PreClinical Safety (PCS) Consultants Ltd

AGAH WORKSHOP

Oncological Drugs: Early Development from Pre-Clinics to Phase II

20th of February 2015, Frankfurt

Non-clinical Safety Assessment of Anti-Cancer Medications and Determination of the First Dose for FIM, an Introduction

S. Plassmann

PCS – The Integrated Drug Development Company

Outline

- **Developmental aspects**
- **Regulatory context**
  - Applicable guidelines
- **Non-clinical testing paradigm**
  - Manufacturing
  - Pharmacology and safety pharmacology
  - DMPK
  - Toxicology
- **Special situations in development**
  - Compassionate use
  - Combination therapies
  - ADCs
- **Determination of dose for first-in-man studies (FIM)**
  - Specific aspects for anti-cancer medications
- **Biomarkers**

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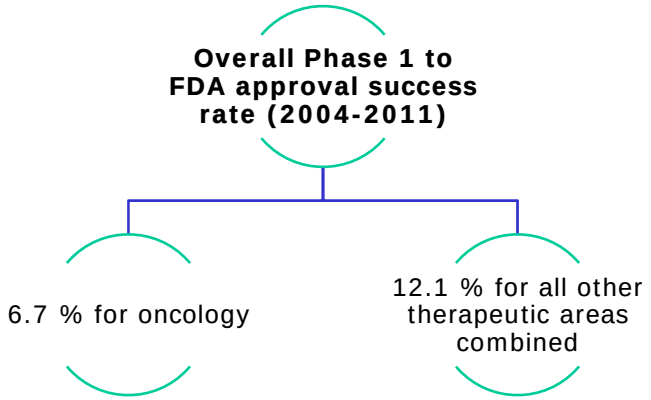
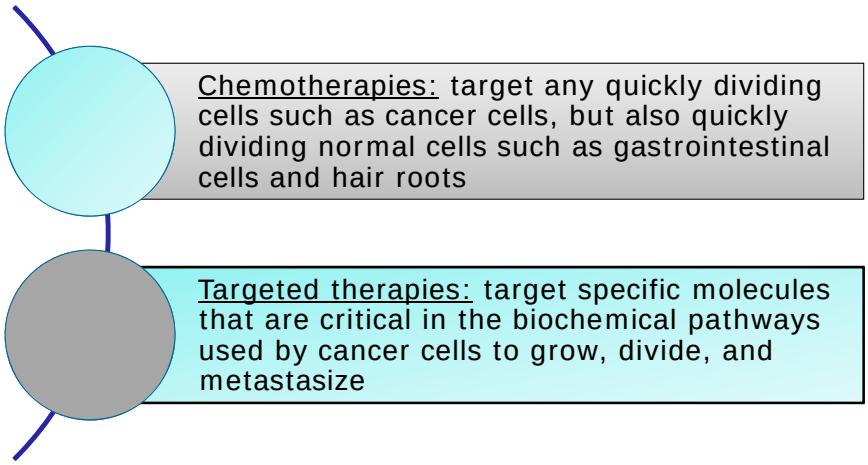
Success Rates During Clinical Development



Source: Inside Bio Industry Analysis, David Thomas www.biotech-now.org
http://www.biotech-now.org/business-and-investments/2012/02/oncology-clinical-trials-secrets-of-success

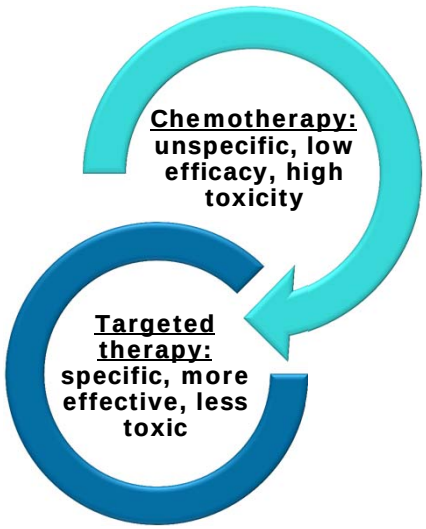
Shift from Chemotherapy to Targeted Therapies



Chemotherapies: target any quickly dividing cells such as cancer cells, but also quickly dividing normal cells such as gastrointestinal cells and hair roots

Targeted therapies: target specific molecules that are critical in the biochemical pathways used by cancer cells to grow, divide, and metastasize

The Hope



Types of Targeted Therapies (1)

- **Hormone therapies**
  - e.g. Tamoxifen for estrogen receptor positive breast cancer
- **Signal transduction inhibitors**
  - e.g. Gleevec (imatinib) for chronic myeloid leukemia
  - e.g. Tarceva (erlotinib) for NSCLC
  - e.g. Erbitux (cetuximab) for colorectal cancer
- **Monoclonal antibodies that deliver toxic molecules (ADC)**
  - Kadcyla (ado-trastuzumab + emtansine): for HER-2 positive breast cancer
  - Adcetris (brentuximab + vedotin): for Hodgkin lymphoma and anaplastic large cell lymphoma

Types of Targeted Therapies (2)

- **Angiogenesis inhibitors**
  - e.g. Avastin (bevacizumab) for renal cell carcinoma
- **Immunotherapies**
  - Provenge (sipuleucel-T) for men with metastatic prostate cancer
- **Cancer vaccines**
  - Hepatitis B virus to prevent liver cancer
  - Human papillomavirus to prevent cervical cancer
- **Gene therapies**
- **Gene expression modulators**

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Applicable Guidance Documents

- **Nonclinical evaluation for anticancer pharmaceuticals (ICH S9)**
  - Patients with advanced disease
  - Higher acceptability for toxicities of new therapies
  - Applicable to small molecules and biopharmaceuticals
- **Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (ICH M3[R2])**
  - Adjuvant therapy or healthy volunteers
  - Lower acceptability for toxicities in this healthier patient population
- **Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6[R1])**
- **FDA CDER Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; 2005**
- **European Medicines Agency: Committee for Medicinal Products for Human Use. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products.**

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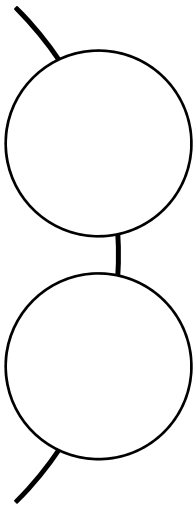
Nonclinical Development Overview (1)



Manufacturing - active substance

- Should be well characterized
- Adequately represent the active substance to be used in clinical trials

Pharmacology

- Provide nonclinical proof of principle
- Provide information for selection of test species for toxicology studies
- Aid in start dose selection for first in human studies
- Guide schedules and dose-escalation schemes in the clinic
- Aid in selection of investigational biomarkers
- Justify pharmaceutical combinations

Nonclinical Development Overview (2)

Safety pharmacology

- Effects on vital organ functions (cardiovascular, respiratory, CNS)

Drug metabolism and pharmacokinetics (DMPK)

Toxicology

- Identification of target organs and recovery
- Toxicokinetics to investigate exposure-response relationship

Pharmacology

- Identification of targets
- Screening compounds
- Lead optimization
- Identification of biomarkers

Screening of Compounds

In vitro

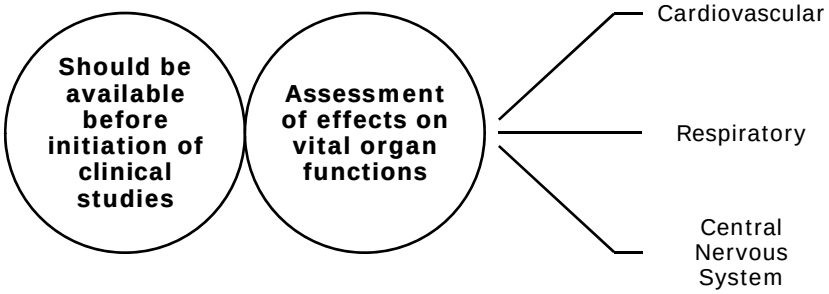
- Biochemical assays
- Cellular systems (proliferation, apoptosis, death, target inhibition, ……)

In vivo

- Transplantation models
- GEM (genetically engineered models)
- Carcinogen-induced models
- Spontaneous
- Metastasis models

All models are wrong, some are useful!

Safety pharmacology (1)



Safety pharmacology (2)

- **Effects are assessed at pharmacological doses and not at high toxicological doses**
- **Parameters can be included in general toxicity studies**
  - Stand alone safety pharmacology studies are not needed
- **Possible approach**
  - Target known to cause cardiac toxicity?
  - *in vitro* hERG assay for small molecules
  - ECG, blood pressure measurements, and respiratory function included in non-rodent (dog or monkey) general toxicology studies
  - CNS evaluation included in rodent toxicology studies
- **If specific concerns have been identified additional studies may be needed**

DMPK – Regulatory Requirements

Limited pharmacokinetic parameters:

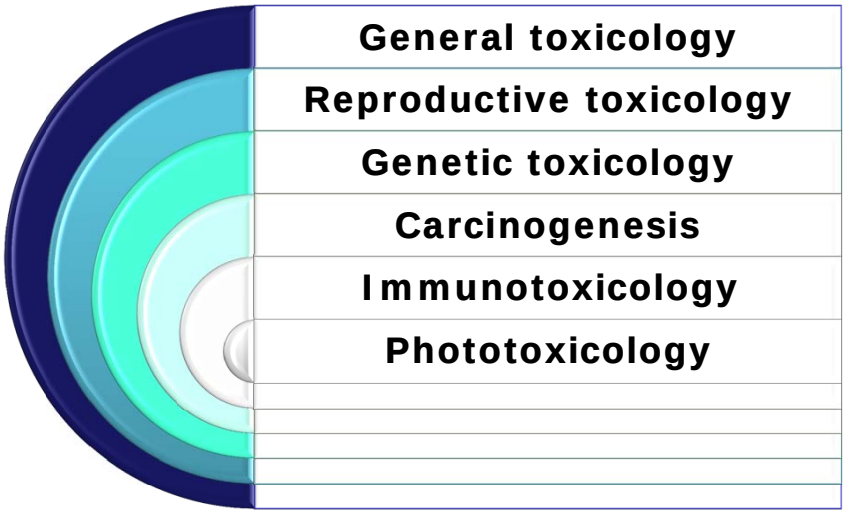
- Peak plasma/serum levels
- Area under the concentration curve (AUC)
- Half-life

Information on distribution, metabolism, and excretion should be generated in parallel with clinical development

DMPK - Differences

Biologics	Small molecules
• No metabolism work • Analytical methods for biologic drug • Analytical method for anti-drug antibodies	• Extensive metabolism work • Analytical assays to measure parent drug concentration • Possibly analytical assays to follow metabolites • Distribution studies • Elimination studies

Toxicology



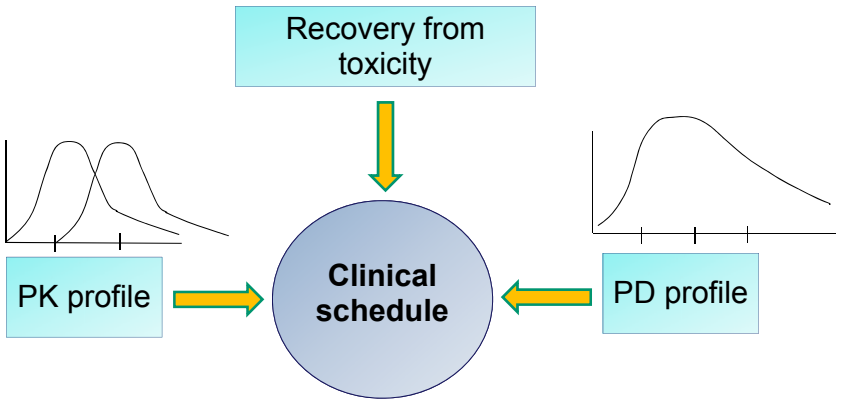
General toxicology

Toxicology studies to determine a No-Observed-Adverse-Effect-Level (NOAEL) or No-Effect-Level (NOEL) are not needed

The potential to recover from toxicity should be evaluated, however demonstration of complete recovery is not considered essential

The clinical schedule should be evaluated in toxicology studies

Determination of Clinical Schedule



Treatment schedule in toxicology studies can be more frequent than in the clinic

Common Schedules and Duration

Clinical schedule	Corresponding non-clinical treatment schedule for 4-week general toxicity studies prior to phase I
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	One a week for 4-5 doses

Selection of Toxicity Species

Small Molecules

- **One rodent (rat) and one non-rodent species (usually dog or monkey) needed**
- **Usually selected based on *in vitro* cross species metabolism data**

Biologics

- **Need pharmacologically relevant species**
  - Homology of the target
  - Target binding affinities
  - Receptor-ligand occupancy
  - Functional activity

Never do a study in a non-relevant species!

Dose Selection for Toxicology Studies

Small Molecule	Biologics
• Based on dose-range finding studies • Establish the maximum tolerated dose	The high dose is the highest of the two below: • A dose that provides the maximum intended pharmacological effect in the preclinical species • A dose that provides approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic
Toxicity driven by unknown endpoints	**Pharmacology driven by known endpoints**

Duration of General Toxicology Studies to Support Clinical Development

Non-Oncology	Oncology
• Non- clinical studies of equal or longer duration needed to support clinical trials	• Treatment can continue according to the patient's response and can continue beyond the duration of the completed toxicology studies • Highest dose or exposure tested in the nonclinical studies **does not** limit the highest dose in cancer patients • Non-clinical data to support Phase 1 are sufficient for moving into Phase 2 • 3-month toxicology studies needed prior to Phase 3 trials

Reproductive Toxicology

Non-Oncology	Oncology
Embryo-fetal toxicity study needed prior inclusion of WOCBP	Only needed for marketing approval
Embryo-fetal toxicity study needed in 2 species	If positive in one species, study in second species not needed
Embryo-fetal development studies needed for genotoxic compounds	Not needed for genotoxic compounds
Special fertility studies needed prior to Phase 3 trials	Not needed. Assessment based on findings in general toxicity studies
Pre- and postnatal development studies needed for marketing approval	Not needed for marketing approval

Genotoxicity and Carcinogenicity

Non-Oncology	Oncology
Gene mutation assay needed prior to single dose in human further genotoxicity studies needed for multiple dose clinical trials	Genotoxicity studies are not needed for clinical development, but to support marketing
Carcinogenicity studies needed for marketing approval for drugs that are used chronically and/or repetitively	Carcinogenicity studies are not needed for compounds to treat patients with advanced cancer

Immunotoxicity and Photosafety

Immunotoxicity endpoints usually integrated in general toxicity studies are sufficient

For immuno-modulatory compounds additional endpoints should be included in general toxicology studies

Phototoxic potential should be assessed based on photochemical properties of the drug

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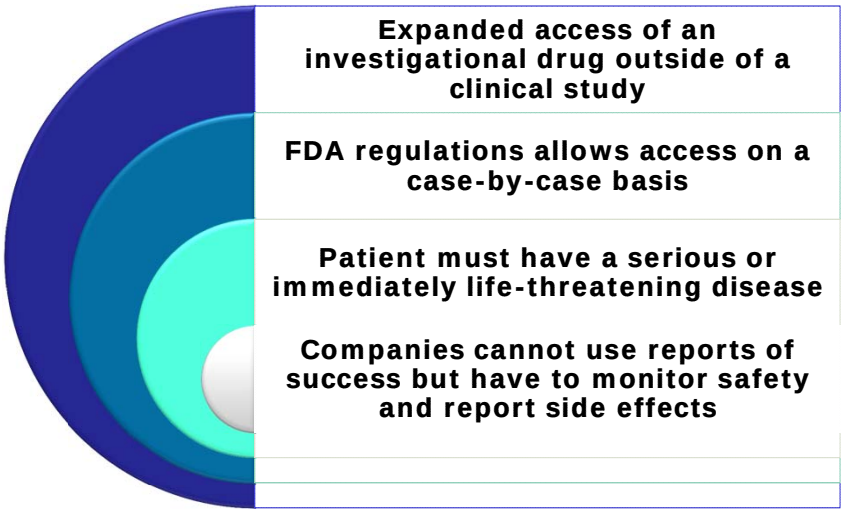
Compassionate Use (1)



Compassionate Use (2)

Gleevec was tested in 2500 people in clinical studies, but Novartis supplied the drug to 5000 additional patients under compassionate use provision

Following a report of the clinical trial results of Gleevec in a New York television station Novartis received 8000 phone calls in one hour

Source: USA today 2001

Combining Oncology Therapies

When given alone the cancer find ways to overcome the anticancer effect → **Combining multiple selective inhibitors**

If one signaling pathway is blocked the tumor activates another → **Designing compounds that inhibit multiple pathways**

Nonclinical Evaluations for Combinations

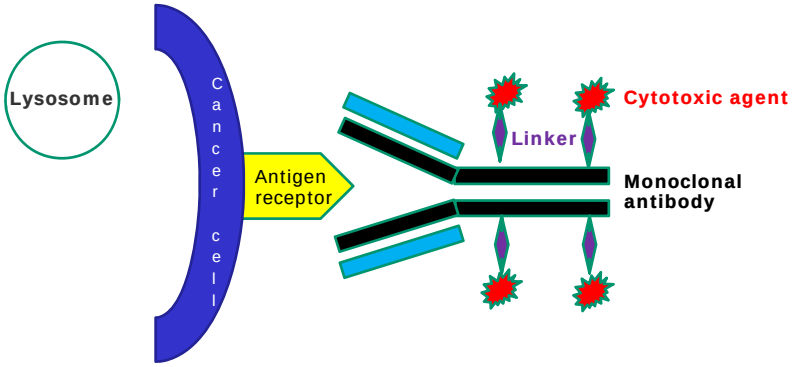
Each compound should be studied individually in toxicology studies

Data to support the rationale for a combination should be provided

If toxicity profile has been characterized in humans, a nonclinical study evaluating the combination is not needed

Approved compound + new drug

Antibody Drug Conjugates (ADCs)



- **Kadcyla (ado-trastuzumab + emtansine): for HER-2 positive breast cancer**
- **Adcetris (brentuximab + vedotin): for Hodgkin lymphoma and anaplastic large cell lymphoma**

Nonclinical Considerations for ADCs

- **DMPK**
  - Assays to detect the ADC, the antibody alone and the drug alone
  - Anti-drug-antibodies can be directed towards the antibody and/or the linker
  - Cross species metabolism needed for the drug
- **Safety Pharmacology**
  - Can be included in general toxicity study in relevant species
  - *In vitro* hERG assay needed for drug
- **Toxicology**
  - Biologically relevant species for ADC
  - Drug can be tested separately in a second species
- **Genotoxicity**
  - Needed for the drug

Antibody Drug Conjugates on the Rise

SP Miksinske and M Shapiro, AAPS Oct 18 2012
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341177.pdf

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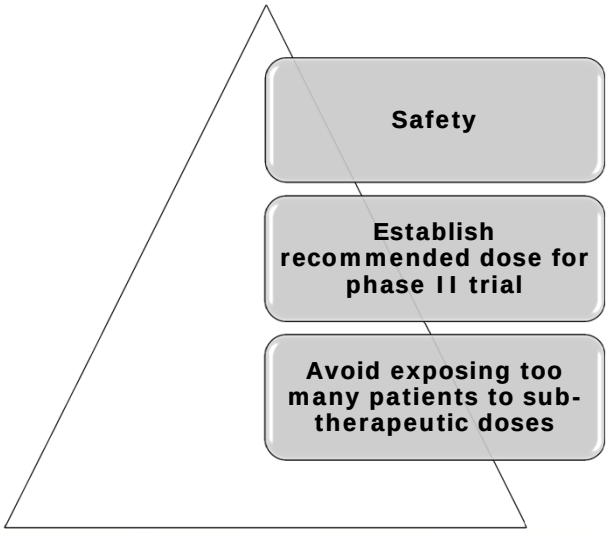
Objectives of a Phase I Study



Determination of Starting Dose for Phase 1

Dose should have pharmacological effects and be reasonably safe

For small molecules interspecies scaling of the animal dose to an equivalent human dose is usually based on body surface area

For biopharmaceuticals the minimally anticipated biologic effect level (MABEL) should be considered

Starting Dose for Non-Oncology Small Molecule Compounds

Determine NOAEL in most sensitive species

↓

Convert dose from mg/kg to human equivalent dose (HED)

↓

Apply safety margin of 10

Determination of Starting Dose for Small Molecule Oncology Compound

Determine dose severely toxic to 10% of rodents (STD_{10}) and convert to mg/m2

Is $1/10^{th}$ of the STD_{10} of rodents severely toxic to non-rodents?

NO → Starting dose

YES → **Determine non-rodent HNSTD** → Take 1/6 as starting dose

Example for Starting Dose Calculation

RAT

Dose mg/kg	Dose mg/m2	Findings	Effect Level
10	60	↓ WBCC	NOAEL
30	180	↓ WBCC, histopathology lesions with tendency of recovery	MTD
100	600	All of the above + 1 animal sacrificed moribund	STD_{10}

1/10 of STD_{10} = 60 mg/m² phase 1 starting dose

DOG

Dose mg/kg	Dose mg/m2	Findings	Effect Level
1	20	↓ WBCC	NOAEL
3	**60**	**↓ WBCC, histopathology lesions with tendency of recovery**	**MTD = HNSTD**
10	200	All of the above + 1 animal sacrificed moribund	Toxic Dose

Examples of 6 Escalation Steps

Step	Dose mg/m2	% increase (modified Fibonacci sequence)
1	60	100%
2	120	67%
3	200	50%
4	300	40%
5	420	30%
6	550	

Among 21 phase 1 trials in the US between 1992-2008 more than half needed 6 or more dose escalation steps (Tourneau et al. J Natl Cancer Inst 2009;101: 708 – 720)

MRSD versus MABEL

Maximum Recommended Starting Dose	Minimal Anticipated Biological Effect Level
• Based on toxicity • Determination of human equivalent dose based on body surface area • Application of safety factor	• Based on pharmacology • Need pharmacology relevant assays in human and animals (*in vitro* and *in vivo*) • Include pharmacokinetic/ pharmacokinetic modeling • Adjust for inter-species differences in affinity and potency
Highest dose thought to be safe	**Lowest dose thought to be active**

TeGenero Case: MRSD versus MABEL (Background)

- TeGenero AG founded in 2000 as a spin-off of the Medical School of the University of Wurzburg
- TGN1412, also known as CD28-Super MAB
- Intended for B cell chronic lymphocytic leukemia and rheumatoid arthritis
- Binds to CD28 and activates T cells without need for T cell receptor pre-activation resulting in IL-2 production = super-agonist
- First in human study in March 2006
- Within 70 minutes 6 volunteers were administered a 3-6 minute IV infusion of 0.1 mg/kg TGN1412
- Within 19 minutes volunteers had a systemic inflammatory response, became critically ill with multiple organ failure = cytokine storm
- One volunteer had all of his toes and tips of several fingers amputated
- All volunteers survived

Horvath CJ, Milton MN: The TeGenero incident and the Duff Report conclusions: a series of unfortunate events or an avoidable event? Toxicol Pathol 2009,37:372-383

TeGenero Case: MRSD versus MABEL (Phase 1 Starting Dose)

Maximum Recommended Starting Dose	Minimal Anticipated Biological Effect Level
• NOAEL: 50 mg/kg • HED: 16 mg/kg • 10-fold safety factor: 1.6 mg/kg • safety factor increased to 160-fold	• Including in vitro T-cell proliferation data from murine equivalent of TGN1412 • Adjust for inter-species differences in affinity and potency • Aim for initial 10% receptor occupancy (generally considered appropriate for agonist)
0.1 mg/kg starting dose	**0.001 mg/kg starting dose**

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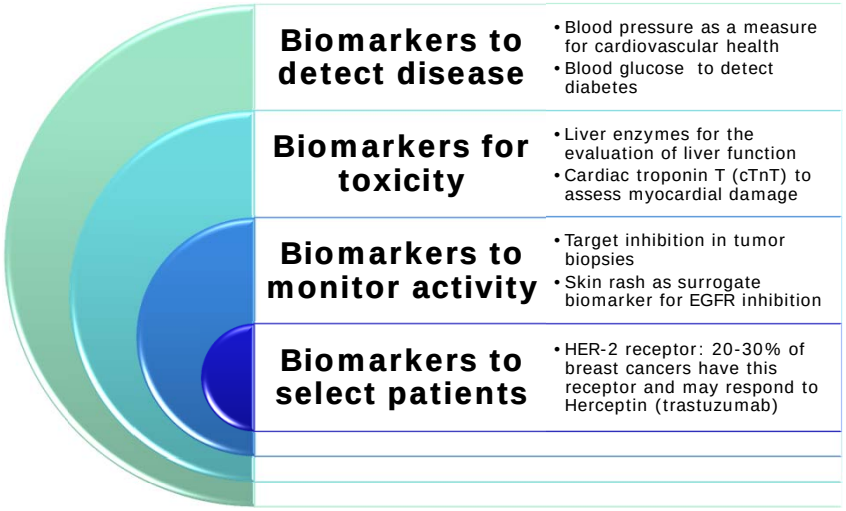
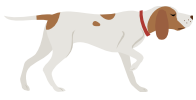
Identification of biomarkers



Biomarker through Development

inhibition of target in in vitro assays

inhibition of target in mouse tumor and/or surrogate (e.g. PBMC, skin)



target inhibition in surrogate (e.g. PBMCs, skin) at tolerated doses in toxicity study

inhibition of target in tumor biopsies and/or surrogates (e.g. PBMCs, skin)

Biomarker Example

- **AEE788: combined EGFR and VEGFR pathway inhibitor from Novartis**
- ***In vitro***
  - EGFR/ErbB-1: IC_{50} of 0.011µM
  - HER2/ErbB-2: IC_{50} of 0.22µM
  - VEGF-2/KDR: IC_{50} of 0.96µM
- **Phase 1**
  - Primary endpoint: MTD based on DLTs
  - Tumor biopsies
  - 2 skin biopsies, each before and after treatment. Second biopsy overlapping the wound from the first biopsy to assess VEGF pathway inhibition.
  - p-EGFR inhibition (IC_{50}): 0.033µM in skin and 0.0125µM in tumor
  - No inhibition of p-VEGFR-2 and cyclin D1 in tumor tissue at tolerated doses

Novartis concluded that AEE788 would provide no additional benefit for currently available EGRF and VEGF inhibitors and terminated further development

Source: Baselga et al. Clin Cancer Res; 18(22) November 15, 2012

What Drug for Which Patient?

Medication	Patient Subpopulation
Tarceva (erlotinib)	NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations (10% USA, 50% Asia)
Herceptin (trastuzumab)	HER-2 overexpressing breast cancer (20-30%)
Zelboraf (vemurafenib)	BRAF V600E mutation melanoma (50%)
Erbitux (cetuximab)	K-Ras mutation negative, EGFR expressing (60%) colorectal cancer

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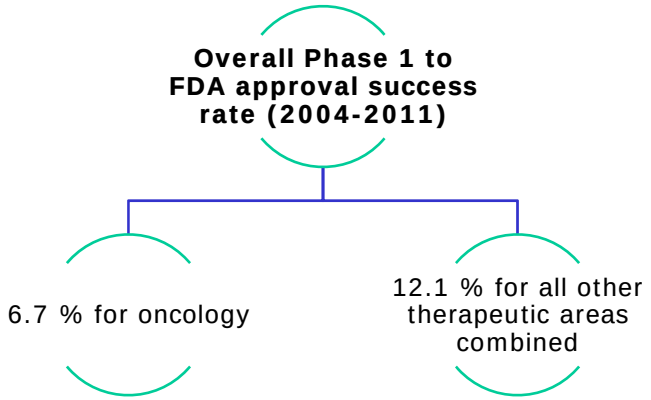

Source: Inside Bio Industry Analysis, David Thomas www.biotech-now.org
http://www.biotech-now.org/business-and-investments/2012/02/oncology-clinical-trials-secrets-of-success

Acknowledgements

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Abbreviations

ADC	=	antibody drug conjugate
AUC	=	area under the curve
BLA	=	biological license application
CHF	=	congestive heart failure
CDER	=	center for drug evaluation and research
CNS	=	central nervous system
CTA	=	clinical trial application
DLT	=	dose limiting toxicity
DMPK	=	drug metabolism and pharmacokinetics
ECG	=	electrocardiogram
EGFR	=	endothelial growth factor receptor
GEM	=	genetically engineered model
FDA	=	food and drug administration
FIM	=	first in man
hERG	=	human Ether-à-go-go-Related Gene
HED	=	human equivalent dose
HNSTD	=	highest non severely toxic dose
IND	=	investigational new drug
ICH	=	international conference on harmonization
LVEF	=	left ventricular ejection fraction
L	=	linker
MABEL	=	minimally anticipated biological effect level
MRSD	=	maximum recommended starting dose
NOAEL	=	no observed adverse effect level
NOEL	=	no observed effect level
MTD	=	maximum tolerated dose
NDA	=	new drug application
NSCLC	=	non-small cell lung cancer
PBMC	=	peripheral blood mononuclear cells
PK	=	pharmacokinetics
PD	=	pharmacodynamics
OS	=	overall survival
STD	=	severely toxic dose
VEGFR	=	vascular endothelial growth factor receptor
WBCC	=	white blood cell count