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CHILDREN'S ONCOLOGY GROUP

ANBL1821

A Phase 2 Randomized Study of Irinotecan/Temozolomide/Dinutuximab with or without Eflornithine (DFMO) ([redacted] in Children with Relapsed, Refractory or Progressive Neuroblastoma

A COG Groupwide Phase 2 Study

IND Sponsor for Eflornithine: COG

[redacted]

CONTACT INFORMATION		
For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (ie, patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

TABLE OF CONTENTS

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[redacted]

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[redacted]

AGENT	NSC#	Supplier
Eflornithine (DFMO)	337250	CPP
Irinotecan	616348	Commercial
Temozolomide	362856	Commercial
Dinutuximab	764038	Commercial
Sargramostim (GM-CSF)	613795	Commercial

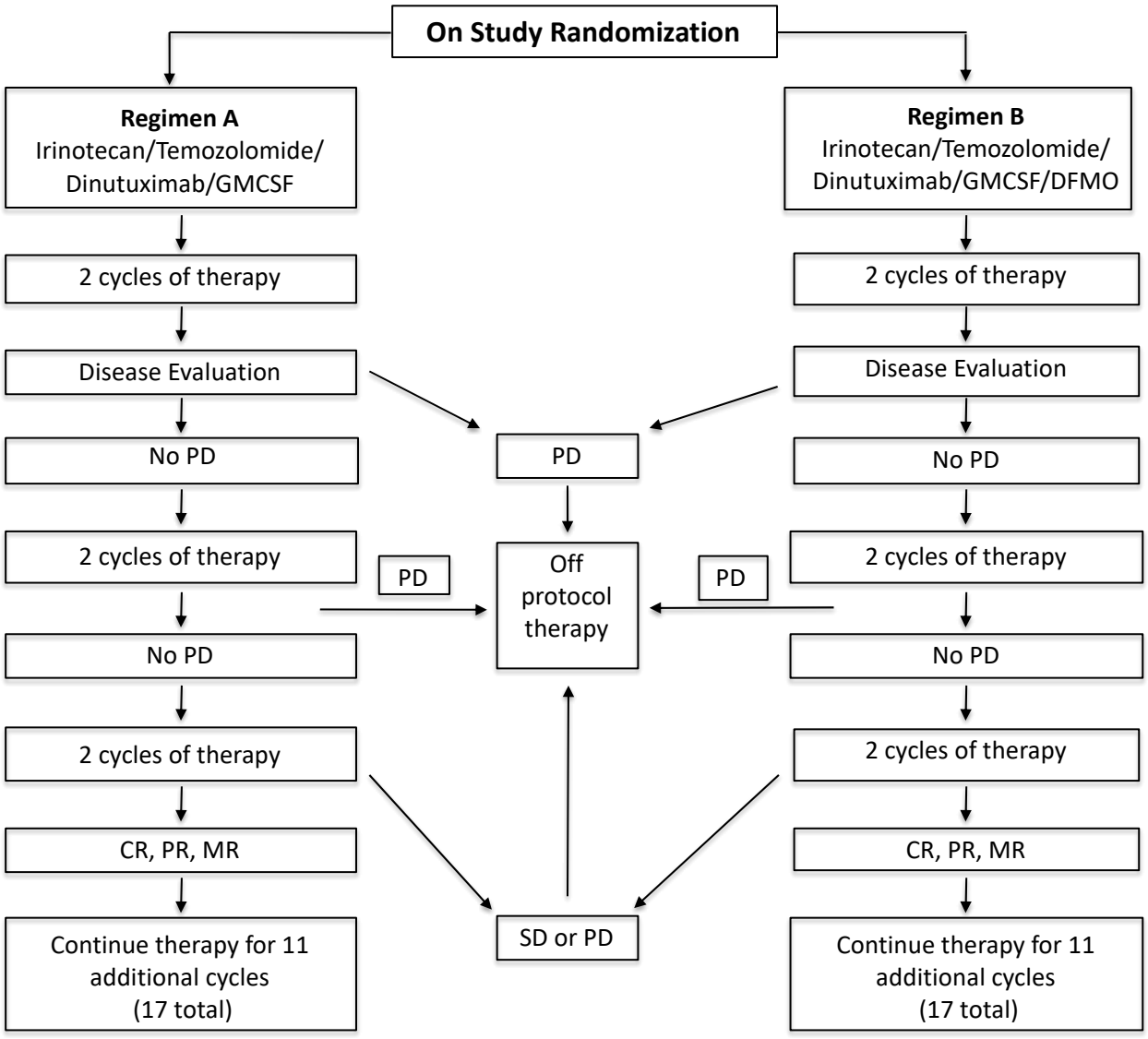
[redacted]
IND Sponsor for Eflornithine: COG

SEE SECTION 14.0 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

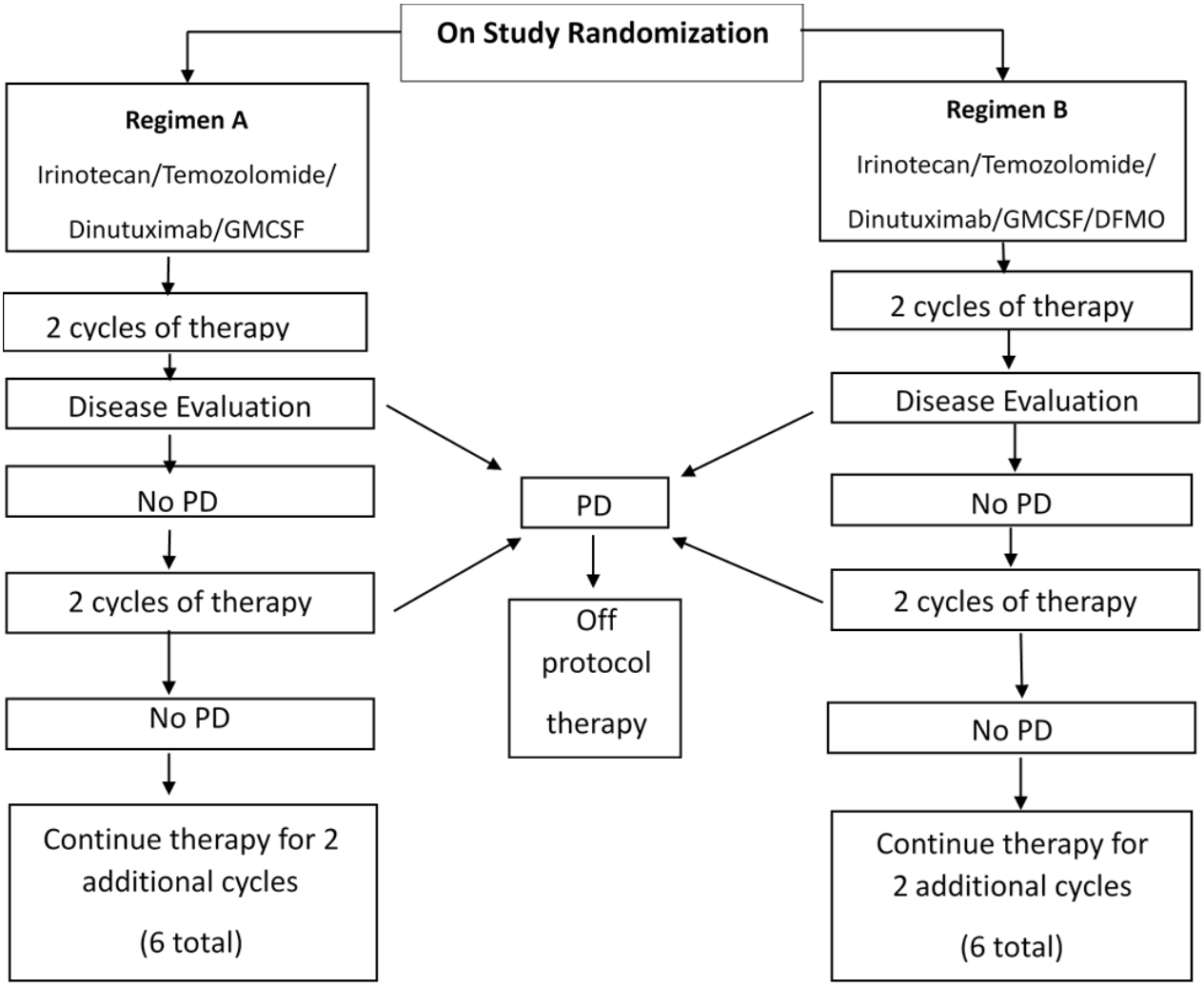
Long-term survival rates for children with high-risk neuroblastoma remain poor. Moreover, survivors experience significant immediate and late toxicities that limit further dose intensification of conventional chemotherapy and radiotherapy. Novel biological therapies are therefore needed. This randomized phase 2 study for patients with refractory or relapsed neuroblastoma is designed to compare response rates (RR) and progression free survival (PFS) for patients treated with dinutuximab, irinotecan and temozolomide alone compared to dinutuximab, irinotecan and temozolomide with difluoromethylornithine (DFMO, Eflornithine). The combination of dinutuximab, irinotecan, and temozolomide has shown promising activity in patients with refractory, relapsed, and progressive neuroblastoma, however the overall objective response rate on a Phase 2 trial of the regimen was less than 50%. This study proposes the addition of DFMO to the chemo-immunotherapy backbone. ODC1 is a downstream transcriptional target of MYCN and a key enzyme in the polyamine synthesis pathway. DFMO is an irreversible inhibitor of ODC1 and thus depletes essential polyamines necessary for tumor survival. DFMO has been studied alone and in combination with chemotherapy in patients with relapsed and refractory neuroblastoma and has shown no significant toxicity. Additionally, preclinical data support a role for DFMO in regulating the tumor microenvironment to reinstate anti-tumor immune responses. These data support the rationale to evaluate the addition of DFMO to the dinutuximab/irinotecan/temozolomide regimen for children with refractory, relapsed or progressive neuroblastoma. Should this trial prove successful, the DFMO/chemotherapy/immunotherapy regimen will be integrated into frontline induction therapy for future patients with high-risk neuroblastoma.

EXPERIMENTAL DESIGN SCHEMA: PATIENTS ENROLLED PRIOR TO AMENDMENT 4



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

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine whether administration of eflornithine (DFMO) in combination with 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.

1.2 Secondary Aims

1.2.1 To compare progression-free survival and overall survival between patients receiving dinutuximab, irinotecan and temozolomide with and without the addition of DFMO.

1.2.2 To define the toxicity profile of DFMO administered with dinutuximab, irinotecan and temozolomide.

1.3 Exploratory Aims

1.3.1 To characterize the immune and cytokine profiles of patients treated with DFMO/chemotherapy/dinutuximab combination and correlate with response to therapy.

1.3.2 To evaluate GD2 levels in tumor cells from patient bone marrow samples and correlate with response to therapy.

1.3.3 To explore whether the addition of DFMO to the dinutuximab and chemotherapy backbone affects pain as determined by patient report and opiate usage.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Despite improvements with intensified therapy, high-risk neuroblastoma (NBL) still portends a poor prognosis, with approximately 50% of patients failing to respond to therapy or relapsing, leaving an unmet critical need to improve upon current therapies with more tumor targeted regimens.[1, 2] The results of a randomized Phase 2 study of irinotecan/temozolomide in combination with either temsirolimus (mTOR inhibitor) or dinutuximab (GD2 targeted chimeric monoclonal antibody) for patients with relapsed or refractory NBL (ANBL1221) showed promising results for patients treated on the dinutuximab arm. In total, 22/53 patients (41.5%) had an objective response.[3] Sixteen (72.7%) of the patients with confirmed responses had partial response or better after the

first 2 cycles with best response seen by Cycle 6. However, this regimen is associated with several important toxicities. Grade 3 or higher pain was observed in 25% of patients assigned to irinotecan/temozolomide/dinutuximab.[3-5] This study represents an effort to improve upon the response rate observed in ANBL1221. The goal of this study is to utilize DFMO to improve response rates in combination with dinutuximab/irinotecan/temozolomide compared to those seen in patients assigned to receive dinutuximab/irinotecan/temozolomide alone. The hypothesis is that DFMO will improve the anti-tumor activity of the ANBL1221 regimen by depleting polyamines, enhancing chemosensitivity, and improving dinutuximab response through immunomodulatory effects on the tumor microenvironment.

Difluoromethylornithine (DFMO, Eflornithine) is an irreversible covalent inhibitor of ODC1 protein[6] with potential for anti-neuroblastoma activity through several pathways. Amplification of the *MYCN* oncogene in neuroblastoma is a predictor of poor outcome. Ornithine decarboxylase (ODC1, encoded by *ODC1*) is a transcriptional target of *MYCN* and the rate-limiting enzyme in polyamine biosynthesis. *ODC1* is not only a *MYC* target gene, but is itself somatically amplified in approximately 15% of neuroblastomas that harbor *MYCN* amplification, further deregulating polyamine signaling.[7] Polyamine homeostasis is essential for cell survival and has been implicated in the pathogenesis of many cancers, including neuroblastoma.[8] *MYCN* amplified tumors have coordinated deregulation of all polyamine regulatory enzymes, including ODC1.[9] *MYCN* non-amplified high-risk neuroblastomas have less profound pathway deregulation, but still demonstrate markedly altered regulation of the rate-limiting polyamine enzyme ODC1, that even in the absence of *MYCN* amplification predicts poor prognosis.[7, 10] While ~40% of high-risk NBL have *MYCN* amplification, expression data assessing "MYC signatures" support the concept that hyperactive MYC signaling occurs in most, if not all, high-risk tumors.[11-13] A COG supported study also showed that a subset of *MYCN* non-amplified primary NBLs have high *C-MYC* protein expression; outcomes for patients with tumors with this feature were poor.[14] Similarly, expression data show that polyamine signaling, which is coordinately regulated by MYC, is broadly deregulated in NBL and correlates with survival.[7] Expression of ODC1, the rate-limiting enzyme in polyamine biosynthesis and the target of DFMO, is not only correlated with survival when analyzed in all NBL patients, but in high-risk patients only, and in high-risk patients whose tumors are absent *MYCN* amplification.[7] Beyond depriving MYC-driven tumor cells of essential polyamines to induce stress, emerging evidence shows a role for arginine-polyamine signaling in maintaining a tumor-permissive and immune-hostile microenvironment.[15]

The goal of this study is to utilize DFMO to improve response rates in combination with dinutuximab/irinotecan/temozolomide compared to those seen in patients assigned to receive dinutuximab/irinotecan/temozolomide alone. DFMO covalently and irreversibly inhibits ODC1. *ODC1* is somatically amplified in a subset of NBL tumors, justifying targeting this enzyme with DFMO. Therefore, this randomized 2-arm study will allow for a direct comparison of chemo-immunotherapy to the same regimen with the addition of DFMO. With the low toxicity profile of DFMO, its MYCN-targeting effects, and the immunomodulatory effects that may potentiate antibody efficacy, DFMO warrants further investigation in combination with neuroblastoma-specific immunotherapy such as dinutuximab. This trial proposes the addition of DFMO to the ANBL1221 backbone of irinotecan/temozolomide/dinutuximab with the hypothesis that DFMO will improve the anti-tumor activity of the ANBL1221 regimen by depleting polyamines, enhancing

chemosensitivity, and improving dinutuximab response through immunomodulatory effects on the tumor microenvironment.

Despite the early success of the dinutuximab/chemotherapy combination in relapsed and refractory neuroblastoma, less than half of all patients assigned to this regimen had an objective response, and biomarkers of response to this chemo-immunotherapy regimen, as well as DFMO, remain to be identified. The effects of DFMO on NK cell number and function are currently unknown; however, prior work supports NK cell activation as a potential mechanism of activity.[16] As the effects of DFMO on key effector cells regulating antibody dependent cellular cytotoxicity (ADCC) deserve further investigation, peripheral blood mononuclear cells (PBMCs) will be collected to assess immune cell subsets during Course 1 of therapy, with a focus on NK fractions. The planned 7-day single agent lead-in with DFMO provides the opportunity to gain specific information about immune cell subsets prior to DFMO treatment, after 7 days of daily DFMO, and prior to chemo-immunotherapy. This trial will allow for the exploration of such biomarkers in a controlled fashion given that the DFMO with chemo-immunotherapy is being compared to chemo-immunotherapy alone.

Rationale for irinotecan, temozolomide, and dinutuximab backbone
ANBL1221 showed that irinotecan/temozolomide/dinutuximab (I/T/DIN) has significant activity when used at first declaration of refractory or relapsed disease. The randomized portion of the trial used a "pick the winner" design to select the preferred molecularly-targeted anti-cancer agent (temsirolimus or dinutuximab) that merited further study. At interim analysis, among the 17 patients assigned to I/T/DIN, 9 had objective responses (5 CR, 4 PR). Responses were observed in patients with both relapsed disease (5/10; 3 PR, 2 CR) and refractory disease (4/7; 3 CR, 1 PR).[3] Among I/T/DIN responders, prior frontline therapy included high dose chemotherapy with stem cell rescue in 5 and anti-GD2 therapy in 3 patients. While I/T/DIN was shown be the optimal combination for further study based on the *a priori* definitions that were part of the selection design, the confidence intervals around the 53% response rate were wide (95% CI: 0.31, 0.74). Therefore, the protocol was amended to permit enrollment of an additional 36 patients, all of whom were to be treated with I/T/DIN. An overall objective response rate of ~41.5% (95% CI: 0.29, 0.55) was observed.[4] Of the 53 patients assigned to the regimen in total, 51 received I/T/DIN therapy. Among these, 22 demonstrated objective responses, including 11 with complete response (CR) and 11 with partial response (PR). In addition, 22 had stable disease (SD) and 7 had progressive disease (PD).[4, 5]

I/T/DIN therapy was generally well tolerated; however, several important toxicities were noted.[4, 5] Of the 51 patients evaluable for toxicity, 13 (25%) had ≥ Grade 3 pain, 8 (16%) had ≥ Grade 3 diarrhea, and 4 (8%) had ≥ Grade 3 vomiting. Neutropenia (≥ Grade 3) was observed in 14 (27%), ≥ Grade 3 thrombocytopenia in 5 (10%), and ≥ Grade 3 fever/infection in 11 (22%). One patient experienced Grade 4 hypoxia and required mechanical ventilation for more than 24 hours. A second patient required discontinuation of dinutuximab therapy due to bronchospasm. One patient developed Grade 3 motor neuropathy which recovered 6 weeks following discontinuation of dinutuximab therapy. One patient died of sudden death 2 days following completion of the 14th cycle of dinutuximab based therapy and cause of death was undetermined despite all investigations including full autopsy. While the response rate to this regimen is quite promising, there remains room for improvement in terms of both response rate and regimen-associated toxicity.

2.2 Preclinical Studies

There is preclinical evidence that the activity of DFMO is related to both cancer cell intrinsic and immunomodulatory mechanisms, making it appealing in this combination setting. Complementary neuroblastoma tumor models demonstrate a benefit for DFMO treatment. Preclinical data recurrently demonstrate anti-tumor activity for DFMO alone and in combination with chemotherapy in mouse models of neuroblastoma, both transgenic models driven by *MYCN* and xenografts of genomically diverse human neuroblastomas.[7, 17] These studies have used 1 gram% DFMO in drinking water, with measured DFMO intake providing an exposure of ~7,000 mg/m^2/day human equivalent dose (HED) when allometrically scaled from rodent to human. DFMO monotherapy was studied in the *TH-MYCN* transgenic neuroblastoma model at doses of 0.25, 0.5 and 1 gram% DFMO ad libitum. Only 1 gram% DFMO extended survival compared to vehicle treated mice ($p < 0.0001$; M. Hogarty, personal communication). Similarly, in a syngeneic mouse NXS2 neuroblastoma model only 1 gram% DFMO extended survival, whereas 0.25 and 0.5 gram% did not ($p < 0.05$; A. Yu, personal communication). Serum concentrations in the mouse models varied widely but maximal concentrations measured were ~50 μM at 0.25 gram%, ~120 μM at 0.5 gram%, and ~140 μM at 1 gram% DFMO (only the higher dose demonstrated anti-tumor activity).

The mechanisms of anti-tumor activity for DFMO beyond depletion of essential polyamines remain under investigation; however, inhibition of oncogenic protein translation and modulation of immune surveillance have been identified as key contributors. The global protein translation factor eIF5A is inactive until activated by a modification requiring the polyamine spermidine. This hypusination step has been shown to be inhibited in neuroblastoma cell lines by DFMO at > 150 μM exposures, with concomitant reduction in global protein translation (M. Hogarty, personal communication).

Along with the tumor intrinsic effects of inhibiting polyamine biosynthesis to induce tumor cell stress, DFMO also influences the tumor microenvironment (TME). Polyamines and their precursor, arginine, regulate the activity of tumor associated lymphocytes, macrophages, NK cells and neutrophils in favor of tumor growth.[18] Through increased ornithine intake and increased synthesis of polyamines, tumor cells increase arginase (ARG1) activity. ARG1 activity contributes to the induction of immunosuppressive ARG1-expressing tumor associated macrophages (TAMs) and the inhibition of anti-tumor NK cells.[19] DFMO inhibits the activity of ARG1 directly as well as indirectly by inhibiting ODC1 to prevent increased ornithine consumption.[15] These ARG1 inhibitory properties credential a role for DFMO in restoring NK cell activity for ADCC.[20] In preclinical mouse models, DFMO given with a polyamine transport inhibitor (AMXT1501) had potent antitumor effects against Myc-driven carcinomas grown in an immune competent mouse, but had no effect on the same tumors grown in an immunocompromised mouse, demonstrating an effect of DFMO through the immune cells themselves.[21] This aspect of the anti-tumor activity of DFMO may be particularly relevant in high-risk neuroblastoma, where the tumor microenvironment has increased regulatory T-cells as well as inhibitory TAMS.[22, 23] Given that anti-GD2 antibody therapy has shown marked efficacy in combination with chemotherapy at relapse[3, 24] and that a major barrier to further improve outcomes is likely the immunosuppressive TME, the immunomodulatory effects of DFMO and its potential to enhance dinutuximab response deserve to be investigated.

2.3 Adult Studies

DFMO is FDA approved for the treatment of Trypanosomiasis, specifically "sleeping sickness" encephalitis and is only distributed in Africa through the World Health Organization (WHO). The adult recommended IV dose is equivalent to 12,000-18,000 mg/m^2/day[25] and the bioavailability of the oral dose is 55%.[26] The main toxicities at the adult MTD were gastrointestinal, with diarrhea, nausea and vomiting in up to 40% of patients.[26] Seizures were seen in 7% of adults treated for encephalitis, which was likely related to the CNS inflammation from infection.[25, 27] Neurologic toxicity has only rarely been reported in cancer trials with DFMO, specifically in patients with gliomas.[28-31] Ototoxicity, defined by modest hearing loss across a range of frequencies, is seen with high dose chronic exposures, increases with older age and is reversible.[32, 33] Interestingly, it appears to affect patients with normal hearing at baseline more than those with baseline hearing deficits.[33] Regular audiologic assessments will be performed on this trial to monitor for this toxicity.

A large trial to assess DFMO safety in trypanosomiasis used a dose of 600 mg/kg/day IV divided every 6 hours, and included 226 children less than 15 years of age.[27]. Despite the high doses of DFMO used in this study, and the debilitated status of many of the patients, toxicity was acceptable. Grade 3 or 4 toxicities were rare and seen in 6.5% of patients. The most common were fever, diarrhea and bacterial infection (all in less than 6% of the patients treated). Neurologic events were seen in this population, although most were Grade 2 or less. Grade 3 or 4 seizures or confusion occurred in 4.8 and 4% of patients, respectively. Grade 1 and 2 toxicities including abdominal pain and headache were frequent. Fever and injection site reactions were also common.[27]

DFMO has been studied extensively in adults with cancer. A Phase 1 trial (n=22) evaluated oral DFMO as a single agent at doses ranging from 3 to 21 g/m^2/day divided every 6 hours.[32] GI and hematologic side effects were seen. Nausea, diarrhea and anorexia were seen in about 65% of patients but were graded as moderate; only 1 patient discontinued DFMO due to GI symptoms. Anorexia was more significant and common at the highest dose level of 21 g/m^2/day. The dose limiting toxicity was reversible thrombocytopenia seen in patients who had received prior chemotherapy. Plasma DFMO concentrations with this dosing reached low mM concentrations sufficient to inhibit ODC activity in vitro. The recommended single agent Phase 2 dose was 9,000 mg/m^2/day (=300 mg/kg/day, orally) divided every 6 hours for patients previously treated with chemotherapy.[32]

A Phase 2 study of DFMO for patients with colorectal or small cell lung cancer tested this dose level (9,000 mg/m^2/day) in a 21-day (out of 28 days) or 28-day continuous regimen.[34, 35] The former schedule was associated with reduced toxicity and better tolerability.[35] A Phase 1/2 study for patients with metastatic breast carcinoma also identified 9,000 mg/m^2/day (divided three times a day) as the MTD of DFMO given orally for 14 days followed by a 14-day rest period.[34] This regimen was well tolerated with only two patients experiencing Grade 3 diarrhea. No other Grade 3 or higher toxicities were observed. Hematologic toxicity was mild (Grade 1-2 anemia, Grade 1 thrombocytopenia) and no transfusions were required. No significant ototoxicity was seen. Only a single patient, who received 18 cycles of DFMO, developed asymptomatic 5-10 dB loss at high frequencies.[34] No objective responses were seen on either trial.[34, 35]

In a Phase 2 trial for patients with malignant glioma, DFMO was given at 10,800 mg/m^2/day divided every 8 hours for 14 days out of 21 days.[28] Grade 3 or 4 diarrhea

was seen in 4 patients (4%) and was controlled with supportive care or by dividing the daily dose over 4-6 times per day. Grade 3 ototoxicity was noted in 12 of 86 patients and was more common in older patients and those exposed to loud noises. Twenty patients (45%) with anaplastic glioma achieved stable disease or better with four patients (9%) demonstrating partial response and 9 (20%) experiencing minor response. Six (17%) patients with GBM experienced stable disease or better with 2 (5.5%) each achieving partial response and minor response.[28]

DFMO has been studied in combination with chemotherapy and radiation therapy. In a phase 1/2 study of DFMO with chemotherapy, 70 adult patients were treated with either standard carcinoma chemotherapy regimens (32 patients) or DFMO in combination with standard chemotherapy regimens. DFMO was given orally at a dose of 5,100 mg/m^2/day divided three times a day. Chemotherapy regimens included tamoxifen, cyclophosphamide-methotrexate-5-fluorouricil (5-FU), cyclophosphamide-vincristine-methotrexate-5FU, doxorubicin-cyclophosphamide with or without cis-platinum.[36] There were no significant differences in hematological toxicities, however, while transient GI toxicities (anorexia, nausea, vomiting, diarrhea) were slightly more common among patients treated with DFMO, these were mainly mild, reversible, and were not dose-limiting. Ototoxicity was dose-limiting with 19% of patients having severe hearing loss (55-80dB); 16% of patients discontinued DFMO therapy for this reason. [36]

Several randomized trials studied the addition of DFMO to radiotherapy or post-radiation chemotherapy regimens for newly diagnosed patients with high-grade gliomas.[29-31] Patients with glioblastoma multiforme (GBM) (n=231) were randomized to receive either standard or hyperfractionated radiation with or without concomitant oral DFMO at 5,400 mg/m^2/day continuously for 1 week prior throughout radiation therapy.[31] The DFMO regimens were well tolerated. Fatigue and GI toxicity were seen more frequently, but most toxicities were Grade 1 or Grade 2. Grade 3 ototoxicity was seen in 3 of 116 patients who received continuous DFMO. There was no improvement in survival compared to radiation alone (standard or hypofractionated).[31] Two randomized trials added oral DFMO at 9,000 mg/m^2/day to post-radiation chemotherapy (procarbazine, lomustine and vincristine; PCV) for either GBM or anaplastic astrocytoma (AA) patients.[29, 30] In both trials, a total of 259 patients (134 GBM, 125 AA) were randomized to receive PCV with oral DFMO given for 14 days out of 28 days. Two patients with AA had Grade 3 sensorineural hearing loss and no ototoxicity above Grade 2 tinnitus was reported in patients with GBM. GI toxicity was more common in the DFMO arm, with diarrhea occurring only in the DFMO+PCV arm (6% v. 0%). No improvement in survival was seen with the addition of DFMO for GBM patients but improved progression-free survival was observed in AA patients who received DFMO (6.3 yrs v. 5.1 yrs).[29, 30]

2.4 Pediatric Studies

The first report of DFMO in children with cancer was reported in 1981 when 8 children with relapsed/refractory ALL received either methylglyoxal bisguanylhydrazone (MGBG, an Amd1 inhibitor) or MGBG and DFMO combined. DFMO was dosed at 3,000 to 15,000 mg/m^2/day over 3-5 days. No toxicity was reported in these 8 patients and half of patients had responses, defined by complete clearance of peripheral blasts.[37] DFMO has been evaluated as a single metronomic agent for one cycle followed by administration in combination with etoposide in a multi-center Phase 1 trial in patients with relapsed/refractory neuroblastoma.[38] Doses of 500-1500 mg/m^2 PO twice daily were very well tolerated and no DLTs were observed.[38]

The NANT N1201 Phase 1 study evaluated the combination of DFMO with celecoxib, cyclophosphamide and topotecan.[39] It included a 7-day lead-in with DFMO (three times per day) and celecoxib (250 mg/m^2/dose orally BID) on Days 1-7. Cyclophosphamide (250 mg/m^2/dose IV) and topotecan (0.75 mg/m^2/dose IV) were given once daily for 5 days on Days 8-12. DFMO was continued on Days 8-21 and celecoxib was continued on Days 8-28 to complete one cycle. DFMO was dose escalated from 3,000 mg/m^2/day, divided TID, to 9000 mg/m^2/day, divided TID. Twenty-four patients were accrued to this study with a median age of 6.8 years. Seven patients had *MYCN* amplified tumors, 13 had *MYCN* non-amplified tumors, and in 4 cases MYCN status was unknown. Twelve patients (50%) had tumor-involved bone marrow at study entry. Patients received 124 total cycles (range, 1-17).

The 4-drug combination was generally well tolerated at all dose levels.[39] The combination of DFMO at dose level 3A (6,750 mg/m^2/day divided 3 times a day) in combination with cyclophosphamide (250 mg/m^2/dose daily x 5 days) and topotecan (0.75 mg/m^2/dose daily x 5 days) and celecoxib (250 mg/m^2 daily) was defined as the recommended Phase 2 dose. This dose of DFMO will be used in this study. Observed toxicities were primarily hematologic and fever related. There were three Cycle-1 DLTs over 4 dose levels (hematologic, in the setting of tumor progression; anorexia; transaminase elevation). One patient had Grade 3 hearing loss which was reversible and did not recur with retreatment. Three (12.5%) patients had Grade 3 diarrhea but none were DLTs. The observed objective response rate [complete response (CR) + partial response (PR)] was 13%. The CR+PR+minor response (MR) rate was 26%, and the CR+PR+MR+stable disease (SD) rate was 69%. Median OS on this trial was 36.2 months, PFS was 13.3 months, and time-to-progression of 19.8 months, at the most recent analysis.[39]

2.5 Dosing Rationale

In this trial, DFMO will be dosed orally. The bioavailability of orally administered DFMO ranges from 50-60% in multiple studies.[26] The dose of DFMO to be used for this trial (6,750 mg/m^2/day divided 3 times a day orally) was the recommended phase 2 dose determined on the NANT consortium N2012-01 trial of DFMO in combination with cyclophosphamide, topotecan and celecoxib. The half-life of DFMO is 3-4 hours when delivered orally, therefore, a TID dosing regimen provides continuously higher plasma concentrations to optimize systemic polyamine depletion. DFMO will be given at this dose during therapy.

Starting with Amendment 2A, DFMO will be given on a discontinuous basis, allowing for a 7-day break without DFMO administration in each cycle, similar to the dosing used in the NANT N2012-01 trial. Four of the first eight patients enrolled on the DFMO containing arm (Regimen B) of this study with available ototoxicity data developed documented Grade 3 hearing loss from their baseline. Hearing loss is a known toxicity of DFMO and is typically reversible. Prior studies have shown that the risk of DFMO-associated ototoxicity is decreased when the DFMO is administered in an intermittent fashion, with a 7-14 day break per cycle. At similar or higher dosing compared to that used in ANBL1821, the incidence of Grade 3 or higher hearing loss with interrupted dosing was less than 5%[40, 30, 29] Similarly, in the NANT2012-01 trial, DFMO dosed at 3000-9000 mg/m^2/day for 21 days out of a 28-day cycle resulted in only 1 of 24 patients experiencing new Grade 3 hearing loss. This hearing loss was reversible and did not recur with re-treatment. [39] The NANT2012-01 trial was conducted in a relapsed NBL population similar to that of ANBL1821 supporting that intermittent dosing of

DFMO may decrease the risk for significant ototoxicity. Therefore, given the incidence of hearing loss seen initially on this study with continuous dosing, this trial will now include a 7-day break in DFMO dosing to decrease the chances of additional hearing loss. Additionally, DFMO will be held at first detection of significant hearing loss.

DFMO PK data for lower DFMO doses in the NMTRC phase 1 study was linear between 1,000 and 3,000 mg/m^2/day with mean C_{max} ranging from 40 μM to 120 μM.[38] On the NANT N2012-01 trial, mean C_{min} was measured at about 20 μM, 90 μM, 135 μM and 130 μM at dose levels of 3,000; 4,500; 6,750 and 9,000 mg/m^2/day, respectively.[39] The estimated C_{max} (2-3 times C_{min} with these PK parameters) would therefore be > 270 μM at 6,750 mg/m^2/day DFMO, the dose to be studied here. This is above the DFMO exposure threshold at which *in vitro* studies demonstrate effects on protein translation, and at which *in vivo* studies demonstrate anti-tumor activity and immunomodulatory effects on the TME.[7]

In this trial, DFMO will be combined with the backbone regimen of irinotecan and temozolomide with dinutuximab, which has been shown to be tolerable on the ANBL1221 study.[3] The irinotecan/temozolomide regimen has fewer hematologic toxicities compared to cyclophosphamide/topotecan used in the previous NANT trial that combined DFMO with chemotherapy.[3, 41] This will likely decrease delays in treatment in a heavily pre-treated population. To limit unexpected or severe toxicities, this trial will closely monitor for increased toxicity on the DFMO arm compared to the standard arm consisting of dinutuximab, irinotecan, temozolomide and sargramostim, with specific attention to DFMO-related toxicities, including diarrhea and hearing loss. Starting with Amendment 4, patients will receive up to 6 cycles of protocol therapy due to changes in drug supply.

2.6 Rationale for Correlative Studies

2.6.1 Rationale for studying immune cell subsets and cytokine profiles

Despite the early success of the dinutuximab/chemotherapy combination in relapsed and refractory neuroblastoma, less than half of all patients assigned to this regimen had an objective response, and biomarkers of response to this chemo-immunotherapy regimen, as well as DFMO, remain to be identified. The effects of DFMO on NK cell number and function are currently unknown, however prior work supports NK cell activation as a potential mechanism of activity.[16] As the effects of DFMO on key effector cells regulating antibody dependent cellular cytotoxicity (ADCC) deserve further investigation, peripheral blood mononuclear cells (PBMCs) will be collected to assess immune cell subsets during course 1 of therapy, with a focus on NK fractions. The planned 7-day single agent lead-in with DFMO provides the opportunity to gain specific information about immune cell subsets prior to DFMO treatment, after 7 days of daily DFMO, and prior to chemo-immunotherapy. This trial will allow for the exploration of such biomarkers in a controlled fashion given that the DFMO with chemo-immunotherapy is being compared to chemo-immunotherapy alone.

An understanding of the baseline status and the nature of changes in activity of immune effector cells in response to immune modulating drugs will be important for the design of future passive immunotherapy regimens for patients with neuroblastoma, specifically, the number of NK and NK-T cells, T cell subsets and expression of NK activation and inhibitory receptors present in patient blood and the influence that DFMO therapy has on these subsets. Preclinical data support a

role for arginine-polyamine signaling in maintaining a tumor-permissive and immune-hostile microenvironment.[15] DFMO regulates this process in favor of reinstating anti-tumor immune response through depleting arginine-regulated immune cell suppression.[15, 19] Therefore, DFMO may also regulate the immune system to enhance antibody dependent cell-mediated cytotoxicity (ADCC) that is critical for dinutuximab effects. Cytokines released by cancer cells or by cells of the tumor microenvironment have a multitude of effects that can either promote tumor cell growth or can potentiate the effect of immunotherapy.[42] It is clear that the polyamine/arginine pathway suppresses the "inflammatory" host state in favor of tumor growth.[19, 21, 43] Thus understanding the changes in cytokine repertoires during the single agent DFMO therapy week and during administration of DFMO with chemo-immunotherapy may identify critical immune biomarkers that are augmented or expressed with the addition of DFMO and positively contribute to therapy response.

2.6.2 Rationale for analysis of GD2 levels in bone marrow

The ganglioside composition of neuroblastoma cells was studied decades ago,[44] yet much remains to be learned regarding the relationship between the presence of gangliosides on neuroblastoma cells (particularly GD2) and response to anti-GD2 based therapy. Lack of GD2 positivity has been observed in 13% of neuroblastoma specimens obtained from children with INSS Stage 4 disease at diagnosis.[45] Assays to assess GD2 presence in real-time are lacking and utilization of an FFPE block has been hampered by loss of antigen. Dr. C. Patrick Reynolds has developed a bi-color flow cytometry assay to detect and quantify GD2 positive neuroblastoma tumor cells in bone marrow aspirates.[46] This allows for sorting of GD2+ and GD2- cells from bone marrow aspirates for further research analysis, such as genomics. Determining GD2 expression in bone marrows may elucidate mechanisms of chemo-immunotherapy resistance as it pertains to differences in cell surface antigen expression for primary and metastatic sites. Determining changes in GD2 expression in bone marrows over time may also provide insight into mechanisms of therapy response and resistance, as well as DFMO and chemotherapy effects specifically on GD2 tumor cell expression.

2.6.3 Rationale for evaluating the effects of DFMO on pain

The randomized design of this study provides a unique opportunity to explore how patient reported outcomes (PROs), or proxy report for young patients, differ with the addition of DFMO. Patient and proxy reported outcomes, including pain, are increasingly important tools which can be used to support the superiority of a treatment arm in randomized studies. GD2 expression in normal tissues is restricted to cerebellar neurons, skin melanocytes and peripheral pain fibers.[47] A well-known side effect of dinutuximab is reversible peripheral pain, necessitating the use of intravenous pain medication, often narcotics, during the dinutuximab infusion.[48-51] Given the role of ODC1 in normal physiology associated with environmental signals including touch,[52-54] this pathway has been investigated for its potential impact on allodynia (pain due to a stimuli which does not normally induce pain, such as touch). Silva *et al.* reported that allodynia and edema induced by Freund's adjuvant injection in paws of rats induced expression and activity of ODC1[55] and that injection of the ODC1 product putrescine or other polyamines induced allodynia and edema in the absence of other stimuli. DFMO

administration decreased allodynia and edema induced by adjuvant in an animal model of inflammation-induced pain.[55]

Preliminary studies evaluating rat models of allodynia demonstrate that DFMO may reduce dinutuximab induced pain sensation (personal communication, Dr. Alice Yu). Furthermore, pro-inflammatory cytokines have been linked to neuropathic pain and the immunomodulatory effects of DFMO may influence such cytokine levels.[56] Therefore, the association between inflammatory serum cytokine levels (IL1, IL6, TNF-alpha, IFN-gamma, etc.), pain, and DFMO therapy merit evaluation. This exploratory aim is to examine the change in pain during dinutuximab infusion in the patients on the DFMO arm compared to the control arm as determined by the Faces Pain Scale. Patients over the age of 5, and proxy for those under the age of 5, will complete the Faces Pain Scale-Revised on Day 1 of chemotherapy with irinotecan and temozolomide, and then daily during the dinutuximab infusion. This will be measured during Cycles 1, 2, 4, and 6. Patients enrolled prior to Amendment 4 will also have the Faces Pain Scale-Revised collected during Cycle 12 of therapy. The Faces Pain Scale-Revised is a simple visual scale validated to provide real-time pain assessment in the pediatric and adolescent and young adult (AYA) population.[57] It has been recommended as the superior PRO measure for pain in pediatric populations based on its excellent psychometric properties and responsiveness to change.[58] The scale scores pain based on a visual cue on a scale of 0 to 10. Pain will also be assessed by measuring the amount of intravenous narcotic administered during the dinutuximab infusion. Patients will also be evaluated for differences in pro-inflammatory cytokine levels during dinutuximab infusion.

2.6.4 Potential use of banked specimens for future research

The goal of this study is to define the impact of polyamine depletion by DFMO on cancer cell survival and response to chemo-immunotherapy, specifically dinutuximab/irinotecan/temozolomide. This trial represents a unique opportunity to collect and bank clinically-annotated specimens from patients treated with chemo-immunotherapy alone or in the setting of polyamine depletion. These valuable specimens will serve as a unique resource for exploratory scientific projects. Future investigation of these specimens may include determination of tumor MYCN expression, ODC1 expression and promotor genotypes, as well as urine polyamine markers, and correlation to response to identify predictive biomarkers.

Stored biological specimens will be available for further and novel research upon initial findings, general technical advances, and newly acquired knowledge of the underlying biology of these tumors. These clinically-annotated tumor, blood, and urine specimens will be available to external investigators interested in studying effects of polyamine depletion and chemo-immunotherapy in neuroblastoma and will provide opportunities for interdisciplinary and collaborative basic research.

2.7 Importance of trial and impact on future clinical practice

Survival of patients with relapsed high-risk neuroblastoma remains poor despite multi-modality therapy. Moreover, despite improvement in overall survival for high-risk neuroblastoma, an unacceptable percentage of patients experience early disease

progression or have disease that is refractory to current induction therapy. It is therefore critical to integrate agents that target specific biologic pathways critical to neuroblastoma survival. DFMO has shown activity against neuroblastoma in both *in vitro* and *in vivo* animal models and has been shown to be safe and tolerable in combination with chemotherapy in pediatric Phase 1 trials. This will be the first attempt to add an immune modifying agent to dinutuximab in combination with chemotherapy. This study will serve as a foundation for future study of such a combination as part of frontline Induction therapy in this important pediatric disease.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue

to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE**' a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster

with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:
- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 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. It is strongly recommended that patients do not start treatment on a Friday or weekend. **Patients who are started on protocol therapy on a Phase 2 study prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.6 Patient Stratification

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)

Please refer to Appendix II for a flowchart for determining the appropriate stratum.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. 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.

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).

3.2.1 Age

Patients ≥ 1 year of age at the time of enrollment are eligible for this study.

3.2.2 Diagnosis

3.2.2.1 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.

3.2.2.2 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.).

3.2.2.3 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 x ULN) **only** are NOT eligible for this study.

3.2.3 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.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.4 Prior Therapy

3.2.4.1 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.

3.2.4.2 Myelosuppressive chemotherapy: At least 14 days must have elapsed since completion of myelosuppressive therapy.

3.2.4.3 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.

3.2.4.4 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.

3.2.4.5 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 ^{131}I-MIBG therapy) as long as hematologic and other eligibility criteria have been met.

3.2.4.6 ^{131}I-MIBG therapy: Patients are eligible ≥ 6 weeks after therapeutic ^{131}I-MIBG provided that all other eligibility criteria are met.

3.2.4.7 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.

3.2.5 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.

3.2.6 Organ Function Requirements

3.2.6.1 Adequate Bone Marrow Function Defined As:

For patients with solid tumors (without marrow involvement) including status post SCT:

- Peripheral absolute neutrophil count (ANC) ≥ 750/μL

- Platelet count ≥ 75,000/μL (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.

3.2.6.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 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 [59] utilizing child length and stature data published by the CDC.

3.2.6.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x ULN for age **AND**
- SGPT (ALT) ≤ 5.0 x ULN for age (≤ 225 U/L). For the purpose of this study, the ULN for SGPT is 45 U/L.

3.2.6.4 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by ECHO, or
- Ejection fraction of ≥ 50% by ECHO or gated radionuclide study.

3.2.6.5 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.

3.2.6.6 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 ≤ Grade 2

3.2.7 Exclusion Criteria

3.2.7.1 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.

3.2.7.2 Patients with only elevated catecholamines (i.e. > 2 x ULN) are NOT eligible for this study.

3.2.7.3 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.

3.2.7.4 Patients must not have received prior treatment with irinotecan and temozolomide.

3.2.7.5 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.)

3.2.7.6 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.

3.2.7.7 Patients must not have been diagnosed with myelodysplastic syndrome or with any malignancy other than neuroblastoma.

3.2.7.8 Patients with symptoms of congestive heart failure are not eligible.

3.2.7.9 Patients must not have ≥ Grade 2 diarrhea.

3.2.7.10 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.

3.2.7.11 Patients must not have uncontrolled infection.

3.2.7.12 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.

3.2.7.13 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.

3.2.8 Regulatory Requirements

3.2.8.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.8.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Patients with high risk neuroblastoma, either primary resistant/refractory or in first relapse or progression, will be randomized to receive one of two arms of therapy: Regimen A consisting of dinutuximab, irinotecan, temozolomide and sargramostim (GM-CSF), or Regimen B, which will include the addition of DFMO to dinutuximab, irinotecan, temozolomide, and GM-CSF. Arms will be balanced with respect to disease category (measurable vs. evaluable), prior anti-GD2 therapy, prior DFMO therapy, and *MYCN* amplification status.

Each cycle of therapy will be 21 days in length, with the exception of Regimen B Cycle 1. Patients randomized to Regimen B will receive a 7-day DFMO pretreatment phase for Days -6 to 0 prior to the start of chemotherapy on Day 1 of Cycle 1 to deplete essential polyamines.

Patients enrolled prior to Amendment 4:
Disease assessments will occur after Cycles 2 and 4. Patients with stable disease or better on disease assessments after Cycles 2 and 4 will continue on protocol therapy. After Cycle 6, patients who achieve a minor response (MR) or better on disease evaluation will continue on protocol therapy. After Cycle 6, patients may remain on study for up to 17 cycles (approximately 1 year of therapy) as long as they maintain a minor response or better on disease assessments performed after every 4th cycle. An end of therapy disease evaluation will be performed after Cycle 17 for patients who complete all planned protocol therapy.

Patients enrolled on Amendment 4 or later:
Disease assessments will occur after Cycles 2 and 4. Patients with stable disease or better on disease assessments after Cycles 2 and 4 will continue on protocol therapy for a maximum of 6 cycles. An end of therapy disease evaluation will be performed after Cycle 6 for patients who complete all planned protocol therapy.

4.2 General Guidelines for therapy

See the Parenteral Chemotherapy Administration Guidelines (CAG) for children on the COG website at:
https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

For COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.2.1 Central line

All patients will have a central venous line placed to facilitate administration of therapy.

4.2.2 Diarrhea prophylaxis

Cefixime (8 mg/kg/day PO once daily) or an available equivalent oral cephalosporin (e.g. cefpodoxime 10 mg/kg/day PO divided BID, maximum dose 400 mg/day) should be started 2 days prior to the first dose of irinotecan and continued until 3 days after the last dose of irinotecan for a total of 10 days in each cycle.

See Appendix V for specific guidelines for supportive care measures for patients who develop therapy-associated diarrhea. Patients receiving prolonged exposure to antibiotics who develop diarrhea should have stool samples evaluated for evidence of infection (viral, C. difficile, etc.). Patients should be tested for infectious etiologies if they have fever with diarrhea, bloody diarrhea, or other concerns for infection.

4.2.3 Pneumocystis jiroveci pneumonia (PJP) prophylaxis

Patients **must** receive PJP prophylaxis during study therapy per institutional guidelines.

4.2.4 Other supportive care

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary.

Use of ototoxic drugs (furosemide, vancomycin, aminoglycosides) should be avoided when possible during this therapy. Reasonable alternatives should be used if they exist.

Note: Steroids (dexamethasone) may not be used as an anti-emetic. Single dose of aprepitant can be used if necessary for anti-nausea; however, multiple day aprepitant regimen may result in moderate CYP3A4 inhibition and should be avoided if reasonable alternatives exist.

4.3 Concomitant Therapy

4.3.1 Chemotherapy or Immunomodulating agents

No other systemic anti-cancer or immunomodulatory therapy (including steroids) will be permitted. Pharmacologic doses of systemic corticosteroids should be used ONLY for life-threatening conditions (i.e. life-threatening allergic reactions and anaphylaxis such as bronchospasm, stridor) unresponsive to other measures. **The use of dexamethasone as an anti-emetic is not permitted.** Corticosteroid therapy can be used as a premedication for transfusion in patients known to have a history of transfusion reactions or for treatment of an unexpected transfusion reaction

(hydrocortisone 2 mg/kg or less or an equivalent dose of an alternative corticosteroid). **The use of steroids during protocol therapy requires clear justification and documentation.**

4.3.2 External Beam radiotherapy
Radiotherapy to localized painful lesions is not permitted on study.

4.3.3 Surgery
Surgical resection or debulking of soft tissue disease is allowed any time after completion of the post-Cycle 6 disease evaluation. Submission of resected residual tumor material per Section 14.2.2.2 is strongly encouraged.

4.3.4 Cytokines or growth factors (G-CSF, Interferon, etc.) not included in the Treatment Plan are prohibited during protocol therapy.

4.3.5 CYP3A4 active agents
See Appendix IV for a list of CYP3A4 active agents.

Irinotecan is a substrate for CYP3A4 (major) and CYP2B6 (major). Patients who have received drugs that are strong inducers or inhibitors of CYP3A4 within 7 days prior to study enrollment are not eligible. The use of strong inhibitors or inducers of CYP3A4 (Appendix IV) and CYP2B6 (e.g. carbamazepine) should be avoided for the duration of protocol therapy. Consult drug information references for further information.

In addition, concomitant use of BCRP inhibitors (cyclosporine, eltrombopag, gefitinib), and UGT1A1 inhibitors (diclofenac, ketoconazole, probenecid, silibinin, nilotinib, and atazanavir) should be avoided due to potential increased risk of irinotecan toxicity.

Moderate inducers or inhibitors of CYP3A4 (Appendix IV) should also be avoided during protocol therapy, if reasonable alternatives exist.

4.4 Regimen A Cycle 1

4.4.1 Therapy Delivery Map –CYCLE 1 Cycle 1 lasts 3 weeks (21 days).	_____ Patient COG ID number _____ DOB

Begin Cycle 2 on Day 22 of Cycle 1 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 5.0 for dose modifications. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temozolomide (TEMO)	PO or via NG or Gtube	For patients ≥ 0.5 m^2: 100 mg/m^2/dose For patients < 0.5 m^2: 3.3 mg/kg/dose See dosing table in Appendix VI.	Days 1 - 5	Max dose = 200 mg Round doses to the nearest 5 mg when using capsules. **Administer at least 1 hour prior to IRIN administration.** Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).
Irinotecan (IRIN)	IV over 90 minutes	50 mg/m^2/dose	Days 1 - 5	Administer at least 1 hour after temozolomide, see Section 4.4.3.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	Days 2 - 5	* Infusion duration may be extended up to 20 hours if needed. Start immediately following NS bolus and irinotecan. See Section 4.4.3 for detailed administration guidelines, including premedications and monitoring during the infusion.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 mcg/m^2/dose	Days 6 - 12	See Section 4.4.3 for administration guidelines.

Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	TEMO ___ mg	IRIN ___ mg	DIN ___ mg	GM-CSF ___ mcg	Studies
			Enter calculated dose above and actual dose administered below				
		1	___ mg	___ mg			a-o
		2	___ mg	___ mg	___ mg		d, o
		3	___ mg	___ mg	___ mg		d, o
		4	___ mg	___ mg	___ mg		d, o
		5	___ mg	___ mg	___ mg		d, o
		6				___ mcg	n
		7				___ mcg	
		8				___ mcg	c, d, e
		9				___ mcg	
		10				___ mcg	
		11				___ mcg	
		12				___ mcg	
		15					c, d, e
		21					
		22	Begin Cycle 2 on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).				

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in Regimen A Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

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. ^{123}I-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 ^{123}I-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.

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

This listing only includes evaluations necessary to address the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Regimen A Cycle 1

4.4.3 Treatment Details for Regimen A Cycle 1 (3 weeks = 1 cycle)

Drug doses should be calculated based on the BSA using height and weight obtained within 1 week prior to the beginning of each cycle.

Suggested administration schedule for chemotherapy and dinutuximab (Days 2-5):

- At hour 0: patient should receive oral temozolomide.
- At hour 1: patient should start IV irinotecan over 90 minutes, and on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 1 hour.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.

Temozolomide: PO daily (NG or G-tube administration is allowed)
Days: 1-5
Dose: Round doses to the nearest 5 mg when using capsules. See dosing table in Appendix VI.

For patients ≥ 0.5 m^2: 100 mg/**m^2/dose**
For patients < 0.5 m^2: 3.3 mg/**kg/dose**
MAX dose = 200 mg

Substitution of IV Temozolomide is not permitted.

Sequencing: when giving with irinotecan, administer temozolomide first and wait 1 hour before giving irinotecan.

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended to prevent nausea and vomiting. When using temozolomide capsules, the dose should be rounded to the nearest 5 mg (round 2.5 mg down, see Appendix VI). For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist. If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose should be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

Administration of oral temozolomide should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures.

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules

Regimen A Cycle 1

needed for the full course must be dispensed at one time. See Section 6.5 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: 50 mg/m^2/dose (regardless of BSA)
Note: Irinotecan should be administered at least 1 hour after the temozolomide has been given.

Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates.

See the Parenteral Chemotherapy Administration Guidelines (CAG) for special precautions, suggestions for patient monitoring, and hydration on the COG website at:
https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf

Dinutuximab: IV over 10 hours* daily
Days: 2-5
Dose: 17.5 mg/m^2/dose

Note: Due to the increased risk of capillary leak and respiratory compromise with dinutuximab administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of dinutuximab. **Before starting dinutuximab**, please obtain a copy of management recommendations for anaphylaxis and hypotension available in Appendix XI and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

Refer to Section 4.4.4 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 1 hour. Bolus should be given concurrently with irinotecan infusion. On Day 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

*The infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of dinutuximab antibody has not been delivered. Antibody administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of dinutuximab is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection (preferred) or IV over 2 hours daily
Days: 6 through 12
Dose: 250 mcg/m^2/dose

Start sargramostim on Day 6 any time after the completion of Day 5 dinutuximab.

The standard route of administration is subcutaneous; in extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.

Sargramostim dose will be held if the total white cell count is > 50,000/μL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/μL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications based on Toxicities.

4.4.4 Premedication and Supportive Care recommended for the prevention of anticipated toxicities associated with dinutuximab

Neuropathic pain, allergic reactions, and fever are commonly seen in patients receiving this antibody. Institutional guidelines for supportive care during this portion of therapy should be followed. The use of the following premedications are recommended:

- IV hydration: Administer NS 20 mL/kg IV over 1 hour just prior to each dinutuximab infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to dinutuximab infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without difficulty, may consider removing the continuous opioid infusion rate in between dinutuximab doses (when dinutuximab is not infusing).
- Recommended starting dose of analgesics:

- Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of dinutuximab infusion. At the same time, start a continuous morphine infusion of 0.02 mg/kg/hr with bolus doses of 0.01 mg/kg/dose q15 minutes prn for pain.
- If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of dinutuximab. At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/hour for opioid naïve patients) with bolus doses of 0.002 mg/kg/dose q15 minutes prn for pain.
- If fentanyl PCA is used, recommend fentanyl 1 mcg/kg 10 minutes prior to starting dinutuximab infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
- Doses should be titrated as needed in accordance with institutional guidelines.

For patients unable to use a PCA, a continuous basal infusion of morphine (or alternative medication) and as-needed boluses of the same medication may be used. Starting doses of the basal infusion and boluses should be based on patient weight, institutional standard practices, and doses required by individual patients for treatment of pain associated with previous interventions.

Have immediately available during the dinutuximab infusion:

a. Albuterol and oxygen
b. Epinephrine
c. Hydrocortisone: Use only for life-threatening reactions (hypotension, bronchospasm, angioedema involving the airway) not responsive to other measures.

Monitoring during the dinutuximab infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until dinutuximab infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.4.5 Additional guidance

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Use of furosemide should be avoided when feasible due to ototoxicity concerns.

- Corticosteroid therapy should be used only for life-threatening conditions (i.e. treatment of increased intracranial pressure in patients with CNS tumors, symptomatic bronchospasm, stridor unresponsive to other measures or life-threatening allergic reactions). Corticosteroids will impair the immune response that is a critical part of the protocol therapy. **The use of steroids at any time during immunotherapy requires clear justification and documentation.**

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

- Cytokines or growth factors (G-CSF, Interferon, etc.) not included in the Treatment Plan are prohibited during immunotherapy.

Following completion of this cycle, Cycle 2 starts on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

4.5 Regimen A Cycle 2 and Subsequent Cycles

4.5.1 Therapy Delivery Map –CYCLE 2 and Subsequent Cycles Each cycle lasts 3 weeks (21 days).	_____ Patient COG ID number _____ DOB

Begin each cycle on Day 22 of the previous cycle or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 5.0 for dose modifications. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temozolomide (TEMO)	PO or via NG or Gtube	For patients ≥ 0.5 m^2: 100 mg/m^2/dose For patients < 0.5 m^2: 3.3 mg/kg/dose See dosing table in Appendix VI.	Days 1 - 5	Max dose = 200 mg Round doses to the nearest 5 mg when using capsules. **Administer at least 1 hour prior to IRIN administration.** Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).
Irinotecan (IRIN)	IV over 90 minutes	50 mg/m^2/dose	Days 1 - 5	Administer at least 1 hour after temozolomide, see Section 4.5.3.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	Days 2 - 5	* Infusion duration may be extended up to 20 hours if needed. Start immediately after completion of NS bolus and irinotecan infusions. See Section 4.5.3 for detailed administration guidelines, including premedications and monitoring during the infusion.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 mcg/m^2/dose	Days 6 - 12	See Section 4.5.3 for administration guidelines.

Cycle # _____ Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	TEMO ___mg	IRIN ___mg	DIN ____ mg	GM-CSF ___mcg	Studies	
			Enter calculated dose above and actual dose administered below				Cycle 2	Subsequent cycles
		1	____mg	____mg			a-e, l, m	a-e, m
		2	____mg	____mg	____mg		d, m	d, m
		3	____mg	____mg	____mg		d, m	d, m
		4	____mg	____mg	____mg		d, m	d, m
		5	____mg	____mg	____mg		d, m	d, m
		6				___mcg		
		7				___mcg		
		8				___mcg	c	c
		9				___mcg		
		10				___mcg		
		11				mcg		
		12				mcg		
		15					c	c
		21					f-k	f-k
		22	Begin next cycle on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).					

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Regimen A Cycle 2 and Subsequent Cycles

4.5.2 Required Observations in Regimen A Cycle 2 and Subsequent Cycles

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. If patients remain on study for > 4 cycles and cytopenias are not observed, CBCs should be obtained at the start of subsequent cycles and as clinically indicated.
d. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus, albumin
e. ALT, total bilirubin
f. Audiogram or BAER (use same mode of testing as baseline). Obtain at the end of Cycle 2 and Cycle 6.
g. Bilateral bone marrow aspirates and biopsies. Obtain at the end of Cycles 2, 4, 6, and every fourth cycle[&] thereafter for patients with bone marrow involvement at baseline (study enrollment) or patients with ***any*** prior history of bone marrow involvement. Obtain at the end of Cycles 2 and 6 for all patients, including those without bone marrow involvement at baseline (study enrollment) and those without ***any*** prior history of bone marrow involvement.*
h. 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 after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle[&] thereafter. Patients with no measurable or non-measurable soft tissue disease (i.e., MIBG avid bone lesions or bone marrow involvement only) at baseline are only required to obtain appropriate cross-sectional imaging (CT and/or MRI) at baseline and at the end of Cycles 2 and 6 (see Section 15.1 for imaging details).*
i. ^{123}I-MIBG scan (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle[&] thereafter.*
j. Curie score profile (patients with MIBG avid disease; see Appendix IX for worksheet) (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle[&] thereafter.
k. FDG-PET scan for patients with ^{123}I-MIBG non-avid disease (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle[&] thereafter. *
l. Specimens for correlative studies (see Section 14 and Appendix X for specimen requirements). On Day 1 of Cycle 2, specimens should be collected prior to initiation of therapy.
m. 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. Obtain for Cycles 2, 4, 6, and 12. See Section 14.1.3 for additional detail.

*Imaging and bilateral bone marrow aspirates and biopsies may be performed within 1 week prior to the start of the next planned cycle of therapy.
[&] Patients enrolled on study prior to Amendment 4 only.

This listing only includes evaluations necessary to address the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.5.3 Treatment Details for Regimen A Cycle 2 and Subsequent Cycles (3 weeks = 1 cycle)

Drug doses should be calculated based on the BSA using height and weight obtained within 1 week prior to the beginning of each cycle.

Suggested administration schedule for chemotherapy and Dinutuximab (Days 2-5):

- At hour 0: patient should receive oral temozolomide.
- At hour 1: patient should start IV irinotecan over 90 minutes, and on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 1 hour.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.

Temozolomide: PO daily (NG or G-tube administration is allowed)
Days: 1-5
Dose: Round doses to the nearest 5 mg when using capsules. See dosing table in Appendix VI.

For patients ≥ 0.5 m^2: 100 mg/**m^2/dose**
For patients < 0.5 m^2: 3.3 mg/**kg/dose**
MAX dose = 200 mg

Substitution of IV Temozolomide is not permitted.

Sequencing: when giving with irinotecan, administer temozolomide first and wait 1 hour before giving irinotecan.

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended to prevent nausea and vomiting. When using temozolomide dose capsules, the dose should be rounded to the nearest 5 mg (round 2.5 mg down, see Appendix VI). For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist.

If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose should be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated.

Administration of oral temozolomide should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See Section 6.5 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: 50 mg/m^2/dose (regardless of BSA)
Note: Irinotecan should be administered at least 1 hour after the temozolomide has been given.

Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates.

See the Parenteral Chemotherapy Administration Guidelines (CAG) for special precautions and suggestions for patient monitoring on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf

Dinutuximab: IV over 10 hours* daily
Days: 2-5
Dose: 17.5 mg/m^2/dose

Note: Due to the increased risk of capillary leak and respiratory compromise with dinutuximab administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of dinutuximab. **Before starting dinutuximab**, please obtain a copy of management recommendations for anaphylaxis and hypotension available in Appendix XI and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

Refer to Section 4.5.4 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 1 hour. Bolus should be given concurrently with irinotecan infusion. On Day 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

*The infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of dinutuximab antibody has not been delivered. Antibody administration should

not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of dinutuximab is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection (preferred) or IV over 2 hours daily.
Days: 6 through 12
Dose: 250 mcg/m^2/dose

Start sargramostim on Day 6 any time after the completion of Day 5 dinutuximab.

The standard route of administration is subcutaneous; in extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.

Sargramostim dose will be held if the total white cell count is > 50,000/µL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/µL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications based on Toxicities.

4.5.4 Premedication and Supportive Care recommended for the prevention of anticipated toxicities associated with dinutuximab

Neuropathic pain, allergic reactions, and fever are commonly seen in patients receiving this antibody. Institutional guidelines for supportive care during this portion of therapy should be followed. The use of the following premedications are recommended:

- IV hydration: NS 20 mL/kg IV over 1 hour just prior to each dinutuximab infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to dinutuximab infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without

difficulty, may consider removing the continuous opioid infusion rate in between dinutuximab doses (when dinutuximab is not infusing).

- Recommended starting dose of analgesics:
  - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of dinutuximab infusion. At the same time, start a continuous morphine infusion of 0.02 mg/kg/hr with bolus doses of 0.01 mg/kg/dose q15 minutes prn for pain.
  - If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of dinutuximab. At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/hour for opioid naïve patients) with bolus doses of 0.002mg/kg/dose q15 minutes prn for pain.
  - If fentanyl PCA is used, recommend fentanyl 1 mcg/kg 10 minutes prior to starting dinutuximab infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
  - Doses should be titrated as needed in accordance with institutional guidelines.

For patients unable to use a PCA, a continuous basal infusion of morphine (or alternative medication) and as-needed boluses of the same medication may be used. Starting doses of the basal infusion and boluses should be based on patient weight, institutional standard practices, and doses required by individual patients for treatment of pain associated with previous interventions.

Have immediately available during the dinutuximab infusion:

a. Albuterol and oxygen
b. Epinephrine
c. Hydrocortisone: Use only for life-threatening reactions (hypotension, bronchospasm, angioedema involving the airway) not responsive to other measures.

Monitoring during the dinutuximab infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until dinutuximab infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.5.5 Additional guidance

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use

of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Use of furosemide should be avoided when feasible due to ototoxicity concerns.

- Corticosteroid therapy should be used only for life-threatening conditions (i.e. treatment of increased intracranial pressure in patients with CNS tumors, symptomatic bronchospasm, stridor unresponsive to other measures or life-threatening allergic reactions). Corticosteroids will impair the immune activation that is a critical part of the protocol therapy. **The use of steroids at any time during immunotherapy requires clear justification and documentation.**

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

- Cytokines or growth factors (G-CSF, Interferon, etc.) not included in the Treatment Plan are prohibited during immunotherapy.

4.6 Regimen B Cycle 1

4.6.1 Therapy Delivery Map –CYCLE 1 Cycle 1 lasts 4 weeks (28 days). This cycle includes a lead-in of 7 days of DFMO (Days -6 to 0) prior to 21 days of chemotherapy.	_____ Patient COG ID number _____ DOB

Begin Cycle 2 on Day 22 of Cycle 1 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 5.0 for dose modifications. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Eflornithine (DFMO) IND# 141913	PO or via NG or Gtube	2250 mg/m^2/dose x 3 doses/day See dosing table in Appendix XII	Days -6 to +7 and Days 15 - 21	Round doses to the nearest 500 mg (see dosing table in Appendix XII). Note: During Days 1-5, consider giving one of the 3 times daily eflornithine doses and temozolomide close together in order to minimize potential for emesis and redosing.
Temozolomide (TEMO)	PO or via NG or Gtube	For patients ≥ 0.5 m^2: 100 mg/m^2/dose For patients < 0.5 m^2: 3.3 mg/kg/dose See dosing table in Appendix VI.	Days 1 - 5	Max dose = 200 mg Round doses to the nearest 5 mg when using capsules. **Administer at least 1 hour prior to IRIN administration.** Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).
Irinotecan (IRIN)	IV over 90 minutes	50 mg/m^2/dose	Days 1 - 5	Administer at least 1 hour after temozolomide, see Section 4.6.3.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	Days 2 - 5	* Infusion duration may be extended up to 20 hours if needed. Start immediately after completion of NS bolus and irinotecan infusions. See Section 4.6.3 for detailed administration guidelines, including premedications and monitoring.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 mcg/m^2/dose	Days 6 - 12	See Section 4.6.3 for administration guidelines.

4.6.1 Therapy Delivery Map –CYCLE 1 Cycle 1 lasts 4 weeks (28 days). This cycle includes a lead-in of 7 days of DFMO (Days -6 to 0) prior to 21 days of chemotherapy.	_____ Patient COG ID number _____ DOB

Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	DFMO ___mg	TEMO ___mg	IRIN ___mg	DIN ____ mg	GM-CSF ___mcg	Studies
			Enter calculated dose above and actual dose administered below					
		-6	____mg					a – o
		-5	____mg					
		-4	____mg					
		-3	____mg					
		-2	____mg					
		-1	____mg					
		0	____mg					
		1	____mg	____mg	____mg			a, c, d, e, n, o
		2	____mg	____mg	____mg	____mg		d, o
		3	____mg	____mg	____mg	____mg		d, o
		4	____mg	____mg	____mg	____mg		d, o
		5	____mg	____mg	____mg	____mg		d, o
		6	____mg				___mcg	n
		7	____mg				___mcg	
		8					___mcg	c, d, e
		9					___mcg	
		10					___mcg	
		11					___mcg	
		12					___mcg	
		13						
		14						
		15	____mg					c, d, e
		16	____mg					
		17	____mg					
		18	____mg					
		19	____mg					
		20	____mg					
		21	____mg					
		22	Begin Cycle 2 on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).					

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Regimen B Cycle 1

4.6.2 Required Observations in Regimen B Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

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. ^{123}I-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 ^{123}I-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 Days -6 and 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.

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

This listing only includes evaluations necessary to address the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.6.3 Treatment Details for Regimen B Cycle 1 (4 weeks = 1 cycle)

Drug doses should be calculated based on the BSA using height and weight obtained within 1 week prior to the beginning of each cycle.

Suggested administration schedule for eflornithine, chemotherapy and dinutuximab (Days 2-5):

- At hour 0: patient should receive oral eflornithine (DFMO) and oral temozolomide. Medications should be given separately, not mixed.
- At hour 1: patient should start IV irinotecan over 90 minutes, and on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 1 hour.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.

Eflornithine (DFMO): PO daily (NG or Gtube administration is allowed)
Days: -6 through +7 and 15 - 21
Dose: 2250 mg/m^2/dose TID (6750 mg/m^2/day). See dosing table in Appendix XII

Note: During Days 1-5, consider giving one of the 3 times daily eflornithine doses and temozolomide close together in order to minimize potential for emesis and redosing.

The eflornithine dose should be rounded to the nearest 500 mg (0.5 g). Please see Appendix XIII for eflornithine administration recommendations. Please provide these instructions to patient families.

If emesis occurs within 20 minutes of taking a dose of eflornithine, then the dose should be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

Administration of oral eflornithine should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures.

Temozolomide: PO daily (NG or Gtube administration is allowed)
Days: 1-5
Dose: Round doses to the nearest 5 mg when using capsules. See dosing table in Appendix VI.

For patients ≥ 0.5 m^2: 100 mg/**m^2/dose**
For patients < 0.5 m^2: 3.3 mg/**kg/dose**
MAX dose = 200 mg

Substitution of IV Temozolomide is not permitted.

Sequencing: when giving with irinotecan, administer temozolomide first and wait 1 hour before giving irinotecan.

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least

1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended to prevent nausea and vomiting. When using temozolomide capsules, the dose should be rounded to the nearest 5 mg (round 2.5 mg down, see Appendix VI). For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist.

If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose should be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

Administration of oral temozolomide should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See Section 6.5 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: 50 mg/m^2/dose (regardless of BSA)
Note: Irinotecan should be administered at least 1 hour after the temozolomide has been given.

Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates.

See the Parenteral Chemotherapy Administration Guidelines (CAG) for special precautions, suggestions for patient monitoring, and hydration pre- and post-cyclophosphamide (or hydrate according to institutional guidelines) on the COG website at:
https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf

Dinutuximab: IV over 10 hours* daily
Days: 2-5
Dose: 17.5 mg/m^2/dose

Note: Due to the increased risk of capillary leak and respiratory compromise with dinutuximab administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of dinutuximab. **Before starting dinutuximab**, please obtain a copy of management recommendations for anaphylaxis and hypotension available in Appendix XI and the training module on

the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

Refer to Section 4.6.4 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 1 hour. Bolus should be given concurrently with irinotecan infusion. On Day 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

*The infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of dinutuximab antibody has not been delivered. Antibody administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of dinutuximab is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection (preferred) or IV over 2 hours
Days: 6 through 12
Dose: 250 mcg/m^2/dose

Start sargramostim on Day 6 any time after the completion of Day 5 dinutuximab.

The standard route of administration is subcutaneous; in extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.

Sargramostim dose will be held if the total white cell count is > 50,000/µL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/µL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications based on Toxicities.

4.6.4 Premedication and Supportive Care recommended for the prevention of anticipated toxicities associated with dinutuximab

Neuropathic pain, allergic reactions, and fever are commonly seen in patients receiving this antibody. Institutional guidelines for supportive care during this portion of therapy should be followed. The use of the following premedications are recommended:

- IV hydration: NS 20 mL/kg IV over 1 hour just prior to each dinutuximab infusion.
  - Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.
  - Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to dinutuximab infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
  - Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
  - Consider use of cetirizine for patients with a history of allergic reactions
  - Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without difficulty, may consider removing the continuous opioid infusion rate in between dinutuximab doses (when dinutuximab is not infusing).
  - Recommended starting dose of analgesics:
    - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of dinutuximab infusion. At the same time, start a continuous morphine infusion of 0.02 mg/kg/hr with bolus doses of 0.01 mg/kg/dose q15 minutes prn for pain.
    - If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of dinutuximab. At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/hour for opioid naïve patients) with bolus doses of 0.002 mg/kg/dose q15 minutes prn for pain.
    - If fentanyl PCA is used, recommend fentanyl 1 mcg/kg 10 minutes prior to starting dinutuximab infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
    - Doses should be titrated as needed in accordance with institutional guidelines.

For patients unable to use a PCA, a continuous basal infusion of morphine (or alternative medication) and as-needed boluses of the same medication may be used. Starting doses of the basal infusion and boluses should be based on patient weight, institutional standard practices, and doses required by individual patients for treatment of pain associated with previous interventions.

<u>Have immediately available during the dinutuximab infusion</u>:

a. Albuterol and oxygen
b. Epinephrine
c. Hydrocortisone: Use only for life-threatening reactions (hypotension, bronchospasm, angioedema involving the airway) not responsive to other measures.

Monitoring during the dinutuximab infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until dinutuximab infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.6.5 Additional guidance

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Use of furosemide should be avoided when feasible due to ototoxicity concerns.

- Corticosteroid therapy should be used only for life-threatening conditions (i.e. treatment of increased intracranial pressure in patients with CNS tumors, symptomatic bronchospasm, stridor unresponsive to other measures or life-threatening allergic reactions). Corticosteroids will impair the immune activation that is a critical part of the protocol therapy. **The use of steroids at any time during immunotherapy requires clear justification and documentation.**

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

- Cytokines or growth factors (G-CSF, Interferon, etc.) not included in the Treatment Plan are prohibited during immunotherapy.

Following completion of this cycle, Cycle 2 starts on Day 22 or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later).

See Section 5.0 for Dose Modifications based on Toxicities.

4.7 Regimen B Cycle 2 and Subsequent Cycles

4.7.1 Therapy Delivery Map –CYCLE 2 and Subsequent Cycles Each cycle lasts 3 weeks (21 days).	_____ Patient COG ID number _____ DOB

Begin each cycle on Day 22 of the previous cycle or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). See Section 5.0 for dose modifications. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Eflornithine (DFMO) IND# 141913	PO or via NG or Gtube	2250 mg/m^2/dose x 3 doses/day See dosing table in Appendix XII	Days 1- 7 and Days 15 - 21	Round doses to the nearest 500 mg (see dosing table in Appendix XII). Note: During Days 1-5, consider giving one of the 3 times daily eflornithine doses and temozolomide close together in order to minimize potential for emesis and redosing.
Temozolomide (TEMO)	PO or via NG or Gtube	For patients ≥ 0.5 m^2: 100 mg/m^2/dose For patients < 0.5 m^2: 3.3 mg/kg/dose See dosing table in Appendix VI.	Days 1 - 5	Max dose = 200 mg Round doses to the nearest 5 mg when using capsules. **Administer at least 1 hour prior to IRIN administration.** Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).
Irinotecan (IRIN)	IV over 90 minutes	50 mg/m^2/dose	Days 1 - 5	Administer at least 1 hour after temozolomide, see Section 4.7.3.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	Days 2 - 5	*Infusion duration may be extended up to 20 hours if needed. Start immediately after completion of NS bolus and irinotecan infusions. See Section 4.7.3 for detailed administration guidelines, including premedications and monitoring during the infusion.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 mcg/m^2/dose	Days 6 - 12	See Section 4.7.3 for administration guidelines.

4.7.1 Therapy Delivery Map –CYCLE 2 and Subsequent Cycles

Each cycle lasts 3 weeks (21 days).

_____
Patient COG ID number

_____
DOB

Cycle # ____ **Ht** ____ **cm** **Wt** ____ **kg** **BSA** ____ **m^2**

Date Due	Date Given	Day	DFMO ___mg	TEMO ___mg	IRIN ___mg	DIN ___mg	GM-CSF ___mcg	Studies	
			Enter calculated dose above and actual dose administered below					Cycle 2	Subsequent cycles
		1	___mg	___mg	___mg			a-e, l, m	a-e, m
		2	___mg	___mg	___mg	___mg		d, m	d, m
		3	___mg	___mg	___mg	___mg		d, m	d, m
		4	___mg	___mg	___mg	___mg		d, m	d, m
		5	___mg	___mg	___mg	___mg		d, m	d, m
		6	___mg				___mcg		
		7	___mg				___mcg		
		8					___mcg	c	c
		9					___mcg		
		10					___mcg		
		11					___mcg		
		12					___mcg		
		13							
		14							
		15	___mg					c	c
		16	___mg						
		17	___mg						
		18	___mg						
		19	___mg						
		20	___mg						
		21	___mg					f-k	f-k
		22	Begin next cycle on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).						

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Regimen B Cycle 2 and Subsequent Cycles

4.7.2 Required Observations in Regimen B Cycle 2 and Subsequent Cycles

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). If patients remain on study for > 4 cycles and cytopenias are not observed, CBCs should be obtained at the start of subsequent cycles and as clinically indicated
d. Electrolytes, BUN, creatinine, magnesium, phosphorus, albumin
e. ALT, total bilirubin
f. Audiogram or BAER (use same mode of testing as baseline). Obtain at the end of Cycle 2 and end of every 2nd cycle thereafter.
g. Bilateral bone marrow aspirates and biopsies. Obtain at the end of Cycles 2, 4, 6, and every fourth cycle& thereafter for patients with bone marrow involvement at baseline (study enrollment) or patients with ***any*** prior history of bone marrow involvement. Obtain at the end of Cycles 2 and 6 for all patients, including those without bone marrow involvement at baseline (study enrollment) and those without ***any*** prior history of bone marrow involvement.*
h. 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 after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle& thereafter. Patients with no measurable or non-measurable soft tissue disease (i.e., MIBG avid bone lesions or bone marrow involvement only) at baseline are only required to obtain appropriate cross-sectional imaging (CT and/or MRI) at baseline and at the end of Cycles 2 and 6 (see Section 15.1 for imaging details).*
i. ^{123}I-MIBG scan (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle& thereafter.*
j. Curie score profile (patients with MIBG avid disease; see Appendix IX for worksheet) (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle& thereafter.
k. FDG-PET scan for patients with ^{123}I-MIBG non-avid disease (submit for central review as soon as scan is obtained after Cycles 2, 4, and 6). Obtain at the end of Cycles 2, 4, 6, and every fourth cycle& thereafter.*
l. Specimens for correlative studies (see Section 14 and Appendix X for specimen requirements). On Day 1 of Cycle 2, specimens should be collected prior to initiation of therapy.
m. 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. Obtain for Cycles 2, 4, 6, and 12. See Section 14.1.3 for additional detail.

*Imaging and bilateral bone marrow aspirates and biopsies may be performed within 1 week prior to the start of the next planned cycle of therapy.
& Patients enrolled on study prior to Amendment 4 only.

This listing only includes evaluations necessary to address the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Regimen B Cycle 2 and Subsequent Cycles

4.7.3 Treatment Details for Regimen B Cycle 2 and Subsequent Cycles (3 weeks = 1 cycle)

Drug doses should be calculated based on the BSA using height and weight obtained within 1 week prior to the beginning of each cycle.

Suggested administration schedule for eflornithine, chemotherapy and dinutuximab (Days 2-5):

- At hour 0: patient should receive oral eflornithine (DFMO) and oral temozolomide. Medications should be given separately, not mixed.
- At hour 1: patient should start IV irinotecan over 90 minutes, and on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 1 hour.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.

Eflornithine (DFMO): PO daily (NG or Gtube administration is allowed)
Days: 1 – 7 and 15 - 21
Dose: 2250 mg/m^2/dose TID (6750 mg/m^2/day). See dosing table in Appendix XII

Note: During Days 1-5, consider giving one of the 3 times daily eflornithine doses and temozolomide close together in order to minimize potential for emesis and redosing.

The eflornithine dose should be rounded to the nearest 500 mg (0.5 g). Please see Appendix XIII for eflornithine administration recommendations. Please provide these instructions to patient families.

If emesis occurs within 20 minutes of taking a dose of eflornithine, then the dose should be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

Administration of oral eflornithine should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures.

Temozolomide: PO daily (NG or Gtube administration is allowed)
Days: 1-5
Dose: Round doses to the nearest 5 mg when using capsules. See dosing table in Appendix VI.

For patients ≥ 0.5 m^2: 100 mg/**m^2/dose**
For patients < 0.5 m^2: 3.3 mg/**kg/dose**
MAX dose = 200 mg

Substitution of IV Temozolomide is not permitted.

Sequencing: when giving with irinotecan, administer temozolomide first and wait 1 hour before giving irinotecan.

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended to prevent nausea and vomiting. When using temozolomide capsules, the dose should be rounded to the nearest 5 mg (round 2.5 mg down, see Appendix VI). For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist.

If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose should be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

Administration of oral temozolomide should be documented; missed doses should be noted on therapy delivery map and/or in accordance with institutional policy/procedures

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See Section 6.5 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: 50 mg/m^2/dose (regardless of BSA)
Note: Irinotecan should be administered at least 1 hour after the temozolomide has been given.

Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates. To avoid extravasation; the use of a central line is suggested.

See the Parenteral Chemotherapy Administration Guidelines (CAG) for special precautions, and suggestions for patient monitoring on the COG website at:
https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf

Dinutuximab: IV over 10 hours* daily
Days: 2-5
Dose: 17.5 mg/m^2/dose

Note: Due to the increased risk of capillary leak and respiratory compromise with dinutuximab administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of dinutuximab. **Before starting dinutuximab**, please obtain a copy of management recommendations for anaphylaxis and hypotension available in Appendix XI and the training module on

the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

Refer to Section 4.7.4 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 1 hour. Bolus should be given concurrently with irinotecan infusion. On Days 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

*The infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of dinutuximab antibody has not been delivered. Antibody administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of dinutuximab is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection (preferred) or IV over 2 hours daily
Days: 6 through 12
Dose: 250 mcg/m^2/dose

Start sargramostim on Day 6 any time after the completion of Day 5 dinutuximab.

The standard route of administration is subcutaneous; in extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.

Sargramostim dose will be held if the total white cell count is > 50,000/µL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/µL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications based on Toxicities.

4.7.4 Premedication and Supportive Care recommended for the prevention of anticipated toxicities associated with dinutuximab

Neuropathic pain, allergic reactions, and fever are commonly seen in patients receiving this antibody. Institutional guidelines for supportive care during this portion of therapy should be followed. The use of the following premedications are recommended:

- IV hydration: NS 20 mL/kg IV over 1 hour just prior to each dinutuximab infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to dinutuximab infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without difficulty, may consider removing the continuous opioid infusion rate in between dinutuximab doses (when dinutuximab is not infusing).
- Recommended starting dose of analgesics:
  - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of dinutuximab infusion. At the same time, start a continuous morphine infusion of 0.02mg/kg/hr with bolus doses of 0.01mg/kg/dose q15 minutes prn for pain.
  - If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of dinutuximab. At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/hour for opioid naïve patients) with bolus doses of 0.002 mg/kg/dose q15 minutes prn for pain.
  - If fentanyl PCA is used, recommend fentanyl 1 mcg/kg 10 minutes prior to starting dinutuximab infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
  - Doses should be titrated as needed in accordance with institutional guidelines.

For patients unable to use a PCA, a continuous basal infusion of morphine (or alternative medication) and as-needed boluses of the same medication may be used. Starting doses of the basal infusion and boluses should be based on patient weight, institutional standard practices, and doses required by individual patients for treatment of pain associated with previous interventions.

<u>Have immediately available during the dinutuximab infusion</u>:

a. Albuterol and oxygen
b. Epinephrine
c. Hydrocortisone: Use only for life-threatening reactions (hypotension, bronchospasm, angioedema involving the airway) not responsive to other measures.

Monitoring during the dinutuximab infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until dinutuximab infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.7.5 Additional guidance

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Use of furosemide should be avoided when feasible due to ototoxicity concerns.

- Corticosteroid therapy should be used only for life-threatening conditions (i.e. treatment of increased intracranial pressure in patients with CNS tumors, symptomatic bronchospasm, stridor unresponsive to other measures or life-threatening allergic reactions). Corticosteroids will impair the immune activation that is a critical part of the protocol therapy. **The use of steroids at any time during immunotherapy requires clear justification and documentation.**

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

- Cytokines or growth factors (G-CSF, Interferon, etc.) not included in the Treatment Plan are prohibited during immunotherapy.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

In addition to dose modifications, this section provides information regarding management of toxicities known to be associated with protocol therapy.

In the sections below, when protocol therapy is to be discontinued, all protocol therapy should be discontinued. If treating clinicians elect to continue to administer dinutuximab, irinotecan and temozolomide, this can be done as part of clinical care but will not be considered protocol therapy.

NOTE: If eflornithine is stopped for any reason (e.g. toxicity or, for patients enrolled prior to Amendment 4, tumor resection after Cycle 6 disease evaluation) and then resumed at same or lower dose, at least 5 days of the resumed/decreased dose of eflornithine should be given prior to starting Day 1 of the next cycle of chemotherapy. The resumed/decreased dose should be given for a total of 12 days. Please HOLD eflornithine for 24 hours prior to tumor resection.

If a subsequent cycle is delayed by ≤ 7 days for any event that is unlikely related to eflornithine (e.g. timing adjustments, count recovery, or toxicity not attributed to eflornithine), the patient should continue eflornithine until the next cycle begins. If a subsequent cycle is delayed > 7 days for any event that is unlikely related to eflornithine, the patient should stop taking eflornithine until he/she meets eligibility to start the subsequent cycle. Once the patient is eligible to start the next cycle, 5 days of eflornithine (Day -4 to Day 0) should be given prior to starting Day 1 of the next cycle of chemoimmunotherapy.

5.1 Dose Modifications for Hematologic Toxicity

Patients must meet hematologic criteria for study entry and at the start of each treatment cycle.

5.1.1 Dose-limiting neutropenia

Patients who experience neutropenia that causes a delay of ≥ 14 days between treatment cycles in the absence of other toxicity requiring dose modification should have the temozolomide dose reduced by 25% for subsequent cycles (see dose reduction nomogram in Appendix VII). If patient experiences neutropenia that causes a delay of ≥ 14 days between treatment cycles after this dose reduction, protocol therapy should be discontinued.

5.1.2 Dose-limiting thrombocytopenia

For patients who experience thrombocytopenia that causes a delay of ≥ 14 days between treatment cycles with or without other hematologic toxicities, the dose of temozolomide should be reduced by 25% for subsequent cycles (see dose reduction nomogram in Appendix VII). If patient experiences thrombocytopenia that causes a delay of ≥ 14 days between treatment cycles after this dose reduction, protocol therapy should be discontinued.

5.1.3 Delayed recovery of platelets and neutrophils

Patients who do not meet criteria to start the next treatment cycle (see Section 4.5.1 or 4.7.1) 21 days after the planned subsequent cycle start date (i.e. there is a ≥ 3 week delay in start of next cycle) must be removed from protocol therapy.

5.2 Dose Modifications for Non-hematologic Toxicity

Patients who have experienced non-hematologic toxicity should receive subsequent doses of study medications as described in the following sections.

NOTE: If eflornithine is stopped for any reason and then resumed at same or lower dose, at least 5 days of the resumed/decreased dose of eflornithine should be given prior to starting Day 1 of the next cycle of chemotherapy.

5.2.1 Dose modifications for diarrhea

See Appendix V for patient/family instructions for supportive care measures for patients who develop therapy-associated diarrhea. Also included are specific instructions for loperamide dosing.

- If Grade 4 therapy-associated diarrhea is experienced by a patient with no evidence of infectious etiology and despite maximal use of anti-diarrheal medications and appropriate use of prophylactic antibiotics, the dose of irinotecan should be reduced by 25% for subsequent cycles (i.e. irinotecan dose 37.5 mg/m^2).
- If diarrhea persists despite maximal use of anti-diarrheal medications and appropriate use of prophylactic antibiotics for Grade 3 diarrhea > 7 days and Grade 4 diarrhea > 3 days after the completion of irinotecan, hold the eflornithine (DFMO) until diarrhea resolves to Grade 1. Then restart at prior dose.
- If Grade 4 therapy-associated diarrhea recurs without an infectious etiology despite reducing the dose of irinotecan by 25%, the dinutuximab dose (Arm A) or both the dinutuximab and eflornithine doses (Arm B) should also be decreased by 25% for subsequent cycles (i.e. dinutuximab dose 13.13 mg/m^2/day and eflornithine dose 5 g/m^2/day divided TID).
- If Grade 4 diarrhea recurs despite maximal use of anti-diarrheals, prophylactic antibiotics, and the dose reductions, the patient should come off protocol therapy.

5.2.2 Dose modifications for nausea and vomiting

- For patients with Grade 4 regimen-related nausea and vomiting and for patients with Grade 3 regimen-related nausea and vomiting > 7 days in duration who did not receive appropriate anti-emetic therapy, adjustments in the anti-emetic regimen should be made during the next cycle of therapy.
- If severe (Grade 4 or Grade 3 > 7 days) regimen-related nausea and vomiting recurs despite optimized anti-emetic usage, doses of irinotecan and temozolomide should both be reduced by 25% for subsequent cycles (i.e. irinotecan dose 37.5 mg/m^2; for temozolomide see dose reduction nomogram in Appendix VII).
- If severe regimen-related nausea and vomiting recurs despite the dose reduction, the patient should come off protocol therapy.

5.2.3 Dose modifications for dehydration

- If dehydration is related to diarrhea or nausea/vomiting, the guidance in

Section 5.2.1 or 5.2.2 should be followed.

- If regimen-related ≥ Grade 3 dehydration persists for > 3 days in the absence of significant diarrhea or nausea/vomiting, doses of irinotecan and temozolomide should both be reduced by 25% for subsequent cycles (i.e. irinotecan dose is 37.5 mg/m^2; for temozolomide see dose reduction nomogram in Appendix VII).
- If ≥ Grade 3 regimen-related dehydration recurs and persists for > 3 days despite the dose reduction, the patient should come off protocol therapy.

5.2.4 Dose modifications for elevations in ALT, AST, or GGT

- If elevations in ALT, AST or GGT occur such that values are > 20x ULN for any duration of time OR > 10x ULN but < 20x ULN and persisting for > 7 days, the dose of dinutuximab should be reduced by 25% for subsequent cycles (i.e. dinutuximab dose 13.13 mg/m^2). For the purposes of this trial the ULN for ALT is defined as 45 U/L; institutional ULN values for AST and GGT should be used.
- If elevations of this magnitude involving same liver enzyme(s) recur despite the first dose reduction, the dose of temozolomide (Arm A) or eflornithine and temozolomide (Arm B) should be reduced by 25% for subsequent cycles (i.e. for temozolomide see dose reduction nomogram in Appendix VII; eflornithine dose 5 g/m^2). If the dose limiting elevations of the same liver enzyme(s) recur despite the temozolomide/eflornithine dose reduction, the patient should come off protocol therapy.
- An elevation in ALT that causes a delay of ≥ 14 days between treatment cycles will also require a 25% reduction in the dose of dinutuximab for all subsequent cycles (i.e. dinutuximab dose 13.13 mg/m^2). If a delay of ≥ 14 days between treatment cycles recurs due to elevation in ALT despite the dose reduction, the patient should come off protocol therapy.

5.2.5 Dinutuximab specific dose modifications and toxicity management recommendations

5.2.5.1 Treatment of dinutuximab-induced hypotension (without evidence of allergic reaction)

a. If hypotension is severe and accompanied by poor perfusion, end organ dysfunction, or acidemia – Pediatric Advanced Life Support (PALS) guidelines should be followed and dinutuximab infusion should be discontinued.
b. In the absence of poor perfusion, end organ dysfunction or acidemia, moderate hypotension is defined as:
   i. symptomatic decreases in blood pressure (BP) and/or
   ii. Systolic BP < 5th percentile based on age and height and baseline BPs OR
   iii. Systolic or diastolic BP decreased by > 20% below baseline

c. For patients with moderate hypotension in the absence of poor perfusion, end organ dysfunction, or acidemia:
   i. Immediately hold dinutuximab
   ii. Give normal saline bolus (20 mL/kg as rapidly as possible)
   iii. Stop or adjust doses of narcotics and sedating H1 blockers

iv. Consider use of Trendelenberg position

d. If hypotension persists after the above measures have been taken:
   i. Reassess perfusion and end organ function
   ii. Follow PALS algorithm if indicated
   iii. Repeat NS bolus OR
   iv. Consider use of albumin if albumin < 3 gm/dL
   v. Consider use of PRBCs if Hb < 10 gm/dL
   vi. Consider use of platelets if count <50,000/μL
   vii. Consider transfer to intensive care setting

e. If hypotension persists following 2 volume boluses, give an additional bolus and prepare to administer pressors
   i. Epinephrine or norepinephrine is preferred over dopamine if possible

f. Resumption of dinutuximab
   i. For patients whose hypotension resolves promptly and completely with limited volume resuscitation (≤ 40 mL/kg) and without requirement for pressor support, dinutuximab may be restarted at 50% of the previous infusion rate. The dinutuximab may be restarted on same day if it is possible to do so within 20 hours of the start of the day's infusion. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient again experiences hypotension requiring multiple volume boluses (e.g. > 40 mL/kg) when dinutuximab is given at full rate but tolerates the 50% infusion rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion. If > 20 hours have elapsed since the start of the infusion, restart dinutuximab the following day.
      - If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given at the full rate
      - If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.
   ii. For patients who require multiple volume boluses for hemodynamic stabilization, dinutuximab should be resumed the following day at 50% of the initial infusion rate.
      - If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given at the full rate

- If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

iii. For patients who require pressors for treatment of hypotension, if blood pressure is stable off pressors for at least 6 hours, administration of dinutuximab may be resumed at 50% of the initial infusion rate on the day following the hypotensive episode. Care should be taken to ensure that the patient is volume replete. Dinutuximab should not be given to patients who continue to require pressor support. Patients who require pressor support for ≥ 24 hours due to treatment-related hypotension despite appropriate volume resuscitation should discontinue protocol therapy. Patients who again require pressor support when dinutuximab is resumed should discontinue protocol therapy.

5.2.5.2 Treatment of Allergic Reactions/Infusion Reactions

a. Mild allergic reactions/infusion reactions to dinutuximab infusion
   i. A mild allergic reaction is limited to rash, flushing, urticaria, mild dyspnea – Grade 1 or 2
   ii. The following recommendations do NOT apply to Grade 3 or 4 allergic reactions, including anaphylaxis
   iii. Management
      - Decrease rate of dinutuximab to 50% of full rate
      - Perform serial exams at bedside
      - Administer H1 blocker (diphenhydramine, cetirizine recommended)
      - Administer H2 blocker
      - When symptoms resolve, resume original infusion rate
      - If symptoms recur when original rate is resumed, decrease to 50% rate again
      - Infusion must be stopped after 20 hours (whether the full dose of dinutuximab has been administered or not); document total amount of drug given in the 20 hour time period

b. Moderate to severe allergic reactions/infusion reactions to dinutuximab infusion
   i. Moderate to severe reactions include any of the following: symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, or anaphylaxis – Grade 3 or 4
   ii. The following recommendations do NOT apply to Grade 1 or

2 allergic reactions

iii. Management
- **Immediately hold dinutuximab**
- Assess airway, breathing and circulation
- Follow institutional guidelines for rapid response team notification if clinically indicated
- For airway concerns
  - Administer oxygen and albuterol immediately for bronchospasm
  - Administer IV diphenhydramine
  - Administer epinephrine (1:1000 IM recommended) immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
  - Administer IV hydrocortisone (1-2 mg/kg) if the patient has frank anaphylaxis with cardiorespiratory collapse OR if ≥ 2 doses of epinephrine are required OR if moderate to severe symptoms recur upon rechallenge with dinutuximab
- For hypotension in the setting of allergic reaction
  - Give normal saline bolus (20 mL/kg as rapidly as possible)
  - Stop or adjust doses of narcotics and sedating H1 blockers
  - Consider use of Trendelenberg position
  - See previous section for management of persistent hypotension
- For patients with mild bronchospasm or angioedema that does not impact breathing, completely resolves without the use of epinephrine and hydrocortisone and for patients whose hypotension resolves following volume bolus, dinutuximab may be resumed at 50% of the previous rate of infusion on the same day as the reaction occurred. If symptomatic angioedema or asymptomatic bronchospasm recurs when the dinutuximab is restarted, discontinue immunotherapy for that day and if symptoms/signs resolve completely that day, resume the next day with additional pre-medication of hydrocortisone 1-2 mg/kg IV. For this re-challenge, the infusion should be given in an ICU setting.
- For patients whose bronchospasm or angioedema requires the use of systemic epinephrine, protocol therapy should be discontinued.
- For patients with bronchospasm or angioedema that does not require systemic epinephrine but whose hypotension requires more extensive volume resuscitation, guidance in Section 5.2.5.1 should be followed.

5.2.5.3 Management of capillary leak syndrome (≥ Grade 3)

- Hold dinutuximab infusion
- Provide oxygen, fluids as needed
- Diuretics should be used with caution and hypotension avoided
- **See Section 5.2.5.1 for management of hypotension, anemia and hypoalbuminemia**
- Do NOT resume dinutuximab therapy if symptoms of severe capillary leak syndrome persist on the same day or subsequent days of a given cycle. Only resume dinutuximab therapy when the capillary leak syndrome resolves or requires less significant intervention (Grade 2 or less).
- If capillary leak resolves, may resume dinutuximab infusion at 50% rate the same day and for subsequent doses during a given cycle. The infusion may be given at the full rate at the start of subsequent cycles
- If mechanical ventilation (any duration) or pressor support for ≥ 24 hours is required due to therapy-related capillary leak syndrome, the patient should discontinue protocol therapy

5.2.5.4 Management of renal insufficiency (unrelated to hypotension)

- Consider the possibility of renal hypoperfusion in the context of borderline hypotension; administer volume if appropriate
- If the patient's creatinine is elevated to ≥ 2 x the upper limit of normal for age/gender (see table in Section 3.2.6.2) and elevation persists despite optimized fluid management, hold dinutuximab
- Modify dosing of concomitant medications that may contribute to or be affected by renal insufficiency
- When urine output returns to normal and creatinine returns to < 2 x upper limit of normal for age/gender, resume dinutuximab at 50% rate. If renal function normalizes by the following day, dinutuximab may be administered at full rate. If renal function is not sufficiently improved (urine output normal and creatinine < 2x ULN for age/gender) by Day 7, no further dinutuximab should be given during that cycle of therapy. If renal function has normalized by the planned start date for the next cycle, retreatment with dinutuximab is permitted

5.2.5.5 Management of hyponatremia (≥ Grade 3; Na < 130 mEq/L and symptomatic or 120-124 mEq/L regardless of symptoms)

- Change hypotonic fluids to isotonic fluids as compatibilities permit
- Avoid administration of oral free water
- Correct fluid losses due to diarrhea
- 3% saline is only indicated in the following settings:
  - hyponatremia leading to seizure
  - drop in sodium level > 10 points in 6 hours or less
  - sodium level < 117 mEq/L
- If Grade 4 hyponatremia persists despite optimal fluid management, discontinue dinutuximab for the remainder of the cycle. Sodium should be monitored closely during the next cycle of therapy. If

hyponatremia improves to Grade 2 or better, or baseline, empiric dose reduction is not required at the start of the next cycle of therapy, though dinutuximab would again be discontinued if Grade 4 hyponatremia were to persist despite optimal fluid management. In such cases, patient should discontinue protocol therapy.

5.2.5.6 Management of fever in the absence of hypotension

- Administer antipyretics
- Adjust fluids to account for insensible losses if fever is persistent
- Obtain blood culture
- Administer empiric antibiotics if suggested by institutional policy

5.2.5.7 Management of treatment-related pain

- No further dinutuximab therapy should be given to patients who experience treatment related Grade 3 pain that cannot be controlled by narcotics during a given cycle. Treatment with gabapentin or similar agent should be initiated if not already being administered. If pain that is not controlled with narcotics recurs during a subsequent cycle, the patient should discontinue protocol therapy
- For patients with treatment-related Grade 3 pain requiring intravenous narcotics for ≥ 48 hours following completion of dinutuximab therapy, gabapentin or similar agent should be initiated if not already being administered. If pain requiring prolonged intravenous narcotics (≥48 hours following completion of dinutuximab therapy) recurs during a subsequent cycle despite this intervention, the patient should discontinue protocol therapy.

5.2.5.8 Management of visual changes

- Dinutuximab may cause impaired accommodation and/or dilated pupils with sluggish light reflex with or without photophobia. No dose modifications, dose reductions, or changes in infusion rate should be made unless there is associated vision loss. If this occurs in conjunction with Grade 3 decrease in vision, dinutuximab should be discontinued. If visual loss improves to Grade 1 or better before the next immunotherapy course is due, the patient should receive dinutuximab at a dose that is 50% reduced compared to the prior dose. Full dose sargramostim (GM-CSF) should be given. If the lower dose of dinutuximab is tolerated without worsening of ocular toxicity, full dose dinutuximab should be given in subsequent courses. If visual toxicity worsens, the patient should discontinue protocol therapy.
- Dose reductions for dilated pupils or changes in accommodation without vision loss are not required.

5.2.5.9 Management of serum sickness

- Identification of serum sickness – signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy,

glomerulonephritis in the presence of persistent fevers, cutaneous eruptions.

- Serum sickness typically develops 1 to 3 weeks after administration of the causative agent, but can develop within 12-36 hours in patients who have previously been sensitized to the causative agent.
- Patients with ≥ Grade 3 serum sickness should discontinue protocol therapy.
- For Grade 2 serum sickness, antihistamines should be prescribed.

5.2.5.10 Management of neurotoxicity

- Patients who develop Grade 4 neurotoxicity should discontinue protocol therapy.
- Dinutuximab should be discontinued for the remainder of the current cycle of therapy for patients who develop Grade 3 sensory neuropathy or Grade 3 motor neuropathy. If abnormalities resolve by start of next cycle of therapy, the patient may receive 50% dose of dinutuximab (i.e. dinutuximab dose 8.75 mg/m^2). If symptoms do not completely resolve or recur with dinutuximab then the patient should discontinue protocol therapy.

5.2.6 Management of sargramostim related toxicities

- Hold sargramostim if total white blood cell count is > 50,000/µL; resume at 50% dose when the count is < 20,000/µL. Administer full dose with subsequent cycles and modify again if the count exceeds 50,000/µL
- Localized skin reactions to sargramostim are common, and sargramostim can be continued when reactions are mild. Rotation of sites of injections is recommended rather than use of insuflon for subcutaneous injection when skin reactions occur. Consider use of antihistamines. If ≥ Grade 3 injection site reactions occur, stop sargramostim for the current cycle and discontinue sargramostim for subsequent cycles of therapy.
- A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the administration of the first dose of sargramostim in a particular cycle. This syndrome generally resolves with symptomatic treatment and usually does not recur with subsequent doses of sargramostim in the same cycle of treatment. For safety purposes in this study, if such a "first dose reaction" occurs, the sargramostim dose will be reduced to 50% for the next dose (i.e. sargramostim dose 125 mcg/m^2). If a similar reaction occurs at the 50% dose, the sargramostim will be discontinued for that patient. If the first dose at 50% does not cause any recurrent severe symptoms, subsequent doses can be escalated back to 100%. If recurrent severe symptoms are observed at 100% dose, then the dose will be reduced to 50%. If 50% is tolerated, that dose should be administered for all subsequent protocol treatment for that patient. If recurrent severe symptoms are seen at the 50% dose, the sargramostim will be discontinued for subsequent cycles of therapy.

5.2.7 Eflornithine (DFMO) specific dose modifications and toxicity management recommendations

5.2.7.1 Hearing Loss

Potential eflornithine-related hearing loss will be identified by audiologic assessment and defined **as ≥ 15 dB increase from baseline in hearing threshold at two contiguous frequencies between 500 and 3000 Hz.** If this hearing deterioration is detected, eflornithine will be held for the remainder of the cycle and for one additional full cycle, and the audiologic testing should be repeated at the end of the entire dose holding period. If hearing sensitivity returns to pre-therapy baseline (or within 5dB of baseline), they will resume eflornithine at same dose. If hearing remains diminished as described above in comparison with pre-enrollment baseline, the eflornithine dose will be reduced by 25% (i.e. eflornithine of 5 g/m^2/day as in Appendix XII) during the next cycle. Patients who have eflornithine held more than once for hearing loss, but return to baseline after hold, will have the eflornithine dose reduced by 25% for subsequent cycles. Patients who are receiving eflornithine at the lowest dose level (3750 mg/m^2/day) for hearing loss and have recurrent or progressive hearing loss despite dose reduction will stop protocol therapy.

5.2.7.2 Diarrhea occurring during single agent eflornithine lead-in (Days -6 to 1)

See Appendix V for patient/family instructions for supportive care measures for patients who develop therapy-associated diarrhea. Also included are specific instructions for loperamide dosing.

If eflornithine is stopped for any reason and then resumed at a lower dose, at least 5 days of the decreased dose of eflornithine should be given prior to starting Day 1 of the next cycle of chemotherapy, per Section 5.2.

If Grade 4 therapy-associated diarrhea is experienced by a patient with no evidence of infectious etiology and despite maximal use of anti-diarrheal medications, the eflornithine dose should be held until diarrhea has resolved to Grade 1 or less and then restarted with a 25% reduction of the original dose (i.e. eflornithine of 5 g/m^2/day).

If Grade 4 therapy-associated diarrhea recurs again without an infectious etiology and despite maximal use of anti-diarrheal medications, the eflornithine dose should be held again until diarrhea has resolved to Grade 1 or less and then decreased by an additional 25% (i.e. eflornithine of 3.75 g/m^2/day).

If Grade 4 diarrhea recurs during single agent lead-in despite maximal use of anti-diarrheals, and the dose reductions, the patient should come off protocol therapy.

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the Commercial Agent Monographs (https://www.cogmembers.org/_files/disc/pharmacy/CommercialAgentsMonographs.pdf) and is provided under Standard Sections for Protocols at: https://cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials.

6.1

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

6.2 DINUTUXIMAB (04/30/19)

(Unituxin®, MoAb 14.18, chimeric; human/murine anti-G_{D2} monoclonal antibody; chimeric anti-G_{D2}; chimeric mAb 14.18; ch14.18) NSC# 764038

Source and Pharmacology:

Dinutuximab (ch14.18, UTC) is an anti-G_{D2} monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.G2a and the human constant region genes for heavy chain IgG_1 and light chain kappa. Dinutuximab exerts its antitumor effect by binding specifically to the disialoganglioside G_{D2}, an antigen found in human tumors of neuroectodermal origin such as melanoma and neuroblastoma. This chimeric antibody has been shown to lyse melanoma and neuroblastoma cells through the process of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. By targeting the G_{D2} antigen on the cell surface, dinutuximab may also prevent attachment of circulating malignant cells to the extracellular matrix. Additionally, dinutuximab mediates lysis of several melanoma and neuroblastoma cell lines in a dose dependent manner in the presence of potent mediators of ch14.18-dependent cytotoxicity, such as human peripheral blood mononuclear cells and granulocytes. This is most profound with neutrophils, especially in the presence of recombinant human granulocyte-macrophage colony-stimulating factor.

The PK profile of dinutuximab has been determined in adults with melanoma and children with neuroblastoma. Although the plasma clearance for both groups of patients follow a two-compartment model, circulating antibody is cleared from the plasma at a much faster rate in children than adults (mean $t_{½}\beta = 66.6 \pm 27.4$ hours in children versus 123 ± 29 hours and 181 ± 73 hours in two adult trials, respectively). Maturation of the hepatic and renal systems with age is thought to impact on drug metabolism and elimination and could account for these differences. In general, the mAb half-life following the first course of treatment was longer than the half-lives following subsequent courses in a given patient.

Patient care implications:

Based on its mechanism of action, dinutuximab may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for two months after the last dose of dinutuximab.

It is not known if dinutuximab is excreted in breast milk. IgG molecules are excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Dinutuximab (MoAb 14.18, chimeric, NSCs 623408 and 764038)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. *Frequency is provided based on 359 patients.* Below is the CAEPR for dinutuximab (MoAb 14.18, chimeric).

Version 2.9, January 10, 2019[60]

Adverse Events with Possible Relationship to dinutuximab (CTCAE 5.0 Term) [n= 359]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Disseminated intravascular coagulation	
		Hemolytic uremic syndrome[61]
CARDIAC DISORDERS		
		Cardiac arrest
		Sinus bradycardia
	Sinus tachycardia	
EYE DISORDERS		
		Eye disorders - Other (eye disorders)[62]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Diarrhea	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fever		
	Generalized edema	
Pain		
		Sudden death NOS
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
	Serum sickness	

Adverse Events with Possible Relationship to dinutuximab (CTCAE 5.0 Term) [n= 359]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
INFECTIONS AND INFESTATIONS		
	Infection[63]	
		Myelitis[64]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Creatinine increased	
Investigations - Other (elevated c-reactive proteins)		
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperkalemia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypokalemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Back pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Neuralgia	
		Peripheral motor neuropathy
	Peripheral sensory neuropathy[65]	
		Reversible posterior leukoencephalopathy syndrome
RENAL AND URINARY DISORDERS		
	Proteinuria	
		Renal and urinary disorders - Other (atonic urinary bladder)[6]
	Urinary retention[65]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Bronchial obstruction	

Adverse Events with Possible Relationship to dinutuximab (CTCAE 5.0 Term) [n= 359]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Cough		
	Dyspnea	
	Hypoxia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	
Rash maculo-papular		
	Urticaria	
VASCULAR DISORDERS		
	Capillary leak syndrome	
	Hypertension	
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]There have been rare instances of atypical hemolytic uremic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anemia, and hypertension.

[3]Neurological disorders of the eye including blurred vision, diplopia, cycloplegia, mydriasis, photophobia, optic nerve disorder, eyelid ptosis, and fixed pupils have been observed.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]Myelitis expressed as transverse myelitis has occurred in patients treated with dinutuximab. Symptoms may include weakness, paresthesia, sensory loss, or incontinence.

[6]Acute urinary retention occurs during therapy and is thought to be due to fluid shifts and narcotic administration that accompany dinutuximab administration. Atonic urinary bladder results in chronic urinary retention (CUR) that requires intermittent urethral catheterization days to weeks following dinutuximab administration.

Adverse events reported on dinutuximab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that dinutuximab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (thrombotic microangiopathy [e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]); Bone marrow hypocellular; Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Cardiac disorders - Other (gallop on exam); Cardiac disorders - Other (N-terminal BNP); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Mobitz (type) II

atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired
ENDOCRINE DISORDERS - Endocrine disorders - Other (transient hypoaldosteronism); Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Papilledema; Periorbital edema; Scleral disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Constipation; Duodenal obstruction; Dysphagia; Enterocolitis; Esophageal stenosis; Esophageal ulcer; Esophagitis; Gastrointestinal disorders - Other (bleeding, NOS); Gastrointestinal disorders - Other (esophageal stricture); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastroparesis; Hemorrhoidal hemorrhage; Ileus; Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Mucositis oral; Oral pain; Rectal hemorrhage; Stomach pain; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Edema trunk; Fatigue; General disorders and administration site conditions - Other (cold and clammy); General disorders and administration site conditions - Other (vascular leak syndrome); Hypothermia; Injection site reaction; Localized edema; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Cholesterol high; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Fibrinogen decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count increased; Urine output decreased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hypoglycemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Chest wall pain; Muscle weakness lower limb; Myalgia; Neck pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Headache; Hydrocephalus; Meningismus; Movements involuntary; Nystagmus; Oculomotor nerve disorder; Paresthesia; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Delirium; Hallucinations; Insomnia; Irritability; Personality change; Restlessness
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Hematuria; Renal and urinary disorders - Other (acute renal insufficiency); Renal and urinary disorders - Other (urethritis); Renal hemorrhage
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Ovarian hemorrhage; Pelvic pain; Penile pain; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Atelectasis; Bronchospasm; Laryngeal edema; Laryngopharyngeal dysesthesia; Laryngospasm; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Stridor; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hyperhidrosis
VASCULAR DISORDERS - Flushing

Note: dinutuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Formulation and Stability:
Dinutuximab is provided as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM Histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8. Intact vials should be stored in the refrigerator at 2ºC to 8ºC (36°F to 46°F); do not freeze. Do not shake. Keep the vial in the outer carton to protect from light. Solutions diluted for infusion should be stored at 2°C to 8°C (36°F to 46°F). Initiate infusion within 4 hours of preparation. Discard diluted solution 24 hours after preparation.

Must be diluted prior to infusion. Withdraw the required dinutuximab volume and inject into a 100 mL bag of NS. Mix by gentle inversion; do not shake. Discard unused vial contents. Initiate infusion within 4 hours of preparation. Do not use if cloudy, discolored (pronounced), or contains particulates. The use of a filter during preparation is not required. The final prepared product of dinutuximab in NS is stable at room temperature for 24 hours when diluted to a concentration between 0.044 mg/mL and 0.56 mg/mL; however, the final dosage form should be prepared immediately prior to administration as there is a maximum infusion time of 20 hours.

Guidelines for Administration:
See Treatment, Dose Modifications and/or Supportive Care sections of the protocol.

Administer as an IV infusion only (the minimum dinutuximab infusion time is 10 hours up to a maximum of 20 hours); **do not administer as an IV push or bolus.** Administer NS 10 mL/kg IV over 1 hour just prior to each dinutuximab infusion. Premedicate with analgesics, an antihistamine, and an antipyretic prior to administration. Infuse in an environment equipped to monitor for and manage infusion reactions. Interrupt infusion for toxicity. Monitor patients closely for signs and symptoms of an infusion reaction during and for at least 4 hours following completion of each dinutuximab infusion.

Supplier:
Commercially available. See package insert for further information.

CANADIAN SITES:
Commercially available through McKesson Canada.

AUSTRALIA AND NEW ZEALAND SITES:
United Therapeutics will provide dinutuximab via expanded access program to the COG sites in Australia and New Zealand that had ANBL0032 study open in the past. Dinutuximab can only be used in accordance with the United States prescribing information. IDIS Managed Access will be utilized for this program. Prescribers can order dinutuximab for new patient starts by requesting a copy of updated IDIS patient access form at global@idispharma.com

6.3 IRINOTECAN (12/18/18)

[CPT-11, Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348

Source and Pharmacology:
Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from *Camptotheca acuminata)*. Irinotecan is a prodrug that requires conversion,

by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN-38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

Toxicity:

Incidence	Toxicities
Common (>20% of patients)	• Anemia • Thrombocytopenia • Neutrophil count decreased • White blood cell count decreased • Nausea • Vomiting • Constipation • Anorexia • Fever • Asthenia • Cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and diarrhea) • Alopecia • Bilirubin increased • Mucositis • Dyspnea • Cough • Weight loss • Pain
Occasional (4-20% of patients)	• Abdominal fullness • Flatulence • Vasodilation • Hypotension

	• Dehydration • Edema • AST increased • Alkaline phosphatase increased • Ascites • Jaundice • Febrile neutropenia • Infection • Headache • Dizziness • Chills • Insomnia • Rash • Dyspepsia • Somnolence • Thromboembolic events • Pneumonia
Rare (≤ 3% of patients)	• Anaphylaxis • Bradycardia • Disorientation/confusion • Colitis • Renal failure (secondary to severe dehydration) • Ileus • Pancreatitis • Pneumonitis (L)
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.

(L) Toxicity may also occur later

Formulation & Stability:
Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL), 100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL). Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

IV Administration: Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in D5W, (preferred) or NS to a final concentration range of 0.12-2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in D5W and stored at refrigerated temperatures (approximately 2°-8°C), and protected from light are

physically and chemically stable for 48 hours. Refrigeration of admixtures using NS is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

Supplier:
Commercially available from various manufacturers. See package insert for more detailed information.

6.4 SARGRAMOSTIM (06/26/18)

(Granulocyte Macrophage Colony Stimulating Factor, rhu GM-CSF, rGM-CSF, GM-CSF, Leukine®) NSC #613795

Source and Pharmacology:
Sargramostim (recombinant human GM-CSF) is a glycoprotein produced in yeast (*S. cerevisiae*) by recombinant DNA technology. rGM-CSF is a hematopoietic growth factor which supports survival, clonal expansion, and differentiation of hematopoietic progenitor cells. rGM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways. rGM-CSF stimulates the production of monocytes, granulocytes, erythrocytes, and sometimes, megakaryocytes in the bone marrow. It also induces mature neutrophil and monocytes to increase phagocytosis, superoxide generation, ADCC, tumoricidal killing and cytokine production (IL-1 and tumor necrosis factor). Recombinant human GM-CSF is a glycoprotein of 127 amino acids characterized by three primary molecular masses of 15500, 16800, and 19500 daltons. The amino acid sequence differs from the natural sequence by a substitution of leucine at position 23 and the CHO moiety may be different from the native protein. After subcutaneous administration of sargramostim, peak levels were obtained in 1-4 hours and were detectable at therapeutic levels for 12-16 hours post injection. The elimination $t_{½}$ ranges from 1.5-2.7 hours after SubQ or IV administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Headache, malaise, fatigue, rash, pruritus, bone pain, myalgia, arthralgia, fever, chills	Abdominal pain, weakness, anorexia, nausea, local injection reactions	Anaphylaxis, "first dose reaction" (hypoxia, dyspnea, hypotension, fever, tachycardia, diaphoresis, flushing, back pain), vomiting, diarrhea, phlebitis, SVT, pericardial effusion
Prompt: Within 2-3 weeks, prior to the next course		Weight gain	In high doses: capillary leak syndrome: (pleural effusion, peripheral edema, ascites, weight gain, hypotension), pneumonitis, peripheral edema, elevation of creatinine, bilirubin and hepatic enzymes in patients with pre-existing renal or hepatic dysfunction
Delayed:		Thrombocytopenia	

Any time later during therapy			
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: It is not known whether sargramostim can cause fetal harm or affect reproduction capacity when administered to a pregnant woman. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Sargramostim is available as a lyophilized sterile, white, preservative free powder with 250 mcg (1.4 million International Units) per vial. The sargramostim reconstituted lyophilized vial contains 40 mg/mL mannitol, *USP*; 10 mg/mL sucrose, NF; and 1.2 mg/mL tromethamine, *USP*, as excipients. Store refrigerated at 2-8°C (36-46°F). Do not freeze or shake.

Guidelines for Administration:
See Treatment and Dose Modifications and Supportive Care sections of the protocol.

Reconstitute lyophilized powder for injection with 1 mL SWFI or 1 mL Bacteriostatic Water for Injection. **Use SWFI without benzyl alcohol for neonates, infants, and children < 2 years of age or patients with hypersensitivity to benzyl alcohol**. During reconstitution, direct the diluent at the side of the vial and gently swirl the contents to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake. Reconstituted solutions prepared with Bacteriostatic Water for Injection (0.9% benzyl alcohol) or the liquid preserved solution may be stored for up to 20 days following the first entry into the vial at 2°-8°C (36°-46°F). Discard reconstituted solution after 20 days have elapsed. Reconstituted solutions prepared with SWFI (without preservative) should be administered as soon as possible and within 6 hours following reconstitution.

Use sargramostim for subcutaneous injection without further dilution. Perform dilution for IV infusion in NS. If the final concentration is < 10 mcg/mL, add albumin (human) at a final concentration of 0.1% to the saline prior to addition of sargramostim to prevent adsorption to the components of the drug delivery system. For a final concentration of 0.1% albumin (human), add 1 mg albumin (human) per 1 mL NS. For example, for a final volume of 50 mL NS, add 50 mg (or 1 mL) of 5% albumin [human]. Intravenous dilutions are stable for up to 48 hours at room temperature or refrigerated but should be used within 6 hours due to microbiological concerns. Do not use an in-line membrane filter for IV infusion.

Supplier:
Commercially available. See package insert for more detailed information.

CANADIAN SITES
Sargramostim is not commercially available in Canada. Sites may purchase and import the USA commercial supply of Lyophylized Leukine® distributed by Partner Therapeutics via an International Distributor (Pharma Exports LLC; [redacted] under the authority of the protocol's No Objection Letter (NOL).

The Canadian Senior Medical Officer (SMO)'s office is responsible for coordinating the "Fax Back" approval with Health Canada's Biologics and Genetic Therapies Directorate for all lots for use in Canada on behalf of all Canadian sites. A list of approved lot numbers is posted on the C17 website (www.c17.ca) under the protocol titled Sargramostim. If an

unapproved lot is received from the distributor, quarantine the lot and contact the COG Canada Regulatory Affairs Office at c17@albertahealthservices.ca.

Canadian sites must keep a drug accountability log (DAL) and must record Lot #'s and expiry dates of shipments received and doses dispensed. Sites may use their own DAL as long as it complies with all elements of ICH GCP and Health Canada's Division 5 of the Food and Drugs Act. Each site is responsible for the procurement (import +/- purchase) of sargramostim. Sites may import and manage a single clinical trial supply for multiple protocols as long as each protocol has an NOL and the protocol the patient is registered on is recorded on the DAL.

6.5 TEMOZOLOMIDE (08/26/20)

(Temodar®, Temodal®) NSC #362856

Source and Pharmacology:
An orally or intravenously administered alkylating agent, a second generation imidazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH.

The cytotoxic effects of MTIC are manifested through alkylation (methylation) of DNA at the O^6, N^7 guanine positions which lead to DNA double strand breaks and apoptosis. Temozolomide is noncell cycle specific.

Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median T_{max} increased by 2-fold (from 1-2.25 hours) when temozolomide was administered after a modified high-fat breakfast. A pharmacokinetic study comparing oral and intravenous temozolomide in patients with primary CNS malignancies showed that at 150 mg/m^2 dose temozolomide IV and oral capsules are bioequivalent with respect to both C_{max} and AUC of temozolomide and MTIC. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%. Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. About 38% of the administered temozolomide total radioactive dose is recovered in the urine. Overall clearance of temozolomide is about 5.5 L/hr/m^2. Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m^2/day. A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

The table below lists the anticipated toxicity profile of temozolomide (oral):

Incidence	Toxicities
Common (>20% of patients)	Constipation, nausea, vomiting, , anorexia, alopecia, headache, seizure, fatigue
Occasional (4-20% of patients)	Peripheral edema, skin rash, pruritus, xeroderma, erythema of skin, diarrhea, dysphagia, dizziness, ataxia, hemiparesis, asthenia, fever, stomatitis, abdominal pain, dysgeusia, weight gain, platelet count decreased, white blood cell count decreased, lymphocyte count decreased, urinary incontinence or frequency, cough, dyspnea, infection, anxiety, depression, insomnia, gait disturbance, amnesia, paresthesia, drowsiness, visual disturbances, back pain, arthralgia/myalgia
Rare (≤ 3% of patients)	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hyperbilirubinemia, transaminitis, injection site reaction (IV formulation), interstitial pneumonitis, pancytopenia (may be prolonged), myelodysplastic syndrome, leukemia secondary to oncology chemotherapy, infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatotoxicity, cholestasis, anemia, aplastic anemia
Pregnancy & Lactation	**Pregnancy Category D** Adequate, well-controlled studies have not been conducted in humans. Women of childbearing potential should be advised against becoming pregnant while taking temozolomide and for at least 6 months following the end of therapy. Temozolomide administration to rats and rabbits at 3/8 and 3/4 the human dose resulted in the development of malformations of the external organs, soft tissues, and skeleton. These animal studies also demonstrated embryolethality (increased resorptions) at similar doses. There is no information available regarding the transmission of temozolomide during lactation; women should avoid breastfeeding while receiving temozolomide.

Formulation and Stability:
Temozolomide capsules are available in six different strengths (5, 20, 100, 140, 180, 250 mg). The capsules vary in size, color, and imprint according to strength. In the US, capsules are packaged in 5-count and 14-count bottles. In other countries temozolomide may be packaged in 5-count, 14-count or 20-count bottles. Temozolomide capsules are stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

There is a potential for medication errors involving temozolomide capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule.

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

Each strength of temozolomide must be dispensed in a separate vial or in its original container (e.g., bottle or sachet). Based on the dose prescribed, determine the number of

each strength of temozolomide capsules needed for the full course as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250 mg capsules, five 20 mg capsules, and five 5 mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each bottle or vial to equal the total daily dose prescribed by the physician. Institutions that have the capability to dispense temozolomide as daily doses in a blister pack may do so, taking specific precautions to ensure that the appropriate dose is provided and that the patient is educated to understand the daily dosing regimen.

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10 mg/mL suspension triturate the contents of ten 100 mg capsules (1000 mg), 500 mg povidone K-30 and 25 mg anhydrous citric acid dissolved in 1.5 mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100 mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension should be stored in the refrigerator at 2°-8°C (36°-46°F) for no more than 2 weeks after preparation. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension.[66]

Extemporaneous temozolomide 10 mg/mL suspension can also be prepared using 100 mg temozolomide capsules mixed in Ora-Mix SF®. Open contents of the required number of 100 mg temozolomide capsules into a mortar and add Ora-Mix SF® until a paste forms. Add more vehicle until a liquid is formed (for each 100 mg capsule add 10 mL of Ora-Mix SF®). Transfer desired volume to a glass or polyethylene terephthalate bottle. Label the container, assigning a beyond-use-date of 30 days, for storage under refrigeration only.[67]

Alternatively, the capsules can be opened and mixed with apple sauce or juice, which should be used immediately after mixing or must be used in 2 hours after mixing (refer to Appendix VIII).

Supplier:
Commercially available. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy & Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

STUDIES TO BE OBTAINED	End of Therapy	Disease Progression	Follow up			
			Year 1	Year 1	Year 1	Years 2 -5
			30 days	6 months*	12 months*	Annually*
History	X					
Physical Exam with VS	X					
Ht, Wt, BSA	X					
Performance Status	X					
CBC, differential, platelets	X					
Electrolytes, BUN, Creatinine	X					
ALT, total bilirubin, albumin	X					
CT/MRI[1]	X[2]	X				
MIBG (or FDG-PET if ^{123}I-MIBG non-avid disease)	X[2]	X				
Bilateral bone marrow aspirates and biopsies	X[2]	X				
Audiogram	X		X[3]		X	
Disease status	X		X	X	X	X
Toxicity/Significant events	X		X	X	X	X
Survival/Vital status	X		X	X	X	X

* +/- 2 months

1. Cross-sectional imaging should be of the original primary site and any non-osseous disease sites present at study enrollment or at time of progression.
2. For patients who experienced their first response (MR, PR, CR) at the time of the end therapy evaluation, a complete confirmatory disease evaluation should be performed *at least* 4 weeks after the end of therapy evaluation.
3. If the patient underwent an audiogram within 28 days prior to end of therapy (ie, at the end of the previous cycle), the end of therapy audiogram should be done 30 days +/- 7 days from the end of therapy date.

7.2 Research Studies for which Patient Participation is Required or Optional

See Section 14.0 for Special Studies requirements. Required studies are detailed in Section 14.1 and optional studies (including specimens for biobanking) are detailed in Section 14.2.

A summary of specimens to be collected is provided in Appendix X. Every effort should be made to obtain samples from all time points, including the pre-therapy time point. However, if the pre-ANBL1821 therapy sample cannot be obtained, subsequent samples should still be collected as specified.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Stable disease after 6 cycles of protocol therapy for patients enrolled prior to Amendment 4.
c) Intolerance of study therapy or unacceptable toxicity due to protocol therapy (see Section 5.0).
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Completion of the maximum allowable number of cycles of therapy (see Section 4.1).
f) Physician determines it is in patient's best interest.
g) Second malignant neoplasm (SMN).
h) Patients who do not meet criteria to start the next treatment cycle within 21 days after the planned subsequent cycle start date (i.e. there is a ≥ 3 week delay in start of next cycle).
i) Pregnancy.
j) Repeat eligibility studies (if required) are outside the parameters required for eligibility (see Section 3.2).

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g. at time of progression or subsequent relapse).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

The proposed randomized Phase 2 study will require enrollment of 90 eligible patients, 45 assigned to each regimen. Enrollment may proceed up to 95 patients to allow up to 5% potentially ineligible patients.

Expected accrual for this study would be similar to the accrual rate of 42 patients/year observed on the ANBL1221 expansion cohort at non-Australian and New Zealand sites as the patient population and eligibility are very similar. We anticipate that given the positive results of ANBL1221 and the reality that this backbone has become widely used for first relapse, there should be similar accrual rates for this trial. Assuming this rate, the trial would take about 2.3 years to complete accrual of up to 95 patients. The study will require an additional 12 months for completion of therapy and toxicity evaluation for a total study duration of approximately 3.3 years.

The sample size may be increased if accrual is fast: specifically, if 30 months after the study commencement the average accrual rate over the previous 3 months is above an annual rate of 41 patients per year, then the study may be amended (blindly to the interim outcome data) and accrual increased to 148 eligible patients. In this case, enrollment may proceed up to 155 patients to allow up to 5% potentially ineligible patients. Assuming an accrual rate of 42 patients/year (this rate would be amended if needed based on observed accrual rate), the trial would take about 3.7 years to complete accrual and a total study duration of ~4.7 years. The amendment would be submitted after the 30-month time point so that the study will not need to be closed to accrual as a result of the increase in the target accrual.

9.2 Study Design

This will be a prospective, randomized phase 2 trial to determine whether the addition of DFMO to the dinutuximab/irinotecan/temozolomide backbone improves the response rate compared to the backbone alone. Patients will be randomized 1:1 to Regimen A (irinotecan/temozolomide/dinutuximab) or Regimen B (DFMO + irinotecan/temozolomide/ dinutuximab), stratified by 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), and *MYCN* status (amplified vs. non-amplified vs. unknown). We will monitor for differences in the response rate between the two regimens for early indication of futility and efficacy.

9.3 Methods of Analysis

9.3.1 Primary Endpoint

The primary endpoint will be the proportion of eligible patients who are responders. Responders are defined as patients who achieve a minor response (MR) or better, per the revised International Neuroblastoma Response Criteria (INRC),[68] as their best overall response by the end of 6 cycles as determined by central review. With Amendment 4, patients with a response of MR, PR, or CR that is qualified by "Not Fully Evaluated (NFE)" will be included as responders. See Section 10.2.3 and Appendix XIV for definition of NFE. Patients with progressive disease (PD) prior to attaining a ≥ MR will be considered non-responders. If a patient becomes a responder and later has PD or later goes off protocol therapy, then the patient will be counted as a responder. Eligible patients without any response assessment will be considered non-responders. All eligible patients will be considered evaluable for response. All analyses of response will be conducted as intent-to-treat.

Patients enrolled prior to Amendment 4: Patients will be assessed for response after every 2 cycles for the first 6 cycles, then after every 4 cycles for up to 11

additional cycles. Patients with stable disease or better during the first 4 cycles will be permitted to continue protocol therapy. However, after 6 cycles, patients not demonstrating a response [complete response (CR), partial response (PR), or MR] will be removed from protocol therapy. The decision to remove patients without response after 6 cycles is based on data from ANBL1221, where the majority of responders to I/T/DIN were found to have objective responses after 2 cycles but some patients did not achieve their best response until later cycles. Data including the expanded cohort of patients treated with I/T/DIN on ANBL1221 indicate that 12 of 22 responders (54.5%) experienced their best response after Cycle 2, with the remaining 10 of 22 (45.5%) responders achieving their best response by Cycle 6.[3]

Patients enrolled on Amendment 4 or later: Patients will be assessed for response after every 2 cycles and may receive a maximum of 6 cycles of protocol therapy. Patients with stable disease or better during the first 4 cycles will be permitted to continue protocol therapy. All patients will go off protocol therapy regardless of response after 6 cycles.

9.3.1.1 Power Calculations

With enrollment of 90 eligible patients (45 to each regimen), this design has 80% power to detect a 20% difference in response rate [40% under the null for Regimen A (as observed on the ANBL1221 including the expanded cohort of patients assigned to the I/T/DIN arm), 60% under the alternative for Regimen B] and type I error of 20%, using a one-sided continuity-corrected test of proportions with pooled variance.

If the study is amended and the sample size is increased to 148 eligible patients (74 on each regimen) due to fast accrual, a 15% difference in response rate will be targeted [40% under the null for Regimen A, 55% under the alternative for Regimen B]. This design has 80% power and type I error of 20%, using a one-sided continuity-corrected test of proportions with pooled variance and interim monitoring for efficacy with a one-sided O'Brien-Fleming rule.

9.3.2 Secondary Endpoints

Progression-free survival (PFS) and overall survival (OS) will be assessed for patients receiving dinutuximab, irinotecan, and temozolomide with and without the addition of DFMO. For PFS, time to event will be calculated from the time of randomization to the occurrence of relapse, progressive disease, or death. For OS, death will be the only event considered and time to death will be calculated from the time of randomization. Patients without a PFS event or death will be censored at the time of last follow-up.

9.3.3 Monitoring for Futility or Efficacy of Regimen B

Monitoring for futility or efficacy of the DFMO arm will be performed. There would be cause to stop the trial early if the response rate on Regimen B appears to be insufficiently efficacious or superior to Regimen A. The response rates will be monitored after 2 cycles to decrease the amount of time the study must be closed for interim analysis. ANBL1221 data showed that most patients that responded on

the I/T/DIN arm did so early, with 16 of the 22 patients with confirmed responses demonstrating partial response or better after the first 2 cycles. With Amendment 4, the interim analysis will be done using overall response, or if overall response was coded as Not Done due to a missing component of the disease evaluation, the response at soft tissue and bone sites will be used as the overall response at the end of Cycle 2.

Futility monitoring will be performed per Ellenberg and Eisenberger (1985):[69] if at half the sample size the observed response rate after 2 cycles for Regimen B is less than that for Regimen A, accrual will be halted and the DSMC will consider permanently stopping accrual. Due to the potential for a drug supply issue, the futility analysis will be performed sooner, after accrual of 40 patients rather than at half the sample size of 45 patients. The futility rule will be executed once, using data from the first 40 eligible patients enrolled. This two-stage rule has been shown to lead to a reduction in the expected sample size if Regimen B is ineffective, with minimal loss in power.[70]

A one-sided O'Brien-Fleming group-sequential boundary will be used to monitor for efficacy of Regimen B if the sample size is increased to 148 eligible patients. Interim monitoring will be performed at 50% of the expected information (N=74, 37 eligible patients per regimen), and 100% information. The critical p-values (upper boundary z-score) for the interim looks (maintaining an overall significance level of 20%) are 0.0699 (1.4763) at the first look, with the final analysis performed at a significance level of 0.1803 (0.9141).

If the futility and efficacy monitoring rules are not triggered, accrual will continue as planned, and the one-sided continuity-corrected test of proportions with pooled variance will be applied.

9.3.4 Assessment of Study Objectives

The primary study aim (1.1.1) will be assessed by a one-sided continuity-corrected test of proportions with pooled variance to compare the response rates after 6 cycles in the two regimens, and the futility and efficacy monitoring rules (Section 9.3.3). The response rate by the end of 6 cycles will be calculated on each regimen, including placement of a 95% confidence interval. If a patient is a responder and later has PD or goes off protocol therapy, then the patient will be counted as a responder. If the response rate on Regimen B is significantly better, then it will be considered a therapeutic regimen worthy of further testing in patients with newly-diagnosed high-risk neuroblastoma. In addition, the response rate by the end of 6 cycles (based on confirmed responses) will also be calculated for each regimen, with responders defined as patients who achieve a confirmed minor response or better per the revised INRC[68] as their best overall response by the end of 6 cycles as determined by central review.

To address secondary objective 1.2.1, Kaplan-Meier curves of PFS and OS will be generated by regimen and compared using log-rank tests. PFS and OS will also be evaluated separately in the cohorts of patients enrolled prior to and post-Amendment 4 given the reduction in maximum cycles of therapy from 17 to 6 cycles.

To assess secondary aim 1.2.2, toxicities (Grade ≥ 3) experienced on Regimen B will be descriptively summarized.

Exploratory aim 1.3.1 will be assessed by exploring the relationship between response (responder vs. non-responder) after 6 cycles on Regimen B with serum cytokine levels (IL1, IL6, TNF-alpha, IFN-gamma, etc.), tumor resident immune cells (NK cells, TAMS, TILS), and critical immune cell suppressing proteins (B7H3, PDL-1) using Fisher's exact test for categorical and Wilcoxon rank-sum test for continuous factors.

To address exploratory objective 1.3.2, GD2 levels in tumor cells from bone marrow samples will be correlated with response (responder vs. non-responder) after 6 cycles using Fisher's exact test for categorical and the Wilcoxon rank-sum test for continuous factors.

To assess exploratory aim 1.3.3, the occurrence of pain on each regimen as reported by patient report and opiate use will be descriptively summarized. Descriptive and summary statistics will be used to describe the scores from the Faces Pain Scale-Revised during the dinutuximab infusion and on Day 1 with irinotecan and temozolomide alone for each arm separately. Confidence intervals will be constructed for the mean and frequency estimates. The Day 1 patient reported outcome data are expected to be similar between the 2 regimens, while differences during or after completion of treatment may be observed.

9.4 Evaluability for Response

All eligible patients will be considered evaluable for response.

9.5 Evaluability for Toxicity

All eligible patients will be evaluable for toxicity from the time of their first treatment with eflornithine, irinotecan, temozolomide, or dinutuximab.

The study committee will review ototoxicity data closely during monthly committee meetings. If a difference in the incidence of hearing loss of >15% in eligible patients treated on the interrupted schedule enacted with Amendment 2A is detected among patients on the DFMO-containing Regimen B as compared to Regimen A, the study committee will notify the DSMC and CTEP and discuss potentially suspending accrual and further modifying the DFMO dose and/or schedule. In this context, hearing loss is defined as "an increase of 15dB or more from baseline in hearing threshold at two contiguous frequencies between 500-3000Hz" as this is the criterion for which DFMO is held for hearing loss.

9.6 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	

American Indian/ Alaska Native	0	0	0	0	0
Asian	0	3	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	8	5	0	0	13
White	18	29	5	10	62
More Than One Race	0	0	0	0	0
Total	26	37	5	10	78

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	0	0	0	0	0
White	4	7	2	0	13
More Than One Race	0	0	0	0	0
Total	5	10	2	0	17

This distribution was derived from ANBL1221.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.0 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria for Patients with Solid Tumors

This study will use the revised International Neuroblastoma Response Criteria (INRC) for disease assessment.[68] The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do **not** include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

10.2.1 Definitions

10.2.1.1 Evaluable for toxicity: All eligible patients will be evaluable for toxicity from the time of their first treatment with eflornithine, or irinotecan, temozolomide or dinutuximab.

10.2.1.2 Evaluable for response: All eligible patients will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

10.2.2 Disease Parameters

10.2.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable if they demonstrate clear evidence of progression after completion of radiation.

10.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed as per RECIST 1.1 criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

10.2.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

10.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.2.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.2.2.6 Bone lesions: Osteomedullary disease will be assessed using ^{123}I-MIBG scans or FDG-PET scans. Technetium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system (see Appendix IX for worksheet). SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

10.2.2.7 Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment time points (baseline and end of Cycles 2, 4, 6 and every 4th cycle thereafter if bone marrow

involvement at study enrollment or ***any*** history of bone marrow disease; end of Cycles 2 and 6 for those patients without bone marrow involvement at study enrollment and without ***any*** history of bone marrow involvement). The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[71] The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

10.2.3 Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

RESPONSE	**ANATOMICAL IMAGING + MIBG (FDG-PET[2]) IMAGING**
Complete Response (CR)	• < 10 mm residual soft tissue at primary site, AND • complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site
Partial Response (PR)	• ≥ 30% decrease in longest diameter (LD) of primary site • MIBG or FDG-PET uptake at primary site stable, improved or resolved
Progressive Disease (PD)	• > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND • a minimum absolute increase of 5 mm in longest dimension[3]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

[1]Not for use in assessment of metastatic sites
[2] For ^{123}I-MIBG non-avid tumors
[3] A mass that has not met PD measurement criteria but has fluctuating ^{123}I-MIBG avidity will not be considered progressive disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES[5]

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[1]) IMAGING

Complete Response (CR)	• Resolution of all sites of disease defined as:
	  • Non-primary target and non-target lesions measure < 10 mm AND
	  • Lymph nodes identified as target lesions decrease to a short axis < 15 mm, AND
	  • MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely

Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following:
	  • Non-target lesions may be stable or smaller in size AND
	  • No new lesions AND
	  • ≥ 50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥ 0.1 to ≤ 0.5 using as a reference the absolute score for bone lesions from time of enrollment[4,6]) or ≥ 50% reduction in number of FDG-PET avid bone lesions[3,4]

Progressive Disease (PD)	Any of the following:
	  • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid;
	  • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma;
	  • Any new bone site that is MIBG avid and that was not seen on the immediate prior scan;
	  • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma;
	  • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions;
	  • Relative MIBG score ≥ 1.2 using as reference the lowest absolute score for bone lesions since enrollment[4, 7]

Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions

[1] Used for MIBG non-avid tumors

[2] Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.

[3] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.
[4] MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes but the same imaging methodology should be used for all evaluations.
[5] Criteria for soft tissue metastasis not applicable if the patient has only bone metastasis; criteria for bone metastasis not applicable if the patient has only soft tissue metastasis.
[6] Relative Curie score when assessing patient for partial response: [Current Curie score for bone sites] / [Curie score for bone sites at enrollment].
[7] Relative Curie score when assessing patient for progressive disease: [Current Curie score for bone sites] / [Lowest Curie score for bone sites since enrollment].

BONE MARROW RESPONSE

RESPONSE	**BONE MARROW STATUS**[1]
Complete response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement
Progressive disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by > 2-fold and has > 20% tumor infiltration upon reassessment.
Minimal disease (MD)	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0-≤ 5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤ 5% tumor infiltration upon reassessment; or • Bone marrow with >5% tumor infiltration that has > 0-≤ 5% tumor infiltration upon reassessment.
Stable disease (SD)	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration upon reassessment but does not meet CR, MD or PD criteria

[1]Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

In determining overall response, Not Fully Evaluated (NFE) will be used when at least one component of response evaluation was not required and not performed for one or more of the 3 components required for overall response (this will be annotated CR, PR, MR, or SD).

If a component was not performed and was required by protocol, that component will be determined to be Not Done (ND) and the overall response will be Not Done.

RESPONSE	CRITERIA
Complete Response (CR)	All components meet criteria for CR
Partial Response (PR)	PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD.*
Stable Disease (SD)	SD in one component with no better than SD or NI in any other component; no component with PD.
Progressive Disease (PD)	Any component with PD

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.
For CR, PR, MR, SD – if one or more component evaluations were not required at that disease evaluation timepoint *AND* they were not performed at the timepoint in question– that response will be annotated as Not Fully Evaluated (NFE).

*Patients who enroll with marrow-only disease who have a marrow response of Minimal Disease will also be coded as having an overall response of Stable Disease.

See Appendix XIV for additional information regarding overall response assessment

10.2.4 Duration of Response

10.2.4.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR, PR, or MR (whichever is first recorded, even if annotated as NFE) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

10.2.4.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.2.5 Progression-Free Survival (PFS)

For PFS, time to event will be calculated from the time of randomization to first occurrence of relapse, progressive disease, or death. Patients without a PFS event will be censored at the time of last follow-up.

10.2.6 Response Review

All patients will have central review of imaging after Cycles 2, 4, and 6 to evaluate for response. See Section 15.2 for central review imaging guidelines and submission requirements.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under an NCI, COG, or industry sponsor IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease progression*" in the system organ class (SOC) "*General disorders and administration site conditions.*" Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (310) 640-9193. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs

to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions"*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero.*" Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss"* under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4, "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g. elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report must be submitted electronically via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

- Expedited AE reporting timelines are defined as:
    - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
    - **7 Calendar Days -** A complete expedited report on the AE must be submitted

within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Fax or email supporting documentation **for AEs related to investigational agents** to COG: Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator.

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (COG) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 **Protocol Specific Additional Instructions and Reporting Exceptions**

For Regimen A and Regimen B:

- **Grade 1-2 dehydration or Grade 3 dehydration ≤ 3 days duration does not require expedited reporting**
- **Grade 1-3 irritability does not require expedited reporting**
- **Grade 1-3 urine output decreased does not require expedited reporting**
- **Grade 1-2 decrease in vision or Grade 3 decrease in vision that resolves within 7 days of onset does not require expedited reporting**
- **Grade 1-3 capillary leak does not require expedited reporting**
- **Grade 1-3 anemia does not require expedited reporting**
- **Grade 1-3 white blood cell or neutrophil count decrease do not require expedited reporting**

11.11 **Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	**Grade 4**		**Grade 5**
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 **Routine Adverse Event Reporting**

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 3 and higher Adverse Events.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g. termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

13.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

No pathology review is planned for this study.

14.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

If the patient consents to banking, any specimens left over after the required and optional research studies described below have been performed will be banked at the Biopathology Center for future research studies.

A table of specimens to be collected is available in Appendix X.

14.1 Required Studies

All patients who provide consent will be eligible for all special studies on ANBL1821.

14.1.1 Immune profiling: Immune phenotyping

14.1.1.1 Specimen Schedule and Requirements

At each time point, collect either two sodium heparin (green top) tubes with 5 mL each of peripheral blood or one sodium heparin (green top) 10 mL tube (total of 10 mL).

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 1, Day 1 (Regimen B only)
- Cycle 1, post-completion of dinutuximab (collect a single sample between Day 6 and Day 9)
- Cycle 2, Day 1 (prior to initiation of Cycle 2 therapy)

Please do not collect the first sample until you contact the Children's Clinical Translation Discovery Core at Emory (CCTDC@emory.edu) to coordinate the date of first sample delivery, and before shipping each sample.

14.1.1.2 Specimen Processing

Samples must be shipped the same day as collected. Sites should plan ahead to avoid Friday or Saturday sample collection. Sample should not be refrigerated or frozen. Samples should be kept at room temperature until shipped. Specimen will be shipped at room temperature for overnight delivery.

14.1.1.3 Specimen Labeling

Tubes must be labeled with:

- The patient's COG ID number
- Specimen type (blood)
- Collection time point (e.g. Cycle 1, Day 6)
- Date collected

14.1.1.4 Specimen Shipping

These specimens will be shipped by FedEx Priority Overnight delivery directly to **the Emory University Children's Clinical and Translational Discovery Core (CCTDC).**

The peripheral blood sample for immune profiling by flow cytometry should be sent on the same day it was obtained. The sample should be shipped at room temperature overnight via FedEx Priority Overnight delivery.

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. **NO Friday or Saturday shipments will be allowed.**

Please do not collect the first sample until you contact the Children's Clinical Translation Discovery Core at Emory (CCTDC@emory.edu) to coordinate the date of first sample delivery, and before shipping each sample.

Specimens should be shipped the same day they are collected at room temperature but in an insulated Styrofoam container (provided by the institution) to prevent temperature fluctuations by Federal Express Priority Overnight delivery to the following address:

For questions about sample processing and shipping, please contact the CCTDC directly.

14.1.1.5 Methodology

We will obtain preliminary data regarding the number of T, B, and NK cells present in the circulation at baseline and after treatment with DFMO and the DFMO/chemo-immunotherapy combination. This T-B-NK panel quantifies these cells using flow cytometry. We will also freeze peripheral blood mononuclear cells (PBMCs), RNA and DNA for these immunogenomic studies.

Flow cytometry panel:

Lineage Panel	Live/Dead (L/D), CD45, CD3, CD4, CD8, CD19, CD14, CD45RA, CCR7, CD25, CD127, HLA-DR
NK Cell Panel	L/D, CD45, CD3, CD8, CD16, CD56, CD57, CD107a, CD158, CD314, CD335

14.1.2 Immune profiling: Cytokine analysis

14.1.2.1 Specimen Schedule and Requirements

At each time point, collect 5 mL of peripheral blood in a sodium heparin (green top) tube and process for plasma.

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 1, Day 1 (Regimen B only)
- Cycle 1, post-completion of dinutuximab (collect a single sample between Day 6 and Day 9)
- Cycle 2, Day 1 (prior to initiation of Cycle 2 therapy)

14.1.2.2 Specimen Processing

Process the sample within 30 minutes of collection. Centrifuge the blood at 1200 x *g* for 15 minutes at 4°C (preferred) or room temperature to separate the plasma (top layer) from the red blood cells (bottom, red layer). Quickly, evenly dispense (aliquot) the plasma into pre-labeled cryoprotective vials and cap the vials securely. Place a minimum of 0.25 mL into each cryovial. Immediately freeze the vials upright in a -70°C to -80°C freezer. Store frozen until ready for shipment.

14.1.2.3 Specimen Labeling and Shipping

Each cryovial must be labeled with:

- The patient's COG ID number
- Specimen type (plasma)
- Collection time point (e.g. Cycle 1, Day 1)
- Date collected

Plasma for cytokine analysis can be batched and shipped on dry ice to **the Emory University Children's Clinical and Translational Discovery Core (CCTDC)** after the Cycle 2, Day 1 sample is drawn and processed.

Specimens should be shipped on dry ice in an insulated Styrofoam container (provided by the institution) to prevent temperature fluctuations. Ship by Federal Express Priority Overnight delivery (see Section 14.1.1). See Section 14.1.1.4 for shipping instructions and address.

14.1.2.4 Methodology

The Emory University Children's Clinical and Translational Discovery Core (CCTDC) will perform ELISA to analyze the cytokines/chemokine changes due to DFMO or chemo-immunotherapy combination during the course of treatment. This testing will be performed using a multiplex cytokine array on a Luminex platform.

39-plex: IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, EGF, Eotaxin, FGF-2, Flt-3-ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, INF-γ, IP-10, MCP-1, MCP-3/CCL7, MDC/CCL22, MIP-1α, MIP-1β, TNFα, TNFβ, VEGF, sCD40L, TGFas, IL-2R

Single-plex: sIL6-R

14.1.3 Patient Reported Outcomes of Pain

Patients or their proxy for those under the age of 5 years, must complete the Faces Pain Scale-Revised. The Faces Pain Scale-Revised is a simple visual scale validated to provide a real-time (current) pain assessment in the pediatric population.[57] The scale scores pain based on a visual cue on a scale of 0 to 10.

14.1.3.1 Timing

Administer the Faces Pain Scale Revised at any time on Day -6 (Cycle 1 of Regimen B only) and Day 1 of therapy with irinotecan and temozolomide alone, and then on Days 2-5 of therapy at least 4 hours after the dinutuximab infusion has begun. It will be administered during Cycles 1, 2, 4, 6 for all patients and Cycle 12 of therapy for patients enrolled prior to Amendment 4.

14.1.3.2 Assessments

The assessments will be performed by the nurse caring for the patient at the appropriate time-points described above. The data will be entered in RAVE. The total daily intravenous narcotic dose will also be entered in RAVE.

14.2 Optional Studies

The following correlative studies are optional, but **strongly encouraged**. All patients will be eligible for all special studies on ANBL1821.

14.2.1 GD2 Biomarkers

14.2.1.1 Specimen Schedule and Requirements

Send 3-5 mL of bone marrow aspirates in heparinized (lithium heparin or sodium heparin) tube whenever they are obtained for disease evaluation.

14.2.1.2 Specimen Processing and Storage

No processing required, bone marrow aspirate samples will be sent fresh to the laboratory of Dr. C. Patrick Reynolds.

14.2.1.3 Specimen Labeling

Heparinized tube must be labeled with:

- The patient's COG ID number
- Specimen type
- Collection Time Point (e.g. Cycle 2, Day 21)
- Collection date

14.2.1.4 Specimen Shipping

The heparinized bone marrow should be sent in aseptic secure containers, at 4°C or room temperature but in an insulated Styrofoam container (provided by the institution) to prevent temperature fluctuations. Please ship overnight to:

Saturday deliveries will be accepted. **Please contact the laboratory by email or phone when shipping for arrival on weekends or holidays.** For questions about sample processing and shipping, please contact Dr. Reynolds' lab directly.

14.2.1.5 Methodology

For bone marrow aspirates, a multi-color flow cytometry with directly labeled dinutuximab as well as antibodies (HSAN + 459) that bind to neuroblastoma (but not to marrow or blood cells) is used to detect all neuroblastoma cells and accurately quantify the amount of dinutuximab bound and the percent of neuroblastoma cells binding to it. These studies will be overseen by Dr. C. Patrick Reynolds at Texas Tech University Health Sciences Center.

14.2.2 Specimens for Biobanking

If the patient has consented to banking of material for future research then tumor tissue, urine, and whole blood should be collected and submitted as detailed below. Every effort should be made to obtain samples from all time points, as appropriate for consenting patients.

All material to be used for future research will be banked at the Biopathology Center.

14.2.2.1 Whole Blood Collection

5 mL of whole blood should be collected (2.5 mL in a PAXgene DNA tube and 2.5 mL in a PAXgene RNA tube).

If consent for specimen biobanking is signed, please contact the CCTDC immediately after patient enrollment to obtain PAXgene tubes.

Phone: 404-727-2342
Email: CCTDC@emory.edu

Collection Time
A single blood sample should be obtained prior to the start of therapy on ANBL1821. The WBC count on the day of the blood draw should be > 1,000/mm^3 (sufficient for DNA extraction).

Specimen Handling
Gently invert the PAXgene tubes 8-10 times after collection. Keep the tubes at room temperature for 2 – 72 hours and then freeze upright in a wire rack (**NOT Styrofoam holder**) for 24 hours at -20°C and then transfer to -70°C or -80°C freezer until ready to batch ship. If a -70°C or a -20°C freezer is unavailable, then freeze on dry ice and ship frozen to BPC on the day of collection.

Labeling
Label each tube with the following information:
- COG patient ID number
- BPC number
- Specimen type (blood)
- Date and time of collection

Shipping
See Section 14.3.2 for details on ordering a specimen procurement kit and shipping frozen specimens to the **Biopathology Center**.

14.2.2.2 Tissue Collection

Please submit representative frozen tumor tissue, as well as matching paraffin embedded tumor tissue, as described below. Frozen tissue is preferred over paraffin embedded tissue.

Collection Time
Tumor tissue samples are requested at the following time points:
- Most recent relapsed tissue biopsy performed before study enrollment. For patients who have refractory or progressive disease, most recent tissue biopsy prior to study registration (2nd look surgery is acceptable). Initial diagnostic tissue is not acceptable unless no other tissue is available to be submitted. Please notify study chair if submitting diagnostic tissue.
- Any time patient undergoes biopsy (or resection) of either primary or metastatic tumor while on study.

- Any soft tissue biopsy done post-completion of ANBL1821 therapy and prior to the start of any other therapy.

Specimen Handling

- *Snap Frozen Tumor Tissue*
  Snap freeze tissue within 15 minutes after surgery for optimal preservation – immediately frozen in vapor phase liquid nitrogen or isopentane/dry ice. Cut at least one specimen from the primary tumor and metastatic areas into maximum 1 gram aliquots. Place each aliquot of tissue in a labeled cryovial and snap freeze in vapor phase liquid nitrogen (do not submerge) or on dry ice.

- *Paraffin Embedded Tumor Tissue*
  Paraffin tissue blocks or slides can be stored at room temperature.

  Submit the following materials:
  - 2 H and E stained slides of tumor from each block
  - 10 unstained slides (5 micron) from the most representative blocks (not necessary to send slides from every block)
  - Additional paraffin embedded blocks not required for diagnosis or institutional quality control (optional)

Labeling

Label the frozen tissue specimens with the following information:

- COG patient ID number
- BPC number
- Specimen type (P for primary, M for metastatic, or BM for bone marrow)
- Collection time point
- Date collected

Label the blocks or slides with the following information:

- COG patient ID number
- Specimen type (P for primary, M for metastatic, or BM for bone marrow)
- Date collected
- Blocks and slides must also be labeled with the surgical pathology ID and block number from the corresponding pathology report

Shipping

See Section 14.3.1 for details on shipping blocks or slides. See Section 14.3.2 for details on ordering a specimen procurement kit and shipping frozen specimens to the **Biopathology Center**.

14.2.2.3 Urine Collection

15 mL of urine should be collected (minimum 5 mL) by clean-catch technique and transferred to a 2 mL clean screw-cap vials. Approximately 10 vials will be needed for each time point.

Collection Time
Urine samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 1, Day 1 (Regimen B only)
- Cycle 1, post-completion of dinutuximab (collect a single sample between Day 6 and Day 9)
- Cycle 2, Day 1 (prior to initiation of Cycle 2 therapy)

Specimen Handling
Urine-containing vials should be frozen at -80°C within 30 minutes of collection (or the specimen can be placed on dry ice for up to 4 hours prior to freezing).

Labeling
Label the tubes with the following information:

- COG patient ID number
- BPC number
- Date and time of sample collection
- Time point (include *treatment cycle*, *day of cycle*)
- Source of material (urine)

Shipping
Urine samples should be batched for individual patients and shipped frozen on dry ice to the **Biopathology Center** as described in Section 14.3.2.

14.2.2.4 Future Studies with Banked Biospecimens

An amendment for any correlative science studies to be performed on biological samples that are biobanked will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

14.3 Shipping Instructions for Specimens Submitted to the Biopathology Center

14.3.1 Blocks/Slides

FFPE blocks or unstained paraffin tissue slides should be sent to the COG Biopathology Center (BPC) at room temperature using the submitting institution's courier account.

An ANBL1821 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen. In addition, the corresponding pathology report must be included with the shipment.

Blocks/slides should not be shipped for Saturday delivery. See Section 14.3.3 for shipping address.

14.3.2 Frozen Specimens

Send in batch shipments to the BPC on dry ice in a specimen procurement kit. Leave enough space in the kit chamber for sufficient dry ice (4-5 lb.) to keep specimens frozen during shipment.

Ordering a Kit for the submission of frozen specimens:
The Biopathology Center (BPC) will provide a specimen procurement kit upon request to institutions in North America for batch shipments of frozen specimens. Kits are ordered via the BPC Kit Management application (https://ricapps.nationwidechildrens.org/KitManagement/).

An ANBL1821 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen. When tissue is submitted, the corresponding pathology report must also be included in the shipment.

Specimen Procurement Kit Instructions

1. Before specimens are placed into the specimen procurement kit, they first need to be placed in three separate layers of packaging. A set of biohazard and Tyvek diagnostic envelopes are provided in the kit for this purpose.
   a. Place the specimens in zip lock bags (**one bag per specimen type/time point**). Because specimens will be batch shipped from multiple time points, it is extremely important that all specimens be clearly labeled with the specimen type and time point.
   b. Place the zip lock bags in a biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope.
   c. Place the biohazard envelope inside a Tyvek envelope. Expel as much air as possible and seal the envelope.
2. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. Place the foam lid on top to insulate the specimens during shipment.
3. Place the transmittal form(s) and pathology report (when applicable) on top of the foam lid.
4. Close the outer lid of the specimen procurement kit and secure with filament or other durable sealing tape.
5. Sites in North American will print a shipping label via the BPC Kit Management application and attach to the top of the kit.
6. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.
7. Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355.

Ship frozen specimens on Monday through Thursday for a Tuesday through Friday delivery. Do not ship frozen specimens the day before a national holiday. See Section 14.3.3 for shipping address.

14.3.3 Shipping Address

Specimens that are designated to be shipped to the Biopathology Center should be shipped to the following address:

Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: NBLPG@nationwidechildrens.org

**Be sure to include the room number. Packages received without the room number may be returned to the sender.*

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

15.1 Timing of Imaging

To document tumor, standard CT, MRI, and MIBG (FDG PET/CT or PET/MRI scan if tumor is not MIBG avid) scans must be performed at the following time points:

- within 3 weeks prior to the start of protocol therapy
- end of Cycles 2*, 4 and 6*, then for patients enrolled prior to Amendment 4 every 4th cycle thereafter
- end of therapy*
- at relapse/progression

* Patients with no soft tissue (non-osseous) disease at baseline (i.e., MIBG avid bone lesions or bone marrow involvement only) are only required to undergo appropriate cross-sectional imaging (CT and/or MRI) of primary tumor site at the end of Cycles 2, 6, and end of therapy only. Additionally, CT and/or MRI are required for confirmatory imaging at least 4 weeks after first response is documented for those patients who do not continue on protocol therapy. This is in addition to MIBG (FDG PET/CT or PET/MRI scan if tumor is not MIBG avid) performed at all disease evaluation time points.

Note: Patients with any soft tissue disease (either measurable or non-measurable) at baseline are required to have CT/MRI, and MIBG (FDG PET/CT or PET/MRI scan if tumor is not MIBG avid) scans at all disease evaluation time points.

15.2 Imaging Required for Confirmation of Response Status

The pertinent imaging studies (CT/MRI and MIBG or FDG PET/CT or PET/MRI) of all patients after Cycles 2, 4, and 6 will be centrally reviewed. Additionally, central review of confirmatory imaging performed at least 4 weeks after first response was documented for those patients who do not continue on protocol therapy will be performed.

Central review will be performed by the Diagnostic Imaging Specialists of the Study Committee. They will review baseline scans and scans after Cycles 2, 4, and 6 for all patients. Radiology scans and corresponding reports will be sent to the IROC Rhode Island (formerly QARC). The results of the central review will not be returned to the institution.

For all patients after Cycles 2, 4, 6, and any patients with confirmatory response imaging after stopping protocol therapy, , the following must be submitted for central review:

Baseline, End of Cycles 2, 4, and 6 imaging and confirmatory response imaging (if applicable see Section 7.1) Scans:

- CT/MRI
- MIBG scan
- Curie Scoring Summary Sheet (submit via RAVE; see Appendix IX)
- FDG PET/CT or PET/MRI scan if tumor is not MIBG avid
- Copies of the reports for the scans submitted

Scans and corresponding reports should be submitted to IROC as soon as they are obtained.

For PET/CT or PET/MRI scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of ^{18}F-FDG PET/CT or PET/MRI scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found at the following link: https://imaging.cancer.gov/programs_resources/reports_publications/publications/clinical_trials_guidelines.htm[72]

15.3 Image Submission

Submission of Diagnostic Imaging data in digital DICOM format is required. These files should be submitted electronically via TRIAD, sFTP or Dicommunicator. Information for TRIAD is below. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Sites using Dicommunicator may submit imaging via that application.

Submission by CD is discouraged. Only when electronic submission is not possible, the imaging may be burned to a CD and mailed to IROC RI. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Contact IROC RI with questions or for additional information. The required Diagnostic Imaging reports should be submitted electronically with the DICOM files.

If submitted via CD send to:
IROC Rhode Island QA Center

Building B, Suite 201
640 George Washington Highway
Lincoln, Rhode Island 02865-4207

For questions regarding data submission please contact:
E-mail to DataSubmission@QARC.org
Phone: (401) 753-7600

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM, DICOM RT and other digital files. The TRIAD software anonymizes, encrypts and validates the images as they are transferred.

Site staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.

To submit images, the site TRIAD user must be on the listed on the enrolling site's roster in CTSU and be assigned the 'TRIAD site user' role. Users should contact their site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit the image files. TRIAD installation documentation can be found by following this link: https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

For support with the TRIAD application, please send an e-mail to TRIAD-Support@ACR.org.

16.0 RADIATION THERAPY GUIDELINES

No radiation therapy is planned for this study.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting
Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and

- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

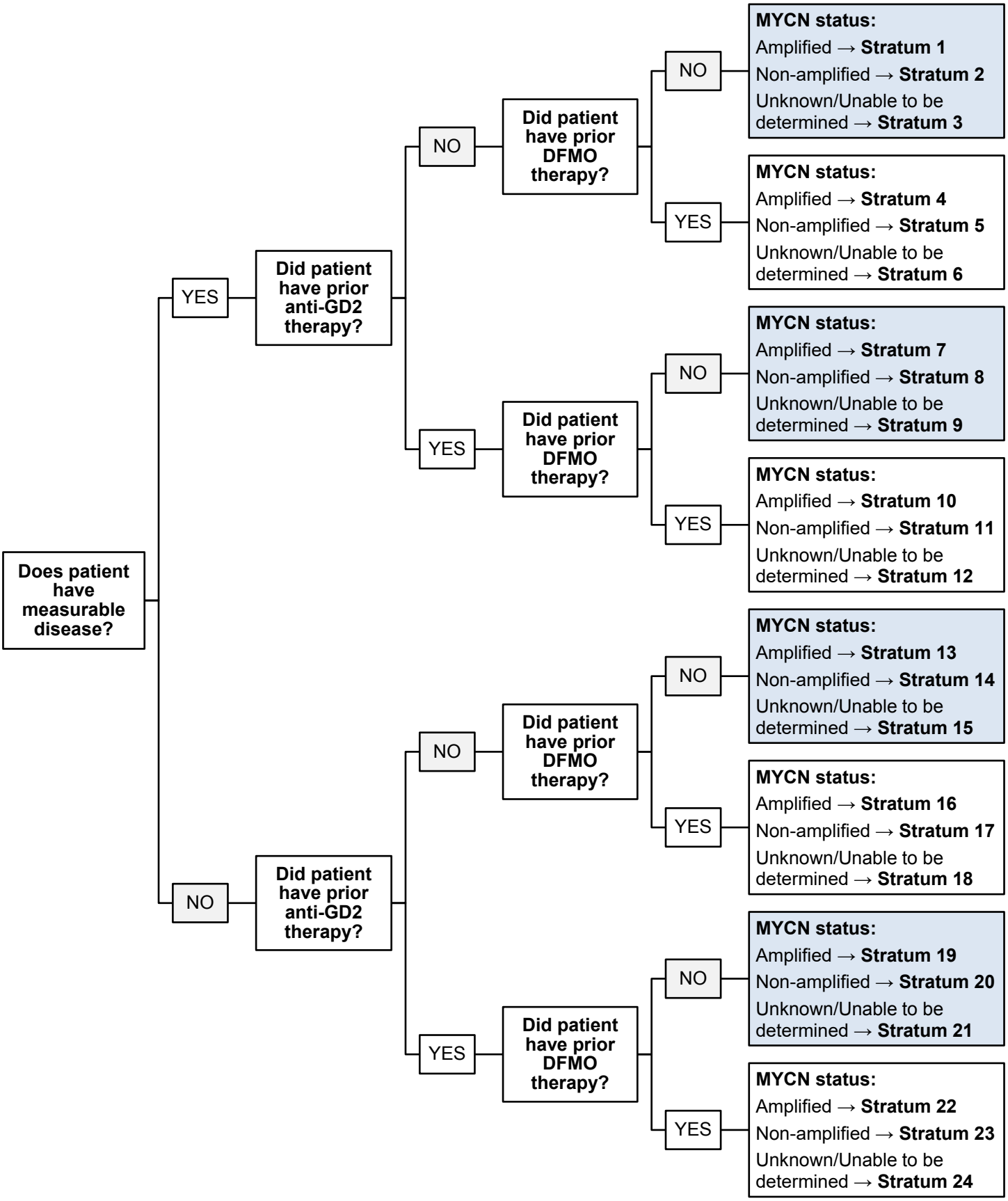
The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

APPENDIX II: PATIENT STRATIFICATION FLOWCHART



APPENDIX III: UNACCEPTABLE ENZYME INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Recommended Non-enzyme inducing anticonvulsants
Clonazepam
Diazepam
Ethosuximide
Ezogabine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Perampanel
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Carbamazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine

APPENDIX IV: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
abemaciclib acalabrutinib[5] alfentanil[4,5] alprazolam[5] amiodarone[4] amlodipine aprepitant/fosaprepitant atorvastatin avanafil[5] axitinib bortezomib bosutinib[5] brexpiprazole brigatinib budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] colchicine[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] ebastine[5] eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] felodipine[5]	atazanavir boceprevir clarithromycin ceritinib cobicistat danoprevir/ritonavir darunavir delavirdine elvitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ ombitasvir +/- dasabuvir posaconazole ritonavir saquinavir telaprevir telithromycin tipranavir/ritonavir tucatinib voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone duvelisib erythromycin fedratinib fluconazole fosamprenavir fosnetupitant grapefruit[3] grapefruit juice[3] imatinib isavuconazole lefamulin letermovir mifepristone netupitant nilotinib ribociclib verapamil	apalutamide barbiturates carbamazepine enzalutamide fosphenytoin lumacaftor/ ivacaftor mitotane phenobarbital phenytoin primidone rifampin St. John's wort	bosentan cenobamate dabrafenib efavirenz eslicarbazepine etravirine lorlatinib modafinil nafcillin pexidartinib rifabutin rifapentin

fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib lomitapide[5] lorlatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil naloxegol[5] nefazodone nilotinib nisoldipine[5] olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen tadalafil[5] telaprevir				

temsirolimus teniposide tetracycline ticagrelor[5] tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.3.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX V: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight.

Early diarrhea
Early onset diarrhea associated with irinotecan is usually preceded by sweating and abdominal cramping. Patients who have the onset of these symptoms followed by diarrhea within several hours after taking irinotecan should contact the treating physician immediately. The treating physician may consider treatment with atropine. If symptoms do not improve with administration of atropine, treatment for late diarrhea (as outlined below) should be started.

Late diarrhea (more than 24 hours after the administration of the first dose of irinotecan)
Each family will be instructed to have antidiarrheal medication available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given loperamide based on body weight.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking loperamide (Imodium). **If he/she does not start taking the loperamide right away, the diarrhea may become severe and last several days or require hospitalization.**

Please follow these directions carefully, using dosing guidelines below:

- Take _____ at the first sign of diarrhea.
- Continue taking _____ every _____ hours until the diarrhea slows or the normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed _____ in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS FOR LATE DIARRHEA (maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg per day (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (1 teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg per day (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg per day (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (one teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg per day (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg per day (80 mL or 16 teaspoonfuls) per day.

APPENDIX VI: TEMOZOLOMIDE DOSING (100 mg/m^2) NOMOGRAM

Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For these patients, doses are rounded to the nearest 5 mg. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).

For patients with a BSA < 0.5 m^2: Use **3.3 mg/kg**.

Examples: For a patient with BSA= 0.3 m^2 and weight= 5 kg, the calculated dose = 5 kg x 3.3 mg/kg = 16.5 mg

Temozolomide oral suspension is compounded to a concentration of 10 mg/mL. When temozolomide suspension is used, consider rounding doses to the nearest 1 mg (0.1 mL) for doses ≤ 22.5 mg and to the nearest 2 mg (0.2 mL) for doses > 22.5 mg for deliverability. In the example above, the dose can be rounded to 16 mg (1.6 mL).

For a patient with BSA= 0.66 m^2 the calculated dose is 0.66 m^2 x 100 mg/m^2 = 66 mg/day; administered dose = 65 mg temozolomide/day.

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.2-0.49	3.3 mg/kg	3.3 mg/kg
0.50-0.52	50-52	50
0.53-0.57	53-57	55
0.58-0.62	58-62	60
0.63-0.67	63-67	65
0.68-0.72	68-72	70
0.73-0.77	73-77	75
0.78-0.82	78-82	80
0.83-0.87	83-87	85
0.88-0.92	88-92	90
0.93-0.97	93-97	95
0.98-1.0	98-100	100
1.01-1.05	100-105	105
1.06-1.14	106-114	110
1.15-1.24	115-124	120
1.25-1.34	125-134	130
1.35-1.44	135-144	140
1.45-1.54	145-154	150
1.55-1.64	155-164	160
1.65-1.74	165-174	170
1.75-1.84	175-184	180
1.85-1.94	185-194	190
1.95-2.00	195-200	200
> 2.0	> 200	200

APPENDIX VII: TEMOZOLOMIDE REDUCED (75 mg/m^2) DOSING NOMOGRAM

Temozolomide is dosed based on body surface area for patients whose BSA is at least 0.5 m^2. For these patients, doses are rounded to the nearest 5 mg. For patients with BSA < 0.5 m^2, dosing is based on body weight (kg).

For patients with a BSA < 0.5 m^2: Use **2.5 mg/kg**.

Examples: For a patient that is 0.3 m^2 and weighs 5 kg, the calculated dose is 5 kg x 2.5 mg/kg = 12.5 mg

Temozolomide oral suspension is compounded to a concentration of 10 mg/mL. When temozolomide suspension is used, consider rounding doses to the nearest 1 mg (0.1 mL) for doses ≤ 22.5 mg and to the nearest 2 mg (0.2 mL) for doses > 22.5 mg for deliverability. In the example above, the dose can be rounded to 12 mg (1.2 mL).

For a patient with a BSA of 0.66 m^2, the calculated dose = 49.5 mg/dose; administered dose = 50 mg temozolomide/dose.

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.2-0.49	2.5 mg/kg	2.5 mg/kg
0.50-0.56	38-42	40
0.57-0.63	43-47	45
0.64-0.70	48-52	50
0.71-0.76	53-57	55
0.77-0.83	58-62	60
0.84-0.90	63-67	65
0.91-0.96	68-72	70
0.97-1.03	73-77	75
1.04-1.10	78-82	80
1.11-1.16	83-87	85
1.17-1.23	88-92	90
1.24-1.30	93-97	95
1.31-1.36	98-102	100
1.37-1.43	103-107	105
1.44-1.50	108-112	110
1.51-1.56	113-117	115
1.57-1.63	118-122	120
1.64-1.70	123-127	125
1.71-1.76	128-132	130
1.77-1.83	133-137	135
1.84-1.90	138-142	140
1.91-1.96	143-147	145
≥ 1.97	148-152	150

APPENDIX VIII: INSTRUCTIONS FOR TEMOZOLOMIDE PREPARATION, ADMINISTRATION AND SAFE HANDLING

Patient Name: _____ Cycle#: _____ Date Range: _____

Temozolomide *is an oral medicine for the treatment of cancer. This information sheet will help you prepare, administer, store, and dispose of the medicine. Please read the information before preparing and giving the medicine. If you have any questions, please contact:_____*

WHAT DO I NEED?

Your Temozolomide dose is: _____mg

- You should use the following number of capsules for each dose):

Number of temozolomide capsules per dose					
5 mg	**20 mg**	**100 mg**	**140 mg**	**180 mg**	**250 mg**

- Give each dose by mouth one time each morning for 5 days in a row.
- You should take the temozolomide on the following days:_____

Supplies:

- Temozolomide capsules (see the table above)
- Disposable pad or paper towels
- Disposable gloves and mask and a pair of goggles (eye protection)
- Disposable cup and disposable spoon
- A container to collect waste (zip top plastic bag or medical waste bag or container)
- A small amount of applesauce or apple juice
  - Two teaspoons (10 mL) should be enough. A single-serving container of applesauce may be used, but the patient must be able to eat the entire contents of the container to ensure the full dose is taken.
  - Food should be cool or close to room temperature when administered; do not use hot or boiling food

HOW DO I STORE THE MEDICINE AND WASTE?

Store the medication in the original bottle away from food and out of the reach of children or pets. Store the waste container out of the reach of children or pets. Return the container to the clinic during your next visit.

WHAT SAFETY MEASURES SHOULD I TAKE?

If the medicine gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. If you spilled the medicine on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention if the skin becomes red, irritated, or if you are concerned. Call your doctor or nurse immediately at:_____
and/or contact the Poison Center at 1-800-222-1222.

HOW DO I PREPARE THE MEDICINE?

CAUTION: If you are pregnant, could become pregnant, or are breast-feeding, DO NOT prepare or administer this medicine.

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Wash your hands with soap and water; dry them well.
4. Put on disposable gloves, disposable mask, and a pair of goggles or eye protection.
5. Place a disposable pad or paper towel on the clean working space and place all supplies on the pad or paper towel.
6. Fill a cup with a small amount of apple juice or applesauce (or use pre-filled applesauce cup).
7. Open each capsule required for the daily dose over the cup with the apple juice or applesauce.
   - Hold one capsule over the center of the cup.
   - To open, pinch both ends of one capsule with gentle pressure. Slowly rotate one end in small, back and forth movements while holding the other end steady until the capsule sections begin to separate.
   - Gently separate the ends so the powder falls into the center of the food. Look inside each end of the capsule. Tap and shake each end of the capsule until all medicine powder is out of the capsule.
   - Repeat the steps above for each capsule needed.
8. The medicine will not dissolve completely if mixing in apple juice. Keep extra apple juice on hand to add to any remaining powder left at the bottom of the cup. If you need more apple juice or applesauce, remove your gloves before touching the main container. Wear new gloves before adding the additional apple juice or applesauce to the medicine to prevent contaminating the main container with any powder that may be on your gloves.
9. Give the medicine mixture to the patient immediately.

HOW DO I TAKE/GIVE THE MEDICINE?

- Take/give an anti-nausea medicine 30-60 minutes before the temozolomide only if instructed to do so by your doctor.
- Take/give temozolomide 1 hour before irinotecan.
- Take/give temozolomide at around the same time each day with or without food. On days where you have special blood tests drawn, take both medicines on an empty stomach, at least 2 hours after food.
- When you are finished, place all used supplies in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- If the dose is vomited within 30 minutes, the dose should be repeated. If the dose is vomited more than 30 minutes after the dose, do not repeat the dose. If the patient is unable to take a dose, or a dose is accidentally missed, place the remaining medicine from this dose in the waste container, seal, and contact your doctor or nurse for instructions.

APPENDIX IX: CURIE SCORING SUMMARY SHEET (Submit this sheet via RAVE)

COG Registration Number: _____ **Radiology reviewer**: _____
(6 digits) *(print name)*

Date of scan: _____ **Type of Scan** (check 1): I-123 MIBG ☐ I-131 MIBG ☐
(DD/MM/YYYY)

Scan time point (circle 1): Baseline End of Cycle 2

End of Cycle 4 End of Cycle 6 End of Cycle 10

End of Cycle 14 End of Cycle 17 Relapse/Progression Other (specify)

Note: For patients enrolled with Amendment 4 or later, the End of Cycle 6 timepoint will be the end of therapy. Please do not fill out End of Cycles 10, 14, and 17 as those timepoints are not relevant.

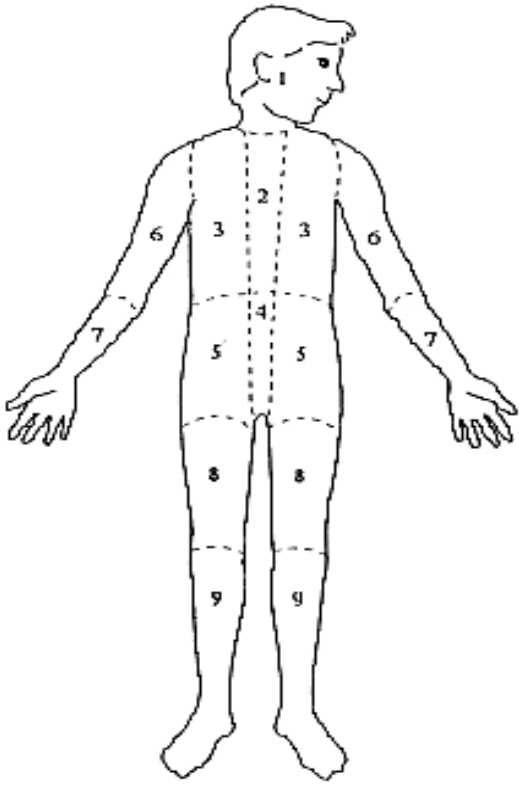
Table 1a. Scoring skeletal disease

Regions 1 – 9	
Scoring	MIBG uptake
0	No MIBG uptake
1	1 focal site
2	> 1 focal site
3	≥ 50% of a region

Table 1b. Scoring soft tissue disease

	Region 10 (Primary soft tissue site)	
	Scoring	MIBG uptake
	0	No soft tissue uptake
	1	1 focal soft tissue site
	2	> 1 focal soft tissue site
	3	≥ 50% of a region (chest, abdomen)

Region	**Site**	**Curie score**
1	Head / Neck	
2	Cervico-Thoracic spine	
3	Ribs / Sternum / Clavicles/ Chest	
4	Lumbar / Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	



10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	

Figure 1.

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 *Banking*	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 *Banking*	BPC	14.2.2.2
	Bone marrow aspirate	3-5 mL	1 tube	Heparinized tube	OPTIONAL; Send fresh overnight *GD2 Biomarkers*	Reynolds	14.2.1
Pre-therapy	Blood[a, b]	2.5 mL	2 tubes	PAXgene RNA tube PAXgene DNA tube	OPTIONAL *Banking*	BPC	14.2.2.1
	Urine	15 mL		Clean-catch; transfer to sterile screw-cap vials	OPTIONAL; Freeze within 30 minutes *Banking*	BPC	14.2.2.3
	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
	Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
Cycle 1, Day 1 (Regimen B only)	Urine	15 mL		Clean-catch; transfer to sterile screw-cap vials	OPTIONAL; Freeze within 30 minutes *Banking*	BPC	14.2.2.3
	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
	Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
Cycle 1, post-completion of dinutuximab (collect a single sample between Day 6 and Day 9)[c]	Urine	15 mL		Clean-catch; transfer to sterile screw-cap vials	OPTIONAL; Freeze within 30 minutes *Banking*	BPC	14.2.2.3
	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
	Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
Cycle 2, Day 1	Urine	15 mL		Clean-catch; transfer to sterile screw-cap vials	OPTIONAL; Freeze within 30 minutes *Banking*	BPC	14.2.2.3
	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1

	Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
Time point	**Sample Type**			**Tube Type / Sample Prep**	**Notes**	**Ship to**	**Section Number**
Any soft tissue collected post-completion of ANBL1821 therapy and prior to start of any other therapy.	Soft tissue tumor			Snap-frozen tumor material and paraffin-embedded tumor tissue	OPTIONAL *Banking*	BPC	14.2.2.2

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/mm^3
c. Collect all specimens at this time point post-completion of dinutuximab

APPENDIX XI: EMERGENCY MANAGEMENT OF DINUTUXIMAB TOXICITIES

This document is for rapid reference. See Section 5.2.5 for further information regarding management of acute toxicities during dinutuximab-containing cycles of therapy

Severe Allergic Reaction

Definition (any of the following): symptomatic bronchospasm with or without urticaria, IV meds required, allergy-related edema/angioedema, or anaphylaxis (Grade 3 or 4)

Treatment:

- Immediately **hold** dinutuximab infusion
- Assess airway, breathing and circulation

For airway concerns:

- Administer oxygen and albuterol immediately for bronchospasm
- Administer diphenhydramine (if not already being given)
- Administer epinephrine immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
- Administer hydrocortisone **if any of the following are true**
    - patient has frank anaphylaxis with cardiorespiratory collapse
    - two or more doses of epinephrine are required
    - moderate to severe symptoms recur upon rechallenge with dinutuximab

For hypotension in setting of allergic reaction:

- Hold dinutuximab and give normal saline bolus (see hypotension guidelines)
- Stop or adjust doses of narcotics
- For patients with hypotension that resolves with initial volume bolus, resume dinutuximab at half rate

Reassess need for additional volume resuscitation, ICU transfer and use of vasopressors

For patients with angioedema that does **not** affect the airway or patients with mild bronchospasm and **no** other symptoms:

- If symptoms resolve rapidly, dinutuximab can be resumed at half rate with very close observation

Minimal criteria for resumption of dinutuximab infusion:

- Complete resolution of airway symptoms
- Complete resolution of hypotension

APPENDIX XII: EFLORNITHINE (DFMO) DOSING TABLES

DOSE LEVEL – 6750 mg/m^2/day (6.75 g/m^2/day) divided TID					
BSA range (m^2) lower	**upper**	**Dose 1 (g)**	**Dose 2 (g)**	**Dose 3 (g)**	**Total daily dose (g)**
0.35	0.40	1	1	0.5	2.5
0.41	0.47	1	1	1	3
0.48	0.55	1.5	1	1	3.5
0.56	0.62	1.5	1.5	1	4
0.63	0.69	1.5	1.5	1.5	4.5
0.70	0.77	2	1.5	1.5	5
0.78	0.84	2	2	1.5	5.5
0.85	0.92	2	2	2	6
0.93	1.03	2.5	2	2	6.5
1.04	1.21	2.5	2.5	2.5	7.5
1.22	1.43	3	3	3	9
1.44	1.66	3.5	3.5	3.5	10.5
1.67	1.88	4	4	4	12
1.89	and above	4.5	4.5	4.5	13.5

DOSE LEVEL – 5000 mg/m^2/day (5 g/m^2/day) divided TID					
BSA range (m^2) lower	**upper**	**Dose 1 (g)**	**Dose 2 (g)**	**Dose 3 (g)**	**Total daily dose (g)**
0.35	0.47	1	0.5	0.5	2
0.48	0.55	1	1	0.5	2.5
0.56	0.63	1	1	1	3
0.64	0.77	1.5	1	1	3.5
0.78	0.84	1.5	1.5	1	4
0.85	0.92	1.5	1.5	1.5	4.5
0.93	1.03	2	1.5	1.5	5
1.04	1.21	2	2	1.5	5.5
1.22	1.43	2.5	2	2	6.5
1.44	1.66	2.5	2.5	2.5	7.5
1.67	and above	3	3	3	9

DOSE LEVEL – 3750 mg/m^2/day (3.75 g/m^2/day) divided TID					
BSA range (m^2)		**Dose 1 (g)**	**Dose 2 (g)**	**Dose 3 (g)**	**Total daily dose (g)**
lower	**upper**				
0.35	0.47	0.5	0.5	0.5	1.5
0.48	0.63	1	0.5	0.5	2
0.64	0.77	1	1	0.5	2.5
0.78	0.84	1	1	1	3
0.85	1.03	1.5	1	1	3.5
1.04	1.21	1.5	1.5	1	4
1.22	1.43	2	1.5	1.5	5
1.44	1.49	2	2	1.5	5.5
1.50	1.88	2	2	2	6
1.89	and above	2.5	2.5	2	7

APPENDIX XIII: INSTRUCTIONS FOR PREPARATION AND ADMINISTRATION OF EFLORNITHINE (DFMO)

Take eflornithine (DFMO) solution by mouth or give through an enteral tube (NG or Gtube), without regard to meals. If you vomit within 20 minutes of taking a dose, an additional dose can be taken once. If you vomit after 20 minutes of taking a dose, the dose should not be repeated.

DFMO is provided as either 0.5 or 1 gram of powdered drug in a single dose sachet. The parent or caregiver will fully dissolve the powder in the appropriate amount of sterile or distilled water for each dose (see table below). This provides a solution of 100 mg DFMO per 1 mL of solution. When preparing each dose, use a disposable cup and discard the cup when the medication has been administered. **Administer each dose immediately after dissolution**. A delay of up to 30 minutes between dissolution and administration is acceptable.

Dilution table to achieve 100 mg/mL solution:

Eflornithine Dose (g)	Number of 0.5 g sachets	Number of 1 g sachets	Amount of sterile/distilled water
0.5	1	0	5 mL
1	0	1	10 mL
1.5	1	1	15 mL
2	0	2	20 mL
2.5	1	2	25 mL
3	0	3	30 mL
3.5	1	3	35 mL
4	0	4	40 mL
4.5	1	4	45 mL

To improve the taste of DFMO solution, an additional liquid can be added to the 100 mg/mL solution. The amount of liquid to be used can be decided by the patient and/or family but typically would include adding juice equal to 2 times the volume of DFMO. For example, a dose of 45 mLs of eflornithine (= 4.5 g) would be added to 90 mLs (= 3 ounces) of juice.

RECOMMENDED juices for this purpose include lemonade, apple juice, cranberry or grape juice (in order of preference).

Juices to be AVOIDED when administering DFMO include grapefruit juice, orange juice and tomato juice (including V8 juice).

DFMO should be taken IMMEDIATELY after it is dissolved, rather than storing it for later use.

Enteral Tube Administration: DFMO should be given via enteral tube (NG or Gtube) the same way other medications are given. Pause the feeds if running, flush the tube with water, administer the medication, flush the tube again with water, and restart feeds. The tube should be flushed with water before and after each medication administration.

Please note:

- Gloves should be worn when preparing DFMO solution.
- Pregnant women should not prepare the medication.
- If DFMO sachet is ripped or broken and the powder gets on skin, wash the exposed area with soap and water. Inform your study doctor or nurse if this occurs.
- If DFMO sachet powder or mixed solution is spilled on the counter or other surface, use a damp paper towel to clean up the area. Then use Clorox to clean the area and dispose of the paper towels when finished.

APPENDIX XIV: OVERALL RESPONSE CRITERIA

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET/CT or PET/MR)	Bone Marrow Metastatic Disease	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	NI	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	NI	NI	SD
SD	SD	NI	SD
SD	SD	SD	SD
SD	NI	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of Not Evaluable for any one of the 3 components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not Evaluable

No response evaluation performed for any of the 3 components that were involved at study entry or explicitly required as a component of disease evaluation at that timepoint during study	Not Done

CR: Complete Response; MD: Minimal Disease; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive disease; NI: not involved; site not involved at study entry and remains not involved. NFE: Not Fully Evaluated; when at least one component of response evaluation was not required AND not performed at that timepoint for one or more of the 3 response components of overall response (this will annotate CR, PR, MR, or SD).

APPENDIX XV: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Some drugs, food, and supplements may interact with irinotecan. Examples include:

Drugs that may interact with irinotecan

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Clozapine, nefazodone
• Antifungals
  • Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine
• Antiretrovirals and antivirals
  • Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir
• Anti-seizure medications
  • Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, carvedilol, dronedenarone, diltiazem, propafenone, quinidine, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Aprepitant, bosentan, cobicistat, conivaptan, ivacaftor, mifepristone, modafinil, natalizumab

Food and supplements that may interact with irinotecan
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with temozolomide. Examples include:

Drugs that may interact with temozolomide
• Clozapine, leflunomide, natalizumab, tofacitinib, valproate products

Food and supplements that may interact with temozolomide
• Echinacea

APPENDIX XVI: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ANBL1821
(for children from 7 through 12 years of age)

A trial to compare 2 ways to treat children with Neuroblastoma (NBL) that is not responding to treatment or has come back after treatment

1. We have been talking with you about your illness, neuroblastoma (NBL). NBL is a kind of cancer that grows in the soft issue in your body. It can grow in different parts of the body. After doing tests, we have found that you have this type of cancer. You have had treatment for this cancer already but the cancer did not go away or has come back after treatment.

2. We are asking you to take part in a research study because you have NBL that is not responding to treatment or has come back after treatment. A research study is when doctors work together to try out new ways to help people who are sick.

3. All children who are part of this study will be treated with chemotherapy. Some children who are part of this study will be treated with chemotherapy and the drug eflornithine (also called DFMO). Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment with DFMO.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is a better chance of getting rid of the cancer for as long as possible. But we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatment may not work as well as other therapies. Also, the study treatment may cause more side effects than other therapies. Your doctors will watch you for signs of any side effects.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We want to learn more about how people respond to treatment with DFMO. In order to take part in this study, you must take part in two tests to help us learn about DFMO. Extra blood will be collected 3-4 times during your treatment and a nurse will ask about any pain you may have on this study.

   We are also asking your permission to collect extra bone marrow, tumor tissue, and urine and use them for research studies. We would take extra when we collect bone marrow, tumor tissue, and urine for regular tests. You can still take part in this study even if you do not agree to let us collect the extra samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY ANBL1821
(for teens from 13 through 17 years of age)

A trial to compare 2 ways to treat patients with NBL that is not responding to treatment or has come back after treatment

1. We have been talking with you about your illness, neuroblastoma (NBL). NBL is a type of cancer that grows in the soft issue in your body. It can grow in different parts of the body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have NBL that is recurrent or refractory. Recurrent means that the cancer has come back after treatment. Refractory means that the cancer has not responded to treatment. A research study is when doctors work together to try out new ways to help people who are sick.

3. All children who are part of this study will be treated with chemotherapy. Some children who are part of this study will be treated with chemotherapy and the drug eflornithine (also called DFMO). Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment with DFMO.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is a better chance of getting rid of your cancer for as long as possible. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that the study treatment may be less effective than other therapy options. It is also possible that the study treatment may cause more side effects than other therapies. Your doctors will monitor you closely for signs of any side effects. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We want to learn more about how people respond to treatment with DFMO. In order to take part in this study, you must take part in two tests to help us learn about DFMO. Extra blood will be collected 3-4 times during your treatment and a nurse will ask about any pain you may have on this study.

   We are also asking your permission to collect extra bone marrow, tumor tissue, and urine and use them for research studies. We would take extra when we collect bone marrow, tumor tissue, and urine for regular tests. You can still take part in this study even if you do not agree to let us collect the extra samples for research.

REFERENCES

1. Matthay KK, Reynolds CP, Seeger RC, et al.: Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. J Clin Oncol 27:1007-13, 2009
2. Pinto NR, Applebaum MA, Volchenboum SL, et al.: Advances in Risk Classification and Treatment Strategies for Neuroblastoma. J Clin Oncol 33:3008-17, 2015
3. Mody R, Naranjo A, Van Ryn C, et al.: Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. Lancet Oncol 18:946-957, 2017
4. Mody R, Naranjo A, Hibbitts E, et al.: Phase II Trial of Irinotecan/Temozolomide with Dinutuximab/GMCSF (I/T/DIN/GMCSF) in Relapsed/Refractory Neuroblastoma: A Report from The Children's Oncology Group (COG). Presented at the Advances in Neuroblastoma Research (ANR), San Francisco, CA, 2018
5. Mody R, Naranjo A, Yu AL, et al.: Phase II trial of irinotecan/temozolomide/dinutuximab/granulocyte macrophage colony stimulating factor (I/T/DIN/GMCSF) in children with relapsed/refractory neuroblastoma (NBL): A report from the Children's Oncology Group (COG). 2018 ASCO Annual Meeting. Chicago, IL, 2018
6. Metcalf BW, Bey P, Danzin C, et al.: Catalytic irreversible inhibition of mammalian ornithine decarboxylase (E.C.4.1.1.17) by substrate and product analogs. Journal of the American Chemical Society 100:2551-2553, 1978
7. Hogarty MD, Norris MD, Davis K, et al.: ODC1 is a critical determinant of MYCN oncogenesis and a therapeutic target in neuroblastoma. Cancer Res 68:9735-45, 2008
8. Casero RA, Jr.,Marton LJ: Targeting polyamine metabolism and function in cancer and other hyperproliferative diseases. Nat Rev Drug Discov 6:373-90, 2007
9. Lutz W, Stohr M, Schurmann J, et al.: Conditional expression of N-myc in human neuroblastoma cells increases expression of alpha-prothymosin and ornithine decarboxylase and accelerates progression into S-phase early after mitogenic stimulation of quiescent cells. Oncogene 13:803-12, 1996
10. Geerts D, Koster J, Albert D, et al.: The polyamine metabolism genes ornithine decarboxylase and antizyme 2 predict aggressive behavior in neuroblastomas with and without MYCN amplification. Int J Cancer 126:2012-24, 2010
11. Fredlund E, Ringner M, Maris JM, et al.: High Myc pathway activity and low stage of neuronal differentiation associate with poor outcome in neuroblastoma. Proc Natl Acad Sci U S A 105:14094-9, 2008
12. Westermann F, Muth D, Benner A, et al.: Distinct transcriptional MYCN/c-MYC activities are associated with spontaneous regression or malignant progression in neuroblastomas. Genome Biol 9:R150, 2008
13. Valentijn LJ, Koster J, Haneveld F, et al.: Functional MYCN signature predicts outcome of neuroblastoma irrespective of MYCN amplification. Proc Natl Acad Sci U S A 109:19190-5, 2012
14. Wang LL, Teshiba R, Ikegaki N, et al.: Augmented expression of MYC and/or MYCN protein defines highly aggressive MYC-driven neuroblastoma: a Children's Oncology Group study. Br J Cancer 113:57-63, 2015
15. Selamnia M, Mayeur C, Robert V, et al.: Alpha-difluoromethylornithine (DFMO) as a potent arginase activity inhibitor in human colon carcinoma cells. Biochem Pharmacol 55:1241-5, 1998
16. Janakiram NB, Mohammed A, Bryant T, et al.: Potentiating NK cell activity by combination of Rosuvastatin and Difluoromethylornithine for effective chemopreventive efficacy against Colon Cancer. Sci Rep 6:37046, 2016

17. Evageliou NF, Haber M, Vu A, et al.: Polyamine Antagonist Therapies Inhibit Neuroblastoma Initiation and Progression. Clin Cancer Res 22:4391-404, 2016
18. Bassiri H, Benavides A, Haber M, et al.: Translational development of difluoromethylornithine (DFMO) for the treatment of neuroblastoma. Transl Pediatr 4:226-38, 2015
19. Rodriguez PC, Quiceno DG, Zabaleta J, et al.: Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. Cancer Res 64:5839-49, 2004
20. Akslen LA, Watnick, Randolph S.: Biomarkers of the Tumor Microenvironment: Basic Studies and Practical Applications (ed 1). Switzerland, Springer International Publishing, 2017
21. Hayes CS, Shicora AC, Keough MP, et al.: Polyamine-blocking therapy reverses immunosuppression in the tumor microenvironment. Cancer Immunol Res 2:274-85, 2014
22. Asgharzadeh S, Salo JA, Ji L, et al.: Clinical significance of tumor-associated inflammatory cells in metastatic neuroblastoma. J Clin Oncol 30:3525-32, 2012
23. Tilak T, Sherawat S, Agarwala S, et al.: Circulating T-regulatory cells in neuroblastoma: a pilot prospective study. Pediatr Hematol Oncol 31:717-22, 2014
24. Federico SM, McCarville MB, Shulkin BL, et al.: A Pilot Trial of Humanized Anti-GD2 Monoclonal Antibody (hu14.18K322A) with Chemotherapy and Natural Killer Cells in Children with Recurrent/Refractory Neuroblastoma. Clin Cancer Res 23:6441-6449, 2017
25. Burri C,Brun R: Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res 90 Supp 1:S49-52, 2003
26. Haegele KD, Alken RG, Grove J, et al.: Kinetics of alpha-difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. Clin Pharmacol Ther 30:210-7, 1981
27. Priotto G, Pinoges L, Fursa IB, et al.: Safety and effectiveness of first line eflornithine for Trypanosoma brucei gambiense sleeping sickness in Sudan: cohort study. Bmj 336:705-8, 2008
28. Levin VA, Prados MD, Yung WK, et al.: Treatment of recurrent gliomas with eflornithine. J Natl Cancer Inst 84:1432-7, 1992
29. Levin VA, Uhm JH, Jaeckle KA, et al.: Phase III randomized study of postradiotherapy chemotherapy with alpha-difluoromethylornithine-procarbazine, N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosurea, vincristine (DFMO-PCV) versus PCV for glioblastoma multiforme. Clin Cancer Res 6:3878-84, 2000
30. Levin VA, Hess KR, Choucair A, et al.: Phase III randomized study of postradiotherapy chemotherapy with combination alpha-difluoromethylornithine-PCV versus PCV for anaplastic gliomas. Clin Cancer Res 9:981-90, 2003
31. Prados MD, Wara WM, Sneed PK, et al.: Phase III trial of accelerated hyperfractionation with or without difluromethylornithine (DFMO) versus standard fractionated radiotherapy with or without DFMO for newly diagnosed patients with glioblastoma multiforme. Int J Radiat Oncol Biol Phys 49:71-7, 2001
32. Abeloff MD, Slavik M, Luk GD, et al.: Phase I trial and pharmacokinetic studies of alpha-difluoromethylornithine--an inhibitor of polyamine biosynthesis. J Clin Oncol 2:124-30, 1984
33. Croghan MK, Aickin MG,Meyskens FL: Dose-related alpha-difluoromethylornithine ototoxicity. Am J Clin Oncol 14:331-5, 1991
34. O'Shaughnessy JA, Demers LM, Jones SE, et al.: Alpha-difluoromethylornithine as treatment for metastatic breast cancer patients. Clin Cancer Res 5:3438-44, 1999
35. Abeloff MD, Rosen ST, Luk GD, et al.: Phase II trials of alpha-difluoromethylornithine, an inhibitor of polyamine synthesis, in advanced small cell lung cancer and colon cancer. Cancer treatment reports 70:843-845, 1986
36. Horn Y, Schechter PJ,Marton LJ: Phase I-II clinical trial with alpha-difluoromethylornithine--an inhibitor of polyamine biosynthesis. European journal of cancer & clinical oncology 23:1103-1107, 1987

37. Siimes M, Seppanen P, Alhonen-Hongisto L, et al.: Synergistic action of two polyamine antimetabolites leads to a rapid therapeutic response in childhood leukemia. Int J Cancer 28:567-70, 1981
38. Saulnier Sholler GL, Gerner EW, Bergendahl G, et al.: A Phase I Trial of DFMO Targeting Polyamine Addiction in Patients with Relapsed/Refractory Neuroblastoma. PLoS One 10:e0127246, 2015
39. Hogarty M, Flynn A, Liu K, et al.: NANT 2012-01: Phase 1 Study of DFMO and Celecoxib with Cyclophosphamide and Topotecan for Relapsed or Refractory High-Risk Neuroblastoma., Advances in Neuroblastoma Research (ANR). San Francisco, CA, 2018
40. Abeloff MD, Rosen ST, Luk GD, et al.: Phase II trials of alpha-difluoromethylornithine, an inhibitor of polyamine synthesis, in advanced small cell lung cancer and colon cancer. Cancer Treat Rep 70:843-5, 1986
41. London WB, Frantz CN, Campbell LA, et al.: Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol 28:3808-15, 2010
42. Pistoia V, Bianchi G, Borgonovo G, et al.: Cytokines in neuroblastoma: from pathogenesis to treatment. Immunotherapy 3:895-907, 2011
43. Sinha P, Clements VK,Ostrand-Rosenberg S: Reduction of myeloid-derived suppressor cells and induction of M1 macrophages facilitate the rejection of established metastatic disease. J Immunol 174:636-45, 2005
44. Schengrund CL, Repman MA,Shochat SJ: Ganglioside composition of human neuroblastomas. Correlation with prognosis. A Pediatric Oncology Group Study. Cancer 56:2640-6, 1985
45. Schumacher-Kuckelkorn R, Volland R, Gradehandt A, et al.: Lack of immunocytological GD2 expression on neuroblastoma cells in bone marrow at diagnosis, during treatment, and at recurrence*. Pediatric Blood & Cancer 64:46-56, 2017
46. Keyel M, Davidson H, Nguyen T, et al.: Association of Anti-Tumor Activity in Neuroblastoma Patient-Derived Xenografts with Levels of GD2 Expression Advances in Neuroblastoma Research (ANR). San Francisco, CA, 2018
47. Schulz G, Cheresh DA, Varki NM, et al.: Detection of ganglioside GD2 in tumor tissues and sera of neuroblastoma patients. Cancer Res 44:5914-20, 1984
48. Saleh MN, Khazaeli MB, Wheeler RH, et al.: Phase I trial of the murine monoclonal anti-GD2 antibody 14G2a in metastatic melanoma. Cancer Res 52:4342-7, 1992
49. Yu AL, Uttenreuther-Fischer MM, Huang CS, et al.: Phase I trial of a human-mouse chimeric anti-disialoganglioside monoclonal antibody ch14.18 in patients with refractory neuroblastoma and osteosarcoma. J Clin Oncol 16:2169-80, 1998
50. Handgretinger R, Anderson K, Lang P, et al.: A phase I study of human/mouse chimeric antiganglioside GD2 antibody ch14.18 in patients with neuroblastoma. Eur J Cancer 31A:261-7, 1995
51. Yu AL, Gilman AL, Ozkaynak MF, et al.: Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 363:1324-34, 2010
52. Pauk J, Kuhn CM, Field TM, et al.: Positive effects of tactile versus kinesthetic or vestibular stimulation on neuroendocrine and ODC activity in maternally-deprived rat pups. Life Sci 39:2081-7, 1986
53. Wang S, Bartolome JV,Schanberg SM: Neonatal deprivation of maternal touch may suppress ornithine decarboxylase via downregulation of the proto-oncogenes c-myc and max. J Neurosci 16:836-42, 1996
54. Schanberg SM, Ingledue VF, Lee JY, et al.: PKC alpha mediates maternal touch regulation of growth-related gene expression in infant rats. Neuropsychopharmacology 28:1026-30, 2003
55. Silva MA, Klafke JZ, Rossato MF, et al.: Role of peripheral polyamines in the development of inflammatory pain. Biochem Pharmacol 82:269-77, 2011

56. Sommer C,Kress M: Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett 361:184-7, 2004
57. Hicks CL, von Baeyer CL, Spafford PA, et al.: The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain 93:173-83, 2001
58. Tomlinson D, von Baeyer CL, Stinson JN, et al.: A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics 126:e1168-98, 2010
59. Schwartz GJ,Gauthier B: A simple estimate of glomerular filtration rate in adolescent boys. The Journal of Pediatrics 106:522-526, 1985
60. Wong KK, Chang S, Weiler SR, et al.: Telomere dysfunction impairs DNA repair and enhances sensitivity to ionizing radiation. Nat Genet 26:85-8, 2000
61. Bae I, Smith ML, Sheikh MS, et al.: An abnormality in the p53 pathway following gamma-irradiation in many wild-type p53 human melanoma lines. Cancer Res 56:840-7, 1996
62. Kabacik S, Mackay A, Tamber N, et al.: Gene expression following ionising radiation: identification of biomarkers for dose estimation and prediction of individual response. Int J Radiat Biol 87:115-29, 2011
63. Liu G,Chen X: The ferredoxin reductase gene is regulated by the p53 family and sensitizes cells to oxidative stress-induced apoptosis. Oncogene 21:7195-204, 2002
64. Martinez A, Hinz JM, Gomez L, et al.: Differential expression of TP53 associated genes in Fanconi anemia cells after mitomycin C and hydroxyurea treatment. Mutat Res 656:1-7, 2008
65. Paul S, Barker CA, Turner HC, et al.: Prediction of in vivo radiation dose status in radiotherapy patients using ex vivo and in vivo gene expression signatures. Radiat Res 175:257-65, 2011
66. Trissel LA, Zhang Y,Koontz SE: Temozolomide stability in extemporaneously compounded oral suspensions. Int J Pharm Compd 10:396-9, 2006
67. Lingertat-Walsh K, Weilnau J, Cober MP, et al.: Stability of extemporaneously compounded temozolomide 10 mg/mL suspensions in Oral Mix SF® in glass and plastic bottles and plastic syringes. J Oncol Pharm Pract:1078155220914349, 2020
68. Park JR, Bagatell R, Cohn SL, et al.: Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587, 2017
69. Ellenberg SS,Eisenberger MA: An efficient design for phase III studies of combination chemotherapies. Cancer Treat Rep 69:1147-54, 1985
70. Wieand S,Therneau T: A two-stage design for randomized trials with binary outcomes. Control Clin Trials 8:20-8, 1987
71. Burchill SA, Beiske K, Shimada H, et al.: Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma on behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer 123:1095-1105, 2017
72. Shankar LK, Hoffman JM, Bacharach S, et al.: Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med 47:1059-66, 2006