

COG-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

FAST FACTS

Eligibility Reviewed and Verified By _____

MD/DO/RN/LPN/CRA Date _____

MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

- ___ 1. Prior to obtaining informed consent and enrolling a patient, a reservation must be made. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Reservations may be held for 7 calendar days.
- ___ 2. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **ten (10) calendar days** after the date of study enrollment. **Patients who are started on protocol therapy on a Phase 2 study prior to study enrollment will be considered ineligible.**
- ___ 3. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, echocardiogram, and bone marrow evaluations, if applicable, must be obtained within 3 weeks prior to start of protocol therapy (repeat the tumor imaging, echocardiogram, and/or bone marrows if necessary).**
- ___ 4. Age
Patients \geq 1 year of age at the time of enrollment are eligible for this study.
- ___ 5. Diagnosis
 - Histologic Diagnosis:
Patients must have had histologic verification of neuroblastoma or ganglioneuroblastoma or demonstration of neuroblastoma cells in the bone marrow with elevated urinary catecholamines [i.e. > 2 x upper limit of normal (ULN)], at the time of initial diagnosis.
 - Active Disease:
For the purposes of this study, aggressive multidrug chemotherapy is defined as chemotherapy including 2 or more agents that must include an alkylating agent and a platinum-containing compound as intended to treat high-risk disease. The doses of chemotherapy must be comparable to those used in frontline high-risk neuroblastoma therapies (examples include A3973, ANBL0532, ANBL09P1, ANBL12P1, and ANBL1531). Patients must have ONE of the following:
 - 1) First episode of recurrent high-risk disease following completion of aggressive multi-drug frontline high-risk therapy.
 - 2) First episode of progressive high-risk disease during aggressive multi-drug frontline high-risk therapy.
 - 3) Primary resistant/refractory disease (less than partial response by INRC) detected at the conclusion of at least 4 cycles of aggressive multidrug induction chemotherapy on or according to a high-risk neuroblastoma protocol (examples include A3973, ANBL0532, ANBL09P1, ANBL12P1, ANBL1531, etc.).

- Documentation of Disease:
Patients must have at least ONE of the following at the time of enrollment:
 - 1) Measurable tumor on MRI or CT scan. Measurable is defined as ≥ 10 mm in at least one dimension on spiral/helical CT that is MIBG avid or demonstrates increased FDG uptake on PET scan.
 - 2) MIBG-avid lesion detected on MIBG scan with positive uptake at a minimum of one site. This site must represent disease recurrence after completion of therapy, progressive disease on therapy, or refractory disease during induction.
 - 3) Patients with resistant/refractory soft tissue disease that is not MIBG avid or does not demonstrate increased FDG uptake on PET scan must undergo biopsy to document the presence of viable neuroblastoma. Biopsy is not required for patients who have a new site of soft tissue disease (radiographic evidence of disease progression) regardless of whether progression occurs while receiving therapy or after completion of therapy.
 - 4) Patients with bone marrow disease only will be eligible if they have **more than 5%** disease involvement (documented neuroblastoma cells) in at least one sample from bilateral bone marrow biopsies.

Note: Patients with elevated catecholamines (i.e. $> 2 \times$ ULN) **only** are NOT eligible for this study.

___ 6. Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients > 16 years of age.

See https://members.childrendoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

___ 7. Prior Therapy

- Primary refractory/resistant patients must have received at least 4 cycles of frontline high-risk chemotherapy. Frontline therapy may also have included surgery, chemotherapy, autologous SCT +/- MIBG, immunotherapy, radiotherapy, and retinoids but must NOT have received second line therapy for resistant/refractory, relapsed, or progressive disease. Patients who received intensified therapy for poor induction response or refractory disease (e.g. MIBG) will be considered to have received second line therapy and will not be eligible.
- Myelosuppressive chemotherapy: At least 14 days must have elapsed since completion of myelosuppressive therapy.
- Biologic (anti-neoplastic agents): Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications.
Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1 .
- XRT: No interim time prior to study entry is required following prior RT for non-target lesions. However, patients must not have received radiation for a minimum of 4 weeks prior to study entry at the site of any lesion that will be identified as a target lesion to measure tumor response. Lesions that have been previously radiated cannot be used as target lesions unless there is radiographic evidence of progression at the site following radiation or a biopsy done following radiation shows viable neuroblastoma. Palliative radiation while on study is not permitted.
- Stem Cell Transplants (SCT): Patients are eligible ≥ 6 weeks after autologous stem cell transplants or stem cell infusions (including stem cell infusions given as supportive care following 131I-MIBG therapy) as long as hematologic and other eligibility criteria have been met.
- ¹³¹I-MIBG therapy: Patients are eligible ≥ 6 weeks after therapeutic 131I-MIBG provided that all other eligibility criteria are met.
- Study specific limitations on prior therapy:
 1. Subjects who have previously received anti-GD2 monoclonal antibodies with or without retinoids for biologic therapy are eligible unless they have had progressive disease while receiving prior anti-GD2 therapy or progressed/relapsed within 3 months of receiving anti-GD2 therapy. However, eligible patients may NOT have received anti-GD2 monoclonal antibodies in combination with chemotherapy.
 2. Subjects who have received autologous marrow infusions or autologous stem cell infusions that were purged using monoclonal antibody linked to beads are eligible.
 3. Subjects who have previously received DFMO are eligible for this study provided they have not had progressive disease while receiving DFMO or progressed/relapsed within 3 months of completing DFMO.

___ 8. Concomitant Medications Restrictions

Please see [Section 4.3](#) for the concomitant therapy restrictions for patients during treatment.

Patients must not have received long-acting myeloid growth factors (e.g. pegfilgrastim) within 14 days of entry on this study. Seven days must have elapsed since administration of a short-acting myeloid growth factor.

9. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
For patients with solid tumors (without marrow involvement) including status post SCT:
 - Peripheral absolute neutrophil count (ANC) $\geq 750/\mu\text{L}$
 - Platelet count $\geq 75,000/\mu\text{L}$ (transfusion independent)
 Patients known to have bone marrow involvement with neuroblastoma are eligible provided that minimum ANC and transfusion independent platelet count criteria are met (as above). However, these patients are not evaluable for hematological toxicity.
- Adequate Renal Function Defined As:
 - Creatinine clearance or radioisotope GFR $\geq 70 \text{ mL/min/1.73 m}^2$ or
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

- Adequate Liver Function Defined As:
 - Total bilirubin $\leq 1.5 \times \text{ULN}$ for age **AND**
 - SGPT (ALT) $\leq 5.0 \times \text{ULN}$ for age ($\leq 225 \text{ U/L}$). For the purpose of this study, the ULN for SGPT is 45 U/L.
- Adequate Cardiac Function Defined As:
 - Shortening fraction of $\geq 27\%$ by ECHO, or
 - Ejection fraction of $\geq 50\%$ by ECHO or gated radionuclide study.
- Adequate Pulmonary Function Defined As:
 - No evidence of dyspnea at rest, no exercise intolerance, no chronic oxygen requirement, and room air pulse oximetry $> 94\%$ if there is a clinical indication for pulse oximetry. Normal pulmonary function tests in patients who are capable of cooperating with testing (including DLCO) are required if there is a clinical indication for determination. For patients who do not have respiratory symptoms, full PFTs are NOT required.
- Adequate Central Nervous System Function Defined As:
 - Patients with a history of CNS disease must have no clinical or radiological evidence of active CNS disease at the time of study enrollment
 - Patients with seizure disorders may be enrolled if seizures are well controlled on anti-convulsants
 - CNS toxicity $\leq \text{Grade } 2$

Assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

- ___ 1. **Pregnancy and Breastfeeding**
Men and women of childbearing potential and their partners must agree to use adequate contraception while enrolled on this study. Based on the established teratogenic potential of alkylating agents, pregnant women will be excluded from this study. Because of potential risks to breastfed infants due to drug metabolites that could be excreted in breast milk, female patients who are lactating must agree to stop breastfeeding or will otherwise be excluded from this study. Females of childbearing potential must have a negative pregnancy test to be eligible for this study.
- ___ 2. Patients with only elevated catecholamines (i.e. > 2 x ULN) are NOT eligible for this study.
- ___ 3. Patients must have been off pharmacologic doses of systemic steroids for at least 7 days prior to enrollment. Patients who require or are likely to require pharmacologic doses of systemic corticosteroids while receiving treatment on this study are ineligible. The only exception is for patients known to require 2 mg/kg or less of hydrocortisone (or an equivalent dose of an alternative corticosteroid) as premedication for blood product administration in order to avoid allergic transfusion reactions. The use of conventional doses of inhaled steroids for the treatment of asthma is permitted, as is the use of physiologic doses of steroids for patients with known adrenal insufficiency. Patients on any other immunosuppressive medications (e.g. cyclosporine, tacrolimus) are not eligible.
- ___ 4. Patients must not have received prior treatment with irinotecan and temozolomide.
- ___ 5. Patients must not have received enzyme-inducing anticonvulsants including phenytoin, phenobarbital, or carbamazepine for at least 7 days prior to study enrollment. Patients receiving non-enzyme inducing anticonvulsants such as gabapentin, valproic acid, or levetiracetam will be eligible. (See [Appendix III](#) for additional enzyme-inducing anticonvulsants and acceptable alternative options.)
- ___ 6. Patients who have received drugs that are strong inducers or inhibitors of CYP3A4 within 7 days prior to study enrollment are not eligible. See [Appendix IV](#) for a list of agents.
- ___ 7. Patients must not have been diagnosed with myelodysplastic syndrome or with any malignancy other than neuroblastoma.
- ___ 8. Patients with symptoms of congestive heart failure are not eligible.
- ___ 9. Patients must not have \geq Grade 2 diarrhea.
- ___ 10. Patients who are unable to tolerate oral/nasogastric/gastrostomy medications will not be eligible for this trial. Additionally, patients with significant malabsorption will not be eligible for this trial.
- ___ 11. Patients must not have uncontrolled infection.
- ___ 12. Patients with a history of Grade 4 allergic reactions to anti-GD2 antibodies or reactions that required permanent discontinuation of the anti-GD2 therapy are not eligible.
- ___ 13. Patients with a significant intercurrent illness (any ongoing serious medical problem unrelated to cancer or its treatment) that is not covered by the detailed exclusion criteria and that is expected to interfere with the action of study agents or to significantly increase the severity of the toxicities experienced from study treatment are not eligible.

INDUCTION STRATIFICATION FACTORS:

Patients will be randomized 1:1 to Regimen A (irinotecan/temozolomide/ dinutuximab) or Regimen B (DFMO + irinotecan/temozolomide/dinutuximab), with stratification according to the following 4 factors:

- Disease category (measurable vs. evaluable)
- Prior anti-GD2 therapy (prior exposure to anti-GD2 antibody vs. no prior exposure to anti-GD2 antibody)
- Prior DFMO therapy (prior exposure to DFMO vs. no prior exposure to DFMO)
- MYCN status (amplified vs. non-amplified vs. unknown)

REQUIRED OBSERVATIONS:

Required Observations in Regimen A Cycle 1

- a. History, physical exam with vital signs, performance status*
- b. Height, weight, BSA*
- c. CBC with differential and platelets (patients who experience Grade 4 neutropenia should have CBCs checked at least twice per week until recovery to Grade 3)*
- d. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus, albumin*
- e. ALT, total bilirubin*
- f. Pregnancy test (obtain for females of childbearing potential)
- g. ECHO or MUGA
- h. Audiogram or BAER – May be obtained within 3 weeks prior to the start of protocol therapy.
- i. Bilateral bone marrow aspirates and biopsies
- j. Cross sectional tumor imaging of original primary site and any non-osseous sites of disease involvement at study entry (MRI or CT) (submit for central review as soon as scan is obtained; see [Section 15.1](#) for imaging details for patients without measurable disease)
- k. ¹²³I-MIBG scan (submit for central review as soon as scan is obtained)
- l. Curie score profile (patients with MIBG avid disease; see [Appendix IX](#) for worksheet) (submit for central review as soon as scan is obtained)
- m. FDG-PET scan for patients with ¹²³I-MIBG non-avid disease (submit for central review as soon as scan is obtained)
- n. Specimens for correlative studies. Post-dinutuximab specimens should be collected at a single time point between Day 6 and Day 9. See [Section 14](#) and [Appendix X](#) for details.
- o. Faces Pain Scale Revised – can be done anytime on Day 1 of therapy. On Days 2-5 of therapy, should be performed at least 4 hours after the dinutuximab infusion has begun. See [Section 14.1.3](#) for additional detail.

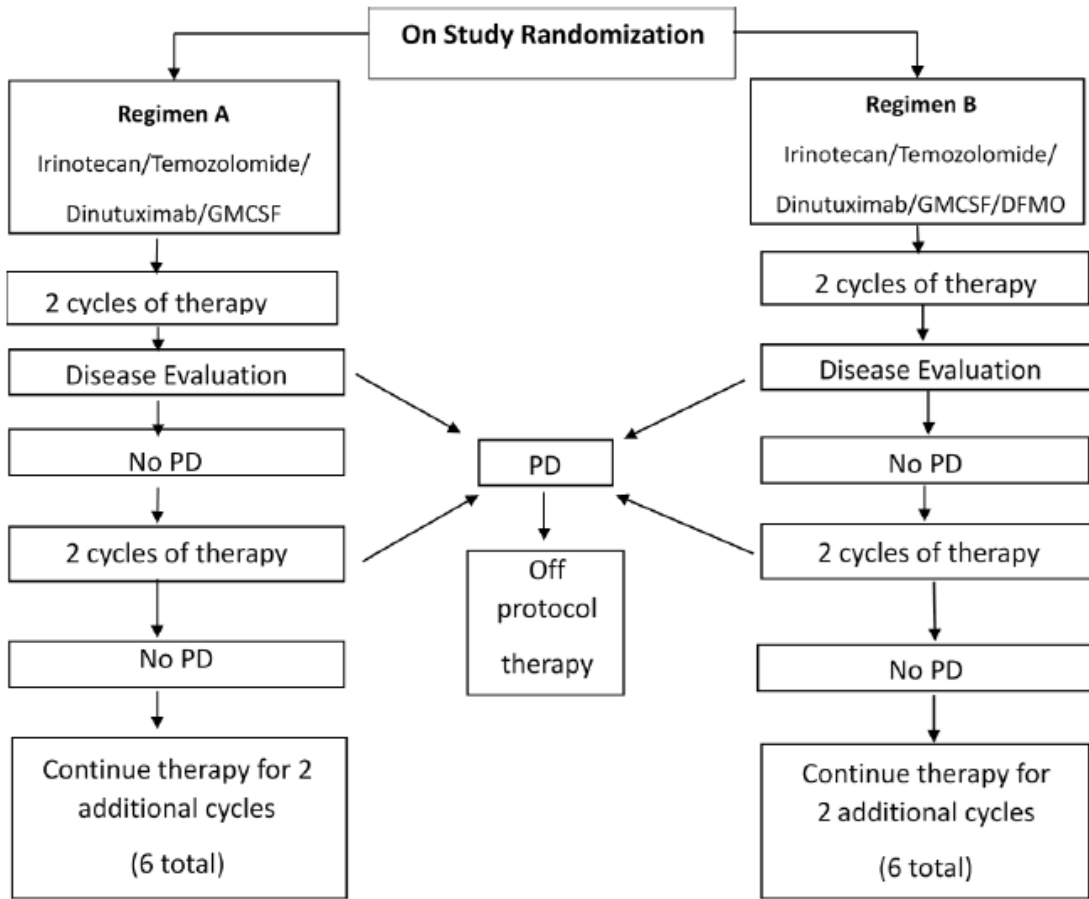
For Regimen A patients:

*These baseline studies must be repeated on Day 1 if not performed within 72 hours of Day 1.

For Regimen B patients

*These baseline studies must be repeated on Day -6 if not performed within 72 hours of Day 06.

**TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA: PATIENTS ENROLLED ON AMENDMENT 4 AND LATER**



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

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

See Appendix X: BIOLOGIC CORRELATIVE LAB STUDIES

Time Point	Sample Type			Tube Type / Sample Prep	Notes	Ship to	Section Number
Most recent biopsy performed before study registration	Biopsy of primary or metastatic site			Snap-frozen tumor material and paraffin-embedded tumor tissue	OPTIONAL <i>Banking</i>	BPC	14.2.2.2
Time point	Sample Type	Volume per tube	Quantity	Tube Type / Sample Prep	Notes	Ship to	Section Number
Any time bone marrow aspirate or tumor tissue is obtained	Biopsy of primary or metastatic site			Snap-frozen tumor material and paraffin-embedded tumor tissue	OPTIONAL <i>Banking</i>	BPC	14.2.2.2
	Bone marrow aspirate	3-5 mL	1 tube	Heparinized tube	OPTIONAL; Send fresh overnight <i>GD2 Biomarkers</i>	Reynolds	14.2.1
Pre-therapy	Blood ^{a, b}	2.5 mL	2 tubes	PAXgene RNA tube PAXgene DNA tube	OPTIONAL <i>Banking</i>	BPC	14.2.2.1
	Urine	15 mL		Clean-catch; transfer to sterile screw-cap vials	OPTIONAL; Freeze within 30 minutes <i>Banking</i>	BPC	14.2.2.3
	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day <i>Immune Phenotyping</i>	Emory	14.1.1
	Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma <i>Cytokine Analysis</i>	Emory	14.1.2

- a. If consent for blood biobanking is signed, please contact the Emory CCTDC immediately after patient enrollment to obtain PAXgene tubes (see Section 14.2.2.1 for contact information)
- b. A single blood sample is requested from each patient consenting to optional banking. This sample should be obtained prior to the start of therapy. The WBC count on the day of the blood draw should be $> 1,000/\text{mm}^3$