SIXTH FRAMEWORK PROGRAMME

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Life Sciences, genomics and biotechnology for health

(LifeSciHealth)

Proposal/Contract no.: 503216

Project acronym: European LeukemiaNet

Project full title: Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe

Network of Excellence

Seventh Annual Activity Report

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Project coordinator: Prof. Rüdiger Hehlmann

Project coordinator organization name: Universität Heidelberg

Publishable Executive Summary

The European Leukemia Net (ELN) stands for more than 8 years cooperative research in a network of excellence (NoE), including over 1000 leukemia specialists from 182 institutions in 34 countries across Europe. ELN has become a landmark in the medical history of leukemia.

Honoring the success of ELN, the contract between the EU and the ELN was extended over the regular period of six years until February 2011. This was the last month of EU funding within the 6th framework programme, but not the last month of ELN. Looking back the ELN has published over 35 guidelines and management recommendations on leukemia diagnosis and therapy. These are the basis for high quality patient care in leukemia across Europe. More leukemia patients survive longer times. In chronic myeloid leukemia the survival time increased almost 10 fold, from 3 years in 1982 to over 25 years in 2011. Will curing the disease be possible in the near future?

ELN funding will continue through the European Science Foundation (ESF), which can secure the ELN Symposia and some of the networking activities until 2015. Together with ESF, the ELN engages in a European initiative to revise the legislation in the field of clinical trials and has taken position in the "Revision of the 'Clinical Trials Directive' 2001/20/EC, Concept Paper'. Motivation and vision has driven the ELN to found the ELN Foundation in 2009, which will sustain and support goals and activities of ELN through donations for ELN research activities. The ELN Foundation website was launched in 2010 (www.elnfoundation.org). In 2011, ELN may assume a new identity, developing from an EU NoE-project to an organisation with legal status. The ELN Steering Committee has taken decisions during the ELN symposium in February 2011 in Mannheim. New collaborations and research goals will be started between partners, new participants will continue to join. ELN has steadily expanded and has made fragmentation of leukemia research in Europe an issue of the past. 2011 and future years will bring many new ideas and good partnerships within the cooperative research of ELNs evolving identity.

In support of this, EUTOS for CML (European treatment and outcome study for chronic myeloid leukemia), a public-private partnership between the ELN and Novartis was recently updated and extended until 2012. This collaboration has already achieved major milestones in CML research by enabling access to the largest CML population ever studied, aiming for a cure of this devastating disease.

The ELN will continue to set high standards for the investigation of all leukemias in Europe and qualify medical doctors and scientists with educational activities on treatment recommendations, new insights in the emergence of the disease and innovative research. Other Public-Private-Partnerships have been established (e.g. EUMDS).

Major achievements during the EU funding period are summarized in the publication "The European LeukemiaNet: achievements and perspectives" (Hehlmann, R; Grimwade, D; Simonsson, B, et al. Haematologica 2011,96:156-162).

Examples are listed below:

- Cooperation instead of fragmentation within the European leukemia research arena
- International cooperation with the US, Japan and Australia.
- Accomplishment of a unique leukemia specific infrastructure given by the three network centers, responsible for management (NMC), information (ELIC) and statistics/biometry (CICS) (WP1-3,17).
- Clinical trials on a European scale through collaboration of the leading national leukemia trial groups of the different leukemia entities (WP4-9) and the interdisciplinary partner groups in diagnostics and therapy research (WP10-15)
- Standardized protocols for clinical trials and diagnostic procedures to achieve comparable data, resulting in better and equal treatment options across national borders
- Networks of reference laboratories in leukemia diagnostics and pharmacokinetics across Europe (WP12, EUTOS for CML)
- Management recommendations for all leukemias
- Patient registries for information on current treatment and best treatment options (EUTOS for CML, EU-MDS)
- Improvement of patient care due to personalized treatment options
- Spread of excellence (ELN Website and publications) and high level training and education to all physicians and researchers within leukemia research.

The ELN is committed to sustain the collaborations within and outside the network and to further develop high quality standards in leukemia research, diagnosis and treatment.

Highlights in 2010 and 2011 include:

- The ELN symposia in Mannheim which attracted 460 ELN participants from 33 countries in 2010 and 425 participants from 34 countries in 2011
- In 2010 acceptance of fourteen new participants to ELN integrating one additional country, namely Estonia
- In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria
- The ELN increased in its last year of EU funding to 182 participants and 34 countries.
- Trials on a European level
- Consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network) and management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms)

- Funding of the ELN Networking Programmes through the European Science Foundation (ESF). ESF will fund the ESF-ELN RNP with more that 80.000 € per year. This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like website, publications, and printed information material.
- Public-private-partnerships between ELN and Novartis successfully continue until 2012, including "A Path to Cure" project.
- In conjunction with the EUTOS elongation, the CML Registry offers access to the largest CML population ever studied (www.eutos.org).
- In European registries in MDS, 1000 included patients have been reached. The follow-up period has been extended by 3 years (www.eumds.org).
- Spread of excellence by close to 80 educational activities at the annual congresses of ASH, EHA and the German/Austrian/Swiss Societies of Hematology and Oncology, the annual CML-educational meetings, more than 15 specialty workshops, publication or completion of more than 550 manuscripts in 2010/2011, the 7th Information Letter, the information booth, the ELN website and more than 800 lectures by ELN-participants.
- The launch of the ELN Foundation website: www.elnfoundation.org to fundraise donations with the aim to cure leukemia.
- An ELN Foundation information newsletter in 7 languages.
- Project websites like ESF-ELN Research Networking Programme.
- A summarizing publication on the ELN: The European LeukemiaNet: Achievements and perspectives, Haematologica. 2011;96:156-62.

ELN as a network recruits larger patient cohorts in shorter time periods from across Europe than any national network and has made a durable impact by promoting leukemia research and improving treatment options.

Uniform definitions, common clinical trials and research projects, prolonged partnerships, new proposals, publications and the steadily increasing number of ELN participants characterise the ELN in 2011. These activities, the international acceptance and the application of ELN criteria point to sustainability and further development of the ELN.

The ELN will continue beyond NoE funding on the forefront of leukemia science, sharing members with the European working groups of EHA (European hematology association), COST-, ESF Research Networking - and EU 7th framework programmes but also public- private partnerships and many more research activities, challenging current knowledge and aiming for a cure of all leukemias.

Section 1: Project objectives and major achievements during the reporting period

1.: Financial sustainability, integration and cooperation, central information and communication, central data management and spread of excellence (WP1-3, 17)

The four network service centers offer a unique leukemia specific infrastructure in regards to network management (NMC), European leukemia information center (ELIC), central infromation and communicating service (CICS), and regstry (WP17).

Sustainability was and is the key project for the **NMC (WP1).** Final reporting of the ELN-EU FP6 project and reorganisation of the ELN beyond EU support constitutes the NMCs actual programme. Inquiring novel funding sources is a continuously ongoing process. Support from the ELN Foundation, from the European Science Foundation (ESF) and through a new EUTOS contract in 2010 could be secured, and applications to the EU 7th framework programme and the German BMBF International bureau were submitted. Contract renewals, stimulation of partners to write new proposals, activation of additional collaborations and organizational support to all ELN activities at national and international levels are major tasks. Leukemia events in 2010 and 2011, including training of young hematologists, communication with industry, patient organizations and public relations as well as the distribution of information on network activities and achievements are managed by the NMC (PR material: flyer, booth, Information Letter). Brainstorming for innovative ideas and new milestones and deliverables are a continuous process.

In 2010, the annual ELN symposium in Mannheim attracted 460 ELN participants from 33 countries and in 2011 425 participants from 34 countries.

In 2010 a workshop on ”Regulatory requirements for the clinical development of cell therapeutics and biologicals” directed by Prof. U. Mansmann, Munich, preceeded the symposium and attracted a major audience.

A session on “Life quality and late effects: activities and future collaboration in the European LeukemiaNet” emphasised an important part of clinical studies and started up the first day of the symposium. The sustainability topic was introduced through the ELN Foundation.

Current collaborations, challenges and new directions in leukemia and related disease entities were highlighted in the WP meetings. The scientific symposium highlighted different methodologies, like whole genome sequencing, molecular biology of MDS, molecular pathogenesis of atypical MPN, the relevance of molecular monitoring for prognosis and treatment of CML and, from a very different point of view, health economic issues in leukemia.

In 2010, the General Assembly accepted fourteen new participants to ELN, integrating one additional country, namely Estonia. In 2010 the ELN comprised 176 institutions from 33 countries working together in now 105 leading national leukemia trial groups and 105 interdisciplinary partner groups.

In 2011, the 8th Annual Symposium of the European LeukemiaNet was held again in Mannheim on February 1-2. This was the last ELN Symposium under EU funding as a Network of Excellence within the6th European Union Framework Programme (2004-2011). NMC organized the scientific program and provided the operational and organizational infrastructure of the symposium and workshops. This includes the scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs. Again it was a major goal and challenge at this annual conference to get the members of all ELN workpackages face-to-face together. In total, 425 participants from 34 countries attended the Symposium in 2011. The ELN is still increasing in 2011. At the end of EU funding the General Assembly agreed, in 2011, on eight new participants integrating one additional country, namely Bulgaria, increasing the number of participants to 182 and the number of countries to 34 (Fig. I.1).

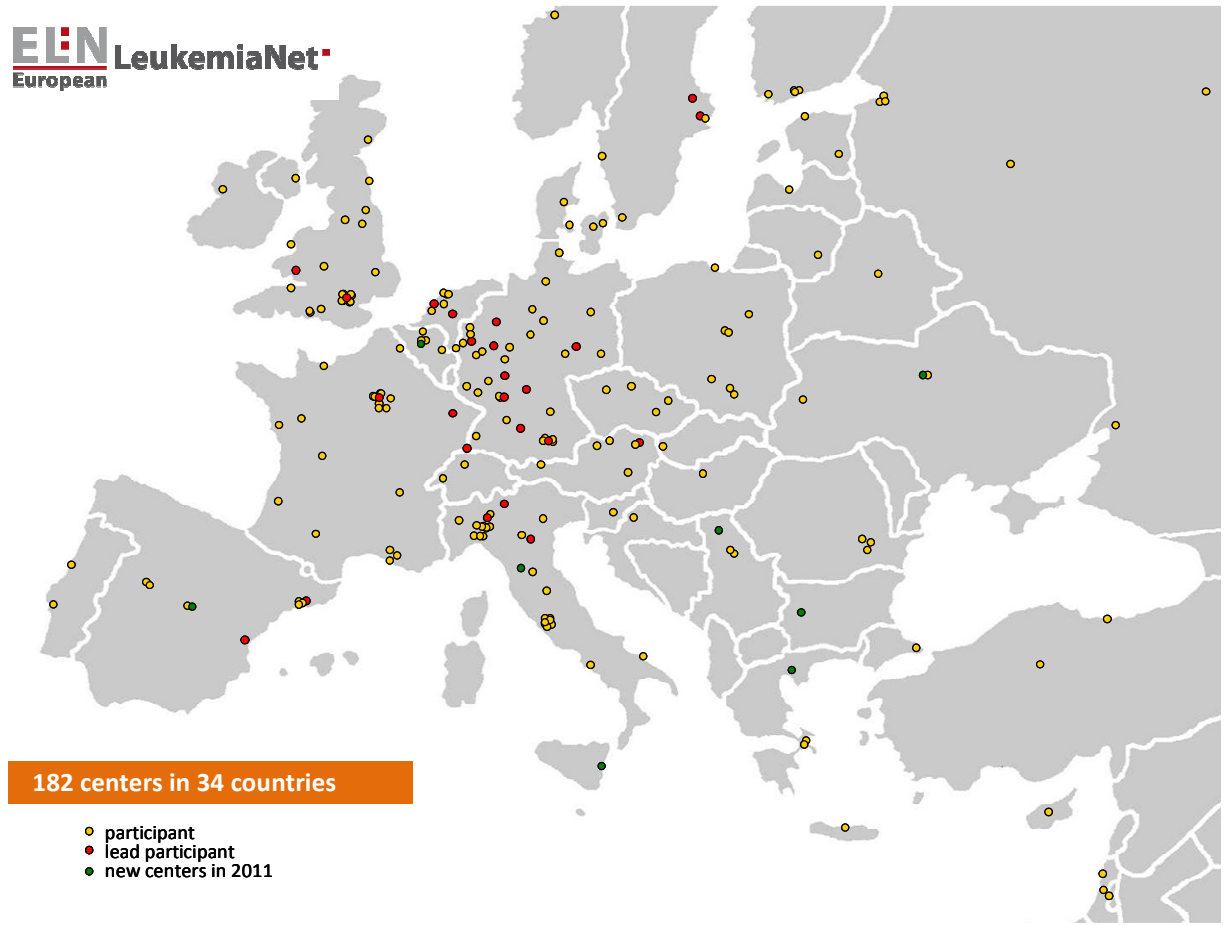

Figure I.1: The 182 centers in 34 countries, which are members of ELN in 2011

About a 1000 internationally recognized clinicians and scientists combine forces within 108 national leukemia study groups and 105 interdisciplinary partner groups in diagnostics, cytogenetics, MRD-research, gene expression profiling and registry, guidelines and industry (Fig. I.2 and I.3).

108 National Leukemia Study Groups

European Networks	CML	AML	ALL	CLL	MDS	CMPD
Austria	●	●	●	●	●	●
Belgium	●	●		●	●	●
Bulgaria	●	●				
Croatia	●		●			
Cyprus	●					
Czechia	●	●	●		●	
Denmark	●	●		●	●	●
Estonia	●					
Finland	●				●	
France	●	● ●	●	●	●	●
Germany	●	●	●	●	●	●
Greece	●		●			
Hungary	●				●	
Ireland	●					
Israel	●	●			●	
Italy	●	●	● ●	●	●	●
Latvia	●					
Luxembourg	●	●				
Netherlands	●	● ●	●	●	●	
Norway	●					
Poland	●	●	●	●		
Portugal	●					
Romania	●		●		●	
Russia	●	●				●
Serbia	●					
Slovakia	●					
Slovenia	●					
Spain	● ●	● ●	●	●	●	●
Sweden	●	●	●	●	●	●
Switzerland	●	●	●		●	
Turkey	●		●			
UK	●	●	●	●	●	●
Ukraine	●			●		
European consortia	EI-CML EBMT	EORTC	EORTC EWALL	ERIC	EBMT EORTC	ECLAP European ET

Figure I.2: 108 National ELN Leukemia Study Groups

105 Interdisciplinary Partner Groups								
Platform for interdisciplinary specialities	Diagnostics	Cyto-genetics	MRD	Gene profiling	SCT	Supportive Care Infections	Registry	Guidelines
Austria	●	●	●		●		●	●
Belarus			●				●	
Belgium		●	●		●	●	●	●
Croatia					●			
Czechia					●		●	●
Denmark		●	●				●	
Finland		●	●	●	●		●	
France	●	●	●	●	●	●	●	●
Germany	●	●	●	●	●	●	●	●
Greece		●						
Hungary					●			
Israel					●	●		
Italy	●	●	●	●	●	●	●	●
Lithuania			●					
Netherlands	●	●	●	●	●	●	●	●
Poland			●		●		●	
Portugal			●					
Russia			●				●	
Serbia			●					
Spain		●	●	●	●	●	●	●
Sweden	●	●	●	●	●	●	●	●
Switzerland	●	●	●		●	●	●	●
Turkey		●	●		●	●	●	
UK	●	●	●	●	●	●	●	●
European consortia	EGIL			EORTC	EBMT CLWP	EBMT		ESH EHA

Figure I.3: 105 Interdisciplinary Partner Groups

Two sessions preceded the Annual Symposium of the European LeukemiaNet in 2011 directly: New developments around the Clinical Trial Directive (CTD)" organized jointly by WP1 and WP2 and the 2nd ESF-ELN Steering Committee Meeting, which was by invitation only.

Dr. Steinhausen, Strasbourg, from the European Science Foundation (ESF) participated in both meetings, introducing the role of ESF ("Forward Look" on Investigator-Driven Clinical Trials) and of the European Medical Research Councils ("Position Paper", CTD, available summer 2011) in the modification process of the CTD and thereafter representing the ESF in the ESF-ELN RNP SC meeting.

The CTD session gave insight into the latest development on Investigator Initiated Trials (IITs) in Europe. Speakers from different stakeholders' perspective, ESF (Dr. Steinhausen), ELN (Ihrig) and the Patient advocacy group (Geissler, Leukämie-Online e.V. / LeukaNET / CML Advocates Network) discussed their efforts in the past and gave direction for future changes. Practical approaches, like a "Voluntary harmonization process for regulatory approval" were introduced by the German Paul-Ehrlich Institute (Krafft). The "Risk-adapted approach to clinical trial regulation and monitoring" was presented by the European Clinical Infrastructure Network (ECRIN, Jaques Demotes). It was stressed that the revision of the *'clinical trials directive' 2001/20/ec concept paper"*

submitted for public consultation will be published by the European commission and that a concerted effort from all groups present is needed to respond.

Challenges and new directions in leukemia and related disease entities were highlighted during the workpackage meeting in three consecutive sessions. Each WP reported on the different projects and discussed future objectives of the group for the coming year.

The Scientific Symposium finalised the symposium with speakers from Europe and the US, presenting outstanding issues within leukemia research such as a revisit of HTLV-I in ATL, a rising CLL incidence after Chernobyl, a new stem cell marker in CLL, progress with MDS and standardized molecular monitoring across Europe. On day two each WP presented the highlights, results and the prospective outlines for the future in a plenary session. The programme was available for download via the ELN homepage (see Figure I.4). The event was further announced at the ESF homepage, at "my medical education" and at the University of Heidelberg homepage (see section 2, Figure 1.7 and 1.8).

WP2 (ELIC) prepared a sponsoring concept to gain funding for the ELN. This will enable the ELN to accept funding for service in return. The ELN will in future have the possibility for sponsoring contracts as an additional tool to get financial support. Characteristics of sponsorship is that the sponsors (main target group: pharmaceutical companies) will receive a specific service in return for their financial support - mainly through the benefits of the network and public relation, like the ELN website. Aim of the sponsoring concept is to generate a budget for the ELN which is distributed according to transparent criteria. It serves as a concept for the financial sustainability of the ELN by attracting sponsors who give regular funds to the ELN with transparent service in return. Target groups will be pharmaceutical companies (one-stop-shop).

Sustainability/ELN Foundation: In contrast, the ELN foundation will collect donations. Its non-profit status does not allow contracts or service to companies in return. Target groups of the ELN foundation are non pharmaceutical companies, private persons and major Foundations. A fundraiser is in charge to contact these target groups.

ELIC is continuously updating the ELN homepage in regards to meetings and conferences, clinical trials, project updates, dissemination of news and the set up of new project sites. In 2010 two new subpages were added informing on the activities of the ELN Foundation and the ESF-ELN-RNP site linking directly to the related homepages www.elnfoundation.org and www.esf.org/esf-eln. The ELN Foundation Website was launched in 2010 as a completely new website. A project to add information about patient advocates has been started to further enhance the benefit of the ELN webpage for patients.

The leukemia trial registry (ELTR) has currently registered up to 100 European leukemia trials and was recently restructured. ELIC also links to and updates the homepage of the public-private partnership "European treatment and outcome study (EUTOS) for CML".

Figure I.4: ELN Homepage with 2 new project sites and the links to the European Leukemia Trial registry and the EUTOS project

The seventh Information Letter was prepared for the symposium in 2011 (**WP2,** ELIC, in cooperation with **WP1**, NMC)., highlighting the current progress on projects, collaborations, meetings, website content and lists upcoming meetings. It fosters cooperation amongst network members and informs the public on hot topics in leukemia.

Figure I.5: The 7th ELN Newsletter 2011

In the name of the ELN ELIC together with the NMC and the European Science Foundation coordinate ELN activities around a response to the *'clinical trials directive' 2001/20/ec concept paper"* which was submitted for public consultation beginning of 2011.

WP3 (CICS) offered computational services to the network:

CICS facilitates computational structures for the network, like data management, algorithmic instruments, statistical networks and profiling structures central registry services help to channel international registry data collection through electronic case report forms (eCRFs).

A central randomization facility accompanies clinical trials

In 2010 the range of functions of the software 'RANDOULETTE' was extended. Randoulette allows online randomisation of individual patients in clinical trials according to Good Clinical Practice The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. The GCP-compliant electronic data capture facility MACRO is also available to research groups within the consortium.

In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports

include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010.
A Microarray – Analysis – Pipeline developed in cooperation with the University Regensburg and designed to automate standard working steps was used on 151 CLL samples to develop a prognostic score for patient survival time and time to treatment.
In 2010 WP3 participated in the planning of pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study), which will start in 2011.
Furthermore, WP3 (IBE, LMU Munich) participates in the FLAMSA 101, 102, 103 studies in high risk AML patients with IT and biometrical services (RANDOULETTE and statistical analysis).

WP17 (Biometry of registry, epidemiology and prognosis) continued to expand the CML and MDS registries together with WP3, WP4 and WP8. Together, both registries account for data from more than 4700 eligible CML and more than 1000 MDS patients. In CML, 24 countries participated in the population-based-registry, collecting baseline and follow up data on new patients diagnosed with CML. A report was provided by WP17. The challenge will be to assure proper monitoring and follow-ups, to reach the goal of developing and validating a comprehensive prognostic model that allows optimization of individual treatment choices.
Recently, an AML-registry, has started in Germany with data input within the AML-Intergroup, aiming towards an European AML-registry.

2. Performance of clinical trials (WP4-9, 14-15)

ELN overcomes national fragmentation of clinical trials, avoids duplication of efforts and accelerates outcome by recruiting larger patient cohorts in shorter periods from across Europe. Uniform definitions, protocols and outcome measures allow comparison of research results and lead to common guidelines and treatment recommendations. This impacts patients, health care economics and society and results in faster implementation of best treatment options for all patients across Europe. 36 recommendations were published in the funding period, three of these in 2010 and 2011 (see Table I.1 below). In leukemia ELN sets the standards, protocols and common data sets. The trial registry on the ELN website informs on all active, but also inactive clinical trials, which are not recruiting but evaluating results and follow-up data

WP4 (CML) has six multicenter clinical trials ongoing. Trials with new signal transduction inhibitors, new immunotherapy (vaccination, interferon) and with attempts to stop imatinib therapy are running successfully across Europe. The European registry and the subregistries have grown rapidly and enrolled more than 4000 patients. Standardization rounds and harmonization for molecular monitoring of residual CML with 58 ELN laboratories (including 28 national reference laboratories) are ongoing. A consensus manuscript on molecular monitoring and a follow up paper were published.

WP4 is closely networking with WPs 1-3, 10-14, 17, CML Study Groups outside EU and pharmaceutical industry. EUTOS (European Treatment and Outcome Study) for CML was prolonged for another 2 years until December 2012. Spread of excellence activities were focussing on hematology conferences and educationals.

In the last funding period the **AML Groups (WP5)** achieved further progress and experience in the field of molecular markers and new drugs targets (Hematologic Malignancies conference in Brussels, 2010). Promising therapeutic results were confirmed mainly in promyelocytic leukemia. First updates suggested a successful cooperation of trials in the AML Intergroup in younger patients, while data and experiences in older age AML increased Europe wide. An increasing availability of data on allogeneic SCT suggested the use in high-risk disease even in older patients (see Annex Section 3, WP5 publication list 2010).

The AML Intergroup as an ELN pilot study has now recruited more than 3000 patients. The latest update allows reliable projections to 5 years. Uniform European recommendations on all clinical aspects of AML were published. Multiple approaches and experiences were reported on the field of allogeneic SCT. The AML Intergroup coordinates European trials and harmonizes treatment protocols, future strategies and comparability parameters according to European guidelines. The comparability of trials across Europe will lead to synergies and improved outcomes in research and patient care.

The successful national European study groups for ALL **(EWALL, WP6)** aim to combine their efforts in order to create a world-wide leading research group for adult ALL. Integrating activities are of major importance and include the development of standardized laboratory procedures for diagnostic confirmation, an overview on prognostic factors and on ongoing European studies in ALL within a study registry. Phase I-III intergroup studies and the combination and standardization of methods, definitions and clinical application of MRD are jointly executed research activities.

The first meeting of the EHA-SWG-EWALL took place at EHA in Barcelona 2010 with about a 100 participants. EWALL was extended by a Slowakian study group for adult ALL. Several publications on studies and standardisation in diagnoses and follow up were published in 2010 and beginning 2011.

In 2010, **WP7 (CLL)**, ERIC has fostered scientific credibility, competence and excellence of ERIC as a European non-profit organization. Furthermore, it connects the European LeukemiaNet and EHA as interacting European promoters of competence in hematology and leukemia. In 2010 three ERIC meetings and one ERIC/EHA SWG workshop were held (between 40 and 120 participants). The outcomes of the clinical trials were presented at ASH 2010 in Orlando.

The **MDS working group (WP8)** has started attempts in 2010 to integrate into the Working group of the European Hematology association, EHA MDS Working group. An EHA MDS working group met in December 2010 to discuss the future EHA meetings and the collaboration on projects on clinical and laboratory research. The second major goal of WP8 is to set up an international MDS clinical trial

platform to standardize methodology of diagnosis (flow cytometry), therapy (Vidaza, Lenalinomide) and follow up in MDS an to allow better comparison of results. Discussions with Dr. Hartmut Kraft (PEI), co-chair of the Clinical Trial facilitation Group (CTFG) are ongoing (http://www.hma.eu/77.html). Therapeutic guidelines on treatment of MDS can be found on the website: http://mds.haematologica.org (Fig. I.6).

Figure I.6: Therapeutic guidelines on treatment of MDS on the website: http://mds.haematologica.org

As the second WP that has started a European MDS-registry (EUMDS) with the private partner Novartis, WP8 has reached the milestone of including 1000 patients to this registry. 15 countries participate currently. The follow-up period has been extended to 3 years. It is the aim to enhance the value of the registry by integrating and matching biobanking. WP8 plans to apply in the EU 7th framework programme "Rare diseases".

The **CMPD working group (WP9)** reported within the ELN in 2010 and 2011 on ongoing clinical trials in myeloproliferative neoplasms (MPN) in Europe. New proposals for the next period 2011 were discussed, like a consensus on the outcome measures for clinical trials in MPNs or a booklet for MPN patients, harmonized throughout Europe. In addition, an update on the MPN&MPNr-EuroNet activities was given (Molecular Diagnosis of MyeloProliferative Neoplasms (MPN) and MPN-related congenital diseases (MPNr) (COST Action BM 0902)).

The **diagnostics platform (WP10)** focussed attention to the development of optimized protocols for flow cytometric detection of MRD. Together with WP12, a joint program was established to investigate the optimal approach for MRD- directed therapy in leukemia patients with AML, which lack a leukemia-specific marker (publications see Annex Section 3).

The **cytogenetics working group (WP11)** aimed to intensify harmonization of cytogenetic techniques between laboratories based on consensus protocols and practical training in other laboratories and to improve analysis of large and complex cytogenetic data sets, using the Cytogenetic Data Analysis System (CyDAS.org). New cases with rare chromosome aberrations were collected in collaboration

with the Atlas of Genetics and Cytogenetics in Oncology and Hematology. Cryptic and complex chromosome aberrations were revealed by SNP microarray analysis. The continuous interlaboratory development and provision of methods lead to a number of publications on chromosomal abnormalities in different leukemias, especially AML and MDS in 2010 and 11.

The minimal residual disease (MRD) working group **(WP12)** established assays from which patients with myeloid leukemias/myeloproliferative disorders (MPDs) can benefit from. Key approach is the monitoring of minimal residual disease (MRD) using real-time quantitative PCR (RQ-PCR). Key objectives over the last year have been to continue to improve standardization of established assays (i.e. *BCR-ABL,* JAK2 V617F in collaboration with WP4 and WP9, respectively), the evaluation of novel RQ-PCR assays (i.e. Wilms' Tumor gene (*WT1*) and nucleophosmin (*NPM1*) mutation) and the validation and implementation of a computer software reporting package to improve standards of reporting of RQ-PCR data to clinicians, which also serves to facilitate comparison of results between laboratories. MRD assessment enables to guide therapies leading to improved management and clinical outcome.

The **gene profiling platform (WP13)** was first interested in using gene expression profiling for investigating basic research topics and the application of microarrays in a clinical setting. Since 2010 next generation sequencing is of high interest and takes over the focus. The evaluation of both screening methodologies is strongly supported by biostatisticians. Microarray data as well as NGS data very recently were collected within the ELN network and involved respective subgroups in WP13 as well as other WPs in close collaborations. The DACH and the MILE studies are published and data is publicly available in the GEO database. In parallel, all biostatistical platforms have been upgraded in 2010 and expanded to NHS data sets: GAP is freely available for all ELN members, and not restricted to the MILE subgroups. In the ELN GAP database, data can easily be stored, exchanged and analyzed within the participating WPs. Many results were published in 2010, many more are in preparation (see Annex Section 3).

Several important deliverables were obtained in the stem **cell transplantation group (WP14)** during 2010. The stem cell transplant survey was performed in Europe and World wide, but also the harmonization process between Europe and the US was continued, providing valid information on changes in indications, frequencies among the different countries but also among diseases. WP14 makes use of synergies with the European Group for Blood and Marrow Transplantation (EBMT). The main activities include regular surveys on the transplantation activity in Europe, recommendations for the use of stem cell transplantation assessment of key factors responsible for outcome and, as a current focus, the adaptation of transplantation conditions to the needs of elderly patients, mainly with AML and ALL. In CML, an improvement of transplantation outcome has been achieved with low transplantation mortality (<10%) and 3-year survival-rates of approximately 90% in chronic phase and more than 50% in advanced phase patients. These favorable developments are mediated by improvements in patient and donor selection, transplantation procedures and supportive care.

The **working group on supportive care and antiinfection prophylaxis (WP15)** initiated collaboration with IDSA regarding guidelines for vaccination of patients with hematological malignancies in general and after stem cell transplantation. These have been presented at the IDSA meeting in Vancouver, Canada in October 2010 and the manuscript is in the final stages of preparation. The 13th training course of the Infectious disease working party (IDWP) was held in 23-25 September, 2010, Paris, France. A 4th European Conference regarding Infections in Leukemia is planned for September 2011, updating previous guidelines and covering new topics.

3. European Leukemia Registries

The ELN established patient registries for CML and ALL in 2005. The CML registry was expanded in 2007 (EUTOS for CML), a MDS registry started in 2008 (EUMDS), both funded by Novartis, currently until 2012. An AML registry was initiated in 2010, intending to act as a data repository for the different AML trial groups.

One of the key objectives is to provide a clear epidemiological picture of the disease and a real world information on patient treatment and outcomes across Europe. EUTOS for CML is collecting baseline, treatment and outcomes data for patients with CML. The final report from the central data centre (CDC) in Munich summarises the current state:

The three sections (in-study, out-study, and population-based) of the EUTOS CML-Registry have been successfully established. With 2389 eligible CML-patients in the in-study and 1582 patients in the out-study section even more patients than initially expected could be recruited.

24 countries participated in the prospective population-based study. It did take time to agree on the research plan, so the majority of the data was collected in 2010. Considering the challenges of a European registry and the differences in ethics and regulatory affairs for each individual country, the reporting of 731 eligible patients is as a success. Alltogether data of 4703 eligible CML-patients have been registered in the reporting period.

Typically registers take years before data can be analysed and manuscripts can be submitted, due to different laws and regulations in each country. In contrast, the EUTOS registry has already provided several detailed reports and presentations, summary articles in the ELN Newsletter and PR documentation. In addition, a manuscript has been finalized about a new prognostic model which allows to predict complete cytogenetic response (CCgR) at 18 months using two variables only (see Hasford et al., Annex Section 3 WP17).

The major challenge in the coming period is to safeguard that all patients are monitored according to the research plan and that the registry receives the follow-up patient data.

The European MDS registry (WP8) has now data on more than 1000 patients from 15 countries and plans to register 2000 patients in the next 3 to 5 years. First results were presented at ASH 2010, Orlando.

A German AML registry started in 2010 with the plan to develop this registry into a common European AML registry, which will provide information on differences in treatment, treatment outcomes, on needs for improvement, and on life expectancy of AML patients across Europe.

4. Diagnosis / Follow-up (WP10-13)

Early diagnostic, proper classification of disease and the follow up on minimal residual disease are essential for optimal treatment of each patient. The cooperation between the diagnostics WPs: morphology (**WP10**), cytogenetics (**WP11**), detection of minimal residual disease (**WP12**) and gene profiling (**WP13**) lead to a European consensus report on blood cell differentiation (Zini et al. 2010, see Annex section 3, WP10) and to a consensus proposal in immunophenotyping of acute leukemia lymphoproliferative disorders (Béné et al., 2011).

WP11 (cytogenetics) and WP13 (gene profiling) developed the "Leukemia Gene Atlas", a new web-based tool for the ELN (leukemia-gene-atlas.org), a new web-based tool for the ELN (leukemia-gene-atlas.org). The IRON study of WP13 was analysing the interlab robustness of next generation sequencing (NGS) data. The future plan is to use NGS in the standardisation process of diagnosis, prognosis and follow up, finding markers in those patients who survive. A gene list of hematological malignancies will be of common interest and needs a concerted effort of all leukemia groups.

WP12 has linked up with the international standardization efforts for RQ-PCR analysis and reporting of *BCR-ABL* results in chronic myeloid leukemia (CML) (WP4). The *BCR-ABL* related work within WP12 has focused on the development of accredited reference reagents as a means to facilitate the implementation of the International Scale (IS) for MRD determination in CML. The documentation describing these experiments was submitted by NIBSC to the World Health Organisation (WHO) in July 2009 and following assessment of the evidence, the materials were approved as primary reference reagents in November 2009. The supply of these reagents will be limited to companies and reference laboratories that are able to generate the secondary reference materials that will actually be used by testing laboratories. This work was presented at EHA 2010 (White *et al*., *Haematologica* 2010;95; Suppl2:84-85) and recently published (White *et al*., *Blood* 2010;116:e111-7).

The EUTOS project (WP4) has focused very productively on the establishment of conversion factors (CFs) for at least one laboratory per country or region. An evaluation concerning the stability of CFs over time has been presented at ASH 2010 (Müller *et al*., *Blood* (ASH Annual Meeting Abstracts), Nov 2010; 116: 893). A control round to assess the ability of laboratories to detect resistance-associated mutations was performed and results presented at ASH 2010 (Ernst *et al*., *Blood* (ASH Annual Meeting Abstracts), Nov 2010; 116**:** 894).

Reference or consensus documents in cytometric methods have also been achieved within the ELN (see Table below: Recommendations and guidelines).

5. Consensus recommendations and guidelines

The ELN published during the EU funding period 41 European standards, consensual recommendations and guidelines in high impact journals (see Table 1). ELN criteria are widely used. This was and still is one of the central aims of ELN. A special article on "The European LeukemiaNet: achievements and perspectives was published this year (2011) in Haematologica. It includes a table summarising 35 of these 41 publications, explains the start of ELN, reflects on past and future highlights and the aera of ELN.

Also in the last funding period, consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network), management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms) and guidelines (antifungal management) were published by ELN.

The table below includes all 41 ELN standards, consensual recommendations and guidelines, published so far.

Table I.1: The ELN standards, consensual recommendations and guidelines, published until 3/2011.

Recommendations and Guidelines	
CML management recommendations	Baccarani et al., Blood 2006; 108: 1809 – 1820 Hehlmann et al., Lancet 2007; 370: 342 – 350 Baccarani et al., J Clin Oncol 2009; 27: 6041 – 6051
CML molecular monitoring	Müller et al., Leukemia 2009: 1957 – 1963 Hughes et al., Blood 2006; 108: 28 – 37 Branford et al., Leukemia 2006: 1925 – 1930
CML-prognosis – EUTOS-score	Hasford et al., Blood 2011, in press
AML management recommendations	Döhner et al., Blood 2009, 10; 115: 453 – 474
APL management recommendations	Sanz et al., Blood 2009; 113: 1875 – 1891
APL molecular monitoring	Grimwade et al.; J Clin Oncol 2009; 27: 3650 – 3658
CLL guidelines	Hallek et al., Blood 2008; 111: 5446 – 5456
CLL molecular and flow-cytometric monitoring	Ghia et al.; Leukemia 2007; 21: 1 – 3 Rawstron et al., Leukemia 2007; 21: 956 – 964
Evidence- and consensus-based European guidelines on MDS	ELN Homepage: http://www.leukemianet.org/content/leukemias/mds/recommendations
CMPD management recommendations (PV, ET, PMF)	Barbui et al., J Clin Oncol 2011; 29: 761 – 770.
Response criteria for ET and PV	Barosi et al., Blood 2009; 113: 4829 –3314
Definition of resistance and intolerance to hydroxyurea in PV and myelofibrosis	Barosi et al., Br J Haematol 2010; 148: 961 – 963
Reference document for four- and five-color flow-cytometry	Arnoulet et al. Cytometry B Clin Cytom 2010, 78: 4 – 10
Flow-cytometry in MDS	van de Loosdrecht et al.; Haematologica 2009: 94: 1124 – 1134
A European consensus report on blood cell identification	Zini et al., Br J Haematol 2010; 151: 359 – 364
Immunophenotyping	Haferlach et al., Genes Chromosomes Cancer 2007; 46: 494 – 499 Béné et al., Leukemia 2011; 25: 567 – 574.
FIP1L1-PDGFRA – recommendations for diagnosis & molecular monitoring	Jovanovic et al., Blood 2007; 109: 4635 – 4640 Score et al. Leukemia 2009; 23: 332 – 339
MRD – standardized approaches to reporting of minimal residual disease	Ostergaard et al., Leukemia 2011; Apr. 15, Epub ahead of print
WT1 PCR standardization	Cilloni et al., J Clin Oncol 2009; 27: 5195 – 5201
Gene expression profiling recommendations	Kohlmann et al., Br J Haematol 2008; 142: 802 – 807
Microarray analyses guidelines	Staal et al., Leukemia 2006; 20: 1385 – 1392
Transplant-□associated microangiopathy recommendations	Ruutu et al., Haematologica 2007; 92: 95 – 100
Stem cell transplantation recommendations in CLL in MDS	 Dreger et al., Leukemia 2007; 21: 12 – 17 De Witte et al., Haematologica 2006; 91: 750 – 756
Recommendations for management of infections • Quinolone prophylaxis for bacterial infections in afebrile neutropenia • HSV, VZV and EBV • CMV, HHV-6, HHV-7 and HHV-8 • Empirical antifungal therapy in febrile neutropenic patients • Primary antifungal prophylaxis • Candida and Aspergillus • Vaccination in stem cell transplant recipients	 Bucaneve et al., EJC Supplements 2007 (Vol. 5, 5 – 12) Styczynski et al., Bone Marrow Transplant 2009; 43: 757 – 770 Ljungman et al., Bone Marrow Transplant 2005; 35, 737 – 746 Marchetti et al., EJC Supplements 2007 (Vol. 5, 32 – 42) Maertens et al., EJC Supplements 2007 (Vol. 5, 43 – 48) Herbrecht et al., EJC Supplements 2007 (Vol. 5, 49 – 59) Ljungman et al. Bone Marrow Transplant 2008; 42: 227 – 240
CML management recommendations	Baccarani et al., Blood 2006; 108: 1809 – 1820 Hehlmann et al., Lancet 2007; 370: 342 – 350 Baccarani et al., J Clin Oncol 2009; 27: 6041 – 6051

6. Synergies, cooperations and sustainability

Leukemia is a rare disease and European clinical trials are a prerequisite to gain a broad patient collective, to discuss and compare results and offer optimal treatment to the patient. European harmonisation efforts are of major importance for progress in all leukemias. In 2011 at the end of EU funding ELN integrates 182 centres in 34 countries. ELN clinicians and researchers aim for the cure of leukemia.

ELN is a network grown by mutual trust, synergies and competition. It stands for innovation in the field of leukemia and offers internationally recognized researchers. ELN integrates a large portfolio of new disease markers, novel targets, drugs, drug-combination and dose-optimisation studies, vaccination approaches and next generation high-throughput technologies developed in a harmonised setting of European collaborations. Joint infrastructures, the research activities and the enormous diversity of ELN member institutions enable durability well beyond the period of EU-funding.

Important activities include consensus decisions in clinical study endpoints, the set up of patient registries for all leukemias, common standardisation procedures and classification systems in diagnosis and follow up (molecular monitoring, cytogenetics, minimal residual disease assessment) but also harmonisation in data evaluation and reporting. Cooperative research is the only way to cure leukemia. The ELN is likely to have a durable impact on leukemia research in Europe. Infrastructure and the productive collaboration provided by the ELN have accomplished a valuable contribution to progress in the field of leukemia.

ELN will continue beyond NoE funding on the forefront of leukemia science, sharing members with the European working groups of EHA (European hematology association), COST-, ESF Research Networking - and EU 7th framework programmes but also within public- private partnerships and non-profit organisations (ELN Foundation), challenging current knowledge and aiming for a cure of all leukemias.

Section 2: Workpackage progress of the period

1 NMC (WP01)

Objectives and starting point of work at the beginning of the reporting period

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

In 2010 an 2011 the key issue for the NMC was to attract funding to sustain the ELN Network. In addition, the final reporting of the ELN project with information to all members on finances and audits was executed. While a new identity of the ELN is in progress, support from the ELN Foundation and through the European Science Foundation (ESF) could be settled. In addition, EUTOS for CML, the public-private partnership between ELN and Novartis was prolonged until 2012. Furthermore applications to the EU 7th framework programme and the German BMBF International bureau were submitted. Contract renewals, stimulation of partners to write new proposals, activation of additional collaborations and organizational support to all ELN activities at national and international level were major tasks. Success is again observed in the international acceptance of ELN and in the growth of ELN in 2011 to 182 institutions from 34 countries.

1.3f Operating management of networking, i.e.legal and contractual, dissemination and knowledge (including 1.14, 1.20)

In 2010 and 11 the NMC offered again a high degree of managerial services, fundraising activities and the presentation of sustainability concepts:

- Meetings organized by NMC:
  - The 7 th and 8th Annual ELN Symposia in 2010 and 2011 with 460 participants from 33 countries and 425 participants from 34 countries, respectively.
  - The WP-meetings at EHA in Barcelona 2010 (more than 200 participants), and the ELN-breakfast meeting and WP meetings at ASH in Orlando in December 2010 (over 150 participants).
  - Educational day for young hematologists in conjunction with EUTOS for CML, Naples, May 2010
  - 19th International CML-Workshop with EUTOS meeting in Heidelberg, July 2010
  - ESH-ELN joined CML meeting in Bordeaux, 2010
  - ELN-CML Educational Symposium (ELN Frontiers) in conjunction with EUTOS for CML including a press conference, Vienna, October 2010

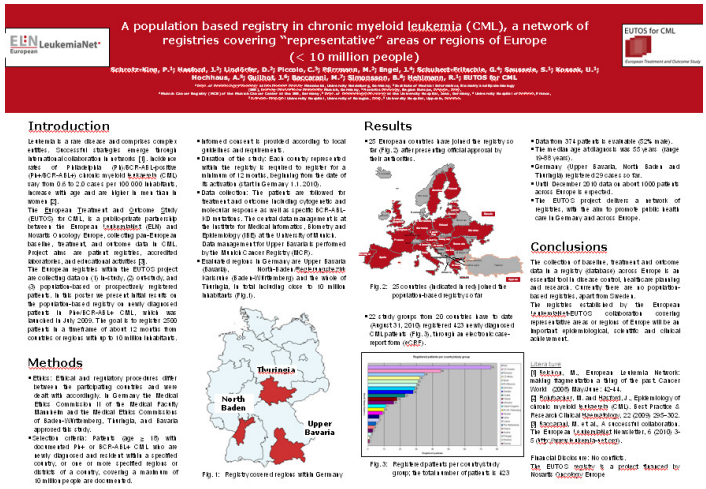

Figure 1.1: Poster on the EUTOS registry presented at the DGHO in 2010.

Figure 1.2: EUTOS brochure: Achievements 2007-2010.

- Presentations:
  - Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010 (Figure 1.1).
  - Summary Information Letter on Achievements: EUTOS 2007-2010 (Figure 1.2).
  - 7th ELN newsletter at the Annual ELN Symposium 2011
  - Presentation of the ELN Foundation and the EUTOS for CML project at ASH 2010.
  - Presentation of the ELN exhibition booth at international hematology meetings in 2010 and 2011 (EHA, ASH, DGHO)

- Publications
    - Dissemination of reprints of research articles, guidelines and recommendations, ELN flyers, newsletters, treatment recommendations in pocket card format, ELN booth exhibition at conferences,
    - Publication on the ELN: The European LeukemiaNet: achievements and perspectives, Haematologica. 2011;96:156-62. Epub 2010 Nov 3.

SPECIAL ARTICLE

The European LeukemiaNet: achievements and perspectives

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ABSTRACT

The only way to cure leukemia is by cooperative research. To optimize research, the European LeukemiaNet integrates 105 national leukemia trial groups and networks, 105 interdisciplinary partner groups and about 1,000 leukemia specialists from 175 institutions. They care for tens of thousands of leukemia patients in 33 countries across Europe. Their ultimate goal is to cure leukemia. Since its inception in 2002, the European LeukemiaNet has steadily expanded and has unified leukemia research across Europe. The European LeukemiaNet grew from two major roots: 1) the German Competence Network on Acute and Chronic Leukemias; and 2) the collaboration of European Investigators on Chronic Myeloid Leukemia. The European LeukemiaNet has improved leukemia research and management across Europe. Its concept has led to funding by the European Commission as a network of excellence. Other sources (European Science Foundation; European LeukemiaNet-Foundation) will take over when the support of the European Commission ends.

Key words: Cooperative leukemia research, European LeukemiaNet, transnational and interdisciplinary cooperation on leukemia, cure of leukemia, leukemia management guidelines.

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Introduction

Before the creation of the European LeukemiaNet (ELN), there were a number of pre-existing networks in Europe that were each individually developing diagnostic methodology, running clinical trials and producing management guidelines.[1] The main goal of the ELN was to create an environment in which these organizations could work more closely together, to harmonize their efforts and bring their advances to a wider community in a more timely fashion.

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Figure 1.3: ELN publication on achievements and perspectives in Hematologica in 2011

In summary: Spread of excellence by close to 90 educational activities at the annual congresses of ASH, EHA and the German/Austrian/Swiss Societies of Hematology and Oncology, the annual CML-educational meeting, more than 20 workshops, by publication or completion of more than 550 manuscripts, the 7th ELN Information Letter, the information booth at ASH EHA and DGHO, an ELN

Foundation Newsletter in 7 languages, the EUTOS-Newsletter, the ELN and ELN Foundation websites, including project sites like ESF-ELN RNP, and more than 500 lectures by ELN-participants.

- Sustainability
  - Funding of the ELN Networking Programmes through the European Science Foundation (ESF), 2010-2015. ESF will fund the ESF-ELN RNP with more than 80.000 € per year. This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like the website, publications, and printed information material.
  - Prolongation of EUTOS for CML public-private-partnership between ELN and Novartis until 2012.
  - The launch of the ELN Foundation website: www.elnfoundation.org to fundraise donations with the aim to cure leukemia.
  - Acceptance of fourteen new participants to ELN integrating one additional country, namely Estonia, in 2010
  - In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria
  - Growth of ELN in 2011 to 182 participants and 34 countries
  - Plans for an infrastructure platform for international studies (for example for MDS and CML), proposals in the 7th framework programme submitted

1.4f Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network, for example setting up the ELN Foundation

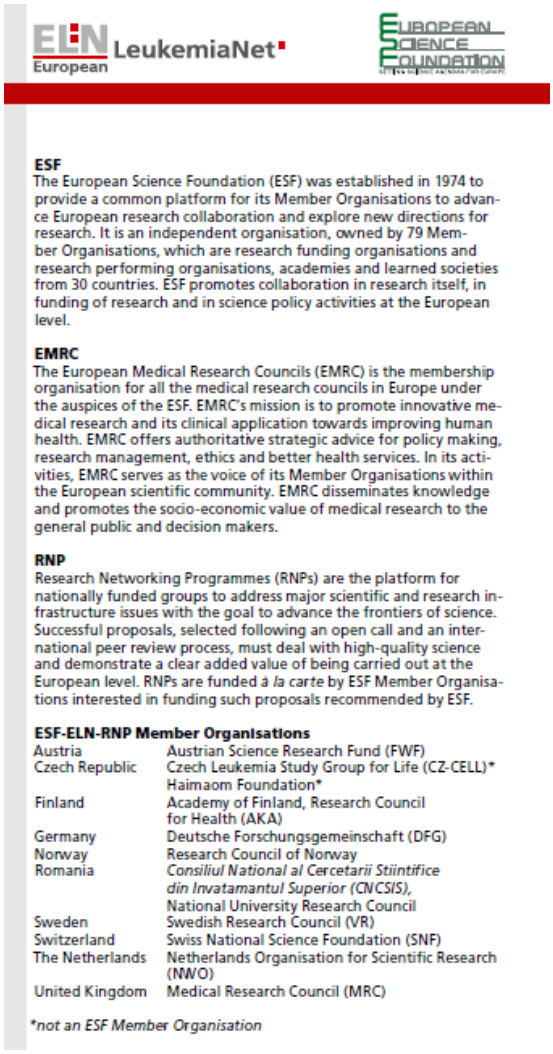
The NMC gave also for the last period advice for the preparation of the financial reports i. e. which costs are eligible and how Forms C are prepared. Due to the constantly increasing number of participants, this is time consuming but also rewarding due to the growing impact of ELN. A new financial plan of budget allocation for the 7th funding period was prepared.

During 2009 and 2010 all institutions were informed on their remaining budget and their expenses. Institutions which did not spend their money were asked to pay it back. More than 120.000€ were returned to the NMC. The General Assembly and the Steering Committee decided to use this money for future ELN symposia.

In addition the NMC centrally managed the reimbursement of all travel costs arising from the Annual Symposia 2010 and 2011 and all WP meetings and workshops.

The ELN proposal to the European Science Foundation was accepted in 2010. The ESF-ELN RNP started in July 2010 with a kick-off meeting in Mannheim. ESF will fund the ESF-ELN RNP for 5 years (2010-2015). This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like the website, publications, and printed information material.

First time in 2011 the ESF partially funded the ELN Annual symposium, reflected in the last page of the Programme brochure 2011.



ELN European LeukemiaNet

EUROPEAN SCIENCE FOUNDATION

ESF
The European Science Foundation (ESF) was established in 1974 to provide a common platform for its Member Organisations to advance European research collaboration and explore new directions for research. It is an independent organisation, owned by 79 Member Organisations, which are research funding organisations and research performing organisations, academies and learned societies from 30 countries. ESF promotes collaboration in research itself, in funding of research and in science policy activities at the European level.

EMRC
The European Medical Research Councils (EMRC) is the membership organisation for all the medical research councils in Europe under the auspices of the ESF. EMRC's mission is to promote innovative medical research and its clinical application towards improving human health. EMRC offers authoritative strategic advice for policy making, research management, ethics and better health services. In its activities, EMRC serves as the voice of its Member Organisations within the European scientific community. EMRC disseminates knowledge and promotes the socio-economic value of medical research to the general public and decision makers.

RNP
Research Networking Programmes (RNPs) are the platform for nationally funded groups to address major scientific and research infrastructure issues with the goal to advance the frontiers of science. Successful proposals, selected following an open call and an international peer review process, must deal with high-quality science and demonstrate a clear added value of being carried out at the European level. RNPs are funded *à la carte* by ESF Member Organisations interested in funding such proposals recommended by ESF.

ESF-ELN-RNP Member Organisations

Austria	Austrian Science Research Fund (FWF)
Czech Republic	Czech Leukemia Study Group for Life (CZ-CELL)*
	Haimaom Foundation*
Finland	Academy of Finland, Research Council for Health (AKA)
Germany	Deutsche Forschungsgemeinschaft (DFG)
Norway	Research Council of Norway
Romania	*Consiliul National al Cercetarii Stiintifice din Invatamantul Superior (CNCSIS),* National University Research Council
Sweden	Swedish Research Council (VR)
Switzerland	Swiss National Science Foundation (SNF)
The Netherlands	Netherlands Organisation for Scientific Research (NWO)
United Kingdom	Medical Research Council (MRC)

**not an ESF Member Organisation*

Figure 1.4: Program of the Annual ELN Symposium 2011 with ESF logo, ESF, EMRC and RNP texts

The EUTOS for CML public private partnership was continued in a new contract until 2012. Now, subcontracts between the University of Heidelberg and the ELN on one hand and ELN member countries on the other hand are being signed.

The ELN Foundation launched its website in 2010 and continued to fundraise donations to support ELN research.

New proposals to the European Commission were sent or are in preparation to the 7th framework programme.

A proposal was sent in 2011 to the International Bureau of the BMBF (Federal Ministry of Education and Research) in Germany to support the scientific networking between Russia and Germany.

1.5f Organization of internal and external reporting ensuring that milestones are effectively reached

During 2010 and 2011 progress reports, meeting minutes, presentations and summary notes of meetings and symposia are collected and available at the management center for external reporting.

1.6f Organization of regular meetings held by the Steering Committee

Two SC meetings were organized in 2010: in February 2010 in Mannheim and in June 2010 in Barcelona. In 2011 an SC Meeting took place at the Annual symposium in Mannheim. Discussed and agreed issues were communicated to all participants for information and coordination of the annual meetings, deliverables, reporting and contractual affairs also in 2011 (see Annex Section 3, WP1-5 and 1-6). In future, the ELN SC-Meetings will be held together with the ESF-ELN RNP SC-Meetings. The next ELN SC-Meeting is planned for June 2011 in London during EHA congress.

1.7f Organization of the Annual Network's Symposium 2010

In 2010, the annual ELN symposium was held in Mannheim on February 1-3. It attracted 460 ELN participants from 33 countries.

A workshop on "Regulatory requirements for the clinical development of cell therapeutics and biologicals" directed by Prof. U. Mansmann preceded the symposium and attracted a major audience.

A session on "Life quality and late effects: activities and future collaboration in the European LeukemiaNet" emphasised an important part of clinical studies and started up the first day of the symposium. The sustainability topic was introduced through the ELN Foundation. Current collaborations, challenges and new directions in leukemia and related disease entities were highlighted in the WP meetings. The scientific symposium highlighted different methodologies, like whole genome sequencing, molecular biology of MDS, molecular pathogenesis of atypical MPN, the relevance of molecular monitoring for prognosis and treatment of CML and from a very different point of view, health economic issues in leukemia.

In 2010, the General Assembly accepted fourteen new participants to ELN integrating one additional country, namely Estonia. In 2010 the ELN included 176 institutions from 33 countries working together in now 105 leading national leukemia trial groups and 105 interdisciplinary partner groups.

1.7g Organization of the Annual Network's Symposium 2011

In 2011, the 8th Annual Symposium of the European LeukemiaNet was held again in Mannheim on February 1-2. This was the last ELN Symposium under EU funding as a Network of Excellence within 6th European Union Framework Programme (2004-2011). NMC organized the scientific program and provided the operational and organizational infrastructure of symposium and workshops. This included the scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs. Again it was a major goal and challenge at this annual conference to get the members of

all ELN workpackages face-to-face together. In total, 425 participants from 34 countries attended the Symposium in 2011. The ELN is still increasing in 2011, at the end of EU funding the General Assembly agreed in 2011 on eight new participants integrating one additional country, namely Bulgaria, increasing the number of participants to 182 and the number of countries to 34.

Figure 1.5: Participants of the 8th annual ELN Symposium 2011and the 12th Annual symposium of the German Competence Network "Acute and chronic Leukemias" in Mannheim, February 1-2, 2011

Two sessions preceded the **8th** Annual Symposium directly: New developments around the Clinical Trial Directive (CTD)" organized jointly by WP1 and WP2 and the 2nd ESF-ELN Steering Committee Meeting, which was by invitation only.

Dr. Steinhausen from the European Science Foundation (ESF) participated in both meetings, introducing the role of ESF ("Forward Look" on Investigator-Driven Clinical Trials) and of the European Medical Research Councils ("Position Paper" CTD, available summer 2011) in the modification process of the CTD and thereafter representing the ESF in the ESF-ELN RNP SC meeting.

The CTD session gave insight into the latest development on Investigator Initiated Trials (IITs) in Europe. Speakers from different stakeholders' perspective, ESF (Dr. Steinhausen), ELN (Ihrig) and the Patient advocacy group (Geissler, Leukämie-Online e.V. / LeukaNET / CML Advocates Network) discussed their efforts in the past and gave directions for future changes. Practical approaches, like a

"Voluntary harmonization process for regulatory approval" were introduced by the German Paul-Ehrlich Institute (Krafft) and the "Risk-adapted approach to clinical trial regulation and monitoring" was presented by the European Clinical Infrastructure Network (ECRIN, Jaques Demotes). It was stressed several times, that the revision of the *'clinical trials directive' 2001/20/ec concept paper"* submitted for public consultation, will be published by the European commission and that a concerted effort from all groups present is needed to respond.

Challenges and new directions in leukemia and related disease entities were highlighted during the workpackage meeting in three consecutive sessions. Each WP reported on the different projects and discussed future objectives of the group for the coming year.

On day two each WP presented the highlights, results and the prospective outlines for the future of their session from the day before in a plenary session. A scientific symposium with invited speakers from Europe and US presenting outstanding issues within leukemia research finalised the ELN Symposium. The NMC organized the scientific program and provided the operational and organizational structure of symposium and workshops. This includes scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs.

The programme invitations for 2010 and 2011 were available for download via the ELN homepage (see Figure 1.6).

Figure 1.6: The invitations and programs of the joint annual symposium of the European LeukemiaNet and the German Competence Network "Acute and chronic Leukemias", February 2010 and 2011

The event in 2010 was further announced at the TMF (Telematik Platform für medizinische Forschungsnetze) homepage.

The programme 2011 was further announced at the ESF homepage, at "my medical education" and at the University of Heidelberg homepage (See Figure 1.10).

Figure 1.7: ESF-ELN homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network "Acute and chronic Leukemias".

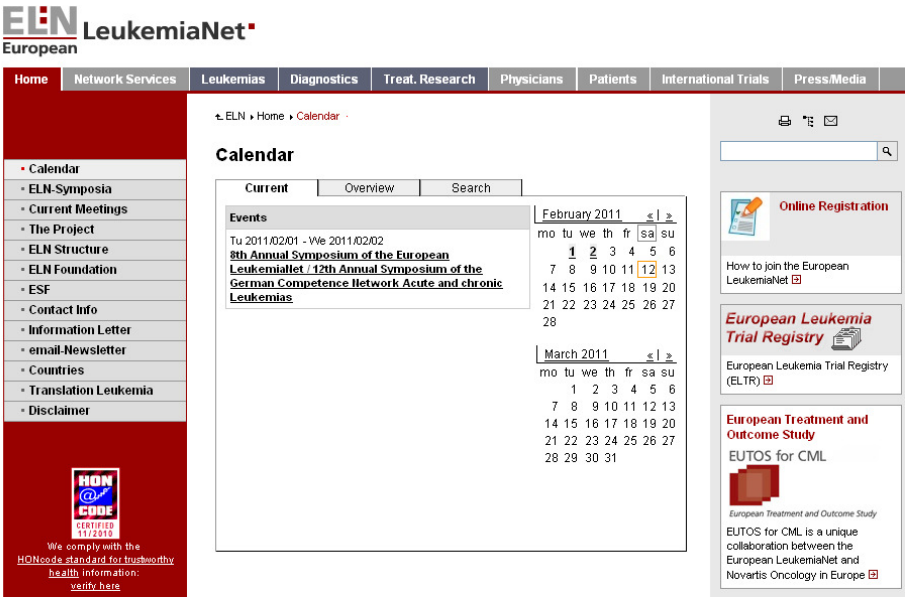


Figure 1.8: ELN homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network "Acute and chronic Leukemias".

Figure 1.9: Mymedicaleducation homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network "Acute and chronic Leukemias".

Figure 1.10: Homepage of the University of Heidelberg,, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network "Acute and chronic Leukemias".

1.9e Continuation of delivering all integrated trials to the integrated web site, progress report in conjunction with ELIC

The trial list and charts were updated in 2010 through ELIC and the NMC and the help of all leukemia clinical trial WPs. Continuous updating of the trials is promoted by the NMC.

1.10f Annual reports to the EC

i) The **activity report,** the comprehensive summary and information on the scientific activities of the project. Reports of all 16 workpackages were collected, edited and combined.

ii) The **management report** (including Form C, Summary Form C and the "Report on the Distribution of the Community's contribution") providing the administrative and financial information. Collecting forms C of 175 funded participants and financial audits of 72 participants funded with 63.333 € was again a tremendous and time-consuming effort. Again, extensive advice had to be provided. Requests especially on Forms C by the EC were answered ASAP; iii) the **new implementation plan** in 2010 with the new list of deliverables was prepared in agreement with the workpackage leaders with approval of the General Assembly; iv) the **financial planning for the seventh period** was prepared on the basis of the new implementation plan) **updated CPF** (contract preparation form) **file, updated Annex I** and **updated list of researchers** were prepared.

1.10g Annual reports to the EC

Organizational work for the report 2010 started in November 2010 with completion of templates for activity and management reports. Due to the cost-neutral prolongation of the financing period to March 2011 further EC deliverables and financial issues are closed by March 2011. For the period after funding through the EC planning of deliverables and financial issues is in progress.

1.11g Continuation of public relations activities to enhance public visibility of the European LeukemiaNet

The ELN-booth was presented at several meetings during 2010 and 2011, DHGO, EHA, ASH, and ELN Frontiers. Flyers, pocket cards, ELN publications, ELN newsletters, ELN Foundation and EUTOS for CML material were distributed at the same occasions.

Publications on the ELN:

- The European LeukemiaNet: achievements and perspectives, Haematologica. 2011 ;96:156-62. Epub 2010 Nov 3.
- Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010.
- Summary Information Letter on Achievements: EUTOS 2007-2010 at the Annual ELN Symposium 2011 (Fig. X).
- 7th ELN Information Letter

Figure 1.11: The invitation to the EUTOS educational meeting on CML in Vienna 2010.

1.12f Issue of the biannual network's Information Letter in conjunction with ELIC

The seventh ELN Information Letter was prepared in 2010 to be available at the ELN Symposium in 2011 (see Annex Section 3, WP1+2).

1.14f, 1.21g Continuation of organization of workshops, seminars, conferences etc.

The ELN was presented at multiple national and international congresses. Time slots for WP meetings were arranged at the Annual ELN Symposium in February, the EHA congress in June 2010 and at the ELN breakfast meeting at the ASH conference in Orlando, December 2010.

1.17g Continuous support of quality control measures, e.g. consensus protocols, quality control rounds, and reference laboratories (see also 1.21.e)

Quality control measures are a major topic at all ELN meetings. They are also a key topic of the EUTOS for CML project regarding all 4 subprojects, registry, molecular and pharmacological monitoring and spread of excellence. The number of reference laboratories across Europe is increasing steadily.

The ELN is supporting the spread of information to physicians across Europe. A table of over 38 recommendations and guidelines on leukemia management is available in this report. A summary table is also shown on the exhibition booth. Recommendations can be ordered by clinicians as pocket card via the ELN homepage. Slide kits for physicians on all four EUTOS subprojects are available on the EUTOS homepage.

1.20g Integrating new partners, industry and key stakeholders including patient organizations, support activities that constitute synergism, e.g. cooperations, partnership, funds

In 2010, fourteen new institutions were included into the consortium after approval by the Assembly on 2. February 2010 (see Annex Section 3, WP1). All documents were adapted accordingly.

1. Russian Research Institute of Hematology and Transfusiology, Russian Federation, represented by Prof. Kudrat Abdulkadyrov, WP4
2. Haematology and Oncology Clinic, Tartu University Hospital, Estonia, represented by Prof. Hele Everaus, WP4
3. SA Pohja-Eesti Regionaalhaigla (foundation North Estonia Medical Centre), Tallinn, Estonia, represented by Dr. Edward Laane, WP4
4. State Institution "Institute of Blood Pathology and Transfusion Medicine of UAMS", Lviv, Ukraine, represented by Prof. Zvenyslava Maslyak, WP4
5. Hellenic Society of Haematology, Athens, Greece, represented by Prof. Panayiotis Panayiotidis, WP4
6. Universitätsklinikum Jena, Germany, represented by Prof. Andreas Hochhaus, WP4
7. Centre Hospitalier Universitaire de Nantes, France, represented by Dr. Sylvie Hermouet, WP9
8. Stockholm South Hospital, Sweden, represented by Dr. Jan Samuelsson, WP9
9. TYKSLAB at Tyks-Sapa utility unit of Hospital District of Southwestern Finland, Turku, Finland, represented by Dr. Veli Kairisto, WP12
10. Universitätsklinikum Aachen, Germany, represented by Prof. Tim Brümmendorf, WP4
11. Université de Liège, Belgium, represented by Prof. Vincent Bours, WP11
12. Rostov State Medical University, Russian Federation, represented by Prof. Sergey Kutsev, WP4
13. Hospices Civils Ce Lyon, France, represented by Dr. Franck Nicolini, WP4
14. University of Copenhagen, Roskilde, Denmark, represented by Prof. Hans Hasselbalch, WP9

Contacts to potential new participants were arranged.

In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria

15. G. Papanicolaou Hospital of Thessalonik,i Thessaloniki, Greece, represented by Dr. C. Kelaidi, WP11
16. Cliniques Universitaires Saint-Luc Brussels, Belgium Dr. L. Knoops, WP9
17. Fundación Investigación Biomédica Hospital Universitario 12 de Octubre, Madrid, Spain, represented by Dr. J. Martinez-Lopez, WP4, 9, 12
18. Azienda Ospedaliero-Universitaria "Policlinico - Vittorio Emanuele", Catania, Italy, represented by Prof. F. Di Raimondo, WP4

19. National Specialized Hospital for Active Treatment of Haematological Diseases EAD, Sofia, Bulgaria, represented by Prof. G. Mihaylov, WP4, 5
20. Clinical Centre of Vojvodina, Novi Sad, Serbia, represented by Prof. S. Popovic, WP4
21. Siena University, Siena, Italy, represented by Prof. M. Bocchia, WP4
22. National Cancer Institute, Kyiv, Ukraine, represented by Dr. K. Filonenko, WP7

The ELN increased in its last year of EU funding to 182 participants and 34 countries.

1.22g Organization of panel meetings and preparation of ELN management recommendations:

In the last period of EU funding further consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network) and management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms, antifungal management) were published.

Panel meetings were organized by NMC especially for the MPN panel.

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

No deviations.

Table 1.1 List of deliverables WP1, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP1 NMC						
1.3f	Operating management of networking, i.e.legal and contractual, dissemination and knowledge	73-86	86	0	20	Saußele Huber Weinreich Manthey
1.4f	Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network, for example setting up the ELN Foundation	73-86	86	0	18	Saußele Hehlmann Weinreich Schrotz-King
1.5f	Organization of internal and external reporting ensuring that milestones are effectively reached	79,86	86	0	2	Saußele Schrotz-King
1.6f	Organization of regular meetings held by the Steering Committee	73,79, 84,86	73, 79, 86	0	2	Hehlmann Saußele
1.7f	Organization of Annual Network's Symposium 2010	73	73	0	10	Saußele Hehlmann
1.7g	Organization of Annual Network's Symposium 2011	86	86	0	10	Saußele Hehlmann
1.10f	Annual reports to EC 2010	74	75	0	18	Saußele Hehlmann
1.10g	Annual reports to EC 2011	86	88	0	18	Saußele Hehlmann
1.11g	Continuation of public relations activities to enhance public visibility of the European LeukemiaNet	73-86	86	0	6	Saußele Hehlmann
1.12f	Issue of the biannual network's Information Letter in conjunction with ELIC	84	85	0	2	Saußele Schrotz-King
1.14f	Continuation of organization of workshops, seminars, scientific meetings, conferences to enhance knowledge transfer from bench to bedside, from research centers to clinical institutions in conjunction with WP4-9	73-86	86	0	4	Saußele Hehlmann Schrotz-King
1.17g	Continous support of quality control measures, e.g., consensus protocols, quality control rounds, reference laboratories	(73)-86	86	0	4	Reiter, Müller M
1.20g	Integrating new partners, industry and key stakeholders including patient organizations, support activities that constitute synergism, e.g. cooperations, partnership, funds	73-86	86	0	6	Hehlmann Saußele
1.21g	Continuous update of project presentations	73-86	86	0	6	Hehlmann Saußele
1.22c	Organization of panel meetings and preparation of ELN management recommendations: • CMPD	73-86	86	0	2	Hehlmann Saußele

*) if available

Table 1.2 List of milestones WP1, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP1	NMC			
1.4f	Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network, for example setting up the ELN Foundation	73-86	86	Saußele Hehlmann Weinreich Schrotz-King
1.7f	Organization of Annual Network's Symposium 2010	73	73	Saußele Hehlmann
1.7g	Organization of Annual Network's Symposium 2011	86	86	Saußele Hehlmann
1.10f	Annual reports to EC 2010	74	75	Saußele Hehlmann
1.10g	Annual reports to EC 2011	86	88	Saußele Hehlmann
1.12f	Issue of the biannual network's Information Letter in conjunction with ELIC	84	85	Saußele Schrotz-King
1.22c	Organization of panel meetings and preparation of ELN management recommendations: • CMPD	73-86	86	Hehlmann Saußele

Section 3: Consortium management

14 new institutions including 1 new country (Estonia) were presented at the General Assembly on 2. February 2010 in Mannheim and 8 new institutions at the Assemböly in 2011 for accession to the contract:

1. Russian Research Institute of Hematology and Transfusiology, St. Petersburg, Russian Federation, Prof. K. Abdulkadyrov (WP4)
2. Haematology and Oncology Clinic, Tartu University Hospital, Tartu, Estonia, Prof. H. Everaus (WP4)
3. SA Pohja-Eesti Regionaalhaigla (foundation North Estonia Medical Centre), Tallinn, Estonia, Dr. E. Laane (WP4)
4. State Institution "Institute of Blood Pathology and Transfusion Medicine of UAMS", Lviv, Ukraine, Prof. Z. Maslyak (WP4)
5. Hellenic Society of Haematology, Athens, Greece, Prof. P. Panayiotidis (WP4)
6. Universitätsklinikum Jena, Germany, Prof. A. Hochhaus (WP4)
7. Centre Hospitalier Universitaire de Nantes, Nantes, France, Dr. S. Hermouet (WP9)
8. Stockholm South Hospital, Stockkholm, Sweden, Pr. Dr. J. Samuelsson
9. TYKSLAB at Tyks-Sapa utility unit of Hospital District of Southwestern Finland, Turku, Finland, Dr. V. Kairisto
10. Universitätsklinikum Aachen, Aachen, Germany, Prof. Dr. T. Brümmendorf
11. Université de Liège, Liège, France, Prof.. V. Bours
12. Rostov State Medical University, Rostov-on-Don, Russion Federation, Prof. S. Kutsev
13. Hospices Civils Ce Lyon, Lyon, France, Dr. F. Nicolini
14. University of Copenhagen, Danmark, Prof. H. Hasselbalch

15. G. Papanicolaou Hospital of Thessalonik,i Thessaloniki, Greece, represented by Dr. C. Kelaidi, WP11
16. Cliniques Universitaires Saint-Luc Brussels, Belgium Dr. L. Knoops, WP9
17. Fundación Investigación Biomédica Hospital Universitario 12 de Octubre, Madrid, Spain, represented by Dr. J. Martinez-Lopez, WP4, 9, 12
18. Azienda Ospedaliero-Universitaria "Policlinico - Vittorio Emanuele", Catania, Italy, represented by Prof. F. Di Raimondo, WP4
19. National Specialized Hospital for Active Treatment of Haematological Diseases EAD, Sofia, Bulgaria, represented by Prof. G. Mihaylov, WP4, 5
20. Clinical Centre of Vojvodina, Novi Sad, Serbia, represented by Prof. S. Popovic, WP4
21. Siena University, Siena, Italy, represented by Prof. M. Bocchia, WP4
22. National Cancer Institute, Kyiv, Ukraine, represented by Dr. K. Filonenko, WP7

Section 4: Other Issues

Ethical issues - none

Competitive calls - none

Section 5: WP-Performance

Performance indicators	**Status**
Number of participating trial groups, centers, researchers	182 institutions
Annual symposia	done
6-monthly workshops of trial groups and interdisciplinary partners	done
Collection and distribution of information on ongoing projects	done

2 ELIC (WP02)

Objectives and starting point of work at beginning of reporting period

- Preparation of a sponsoring concept for the ELN
- Maintenance of current website with a content-management-system (CMS)
- Maintenance and improvement of the European Leukemia Trial Registry (ELTR)
- Classification of the clinical trials in the ELTR has been restructured
- Launch of the website www.elnfoundation.org
- Browser-based opportunity of editing special parts of the website by web-editors
- Web-contents for all different user groups and all parts of the website
- Preparation of the 7th Information Letter and e-mail Newsletters, to present the network towards the network members, as well as to spread information to public, press and media

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

2.24e Maintenance and extension of website-contents

Existing content was continuously revised. ELIC verified and updated relevant content of the website. All recommendations within the ELN network have been presented at the website with a direct link to pubmed.gov. Contact information of all WP members as well as promotion slides with information of the ELN structure and member status of the ELN have been updated regularly. A subpage of ESF has been integrated to the ELN website with further information about the collaboration. A project to update and add useful information about patient advocats has been started to enhance the benefit of the ELN webpage for patients and to attract more visitors.

An enquiry to provide slidesets of specific actual topics in present research for further education and advanced training purposes to be presented on the website for the ELN members remained as an unsuccessful call and could not be realised so far.

Pageviews, visits and average time on site of the website users have been continuously analysed and evaluated statistically. User rates and usage characteristics of the website have been analysed continuously throughout 2010. There was a 20% increase of visits compared to 2009. Around 48.000 visits from 148 countries were registered in 2010.

A major work task was to launch the website www.elnfoundation.org within the corporate design of the ELN website. This site has been completely structured and optimised to attract potential donators for the ELN to generate further budget to continue with the ELN. Furthermore it has been laid out with the possibility to present videos directly from that website to cover upcoming demands of the internet user community (cf. web2.0).

2.35c Maintenance of ELTR (entry of new studies provided by the WPs)

The completion of the European Leukemia Trial Registry (ELTR) was intensified and this was a major work topic. All study leaders were contacted and requested to insert their leukemia trials into the ELTR. ELIC kept on screening the NCI register www.clinicaltrials.gov for listed leukemia trials to transfer them to the ELTR. All leukemia-diseases and all countries, represented in the ELN, were included into that survey. Responsible study leaders were contacted to update the studies, before integrating them into the ELTR. To facilitate this process of updating the trials a reminder function has been implemented and can be used to automatise the sending of reminder emails to the study leaders. This process will automatically sort out studies which have not been revised for a certain time and request the study leaders to check the trials if updating is necessary.

The classification of the ongoing studies has been adapted to practical requirements and restructured with the assistance of the WP leaders. This process is still ongoing.

At present up to 100 European Leukemia trials were provided in the ELTR:

- Acute lymphoblastic leukemia (ALL)
- Acute myeloblastic leukemia (AML)
- Chronic lymphoblastic leukemia (CLL)
- Chronic myeloblastic leukemia (CML)
- Chronic myelodysplastic Disease (CMPD)
- Myelodydysplastic Syndrome (MDS)
- Stem Cell Transplantation (SCT)

2.47b Continuous website-linking with European institutions

Manual cross-linking with all major hematology associations and patient groups was continued. The idea of taking the ELN website forward with a project for GOOGLE optimization and backlinking was not realized due to lack of funding.

58% of the users came from search engines. This result indicates that an improved ranking in major search engines due to persistent cross-linking to relevant sites has been achieved.

2.48b Realization of website sponsoring and acquisition of support

A sponsor-concept including fundraising was developed by ELIC. It has been discussed with the network management center at several occasions intensively with regard to integration in the future ELN fundraising strategy. Two main options for sponsorship are being considered: sponsoring the ELN in general or sponsoring parts of the ELN with a specific service in return. The realization of the sponsor-concept will continue after the acceptance of the steering committee.

2.49b Participation in an international expert group for novellation of the European Drug Law and coauthorship for recommendations

The EU-directive 2001/20/EC aimed to implement good clinical practice in the conduct of clinical trials on medicinal products for human use in the EU member states. But it turns out that the changes have caused huge and negative effects for investigator-initiated ("investigator-driven"; "investigator-sponsored") trials (IITs): administrative burden and costs were extremely rising and independence and trial performance particularly in an optimum-use scenario are dramatically damaged.

To react on the poor situation ELIC is participating in the Road Map Initiative for Clinical Research in Europe, which organizes workshops for stakeholders in the area of clinical trials.

Workshop schedule:

- 18 January 2010: Meeting in Barcelona (Spain): Risk based approach organised by ECRIN
- 19 January 2010: Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe organised by ECRIN
- 8 February 2010: Meeting in Brussels (The Netherlands): Towards a better Future for Pharmacovigilance in Clinical Trials organised by EORTC
- 17 March 2010: Meeting in Brussels (The Netherlands): Designing the Future Conditions for Clinical Research in Europe by EFGCP

Details to the workshops are disseminated on the website.

3rd Workshop of the ELN in 2011:

- 1 February 2011: Workshop in Mannheim about European Clinical Trials Directive: Suggestions for modification and practical approaches

This workshop has been organised and chaired by ELIC.

2.52 Contribution to the impact assessment of the EU directive on clinical trials

The ELIC group has prepared in collaboration with other European societies a comprehensive contribution to the impact assessment of the CT directive. The document which places a focus on the specific tremendous problems of academic clinical trials is made available on the website (http://www.leukemia-net.org/content/international_trials/basic_information/).

A step towards building up a strong group was the visit at the Directorate General in Brussels and a fruitful discussion with S. Fuehring. The aim is to elaborate detailed suggestions for changes in the legislation and to estimate the practical approaches to be considered in the upcoming proposal to the EU.

2.53 7th Information Letter

In 2010 the 7th Information Letter has been prepared to be presented at the network meeting in February 2011. The newsletters are available online.

2.54 Quality of life WS

At the network meeting in 2010 in Mannheim an internal workshop for Quality of life and late effects has been organised and chaired by ELIC.

Internal Workshop of the ELN in 2010:

- February 2010: Workshop in Mannheim about Quality of Life and Late Effects in Hematolgocial Malignancies

2.55 Coordination and monitoring of website contents entered by other WPs

Website contents have been entered by other WPs via the CMS System and/or via delivering the data by email to the webmaster.

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

WP2 is a workpackage with mainly service purposes for other WPs – in contrast to the other scientific workpackages. In 2010 the work had nevertheless to be provided without any funding. The payment of staff had to be made from other projects at the University of Frankfurt, which cannot be continued. Nevertheless we tried to maintain and extend the function of the website as the essential communication and information platform and even started new projects. With regard to the future maintenance of the existing websites www.leukemia-net.org and www.elnfoundation.org and to carry out the sponsoring concept it is necessary to get financial support for previous expenses to pay staff and technical equipment.

Table 2.1 List of deliverables WP2, 2010

Deliv. No.	Deliverable Name	Date due	Actual/ Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP2 ELIC						
2.2	LP reports to NMC regarding structure, activities (1 page, bullet point style)	**79,86**	79, 86	0	1	Gökbuget
2.24e	Maintenance of existing website-contents	**73-86**	86	0	6	Schäfer
2.35c	Maintenance of ELTR (entry of new studies provided by the WPs)	**73-86**	86	0	4	Schäfer
2.47b	Continuous website-linking with European institutions	**73-86**	86	0	6	Schäfer
2.48b	Realization of website sponsoring and acquisition of support	**73-86**	86	0	2	Gökbuget
2.49b	Participation in an international expert group for novellation of the European Drug Law and coauthorship for recommendations	**73-86**	86	0	4	Gökbuget
2.52	Contribution to the impact assessment of the EU directive on clinical trials	**75-86**	86	0	4	Gökbuget Ihrig
2.53	7th Information Letter	**85**	86	0	4	Schäfer
2.54	Quality of life WS	**73,86**	73	0	2	Gökbuget Ihrig
2.55	Coordination and monitoring of website contents entered by other WPs	**73-86**	86	0	3	Schäfer
2.56	Cooperation with set-up of sponsoring concept	**73-86**	86	0	2	Gökbuget Schäfer

*) if available

Table 2.2 List of milestones WP2, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP2 ELIC				
2.24e	Maintenance of existing website-contents	**73-86**	continuously	Schäfer
2.35c	Maintenance of ELTR (entry of new studies provided by the WPs)	**73-86**	continuously	Schäfer
2.53	7th Information Letter	**85**	January 2011	Schäfer

Section 4: Other Issues

Ethical issues - none

Competitive calls - none

3 CICS (WP03)

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

3.3 LP reports to NMC regarding structure, activities and integration of national groups

Reports were sent as requested.

3.31 Operation of central web-based recruitment and randomisation facility

This deliverable covers operation of the facility from project month 73 (1.1.2010) to month 86 (28.2.2011). See also deliverable D3.7, D3.12, D3.16 and D3.18.

The central web-based facility 'RANDOULETTE' for conducting randomisation in clinical trials has been developed, operated and provided for use in clinical trials of the network. Randoulette allows for online randomisation of individual patients at any time using a standard web browser.

The software Randoulette has been implemented as a java web application and is hosted on a server at the IBE, LMU Munich. Randoulette provides a randomisation result for patients in stratified, blinded clinical trials with block randomisation with or without stratification or alternatively full randomisation. The block lengths can be defined as randomly variable. The number of appliable treatment arms and study centers is unlimited and treatment arms can be parametrized by weighting. Stratification by centers or other factors is also possible limitless. Lists of blinded labels of drug packages can be created and provided for blinded drug manufacturing. The sections of a list are assignable to one or more trial sites for random assignment. Breaking of single blinded codes is supported and available online. In all processes Randoulette offers full conformity to concerns of Good Clinical Practice (GCP).

In 2010 the range of functions of the software 'RANDOULETTE' was extended. Reporting facilities were implemented and are now available for authorized trial coordinators. Quality assurance measures are customable for each trial. The user interfaces were redesigned. Randomisation notifications can be sent by email to all authorized persons.

The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. Interested trial group leaders should contact WP3 participant A. Fischer by randoulette@ibe.med.uni-muenchen.de or the Network Management Center.

3.32 Operation of central electronic data capture facility

This deliverable extends the results of deliverables D3.8, D3.13, D3.17, D.3.19 and D3.27 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The GCP-compliant electronic data capture facility MACRO has been installed. Both services are available to research groups within the consortium, but there will be extra license-costs for additional users. For further information see deliverable D3.8 and D.3.14.

In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010. The system is based on proven open source software components such as the Linux plattform, the Apache webserver, and the PostgreSQL database as well as several tools stemming from in-house development that have been sucessfully used in a number of web-based projects and continuously enhanced. Due to pre-existing structures, the allocation of responsibilities differs in various member countries and regions. This is accommodated by a simple and yet versatile role-based authorisation scheme.

3.33 Operation of the PID-Generator

This deliverable extends the results of deliverables D3.21, D3.25 and D3.28 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The second version of the PID-Generator developed by the TMF has been installed on a server at the IBE Munich. The various configuration possiblities the software offers have been deployed and tested by WP3 participants.
The software which implements an algorithm providing unique pseudonyms for subjects of research collectives such as trials and disease registers is available for all ELN member projects.
WP3 offers interested research projects guidance in concerns of data protection and pseudonymization.

In 2010 WP3 installed the infrastructure to handle pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study). An implementation scenario integrating the PID service in the existing data collection plattform has been developed. In this context the PID-Generator service has been custom-configured and was tested against available real-life datasets. The planning of the AMLSG-BiO study is finished and it the inclusion of patient started in 2010.

3.34 Enhancement and Operation of the analysis pipeline for DNA-Microarrays

This deliverable extends the results of deliverables D3.23 and D3.29 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The Microarray – Analysis – Pipeline has been designed to automate standard working steps in microarray data analysis such as preprocessing, assessment of differentially expressed genes or annotation. In 2009 it was used on 151 CLL samples to create preprocessed and normalized data which were then used to develop a prognostic score for patient survival time and time to treatment.
The pipeline was developed in cooperation with the "Computational Diagnostics Group" at the University Regensburg (http://www-compdiag.uni-regensburg.de). Two projects were started and finished. Work on a CLL prognostic gene signature by Herold, Jurinovic eta al. is completed and a manuscript is submitted. Herold & Jurinovic also studied ranscription activities of genes located in the minimally deleted regions of 13q14 and 11q22-23 in chronic lymphocytic leukemia and explored vidence for a common pathogenetic pathway. This paper is in print.

3.35 Development of a concept for extending the German AML register to a European level

A pilot for the German AML register was presented during the annual meeting of the ELN in Mannheim (February 2011). A national and European framework to use this registry was discussed. This registry acts as a meta-registry which does not contain the patient information but information on the availability of patient data. The meta register also offers the infrastructure to use this meta-information to produce specific data sets related to research questions of the consortium.

Table 3.2 List of deliverables WP3, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP3	**CICS**					
3.3	LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)	79,85	86	1	2	Mansmann
3.31	Operation of central web-based recruitment and randomization facility	73-86	86	2	2	Mansmann
3.32	Operation of central electronic data capture facility	73-86	86	3	2	Mansmann
3.33	Operation of the PID-Generator	73-86	86	2	2	Mansmann
3.34	Enhancement and Operation of the analysis pipeline for DNA-Microarrays	73-86	86	7	2	Mansmann
3.35	Development of a concept for extending the German AML register to a European level	73-86	86	9	2	Mansmann

*) if available

Table 3.3 List of milestones WP3, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP3	**CICS**			
3.34	Enhancement and Operation of the analysis pipeline for DNA-Microarrays	73-86	presented in February 2011	Mansmann
3.35	Development of a concept for extending the German AML register to a European level	73-86	presented in February 2011	Mansmann

Section 5: Workpackage performance

Performance indicators	Status
Number of patients randomized in clinical studies 2011	1132
Number and quality of papers published or presented based on then achieved research results of the network	See WP1 and Section3
Number of visits at the homepage	Prospectively done by WP2

4 CML (WP04)

Cooperation between European study groups on CML has a long standing tradition since establishment of the group of "European investigators on CML" (EICML) in 1992. Thus, EICML represents one of the founding collaborative groups for the European LeukemiaNet. Another important background structure is the "German Competence Network Leukemias", which was founded in 1999. WP4 has now (2010) 62 participants representing 34 countries. Major goals of the WP with regard to the optimization of treatment strategies in CML are:

- Establishment of comprehensive registries for patients across Europe
- Elaboration and updating of common definitions and guidelines for diagnostic and therapeutic procedures
- Creation of a European trial platform
- Standardization and harmonization of molecular methodologies for diagnosis and follow up
- Laboratory and experimental studies of different aspects of CML
- Spread of excellence

This seventh period was characterized by an active communication process with three WP meetings and several meetings of specific groups working on particular deliverables (e.g registries, sub-registries, standardization and harmonization of molecular monitoring, different clinical trials, implementation of guidelines, spread of excellence activities).

WP4 is closely networking with WPs 1-3, 10-14, 17, CML Study Groups outside EU and pharmaceutical industry. The collaboration atmosphere is indeed creative. The five WP lead participants have a tight communication by mail and phone and at meetings.

Highlights of the cooperative work include:

- EUTOS (European Treatment and Outcome Study) for CML
- Standardization rounds with 58 ELN laboratories (including 28 national reference labs) for molecular monitoring of residual CML in cooperation with WP12
- Consensus manuscript on molecular monitoring and a follow up paper published
- Trials with new signal transduction inhibitors, new immunotherapy (vaccination, interferon) and with attempts to stop imatinib therapy are running successfully across Europe
- Six ongoing collaborative trials on an European level (EICML)
- The European registry and the subregistries have grown rapidly and now enrolled more than 5000 patients .
- A European population based registry was launched in 2009 - 10
- Several multicenter upfront clinical trials have been reported in high input journals

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

4.5 Regular WP meetings

Three WP meetings were organized in February (Mannheim), June (EHA, Barcelona) and December (ASH, Orlando) (see Annex section II).

4.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

Reports (as minutes from WP meetings) on the status of the deliverables have been sent to NMC.

Deliverables

Registries

4.14e Report of study patients to registries (n > 400 per year)

1. *In-Study registry (i.e. on patients enrolled in clinical trials):*

Registry for prognosis of imatinib treated patients: All new cases of CML from the Italian GIM-EMA, the German CML IV, the Nordic (Denmark, Finland, Norway, Sweden) the Spanish (from Barcelona), the French, the Netherlands and the UK study groups have been made available. Total number of registered cases over a 5-year period (2002-2006) amounts to 2389 patients. Reports were given at ISH and ASH 2010. For more details see also Annual Activity Report of WP17.

2. *Out-Study registry (i.e. on patients not enrolled in clinical trials):*

Patients (n=1582) registrered in Spain (Madrid), Czech Republic (Infinity), Czech Republic (Camelia), Russia (Moscow and St. Petersburg), Romania, UK (Hammersmith) and Poland are included . In- and out-study registry contains altogether 3971 patients.

3. *Population-based registry:*

National/international based registries are running in Czech Republic, Finland, the Netherlands, Poland, Sweden and Spain and a new common European population based registry was launched in 2009. This registry is now active in 24 European countries. More than 800 patients from 25 Study groups are included.

4. *The subregistry of patients with additional cytogenetic abnormalities in Ph-positive and Ph-negative hematopoiesis after imatinib therapy has enrolled 40 patients.*

Direct results out of registries: See also Annual Activity Report from WP17.

5. *Imatinib-discontinuation registry:*

This registry was reorganized within the Imatinib failure patients (IFP)-Registry. Additional projects are defined under 4.46 and 4.49. The IFP-registry is organized under the European CML Registry (WP4). It is supported by a grant from the 6th European Framework program and by Novartis Pharma. French authorities approved it in accordance with the European Community and the Helsinki protocol. Currently, 1029 cases have been registered from 15 European countries. The registry is now closed for

registration. Data completion is ongoing. Results were presented at EHA 2010. A final draft of a manuscript is planned for Q2 2011.

Studies

4.19f Study imatinib + IFN or AraC, progress reports

Prospective studies investigating standard dose imatinib and the combination of imatinib and IFN or imatinib and ara-C are running in Germany (recombinant IFN, ara-C) and France (Peg-IFN, ara-C), the Nordic countries (Denmark, Finland, Norway and Sweden; Peg-IFN), and UK (Peg-IFN). In total, more than 2500 patients have been enrolled. Analyses from German, French and Nordic groups have been presented at several international meetings (see Annex/Section 3 WP4) and demonstrate the feasibility of the combinations.

The phase III prospective randomized trial investigating the impact of higher dose imatinib and of the combination of imatinib and Peg-IFN or imatinib and ara-C is still running in France (SPIRIT study). As of December 31 2010, 789 patients were included and accrual was stopped. The data were presented for the first time at ASH 2008. The final results of the first part of the trial has been recently published (Preudhomme C, et al N Engl J Med, 2010, 363: 2511-21). The Major Molecular Response (MMR) rate at 24 months is significantly improved with combination of imatinib plus Peg-IFN. The patients will be followed until December 2013. Patients are still treated according to their treatment assignment. The dose of Peg-IFN has been reduced to 45µg for the first 2 months and then patients are asked to increase the dose up to 90µg/week if tolerability is good.

In the Nordic study (n=112), also reported at ASH 2009 and EHA 2010, imatinib was compared with imatinib + Peg-IFN. The 12 month rate of MMR was also here significantly improved in the combination arm. A manuscript has been submitted for publication.

The German group found no effect on 24 months molecular or cytogenetic reponses by adding regular IFN to imatinib (n=562) (GEIST-study, reported at ASH 2009). To analyse a non-significant survival advantage for the combination with IFN after a median survival of 5 years, a survival update is currently performed. Concerning the combination with ara-C, an evaluation of the combined German and French patient groups is planned.

4.21d Study high dose Imatinib in high risk chronic phase CML, update and follow up

120 high risk patients who were assigned to receive 400 or 800 mg Imatinib front-line have been regularly followed and updated, for a final report, that will be completed and published in 2011.

4.22d Study high dose imatinib vs imatinib in standard dose (CML-Study IV), progress report, publication

The German CML Study Group compared imatinib 800 mg with standard dose imatinib +/- IFN. 1014 newly diagnosed CP-CML patients were randomly assigned to imatinib 800 mg (n=338), imatinib 400 mg (n=325) or imatinib 400 + IFN (n=351). Dose adaptation to avoid higher-grade toxicity was recommended. First primary endpoint was MMR at 12 months. A higher rate of MMR at 12 months occurred with tolerability-adapted imatinib 800 mg than with imatinib 400 mg (59% [95%CI: 53-65%] vs 44% [95%CI: 37-50%]; p= 0.0003) or imatinib 400 mg + IFN (59% vs 46% [95%CI: 40-52%], p= 0.002). Median average dose in the 800mg arm was 628 mg with a maximum of 737 mg during months 4 – 6 and a maintenance-dose of 600 mg. All three treatment approaches were well tolerated with similar grade 3 and 4 adverse events (AEs). Independent of treatment approach, MMR at 12 months showed better progression-free (99% vs. 94%;p=0.0023) and overall survival (99% vs 93%; p= 0.0011) at 3 years if compared to >1% International Scale (IS) or no MMR, but showed no difference to 0.1% - < 1% IS which closely correlates with CCgR. It is concluded that treatment of early-phase CML with imatinib can be optimized. Early high-dose followed by rapid adaptation to good tolerability increases rate of MMR at 12 months. Achievement of MMR by month 12 is directly associated with improved survival. (See also Tabler 4.1).

4.30e Preclinical and phase 1 – 2 clinical studies of tyrosine kinase and Src inhibitors

A prospective, multicentre study of nilotinib and imatinib, given in a 3-month rotation, frontline in CP CML has enrolled 120 patients who have now a follow up close to 12 months.

4.36d Phase II study of peptide vaccine to potentiate and stabilize imatinib effect in CP

Sixty patients who were in CCgR on imatinib have been enrolled in a phase II study of a B3A2 peptidic vaccine, and have been treated and observed for 12-24 months. A full report is scheduled for 2011.

4.38d Nilotinib upfront in CP, progress report

A cohort of 73 patients who have been treated frontline with Nilotinib 800 mg has been followed-up for a minimum of 30 months, to assess CMR rate and the frequency of mutations. A full report will be presented in 2011.

Table 4.1: Cumulative Incidences of MMR, CMR[4] and CCgR.

Time after start of treatment (months)	**Cumulative incidences (95%CI)**				
	IM400 n=306	*Δ*	IM800 n=328	*Δ*	IM400 +IFN n=336
	MMR (%)				
6	8.6 (5.2-11.3)	*9.5*	18.1 (13.8-22.9)	*9.7*	8.4 (5.2-11.0)
12	30.8 (26.6-36.1)	*24.0*	54.8 (48.7-59.7)	*20.1*	34.7 (29.0-39.2)
18	50.3 (44.0-55.5)	*18.1*	68.4 (62.2-73.0)	*14.3*	54.1 (48.4-59.4)
24	63 (56.7-68.0)	*13.0*	76.0 (70.5-80.6)	*13.2*	62.8 (56.7-67.6)
36	79.3 (73.9-83.7	*2.3*	81.6 (76.0-86.0)	*10.9*	70.7 (64.6-75.1)
	CMR[4] (%)				
6	3 (1.2-4.9)	*0.7*	3.7 (1.6-5.4)	*1.3*	2.4 (0.9-4.1)
12	7.5 (4.8-10.8)	*12.3*	19.8 (15.2-24.0)	*7.4*	12.4 (8.8-15.8)
18	21.2 (16.6-26.1)	*12.2*	33.4 (28.0-39.0)	*9.8*	23.6 (19.0-28.5)
24	30.7 (24.9-35.8)	*12.3*	43 (36.8-49.0)	*13*	30.0 (24.9-35.3)
36	45.5 (38.7-51.0)	*11.3*	56.8 (49.4-63.5)	*16.3*	40.5 (34.6-46.3)
	CCgR(%)*				
6	21.3 (16.4-25.8)	*10.2*	31.5 (25.9-36.6)	*12.0*	19.5 (15.0-23.8)
12	49.4 (42.6-54.4)	*13.5*	62.9 (56.4-67.9)	*13.2*	49.7 (43.5-54.9)
18	66.0 (59.4-70.9)	*8.9*	74.9 (68.6-79.3)	*5.7*	69.2 (63.4-74.3)
24	74.3 (67.6-78.9)	*8.0*	82.3 (77.0-86.6)	*5.8*	76.5 (70.3-80.7)

Δ: Difference between IM 800 and IM 400, or IM 800 and IM 400+IFN, respectively.
*number of patients with cytogenetic evaluations: IM 400, n= 303; IM 800, n= 311; IM + IFN, n= 326

4.40b Long term effects of imatinib therapy, progress

Imatinib slows development of CML. However, available information on morbidity and mortality is largely based on sponsored trials whereas independent long-term field studies are lacking.

The independent, multicenter Imatinib Long Term side Effects study assessed overall survival, loss of CCgR, attainment of CMR, SAEs, and toxicities not qualifying as SAE (NSAE) but judged by treating physicians as substantially affecting quality of life. Consecutive CML patients who started imatinib before 2005 and who were in CCgR after two years (plus or minus 3 months) were eligible. Overall survival, incidence of the first adverse events, and loss of CCgR were estimated according to the Kaplan-Meier method and compared with the standard log-rank test. Cumulative incidence of death was broken down into incidence related or unrelated to CML, accounting for competing risks, according to the Kalbfleisch-Prentice method. Standardized incidence ratios were calculated based on population rates specific for gender and age classes. Confidence intervals were calculated by the exact method based on the chi-square distribution. All statistical tests were two-sided.

Overall, 832 patients were enrolled with a median treatment duration of 5.8 years. Twenty deaths were observed (6 [30%] associated with CML), with a 4.8% mortality incidence rate (standardized incidence ratio = 0.7, 95% confidence interval = 0.40 to 1.01, P = 0.08). There were 139 recorded SAEs, of which 19.4% were related to imatinib. Among the 830 NSAEs (which developed in 53% of patients), the most frequent were muscle cramps, asthenia, edema, skin fragility, diarrhea, tendon or ligament lesions (68 % were imatinib-related). Nineteen patients (2.3%) discontinued imatinib because of drug-related toxicities. Forty-five patients lost CCgR, corresponding to a rate of 1.4 per 100 person years. Durable (> 1 year) CMR was attained by 179 patients.

CML-related deaths are uncommon in CML patients who are in CCgR two years after starting imatinib and survival is not statistically significantly different from that of the general population.

The results presented here have been accepted as full article in the Journal of National Cancer Institute.

4.41 Allo-SCT after second generation TKI

Work in progress.

4.44b Imatinib +/- hydroxyurea

After a phase I study in newly diagnosed (n=18) or IFN refractory (n=2) CML patients, 80 newly diagnosed patients were randomized 2:1 for the combination treatment imatinib 400mg + hydroxyurea 500mg (n=53) with a progressive escalation of the hydroxyurea dose to attain mild leukopenia (3-4 Gpt/l) or imatinib 400mg alone (n=27). The primary endpoint of the study is the achievement of MMR after 18 months.

Until now the combination of imatinib 400 mg with hydroxyurea doses up to 3000 mg results in a low toxicity profile compared to other combination treatment strategies. Looking at the most recent interim

analysis favourable responses have been observed in the combination arm. Statistical analysis together with CML IV data have been planned for 2011.

4.46b European study on imatinib withdrawal

After a long discussion during the last year we have now decided to go for a common European study, hopefully starting this year which is entitled EURO-SKI (EURO-StoptyrosineKinaseInhibitors). A large number of countries and study groups have accepted the study design and to join the study.

4.49b Imatinib D/C in patients with CMR (STIM)

In a pilot study of imatinib treated patients achieving CMR for at least two years and thereafter stopped treatment, a molecular relapse rate of 50% was observed. All patients had prior to imatinib been treated with IFN. Then, we performed a prospective new multicentre study "Stop Imatinib" (STIM), including also newly-diagnosed patients, initiated in July 2007 to evaluate the persistence of CMR after discontinuation of the drug, and to determine the factors that could be associated with CMR persistence. The research team enrolled 100 patients with CP or AP CML with a sustained CMR, defined as a 5 log reduction in BCR-ABL and ABL levels as well as undetectable transcripts on RT-PCR, for at least two years. Fifty-one patients were previously treated with IFN. After stopping imatinib, molecular relapse was seen in 54 patients after a median follow-up of 17 months. Forty-six patients remained in CMR at a median follow-up of 14 months, with the overall probability of maintaining a CMR at 12 months of 43%. In the subset of 69 patients with follow-up over one year (median 24 months), molecular relapse occurred in 42, usually within 6 months. Molecular relapse free survival in this group was 41% at one year and 38% at 2 years. Patients treated with IFN prior to imatinib showed no differences in relapse rates compared to those treated with imatinib only. Molecular relapse at or before 18 months occurred in 70% of men and 46% of women. Among patients with high, intermediate and low Sokal risk scores molecular relapses were detected in 88%, 65%, and 49%, respectively. Further, patients with a duration of imatinib therapy of at least 50 months had a 53% likelihood of molecular relapse, whereas 78% of patients with shorter duration of treatment relapsed.. When these three factors, gender, Sokal group and duration of treatment, were entered into a Cox regression model they all significantly and independently predicted likelihood of molecular relapse. All patients who relapsed were retreated with imatinib and all patients responded well. No loss of hematologic response was seen or progression to advanced phase. Of the 42 who relapsed, 26 achieved a CMR with imatinib retreatment at the time of the analysis. The identification of patients who would benefit most from discontinuation of imatinib remains a key issue.(Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial (Mahon, Lancet Oncol. 2010; 11:1029-35.)

4.50 IFN plus dasatinib front line and in MMR patients

No update.

4.51 Optimization of the treatment with dasatinib for newly diagnosed chronic phase CML

The French group started in 2009 a new trial entitled: ”A prospective randomized phase II study evaluating the optimization of the residual plasmatic level of dasatinib (Sprycel®) in patients newly diagnosed with CP CML”.

Dasatinib is a new, multitargeted, tyrosine kinase inhibitor with a 300 fold more potent activity on the BCR-ABL tyrosine kinase in vitro compared to imatinib mesylate. Dasatinib has been extensively studied in the setting of imatinib failure with a rate of 40% of CCR in case of failure to imatinib. The dose of 100mg QD of dasatinib is now labelled for patients with CP CML. Based on preliminary results of dasatinib in de novo CML, the estimated rates of MMR at 6 and 12 months are 19% and 33% respectively. The estimated rates of CCR at 3, 6 and 12 months are 72%, 94% and 100% respectively. A CCR rate of 81% is expected from the assumption made for the sample size calculation of the BMS 056 dasatinib front line study.

AEs observed with dasatinib include fluid retention, pleural effusions and cytopenia (especially thrombocytopenia). These AEs require dose reduction or dasatinib interruption.

A subanalysis of the BMS 034 study indicated that the main factor associated with these adverse events is the level of the residual dosage of dasatinib (Cmin). Cmin correlates with the risk of adverse events such as fluid retention, pleural effusion and thrombocytopenia. In this study, the cut off value for Cmin was below 5nM. This analysis demonstrated also that the cumulative duration of dasatinib interruption is an independent factor inversely correlated to the quality of the response (Nicaise et al. EHA 2008).

We propose to prospectively assess the Cmin values of patients with de novo chronic phase CML treated with dasatinib as a first line therapy. Patients with a dasatinib plasmatic Cmin over 5nM will be randomized between a prospective adaptation strategy of the dasatinib daily dose based on the monitoring of the Cmin value (arm A1) versus observation only (arm A2). The other patients with a dasatinib plasmatic Cmin value below 5nM will be follow up according the ELN recommendation (arm A3). Dasatinib plasmatic Cmin will then be rechecked at two weeks interval (arms A1 and A2) until reaching the optimal dosage of dasatinib (arm A1) and every month in arm A3. The objective of the study is to reduce the rate of adverse events in arm A1 compared to arm A2. Patients in arm A3 will provide an estimate of the best expected difference between arm A1 and arm A2.

Initial results of this trial were presented during EHA 2010 and ASH 2010 (see Rousselot et al., Annex section 3 WP4).

4.57 Induction/Maintenance strategies in newly diagnosed CML patients using nilotinib and IFN – German CML study V. Start 2010

A prospective study on nilotinib vs. nilotinib + IFN induction therapy and nilotinib vs. Peg-IFN maintenance therapy after confirmed MMR and treatment discontinuation after >12 mo. stable CMR is in preparation in Germany and Switzerland. The protocol has been discussed in the steering board, the budget is in place. The study will start after stop of recruitment of ENEST1st. n=644 patients will be recruited.

Laboratory issues

4.29e Dynamics of response and resistance in CML patients treated with tyrosine kinase inhibitors beyond imatinib (AMN 107, BMS 354825). Progress reports.

Nilotinib and dasatinib are novel BCR-ABL inhibitors and are tested in clinical phase II/III trials. Levels of residual disease, BCR-ABL mutation analysis, and proportion of phosphorylated CRKL are determined in laboratories in Mannheim, Torino and Bologna.

Dasatinib efficacy was analyzed in patients recruited to phase II/III trials with CP CML with or without BCR-ABL mutations after prior imatinib. Among 1043 patients, 39% had a preexisting BCR-ABL mutation, including 48% of 805 patients with imatinib resistance or suboptimal response. Sixty-three different BCR-ABL mutations affecting 49 amino acids were detected at baseline, with G250, M351, M244, and F359 most frequently affected. After 2 years of follow-up, dasatinib treatment of imatinib-resistant patients with or without a mutation resulted in notable response rates (CCgR: 43% vs 47%) and durable progression-free survival (70% vs 80%). High response rates were achieved with different mutations except T315I, including highly imatinib-resistant mutations in the P-loop region. Impaired responses were observed with some mutations with a dasatinib median inhibitory concentration (IC(50)) greater than 3nM; among patients with mutations with lower or unknown IC(50), efficacy was comparable with those with no mutation. Overall, dasatinib has durable efficacy in patients with or without BCR-ABL mutations (see Annex Section 3, WP4).

In a subanalysis of a phase II nilotinib registration trial study in patients with imatinib-resistant or imatinib-intolerant CML-CP, the occurrence and impact of baseline and newly detectable BCR-ABL mutations were assessed. Baseline mutation data were assessed in 281 (88%) of 321 patients. Among imatinib-resistant patients, the frequency of mutations at baseline was 55%. After 12 months of therapy, MCyR was achieved in 60%, CCyR in 40% and MMR in 29% of patients without baseline mutations versus 49% (P = .145), 32% (P = .285), and 22% (P = .366), respectively, of patients with mutations. Responses in patients who harbored mutations with high in vitro sensitivity to nilotinib (50% inhibitory concentration [IC(50)] <or= 150 nM) or mutations with unknown nilotinib sensitivity were equivalent to those responses for patients without mutations (not significant). Patients with mutations that were less sensitive to nilotinib in vitro (IC(50) > 150 nM; Y253H, E255V/K, F359V/C)

had less favorable responses, as 13%, 43%, and 9% of patients with each of these mutations, respectively, achieved PCyR. For most patients with imatinib resistance and with mutations, nilotinib offers a substantial probability of response. However, mutational status at baseline may influence response. Less sensitive mutations that occurred at three residues defined in this study, as well as the T315I mutation, may be associated with less favorable responses to nilotinib (see Annex Section 3, WP4).

Molecular responses to first line nilotinib and dasatinib therapies were reported at ASH 2010 (Rosti, Hochhaus, Hughes, Shah, see Annex Section 3, WP4).

4.34d European control round for BCR-ABL mRNA quantification (overlap with WP12), Progress report

The rationale for the development of this subproject was to

(i) improve the early recognition of relapse

(ii) provide prognostic information

Thus this project aims to bring about the standardization of RQ-PCR throughout Europe ensuring an alignment with the International Scale (IS). A good network of standardized labs currently exists across Europe: 58 labs are participating in this project with 28 national reference labs (including Mannheim) validated across Europe so far (see Figure 4.3). Preliminary conversion factors (CFs) are calculated using standard samples sent from the central laboratory in Mannheim to national labs and then validation of these CFs occurs by sending patient samples from the national labs to the central lab. Once validated, the national reference labs are equipped to propagate validated CFs and allow local labs in their respective countries to express their BCR-ABL levels on the IS. Recommendations for the propagation of the IS by national or regional laboratory networks were recently published in Leukemia (see Annex Section 3, WP4).

The validation of CFs to the International Scale within the network was reported at ASH 2010 (Müller et al.). The Mannheim lab has received patient samples (each 25-35 samples) from 25 laboratories in 2010, worked them up and calculated or validated CFs by mathematical comparison with the results obtained in the sending laboratories. So far, 32 laboratories have sent two rounds of patient samples and received a certificate until the end of 2010.

Exchange programs were initiated to educate the personnel from laboratories starting with the Q-PCR and mutations analyses in order to allow rapid implementation of the standards in all participating European countries. Importantly, the whole process will be adapted to the international standardization process allowing implementation of the international standard to all European countries, but avoiding the risk of heterogeneous standards in different parts of the world. Workshops were performed in Mannheim for 7 colleagues from 4 participating laboratories (03/10 Jena, 09/10 Kiev, 10/10 Krakow, 11/10 Hamburg) to improve performance and standardization.

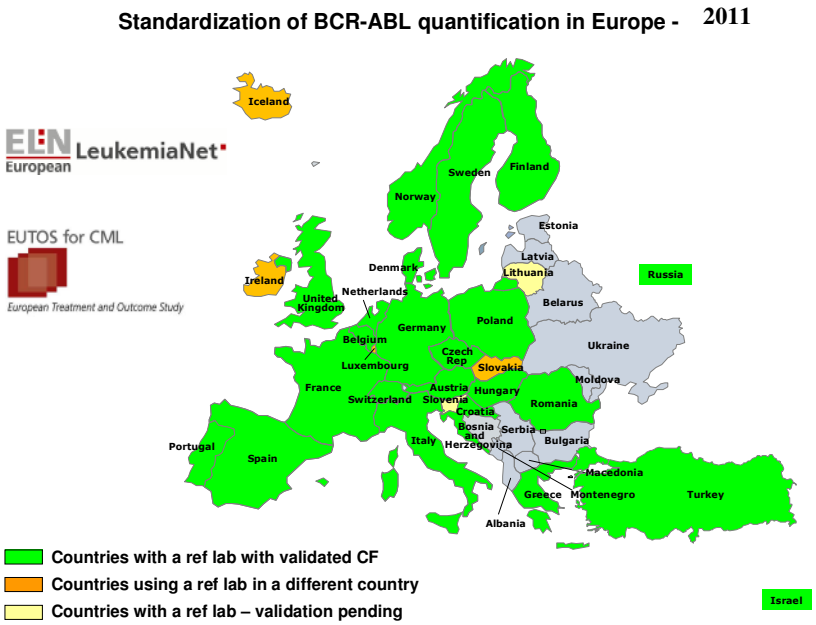


Figure 4.1: A summary of the standardization progress of BCR-ABL quantification in Europe between 2006 and 2011.

4.58 Definition and European Standardization of CMR

Standardization of CMR assessment is a crucial topic for future trials since most trials will include CMR as primary or secondary endpoint.

Thirteen labs have been selected to serve as reference laboratories for Q-PCR within the ENEST1st study and to establish and validate definitions of CMR on various sensitivity levels (CMR^{4}, $CMR^{4.5}$, CMR^{5}). A survey was conducted to establish common pre-analytical and analytical procedures and to estimate the sensitivity level achieved in each lab. Improvement of the performance will be achieved by workshops and ongoing control rounds.

CMR data have been reported from the German CML Study IV and the French SPIRIT study in two publications.

4.35b Mutated bcr-abl clones – level, control rounds

Harmonized Testing for BCR-ABL Kinase Domain Mutations In CML: Results of a Survey and First Control Round within 28 National Reference Laboratories In Europe.

Standardized techniques and protocols for the detection of BCR-ABL mutations will be necessary in the future to obtain comparable mutation results within clinical studies. The first objective of this study conducted within the EUTOS (European Treatment and Outcome Study) for CML program was to record the mutation analysis techniques and protocols that are used for routine diagnostics by 28 national reference laboratories in 23 European countries, 9 of whom perform regular mutation analyses as a central laboratory for national or international clinical trials. A web-based survey was

conducted with a total of 39 technical and PCR-specific questions. The second objective was to evaluate the techniques by analysis of blinded samples containing various BCR-ABL kinase domain mutations. Control samples were prepared and distributed in a blinded fashion to testing laboratories. Seventeen Ba/F3$^{BCR-ABL}$ cell lines harboring various BCR-ABL kinase domain mutations were mixed with non-mutated Ba/F3$^{BCR-ABL}$ to produce dilutions ranging from 1% to 100% of mutant alleles. Mutated and non-mutated Ba/F3$^{BCR-ABL}$ cell lines were diluted into HL60 cells to simulate a BCR-ABL level of 10% on the International Scale. Twenty blinded cDNA samples were sent out on dry ice to each participating laboratory (total of 560 samples). The results have shown that Sanger sequencing is the most frequently applied technique for routine analysis of BCR-ABL kinase domain mutations in CML in Europe. In general it reliably identifies mutations when the proportion of mutant alleles comprise 20% or more. Nevertheless, false negative and false positive results were reported in a substantial proportion of samples with ≥ 20% mutation level (35/253, 14%). For mutations that are present at 10% or less mutant alleles, routine methods mainly failed to identify mutations. The study provides a basis for further comparisons and standardization efforts comparable with the introduction of the international scale for quantification of BCR-ABL transcripts. The study was presented as an oral presentation at the 52nd ASH annual meeting 2010 in Orlando, Florida (see Annex Section 3 WP4). A manuscript will be submitted in 2011.

4.45 Allo-HSCT in low risk patients. Second report

The evaluation of allo-SCT in low risk Gratwohl score CML patients has been published (Saussele et al, see Annex Section 3 WP4).

Patients with CML and a low EBMT risk score have an excellent survival with a transplant related mortality of 10% only and a survival which was not different from a similar cohort of patients without a donor but treated within the prospective controlled German-Swiss CML IV study. Similar excellent survival was documented in a cohort of more than a 100 patients of the EBMT.

Other

4.43b Dasatinib and immunomodulation, progress report

Background:

Targeted inhibition of the oncogenic BCR-ABL tyrosine kinase by TKIs has profoundly changed the therapy of CML. Imatinib mesylate was the first drug approved for clinical use and currently is the standard first-line therapy for all CML patients. Imatinib is well tolerated and has few significant side-effects, as it predominantly only targets cells with the mutated kinase. However, the inhibition profile of many 2nd generation TKIs is much broader. This may be therapeutically advantageous, but as long-term effects on normal cells are largely unknown, significant side-effects may emerge.

We have recently observed a massive clonal expansion of cytotoxic LGL (large granular lymphocyte)-cells in blood of several CML and acute lymphoblastic leukemia patients during dasatinib (2nd

generation TKI) therapy. The aim of this project has been to characterize the clinical features of the phenomenon and to study background mechanisms.

Current status of the project (January 2011).

We have collected a case series of patients with LGL expansion during dasatinib therapy (n>25) from different centers in Europe and US. Several clinical and basic research investigators (from Finland, Norway, Sweden, Germany, France, Spain and US) have participated in the project. We have found that the expansion of immune effector cells is linked to autoimmune reactivity, such as severe diarrhea and lung toxicity, as accumulation of clonal T -cells was also observed in these organs. Furthermore, several patients with advanced, poor-prognosis leukemia achieved long-lasting complete responses to dasatinib, thus strongly suggesting an antitumor effect of the expanded cytotoxic cells. We postulate that by inhibiting kinases in immune effector cells, dasatinib induces a reversible state of autoimmune reactivity resulting in host organ damage and in enhanced anti-leukemic control, both driven by cytotoxic T/NK LGL cells. These results have now been published in *Leukemia* journal (see Annex Section 3, WP4).

In our follow-up projects, we discovered that the expanding lymphocyte clones exist already before start of dasatinib therapy and remarkably, they can be detected at low levels already at the diagnostic phase of CML. Therefore our current working hypothesis is that clonal lymphocytes present at CML diagnosis are anergic/exhausted anti-leukemic lymphocytes and part of the immune escape mechanisms inherent to leukemogenesis. Dasatinib therapy may break this immune tolerance and revert anti-leukemic potential of pre-existing cytotoxic lymphocytes. Results were published recently in *Blood* journal (Kreutzman et al) (see Annex Section 3, WP4).

As in our previous studies we noticed that lymphocytosis is oscillating in most patients, we collected follow-up samples from dasatinib treated patients before and after (0, 1, 2 and 4 hours) drug oral administration to assess the relation of drug intake, plasma level and lymphocyte counts. To our surprise, in all patients and in one healthy control dasatinib induced a rapid and marked mobilization of blood leukocytes with peak values after 1-2 hours of oral drug intake. Most substantial mobilization was observed for lymphocytes and it correlated closely with dasatinib plasma concentration. In other TKI treated patients (imatinib, nilotinib, bosutinib), no similar changes were observed. These results were presented at ASH with the poster presentation (Mustjoki et al) and manuscript is under preparation.

Further aims and future activities:

Currently we are studying *in vitro* the effects of TKIs on immune effector cells and we aim to isolate target kinase(s) (for example kinases related to downstream signalling of adhesion molecules), which, when inhibited by dasatinib, cause mobilization of cytotoxic T/NK cells. We also aim to identify the antigen targets of the activated cytotoxic cells on both normal and malignant cells and to assess the role of these cytotoxic cells in autoimmune/anti-leukemia manifestations in patients treated with TKI

therapy. Further, we try to find the genetic factors, which determine weather the patients develop lymphocytosis during dasatinib therapy and have therefore better therapy response. We hypothesize that KIR/HLA mismatch could be one of the mechanisms and we are currently collecting samples from different centers in order to have big enough patient material.
Collaboration with international investigators continues actively as we try to study patient samples *in vitro* to be able to draw direct conclusions to patient care.

Importance of the study
The aim of this project is to uncover the cellular and molecular mechanisms of TKI-induced anti-leukemia immune response in order to develop a novel, specific immunotargeting drug.
If successful, this project will introduce a significant addendum to the armament of treating leukemia: use of a molecularly targeted drug to induce a potent, durable anti-leukemia immune response.
(See Annex Section 3 WP4, Kreutzmann et al., Mustjoki et al.)

4.48b Quality of life during imatinib treatment

Monitoring the quality of life should be an essential part of treatment of patients with CML. Validated testing methods enable us to monitor the physical, mental and social state together with spiritual aspects of patients. There exists a wide range of validated questionnaires which assess how patients feel about their quality of life in different stages of treatment and which compare the achieved quality of life when introducing new medicaments and medical methods. The aim of all testings is to know the needs of patients and to improve the quality of their lives during and after the treatment. The achieved results of the quality of life measurements need to be statistically processed and evaluated in short studies and both semi-longitudinal and longitudinal research. Instruments: Generic questionnaires: SF 36 (Short Form 36 Health Subject Questionnaire), EuroQolEQ-5D (European Duality of Life Questionnaire Version EQ-5D). Specific questionnaires: EORTC QLQ-C30, QHOQOL 100, FACT).
Work done: Extensive questionnaire testing of 50 imatinib treated patients at least 1 year on treatment.
Plans for the year 2011: Manuscript will be submitted for publication.

4.55b Immunosuppressive mechanisms in CML

We have screened CML patients at the time of diagnosis for their immunological status. Similarly to that of many other cancer types, the level of Tregs in CML patients was increased compared to healthy controls . We have previously published that sCD25 is used by Tregs to suppress T-cell proliferation (Lindqvist C et al, Immunology 2010). In CML patients, sCD25 was markedly increased in plasma but TKI therapy decreased the release of this modulator significantly. Similarly, CML patients have an increase of the T-cell suppressor IL10 in plasma.
Furthermore, the CML tumor was shown to express the regulator PDL1 on the cell surface and we are currently evaluating the capability of those to directly suppress T-cells since the PDL1 receptor PD1 is

expressed on activated T-cells. Preliminary results on four patients demonstrate that CML cells are able to inhibit the proliferation of autologous T-cells but blocking PDL1 on CML cells by antibodies will increase T-cell proliferation in patients and to some extent in healthy controls .

We have created a peptide mix of bcr-abl that can activate both $CD4^+$ and $CD8^+$ T-cells independently of HLA background. Using this peptide mix we can activate and thereby detect T-cells from CML patients that react against bcr-abl (tumor-reactive T-cells). Using this peptide-stimulation we will determine if TKI therapy will affect the number of tumor-reactive T-cells. Similar protocols for detection of CMV positive cells are available at our laboratory.

In patients with B-cell malignancies we have shown that the $FoxP3^+$ Treg cells express increased levels of CD107a which is a marker for degranulation/effector function. However, this increase was more prominent in the $CD127^+$ Treg cells then in the $CD127^-$ Tregs. These cells were then used in a cytotoxic assay against the patients circulating B-cells consisting mostly of tumor cells. The results revealed that the patients Treg cells were capable of killing tumor cells in vitro . Hence, the Tregs in patients with leukemia may not only control anti-tumor T-cells and NK-cells but may as well be controlling the tumor cell since it is derived from the immune system. These results have recently been submitted to Immunology. Tregs may have a similar function in CML patients which we will further investigate in the proposed project.

4.59 Relevant definitions for future trials.

A manuscript is in preparation, including consideration about Imatinib and also 2^{nd} generation of TKIs. To be published 2011.

4.60 Clinical Recommendations for mutation analysis in CML

No updating

4.61 A phase II trial comparing the depletion of malignant stem cells with dasatinib vs imatinib in newly diagnosed CP CML

Background

Imatinib efficiently induces rapid hematologic and cytogenetic remission in most CML patients. However, a small population of resistant primitive leukemia stem cells remains even after years on therapy. Also in vitro experiments have shown that CML stem cells are resistant to TKIs. The clinical implication of stem cell resistance is a rapid leukemia relapse in patients who discontinue imatinib. This residual population also serves as a reservoir for development of drug resistant clones, as it has been shown that most often drug resistance arises as a result of kinase domain mutations in the stem or progenitor cell compartment that affect imatinib binding.

Although the precise phenotype of CML stem cell is not fully characterized, it is likely that the most primitive leukemic stem cells reside in the CD38-negative fraction of CD34-positive hematopoietic

stem cells. The effects of TKI therapy on different fractions of stem cells in vivo are largely unknown. Recent in vitro data on human primary cells have indicated that dasatinib targets an earlier stem cell population than imatinib. Preclinical data need to be confirmed in patients by utilizing state-of-the-art stem cell enumeration and kinetics assays. The aim of this project is to set up a program to routinely enumerate the BM stem cell pool (both malignant and non-malignant) with flow cytometry and fluorescence in situ hybridization (FISH). The correlation between the malignant stem cell burden and the clinical response in CML patients participating in the proposed trial will be monitored. In addition, we hypothesize that initial leukemia burden at the early progenitor and stem cell level may predict therapeutic response. Close monitoring of the kinetics of drug response at the progenitor and stem cell level might serve as an important surrogate marker for long term response and may predict likelihood of early relapse.

Current status of the project (January 2011):

The clinical study (NordCML006) started in Nordic countries (Denmark, Finland, Norway and Sweden) in 2009 and the first patient was recruited in March 2009. The study was closed for inclusion in September 2010 when all 46 planned patients were recruited. Patients were randomized to receive dasatinib at a starting dose of 100 mg QD or imatinib at a starting dose of 400 mg QD. The primary endpoint of the study was the comparison of proportion of Ph^+ cells in stem cell compartments ($CD34^+CD38^-$ and $CD34^+CD38^+$) at 6 months between the study arms. This was analyzed by counting Ph^+ cells from flow cytometry separated stem cell fractions by FISH method. The secondary aims of the study were: correlate the size of the Ph^+ stem cell compartment at diagnosis with (a) therapeutic response at 12 months, (b) kinetics of response at 1, 3, and 12 months (c) hematological toxicity.

First interim results of the diagnostic phase situation were analysed in July 2010 and presented orally at ASH 2010 (Mustjoki et al,). The results showed that the proportion of Ph^+ stem cells at the time of diagnosis varied from 1 to 100% between individual CML patients. It was correlated with hemoglobin concentration, leukocyte count, blast percentage and spleen size at diagnosis and with hematological toxicity during early course of treatment, mirroring paucity of healthy hematopoietic stem cell reservoir. The size of the leukemic stem cell pool at diagnosis may be a powerful prognostic marker and a major biological determinant for the high Sokal risk group.

Further aims and future activities:

The effect of TKI therapy on the malignant stem cell pool size and correlation to therapy responses will be evaluated when all patients have reached the primary study endpoint of 6 months. We plan to present the data from these results at EHA 2011 and/or ASH 2011 meetings.

Importance of the study

The first-line treatment of CML is currently changing with the invention of 2^{nd} generation TKIs. However, probably not all newly diagnosed patients would require more broad spectrum drugs and imatinib could be still drug of choice for them. If the proportion of malignant stem cell pool at the

diagnosis is the major determinant of therapy response, it could serve as a prognostic marker when considering which patients need more robust treatment at the beginning. Furthermore, the proportion of malignant stem cells could be an important biological determinant of the disease and could define a group of patients, who are able to discontinue the treatment after receiving complete molecular response. This needs to be evaluated in future clinical trials. (Reference abstract: see Annex Section 3 WP4, Mustjoki et al.)

4.62 Recommendations regarding CML biobank

Delivery will not occur

4.63 A vaccination trial with *WT1* mRNA-electroporated dendritic cells in TKI treated CML patients

No updating

Table 4.2 List of deliverables WP4, 2011

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP4	**CML**					
	Management					
4.5	Regular WP meetings	78,84,86		0		Simonsson, Guilhot, Hehlmann, Hochhaus
4.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)	79,86		0		Simonsson
	Registry					
4.14e	Report of study patients to registries (n > 400 per year)	73-86		0		Baccarani, Guilhot, Hasford, Hehlmann, O'Brien, Simonsson, Thaler, Cervantes, Steegmann, Ossenkoppele
	Studies					
4.19f	Study imatinib + IFN or AraC, progress reports	73-86		0		Hehlmann, Guilhot, O'Brien Simonsson,Thaler
4.22d	Study high dose imatinib vs imatinib in standard dose (CML-Study IV), progress report, publication	84		0		Hehlmann
4.30e	Preclinical and phase 1 – 2 clinical studies of tyrosine kinase and Src inhibitors	73-86		0		Baccarani
4.36d	Phase II study of peptide vaccine to potentiate and stabilize imatinib effect in CP	73-86		0		Bocchia(1), Baccarani
4.38d	Nilotinib upfront in CP, progress report	73-86		0		Baccarani

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
4.40b	Long term effects of imatinib therapy, progress	73-86		0		Gambacorti
4.41	Allo-SCT after second generation TKI	73-86		0		F. Guilhot
4.44b	Imatinib +/- hydroxyurea	73-86		0		Lange, Niederwieser
4.46b	European study on imatinib withdrawal	73-86		0		Mahon
4.49b	Imatinib D/C in patients with CMolR (STIM)	73-86		0		Mahon
4.50b	IFN plus dasatinib front line and in MMR patients	73-86		0		Roy, F. Guilhot
4.51b	Optimization of imatinib treatment based on plasma imatinib level (OPTIM)	73-86		0		F. Guilhot
4.57	Induction/Maintenance strategies in newly diagnosed CML patients using nilotinib, dasatinib and Interferon alpha – German CML study V. Start 2010	73-86		0		Hochhaus, Hehlmann
	Lab					
4.29e	Dynamics of response and resistance in CML patients treated with tyrosine kinase inhibitors beyond imatinib (AMN 107, BMS 354825). Progress reports.	73-86		0		Hochhaus, Saglio
4.34d	European control round for BCR-ABL mRNA quantification (overlap with WP12), progress report	73-86		0		Cross, Hochhaus, Saglio, Müller
4.58	Definition and European Standardization of CMR	73-86		0		Cross, Müller, Hochhaus, Saglio
4.35b	Mutated bcr-abl clones – level, control rounds	73-86		0		Müller, Gruber, Lange, Ernst
4.45	Allo-HSCT in LR patients. Second report	73-86		0		Gratwohl, Niederwieser
4.47b	DNA microassays in CD34+ CML cells	73-86		0		Mayer
	Others					
4.43b	Dasatinib and immunomodulation, progress report	73-86		0		Porkka
4.48b	Quality of life during imatinib treatment	73-86		0		Mayer
4.55b	Immunosuppressive mechanisms in CML	73-86		0		Simonsson
4.59	Relevant definitions for future trials, Manuscript 2010	73-86		0		J Guilhot
4.60	Clinical Recommendations for mutation analysis in CML	73-86		0		Martinelli, Souverini
4.61	A phase II trial comparing the depletion of malignant stem cells with dasatinib vs imatinib in newly diagnosed CP CML	73-86		0		Mustjoki, Hjorth-Hansen, Richter
4.62	Recommendations regarding CML biobanks	73-86		0		Goldman
4.63	A vaccination trial with WT1 mRNA- electroporated dendritic cells in TKI treated CML patients	73-86		0		Berneman

*) if available

Table 4.3 List of milestones WP4, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP4	**CML**			
4.14e	Report of study patients to registries (n > 400 per year)	73-86		Baccarani, Guilhot, Hasford, Hehlmann, O'Brien, Simonsson, Thaler, Cervantes, Steegmann, Ossenkoppele
4.58	Definition and European Standardization of CMR	73-86		Cross, Müller, Hochhaus, Saglio
4.35b	Mutated bcr-abl clones – level, control rounds	73-86		Müller, Gruber, Lange, Ernst
4.43b	Dasatinib and immunmodulation, progress report	73-86		Porkka
4.59	Relevant definitions for future trials, Manuscript 2010	73-86		J Guilhot

Section 3: Consortium management

WP4 in conjunction with the group of European Investigators on CML (EICML) has been a successful group of scientists, which is well recognized internationally. This group represents a solid basis for setting standards and for the rapid investigation of new drugs.

WP4 is managed by five lead participants with the help of the NMC in Mannheim. Three successful WP meetings (and one EICML meeting) demonstrate the active work in this group.

Communication between participants and with the NMC is running well.

Section 4: Other Issues

Ethical issues – none, Competitive calls - none

Section 5: WP-Performance

Performance indicators	Status
Number of clinical trials started and/or completed	6
Number of patients included into registries	approx. 3500
Improved predictive, prognostic or quality of life assessments	Guidelines of diagnostic and therapeutic procedures updated for submission, inter-laboratory control rounds continue
Degree of harmonization of trials	4 collaborative trials on an European level
Number of SOPs and consensus papers	2
Number of publications	85
Number of meetings	6
Number of meta-analyses	0
Number of accredited trials	see website

5 AML (WP05)

Objectives and starting point of work at beginning of the reporting period

At the beginning of 2010 the situation was characterized by further progress and experience in the field of molecular markers. Besides their role as risk factors, the genetic and metabolic peculiarities of AML cells increasingly appeared as targets for new drugs. Promising therapeutic results were confirmed mainly in promyelocytic leukemia. First updates suggested a successful cooperation of trials in the AML Intergroup in younger patients, while data and experiences in older age AML increased Europe wide. An increasing availability of data on allogeneic SCT suggested the use in high-risk disease even in older patients. Publications see Annex Section 3, WP5.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

During 2010 further progress has been achieved in the European AML network (WP5). At the annual Reisensburg Symposium new data on gene mutations have been presented and T.Haferlach gave a comprehensive overview of the field (see minutes). New drugs and targets were updated at the Hematologic Malignancies conference in Brussels and by a survey. Epigenetic changes in AML related to age became the subject of a DFG funded research project (see application summary) and also a therapeutic target. The AML Intergroup as an ELN pilot study has now recruited more than 3000 patients. The latest update allows reliable projections to 5 years, (7). As another ELN pilot study a scoring system of older age AML was elaborated in a large multicenter trial and validated in an independent trial (8,9). Uniform European recommendations on all clinical aspects of AML were published for both general AML (13) and APL (4). APL relapse, data and treatment, were contributed in an own publication (5,6). Multiple approaches and experiences were reported on the field of allogeneic SCT (11,14). The role of growth factor priming in AML could be elucidated in a large multicenter trial as an ELN pilot project (see Annex section 3, WP5-2).

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

No substantial deviations of the workprogram.

5.5 Regular WP meetings

WP5 Meeting at ELN Symposium Mannheim, 03.02.2010

AML Intergroup Meeting, Frankfurt, 03.05.2010

WP5 Meeting at EHA Barcelona, 10.06.2010

AML Intergroup Meeting, at ASH Orlando, 05.12.2010

WP5 Meeting at ELN Symposium Mannheim, 02.02.2011

5.6 LP Reports to NMC regarding structure, trial activities and integration of national leukemia trial groups, continued

AML Intergroup Symposium Reisensburg, 12.02.2010 (see minutes)

AML Intergroup Symposium Reisensburg, 11.02.2011 (see minutes)

WP5 meetings (see 5.5).

5.12g Current trials on novel therapies in Europe (new drugs new targets), continued

Report at International Symposium Hematological Malignancies, Brussels 01.10.2009

5.13f Pilot study treatment in subgroups defined by genetic markers, up-front randomized, intention-to-treat, continued

Büchner et al, JCO 2009 (see Annex section 3, WP5).

5.15f Pilot study AML Intergroup and a European AML network, continued

New update from the AML Intergroup: Participation of 5 trial groups, recruitment of 3602 patients age 16 to 60 years, median observation time between 2.0 and 4.8years, 358 patients (10% from all groups) in the common standard arm, overall survival probability at 5 years standard arm 0,41, all 5 participating trials within the 95% CI.. Büchner et al. ASH 2010 (see Annex section 3, WP5).

5.16f Establishing a European network on management of Acute Promyelocytic Leukemia

Sanz et al., Blood 2009 (see Annex section 3, WP5).

5.17f Establishing a European network on management of AML in older patients

As a pilot project a scoring system of elderly AML has been established in the AML Intergroup (Krug et al. 2010 Lancet (see Annex section 3, WP5).

5.18f Develop frailty index for leukemia in older patients, continuation

A novel risk score that predicts the likelihood of a complete remission after intensive induction therapy in older patients has been published in 2009. A publication on the frailty index in older patients is in preparation (see Annex section 3, WP5).

A publication by Lübbert M. et al. concerning the frailty index in older patients with AML has been prepared.

5.21e Harmonizing the criteria of biologic subgroups, risk categories and treatment strategies for patients with AML in Europe, continued

Recommendations for the diagnosis and management of AML in adults have been published in 2009 Döhner H et al. Blood 2010 (see Annex section 3, WP5).

5.25b Epigenetic pattern of AML with respect to patients age and risk profile

The project “Die Bedeutung altersabhängiger genomweiter DNA-Methylierungsmuster bei der Akuten Myeloischen Leukämie/ Kennwort: Biologie der AML im Alter”, submitted by C. Müller-Tidow and T. Büchner, has been accepted for funding by the DFG/German Research Community.

5.26b Growth factor priming in AML: Long-term results

Long-term results in patients with acute myeloid leukemia (AML) and data of the AMLCG 1999 trial were published in Blood 2009 and in ASH Highlights (see Annex section 3, WP5).

There was a contribution of WP5 to the current ELN Information Letter concerning the prospective assessment of outcome determinants in AML (see Annex section 3, WP2).

5.27b European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation

WP5 maintained several fruitful cooperation with European trialists, resulting in 3 publications in 2010 (see Annex section 3, WP5).

5.28 European recommendation on diagnostic, classification and treatment of AML

Döhner et al. Blood 2010 (13) (See Annex section 3, WP5)

Table 5.1 List of Deliverables WP5, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP5	**AML**					
5.5	Regular WP meetings	**78,84,86**	86 and beyond	0	4	Büchner Ossenkoppele
5.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style), continued	**79,86**	86	0	2	Büchner Ossenkoppele Sanz
5.12g	Current trials on novel therapies in Europe (new drugs new targets), continued	**86**	**86 and beyond**	0	2	Berdel Müller-Tidow Krug Serve Holowiecki Lübbert
5.13f	Pilot study, treatment in subgroups defined by genetic markers, up-front randomized, intention-to-treat, continued	**86**	**86 and beyond**	0	4	Büchner Berdel Kienast, Heinecke Serve
5.15f	Pilot study AML Intergroup and a European AML network, continued	**86**	**86 and beyond**	0	12	Büchner Döhner Ehninger Ganser Niederwieser Pfirrmann Gratwohl
5.16f	Establishing a European network on management of acute promyelocytic leukemia, continued	**86**	**86 and beyond**	0	2	Sanz Lengfelder
5.17f	Establishing a European network on management of AML in older patients, continued	**86**	**86 and beyond**	0	6	Büchner Burnett Niederwieser Lübbert
5.18f	Develop frailty index for leukemia in older patients, continued	**86**	**86 and beyond**	0	4	Lübbert Büchner Krug
5.21e	Harmonizing the criteria of biologic subgroups, risk categories and treatment strategies for patients with AML in Europe, continued	**86**	**86 and beyond**	0	6	Ossenkoppele Sierra Büchner Lübbert
5.25b	Epigenetic pattern of AML with respect to patients age and risk profile, continued	**86**	**86 and beyond**	0	6	Müller-Tidow Haferlach Löwenberg
5.26b	Growth factor priming in AML: Long-term results, continued	**78**	78	0	2	Löwenberg, Amadori Büchner
5.27b	European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation, continued	**86**	**86 and beyond**	0	6	Kienast Gratwohl Wheatley Krug Löwenberg Ehninger
5.28	European recommendation on diagnostic, classification and treatment of AML	**86**	**86 and beyond**	0	4	Niederwieser Döhner Büchner Löwenberg

Table 5.2: List of milestones WP5, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP5	**AML**			
5.15f	Pilotstudy, AML Intergroup and a European AML network, continued	**86 and beyond**	12	Büchner Döhner Ehninger Ganser Niederwieser Pfirrmann Gratwohl
5.16f	Establishing a European network on management of acute promyelocytic leukemia, continued	**86 and beyond**	2	Sanz Lengfelder
5.17f	Scoring of elderly AML	**86 and beyond**	6	Krug Röllig Müller-Tidow Büchner
5.27b	European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation	**86 and beyond**	6	Kienast Gratwohl Wheatley Krug Löwenberg Ehninger Niederwieser
5.28	European recommendation on diagnostic, classification and treatment of AML	**86 and beyond**	4	Döhner Büchner Löwenberg

Section 4: Other Issues

Ethical issues -none

Competitive calls – none

Section 5: WP-Performance

No major changes since 03/07

Performance indicators	Status
Number of clinical trials started and/or completed	3
Number of patients recruited into clinical trials	approx. 1500
Number of patients included into registries	approx. 1500
Improved predictive, prognostic or quality of life assessments	New AML European guidelines published (Blood 2009)
Degree of harmonization of trials	see publication (Blood 2009)
Number of SOPs and consensus papers	6
Number of publications	120
Number of meetings	10
Number of meta-analyses	2
Number of accredited trials	20

6 ALL (WP06)

The successful national European study groups for ALL aim to combine their efforts in order to create a world-wide leading research group for adult ALL. Thus the essential aims of WP6 remained the same since the beginning of the funding. Major aim is to strengthen collaboration between the national European ALL study groups, to initiate new national study groups, to provide a platform for trustfull discussion of data and future plans and to encourage and initiate collaborative projects.

Integrating activities

- Maintenance of central management structures
- Development of standardized laboratory procedures for diagnostic confirmation
- Overview on prognostic factors used in the different trials
- Overview on ongoing European studies in ALL with a study registry
- Discussion of results and future plans of the national ALL study groups

Jointly executed research activities

- Combination and standardization of methods, definitions and clinical application of MRD
- Phase I-III intergroup studies

Spread of excellence

- Internet-based information on adult ALL
- Evidence-based guidelines for diagnosis and treatment of ALL
- Presentation of the network at national and international meetings
- Extension of network

Integrating activities

Management and structure of the working group:

The collaboration within EWALL was further extended. According to a defined meeting plan three meetings were organised by EWALL alone or in collaboration with other groups. The communication between the participants is based on regular e-mail exchange.

New members in 2010

In 2010 the newly founded Slowakian working group for adult ALL joined the EWALL.

Meetings in 2010

Two meetings were organised in the context of other international meetings (Heidelberg, Network Symposium; informal come-together at ASH, Orlando). Beyond this the EWALL organised two separate 1 day internal meetings. One of these traditionally takes place in Frankfurt and the other by rotation in different member countries. The collaboration with the ESG-MRD group and joint meetings for standardisation of bcr-abl diagnostics continued.

EWALL meeting February 2010, Mannheim:

The meeting covered two major topics. (1) **Ph-positive ALL**. Contributions were made regarding BCR-ABL diagnostics and mutation analysis. An update on the EWALL elderly trial with Dasatinib was presented and the planned GIMEMA combination trial was discussed. (2) **New drugs in Ph-negative ALL**. Planned or ongoing studies with Clofarabine, MT103, Erythroczyte-encapsulated asparaginase and antifungal prophylaxis were presented.

EWALL meeting June 2010, Milano

Before EWALL and EHA relationships were discussed with the aim to develop the ALL-EHA-Scientific Working group. Two major topics were discussed. (1) **Relapsed and Refractory ALL**. (a) Clofarabine/ Cyclophosphamide protocol for relapsed/refractory ALL, (b) GIMEMA experience with clofarabine for highly resistant ALL, (c) FLAM and FLAM-Cam for relapsed/refractory ALL (PALG studies), (d) Relapse treatment in the GMALL studies, (e) PETHEMA studies in refractory/ relapsed ALL and (e) Considerations on biology of relapse in Ph+ ALL were presented. The second major topic was (2) **Treatment of T-ALL**. Results from ongoing (a) GMALL- studies, (b) NILG studies, (c) PETHEMA studies were discussed and as a guest A.Biondi presented (d) data from pediatric patients. Additional topics were (3) Ofatumumab in association with chemotherapy in Burkitt Lymphoma and B-ALL and (4) Haploidentical SCT for highly resistant ALL

EWALL meeting November 2010, Frankfurt

Two major topics and a number of specific topics were discussed. (1) **New drugs for ALL.** Presentations were given on (a) Clofarabine in de novo ALL, (b) Protocols with Notch 1 inhibitors and (c) Erythrocyte encapsulated asparaginase. (2) **Ph+ ALL – Results of stem cell transplantation**. Data from the (a) GRAALL, (b) Pethema, (c) GIMEMA, (d) NILG, (e) GMALL and (f) MRC were presented. Furthermore a joint project on (3) Prophylactic use of G-CSF during induction and consolidation in ALL (a joint analysis of five randomized trials) was discussed. (4) The collaborative study of Gilead Sciences and EWALL was presented and discussed. (5) Updates on ongoing and planned studies with 2nd generation inhibitors in Ph+ ALL (Dasatinib, Nilotinib) were presented and 3rd generation inhibitors for relapsed Ph+ ALL were discussed. (6) Final decisions on the EWALL standard recommendation were made and (7) future meetings, particularly the EWALL meeting in London discussed.

EWALL meeting, ASH New Orleans, December 2010: The group presented in the plenary session major achievements and future plans to the other network members. Thereafter an informal come-together took place.

Web presentation

Further website contents were entered by WP2.

Study registry

The registry with ongoing European studies on adult ALL was maintained and extended.

Jointly executed research activities

Collaborative trials

The initiation of international joint European trials still is in practice extremely difficult and time-consuming – actually nearly impossible without large funds.

The following studies are ongoing or in preparation:

- GMALL B-ALL/NHL 2002

  The study conducted by the German ALL Study Group (GMALL) is ongoing in the Northern Italian Leukemia Group (NILG), the Polish Leukemia Group and the Spanish PETHEMA group. Since 2007 the Swedish group uses the protocol.
- EWALL Depocyte Trials

  The NILG study with Depocyte in prophylaxis was started. In the GMALL elderly study the planned patient number was achieved and follow-up is awaited.
- EWALL Chemotherapy Backbone for Elderly ALL

  The trial with Dasatinib for elderly Ph+ ALL was extended in order to achieve a sufficient number of Dasatinib treated patients. A trial with Nilotinib was prepared and will start in 2011.
- Clofarabine in relapsed ALL

  A new study with a clofarabine combination in relapsed ALL was initiated by R.Bassan.
- Blinatumomab

  A joint European trial with Blinatumomab in MRD positive ALL was started as a company sponsored trial
- Antifungal prophylaxis

  An international trial with Ambisome prophylaxis during induction therapy of ALL was started as a company sponsored trial.

Spread of excellence

With the website of the project a basis for internet-based information exchange and creation of a virtual center of excellence on adult ALL was maintained.

Members of the WP were also active speakers of educational sessions on national and international meetings and made contributions to textbooks.

Ottmann O.G.: Treatment of Ph+ adult ALL (EHA Education Session 2010)

Ribera J.M.: MRD oriented treatment in PH-adult ALL (EHA Education Session 2010)

Marks D.: Treating the "Older" Adult With Acute Lymphoblastic Leukemia (ASH Education Session 2010)

Foundation of a EHA-EWALL Working Group

A first workshop of the newly founded EHA-EWALL working group was organized during the EHA meeting in Barcelona and well attended (100 participants).

- Interim results of the new MRD and risk oriented study 10/07 (R.Bassan)
- Results of the GRAALL Studies 2003 and 2005 in Ph-negative ALL (H.Dombret)
- MRD-based treatment in GMALL study 07/2003 (N.Gökbuget)
- The GIMEMA strategy for Ph+ ALL (R.Foa)
- UKALL12 final analysis of Imatinib in Ph+ ALL (A.Fielding)
- Results of specific immunochemotherapy in HIV-related Burkitts leukemia and lymphoma (J.Ribera)

Extension of the network

Another important goal was the extension of network by inclusion of additional network participants from other European countries. The aim is to integrate countries which have national study groups dedicated to ALL but not individual hospitals. The EWALL supported the foundation of a Slowakian study group for adult ALL headed by Eva Demeckova.

Publications

The members of the workpackage have developed a large number of national and international publications and were international opinion-leaders in many respects although these publications were not directly initiated by the network.

Deviation from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

In 2010 the work of the European Working Group for Adult ALL (EWALL) was continued although – despite travel expenses for one working group meeting - no funding was available.

Table 6.1 List of deliverables WP6, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP6	**ALL**					
6.5	Regular WP meetings and symposiums (during international meetings)	78,80,86	78, 80, 83, 86	0	4	Hoelzer, Gökbuget
6.20	WP Management including reports	79,86	86	0	2	Gökbuget, Hoelzer
6.21d	Extension of web-based information and communication services on ALL, continued	73-86	86	0	4	Gökbuget, Hoelzer
6.24e	Support of newly funded European study groups and education	73-86	86	0	3	Hoelzer, Gökbuget
6.25e	Extension of registry of ongoing European ALL studies	73-86	86	0	6	Gökbuget, Hoelzer
6.27e	Activation of further European studies	73-86	86	0	6	Hoelzer, Gökbuget
6.28e	Publication of Consensus Paper	73-86	86	0	6	Gökbuget, Hoelzer
6.29e	Coordination of the EHA ALL Working Group	73-86	86	0	4	Gökbuget, Hoelzer

*) if available

Table 6.2 List of milestones WP6, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP6	**ALL**			
6.28e	Publication of Consensus Papaer	73-86	ongoing	Gökbuget, Hoelzer
6.29e	Coordination of the EHA ALL Working Group	73-86	86	Gökbuget, Hoelzer

Section 3: Consortium management

New participants of the WP: The Slowakian ALL study group with the following representatives joined the EWALL: E.Demeckova.

Section 4: Other Issues

Ethical issues: none, Competitive calls: none

Section 5: WP-Performance

Performance indicators	Status
Number of clinical trials started and/or completed	European joint studies: 5 (4 planned)
Improved predictive, prognostic or quality of life assessments	Analysis of prognostic factors in European ALL trials, Joint proposal for a geriatric score, Consensus for MRD-analysis (BCR-ABL, gene rearrangements)
Degree of harmonization of trials	Ongoing
Number of SOPs and consensus papers	2 consensus paper prepared for website Patient info.,prepared for website (8 languages
Number of publications	1 paper, 1 submitted, 38 additional papers
Number of meetings	5
Number of meta-analyses	0
Number of accredited trials	>20

7 CLL (WP07)

Objectives and starting point of work at beginning of report period:

The European Research Initiative on Chronic Lymphocytic Leukemia (ERIC/WP7) comprises a well established association of more than 300 European/international clinicians and/or scientists, dedicated to creating a translational platform for clinical and basic research activities in the field of chronic lymphocytic leukemia (CLL). Over the past 9 years, ERIC has established an excellently working information- and communication structure and a notable core of world-wide recognized CLL specialists. With the election of a new board of directors, including Professor Emili Montserrat (Barcelona/Spain) as the executive chairman of ERIC in December 2008, ERIC has entered a new era of further development, restructuring and activities. During 2010, the main ERIC Secretariat office was consolidated in Barcelona. However, parts of the ELN related administration and representation of ERIC are still carried out in Germany thanks to the support of the former ERIC chairman Professor Michael Hallek and the Cologne office (University of Cologne, Department of Internal Medicine I). 2010 was the second year that ERIC has successfully performed as a Scientific Working Group (SWG) within the European Hematology Association (EHA). As per the deliverables of WP7/ERIC, the following activities have been carried out during the past 12 months:

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

7.5 Regular WP meetings

3 business meetings, one scientific symposium and one scientific workshop were held by ERIC/WP7 in 2010:

1. 22nd ERIC Meeting at the 7th Annual Symposium of the ELN, Tuesday, February 02, 2010
   Attendance: Approximately 50 participants from EU and non EU countries
   The major results of this ERIC/WP7 meeting, were:
   - An Executive Committee presentation by Professor Montserrat.
   - A presentation on 'Potential collaboration to evaluate prognostic role and potential role as therapeutic target of Cdc7 in CLL´ by Prof. M. O'Dwyer
   - A decision to add Dr Sarka Pospisilova to the ERIC Board, accepted by meeting participants.
   - A plan for an 'ERIC retreat' of key members prior to the next ERIC General Meeting
     The meeting was kept informal for open discussion.
2. 23rd ERIC Meeting at the European Hematology Association (EHA) Congress, Barcelona, Thursday 10th June 2010.
   Attendance: Approximately 55 participants from EU and non EU countries
   As mentioned in recent reports, for the past years the annual EHA congress has become a

fixed meeting venue for a series of very successful Scientific Workshops/Symposiums, carried out by ERIC/WP7. In 2010, the tradition was continued by ERIC, now additionally representing a Scientific Working Group of EHA, with a series of invited top speakers from Europe and the U.S. (see two events detailed below). The topic of "CLL/T-PLL transplants" was selected by the Scientific Committees of ERIC for a special symposium dedicated to the memory of a recently departed and dearly loved colleague. The p53 scientific workshop was also well anticipated and visited by members and other EHA congress attendees.

3. EHA/ERIC Symposium on CLL/T-PLL transplants at the European Hematology Association (EHA) Congress, Barcelona. Thursday 10th June 2010. *Dedicated to the memory of Dr. Jasper Jurlander*. Chairpersons: E. Kimby and E. Montserrat, Meeting Organizer: P. Dreger. Final Programme available at the ERIC website: www.ericll.org
4. ERIC p53 scientific workshop at the European Hematology Association (EHA) Congress, Barcelona. Thursday 10th June 2010. Organisers: Stephen Stilgenbauer and Thorsten Zenz. Attendance: Approximately 45 participants from EU and non EU countries.
   Final agenda and minutes available at the ERIC website: www.ericll.org
5. 24th General Meeting of ERIC Members, Orlando, 5th December 2010
   Attendance: Approximately 50 participants from EU and non EU countries
   As every year, the ERIC/WP7 community was gathering in context of the "ASH Breakfast Meeting" carried out by the ELN at the annual congress of the American Society of Hematology (ASH, Orlando, USA). A major section of the agenda was given over to working group/project updates and in particular the 'resetting' of working group activities within a new detailed 'project' modality with improved reporting lines. Final agenda and minutes available at the ERIC website: www.ericll.org.
6. The next ERIC assembly took place in Mannheim/Germany during the 8th Annual Symposium of the European LeukemiaNet (Feb 1, 2011).

7.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

See schedules for the ERIC/WP07 meetings in Mannheim, Barcelona and Orlando 2010.

7.8f Treatment of early stage, high risk CLL with FCR continued

The results of this important clinical randomized trials led by Professor Michael Hallek as principal investigator, the German CLL Study Group and many other European CLL Working Groups, most of them linked to ERIC, have been presented at different international meetings and successfully published in Lancet.

7.9f Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups

The development of new potential curative treatment modalities for CLL and related diseases is one long-term goal of WP7/ERIC. Therefore, one ERIC objective is to support phase I/II/III trials with new agents alone or in combination with established therapies (purine analogues, alkylating agents) in CLL and/or related entities. According to previous reports, the following protocol exchanges have been active within ERIC:

- Protocol on chemoimmuntherapy with FCR versus watch and wait in early CLL; German/French study group (GCLLSG/FCGCLL)
- Protocol on recommendations for stem cell transplantation in T prolymphocytic leukemia (T-PLL) and development of a national registry documentation for transplant cases in T-PLL (responsible: P. Dreger, Heidelberg/Germany, see D7.16c)

CLL cases with p53-abnormalities are continuously collected on a molecular and clinical basis (including sequence characteristics but also clinical routine data) by the p53 working group (responsible: Stephan Stilgenbauer, Ulm, Germany), as previously described. Deliverable D7.9 belongs to the long-term efforts of WP7/ERIC and fulfilment will last up to and exceed month 91.

Moreover, ERIC has collected information on other clinical trials for CLL across Europe that are available at ERIC webpage (www.ericll.org). ERIC will update this information on a yearly basis.

7.10d Common data safety monitoring boards in clinical trial on CLL in Europe

The first exemplary Data Safety Monitoring Board (DSMB) within ERIC was constituted for the ERIC supported clinical trial protocol on early stage CLL patients, which is part of deliverable 7.8. Eva Kimby (Stockholm/Sweden) and Peter Hillmen (Leeds/UK) have been selected as independent reviewers of data acquired within this transnational study for any interim, final or follow up analysis in future. The DSMB has been instituted by the German and French CLL study groups to review the clinical plausibility and safety of data collected during the study, as previously described. With finished patient recruitment for deliverable 7.8e, data for a first interim analysis are expected to be available in fall 2011.

7.11f Web-based information- and communication services on CLL refined and up-dated

One of the major goals of deliverable 7.11 is to maintain and spread updated information on the mission, goals and activities of ERIC/WP7 to clinicians/scientists, who are interested and/or active in the field of CLL. During the past 12 months the content of the ERIC core webpage (http://www.ericll.org) has been maintained and updated on a regular basis. Upcoming meetings, meeting agendas and minutes have been announced on the web page regularly. In addition to the core web page, the concordance of project specific web pages for “the harmonization of MRD analysis in CLL” (deliverable 7.24, www.mrd-cll.org) and the “ERIC consensus and review board on IGHV-

analysis in CLL" (deliverable 7.23, www.ericll.org/projects/IGVHMutationalAnalysis.php) require additional web skills and high maintenance efforts: Continuous improvements and further development of the webpage setup, programming, structure and contents are ongoing. This task will be continued as deliverable 7.11. of WP7 beyond month 91.

7.16f Harmonisation of clinical study protocols and trial accessories between national CLL study groups

The harmonization of clinical study protocols and trial accessories between national CLL study groups has been exemplary initiated within deliverable D7.8 (treatment of early stage, high risk CLL with FCR versus watch and wait). In this pilot trial, the harmonization of the complete data management process including data documentation, handling of queries, adverse events, SOPs etc. between the cooperating study groups in Germany, France and other participating countries has been difficult, and by far more time and man power consuming than originally assumed. It also exceeded the input and operating expenses provided by each country for the "regular" trial conduction. As one successful step within the past 12 months, two data bases with an agreed framework consensus of patient data items have been established between German and French study groups in collaboration with the company WISP (Wissenschaftlicher Service Pharma GmbH, Langenfeld, Germany). While quality control and assurance activities by data base programmers on both sides are ongoing, both countries continue to collect completed CRFs and continue to perform continuous medical review, query processing and monitoring of participating study sites. The goal of deliverable 7.16 is to create exemplary harmonized trial accessories required to ensure high data quality in transnationally performed clinical trials. Setup of a completely harmonized and audit-withstanding clinical trial between several countries continues to stay a big challenge for established study groups. According to our experience it is not accomplishable for public study groups without industrial support and funding. Further progress of this deliverable will take at least further months up to month 91 and requires more person-months.

7.19d Continued follow-up of patients with advanced CLL treated with FCR/FC – progress report

Albeit this trial has been terminated and published, continuous follow up of patients is planned as per the rules established in the protocol. The deliverable confirmed that treatment with FCR chemoimmunotherapy is more effective than FC chemotherapy in previously untreated CLL patients. Furthermore, for the first time a survival benefit was demonstrated in a randomized setting for first-line treatment in CLL. The partial failure to demonstrate a benefit for FCR treatment in Binet stage C patients was discussed as potentially related to the higher tumor load in such patients. However, the results corroborate the recommendation to use FCR as standard treatment in physically fit patients with CLL and in need of therapy.

7.20e European platform for phase I/II trials

Some approaches have been made with Pharma, particularly with GSK and we are now in the process of negotiating.

In the past funding periods the difficult aspects of performing clinical trials in rare disease entities have been discussed intensively in our activity reports at the examples of the following ERIC-supported trial protocols (deliverable 7.26):

- Protocol of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria)
- Protocol of primary or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany.

Despite tremendous efforts by local and European wide study groups, the spread of trial information via ERIC and negotiations with companies and application for public funding, as previously described, it was not possible to overcome financial and regulatory requirements to launch these trials in the sponsoring countries so far. This has been disappointing for responsible investigators, the ERIC community and patients. Current rescue strategies are considering re-application to public funding opportunities and design of a register trial. Further ideas and strategies are currently discussed among ERIC investigators and will be topic of future ERIC meetings. Thus deliverable will be a continuous task of ERIC/WP beyond month 78.

7.21e European survey on treatment modalities in CLL patients

Under guidance of Vincent Levy (Paris), ERIC is performing a prospective multicenter international internet-based survey on clinical CLL practice. Aim of the project is the evaluation of treatment modalities and behaviour of clinicians in selecting diagnostic and treatment regimens for CLL patients in different situations of clinical disease presentation. As an assessment tool, 7 CLL specific case vignettes are used, which have been shown to be valid tools to assess the quality of clinical practice. The study is conducted among hematologists within Europe, Israel, South America and Australia, actively engaged in treating CLL patients, participating or not in clinical trials and from all types of medical structures (from private practice to large tertiary centres). Within the past 12 months the following steps have been accomplished:

After an initial phase of vignette quality assessment and control the study is currently running in second phase and evaluated as a large-scale European and International survey. Contacts to European and other countries interested in participation have been partially established via ERIC.

Responsible contact person for the project is Vincent Lévy (Centre d'Investigations Cliniques, Hôpital Saint Louis, Paris, France). This interesting and innovative deliverable is not yet fulfilled and will last

until month 78 for being fully accomplished.

7.23d Harmonization, consensus, online support for interpretation and collection of "problematic cases" in IGHV gene mutational analysis

The "IGHV"-working group is dedicated to standardize, harmonize and teach the correct way of mutation-analysis of rearranged immunoglobulin heavy chain variable (IGHV) region genes in patients with CLL. In several trials the IgHV mutation status has been proven to be one of the most potent prognostic factors for treatment and long-term outcome in CLL patients. This WG has now been divided in two relevant projects on the analysis of IgHV genes:

1) Towards standardization of immunoglobulin gene analysis in CLL.

General aims are to investigate how laboratories currently are performing and interpreting immunoglobulin gene analysis in CLL, a comprehensive online questionnaire will be created which will cover important technical and bioinformatic aspects as well as their interpretation of results.

As a second step, we will develop a program for quality control of immunoglobulin gene analysis for ERIC laboratories and our plan is to annually send around a number of "unknown" CLL samples for analysis and interpretation.

2) Immunoglobulin gene analysis in CLL: Prognostic and biological implications of cases difficult to categorize

With the aims of creating a comprehensive catalogue of all possible types of problems that may be encountered during immunoglobulin gene analysis, the collection of clinical information and biological material from all cases with problematic IGHV-IGHD-IGHJ sequences is planned in order to reach a significant number of each category, thus enabling to investigate potential prognostic and biological implications

The IGHV group has established a very successful online system, offering online consultation/support for centers having difficulties in interpreting IGHV sequences and collecting IGHV sequences from participating centers throughout Europe (see previous activity reports). In 2010 the IGHV group had the following activities:

1. Continuous web-based/online support for trouble-shooting in IGHV sequence analyses: Over the year 15 queries from several countries throughout Europe and the US were received. Most frequently, "troubled" sequences included insertions and/or deletions or single unproductive rearrangements, which hindered complete alignment with IGHV germline sequences.
2. The IGHV group is definitely collaborating with IMGT (International Immunogenetics Information System) in order to refine the programmed analytical tools for the automated IGHV sequence analysis and alignment with germline sequences offered by www.imgt.org (IMGT/V-Quest). With the implementation of new bioinformatic/programmed tools, the detection and denomination of insertions, duplications and deletions with the IMGT/V-Quest

system has been improved tremendously. Clinicians/scientists using IMGT/V-Quest can now retrieve more comprehensive and detailed information about inserted/deleted or duplicated nucleotides, when analyzing an affected IGHV sequence case. Everybody can connect to http://imgt.cines.fr/, to scroll down to "Databases" and you will find to "IMGT/CLL-DB (bylaws) LIGM, Montpellier, France IG sequences from CLL, an initiative of the IMGT/CLL-DB group"

3. An educational workshop on IGHV sequence analysis in CLL in Stressa (Italy) is planned for the next 6th-7th April 2011, sponsored by the ELN/ERIC and industrial support.
4. Following the very successful first book release (title: "Immunoglobulin gene analysis in chronic lymphocytic leukemia"), which was also supported by the ELN/ERIC, a second book about "biological diagnostic markers in CLL" has already been published and distributed among ERIC members. It includes modern diagnostic tools, like the immunoglobulin analysis, MBL diagnostics, flow cytometry, microRNA analysis etc. and focus on the future clinical application and potential of such diagnostic parameters.

7.24d Harmonization and quality control of MRD diagnostics

The MRD (minimal residual disease) working group under guidance of Andy Rawstron (Leeds, UK) focuses on continuous improvements and standardization of MRD analysis techniques in CLL, as described in earlier activity reports. Besides the ongoing online support provided by the management and maintenance of an ERIC-connected MRD web page (www.mrd-cll.org), the working group continues to work on the following goals:

- To develop a quality control system for MRD analysis which simplifies a sort of "screening" assay for routine MRD assessment in CLL
- To develop a standardized 6-colour flow cytometric assay running under the quality control aspects developed above.

Compared to 2008, ongoing activities of the working group in 2009 have not changed and concentrate on the following aspects.

- To determine optimal antibody combinations by investigating electronically manipulated data in 4/5/6-color formats
- To conduct dilution studies between European wide participating centers: representative data files were sent to Milano, Kiel & Barcelona and are under investigation
- To establish/re-develop a "rapid screening approach" of MRD by flow cytometry using the minimally required antibody combination for the highest number of correct MRD estimations (500 cases are tested so far, further tests are ongoing, this approach may be highly effective during treatment but response assessment usually requires a full MRD panel)
- To establish, evaluate and improve an MRD quality control data analysis scheme: First e-trial-results have been collected from 16 centres (of 31 registered, each centre has to process a

given CLL case with a certain amount of residual CLL cells and denominate the number/percentage of detected CLL cells).

- Collection and review of difficult MRD cases, discussion and continuous online support.

The accomplishment of these tasks has to be continued under the auspices of ERIC beyond month 91. First results will be presented and discussed in the ERIC community in 2011.

7.26d Collection & investigation of functional aspects of p53 mutation

The "p53 working group" within ERIC comprises a very active subgroup of scientists/clinicians from 9 European countries interested in p53 (a tumor suppressor inactivated in several tumor subtypes, also in a subgroup of CLL patients with very poor prognosis) related translational and basic research.
Within the past year the following activities have been accomplished:

- A large series of 268 different p53 mutations in 254 patients has been collected and characterized. Mutations have been identified as mostly missense mutations (74%), followed by deletions/insertions (20%), nonsense mutations (4%) and affecting splice sites (2%). The most frequent amino acid positions of mutations have been determined (i.e. AA 175, 179, 248, 273). Detailed results were published by the p53 working group in several journals or at ASH (see Annex Section 3, WP7).
- Further focus of the p53 working group is to retrieve clinical correlations between p53 mutations and treatment outcome and longterm prognosis in clinical trials. Therefore, the group is promoting "p53 trials", where refractory CLL patients with or without affected p53 gene loci can be included. One example is the CLL2O trial by the German CLL study group (phase II study of subcutaneous alemtuzumab combined with oral dexamethasone, followed by alemtuzumab maintenance or allogeneic stem-cell transplantation, in CLL associated with 17p deletion or refractory to fludarabine) or the meanwhile closed CLL206 NCRI trial (phase II study investigating the role of alemtuzumab (iv or sc) plus methylprednisolone in CLL patients with p53 deletion)
- A "p53 workshop" for ERIC members and interested non-members to encourage scientific exchange and discussion on p53-related topics in CLL was performed in context of the ERIC meeting at the EHA congress in Barcelona, June 2010. The workshop was very well anticipated and visited by ca. 50 participants. Due to its success, the working group is planning to set up p53-workshops on an annual basis, if respective funding is available.

The deliverable has been successfully established and produced publishable results. However, due to the biological and clinical high relevance of p53-aberrations for CLL treatment outcome and prognosis, the deliverable will be an ongoing and long-lasting "task-force" of ERIC. Several iniatitives have emerged from this group:

1. Establish clinical use of p53 pathway analysis in CLL.

Scientific deliverables: Guideline p53 mutation detection, Assess clinical impact of MDM2SN309 SNP by individual patient data metaanalysis (publication early 2011)(with Rosenquist, Rossi, Majid, Linderholm, Greil, Pospisilova & Trbusek), Metaanalysis of clinical impact of different p53 mutations in CLL (prospective trial data) (publication)

2. Development and harmonization of functional p53 assays. General aims include the development of clinically applicable functional p53 assays, development of MLPA-based functional p53 kit, testing application of functional assays in prospective trials, compare results of different functional assays using specific set of samples, harmonize functional p53 assays among groups and countries.

Scientific deliverables: Development of novel techniques (publication), Test clinical relevance of p53-assays in prospective trials (publication), Harmonization (guidelines)

7.27d Phase I/II trial platform for the treatment of rare subentities T-PLL and B-PLL

With the phase I/II trial platform launched in deliverable 7.20 focusing on the so far NOT successfully activated studies on

- the reatment of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria),
- the treatment or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany,

Deliverable 7.20 covers contents of 7.27, please see there for details. The creation of a common diagnostic platform on prolymphocytic diseases in Germany with a new central reference laboratory in Cologne (responsible: Dr. Marco Herling, University of Cologne) has been one step forward within the past year. First diagnostic samples have been received and processed by the Cologne laboratory. Other European diagnostic laboratories interested in PLL-diagnostics have shown their interest and willingness to collaborate for future European wide trials on PLL-related diseases. Deliverable D7.27 is ongoing beyond month 91.

7.28b Recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)

ERIC and the CLL subcommittee of the EBMT (European group for blood and bone marrow transplant, responsible subcommittee chairman: Johannes Schetelig) consolidated on the occasion of the last meeting held in Manheim an ad hoc joint group Both groups have been collaborating to define "recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)". The final edition of the recommendations has been published on the ERIC webpage

(www.ericll.org), as previously described (deliverable partially fulfilled). Since it has been impossible under the current regulatory framework to perform an international prospective trial on stem cell transplantation in T-PLL (see deliverable 7.27), this group has established a register trial, were transplanted T-PLL patients can be registered and be evaluated retrospectively. In addition to retrospective patient registration and analysis, 23 European centers have agreed to register T-PLL patients prospectively, prior performance of their transplantation, to allow early data collection and evaluation. The trial is supported by ERIC and first data status and results of 13 autologous transplanted patients, 52 allogeneic transplanted patients and 27 prospectively registered patients were discussed at the latest ERIC meeting in New Orleans. Deliverable 7.28 will stay a long-lasting activity of ERIC/WP7 with fulfilment beyond month 91. Main goal of the activity is to intensify networking between WP7 and WP14 as well as the exchange and spread of expertise and trial efforts on stem cell transplantation in CLL.

7.29b Improvement of long-term follow-up of CLL patients in European trials

One of the recently launched ERIC projects is the implementation of a new trial system to collect long-term follow-up data in randomized phase III trials within Europe. Previously published phase III trials in CLL show median observation times ranging from 22 to 41 months, most of the trials exhibit only around 2 years of observation time. One reason for the unacceptable availability of long-term follow up data in clinical trials is the limited affordability for non-commercial study groups to accomplish long-term follow up data collection, management and evaluation. The ERIC trial system is planned to be conducted as a web-based repository, further details have been described in the last activity report. The project is aiming to collect long-term data including the following items: the date of the annual follow-up, status of the patient (alive/dead), disease status (CR, PR, SD or PD), incidence of secondary diseases, further therapies and responses and death related informations. Responsible leaders of this project are Peter Hillmen (Leeds, UK) and Barbara Eichhorst (Cologne, Germany). Within the past year negotiations with companies have been carried out to set up legal, ethical and practical requirements for the project. In collaboration with a CRO company, ICON, first steps to realize the follow up trial system have been undertaken and were presented and discussed at the last ERIC meeting in New Orleans. Currently, the group is working on solutions for the complex ethical situation regarding approval to acquire long-term follow up data on a European level, the setup of the remote trial system available for multiple countries, the governance of data flow, management and the overall system, and the maintenance of long-term confidence of investigators participating in the long-term follow-up system. Deliverable 7.28 is ongoing beyond month 91.

7.30b Promotion of ERIC for sustainability of WP7

The main goal of ERIC is to promote the development and sustainability of clinical, translational and basic research activities on CLL. In order to accomplish this goal on a long-term basis and sustain

ERIC as a European and world-wide recognized platform for CLL research, the ERIC Board initiated a strategic review process during 2010. This process kicked off with a half-day retreat of key ERIC members prior to the EHA Congress in Barcelona. From this platform the key members split into taskforces to develop strategic objectives and priorities for the following themes:

1. ERIC legal structure, board and bylaws
2. ERIC and its relationship with other organisations
3. ERIC webpage
4. ERIC Working Groups
5. ERIC visibility and marketing
6. The clinical side of ERIC
7. ERIC fundraising

Implementation of the results of the strategic review by the ERIC Board and Subcommittees continue into 2011and beyond 2011.
Deliverable 7.28 is ongoing long-term effort beyond month 91.

Deliverable List WP7, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months	Used indicative person months*)	Lead contractor
WP7	**CLL**					
7.5	Regular WP meetings	**78,84,86**	3 per year	0	2	Montserrat
7.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)	**79,86**	90,98	0	2	Montserrat
7.8f	Treatment of early stage, high risk CLL with FCR -continued	**73-86**	86-98	0	4	Hallek
7.9f	Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups	**73-86**	86-98	0	2	Montserrat/ Moreno
7.10d	Common data safety monitoring boards in clinical trial on CLL in Europe	**73-86**	86-98	0	2	Kimby
7.11f	Web-based information- and communication services on CLL refined and up-dated	**73-86**	Ongoing	0	4	Dan Wilde
7.16f	Harmonization of clinical study protocols and trial accessories between national CLL study groups	**73-86**	86-98	0	2	Eichorst/Hillmen
7.19d	Continued follow-up of patients with advanced CLL treated with FCR/FC – progress report	**73-86**	86-98	0	4	Hallek
7.20e	European platform for phase I/II trials	**73-86**	86-98	0	3	Levy

7.21e	European survey on treatment modalities in CLL patients	**73-86**	86-98	0	2	Levy
7.23d	Harmonization, consensus, online support for interpretation and collection of "problematic cases" in IGHV gene mutational analysis	**73-86**	86-98	0	2	Ghia
7.24d	Harmonization and quality control of MRD diagnostics	**73-86**	86-98	0	2	Hallek
7.26d	Collection & investigation of functional aspects of p53 mutation	**73-86**	86-98	0	2	Stilgenbauer
7.27d	Phase I/II trial platform for the treatment of rare subentities T-PLL and B-PLL	**73-86**	86-98	0	2	Montserrat
7.28b	Recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)	**73-86**	86-98	0	2	Dreger/Schetelig
7.29b	Improvement of long-term follow-up of CLL patients in European trials	**73-86**	86-98	0	4	Kimby/Hillmen
7.30b	Promotion of ERIC for sustainability of WP7	**73-86**	Ongoing	0	4	Montserrat

*) if available

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

None

List of milestones WP7, 2011

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP7	**CLL**			
7.5	Spread of excellence by high-quality scientific and educational meetings and workshops	**78,84,86**	Ongoing	Hallek
7.23d	Harmonization, consensus, online support for interpretation and collection of "problematic cases" in IGHV gene mutational analysis	**73-86**	86-98	Ghia
7.24d	Harmonization and quality control of MRD diagnostics	**73-86**	86-98	Hallek
7.26d	Collection & investigation of functional aspects of p53 mutation	**73-86**	86-98	Stilgenbauer

Section 3: Consortium management

The European Research Initiative on CLL (ERIC/WP7) is a continuously growing institution, which is more and more anticipated and recognized in Europe and world wide. 2010 has been an important year for ERIC as a Scientific Working Group of the European Society of Hematology (EHA): Both the Symposium and Scientific Workshop offered by ERIC at the annual EHA congress attracted increasing numbers of clinicians and scientists and stood out due to their leading specialist speakers and state-of-the-art presentations. ERIC/WP7 is continuously active in the education/spread of

excellence on clinical and scientific topics in CLL, predominantly by the p53- and IGHV-working groups.

With the notarial registration of ERIC in 2010, the association achieved recognised legal status in Germany.

Under the new chairman Professor Emili Montserrat, transfer of the ERIC office to Barcelona was completed in 2010. Implementation of strategic development objectives will be an important focus in the upcoming months. Overall ERIC/WP7 continuous to be an active and well prospering group within the ELN and EHA, dedicated to the improvement of clinical and basic science and treatment of CLL patients in and outside of Europe.

Section 4: Other Issues

Ethical issues - none

Competitive calls – none

Section 5: WP-Performance

Performance indicators	**Status**
Number of clinical trials started and/or completed	5
Number of patients recruited into clinical trials	>1500
Number of patients included into registries	n.a.
Improved predictive, prognostic or quality of life assessments	~1500
Degree of harmonization of trials	Well established
Number of SOPs and consensus papers	5
Number of publications	39
Number of meetings	3 (+2)
Number of meta-analyses	0
Number of accredited trials	2

8 MDS (WP08)

Objectives and starting point of work at beginning of reporting period

The collaborators of this network have established a European platform for integration of MDS trial groups and their interdisciplinary partners. This infrastructure prevents European fragmentation and augments scientific interaction and collaboration. The platform communicates and decides about diagnostic standards, prognostic tools, new molecular targets for new treatment modalities, and guidelines for various treatment approaches. Clinical trials are initiated and performed on a European scale. In addition, international registries have been developed to determine incidence, disease patterns and the prognostic impact of standard treatment according to well established guidelines. The starting point of work at beginning of the reporting period was as follows. We had interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11 (cytogenetics in diagnostic guidelines in MDS), AML WP5 (development of a common prognostic score), Minimal Residual Disease WP12 and Gene Profiling WP13, for translational studies. WP-MDS interacted actively internationally with the EORTC Leukemia Group, several national MDS study groups (GFM-France, Nordic MDS study group, German MDS study group and the Czech MDS study group), with the international MDS Foundation (several members of the steering committee are board members of the MDS Foundation), with the European Hematology Association (EHA), with European School of Hematology (ESH), and with numerous pharmaceutical companies which actively support the MDS registry and other clinical or translational projects. Knowledge like new treatment modalities and diagnostic and therapeutic guidelines were disseminated by meetings and presentation on the ELN website.

Close cooperation with numerous European MDS study groups resulted in a well running European MDS Registry Study. All planned deliverables for this project have been fulfilled and patient inclusion started in April 2008. The second interim analysis of the EUMDS registry has been performed on the first 800 registered patients and these data have been presented at the 2010 ASH meeting. The milestone of 1000 included patients has been reached in January 2011. A clinical platform has been initiated and is being developed to create collaboration between individual national studies with the aim to reduce duplication of trials, to exchange results at an early stage and to develop common control for investigational drugs. This will allow a reduced number of patients in the control arms and comparison of the study arms in different studies using the identical control arm. Furthermore the European guidelines for treatment of primary myelodysplastic syndromes has been finalized. The aim of these guidelines is to provide clinical practice recommendations that support the appropriate choice of therapeutic interventions in adult patients with primary MDS. On top of these guidelines, a web based scenario analysis on the treatment of myelodysplastic syndromes has been developed and a training how to use this scenario has been created.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

8.5 Regular WP meetings

2010

1. Annual ELN Symposium, MDS WP meeting, Mannheim, 2 February; 103 registered participants
2. European MDS Registry project, Steering Committee meeting, Mannheim, February 2, 10 participants and Operational team meeting February 1; 14 participants
3. European MDS Registry project, Steering Committee and operational team meeting, Barcelona , June 9; 18 and 10 participants respectively
4. European MDS Registry project, Operational team teleconferences: March 1 (13 participants), April 6 (8 participants), May 10 (10 participants), September 6 (6 participants)
5. ELN Steering committee meeting, Barcelona, June 10; 18 participants
6. European MDS Registry project, Steering Committee meeting, at ASH congress, Orlando, December 3; 11 participants
7. ELN breakfast meeting at the Annual ASH meeting Orlando, December 5
8. ELN Frontiers meeting, Vienna, October 23-24
9. MDS Iron Forum, Rome, September 25

2011

1. Annual ELN Symposium, MDS WP meeting, Mannheim, February 1; 90 participants (68 registered)
2. European MDS Registry project, Steering Committee meeting, Mannheim, January 31 (17 participants) and Operational team meeting January 31 (13 participants)

8.6 LP reports to NMC regarding structure, trial activities and integration of national trial groups

LP reports have been sent to NMC as requested.

8.49b Maintenance of the MDS WP8 section of ELN website

The MDS WP8 section of ELN website has been updated regularly. Currently some WP8 reports and presentations have to be put on the website by ELIC.

Diagnostic Guidelines

8.25a Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website

The MDS guidelines are revised on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website. E. Hellström Lindberg and A. Porwit prepared a revised version of the guidelines: updated according to WHO and revised regarding flowcytometry, according to minutes from the previous meeting. The document was sent to all participants of the MDS WP. Many comments were received by email and E. Hellström Lindberg summarized the major comments during

the Mannheim ELN MDS WP8 meeting in 2010. The guidelines include a work-up of suspected MDS or mixed MDS/MPNs. It was proposed and agreed to keep the MDS and AML guidelines separated because of the new WHO classification. Both IPSS and WPSS are included in the guidelines (WPSS is less validated compared to IPSS). It was proposed and agreed to remove the WHO classification 2001. E. Hellstrom-Lindberg has prepared a new version of the guidelines using the comments of the MDS WP participants. These guidelines have been presented during the ELN MDS WP8 meeting in Mannheim in 2011.The new version is published on the ELN website and will be evaluated after one year.

8.25b Addition of information on Immunophenotyping in diagnostic guidelines in MDS/AML

After the start of the working group on flow cytometry in myelodysplastic syndromes in Amsterdam in 2008, the WP focussed on minimal flow cytometric criteria in the diagnosis of MDS. The group defined in its first publication [Haematologica 2009] the role of flow cytometry not only in the diagnosis but also its contribution in classification and prognostification of MDS. This report describes in detail a standard flowcytometric method dealing with sampling handling, use of antibodies as well as defining antigens involved in dyshematopoiesis primarily concerning the erythroid, granulocytic and monocytic cell lineages. In 2009, the second workshop (MLL Munich Lab, chair AA van de Loosdrecht, co-chair W. Kern) discussed in more detail the immature and maturing granulocytic and monocytic cell lineages to define those antigens expressed during differentiation which might be of relevance to distinguish normal from dysplastic hematopoietic cells. This critical multidimensional approach is needed to translate potential aberrant profiles to a numerical scoring system. A newly defined scoring system could be instrumental for diagnostic and prognostic purposes. The latter has been discussed in the third international flow cytometry meeting of the WP8 on flow and MDS which has been held in London in November 2010 (co-chair R. Ireland). An ELN consensus guideline for flow cytometry in MDS is available and will be submitted to a high-ranking international journal in 2011. Also a rationale for clinical use of flow cytometry is defined and will be submitted for publication in 2011. The diagnostics, revision of FCSS (flowcytometry scoring system), erythroid4 lineage, clinical reporting and incorporate software tools for analysis/statistics will be discussed during the fourth workshop in October 2011. WP10 will be involved in the planned meetings.

8.25f The results of the second Workshop on flow cytometry in MDS (Oct 2009 in Munich, Germany) have been submitted for publication.

The results of the second Workshop on flow cytometry in MDS has been submitted for publication. This report also contains the results of the third Workshop on flow cytometry in MDS (October 2010 in London, UK).

8.25g The third international Workshop on flow cytometry in MDS has been held on October 2010 in London, UK (host: dr. R. Ireland, chair: Dr. van de Loosdrecht)

28 Representatives from 12 countries attended this meeting (including Australia, Japan and the United States). The minimal flow cytometry criteria have been defined and have been published in Haematologica (2009). The results of this Workshop has been submitted for publication. The Flow Score has been developed as a prognostic tool. Guidelines for the Flow Score Flow will be defined and described in 2 consensus documents to be submitted in first months of 2011. Recommendations are identified for the analysis of subsets in the BM. Publications have been reported on: analysis of a minimized multiparameter panel, analysis of myelomonopoiesis and FCSS related to transfusiondependancy and progression to AML.
An ELN consensus guideline for flow cytometry in MDS is available. And a rationale for clinical use of flow cytometry has been defined (see also item 8.25b)

Therapeutic Guidelines

8.27a Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website

The guidelines have been developed by a European expert panel and a systemic review of literature. The European guidelines for treatment of primary myelodysplastic syndromes have been finalized. The aim of these guidelines is to provide clinical practice recommendations that can support the appropriate choice of therapeutic interventions in adult patients with primary MDS. A final manuscript is in preparation and will be submitted to Blood in 2011.

8.27c Web based scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS

Consensus was achieved for key clinical questions and a list of treatment indications. The treatment guidelines include a summary of the diagnostic guidelines. On top of these guidelines, a web based scenario analysis on the treatment of myelodysplastic syndromes has been made and a training on how to use this is created and distributed as well.

8.27d Report on web based training program based on scenario analyses and consensus based guidelines for therapy of MDS developed by experts in this field

The final manuscript will be submitted to Blood in 2011. The next version will include international, nonEuropean experts as well.

8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians

Scenario analysis of more than 50 scenarios has been developed and reviewed by the expert panels. The recommendations for the 50 scenarios are available at the website of Haematologica.

8.29a Evaluation of web based scenario analysis experts versus trainees.

An evaluation of the web based scenario analysis by experts and non-experts (trainees) is planned for 2011.

Trials

8.31 Yearly update of a list of all trials by MDS study groups in Europe

The list of MDS trials is presented on the LeukemiaNet website. The updated list is sent to the ELIC and they will put it on the website as soon as migration to the ELTR is ready.

New List of trials and studies in Myelodysplastic Syndromes

Different risk groups:

- 5-Azacytidine II: Study of maintenance with Azacitidine in MDS patients achieving complete or partial remission (CR or PR) after intensive chemotherapy
- MDS Azacitidine: Study of Maintenance With Azacitidine in MDS Patients
- Bevacizumab: A Trial of Bevacizumab in Myelodysplastic Syndromes (Int-1, Int-2 and High Risk According to International Prognostic Scoring System (IPSS)) With Excess of Marrow Blasts
- MDS Decitabine: Study of Decitabine

Low risk and intermediate I:

- Azacitidine-Epoetin Beta: Study of Azacitidine (Vidaza) combined to Epoetin Beta (NeoRecormon) in IPSS low-risk and intermediate-1 MDS patients, resistant to ESA
- Azacitidine-Epoetin Beta II: Azacitidine and Beta Erythropoietin Treatment
- Erythropoetin: Comparison Between Erythropoietin and Erythropoietin Associated to Differentiating Therapy With Acid 13-Cis-Retinoic and Dihydroxyvitamin D3
- European Registry: European Registry for Newly Diagnosed Patients With MDS of IPSS Low and Intermediate-1 Subtypes
- HOVON 89 MDS: Study to assess the efficacy of lenalidomide with or without erythropoietin and granulocyte-colony stimulating factor in patients with low and intermediate-1 risk MDS
- MDS Lenalidomide II (pending) : A phase II tial to assess the efficacy Lenalidomide with or without Erythropoietin and G-SCF in low- and intermediate-1 MDS
- MDS Lintuzumab (temporary halt) : Monoclonal antibody therapy in treating patients with primary MDS

Intermediate II and high risk:

- 5-Azacitidine: Subcutaneous Azacitidine + best supportive care vs. conventional regimens + best supportive care
- Erlotinib: Erlotonib in high risk MDS
- HOVON 81 AML: Study to assess the tolerability and efficacy of the addition of Bevacizumab to standard induction therapy in AML and high risk MDS above 60 years.
- MDS Antithymocyte Globulin-Cyclosporine (temporary halt) : A randomized trial comparing ATG + CSA with best supportive care
- MDS Clofarabine: Clofarabine in combination with a standard remission induction regimen (AraC and idarubicin) in patients 18-60 years old with previously untreated intermediate and bad risk acute AML or high risk MDS
- MDS Combi-Chemo (active): Combination chemotherapy with or without Gemtuzumab or Tipifarnib in high-risk MDS
- MDS-005 Lenalidomid: Study of the Efficacy and Safety of Lenalidomide (Revlimid) versus Placebo in Subjects with Transfusion-Dependent Anemia due to IPSS Low or Intermediate 1 Risk MDS without Deletion 5Q
- Velcade Zarnestra: Bortezomib and Tipifarnib in MDS
- Vorinostat: Study of Vorinostat in Combination With Low Dose Ara-C

Monosomie 5 or del5q:

- Lenalidomide I: Lenalidomide vs Placebo in RBC-dependent low- or intermediate-1 risk MDS with 5q-
- Lenalidomide III: This is a study of oral lenalidomide administered in adult subjects

Supportive studies MDS

- MDS/AML Eltrombopag: Eltrombopag bei MDS und AML
- MDS Exjade (Active): Exjade(ICL670) in transfusion dependent iron overload (2008)
- Darbepoetin-Filgrastim: Darbepoetin alpha and G-CSF vs. best supportive care
- Darbepoietin alpha II: Darbepoietin in low- or intermediate-1 risk MDS with anemia
- Romiplostim I: Evaluating the Safety of Long Term Dosing of Romiplostim (formerly AMG 531)

Diagnostic /biomarker studies MDS

- Biomarkers: Biomarkers in Patients at Risk of Developing Myelodysplastic Syndrome or Other Disorders and in Healthy Participants
- MDS Biomarkers : Molecular and functional characterization of bone marrow function in patients with MDS and secondary disorders of hematopoiesis

- CytogenicAnalysis: Cytogenetic Analysis Using Blood and Tissue Samples From Young Patients With Myelodysplastic Syndromes, Juvenile Myelomonocytic Leukemia, or Down Syndrome and Acute Myeloid Leukemia

Quality of Life

- NMDSG03A MDS Quality of life I (active): Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS QOL II: Quality of Life and Symptoms

SCT: Stem cell transplantation

MDS

- AML RICMAC/MDSsAML: Dose reduced vs. standard conditioning + SCT in MDS or sAML
- Allo SCT after treosulfan fludarabine: Allogeneic stem cell transplantation after toxicityreduced conditioning regimen with treosulfan and fludarabine for patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukaemia (sAML) who were not eligible for a standard conditioning regimen
- StemCellTransplant II: Pilot Study of Reduced Intensity Haematopoietic Stem Cell Transplantation in Patients With Poor Risk MDS and AML Utilising Conditioning With Fludarabine, Busulphan and Thymoglobulin (FB-ATG)
- Velcade: Phase II Study of PS341 (VELCADE) in MDS
- MDS AlloSCT-Clofarabine: Allogeneic Stem Cell Transplant With Clofarabine, Busulfan and Antithymocyte Globulin (ATG) for Adult Patients With High-Risk AML/MDS or ALL

8.51d Impact of frailty index on various therapeutic approaches, supportive care, hypomethylating agents, intensive anti-leukemic therapy

The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. Multicenter evaluation was feasible. Multivariate analysis revealed "Activities of daily living" (ADL) and fatigue measured with the QLQ C30 questionnaire as highly prognostic for survival in the entire patient cohort. Follow-up assessments revealed that no severe deterioration in geriatric and QOL (quality of life) domains occurred within 6 months under treatment. Statistical calculations are currently being performed to define a risk score. Final publication of data is planned for 2011.

8.57 GIMEMA-ELN Qol – MDS 0108 study, Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes.

The obtained data of this Quality of Life study has been published in 2009 in Expert Review Hematology, 2009 Feb; 2(1):69-80, G. Caocci, G. La Nasa, F. Efficace. Further publications are expected after completion of the full study.

MDS registry

8.54 Monthly progress reports of the prospective, non-interventional multicenter European MDS Registry (IPSS low and intermediate-1) project

Monthly reports have been sent to Novartis, the sponsor of the registry and to all participating registries. It is clear that the quality of the data is very high and informative. The registry is collecting a unique data set which will prove to be very valuable for future questions and studies as well. The accrual has risen again to an accrual of 1000 patients in January 2011 (980 per 31 December 2010). The registry continues to consider to merge the low risk MDS- registry with the high risk registry if the support will come from a Pharma consortium or other funding (outreach programs, FP-EU programs), but for the time being the focus will be on lower risk MDS. The follow-up time is extended to 3 years with support from Novartis.

8.54f First presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010

Summary from the steering committee meeting in Orlando, December 3, 2010. The EU-MDS Registry had 3 poster presentations at ASH based on the interim analyses of the first 800 patients:

1. Dr. Smith and Dr. Bowen: **Population based real world of low risk MDS**. European countries are participating to the registry. France, Spain, UK and Greece are major contributors. Cytogenetic data are available in 93% of the patients. Epo levels are low in majority of patients: <100U/l in 68% of the patients. The basal EPO-levels have no significant relationship to Hb-levels.

2. Dr. Stauder: Quality of Life at base line. The Hb-levels show no correlation with age in contrast to nonMDS elderly people. Patients having problems with daily activities have a decreased median Hblevel: 9.5 vs 10.4 g/dl when no problems with daily activities. The Sorror score (co-morbidity index) showed a clear relationship with EQ-5D Visual Analogue scale.

3. Drs. de Swart: Disease management during the first 18 months. About 35% of the patients have received EPO with or without G-CSF. 303/800 Patients were transfusion dependent. Transfusion dependency and high ferritin levels in transfusion dependent patients were independent prognostic factors for survival and progression-free survival.

8.54g Second interim analysis (800 patients) entered in the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1)

The statistician, Dr. Smith, has created the second interim analysis on the first 800 registered patients. She has presented the analysis at the steering committee meetings in Orlando (December 2010) and Mannheim (January 2011).

8.54h Inclusion of next patients to 1000

In February 2011 the milestone of 1000 included patients has been reached.

8.54i Extension of follow-up, 2-5 years

The follow-up period has been extended from 2 to 3 years.

8.54j Extension to more registries (new countries)

Portugal, Poland and Denmark have joined the EUMDS Registry in 2010. Israel has joined thesteering committee in 2010. Israel is expected to enter patients in 2011.

8.54k Extension of Registry after 1000 patients

Continuation of the support of Novartis after the first 1000 patients is under discussion. Several participating countries in the Registry have committed themselves to continue the Registry with local funding.

8.73-8.79 A prospective, non-interventional multicenter European high-risk MDS Registry

The steering committee discussed the progress of the development of this registry during the ELN annual meeting in Mannheim 2010 and at the EHA congress in London 2010. A consortium of sponsors are being invited to support the study. The CRFs and the web-based reporting will be adapted from the low risk registry system developed by the University of York. Merging of the low risk and high risk registries is foreseen after completion of the low risk MDS registry project.

Translational research

8.80 and 8.80a: Iron Pathophysiology and imaging of iron overload: side studies of the low risk MDS registry study.

The protocol has been finalized by the steering committee in May 2009. The contract of the sponsor has been signed in October 2009. Collection of necessary samples has already been performed for more than 300 patients. In 6 countries (34 sites) samples have been collected: UK, GR, NL, SW, CZ, RU. In total samples of 810 different visits are collected. Already 37 patients have completed the substudy (= 5 samples collected). The samples will be transported to the UMCN in The Netherlands and laboratory analysis of the samples will be performed before the end of 2011.

8.81 Side study of Low Risk MDS Registry: Cytomorphologic sub-study. Meeting in Düsseldorf planned June 2010

The aim of this cytomorphologic substudy is to assess the reproducibility of diagnosis. Methods have already been defined: review of randomly selected slides from all participating countries; reviewer panel includes both „experts“ as well as physicians in training; description of results and correlation with original findings and calculation of degree of discrepancy using k-test. The side study and progress of the protocol and logistics have been presented and discussed during the EUMDS-steering committee meeting and the ElN-WP8 meeting in Mannheim in 2011. The final protocol of this review is expected in April 2011.

8.82 Side study of Low Risk MDS Registry: Geriatric Assessment: presentation at EHA 2010, Barcelona

B. Deschler presented the effects of different treatment regimens on the various geriatric assessment tools and the quality of life in elderly MDS patients. Careful geriatric assessment evokes awareness of relevant changes in elderly MDS/AML that otherwise might be unnoticed (Deschler et all, abstract 0464 Haematologica 2010; 95: 189).

8.83 Evaluation of the prognostic value of TET-2 mutations in MDS

Based on the experience of techniques used to detect and to describe the incidence and prognosis of TET-2 mutation in MDS (S. Langemeijer et al Nat Genet. 2009;4:838-42) we identified a new mutation in chromosome 7 of MDS patients (G. Nikoloski, et al. Nature Genetics 2010; 42: 665–667) In MDS deletions of chromosome 7 or 7q are common and correlate with a poor prognosis. The relevant genes on chromosome 7 are unknown. *EZH2*, located at 7q36.1, is frequently targeted in MDS. Analysis of *EZH2* deletions, missense and frameshift mutations strongly suggests that *EZH2* is a tumor suppressor. As EZH2 functions as a histone methyltransferase, abnormal histone modification may contribute to epigenetic deregulation in MDS. This may have therapeutic implications.

8.84 Evaluation of the prognostic value of TET-2 mutations in AML

Ten-Eleven-Translocation 2 (TET2) gene mutations and deletions have been detected in myelodysplastic syndromes, acute myeloid leukemias (AML) and other myeloid malignancies. TET2 mutations are found in 8–19% of adult AML and the expression of TET2 is high in granulocytes as compared with other hematopoietic and non-hematopoietic cells, where it is increased during myeloid differentiation. S. Langemeijer described novel TET2 mutations in 3.8% of pediatric AML. Despite the lower incidence compared with adult AML, this observation may be instrumental for the design of ovel targeted therapies in pediatric acute myeloid leukemia (Leukemia. 2011;25:189-92).

8.59 ESH-EHA Scientific Workshop on Experimental Haematopoiesis and Therapeutics 2010. (MRD, Gene Profiling, Immunophenotyping, Cytogenetics, in AML and MDS)

The scientific Workshop took place at Frankfurt during September 16-18, 2010. Altogether 27 distinguished speakers from 10 different countries including the US and Australia. The topics ranged from normal and leukemic stem cell biology to new molecular pathways including epigenetic biology in leukemia, myelodysplastic syndromes and myeloproliferative disorders.

Table 8.1: List of deliverables WP8, 2010 and 2011.

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months	Used indicative person months*)	Lead contractor
WP8	**MDS**					
8.5	Regular WP meetings	78,84,86	78, 80, 82, 83, 84, 86	1.5	3	De Witte
8.6	LP reports to NMC regarding structure, trial activities and integration of national trial groups (1 page, bullet point style)	79,86	86	1,5	2	De Witte
8.49b	Maintenance of the MDS WP8 section of ELN website	73-86	86	1	4	De Witte
	Diagnostic Guidelines					
8.25a	Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website	73-78	86	2	4	Hellström-Lindberg
8.25b	Integration of immunophenotypind in diagnostic guidelines in MDS	73-86	86 ongoing	2	6	Hellström-Lindberg, Van de Loosdrecht
8.25g	The third international workshop on flow cytometry in MDS- was held on 30-31 Oct 2010 in London, UK (host: Dr. R. Ireland; chair: AA van de Loosdrecht)	70	82	2	4	Van de Loosdrecht
	Therapeutic Guidelines					
8.27a	Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website	73-86	86	1	6	Malcovati, Cazzola
8.27c	Web-based scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS	73-86	86	1	4	Malcovati, Cazzola
8.27d	Report on web based training program based on scenario analysis and consensus based guidelines for therapy of MDS developed by experts in this field	78	86	1	2	Malcovati, Cazzola
8.29	Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians	78	78	1	4	Malcovati, Cazzola
8.29a	Evaluation of web-based scenario analysis experts versus trainees	78	86	1	3	Malcovati, Cazzola
	Trials					
8.31	Yearly update of a list of all trials by MDS study groups in Europe	73-86	86	2	2	De Witte

8.57	GIMEMA-ELN QoL - MDS 0108 study Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes. Obtain additional key data to further facilitate clinical decision-making in MDS patients.	78	78	2	3	Efficace
	MDS registry					
8.54	Monthly progress reports of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) project	73-86	73-89	2	3	De Witte
8.54f	First presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010	85	85	2	4	Bowen
8.54g	Second interim analysis (800 patients) entered in the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1)	79	85	2	3	De Witte
8.54h	Inclusion of next patients 600 to 1,000	73-86	86	2	4	De Witte, Bowen
8.54i	Extension of follow-up, 2-5 years	78	86	2	3	De Witte, Bowen
8.54j	Extension to three more registries (new countries): Portugal, Poland and Denmark	73-76	80	2	2	De Witte
8.54k	Extension of registry after 1000 patients	86	Ongoing	2	2	De Witte, Bowen
	Translational Research					
8.59	ESH-EHA Scientific Workshop on Experimental Haematopoiesis and Therapeutics 2010. (MRD, Gene Profiling, Immunophenotyping, Cytogenetics in AML and MDS)	78	80	2	3	Padua
8.80	Side study of Low Risk MDS Registry: Iron pathophysiology.	78	86	3	3	McKenzie
8.80a	Side study of Low Risk MDS Registry: Imaging of iron overload	75	86	3	4	De Witte
8.82	Side study of Low Risk MDS Registry: Geriatric Assessment: presentation at EHA 2010, Barcelona	78	78	0	4	Stauder
8.83	Evaluation of the prognostic value of TET-2 mutations in MDS	76	86	0	4	Jansen
8.84	Evaluation of the prognostic value of TET-2 mutations in AML	76	86	0	4	Jansen

Table 8.2 List of milestones WP8, 2010 and 2011

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP8	**MDS**			
8.25	Publication of the results of the second Workshop on flow cytometry in MDS (Oct 2009 in Munich, Germany)	73-86	86	Hellström-Lindberg, Van de Loosdrecht
8.54m	Second presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010	104	73-86	Bowen
8.75	Establishment of a high-risk European MDS registry: Setting up central IT structure	78-86	86	Bowen
8.83	Evaluation of the prognostic value of TET-2 mutations in MDS	76	86	Jansen

Section 3: Consortium management

In general, we speculate that MDS WP8 has been an active and productive WP within the European LeukemiaNet, as indicated by this report and the website content of WP8. We have interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11, (cytogenetics in diagnostic guidelines in MDS), AML WP5 (integration of diagnostic guidelines in AML and MDS, shared criteria of response for AML and MDS) and Gene Profiling WP13 (Multi-Center Microarray Study for the Molecular Classification of Leukemia).

The cooperation with WP11 and WP13 is coordinated within the COST action (coordinator: Dr Ken Mills) and Eugesma (coordinated by Dr Rose-Ann Padua) They organised two Working group meetings each attended by ~95 participants from 20 countries. Cost (Action) and Eugesma participants organized two major FP7 applications:

- MATRIX involving participants from WG's 1,2, 3 & 4
  - ✓ Resistance in AML and MDS
  - ✓ Selected from 460 Stage I applications for Stage II
- DCDVACL, a one-stage application, from WG4
  - ✓ Innovative Therapeutic Approaches and Interventions (DNA Vaccines)
  - ✓ One-stage application – currently in EU review

Close cooperation of many European MDS study groups resulted in much progress on the European MDS Registry Study (see Annex Section 3, WP8 (del. 8.53e). The inclusion started April 1st 2008. At the end of December 2009, the overall recruitment was 650 patients in 12 countries.

The study entitled "Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS) is progressing well. This

international multicenter observational study" GIMEMA-ELN QoL - MDS 0108 aims to obtain additional key data to further facilitate clinical decision-making in MDS patients. This initiative fits very well in our deliverables on developing a frailty index for treatment decision-making for older patients with MDS or AML. Therefore, this study is incorporated in our LeukemiaNet activities. Finally, much progress was made for the translational studies: Using SNP-arrays 40 novel recurrent genetic loci in MDS were identified (del.8.57). This resulted in three high ranking papers (see: 8.83 and 8.84).

The present steering committee of our workpackage has been in office for more than 6 years. The steering committee felt it important to continue and to extend its activities through active participation of "junior experts" in our field. The steering committee discussed the extension of the steering committee with young investigators during the ESH-EHA MDS postgraduate course, in Mandelieu France. Uwe Platzbecker Dresden), Lionel Ades (Avicenne), Arjan van de Loosdrecht (Amsterdam), Luca Malcovati (Pavia), Wolf-Karsten Hofmann (Mannheim) and Martin Jadersten (Huddinge) have been invited as steering committee members. We shall identify the topics which the junior steering committee members will coordinate.

Section 4: Other Issues

Ethical issues – none,

Competitive calls -none

Section 5: WP-Performance

Performance indicators	Status
Number of clinical trials started and/or completed	8
Number of patients re-cruited into clinical trials	Not reported
Number of patients included into registries	The inclusion started April 1st 2008. In February 2011, the overall recruitment was 1000 patients in 12 countries.
Improved predictive, prognostic or quality of life assessments	See del. 8.25b Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website. The MDS guidelines were adapted on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website. See del. 8.25b Addition of information on Immunophenotyping in diagnostic guidelines in MDS/AML. This concerns a cooperation of WP8 and WP10 (Diagnostics). The second International ELN Workshop on standardization of flow cytometry in MDS in Munich, October 2009 was very successful. A general consensus protocol developed during the first Workshop has been published and became operational in the beginning of 2009. See del. 8.51d Frailty index for treatment decision-making for older patients with MDS or AML. The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. This index has been validated in a group of patients with myeloid malignancies candidates for allogeneic stem cell transplantation. In addition, this model is tested prospectively in the study entitled "Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS). An international multicenter observational study" GIMEMA-ELN QoL - MDS 0108 which has started in 2008.

Performance indicators	Status
Degree of harmonization of trials	Multiple deliverables regarding harmonization of trials have been fulfilled and the results are presented on the ELN website: See del. 8.25b Guidelines for diagnostic standards. See del. 8.25b Immunophenotyping in diagnostic guidelines, a cooperation of WP8 and WP10 (Diagnostics). A general consensus protocol developed during the first Workshop has been published (see pdf 8.5) and became operational in the beginning of 2009. See del. 8.27c Webbased scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS (see attachment 8.13) See del. 8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians http://mds.haematologica.org See del. 8.31b We updated the list of all trials by MDS study groups in Europe. See del. 8.32 Every year an inventory on new drugs/treatments is made, by asking all partcipants of the MDS WP for input regarding this issue. Furthermore, new drugs/treatments is discussed at several MDS WP8 meetings. If necessary an investigator meeting on a particular new drug/treatment is organized.
Number of SOPs and consensus papers	4
Number of publications	56
Number of meetings	11
Number of accredited trials	See 8.31b

9 CMPD (WP09)

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

9.5 Regular WP meetings

WP9 participants met 3 times in 2010 during International congresses: in Mannheim on February, in Barcelona on June 10 (EHA meeting), and in Orlando on December 5 (ASH meeting). Written minutes of those meetings were provided to WP9 members, and are available upon request.

9.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group

Minutes of meetings were sent to the NMC.

9.26e Phase II study of imatinib therapy in PV patients – (recruitment closed, progress report)

The recruitment was completed in June 2009.

Primary objective: To determine the antiproliferative effects of imatinib on the major parameters of the increased myeloproliferation in patients with PV, utilizing a dose escalation schedule.

The main endpoint of the study is the response rate to the therapy (reduction of the phlebotomy rate, of platelet count, of white blood cell count, of spleen size) after one year of treatment.

Secondary objectives: To determine the rate and severity of side effects of the therapy; to determine the PV-related complications and symptoms (thrombosis, bleeding, microvascular disturbances, pruritus) under therapy with imatinib.

Main inclusion criteria: Newly diagnosed or pretreated patients with PV according to the WHO criteria. Patients ≥18 years of age no upper age limit.

Main exclusion criteria: Postpolycythemic myelofibrosis. Secondary acute leukemia. Pretreatment with ^{32}P. Other malignant disease requiring therapy or with life expectancy of less than one year.

Treatment: Imatinib starting dose of 400mg daily. During follow up, the dose will be adapted to response and tolerability (stepwise dose escalation to 600mg and 800mg or reduction to 300mg in adaptation to blood counts, spleen size and side effects).

Results:

Included patients: 34 patients (17f / 17 m) from 9 German centers

Median age (64 (44 – 84) years

Previous therapy: phlebotomy (n = 17), cytoreductive therapy (n = 13)

Median duration of imatinib therapy: 13 (0,1 – 35) months

Response rate of at least one parameter (erythrocytosis, leukocytosis, thrombocytosis , splenomegaly): observed in approximately 60% of patients.

9.28e Advancement in a registry of pregnancies in ET (ongoing)

There is an ongoing registry of pregnancies in MPD patients, with forms available on the ELN web site, chaired by M. Griesshammer (Minden). At last evaluation, 143 pregnancies were reported in 71 patients, implemented by hematologists from 6 different EU countries. The majority of patients had ET (57/71), but several pregnancies in PV (10 patients) and PMF (4 patients) patients were also reported. Pregnancy outcome could be evaluated in 125 pregnancies. Live birth rate was 70%, including 63% of full term normal deliveries, a rate significantly higher than previously reported (about 50% in the literature). Spontaneous abortions remained the main complication, occurring in 28% of pregnancies. Maternal complications were low, but clearly higher than in "normal" pregnancies: preeclampsia (4%), major bleeding (5%), venous thromboembolism (4%). Implementation of this registry will allow better knowledge and recommendation for management of pregnancies in MPD patients.

9.30e Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients)

Patients: PV diagnosed according to WHO criteria, age > 18 years.

Randomization: between standard target hematocrit at less than 45%, and the experimental arm with a target hematocrit between 45 and 50%. The study aim is to recruit 500 PV patients in each arm.

Primary endpoint: To demonstrate that, in patients with PV and treated at the best of recommended therapies (i.e., low-dose aspirin when indicated and adequate control of standard cardiovascular risk factors), long term, aggressive cytoreductive therapy aimed at maintaining HCT < 45% (either with phlebotomy and/or HU) is more effective than cytoreductive therapy aimed at maintaining HCT in the range 45-50% (either with phlebotomy and/or HU) in reduction of:

CV deaths plus thrombotic events (stroke, acute coronary syndrome [**ACS**], transient ischemic attack [**TIA**], pulmonary embolism [**PE**], abdominal thrombosis, deep vein thrombosis [**DVT**], and peripheral arterial thrombosis).

Secondary endpoints: The events included in the PEP, arterial and venous thrombosis, major and minor thrombosis as well as hospitalization for any reason, hospitalization for CV reason, malignancy, and PV-related malignancy (progression to myelofibrosis, myelodysplastic or leukemic transformation) will be analyzed separately to assess the full benefit/risk profile of experimental treatments.

Recruitment has started in May 2008. As of January 2011, 343 patients were registered and 300 were randomized. The study is still ongoing.

9.31e Advancement in a registration study of high-risk ET patients treated with Anagrelide – (recruitment closed, progress report)

The Exels study is a non-interventional, multicenter, European observational study of a large cohort of at-risk ET patients on cytoreductive therapy. The study was a prerequisite for the registration of

Xagrid® (anagrelide) as an orphan drug by EMEA. 125 centres in Europe have now completed the recruitment of 3600 patients. The inclusion was closed in April 2009. The patients will be followed for 5 years, and the first patient to complete the study will do so in March 2010.

The patients are followed with 6-monthly data collections regarding disease complications, toxicity, drug use, efficacy of therapy, death and pregnancy. Reports to the DSMB every 6 months have not shown any new safety concerns.

The analysis of collected data shows that the treatment pattern is rather homogenous throughout Europe with a couple of exceptions. Hydroxyurea is first line treatment except in patients under 50 years of age, where anagrelide is more common.

The cohort consists of two large treatment groups, hydroxyurea (around 2000 patients), anagrelide (around 900 patients) as well as more than 150 patients with combination therapy and about 150 treated with interferon. Pipobroman is used only in a couple of countries in Europe.

The number of events is still too low to allow statistical comparison of various treatment groups. A total of 101 thrombohemorrhagic events were reported at the latest data-cut in September 2009.

This study, which is sponsored by Shire, the manufacturer of Xagrid, now encompasses a large cohort of ET patients, and results are expected to include frequency of thrombosis, bleeding, transformation to myelofibrosis and leukaemia as well as safety data. Final reports will be due after the completion of the last patient in 2014, and an interim report will be produced after the September 2011 datacut. Publications on demography, treatment patterns in Europe, treatment in elderly ET patients are forthcoming during 2011 and 2012.

9.34e Protocol for a multicenter study of vorinostat in CMPDs (started in 2009, still recruiting patients)

The COSMYD protocol "Safety and Efficacy of Vorinostat in the Treatment of Polycythemia Vera and Essential Thrombocythemia" - a multicenter study enrolling patients from centers within the COSMYD-group (UK,Holland, Sweden and Denmark).

This is an investigator-driven study in several countries within the European LeukemiaNet. H.C. Hasselbalch is the representative of the Sponsor for this Study – University of Copenhagen, Department of Hematology, Herlev Hospital – and Professor Mary Frances McMullin, Belfast City Hospital, is the representative for the UK –sites in the study. The study has now concluded enrolment of the target cohort of 60 patients. H.C. Hasselbalch has been currently involved in monitoring timely enrolment of patients and several News Letters have been forwarded to the participating centres. Preliminary data are encouraging. An abstract on preliminary results has been forwarded to EHA, London June 2011. Since vorinostat seems to have a striking effect, including a marked reduction in huge splenomegaly in one of the patients HCH has elaborated a protocol aiming at enrolling 20 patients with myelofibrosis and large splenomegaly. This study will be conducted in Denmark only. Furthermore, an application has been forwarded to extend the study period in order to obtain long-term

efficacy and safety data on vorinostat in the treatment of patients with Ph-negative chronic myeloproliferative neoplasms. This study will be conducted in UK only.

9.36b Survey and harmonization of assay methods for JAK2-V617F (ongoing)

This deliverable refers to a project in common with WP12, MRD. In this year, we have performed additional experiments to characterize different published quantitative assays for JAK2V617F mutation, and we have now resolved that three of the initial 8 assays present acceptable characteristics of reproducibility and specificity. These are being used in current experiments. In collaboration with Ipsogen, that is involved in WP12, we have also performed a RQ assay using different plasmid preparations of JAK2 wild-type and V617F-mutated, as well as progressive dilutions of JAK2V617F mutated HEL cells. The data have been centrally collected and analyzed, and they have been discussed at the WP12 meeting held in Orlando, December 2010. Furthermore, the laboratory of A. Vannucchi has prepared and distributed to all participant laboratories progressive dilutions of a different JAK2V617F-mutated cell line, UKE-1, both as cell dilutions in normal mononuclear cells and as dilutions of purified DNA. Analysis of these preparations has been accomplished by most of involved laboratories, and overall results are planned to be presented in Mannheim, February 2012. Finally, this WP has interacted with the MPN&MPNr-Euronet action COST action BM-0902, coordinated by Dr Sylvie Hermouet, which aims at the standardization and dissemination in Europe of molecular techniques for the study of MPN.

9.37b Registry of IFN-treated MPD patients (started in 2010)

Last year, H.C. Hasselbalch forwarded a proposal for a deliverable "A Registry of Patients with Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis treated with Alpha-Interferon within European LeukemiaNet". This was further discussed during the ELN annual meeting in Mannheim.

“The Nordic Long-Term IFN-Efficacy Study in Patients with Polycythaemia Vera and Essential Thrombocythemia”

On the initiative of H.C. Hasselbalch this study aims at collecting a large cohort of patients with ET and PV being treated long term with pegylated Interferon-alpha2. The impetus for this study is the observation in several Danish Patients that long-term treatment with IFN-alpha is able to induce a state of “minimal residual disease “ with normalisation of the bone marrow and “complete molecular remission“ with JAK2V617F mutation load below 1 %, even after discontinuation of IFN-alpha2 for up to 24 months (operational cure?). A total of 75 Danish patients have been enrolled and additional Danish patients are expected to be included in the study. An interim analysis will hopefully be presented at ASH 2011.

9.38 A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2010)

"Erlotonib in the Treatment of Polycythemia Vera and Essential Thrombocythemia. A Pilot Study of Efficacy and Safety"

The study has been delayed owing to lack of financial support in the Clinical Research Unit. The protocol is expected to be activated at the Department of Oncology-Hematology , Roskilde Hospital, University of Copenhagen, within the next 6 months. It is a Pilot Study which will include a total of 10 patients. Based upon the experience in the pilot study it will be decided whether to extend the study to other centres.

Status April 12, 2011: Unfortunately, this study – ready to include patients – had to be cancelled due to the retraction of the manufacturer of erlotinib.

9.39 Study of MPD leukemic transformations (publication in progress)

Transformation to acute myeloid leukemia (AML) is a known complication of myeloproliferative neoplasia (MPN). Recent studies have reported the high incidence (53%) of JAK2 negative blasts from transformed *JAK2*V617F-MPN. We collected blasts and mature myeloid cells from BM of 40 newly diagnosed patients with AML secondary to MPN and analyzed the *JAK2* status before and after leukemic transformation by ASO-PCR and (QRT)-PCR assay. At the time of MPN, JAK2V617F was detectable in 28 of 40 patients. No cytogenetic abnormalities or MPL and JAK2-exone 12 mutations were detected at this stage. A significantly shorter (p= 0.02) time to progression was found in previously JAK2 mutated MPN patients. In our cohort of patients we found that JAK2V617F mutation was still present at the blast transformation in both compartments: CD34+ cells and CD15+ cells in 26 of 28 JAK2 mutated MPN (92%). Two of 28 patients (7%) developed JAK2V617F negative AML starting from a mutated PV with a mean TTP of 5.14 yrs. No differences (p= 0.3) in the allele burden were found comparing MNCs from chronic phase with MNCs of leukemic transformations or comparing GRA with blasts in AML phase. CONCLUSIONS: In our work, the loss of JAK2V617F mutation during AML progression is a rare event (7%).

9.40 Myeloproliferative Neoplasms: Management recommendations of the ELN

New project achieved in 2010: Definition of resistance / intolerance to hydroxyurea in PV and PMF

The ELN WP9 decided to review recent data regarding therapy, standard monitoring procedures, and definitions of responses and to produce recommendations aimed at contributing to the optimization and standardization of management of the three Ph-negative classical MPNs. An expert panel of 21 experts, including several experts from the USA, was selected for their expertise in research and clinical practice of management of MPNs. Using a consensus process, the expert panel produced updated recommendations, that were published in the Journal of Clinical Oncology.

Publications: See Annex Section 3, WP9.

List of deliverables WP9, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP9	**MDS**					
9.5	Regular WP meetings	**78,84,86**	78,84,86	0	2	Barbui Barosi
9.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group (1 page, bullet point syle)	**79,86**	86	0	2	Kiladjian
9.26e	Phase II study of imatinib therapy in Pv patients – (recruitment closed, progress report)	**78**	78	0	2	Lengfelder
9.28e	Advancement in a registry of pregnancies in ET (ongoing)	**73-86**	86	0	3	Griesshammer
9.30e	Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients)	**73-86**	86	0	3	Barbui Finazzi
9.31e	Advancement in a registration study of high-risk ET patients treated with Anagrelide – (recruitment closed, progress report)	**73-86**	86	0	4	Birgegard
9.34e	Protocol for a multicenter study of vorinostat in CMPDs (started in 2009, still recruiting patients)	**73-86**	86	0	4	Hasselbalch
9.36b	Survey and harmonization of assay methods for JAK2-V617F (ongoing)	**73-86**	86	0	5	Vannucchi
9.37b	Registry of IFN-treated MPD patients (to be started in 2010)	**73-86**	86	0	3	Kiladjian Hasselbalch
9.38	A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2010)	**73-86**	Nd	0	0	Hasselbalch
9.39	Study of MPD leukemic transformations (publication in progress)	**73-86**	86	0	4	Rinaldi
9.40	Myeloproliferative Neoplasms: Management recommendations of the ELN	**73-86**	83	0	8	Barbui

List of milestones WP9, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP9	**CMPD**			
9.36b	Survey and harmonization of assay methods for JAK2-V617F	**73-86**	86	Vannucchi
9.40	Myeloproliferative Neoplasms: Management recommendations of the ELN	**73-86**	82	Barbui

Section 4: Other Issues

Ethical issues - none

Competitive calls - none

Section 5: WP-Performance:

Performance indicators	Status
Number of clinical trials started and/or completed	4
Number of patients recruited into clinical trials	About 1500
Number of patients included into registries	About 500
Improved predictive, prognostic or quality of life assessments	2
Degree of harmonization of trials	0
Number of SOPs and consensus papers	1
Number of publications	48
Number of meetings	5
Number of meta-analyses	0
Number of accredited trials	0

10 Diagnostic platform (WP10)

Objectives and starting point of work at beginning of reporting period

The major goals this year were to publish information on morphology and consensual flow recommendations for leukemia diagnosis which was indeed the case.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

10.5 Regular WP meetings, telephone conferences

WP10 participants met at the ELN annual meeting in Mannheim. Some of the team met also at the EGIL meeting in Berlin in March, at the MDS meeting in Munich in October and at the EHA European School in Cascais in November 2010.

10.6 LP reports to NMC regarding structure, activities and integration of national groups

Reports have been forwarded to the ELN management as requested.

10.11f Ongoing European quality control rounds on (morphological) leukemia diagnostics on the 'reference center level'

The morphology faculty completed a comprehensive and published study, available also on line on the ELN website.

10.18e Ongoing extension of internet library of microscopical pictures (incl. immuncytology), case reports, leukemia diagnostics

All of the activities of WP10 that are posted on the website of the ELN are potentially useful for self-training or as teaching material. This seems, from feedback in Mannheim, to be indeed well used. Pr Gina Zini obtained from the ELIC interesting data on the use of our pages. The participation of WP10 to educational sessions especially within the European School of Hematology should also be mentioned. WP10 applied this year to be one of the EHA SWGs.

The internet library of powerpoint presentations on leukemia diagnostics that was established (www.leukemia-diagnostics.org**).**

10.22e Interaction with other groups in diagnostic for design of algorithms

Interaction is fruitfully ongoing on the MDS topic, with published and submitted papers (see Annex section 3, WP10).

10.24e Specific project on microarray for preDC leukemia with WP13-continued

Published joint paper and ongoing discussions about pDC ALL.

10.25 European workshop on Minimal Residual Disease strategies in immunophenotyping

Review paper published and planned meeting in October with MRD as the major flow topic.

10.26 Ongoing cooperation with WP9 on MDS immunophenotyping

See 10.22

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

Table 10.2: List of Deliverables WP10, 2010

Deliv. No.	Deliverable Name	Delivery/ Achieve date	Actual/Forecast delivery date	Estimated indicative person months	Used indicative person months*)	Respon-sible lead participant/ investigator
WP10	**Diagnostics**					
10.5	Regular WP meetings, Telephone conferences	**78,80**	78, 79, 80, 83, 86	0	2	Béné
10.6	LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)	**79,86**	86	0	2	Béné
10.11f	Ongoing European quality control rounds on (morphological) leukemia diagnostics on the 'reference center level'	**73-86**	86	0	4	Zini
10.18e	Ongoing extension of internet library of microscopical pictures (incl. immuncytology), case reports, leukemia diagnostics	**73-86**	86	0	4	Link Hastka
10.22e	Interaction with other groups in diagnostic for design of algorithms	**66-78**	86	0	6	Béné
10.24e	Specific project on microarray for preDC leukemia with WP13-continued	**73-86**	86	0	3	Béné
10.25	European workshop on Minimal Residual Disease strategies in immunophenotyping	**80**	86, ongoing	0	4	Béné
10.26	Ongoing cooperation with WP9 on MDS immunophenotyping	**73-86**	86	0	2	Béné

Table 10. 3: List of milestones WP10, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP10	**Diagnostics**			
10.18e	Ongoing extension of internet library of microscopical pictures (incl. immuncytology), case reports, leukemia diagnostics	**73-86**	On line	Link Hastka
10.25	European workshop on Minimal Residual Disease strategies in immunophenotyping	**80**	Planned for October 2011	Béné
10.26	Ongoing cooperation with WP9 on MDS immunophenotyping	**73-86**	Papers pending next meeting end of 2011 in Pavia	Béné

Section 3: Consortium management

Management of the WP10 is going smoothly, with a lot of electronic communication. New members are joining. It is sometimes required to renew call for papers revision or documentation but the electronic way chosen costs only time. Cooperation with other programs is effective with WP8, WP13 and WP12. Contacts have been made with the clinical WP and will be reinforced.

Section 4: Other Issues

Ethical issues-none

Competitive calls-none

Section 5: WP10-Performance

Performance indicators	**Status**
Establishment of European reference panels	done
Organization of interdisciplinary consensus conferences	done
Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes	done
Organization of quality control rounds	Done, new round in progress
Establishment of European telemicroscopical networks	ongoing
Set up of internet forum	done
Training courses and improvement of teaching facilities with new technologies	done
Number and quality of publications within the network	12

11 Cytogenetics (WP11)

Objectives and starting point of work at beginning of reporting period

- Intensify harmonization of cytogenetic techniques between laboratories based on consensus protocols and practical training in other laboratories.
- Establish working groups on distinct cytogenetic questions
- Improve analysis of large and complex cytogenetic data sets

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

11.5 Regular WP meetings

- WP meeting at the annual network symposion in Mannheim, 3.-4. February 2010
- 4th Work Group meeting and 5th Management Committee meeting Munich of COST and ELN, held at the Munich Leukemia Laboratory, Munich 18.-19. October 2010
- WP meeting at the annual network symposium in Mannheim, 2.-3- February 2011

11.6 LP reports to NMC regarding structure, activities and integration of national cytogenetics groups:

LP reports were prepared in time.

11.10f Further presentation of difficult cases

For questions regarding cytogenetic methods, nomenclature, FISH-probes, and help in difficult cases technical support was continuously offered in the WP11 website and an email address to contact experts of the field was presented.

11.16f Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases

The online Cytogenetic Data Analysis System (CyDAS.org) was continued for the analysis of large cytogenetic data sets.

11.17f Continuation of data collection on rare abnormalities

New cases with rare chromosome aberrations were collected in collaboration with the Atlas of Genetics and Cytogenetics in Oncology and Hematology which is edited by Dr. Huret such as t(8;9)(p12;q33); t(1;21)(p32;q22).

11.18f Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods

SNP microarray analysis revealed cytogenetically cryptic 17q11 deletion encompassing the NF1 gene in 6 out 37 AML with CBFB-MYH11 positive AML. Based on this finding a new project on the identification of NF1 deletions using interphase FISH in other myeloid malignancies was started. 889 myeloid malignancies were analyzed by FISH for *NF1* deletions. *NF1* deletions occur in 7.3% of de novo AML, 4% of CMML, 1.2% of MDS and 5.1% of MPN and therefore are a frequent and important alternative genetic mechanism for activating the RAS pathway in adult myeloid malignancies. As the majority of *NF1* deletions are not detectable by chromosome banding analysis due to the small size of the deletion, FISH analysis is required. Furthermore, in 58% of cases with *NF1* deletion as detected by FISH a *NF1* mutation was observed in the remaining allele.

Two novel cytogenetically cryptic EVI1 rearrangements were characterized by SNP arrays and sequencing.

By combining SNP arrays, banding analysis and sequencing a novel acquired deletion of RAD51 could be identified in a case of MDS with isolated del(5q) by chromosomal banding analysis.

11.20f Continuous development and provision of additional methods

An additional interlaboratory test of the chromosome banding analysis procedure using viable leukemia cells involving 46 laboratories was initiated. An AML cell line carrying typical chromosome aberrations was used. The results are still pending.

11.23d/e Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain

A publication on cytogenetic findings of 2124 MDS patients of Germany and Austria appeared in December 2007 in BLOOD (Haase et al., Bood, 2007). The data collection and merging of the databases are still in progress:

Up to date, 3856 cases of primary and secondary MDS were collected of whom 2901 patients received no disease-altering therapy. The patients included are coalesced from the IMRAW- (Greenberg et al.; n=816), the German-Austrian (n=2011), and the Spanish (Solé et al.; n=975) databases. Additionally, 53 patients from an ICWG-cooperative project, supported by the MDS-Foundation, were included. Based on the 2901 primary, untreated patients mentioned above, a new comprehensive cytogenetic scoring system was designed. Dr. Schanz from Prof. Haases group wrote the manuscript regarding this project, statistic evaluation has been performed by Heinz Tüchler, Vienna. The manuscript has been submitted to JCO, was reviewed and is now under revision.

Dr. Schanz from Prof. Haases group also has performed a multicentric analysis on 2855 MDS patients that indicates an underestimation of poor risk cytogenetics in the IPSS. The manuscript has been submitted and was just accepted for publication in JCO (see Schanz et all, Annex section 3, WP11).

The data collection and merging of the databases is still in progress.

11.25d Cytogenetically unrelated clones in MDS

A recent update of this project yielded 95 cases with MDS cytogenetically unrelated clones which were collected from 11 different national and international (Greece, USA, Sweden, Japan, Spain, France) laboratories. The incidence, based on the international database described in 11.23c, is 0.7%. The most frequent combination was a clone with 5q deletion and a clone with trisomy 8 (43%). Overall, trisomy 8 is overrepresented in independent clones. The median survival of all patients with unrelated clones was 26.2 months, which has to be classified as an intermediate prognosis. Combinations of 5q-/+8 and isolated 5q- showed no statistically significant difference in survival (median survival: 42.7 months). Patients with a trisomy 8 clone and a clone with any other aberration showed an adverse progress (median survival 20.5 months). Combinations of 5q-/+8 had, in comparison to cases with +8 plus a clone with any other aberration, to a significant better survival (p=0.004).

Data have been presented recently at the annual meeting of the German Society of Hematology and Oncology, October 2010. A manuscript is in preparation.

11.26b Provide data for the establishment of a European external quality assessment to EUROGENTEST

The pilot Cytogenetic External Quality Assessment (CEQA) Scheme in Hematology of the EUROGENTEST has been established.

11.27b Administration of WP11 website and spreading of excellence by promotion of web-based information

The contents of the WP11 site were kept up to date by the WP11. E.g., the minutes of the annual Symposium were integrated.

Table 11.1: List of Deliverables WP11, 2010

Deliv. No.	Deliverable Name	Delivery/ Achieve date	Actual/Forecast delivery date	Estimated indicative person months	Used indicative person months*)	Respon-sible lead participant/ investigator
WP11 Cytogenetics						
11.5	Regular WP meetings	**78,86**	78, 86	0	10	Fonatsch, Haferlach C.
11.6	LP reports to NMC regarding structure, activities and integration of national cytogenetics groups (1 page, bullet point style)	**79,86**	86	0	2	Fonatsch
11.10f	Further presentation of difficult cases	**73-86**	86	0	2	Rieder Haferlach C
11.16f	Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases	**73-86**	86	0	2	Rieder
11.17f	Continuation of data collection on rare abnormalities	**73-86**	86	0	2	Haferlach C Rieder Fonatsch
11.18f	Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods	**73-86**	86	0	2	Rieder Haferlach C Fonatsch
11.20f	Continuous development and provision of additional methods	**73-86**	86	0	2	Fonatsch Rieder
11.23d	Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain	**73-86**	86	0	6	Haase
11.25d	Cytogenetically unrelated clones in MDS	**73-86**	86	0	4	Haase Haferlach C Fonatsch
11.26b	Provide data for the establishment of a European external quality assessment to EUROGENTEST	**73-86**	86	0	4	Rieder Dastugue
11.27b	Administration of the WP11 website and spreading of excellence by promotion of web-based information	**73-86**	86	0	4	Rieder

List of milestones WP11, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP11 Cytogenetics				
11.23e	Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain	**73-86**	86	Haase
11.26b	Provide data for the establishment of a European external quality assessment to EUROGENTEST	**73-86**	86	Rieder, Dastugue

Section 3: Consortium management

Cooperation with other workpackages is effective especially with WP6, WP8, WP9 and WP13.

Section 4: Other Issues

Ethical issues-none

Competitive calls-none

Section 5: WP-Performance

Performance indicators	Status
Establishment of European reference panels	in progress
Organization of interdisciplinary consensus conferences	COST meeting in cooperation with WP8 (MDS) took place
Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes	first consensus protocol published in Genes Chromosomes Cancer
Set up of internet forum	done
Number of rare abnormalities for which the prognostic impact could be clarified	1
Number of new recurrent abnormalities identified	2
Number and quality of publications within the network 2010	57
Implementation of technology transfer	in progress
Improved techniques with better results	in progress

12 Minimal residual disease (WP12)

Objectives and starting point of work at beginning of reporting period

A coordinated and integrated working group was successfully established to develop new assays to increase the proportion of patients with myeloid leukemias/myeloproliferative disorders (MPDs) who could potentially benefit from minimal residual disease (MRD) monitoring using real-time quantitative PCR (RQ-PCR) approaches. Key objectives over the last year have been to continue to improve standardization of established assays (i.e. *BCR-ABL,* JAK2 V617F in collaboration with WP4 and WP9, respectively), the evaluation of novel RQ-PCR assays (i.e. Wilms' Tumor gene (*WT1*) and nucleophosmin (*NPM1*) mutation) and the validation and implementation of a computer software reporting package to improve standards of reporting of RQ-PCR data to clinicians, which also serves to facilitate comparison of results between laboratories.

While development of RQ-PCR assays for fusion genes associated with myeloproliferative disorders enables sequential MRD assessment to guide therapy with tyrosine kinase inhibitors (Jovanovic *et al*, *Blood* 2007; Metzgeroth *et al*, *Br J Haematol* 2008; Score *et al*, *Leukemia* 2009; Müller *et al*, *Leukemia* 2009; Hochhaus *et al*, *Leukemia* 2009), in acute myeloid leukemia (AML) we have been exploring a number of approaches whereby MRD detection could lead to improved management and clinical outcome. For leukemia-specific markers that afford relatively high levels of assay sensitivity (i.e. leukemic fusion genes e.g. *PML-RARA*, *NPM1* mutation) it is possible to use MRD monitoring to pinpoint those patients destined to fail first-line therapy, thereby allowing the administration of additional treatment in first remission – this approach has been evaluated initially in acute promyelocytic leukemia (APL) (Grimwade *et al*, *J Clin Oncol* 2009). For AML cases lacking a leukemia-specific molecular marker, MRD monitoring relies upon flow cytometry to detect a leukemia-associated aberrant phenotype or RQ-PCR analysis of genes that are highly expressed in the blast population (e.g. *WT1*). In this situation, evidence to date suggests that MRD assessment is best suited to investigate the degree of leukemic blast reduction during early phases of therapy and its relationship to subsequent risk of relapse (reviewed Freeman *et al*, *Semin Oncol* 2008; Béné & Kaeda, *Haematologica* 2009; Grimwade *et al*, *Curr Opin Oncol* 2010; Smith *et al*, *Blood Rev* 2011). We have recently shown that determination of depth of response to induction chemotherapy using an optimized ELN *WT1* assay provides an independent prognostic factor in AML suggesting that it could be used to enhance risk stratification (Cilloni *et al*, *J Clin Oncol* 2009; Grimwade & Hills, *Hematology Am Soc Hematol Educ Program* 2009). Development of optimized protocols for flow cytometric detection of MRD has been a focus of attention for the "Diagnostic Platform" workpackage (WP10) and we have established a joint program to investigate the optimal approach for MRD-directed therapy in AML cases lacking a leukemia-specific molecular target. Prospective parallel analysis of flow cytometry and optimized RQ-PCR assays is now being evaluated by ELN MRD laboratories within the context of large scale clinical trials. These studies will establish the extent to which MRD assessment affords additional prognostic information as compared to conventional risk factors, facilitating the

development of enhanced risk stratified treatment approaches to AML and providing more insights into the role of autologous or allogeneic transplantation in first remission.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives:

12.5 Regular WP meetings

Instrumental to the progression and development of the experimental program for WP12 over the course of the last year has been the provision for regular meetings. WP12 meetings were linked to international hematology meetings: LeukemiaNet Annual Symposium, Mannheim (2nd February 2010 & 1st February 2011) and the European Hematology Association (EHA), Barcelona (10th June 2010). A separate EUTOS *BCR-ABL* molecular monitoring group meeting was held on 9th June 2010 in Barcelona.

12.6 LP reports to NMC regarding structure, activities and integration of national groups

Minutes from each WP12 meeting are drawn up by the lead participant and submitted to ELN NMC following approval by the membership of WP12. Updates from international *BCR-ABL* standardization meetings chaired by Prof Cross are fed back to the relevant national groups, such as the UK network of molecular diagnostic laboratories (meeting 25th June, 2010), the German Kompetenznetz "Akute und chronische Leukämien", the Italian and the Nordic networks.

12.10c Evaluation of expression levels of target genes in diagnostic material

Prior to this reporting period, WP12 projects had established through application of optimized RQ-PCR assays that leukemic fusion genes e.g. *FIP1L1-PDGFRA* in hypereosinophilic syndrome (Jovanovic *et al*, *Blood* 2007; Reiter *et al*, *Haematologica* 2007) and *PML-RARA* in acute promyelocytic leukemia (Grimwade *et al*, *J Clin Oncol,* 2009) exhibit significant variation in expression in diagnostic samples (~ 3-log range), which impacts significantly upon sensitivity of assays to detect MRD. Over the course of this year WP12 participants have continued to focus on the analysis of *NPM1* mutations and *WT1*, which afford the opportunity to evaluate response to therapy using a molecular marker in a substantial proportion of AML cases.

NPM1: RQ-PCR assays have been developed for the commonest *NPM1* mutations (types A, B & D) by Prof Saglio's group (Gorello *et al*, *Leukemia* 2006) and evaluated more widely within WP12. In addition, RQ-PCR assays that have been shown to be mutant specific have been developed for a number of rarer mutations, including Types G, H, I, J, N, Om, S and previously unreported mutations. Analysis of diagnostic samples has shown that the *NPM1* mutant allele is highly expressed, typically affording assay sensitivities of 1 in 10^5 (Figure 12.1).

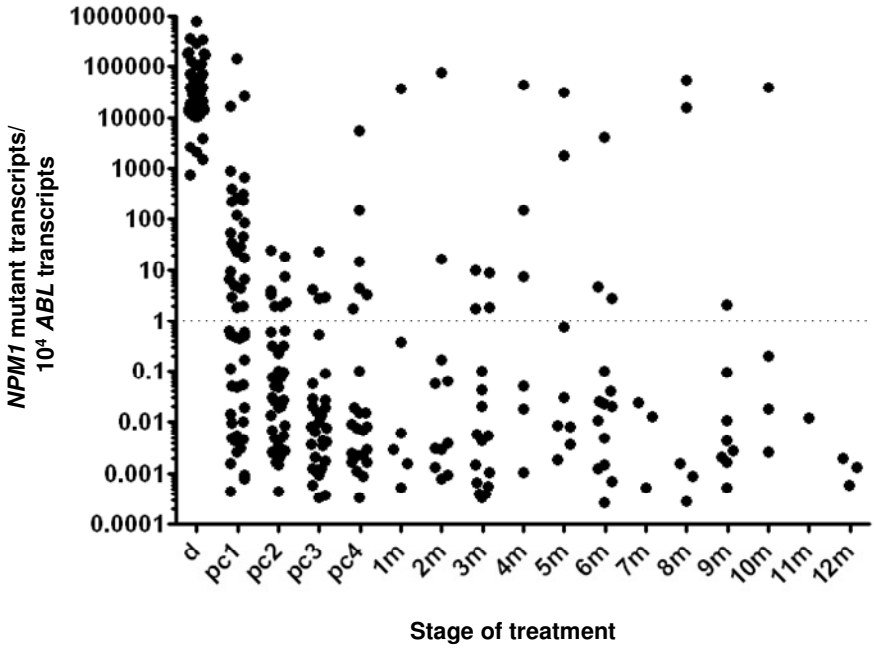


Figure 12.1: Normalized *NPM1* mutant transcript level in diagnostic and follow-up samples from patients recruited to the UK National Cancer Research Institute (NCRI) AML17 trial. *NPM1* mutant transcripts were highly expressed at diagnosis, typically allowing detection of MRD at a sensitivity of 1 in 10^5 in follow-up samples. Abbreviations: d, diagnosis, pc, post-course; m, months.

WT1: This is an interesting potential target for MRD detection in that it has been reported to be over-expressed in approximately 70% of AML and is being investigated as a target for immunotherapy in this disease. In a project led by Daniela Cilloni and Giuseppe Saglio involving 11 WP12 laboratories, 9 published or "in-house" *WT1* assays were systematically analyzed in parallel prior to this reporting year, leading to the selection of an assay located within exons 1 and 2, which was confirmed to be RNA specific and afforded greatest sensitivity. The selected "ELN *WT1*" assay also has the distinct advantage that it is located in a region of the gene that is rarely subject to mutation in AML. Indeed *WT1* mutations which occur in ~10% of normal karyotype AML typically involve exons 7 and 9, where many published *WT1* RQ-PCR assays are located thereby giving rise to the potential for "false negative" results. A full length *WT1* plasmid was developed in conjunction with Ipsogen, Marseille and included in an "ELN *WT1* kit" including primers and probe for the ELN *WT1* assay, *ABL* control gene assay (Europe Against Cancer) and respective plasmid standards. ELN *WT1* kits were centrally distributed to participating laboratories for evaluation in large numbers of AML and non-leukemic samples (620 pre-treatment AML samples and 204 control PB, BM and PBSC samples). This allowed us to establish thresholds for background levels of expression of *WT1* in normal PB and BM (upper limit 50 and 250 copies/ 10^4 *ABL* copies, respectively). This relatively high background level of expression limits the sensitivity of *WT1* RQ-PCR assays to detect residual disease as compared to use of leukemia-specific markers (e.g. mutant NPM1, *PML-RARA*), suggesting that *WT1* is most appropriately used to measure kinetics of disease response during early phases of therapy rather than

for serial MRD monitoring to track impending relapse. Based upon the differential expression of *WT1* in AML blasts and normal PB and BM, PB was considered to provide the preferred sample source allowing at least a 2-log reduction in transcripts to be discriminated in approximately half of AML patients.

No significant difference in *WT1* expression level as determined by the ELN assay was observed in AML cases harboring mutations in exons 7 and 9 of the gene as compared to those with wild type *WT1* (p=0.2). However, sequence analysis of a series of 32 cases of AML in which the ELN assay suggested a low level of *WT1* transcript expression (<250 copies/ 10^4 *ABL* copies), showed that they were enriched for mutations in exons 1 and 2 that disrupted primer and/or probe binding sites. The QC rounds and results of the final validation of the selected ELN *WT1* assay were recently published (Cilloni *et al*, *J Clin Oncol* 2009). The optimized ELN *WT1* assay has now been taken forward to assess MRD in multicenter clinical trials including the UK NCRI AML17 trial as a tool to enhance risk stratification and in the Epicept study (EPC2008-02) to evaluate response to histamine dihydrochloride and IL-2 as maintenance therapy in AML (12.15d).

12.11d Establish the additional proportion of leukemic patients that can be monitored using novel targets

The major focus of this work was the development of optimized RQ-PCR assays for detection of *WT1* and numerous different *NPM1* mutations, thereby substantially extending the proportion of AML patients that can be monitored for disease response beyond the range of fusion gene assays developed in the Europe Against Cancer program, which are applicable to only ~25% of AML.

NPM1

Over the course of the last year significant progress has been made, with the Munich, Ulm, Lille and UK groups providing strong evidence that *NPM1* mutations provide highly promising MRD targets that could allow the development of individualized treatment approaches in a significant proportion of AML patients. The Munich Leukemia Laboratory developed assays for 17 different *NPM1* mutation types based on the Lightcycler platform to analyze 252 AML cases (Schnittger *et al*, *Blood* 2009). Relapses were predicted by failure to reduce *NPM1* mutant level by more than 3 logs or by more than a 1 log rise in the mutant level. In this study *NPM1* mutant level was the most important predictor of relapse in multivariable analysis considering age and FLT3-ITD status. In a study led by Jan Krönke, the Ulm group has undertaken MRD detection in over 1600 samples from 245 adult AML patients (aged 16-60 years) with NPM1 mutations (Krönke *et al*, *J Clin Oncol* 2011, in press). MRD positivity following the second induction and at the post-consolidation timepoint were both predictive of subsequent risk of relapse. On longitudinal monitoring, median time from PCR positivity to relapse was 3 months; in some patients the time from molecular conversion to relapse was very prolonged and

the Lille group (Aline Renneville & Claude Preudhomme, unpublished data) has shown that very late relapses (up to 12 years from diagnosis) with stability of the *NPM1* mutation can occur.

Since it is anticipated that *NPM1* MRD monitoring data will increasingly be used to guide patient therapy, a major focus of WP12 has been to establish predictive thresholds, evaluate the optimal sample type for monitoring (PB vs BM), investigate the kinetics of disease relapse, and consider the stability of the *NPM1* mutation as an MRD target. The Ulm group have reported that a threshold of 200 *NPM1* mutant copies/ 10^4 *ABL* copies to be an informative threshold for relapse. While, detailed mathematical modelling of the raw data provided from the Munich study, performed by Hans Ommen (Aarhus, Denmark), has suggested that *NPM1* mutant levels above a threshold of 5 x 10^{-5} relative to *ABL* are indicative of MRD (Ommen *et al*, *Blood* 2010). To investigate the optimal sample source for MRD monitoring, 174 paired PB and BM follow-up samples have been analyzed using the Gorello assays for Type A, B and D mutations by the Lille group. Good concordance was observed in *NPM1* MRD results obtained with the two sample sources, with bone marrow typically affording ~0.5log greater sensitivity. Kinetics of disease relapse have been investigated in the Munich data set, showing that speed of relapse is significantly more rapid in the group with coexistant FLT3-ITD mutations than in *NPM1*^{mut} cases with wild type FLT3 (Schnittger *et al*, *Blood* 2009; Ommen *et al*, *Blood* 2010). A key aim of WP12 is to establish optimal MRD monitoring schedules to predict disease recurrence and allow time for pre-emptive therapy to be delivered to prevent clinical relapse. Applying the mathematical model which is independent of assay sensitivity, the relationship between sampling interval and likelihood of relapse detection in NPM1 mutant AML in relation to other molecular subsets was defined. Thus, taking a 3 month bone marrow sampling interval as an example, the median time from molecular positivity to hematological relapse was 120 days for *NPM1*^{mut} *AML* as compared to 200 days for *CBFB-MYH11*+ patients, 90 days in *RUNX1-RUNX1T1*+ cases, but as short as 45 days in *PML-RARA*+ patients (Ommen *et al*, *Blood* 2010). Application of the mathematical model to the Munich data set showed that 6 monthly and 4 monthly BM examinations are required to achieve a relapse detection frequency of at least 90% with a window of at least 60 days to hematological relapse in *NPM1c+/FLT3*-ITD- and *NPM1c+/FLT3*-ITD+ AML, respectively. Optimal MRD sampling frequencies are currently being prospectively validated in multi-center clinical trials such as the UK NCRI AML17 trial.

The stability of the *NPM1* mutation as an MRD marker has also been considered. The Munich group reported stability of the *NPM1* mutation in 84 of 84 paired diagnostic and relapse samples (Schnittger *et al*, *Blood* 2009). The Lille group have also found that the *NPM1* mutation is stable based on an analysis of 55 paired diagnostic and relapse samples (Aline Renneville, Claude Preudhomme unpublished data). However, the Ulm group have observed occasional cases in which the *NPM1* mutation is lost at "relapse", including cases with acquisition of trisomy 8, *RUNX1* mutation and MLL-PTD, which most likely reflect development of t-AML rather than relapse of the original clone (Krönke *et al*, *J Clin Oncol* 2011, in press). These studies support the notion that *NPM1* mutation is a

primary lesion in the pathogenesis of AML, but also serve to highlight the importance of comprehensive molecular and cytogenetic characterization of patients with "relapsed" AML.

The Munich *NPM1*^{mut} assays involve use of a mutation-specific forward primer and common reverse primer, which do not amplify the mutation-specific plasmid standards originally developed by Ipsogen to be used in conjunction with the Gorello assays. Therefore, in collaboration with Ipsogen (Marseille), a set of universal plasmid standards for the commonest mutation types (A, B & D), accounting for ~90% of cases that can be used in conjunction with all RNA- and genomic DNA-based assays has been developed. These have been evaluated within WP12, showing good performance profile and will allow for standardized reporting of *NPM1* MRD data across different RQ-PCR platforms.

WT1:

As part of the validation process the optimized ELN *WT1* assay has been tested in samples derived from a cohort of 142 AML patients with high level *WT1* expression at diagnosis (>20,000 *WT1* copies/ 10^4 *ABL* copies) treated with standard anthracycline and cytarabine-based therapy (Grimwade & Hills, *Hematology Am Soc Hematol Educ Program* 2009; Grimwade *et al*, *Curr Opin Oncol* 2010). In this informative group, greater *WT1* transcript reduction after induction predicted reduced relapse risk (hazard ratio, 0.54 per log reduction; 95% CI, 0.36 to 0.83; P =0.004) that remained significant when adjusted for age, WBC count, and cytogenetics (Figure 12.2). Failure to reduce *WT1* transcripts below the threshold limits defined in normal controls by the end of consolidation also predicted increased relapse risk (P= 0.004).

Integrated approaches to MRD detection:

This aim is being addressed in conjunction with WP10, with current data indicating that virtually all AML patients can be subject to assessment of MRD using flow cytometry- and/or RQ-PCR- based approaches (reviewed Béné & Kaeda, *Haematologica* 2009; Grimwade *et al*, *Curr Opin Oncol* 2010). A major aim of WP10 is to achieve greater collaboration between groups performing flow cytometry within the context of national clinical trials. Vincent van der Velden (Rotterdam) has been comparaing RQ-PCR and flow cytometric approaches for MRD detection in pediatric AML (van der Velden *et al*, *Leukemia* 2010). Moreover, Gerrit Schuurhuis has led a national Dutch study prospectively evaluating flow cytometry-based MRD detection to predict outcome in AML and which is comparing flow data with molecular approaches to MRD detection using RQ-PCR. This theme is also being developed in the UK NCRI AML17 trial which commenced in April 2009 in which RQ-PCR (using EAC and ELN standardized assays) and flow-cytometry are being evaluated prospectively in parallel to establish whether early MRD assessment provides greater discriminatory power than current conventional criteria to identify those patients most and least likely to benefit from allogeneic transplantation in first remission.

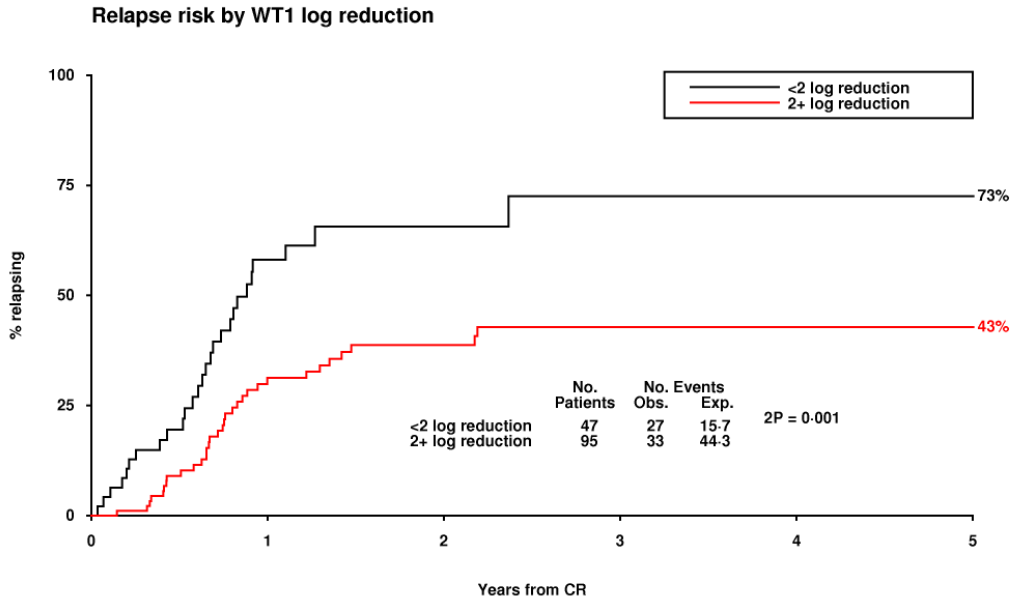


Figure 12.2: Kinetics of minimal residual disease response following induction therapy are predictive of subsequent relapse risk in AML. The predictive value of MRD assessment by standardized ELN *WT1* RQ-PCR assay was determined in a cohort of 142 AML patients treated with conventional anthracycline and cytarabine based treatment. Analysis was undertaken in AML cases with *WT1* expression exceeding 2 x10^4 copies/ 10^4 *ABL* copies in pre-treatment samples, allowing the detection of at least a 2-log reduction in *WT1* transcripts following induction, taking into account the background level of expression observed in normal hematopoietic tissues. The patient cohort included 91 cases reported previously (Cilloni *et al, J Clin Oncol* 2009) combined with a further 51 cases treated in the MRC AML15 trial (samples kindly provided by John Yin and Michelle Sale, Manchester Royal Infirmary and analyzed at Guy's Hospital, London, UK).

FIP1L1-PDGFRA:

A further focus of WP12 has been to develop RQ-PCR assays to direct molecularly targeted therapies in myeloproliferative disorders, in collaboration with WP9. Indeed the structure of WP12 has enabled our group to continue to collect clinical material from patients with relatively rare conditions such as *FIP1L1-PDGFRA*+ hypereosinophilic syndrome which we have found to account for ~10% cases of persistent unexplained eosinophilia (Jovanovic *et al*, *Blood* 2007), enabling us to gain further biological insights into this subset of disorders, complementing the work of WP9 (Burgstaller *et al*, *Leukemia* 2007; Reiter *et al*, *Haematologica* 2007; Metzgeroth *et al*, *Br J Haematol* 2008; Walz *et al*, *Leukemia* 2009). Indeed, in a study led by Prof Nick Cross, we also showed that genomic DNA based RQ-PCR assays for the *FIP1L1-PDGFRA* fusion can detect MRD following imatinib therapy with significantly greater sensitivity than RNA-based assays (Score *et al*, *Leukemia* 2009). The ELN is ideally suited to the conduct of such studies, which would not have been feasible at the national level.

12.13c Development of standardized protocols for MRD assessment (from bedside to clinical report)

BCR-ABL:

In order to achieve this aim, WP12 has linked up with the international standardization efforts for RQ-PCR analysis and reporting of *BCR-ABL* results in chronic myeloid leukemia (CML), led by Prof Nick Cross. This ongoing effort will establish key principles that will be relevant to development of standardized protocols for other MRD targets. The *BCR-ABL* related work within WP12 has focused on the development of accredited reference reagents as a means to facilitate the implementation of the International Scale (IS) for MRD determination in CML. Following a series of successful pilot experiments and control rounds we commissioned ECACC (European Collection of Cell Cultures) to grow 40 litres of HL60 cells in Autumn 2008, from which we made four mixtures of K562/HL60 to approximate 10%, 1%, 0.1% and 0.01% on the IS. These mixtures were prepared as rapidly as possible and transported to the National Institute of Biological Standards and Control (NIBSC) for aliquoting into ampoules and freeze drying, yielding approximately 3000 vials per dilution. Following initial successful in house evaluation of the freeze dried material we performed a field trial in January-March 2009 that aimed to establish IS values for each dilution. Laboratories were selected that had validated conversion factors (CF), with at least three laboratories for each of the three internationally accepted control genes: *ABL*, *BCR* and *GUSB*. A total of 10 laboratories were involved (6 from the EU) using 4 different protocols and 8 different RQ-PCR platforms. Each lab received 3 vials at each of the four dilution levels. RNA was extracted from each vial and reverse transcribed twice on different days yielding 24 datapoints/lab. The amounts of RNA extracted, absolute copy numbers of control gene, *BCR-ABL*/control gene before and after conversion were calculated and the mean for the laboratories used to calculate the IS values for each dilution (Figure 12.3).

In addition, the performance of the freeze dried materials was evaluated by homogeneity and stability testing. The coefficients of variation of 17 randomly selected freeze dried vials for each dilution were similar to the variation seen in 17 aliquots of non-freeze dried material and also patient replicates, confirming batch homogeneity. In accelerated degradation studies, the amounts of extractable RNA fell significantly when the vials were maintained at >20°C for 10 months, but the *BCR-ABL/ABL* ratios were distorted only in samples that had been maintained at 45 degrees or higher (Figure 12.4).

The documentation describing these experiments was submitted by NIBSC to the World Health Organisation (WHO) in July 2009 and following assessment of the evidence, the materials were approved as primary reference reagents in November 2009. The supply of these reagents will be limited to companies and reference laboratories that are able to generate the secondary reference materials that will actually be used by testing laboratories. This work was presented at EHA 2010 (White *et al*., *Haematologica* 2010;95; Suppl2:84-85) and recently published (White *et al*., *Blood* 2010;116:e111-7).

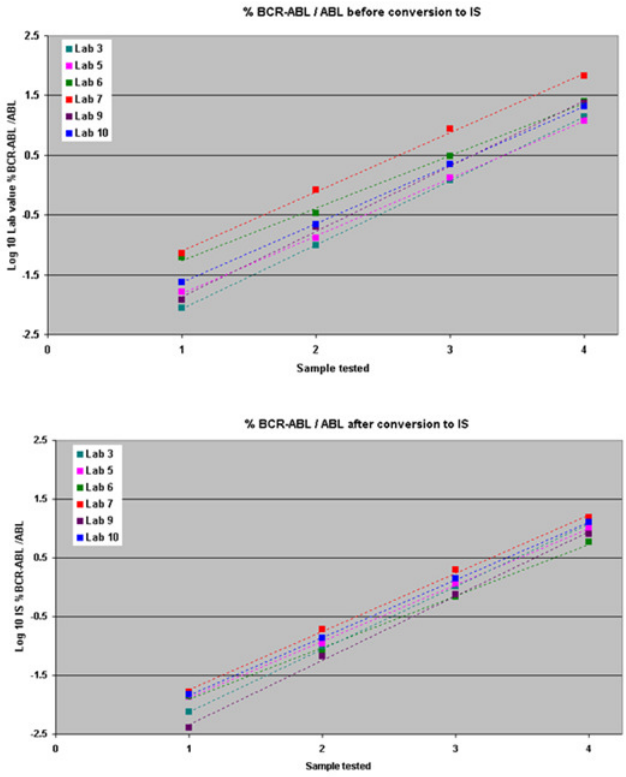


Figure 12.3: *BCR-ABL* QC results of freeze dried cell dilution analysis for the 6 laboratories that used *ABL* as the control gene. Top panel: before conversion; bottom panel: after conversion using local CFs. The mean of the converted values were assigned as IS values to each dilution.

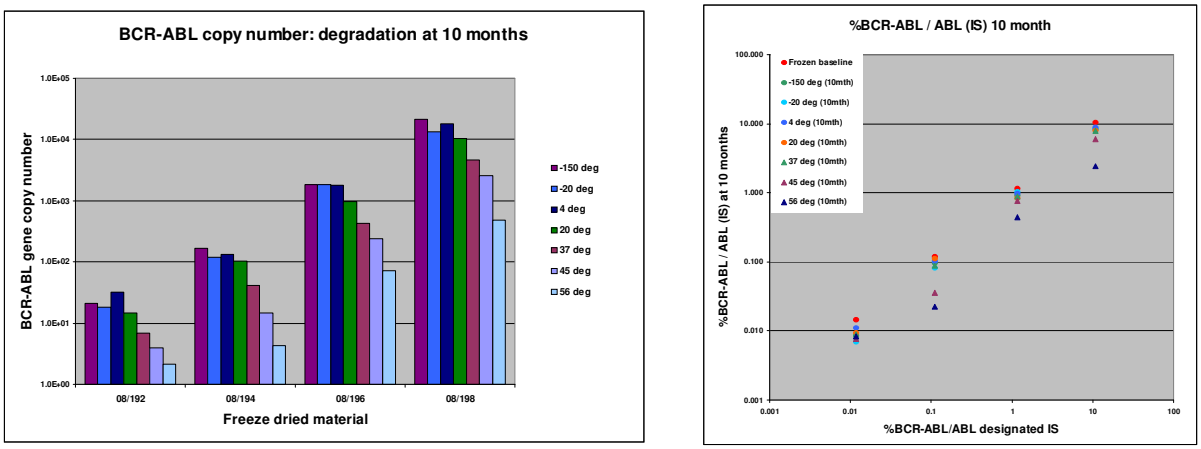


Figure 12.4: Stability of *BCR-ABL* transcripts in freeze dried cells in accelerated degradation studies. Left panel: absolute copy numbers for each of the four dilutions extracted from vials of freeze dried cells that had been maintained at 7 different temperatures for 10 months. Right panel: Values plotted as *BCR-ABL/ABL* ratios.

In addition to the work above, the EUTOS group has focused very productively on the establishment of conversion factors (CFs) for at least one laboratory per country or region following the protocol developed by the Adelaide laboratory. An evaluation concerning the stability of CFs over time has been presented at ASH 2010 (Müller *et al.*, *Blood* (ASH Annual Meeting Abstracts), Nov 2010; 116: 893). A control round to assess the ability of laboratories to detect resistance-associated mutations was

performed and results presented at ASH 2010 (Ernst *et al*., *Blood* (ASH Annual Meeting Abstracts), Nov 2010; 116**:** 894).

QC1: The first QC round involved distribution of dilutions of HEL and K562 cells, which harbor JAK2-V617F and wild type JAK2 alleles respectively, which were tested in 4 laboratories using the three best-performing published wild type and mutant assays (Larsen, Lippert & Nussenzveig), that were taken forward from previous experiments conducted within WP12 (that led to the elimination of 3 published assays, shown to exhibit suboptimal performance). The Larsen mutant assay was found to be the most efficient and afforded greater sensitivity, as compared to the Lippert and Nussenzveig assays. There was limited crossover of the Larsen mutant assay when tested on K562 cells (100% wild type JAK2), but much more crossover with the Lippert assay. The wild type JAK2 assays showed significant crossover as evidenced by amplification of the mutant allele in HEL cells, which was less marked with the Nussenzveig and Lippert assays than with the Larsen assay.

QC2: The second round involved 8 laboratories (Florence, Freiburg, Cambridge, Paris, Bern, London, Nantes, Bordeaux) and investigated 8 JAK2 assays (4 V617F mutant assays [Larsen, Lippert, Nussenzveig & Bern (Oppliger) "in house" assay]; 3 wild type assays [Larsen, Lippert & Nussenzveig]; total JAK2 [Oppliger "in house" assay]) and parallel amplification of independent control gene assays (albumin [BIOMED] and cyclophilin A [Pallisgaard "in house"]) to control for variations in template in each reaction. Plasmid standards for the wild type JAK2, mutant JAK2 and control gene assays were developed by Ipsogen, Marseille on behalf of WP12 and were found to perform well (Figure 5 and Table 1). Genomic DNA extracted from serial dilutions of HEL in K562 cells and K562 dilutions in HEL cells, reaction mixes for each RQ-PCR assay and plasmid standards for wild type and mutant JAK2 and the independent control genes were prepared and centrally distributed by Nicolas Maroc, Ipsogen. A standardized format for performing the QC exercise was distributed to the participating laboratories and data were returned to Nicolas Maroc and David Grimwade/Jelena Jovanovic (Guy's Hospital, London) for centralized analysis. The identities of the JAK2 mutant and wild type assays were blinded to all participants by Ipsogen, and which were not revealed until after the results of the analyses had been completed. The design of the QC exercise that included HEL and K562 cells which harbor only mutant and wild type JAK2 alleles respectively allowed the specificity of the wild type assays to be assessed, in conjunction with assessment of the specificity and sensitivity of the mutant assays. Despite the different platforms (ABI7300, ABI7000, ABI7500 n=2, ABI7900 n=2, LC480, RG6000) and consequent differences in run conditions, marked concordance in the results obtained with all of the respective assays between the laboratories was observed, highlighting the validity of the exercise to draw firm conclusions.

In accordance with previous QC rounds, both the wild type and mutant Nussenzveig assays exhibited poor amplification plots and markedly inferior efficiency (median slopes -3.69 & -3.77, respectively). The Lippert wild type assay exhibited greater specificity than the Larsen wild type assay, in accordance with previous QC rounds. The Oppliger and Larsen mutant assays were found to be the most specific, yielding Ct values >40 when applied to neat K562 cells in the majority of laboratories,

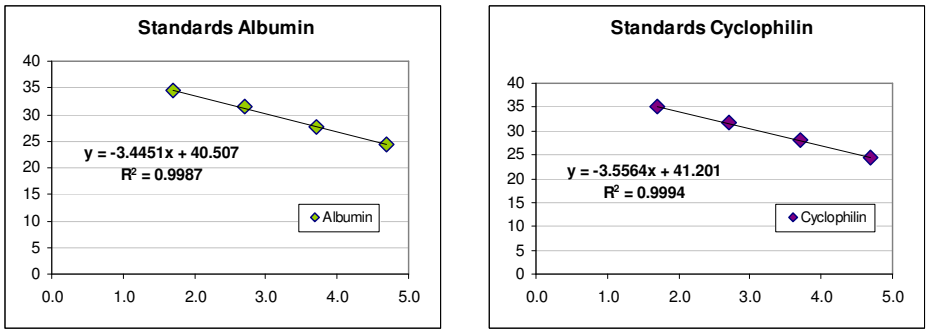


Figure 12.5: Development of plasmid standards for independent control genes to normalize MRD data for DNA-based Q-PCR assays.

irrespective of platform. Taking into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to the Europe Against Cancer [EAC] program consensus) and the level of background amplification observed for the mutant assays in neat K562 cells, the level of sensitivity of the mutant assays was determined in serial dilutions of HEL in K562 cells (taking detection limit as □1 Ct below background amplification).

Table 12.1: Comparison of performance of wild type (WT) and mutant (MUT) JAK2 assays in QC exercise conducted in 8 laboratories. The values provided are slopes reported for plasmid standard curves generated with centrally distributed reagents; assays with maximal efficiency exhibit a slope value of -3.3. Data for the independent control gene assays Albumin (ALB) and Cyclophilin (CYC) are also shown.
Design A: Lippert assay
Design B: Bern (Oppliger) "in house" assay. For this assay the "WT" data relate to total JAK2 (i.e. wild type and mutant)
Design C: Nussenzveig assay
Design D: Larsen assay

		Vannucchi (ABI 7300)	Pahl (ABI 7000)	Bench (ABI 7500)	Cassinat (ABI 7500 fast)	Oppliger (ABI 7900)	Tobal (ABI 7900HT)	Lippert (LC480)	Hermouet (RG 6000)
Design A	WT	-3.54	-3.36	-3.61	-3.91	-3.44	-3.45	-3.46	-3.55
	MUT	-3.86	-3.56	-3.71	-3.72	-3.55	-3.29	-3.60	-3.61
Design B	WT	-3.44	-3.29	-3.79	-3.18	-3.34	-3.43	-3.27	-3.50
	MUT	-3.53	-3.36	-3.53	-3.47	-3.47	-3.35	-3.52	-3.67
Design C	WT	-3.73	-3.38	-3.71	-3.66	-3.01	-3.56	-3.98	-3.76
	MUT	-3.72	-3.48	-3.81	-4.06	-3.83	-3.72	-4.21	-3.68
Design D	WT	-3.32	-3.35	-3.38	-3.34	-3.44	-3.24	-3.43	-3.55
	MUT	-3.49	-3.49	-3.75	-3.66	-3.55	-3.71	-3.50	-3.61
	ALB (avg)	-3.37	-3.43	-3.63	-3.56	-3.30	-3.45	-3.61	-3.65
	CYC (avg)	-3.49	-3.45	-3.73	-3.73	-3.24	-3.36	-3.65	-3.80

The mutant assays differed in their sensitivities (Table 2), with the Oppliger assay capable of detecting an estimated 0.008% mutant JAK2, the Larsen assay detected 0.08-008%, the Lippert assay was consistently less sensitive – 0.08% and the Nussenzveig assay the least sensitive due to inferior efficiency (0.8%). These data are in accordance with those of previous experiments showing that the Larsen assay exhibited better performance than the Lippert assay, with both assays being superior to the Nussenzveig assay.

Table 12.2: Determination of relative sensitivity of 4 assays to detect JAK2-V617F mutant allele in serial dilution of HEL cells in K562 cells in QC exercise conducted in 8 laboratories.
The sensitivity quoted for each assay (0.8%-0.008%) by each laboratory takes into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to EAC) and the level of background amplification observed for the mutant assays in neat K562 cells (taking detection limit as ≤ 1 Ct below background amplification).
Design A: Lippert assay
Design B: Bern (Oppliger) "in house" assay
Design C: Nussenzveig assay
Design D: Larsen assay

	Vannucchi (ABI 7300)	Pahl (ABI 7000)	Bench (ABI 7500)	Cassinat (ABI 7500 fast)	Oppliger (ABI 7900)	Tobal (ABI 7900HT)	Lippert (LC480)	Hermouet (RG 6000)	Max
Design A	0.08	0.8	0.08	0.08	0.8	0.8	0.08	0.08	0.08
Design B	0.008	0.008	47.1	0.008	0.08	0.08	0.008	0.008	0.008
Design C	0.8	0.8	0.8	0.8	0.8	0.8	7.5	0.8	0.8
Design D	0.08-0.008	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08-0.008

QC3: The third round involved evaluation of 5 assays which were blind tested by 6 participating labs on serial dilutions of HEL in K562, as well as against plasmid standards. All materials were prepared and centrally distributed by Ipsogen. JAK2 V617F mutant level was quantified relative to total JAK2 and albumin (standardized BIOMED assay). The JAK2 V617F assays tested were those with a good performance profile in previous QC rounds (i.e. Larsen assay, Oppliger "in house" assay & Lippert assay). In addition, two further "in house" assays were tested – provided by Bert van der Reijden and Jean Gabert. An aliquot of DNA from each HEL cell line dilution was subject to pyrosequencing to check mutant percentage. Concordance of data between the labs was generally very good, despite deployment of 6 different Q-PCR platforms (4 ABI platforms, LC480 & RG6000). The Nijmegen assay showed poorer performance and it was agreed that this was likely due to assay conditions, since the assay performs much better in the "in house" setting. In accordance with previous QC rounds, the Oppliger "in house" assay performed well, affording greatest sensitivity and showing good concordance of results across platforms.

QC4: Taking into account reports that in a recent US QC study conducted by Erasmus Schneider (Albany, New York) that the Nussenzveig assay performed well "in-house" in relation to the Ipsogen MutaQuant kit (Lippert assay) when used to test samples mimicking JAK2-V617F allele loads

observed in the diagnostic setting, a further QC study was conducted. This involved testing of serial dilutions of K562 and HEL cell lines and plasmid controls dispatched to the London, Florence, Bordeaux and ARUP laboratories (Todd Kelley & Joseph Prchal, Salt Lake City – where the Nussenzveig assay was established). The Oppliger, Larsen, Lippert and Nussenzveig assays were tested using reagents centrally distributed by Nicolas Maroc from Ipsogen and where possible "in-house" reagents were used on the test materials in parallel. This QC round again showed that the Larsen and Oppliger assays afford greatest sensitivity to detect JAK2-V617F, exhibiting better performance than the other two assays. In accordance with these data, the Larsen assay actually performed better in Eric Lippert's laboratory, than his own assay when using centrally distributed or in house reagents. There were discrepant results with the Nussenzveig assay, which performed much better "in-house" in the ARUP laboratory than in the other laboratories when using centrally distributed reagents with published conditions for the assay. This will be addressed in a further QC round to be conducted in Spring 2011, which should allow a final decision to be made regarding the optimal assay at the EHA meeting in June 2011. It is anticipated that this assay will be of value for routine diagnostics, given that a 1-2% level of the mutant allele may be clinically relevant in the diagnosis of myeloproliferative neoplasms, as well as for accurately measuring treatment response, including tracking of disease following allogeneic transplant.

12.14c Validation of "leukemia-specific" targets by determination of expression levels in normal peripheral blood, bone marrow and regenerating bone marrow

The development of novel RQ-PCR assays requires confirmation that they are RNA-specific and determination of background levels of amplification due to non-leukemic cells. RNA-specificity was previously confirmed in novel assays designed to amplify *FIP1L1-PDGFRA* fusion transcripts in chronic eosinophilic leukemia (Jovanovic *et al*, *Blood* 2007). In AML we have shown that levels of background amplification in *NPM1* mutation assays due to the wild type allele are too low to compromise assay sensitivity.

Since *WT1* is expressed in normal hematopoietic progenitors and is therefore not a leukemia-specific target we have previously undertaken extensive analyses using centrally distributed ELN *WT1* kits to establish reference ranges for levels of expression of *WT1* transcripts in normal blood (n=118, median 0.01 *WT1* copies/10^4 *ABL* copies, 0.01-47.6), marrow (n=61, median 19.8, 0-213), and peripheral blood stem cells (n=25, median 6.1, 0-39) (Figure 6, left panel). Sequential analysis of PB and BM samples from 15 AML cases with low *WT1* expression (<250 copies) showed no significant modulation in transcript level on regeneration after chemotherapy (Figure 6, right panel), indicating that in *WT1*+ AML, transcript levels detected in follow-up samples reliably reflect disease status.

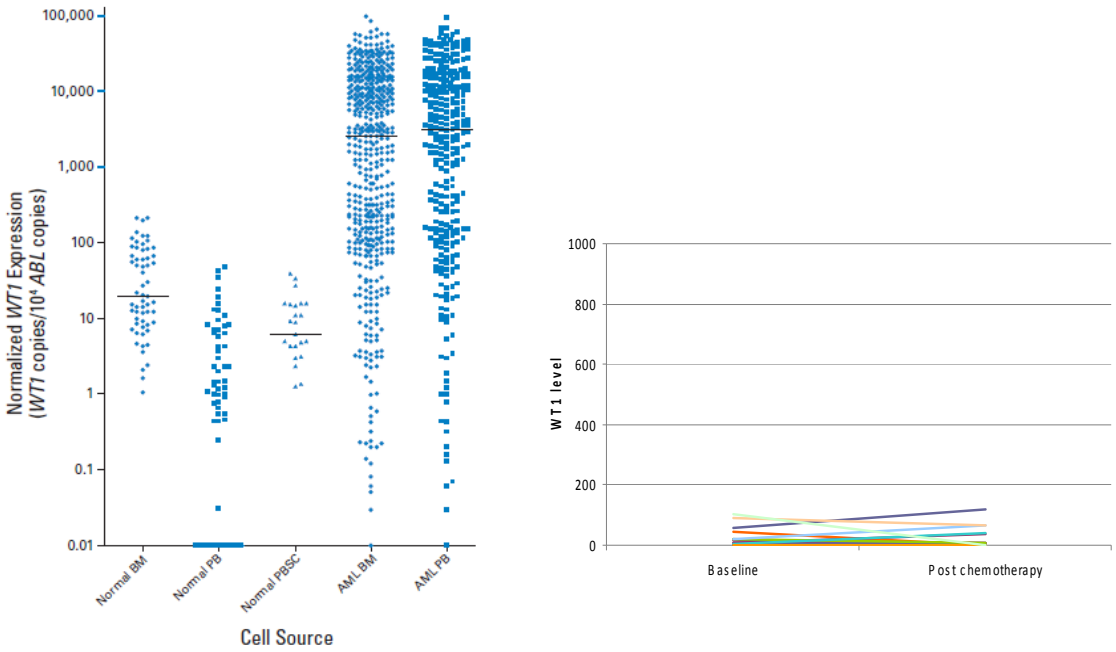


Figure 12.6: Evaluation of standardized ELN *WT1* assay for MRD detection in AML
Left panel: Relative expression of *WT1* (*WT1* copies/10^4 *ABL* copies) in pre-treatment PB and BM samples from AML patients relative to control PB, BM and peripheral blood stem cell (PBSC) samples derived from normal volunteers. Median values denoted by a horizontal bar
Right panel: Comparison of WT1 transcripts between diagnosis and follow-up samples taken on regeneration following intensive chemotherapy in patients lacking over-expression of WT1 in leukemic blasts. These data provide evidence that WT1 expression is not modulated on regeneration following chemotherapy, supporting its use as a valid MRD target.

12.15d Evaluation of validated RQ-PCR assays in national clinical trials

Prospective detection of *PML-RARA* transcripts to direct treatment of acute promyelocytic leukemia patients:

A key premise is that molecular detection of MRD using RQ-PCR can reliably predict relapse, thereby allowing early treatment intervention which could potentially avert full-blown relapse and improve overall chances of cure. There was preliminary evidence from the GIMEMA and PETHEMA groups to support this notion in acute promyelocytic leukemia (APL), although this had not been evaluated prospectively in multi-center clinical trials using RQ-PCR. In a project led by David Grimwade, this was addressed in collaboration with Alan Burnett and Francesco Lo Coco in WP5 (AML) in the UK Medical Research Council (MRC) AML15 trial. First-line treatment involved ATRA and anthracycline-based chemotherapy, with RQ-PCR used to identify patients with persistent disease or molecular relapse to direct pre-emptive therapy with arsenic trioxide prior to transplantation, with type of transplant (autologous vs allogeneic) being dependent upon molecular response as well as donor availability. Over 6,000 samples were prospectively analyzed by RQ-PCR from 303 patients, including over 2,000 paired BM and PB samples. The majority of samples were analyzed by Jelena Jovanovic, who was jointly supported by ELN WP12 and charitable funding (Leukaemia & Lymphoma Research). MRD monitoring according to the recommended schedule (3 monthly BM examination – based upon the data acquired concerning maximal assay sensitivity and kinetics of disease relapse) successfully identified the majority of patients subject to relapse and provided the most powerful predictor of relapse free survival (RFS) in multivariable analysis (HR 17.87, 95% CI 6.88-46.41, $p<0.0001$), far superior to presenting WBC (HR 1.02, CI 1.00-1.03, $p=0.02$) which is currently widely used to guide therapy. In patients who were predicted to experience relapse on the basis of MRD monitoring, early treatment intervention with arsenic trioxide prevented progression to overt relapse in the majority, associated with 73% relapse free survival at 1 year (Grimwade *et al*, *J Clin Oncol* 2009).

Applying the strategy of sequential MRD monitoring to direct pre-emptive therapy within AML15 was associated with a cumulative incidence of clinical relapse (CIR) of only 5% at 3 years. This was lower than the 12% rate of CIR ($p=0.02$) observed in the previous MRC AML12 trial involving patients treated with combination MRC chemotherapy with extended ATRA, but in which MRD monitoring was not performed (Figure 7). While it is recognized that AML12 represents a historical control group, treatment was less intensive in half the patients in AML15 who were randomized to receive the PETHEMA schedule. The lower relapse rate in AML15 could not be accounted for by differences in the distribution of Sanz risk groups, the rate or relative timing of relapses between MRC and PETHEMA treatment schedules.

Based on comparison of survival of patients treated with MRC chemotherapy in the successive trials, with RQ-PCR assays costing an average of $5,370 per patient and assuming a life expectancy of 25 years for patients successfully salvaged, MRD monitoring was found to be most cost-effective in high risk patients (WBC >10) with a 10% survival benefit at 5 years giving $2,415/quality adjusted life year (QALY) compared to those with WBC<10 (1% survival benefit at 5 years giving $25,600/QALY). This prospective multi-center study has been very helpful in establishing the most appropriate MRD monitoring schedules in APL, that have been taken into account in the British Committee for Standards in Haematology (BCSH) AML guidelines (Milligan *et al*, *Br J. Haematol* 2006) and International APL guidelines developed by an expert working group convened by ELN and led by Prof Miguel Sanz on behalf of WP5 (Sanz *et al*, *Blood*, 2009). The role of MRD monitoring in the management of APL has recently been reviewed (Grimwade & Tallman, *Leuk Res* 2011).

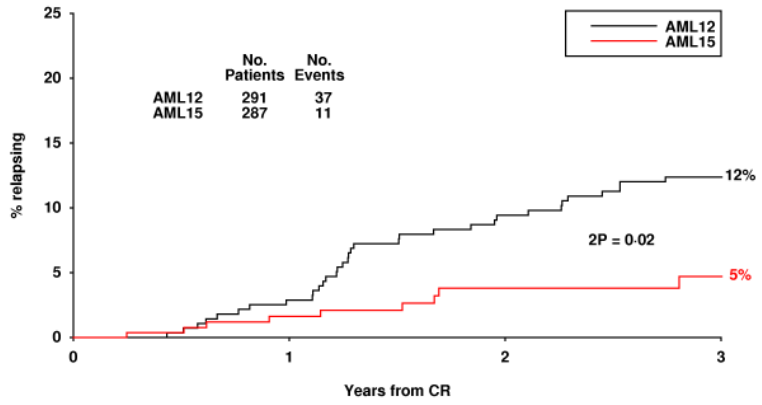


Figure 12.7: Evaluation of minimal residual disease (MRD) monitoring and pre-emptive therapy to reduce rates of frank relapse in *PML-RARA*+ acute promyelocytic leukemia (APL) in the Medical Research Council Acute Myeloid Leukaemia 15 (MRC AML15) trial.
Cumulative incidence of clinical relapse was compared between patients with APL treated with extended all-*trans*retinoic acid (ATRA) and anthracycline-based chemotherapy in the MRC AML12 trial, in which MRD monitoring and pre-emptive therapy were not routinely undertaken, and the MRC AML15 trial, in which this was performed. The ADE/ADE/MACE/MiDAC schedule from AML12 was given to half the patients in MRC AML15, and the remaining patients were randomized to receive the less intensive PETHEMA schedule involving ATRA and anthracycline mono-chemotherapy. A significant reduction in relapse rate was observed in AML15, which was apparent across risk groups defined by presenting white blood count (WBC) (10 *v* 10 x 10^9/L) or Sanz risk group.

Analysis of RQ-PCR profiles in APL has served to highlight important principles that enable the development of optimized schedules for MRD detection, suitable for guiding therapy according to the needs of the individual patient. This is becoming increasingly relevant with interest in investigation of de-intensified treatment protocols for APL, placing greater reliance on MRD monitoring to identify patients who need additional therapy to secure cure of their disease. RQ-PCR using the standardized assay is being used prospectively to guide the management of APL patients in a number of multi-

center European studies being conducted by the GIMEMA, DSIL, AMLSG and UK NCRI groups evaluating the use of chemotherapy-free schedules comprised solely of molecular-targeted therapies (i.e. arsenic + ATRA) as compared to conventional ATRA+anthracycline-based therapy. The results of the MRC AML15 trial have also helped inform the International Pediatric APL trial (ICC-APL01) in which treatment reduction is being investigated in low-risk disease and which uses MRD monitoring to guide treatment approach.

12.23 Development and enhancement of computerized RQ-PCR reporting systems:

This project has been led by Peter Hokland (Aarhus) in collaboration with a Danish software house – Langtved Data, with the aim of developing a program to report RQ-PCR results from any platform in a standardized manner (see Figure 8), since this could have a major benefit in management of patients. A beta version of the program was generated in Spring 2005. Further modifications to the program were made following a users' group meeting and intermittent system review.

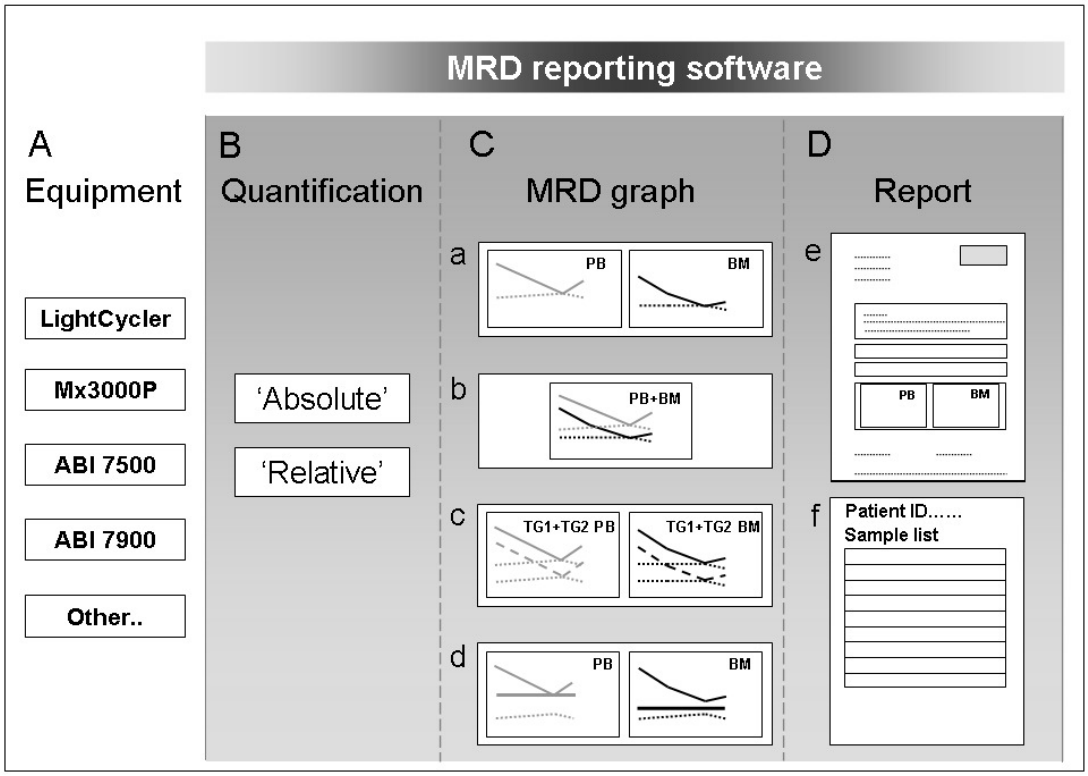


Figure 12.8: MRD reporting program software overview
A) The software accommodates raw data from a broad range of qPCR hardware (carousel/plate/microplate principle). B) Two standard modes of MRD calculation, 'absolute' and 'relative' quantification, as well as two different ways of assessing assay sensitivity can be employed – based on control gene copy number or ΔCt as reported (Grimwade *et al*, *J Clin Oncol* 2009). C) A number of different MRD graphs (solid lines) and sensitivity graphs (hatched lines) can be produced, e.g. a) peripheral blood (PB) and bone marrow (BM) in either separate or b) combined graphs, c) with up to three different target genes (TG) in one graph, and d) inclusion of a fixed threshold line (in bold), e.g. for illustration of the normal expression level for *WT1* assessments. Graph colors and styles are editable. D) A premade report template allows for fast and easy completion and printing of e) a PDF report to the referring department, or f) a list of all results from a given patient (exportable to Excel).

The software program was installed in September 2006 for evaluation in two laboratories in London (Guy's Hospital and King's College Hospital) using ABI platforms (ABI7700/7900) and in the Munich Leukemia Laboratory which employs Lightcycler technology. Installation was successful; however, a number of minor operational issues were identified regarding the display of sensitivity values for follow-up samples, selection of a reference standard and export of data from the Lightcycler platform. These prompted further modifications to the program and an installation guide and "User manual" were prepared by Mette Østergaard and Charlotte Guldborg Nyvold.

The reporting program has been installed and tested in 8 WP12 laboratories (Aarhus, Copenhagen, Frankfurt, Istanbul, London [King's College & Guy's Hospital], Turku & Vejle). The capacity of the program to allow reporting of MRD data in a standardized fashion irrespective of RQ-PCR platform was evaluated through a QC exercise that was coordinated by Charlotte Nyvold (Aarhus). This involved centralized distribution of leukemic cDNA samples (provided by Aarhus), RQ-PCR primers/probes and plasmid standards (provided by Ipsogen, Marseille) to the 8 laboratories (3 labs with some experience of the MRD reporting program, 5 labs in which the program had just been installed and were testing it for the first time).

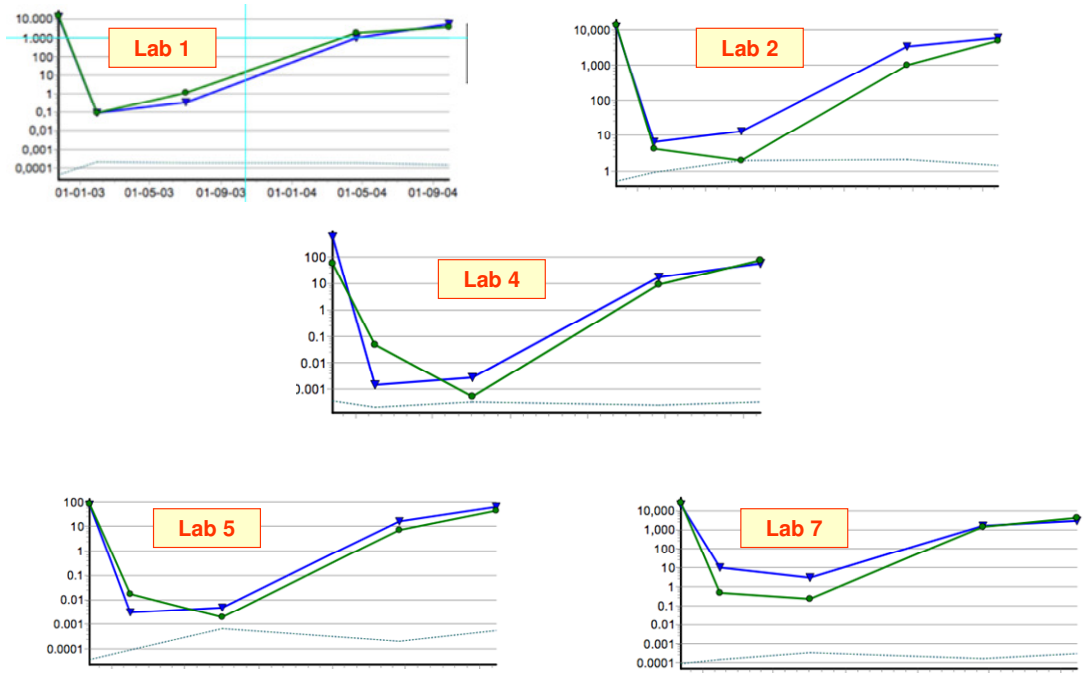


Figure 12.9: Generation of standardized MRD reports using ELN Reporting Program
Complementary DNAs derived from diagnostic and follow-up samples from (inv)16 related AML were dispatched to laboratories participating in the QC exercise, analyzed using centrally distributed assay reagents (*CBFB-MYH11*, *WT1*, *ABL*) and reported in a standardized fashion using the ELN MRD reporting program. Good concordance was observed between normalized MRD results obtained using the Europe Against Cancer *CBFB-MYH11* (green line – labs 2, 4 & 5; blue line – labs 1 & 7) and ELN *WT1* (blue line – labs 2, 4 & 5; green line – labs 1 & 7) assays. Good concordance was also observed in the reports generated with the program, although differences in the scale of the y-axis reflect normalization to 100 or 10^4 *ABL* copies.

Serial samples were provided from a CML patient (5 consecutive samples + cDNA from the K562 cell line as a reference) and also from an AML patient (5 consecutive samples), to be monitored by *CBFB-MYH11* and *WT1* assays in parallel (using the standardized EAC and ELN assays, respectively). Data were normalized to the *ABL* control gene. Between the participating laboratories, 4 platforms were used (ABI 7500/7900, Mx3000 & Lightcycler 480). Relative quantification based on ΔΔCt (compared to the diagnostic sample and K562 for the CML sample) and absolute quantification (comparison to plasmid standards) methods for RQ-PCR data reporting were evaluated. For the *BCR-ABL* samples, remarkable intra- and inter-laboratory concordance was observed in the results irrespective of whether data were reported relative to the diagnostic sample, to the K562 cell line, or whether absolute quantification based on plasmid standards was used. A high degree of concordance was also observed between laboratories in the reporting of *WT1* and *CBFB-MYH11* data, when using diagnostic levels as reference or absolute quantification (Figure 9). Moreover, very close concordance was observed between the *WT1* and *CBFB-MYH11* MRD profiles in each laboratory; although, there were some discrepancies where particular labs had adopted different cut-off thresholds to define samples as PCR positive (e.g Ct <41 and Ct <45) or had normalized target gene expression to different numbers of *ABL* copies (e.g. per 100 or per 10e4 copies).

The QC exercise usefully revealed some minor teething problems in the installation and use of the program; these included difficulties in uploading data to the program, generating certain report types and failure of some labs to use recommended settings. These issues were easily rectified following advice provided by Aarhus or Langtved Data. The QC exercise clearly highlighted the potential of the program to facilitate greater standardization in reporting of MRD data between laboratories and the revised program is now used routinely for reporting of all MRD results by the APL reference laboratory at Guy's Hospital, London, including all samples from the UK NCRI AML17 trial.

In the current reporting year a further QC study was conducted involving 5 laboratories with established *BCR-ABL* conversion factors, required to analyze a series of CML samples, and report MRD data using the program according to the International Scale. This was confirmed to lead to greater concordance in the MRD results, suggesting that the reporting program could be a useful tool in achieving greater standardization in the reporting of RQ-PCR data between laboratories (Østergaard & Nyvold *et al*, *Leukemia* 2011, in press). It is anticipated that the MRD reporting program, which is available free of charge to all ELN members, will be disseminated even more widely. Measures are being put in place for Langtved Data to provide a user help desk to support the program, covered by a service charge (~€2,200 per annum). The legal agreement regarding the future of the program, service agreement, escrow and intellectual property issues has been drawn up between Langtved Data and the ELN Management Center.

12.21c Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines

WP12 members have contributed to practice guidelines and recommendations on the use of MRD monitoring by RQ-PCR approaches to guide therapy in patients with CML, APL and AML (Hughes *et al*, *Blood* 2006; Baccarani *et al*, *Blood* 2006; Milligan *et al*, *Br J Haematol* 2006; Sanz *et al*, *Blood* 2009; Döhner *et al*, *Blood* 2010; Foroni *et al*, *Br J Haematol* 2011).

12.22c Analysis of gender specific issues

A major source of interest to the group is the male preponderance of *FIP1L1-PDGFRA* associated leukemia. Andreas Reiter is leading the project to define the genomic anatomy of the chromosomal rearrangement underlying this condition which may provide some insights into the sex bias associated with this disease and which could be pertinent to the pathogenesis of other subsets of leukemia. Recently, his group analyzed *FIP1L1-PDGFRA* junction sequences from 113 patients at the mRNA (n=113) and genomic DNA (n=85) levels (Walz *et al*, *Leukemia* 2009). Transcript types could be assigned in 109 patients as type A (n=50, 46%) and type B (n=47, 43%), which were created by cryptic acceptor splice sites in different introns of *FIP1L1* (type A) or within *PDGFRA* exon 12 (type B). A new transcript type was identified – type C (n=12, 11%) in which both genomic breakpoints fell within coding sequences creating a hybrid exon without use of a cryptic acceptor splice site. The location of genomic breakpoints within *PDGFRA* and the availability of AG splice sites determine the transcript type and restrict the *FIP1L1* exons used for the creation of the fusion. Stretches of overlapping sequences were identified at the genomic junction site, suggesting that the *FIP1L1-PDGFRA* fusion is created by illegitimate non-homologous end-joining. Statistical analyses provided evidence for clustering of breakpoints within *FIP1L1* that may be related to DNA- or chromatin-related structural features. The variability in the anatomy of the *FIP1L1-PDGFRA* fusion has important implications for strategies to detect the fusion at diagnosis or for monitoring response to treatment.

In a related study, current detection methods for *FIP1L1-PDGFRA* were evaluated by developing a means to rapidly amplify genomic breakpoints (Score *et al*, *Leukemia* 2009). Two hundred and two cases were screened and genomic junctions detected in all samples previously identified as RT-PCR positive (n=43). Genomic fusions were amplified by single step PCR in all cases, whereas only 22 (51%) were single step RT-PCR positive. Importantly, *FIP1L1-PDGFRA* was detected in two cases that initially tested negative by RT-PCR or fluorescence in situ hybridization. Absolute quantification of the fusion by real-time PCR from genomic DNA (gDNA) using patient-specific primer/probe combinations at presentation (n=13) revealed a 40-fold variation between patients (range, 0.027-1.1 *FIP1L1-PDGFRA* copies/haploid genome). In follow up samples, quantitative analysis of gDNA gave 1-2 log greater sensitivity than RQ-PCR of cDNA. Minimal residual disease assessment using gDNA showed that 11 of 13 patients achieved complete molecular response to imatinib within a median of 9

months (range, 3-17) of starting treatment, with a sensitivity of detection of up to 1 in 10^5. One case relapsed with an acquired D842V mutation. Detection of *FIP1L1-PDGFRA* from gDNA is thus a useful adjunct to standard diagnostic procedures and enables more sensitive follow up of positive cases after treatment.

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved.

Not applicable

Table 12.3: List of deliverables WP12, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP12	**MRD**					
12.5	Regular WP meetings	73,78,85	done	15	15	Grimwade, Hochhaus, Reiter
12.6	LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)		done	5	3	Grimwade
12.11d	Establish the additional proportion of leukemic patients that can be monitored using novel targets	66	done	8	8	Grimwade Saglio Preudhomme
12.15d	Evaluation of validated RQ-PCR assays in national clinical trials	78	done	15	10	Grimwade
12.21c	Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	78	ongoing	4	1	Grimwade
12.22c	Analysis of gender specific issues	66	done	2	2	Reiter
12.23	Installation and implementation of Q-PCR reporting program within ELN member laboratories	66	done	4	4	Grimwade Hokland
12.24	Evaluation of MRD monitoring to predict relapse and direct donor leucocyte administration following allogeneic transplant	78	ongoing	8	2	Grimwade
12.25	Conduct of QC exercises for mutation targets	66	done	2	2	Grimwade
12.26	Compare sensitivity and specificity of published JAK2 V617F Q-PCR assays to establish best-performing assay	72	ongoing	6	3	Grimwade
12.27	Compare performance of reference gene assays for JAK2 V617F quantification	72	done	2	2	Grimwade
12.28	Develop plasmid standards for JAK2 V617F and selected reference gene assay	72	done	2	2	Hermitte
12.29	Comparison of RNA- and DNA-based Q-PCR assays for NPM1 mutations	72	done	2	1	Grimwade

*) if available

Table 12.4: List of milestones WP12, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP12	**MRD**			
12.13c	Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)	66	66	Grimwade Hochhaus Cross Hokland
12.15d	Establish prognostic significance of validated Q-PCR assays in national clinical trials	66	66	Grimwade Saglio
12.23	Service implementation of ELN MRD reporting program	66	66	Grimwade
12.26-8	Establish optimal assay for quantification of JAK2 V617F mutant allele load	72	91	Grimwade

Section 3: Consortium management

Not applicable

Section 4: Other Issues

Ethical issues - none

Competitive calls- none

Section 5: WP-Performance

Performance indicators	Status
Organization of interdisciplinary consensus conferences	Done
Development of consensus protocols for the diagnostic work up to identify MRD targets in leukemia	Ongoing
Organization of quality control rounds	Ongoing
Set up of internet forum	In progress
Number and quality of publications within the network	16 published papers 7 abstracts
Number of researchers in exchange programs	0
Implementation of technology transfer	In progress
RQ-PCR assays for rare fusion gene transcripts, leukemia associated mutations and for novel overexpressed genes	4
Evaluation of validated RQ-PCR assays in national clinical trials	In progress
Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)	Done
Development of optimized sensitive validated assays for MRD detection	Done

13 Gene profiling and Next Generation Sequencing (NGS) (WP13)

Objectives and work within reporting period

WP13 is an established and still growing working group of MDs and PhDs who were first interested in using gene expression profiling both for investigating basic research topics and the application of microarrays in a clinical setting. Since 2010 next generation sequencing is of high interest for the same members and mainly takes over the focus of WP13. Both tasks are strongly supported by biostatisticians. Microarray data as well as NGS data very recently were collected within the ELN network and involved respective subgroups in WP13 as well as other WPs in close collaborations.

The DACH and the MILE studies are published and data is public available in GEO.

In parallel, all biostatistical platforms have been upgraded in 2010 and expanded to NHS data sets: GAP is freely available for all ELN members, and not restricted to the MILE subgroups. In the ELN GAP database, data can easily be stored, exchanged and analyzed within the participating WPs (see below and a new data base was placed on the same homepage together with WP13 and COST members (see below).

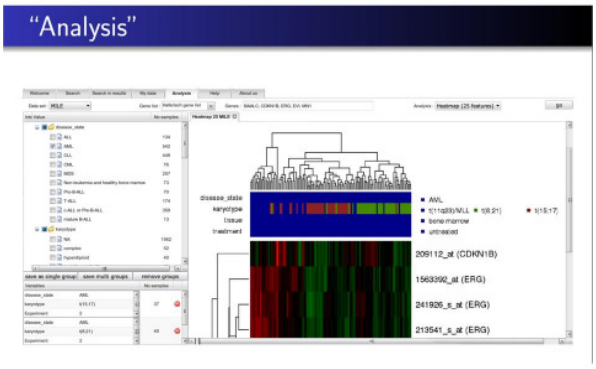
Many publications were published in 2010 using parts of the MILE data set anf form the MDS paper (K. Mills, Blood 2009) and more are upcoming and started to be performed in WP13 (see below).

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

13.1e Expand of WP information and communication structures

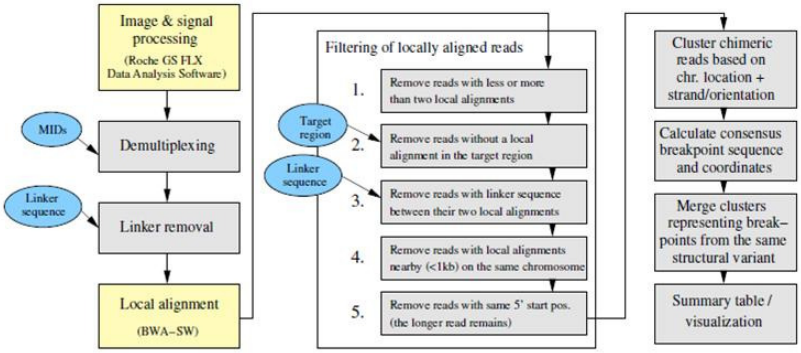
The GAP database in Münster was further improved and includes now much more multiple statistical packages for analysis of gene expression microarray data (for details see http://imiblinux05.uni-muenster.de/). This is all only possible due to the strong support of this outstanding statistic group (Head Prof. Dugas) within and through the WP13. Furthermore the new Leukemia Atlas was posted in 2/2011 and is sponsored in part by the ELN. Also several highly ranked biostatistical papers were published together:

http://www.leukemia-gene-atlas.org/



Toolbox for 454 data: use cases

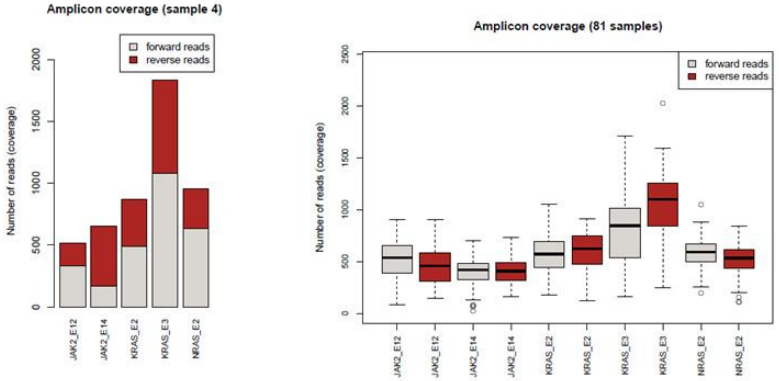
- Detection of fusion genes by targeted NGS



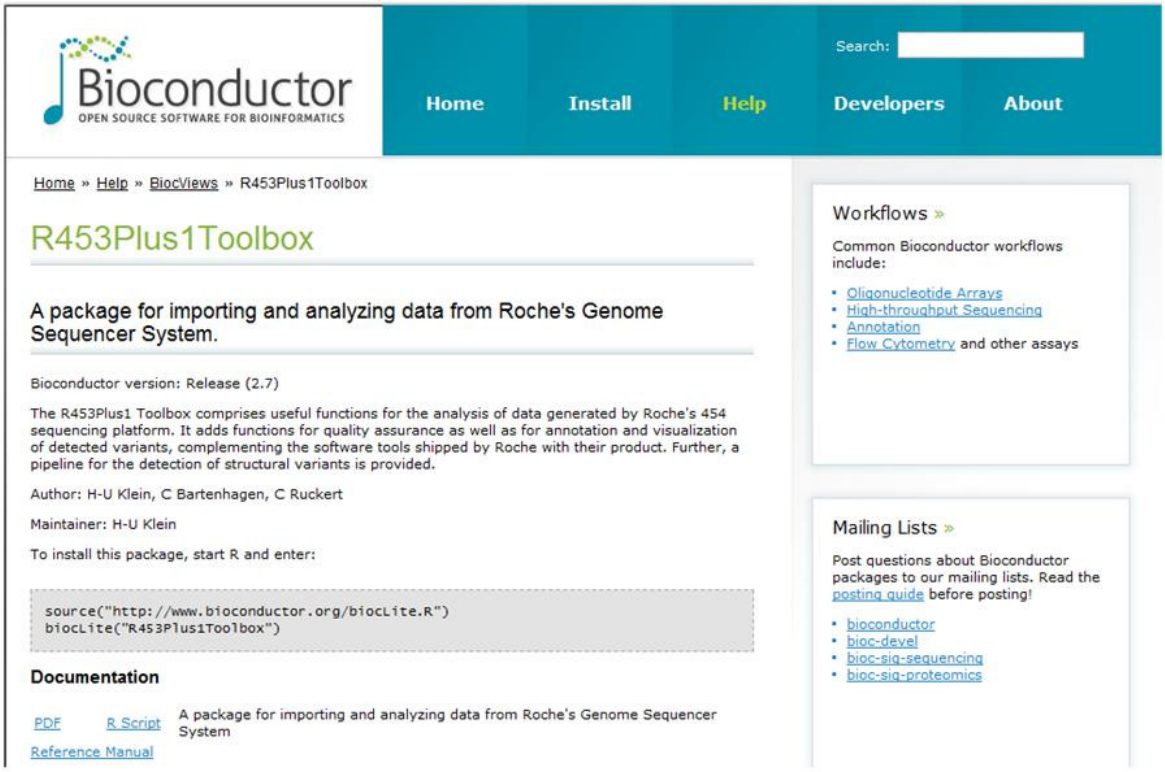
[Grossmann et al., Leukemia. 2011 Jan;]

Toolbox for 454 data: use cases

- Amplicon sequencing:
  Monitor amplicon coverage and
  Annotate/Filter detected variants



[Kohlmann et al., J Clin Oncol. 2010 Aug; 28(24)]

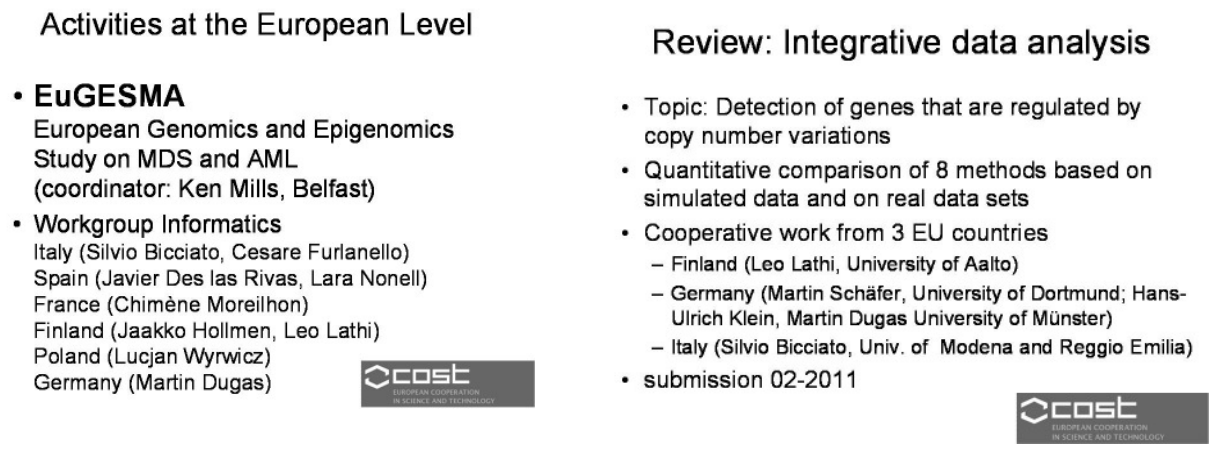


http://www.bioconductor.org/help/bioc-views/release/bioc/html/R453Plus1Toolbox.html

13.4f Optimize European gene profiling platform

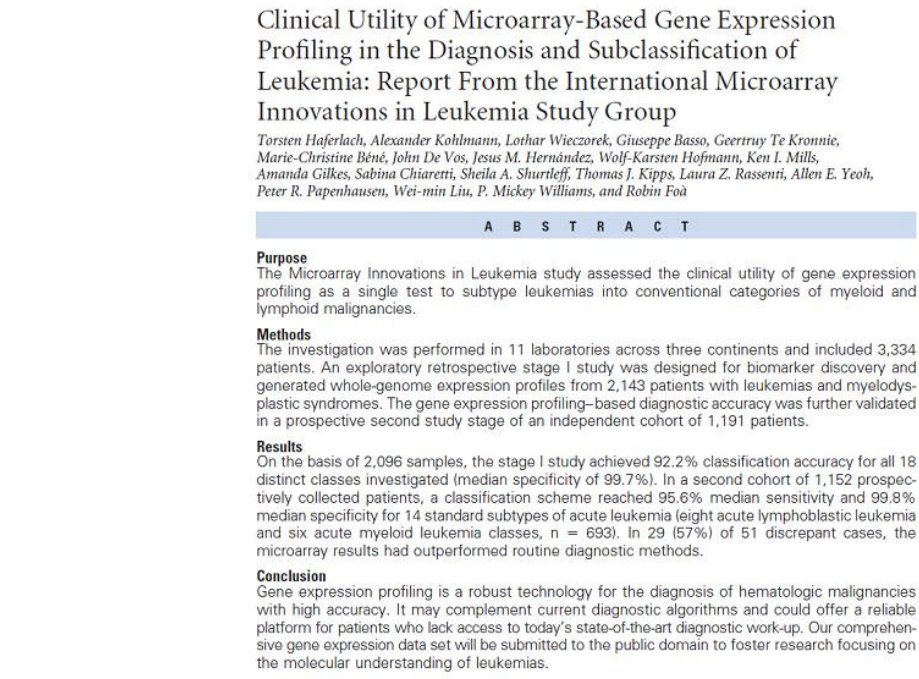
See D13.1d

Due to strong efforts from members of WP13 (**Mills**, Dugas, Haferlach) the EU funded a new project bridging ELN WP13 and other future activities and leading to shared meetings, data and personnel and lab exchanges (see below):



The most important paper published by WP13 was:

MILE Study



Clinical Utility of Microarray-Based Gene Expression Profiling in the Diagnosis and Subclassification of Leukemia: Report From the International Microarray Innovations in Leukemia Study Group

Torsten Haferlach, Alexander Kohlmann, Lothar Wieczorek, Giuseppe Basso, Geertruy Te Kronnie, Marie-Christine Béné, John De Vos, Jesus M. Hernández, Wolf-Karsten Hofmann, Ken I. Mills, Amanda Gilkes, Sabina Chiaretti, Sheila A. Shurtleff, Thomas J. Kipps, Laura Z. Rassenti, Allen E. Yeoh, Peter R. Papenhausen, Wei-min Liu, P. Mickey Williams, and Robin Foà

A B S T R A C T

Purpose
The Microarray Innovations in Leukemia study assessed the clinical utility of gene expression profiling as a single test to subtype leukemias into conventional categories of myeloid and lymphoid malignancies.

Methods
The investigation was performed in 11 laboratories across three continents and included 3,334 patients. An exploratory retrospective stage I study was designed for biomarker discovery and generated whole-genome expression profiles from 2,143 patients with leukemias and myelodysplastic syndromes. The gene expression profiling–based diagnostic accuracy was further validated in a prospective second study stage of an independent cohort of 1,191 patients.

Results
On the basis of 2,096 samples, the stage I study achieved 92.2% classification accuracy for all 18 distinct classes investigated (median specificity of 99.7%). In a second cohort of 1,152 prospectively collected patients, a classification scheme reached 95.6% median sensitivity and 99.8% median specificity for 14 standard subtypes of acute leukemia (eight acute lymphoblastic leukemia and six acute myeloid leukemia classes, n = 693). In 29 (57%) of 51 discrepant cases, the microarray results had outperformed routine diagnostic methods.

Conclusion
Gene expression profiling is a robust technology for the diagnosis of hematologic malignancies with high accuracy. It may complement current diagnostic algorithms and could offer a reliable platform for patients who lack access to today's state-of-the-art diagnostic work-up. Our comprehensive gene expression data set will be submitted to the public domain to foster research focusing on the molecular understanding of leukemias.

Haferlach T et al., J Clin Oncol. 2010;28:2529-37

Further WP13 publications included:

WP13 Publications

Gene expression-based classification as an independent predictor of clinical outcome in juvenile myelomonocytic leukemia.
Bresolin S, Zecca M, Flotho C, Trentin L, Zangrando A, Sainati L, Stary J, de Moerloose B, Hasle H, Niemeyer CM, Te Kronnie G, Locatelli F, Basso G.
J Clin Oncol. 2010 Apr 10;28(11):1919-27.

Clinical utility of microarray-based gene expression profiling in the diagnosis and subclassification of leukemia: report from the International Microarray Innovations in Leukemia Study Group.
Haferlach T, Kohlmann A, Wieczorek L, Basso G, Kronnie GT, Béné MC, De Vos J, Hernández JM, Hofmann WK, Mills KI, Gilkes A, Chiaretti S, Shurtleff SA, Kipps TJ, Rassenti LZ, Yeoh AE, Papenhausen PR, Liu WM, Williams PM, Foà R.
J Clin Oncol. 2010 May 20;28(15):2529-37.

Gene expression profiling in AML with normal karyotype can predict mutations for molecular markers and allows novel insights into perturbed biological pathways.
Kohlmann A, Bullinger L, Thiede C, Schaich M, Schnittger S, Döhner K, Dugas M, Klein HU, Döhner H, Ehninger G, Haferlach T.
Leukemia. 2010 Jun;24(6):1216-20.

WP13 Publications

Gene expression profiling identifies a subset of adult T-cell acute lymphoblastic leukemia with myeloid-like gene features and over-expression of miR-223.
Chiaretti S, Messina M, Tavolaro S, Zardo G, Elia L, Vitale A, Fatica A, Gorello P, Piciocchi A, Scappucci G, Bozzoni I, Fozza C, Candoni A, Guarini A, Foà R.
Haematologica. 2010 Jul;95(7):1114-21. Epub 2010 Apr 23.

Molecular Genetics of Adult Acute Myeloid Leukemia: Prognostic and Therapeutic Implications.
Marcucci G, Haferlach T, Döhner H.
J Clin Oncol. 2011 Jan 10., e-pub

A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases.
Grossmann V, Kohlmann A, Zenger M, Schindela S, Eder C, Weissmann S, Schnittger S, Kern W, Müller MC, Hochhaus A, Haferlach T, Haferlach C.
Leukemia. 2011 Jan 28. e-pub

A very recent paper form ELN WP13 and COST was published 3/2011:

Leukemia (2011), 1–12

www.nature.com/leu

REVIEW

Gene expression profiling in MDS and AML: potential and future avenues

K Theilgaard-Mönch[1,2], J Boultwood[3], S Ferrari[4], K Giannopoulos[5], JM Hernandez-Rivas[6], A Kohlmann[7], M Morgan[8], B Porse[1], E Tagliafico[4], CM Zwaan[9], J Wainscoat[3], MM Van den Heuvel-Eibrink[9], K Mills[10,12] and L Bullinger[11,12]

[1]Biotech Research and Innovation Centre & Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Department of Hematology, Lund University Hospital, Lund University, Lund, Sweden; [3]LRF Molecular Haematology Unit, Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, University of Oxford, Oxford, UK; [4]Department of Biomedical Sciences University of Modena and Reggio Emilia, Modena, Italy; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Servicio de Hematologia, Hospital Universitario de Salamanca and IBMCC, Centro de Investigacion del Cancer, Universidad de Salamanca-CSIC, Salamanca, Spain; [7]MLL Munich Leukemia Laboratory, Munich; Department of Microarrays and Next-Generation Sequencing, Munich, Germany; [8]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [9]Erasmus MC—Sophia Children's Hospital, Erasmus University, Rotterdam, The Netherlands; [10]Center for Cancer Research & Cell Biology, Queen's University Belfast, Belfast, Northern Ireland and [11]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany

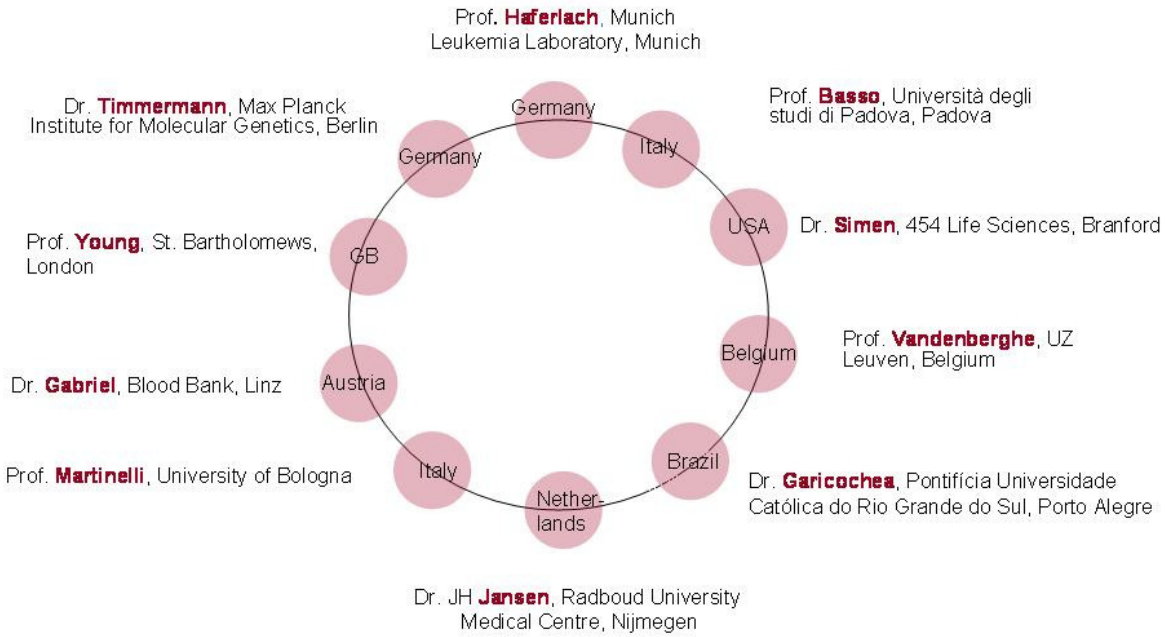
The WP13 then started to focus on NGS and established a 454 hematology focus group that first met in May 2010 in Munich. From this group a first proof-of principle study was initiated, performed and presented as a poster at the ASH 2010; the manuscript was submitted for publication on 3/26/2011.

454 Hematology Focus Group

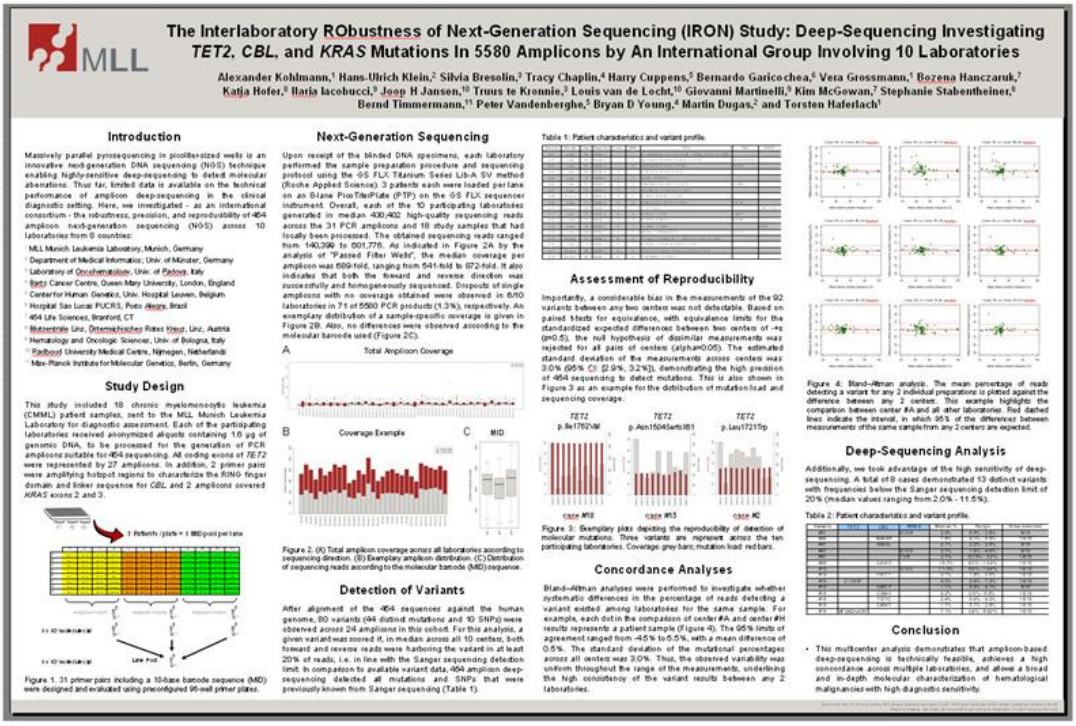
Meeting from Monday 10th May - Tuesday 11th May 2010, Munich

- 50 participants from 12 countries, 3 continents
- Topic: Next-generation sequencing applications
- **Results:** Interlaboratory Robustness Of NGS (IRON) study

IRON Study: Participants and Laboratories



IRON Study: Poster Presentation ASH 2010



The Interlaboratory RObustness of Next-Generation Sequencing (IRON) Study: Deep-Sequencing Investigating *TET2*, *CBL*, and *KRAS* Mutations In 5580 Amplicons by An International Group Involving 10 Laboratories

Alexander Kohlmann,[1] Hans-Ulrich Klein,[2] Silvia Bresolin,[3] Tracy Chaplin,[4] Harry Cuppens,[5] Bernardo Garicochea,[6] Vera Grossmann,[1] Bozena Hanczaruk,[7] Katja Hofer,[8] Ilaria Iacobucci,[9] Joop H Jansen,[10] Truus te Kronnie,[3] Louis van de Locht,[10] Giovanni Martinelli,[9] Kim McGowan,[7] Stephanie Stabentheiner,[8] Bernd Timmermann,[11] Peter Vandenberghe,[5] Bryan D Young,[4] Martin Dugas,[2] and Torsten Haferlach[1]

Introduction

Massively parallel pyrosequencing in picoliter-sized wells is an innovative next-generation DNA sequencing (NGS) technique enabling highly-sensitive deep-sequencing to detect molecular aberrations. Thus far, limited data is available on the technical performance of amplicon deep-sequencing in the clinical diagnostic setting. Here, we investigated - as an international consortium - the robustness, precision, and reproducibility of 454 amplicon next-generation sequencing (NGS) across 10 laboratories from 8 countries:

- MLL Munich Leukemia Laboratory, Munich, Germany
- Department of Medical Informatics, Univ. of Münster, Germany
- Laboratory of Oncohematology, Univ. of Padova, Italy
- Barts Cancer Centre, Queen Mary University, London, England
- Center for Human Genetics, Univ. Hospital Leuven, Belgium
- Hospital São Lucas PUCRS, Porto Alegre, Brazil
- 454 Life Sciences, Branford, CT
- Blutzentrale Linz, Österreichisches Rotes Kreuz, Linz, Austria
- Hematology and Oncologic Sciences, Univ. of Bologna, Italy
- Radboud University Medical Centre, Nijmegen, Netherlands
- Max-Planck Institute for Molecular Genetics, Berlin, Germany

Study Design

This study included 18 chronic myelomonocytic leukemia (CMML) patient samples, sent to the MLL Munich Leukemia Laboratory for diagnostic assessment. Each of the participating laboratories received anonymized aliquots containing 1.6 µg of genomic DNA, to be processed for the generation of PCR amplicons suitable for 454 sequencing. All coding exons of *TET2* were represented by 27 amplicons. In addition, 2 primer pairs were amplifying hotspot regions to characterize the RING finger domain and linker sequence for *CBL*, and 2 amplicons covered *KRAS* exons 2 and 3.

Next-Generation Sequencing

Upon receipt of the blinded DNA specimens, each laboratory performed the sample preparation procedure and sequencing protocol using the GS FLX Titanium Series Lib-A SV method (Roche Applied Science). 3 patients each were loaded per lane on an 8-lane PicoTiterPlate (PTP) on the GS FLX sequencer instrument. Overall, each of the 10 participating laboratories generated in median 400,402 high-quality sequencing reads across the 31 PCR amplicons and 18 study samples that had locally been processed. The obtained sequencing reads ranged from 140,399 to 601,776. As indicated in Figure 2A by the analysis of "Passed Filter Wells", the median coverage per amplicon was 689-fold, ranging from 541-fold to 872-fold. It also indicates that both the forward and reverse direction was successfully and homogeneously sequenced. Dropouts of single amplicons with no coverage obtained were observed in 6/10 laboratories in 71 of 5580 PCR products (1.3%), respectively. An exemplary distribution of a sample-specific coverage is given in Figure 2B. Also, no differences were observed according to the molecular barcode used (Figure 2C).

Detection of Variants

After alignment of the 454 sequences against the human genome, 80 variants (64 distinct mutations and 10 SNPs) were observed across 24 amplicons in this cohort. For this analysis, a given variant was scored if, in median across all 10 centers, both forward and reverse reads were harboring the variant in at least 20% of reads, i.e. in line with the Sanger sequencing detection limit. In comparison to available variant data, 454 amplicon deep-sequencing detected all mutations and SNPs that were previously known from Sanger sequencing (Table 1).

Assessment of Reproducibility

Importantly, a considerable bias in the measurements of the 92 variants between any two centers was not detectable. Based on paired t-tests for equivalence, with equivalence limits for the standardized expected differences between two centers of +s (p=0.5), the null hypothesis of dissimilar measurements was rejected for all pairs of centers (alpha=0.05). The estimated standard deviation of the measurements across centers was 3.0% (95% CI: [2.9%, 3.2%]), demonstrating the high precision of 454 sequencing to detect mutations. This is also shown in Figure 3 as an example for the distribution of mutation load and sequencing coverage.

Concordance Analyses

Bland–Altman analyses were performed to investigate whether systematic differences in the percentage of reads detecting a variant existed among laboratories for the same sample. For example, each dot in the comparison of center #A and center #H results represents a patient sample (Figure 4). The 95% limits of agreement ranged from -4.5% to 5.5%, with a mean difference of 0.5%. The standard deviation of the mutational percentages across all centers was 3.0%. Thus, the observed variability was uniform throughout the range of the measurements, underlining the high consistency of the variant results between any 2 laboratories.

Deep-Sequencing Analysis

Additionally, we took advantage of the high sensitivity of deep-sequencing. A total of 8 cases demonstrated 13 distinct variants with frequencies below the Sanger sequencing detection limit of 20% (median values ranging from 2.0% - 11.5%).

Conclusion

- This multicenter analysis demonstrates that amplicon-based deep-sequencing is technically feasible, achieves a high concordance across multiple laboratories, and allows a broad and in-depth molecular characterization of hematological malignancies with high diagnostic sensitivity.

To combine all activities and open up new areas of interest the WP13 met with COST and EuGESMA in October 2010 in Munich:

Joint ELN WP13 – EuGESMA Meeting

Meeting from Monday 18th October - Tuesday 19th October 2010, Munich

Chairs: Ken Mills (COST) and **Torsten Haferlach** (ELN, WP13)

- 80 participants
- 21 countries
- ~50% early stage researchers
- 24 presentations
- 5 break-out work groups
- Strengthen networks

cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

Translating Genomic and Epigenetic Studies of MDS and AML (EuGESMA)

ELN European LeukemiaNet

New collaborations initiated: SNP and mutational analyses; epigenetics

This meeting led to the following subgroups and activities since 10/2010 and with increasing output and cooperation in 2011:

Activities 2011+: IRON Study Phase II

List of centers with interest in participation (>20 laboratories; 10 countries):

Dr. Christian Gabriel	Linz	AUSTRIA	
Prof. Peter Vandenberghe	Leuven	BELGIUM	**T-ALL**
Dr. Bernardo Garicochea	Porto Alegre	BRASIL	**AML**
Prof. Claude Preudhomme	Lille	FRANCE	**AML**
Prof. Christian Thiede	Dresden	GERMANY	**AML**
Prof. Brigitte Schlegelberger	Hannover	GERMANY	**AML, MDS, MPN**
Prof. Andreas Hochhaus	Jena	GERMANY	**CML, MPN, MDS**
Prof. Wolf-Karsten Hofmann	Mannheim	GERMANY	**MDS**
Prof. Torsten Haferlach	Munich	GERMANY	**AML, MDS, ALL., MPN, CLL**
Dr. Lars Bullinger	Ulm	GERMANY	**AML, MDS, CLL, Lymphoma**
Dr. Orietta Spinelli	Bergamo	ITALY	**B-ALL, T-ALL, Myelofibrosis, AML**
Prof. Giovanni Martinelli	Bologna	ITALY	**ALL, AML, CML**
Prof. Enrico Tagliafico	Modena	ITALY	**MPN**
Dr. Giovanni Cazzaniga	Monza	ITALY	**childhood AML and ALL, JMML**
Prof. Giuseppe Basso	Padova	ITALY	**ALL**
Prof. Robin Foa	Rome	ITALY	**ALL, CLL**
Prof. Allen Yeoh	Singapore	SINGAPORE	**ALL**
Prof. Jesus M Hernandez	Salamanca	SPAIN	**AML, MDS, ALL, CLL**
Dr. Joop H Jansen	Nijmegen	THE NETHERLANDS	**MDS, MPN**
Prof. Peter Valk	Rotterdam	THE NETHERLANDS	**AML, MDS**
Dr. Jude Fitzgibbon	London	UK	**Lymphoma**

Supported by ROCHE the first tools to be investigated using NGS performed on 454 FLX or Junior instruments are the following:

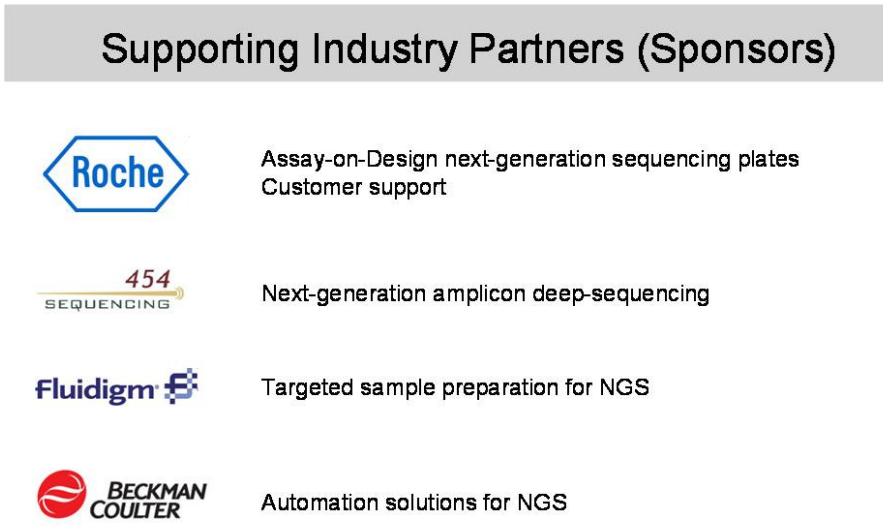
IRON: Assay-on-Demand Plates

96-well plate format with **pre-configured primers** (MID)

- **Design proposal #1:**
  - ✓ *TET2* (complete coding region; 27 amplicons)
  - ✓ *CBL* (Ring + linker domain, exons 8 and 9)
  - ✓ *KRAS* (exons 2 and 3)
  - ➔ 3 patients per plate
- **Design proposal #2:**
  - ✓ *RUNX1* (complete coding region; 7 amplicons)
  - ➔ 12 patients per plate

Roche Applied Science intends to launch these products in second half of 2011

For better maintenance WP13 included an increasing number of industry partners to make all these future activities in NGS and GEP including also SNP arrays possible:



All these new activities will closely cooperate with WP13 in the ELN to spread information in the upcoming years.

13.5 Regular WP meetings

One regular WP meeting for all WP13 members, combined in part with WP11, had been organized in Heidelberg in February 2010. Furthermore, some members of WP13 - mostly representing members also of the European part of the MILE study - met together with WP10, 11 and 12 in Munich in May 2010 and in October 2010 for new activities together with COST and EuGESMA (see above).

13.6 LP reports to NMC regarding structure, activities and integration of national GEP groups

- Ongoing exchange of information regarding GEP and NGS data management and analysis strategies with ELN and COST and EuGESMA partners
- Regular updates to the European biostatistical data analysis platform (GAP) and new Leukemia Atlas in Münster based on input from ELN participants available for all WP13 partners, also making new data sets public (see above)

13.10e Develop new biostatistical approaches and expand the centralized data base

See in detail above.

13.11e Detect further new subgroups of leukemia according to gene expression profiles

As part of a collaboration between Dresden, Munich and Ulm on AML with normal karyotype over 250 cases predefined by NPM1, MLL-PTD, FLT3-ITD, CEPBA and WT1 status were analyzed with

HG-U133 Plus 2.0 microarrays. Data are published in Leukemia in 2010; see in detail 13.1d above. Another manuscript addressing FLT3 signatures is ready to be submitted (L. Bullinger et al.).

13.12e Further evaluation of new genes for therapeutic and diagnostic purposes

Studies by Müller-Tiedow began in 2009 and manuscript will be circulating soon.

13.16d Further evaluation of new biostatistical methods

Has been published or made publically available in 2009 and 2010/11 (see 13.1d) and is still ongoing, now strongly expanding to next-generation sequencing data.

13.18e Find new diagnostic markers and MRD markers with WP10, 11, 12

No further input in 2010.

13.19e Define new entities in AML with WP5 with respect to prognosis in intermediate risk group

Done, paper by Kohlmann et al. Leukemia 2010 and ongoing with same data set (Bullinger et al. manuscript to be submitted soon).

13.21 Use broadly data of WP13 studies and MILE study for all ELN members

See for new tools implemented in 2009 and 2010: (http://imiblinux05.uni-muenster.de/), see above.

13.22 Include SNP data and further projects of WP13 members

See 13.21

13.23 Set up a NGS working group

Done, see above

13.24 Use already available NGS data for new analyses and develop new biostatistic approaches

Ongoing and already published in part, see above.

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

Not applicable.

Table 13.1: List of all Deliverables WP13, 2011

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP13 Gene profiling						
13.1e	Expand of WP information and communication structures	**73-86**	86, ongoing	0	6	Haferlach Dugas
13.4f	Optimize European gene profiling platform	**73-86**	86, ongoing	0	8	Haferlach Dugas
13.5	Regular WP meetings	**80,86**	86, ongoing	0	2	Haferlach
13.6	LP reports to NMC regarding structure, activities and integration of national GEP groups (1 page, bullet point style)	**79,86**	86	0	2	Haferlach
13.10e	Develop new biostatistical approaches and expand the centralized data base	**73-86**	86, ongoing	0	6	Dugas
13.11e	Detect further new subgroups of leukemia according to gene expression profiles	**73-86**	86, ongoing	0	4	Haferlach Dugas
13.12e	Further evaluation of new genes for therapeutic and diagnostic purposes	**73-86**	86, ongoing	0	2	Haferlach
13.16d	Further evaluation of new biostatistical methods	**73-86**	86, ongoing	0	4	Dugas
13.18e	Find new diagnostic markers and MRD markers with WP10, 11, 12	**73-86**	86, ongoing	0	3	Haferlach Grimwade Foa Bene
13.19e	Define new entities in AML with WP5 with respect to prognosis in intermediate risk group	**73-86**	86	0	4	Haferlach Döhner Thiede
13.21	Use broadly data of WP13 studies and MILE study for all ELN members	**73-86**	86	0	4	Haferlach Dugas
13.22	Include SNP data and further projects of WP13 members	**73-86**	86	0	3	Haferlach Dugas
13.23	Set up a NGS working group	**73-86**	86	0	6	Haferlach Kohlmann Dugas
13.24	Use already available NGS data for new analyses and develop new biostatistic approaches	**73-86**	86, ongoing	0	4	Haferlach Kohlmann Dugas

*) if available

List of milestones WP13, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP13	**Gene profiling**			
13.16d	Further evaluation of new biostatistical methods	**73-86**	86, ongoing	Dugas
13.18e	Find new diagnostic markers and MRD markers with WP10, 11, 12	**73-86**	86, ongoing	Haferlach Grimwade Foa Bene
13.19e	Define new entities in AML with WP5 with respect to prognosis in intermediate risk group	**73-86**	86	Haferlach Döhner Thiede
13.21	Use broadly data of WP13 studies and MILE study for all ELN members	**73-86**	86	Haferlach Dugas
13.22	Include SNP data and further projects of WP13 members	**73-86**	86	Haferlach Dugas
13.23	Set up a NGS working group	**73-86**	86	Haferlach Kohlmann Dugas
13.24	Use already available NGS data for new analyses and develop new biostatistic approaches	**73-86**	86, ongoing	Haferlach Kohlmann Dugas

Section 3: Consortium management

Workshop together with WP10 and WP8 and COST and EuGESMA were held in Munich in May and October 2010.

Participants of WP13 further played a major role at important international and national conferences on microarray data and NGS data in leukemia and chaired several sessions or presented their individual data in talks or as posters.

Section 4: Other Issues

Ethical issues - none

Competitive calls – none

Section 5: WP13-Performance

Performance indicators	Status
Establishment of European reference panels	See published papers
Organization of interdisciplinary consensus conferences	See published papers
Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes	See published papers
Organization of quality control rounds	done
Number and quality of publications within the network	See 13.1.d
Implementation of technology transfer	In further progress
Number of difficult cases presented in the expert forum	n.d.
Number of new cooperations between network participants	New cooperations in WP13 and with COST and EuGESMA and 454 hematology focus group

14 Stem cell transplantation (WP14)

Objectives and starting point of work at beginning of reporting period

Many important deliverables were obtained in WP14 during 2010. This was possible through regular working party meetings and continuing the important work started previously with the EBMT/ELN network. As in previous years, the stem cell transplant survey was performed in Europe and World wide, but also the harmonization process between Europe and the US was continued, providing valid information on changes in indications, frequencies among the different countries but also among diseases. In this regard a global survey was continued in 2007/2008.

The main aim consisted in connecting the activities of the different disease-oriented WP of the ELN with the WP hematopoetic cell transplantation (HCT) but also in improving procedure related issues.

In AML the first randomized study comparing transplant vs. non-transplant treatment and involving the major AML study groups has started in January 2010 and 19 patients were already included. The second study on reduced intensity conditioning for patients with related donors in comparison to non-transplant treatment has included now more than 130 patients. Analysis on molecular risk factors and there role for patients with or without SCT were initiated in retrospective analysis. The possibility to use a common arm in Europe raised considerable discussions and has still to be developed in more detail. In MDS the significance of reduced intensity conditioning in comparison to conventional SCT is being studied in the RICMAC study.

In ALL, phase II protocols for older patients using allogeneic HCT after reduced intensity conditioning have been initiated. The results are very encouraging and justify a prospective protocol investigating the role of allogeneic HCT in high risk patients. Especially in high risk patients, an advantage of reduced intensity conditioning regimen seems apparent. More patients are required, however, to set up a randomized study.

In CML analyses on SCT outcome after second generation TKI are very important. In addition, indication for SCT has to be defined considering the improvements and definition of risk factors of the last years. Therefore outcome of patients with low risk Gratwohl score has been analyzed. A prospective study investigating the role of Dasatinib in patients relapsing after SCT has been finalized and the results of Donor Lymphocyte updated.

In T-PLL the survival of patients after autologous and allogenic SCT was updated and a prospective registration audit initiated.

In regard to multiple myeloma the NMMA 2000 study has been accepted as publication in JCO. For patients relapsing after autologous HCT a randomized study comparing Velcade, Thalidomide and Steroids with Thalidomide and steroids has recruited already more than 240 patients and will be presented at the EBMT 2011 as best abstract.

Procedure related questions:

A significant improvement in reducing complications after STC was obtained in the pediatric randomized study for VOD prevention. Defibrotide was able to reduce VOD but also the incidence of GvHD. This work received the VanBekkum Award in March 2010 and the manuscript has been submitted to the NEJM.

In addition standardization and spreading of excellence was pursued by training courses and by standardizing indications for SCT. The DMSO prosepective audit is proceeding as expected and complications registered. A standardization of DMSO concentration is urgently needed. Also the standardization of GvHD treatment is making progress. As a first step, the current practice has been evaluated and a manuscript written. Subsequently recommendations have to be established. Accreditation of stem cell transplantation centers is making considerable progress in Europe. The outcome of second stem cell transplantation has been analyzed in detail.

WP SCT report 1+2/4 2010

Nothing has changed in Europe regarding prospective investigator driven studies after the directive 2001. Despite many meetings at the European Level in Bruselles and London and participation to consultations nothing really improved. Insurance fees are especially high in Germany, founding is restricted to individual member states (e.g. DFG) and national authorities request increasingly more burocracy, making clinical studies almost impossible.

Despite all this problems we managed to have approval for the AML study and even foundings from a national cancer aid society. Using this generous financial support and other financial means we were able to start the AML EBMT study for elderly patients. Many other studies could not be started. Many new studies have a moratorio. The majority of the analysis concentrate on retrospective analysis of registry data, which are still important and valuable, but not able to replace prospective studies. In addition observational audits were started within the EBMT.

As described in the minutes, the results achieved during this period were otherwise impressive. More than 25.000 new SCT performed in 2010 were entered in the registry (total >380.000). The RICMAC study recruited patients in four European Countries and the mmvar study completed accrural. The annual EBMT meeting in Vienna attracted more than 4000 persons around the globe to discuss and present the newest achievements in SCT.

WP SCT report 3/4 2010

During this period further activities on deliverables and non-deliverables were continued. In this period the global survey for 2007-2008 was completed and an increase of more than 40% in certain regions in the world noted (e.g. Asia Pacific Region). Now, all transplant activity around the world is registered with the WBMT, the world blood and marrow transplantation network (a federation of the 18 societies involved in stem cell transplantation around the world) on an annual basis. This powerfull tool can be used to recognize differences in frequencies, indications and tendencies from one continent

or even country to the other. New studies were discussed and collaboration within Europe intensified. Procedure related questions were addressed in order to reduce relapse or treat relapse.

WP SCT report 4/4 2010

The main aim of this period was to intensify the cooperation with other working groups of the ELN like WP AML and WP CML. The study on defibrotide was updated and the results presented at ASH. Some of the observational studies were completed (e.g. DMSO; second generation TKI before SCT) or the protocols finalized (Dasatinib for relapse after SCT in CML) and retrospective studies updated (second SCT).

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

14.5 Regular WP meetings:

8 meetings were held during 2010 including joint WP meetings with WP 4 and WP5

- EBMT CLWP/ELN; Hotel Merian, Basel, Switzerland, January 22-23, 2010
- ELN Meeting, Mannheim, February 1-3, 2010
- EBMT annual meeting, Vienna, March 21, 2010
- EHA/ELN FIRA, Gran Via Conf. Center, Barcelona, June 10, 2010
- Subcommittee chair meeting in Leiden 17/06/10
- EBMT CLWP/ELN; "La Distillerie", Mons, Belgium, September 17- 18, 2010
- Subcommittee chair meeting in Leiden 12/11/10
- ELN Meeting WP5/WP14 JW Marriott Orlando Grande Lakes December 05, 2010

14.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

Reports have been sent to NMC.

14.14f Report of study patients to registry

Information on 386887 SCT in 329096 patients are now available in the EBMT Registry and describe patients with autologous and allogeneic SCT (241805 and 144565 respectively; 517 unknown type), transplants from related and unrelated donors (86631 and 42499 respectively; 784 unknown type), from cord blood, bone marrow and peripheral stem cell grafts (6233, 97115 and 288046 respectively; of which 5940 have more than one type of source and 4134 are of unknown source).

The EBMT Registry also allows the registration of other type of cell therapy procedures such as mesenchymal cells, whether performed for similar or new indications, and whether performed by themselves or in association with haematopoietic stem cell transplantation. Currently there are 464

patients for which such procedures have been registered, including 408 mesenchymal cells therapy and 59 dendritic cells therapy.

14.42d Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning (EBMT study)

The study has been started in January 2010 and more than 17 patients were registered till January 2011. The study is proceeding as planned with the Nederlandes and Germany involved. Switzerland and France did not start yet for administrative reasons, but center initiations are planned in April. The goal of including 210 patients is expected to be reached in 2 years from now.

14.45c Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start

The RICMAC is a European EBMT-trial comparing a dose-reduced conditioning versus a standard myeloablative conditioning regimen followed by allogeneic SCT in patients with myelodysplastic syndome or secondary acute myeloid leukaemia. Accrual is ongoing and has substantially improved this year. 72 of the planned 140 patients are randomized so far.

14.46d MMVAR Study to treat relapse in myeloma after autologous SCT

246 patients entered the study and recruitment stopped. The following abstract was submitted to the EBMT meeting in Paris 2011 and a manuscript is in preparation. The abstract will reveice the prestigious Van Bekkum award.

Bortezomib(Velcade®)-Thalidomide-Dexamethasone (VTD) is superior to Thalidomide-Dexamethasone (TD) in patients with multiple myeloma (MM) progressing or relapsing after autologous transplantation

In 2006, the EBMT and the IFM initiated a prospective, randomized, parallel-group, open-label phase III, multicenter study, comparing VTD (arm A) with TD (arm B) for MM patients in first progression/relapse after at least one autologous transplantation. TTP was the primary end point. Treatment was: bortezomib 1.3 mg/m2 as an i.v bolus on days 1, 4, 8 and 11, followed by a 10-day rest period (days 12 to 21), for 8 cycles (6 months) and then on days 1, 8, 15 and 22, followed by a 20-day rest period (days 23 to 42), for 4 cycles (6 months). In both arms, thalidomide was administered at 200 mg/day for 1 year and dexamethasone at 40 mg/day orally for 4 days every 3 weeks for 1 year. Response was assessed by EBMT criteria. Adverse events were graded by the NCI-CTCAE, Version 3.0. Results: On 01/07/10, a first interim analysis based on 246 patients and 134 events was performed. The trial was then stopped because of superiority of VTD over TD. We report an updated analysis as of 02/12/10. 267 patients (135 in arm A, 132 in arm B) had been enrolled in the study and 157 events had been observed. The median age was 61 years (range 29-76) The stage according to the ISS was I in 56 %, II in 27 %, III in 17 %. The number of previous autologous transplants was one in

71 vs 69 patients and two or more in 64 vs 63 patients, in arms A and B respectively. The median follow-up was 27 months. The median TTP was 19.5 vs 13.8 months respectively in arms A and B, with a cumulative incidence of relapse/progression at 2 years of 56% vs 71% (p=0.0011). The median PFS was 18.6 vs 12.7 months with a cumulative incidence at 2 years of 37% vs 23% (A vs B, p=0.0011). The OS in the first two years was 72% vs 68% (p=0.18). The probability of achieving CR and CR+PR during the first year was 32% vs 12% and 90% vs 69% with VTD and TD (p=0.0001, and p=0.0001). In the VTD and TD arms, the mean number of treatment cycles for the first 8 cycles were 6.25 vs 6.88 and for the 12 cycles, 7.56 vs 9.93 respectively. Treatment was discontinued due to toxicity in 48 patients (VTD= 36, TD=12). 33 patients died during the treatment period (VTD= 14, TD= 19).The incidence of thrombo-embolic events >= grade 3 was similar in the two arms (6.6% vs 5.2%, p=ns, VTD vs TD) while >= grade 3 thrombocytopenia was higher with VTD (16% vs 7%, p= 0.025). Conclusion: VTD resulted in significantly longer TTP and PFS in patients relapsing after ASCT with an acceptable toxicity. Protocol EU-DRACT number: 2005-001628-35.

14.47d Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1 (Brune)

This is an academic study, comparing reduced intensity transplants (RICT) with standard of care in AML. Based on the availability of an HLA identical sibling, patients in their first remission are allocated to a RICT group or a control group. Primary endpoint is survival and the study is supported by the Canadian BMT Group and several funds. PI is Mats Brune Göteborg, Sweden.

At this point, >130 pts have been enrolled from centers in Canada, Norway, Finland, Germany, New Zealand and Sweden. The study has been open also to patients with unrelated donors.

14.48d AlloSCT after tyrosine kinase inhibitors (TKI) in CML

The retrospective study on second generation TKI use prior to allo-transplant is in its final analysis. A total of 19 centres (11 EBMT centres, 8 non EBMT centres) participated. 56 pts. with CML have been identified. At SCT, 37% of the patients were in accelerated or in blast phase, 36% in CP2 and 27% in first chronic phase. In two pts primary graft failure occured. At 24 months the estimated non-relapse mortality was 33% and the relapse incidence 15%. The conclusions of the study were that allotransplants remain a reasonable treatment option for pts. with CML after TKI treatment. Results are promising if pts are transplanted while still in 1st CP. These results have to be confirmed in a larger prospective study. There were differences in outcome after SCT depending on the TKI used before SCT.

The prospective non interventional study (ONIS) has been started. 57 centres have registered, expecting to recruit 422 pts. At this time 46 pts. have been included. For 29 pts data are available. 1/3 were transplanted in 1st CP, 80% were beyond 1 year after diagnosis and 75% had an unrelated donor. No graft failure was observed. The NRM amounted 14% and the RR 7%.

14.49d Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study).

The study did not start because of lack of fundings. Several talks were undertaken with pharmaceutical companies to obtain grants. The interest is high especially for maintanence therapy after SCT, but no definitive decision about funding was given.

14.50d Study investigating the role of Kepivance for treating Mucositis after autologous SCT (350 patients)

Study is complete and a manuscript submitted to JCO. The study was presented at different meetings.

In a high-dose melphalan setting, palifermin compared to placebo did not show an effect on oral mucositis or related patient's burden.

This RCT aimed to study the efficacy of palifermin when administered in two different dosing regimens in a chemotherapy-only conditioning setting, to reduce maximum severity of oral mucositis (OM), patient-reported outcome (PRO) and health care burden including medical resource use, significant infections and duration of hospitalization. The efficacy of palifermin relative to placebo was investigated with palifermin given either pre/post-HDM or pre-HDM in patients with MM undergoing ASCT at 39 European centres. Oral cavity assessment (WHO grades (0/1, 2, 3 or 4)), patient reported outcome (PRO) questionnaires (Oral Mucositis Daily Questionnaire [OMDQ], Functional Assessment of Cancer Therapy Esophageal [FACT-E], European Quality of Life Utility Scale [EQ 5D], Mucositis Chronic Symptoms Questionnaire [MCSQ]) were used until 30 days post transplant or hospital discharge. 281 patients (mean age 56, ±SD= 8 years) were enrolled; 109 patients were randomized to pre-HDM, receiving palifermin (60 μg/kg/day) iv for 3 consecutive days before HDM and 115 subjects were randomized to pre/post-HDM receiving palifermin on 3 consecutive days before HDM and on 3 consecutive days after ASCT. 57 patients were randomized to receive placebo. There was no statistically significant difference in the primary endpoint maximum severity of OM between placebo and palifermin administered pre/post-HDM or pre-HDM. Severe OM (WHO grade 3 and 4) occurred in 37% (placebo), 38% (pre/post-HDM) and 24% (pre-HDM) of the patients. No difference was observed between placebo and palifermin pre/post-HDM, nor pre-only-HDM with respect to PRO assessments or medical resource use i.v. anti-infective drugs or non-opioid drug use, whereas use of opioids was somewhat lower in the palifermin treated arms (eg. 77, 67 and 64%, respectively). A higher incidence of febrile neutropenia and more significant infections were reported in the pre/post-HDM versus placebo group (eg. 51% and 26%). The lack of efficacy of palifermin in this study might be explained by the timing of the palifermin post-dose relative to the development of OM. Usually, OM develops about 10-14 days after start of conditioning. HDM is an exceptionally short (one day) conditioning regimen leading to an interval of two days from start of conditioning to day of transplant and start of post dose, compared to about a week for all common conditioning regimens. This has influenced the outcome of the trial, as the post dose of palifermin should be timed relative to the development of OM. To conclude, palifermin did not show an effect on OM in the

HDM setting, most likely due to the timing interval influenced by the short, one day course of HDM. Consequently, palifermin was not able to reduce OM or patient's burden related to OM after HDM conditioning used to prepare patients before ASCT.

14.55c Comprehensive survey outside Europe (Alois Gratwohl)

The WBMT, has collected information from >1,350 transplant centers over all continents on the numbers of HSCT by indication and donor type for 2007 and 2008. A preliminary analysis was presented at the cIBMTR meeting in Honolulu (Hawaii) February 2011. The transplant rates are increasing and the reporting standardized. A manuscript will be written in summer 2011.

14.56d Integration of risk factor profiling into risk adapted therapy pilot AML HOVON/SAKK <60 years (Alois Gratwohl)

This analysis is still being performed and will be finalized in 2011.

14.59c Guidelines for secondary allotransplantation after relapse (retrospective analysis)

This megafile analysis involves 1631 patients undergone second SCT between 1994-2005 (all malignant disorders with emphasis on transplantation complications and NRM). The relevant clinical questions involve the donor (same or other donor), sibling or MUD, BM or PBSC and which intensity of conditioning? The factors affecting results were identified as: disease type, phase of disease, age, EBMT score, interval between the transplantations, conditioning, same or other donor, sibling vs. MUD and year of transplantation. The analysis will be finalized and presented during one of the meetings in 2011. A manuscript will be prepared as well.

14.60c Prospective feasibility study phase II Dasatinib for relapse in CML after allo (Olavarria)

Regulatory approval has been obtained and the study is open for recruitment in four countries (UK, Germany, Switzerland and France). Currently, no more countries are planned but additional countries may potentially be added in the future (Hungary is expected).

This Phase II efficacy study analyzes the role of dasatinib in patients with chronic and accelerated phase chronic myeloid leukemia relapsing after allogeneic blood or bone marrow transplantation. Patients $\geq$ 18 years of age with Ph+ CML, whose disease is relapsed after transplant from an HLA-identical sibling or an HLA-matched unrelated donor (MUD) and have not responded to withdrawal of immunosuppressive treatment where this is possible, are entered. The primary objective is to assess the efficacy of dasatinib therapy in chronic and accelerated phase BCR-ABL (+) CML patients that undergo molecular, cytogenetic or hematological relapse following SCT. The secondary objectives determine the impact of dasatinib therapy on patient survival after relapse post-SCT and the incidence of any subsequent need for 'rescue' DLI and the safety of dasatinib in this clinical context using this specific dose regimen. The study is recruiting very slowly and the interest of the centers low. If the recruitment will not improve, the study will be closed.

14.61c T-PLL after autologous and allogeneic SCT (Wieslaw Jedrzejczak)

It is the largest group ever evaluated with this disease (54 patients). A first draft was written and the possibility to increase patient's number considered (adding more patients from Claire Dearden). The analysis is now restricted to allogeneic only. A final draft is in preparation, which should be submitted in summer 2011.

14.62c Prospective registration audit for T-PLL (Wieslaw Jedrzejczak)

Prospective study is very close to meet the original planned number of 50 patients. Last information was 47 patients and an analysis is expected within May 2011.

14.65b Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling (Guglielmi)

500 patients were analyzed. 16% had molecular relapse, 30% cytogenetic relapse, 42% chronic hematological relapse and 12% accelerated relapse. The response rate was 68% with a median time to response of 7.5 mts. The GvHD rate amounted 44% with a median onset of 3 months after donor lymphocyte infusion. The relapse rate after response was seen only in 16 patients a median of 19 months after response. A manuscript is planed.

14.66b Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal (Wieslaw Jedrzejczak)

Recommendations are written and are waiting for submission after the retrospective analysis would be accepted for publication

14.67b Cytogenetic high risk AML: results of a biological randomizated study in patients under the age of 60 a

The analysis was published in Leukemia 2009 and showed the important role of allogeneic SCT in high risk patients. The results determine the approach to patients with high risk leukemia and favour SCT as soon as CR is reached.

14.68b DMSO prospective audit (Curly Morris)

An increased risk of side effects is expected with the use of DMSO, especially with the highest doses (side effects are NCI definitions). There are huge center variations in the side effects observed. Some unexpected observations: apparently, DMSO would have a protective effect in young lymphoma patients and on the contrary more side effects seem to be present in old MM patients? The role of the different factors and their interactions can now be analyzed. A manuscript will be prepared.

14.69b ATG-depending outcome in MUD patients transplanted for CML (F. Schleuning)

This analysis is written up for a manuscript and will be submitted.

14.70b Prophylaxis and treatment of GvH-D: an EBMT survey (B. Hertenstein, T. Ruutu)

Reports from 81 EBMT centres from 23 countries are available to document the heterogeneity of GvHD prophylaxis and treatment strategies, to form a platform for efforts to standardize transplantation methods and to help in planning clinical trials. A manuscript has been written

Clear recommendations on indications for allogeneic haematopoietic stem cell transplantation have been established. In contrast, the techniques used have remained poorly standardized. Reported outcomes vary markedly, and it would be important to know, to what extent this is due to differences in treatment procedures. EBMT performed in 2010 a survey among its member centres about their strategies in preventing and treating graft versus host disease (GvHD). Seventy-nine centres from 23 countries participated. The survey showed marked variability in the GvHD prophylaxis and treatment strategies applied in the centres. Even superficially similar methods differed in relevant practical details. It is likely that these differences have a bearing on the outcome of allogeneic transplantations. The present findings underline the need for standardization and prospective controlled studies in GvHD prevention and treatment. The aim is to set recommandation for prophylaxis and treatment of GvHD.

14.71b Analysis of non-disease related complications after HCT (T. Ruutu)

M. Stern is working on an analysis on GvHD as surrogate marker for GvL on relapse using the CLWP megafile. The following questions should be answer a.) How do different diseases compare? b.) How do different transplant settings compare c.) Are there differences between unrelated and related sibling transplantations d.) Are there differences between TCD and non-TCD grafts?

A further topic is the topical tacrolimus for chronic cutaneous GvHD**.** The recruitment will start in March 2010 and will end October 2011. The Follow-Up time of this study will be six months after recruitment. The target will be to recruit 100 patients to this study.

Finally the role of comorbidity on stem cell transplantation will be defined in detail. This study will be a prospective study, which is now in a very preliminary status. No update is available on this evaluation.

14.72b Randomized study on VOD in pediatric patients n=360 (Corbacioglu)

The manuscript has been submitted to NEJM

Hepatic veno-occlusive disease (VOD) is a leading cause of morbidity and mortality after hematopoietic stem-cell transplantation (HSCT).

In this international, randomized, controlled, open-label trial, we compared defibrotide (Gentium S.p.A.) prophylaxis with no prophylaxis in pediatric HSCT patients at high risk for developing VOD. The primary endpoint was the incidence of VOD by Day+30 post-HSCT, adjudicated by a blinded, independent review committee. Secondary endpoints included graft-versus-host disease (GVHD), VOD-related organ failure and mortality.

A total of 356 patients met the inclusion criteria and gave informed consent to be randomized to the i.v. defibrotide arm (n=180) or the control arm (n=176). VOD was reported in 22 patients (12%) in the defibrotide arm and in 35 patients (20%) in the control arm (competing risk, P=0.05; Kaplan-Meier, P=0.05). The incidence and severity of acute GVHD were significantly reduced (P=0.005 and P=0.003, respectively) in the allogeneic recipients. VOD-associated organ failures were lower in the defibrotide arm with a significant reduction in the incidence of renal failure (1% vs. 6%, P=0.02). A significantly higher Day+100 mortality was observed in patients with VOD (25% vs. 6%; P<0.001). Although mortality after VOD diagnosis was lower in the defibrotide arm (4 vs. 10 patients, P=0.1), overall mortality was similar in the two arms. There was no difference in the incidence of adverse events between arms (87% vs. 88%).

Defibrotide reduced the incidence of VOD by 40%, as well as the incidence and severity of acute GVHD, and has a good safety profile. (ClinicalTrials.gov number, NCT00272948.)

14.73a Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD (Mary Eapen and Vanderson Rocha, on behalf of CIBMTR, Eurocord and ALWP of EBMT)

Data support the use of UCB as first line therapy for adults with acute leukemia, especially when transplant is urgently needed or when an HLA-matched unrelated adult donor is lacking. The manuscript is currently being written.

14.74 Non interventional studies (Passweg). Manuscript ready

The possibility to enter patients in non-interventional studies has been exploited by J. Passweg. Using this possibility patients are treated according to established treatment modalities, but outcome can be still evaluated.

14.75 CML RIC vs. standard (Crawley).

The manuscript is in preparation.

14.76 Allo-SCT in T315I mutation (W Wiesław Jędrzejczak) data collection

We have collected 23 reports with T513I mutations. There was recently extensive correspondence between members of the WP since additional 40 patients were collected in another country. The data are now collected and will be analyzed for a manuscript.

14.77 Punctal plugs for dry eyes after allotransplantation. M van Gelder

The protocol has been finalized and 8 patients of the 48 are included. The study will be advertised in a forthcoming newsletter.

14.78 Graft failure after reduced intensity conditioning. B Hertenstein

The paper was rejected by Haematologica and is now being prepared for submission to BMT.

14.79 Cytokine gene polymorphism A Dickinson/ J Norden. Manuscript submission

The manuscript has been published:

Impact of genomic risk factors on outcome after hematopoietic stem cell transplantation for patients with chronic myeloid leukemia. Haematologica. 2010 Jun;95(6):922-7. Epub 2010 Mar 19.

BACKGROUND: Non-HLA gene polymorphisms have been shown to influence outcome after allogeneic hematopoietic stem cell transplantation. Results were derived from heterogeneous, small populations and their value remains a matter of debate.

DESIGN AND METHODS: In this study, we assessed the effect of single nucleotide polymorphisms in genes for interleukin 1 receptor antagonist (IL1RN), interleukin 4 (IL4), interleukin 6 (IL6), interleukin 10 (IL10), interferon (IFNG), tumor necrosis factor (TNF) and the cell surface receptors tumor necrosis factor receptor II (TNFRSFIB), vitamin D receptor (VDR) and estrogen receptor alpha (ESR1) in a homogeneous cohort of 228 HLA identical sibling transplants for chronic myeloid leukemia. Three good predictors of overall survival, identified via statistical methods including Cox regression analysis, were investigated for their effects on transplant-related mortality and relapse. Predictive power was assessed after integration into the established European Group for Blood and Marrow Transplantation (EBMT) risk score.

RESULTS: Absence of patient TNFRSFIB 196R, absence of donor IL10 ATA/ACC and presence of donor IL1RN allele 2 genotypes were associated with increased transplantation-related mortality and decreased survival. Application of prediction error and concordance index statistics gave evidence that integration improved the EBMT risk score.

CONCLUSIONS: Non-HLA genotypes were associated with survival after allogeneic hematopoietic stem cell transplantation. When three genetic polymorphisms were added into the EBMT risk model they improved the goodness of fit. Non-HLA genotyping could, therefore, be used to improve donor selection algorithms and risk assessment prior to allogeneic hematopoietic stem cell transplantation.

14.80 Organ transplantation after allogeneic SCT. Manuscript ready. C Koenecke

The manuscript has been published with the following title:

Solid organ transplantation after allogeneic hematopoietic stem cell transplantation: a retrospective, multicenter study of the EBMT. Am J Transplant. 2010 Aug;10(8):1897-906.

To analyze the outcome of solid organ transplantation (SOT) in patients who had undergone allogeneic hematopoietic stem cell transplantation (HSCT), a questionnaire survey was carried out within 107 European Group of Blood and Marrow Transplantation centers. This study covered HSCT between 1984 and 2007 in Europe. Forty-five SOT in 40 patients were reported. Fifteen liver, 15 renal, 13 lung, 1 heart and 1 skin transplantations were performed in 28 centers. Overall survival (OS) of patients after SOT was 78% at 5 years (95% confidence interval [CI], 64% to 92%). OS at 5 years was 100% for renal, 71% (95% CI, 46% to 96%) for liver and 63% (95% CI, 23% to 100%) for lung transplant recipients. The 2-year-incidence of SOT failure was 20% (95% CI, 4% to 36%) in patients with graft-versus-host disease (GvHD) and 7% (95% CI, 0% to 21%) in patients without GvHD before

SOT. The relapse incidence for underlying malignant diseases was 4% at 5 years (95% CI, 0% to 12%). In summary, this study shows that selected patients receiving SOT after HSCT have a remarkably good overall and organ survival. These data indicate that SOT should be considered in selected patients with single organ failure after HSCT.

14.81 HLA-identical siblings: Impact on cytogenetics and outcome (Francesco Onida). Cytogenetics (CG) represent one of the most important prognostic factors in MDS. However, it is uncertain whether the negative effect of poor CG could be counteracted by allo-HSCT as a curative strategy in patients with MDS. With the aim of evaluating the impact of cytogenetics in patients with primary MDS undergoing allogeneic transplant from HLA-identical siblings, the MDS subcommittee of the CLWP has performed a retrospective analysis on 510 patients who underwent this transplant strategy from 1981 to 2006 and were reported to EBMT with full cytogenetic data.

This study provides evidence that poor risk cytogenetics as classified by the IPSS have strong prognostic impact on outcome of patients undergoing allo-HSCT from HLA-identical siblings for MDS. However, the overall outcome after alloSCT compared to the outcome of nontransplant approaches, makes alloSCT the treatment of choice for this group of patients. The manuscript is currently under its last finalization and will be submitted within next month of April.

14.82 Survey in Europe (annual) A. Gratwohl

The EBMT activity survey 2009: trends over the past 5 years. Bone Marrow Transplant. 2011 Feb 28. [Epub ahead of print] has been accepted for publication.

Six hundred and twenty-four centers from 43 countries reported a total of 31 322 hematopoietic SCT (HSCT) to this 2009 European Group for Blood and Marrow Transplantation (EBMT) survey with 28□033 first transplants (41% allogeneic, 59% autologous). The main indications were leukemias (31%; 92% allogeneic), lymphomas (58%; 12% allogeneic), solid tumors (5%; 6% allogeneic) and non-malignant disorders (6%; 88% allogeneic). There were more unrelated than HLA-identical sibling donors (51 vs 43%) for allogeneic HSCT; the proportion of peripheral blood as stem cell source was 99% for autologous and 71% for allogeneic HSCT. Allogeneic and autologous HSCT continued to increase by about 1000 HSCT per year since 2004. Patterns of increase were distinct and different. In a trend analysis, allogeneic HSCT increased in all World Bank Categories (P=0.01, two sided; all categories), autologous HSCT increased in middle- (P=0.01, two sided) and low-income (P=0.01, two sided) countries. EBMT practice guidelines appeared to have an impact on trend, with a clear increase in absolute numbers within the categories 'standard' and 'clinical option' for both allogeneic and autologous HSCT (P=0.01, two sided; for both allogeneic and autologous HSCT) and a clear decrease in autologous HSCT for the 'developmental' and 'generally not recommended' indications (P=0.01, two sided). These data illustrate the status and trends of HST in Europe.Bone Marrow Transplantation advance online publication, 28 February 2011; doi:10.1038/bmt.2011.11.

14.83 Accreditation in Europe

A study led by Alois Gratwohl (Basel, CH) looked at the effects of implementing quality management in transplant programmes on patient outcome. Their conclusions pointed to a strong correlation between quality management and improvements in patient outcome. Prof. Gratwohl presented the study at the EBMT meeting in Vienna and an article was accepted for publication in the Journal of Clinical Oncology and is expected in print in Spring 2011.

The review process to prepare the 5th edition of the FACT-JACIE Standards commenced in June 2010 with a meeting in Barcelona. The draft text will go to public consultation in April 2011 and release of the final text is expected at the end of 2011.

At the 2010 EBMT Annual Meeting in Vienna, the 2nd Quality Management Meeting took place as part of the congress programme. This proved very successful with approximately 150 attendees participating in a varied programme with opportunities to ask questions and share experience. The meeting has now become a regular part of EBMT Annual Meetings.

In 2010, 11 training courses and other events were run on the initiative of national societies or individuals with JACIE support or directly by JACIE. A total of 73 participants received training either as inspectors, preparing their centre for accreditation or internal audits.

The number of trained inspectors continues to grow and now stands at over 230 from 19 countries.

Accreditation Programme Status:

a. 20 new applications received and 17 applications for reaccreditation.
b. 30 audits were performed (17 first-time and 5 reaccreditation)
c. 21 centres were accredited for the first time and 5 were reaccredited.

Total centres/facilities registered:	230
Centres in progress:	68
Centres inspected:	206
Accredited:	102
Countries:	17

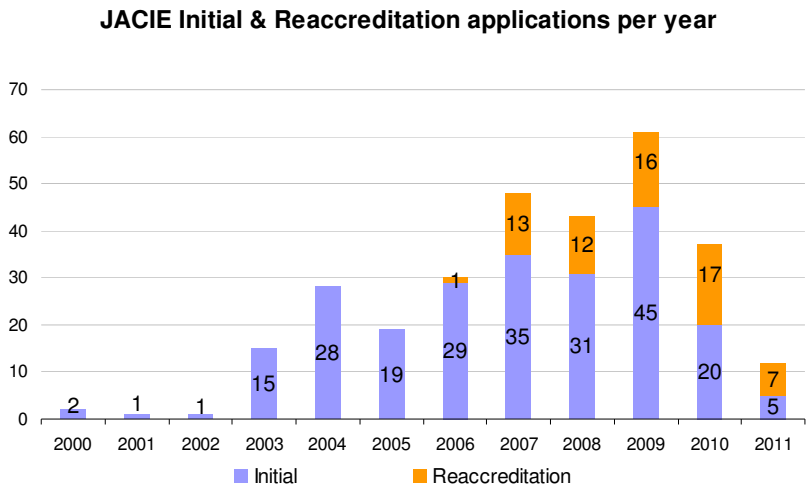


Figure 14.1: Reaccredition applications per year.

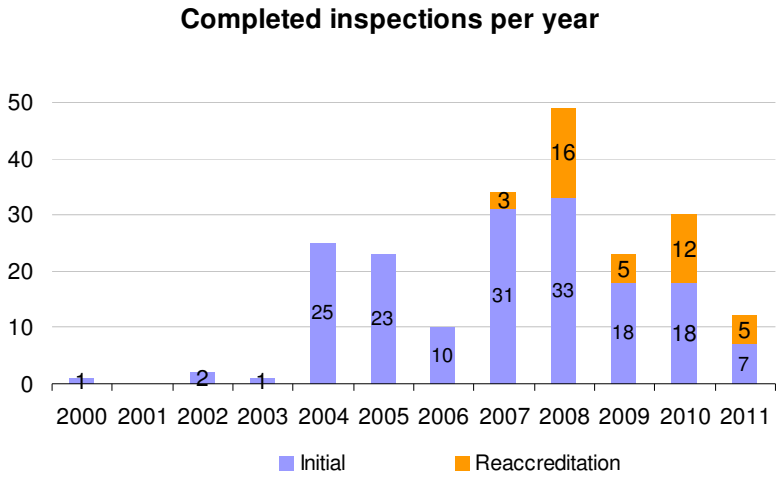


Figure 14.2: Completed inspections per year.

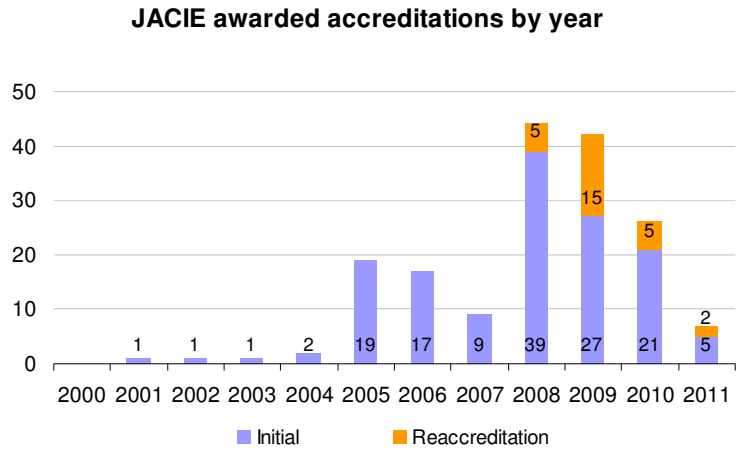


Figure 14.3: awarded accrediations by year.

14.84 Outcome in centers with JACIE accreditation manuscript ready A. Gratwohl

The manuscript has been accepted by the Journal of Clinical Oncology:

INTRODUCTION OF A QUALITY MANAGEMENT SYSTEM AND OUTCOME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

The comprehensive quality management system "JACIE" was introduced to improve quality of care in hematopoietic stem cell transplantation (HSCT). The justification for these investments remained open. We therefore tested the hypothesis that the introduction of JACIE improved patient survival stepwise and more than expected by calendar time alone.

Data on 41,623 allogeneic (39%) and 66,281 autologous (61%) HSCT for an acquired hematological disorder performed between 1999 and 2007 by 421 teams in Europe were used to assess outcome of patients transplanted in teams at *baseline* (> 3 years prior to application or no application), during *preparation* (3 years prior to application), during *application* (time from application to accreditation) and after JACIE *accreditation*. The analysis was clustered by team, stratified for donor type, disease, year of HSCT, conditioning and Gross National Income per capita of the respective country. Patient's risks were adjusted for by the EBMT score.

Outcome improved stepwise from baseline up to JACIE accreditation. This improvement was systematic and robust for patients after allogeneic HSCT, quantified for relapse free survival compared to baseline by a HR of 0.96 (0.90-1.03; p = 0.22) for *preparation*, 0.95 (0.88-1.03; p = 0.20) for *application*, and 0.86 (0.78-0.95; p = 0.01) for the *accreditation* (test for trend: p=0.01). Improvement from baseline was of similar order of magnitude after autologous HSCT (HR for *accreditation* 0.83, 0.74-0.93; p<0.01).

These findings support the hypothesis that introduction of a comprehensive clinical quality management system is associated with improved outcome of patients after HSCT.

Table 14.1: Deliverables WP14, 2010 and 2011

WP14	Stem cell transplantation					
Deliv. No.	**Deliverable Name**	**Date due**	**Actual/Forecast delivery date**	**Estimated indicative person months*)**	**Used indicative person months*)**	**Lead contractor**
14.5	Regular WP meetings	**76,78, 84,86**	76,78,84,86	0	2	Niederwieser
14.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)	**79,86**	86	0	2	Niederwieser
14.14f	Report of study patients to registry	**73-86**	86	0	2	Brand
14.42d	Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning. Start study	**73-86**	86	0	2	Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha
14.45c	Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start	**73-86**	86	0	2	Kröger deWitte
14.46d	MMVAR Study to treat relapse in myeloma after autologous SCT (40 patients)	**73-86**	86	0	2	Gahrton
14.47d	Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1 (Brune)	**73-86**	86	0	2	Brune
14.48d	AlloSCT after TKI in CML	**73-86**	86	0	2	Schleuning, Guilhot
14.49d	Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study).	**73-86**	86	0	2	Niederwieser, Gahrton, Gratwohl,
14.50d	Study investigating the role of Kepivance for treating Mucositis after autologous SCT (350 patients).	**73-86**	86	0	2	Niederwieser, Blijlevens, deWitte,
14.55c	Comprehensive survey outside Europe (publication)	**73-86**	86	0	2	Gratwohl, Niederwieser
14.56d	Integration of risk factor profiling into risk adapted therapy pilot AML HOVON/SAKK <60 years	**73-86**	86	0	2	Gratwohl
14.59c	Guidelines for secondary allotransplantation after relapse (retrospective analysis)	**73-86**	86	0	2	Ruutu
14.60c	Prospective feasibility study phase II Dasatinib for relapse in CML after allo	**73-86**	86	0	2	Olavarria, Schleuning (2)
14.61c	T-PLL after autologous and allogeneic SCT (44 patients)	**73-86**	86	0	2	Jedrzejczak
14.62c	Prospective registration audit for T-PLL	**73-86**	86	0	2	Jedrzejczak

WP14	Stem cell transplantation					
Deliv. No.	**Deliverable Name**	**Date due**	**Actual/Forecast delivery date**	**Estimated indicative person months*)**	**Used indicative person months*)**	**Lead contractor**
14.65b	Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling	**73-86**	86	0	2	Guglielmi
14.66b	Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal	**73-86**	86	0	2	Jedrzejczak
14.67b	Cytogenetic high risk AML: results of a biological randomizated study in patients under the age of 60 a	**73-86**	86	0	2	Basara (Leipzig)
14.68b	DMSO prospective audit	**73-86**	86	0	2	Morris
14.69b	ATG-depending outcome in MUD patients transplanted for CML	**73-86**	86	0	2	Schleuning
14.70b	Prophylaxis and treatment of GvH-D: an EBMT survey	**73-86**	86	0	2	Hertenstein
14.71b	Analysis of non-disease related complications after HCT	**73-86**	86	0	2	Ruutu
14.73	Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD	**73-86**	86	0	2	Rocha
14.74	Non interventional studies (Passweg). Manuscript ready	**73-86**	86	0	2	Passweg
14.75	CML RIC vs. standard (Crawley). Manuscript ready	**73-86**	86	0	2	Crawley
14.76	Allo-SCT in T315I mutation (W Wiesław Jędrzejczak) data collection	**73-86**	86	0	2	Jędrzejczak
14.77	Punctal plugs for dry eyes after allotransplantation. M van Gelder	**73-86**	86	0	2	Van Gelder
14.78	Graft failure after reduced intensity conditioning. B Hertenstein	**73-86**	86	0	2	Hertenstein
14.79	Cytokine gene polymorphism A Dickinson/ J Norden. Manuscript submission	**73-86**	86	0	2	Dickinson, Norden
14.80	Organ transplantation after allogeneic SCT. Manuscript ready. C Koenecke	**73-86**	86	0	2	Koenecke
14.81	HLA-identical siblings: Impact on cytogenetics and outcome (Francesco Onida). Manuscript ready	**73-86**	86	0	2	Onida
14.82	Survey in Europe (annual) A. Gratwohl	**73-86**	86	0	2	Gratwohl
14.83	Accreditation in Europe	**73-86**	86	0	2	EOIN
14.84	Outcome in centers with JACIE accreditation manuscript ready A. Gratwohl	**73-86**	86	0	2	Gratwohl

Table 14.2: List of milestones WP14, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP14	**SCT**			
14.42	Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning	78	Started recruitment , recruitment will last 2-3 years.	Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha
14.57	Autologous SCT for CML (30 patients reported to the EBMT). Evaluation	78	86	Heim, Gratwohl
14.58	Outcome of patients with low risk Gratwohl score CML	78	Ongoing	Heim, Gratwohl
14.61b	T-PLL after autologous and allogeneic SCT (44 patients)	78	ongoing	Jedrzejczak
14.65	Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling	78	Ongoing	Guglielmi
14.66	Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal	78	Ongoing	Jedrzejczak
14.70	Prophylaxis and treatment of GvH-D: an EBMT survey	78	86	Hertenstein
14.71	Analysis of non-disease related complications after HCT	78	86	Ruutu
14.72	Randomized study on VOD in pediatric patients n=360	78	Delivery of the manuscript	Corbaciouglou (Ulm)
14.73	Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD (manuscript ready)	78	86	Rocha

Section 4: Other Issues

Ethical issues - none

Competitive calls - none

Section 5: WP-Performance

Performance indicators	Status
Number of clinical trials	12
Number of patients registered in the survey	50000
Number of metaanalyses	7
Development of standardization and guidelines	done

15 Supportive care/anti-infection prophylaxis and treatment (WP15)

Project objectives and major achievements during the reporting period

The work with guidelines has continued during the period. One paper was submitted for publication in Bone Marrow Transplantation and two other papers are in final stages of preparation. .In addition collaboration has been initiated with the Infectious Diseases Society of America (IDSA) regarding update of vaccination guidelines in patients with leukemia and other hematological malignancies. This work was presented at the IDSA meeting in Vancouver October 2010.

15.5 Regular WP meetings

The WP has held meetings at the ELN meeting in Mannheim in February, at the EBMT meeting in Vienna in March, and in Paris in October

15.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

No new activity.

15.22e Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial

The protocol is finalized but the sponsor did not want to fund the prospective study. Thus, the protocol is currently on hold

15.27d Develop common protocols for molecular diagnosis of fungal infections by PCR

This topic has been developed into an international collaboration (EAPCRI; European Aspergillus PCR Initiative)

15.29d Arrange courses in infectious diseases in stem cell transplant recipients

A training course was held in Paris September 23-25 with approximately 30 participants.

15.30b Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines

Collaboration has been initiated with IDSA regarding guidelines for vaccination of patients with hematological malignancies and after stem cell transplantation. These have been presented at the IDSA meeting in Vancouver, Canada in October 2010 and the manuscript is in the final stages of preparation. From the 3d ECIL meeting, one manuscript has been published, one manuscript has been submitted and two are in the final stages of preparation from the 3d ECIL meeting. Slide sets regarding the recommendations have been published on the ELN website. A 4th European Conference regarding Infections in Leukemia is in planning for September 2011 updating previous guidelines (slides not published on the ELN website), and covering new topics.

Table 15.1: List of deliverables WP15, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months	Used indicative person months*)	Respon-sible lead participant/ investigator
WP15	**Supportive care, anti-infection prophylaxis and treatment**					
15.5	Regular WP meetings	**86**	73,75,80	0	2	Ljungman Einsele
15.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)	**79,86**	86	0	2	Ljungman Einsele
15.22e	Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial	**73-86**	86	0	0	Einsele Ljungman
15.27d	Develop common protocols for molecular diagnosis of fungal infections by PCR	**86**	86 ongoing	0	0	Einsele Maertens
15.29d	Arrange courses in infectious diseases in stem cell transplant recipients	**78**	80	0	1	Einsele Ljungman Cordonnier
15.30b	Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines	**73-86**	86	0	2	Einsele Ljungman Cordonnier

Table 15.2: List of milestones WP15, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP15	**SCT**			
15.27d	Develop common protocols for molecular diagnosis of fungal infections by PCR	**86**	86 ongoing	Einsele Maertens
15.30	Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines	**73-86**	86	Einsele Ljungman Cordonnier

Section 3: Consortium management

All deliverables and milestones that had to get revised timetables as described in 2010. The two subcommittees have continued to function. One subcommittee handles the specific topic of infections in stem cell transplant recipients. This subcommittee is lead by Hermann Einsele. The second subcommittee did the planning for the 3d European Guidelines meeting and is now working on the publications and is planning the 4th meeting.. This group is chaired by Catherine Cordonnier and incorporates representatives for the ELN, the EBMT, the ICHS, and the EORTC.

Section 4: Other Issues

Ethical issues - none

Competitive calls -none

Section 5: WP-Performance

Performance indicators	Status
European guidelines for anti-infection prophylaxis and therapy in neutropenic patients	Finalized and expanded

17 Biometry of Registry, Epidemiology, Metaanalyses and Prognosis (WP17)

With regard to the major objectives as stated in the original grant application many years ago, most of them have been achieved in the field of CML. This is partly due to the fact that there had been already a close collaboration among the premier European CML study groups since 1992. But a major reason why comparable achievements were missing for a long time for the other leukemia entities was lack of funds. Initially a considerably higher funding (actually 4 times as much as finally awarded) was expected and planned for. To establish a registry requires considerable and enduring activities over a long time without the hope of immediate rewards like presentations and publications. This in combination with lack of funds is certainly not a good starting point. Over time and certainly influenced by the constant flow of presentations of the CML Registry, the situation has changed. Thus an ELN-MDS-Registry has been initiated with the support of Novartis which will become productive once a sufficiently sized sample has been recruited and observed for an adequate period of time.

Quite recently similar first activities have been started for AML, too. Guided by the German AML Study Groups and U. Mansmann (IBE, University of Munich) planning and design activities have started. A decisive factor for the outcome of these activities is of course the access to funding.

Considering that the establishment of European Leukemia Registries is pioneer work there are considerable achievements. In this context one should not forget that the legal situation with regard to registries, clinical eand epidemiological research and data confidentiality issues differs from country to country and is thus rather complicated, and difficult to overcome.

Objectives and starting point of work at beginning of reporting period

There were one major objectives for the current reporting period:

to expand and update the European CML-registry which collects data about the epidemiology and the clinical management of patients with CML in the various member states of the EU.

Considerable progress has been achieved.

European CML-registry

The three sections (in-study, out-study, and population-based) of the EUTOS CML-Registry have been successfully established. With 2389 eligible CML-patients in the in-study and 1582 patients in the out-study section even more patients than initially expected could be recruited.

The prospective population-based section took a bit longer to get started as many difficulties had to be solved to get the research plan agreed upon by all participants and to get the data collection started. Thus the majority of the 24 participating countries began with data collection in 2010 only.

Considering this background the reporting of 731 eligible patients should be considered as a success too. Alltogether data of 4703 eligible CML-patients have been registered in the reporting period.

The collaboration between the Scientific Headquarter in Bologna, the Management Center in Mannheim and the Central Data Center in Munich worked very well. Although the workload at the CDC is heavy we managed to got good relations with all participants and there is a constant flow of queries, responses, and questions and answers.

Typically registers take years before they get productive in the sense of analysing data, providing presentations and submitting manuscripts. The major reason is that a research plan has to be prepared and agreed upon and all the country-wise different laws and regulations have to be identified and complied with. The CDC has provided numerous reports both for the sponsor and for the various committees and boards of EUTOS. We are proud that a manuscript has been finalized about a new prognostic model which allows to predict CCgR at 18 months using two variables only (Hasford e al., Blood in pess, see section 3 WP17).

The major challenge in the coming period is to safeguard that all patients are monitored according to the research plan and that the registry receives proper follow-ups.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

17.5 Regular WP meetings

WP meetings took place at the annual ELN meeting in Mannheim (1/2010), Barcelona (EHA 6/2010), Mannheim (CML 7/2010)). Most often these WP meetings were joint meetings of WP17 and WP4.

17.6 LP reports to NMC regarding structure, activities and integration

There were regular reports to the NMC regarding structure, activities and integration.

17.13c Collect data for prognostic model analyses and meta-analyses (European CML registry)

Data of more than 3900 patients from Austria, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Norway, Poland, Romania, Russia, Spain , Sweden and Switzerland have been checked and included in the registry.

17.14c Quality control of incoming data

Quality control of incoming data is a prerequisite of any data evaluation. There are plausibility checks of each variable, concerning completeness, minimum and maximum, valid numbers, valid dates etc. Furthermore there are two-dimensional plausibility checks concerning more than one variable. Finally

comparisons between centres are being conducted to find outliers, which can be due to misinterpretations or erroneous documentation.

There will be send queries to the centres to complete the documentation and improve the quality of the data. The results of the quality control of incoming data are being presented to all participants. This activity has to continue as long as the registry collects data.

There were considerable problems due to many languages used to describe and explain the variables and items, and the 'translation´ to English took some extra time. But we are confident now that we have solved this problem. It is very helpful for us to get the documentation in the Excel template sheets that are provided by us, the participants can cross-check their documentation by filling in them so the number of queries can be reduced.

17.15d Spreading of Excellence by promotion of web-based information, educational training courses etc.

- A major point of basically all presentations was to encourage the physicians in the audience to treat elderly patients with modern treatments like Imatinib.
- In May, Joerg Hasford and Markus Pfirrmann participated in the "European investigators in CML" meeting. in Prague. Hasford and Pfirrmann met most European coordinators of studies in CML. The occasion was used to promote the CML registry. In addition results of our analyses were presented and discussed.
- In July Joerg Hasford presented results at the annual CML-Symposium in Mannheim

17.16d Update of the CML registry

As already mentioned in 2008 and 2009, we tried hard to update the information in the registry. In the last quarter, many study groups provided updates so that we can proceed with the analysis plan.

17.17b Gender specific issues

- To analyse the influence of gender is an obligate issue in each analysis. Gender and age are considered as potential prognostic variables in each standard evaluation of leukaemia studies and therefore compulsory. But it is planned to check for sex-specific disease-, treatment-, and outcome characteristics, too. Due to the fact that most data provided by the study groups consisted of baseline data, our plans of first analyses could not yet be fulfilled with the registry.

17.21bAnalysis and Validation of prognostic models

Due to the delays in updating the data and the comparable few events (e.g. death, relapse) seen under Imatinib, we could not yet analyse prognostic factors. We hope to progress in 2009.

Table 17.1: List of Deliverables WP17, 2010

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP17	**Biometry of Registry, Epidemiology, Metaanalyses and Prognosis**					
17.5	Regular WP meetings	78,84,86	78,84,86	0	2	Hasford
17.6	LP reports to NMC regarding structure, activities and integration (1 page, bullet point style)	79,86	86	0	2	Hasford
17.13d	Collect data for prognostic model analyses and epidemiological and treatment survey	73-86	86	0	6	Hasford
17.14d	Quality control of incoming data-continued	73-86	86	0	6	Hasford, Müller
17.15e	Spreading of excellence by promotion of web-based information, educational training courses etc	73-86	86	0	2	Simonsson, Hasford, J Guilhot, Baccarani
17.16e	Update of CML-Registry	73-86	86	0	4	Hasford, J Guilhot, Baccarani, Simonsson
17.17c	Analysis of gender specific issues	76	86	0	1	Hasford
17.21c	Analysis and Validation of prognostic models	73-86	86	0		Hasford

*) if available

Table 17.2 List of milestones WP17, 2010

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP17	**Biometry of Registry, Epidemiology, Metaanalyses and Prognosis**			
17.21c	Analysis and Validation of prognostic models	73-86	86	Hasford
17.22c	Estimates of incidence of CML and treatment survey	73-86	86	Hasford

Section 4: Other Issues

Ethical issues – none, Competitive calls – none

Section 5: WP-Performance

Performance indicators	Status
Development of core data sets	done (for CML, MDS)
Number of clinical trials performed with standardized common data sets	CML trials
Number of involved countries	24
Number of involved/registered patients	4703

Annex - Plan for using and disseminating the knowledge

16 Section 1: Exploitable knowledge and its use

Is not relevant and not the primary aim of the network.

17 Section 2: Dissemination of knowledge: WP-Meetings

WP-Meetings WP1

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 450 participants from EU and non EU countries

- WP-meetings, EHA, Barcelona, June 2010

Attendance: Approximately 210 participants from EU countries

- ELN ASH Breakfast Meeting 2010, Orlando, December 05 th, 2010

Attendance: Approximately 180 participants from European countries

WP-Meetings WP2

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 60 participants EU countries

- Internal Workshop of the ELN for Quality of life and late effects in Hematolgocial Malignancies, Mannheim, 1 February 2011

Attendance: Approximately 90 participants EU countries

- Workshop in Mannheim about European Clinical Trials Directive: Suggestions for modification and practical approaches, Mannheim, 1 February 2011

Attendance: Approximately 40 participants EU countries

Road Map Initiative for Clinical Research in Europe:

- 18 January 2010: Meeting in Barcelona (Spain): Risk based approach organised by ECRIN
- 19 January 2010: Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe organised by ECRIN
- 8 February 2010: Meeting in Brussels (The Netherlands): Towards a better Future for Pharmacovigilance in Clinical Trials organised by EORTC
- 17 March 2010: Meeting in Brussels (The Netherlands): Designing the Future Conditions for Clinical Research in Europe by EFGCP

WP-Meetings WP3

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 45 participants from EU and non EU countries

WP-Meetings WP4

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 100 participants from EU and non EU countries

- Annual ELN Symposium, EUTOS Meeting, Mannheim, February 3rd

Attendance: Approximately 75 participants from EU and non EU countries

- EI-CML meeting, Spineto, Italy, May 2010

Attendance: Approximately 40 participants from EU

- WP meeting, EHA, Barcelona, June 4

Attendance: Approximately 50 participants from EU

- CML symposium, Heidelberg July 2

Attendance: Approximately 120 participants from EU and non-EU

- ELN Frontiers meeting, Wien, September 2010

Attendance: 400 participants from EU

- ESH-ELN joined CML meeting, Bordeaux, September 2009

Attendance: 300 participants from EU

- ELN Breakfast meeting at ASH, Orlando, December 5

Attendance: Approximately 55 participants from European countries

- EUTOS registry meeting WP4, ASH, New Orleans, New Orleans December 05

Attendance: Approximately 10 participants from EU countries

WP-Meetings WP5

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 60 participants from EU and non EU countries

- 6th Symposium of the AML Intergroup, Reisensburg February 11 2011

Attendance: Approximately 25 participants from EU and non EU countries

- WP meeting, EHA, Barcelona, June 10

Attendance: Approximately 50 participants from EU

- AML Intergroup Meeting, Frankfurt, 05/2010

Attendance: Approximately 20 participants from EU countries

- AML Intergroup Meeting, Frankfurt, 09/2010

Attendance: Approximately 20 participants from EU countries

- ELN Breakfast meeting at ASH, Orlando, December 5

Attendance: Approximately 20 participants from European countries

WP-Meetings WP6

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 45participants from EU and non EU countries

- EWALL, Milano June 2010

Attendance: Approximately 20 participants; EWALL internal meeting

- EWALL, Frankfurt, November 2010

Attendance: Approximately 20 participants from EU countries

- ASH, Orlando, December 2010

Informal meeting during the ELN breakfast meeting; approximately 10 EWALL members

WP-Meetings WP7

- 19th ERIC Meeting at the 6th Annual Symposium of the ELN, Mannheim, February 02, 2010

Attendance: Approximately 45 participants from EU and non EU countries

- 23rd ERIC Meeting at the European Hematology Association (EHA) Congress, Barcelona, Thursday 10th June 2010.

Attendance: Approximately 55 participants from EU and non EU countries ERIC/EHA

- 24th General Meeting of ERIC Members, Orlando, 5th December 2010

Attendance: Approximately 50 participants from EU and non EU countries

- 21st General Meeting of ERIC Members, Orlando, December 05 th, 2010

Attendance: Approximately 50 participants from EU and non EU countries

WP-Meetings WP8

- Annual ELN Symposium, MDS WP meeting, Mannheim, 2 February; 2010

Attendance: 103 participants from EU

- European MDS Registry project, Operational team meeting, Mannheim, February 1, 2010

Attendance: 14 participants

- European MDS Registry project, Steering Committee meeting, Mannheim, February 2, 2010

Attendance: 10 participants

- European MDS Registry project, Operational team meeting, Barcelona, June 9, 2010

Attendance: 18 participants

- European MDS Registry project, Steering Committee meeting, Barcelona, June 9, 2010

Attendance: 10 participants

- European MDS Registry project, Operational team teleconferences, March 1, 2010

Attendance: 13 participants

- European MDS Registry project, Operational team teleconferences, April 6, 2010

Attendance: 8 participants

- European MDS Registry project, Operational team teleconferences, May 10, 2010

Attendance: 10 participants

- European MDS Registry project, Operational team teleconferences, September 6, 2010

Attendance: 6 participants

- ELN steering committee meeting, ASH congress, Orlando, December 3 2010

Attendance: 11 participants

- ELN breakfast meeting, ASH congress, Orlando, December 5 2010
- ELN Frontiers meeting, Vienna, October 23-24 2010
- MDS Iron Forum, Rome September 25, 2010
- Annual ELN Symposium, MDS WP meeting, Mannheim, 1 February; 2011

Attendance: 90 participants from EU

- European MDS Registry project, Steering Committee meeting, Mannheim, January 31, 2011

Attendance: 17 participants

- European MDS Registry project, Operational team meeting, Mannheim, February 1, 2010

Attendance: 13 participants

WP-Meetings WP9

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 60 participants from EU and non EU countries

- European Hematology Association (EHA) Congress, Barcelona, June 10th

Attendance: 15 participants from European countries

- ELN Breakfast meeting, ASH, Orlando, December 5th

Attendance: 20 participants from European countries

WP-Meetings WP10

- Annual ELN Symposium, Mannheim, February 2nd 2010

Attendance: Approximately 60 participants from EU and non EU countries

- EGIL meeting in Berlin, March 2010

Attendance: Approximately 10 participants from EU and non EU countries

- MDS meeting, Munich, October 2010

Attendance: Approximately 15 participants from EU and non EU countries

- EHA European School in Cascais, November 2010

Attendance: Approximately 15 participants from EU countries

WP-Meetings WP11

- Annual ELN Symposium, Mannheim, February 2nd
- EHA, Barcelona, June 10th 2010

Attendance: Approximately 30 participants from EU countries

- Annual ELN Symposium, Mannheim, February 1st 2011

Attendance: Approximately 8 participants from EU and non EU countries

WP-Meetings WP12 (2010-2011)

- Annual ELN Symposium, Mannheim, February 2nd 2010

Attendance: Approximately 85 participants from EU and non EU countries

- EHA, Barcelona, June 10th 2010

Attendance: Approximately 20 participants from EU countries

- Annual ELN Symposium, Mannheim, February 1st 2011

Attendance: Approximately 70 participants from EU and non EU countries

WP-Meetings WP13

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 60 participants from EU and non-EU countries

- MILE study - met together with WP10, 11 and 12 in Munich in May 2010

Attendance: Approximately 60 participants from EU and non-EU countries

- MILE study - met together with WP10, 11 and 12 in Munich in May 2010

Attendance: Approximately 60 participants from EU and non-EU countries

One regular WP meeting for all WP13 members, combined in part with WP11, had been organized in Heidelberg in February 2010. Furthermore, some members of WP13 - mostly representing members also of the European part of the MILE study - met together with WP10, 11 and 12 in Munich in May 2010 and in October 2010 for new activities together with COST and EuGESMA (see above).

WP-Meetings WP14

- EBMT CLWP/ELN; Hotel Merian, Basel, Switzerland, January 22-23, 2010

Attendance: n.a.

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 80 participants from EU and non-EU countries

- EBMT annual meeting, Vienna, March 21, 2010

Attendance: Approximately 70 participants from EU and non-EU countries

- WP5/WP14 meeting at EHA/ELN FIRA, Gran Via Conf. Center, Barcelona June 10, 2010

Attendance: Approximately 50 participants from EU and non-EU countries

- Subcommittee meeting in Leiden, June 17 2010

Attendance: Approximately 30 participants from EU and non-EU countries

- EBMT CLWP/ELN; "La Distillerie", Mons, Belgium, September 17- 18, 2010

Attendance: Approximately 70 participants from EU and non-EU countries

- CLWP Subcommittee chair meeting in Leiden November 13 2010

Attendance: Approximately 30 participants from EU and non-EU countries

- ELN Breakfast meeting, ASH, WP5/WP14 JW Marriott Orlando, December 05, 2010

Attendance: Approximately 40 participants from EU and non-EU countries

WP-Meetings WP15

- Annual ELN Symposium, Mannheim, February 2nd

Attendance: Approximately 10 participants from EU and non EU countries

- EBMT meeting in Vienna March 2010

Attendance: Approximately 30 participants from EU and non-EU countries

- EBMT meeting in Paris October 2010

Attendance: Approximately 30 participants from EU and non-EU countries

WP-Meetings WP17

- Annual ELN Symposium together with WP4 and WP5, Mannheim, February 2nd

Attendance: Approximately 100 participants from EU and non EU countries

- EI-CML Meeting, Spineto, Italy, May 2010

Attendance: Approximately 40 participants from EU countries

- 18th International CML Workshop, 2 July 2010, Heidelberg

Attendance: Approximately 120 participants from EU and non EU countries

- ELN-Frontiers meeting, CML Educational, September 2010, Vienna

Attendance: Approximately 400 participants from EU and non EU countries

- ELN Breakfast meeting together with WP4, ASH, Orlando, December 05, 2010

Attendance: Approximately 40 participants from EU and non-EU countries

- EUTOS registry meeting WP4, ASH, Orlando, December 05, 2010

Attendance: Approximately 10 participants from EU countries

Presentations / Spread of excellence

Table Annex 1: (Press release (PR), oral presentations (OP), organization (O), Exhibition (E), Congress/ Symposium (CS), Poster (PO), email, Website (www), Workshop (WS))

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
All	permanent	www	Website www.leukemia-net.org	Network members & General public	all	See ELIC report	ELIC
1/2	10-2010	E	DGHO Berlin, Germany	Researcher	Germany Austria, Siwtzerland	2500-3000	NMC,ELIC
1/2	10-2010	E	EHA Barcelona, Spain	Researcher	European	5500-6500	NMC,ELIC
1/2	10-2010	E	ASH Orlando, USA	Researcher	International	10000	NMC,ELIC
1/2	12-10	PR	Information Letter	All	all	>1000	NMC
1	02.02.09	CS	Mannheim, ELN/KNL-Symposium „Welcome to the ELN-Symposium 2009“	Research	European	350	NMC, Hehlmann
1	02-2010	CS	Assembly, European LeukemiaNet meeting Mannheim	Research	European	350	NMC, Saußele
1	11.02.2011	CS	AML Intergroup, Reisensburg, Germany	Physicians and Scientists	Germany	50	Hehlmann
1/4	1.-7.12. 2010	OP	Orlando, ASH	Physicians and Scientists	International	3000-10.000	Hehlmann Saußele Kossak-Roth
1	05.12.2010	CS	Orlando, ELN-Breakfast meeting. Overview ELN 2010	Physicians and Scientists	International	150	Hehlmann Saußele
1	02.02.2010	OP	ELN Symposium Update ELN-Foundation	Physicians and Scientists	International	300	P.Schrotz-King
1	01.02.10	CS	Mannheim, ELN/KNL-Symposium „Welcome to the ELN-Symposium 2010“	Physicians and Scientists	European	350	NMC, Hehlmann
All	permanent	www	Website www.leukemia-net.org	Network members & General public	all	See ELIC report	ELIC
1/2	10-2010	E	DGHO Berlin, Germany	Researcher	Germany Austria, Siwtzerland	not applicable	NMC,ELIC
1/2	12-10	PR	Information Letter	All	all	not applicable	NMC
1/4	20.01.10	OP	Tannheimer Tal, Vortrag: “ Historische und aktuelle Entwicklung der CML-Therapie“	Physicians and Scientists	European	50	Hehlmann
1	02-2010	CS	Assembly, European LeukemiaNet meeting Mannheim	Physicians and Scientists	European	350	NMC, Saußele
1	11.02.2011	CS	AML Intergroup, Reisensburg, Germany	Physicians and Scientists	Germany	50	Hehlmann
1	17.-19.4.10	CS	AACR Meeting. European LeukemiaNet, enabling personalized Leukemia diagnosis in Europe and beyond, Washington	Physicians and Scientists	International	150	Hehlmann

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
1	10.6.10	CS	CMPD Panel Meeting	Physicians and Scientists	European	20	Hehlmann
1	13.-14.10.10	OP	ECPC Cancer Summit, Brüssel: The European LeukemiaNet: Cooperative research to cure leukemia	Public	European	200	Hehlmann
1/4	1.-7.12. 2010	OP	Orlando, ASH	Physicians and Scientists	International	3000-10.000	Hehlmann Saußele Kossak-Roth
1	05.12.2010		Orlando, ELN-Breakfast meeting. Overview ELN 2010	Physicians and Scientists	International	150	Hehlmann Saußele
1	02.02.2010	OP	ELN Symposium Update ELN-Foundation	Physicians and Scientists	International	300	P.Schrotz-King
2	1.02.11	WS	IIT Workshop: Clinical trials directive – new developments	Physicians and Scientists	International	80	Gökbuget
2	2.02.10	WS	Life quality and late effects: activities and future collaboration in the European LeukemiaNet	Physicians and Scientists	International	150	Gökbuget,Ihrig
2	18 02 2010	WS	Meeting in Barcelona (Spain): Risk based approach organised by ECRIN	Physicians and Scientists	European	110	Gökbuget ECRIN
2	19 01 2010	WS	Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe	Physicians and Scientists	European	na	Gökbuget ECRIN
2	8 02 2010	WS	Meeting in Brussels (The Netherlands): Towards a better Future for Pharmacovigilance in Clinical Trials	Physicians and Scientists	European	na	Gökbuget EORTC
2	17 03 2010	WS	Meeting in Brussels (The Netherlands): Designing the Future Conditions for Clinical Research in Europe	Physicians and Scientists	European	na	Gökbuget EFGCP
3	1.02.10	WS	Workshop ”Regulatory requirements for the clinical development of cell therapeutics and biologicals“	Physicians and Scientists	International	50	Mansmann
4	3.-7.3.10	CS	CML GOLS The revised ELN recommendations CML GOLS, Dresden	Physicians and Scientists	European	650	Hehlmann
4	5.-6.3.10	WS	Advisory Board Meeting on CML, Dresden	Physicians and Scientists	Germany	20	Hehlmann
4	7.-10.4.10	WS	Workshop „Modern diagnostic and treatment approach to CML“, OP: On the path to cure CML. New developments, Kiew	Physicians and Scientists	National	200	Hehlmann
4	12.4.2010	CS	International Meeting on CML: Updated ELN recommendations for the management of CML, Genua	Physicians and Scientists	European	50	Hehlmann

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
4	15.-17.4.10	CS	Novartis 6th Nilotinib Global Investigators Meeting: The treatment of patients with newly diagnosed CML: A decade of progress, Rome	Physicians and Scientists	European	200	Hehlmann
4	17.-19.4.10	CS	Polish School of Hematology: First and second line therapy of CML, Warzwa	Physicians and Scientists	National	150	Hehlmann
4	13.-16.5.10	CS	EI-CML-Meeting: High dose Imatinib, Introduction, Spineto, Italy	Physicians and Scientists	European	45	Hehlmann Saußele Müller
4	17.-18.5.10	CS	European fellows educational day: EUTOS for CML. An innovative collaboration between ELN and Novartis, Naples	Young Physicians and Scientists	European	60	Hehlmann Saußele
4	4.6.10	CS	Imidex: Current best practice for management of accelerated/blastic phase CML, Chicago, ASCO	Physicians and Scientists	International	1000	Hehlmann
4	7.6.10	PO	Treatment optimization by high-dose imatinib: Randomized comparison of imatinib 800 mg versus imatinib 400 mg ± IFN in newly diagnosed BCR-ABL positive chronic phase (CP) CML: The German CML-study IV, ASCO	Physicians and Scientists	International	40,000	Hehlmann
4	10.6.10	CS	WP4 meeting at EHA, Barcelona	Physicians and Scientists	European	70	Hehlmann
4	8.5.10	CS	COHEM, High dose Imatinib, Introduction, Split	Physicians and Scientists	European	50	Hehlmann
4	13.6.10	CS	EHA 2010: Treatment optimization by high-dose imatinib: Randomized comparison of imatinib 800 mg vs. imatinib 400 mg vs. imatinib 400 mg ± IFN in newly diagnosed BCR-ABL positive chronic phase (CP) CML with regard to MMR at month 12: The German CML-study IV	Physicians and Scientists	European	1500	Hehlmann
4	2.-3.7.10	CS	CML Studientreffen mit 19. Internat. Workshop: Cooperation on Leukemia in Europe. The European LeukemiaNet, Heidelberg	Physicians and Scientists	European	200	Hehlmann Saußele Müller
4	3.7.10	CS	EUTOS Meeting	Physicians and Scientists	European	100	Hehlmann Saußele Mülelr

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
4	2.-5.9.10	OP	1. World Congress Controversies in Hematology: Should first line imatinib treatment be optimized by combination with IFN or by higher imatinib dose? Rome	Physicians and Scientists	European	150	Hehlmann
4	10.06.2010	OP	EHA: "Randomized clinical trial for the optimization of imatinib therapy by combination, dose escalation and trans-plantation. Designed first interim analysis of the German CML Study IV"	Physicians and Scientists	International	2000	Hehlmann
4	2.-3.7.10	OP	international CML-Workshop, EUTOS Meeting: CML Study IV	Physicians and Scientists	International	120	Hehlmann
4	9.7.10	OP	Rotary-Kurpfalz: European LeukemiaNet – europäische Antwort auf das Leukämieproblem	Public	National	70	Hehlmann Saußele
4	23.-27.9.10	CS	ESH-Symposium, Washington	Physicians and Scientists	International	300	Hehlmann Müller
4	2.-5.10.10	OP	DGHO, Mannheim, Vortrag: CML IV	Physicians and Scientists	Germany	300	Hehlmann
4	2.-5.10.10	OP	DGHO, Berlin, Vortrag: CML IV	Physicians and Scientists	Germany	150	Saußele Müller
4	20.-25.10.10	OP	ELN Frontiers 2010, Vienna: The concept of cure and the path to cure	Physicians and Scientists	European	550	Hehlmann
1/4	21.10.10	PR	EUTOS-Press event	Physicians and Scientists	European	50	Hehlmann
4	27.-28.10.10	OP	Society of Hematology, Romania: Current options for first line treatment of CML and impact on prognosis	Physicians and Scientists	European	200	Hehlmann
4	7.-8.12.10	OP	Mission Inn, Orlando: Treatment optimization in CML by tolerability adapted high dose imatinib	Physicians and Scientists	International	50	Hehlmann
4	17-23.1.10		Fortschritte in der Hämatologie: Historische und aktuelle Entwicklung der CML-Therapie	Physicians and Scientists	International	50	Hehlmann
4	2.-7.12.10	OP	Orlando, ASH, OP: How to optimize TKI treatment Dose? Schedule? Interferon? 4.12.10 Superior CMR-Rates with Tolerability-Adapted Imatinib 800 mg vs. 400 mg vs. 400 mg + IFN in CML: The German Randomized CML-Study IV	Physicians and Scientists	International	2000	Hehlmann
5	01.02.-03.02.10	OP	European LeukemiaNet Symposium, Mannheim, Germany	Physicians and Scientists	International	ca. 400	Büchner

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
5	12.02.10	OP	AML Intergroup Meeting, Reisensburg, Germany	Physicians and Scientists	International	40	Büchner
5	26.03.2010	OP	Amonafide Advisory Board Meeting, London, GB	Physicians and Scientists	International	20	Büchner
5	03.05.10	OP	AML Intergroup Meeting, Frankfurt, Germany	Physicians and Scientists	Germany	20	Büchner
5	10.06.10	OP	European LeukemiaNet Meeting at EHA, Barcelona, Spain	Physicians and Scientists	International	40	Büchner
5	19.08.2010	OP	AML Register Meeting, München, Deutschland	Physicians and Scientists	Germany	8-10	Büchner
5	14.-15.09.2010	OP	Advisory Board Meeting, Barcelona, Spain	Physicians and Scientists	International	50	Büchner
5	18.-20.09.2010	OP	Raissa Gorbacheva Memorial Lecture, St. Petersburg, Russia	Physicians and Scientists	International	100	Büchner
5	01.-05.10.2010	OP	DGHO Satellitensymposium Berlin, Germany	Physicians and Scientists	Germany	50	Büchner
5	10.-12.10.2010	OP	XXXIII World Congress of ISH, Jeruslem, Israel	Physicians and Scientists	International	ca. 500	Büchner
5	15.10.2010	OP	Turku XII Stem Cell Symposium, Turku, Finnland	Physicians and Scientists	International	100	Büchner
5	18.10.2010	OP	AML Intergroup Meeting, Frankfurt, Germany	Physicians and Scientists	Germany	20	Büchner
5	22.-24.10.2010	OP	ELN Frontiers Meeting, Vienna, Austria	Physicians and Scientists	International	200	Büchner
5	05.12.2010	PO	ASH Annual Meeting, Orlando, USA	Physicians and Scientists	International	100	Büchner
5	02.12.2010	OP	ELN Breakfast Meeting at ASH, Orlando, USA	Physicians and Scientists	“	25	Büchner
6	1.2.-2.2.11	OP	European Leukemia Net und Netzwerksymposium Kompetenznetz Leukämien EWALL WP6	Physicians and Scientists	International	40-100	Bassan, Holowiecki, Hoelzer, Ribera, Hunault, Gökbuget, Ottmann, Iacobucci, Martinelli
6	06 2010	WS	first workshop of the newly founded EHA-EWALL working group (EHA meeting in Barcelona)	Physicians and Scientists	International	100	Bassan Dombret Gökbuget Foa Fielding Ribera
6	EHA Education Session 12/2010	OP	Ottmann O.G.: Treatment of Ph+ adult ALL	Physicians and Scientists	International	2500	Ottmann
6	EHA Education Session 12/2010	OP	MRD oriented treatment in PH-adult ALL	Physicians and Scientists	International	1500	Ribera
6	ASH Education Session 12/20100	OP	Treating the "Older" Adult With Acute Lymphoblastic Leukemia	Physicians and Scientists	International	3500	Marks

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
7	02.02.10	CS	20th ERIC Meeting Annual Symposium of the European LeukemiaNet, Mannheim	clinical + basic researchers	International	45	Hallek
7	05.12.09	CS, WS, OP, PO	ERIC/ELN Breakfast Meeting at the 52th Annual Congress of the American Society of Hematolgy, Orlando, USA	clinical + basic researchers	International	50	Hallek
8	02.02.10	CS	Annual ELN Symposium, MDS WP meeting, Mannh.	clinical + basic researchers	European	95	De Witte
9	03.02.10		Annual ELN Symposium	clinical + basic researchers	European	30	Barbui
9	10.06.2010		WP meeting at the EHA Congress in Barcelona	clinical + basic researchers	European	35	Barbui
9	05.12.10		WP meeting at the ASH in Orlando, US	clinical + basic researchers	International	20	Barbui
10	03.02.10	CS	Annual ELN Symposium	clinical + basic researchers	European	20	Béné
12	20.05.2010	OP	British Medical Journal Masterclass for Physicians Haematology, London	clinical + basic researchers	UK	150	Grimwade
12	09-13.06.2010	OP	European Hematology Association meeting, Barcelona	clinical + basic researchers	UK	200	Grimwade
12	28.06.2010	OP	Advances in Haematology Research 2010, The Christie Hospital, Manchester	clinical + basic researchers	UK	100	Grimwade
12	02.09.2010	OP	Haematological Malignancies Conference, Institute. of Physics, London	clinical + basic researchers	UK	50	Grimwade
12	03.-05.09.2010	OP	Controversies in Haematology meeting, Rome	clinical + basic researchers	international	200	Grimwade
12	16.-18.9.2010	OP	"Molecular Pathogenesis of Leukemia, Insights & Challenges", Frankfurt	clinical + basic researchers	european	75	Grimwade
12	27.9.2010	OP	Acute Leukaemia Day, Birmingham	clinical + basic researchers	UK	100	Grimwade
12	03.10.2010	OP	DGHO meeting, Berlin	clinical + basic researchers	international	80	Grimwade
12	25.10.2010	OP	Advances in the Management of Haematological Malignancies, Birmingham	clinical + basic researchers	UK	30	Grimwade
12	29 Nov 2010	OP	NCRI Paediatric AML	clinical + basic researchers	UK	30	Grimwade
13	02.02.10	WS	WP meeting for all WP13 members, combined in part with WP11, in Mannheim, Germany	Research + Clinical	International	70	Haferlach
13	9-11.5.10	WS	IRON workshop in Munich for NGS testing	Research + Clinical	International	60	Haferlach
13	17-19.10.10	WS	WP13 members representing the European met together with WP10, and COST group for NGS future in Munich	Research + Clinical	International	90	Haferlach / Mills

WP	Planned/actual Dates	Type	Event	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
13	6.12.10	PO	Poster on IRON study at ASH Orlando	Research + Clinical	International	ASH	Kohlmann / Haferlach
14	12.10	CS	ELN meeting WP5/WP14 Orlando	Research + Clinical	International		Niederwieser
15	02.10		WP meeting at the ELN symposium in Mannheim, Germany, and in Paris.	Clinicians and basic researchers	international	20	Ljungman
15	03.10		WP meeting at the EBMT meeting in Vienna,	Clinicians and basic researchers	international	100	Ljungman
15	09.10		WP meeting at the EBMT meeting in Juan-les-Pins	Clinicians and basic researchers	international	50	Ljungman
15	10.10		WP meeting at the EBMT meeting in Paris	Clinicians and basic researchers	international	15	Ljungman
17	02/2011	OP	ELN Symposium Mannheim	Physicians and Scientists	European	100	J. Hasford
17	04/2010	OP	Cancers in the Elderly, Rome	Physicians	European	500	J. Hasford

18 Section 3: Publishable results

WP1 (NMC) and WP2 (ELIC)

1-1 N. Gökbuget, D. Hoelzer, S. Saussele, R. Hehlmann (Editors). WP2 in cooperation with WP1, 01/2011: 7th ELN Information Letter.

1-2 ELN Booth, EHA, Barcelona 06/2010

1-3 ELN Booth, DGHO, ÖGH, SGH, Berlin, 10/2010

1-4 ELN Booth, ELN-Frontiers,Vienna, 10/2010

1-5 ELN Booth, ASH, Orlando, 12/2010

1-6 Steering Committee 2010, Minutes

1-7 Steering Committee 2011, Minutes

1-8 ELN Assembly minutes 2010

1-9 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

1-10 Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010.

1-11 Summary Information Letter on Achievements: EUTOS 2007-2010 at the Annual ELN Symposium 2011.

WP2 (ELIC) Publications:

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

2-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

2-2 Frewer LJ, Coles D, Champion K, Demotes-Mainard J, Goetbuget N, Ihrig K, et al. Has the European Clinical Trials Directive been a success? British Medical Journal [Editorial] 2010; 340:937-8.

WP3 (CICS) Publications:

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

3-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

WP4 (CML)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

4-1 Baruzzi A, Iacobucci I, Soverini S, Lowell CA, Martinelli G, Berton G. c-Abl and Src-family kinases cross-talk in regulation of myeloid cell migration. Febs Letters 2010; 584(1):15-21.

4-2 Breccia M, Capria S, Iori AP, Foa R, Alimena G, Meloni G. Clofarabine-Based Regimen as Useful Bridge Therapy for Allogeneic Transplantation in Myeloid Blast Crisis of Philadelphia-Positive Chronic Myeloid Leukemia Resistant to Imatinib and Dasatinib. Acta Haematologica [Article] 2010; 124(3):150-2.

4-3 Breccia M, Orlandi SM, Latagliata R, Grammatico S, Diverio D, Mancini M, et al. Suboptimal response to imatinib according to 2006-2009 European LeukaemiaNet criteria: a 'grey zone' at 3, 6 and 12 months identifies chronic myeloid leukaemia patients who need early intervention. British Journal of Haematology 2011; 152(1):119-21.

4-4 Breccia M, Palandri F, Iori AP, Colaci E, Latagliata R, Castagnetti F, et al. Second-generation tyrosine kinase inhibitors before allogeneic stem cell transplantation in patients with chronic myeloid leukemia resistant to imatinib. Leukemia Research [Article, mit ELN] 2010; 34(2):143-7.

4-5 Castagnetti F, Testoni N, Luatti S, Marzocchi G, Mancini M, Kerim S, et al. Deletions of the Derivative Chromosome 9 Do Not Influence the Response and the Outcome of Chronic Myeloid Leukemia in Early Chronic Phase Treated With Imatinib Mesylate: GIMEMA CML Working Party Analysis. Journal of Clinical Oncology 2010; 28(16):2748-54.

4-6 Catellani S, Pierri I, Gobbi M, Poggi A, Zocchi MR. Imatinib Treatment Induces CD5+B Lymphocytes and IgM Natural Antibodies with Anti-Leukemic Reactivity in Patients with Chronic Myelogenous Leukemia. Plos One 2011; 6(4):Article No.: e18925.

4-7 Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011:prepublished online.

4-8 Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Muller MC, Pletsch N, et al. Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon-alpha in Newly Diagnosed Chronic Myeloid Leukemia. Journal of Clinical Oncology [ELN] 2011; 29(12):1634-42.

4-9 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

4-10 Kreil S, Waghorn K, Ernst T, Chase A, White H, Hehlmann R, et al. A polymorphism associated with STAT3 expression and response of chronic myeloid leukemia to interferon alpha. Haematologica-the Hematology Journal 2010; 95(1):148-52.

4-11 Kreutzman A, Juvonen V, Kairisto V, Ekblom M, Stenke L, Seggewiss R, et al. Mono/oligoclonal T and NK cells are common in chronic myeloid leukemia patients at diagnosis and expand during dasatinib therapy. Blood 2010; 116(5):772-82.

4-12 Leitner AA, Hehlmann R. Modern therapy of chronic myeloid leukemia. Internist 2011; 52(2):209-17.

4-13 Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncology 2010; 11(11):1029-35.

4-14 Mustjoki S, J Richter, G Barbany, I Dybedal, T Fioretos, T Gedde-Dahl, B Gjertsen, R Hovland, S Jalkanen, D Josefsen, P Koskenvesa, C Lassen, K Latvala, W Majeed, C Malm, B Markevärn, A Moshfegh, L Ohm, T Olofsson, U Strömberg, K Rapakko, K Remes, J Stentoft, L Stenke, M Suominen, S Thunberg, O Weiss Bjerrum, B Simonsson, K Porkka, and HHjorth-Hansen. The Proportion of Ph+ CD34+CD38neg Leukemic Stem Cells In the Bone Marrow of Newly Diagnosed Patients with Chronic Myeloid Leukemia (CML) In Chronic Phase (CP) Is Variable and Correlates with High Sokal Risk, High Leukocyte Count, Low Hemoglobin Concentration, Splenomegaly and Increased Hematological Toxicity During Initial TKI-Therapy.

4-15 Pfirrmann M, Hochhaus A, Lauseker M, Sausele S, Hehlmann R, Hasford J. Recommendations to meet statistical challenges arising from endpoints beyond overall survival in clinical trials on chronic myeloid leukemia. Leukemia 2011:in press.

4-16 Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010; 115(10):1880-5.

4-17 Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, et al. Bcr-Abl kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 2011:in press.

4-18 Zaccaria A, Testoni N, Valenti AM, Luatti S, Tonelli M, Marzocchi G, et al. Chromosome abnormalities additional to the Philadelphia chromosome at the diagnosis of chronic myelogenous leukemia: pathogenetic and prognostic implications. Cancer Genetics and Cytogenetics [Article, mit ELN] 2010; 199(2):76-80.

*Abstracts (**with** a reference to the European LeukemiaNet):*

4-19 Baccarani M. Chronic Myeloid Leukemia: How Can Minimal Cytogenetic Response After 3 Months of Treatment Be Classified According to the New European LeukemiaNet Recommendations? Reply. Journal of Clinical Oncology 2010; 28(18):E311-E.

4-20 Cortes JE, Shah NP, Schiffer CA, Doz P, Saglio G, Cardama AQ, et al. Significance of ELN Provisional Response Definitions In Predicting Long Term Outcomes of Patients with CP CML Treated with Dasatinib After Imatinib Failure. Blood 2010; 116(21):1410-1.

4-21 Guilhot J, Tartarin F, Hochhaus A, Saussele S, Nicolini F, Rosti G, et al. European sub-registry of chronic myeloid leukemia (CML) patients (PTS) in failure after imatinib therapy (IFP): rationale, study design and current status. A study from the European LeukemiaNet (ELN). Haematologica-the Hematology Journal 2010; 95(Suppl. 2):60-1.

4-22 Hurtz C, Duy C, Cerchietti L, Chatzi K, Park E, Klemm L, et al. BCL6 Is Required for the Maintenance of Leukemia Initiating Cells In Chronic Myeloid Leukemia. Blood 2010; 116(21):92-3.

4-23 Mustjoki S, Richter J, Barbany G, Dybedal I, Fioretos T, Dahl TG, et al. The Proportion of Ph+CD34(+)CD38(neg) Leukemic Stem Cells In the Bone Marrow of Newly Diagnosed Patients with Chronic Myeloid Leukemia (CML) In Chronic Phase (CP) Is Variable and Correlates with High Sokal Risk, High Leukocyte Count, Low Hemoglobin Concentration, Splenomegaly and Increased Hematological Toxicity During Initial TKI Therapy Data From a Randomized Phase II NordCML006 Study. Blood 2010; 116(21):291-2.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

4-24 Baccarani M, Dreyling M, Grp EGW. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology [Article] 2010; 21:v165-v7.

4-25 Bazeos A, Marin D, Reid AG, Gerrard G, Milojkovic D, May PC, et al. hOCT1 transcript levels and single nucleotide polymorphisms as predictive factors for response to imatinib in chronic myeloid leukemia. Leukemia 2010; 24(6):1243-5.

4-26 Beider K, Begin M, Abraham M, Wald H, Weiss ID, Wald O, et al. CXCR4 antagonist 4F-benzoyl-TN14003 inhibits leukemia and multiple myeloma tumor growth. Experimental Hematology 2011; 39(3):282-92.

4-27 Burchert A, Muller MC, Kostrewa P, Erben P, Bostel T, Liebler S, et al. Sustained Molecular Response With Interferon Alfa Maintenance After Induction Therapy With Imatinib Plus Interferon Alfa in Patients With Chronic Myeloid Leukemia. Journal of Clinical Oncology [ohne ELN] 2010; 28(8):1429-35.

4-28 Castagnetti F, Testoni N, Luatti S, Marzocchi G, Mancini M, Kerim S, Giugliano E, Albano F, Cuneo A, Abruzzese E, Martino B, Palandri F, Amabile M, Iacobucci I, Alimena G, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Deletions of the derivative chromosome 9 do not influence the response and the outcome of chronic myeloid leukemia in early chronic phase treated with imatinib mesylate: GIMEMA CML Working Party analysis. J Clin Oncol. 2010 Jun 1;28(16):2748-54. Epub 2010 May 3. PubMed PMID: 20439635.

4-29 Cervantes F, Lopez-Garrido P, Montero MI, Jonte F, Martinez J, Hernandez-Boluda JC, et al. Early intervention during imatinib therapy in patients with newly diagnosed chronic-phase chronic myeloid leukemia: a study of the Spanish PETHEMA group. Haematologica-the Hematology Journal 2010; 95(8):1317-24.

4-30 Chomel JC, Sorel N, Bonnet ML, Bertrand A, Brizard F, Roy L, et al. Extensive analysis of the T315I substitution and detection of additional ABL mutations in progenitors and primitive stem cell compartment in a patient with tyrosine kinase inhibitor-resistant chronic myeloid leukemia. Leukemia & Lymphoma 2010; 51(11):2103-11.

4-31 Daghistani M, Marin D, Khorashad JS, Wang LH, May PC, Paliompeis C, et al. EVI-1 oncogene expression predicts survival in chronic-phase CML patients resistant to imatinib treated with second-generation tyrosine kinase inhibitors. Blood 2010; 116(26):6014-7.

4-32 de Lavallade H, Finetti P, Carbuccia N, Khorashad JS, Charbonnier A, Foroni L, et al. A gene expression signature of primary resistance to imatinib in chronic myeloid leukemia. Leukemia Research 2010; 34(2):254-7.

4-33 Deau B, Montveneur M, Coiteux V, Renneville A, Huguet FR, Delabesse E, et al. Clinical Phenotype and Response to Imatinib of Chronic Myelogenous Leukemia Patients Harbouring Atypical BCR ABL Transcripts A Retrospective Analysis From the French Group of CML (Fr LMC) and the French Group of Molecular Biologists for Hematological Malignancies (GBMHM). Blood 2010; 116(21):1382-3.

4-34 Deenik W, Janssen J, van der Holt B, Verhoef GEG, Smit WM, Kersten MJ, et al. Efficacy of escalated imatinib combined with cytarabine in newly diagnosed patients with chronic myeloid leukemia. Haematologica-the Hematology Journal 2010; 95(6):914-21.

4-35 Deenik W, van der Holt B, Janssen J, Chu IWT, Valk PJM, Ossenkoppele GJ, et al. Polymorphisms in the multidrug resistance gene MDR1 (ABCB1) predict for molecular resistance in patients with newly diagnosed chronic myeloid leukemia receiving high-dose imatinib. Blood 2010; 116(26):6144-5.

4-36 Faber E, Friedecky D, Micova K, Divoka M, Katrincsakova B, Rozmanova S, et al. Imatinib dose escalation in two patients with chronic myeloid leukemia, with low trough imatinib plasma levels measured at various intervals from the beginning of therapy and with suboptimal treatment response, leads to the achievement of higher plasma levels and major molecular response. International Journal of Hematology 2010; 91(5):897-902.

4-37 Fava C, Saglio G. Can We and Should We Improve on Frontline Imatinib Therapy for Chronic Myeloid Leukemia? Seminars in Hematology 2010; 47(4):319-26.

4-38 Flamant S, Ritchie W, Guilhot J, Holst J, Bonnet ML, Chomel JC, et al. Micro-RNA response to imatinib mesylate in patients with chronic myeloid leukemia. Haematologica-the Hematology Journal 2010; 95(8):1325-33.

4-39 Foroni L, Wilson G, Gerrard G, Mason J, Grimwade D, White HE, et al. Guidelines for the measurement of BCR-ABL1 transcripts in chronic myeloid leukaemia. British Journal of Haematology 2011; 153(2):179-90.

4-40 Gambacorti-Passerini C, Antolini L, Mahon FX, Guilhot F, Deininger M, Fava C, et al. Multicenter Independent Assessment of Outcomes in Chronic Myeloid Leukemia Patients Treated With Imatinib. Journal of the National Cancer Institute 2011; 103(7):553-61.

4-41 Garland P, Apperley J. Nilotinib: evaluation and analysis of its role in chronic myeloid leukemia. Future Oncology 2011; 7(2):201-18.

4-42 Giles FJ, Abruzzese E, Rosti G, Kim DW, Bhatia R, Bosly A, et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. Leukemia 2010; 24(7):1299-301.

4-43 Giles FJ, Yin O, Chia YL, le Coutre PD, Woodman RC, Ottmann OG, et al. Nilotinib Exposure Response Analysis In Patients with Imatinib Resistant or Intolerant Chronic Myeloid Leukemia (CML). Blood 2010; 116(21):390-.

4-44 Grossmann V, Kohlmann A, Zenger M, Schindela S, Eder C, Weissmann S, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 2011; 25(3):557-60.

4-45 Gruber FX, Ernst T, Kiselev Y, Hochhaus A, Mikkola I. Detection of Drug-Resistant Clones in Chronic Myelogenous Leukemia Patients during Dasatinib and Nilotinib Treatment. Clinical Chemistry 2010; 56(3):469-73.

4-46 Guilhot F, Guilhot J. Predicting response in CML. Blood [Editorial Material] 2011; 117(6):1773-4.

4-47 Hanfstein B, Muller MC, Kreil S, Ernst T, Schenk T, Lorentz C, et al. Dynamics of mutant BCR-ABL-positive clones after cessation of tyrosine kinase inhibitor therapy. Haematologica-the Hematology Journal 2011; 96(3):360-6.

4-48 Hehlmann R, Jung-Munkwitz S, Saussele S. Treatment of chronic myeloid leukemia when imatinib fails. Expert Opinion on Pharmacotherapy 2011; 12(2):269-83.

4-49 Hochhaus A, Burchert A. How Cells Respond to Interferons Reply. Journal of Clinical Oncology [Letter] 2010; 28(25):E440-E.

4-50 Hochhaus A, Duyster J, Haferlach T, Lange T, Jakob A, Overkamp F, et al. Therapy of chronic myeloid leukemia in elderly patients. Onkologe 2010; 16(1):67-72.

4-51 Hochhaus A, La Rosee P, Muller MC, Ernst T, Cross NCP. Impact of BCR-ABL mutations on patients with chronic myeloid leukemia. Cell Cycle 2011; 10(2):250-60.

4-52 Hochhaus A, Overkamp F, Lange T, Mohr A, Ottmann O, Coutre P, et al. Recommendations on monitoring and second-line therapy for chronic myeloid leukemia. Onkologe 2010; 16(7):701-8.

4-53 Hughes TP, Hochhaus A, Branford S, Muller MC, Kaeda JS, Foroni L, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood 2010; 116(19):3758-65.

4-54 Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood 2011; 117(14):3733-6.

4-55 Ibrahim AR, Paliompeis C, Bua M, Milojkovic D, Szydlo R, Khorashad JS, et al. Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. Blood 2010; 116(25):5497-500.

4-56 Jabbour E, Deininger M, Hochhaus A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia 2011; 25(2):201-10.

4-57 Jabbour E, Hochhaus A, Cortes J, La Rosee P, Kantarjian HM. Choosing the best treatment strategy for chronic myeloid leukemia patients resistant to imatinib: weighing the efficacy and safety of individual drugs with BCR-ABL mutations and patient history. Leukemia 2010; 24(1):6-12.

4-58 Janssen J, Denkers F, Valk P, Cornelissen JJ, Schuurhuis GJ, Ossenkoppele GJ. Methylation patterns in CD34 positive chronic myeloid leukemia blast crisis cells. Haematologica-the Hematology Journal [Letter] 2010; 95(6):1036-7.

4-59 Joha S, Dauphin V, Lepretre F, Corm S, Nicolini FE, Roumier C, et al. Genomic characterization of Imatinib resistance in CD34(+) cell populations from chronic myeloid leukaemia patients. Leukemia Research 2011; 35(4):448-58.

4-60 Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. New England Journal of Medicine 2010; 362(24):2260-70.

4-61 Kantarjian HM, Baccarani M, Jabbour E, Saglio G, Cortes JE. Second-Generation Tyrosine Kinase Inhibitors: The Future of Frontline CML Therapy. Clinical Cancer Research 2011; 17(7):1674-83.

4-62 Kantarjian HM, Cortes J, La Rosee P, Hochhaus A. Optimizing Therapy for Patients With Chronic Myelogenous Leukemia in Chronic Phase. Cancer 2010; 116(6):1419-30.

4-63 Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 2011; 117(4):1141-5.

4-64 Kuwabara A, Babb A, Ibrahim A, Milojkovic D, Apperley J, Bua M, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010; 116(6):1014-6.

4-65 La Rosee P, Hochhaus A. Molecular pathogenesis of tyrosine kinase resistance in chronic myeloid leukemia. Current Opinion in Hematology 2010; 17(2):91-6.

4-66 Latagliata R, Breccia M, Carmosino I, Cannella L, De Cuia R, Diverio D, et al. "Real- life" results of front-line treatment with Imatinib in older patients (>= 65 years) with newly diagnosed chronic myelogenous leukemia. Leukemia Research 2010; 34(11):1472-5.

4-67 Leitner AA, Hochhaus A, Muller MC. Current Treatment Concepts of CML. Current Cancer Drug Targets 2011; 11(1):31-43.

4-68 Li-Wan-Po A, Farndon P, Craddock C, Griffiths M. Integrating pharmacogenetics and therapeutic drug monitoring: optimal dosing of imatinib as a case-example. European Journal of Clinical Pharmacology 2010; 66(4):369-74.

4-69 Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, et al. Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib. Journal of Clinical Oncology 2010; 28(14):2381-8.

4-70 Milojkovic D, Nicholson E, Apperley JF, Holyoake TL, Shepherd P, Drummond MW, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Haematologica-the Hematology Journal 2010; 95(2):224-31.

4-71 Nicolini FE, Chomel JC, Roy L, Legros L, Chabane K, Ducastelle S, et al. The Durable Clearance of the T315I BCR-ABL Mutated Clone in Chronic Phase Chronic Myelogenous Leukemia Patients on Omacetaxine Allows Tyrosine Kinase Inhibitor Rechallenge. Clinical Lymphoma Myeloma & Leukemia 2010; 10(5):394-9.

4-72 Nowak D, Ogawa S, Muschen M, Kato M, Kawamata N, Meixel A, et al. SNP array analysis of tyrosine kinase inhibitor-resistant chronic myeloid leukemia identifies heterogeneous secondary genomic alterations. Blood 2010; 115(5):1049-53.

4-73 Olsson-Stromberg U, Hermansson M, Lundan T, Ohm AC, Engdahl I, Hoglund M, et al. Molecular monitoring and mutation analysis of patients with advanced phase CML and Ph plus ALL receiving dasatinib. European Journal of Haematology 2010; 85(5):399-404.

4-74 Palandri F, Castagnetti F, Iacobucci I, Martinelli G, Amabile M, Gugliotta G, et al. The response to imatinib and interferon-alpha is more rapid than the response to imatinib alone: a retrospective analysis of 495 Philadelphia-positive chronic myeloid leukemia patients in early chronic phase. Haematologica-the Hematology Journal 2010; 95(8):1415-9.

4-75 Pavlu J, Kew AK, Taylor-Roberts B, Auner HW, Marin D, Olavarria E, et al. Optimizing patient selection for myeloablative allogeneic hematopoietic cell transplantation in chronic myeloid leukemia in chronic phase. Blood 2010; 115(20):4018-20.

4-76 Pavlu J, Szydlo RM, Goldman JM, Apperley JF. Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood 2011; 117(3):755-63.

4-77 Petzer AL, Wolf D, Fong D, Lion T, Dyagil I, Masliak Z, et al. High-dose imatinib improves cytogenetic and molecular remissions in patients with pretreated Philadelphia-positive, BCR-ABL-positive chronic phase chronic myeloid leukemia: first results from the randomized CELSG phase III CML 11 "ISTAHIT" study. Haematologica-the Hematology Journal 2010; 95(6):908-13.

4-78 Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, et al. Imatinib plus Peginterferon Alfa-2a in Chronic Myeloid Leukemia. New England Journal of Medicine 2010; 363(26):2511-21.

4-79 Rosti G, Castagnetti F, Gugliotta G, Palandri F, Martinelli G, Baccarani M. Dasatinib and nilotinib in imatinib-resistant Philadelphia-positive chronic myelogenous leukemia: a 'head-to-head comparison'. Leukemia & Lymphoma 2010; 51(4):583-91.

4-80 Saglio G, Baccarani M. First-line Therapy for Chronic Myeloid Leukemia: New Horizons and an Update. Clinical Lymphoma Myeloma & Leukemia 2010; 10(3):169-76.

4-81 Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, et al. Dasatinib in Imatinib-Resistant or Imatinib-Intolerant Chronic Myeloid Leukemia in Blast Phase After 2 Years of Follow-Up in a Phase 3 Study

Efficacy and Tolerability of 140 Milligrams Once Daily and 70 Milligrams Twice Daily. Cancer 2010; 116(16):3852-61.

4-82 Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. New England Journal of Medicine 2010; 362(24):2251-9.

4-83 Salomon O, Tohami T, Trakhtenbrot L, Meirov R, Kneller A, Berkowitz M, et al. BCR-ABL transcripts are not detected in cord blood or the peripheral blood of the newborn child whose mother developed chronic myeloid leukemia while pregnant. Leukemia Research 2010; 34(2):E78-E81.

4-84 Santos FPS, Kantarjian H, Fava C, O'Brien S, Garcia-Manero G, Ravandi F, et al. Clinical impact of dose reductions and interruptions of second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukaemia. British Journal of Haematology 2010; 150(3):303-12.

4-85 Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PED, Enrico A, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica-the Hematology Journal 2010; 95(2):232-40.

4-86 Simonsson B, Hjorth-Hansen H, Bjerrum OW, Porkka K. Interferon alpha for Treatment of Chronic Myeloid Leukemia. Current Drug Targets 2011; 12(3):420-8.

4-87 Sobrinho-Simoes M, Wilczek V, Score J, Cross NCP, Apperley JF, Melo JV. In search of the original leukemic clone in chronic myeloid leukemia patients in complete molecular remission after stem cell transplantation or imatinib. Blood 2010; 116(8):1329-35.

4-88 Sorel N, Mayeur-Rousse C, Deverriere S, Roy L, Brottier-Mancini E, Guilhot F, et al. Comprehensive Characterization of a Novel Intronic Pseudo-Exon Inserted within an e14/a2 BCR-ABL Rearrangement in a Patient with Chronic Myeloid Leukemia. Journal of Molecular Diagnostics 2010; 12(4):520-4.

4-89 Soverini S, Angelini S, Turrini E, Burnett M, Ravegnini G, Thornquist M, et al. Specific Drug Transporter Genotypes Are Significantly Associated with Increased Rates of Major and Complete Molecular Responses In Newly Diagnosed Chronic Myeloid Leukemia Patients Treated with Imatinib - A TOPS Correlative Substudy. Blood 2010; 116(21):293-4.

4-90 Soverini S, Poerio A, Ferrarini A, Iacobucci I, Sazzini M, Score J, et al. Whole Transcriptome Sequencing In Chronic Myeloid Leukemia Reveals Novel Gene Mutations That May Be Associated with Disease Pathogenesis and Progression. Blood 2010; 116(21):387-.

4-91 Soverini S, Score J, Iacobucci I, Poerio A, Lonetti A, Gnani A, et al. IDH2 somatic mutations in chronic myeloid leukemia patients in blast crisis. Leukemia 2011; 25(1):178-81.

4-92 Vianello F, Villanova F, Tisato V, Lymperi S, Ho KK, Gomes AR, et al. Bone marrow mesenchymal stromal cells non-selectively protect chronic myeloid leukemia cells from imatinib-induced apoptosis via the CXCR4/CXCL12 axis. Haematologica-the Hematology Journal 2010; 95(7):1081-9.

4-93 Zaccaria A, Testoni N, Valenti AM, Luatti S, Tonelli M, Marzocchi G, Cipriani R, Baldazzi C, Giannini B, Stacchini M, Gamberini C, Castagnetti F, Rosti G, Azzena A, Cavazzini F, Cianciulli AM, Dalsass A, Donti E, Giugliano E, Gozzetti A, Grimoldi MG, Ronconi S, Santoro A, Spedicato F, Zanatta L, Baccarani M; GIMEMA Working Party on CML. Chromosome abnormalities additional to the Philadelphia chromosome at the diagnosis of chronic myelogenous leukemia: pathogenetic and prognostic implications. Cancer Genet Cytogenet. 2010 Jun;199(2):76-80. PubMed PMID: 20471509.

4-94 Zackova D, Klamova H, Dusek L, Muzik J, Polakova KM, Moravcova J, et al. Imatinib as the first-line treatment of patients with chronic myeloid leukemia diagnosed in the chronic phase: Can we compare real life data to the results from clinical trials? American Journal of Hematology 2011; 86(3):318-21.

Abstracts oral presentations

4-95 Arpinati M, Amabile M, Bochicchio MT, Poerio A, Bandini G, Bonifazi F, Stanzani M, Castagnetti F, Rosti G, Martinelli G, Baccarani M. Long Term Study of the Impact of Quantitative Molecular Monitoring of Bcr-Abl Transcripts on the Risk of Relapse of CML After Allogeneic HSCT. Blood. 2010 (ASH Annual Meeting); Abstract n. 1287

4-96 Baccarani M, Rosti G, Martinelli G, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Testoni N. Evaluating the Response to Imatinib In Philadelphia-Positive Chronic Myeloid Leukemia (Ph+ CML): The Value of Major Molecular Response (MMolR) at 12 Months.. Blood. 2010 (ASH Annual Meeting); Abstract n. 668.

4-97 Bocchia M, Defina M, Ippoliti M, Abruzzese A, Castagnetti F, Tiribelli M, Rosti G, Breccia M, Trawinska MM, Crupi R, Aprile L, Salvucci M, Baratè C, Gozzini A, Rondoni M, Zaccaria A, Alimena G, Santini V, Specchia G, Fanin R, Gozzetti A, Lauria F. Evaluation of Residual CD34+/Ph+ Stem Cells In Chronic Myeloid Leukemia Patients In Complete Cytogenetic Response during First Line Nilotinib Therapy. Blood. 2010 (ASH Annual Meeting); Abstract n. 3413.

4-98 Castagnetti F, Palandri F, Poerio A, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Intermesoli T, Castagnetti F, Gugliotta G, Palandri F, Levato L, Abruzzese E, Russo Rossi A, Palmieri F, Capucci A, Pierri I, Turri D, Zaccaria A, Cavazzini F, Stagno F, Musolino C, Morandi S, Breccia M, Rege-Cambrin G, Amabile M, Iacobucci I, Testoni N, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Imatinib 400 mg vs 800 mg daily as a front-line treatment of Sokal high-risk Ph+ Chronic Myeloid Leukemia: 4-year results of a prospective randomized study of the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):132-3. Abstract n. P156.

4-99 Castagnetti F, Gugliotta G, Palandri F, Breccia M, Specchia G, Abruzzese E, Intermesoli T, Capucci A, Martino B, Stagno F, Pregno P, Amabile M, Soverini S, Testoni N, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. BCR-ABL Fusion Transcript Do Not Significantly Influence the Outcome of Chronic Myeloid Leukemia Patients In Early Chronic Phase Treated with Imatinib Mesylate: a GIMEMA CML WP Analysis. Blood. 2010 (ASH Annual Meeting); Abstract n. 1230

4-100 Castagnetti F, Palandri F, Gugliotta G, Breccia M, Specchia G, Abruzzese E, Levato L, Intermesoli T, Martino B, Pregno P, Orlandi E, Iacobucci I, Soverini S, Testoni N, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Long term outcome of 559 Ph+ chronic myeloid leukemia patients treated front-line with imatinib: 5-year results of 3 independent studies of the GIMEMA CML Working Party. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):54. Abstract n. 134.

4-101 Castagnetti F, Palandri F, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Bocchia M, Cuneo A, Stagno F, Specchia G, Musso M, Gugliotta G, Testoni N, Alimena G, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Nilotinib 400 mg bid daily as frontline therapy of ph chronic myeloid leukemia: dose delivery and safety profile at 2 years. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):340-1. Abstract n. 814.

4-102 Ernst T, Lin F, White H, La Rosée P, Lion T, Mitterbauer-Hohendanner G, Vandenberghe P, Zadro R, Machova Polakova K, Plachy R, Guldborg Nyvold C, Lundán T, Cayuela J, Lange T, Müller M, Zoi K, Andrikovics H, Tohami T, Pane F, Soverini S, Arruga F, Eggen L, Sacha T, Diamond J, Talmaci R, Pajic T, Colomer D, Hermanson M, Oppliger Leibundgut E, Valk P, Ozbek U, Gerrard G, Saglio G, Hochhaus A, Cross NCP: Harmonized Testing for BCR-ABL Kinase Domain Mutations In CML: Results of a Survey and First Control Round within 28 National Reference Laboratories In Europe. Blood 2010; 116(21): abstract #894

4-103 Gnani A, Soverini S, Colarossi S, Castagnetti F, Astolfi A, Formica S, Palandri F, Iacobucci I, Gugliotta G, Poerio A, Amabile M, Marzocchi G, Testoni N, Abruzzese E, Rosti G, Capranico G, Baccarani M, Martinelli G. High-Resolution Molecular Karyotyping of Chronic Myeloid Leukemia Patients in Blast Crisis by 6.0 SNP-Arrays Identifies Focal Copy Number Alterations Affecting the Whole Sequence or Specific Exons of Oncogenes and Tumor Suppressor Genes. AACR Meeting Abstracts 2010. Abstract n. 2143.

4-104 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Radaelli F, Capucci A, Cavazzini F, Ferrero D, Stagno F, Gherlinzoni F, Di Lorenzo R, Leoni P, Rege Cambrin G, Ferrara F, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Second malignancies in 559 patients with chronic myeloid leukemia treated with imatinib frontline: data from the GIMEMA CML Working Party. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):337. Abstract n. 805.

4-105 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Cavazzini F, Di Lorenzo R, Levato L, Girasoli M, Leone G, Abruzzese E, Tiribelli M, Meneghini V, Galieni P, Trabacchi E, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Incidence and Mortality of Second Malignancies In 559 Patients with Chronic Myeloid Leukemia (CML) Treated with Imatinib Frontline: Data From the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2281.

4-106 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Soverini S, Girasoli M, Levato L, Cavazzini F, Pregno P, Bigazzi C, Sica S, Abruzzese E, Di Lorenzo R, Ciccone F, Capucci A, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Incidence of second malignancies in 559 patients with Chronic Myeloid Leukemia treated with imatinib front-line: data from the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):133. Abstract n. P157.

4-107 Martinelli G, Poerio A, Amabile M, Iacobucci I, Soverini S, Castagnetti F, Palandri F, Gugliotta G, Cappucci A, Tiribelli M, Stagno F, Zaccaria A, Intermesoli T, Martino B, Bocchia M, Cedrone M, Testoni N, Breccia M, Alimena G, Levato L, Papayannidis C, Lonetti A, Terragna C, Russo D, Pane F, Saglio G, Rosti G, Baccarani M. First Line Treatment with Nilotinib 800 Mg Daily Results In Unprecedentedly High Rate of Rapid, "Deep" and Stable Molecular Responses as Assessed by a High Sensitive Nanofluidic Array for the Detection of Rare Copies of BCR-ABL1 Transcript: Results of a Phase 2 Trial of the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2720.

4-108 Martinelli G, Poerio A, Soverini S, Saglio G, Pane F, Castagnetti F, Capucci A, Tiribelli M, Stagno F, Palandri F, Gugliotta G, Zaccaria A, Intermesoli T, Martino B, Bocchia M, Cedrone M, Testoni N, Amabile M, Iacobucci I, Breccia M, Alimena G, Levato L, Baccarani M, Rosti G. Improving on imatinib for targeted therapy of chronic myeloid leukemia: first line treatment with nilotinib 800 mg daily results in unprecedently high rate of rapid, "deep" and stable molecular responses – Results of a phase 2 trial of the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):56. Abstract n. C065.

4-109 Martinelli G, Poerio A, Soverini S, Saglio G, Pane F, Castagnetti F, Capucci A, Tiribelli M, Stagno F, Palandri F, Gugliotta G, Zaccaria A, Intermesoli T, Martino B, Biasco G, Bocchia M, Cedrone M, Testoni N, Amabile M, Iacobucci I, Breccia M, Alimena G, Levato L, Baccarani M. Improving on Imatinib for targeted therapy of

chronic myeloid leukemia: First line treatment with Nilotinib 800 mg daily results in unprecedentedly high rate of rapid, “deep” and stable molecular responses - Results of a phase 2 trial of the GIMEMA CML working party. AACR Meeting Abstracts 2010. Abstract n. 1805.

4-110 Martino B, Cedrone M, Bocchia M, Cavazzini F, Stagno F, Specchia G, Musso M, Soverini S, Gugliotta G, Testoni N, Alimena G, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Nilotinib 400 mg BID in early Chronic Phase Ph+ Chronic Myeloid Leukemia: results at 2 years of a phase II trial of the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):132. Abstract n. P154.

4-111 Marzocchi G, Luatti S, Castagnetti F, Baldazzi C, Stacchini M, Gamberini C, Amabile M, Soverini S, Colarossi S, Specchia G, Sessarego M, Giussani U, Zanatta L, Valori L, Discepoli G, Montaldi A, Santoro A, Sebastio L, Giudici G, Bonaldi L, Cianciulli A, Giacobbi F, Palandri F, Rosti G, Baccarani M, Testoni N. Variant Ph translocation in early chronic phase of chronic myeloid leukemia: cytogenetic-molecular characterization and correlation to imatinib mesylate therapy (a GIMEMA WP on CML analysis). Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):333. Abstract n. 794.

4-112 Rosti G, Castagnetti F, Gugliotta G, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Bocchia M, Cuneo A, Stagno F, Specchia G, Porretto F, Martino B, Cedrone M, Intermesoli T, Palandri F, Amabile M, Soverini S, Testoni N, Alimena G, Pane F, Saglio G, Martinelli G, Baccarani M. Excellent Outcomes at 3 Years with Nilotinib 800 Mg Daily In Early Chronic Phase, Ph+ Chronic Myeloid Leukemia (CML): Results of a Phase 2 GIMEMA CML WP Clinical Trial. Blood. 2010 (ASH Annual Meeting); Abstract n. 359

4-113 Soverini S, Poerio A, Ferrarini A, Iacobucci I, Sazzini M, Score J, Giacomelli E, Xumerle L, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Cross NC, Delledonne M, Martinelli G. Whole-Transcriptome Sequencing In Chronic Myeloid Leukemia Reveals Novel Gene Mutations That May Be Associated with Disease Pathogenesis and Progression. Blood. 2010 (ASH Annual Meeting); Abstract n. 885.

4-114 Soverini S, Poerio A, Ferrarini A, Iacobucci I, Sazzini M, Xumerle L, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Delledonne M, Martinelli G. Novel gene mutations revealed by massively parallel sequencing of the transcriptome of a chronic myeloid leukemia patient at diagnosis and at the time of progression to blast crisis. Haematologica. 2010 (SIES Meeting); 95(s3):57. Abstract n. C067.

4-115 Soverini S, Poerio A, Debenedittis C, Iacobucci I, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. Low-Level Bcr-Abl Kinase Domain Mutations Are Very Rare In Chronic Myeloid Leukemia Patients Who Are In Major Molecular Response After 12 Months of First-Line Nilotinib Therapy. Blood. 2010 (ASH Annual Meeting); Abstract n. 1666.

4-116 Soverini S, Gnani A, Colarossi S, Castagnetti F, Iacobucci I, Breccia M, Abruzzese E, Pane F, Saglio G, Russo D, Specchia G, Pregno P, Sorà F, Tiribelli M, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. Bcr-Abl Kinase Domain Mutations in Imatinib and in Second-Generation Tyrosine Kinase Inhibitor Eras: Seven Years of Mutation Analysis, a Report by the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2279.

4-117 Soverini S, Poerio A, Debenedittis C, Iacobucci I, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. In Chronic Myeloid Leukemia patients who are in major molecular response after 12 months on first-line nilotinib therapy, low -level BCR-ABL kinase domain mutations are very rare. Haematologica. 2010 (SIES Meeting); 95(s3):122. Abstract n. P129.

4-118 Soverini S, Colarossi S, Gnani A, Poerio A, Castagnetti F, Astolfi A, Formica S, Palandri F, Iacobucci I, Amabile M, Marzocchi G, Luatti S, Testoni N, Gugliotta G, Rosti G, Baccarani M, Martinelli G. High-resolution molecular karyotyping of chronic myeloid leukemia patients in blast crisis by 6.0 snp-arrays identifies focal copy number alterations affecting oncogenes and tumor suppressor genes. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):49. Abstract n. 122.

4-119 Soverini S, Poerio A, Gnani A, Colarossi S, Rosti G, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Baccarani M, Martinelli G. In chronic myeloid leukemia patients who are in major molecular response after 12 months of first-line nilotinib therapy, low-level BCR-ABL kinase domain mutations are very rare. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):341. Abstract n. 815.

4-120 Rosti G, Castagnetti F, Palandri F, Poerio A, Soverini S, Breccia M, Pane F, Martinelli G, Baccarani M, Saglio G. Efficacy and safety of nilotinib 800 mg daily in early chronic phase Ph+ chronic myeloid leukemia: Results of a phase II trial at 2 years. J Clin Oncol. 2010 (ASCO Annual Meeting Abstracts); 28(7s), abstr n. 6515.

4-121 Rosti G, Castagnetti F, Palandri F, Poerio A, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Intermesoli T, Martino B, Cedrone M, Gugliotta G, Amabile M, Testoni N, Alimena G, Pane F, Saglio G, Martinelli G, Baccarani M. Nilotinib 400 mg bid in early chronic phase Ph+ chronic myeloid leukemia: results at 2 years of a phase II trial. Haematologica. 2010 (EHA Annual Meeting); 95(s2):459. Abstract n. 1114

4-122 Satu Mustjoki, Philippe Rousselot, Sari Jalkanen, Anna Kreutzman, Teresa Melo, Anna-Maria Lahesmaa, Sampsa Hautaniemi, Mathieu Molimard, Richard Smykla, Francis Lee, Jukka Vakkila, and Kimmo Porkka. Dasatinib Induces a Rapid, Dose-Controllable Mobilization of Cytotoxic Lymphocytes: A Novel Immunomodulatory Effect Associated with Prolonged Therapy Responses In Advanced Leukemia. ASH 2010.

4-123 Terragna C, Durante S, Astolfi A, Palandri F, Castagnetti F, Testoni N, Amabile M, Iacobucci I, Soverini S, Alimena G, Breccia M, Pane F, Saglio G, Rosti G, Baccarani M, Martinelli G. The Elevated Expression of FBP1, a Key-Enzyme of Gluconeogenesis Gene, Is Associated to High Sokal Risk In Chronic Myeloid Leukemia Patients. Blood. 2010 (ASH Annual Meeting); Abstract n. 3399.

4-124 Terragna c, Durante S, Astolfi A, Palandri F, Castagnetti F, Testoni N, Iacobucci I, Soverini S, Amabile M, Poerio A, Alimena G, Breccia M, Pane F, Saglio G, Rosti G, Baccarani M, Martinelli G. Dissecting molecular bases of high Sokal versus low Sokal risk in chronic myeloid leukemia patients by gene expression profiles of cd34 cells at diagnosis. Haematologica. 2010 (EHA Annual Meeting); 95(s2):243-4. Abstract n. 584.

Abstracts poster presentations

4-125 Arpinati M, Amabile M, Bochicchio MT, Poerio A, Bandini G, Bonifazi F, Stanzani M, Castagnetti F, Rosti G, Martinelli G, Baccarani M. .Long Term Study of the Impact of Quantitative Molecular Monitoring of Bcr-Abl Transcripts on the Risk of Relapse of CML After Allogeneic HSCT. Blood. 2010 (ASH Annual Meeting); Abstract n. 1287

4-126 Bocchia M, Defina M, Ippoliti M, Abruzzese A, Castagnetti F, Tiribelli M, Rosti G, Breccia M, Trawinska MM, Crupi R, Aprile L, Salvucci M, Baratè C, Gozzini A, Rondoni M, Zaccaria A, Alimena G, Santini V, Specchia G, Fanin R, Gozzetti A, Lauria F. Evaluation of Residual CD34+/Ph+ Stem Cells In Chronic Myeloid Leukemia Patients In Complete Cytogenetic Response during First Line Nilotinib Therapy. Blood. 2010 (ASH Annual Meeting); Abstract n. 3413.

4-127 Castagnetti F, Gugliotta G, Palandri F, Breccia M, Specchia G, Abruzzese E, Intermesoli T, Capucci A, Martino B, Stagno F, Pregno P, Amabile M, Soverini S, Testoni N, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. BCR-ABL Fusion Transcript Do Not Significantly Influence the Outcome of Chronic Myeloid Leukemia Patients In Early Chronic Phase Treated with Imatinib Mesylate: a GIMEMA CML WP Analysis. Blood. 2010 (ASH Annual Meeting); Abstract n. 1230

4-128 Castagnetti F, Palandri F, Poerio A, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Intermesoli T, Martino B, Cedrone M, Bocchia M, Cavazzini F, Stagno F, Specchia G, Musso M, Soverini S, Gugliotta G, Testoni N, Alimena G, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Nilotinib 400 mg BID in early Chronic Phase Ph+ Chronic Myeloid Leukemia: results at 2 years of a phase II trial of the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):132. Abstract n. P154.

4-129 Castagnetti F, Gugliotta G, Palandri F, Levato L, Abruzzese E, Russo Rossi A, Palmieri F, Capucci A, Pierri I, Turri D, Zaccaria A, Cavazzini F, Stagno F, Musolino C, Morandi S, Breccia M, Rege-Cambrin G, Amabile M, Iacobucci I, Testoni N, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Imatinib 400 mg vs 800 mg daily as a front-line treatment of Sokal high-risk Ph+ Chronic Myeloid Leukemia: 4-year results of a prospective randomized study of the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):132-3. Abstract n. P156.

4-130 Castagnetti F, Palandri F, Gugliotta G, Breccia M, Specchia G, Abruzzese E, Levato L, Intermesoli T, Martino B, Pregno P, Orlandi E, Iacobucci I, Soverini S, Testoni N, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Long term outcome of 559 Ph+ chronic myeloid leukemia patients treated front-line with imatinib: 5-year results of 3 independent studies of the GIMEMA CML Working Party. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):54. Abstract n. 134.

4-131 Castagnetti F, Palandri F, Breccia M, Levato L, Capucci A, Tiribelli M, Zaccaria A, Bocchia M, Cuneo A, Stagno F, Specchia G, Musso M, Gugliotta G, Testoni N, Alimena G, Pane F, Martinelli G, Saglio G, Baccarani M, Rosti G. Nilotinib 400 mg bid daily as frontline therapy of ph chronic myeloid leukemia: dose delivery and safety profile at 2 years. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):340-1. Abstract n. 814.

4-132 Gnani A, Soverini S, Colarossi S, Castagnetti F, Astolfi A, Formica S, Palandri F, Iacobucci I, Gugliotta G, Poerio A, Amabile M, Marzocchi G, Testoni N, Abruzzese E, Rosti G, Capranico G, Baccarani M, Martinelli G. High-Resolution Molecular Karyotyping of Chronic Myeloid Leukemia Patients in Blast Crisis by 6.0 SNP-Arrays Identifies Focal Copy Number Alterations Affecting the Whole Sequence or Specific Exons of Oncogenes and Tumor Suppressor Genes. AACR Meeting Abstracts 2010. Abstract n. 2143.

4-133 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Cavazzini F, Di Lorenzo R, Levato L, Girasoli M, Leone G, Abruzzese E, Tiribelli M, Meneghini V, Galieni P, Trabacchi E, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Incidence and Mortality of Second Malignancies In 559 Patients with Chronic Myeloid Leukemia (CML) Treated with Imatinib Frontline: Data From the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2281.

4-134 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Radaelli F, Capucci A, Cavazzini F, Ferrero D, Stagno F, Gherlinzoni F, Di Lorenzo R, Leoni P, Rege Cambrin G, Ferrara F, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Second malignancies in 559 patients with chronic myeloid leukemia treated with imatinib frontline: data from the GIMEMA CML Working Party. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):337. Abstract n. 805.

4-135 Gugliotta G, Castagnetti F, Palandri F, Breccia M, Soverini S, Girasoli M, Levato L, Cavazzini F, Pregno P, Bigazzi C, Sica S, Abruzzese E, Di Lorenzo R, Ciccone F, Capucci A, Alimena G, Martinelli G, Pane F, Saglio G, Baccarani M, Rosti G. Incidence of second malignancies in 559 patients with Chronic Myeloid Leukemia treated with imatinib front-line: data from the GIMEMA CML Working Party. Haematologica. 2010 (SIES Meeting); 95(s3):133. Abstract n. P157.

4-136 Martinelli G, Poerio A, Amabile M, Iacobucci I, Soverini S, Castagnetti F, Palandri F, Gugliotta G, Cappucci A, Tiribelli M, Stagno F, Zaccaria A, Intermesoli T, Martino B, Bocchia M, Cedrone M, Testoni N, Breccia M, Alimena G, Levato L, Papayannidis C, Lonetti A, Terragna C, Russo D, Pane F, Saglio G, Rosti G, Baccarani M. First Line Treatment with Nilotinib 800 Mg Daily Results In Unprecedentedly High Rate of Rapid, "Deep" and Stable Molecular Responses as Assessed by a High Sensitive Nanofluidic Array for the Detection of Rare Copies of BCR-ABL1 Transcript: Results of a Phase 2 Trial of the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2720.

4-137 Martinelli G, Poerio A, Soverini S, Saglio G, Pane F, Castagnetti F, Capucci A, Tiribelli M, Stagno F, Palandri F, Gugliotta G, Zaccaria A, Intermesoli T, Martino B, Biasco G, Bocchia M, Cedrone M, Testoni N, Amabile M, Iacobucci I, Breccia M, Alimena G, Levato L, Baccarani M. Improving on Imatinib for targeted therapy of chronic myeloid leukemia: First line treatment with Nilotinib 800 mg daily results in unprecedentedly high rate of rapid, "deep" and stable molecular responses - Results of a phase 2 trial of the GIMEMA CML working party. AACR Meeting Abstracts 2010. Abstract n. 1805.

4-138 Marzocchi G, Luatti S, Castagnetti F, Baldazzi C, Stacchini M, Gamberini C, Amabile M, Soverini S, Colarossi S, Specchia G, Sessarego M, Giussani U, Zanatta L, Valori L, Discepoli G, Montaldi A, Santoro A, Sebastio L, Giudici G, Bonaldi L, Cianciulli A, Giacobbi F, Palandri F, Rosti G, Baccarani M, Testoni N. Variant Ph translocation in early chronic phase of chronic myeloid leukemia: cytogenetic-molecular characterization and correlation to imatinib mesylate therapy (a GIMEMA WP on CML analysis). Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):333. Abstract n. 794.

4-139 Rosti G, Castagnetti F, Palandri F, Poerio A, Soverini S, Breccia M, Pane F, Martinelli G, Baccarani M, Saglio G. Efficacy and safety of nilotinib 800 mg daily in early chronic phase Ph+ chronic myeloid leukemia: Results of a phase II trial at 2 years. J Clin Oncol. 2010 (ASCO Annual Meeting Abstracts); 28(7s), abstr n. 6515.

4-140 Rousselot Philippe, Stéphane Boucher, Gabriel Etienne, Franck E Nicolini, Emmanuelle Chauzit, Pascale Cony Makhoul, Valérie Coiteux, Agnès Guerci, Martine Gardembas, Laurence Legros, Lydia Roy, Caroline Dartigeas, Maud Janvier, Christian Berthou, Lambert Busque, Mathieu Molimard, Joelle Guilhot, Luigina Mollica, and Francois-Xavier Mahon. Pharmacokinetics of Dasatinib as a First Line Therapy In Newly Diagnosed CML Patients (OPTIM dasatinib trial): Correlation with Safety and Response. Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 3432.

4-141 Soverini S, Poerio A, Debenedittis C, Iacobucci I, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. Low-Level Bcr-Abl Kinase Domain Mutations Are Very Rare In Chronic Myeloid Leukemia Patients Who Are In Major Molecular Response After 12 Months of First-Line Nilotinib Therapy. Blood. 2010 (ASH Annual Meeting); Abstract n. 1666.

4-142 Soverini S, Gnani A, Colarossi S, Castagnetti F, Iacobucci I, Breccia M, Abruzzese E, Pane F, Saglio G, Russo D, Specchia G, Pregno P, Sorà F, Tiribelli M, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. Bcr-Abl Kinase Domain Mutations in Imatinib and in Second-Generation Tyrosine Kinase Inhibitor Eras: Seven Years of Mutation Analysis, a Report by the GIMEMA CML Working Party. Blood. 2010 (ASH Annual Meeting); Abstract n. 2279.

4-143 Soverini S, Poerio A, Debenedittis C, Iacobucci I, Colarossi S, Gnani A, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Rosti G, Baccarani M, Martinelli G. In Chronic Myeloid Leukemia patients who are in major molecular response after 12 months on first-line nilotinib therapy, low -level BCR-ABL kinase domain mutations are very rare. Haematologica. 2010 (SIES Meeting); 95(s3):122. Abstract n. P129.

4-144 Soverini S, Colarossi S, Gnani A, Poerio A, Castagnetti F, Astolfi A, Formica S, Palandri F, Iacobucci I, Amabile M, Marzocchi G, Luatti S, Testoni N, Gugliotta G, Rosti G, Baccarani M, Martinelli G. High-resolution molecular karyotyping of chronic myeloid leukemia patients in blast crisis by 6.0 snp-arrays identifies focal copy number alterations affecting oncogenes and tumor suppressor genes. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):49. Abstract n. 122.

4-145 Soverini S, Poerio A, Gnani A, Colarossi S, Rosti G, Castagnetti F, Palandri F, Gugliotta G, Amabile M, Baccarani M, Martinelli G. In chronic myeloid leukemia patients who are in major molecular response after 12 months of first-line nilotinib therapy, low-level BCR-ABL kinase domain mutations are very rare. Haematologica. 2010 (EHA Annual Meeting Abstracts); 95(s2):341. Abstract n. 815.

4-146 Terragna C, Durante S, Astolfi A, Palandri F, Castagnetti F, Testoni N, Amabile M, Iacobucci I, Soverini S, Alimena G, Breccia M, Pane F, Saglio G, Rosti G, Baccarani M, Martinelli G. The Elevated Expression of FBP1, a Key-Enzyme of Gluconeogenesis Gene, Is Associated to High Sokal Risk In Chronic Myeloid Leukemia Patients. Blood. 2010 (ASH Annual Meeting); Abstract n. 3399.

WP5 (AML)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

5-1 Minutes from the Reisensburg-Meeting, February 6, 2009

5-2 Döhner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010; 115(3):453-74.

5-3 Haferlach T. Die Zukunft der Diagnostik akuter Leukämien. Reisensburg Meeting Feb. 2010

5-4 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

5-5 Metzeler KH, Maharry K, Radmacher MD, Mrozek K, Margeson D, Becker H, et al. TET2 Mutations Improve the New European LeukemiaNet Risk Classification of Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. Journal of Clinical Oncology 2011; 29(10):1373-81.

5-6 Sanz MA, Grimwade D, Tallman MS, et al: Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 113:1875-1891, 2009

5-7 Wierzbowska A, Pluta A, Robak T. Standards of diagnostic and treatment procedures in adult patients with acute myeloid leukemia according to European LeukemiaNet. Acta Haematologica Polonica 2010; 41(3):371-9.

*Abstracts (**with** a reference to the European LeukemiaNet)*

5-8 Hoyos M, Brunet S, Nomdedeu JF, Esteve J, Duarte RF, Ribera JM, et al. Validation of the European Leukemia Net (ELN) Genetic Classification of Acute Myeloid Leukemia Inclusion of Monosomal Karyotype Improves Prognostic Discrimination. Blood 2010; 116(21):717-.

5-9 Metzeler KH, Maharry K, Radmacher MD, Mrozek K, Margeson D, Becker H, et al. Mutations In the Tet Oncogene Family Member 2 (TET2) Gene Refine the New European LeukemiaNet Risk Classification of Primary, Cytogenetically Normal Acute Myeloid Leukemia (CN AML) In Adults A Cancer and Leukemia Group B (CALGB) Study. Blood 2010; 116(21):48-9.

5-10 Röllig C, Thiede C, Aulitzky W, Bornhauser M, Bodenstein H, Stuhlmann R, et al. Long-term outcome of AM patients according to the new genetic risk classification of the Euorpean LeumeiaNet recommendations. Evaluation of the proposed reporting system in a cohort of 1507 patients. . Haematologica-the Hematology Journal 2010; 95(Suppl. 2):224.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet*)

5-11 Ades L, Guerci A, Raffoux E, Sanz M, Chevallier P, Lapusan S, et al. Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Group experience. Blood 2010; 115(9):1690-6.

5-12 Al-Ali HK, Cross M, Lange T, et al. Low-dose total body irradiation-based regimens as a preparative regimen for allogeneic haematopoietic cell transplantation in acute myelogenous leukaemia. Curr Opin Oncol. 2009 Jun;21 Suppl 1:S17-22. (Senior Author: Niederwieser D)

5-13 Alvarez S, Suela J, Valencia A, Fernandez A, Wunderlich M, Agirre X, et al. DNA Methylation Profiles and Their Relationship with Cytogenetic Status in Adult Acute Myeloid Leukemia. Plos One 2010; 5(8):e12197 (12 pages).

5-14 Amadori S, Suciu S, Selleslag D, Stasi R, Alimena G, Baila L, et al. Randomized trial of two schedules of low-dose gemtuzumab ozogamicin as induction monotherapy for newly diagnosed acute myeloid leukaemia in older patients not considered candidates for intensive chemotherapy. A phase II study of the EORTC and GIMEMA leukaemia groups (AML-19). British Journal of Haematology 2010; 149(3):376-82.

5-15 Ammatuna E, Montesinos P, Hasan SK, Ramadan SM, Esteve J, Hubmann M, et al. Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis. Haematologica-the Hematology Journal 2011; 96(4):621-5.

5-16 Boissel N, Nibourel O, Renneville A, Gardin C, Reman O, Contentin N, et al. Prognostic Impact of Isocitrate Dehydrogenase Enzyme Isoforms 1 and 2 Mutations in Acute Myeloid Leukemia: A Study by the Acute Leukemia French Association Group. Journal of Clinical Oncology 2010; 28(23):3717-23.

5-17 Boissel N, Nibourel O, Renneville A, Huchette P, Dombret H, Preudhomme C. Differential prognosis impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood [Letter] 2011; 117(13):3696-7.

5-18 Bommer M, von Harsdorf S, Dohner H, Bunjes D, Ringhoffer M. Neoplastic meningitis in patients with acute myeloid leukemia scheduled for allogeneic hematopoietic stem cell transplantation. Haematologica-the Hematology Journal 2010; 95(11):1969-72.

5-19 Bullinger L, Ehrich M, Dohner K, Schlenk RF, Dohner H, Nelson MR, et al. Quantitative DNA methylation predicts survival in adult acute myeloid leukemia. Blood 2010; 115(3):636-42.

5-20 Bullinger L, Kroenke J, Schoen C, Radtke I, Urlbauer K, Botzenhardt U, et al. Identification of acquired copy number alterations and uniparental disomies in cytogenetically normal acute myeloid leukemia using high-resolution single-nucleotide polymorphism analysis. Leukemia (Basingstoke) 2010; 24(2):438-49.Brunnberg U, Mohr M, Noppeney R, et al. Induction Therapy by Ara-C Plus Daunorubicin Versus Ara-C Plus Gemtuzumab Ozogamicin: Interim Analysis of a Randomized Phase II Trial of the SAL In Elderly Patients with Acute Myeloid Leukemia. Blood Nov 2010; 116: 335 *(Senior Author: Berdel)*

5-21 Buchner T. Strategies against relapse in AML. Cellular Therapy and Transplantation (CTT) 3, No. 9, 2010 (abstract 75)APL. Blood, Nov 2010; 116: 15.

5-22 Buchner T, Berdel WE, Haferlach C, et al: Age-Related Risk Profile and Chemotherapy Dose Response in Acute Myeloid Leukemia: A Study by the German Acute Myeloid Leukemia Cooperative Group. Journal of Clinical Oncology 27:61-69, 2009

5-23 Buchner T, Berdel WE, Schoch C, et al: Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. J Clin Oncol 24:2480-9, 2006

5-24 Buchner T, Berdel WE, Haferlach C, et al. Long-Term Results in Patients with Acute Myeloid Leukemia (AML): The Influence of High-Dose AraC, G-CSF Priming, Autologous Transplantation, Prolonged Maintenance, Age, History, Cytogenetics, and Mutation Status. Data of the AMLCG 1999 Trial. Blood Nov 2009; 114: 485.

5-25 Büchner T, Schlenk R, Schaich M, et al. Prospective comparison of different treatments with a common standard treatment - a study by the German AML Intergroup. Blood Nov 2010; 116: 2175

5-26 Creutzig U, Buchner T, Sauerland MC, et al: Significance of age in acute myeloid leukemia patients younger than 30 years: a common analysis of the pediatric trials AML-BFM 93/98 and the adult trials AMLCG 92/99 and AMLSG HD93/98A. Cancer 112:562-71, 2008

5-27 Callens C, Coulon S, Naudin J, Radford-Weiss I, Boissel N, Raffoux E, et al. Targeting iron homeostasis induces cellular differentiation and synergizes with differentiating agents in acute myeloid leukemia. Journal of Experimental Medicine 2010; 207(4):731-50.

5-28 Capria S, Gentile G, Capobianchi A, Cardarelli L, Gianfelici V, Trisolini SM, et al. Prospective Cytomegalovirus Monitoring During First-Line Chemotherapy in Patients With Acute Myeloid Leukemia. Journal of Medical Virology 2010; 82(7):1201-7.

5-29 Cervera J, Montesinos P, Hernandez-Rivas JM, Calasanz MJ, Aventin A, Ferro MT, et al. Additional chromosome abnormalities in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Haematologica-the Hematology Journal 2010; 95(3):424-31.

5-30 Chevallier P, Fornecker L, Lioure B, Bene MC, Pigneux A, Recher C, et al. Tandem versus single autologous peripheral blood stem cell transplantation as post-remission therapy in adult acute myeloid leukemia patients under 60 in first complete remission: results of the multicenter prospective phase III GOELAMS LAM-2001 trial. Leukemia 2010; 24(7):1380-5.

5-31 Corbacioglu A, Scholl C, Schlenk RF, Eiwen K, Du JA, Bullinger L, et al. Prognostic Impact of Minimal Residual Disease in CBFB-MYH11-Positive Acute Myeloid Leukemia. Journal of Clinical Oncology 2010; 28(23):3724-9.

5-32 Coskun E, von der Heide EK, Schlee C, Kuhnl A, Gokbuget N, Hoelzer D, et al. The role of microRNA-196a and microRNA-196b as ERG regulators in acute myeloid leukemia and acute T-lymphoblastic leukemia. Leukemia Research 2011; 35(2):208-13.

5-33 Damm F, Heuser M, Morgan M, Yun HY, Grosshennig A, Gohring G, et al. Single Nucleotide Polymorphism in the Mutational Hotspot of WT1 Predicts a Favorable Outcome in Patients With Cytogenetically Normal Acute Myeloid Leukemia. Journal of Clinical Oncology 2010; 28(4):578-85.

5-34 Damm F, Oberacker T, Thol F, Surdziel E, Wagner K, Chaturvedi A, et al. Prognostic Importance of Histone Methyltransferase MLL5 Expression in Acute Myeloid Leukemia. Journal of Clinical Oncology 2011; 29(6):682-9.

5-35 de Leeuw DC, van den Ancker W, Westers TM, Loonen AH, Bhola SL, Ossenkoppele GJ, et al. Challenging diagnosis in a patient with clear lymphoid immunohistochemical features and myeloid morphology: Mixed phenotype acute leukemia with erythrophagocytosis. Leukemia Research [Editorial] 2011; 35(5):693-6.

5-36 Dufour A, Schneider F, Metzeler KH, Hoster E, Schneider S, Zellmeier E, et al. Acute Myeloid Leukemia With Biallelic CEBPA Gene Mutations and Normal Karyotype Represents a Distinct Genetic Entity Associated With a Favorable Clinical Outcome. Journal of Clinical Oncology 2010; 28(4):570-7.

5-37 Falini B, Macijewski K, Weiss T, Bacher U, Schnittger S, Kern W, et al. Multilineage dysplasia has no impact on biologic, clinicopathologic, and prognostic features of AML with mutated nucleophosmin (NPM1). Blood 2010; 115(18):3776-86.

5-38 Falini B, Martelli MP, Bolli N, Sportoletti P, Liso A, Tiacci E, et al. Acute myeloid leukemia with mutated nucleophosmin (NPM1): is it a distinct entity? Blood 2011; 117(4):1109-20.

5-39 Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia. Journal of Clinical Oncology 2010; 28(4):562-9.

5-40 Fiedler W, Krauter J, Gotze K, Salih HR, Bokemeyer C, Spaeth D, et al. A Phase I/II Study Combining Sunitinib with Standard Ara C/Daunorubicin Chemotherapy In Patients 60 Years or Older with FLT3 Mutated AML. Blood 2010; 116(21):1346-.

5-41 Gaidzik VI, Bullinger L, Schlenk RF, Zimmermann AS, Rock J, Paschka P, et al. RUNX1 Mutations in Acute Myeloid Leukemia: Results From a Comprehensive Genetic and Clinical Analysis From the AML Study Group. Journal of Clinical Oncology 2011; 29(10):1364-72.

5-42 Gorin NC, Labopin M, Reiffers J, Milpied N, Blaise D, Witz F, et al. Higher incidence of relapse in patients with acute myelocytic leukemia infused with higher doses of CD34(+) cells from leukapheresis products autografted during the first remission. Blood 2010; 116(17):3157-62.

5-43 Gratwohl A, Baldomero H, Aljourf M, et al. Hematopoietic Stem Cell Transplantation. JAMA. 2010;303(16):1617-1624

5-44 Groschel S, Lugthart S, Schlenk RF, Valk PJM, Eiwen K, Goudswaard C, et al. High EVI1 Expression Predicts Outcome in Younger Adult Patients With Acute Myeloid Leukemia and Is Associated With Distinct Cytogenetic Abnormalities. Journal of Clinical Oncology 2010; 28(12):2101-7.

5-45 Harrison CJ, Hills RK, Moorman AV, Grimwade DJ, Hann I, Webb DKH, et al. Cytogenetics of Childhood Acute Myeloid Leukemia: United Kingdom Medical Research Council Treatment Trials AML 10 and 12. Journal of Clinical Oncology 2010; 28(16):2674-81.

5-46 Hasan SK, Buttari F, Ottone T, Voso MT, Hohaus S, Marasco E, et al. Risk of acute promyelocytic leukemia in multiple sclerosis Coding variants of DNA repair genes. Neurology 2011; 76(12):1059-65.

5-47 Hasan SK, Ottone T, Schlenk RF, Xiao YY, Wiemels JL, Mitra ME, et al. Analysis of t(15;17) Chromosomal Breakpoint Sequences in Therapy-Related Versus De Novo Acute Promyelocytic Leukemia: Association of DNA Breaks with Specific DNA Motifs at PML and RARA Loci. Genes Chromosomes & Cancer 2010; 49(8):726-32.

5-48 Homme C, Krug U, Tidow N, Schulte B, Kohler G, Serve H, et al. Low SMC1A protein expression predicts poor survival in acute myeloid leukemia. Oncology Reports 2010; 24(1):47-56.

5-49 Kayser S, Dohner K, Krauter J, Kohne CH, Horst HA, Held G, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011; 117(7):2137-45.

5-50 Krug U, Lubbert M, Buchner T. Maintenance therapy in acute myeloid leukemia revisited: will new agents rekindle an old interest? Current Opinion in Hematology 2010; 17(2):85-90.

5-51 Krug UO, Rohde C, Heinecke A, Sauerland MC, Koschmieder A, Rollig C, et al. Estimating the Chances of Older AML Patients to Achieve a Complete Remission Upon Intensive Induction Chemotherapy An AMLCG and SAL Study. Blood 2010; 116(21):1111-.

5-52 Krug U, Röllig C, Koschmieder A, et al: Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 376:2000-2008, 2010Lengfelder E, Lo-Coco F, Montesinos P, et al. Treatment of Molecular and Clinical Relapse of Acute Promyelocytic Leukemia (APL) with Arsenic Trioxide: Results of the European Registry of Relapsed

5-53 Krug U, Lubbert M, Buchner T. Maintenance therapy in acute myeloid leukemia revisited: will new agents rekindle an old interest? Curr Opin Hematol 2:85-90, 2010

5-54 Kuhn WMM, Radtke I, Bullinger L, Goorha S, Cheng JJ, Edelmann J, et al. High Resolution Genomic Profiling of Adult and Pediatric Core Binding Factor Acute Myeloid Leukemia Reveals New Recurrent Genomic Aberrations. Blood 2010; 116(21):369-70.

5-55 Lange T, Hubmann M, Burkhardt R, Franke GN, Cross M, Scholz M, et al. Monitoring of WT1 expression in PB and CD34(+) donor chimerism of BM predicts early relapse in AML and MDS patients after hematopoietic cell transplantation with reduced- intensity conditioning. Leukemia (Basingstoke) 2011; 25(3):498-505.

5-56 Lengfelder E, Haferlach C, Saussele S, et al. High dose ara-C in the treatment of newly diagnosed acute promyelocytic leukemia: long-term results of the German AMLCG. Leukemia 23:2248-58, 2009.

5-57 Lowenberg B, Pabst T, Vellenga E, van Putten W, Schouten HC, Graux C, et al. Cytarabine Dose for Acute Myeloid Leukemia. New England Journal of Medicine 2011; 364(11):1027-36.

5-58 Luck SC, Russ AC, Du J, Gaidzik V, Schlenk RF, Pollack JR, et al. KIT mutations confer a distinct gene expression signature in core binding factor leukaemia. British Journal of Haematology 2010; 148(6):925-37.

5-59 Lugthart S, Groschel S, Beverloo HB, Kayser S, Valk PJM, van Zelderen-Bhola SL, et al. Clinical, Molecular, and Prognostic Significance of WHO Type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and Various Other 3q Abnormalities in Acute Myeloid Leukemia. Journal of Clinical Oncology 2010; 28(24):3890-8.

5-60 Marcucci G, Haferlach T, Dohner H. Molecular Genetics of Adult Acute Myeloid Leukemia: Prognostic and Therapeutic Implications. Journal of Clinical Oncology 2011; 29(5):475-86.

5-61 Martin V, Valencia A, Agirre X, Cervera J, Jose-Eneriz ES, Vilas-Zornoza A, et al. Epigenetic regulation of the non-canonical Wnt pathway in acute myeloid leukemia. Cancer Science 2010; 101(2):425-32.

5-62 Mays AN, Osheroff N, Xiao YY, Wiemels JL, Felix CA, Byl JAW, et al. Evidence for direct involvement of epirubicin in the formation of chromosomal translocations in t(15;17) therapy-related acute promyelocytic leukemia. Blood 2010; 115(2):326-30.

5-63 Montesinos P, Gonzalez JD, Gonzalez J, Rayon C, de Lisa E, Amigo ML, et al. Therapy-Related Myeloid Neoplasms in Patients With Acute Promyelocytic Leukemia Treated With All-Trans-Retinoic Acid and Anthracycline-Based Chemotherapy. Journal of Clinical Oncology 2010; 28(24):3872-9.

5-64 Montesinos P, Rayon C, Vellenga E, Brunet S, Gonzalez J, Gonzalez M, et al. Clinical significance of CD56 expression in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based regimens. Blood 2011; 117(6):1799-805.

5-65 Nibourel O, Kosmider O, Cheok M, Boissel N, Renneville A, Philippe N, et al. Incidence and prognostic value of TET2 alterations in de novo acute myeloid leukemia achieving complete remission. Blood 2010; 116(7):1132-5.

5-66 Niederwieser D. Studienstrategien der OSHO bei AML 60+ : Vidaza, Clofarabine, alloSCT (EBMT), und Networking (Intergroup). Reisensburg Meeting Feb 2011.

5-67 Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Kronke J, Bullinger L, et al. IDH1 and IDH2 Mutations Are Frequent Genetic Alterations in Acute Myeloid Leukemia and Confer Adverse Prognosis in Cytogenetically Normal Acute Myeloid Leukemia With NPM1 Mutation Without FLT3 Internal Tandem Duplication. Journal of Clinical Oncology 2010; 28(22):3636-43.

5-68 Pautas C, Merabet F, Thomas X, Raffoux E, Gardin C, Corm S, et al. Randomized Study of Intensified Anthracycline Doses for Induction and Recombinant Interleukin-2 for Maintenance in Patients With Acute Myeloid Leukemia Age 50 to 70 Years: Results of the ALFA-9801 Study. Journal of Clinical Oncology 2010; 28(5):808-14.

5-69 Pigneux A, Harousseau JL, Witz F, Sauvezie M, Bene MC, Luquet I, et al. Addition of Lomustine to Idarubicin and Cytarabine Improves the Outcome of Elderly Patients With De Novo Acute Myeloid Leukemia: A Report From the GOELAMS. Journal of Clinical Oncology 2010; 28(18):3028-34.

5-70 Rawat VPS, Arseni N, Ahmed F, Mulaw MA, Thoene S, Heilmeier B, et al. The vent-like homeobox gene VENTX promotes human myeloid differentiation and is highly expressed in acute myeloid leukemia. Proceedings of the National Academy of Sciences of the United States of America 2010; 107(39):16946-51.

5-71 Roellig C, Thiede C, Gramatzki M, Aulitzky W, Bodenstein H, Bornhaeuser M, et al. A novel prognostic model in elderly patients with acute myeloid leukemia: results of 909 patients entered into the prospective AML96 trial. Blood 2010; 116(6):971-8.

5-72 Rucker FG, Bullinger L, Gribov A, Sill M, Schlenk RF, Lichter P, et al. Molecular Characterization of AML with ins(21;8)(q22;q22q22) Reveals Similarity to t(8;21) AML. Genes Chromosomes & Cancer 2011; 50(1):51-8.

5-73 Rucker FG, Bullinger L, Stegelmann F, Blersch C, Lichter P, Krauter J, et al. NF1 Alterations Are Common In AML with Complex Karyotype and Correlate with Specific Genomic Imbalances. Blood 2010; 116(21):1700-.

5-74 Sanz J, Sanz MA, Saavedra S, Lorenzo I, Montesinos P, Senent L, et al. Cord Blood Transplantation from Unrelated Donors in Adults with High-Risk Acute Myeloid Leukemia. Biology of Blood and Marrow Transplantation 2010; 16(1):86-94.

5-75 Sanz MA, Lo-Coco F. Modern Approaches to Treating Acute Promyelocytic Leukemia. Journal of Clinical Oncology 2011; 29(5):495-503.

5-76 Sanz MA, Montesinos P, Rayon C, Holowiecka A, de la Serna J, Milone G, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood 2010; 115(25):5137-46.

5-77 Sauter D, Ringel K, Braess J, Hiddemann W, Spiekermann K, Subklewe M. Minimal Residual Disease Assessment by Flow Cytometry In AML Patients at Time of Aplasia Post Induction Is Highly Predictive of Outcome and Strongly Correlates with Molecular MRD In a Subgroup of NPM1 Positive Patients. Blood 2010; 116(21):721-.

5-78 Schachter-Tokarz E, Kelaidi C, Cassinat B, Chomienne C, Gardin C, Raffoux E, et al. PML-RAR alpha ligand-binding domain deletion mutations associated with reduced disease control and outcome after first relapse of APL. Leukemia 2010; 24(2):473-6.

5-79 Schlenk RF, Dohner K, Mack S, Stoppel M, Kiraly F, Gotze K, et al. Prospective Evaluation of Allogeneic Hematopoietic Stem-Cell Transplantation From Matched Related and Matched Unrelated Donors in Younger Adults

With High-Risk Acute Myeloid Leukemia: German-Austrian Trial AMLHD98A. Journal of Clinical Oncology 2010; 28(30):4642-8.

5-80 Schuurhuis GJ, Ossenkoppele G. Minimal residual disease in acute myeloid leukemia: already predicting a safe haven? Expert Review of Hematology 2010; 3(1):1-5.

5-81 Serve H, Wagner R, Sauerland C, et al. Sorafenib In Combination with Standard Induction and Consolidation Therapy In Elderly AML Patients: Results From a Randomized, Placebo-Controlled Phase II Trial. Blood, Nov 2010; 116: 333.

5-82 Stelljes M, Beelen D, Braess J, et al. Allogeneic transplantation as postremission therapy for cytogenetically high risk acute myeloid leukemia (AML): Landmark analysis from a single prospective multicenter trial. Haematologica 2011, in press

5-83 Stringaris K, Barrett AJ, Hills R, Linch DC, Gale R, Allen C, et al. A Distinct Signature of Natural Killer Cell MR Gene Frequencies In Secondary AML Compared with De Novo AML and Normal Controls. Blood 2010; 116(21):711-2.

5-84 Such E, Cervera J, Valencia A, Barragan E, Ibanez M, Luna I, et al. A novel NUP98/RARG gene fusion in acute myeloid leukemia resembling acute promyelocytic leukemia. Blood 2011; 117(1):242-5.

5-85 Tallman MS, Kim HT, Montesinos P, Appelbaum FR, de la Serna J, Bennett JM, et al. Does microgranular variant morphology of acute promyelocytic leukemia independently predict a less favorable outcome compared with classical M3 APL? A joint study of the North American Intergroup and the PETHEMA Group. Blood 2010; 116(25):5650-9.

5-86 Taskesen E, Bullinger L, Corbacioglu A, Sanders MA, Erpelinck CAJ, Wouters BJ, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. Blood 2011; 117(8):2469-75.

5-87 Thol F, Damm F, Wagner K, Gohring G, Schlegelberger B, Hoelzer D, et al. Prognostic impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood [Article] 2010; 116(4):614-6.

5-88 Thomas X, Raffoux E, Renneville A, Pautas C, de Botton S, Terre C, et al. Which AML Subsets Benefit From Leukemic Cell Priming During Chemotherapy? Long-Term Analysis of the ALFA-9802 GM-CSF Study. Cancer 2010; 116(7):1725-32.

5-89 Valencia A, Cervera J, Such E, Ibanez M, Barragan E, Fuster O, et al. A new reliable fluorescence in situ hybridization method for identifying multiple specific cytogenetic abnormalities in acute myeloid leukemia. Leukemia & Lymphoma 2010; 51(4):680-5.

5-90 van den Ancker W, van Luijn MM, Westers TM, Bontkes HJ, Ruben JM, de Gruijl TD, et al. Recent advances in antigen-loaded dendritic cell-based strategies for treatment of minimal residual disease in acute myeloid leukemia. Immunotherapy 2010; 2(1):69-83.

5-91 van Luijn MM, Chamuleau MED, Ressing ME, Wiertz EJ, Ostrand-Rosenberg S, Souwer Y, et al. Alternative Ii-independent antigen-processing pathway in leukemic blasts involves TAP-dependent peptide loading of HLA class II complexes. Cancer Immunology Immunotherapy 2010; 59(12):1825-38.

5-92 van Luijn MM, Chamuleau MED, Thompson JA, Ostrand-Rosenberg S, Westers TM, Souwer Y, et al. Class II-associated invariant chain peptide down-modulation enhances the immunogenicity of myeloid leukemic blasts resulting in increased CD4(+) T-cell responses. Haematologica-the Hematology Journal 2010; 95(3):485-93.

5-93 van Luijn MM, van den Ancker W, Chamuleau MED, Ossenkoppele GJ, van Ham SM, van de Loosdrecht AA. Impaired antigen presentation in neoplasia: basic mechanisms and implications for acute myeloid leukemia. Immunotherapy 2010; 2(1):85-97.

5-94 van Luijn MM, van den Ancker W, Chamuleau MED, Zevenbergen A, Westers TM, Ossenkoppele GJ, et al. Absence of Class II-Associated Invariant Chain Peptide on Leukemic Blasts of Patients Promotes Activation of Autologous Leukemia-Reactive CD4(+) T Cells. Cancer Research 2011; 71(7):2507-17.

5-95 Vellenga E, van Putten W, Ossenkoppele GJ, Fey M, Kuball J, Theobald M, et al. Autologous Blood Stem Cell Transplantation Results In Better Relapse Free Survival Than Consolidation Chemotherapy Results of a HOVON/SAKK Phase III Trial In 519 AML Patients In First Complete Remission. Blood 2010; 116(21):166-.

5-96 Wandt H, Haferlach T, Thiede C, Ehninger G. WHO classification of myeloid neoplasms and leukemia. Blood 2010; 115(3):748-9.

WP6 (ALL)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)

6-1 Brueggemann M, Schrauder A, Raff T, Pfeifer H, Dworzak M, Ottmann OG, et al. Standardized MRD quantification in European ALL trials: Proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia (Basingstoke) 2010; 24(3):521-35.

6-2 Folber F, Sálek C, Doubek M, Soukupová Maaloufová J, Valová T, Trka J, Gökbuget N, Vydra J, Kozák T, Horácek JM, Zák P, Cetkovský P, Hoelzer D, Mayer J. [Treatment of adult acute lymphoblastic leukemia according to GMALL 07/2003 study protocol in the Czech Republic - the first experience]. Vnitr Lek. 2010 Mar;56(3):176-82. Czech.

6-3 Giebel S, Stella-Holowiecka B, Krawczyk-Kulis M, Gokbuget N, Hoelzer D, Doubek M, et al. Status of minimal residual disease determines outcome of autologous hematopoietic SCT in adult ALL. Bone Marrow Transplantation 2010; 45(6):1095-101.

6-4 Goekbuget N, Hartog C-M, Bassan R, Derigs H-G, Dombret H, Greil R, et al. Liposomal cytarabine is effective and tolerable in the treatment of central nervous system relapse of acute lymphoblastic leukemia and very aggressive lymphoma. Haematologica-the Hematology Journal 2011; 96(2):238-44.

6-5 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

*International publications that are the not a direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

6-6 Asnafi V, Le Noir S, Lhermitte L, Gardin C, Legrand F, Vallantin X, Malfuson JV, Ifrah N, Dombret H, Macintyre E. JAK1 mutations are not frequent events in adult T-ALL: a GRAALL study.Br J Haematol. 2010 Jan;148(1):178-9. Epub 2009 Sep 18. No abstract available

6-7 Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011 Feb 10;29(5):532-43. Epub 2011 Jan 10. Review.

6-8 Bassan R, Rossi G, Pogliani EM, Di Bona E, Angelucci E, Cavattoni I, et al. Chemotherapy-Phased Imatinib Pulses Improve Long-Term Outcome of Adult Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Northern Italy Leukemia Group Protocol 09/00. Journal of Clinical Oncology 2010; 28(22):3644-52.

6-9 Burmeister T, Gökbuget N, Schwartz S, Fischer L, Hubert D, Sindram A, Hoelzer D, Thiel E. Clinical features and prognostic implications of TCF3-PBX1 and ETV6-RUNX1 in adult acute lymphoblastic leukemia. Haematologica. 2010 Feb;95(2):241-6. Epub 2009 Aug 27.

6-10 Chiaretti S, Messina M, Tavolaro S, Zardo G, Elia L, Vitale A, et al. Gene expression profiling identifies a subset of adult T-cell acute lymphoblastic leukemia with myeloid-like gene features and over-expression of miR-223. Haematologica-the Hematology Journal 2010; 95(7):1114-21.

6-11 Cimino G, Cenfra N, Elia L, Sica S, Luppi M, Meloni G, et al. The therapeutic response and clinical outcome of adults with ALL1(MLL)/AF4 fusion positive acute lymphoblastic leukemia according to the GIMEMA experience. Haematologica-the Hematology Journal 2010; 95(5):837-40.

6-12 Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010; 115(16):3206-14.

6-13 Coskun E, von der Heide EK, Schlee C, Kuhnl A, Gokbuget N, Hoelzer D, et al. The role of microRNA-196a and microRNA-196b as ERG regulators in acute myeloid leukemia and acute T-lymphoblastic leukemia. Leukemia Research 2011; 35(2):208-13.

6-14 de Vries JF, Marvelde JGT, Wind HK, van Dongen JJM, van der Velden VHJ. The potential use of basigin (CD147) as a prognostic marker in B-cell precursor acute lymphoblastic leukaemia. British Journal of Haematology 2010; 150(5):624-6.

6-15 Domenech C, Thomas X, Chabaud S, Baruchel A, Gueyffier F, Mazingue F, et al. L-asparaginase loaded red blood cells in refractory or relapsing acute lymphoblastic leukaemia in children and adults: results of the GRASPALL 2005-01 randomized trial. British Journal of Haematology 2011; 153(1):58-65.

6-16 Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, Hoelzer D, et al. Adult Acute Lymphoblastic Leukemia Concepts and Strategies. Cancer 2010; 116(5):1165-76.

6-17 Ferra C, Sanz J, de la Camara R, Sanz G, Bermudez A, Valcarcel D, et al. Unrelated Transplantation for Poor-Prognosis Adult Acute Lymphoblastic Leukemia: Long-Term Outcome Analysis and Study of the Impact of Hematopoietic Graft Source. Biology of Blood and Marrow Transplantation 2010; 16(7):957-66.

6-18 Fielding AK. How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia. Blood 2010; 116(18):3409-17.

6-19 Fielding AK. Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 2010; 95(1):8-12.

6-20 Fielding AK. Philadelphia-Positive Acute Lymphoblastic Leukemia--Is Bone Marrow Transplant Still Necessary? Biology of Blood and Marrow Transplantation [doi: 10.1016/j.bbmt.2010.11.023] 2011; 17(1, Supplement 1):S84-S8.

6-21 Folber F, Salek C, Doubek M, Soukupova Maaloufova J, Valova T, Trka J, et al. [Treatment of adult acute lymphoblastic leukemia according to GMALL 07/2003 study protocol in the Czech Republic - the first experience]. Vnitr Lek 2010; 56(3):176-82.

6-22 Gokbuget N, Hartog CM, Bassan R, Derigs HG, Dombret H, Greil R, et al. Liposomal cytarabine is effective and tolerable in the treatment of central nervous system relapse of acute lymphoblastic leukemia and very aggressive lymphoma. Haematologica-the Hematology Journal 2011; 96(2):238-44.

6-23 Gorello P, La Starza R, Varasano E, Chiaretti S, Elia L, Pierini V, et al. Combined interphase fluorescence in situ hybridization elucidates the genetic heterogeneity of T-cell acute lymphoblastic leukemia in adults. Haematologica-the Hematology Journal 2010; 95(1):79-86.

6-24 Hagemeijer A, Graux C. ABLI Rearrangements in T-Cell Acute Lymphoblastic Leukemia. Genes Chromosomes & Cancer 2010; 49(4):299-308.

6-25 Heesch S, Bartram I, Neumann M, Reins J, Mossner M, Schlee C, et al. Expression of IGFBP7 in acute leukemia is regulated by DNA methylation. Cancer Science 2011; 102(1):253-9.

6-26 Heesch S, Goekbuget N, Stroux A, Tanchez JO, Schlee C, Burmeister T, et al. Prognostic implications of mutations and expression of the Wilms tumor 1 (WT1) gene in adult acute T-lymphoblastic leukemia. Haematologica-the Hematology Journal 2010; 95(6):942-9.

6-27 Heesch S, Schlee C, Neumann M, Stroux A, Kuhnl A, Schwartz S, et al. BAALC-associated gene expression profiles define IGFBP7 as a novel molecular marker in acute leukemia. Leukemia 2010; 24(8):1429-36.

6-28 Hertzberg L, Vendramini E, Ganmore I, Cazzaniga G, Schmitz M, Chalker J, et al. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Blood 2010; 115(5):1006-17.

6-29 Heuser M, Ganser A, Hoelzer D. The hematopoietic growth factors in acute leukemia: a European perspective. Cancer Treat Res 2011; 157:339-62.

6-30 Hornakova T, Chiaretti S, Lemaire MM, Foa R, Ben Abdelali R, Asnafi V, et al. ALL-associated JAK1 mutations confer hypersensitivity to the antiproliferative effect of type I interferon. Blood 2010; 115(16):3287-95.

6-31 Hunault-Berger M, Leguay T, Thomas X, Legrand O, Huguet F, Bonmati C, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. Haematologica-the Hematology Journal 2011; 96(2):245-52.

6-32 Hutter G, Kaiser M, Neumann M, Mossner M, Nowak D, Baldus CD, et al. Epigenetic regulation of PAX5 expression in acute T-cell lymphoblastic leukemia. Leukemia Research 2011; 35(5):614-9.

6-33 Iacobucci I, Lonetti A, Messa F, Ferrari A, Cilloni D, Soverini S, et al. Different isoforms of the B-cell mutator activation-induced cytidine deaminase are aberrantly expressed in BCR-ABL1-positive acute lymphoblastic leukemia patients. Leukemia 2010; 24(1):66-73.

6-34 Iacobucci I, Lonetti A, Paoloni F, Papayannidis C, Ferrari A, Storlazzi CT, et al. The PAX5 gene is frequently rearranged in BCR-ABL1-positive acute lymphoblastic leukemia but is not associated with outcome. A report on behalf of the GIMEMA Acute Leukemia Working Party. Haematologica-the Hematology Journal 2010; 95(10):1683-90.

6-35 Kleppe M, Lahortiga I, El Chaar T, De Keersmaecker K, Mentens N, Graux C, et al. Deletion of the protein tyrosine phosphatase gene PTPN2 in T-cell acute lymphoblastic leukemia. Nature Genetics 2010; 42(6):530-U84.

6-36 Kuhnl A, Gokbuget N, Stroux A, Burmeister T, Neumann M, Heesch S, et al. High BAALC expression predicts chemoresistance in adult B-precursor acute lymphoblastic leukemia. Blood 2010; 115(18):3737-44.

6-37 Lankester AC, Bierings MB, van Wering ER, Wijkhuijs AJM, de Weger RA, Wijnen JT, et al. Preemptive alloimmune intervention in high-risk pediatric acute lymphoblastic leukemia patients guided by minimal residual disease level before stem cell transplantation. Leukemia 2010; 24(8):1462-9.

6-38 Lilly MB, Ottmann OG, Shah NP, Larson RA, Reiffers JJ, Ehninger G, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. American Journal of Hematology 2010; 85(3):164-70.

6-39 Maggio R, Peragine N, De Propris MS, Vitale A, Elia L, Calabrese E, et al. Immunocompetent cell functions in Ph+ acute lymphoblastic leukemia patients on prolonged Imatinib maintenance treatment. Cancer Immunology Immunotherapy 2011; 60(4):599-607.

6-40 Matteucci C, Barba G, Varasano E, Vitale A, Mancini M, Testoni N, et al. Rescue of genomic information in adult acute lymphoblastic leukaemia (ALL) with normal/failed cytogenetics: a GIMEMA centralized biological study. British Journal of Haematology 2010; 149(1):70-8.

6-41 Maury S, Huguet F, Leguay T, Lacombe F, Maynadie M, Girard S, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. Haematologica-the Hematology Journal 2010; 95(2):324-8.

6-42 Messina M, Chiaretti S, Iacobucci I, Tavolaro S, Lonetti A, Santangelo S, et al. AICDA expression in BCR/ABL1-positive acute lymphoblastic leukaemia is associated with a peculiar gene expression profile. British Journal of Haematology 2011; 152(6):727-32.

6-43 Messina M, Chiaretti S, Tavolaro S, Peragine N, Vitale A, Elia L, et al. Protein Kinase Gene Expression Profiling and In Vitro Functional Experiments Identify Novel Potential Therapeutic Targets in Adult Acute Lymphoblastic Leukemia. Cancer 2010; 116(14):3426-37.

6-44 Nijmeijer BA, van Schie MLJ, Halkes CJM, Griffioen M, Willemze R, Falkenburg JHF. A mechanistic rationale for combining alemtuzumab and rituximab in the treatment of ALL. Blood 2010; 116(26):5930-40.

6-45 Okamoto R, Ogawa S, Nowak D, Kawamata N, Akagi T, Kato M, et al. Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica-the Hematology Journal 2010; 95(9):1481-8.

6-46 Oriol A, Vives S, Hernandez-Rivas JM, Tormo M, Heras I, Rivas C, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica-the Hematology Journal 2010; 95(4):589-96.

6-47 Patel B, Rai L, Buck G, Richards SM, Mortuza Y, Mitchell W, et al. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. British Journal of Haematology 2010; 148(1):80-9.

6-48 Pieters R, Hunger SP, Boos J, Rizzari C, Silverman L, Baruchel A, et al. L-Asparaginase Treatment in Acute Lymphoblastic Leukemia. Cancer 2011; 117(2):238-49.

6-49 Rai L, Casanova A, Moorman AV, Richards S, Buck G, Goldstone AH, et al. Antigen receptor gene rearrangements reflect on the heterogeneity of adult Acute Lymphoblastic Leukaemia (ALL) with implications of cell-origin of ALL subgroups - a UKALLXII study. British Journal of Haematology 2010; 148(3):394-401.

6-50 Ramadanova K, Hoff H, Gokbuget N, Reuner U, Hamann S, Ehninger G, et al. Toxic non-resorptive internal hydrocephalus as a result of haemorrhagic ventriculitis during induction chemotherapy of Bcr-Abl positive acute lymphoblastic leukaemia. Annals of Hematology [Letter] 2010; 89(2):221-3.

6-51 Raponi S, Stefania De Propris M, Intoppa S, Laura Milani M, Vitale A, Elia L, et al. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. Leuk Lymphoma 2011; 52(6):1098-107.

6-52 Ribera JM, Oriol A, Gonzalez M, Vidriales B, Brunet S, Esteve J, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final resullts of the CSTIBES02 trial. Haematologica-the Hematology Journal 2010; 95(1):87-95.

6-53 Soverini S, Vitale A, Poerio A, Gnani A, Colarossi S, Iacobucci I, et al. Philadelphia-positive acute lymphoblastic leukemia patients already harbor BCR-ABL kinase domain mutations at low levels at the time of diagnosis. Haematologica-the Hematology Journal 2011; 96(4):552-7.

6-54 Szczepanski T, van der Velden VHJ, Waanders E, Kuiper RP, Van Vlierberghe P, Gruhn B, et al. Late Recurrence of Childhood T-Cell Acute Lymphoblastic Leukemia Frequently Represents a Second Leukemia Rather Than a Relapse: First Evidence for Genetic Predisposition. Journal of Clinical Oncology 2011; 29(12):1643-9.

6-55 Waanders E, van der Velden VHJ, van der Schoot CE, van Leeuwen FN, van Reijmersdal SV, de Haas V, et al. Integrated use of minimal residual disease classification and IKZF1 alteration status accurately predicts 79% of relapses in pediatric acute lymphoblastic leukemia. Leukemia (Basingstoke) 2011; 25(2):254-8.

6-56 Wu SL, Fischer L, Gokbuget N, Schwartz S, Burmeister T, Notter M, et al. Expression of Interleukin 15 in Primary Adult Acute Lymphoblastic Leukemia. Cancer 2010; 116(2):387-92.

6-57 Xicoy B, Ribera JM, Miralles P, La Cruz J, Oriol A, Valencia E, et al. Comparison of CHOP treatment with specific short-intensive chemotherapy in AIDS-related Burkitt's lymphoma or leukemia. Medicina Clinica 2011; 136(8):323-8.

6-58 Yoda A, Yoda Y, Chiaretti S, Bar-Natan M, Mani K, Rodig SJ, et al. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. Proceedings of the National Academy of Sciences of the United States of America 2010; 107(1):252-7.

WP7 (CLL))

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

7-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

International publications that are the direct result of the European LeukemiaNet
(**without** a reference to the European LeukemiaNet)

7-2 Baldazzi C, Iacobucci I, Luatti S, Ottaviani E, Marzocchi G, Paolini S, et al. B-cell acute lymphoblastic leukemia as evolution of a 8p11 myeloproliferative syndrome with t(8;22)(p11;q11) and BCR-FGFR1 fusion gene. Leukemia Research [Letter] 2010; 34(10):E282-E5.

7-3 Bhattacharya N, Diener S, Idler IS, Barth TF, Rauen J, Habermann A, et al. Non-malignant B cells and chronic lymphocytic leukemia cells induce a pro-survival phenotype in CD14(+) cells from peripheral blood. Leukemia 2011; 25(4):722-6.

7-4 Boll B, Eichenauer DA, Von Tresckow B, Peine D, Hallek M, Engert A, et al. Activity of cetuximab as single agent in a patient with relapsed multiple myeloma. Leukemia & Lymphoma 2010; 51(3):562-4.

7-5 Cartron G, Trappe RU, Solal-Celigny P, Hallek M. Interindividual Variability of Response to Rituximab: From Biological Origins to Individualized Therapies. Clinical Cancer Research 2011; 17(1):19-30.

7-6 Cheson BD, Wendtner CM, Pieper A, Dreyling M, Friedberg J, Hoelzer D, et al. Optimal Use of Bendamustine in Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphomas, and Multiple Myeloma: Treatment Recommendations From an International Consensus Panel. Clinical Lymphoma Myeloma & Leukemia 2010; 10(1):21-7.

7-7 Chiaretti S, Tavolaro S, Marinelli M, Messina M, Del Giudice I, Mauro FR, et al. Evaluation of TP53 Mutations with the AmpliChip p53 Research Test in Chronic Lymphocytic Leukemia: Correlation with Clinical Outcome and Gene Expression Profiling. Genes Chromosomes & Cancer 2011; 50(4):263-74.

7-8 Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia-what do we need to know? Nature Reviews Clinical Oncology 2011; 8(1):38-47.

7-9 Crowther-Swanepoel D, Broderick P, Di Bernardo MC, Dobbins SE, Torres M, Mansouri M, et al. Common variants at 2q37.3, 8q24.21, 15q21.3 and 16q24.1 influence chronic lymphocytic leukemia risk. Nature Genetics 2010; 42(2):132-U59.

7-10 Crowther-Swanepoel D, Mansouri M, Enjuanes A, Vega A, Smedby KE, Ruiz-Ponte C, et al. Verification that common variation at 2q37.1, 6p25.3, 11q24.1, 15q23, and 19q13.32 influences chronic lymphocytic leukaemia risk. British Journal of Haematology 2010; 150(4):473-9.

7-11 Dal-Bo M, Del Giudice I, Bomben R, Capello D, Bertoni F, Forconi F, et al. B-cell receptor, clinical course and prognosis in chronic lymphocytic leukaemia: the growing saga of the IGHV3 subgroup gene usage. British Journal of Haematology 2011; 153(1):3-14.

7-12 Dreger P, Dohner H, Ritgen M, Bottcher S, Busch R, Dietrich S, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood 2010; 116(14):2438-47.

7-13 Eichhorst B, Hallek M, Dreyling M, Grp EGW. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology [Article] 2010; 21:v162-v4.

7-14 Eichhorst BF, Fischer K, Fink AM, Elter T, Wendtner CM, Goede V, et al. Limited clinical relevance of imaging techniques in the follow-up of patients with advanced chronic lymphocytic leukemia: results of a meta-analysis. Blood 2011; 117(6):1817-21.

7-15 Foon KA, Hallek MJ. Changing paradigms in the treatment of chronic lymphocytic leukemia. Leukemia 2010; 24(3):500-11.

7-16 Frenzel LP, Patz M, Pallasch CP, Brinker R, Claasen J, Schulz A, et al. Novel X-linked inhibitor of apoptosis inhibiting compound as sensitizer for TRAIL-mediated apoptosis in chronic lymphocytic leukaemia with poor prognosis. British Journal of Haematology 2011; 152(2):191-200.

7-17 Gandhirajan RK, Staib PA, Minke K, Gehrke I, Plickert G, Schlosser AA, et al. Small Molecule Inhibitors of Wnt/beta-Catenin/Lef-1 Signaling Induces Apoptosis in Chronic Lymphocytic Leukemia Cells In Vitro and In Vivo. Neoplasia [Article] 2010; 12(4):326-U50.

7-18 Giannopoulos K, Dmoszynska A, Kowal M, Rolinski J, Gostick E, Price DA, et al. Peptide vaccination elicits leukemia-associated antigen-specific cytotoxic CD8(+) T-cell responses in patients with chronic lymphocytic leukemia. Leukemia 2010; 24(4):798-805.

7-19 Goede V, Hallek M. Optimal Pharmacotherapeutic Management of Chronic Lymphocytic Leukaemia Considerations in the Elderly. Drugs & Aging 2011; 28(3):163-76.

7-20 Hallek M. Therapy of chronic lymphocytic leukaemia. Best Practice & Research Clinical Haematology 2010; 23(1):85-96.

7-21 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Defining response criteria in CLL patients treated in clinical research trials Response. Blood [Letter] 2010; 116(10):1817-8.

7-22 Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010; 376(9747):1164-74.

7-23 Hallek M, Pflug N. Chronic lymphocytic leukemia. Annals of Oncology 2010; 21:154-64.

7-24 Hallek M, Pflug N. State of the art treatment of chronic lymphocytic leukaemia. Blood Reviews 2011; 25(1):1-9.

7-25 Idler I, Giannopoulos K, Zenz T, Bhattacharya N, Nothing M, Dohner H, et al. Lenalidomide treatment of chronic lymphocytic leukaemia patients reduces regulatory T cells and induces Th17 T helper cells. British Journal of Haematology 2010; 148(6):948-50.

7-26 Kienle D, Benner A, Laufle C, Winkler D, Schneider C, Buhler A, et al. Gene expression factors as predictors of genetic risk and survival in chronic lymphocytic leukemia. Haematologica-the Hematology Journal 2010; 95(1):102-9.

7-27 Krause G, Hallek M. On the assessment of dasatinib-induced autophagy in CLL. Leukemia Research [Letter] 2011; 35(1):137-8.

7-28 Langerak AW, Davi F, Ghia P, Hadzidimitriou A, Murray F, Potter KN, et al. Immunoglobulin sequence analysis and prognostication in CLL: guidelines from the ERIC review board for reliable interpretation of problematic cases. Leukemia 2011:in press.

7-29 Laurenti L, De Padua L, Tarnani M, Piccirillo N, Falcucci P, D'Arena G, et al. Comparison between oral and intravenous fludarabine plus cyclophosphamide regime as front-line therapy in patients affected by chronic lymphocytic leukaemia: influence of biological parameters on the clinical outcome. Annals of Hematology 2011; 90(1):59-65.

7-30 Marinelli M, Raponi S, Del Giudice I, De Propris MS, Nanni M, Intoppa S, et al. Is the Aberrant Expression of p53 by Immunocytochemistry a Surrogate Marker of TP53 Mutation and/or Deletion in Chronic Lymphocytic Leukemia? American Journal of Clinical Pathology [Letter] 2011; 135(1):173-4.

7-31 Michallet M, Dreger P, Sutton L, Brand R, Richards S, van Os M, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. Blood 2011; 117(5): 1516-21.

7-32 Michallet M, Sobh M, Milligan D, Morisset S, Niederwieser D, Koza V, et al. The impact of HLA matching on long-term transplant outcome after allogeneic hematopoietic stem cell transplantation for CLL: a retrospective study from the EBMT registry. Leukemia 2010; 24(10):1725-31.

7-33 Mohr J, Helfrich H, Fuge M, Eldering E, Buhler A, Winkler D, et al. DNA damage-induced transcriptional program in CLL: biological and diagnostic implications for functional p53 testing. Blood 2011; 117(5):1622-32.

7-34 Molica S, Mauro FR, Callea V, Giannarelli D, Lauria F, Rotoli B, et al. The utility of a prognostic index for predicting time to first treatment in early chronic lymphocytic leukemia: the GIMEMA experience. Haematologica-the Hematology Journal 2010; 95(3):464-9.

7-35 Molica S, Mauro FR, Giannarelli D, Lauria F, Cortelezzi A, Brugiatelli M, et al. Differentiating chronic lymphocytic leukemia from monoclonal B-lymphocytosis according to clinical outcome: on behalf of the GIMEMA chronic lymphoproliferative diseases working group. Haematologica-the Hematology Journal 2011; 96(2):277-83.

7-36 Montserrat E. Advances in Biology and Therapy of Chronic Lymphocytic Leukemia Preface. Best Practice & Research Clinical Haematology [Editorial Material] 2010; 23(1):1-2.

7-37 Moreno C, Hodgson K, Ferrer G, Elena M, Filella X, Pereira A, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. Blood 2010; 116(23):4771-6.

7-38 Moreno C, Montserrat E. Genetic lesions in chronic lymphocytic leukemia: what's ready for prime time use? Haematologica-the Hematology Journal 2010; 95(1):12-5.

7-39 Paesler J, Gehrke I, Gandhirajan RK, Filipovich A, Hertweck M, Erdfelder F, et al. The Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors Vatalanib and Pazopanib Potently Induce Apoptosis in Chronic Lymphocytic Leukemia Cells In vitro and In vivo. Clinical Cancer Research 2010; 16(13):3390-8.

7-40 Papayannidis C, Iacobucci I, Abbenante MC, Curti A, Parisi S, Paolini S, et al. Philadelphia positive (Ph plus) acute lymphoblastic leukemia (ALL) patient with breast infiltration. Leukemia Research [Letter] 2010; 34(9):E246-E7.

7-41 Patz M, Isaeva P, Forcob N, Muller B, Frenzel LP, Wendtner CM, et al. Comparison of the in vitro effects of the anti-CD20 antibodies rituximab and GA101 on chronic lymphocytic leukaemia cells. British Journal of Haematology 2011; 152(3):295-306.

7-42 Philippen A, Diener S, Zenz T, Dohner H, Stilgenbauer S, Mertens D. SYK carries no activating point mutations in patients with chronic lymphocytic leukaemia (CLL). British Journal of Haematology 2010; 150(5):633-6.

7-43 Razavi R, Gehrke I, Gandhirajan RK, Poll-Wolbeck SJ, Hallek M, Kreuzer KA. Nitric Oxide-Donating Acetylsalicylic Acid Induces Apoptosis in Chronic Lymphocytic Leukemia Cells and Shows Strong Antitumor Efficacy In vivo. Clinical Cancer Research 2011; 17(2):286-93.

7-44 Rocha CK, Wendtner CM, Hallek M, Kreuzer KA. Conventional cytogenetics in chronic lymphocytic leukemia (CLL). Leukemia Research [Letter] 2011; 35(3):E25-E.

7-45 Rossi D, Spina V, Deambrogi C, Rasi S, Laurenti L, Stamatopoulos K, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood 2011; 117(12):3391-401.

7-46 Seiffert M, Schulz A, Ohl S, Dohner H, Stilgenbauer S, Lichter P. Soluble CD14 is a novel monocyte-derived survival factor for chronic lymphocytic leukemia cells, which is induced by CLL cells in vitro and present at abnormally high levels in vivo. Blood 2010; 116(20):4223-30.

7-47 Shehata M, Demirtas D, Schnabl S, Hilgarth M, Hubmann R, Fonatsch C, et al. Sequential gene expression profiling during treatment for identification of predictive markers and novel therapeutic targets in chronic lymphocytic leukemia. Leukemia 2010; 24(12):2122-7.

7-48 Tavolaro S, Chiaretti S, Messina M, Peragine N, Del Giudice I, Marinelli M, et al. Gene expression profile of protein kinases reveals a distinctive signature in chronic lymphocytic leukemia and in vitro experiments support a role of second generation protein kinase inhibitors. Leukemia Research 2010; 34(6):733-41.

7-49 Wierda WG, Chiorazzi N, Dearden C, Brown JR, Montserrat E, Shpall E, et al. Chronic Lymphocytic Leukemia: New Concepts for Future Therapy. Clinical Lymphoma Myeloma & Leukemia 2010; 10(5):369-78.

7-50 Winkler D, Schneider C, Zucknick M, Bogelein D, Schulze K, Zenz T, et al. Protein expression analysis of chronic lymphocytic leukemia defines the effect of genetic aberrations and uncovers a correlation of CDK4, P27 and P53 with hierarchical risk. Haematologica-the Hematology Journal 2010; 95(11):1880-8.

7-51 Zenz T, Eichhorst B, Busch R, Denzel T, Habe S, Winkler D, et al. TP53 Mutation and Survival in Chronic Lymphocytic Leukemia. Journal of Clinical Oncology 2010; 28(29):4473-9.

7-52 Zenz T, Frohling S, Mertens D, Dohner H, Stilgenbauer S. Moving from prognostic to predictive factors in chronic lymphocytic leukaemia (CLL). Best Practice & Research Clinical Haematology 2010; 23(1):71-84.

7-53 Zenz T, Mertens D, Kuppers R, Dohner H, Stilgenbauer S. From pathogenesis to treatment of chronic lymphocytic leukaemia. Nature Reviews Cancer 2010; 10(1):37-50.

7-54 Zenz T, Vollmer D, Trbusek M, Smardova J, Benner A, Soussi T, et al. TP53 mutation profile in chronic lymphocytic leukemia: evidence for a disease specific profile from a comprehensive analysis of 268 mutations. Leukemia 2010; 24(12):2072-9.

WP8 (MDS)

International publications that are the direct result of the European LeukemiaNet (**with** *a reference to the European LeukemiaNet*)

8-1 de Swart L, Smith A, Fenaux P, Symeonidis A, Lindberg EH, Sanz G, et al. Disease Management of Low and Intermediate 1 Risk Myelodysplastic Syndromes Report on 800 Newly Diagnosed MDS Patients From the European LeukemiaNet MDS Registry. Blood 2010; 116(21):1201-2.

8-2 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

8-3 Stauder R, Smith A, de Witte T, Droste J, Fenaux P, Symeonidis A, et al. Health Related Quality of Life In Newly Diagnosed Low Risk and Intermediate 1 Risk MDS Report on the First 683 Patients From the European LeukemiaNet Registry. Blood 2010; 116(21):1630-.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

8-4 Aggarwal S, van de Loosdrecht AA, Alhan C, Ossenkoppele GJ, Westers TM, Bontkes HJ. Role of immune responses in the pathogenesis of low-risk MDS and high-risk MDS: implications for immunotherapy. Br J Haematol 2011; 153(5):568-81.

8-5 Aul C, Giagounidis A, Germing U. [Myelodysplastic syndromes]. Internist (Berl) 2010; 51(2):169-82; quiz 83-4.

8-6 Bontkes HJ, Ruben JM, Westers TM, Ossenkoppele GJ, Van de Loosdrecht AA. Azacitidine Induces A Shift In Th1/Th17 Ratio and FoxP3 Expression In Anti CD3 Stimulated CD4+T Cells, Implications for the Treatment of Myelodysplastic Syndromes. Blood 2010; 116(21):1640-1.

8-7 Boultwood J, Perry J, Pellagatti A, Fernandez-Mercado M, Fernandez-Santamaria C, Calasanz MJ, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. Leukemia 2010; 24(5):1062-5.

8-8 Carlsten M, Baumann BC, Simonsson M, Jadersten M, Forsblom AM, Hammarstedt C, et al. Reduced DNAM-1 expression on bone marrow NK cells associated with impaired killing of CD34+ blasts in myelodysplastic syndrome. Leukemia 2010; 24(9):1607-16.

8-9 Cazzola M, Malcovati L. Prognostic classification and risk assessment in myelodysplastic syndromes. Hematol Oncol Clin North Am 2010; 24(2):459-68.

8-10 Chen C, Bowen DT, Giagounidis AA, Schlegelberger B, Haase S, Wright EG. Identification of disease- and therapy-associated proteome changes in the sera of patients with myelodysplastic syndromes and del(5q). Leukemia 2010; 24(11):1875-84.

8-11 Chun K, Hagemeijer A, Iqbal A, Slovak ML. Implementation of standardized international karyotype scoring practices is needed to provide uniform and systematic evaluation for patients with myelodysplastic syndrome using IPSS criteria: An International Working Group on MDS Cytogenetics Study. Leukemia Research 2010; 34(2):160-5.

8-12 Cuijpers ML, Raymakers RA, Mackenzie MA, de Witte TJ, Swinkels DW. Recent advances in the understanding of iron overload in sideroblastic myelodysplastic syndrome. Br J Haematol 2010; 149(3):322-33.

8-13 Czibere A, Bruns I, Kroger N, Platzbecker U, Lind J, Zohren F, et al. 5-Azacytidine for the treatment of patients with acute myeloid leukemia or myelodysplastic syndrome who relapse after allo-SCT: a retrospective analysis. Bone Marrow Transplant 2010; 45(5):872-6.

8-14 Della Porta MG, Malcovati L, Strupp C, Ambaglio I, Kuendgen A, Zipperer E, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica 2011; 96(3):441-9.

8-15 Fenaux P, Bowen D, Gattermann N, Hellstrom-Lindberg E, Hofmann WK, Pfeilstocker M, et al. Practical use of azacitidine in higher-risk myelodysplastic syndromes: an expert panel opinion. Leuk Res 2010; 34(11):1410-6.

8-16 Fenaux P, Gattermann N, Seymour JF, Hellstrom-Lindberg E, Mufti GJ, Duehrsen U, et al. Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: azacitidine compared with low dose ara-C. Br J Haematol 2010; 149(2):244-9.

8-17 Gattermann N, Finelli C, Porta MD, Fenaux P, Ganser A, Guerci-Bresler A, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. Leuk Res 2010; 34(9):1143-50.

8-18 Giagounidis A, Leto di Priolo S, Ille S, Fenaux P. A European survey on the detection and management of iron overload in transfusion-dependent patients with MDS. Ann Hematol 2011; 90(6):667-73.

8-19 Gohring G, Giagounidis A, Busche G, Hofmann W, Kreipe HH, Fenaux P, et al. Cytogenetic follow-up by karyotyping and fluorescence in situ hybridization: implications for monitoring patients with myelodysplastic syndrome and deletion 5q treated with lenalidomide. Haematologica 2011; 96(2):319-22.

8-20 Gohring G, Giagounidis A, Busche G, Kreipe HH, Zimmermann M, Hellstrom-Lindberg E, et al. Patients with del(5q) MDS who fail to achieve sustained erythroid or cytogenetic remission after treatment with lenalidomide have an increased risk for clonal evolution and AML progression. Ann Hematol 2010; 89(4):365-74.

8-21 Grovdal M, Karimi M, Khan R, Aggerholm A, Antunovic P, Astermark J, et al. Maintenance treatment with azacytidine for patients with high-risk myelodysplastic syndromes (MDS) or acute myeloid leukaemia following MDS in complete remission after induction chemotherapy. Br J Haematol 2010; 150(3):293-302.

8-22 Gueller S, Komor M, Nowak D, Baldus CD, de Vos S, Hoelzer D, et al. Identification of defects in the transcriptional program during lineage-specific in vitro differentiation of CD34(+) cells selected from patients with both low- and high-risk myelodysplastic syndrome. Experimental Hematology 2010; 38(9):718-32.

8-23 Hellstrom-Lindberg E. Erythropoiesis-stimulating agents in myelodysplastic syndromes. Leuk Lymphoma 2010; 51(7):1155-6.

8-24 Hellstrom-Lindberg E. Significance of JAK2 and TET2 mutations in myelodysplastic syndromes. Blood Rev 2010; 24(2):83-90.

8-25 Jadersten M, Hellstrom-Lindberg E. New clues to the molecular pathogenesis of myelodysplastic syndromes. Exp Cell Res 2010; 316(8):1390-6.

8-26 Jadersten M, Saft L, Smith A, Kulasekararaj A, Pomplun S, Gohring G, et al. TP53 Mutations in Low-Risk Myelodysplastic Syndromes With del(5q) Predict Disease Progression. J Clin Oncol 2011; 29(15):1971-9.

8-27 Kantarjian H, Fenaux P, Sekeres MA, Becker PS, Boruchov A, Bowen D, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol 2010; 28(3):437-44.

8-28 Kroger N, Zabelina T, van Biezen A, Brand R, Niederwieser D, Martino R, et al. Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis. Haematologica 2011; 96(2):291-7.

8-29 Kuhne F, Mittendorf T, Germing U, Tesch H, Weinberg R, Grabenhorst U, et al. Cost of transfusion-dependent myelodysplastic syndrome (MDS) from a German payer's perspective. Ann Hematol 2010; 89(12):1239-47.

8-30 Loeffler-Ragg J, Germing U, Sperr WR, Herrmann H, Zwierzina H, Valent P, et al. Serum CD44 levels predict survival in patients with low-risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2011; 78(2):150-61.

8-31 Lubbert M, Suciu S, Baila L, Ruter BH, Platzbecker U, Giagounidis A, et al. Low-Dose Decitabine Versus Best Supportive Care in Elderly Patients With Intermediate- or High-Risk Myelodysplastic Syndrome (MDS) Ineligible for Intensive Chemotherapy: Final Results of the Randomized Phase III Study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011; 29(15):1987-96.

8-32 Mallo M, Cervera J, Schanz J, Such E, Garcia-Manero G, Luno E, et al. Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia 2011; 25(1):110-20.

8-33 Matsuda A, Germing U, Jinnai I, Araseki K, Kuendgen A, Strupp C, et al. Differences in the distribution of subtypes according to the WHO classification 2008 between Japanese and German patients with refractory anemia according to the FAB classification in myelodysplastic syndromes. Leuk Res 2010; 34(8):974-80.

8-34 Nikoloski G, Langemeijer SMC, Kuiper RP, Knops R, Massop M, Tonnissen E, et al. Somatic mutations of the histone methyltransferase gene EZH2 in myelodysplastic syndromes. Nature Genetics 2010; 42(8):665-7.

8-35 Nolte F, Hofmann WK. [Current treatment options for myelodysplastic syndromes]. Dtsch Med Wochenschr 2010; 135(38):1863-9.

8-36 Nolte F, Hofmann WK. Molecular mechanisms involved in the progression of myelodysplastic syndrome. Future Oncol 2010; 6(3):445-55.

8-37 Passweg JR, Giagounidis AAN, Simcock M, Aul C, Dobbelstein C, Stadler M, et al. Immunosuppressive Therapy for Patients With Myelodysplastic Syndrome: A Prospective Randomized Multicenter Phase III Trial Comparing Antithymocyte Globulin Plus Cyclosporine With Best Supportive Care-SAKK 33/99. Journal of Clinical Oncology 2011; 29(3):303-9.

8-38 Pellagatti A, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, et al. Deregulated gene expression pathways in myelodysplastic syndrome hematopoietic stem cells. Leukemia 2010; 24(4):756-64.

8-39 Pellagatti A, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, et al. Marked down-regulation of nucleophosmin-1 is associated with advanced del(5q) myelodysplastic syndrome. Br J Haematol 2011:in press.

8-40 Platzbecker U, Aul C, Ehninger G, Giagounidis A. Reduction of 5-azacitidine induced skin reactions in MDS patients with evening primrose oil. Ann Hematol 2010; 89(4):427-8.

8-41 Reins J, Mossner M, Neumann M, Platzbecker U, Schumann C, Thiel E, et al. Transcriptional down-regulation of the Wnt antagonist SFRP1 in haematopoietic cells of patients with different risk types of MDS. Leuk Res 2010; 34(12):1610-6.

8-42 Santini V, Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Silverman LR, List A, et al. Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*. Eur J Haematol 2010; 85(2):130-8.

8-43 Schanz J, Steidl C, Fonatsch C, Pfeilstocker M, Nosslinger T, Tuechler H, et al. Coalesced multicentric analysis of 2,351 patients with myelodysplastic syndromes indicates an underestimation of poor-risk cytogenetics of myelodysplastic syndromes in the international prognostic scoring system. J Clin Oncol 2011; 29(15):1963-70.

8-44 Schanz J, Stephanie F, Haferlach C, Bardi G, Slovak ML, Eclache V, et al. Unrelated Clones In Myelodysplastic Syndromes and Acute Myeloid Leukemia Characterization and Prognostic Relevance. Blood 2010; 116(21):1639-.

8-45 Schroeder T, Ruf L, Bernhardt A, Hildebrandt B, Aivado M, Aul C, et al. Distinguishing myelodysplastic syndromes (MDS) from idiopathic cytopenia of undetermined significance (ICUS): HUMARA unravels clonality in a subgroup of patients. Ann Oncol 2010; 21(11):2267-71.

8-46 Seymour JF, Fenaux P, Silverman LR, Mufti GJ, Hellstrom-Lindberg E, Santini V, et al. Effects of azacitidine compared with conventional care regimens in elderly (>/= 75 years) patients with higher-risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2010; 76(3):218-27.

8-47 Silverman LR, Fenaux P, Mufti GJ, Santini V, Hellstrom-Lindberg E, Gattermann N, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. Cancer 2011:in press.

8-48 Sperr WR, Wimazal F, Kundi M, Baumgartner C, Nosslinger T, Makrai A, et al. Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group. Ann Oncol 2010; 21(1):114-9.

8-49 Thiel A, Beier M, Ingenhag D, Servan K, Hein M, Moeller V, et al. Comprehensive array CGH of normal karyotype myelodysplastic syndromes reveals hidden recurrent and individual genomic copy number alterations with prognostic relevance. Leukemia 2011; 25(3):387-99.

8-50 Thol F, Friesen I, Damm F, Yun H, Weissinger EM, Krauter J, et al. Prognostic Significance of ASXL1 Mutations in Patients With Myelodysplastic Syndromes. J Clin Oncol 2011:in press.

8-51 Thol F, Weissinger EM, Krauter J, Wagner K, Damm F, Wichmann M, et al. IDH1 mutations in patients with myelodysplastic syndromes are associated with an unfavorable prognosis. Haematologica 2010; 95(10):1668-74.

8-52 Tobiasson M, Olsson R, Hellstrom-Lindberg E, Mattsson J. Early detection of relapse in patients with myelodysplastic syndrome after allo-SCT. Bone Marrow Transplant 2011; 46(5):719-26.

8-53 Valent P, Orazi A, Busche G, Schmitt-Graff A, George TI, Sotlar K, et al. Standards and impact of hematopathology in myelodysplastic syndromes (MDS). Oncotarget 2010; 1(7):483-96.

8-54 van de Loosdrecht AA, Westers TM. Flow cytometry in myelodysplastic syndromes: Ready for translation into clinical practice. Leuk Res 2011:in press.

8-55 Westers TM, Alhan C, Chamuleau MED, van der Vorst M, Eeltink C, Ossenkoppele GJ, et al. Aberrant immunophenotype of blasts in myelodysplastic syndromes is a clinically relevant biomarker in predicting response to growth factor treatment. Blood 2010; 115(9):1779-84.

8-56 Wimazal F, Germing U, Kundi M, Noesslinger T, Blum S, Geissler P, et al. Evaluation of the prognostic significance of eosinophilia and basophilia in a larger cohort of patients with myelodysplastic syndromes. Cancer 2010; 116(10):2372-81.

WP9 (CMPD)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

9-1 Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, et al. Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet. Journal of Clinical Oncology 2011; 29(6):761-70.

9-2 Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch H, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. British Journal of Haematology 2010; 148(6):961-3.

9-3 Carobbio A, Finazzi G, Antonioli E, Vannucchi AM, Barosi G, Ruggeri M, et al. Hydroxyurea in essential thrombocythemia: rate and clinical relevance of responses by European LeukemiaNet criteria. Blood 2010; 116(7):1051-5.

9-4 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

9-5 Hernandez-Boluda JC, Alvarez-Larran A, Gomez M, Angona A, Amat P, Bellosillo B, et al. Clinical evaluation of the European LeukaemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia. British Journal of Haematology 2011; 152(1):81-8.

9-6 Hernandez-Boluda J-C, Alvarez-Larran A, Gomez M, Angona A, Amat P, Bellosillo B, et al. Clinical evaluation of the European LeukaemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia. British Journal of Haematology 2011; 152(1):81-8.

9-7 Rinaldi CR, Rinaldi P, Alagia A, Gemei M, Del Vecchio L, Martino B, et al. JAK2V617F Mutation Persists IN Blasts and Mature CELLS of Transformed JAK2V617F POSITIVE MYELOPROLIFERATIVE Neoplasia A European LEUKEMIA NET (ENL) STUDY. Blood 2010; 116(21):1664-5.

9-8 Rinaldi CR, Rinaldi P, Gemei M, Grimaldi F, Battipaglia G, Del Vecchio L, et al. JAK2V617F mutation persists in blasts and mature cells of transformed JAK2V617F-positive-myeloproliferative neoplasia: A European Leukemia Net (ENL) study. American Journal of Hematology 2010; 85(5):383-6.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

9-9 Bacher U, Haferlach T, Schnittger S, Kreipe H, Kroger N. Recent advances in diagnosis, molecular pathology and therapy of chronic myelomonocytic leukaemia. British Journal of Haematology 2011; 153(2):149-67.

9-10 Baran-Marszak F, Magdoud H, Desterke C, Alvarado A, Roger C, Harel S, et al. Expression level and differential JAK2-V617F-binding of the adaptor protein Lnk regulates JAK2-mediated signals in myeloproliferative neoplasms. Blood 2010; 116(26):5961-71.

9-11 Barbui T, Carobbio A, Cervantes F, Vannucchi AM, Guglielmelli P, Antonioli E, et al. Thrombosis in primary myelofibrosis: incidence and risk factors. Blood 2010; 115(4):778-82.

9-12 Barbui T, Carobbio A, Finazzi G, Vannucchi AM, Barosi G, Antonioli E, et al. Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3. Haematologica-the Hematology Journal 2011; 96(2):315-8.

9-13 Barosi G, Gale RP. Bone marrow fibrosis in myeloproliferative neoplasms-associated myelofibrosis: Deconstructing a myth? Leukemia Research [Article] 2011; 35(5):563-5.

9-14 Barosi G, Magrini U, Gale RP. Does auto-immunity contribute to anemia in myeloproliferative neoplasms (MPN)-associated myelofibrosis? Leukemia Research [Editorial Material] 2010; 34(9):1119-20.

9-15 Besses C, Larran AA, Gomez M, Angona A, Amat P, Bellosillo B, et al. Clinical Evaluation of the European LeukemiaNet Criteria for Resistance/Intolerance to Hydroxyurea In Essential Thrombocythemia. Blood 2010; 116(21):1663-.

9-16 Campanelli R, Rosti V, Villani L, Castagno M, Moretti E, Bonetti E, et al. Evaluation of the bioactive and total transforming growth factor beta 1 levels in primary myelofibrosis. Cytokine 2011; 53(1):100-6.

9-17 Cella G, Marchetti M, Vianello F, Panova-Noeva M, Vignoli A, Russo L, et al. Nitric oxide derivatives and soluble plasma selectins in patients with myeloproliferative neoplasms. Thrombosis and Haemostasis 2010; 104(1):151-6.

9-18 De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, et al. Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia. American Journal of Hematology [Article] 2010; 85(2):97-100.

9-19 De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, et al. Increased risk of recurrent thrombosis in patients with essential thrombocythemia carrying the homozygous JAK2 V617F mutation. Annals of Hematology 2010; 89(2):141-6.

9-20 Elling C, Erben P, Walz C, Frickenhaus M, Schemionek M, Stehling M, et al. Novel imatinib-sensitive PDGFRA-activating point mutations in hypereosinophilic syndrome induce growth factor independence and leukemia-like disease. Blood 2011; 117(10):2935-43.

9-21 Fleischman AG, Aichberger KJ, Petersen CL, Doratotaj S, Bumm TG, Pahl HL, et al. Jak2 V617F Induced TNF Resistance as a Mechanism of Clonal Expansion In Myeloproliferative Neoplasm. Blood 2010; 116(21):348-.

9-22 Gale RP, Barosi G, Barbui T, Cervantes F, Dohner K, Dupriez B, et al. What are RBC-transfusion-dependence and -independence? Leukemia Research [Article] 2011; 35(1):8-11.

9-23 Guglielmelli P, Biamonte F, Spolverini A, Pieri L, Isgro A, Antonioli E, et al. Frequency and clinical correlates of JAK2 46/1 (GGCC) haplotype in primary myelofibrosis. Leukemia 2010; 24(8):1533-7.

9-24 Harrison C, Barbui T. Aspirin in low-risk essential thrombocythemia, not so simple after all? Leukemia Research 2011; 35(3):286-9.

9-25 Hasselbalch HC, Larsen TS, Riley CH, Jensen MK, Kiladjian JJ. Interferon-Alpha in the Treatment of Philadelphia-Negative Chronic Myeloproliferative Neoplasms. Status and Perspectives. Current Drug Targets 2011; 12(3):392-419.

9-26 Hidalgo-Curtis C, Apperley JF, Stark A, Jeng M, Gotlib J, Chase A, et al. Fusion of PDGFRB to two distinct loci at 3p21 and a third at 12q13 in imatinib-responsive myeloproliferative neoplasms. British Journal of Haematology 2010; 148(2):268-73.

9-27 Hidalgo-Curtis C, Apperley JF, Stark A, Jeng M, Gotlib J, Chase A, et al. Fusion of PDGFRB to two distinct loci at 3p21 and a third at 12q13 in imatinib-responsive myeloproliferative neoplasms (vol 148, pg 268, 2010). British Journal of Haematology 2010; 148(6):964-.

9-28 Kiladjian JJ, Masse A, Cassinat B, Mokrani H, Teyssandier I, le Couedic JP, et al. Clonal analysis of erythroid progenitors suggests that pegylated interferon alpha-2a treatment targets JAK2(V617F) clones without affecting TET2 mutant cells. Leukemia 2010; 24(8):1519-23.

9-29 Massa M, Campanelli R, Lupo L, Fois G, Viarengo G, Jemos V, et al. Splenectomy produces a rapid but transient decrease of the frequency of circulating CD34+haematopoietic progenitor cells in primary myelofibrosis. British Journal of Haematology 2011; 152(5):665-7.

9-30 Palandri F, Polverelli N, Ottaviani E, Castagnetti F, Baccarani M, Vianelli N. Long-term follow-up of essential thrombocythemia in young adults: treatment strategies, major thrombotic complications and pregnancy outcomes. A study of 76 patients. Haematologica-the Hematology Journal [Letter] 2010; 95(6):1038-40.

9-31 Panova-Noeva M, Marchetti M, Spronk HM, Russo L, Diani E, Finazzi G, et al. Platelet-induced thrombin generation by the calibrated automated thrombogram assay is increased in patients with essential thrombocythemia and polycythemia vera. American Journal of Hematology 2011; 86(4):337-42.

9-32 Pardanani A, Vannucchi AM, Passamonti F, Cervantes F, Barbui T, Tefferi A. JAK inhibitor therapy for myelofibrosis: critical assessment of value and limitations. Leukemia 2011; 25(2):218-25.

9-33 Passamonti F, Elena C, Schnittger S, Skoda RC, Green AR, Girodon F, et al. Molecular and clinical features of the myeloproliferative neoplasm associated with JAK2 exon 12 mutations. Blood 2011; 117(10):2813-6.

9-34 Rambaldi A, Dellacasa CM, Finazzi G, Carobbio A, Ferrari ML, Guglielmelli P, et al. A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. British Journal of Haematology 2010; 150(4):446-55.

9-35 Rosti V, Bonetti E, Bergamaschi G, Campanelli R, Guglielmelli P, Maestri M, et al. High Frequency of Endothelial Colony Forming Cells Marks a Non-Active Myeloproliferative Neoplasm with High Risk of Splanchnic Vein Thrombosis. Plos One 2010; 5(12):e15277 (6 pages).

9-36 Spolverini A, Jones AV, Hochhaus A, Pieri L, Cross NCP, Vannucchi AM. The myeloproliferative neoplasm-associated JAK2 46/1 haplotype is not overrepresented in chronic myelogenous leukemia. Annals of Hematology [Letter] 2011; 90(3):365-6.

9-37 Stegelmann F, Bullinger L, Griesshammer M, Holzmann K, Habdank M, Kuhn S, et al. High-resolution single-nucleotide polymorphism array-profiling in myeloproliferative neoplasms identifies novel genomic aberrations. Haematologica-the Hematology Journal 2010; 95(4):666-9.

9-38 Thepot S, Itzykson R, Seegers V, Raffoux E, Quesnel B, Chait Y, et al. Treatment of progression of Philadelphia-negative myeloproliferative neoplasms to myelodysplastic syndrome or acute myeloid leukemia by azacitidine: a report on 54 cases on the behalf of the Groupe Francophone des Myelodysplasies (GFM). Blood 2010; 116(19):3735-42.

9-39 Ugo V, Tondeur S, Menot M-L, Bonnin N, Le Gac G, Tonetti C, et al. Interlaboratory Development and Validation of a HRM Method Applied to the Detection of JAK2 Exon 12 Mutations in Polycythemia Vera Patients. Plos One 2010; 5(1):Article No.: e8893 (6 pages).

9-40 Wang W, Schwemmers S, Hexner EO, Pahl HL. AML1 is overexpressed in patients with myeloproliferative neoplasms and mediates JAK2(V617F)-independent overexpression of NF-E2. Blood 2010; 116(2):254-66.

WP10 (Diagnostics)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

10-1 Arnoulet C, Bene MC, Durrieu F, Feuillard J, Fossat C, Husson B, et al. Four- and Five-Color Flow Cytometry Analysis of Leukocyte Differentiation Pathways in Normal Bone Marrow: A Reference Document Based on a Systematic Approach by the GTLLF and GEIL. Cytometry 2010; 78B(1):3-10.

10-2 Béné MC, Kaeda JS. How and why minimal residual disease studies are necessary in leukemia: a review from WP10 and WP12 of the European LeukaemiaNet. Haematologica. 2009;94(8):1135-50.

10-3 Béné MC, Nebe T, Bettelheim P, Buldini B, Bumbea H, Kern W, Lacombe F, Lemez P, Marinov I, Matutes E, Maynadié M, Oelschlagel U, Orfao A, Schabath R, Solenthaler M, Tschurtschenthaler G, Vladareanu AM, Zini G, Faure GC, Porwit A. Immunophenotyping of acute leukemia and lymphoproliferative disorders: a consensus proposal of the European LeukemiaNet Work Package 10. Leukemia. 2011;25(4):567-74.

10-4 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

10-5 van de Loosdrecht AA, Alhan C, Béné MC, Della Porta MG, Dräger AM, Feuillard J, Font P, Germing U, Haase D, Homburg CH, Ireland R, Jansen JH, Kern W, Malcovati L, Te Marvelde JG, Mufti GJ, Ogata K, Orfao A, Ossenkoppele GJ, Porwit A, Preijers FW, Richards SJ, Schuurhuis GJ, Subirá D, Valent P, van der Velden VH, Vyas P, Westra AH, de Witte TM, Wells DA, Loken MR, Westers TM. Standardization of flow cytometry in myelodysplastic syndromes: report from the first European LeukemiaNet working conference on flow cytometry in myelodysplastic syndromes. Haematologica. 2009;94(8):1124-34.

10-6 Zini G, Bain B, Bettelheim P, Cortez J, d'Onofrio G, Faber E, et al. A European consensus report on blood cell identification: terminology utilized and morphological diagnosis concordance among 28 experts from 17 countries within the European LeukemiaNet network WP10, on behalf of the ELN Morphology Faculty. British Journal of Haematology 2010; 151(4):359-64.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

10-7 Béné MC. Biphenotypic, bilineal, ambiguous or mixed lineage: strange leukemias! Haematologica. 2009;94(7):891-3.

10-8 Faure GC, Amsellem S, Arnoulet C, Bardet V, Campos L, De Carvalho-Bittencourt M, et al. Mutual benefits of B-ALL and HLDA/HCDM HLDA 9th Barcelona 2010. Immunology Letters 2011; 134(2):145-9.

10-9 Haferlach T, Kohlmann A, Wieczorek L, Basso G, Kronnie GT, Béné MC, De Vos J, Hernández JM, Hofmann WK, Mills KI, Gilkes A, Chiaretti S, Shurtleff SA, Kipps TJ, Rassenti LZ, Yeoh AE, Papenhausen PR, Liu WM, Williams PM, Foà R. Clinical utility of microarray-based gene expression profiling in the diagnosis and subclassification of leukemia: report from the International Microarray Innovations in Leukemia Study Group. J Clin Oncol. 2010;28(15):2529-37.

10-10 Lemez P, Attarbaschi A, Bene MC, Bertrand Y, Castoldi G, Forestier E, et al. Childhood near-tetraploid acute lymphoblastic leukemia: an EGIL study on 36 cases. European Journal of Haematology 2010; 85(4):300-8.

10-11 Matutes E, Pickl WF, van't Veer M, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood 2011; 117(11):3163-71

10-12 Kern W, Bacher U, Haferlach C, Schnittger S, Haferlach T. The role of multiparameter flow cytometry for disease monitoring in AML. Best Practice & Research Clinical Haematology 2010; 23(3):379-90.

10-13 Kern W, Bacher U, Haferlach C, Schnittger S, Haferlach T. Acute monoblastic/monocytic leukemia and chronic myelomonocytic leukemia share common immunophenotypic features but differ in the extent of aberrantly expressed antigens and amount of granulocytic cells. Leukemia & Lymphoma 2011; 52(1):92-100.

10-14 Kern W, Haferlach C, Schnittger S, Haferlach T. Clinical Utility of Multiparameter Flow Cytometry in the Diagnosis of 1013 Patients With Suspected Myelodysplastic Syndrome Correlation to Cytomorphology, cytogenetics, and Clinical Data. Cancer 2010; 116(19):4549-63.

WP11 (Cytogenetics)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

11-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

11-2 Bacher U, Haferlach T, Kern W, Alpermann T, Schnittger S, Haferlach C: Correlation of cytomorphology, immunophenotyping, and interphase fluorescence in situ hybridization in 381 patients with monoclonal gammopathy of undetermined significance and 301 patients with plasma cell myeloma. Cancer Genet Cytogenet 2010;203:169-175.

11-3 Bacher U, Haferlach T, Schnittger S, Weiss T, Burkhard O, Bechtel B, Kern W, Haferlach C: Detection of a t(4;14)(p16;q32) in two cases of lymphoma showing both the immunophenotype of chronic lymphocytic leukemia. Cancer Genet Cytogenet 2010;200:170-174.

11-4 Bacher U, Haferlach T, Alpermann T, Zenger M, Kroger N, Beelen DW, Kern W, Schnittger S, Haferlach C: Comparison of cytogenetic clonal evolution patterns following allogeneic hematopoietic transplantation versus conventional treatment in patients at relapse of AML. Biol Blood Marrow Transplant 2010;16:1649-1657.

11-5 Bacher U, Haferlach C, Schnittger S, Kohlmann A, Kern W, Haferlach T: Mutations of the TET2 and CBL genes: novel molecular markers in myeloid malignancies. Ann Hematol 2010;89:643-652.

11-6 Bacher U, Haferlach C, Kroger N, Schnittger S, Kern W, Wiedemann B, Zander AR, Haferlach T: Diagnostic tools in the indications for allogeneic stem cell transplantation in myelodysplastic syndromes. Biol Blood Marrow Transplant 2010;16:1-11.

11-7 Braulke F, Schanz J, Jung K, Shirneshan K, Schulte K, Schuetze C, Steffens R, Trumper L, Haase D: FISH analysis of circulating CD34+ cells as a new tool for genetic monitoring in MDS: verification of the method and application to 27 MDS patients. Leuk Res 2010;34:1296-1301.

11-8 Clappier E, Collette S, Grardel N, Girard S, Suarez L, Brunie G, Kaltenbach S, Yakouben K, Mazingue F, Robert A, Boutard P, Plantaz D, Rohrlich P, Van VP, Preudhomme C, Otten J, Speleman F, Dastugue N, Suciu S, Benoit Y, Bertrand Y, Cave H: NOTCH1 and FBXW7 mutations have a favorable impact on early response to treatment, but not on outcome, in children with T-cell acute lymphoblastic leukemia (T-ALL) treated on EORTC trials 58881 and 58951. Leukemia 2010;24:2023-2031.

11-9 Couronne L, Lippert E, Andrieux J, Kosmider O, Radford-Weiss I, Penther D, Dastugue N, Mugneret F, Lafage M, Gachard N, Nadal N, Bernard OA, Nguyen-Khac F: Analyses of TET2 mutations in post-myeloproliferative neoplasm acute myeloid leukemias. Leukemia 2010;24:201-203.

11-10 Coyaud E, Struski S, Dastugue N, Brousset P, Broccardo C, Bradtke J: PAX5-AUTS2 fusion resulting from t(7;9)(q11.2;p13.2) can now be classified as recurrent in B cell acute lymphoblastic leukemia. Leuk Res 2010;34:e323-e325.

11-11 Coyaud E, Struski S, Prade N, Familiades J, Eichner R, Quelen C, Bousquet M, Mugneret F, Talmant P, Pages MP, Lefebvre C, Penther D, Lippert E, Nadal N, Taviaux S, Poppe B, Luquet I, Baranger L, Eclache V, Radford I, Barin C, Mozziconacci MJ, Lafage-Pochitaloff M, Antoine-Poirel H, Charrin C, Perot C, Terre C, Brousset P, Dastugue N, Broccardo C: Wide diversity of PAX5 alterations in B-ALL: a Groupe Francophone de Cytogenetique Hematologique study. Blood 2010;115:3089-3097.

11-12 De KK, Real PJ, Gatta GD, Palomero T, Sulis ML, Tosello V, Van VP, Barnes K, Castillo M, Sole X, Hadler M, Lenz J, Aplan PD, Kelliher M, Kee BL, Pandolfi PP, Kappes D, Gounari F, Petrie H, Van der Meulen J, Speleman F,

Paietta E, Racevskis J, Wiernik PH, Rowe JM, Soulier J, Avran D, Cave H, Dastugue N, Raimondi S, Meijerink JP, Cordon-Cardo C, Califano A, Ferrando AA: The TLX1 oncogene drives aneuploidy in T cell transformation. Nat Med 2010;16:1321-1327.

11-13 De Keersmaecker K, Real PJ, Della Gatta G, Palomero T, Sulis ML, Tosello V, et al. The TLX1 oncogene drives aneuploidy in T cell transformation. Nature Medicine 2010; 16(11):1321-U65.

11-14 Dicker F, Haferlach C, Sundermann J, Wendland N, Weiss T, Kern W, Haferlach T, Schnittger S: Mutation analysis for RUNX1, MLL-PTD, FLT3-ITD, NPM1 and NRAS in 269 patients with MDS or secondary AML. Leukemia 2010;24:1528-1532.

11-15 Fiegl M, Erdel M, Tinhofer I, Brychtova Y, Panovska A, Doubek M, et al. Clinical outcome of pretreated B-cell chronic lymphocytic leukemia following alemtuzumab therapy: a retrospective study on various cytogenetic risk categories. Annals of Oncology 2010; 21(12):2410-9.

11-16 Erben P, Gosenca D, Muller MC, Reinhard J, Score J, Del VF, Walz C, Mix J, Metzgeroth G, Ernst T, Haferlach C, Cross NC, Hochhaus A, Reiter A: Screening for diverse PDGFRA or PDGFRB fusion genes is facilitated by generic quantitative reverse transcriptase polymerase chain reaction analysis. Haematologica 2010;95:738-744.

11-17 Falini B, Macijewski K, Weiss T, Bacher U, Schnittger S, Kern W, Kohlmann A, Klein HU, Vignetti M, Piciocchi A, Fazi P, Martelli MP, Vitale A, Pileri S, Miesner M, Santucci A, Haferlach C, Mandelli F, Haferlach T: Multilineage dysplasia has no impact on biologic, clinicopathologic, and prognostic features of AML with mutated nucleophosmin (NPM1). Blood 2010;115:3776-3786.

11-18 Falini B, Martelli MP, Pileri SA, Mecucci C: Molecular and alternative methods for diagnosis of acute myeloid leukemia with mutated NPM1: flexibility may help. Haematologica 2010;95:529-534.

11-19 Fiegl M, Erdel M, Tinhofer I, Brychtova Y, Panovska A, Doubek M, Eigenberger K, Fonatsch C, Hopfinger G, Muhlberger H, Zabernigg A, Falkner F, Gastl G, Mayer J, Greil R: Clinical outcome of pretreated B-cell chronic lymphocytic leukemia following alemtuzumab therapy: a retrospective study on various cytogenetic risk categories. Ann Oncol 2010;21:2410-2419.

11-20 Flach J, Dicker F, Schnittger S, Kohlmann A, Haferlach T, Haferlach C: Mutations of JAK2 and TET2, but not CBL are detectable in a high portion of patients with refractory anemia with ring sideroblasts and thrombocytosis. Haematologica 2010;95:518-519.

11-21 Flach J, Dicker F, Schnittger S, Schindela S, Kohlmann A, Haferlach T, et al. An accumulation of cytogenetic and molecular genetic events characterizes the progression from MDS to secondary AML: an analysis of 38 paired samples analyzed by cytogenetics, molecular mutation analysis and SNP microarray profiling. Leukemia 2011; 25(4):713-8.

11-22 Fonatsch C. The Role of Chromosome 21 in Hematology and Oncology. Genes Chromosomes & Cancer 2010; 49(6):497-508.

11-23 Fonatsch C: The role of chromosome 21 in hematology and oncology. Genes Chromosomes Cancer 2010;49:497-508.

11-24 Giehl M, Leitner A, Haferlach C, Duesberg P, Hofmann WK, Hofheinz R, Seifarth W, Hochhaus A, Fabarius A: Detection of centrosome aberrations in disease-unrelated cells from patients with tumor treated with tyrosine kinase inhibitors. Eur J Haematol 2010;85:139-148.

11-25 Gorello P, La SR, Di GD, Messina M, Puzzolo MC, Crescenzi B, Santoro A, Chiaretti S, Mecucci C: SQSTM1-NUP214: a new gene fusion in adult T-cell acute lymphoblastic leukemia. Haematologica 2010;95:2161-2163.

11-26 Gorello P, La SR, Varasano E, Chiaretti S, Elia L, Pierini V, Barba G, Brandimarte L, Crescenzi B, Vitale A, Messina M, Grammatico S, Mancini M, Matteucci C, Bardi A, Guarini A, Martelli MF, Foa R, Mecucci C: Combined interphase fluorescence in situ hybridization elucidates the genetic heterogeneity of T-cell acute lymphoblastic leukemia in adults. Haematologica 2010;95:79-86.

11-27 Gotze K, Platzbecker U, Giagounidis A, Haase D, Lubbert M, Aul C, Ganser A, Germing U, Hofmann WK: Azacitidine for treatment of patients with myelodysplastic syndromes (MDS): practical recommendations of the German MDS Study Group. Ann Hematol 2010;89:841-850.

11-28 Haferlach C, Dicker F, Weiss T, Schnittger S, Beck C, Grote-Metke A, Oruzio D, Kern W, Haferlach T: Toward a comprehensive prognostic scoring system in chronic lymphocytic leukemia based on a combination of genetic parameters. Genes Chromosomes Cancer 2010;49:851-859.

11-29 Haferlach C, Dicker F, Kohlmann A, Schindela S, Weiss T, Kern W, Schnittger S, Haferlach T: AML with CBFB-MYH11 rearrangement demonstrate RAS pathway alterations in 92% of all cases including a high frequency of NF1 deletions. Leukemia 2010;24:1065-1069.

11-30 Haferlach C, Bacher U, Schnittger S, Weiss T, Kern W, Haferlach T: Similar patterns of chromosome abnormalities in CML occur in addition to the Philadelphia chromosome with or without tyrosine kinase inhibitor treatment. Leukemia 2010;24:638-640.

11-31 Kaune KM, Baumgart M, Schmitke E, Haase D, Middel P, Ghadimi BM, Bertsch HP, Neumann C, Emmert S: Papular exanthem discloses acute myeloid leukaemia: interphase fluorescence in situ hybridization revealed deletion of p53 and gain at 8q22/8q24/Tel8q without trisomy 8. Clin Exp Dermatol 2010;35:160-164.

11-32 Kern W, Haferlach C, Schnittger S, Haferlach T: Clinical utility of multiparameter flow cytometry in the diagnosis of 1013 patients with suspected myelodysplastic syndrome: correlation to cytomorphology, cytogenetics, and clinical data. Cancer 2010;116:4549-4563.

11-33 Kern W, Bacher U, Haferlach C, Schnittger S, Haferlach T: The role of multiparameter flow cytometry for disease monitoring in AML. Best Pract Res Clin Haematol 2010;23:379-390.

11-34 Kohlmann A, Grossmann V, Klein HU, Schindela S, Weiss T, Kazak B, Dicker F, Schnittger S, Dugas M, Kern W, Haferlach C, Haferlach T: Next-generation sequencing technology reveals a characteristic pattern of molecular mutations in 72.8% of chronic myelomonocytic leukemia by detecting frequent alterations in TET2, CBL, RAS, and RUNX1. J Clin Oncol 2010;28:3858-3865.

11-35 Krug U, Rollig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, Thiede C, Kramer M, Braess J, Spiekermann K, Haferlach T, Haferlach C, Koschmieder S, Rohde C, Serve H, Wormann B, Hiddemann W, Ehninger G, Berdel WE, Buchner T, Muller-Tidow C: Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 2010;376:2000-2008.

11-36 La Starza R, Matteucci C, Gorello P, Brandimarte L, Pierini V, Crescenzi B, et al. NPM1 Deletion Is Associated with Gross Chromosomal Rearrangements in Leukemia. Plos One 2010; 5(9):Article Number: e12855.

11-37 Lippert E, Etienne G, Mozziconacci MJ, Laibe S, Gervais C, Girault S, Gachard N, Tigaud I, Dastugue N, Huguet F, Fort MP, Legros L, Eclache V, Mahon FX: Loss of the Y chromosome in Philadelphia-positive cells predicts a poor response of chronic myeloid leukemia patients to imatinib mesylate therapy. Haematologica 2010;95:1604-1607.

11-38 Lundin C, Horvat A, Karlsson K, Olofsson T, Paulsson K, Johansson B: t(9;11)(p22;p15) [NUP98/PSIP1] is a poor prognostic marker associated with de novo acute myeloid leukaemia expressing both mature and immature surface antigens. Leuk Res 2010.

11-39 Mallo M, Cervera J, Schanz J, Such E, Garcia-Manero G, Luno E, Steidl C, Espinet B, Vallespi T, Germing U, Blum S, Ohyashiki K, Grau J, Pfeilstocker M, Hernandez JM, Noesslinger T, Giagounidis A, Aul C, Calasanz MJ, Martin ML, Valent P, Collado R, Haferlach C, Fonatsch C, Lubbert M, Stauder R, Hildebrandt B, Krieger O, Pedro C, Arenillas L, Sanz MA, Valencia A, Florensa L, Sanz GF, Haase D, Sole F: Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia 2011;25:110-120.

11-40 Matteucci C, Barba G, Varasano E, Vitale A, Mancini M, Testoni N, Cuneo A, Rege-Cambrin G, Elia L, La SR, Pierini V, Brandimarte L, Vignetti M, Foa R, Mecucci C: Rescue of genomic information in adult acute lymphoblastic leukaemia (ALL) with normal/failed cytogenetics: a GIMEMA centralized biological study. Br J Haematol 2010;149:70-78.

11-41 Miesner M, Haferlach C, Bacher U, Weiss T, Macijewski K, Kohlmann A, Klein HU, Dugas M, Kern W, Schnittger S, Haferlach T: Multilineage dysplasia (MLD) in acute myeloid leukemia (AML) correlates with MDS-related cytogenetic abnormalities and a prior history of MDS or MDS/MPN but has no independent prognostic relevance: a comparison of 408 cases classified as "AML not otherwise specified" (AML-NOS) or "AML with myelodysplasia-related changes" (AML-MRC). Blood 2010;116:2742-2751.

11-42 Nguyen-Khac F, Lesty C, Eclache V, Couronne L, Kosmider O, Andrieux J, Collonge-Rame MA, Penther D, Lafage M, Bilhou-Nabera C, Chapiro E, Mozziconacci MJ, Mugneret F, Gachard N, Nadal N, Lippert E, Struski S, Dastugue N, Cabrol C, Bernard OA: Chromosomal abnormalities in transformed Ph-negative myeloproliferative neoplasms are associated to the transformation subtype and independent of JAK2 and the TET2 mutations. Genes Chromosomes Cancer 2010;49:919-927.

11-43 Nosslinger T, Tuchler H, Germing U, Sperr WR, Krieger O, Haase D, Lubbert M, Stauder R, Giagounidis A, Valent P, Pfeilstocker M: Prognostic impact of age and gender in 897 untreated patients with primary myelodysplastic syndromes. Ann Oncol 2010;21:120-125.

11-44 Nowak D, Ogawa S, Muschen M, Kato M, Kawamata N, Meixel A, Nowak V, Kim HS, Kang S, Paquette R, Chang MS, Thoennissen NH, Mossner M, Hofmann WK, Kohlmann A, Weiss T, Haferlach T, Haferlach C, Koeffler HP: SNP array analysis of tyrosine kinase inhibitor-resistant chronic myeloid leukemia identifies heterogeneous secondary genomic alterations. Blood 2010;115:1049-1053.

11-45 Ochsenreither S, Fusi A, Busse A, Letsch A, Haase D, Thiel E, Scheibenbogen C, Keilholz U: Long term presence of a single predominant tyrosinase-specific T-cell clone associated with disease control in a patient with metastatic melanoma. Int J Cancer 2010;126:2497-2502.

11-46 Okamoto R, Ogawa S, Nowak D, Kawamata N, Akagi T, Kato M, Sanada M, Weiss T, Haferlach C, Dugas M, Ruckert C, Haferlach T, Koeffler HP: Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica 2010;95:1481-1488.

11-47 Paulsson K, Haferlach C, Fonatsch C, Hagemeijer A, Andersen MK, Slovak ML, Johansson B: The idic(X)(q13) in myeloid malignancies: breakpoint clustering in segmental duplications and association with TET2 mutations. Hum Mol Genet 2010;19:1507-1514.

11-48 Reindl L, Bacher U, Dicker F, Alpermann T, Kern W, Schnittger S, Haferlach T, Haferlach C: Biological and clinical characterization of recurrent 14q deletions in CLL and other mature B-cell neoplasms. Br J Haematol 2010;151:25-36.

11-49 Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, Kolb HJ, Ho AD, Falge C, Holler E, Schlimok G, Zander AR, Arnold R, Kanz L, Dengler R, Haferlach C, Schlegelberger B, Pfirrmann M, Muller MC, Schnittger S, Leitner A, Pletsch N, Hochhaus A, Hasford J, Hehlmann R: Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-1885.

11-50 Savage NM, Kota V, Manaloor EJ, Kulharya AS, Pierini V, Mecucci C, Ustun C: Acute leukemia with PICALM-MLLT10 fusion gene: diagnostic and treatment struggle. Cancer Genet Cytogenet 2010;202:129-132.

11-51 Schlenk RF, Dohner K, Mack S, Stoppel M, Kiraly F, Gotze K, Hartmann F, Horst HA, Koller E, Petzer A, Grimminger W, Kobbe G, Glasmacher A, Salwender H, Kirchen H, Haase D, Kremers S, Matzdorff A, Benner A, Dohner H: Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. J Clin Oncol 2010;28:4642-4648.

11-52 Schnittger S, Haferlach C, Ulke M, Alpermann T, Kern W, Haferlach T: IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated NPM1 status. Blood 2010;116:5486-5496.

11-53 Schnittger S, Dicker F, Kern W, Wendland N, Sundermann J, Alpermann T, Haferlach C, Haferlach T: RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. Blood 2011;117:2348-2357.

11-54 Schnittger S, Bacher U, Eder C, Lohse P, Haferlach C, Kern W, Haferlach T: A copy number repeat polymorphism in the transactivation domain of the CEPBA gene is possibly associated with a protective effect against acquired CEBPA mutations: an analysis in 1135 patients with AML and 187 healthy controls. Exp Hematol 2011;39:87-94.

11-55 Schnittger S, Bacher U, Dicker F, Kern W, Alpermann T, Haferlach T, Haferlach C: Associations between imatinib resistance conferring mutations and Philadelphia positive clonal cytogenetic evolution in CML. Genes Chromosomes Cancer 2010;49:910-918.

11-56 Shehata M, Demirtas D, Schnabl S, Hilgarth M, Hubmann R, Fonatsch C, Schwarzinger I, Hopfinger G, Eigenberger K, Heintel D, Porpaczy E, Vanura K, Hauswirth A, Schwarzmeier JD, Gaiger A, Stilgenbauer S, Hallek M, Bilban M, Jager U: Sequential gene expression profiling during treatment for identification of predictive markers and novel therapeutic targets in chronic lymphocytic leukemia. Leukemia 2010;24:2122-2127.

11-57 Sportoletti P, Baldoni S, Cavalli L, Del PB, Bonifacio E, Ciurnelli R, Bell AS, Di TA, Rosati E, Crescenzi B, Mecucci C, Screpanti I, Marconi P, Martelli MF, Di IM, Falzetti F: NOTCH1 PEST domain mutation is an adverse prognostic factor in B-CLL. Br J Haematol 2010;151:404-406.

11-58 Taussig DC, Vargaftig J, Miraki-Moud F, Griessinger E, Sharrock K, Luke T, Lillington D, Oakervee H, Cavenagh J, Agrawal SG, Lister TA, Gribben JG, Bonnet D: Leukemia-initiating cells from some acute myeloid leukemia patients with mutated nucleophosmin reside in the CD34(-) fraction. Blood 2010;115:1976-1984.

11-59 Tehranchi R, Woll PS, Anderson K, Buza-Vidas N, Mizukami T, Mead AJ, Astrand-Grundstrom I, Strombeck B, Horvat A, Ferry H, Dhanda RS, Hast R, Ryden T, Vyas P, Gohring G, Schlegelberger B, Johansson B, Hellstrom-Lindberg E, List A, Nilsson L, Jacobsen SE: Persistent malignant stem cells in del(5q) myelodysplasia in remission. N Engl J Med 2010;363:1025-1037.

11-60 Walz C, Grimwade D, Saussele S, Lengfelder E, Haferlach C, Schnittger S, Lafage-Pochitaloff M, Hochhaus A, Cross NC, Reiter A: Atypical mRNA fusions in PML-RARA positive, RARA-PML negative acute promyelocytic leukemia. Genes Chromosomes Cancer 2010;49:471-479.

11-61 Wieser R, Scheideler M, Hackl H, Engelmann M, Schneckenleithner C, Hiden K, Papak C, Trajanoski Z, Sill H, Fonatsch C: microRNAs in acute myeloid leukemia: expression patterns, correlations with genetic and clinical parameters, and prognostic significance. Genes Chromosomes Cancer 2010;49:193-203.

WP12 (MRD)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

12-1 Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Lowenberg B, Bloomfield CD. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-74.

12-2 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, Barosi G, Bassan R, Béné MC, Berger U, Büchner T, Burnett A, Cross NC, de Witte TJ, Döhner H, Dombret H, Einsele H, Engelich G, Foà R, Fonatsch C, Gökbuget N, Gluckman E, Gratwohl A, Guilhot F, Haferlach C, Haferlach T, Hallek M, Hasford J, Hochhaus A, Hoelzer D, Kiladjian JJ, Labar B, Ljungman P, Mansmann U, Niederwieser D, Ossenkoppele G, Ribera JM, Rieder H, Serve H, Schrotz-King P, Sanz MA, Saussele S; European LeukemiaNet. The European LeukemiaNet: achievements and perspectives. Haematologica. 2011; 96(1):156-62

12-3 Ommen HB, Schnittger S, Jovanovic JV, Ommen IB, Hasle H, Østergaard M, Grimwade D, Hokland P. Strikingly different molecular relapse kinetics in NPM1c, PML-RARA, RUNX1-RUNX1T1 and CBFB-MYH11 acute myeloid leukemias. Blood. 2010; 115: 198-205.

12-4 Østergaard M, Nyvold CG, Jovanovic JV, Andersen MT, Kairisto V, Morgan YG, Tobal K, Pallisgaard N, Özbek U, Pfeifer H, Schnittger S, Grubach L, Larsen JK, Grimwade D, Hokland P. Development of standardized approaches to reporting of minimal residual disease data using a reporting software package designed within the European LeukemiaNet (ELN). Leukemia 2011, in press.

12-5 Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, Pane F, Müller MC, Ernst T, Rosti G, Porkka K, Baccarani M, Cross NCP, and Martinelli G. Bcr-Abl kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet Blood published 19 May 2011, 10.1182/blood-2010-12-326405

12-6 White HE, Matejtschuk P, Rigsby P, Gabert J, Lin F, Lynn Wang Y, Branford S, Müller MC, Beaufils N, Beillard E, Colomer D, Dvorakova D, Ehrencrona H, Goh HG, El Housni H, Jones D, Kairisto V, Kamel-Reid S, Kim DW, Langabeer S, Ma ES, Press RD, Romeo G, Wang L, Zoi K, Hughes T, Saglio G, Hochhaus A, Goldman JM, Metcalfe P, Cross NC. Establishment of the first World Health Organization International Genetic Reference Panel for quantitation of BCR-ABL mRNA. Blood. 2010;116(22):e111-7

International publications to which the European leukemia Network has made a contribution

*(**without** a reference to the European leukemia Network)*

12-7 Erben P, Gosenca D, Muller MC, Reinhard J, Score J, del Valle F, et al. Screening for diverse PDGFRA or PDGFRB fusion genes is facilitated by generic quantitative reverse transcriptase polymerase chain reaction analysis. Haematologica-the Hematology Journal 2010; 95(5):738-44.

12-8 Ernst T, Chase A, Zoi K, Waghorn K, Hidalgo-Curtis C, Score J, et al. Transcription factor mutations in myelodysplastic/myeloproliferative neoplasms. Haematologica-the Hematology Journal 2010; 95(9):1473-80.

12-9 Ernst T, Chase AJ, Score J, Hidalgo-Curtis CE, Bryant C, Jones AV, et al. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. Nature Genetics [Article] 2010; 42(8):722-U109.

12-10 Falini B, Macijewski K, Weiss T, Bacher U, Schnittger S, Kern W, et al. Multilineage dysplasia has no impact on biologic, clinicopathologic, and prognostic features of AML with mutated nucleophosmin (NPM1). Blood 2010; 115(18):3776-86.

12-11 Falini B, Martelli MP, Pileri SA, Mecucci C. Molecular and alternative methods for diagnosis of acute myeloid leukemia with mutated NPM1: flexibility may help. Haematologica-the Hematology Journal 2010; 95(4):529-34.

12-12 Grimwade D, Vyas P, Freeman S. Assessment of minimal residual disease in acute myeloid leukemia. Curr Opin Oncol. 2010;22(6):656-63.

12-13 Foroni L, Wilson G, Gerrard G, Mason J, Grimwade D, White HE, de Castro DG, Austin S, Awan A, Burt E, Clench T, Farruggia J, Hancock J, Irvine AE, Kizilors A, Langabeer S, Milner BJ, Nickless G, Schuh A, Sproul A, Wang L, Wickham C, Cross NC. Guidelines for the measurement of BCR-ABL1 transcripts in chronic myeloid leukaemia. Br J Haematol. 2011 Mar 8.

12-14 Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 2010; 116(3):354-65

12-15 Grimwade D, Jovanovic JV, Hills RK, Solomon E, Lo-Coco F, Wheatley K, et al. How Should We Prevent Hematologic Relapse of Acute Promyelocytic Leukemia? Reply. Journal of Clinical Oncology [Letter] 2010; 28(4):E63-E4.

12-16 Grimwade D, Mistry AR, Solomon E, Guidez F. Acute Promyelocytic Leukemia: A Paradigm for Differentiation Therapy. Acute Myelogenous Leukemia:GENETICS, BIOLOGY AND THERAPY 2010:219-35.

12-17 Grimwade D, Tallman MS. Should minimal residual disease monitoring be the standard of care for all patients with acute promyelocytic leukemia? Leukemia Research 2011; 35(1):3-7.

12-18 Grimwade D, Vyas P, Freeman S. Assessment of minimal residual disease in acute myeloid leukemia. Current Opinion in Oncology 2010; 22(6):656-63.

12-19 Hochhaus A, La Rosee P, Muller MC, Ernst T, Cross NCP. Impact of BCR-ABL mutations on patients with chronic myeloid leukemia. Cell Cycle 2011; 10(2):250-60.

12-20 Hokland P, Ommen HB. Towards individualized follow-up in adult acute myeloid leukemia in remission. Blood 2011; 117(9):2577-84.

12-21 Joannides M, Grimwade D. Molecular biology of therapy-related leukaemias. Clinical & Translational Oncology 2010; 12(1):8-14.

12-22 Krönke J, Schlenk RF, Jensen K-O, Tschürtz F, Corbacioglu A, Gaidzik VI, et al. Monitoring of Minimal Residual Disease in NPM1-Mutated Acute Myeloid Leukemia: A Study From the German-Austrian Acute Myeloid Leukemia Study Group. Journal of Clinical Oncology 2011:in press.

12-23 Kuiper RP, Waanders E, van der Velden VHJ, van Reijmersdal SV, Venkatachalam R, Scheijen B, et al. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. Leukemia 2010; 24(7):1258-64.

12-24 Ommen HB, Schnittger S, Jovanovic JV, Ommen IB, Hasle H, Ostergaard M, et al. Strikingly different molecular relapse kinetics in NPM1c, PML-RARA, RUNX1-RUNX1T1, and CBFB-MYH11 acute myeloid leukemias. Blood 2010; 115(2):198-205.

12-25 Ossenkoppele GJ, van de Loosdrecht AA, Schuurhuis GJ. Review of the relevance of aberrant antigen expression by flow cytometry in myeloid neoplasms. British Journal of Haematology 2011; 153(4):421-36.

12-26 Schnittger S, Alpermann T, Eder C, Schindela S, Grossmann V, Kern W, et al. The Role of Different Genetic Subtypes In CEBPA Mutated AML. Blood 2010; 116(21):330-1.

12-27 Schnittger S, Bacher U, Eder C, Lohse P, Haferlach C, Kern W, et al. A copy number repeat polymorphism in the transactivation domain of the CEPBA gene is possibly associated with a protective effect against acquired CEBPA mutations an analysis in 1135 patients with AML and 187 healthy controls. Experimental Hematology 2011; 39(1):87-94.

12-28 Schnittger S, Bacher U, Haferlach C, Alpermann T, Dicker F, Sundermann J, et al. Characterization of NPM1-mutated AML with a history of myelodysplastic syndromes or myeloproliferative neoplasms. Leukemia 2011; 25(4):615-21.

12-29 Schnittger S, Dicker F, Kern W, Wendland N, Sundermann J, Alpermann T, et al. RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. Blood 2011; 117(8):2348-57.

12-30 Schnittger S, Haferlach C, Ulke M, Alpermann T, Kern W, Haferlach T. IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated NPM1 status. Blood 2010; 116(25):5486-96.

12-31 Schuurhuis GJ, Ossenkoppele G. Minimal residual disease in acute myeloid leukemia: already predicting a safe haven? Expert Review of Hematology 2010; 3(1):1-5.

12-32 Smith ML, Hills RK, Grimwade D. Independent prognostic variables in acute myeloid leukaemia. Blood Reviews 2011; 25(1):39-51.

12-33 Staal FJT, de Ridder D, Szczepanski T, Schonewille T, van der Linden ECE, van Wering ER, et al. Genome-wide expression analysis of paired diagnosis-relapse samples in ALL indicates involvement of pathways related to DNA replication, cell cycle and DNA repair, independent of immune phenotype. Leukemia 2010; 24(3):491-9.

12-34 Szczepanski T, Harrison CJ, van Dongen JJM. Genetic aberrations in paediatric acute leukaemias and implications for management of patients. Lancet Oncology 2010; 11(9):880-9.

12-35 van der Velden VHJ, van der Sluijs-Geling A, Gibson BES, Marvelde JGT, Hoogeveen PG, Hop WCJ, et al. Clinical significance of flowcytometric minimal residual disease detection in pediatric acute myeloid leukemia patients treated according to the DCOG ANLL97/MRC AML12 protocol. Leukemia 2010; 24(9):1599-606.

12-36 Walz C, Grimwade D, Saussele S, Lengfelder E, Haferlach C, Schnittger S, et al. Atypical mRNA Fusions in PML-RARA Positive, RARA-PML Negative Acute Promyelocytic Leukemia. Genes Chromosomes & Cancer 2010; 49(5):471-9.

Abstracts

12-37 Ernst T., Feng Lin, Helen E White, Paul La Rosée, Thomas Lion, Gerlinde Mitterbauer-Hohendanner, Peter Vandenberghe, Renata Zadro, Katerina Machova Polakova, Radek Plachy, Charlotte Guldborg Nyvold, Tuija Lundán, Jean-Michel Cayuela, Thoralf Lange, Martin C. Müller, Katerina Zoi, Hajnalka Andrikovics, Tali Tohami, Fabrizio Pane, Simona Soverini, Francesca Arruga, Lene Eggen, Tomasz Sacha, Joana Diamond, Rodica Talmaci, Tadej Pajic, Dolors Colomer, Monica Hermanson, Elisabeth Oppliger Leibundgut, Peter J. M. Valk, Ugur Ozbek, Gareth Gerrard, Giuseppe Saglio, Andreas Hochhaus, Nicholas C.P. Cross. Harmonized testing for BCR-ABL kinase domain mutations in CML: Results of a survey and first control round within 28 National Reference Laboratories in Europe
Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 894.

12-38 Lengfelder E., Francesco Lo-Coco, Pau Montesinos, David Grimwade, Lionel Ades, Bhuvan Kishore, Maria Pagoni, Safaa M. Ramadan, Massimo Breccia, Alexandra Holowiecka, Anne Pradel, Maria Cristina Sauerland, Pierre Fenaux,

Miguel Angel Sanz. Treatment of Molecular and Clinical Relapse of Acute Promyelocytic Leukemia (APL) with Arsenic Trioxide: Results of the European Registry of Relapsed APL Blood. 116, abstract 15, Oral presentation, ASH 2010.

12-39 Müller MC, Umang Munjal, Philipp Erben, Thomas Lion, Gerlinde Mitterbauer-Hohendanner, Hakim El Housni, Nancy Boeckx, Renata Zadro, Jiri Mayer, Peter Rohon, Jana Rulcova, Lykke Grubach, Kadri Raudsepp, Veli Kairisto, Francois-Xavier Mahon, Claude Preudhomme, Sandrine Hayette, Jean Gabert, Jean-Michel Cayuela, Christian Thiede, Lars Galonska, Heike Pfeifer, Carsten Hirt, Philippe Schafhausen, Nils von Neuhoff, Martin Roskos, Christiane Pott, Thoralf Lange, Georg Hess, Susanne Schnittger, Annika Dufour, Steffen Koschmieder, Frank Stegelmann, Katerina Zoi, Kostas Stamatopoulos, Hajnalka Andrikovics, Tali Tohami, Giovanni Martinelli, Barbara Izzo, Enrico Gottardi, Mindaugas Stoskus, Dag Andre Nymoen, Tomasz Sacha, Joana Diamond, Rodica Talmaci, Andrey Misyurin, Michael V. Dubina, Tadej Pajic, Josep F. Nomdedeu, Dolors Colomer, Gisela Barbany-Bustinza, Hans Ehrencrona, Elisabeth Oppliger Leibundgut, Jeroen Janssen, Vincent H. J. van der Velden, Peter J.M. Valk, Ugur Ozbek, Lihui Wang, Gareth Gerrard, Helen E White, Thomas Schenk, Thomas Ernst, Rüdiger Hehlmann, Giuseppe Saglio, Andreas Hochhaus, Nicholas C. P. Cross. Stability of conversion factors for BCR-ABL monitoring -– Implications for the frequency of validation rounds. Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 893.

12-40 Terwijn M., Angèle Kelder, Wim L.J. van Putten, Alexander N. Snel, Vincent H.J. van der Velden, Rik A. Brooimans, Nancy Boeckx, Frank W.M.B. Preijers, Bob Löwenberg, Angelika M. Dräger, Peter C. Huijgens, Peter J.M Valk, Johan Maertens, Thomas Pabst, Gert J. Ossenkoppele, Gerrit J. Schuurhuis. High prognostic impact of flowcytometric minimal residual disease detection in acute myeloid leukemia: Prospective Data From the HOVON/SAKK 42a Study. Blood. 116, abstract 760, Oral presentation, ASH 2010.

12-41 Terwijn M., A.P. Rutten, A. Kelder, A.N. Snel, W. Scholten, S. Zweegman, G.J. Ossenkoppele, G.J. Schuurhuis. Accurate detection of residual leukemic stem cells in remission bone marrow predicts relapse in acute myeloid leukemia patients. Blood. 116, abstract 759, Oral presentation, ASH 2010.

12-42 Tsaur G., A. Ivanova, A. Popov, Y. Yakovleva, T. Riger, O. Plekhanova, Y. Ivanets, A. Misyurin, M. Suchkova, E. Shorikov, L. Saveliev, L. Fechina. Evaluation of BCR-ABL/ABL ratio increase that corresponds to BCR-ABL mutation in chronic myeloid leukemia patients treated by imatinib. Blood. 116, abstract 3422. ASH 2010.

12-43 White HE, Matejtschuk P, Rigsby P, Gabert J, Lin F, Wang YL, Branford S, Müller MC, Beaufils N, Beillard E, Colomer D, Dvorakova D, Ehrencrona H, Goh HG, El Housni H, Jones D, Kairisto V, Kamel-Reid S, Kim DW, Langabeer S, Ma ES, Press RD, Romeo G, Wang L, Zoi K, Hughes T, Saglio G, Hochhaus A, Goldman JM, Metcalfe P, Cross NCP. Establishment of the 1st World Health Organization International Genetic Reference Panel for quantitation of BCR-ABL mRNA. Haematologica. 2010;95; Suppl2:84-85. EHA June 2010.

WP13 (Gene profiling)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

13-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

13-2 Bacher U, Kohlmann A, Haferlach T. Gene expression profiling for diagnosis and therapy in acute leukaemia and other haematologic malignancies. Cancer Treatment Reviews 2010; 36(8):637-46.

13-3 Bresolin S, Zecca M, Flotho C, Trentin L, Zangrando A, Sainati L, et al. Gene Expression-Based Classification As an Independent Predictor of Clinical Outcome in Juvenile Myelomonocytic Leukemia. Journal of Clinical Oncology 2010; 28(11):1919-27.

13-4 Bullinger L, Armstrong SA. HELP for AML: methylation profiling opens new avenues. Cancer Cell 2010; 17(1):1-3.

13-5 Bullinger L, Ehrich M, Dohner K, Schlenk RF, Dohner H, Nelson MR, et al. Quantitative DNA methylation predicts survival in adult acute myeloid leukemia. Blood 2010; 115(3):636-42.

13-6 Bullinger L, Kronke J, Schon C, Radtke I, Urlbauer K, Botzenhardt U, et al. Identification of acquired copy number alterations and uniparental disomies in cytogenetically normal acute myeloid leukemia using high-resolution single-nucleotide polymorphism analysis. Leukemia 2010; 24(2):438-49.

13-7 Chiaretti S, Messina M, Tavolaro S, Zardo G, Elia L, Vitale A, et al. Gene expression profiling identifies a subset of adult T-cell acute lymphoblastic leukemia with myeloid-like gene features and over-expression of miR-223. Haematologica 2010; 95(7):1114-21.

13-8 Grossmann V, Kohlmann A, Eder C, Haferlach C, Kern W, Cross NCP, et al. Molecular profiling of chronic myelomonocytic leukemia reveals diverse mutations in >80% of patients with TET2 and EZH2 being of high prognostic relevance. Leukemia 2011; 25(5):877-9.

13-9 Grossmann V, Kohlmann A, Klein HU, Schindela S, Schnittger S, Dicker F, et al. Targeted next-generation sequencing detects point mutations, insertions, deletions and balanced chromosomal rearrangements as well as identifies novel leukemia-specific fusion genes in a single procedure. Leukemia 2011; 25(4):671-80.

13-10 Grossmann V, Kohlmann A, Zenger M, Schindela S, Eder C, Weissmann S, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 2011; 25(3):557-60.

13-11 Haferlach T, Kohlmann A, Wieczorek L, Basso G, Kronnie GT, Bene MC, et al. Clinical Utility of Microarray-Based Gene Expression Profiling in the Diagnosis and Subclassification of Leukemia: Report From the International Microarray Innovations in Leukemia Study Group. Journal of Clinical Oncology 2010; 28(15):2529-37.

13-12 Hiddemann W. Current tumor pathology. Pathologe [Article] 2010; 31(1):6-8.

13-13 Jenal M, Batliner J, Reddy VA, Haferlach T, Tobler A, Fey MF, et al. The anti-apoptotic gene BCL2A1 is a novel transcriptional target of PU.1. Leukemia 2010; 24(5):1073-6.

13-14 Klein HU, Bartenhagen C, Kohlmann A, Grossmann V, Ruckert C, Haferlach T, et al. R453Plus1Toolbox: an R/Bioconductor package for analyzing Roche 454 Sequencing data. Bioinformatics [Article] 2011; 27(8):1162-3.

13-15 Kohlmann A, Bullinger L, Thiede C, Schaich M, Schnittger S, Dohner K, et al. Gene expression profiling in AML with normal karyotype can predict mutations for molecular markers and allows novel insights into perturbed biological pathways. Leukemia 2010; 24(6):1216-20.

13-16 Kohlmann A, Grossmann V, Klein HU, Schindela S, Weiss T, Kazak B, et al. Next-Generation Sequencing Technology Reveals a Characteristic Pattern of Molecular Mutations in 72.8% of Chronic Myelomonocytic Leukemia by Detecting Frequent Alterations in TET2, CBL, RAS, and RUNX1. Journal of Clinical Oncology 2010; 28(24):3858-65.

13-17 Marcucci G, Haferlach T, Döhner H. Molecular Genetics of Adult Acute Myeloid Leukemia: Prognostic and Therapeutic Implications. Journal of Clinical Oncology 2011; 29(5):475-86.

13-18 Theilgaard-Monch K, Boultwood J, Ferrari S, Giannopoulos K, Hernandez-Rivas JM, Kohlmann A, et al. Gene expression profiling in MDS and AML: potential and future avenues. Leukemia 2011:published online.

13-19 Thoennissen NH, Krug UO, Lee DHT, Kawamata N, Iwanski GB, Lasho T, et al. Prevalence and prognostic impact of allelic imbalances associated with leukemic transformation of Philadelphia chromosome-negative myeloproliferative neoplasms. Blood 2010; 115(14):2882-90.

WP14 (SCT)

*International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)*

14-1 Gratwohl A, Brand R, Niederwieser D, Baldomero H, Chabannon C, Cornelissen J, et al. Introduction of a Quality Management System and Outcome After Hematopoietic Stem-Cell Transplantation. Journal of Clinical Oncology 2011; 29(15):1980-6.

14-2 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet):*

14-3 Auner HW, Mazzarella L, Cook L, Szydlo R, Saltarelli F, Pavlu J, et al. High rate of stem cell mobilization failure after thalidomide and oral cyclophosphamide induction therapy for multiple myeloma. Bone Marrow Transplantation 2011; 46(3):364-7.

14-4 Bacher U, Haferlach C, Kroger N, Schnittger S, Kern W, Wiedemann B, et al. Diagnostic Tools in the Indications for Allogeneic Stem Cell Transplantation in Myelodysplastic Syndromes. Biology of Blood and Marrow Transplantation 2010; 16(1):1-11.

14-5 Bacigalupo A, Soraru M, Dominietto A, Pozzi S, Geroldi S, Van Lint MT, et al. Allogeneic hemopoietic SCT for patients with primary myelofibrosis: a predictive transplant score based on transfusion requirement, spleen size and donor type. Bone Marrow Transplantation 2010; 45(3):458-63.

14-6 Baldomero H, Gratwohl M, Gratwohl A, Tichelli A, Niederwieser D, Madrigal A, et al. The EBMT activity survey 2009: trends over the past 5 years. Bone Marrow Transplantation 2011; 46(4):485-501.

14-7 Chalandon Y, Passweg JR, Schmid C, Olavarria E, Dazzi F, Simula MP, et al. Outcome of patients developing GVHD after DLI given to treat CML relapse: a study by the chronic leukemia working party of the EBMT. Bone Marrow Transplantation 2010; 45(3):558-64.

14-8 Clare S, Mank A, Stone R, Davies M, Potting C, Apperley JF, et al. Management of related donor care: a European survey. Bone Marrow Transplantation 2010; 45(1):97-101.

14-9 Cohen YC, Scaradavou A, Stevens CE, Rubinstein P, Gluckman E, Rocha V, et al. Factors affecting mortality following myeloablative cord blood transplantation in adults: a pooled analysis of three international registries. Bone Marrow Transplantation 2011; 46(1):70-6.

14-10 Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, et al. Hepatic Veno-Occlusive Disease following Stem Cell Transplantation: Incidence, Clinical Course, and Outcome. Biology of Blood and Marrow Transplantation 2010; 16(2):157-68.

14-11 Cordonnier C, Labopin M, Chesnel V, Ribaud P, De La Camara R, Martino R, et al. Immune response to the 23-valent polysaccharide pneumococcal vaccine after the 7-valent conjugate vaccine in allogeneic stem cell transplant recipients: Results from the EBMT IDWP01 trial. Vaccine 2010; 28(15):2730-4.

14-12 de Lavallade H, Garland P, Sekine T, Hoschler K, Marin D, Stringaris K, et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica-the Hematology Journal 2011; 96(2):307-14.

14-13 Dickinson AM, Pearce KF, Norden J, O'Brien SG, Holler E, Bickeboller H, et al. Impact of genomic risk factors on outcome after hematopoietic stem cell transplantation for patients with chronic myeloid leukemia. Haematologica-the Hematology Journal 2010; 95(6):922-7.

14-14 Drake MB, Iacobelli S, van Biezen A, Morris C, Apperley JF, Niederwieser D, et al. Primary plasma cell leukemia and autologous stem cell transplantation. Haematologica-the Hematology Journal 2010; 95(5):804-9.

14-15 Feuchtinger T, Opherk K, Bethge WA, Topp MS, Schuster FR, Weissinger EM, et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. Blood 2010; 116(20):4360-7.

14-16 Frewer LJ, Coles D, van der Lans IA, Schroeder D, Champion K, Apperley JF. Impact of the European Clinical Trials Directive on prospective academic clinical trials associated with BMT. Bone Marrow Transplantation 2011; 46(3):443-7.

14-17 Garderet L, Iacobelli S, Moreau P, Dib M, Caillot D, Niederwieser DW, et al. Bortezomib(Velcade (R)) Thalidomide-Dexamethasone (VTD) Is Superior to Thalidomide Dexamethasone (TD) In Patients with Multiple Myeloma (MM) Progressing or Relapsing After Autologous Transplantation. Blood 2010; 116(21):1254-.

14-18 Giebel S, Labopin M, Mohty M, Blaise D, Craddock C, Nagler A, et al. The Impact of Center Experience on Results of Reduced Intensity - Allogeneic Hematopoietic Stem Cell Transplantation A Survey From the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). Blood 2010; 116(21):1445-6.

14-19 Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al. Hematopoietic Stem Cell Transplantation A Global Perspective. Jama-Journal of the American Medical Association 2010; 303(16):1617-24.

14-20 Gratwohl A, Baldomero H, Schwendener A, Gratwohl M, Apperley J, Frauendorfer K, et al. The EBMT activity survey 2008: impact of team size, team density and new trends. Bone Marrow Transplantation 2011; 46(2):174-91.

14-21 Gratwohl A, Schwendener A, Baldomero H, Gratwohl M, Apperley J, Niederwieser D, et al. Changes in the use of hematopoietic stem cell transplantation: a model for diffusion of medical technology. Haematologica-the Hematology Journal 2010; 95(4):637-43.

14-22 Hebart H, Lengerke C, Ljungman P, Paya CV, Klingebiel T, Loeffler J, et al. Prospective comparison of PCR-based vs late mRNA-based preemptive antiviral therapy for HCMV infection in patients after allo-SCT. Bone Marrow Transplantation 2011; 46(3):408-15.

14-23 Koenecke C, Hertenstein B, Schetelig J, van Biezen A, Dammann E, Gratwohl A, et al. Solid Organ Transplantation After Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective, Multicenter Study of the EBMT. American Journal of Transplantation 2010; 10(8):1897-906.

14-24 Krenauer A, Moll A, Ponisch W, Schmitz N, Niedobitek G, Niederwieser D, et al. EBV-associated post-transplantation B-cell lymphoproliferative disorder following allogenic stem cell transplantation for acute lymphoblastic leukaemia: tumor regression after reduction of immunosuppression - a case report. Diagnostic Pathology 2010; 5.

14-25 Kroeger N, Putter H, Brand R, Kuendgen A, de Witte T, Germing U, et al. Comparison of allogeneic stem cell transplantation and best supportive care in elderly patients with advanced MDS. Bone Marrow Transplantation 2010; 45(Suppl. 2):ISSN 0268-3369(print)|1476-5365(electronic).

14-26 Kroeger N, Shimoni A, Schilling G, Schwerdtfeger R, Bornhaueser M, Nagler A, et al. Unrelated stem cell transplantation after reduced intensity conditioning for patients with multiple myeloma relapsing after autologous transplantation. British Journal of Haematology 2010; 148(2):323-31.

14-27 Kroeger N, Zabelina T, van Biezen A, Brand R, de Witte T. Bone marrow fibrosis on outcomes of patients with MDS/sAML undergoing allogeneic stem cell transplantation. Bone Marrow Transplantation 2010; 45(Suppl. 2):ISSN 0268-3369(print)|1476-5365(electronic).

14-28 Kroeger N, Zabelina T, van Biezen A, Brand R, Niederwieser D, Martino R, et al. Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis. Haematologica-the Hematology Journal 2011; 96(2):291-7

14-29 Kyriakou C, Canals C, Sibon D, Cahn JY, Kazmi M, Arcese W, et al. High-Dose Therapy and Autologous Stem-Cell Transplantation in Waldenstrom Macroglobulinemia: The Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Journal of Clinical Oncology 2010; 28(13):2227-32.

14-30 Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al. Allogeneic Hematopoietic Stem-Cell Transplantation for Patients 50 Years or Older With Myelodysplastic Syndromes or Secondary Acute Myeloid Leukemia. Journal of Clinical Oncology 2010; 28(3):405-11.

14-31 Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. Bone Marrow Transplantation 2010; 45(2):219-34.

14-32 Loren AW, Chow E, Jacobsohn DA, Gilleece M, Halter J, Joshi S, et al. Pregnancy after Hematopoietic Cell Transplantation: A Report from the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). Biology of Blood and Marrow Transplantation 2011; 17(2):157-66.

14-33 Michallet M, Dreger P, Sutton L, Brand R, Richards S, van Os M, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. Blood 2011; 117(5):1516-21.

14-34 Mohty M, Labopin M, Volin L, Gratwohl A, Socie G, Esteve J, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood 2010; 116(22):4439-43.

14-35 Morris C, Drake M, Apperley J, Iacobelli S, van Biezen A, Bjorkstrand B, et al. Efficacy and outcome of autologous transplantation in rare myelomas. Haematologica-the Hematology Journal 2010; 95(12):2126-33.

14-36 Mutis T, Brand R, Gallardo D, van Biezen A, Niederwieser D, Goulmy E, et al. Graft-versus-host driven graft-versus-leukemia effect of minor histocompatibility antigen HA-1 in chronic myeloid leukemia patients. Leukemia 2010; 24(7):1388-92.

14-37 Nagler A. Introduction: advances and promise in human umbilical cord blood Preface. Best Practice & Research Clinical Haematology [Editorial Material] 2010; 23(2):169-70.

14-38 Ohrmalm L, Lindblom A, Omar H, Norbeck O, Gustafson I, Lewensohn-Fuchs I, et al. Evaluation of a surveillance strategy for early detection of adenovirus by PCR of peripheral blood in hematopoietic SCT recipients: incidence and outcome. Bone Marrow Transplantation 2011; 46(2):267-72.

14-39 Omar H, Ahmed R, Rane L, Bjorklund A, Gustafsson-Jernberg A, Ljungman P, et al. Decreased IL-7 Signaling in T Cells From Patients With PTLD After Allogeneic HSCT. Journal of Immunotherapy 2011; 34(4):390-6.

14-40 Ostrovsky O, Shimoni A, Rand A, Vlodavsky I, Nagler A. Genetic variations in the heparanase gene (HPSE) associate with increased risk of GVHD following allogeneic stem cell transplantation: effect of discrepancy between recipients and donors. Blood 2010; 115(11):2319-28.

14-41 Powles R, Sirohi B, Niederwieser D. The role of the European haematologist in a large irradiation emercency. The European Blood and Marrow Transplantation Society (EBMT) Nuclear Accident Committee (NAC). Health Physics 2010; 98(6):810-4.

14-42 Robin M, Sanz GF, Ionescu I, Rio B, Sirvent A, Renaud M, et al. Unrelated cord blood transplantation in adults with myelodysplasia or secondary acute myeloblastic leukemia: a survey on behalf of Eurocord and CLWP of EBMT. Leukemia 2011; 25(1):75-81.

14-43 Schlaak M, Schwind S, Wetzig T, Maschke J, Treudler R, Basara N, et al. UVA (UVA-1) therapy for the treatment of acute GVHD of the skin. Bone Marrow Transplantation 2010; 45(12):1741-8.

14-44 Shaughnessy PJ, Bolwell BJ, van Besien K, Mistrik M, Grigg A, Dodds A, et al. Extracorporeal photopheresis for the prevention of acute GVHD in patients undergoing standard myeloablative conditioning and allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplantation 2010; 45(6):1068-76.

14-45 Shaw BE, Mayor NP, Russell NH, Apperley JF, Clark RE, Cornish J, et al. Diverging effects of HLA-DPB1 matching status on outcome following unrelated donor transplantation depending on disease stage and the degree of matching for other HLA alleles. Leukemia 2010; 24(1):58-65.

14-46 Shimoni A, Hardan I, Shem-Tov N, Yerushalmi R, Nagler A. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: long-term follow-up. Leukemia 2010; 24(5):1050-2.

14-47 Shustov AR, Gooley TA, Sandmaier BM, Shizuru J, Sorror ML, Sahebi F, et al. Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. British Journal of Haematology 2010; 150(2):170-8.

14-48 Stelljes M, Beelen DW, Braess J, Sauerland MC, Heinecke A, Berning B, et al. Allogeneic transplantation as postremission therapy for cytogenetically high risk acute myeloid leukemia: Landmark analysis from a single prospective multicenter trial. Haematologica 2011:in press.

14-49 Stewart WA, Pearce R, Kirkland KE, Bloor A, Thomson K, Apperley J, et al. The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study. Bone Marrow Transplantation 2010; 45(11):1587-93.

14-50 Szydlo RM, Gabriel I, Olavarria E, Apperley J. Sign of the Zodiac as a Predictor of Survival for Recipients of an Allogeneic Stem Cell Transplant for Chronic Myeloid Leukaemia (CML): An Artificial Association. Transplantation Proceedings 2010; 42(8):3312-5.

14-51 Uprichard J, Dazzi F, Apperley JF, Laffan MA. Haemopoietic stem cell transplantation induces tolerance to donor antigens but not to foreign FVIII peptides. Haemophilia 2010; 16(1):143-7.

14-52 Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biology of Blood and Marrow Transplantation 2011; 17(1):1-17.

WP15 (Supportive care/anti-infection prophylaxis and treatment)

*International publications that are the direct result of the European leukemia Network (**with** a reference to the European leukemia Network)*

15-1 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

15-2 Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in Hematopoietic Stem Cell Transplant Recipients. Infectious Disease Clinics of North America 2010; 24(2):319-+.

15-3 Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in Hematopoietic Stem Cell Transplant Recipients. Hematology-Oncology Clinics of North America 2011; 25(1):151-+.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

15-4 Bjorklund AT, Schaffer M, Fauriat C, Ringden O, Remberger M, Hammarstedt C, et al. NK cells expressing inhibitory KIR for non-self-ligands remain tolerant in HLA-matched sibling stem cell transplantation. Blood 2010; 115(13):2686-94.

15-5 Blennow O, Remberger M, Klingspor L, Omazic B, Fransson K, Ljungman P, et al. Randomized PCR-based therapy and risk factors for invasive fungal infection following reduced-intensity conditioning and hematopoietic SCT. Bone Marrow Transplantation 2010; 45(12):1710-8.

15-6 Cordonnier C, Labopin M, Jansen KU, Pride M, Chesnel V, Bonnet E, et al. Relationship between IgG titers and opsonocytophagocytic activity of anti-pneumococcal antibodies after immunization with the 7-valent conjugate vaccine in allogeneic stem cell transplant. Bone Marrow Transplantation 2010; 45(9):1423-6.

15-7 Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica-the Hematology Journal 2010; 95(10):1762-8.

15-8 Cornely OA, Maertens J, Bresnik M, Ullmann AJ, Ebrahimi R, Herbrecht R. Treatment outcome of invasive mould disease after sequential exposure to azoles and liposomal amphotericin B. Journal of Antimicrobial Chemotherapy 2010; 65(1):114-7.

15-9 Cornely OA, Pappas PG, Young JAH, Maddison P, Ullmann AJ. Accumulated safety data of micafungin in therapy and prophylaxis in fungal diseases. Expert Opinion on Drug Safety 2011; 10(2):171-83.

15-10 Cornely OA, Ullmann AJ. Lack of Evidence for Exposure-Response Relationship in the Use of Posaconazole as Prophylaxis Against Invasive Fungal Infections. Clinical Pharmacology & Therapeutics 2011; 89(3):351-2.

15-11 Dalianis T, Ljungman P. Full Myeloablative Conditioning and an Unrelated HLA Mismatched Donor Increase the Risk for BK Virus-positive Hemorrhagic Cystitis in Allogeneic Hematopoetic Stem Cell Transplanted Patients. Anticancer Research 2011; 31(3):939-44.

15-12 Einsele H, Knop S, Straka C. Progress in treating patients with multiple myeloma. High-dose chemotherapy and stem cell transplantation. Onkologe 2010; 16(3):263-+.

15-13 Emery VC, Einsele H, Atabani S, Haque T. Immunotherapy and Vaccination After Transplant: The Present, the Future. Hematology-Oncology Clinics of North America 2011; 25(1):215-+.

15-14 Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. Bone Marrow Transplantation 2010; 45(7):1227-33.

15-15 Horn DL, Ostrosky-Zeichner L, Morris MI, Ullmann AJ, Wu C, Buell DN, et al. Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. European Journal of Clinical Microbiology & Infectious Diseases 2010; 29(2):223-9.

15-16 Kohl V, Muller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, et al. Factors Influencing Pharmacokinetics of Prophylactic Posaconazole in Patients Undergoing Allogeneic Stem Cell Transplantation. Antimicrobial Agents and Chemotherapy 2010; 54(1):207-12.

15-17 Kroger N, Einsele H, Derigs G, Wandt H, Krull A, Zander A. Long-Term Follow-Up of an Intensified Myeloablative Conditioning Regimen with In Vivo T Cell Depletion Followed by Allografting in Patients with Advanced Multiple Myeloma. Biology of Blood and Marrow Transplantation 2010; 16(6):861-4.

15-18 Ljungman P. Molecular monitoring of viral infections after hematopoietic stem cell transplantation. International Journal of Hematology 2010; 91(4):596-601.

15-19 Ljungman P. Solid-organ transplants and the risks of pandemic influenza. Lancet Infectious Diseases 2010; 10(8):506-7.

15-20 Loeffler J, Ok M, Morton OC, Mezger M, Einsele H. Genetic Polymorphisms in the Cytokine and Chemokine System: Their Possible Importance in Allogeneic Stem Cell Transplantation. Chemokine System in Experimental and Clinical Hematology 2010; 341:83-96.

15-21 Lokhorst H, Einsele H, Vesole D, Bruno B, Miguel JS, Perez-Simon JA, et al. International Myeloma Working Group Consensus Statement Regarding the Current Status of Allogeneic Stem-Cell Transplantation for Multiple Myeloma. Journal of Clinical Oncology 2010; 28(29):4521-30.

15-22 Mezger M, Einsele H, Loeffler J. Genetic susceptibility to infections with Aspergillus fumigatus. Critical Reviews in Microbiology 2010; 36(2):168-77.

15-23 Morton CO, Varga JJ, Hornbach A, Mezger M, Sennefelder H, Kneitz S, et al. The Temporal Dynamics of Differential Gene Expression in Aspergillus fumigatus Interacting with Human Immature Dendritic Cells In Vitro. Plos One 2011; 6(1):e16016.

15-24 Mui TS, Kapp M, Einsele H, Grigoleit GU. T-cell therapy for cytomegalovirus infection. Current Opinion in Organ Transplantation 2010; 15(6):744-50.

15-25 Omar H, Yun Z, Lewensohn-Fuchs I, Perez-Bercoff L, Orvell C, Engstrom L, et al. Poor outcome of adenovirus infections in adult hematopoietic stem cell transplant patients with sustained adenovirus viremia. Transplant Infectious Disease 2010; 12(5):465-9.

15-26 Rueping MJGT, Heinz WJ, Kindo AJ, Rickerts V, Lass-Floerl C, Beisel C, et al. Forty-one recent cases of invasive zygomycosis from a global clinical registry. Journal of Antimicrobial Chemotherapy 2010; 65(2):296-302.

15-27 Schempp S, Topp M, Kessler T, Sampaio KL, Dennehy KM, Einsele H, et al. Deletion mutant of human cytomegalovirus lacking US2-US6 and US11 maintains MHC class I expression and antigen presentation by infected dendritic cells. Virus Research 2011; 155(2):446-54.

15-28 Schneider CK, Salmikangas P, Jilma B, Flamion B, Todorova LR, Paphitou A, et al. Challenges with advanced therapy medicinal products and how to meet them. Nature Reviews Drug Discovery 2010; 9(3):195-201.

15-29 Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood 2010; 115(19):3861-8.

15-30 Spinnler K, Mezger M, Steffens M, Sennefelder H, Kurzai O, Einsele H, et al. Role of Glycogen Synthase Kinase 3 (GSK-3) in innate immune response of human immature dendritic cells to Aspergillus fumigatus. Medical Mycology 2010; 48(4):589-97.

15-31 Springer J, Loeffler J, Heinz W, Schlossnagel H, Lehmann M, Morton O, et al. Pathogen-Specific DNA Enrichment Does Not Increase Sensitivity of PCR for Diagnosis of Invasive Aspergillosis in Neutropenic Patients. Journal of Clinical Microbiology 2011; 49(4):1267-73.

15-32 Straka C, Sandherr M, Salwender H, Wandt H, Metzner B, Hubel K, et al. Testing G-CSF responsiveness predicts the individual susceptibility to infection and consecutive treatment in recipients of high-dose chemotherapy. Blood 2011; 117(7):2121-8.

15-33 Vehreschild JJ, Ruping M, Wisplinghoff H, Farowski F, Steinbach A, Sims R, et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. Journal of Antimicrobial Chemotherapy 2010; 65(7):1466-71.

WP17 (Biometry of Registry, Epidemiology, Metaanalyses and Prognosis)

International publications that are the direct result of the European LeukemiaNet (**with** a reference to the European LeukemiaNet)

17-1 Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011:prepublished online.

17-2 Hehlmann R, Grimwade D, Simonsson B, Apperley J, Baccarani M, Barbui T, et al. The European LeukemiaNet: achievements and perspectives. Haematologica-the Hematology Journal 2011; 96(1):156-62.

17-3 Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Muller MC, Pletsch N, et al. Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon-alpha in Newly Diagnosed Chronic Myeloid Leukemia. Journal of Clinical Oncology 2011; 29(12):1634-42.

17-4 Pfirrmann M, Hochhaus A, Lauseker M, Sausele S, Hehlmann R, Hasford J. Recommendations to meet statistical challenges arising from endpoints beyond overall survival in clinical trials on chronic myeloid leukemia. Leukemia 2011:in press.

17-5 Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010; 115(10):1880-5.

Abstracts with reference to the ELN:

17-6 Hasford J, Rosti G, Hoffmann V, Hehlmann R, Guilhot J, Nicolini F, et al.Only a high relative risk (Sokal or Euro) predicts for response to imatinib. An European LeukemiaNet EUTOS study. Haematologica-the Hematology Journal 2010; 95:0136.

*International publications that are the direct result of the European LeukemiaNet (**without** a reference to the European LeukemiaNet)*

17-7 Stausberg J, Hasford J. Identification of Adverse Drug Events The Use of ICD-10 Coded Diagnoses in Routine Hospital Data. Deutsches Arzteblatt International 2010; 107(3):23-U10.