ANBL1821: *A Phase 2 Randomized Study of Irinotecan/Temozolomide/Dinutuximab with or without Eflornithine (DFMO) (IND# 141913) in Children with Relapsed, Refractory or Progressive Neuroblastoma*

Satellite Investigator Training

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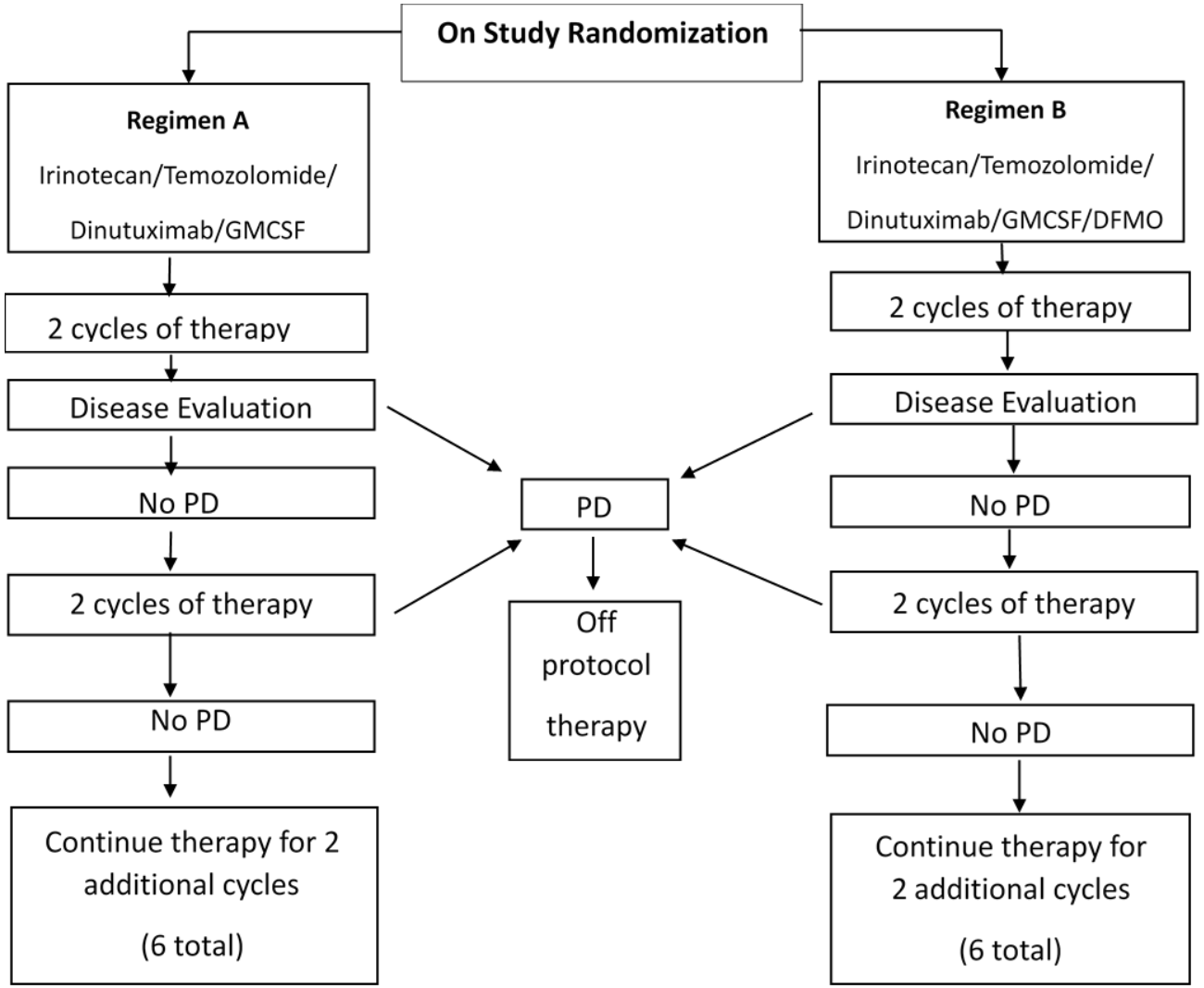
Current Study Schema



PD: Progressive Disease; CR: Complete Response; PR: Partial Response; MR: Minor Response; SD: Stable Disease

Study Goal

- To determine if adding difluoromethylornithine (DFMO, Eflornithine) to a chemo-immunotherapy backbone (dinutuximab, irinotecan and temozolomide) results in an improved response rate compared to dinutuximab, irinotecan and temozolomide in patients with relapsed or refractory neuroblastoma and therefore is a therapeutic regimen worthy of further testing in patients with newly-diagnosed high-risk neuroblastoma (NBL).

Relapsed Neuroblastoma

- Despite multiple improvements in front-line high risk neuroblastoma therapy, up to 50% of patients will fail to respond or relapse from front line therapy
- Recently a COG study (ANBL 1221) showed promising results combining traditional cytotoxic chemotherapy (temozolomide and irinotecan) with immunotherapy (dinutuximab + sargramostim)
- ANBL 1821 aims to improve on the ANBL 1221 results by the randomized addition of DFMO (difluoromethylornithine)

Regimen A: Temo/Irino/Dinutux/Sargramostim

- All cycles are 21 days
- **Days 1 to 5:** Temozolomide (orally) and Irinotecan
- **Days 2 to 5:** Dintuximab infusion (inpatient)
- **Days 6 to 12:** Sargramostim (subcutaneous)

Temozolomide and Irinotecan

- Generally well tolerated, some myelosuppression may be experienced
- Irinotecan induced diarrhea
  - All patients will be started on Cefixime (8 mg/kg/day PO once daily) 2 days before starting irinotecan and 3 days after for a total of 10 days as prophylaxis
  - Families should be aware of when and how to dose loperamide as needed for breakthrough diarrhea
  - Patients with persistent heavy diarrhea despite prophylaxis and loperamide use should be assessed for hydration status and their management discussed with the referring centre

Dinutuximab

- Chimeric antibody given by slow infusion
- Common infusional toxicities include pain, fever, rash and cough
- During infusions, patients require close nursing care with opioid infusions and other other supportive care
- Toxicities tend to resolve by time of discharge, but any new unexpected symptoms should be discussed with referring teams for consideration of reporting

Sargramostim (GM-CSF)

- Human recombinant glycoprotein that supports survival, clonal expansion, and differentiation of hematopoietic progenitor cells.
- Used to stimulate immune cells to increase activity against dinutuximab bound cells
- Given SC for 7 days following dinutuximab
- Common Toxicities: Headache, bone pain, fever, malaise
- *Local Skin Reactions*: Common, discuss strategies with referring team (rotating sites, avoiding insuflons, etc.)

Regimen B: Temo/Irino/Dinutux/Sargramostim

- All cycles are 21 days
- **Days -6 to 0 (Cycle 1 only):** DFMO orally 3 times daily
- **Days 1 to 7 (Cycle 2 and beyond):** DFMO orally 3 times daily
- **Days 1 to 5:** Temozolomide (orally) and Irinotecan
- **Days 2 to 5:** Dinutuximab infusion (inpatient)
- **Days 6 to 12:** Sargramostim (subcutaneous)
- **Days 15 to 21:** DFMO orally 3 times daily

DFMO

- Approved agent for treatment of Trypanosomiasis (sleeping sickness)
- irreversible covalent inhibitor of ODC1 protein6 with potential for anti-neuroblastoma activity through several pathways, including *MYCN*
- Has been shown to be well tolerated as monotherapy and in combination with cytotoxic therapy, with the primary dose limiting toxicity being diarrhea
- Given orally or by NG tube as powdered drug in sachets that caregivers dissolve in water at the time of administration
- The goal of DFMO inclusion in the study to assess if exposure to DFMO improves response rate to the dinutuximab/irinotecan/temozolomide backbone

DFMO

- Toxicities
  - Hearing Loss: Referring Centres will be responsible for monitoring and will be responsible for holding DFMO and restarting at a reduced dose
  - Diarrhea:
    - Families should be provided with education on the use of loperamide to treat DFMO-associated diarrhea
    - Severe Diarrhea without infectious cause and not controlled by loperamide administration may require DFMO to be held: Discuss with referring centre
- Patients admitted for complications should have DFMO CONTINUED routinely until discussion with referring centre

Summary

- ANBL 1821 attempts to improve outcomes in an often highly treated poor prognosis population
- While therapy will primarily be delivered by referring specialized childhood cancer programs, satellite teams should be aware of potential toxicities of therapy, particularly diarrhea
- DFMO is an investigational agent that may require administration in hospital for patients admitted for toxicities such as fever and neutropenia
- As always, all adverse events and toxicities should be discussed and shared with referring centres

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