CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

May 19, 2017

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Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
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Dear Ms. Kruhm,

Enclosed please find Amendment #6 to protocol **ANBL1221**, *A Phase II Randomized Trial of Irinotecan/Temozolomide with Temsirolimus (NSC# 683864, IND# 61010) or Chimeric 14.18 Antibody (ch14.18) (NSC# 764038, IND# 4308) in Children with Refractory, Relapsed or Progressive Neuroblastoma*, for CTEP review.

This amendment is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. Jeffrey Moscow, dated May 10, 2017. In this amendment, the revised CAEPR for MoAb 14.18, chimeric (Version 2.8, April 10, 2017) has been inserted in the protocol and the associated risk information in the informed consent document has been revised accordingly. Revisions to the protocol and consent are detailed in the pages below.

The ANBL1221 study team looks forward to approval of this amendment. Please let me know if we can offer further information.

Sincerely,

Jeannette Cassar, Protocol Coordinator (for)
Rajen Mody, MD, ANBL1221 Study Chair
Peter Adamson, MD, COG Group Chair

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	Title Page	1	Protocol version date and amendment number have been updated.
2.	Table of Contents	2-5	Table of contents has been updated to account for repagination.

3.	6.1	44-50	The revised CAEPR for MoAb 14.18, chimeric (Version 2.8, April 10, 2017) has been inserted. The specific changes are as follows:
			• Added New Risk:
			  • Also Reported on MoAb 14.18, chimeric Trials But With Insufficient Evidence for Attribution: Cardiac disorders - Other (gallop on exam); Cardiac disorders - Other (N-terminal BNP); General disorders and administration site conditions - Other (cold and clammy); Syncope
			• Increase in Risk Attribution:
			  • Changed to Less Likely from Also Reported on MoAb 14.18, chimeric Trials But With Insufficient Evidence for Attribution: Hypocalcemia
			  • Changed to Rare but Serious from Also Reported on MoAb 14.18, chimeric Trials But With Insufficient Evidence for Attribution: Myelitis; Reversible posterior leukoencephalopathy syndrome; Sudden death NOS
			• A typo in the word "a typical" has been corrected to "**atypical**."
			Minor administrative edits have been made throughout the section, and information about investigator brochure availability and useful links and contacts have been added.

SUMMARY OF CHANGES: INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	All		The version date in the footer has been updated.
2.	Risks of Study	7	Updated the section to reflect the current NCI Consent Form Template, including the following wording requested in the RRA: **"If you choose to take part in this study, there is a risk that:** • **You may lose time at work or home and spend more time in the hospital or doctor's office than usual** • **You may be asked sensitive or private questions which you normally do not discuss** **The MoAb 14.18, chimeric used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.** **There is also a risk that you could have side effects from the study drug(s)/study approach.**

			Here are important points about side effects: • **The study doctors do not know who will or will not have side effects.** • **Some side effects may go away soon, some may last a long time, or some may never go away.** • **Some side effects may interfere with your ability to have children.** • **Some side effects may be serious and may even result in death.** **Here are important points about how you and the study doctor can make side effects less of a problem:** • **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.** • **The study doctor may be able to treat some side effects.** • **The study doctor may adjust the study drugs to try to reduce side effects.** **The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."**

3.	Possible Side Effects of MoAb 14.18, Chimeric (dinutuximab)	8	Updated the consent risk profile for MoAb 14.18, chimeric to reflect the current CAEPR. The specific changes are as follows:
			
			• Increase in Risk Attribution:
			  • Changed to Rare from Also Reported on MoAb 14.18, chimeric Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Death; Swelling of the spinal cord; Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome).
			
			• Provided Further Clarification:
			  • Anemia which may cause tiredness, or may require blood transfusion (under Occasional) and Anemia, kidney problems which may cause swelling, or may require dialysis (under Rare) are now reported as Anemia, kidney problems which may cause tiredness, or may require blood transfusion or dialysis (under Occasional).
			  • High blood pressure which may cause headaches, dizziness, blurred vision (under Occasional) is now reported as High blood pressure which may cause dizziness, blurred vision (under Occasional).

Activated: 02/04/13
Closed:
Version Date: 05/18/2017
Amendment: #6

CHILDREN'S ONCOLOGY GROUP

ANBL1221

A Phase II Randomized Trial of Irinotecan/Temozolomide with Temsirolimus (NSC# 683864, IND# 61010) or Chimeric 14.18 Antibody (ch14.18) (NSC# 764038, IND# 4308) in Children with Refractory, Relapsed or Progressive Neuroblastoma

A Groupwide Phase II Study

NCI Supplied Agents: Chimeric 14.18 Antibody (ch14.18, dinutuximab) (NSC# 764038, IND# 4308)

IND sponsor for ch14.18 (dinutuximab): DCTD, NCI

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AGENT	NSC#	IND#
ch14.18 (dinutuximab)	764038	4308
GM-CSF	613795	Exempt
Irinotecan	616348	Exempt
Temozolomide	362856	Exempt

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IND sponsor for ch14.18 (dinutuximab):DCTD, NCI

SEE SECTION 13.0 FOR SPECIMEN SHIPPING ADDRESSES

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
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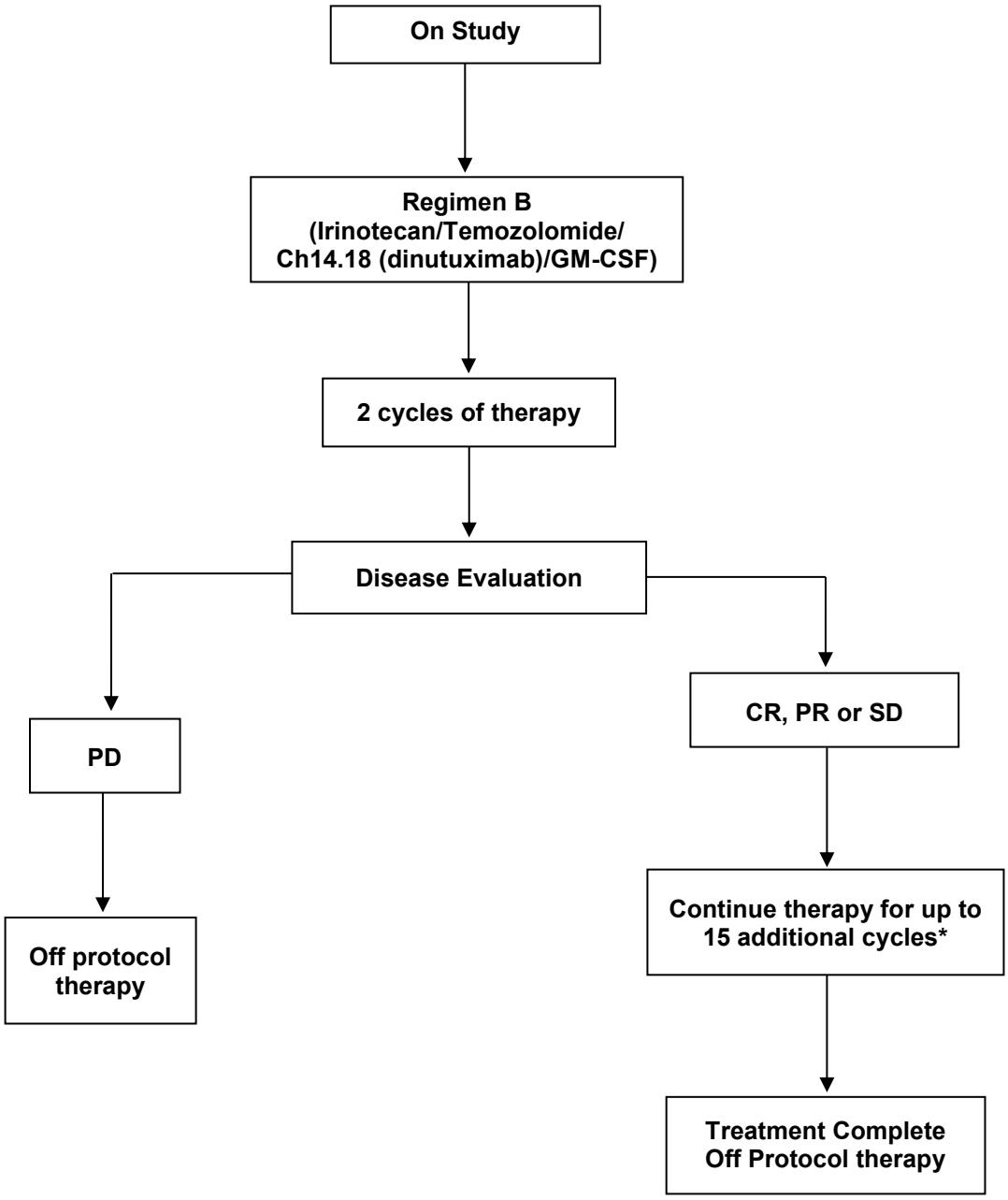
ABSTRACT

Long-term survival rates for children with high-risk neuroblastoma remain poor. In addition, survivors experience significant immediate and late toxicities limiting further dose intensification with conventional chemotherapy agents. Novel biological therapies are therefore needed. This “Pick the Winner” Phase II study is designed to compare the response rates (RR) and progression free survival (PFS) for patients with refractory, relapsed or progressive neuroblastoma receiving temsirolimus or ch14.18 (dinutuximab) in combination with irinotecan and temozolomide. The irinotecan and temozolomide combination has shown activity against relapsed/refractory neuroblastoma. Furthermore, its favorable toxicity profile makes it an attractive backbone chemotherapy regimen for assessment of the contribution of novel molecularly targeted agents. Neuroblastoma cells have shown sensitivity to mTOR inhibitors both *in vitro* and *in vivo*. mTOR inhibitors have also been shown to have synergistic or additive effects when combined with several conventional chemotherapeutic drugs, including those frequently used in the treatment of neuroblastoma. The combination of irinotecan and temozolomide with the mTOR inhibitor temsirolimus is well tolerated in children, and this 3-drug regimen will comprise one regimen of this study. The second regimen will include irinotecan and temozolomide in combination with the chimeric anti-GD2 antibody ch14.18 (dinutuximab). The disialoganglioside GD2 is expressed on neuroblastoma cells, but its expression in normal human tissues is limited. A randomized Phase III study (COG ANBL0032) compared the event free survival of patients with high risk neuroblastoma treated with ch14.18 (dinutuximab) combined with GM-CSF, interleukin 2 and isotretinoin to that of patients treated with isotretinoin alone as post-consolidation therapy. Randomization was stopped early because of superior survival associated with the antibody-containing regimen. Preclinical studies of anti-GD2 antibodies combined with cytotoxic chemotherapy have shown synergistic or additive effects on neuroblastoma cells. These data support evaluation of the addition of ch14.18 (dinutuximab) to chemotherapy for children with refractory, relapsed or progressive neuroblastoma. The agent selected for further study as a result of this trial will be integrated into frontline induction therapy for future patients with high-risk neuroblastoma.

EXPERIMENTAL DESIGN SCHEMA



* Disease re-evaluation after Cycle 4 and 6, and every 4 cycles thereafter. May continue therapy up to a maximum of 17 cycles in total in the absence of PD or unacceptable toxicity.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Specific hypothesis:
The addition of a molecularly-targeted anti-cancer agent (temsirolimus or ch14.18, dinutuximab) to the chemotherapy backbone of irinotecan and temozolomide will be tolerable and will result in improved response rates in patients with refractory, relapsed or progressive neuroblastoma.

1.1 Primary Objective

1.1.1 To identify whether temsirolimus or ch14.18 (dinutuximab) is the optimal therapeutic agent to consider for further testing in a future Phase III randomized trial for treatment of newly diagnosed high-risk neuroblastoma.

1.1.2 To determine the response rate of patients with relapsed, refractory or progressive neuroblastoma following treatment with irinotecan, temozolomide and ch14.18 (dinutuximab) and to compare this with the known response rate of patients treated with irinotecan and temozolomide alone.

1.2 Exploratory Objectives

1.2.1 To compare the response rates (RR) for patients receiving temsirolimus or ch14.18 (dinutuximab) in combination with irinotecan and temozolomide.

1.2.2 To compare the progression free survival (PFS) and overall survival (OS) rates for patients receiving temsirolimus or ch14.18 (dinutuximab) in combination with irinotecan and temozolomide.

1.2.3 To compare the toxicities associated with temsirolimus or ch14.18 (dinutuximab) when combined with irinotecan and temozolomide in patients with refractory, relapsed or progressive neuroblastoma.

1.2.4 To compare the ability to maintain intended dose intensity of all agents when temsirolimus or ch14.18 (dinutuximab) is combined with irinotecan and temozolomide in patients with refractory, relapsed or progressive neuroblastoma.

1.2.5 To determine the concordance between tumor responses as defined by standard International Neuroblastoma Response Criteria (INRC) versus response per the revised INRC.

1.2.6 To study the clinical relevance of naturally occurring anti-glycan antibodies in patients receiving ch14.18 (dinutuximab) antibody.

1.2.7 To study the clinical relevance of NK receptor NKp30 isoforms in patients receiving ch14.18 (dinutuximab) antibody or temsirolimus.

1.2.8 To study the association between host factors and response to irinotecan, temozolomide and ch14.18 (dinutuximab).

1.2.9 To characterize the tumor immune-microenvironment (gene expression; immune effector cells, activities and signaling molecules; immune target expression) following treatment with irinotecan, temozolomide and ch14.18 (dinutuximab).

1.2.10 To study the association between changes in the tumor immune-microenvironment (gene expression; immune effector cells, activities and signaling molecules; immune target expression) with response following treatment with irinotecan, temozolomide and ch14.18 (dinutuximab).

1.2.11 To study the association between tumor genomic and transcriptomic aberrations as well as levels of circulating GD2 with response to irinotecan, temozolomide and ch14.18 (dinutuximab).

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Neuroblastoma remains an important clinical problem, with approximately 50% of patients presenting with advanced-stage disease. Despite significant intensification of conventional chemotherapy regimens, the long-term survival rates for these children remain less than 40%.[1] Significant immediate and late toxicities limit further dose intensification with conventional chemotherapy agents.[2-4]

New therapeutic strategies must build upon our knowledge of neuroblastoma biology by combining molecularly targeted agents with conventional chemotherapeutic drugs. The COG ANBL0421 protocol was developed to both assess the anti-tumor activity of irinotecan/temozolomide in the setting of refractory or relapsed disease and, perhaps more importantly, to provide a backbone on which to integrate rationally selected molecularly targeted agents.[5] The proposed Phase II ANBL1221 study builds from this strategy. The proposed biologic agents, temsirolimus and ch14.18 (dinutuximab), have activity against neuroblastoma in pre-clinical models and have demonstrated synergy with conventional cytotoxic chemotherapy in these models.[6-9] Pediatric dosing and safety data exist for both agents[10,11] and there is a strong rationale to proceed with the first prospective clinical trial to evaluate the combination of a molecularly targeted agent with conventional chemotherapy in the treatment of neuroblastoma.

The primary objective of ANBL1221 is to use a randomized, Phase-II sequential and selection design[12-14] to identify whether temsirolimus or ch14.18 (dinutuximab) warrants further testing in a future upfront randomized Phase III clinical trial for treatment of high-risk neuroblastoma. Specifically, ANBL1221 will compare the response rate, toxicity, and feasibility of administration of temsirolimus or ch14.18 (dinutuximab) when combined with a backbone chemotherapy regimen of irinotecan and temozolomide. As appropriate for a Phase II selection design trial,[14,15] a standard irinotecan and temozolomide only control arm will not be included. Rather, the completed COG Phase II trial ANBL0421 will be used as a historical comparator for response rates and toxicity of irinotecan and temozolomide.

2.2 Rationale for Irinotecan and Temozolomide Chemotherapy Backbone

Relapse following myeloablative therapy for neuroblastoma is almost invariably fatal, and thus no "standard" salvage regimen exists. The anti-neuroblastoma activity of irinotecan and temozolomide together with its tolerable toxicity profile make it a reasonable backbone chemotherapy regimen with which to assess the contribution of novel molecularly targeted agents in refractory/recurrent neuroblastoma. Irinotecan is a camptothecin prodrug that is metabolized to the active topoisomerase I poison SN-38. Temozolomide is an imidazotetrazine prodrug that undergoes hydrolysis to the active metabolite MTIC, which induces cytotoxicity by methylating DNA and generating O^6-methylguanine adducts. The combination of irinotecan and temozolomide has been shown to be active *in vitro* and *in vivo* against neuroblastoma.[16]

A Phase I trial conducted by Wagner and colleagues established the maximum tolerated doses (MTDs) of intravenous irinotecan together with oral temozolomide, and objective responses in patients with neuroblastoma were observed.[17] The COG study ANBL0421 was a multicenter Phase II trial of irinotecan

plus temozolomide in the setting of refractory or relapsed neuroblastoma.[5] A protracted schedule of irinotecan (10 mg/m^2/dose administered IV for 5 consecutive days given each week for 2 weeks) in combination with temozolomide (100 mg/m^2/dose) PO for 5 days, was used. Cycles of chemotherapy were repeated every 21 days. Fifty-five eligible patients were enrolled, and the objective response rate was 15%. Twenty nine patients (53%) had stable disease. The therapy was well tolerated as less than 5% of patients experienced ≥ Grade 3 diarrhea. Although 18% of patients with disease measurable by CT/MRI and 35% of patients with disease assessable only by MIBG and/or bone marrow aspirate/biopsy experienced ≥ Grade 3 neutropenia during the first 3 cycles of therapy, less than 10% of all patients developed evidence of infection while neutropenic.[5] The irinotecan + temozolomide combination is thus a backbone onto which newer, biologically based agents may be added for use in the relapse setting or as part of initial therapy.

Two intravenous schedules of irinotecan have been studied in the treatment of refractory pediatric cancers: the daily x 5 days schedule and a protracted schedule of daily x 5 days for 2 consecutive weeks. ANBL0421 made use of the protracted irinotecan schedule based upon xenograft data.[18] Recent clinical data suggest that a shorter irinotecan administration schedule (daily x 5 for 1 week) maintains anti-tumor activity with less burden to the patient. A completed rhabdomyosarcoma study (COG ARST0121) showed no statistically significant difference in response rates comparing a daily x 5 schedule of IV irinotecan (50 mg/m^2/dose) to a daily x 5 x 2 week schedule (20 mg/m^2/dose).[19] The ANBL1221 trial will make use of a temozolomide dose of 100 mg/m^2/dose PO x 5 days combined with IV irinotecan at a dose of 50 mg/m^2/dose x 5 days.

The other backbone considered for use in this study was topotecan and cyclophosphamide. This combination was used in the POG/CCG 9642 study for patients with relapsed/refractory neuroblastoma.[20] For two reasons this regimen was not selected for incorporation into the current trial. First, the 25-30% response rate observed in the 9642 trial prompted incorporation of topotecan/cyclophosphamide into a pilot study (ANBL02P1) and subsequently into the most recent COG Phase III trial for patients with newly diagnosed high-risk neuroblastoma (ANBL0532). Therefore, most patients with high-risk neuroblastoma treated at COG centers who develop disease relapse will have received this combination during up-front therapy, making its use in the relapse setting sub-optimal. Second, the topotecan/cyclophosphamide regimen is associated with considerably higher rates of toxicity than is the irinotecan/temozolomide regimen. This is particularly important because the patients enrolled on the current trial will have already received the prolonged and intensive multimodality therapy that is presently standard of care for this disease. Nineteen percent of the patients treated with topotecan and cyclophosphamide on P9462 developed ≥ Grade 3 infection, and there was one toxic death. Forty four percent had Grade 3 or 4 neutropenia, and 60% had Grade 3 or 4 thrombocytopenia. In a study by the NANT consortium for a similar patient population, the combination of irinotecan (administered orally) and temozolomide was also tolerated very well.[21] In this smaller study, only 7% of patients developed Grade 4 neutropenia and Grade 4 thrombocytopenia, and 6% received blood product transfusions. As on the ANBL0421 study, dose-limiting diarrhea was rare. Thus, the combination of irinotecan and temozolomide is attractive for current-era patients with relapsed and refractory neuroblastoma both due to its acceptable toxicity profile and because previous exposure to this combination is expected to be considerably less frequent than prior exposure to topotecan/cyclophosphamide.

2.3 Rationale for mTOR Inhibition in Pediatric Solid Tumors

2.3.1 Pre-Clinical Studies

When activated and associated with appropriate members of a functional complex, mTOR plays an important role in regulation of protein synthesis, cell growth, and proliferation.[22] Rapamycin and rapamycin analogs form complexes with mTOR and FK506-binding protein, leading to inhibition of mTOR signaling. The Pediatric Preclinical Testing Program (PPTP) has evaluated the single-agent activity of an mTOR

inhibitor (rapamycin) using a standardized testing system comprised of over 30 models representing the major pediatric solid tumor types.[23] Inhibition of cell growth/proliferation following exposure to rapamycin was variable across the cell lines tested *in vitro*. Objective responses to rapamycin were seen in 4 of 36 *in vivo* solid tumor models. Growth inhibition following administration of rapamycin was seen in a neuroblastoma model, though an objective response was not observed in the PPTP experiments.[23] Other investigators have also shown that neuroblastoma cells are sensitive to mTOR inhibitors both *in vitro* and *in vivo*.[6]

mTOR inhibitors have been shown to have synergistic or additive effects when combined with several conventional chemotherapeutic drugs, including those frequently used in the treatment of pediatric malignancies.[24,25] Rapamycin has been shown to have synergistic antiproliferative effects *in vitro* when combined with carboplatin, and additive effects were observed when rapamycin was combined with doxorubicin.[24] *In vivo*, treatment with rapamycin in combination with doxorubicin resulted in greater inhibition of angiogenesis and tumor growth than did exposure to either agent administered alone.[25] Similarly, Teachey and colleagues have shown that the combination of methotrexate and the mTOR inhibitor temsirolimus resulted in long term disease control in a xenograft model of human acute leukemia while each agent alone provided only short term disease control.[26] Rapamycin has also been shown to reverse resistance to topotecan and mitoxantrone in a breast cancer model.[27] Furthermore, rapamycin has been shown to sensitize tumors to irinotecan in xenograft models of colon cancer. Marked decreases in tumor volume were observed following exposure to irinotecan + rapamycin.[28] Residual masses evaluated following exposure to the combination were found to have extensive necrosis and fibrosis.[28] Taken together, these data suggest that the combination of an mTOR inhibitor with chemotherapy, including irinotecan, may be a promising strategy for treatment of solid tumors.

2.3.2 Clinical Experience with Temsirolimus

2.3.2.1 Adult Studies with Temsirolimus:

In a Phase I study of temsirolimus given as a weekly infusion, 24 adults received doses ranging 7.5 to 220 mg/m^2.[29] Grade 3 thrombocytopenia was observed in a patient treated at a dose of 34 mg/m^2 and in a patient treated at a dose of 45 mg/m^2. Dose escalation continued without additional dose-limiting toxicity up to a dose of 220 mg/m^2. Toxicities noted at that dose level included manic-depressive syndrome, stomatitis, and asthenia in 2 of 9 patients. The most frequent drug-related toxicities were rashes and mucositis or stomatitis. Toxicities were reversible upon discontinuation of treatment.[29]

A Phase II study of temsirolimus in adults with relapsed or refractory mantle cell lymphoma has been conducted.[30] Thirty-five patients were treated with this agent at a dose of 250 mg IV weekly. Objective responses were seen in 13 of 34 patients (one CR and 12 PR). The median time-to-progression in all patients was 6.5 months, and the median duration of response for the responders was 6.9 months. Hematologic toxicities were common, and thrombocytopenia was the most frequent cause of dose reductions. The thrombocytopenia was brief, however, with resolution typically observed within one week.[30]

In a multicenter, Phase III trial in patients with poor prognosis renal cell carcinoma, 626 patients were randomized to receive 25 mg of intravenous temsirolimus weekly, 3 million U of interferon alfa (with an increase to 18 million U) subcutaneously three times weekly, or combination therapy with 15 mg of temsirolimus weekly plus 6 million U of interferon alfa three times weekly.[31] Patients who received temsirolimus alone had longer overall survival and progression-free survival than those who received interferon alone or interferon + temsirolimus. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group; asthenia was more common in the interferon group.[31] There were fewer patients with serious adverse events in the temsirolimus group than in the interferon group. Following an interim analysis of the data from this study, temsirolimus was approved by the FDA for the treatment of advanced renal cell carcinoma.[31]

Data from studies of temsirolimus as a component of multi-agent therapy are emerging. Concerns regarding an increased risk of infection were raised after a patient with glioblastoma multiforme developed fatal pneumocystis pneumonia following administration of temsirolimus in combination with temozolomide and radiotherapy.[32] Antibiotic prophylaxis was subsequently mandated for patients on this trial. Two other patients developed fatal gram negative sepsis during the study, and the investigators note that there appeared to be an increased risk of opportunistic infections in patients treated with the combination regimen compared with the population of patients treated with temsirolimus as a single agent.[32]

Although administration of weekly temsirolimus in combination with paclitaxel and carboplatin in patients with advanced solid tumors was not feasible due to myelosuppression, a regimen including all 3 drugs on Day 1 followed by temsirolimus (25 mg) on Day 8 of a 3 week cycle was well-tolerated. Toxicities associated with this regimen did not differ substantially from those associated with carboplatin and paclitaxel alone.[33]

2.3.2.2 Pediatric Studies with Temsirolimus:

A pediatric Phase I study of single agent temsirolimus in patients with recurrent solid tumors has been completed.[10] Nineteen patients were enrolled on study. Dose limiting toxicities at 150 mg/m^2 included Grade 4 thrombocytopenia and Grade 3 anorexia. Other Grade 3 or 4 toxicities included leukopenia (17%), anemia (11%), neutropenia (22%) and elevated ALT. A dose of 75 mg/m^2 weekly IV was recommended for study in the Phase II pediatric setting.[10] The results of the pediatric Phase II single agent trial of temsirolimus have also been published. Among the 19 children with neuroblastoma treated on this study, one experienced a partial response while 6 were found to have stable disease. Five of these patients experienced stable disease or better for more than 6 months.[34]

COG ADVL0918 is a Phase I study of irinotecan, temozolomide, and temsirolimus. Irinotecan (90 mg/m^2/dose) and temozolomide (dose being escalated stepwise from 100 to 150 mg/m^2/dose) are both given orally on a daily x 5 days schedule. Doses of temsirolimus are delivered intravenously on Days 1 and 8 of a 3-week cycle. The 3-drug combination was well tolerated when temsirolimus was given at doses up to 35 mg/m^2/dose. Observed toxicities included neutropenia, thrombocytopenia, lymphopenia, nausea/vomiting, mucositis, and elevated transaminases. Following administration of fixed doses of irinotecan and temozolomide in combination with 25 mg/m^2/dose temsirolimus, 2 patients who had been receiving chronic steroids developed dose-limiting hyperlipidemia.

The study was amended to preclude enrollment of children who require chronic steroid administration, and dose-limiting lipidemia was not observed at this or subsequent dose levels. The combination of a temsirolimus dose of 35 mg/m^2/dose in combination with irinotecan (90 mg/m^2/dose daily x 5 days) and temozolomide (100 mg/m^2/dose daily x 5 days) has been shown to be well tolerated, and this dose of temsirolimus will be used in this study.

Among 39 evaluable patients with solid tumors treated with these drug doses, 4 have had objective responses to protocol therapy. A total of 10 patients with neuroblastoma had been enrolled as of May 2012. One of these children experienced a prolonged partial response (14 cycles; confirmed by central review) and 2 experienced stable disease for >7 months.[35]

2.3.3 Rationale for closure of Regimen A (Amendment #5)

A total of 18 eligible patients were randomized to ANBL1221 Regimen A during Stage 1 of the activity design. The regimen was found to be safe and feasibility was demonstrated, however only 1 objective response (PR) was observed. As per Section 9.3.4 of this protocol, if there are 3 or fewer responders on a given regimen, this constitutes insufficient evidence of activity for the regimen. For this reason, there will be no further enrollments to Regimen A.

2.4 Rationale for GD2 Directed Therapy

2.4.1 Pre-Clinical Studies

The disialoganglioside GD2 is expressed on neuroblastoma cells, but its expression in normal human tissues is restricted to neurons, skin melanocytes and peripheral pain fibers.[36-38] Because of this pattern of expression, anti-GD2 monoclonal antibodies are an attractive form of targeted immunotherapy for children with neuroblastoma. Over the past 3 decades, antibodies directed against GD2 have been studied extensively. Early studies were performed using the murine IgG3 monoclonal antibody 3F8.[36,37] and murine IgG2a,14G2a.[39,40] 3F8 has been shown to mediate very efficient antitumor antibody dependent cytotoxicity (ADCC) *in vitro* in the presence of GM-CSF.[41] However, murine antibody therapy can be accompanied by development of a human anti-mouse antibody response (HAMA), which results in the formation of neutralizing antibodies. This can be particularly problematic in patients who have not received high dose chemotherapy or undergone myeloablative treatment within 90 days preceding murine antibody treatment.[42] To address this challenge, alternative antibody constructs have been developed. Ch14.18 (dinutuximab) consists of the variable regions of murine IgG3 b 14.18 and the constant regions of human IgG1-κ. Pharmacokinetic and immunological studies have shown that ch14.18 (dinutuximab) has longer plasma half life and less immunogenicity when compared to the murine antibody, making it potentially more effective.[11,43] Preclinical studies performed both *in vitro* and *in vivo* indicate that its anti-neuroblastoma activity involves complement dependent cytotoxicity (CDC) and ADCC when ch 14.18 is used alone[44] or in combination with GM-CSF.[45]

2.4.2 Clinical Studies using anti-GD2 Antibodies

The murine anti-GD2 antibody 3F8 was tested in a Phase I trial in patients with neuroblastoma, and in a Phase II trial of 3F8 in combination with GM-CSF. The 2 agent combination appeared to have efficacy, especially in patients with bone marrow disease.[46] Phase I and II clinical trials of ch14.18 (dinutuximab) or 14G2a, alone or combined with cytokines such as GM-CSF or IL2 respectively, also showed signals of activity in patients with neuroblastoma.[47,48] Subsequent clinical trials have demonstrated a significant decrease in risk of relapse and an improvement in survival for patients with high risk neuroblastoma in remission after initial multi-modality therapy. An early analysis of results of a German study of ch14.18 (dinutuximab) therapy alone administered to patients > 1 year of age with Stage 4 neuroblastoma did not demonstrate a decrease in recurrence risk compared to no further therapy.[49] However, analyses at 9 years from therapy revealed a statistically significant improvement in EFS for those patients who received ch14.18 (dinutuximab).[50] A randomized Phase III study (COG ANBL0032) of ch14.18 (dinutuximab) combined with GM-CSF, interleukin 2 and isotretinoin compared with isotretinoin alone as post-consolidation therapy for patients in remission was stopped early because the EFS of patients treated with the antibody containing regimen was clearly superior to that of patients treated with isotretinoin alone.[51] Thus, although few patients with measurable bulk disease experienced objective responses to ch14.18 (dinutuximab) as a single agent in early phase clinical trials, ch14.18 (dinutuximab) plus cytokine therapy is now considered standard post-consolidation care for patients with high-risk neuroblastoma.

The clinical evaluation of various anti-GD2 monoclonal antibodies in children with neuroblastoma has been largely focused on treatment of minimal residual disease to date. However, several studies conducted in adults with cancer suggest that monoclonal antibodies can be effectively combined with chemotherapy to treat patients, including those with measurable disease.[52-59]

2.4.3 Combination of ch14.18 (dinutuximab) with chemotherapy

In the currently proposed study, ch14.18 (dinutuximab) will be given in combination with irinotecan and temozolomide in an effort to augment the activity of the antibody in a setting other than that of minimal residual disease. Preclinical studies also indicate that anti-GD2 antibodies enhance the effects of

chemotherapy. This has been shown in a small cell lung cancer (SCLC) cell line[60] and in a neuroblastoma cell line.[61] In the first study with SCLC cell line, the combination of cisplatin (CDDP) with an anti-GD2 mAb resulted in prominent enhancement of cytotoxicity even in cells with low to moderate GD2 expression. The anti-GD2 monoclonal antibody induced weak activation of c-Jun terminal kinase (JNK) in SCLC cells, and all anti-cancer drugs also induced its activation to various degrees. When CDDP and an anti-GD2 antibody were used together, significantly augmented JNK activation was observed with corresponding cytotoxic effects, suggesting that synergistic phosphorylation of JNK with 2 reagents induced apoptosis. This study suggests that in addition to the ADCC, anti-GD2 antibodies induced direct apoptosis of SCLC cells.[60] In a later study with a neuroblastoma cell line, the anti-GD2 14G2a antibody was found to have at least additive (carboplatin) or synergistic (doxorubicin, topotecan) effects on cell killing.[61] These data provide compelling reasons to evaluate the addition of an anti-GD2 antibody to chemotherapy outside the setting of minimal residual disease for treatment of children with relapsed or refractory neuroblastoma. To optimize the effect of the antibody, GM-CSF will also be administered.

2.4.4 Use of monoclonal antibodies with chemotherapy in clinical trials in adults

Rituximab, a chimeric monoclonal antibody directed against the B-cell specific antigen CD20, causes complement and antibody-dependent cell-mediated toxicity. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was associated with statistically significantly higher complete response rates in patients with diffuse large B-cell lymphoma compared to CHOP alone. The addition of rituximab to standard chemotherapy was shown to significantly decrease the risk of treatment failure and death among patients in this trial.[62] Subsequent studies confirmed the contribution of rituximab in combination with CHOP in adults with lymphoma, and the long-term benefit of this combination has been demonstrated.[52]

Although the mechanism of action of monoclonal antibodies that interfere with signal transduction within tumor cells is somewhat different from that of antibodies that mediate ADCC, the concept of using monoclonal antibodies together with chemotherapy is also supported by the trastuzumab and cetuximab experiences. Trastuzumab binds to the extracellular domain of the HER-2/neu receptor tyrosine kinase and disrupts receptor dimerization.[63] This antibody has been successfully combined with chemotherapy (doxorubicin and cyclophosphamide) for women with HER-2 positive metastatic breast cancer for more than a decade, leading to increased response rate, prolonged progression free and overall survival.[53] Cetuximab is a chimeric antibody that binds to the epidermal growth factor receptor (EGFR) and competitively inhibits the binding of ligands including epidermal growth factor (EGF) and transforming growth factor alpha. Binding of cetuximab to the EGFR decreases activation of receptor-associated kinases and inhibits cell growth and proliferation.[64] This agent is approved for use in combination with irinotecan in patients with EGFR-expressing metastatic colorectal cancer refractory to irinotecan-based therapy.[65]

2.5 Transition from NCI Manufactured Ch14.18 to UTC Manufactured Ch14.18 (dinutuximab)

The investigational agent, chimeric monoclonal anti-GD2, ch14.18, used in ANBL0032 and ANBL1221 was provided and manufactured by NCI since study activation in October 2001 and February 2013, respectively.

As of January 21, 2014, the ch14.18, dinutuximab (NSC 764038) distributed by the NCI is manufactured by United therapeutics, Inc. The ch14.18 (NSC 623408) manufactured by the NCI is no longer being utilized in NCI sponsored protocols. The NCI has continued to distribute the agent through the Pharmaceutical Management Branch, under the same IND. However, the dosing calculation was adjusted in order to reflect the change from a theoretical extinction coefficient used by the NCI to a calculated extinction coefficient used by United Therapeutics. This adjustment was necessary in order to ensure the delivery of the same amount of ch14.18 (dinutuximab) as for those patients treated prior to Jan 21, 2014.

2.6 Rationale for Further Study of Regimen B

A total of 17 patients were randomized to Regimen B therapy. Sixteen of these received treatment while one declined therapy following randomization. During a safety phase in which 6 patients were treated, one patient experienced unacceptable toxicity as defined in Section 9.3.3. This patient experienced Grade 4 hypoxia and required mechanical ventilation for more than 24 hours. Of the 16 patients treated with Regimen B therapy, 11 patients required dose modifications. Among these patients, five required temozolomide dose modifications. In one patient the dose was modified due to a formulation issue, and in one the temozolomide dose was modified due to emesis. In 3 patients temozolomide dosing was modified due to hematologic toxicity (neutropenia and thrombocytopenia), mostly during later cycles, however all patients continued protocol therapy uninterrupted. An additional six patients required dinutuximab dose modifications, including one patient with protocol-defined unacceptable toxicity, and one with Grade 4 bronchospasm. In both cases protocol therapy was discontinued. The remaining four patients required dinutuximab dose modifications due to pain (two), infection (one) and hypotension (one). However these patients all continued therapy without toxicity that required additional dose modification. After review of the cases in which doses were modified, the study committee and the data safety monitoring committee determined that no changes in drug dosing as described in Section 4 are required. However, to further assess the feasibility of delivering this regimen, evaluation of toxicity in additional patients is needed.

Response to therapy was also assessed. Analysis of data available as of January 15, 2016 shows that among the 17 patients assigned to Regimen B, nine had objective responses (5 CR, 4 PR). Responses were observed in patients with both relapsed/progressive disease (5/10; 3 PR, 2 CR) and refractory (4/7; 3 CR, 1 PR) disease. Among Regimen B responders, prior frontline therapy included high dose chemotherapy with stem cell rescue in 5 and anti-GD2 therapy in 3 patients. The protocol-defined minimum number of responses required to deem Regimen B worthy of additional study was exceeded during Stage 1. However, the confidence intervals around the 53% response rate for Regimen B are wide (95% CI: 0.31, 0.74). In addition, the small number of patients treated with Regimen B therapy precludes subgroup analyses that are important for application of the findings to the overall population of patients with neuroblastoma. To allow further study of feasibility and to more accurately estimate the response rate to this therapy, additional patients will be assigned to Regimen B to permit accrual of a total of 50 eligible patients.

2.7 Additional Studies

2.7.1 Rationale for studying naturally occurring anti-glycan antibodies

Administration of ch14.18 (dinutuximab) is often associated with allergic reactions, which may occur even during the first infusion. Natural occurring antibodies to non-human glycans, galactose alpha-1,3-galactose (alpha-gal) and Neu5Gc, are present in all humans.[66] Ch14.18 (dinutuximab), which is produced in rodent cells, contains alpha-gal and Neu5Gc. Levels of anti-alpha-gal have been correlated with allergic reactions to cetuximab (Erbitux), a chimeric antibody against the EGF receptor that is extensively modified with these glycans.[67] Thus, it is possible that the presence and/or levels of antibodies to these non-human glycans may correlate with allergic reactions to ch14.18 (dinutuximab), and the levels of anti-glycan antibodies may increase after serial courses of immunotherapy. The presence and/or level of antibodies to non-human glycans may affect the blood levels of ch14.18 (dinutuximab) and ultimately impact response to therapy.

2.7.2 Rationale for NK cell receptor NKp30 isoform

The natural killer (NK) cell receptor NKp30 is selectively expressed by all human NK-cells and plays an important role in triggering NK-mediated cytotoxicity. NKp30 is also involved in the cross-talk between NK and dendritic cells. The three NKp30 splice variants[68] have been shown to be of prognostic significance in gastrointestinal sarcoma (GIST), a malignancy that expresses NKp30 ligands and that is treated with NK-stimulatory KIT tyrosine kinase inhibitors. Healthy individuals and those with GIST show distinct patterns of transcription of functionally different NKp30 isoforms. In individuals with GIST, predominant expression of the immunosuppressive NKp30*c* isoform (compared to the immunostimulatory NKp30a and

NKp30b isoforms) was associated with reduced survival, decreased NKp30-dependent tumor necrosis factor-α (TNF-α), IL10 and CD107a release, and defective secretions of interferon-γ (IFN-γ) and interleukin-12 (IL-12) in the NK-DC cross-talk that could be restored by blocking of IL-10.[69] In a recent French study, an association between high levels of the immunosuppressive Nkp30*c*-isoform and worse prognosis (PFS *p-value= 0.01*) of patients with high risk neuroblastoma has been reported. No impact of the Nkp30*a*-isoform was noted.[70] Treatment of glioblastoma patients with temsirolimus, temozolomide and radiation suppressed helper and cytotoxic T cells, B cells, and natural killer cells but increased numbers of regulatory T cells. These cells recovered to baseline levels during adjuvant temozolomide.[71] Since NK cytotoxicity plays a major role in tumor immunity in general, and in anti-GD2-mediated tumor cell kill in particular, the impact of NKp30 isoforms including the NKp30*c*-isoform may be more pronounced in patients receiving either ch14.18 (dinutuximab) or temsirolimus therapy.

2.7.3 Rationale for KIR/KIR-L genotyping

Killer-Immunoglobulin-like Receptors (KIR) recognize specific HLA molecules, regulate function of human NK cells and control their self-tolerance. The interactions between KIR on donor NK cells and KIR ligands (KIR-L) on recipient tissues influence anti-tumor efficacy of allogeneic hematopoietic stem cell transplantation, and influence the antitumor effects of autologous transplantation. Since the genes encoding KIR and KIR-L are inherited independently, it is possible for an individual to be KIR-receptor ligand mismatched with oneself. In a COG phase II study of 38 relapsed/refractory neuroblastoma receiving *humanized* anti-GD2 linked to IL2, 7 of 24 mismatched patients experienced either complete response or improvement of their disease after immunocytokine therapy, while there was no response or comparable improvement of disease in 14 patients who were matched ($p = 0.03$)[72]. These data suggest that patients with KIR receptor-ligand mismatch may be associated with better clinical response to immunotherapy with an anti-GD2 antibody. KIR and KIR ligand genotyping will therefore be performed as part of this trial.

2.7.4 Rationale for Fc receptor genotyping

In general, the anti-tumor activities of unconjugated monoclonal antibodies require the contribution of either complement or Fcγ receptor (FcγR)-expressing effector cells in order to achieve tumor cell killing. However, because most tumor cells, including neuroblastoma, express increased amounts of complement-inhibiting proteins that protect the cells against lysis by complement, antibody-dependent cell cytotoxicity (ADCC) is considered the key antitumor mechanism of therapeutic antibodies *in vivo*. Most natural killer (NK) cells, certain subpopulations of T lymphocytes, as well as monocytes and granulocytes are capable of mediating ADCC against antibody-coated targets via their expression of FcγR for IgG. The FcγR genes display polymorphisms that greatly influence the affinity of IgG for the Fcγ receptor. NK cells bearing the FcγRIIIa-158V/V allele mediate ADCC more effectively than those with F/F allele. Similarly, for FcγRIIA, the high-affinity H allele at 131 results in greater affinity of FcγRIIa for IgG, whereas the low-affinity R allele correlates with decreased binding. Fc receptor polymorphisms have been reported to influence the response of lymphoma to rituximab (anti-CD20)[73,74]. More recently the FcγRIIc molecules have also been shown to influence ADCC; polymorphisms at this locus can influence expression vs. lack of expression (function vs. lack of function) of this FcγRIIc. Recently, it has been shown that an algorithm incorporating polymorphism data for FcγRIIa, FcγRIIIa and FcγRIIc is associated with clinical benefit in an immunotherapy trial for adults with renal cell carcinoma.[75] Because dinutuximab is very effective in mediating ADCC, its efficacy in neuroblastoma may be associated with Fc receptor genotype. The association between Fc receptor genotype and response to irinotecan/temozolimide/dinutuximab therapy will be examined.

2.7.5 Rationale for HACA testing

Analysis of samples from a Phase 1 trial of a humanized anti-GD2 antibody (hu14.18K322A) conducted at St. Jude Children's Research Hospital[76] has shown that sera obtained prior to therapy from 9 of 38 patients contained **P**re-existing **A**nti-**T**herapeutic **A**ntibodies (PATA) that reacted against the anti-GD2 antibody

although there subjects had no prior exposure to any monoclonal antibody. Initial analyses of the immunologic reactivity pattern of the sera from these 9 PATA+ patients revealed that these PATA are not anti-idiotypic antibodies against the therapeutic hu14.18K322A mAb. Unexpectedly, these PATA bound to other human IgG1 mAbs (rituximab, trastuzumab), pooled human IgG (Gammagard), and also to the anti-GD2 chimeric antibody dinutuximab. However, they did not bind to the parental mouse anti-GD2 mAb (14.G2a). The presence of PATA may be linked to patient outcome. Of the 38 initially evaluable patients, only 4 were known to be in remission or without progression 2.5 years following treatment. All 4 of these patients were among the 9 found to to PATA positive (p= 0.002). (Paul Sondel, personal communication) This preliminary observation requires further study, however it suggests that these PATA recognize a shared IgG1 epitope (also known as an antibody-allotype)[77] that is found on most human IgG1 antibodies, but is "foreign" to the 9 PATA+ patients who may have been immunized via exposure to allo-IgG1 in prior transfusions). PATA/anti-alloantibodies may potentially augment the efficacy of tumor reactive therapeutic antibodies and may represent some of the antibody reactivity identified in prior "human anti-chimeric antibody (HACA)" assays. An understanding of the role of PATA/anti-allotype biology may aid in the selection of patients for GD2 directed immunotherapy. The association between results of testing for the presence HACA, anti-idiotype and PATA/anti-allotype antibody (not directed against the dinutuximab idiotype) with response to study therapy will be examined.

2.7.6 Rationale for immune function studies

Understanding the state of the immune effector cells may be crucial to the design of future passive immunotherapies for cancer. Specifically, the number of NK and NK-T cells, T cell subsets and expression of NK activation and inhibitory receptors present in patient blood may have an association with clinical responses to immunotherapies, including dinutuximab. In addition, cytokine levels may be important in understanding responses to immunotherapy for children with neuroblastoma. 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.[78] In addition, proinflammatory cytokines have been linked to neuropathic pain. Therefore the association between serum cytokine levels (IL1, IL6, TNF-alpha, IFN-gamma, etc) with toxicity and response to therapy merit evaluation.

2.7.7 Rationale for assessment of the tumor microenvironment

Tumor-infiltrating leukocytes (TILs) can act as critical participants in tumor progression, and the presence of tumor-associated macrophages (TAMs) has been associated with poor prognosis in many adult cancers. In neuroblastoma, expression levels of genes related to M2 polarization of macrophages may be prognostic in patients with high-risk disease.[79] The importance of inflammatory pathways in neuroblastoma progression reinforces the concept that the tumor microenvironment may be important in resistance to therapies including immunotherapies in neuroblastomas and other pediatric malignancies.[80,81] In this study, the association between levels of infiltrating TILs (including TAMs) in tumor samples with response and outcome following dinutuximab and irinotecan/temozolomide will be examined. In addition, because immune checkpoint proteins CD274 (PDL1) and CD276 (B7H3) affect the activity of T and NK cells,[82-84] expression of these proteins in tumor samples will also be evaluated. Finally, expression of GD2 itself will also be assessed in tumor samples.

2.7.8 Rationale for analysis of gene expression studies

Expression of immune response related genes may be predictive of ADCC and anti-tumor effect in patients treated with dinutuximab and irinotecan/temozolomide. RNA samples obtained prior to and following therapy and samples collected after administration of dinutuximab/irinotecan/temozolomide will be used for analysis of expression of a panel of genes related to immune function (including cell surface receptors, proteases, cytokines and cytokine receptors, cell cycle and protein kinases, etc) and for more global analysis via RNASeq. Gene expression studies will also include assessment of tumor burden in the circulating blood using the NB5 assay. This assay quantifies expression of CHGA, DCX, DDC, PHOX2B, and TH with a sensitivity of one tumor cell among 10^6 normal blood mononuclear cells. The results of this assay can be

used to correlate expression of immune related genes to tumor burden levels.

2.7.9 Rationale for analysis of circulating GD2 levels

The ganglioside composition of neuroblastoma cells was studied decades ago,[85] 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. Because serial tumor sampling is not possible in young children receiving neuroblastoma therapy, methods for detection of GD2 shed from the surface of neuroblastoma cells have been developed. A high performance liquid chromatography (HPLC)/tandem mass spectrometry (MS/MS) assay for enhanced detection of GD2 in plasma and serum has recently been validated (A. Desai, personal communication). The level of GD2 detectable at baseline may be predictive of response to the combination of irinotecan, temozolomide and dinutuximab. Alternatively, changes in levels of GD2 following treatment with this combination may be more informative.

2.7.10 Rationale for tumor exome and transcriptome sequencing

Next generation sequencing studies have demonstrated that recurring genomic aberrations may have both prognostic and therapeutic significance in neuroblastoma.[86] Recurrent molecular aberrations in tumor may provide critical insights into the basis for the differential response to irinotecan, temozolomide and dinutuximab. Available tumor samples collected for clinical purposes will be analyzed by deep exome sequencing and by transcriptome sequencing. To facilitate the analysis, results will be interpreted in the context of results from exome sequencing of DNA derived from peripheral blood. The number of patients to be studied in the proposed expanded cohort to be enrolled on this study is small, however findings from these sequencing studies together with results from studies described in the preceeding paragraphs may be critical in identifying future patients most likely to benefit from the combination of irinotecan, temozolimide and dinutuximab.

2.7.11 Revised International Neuroblastoma Response Criteria

The International Neuroblastoma (NB) Response Criteria (INRC) provide a common basis for comparisons of response across clinical trials conducted throughout the world. While these criteria have proven to be extremely helpful over time, they were last updated in 1993. Since that time, it has become apparent that the current INRC guidelines suffer from significant limitations, particularly with respect to definitions of response at metastatic sites (bone and bone marrow). The INRC provide limited guidance for incorporation of now-standard imaging modalities (^{123}I-MIBG imaging), and they provide no guidance for incorporation of FDG-PET. Furthermore, the criteria that were applicable in the early to mid-1990s do not address modern techniques for quantification of marrow disease. A National Cancer Institute-sponsored international meeting was held in 2012 to develop updated consensus guidelines for assessment of response in patients with neuroblastoma. Data obtained from COG, New Agents for Neuroblastoma Therapy (NANT), Society of Paediatric Oncology European Neuroblastoma Network (SIOP-EN) and Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) contemporary clinical trials were analyzed. Individual response components of a revised INRC will include primary tumor dimensions using anatomic imaging, and metastatic disease assessment using ^{123}I-MIBG imaging. For patients with MIBG non-avid disease, FDG-PET will be used for metastatic imaging. Furthermore, in addition to bone marrow morphologic assessment, immunocytochemistry will be used to assess the burden of neuroblastoma in the marrow. An updated version of the INRC (including definitions of complete response, partial response, stable disease, and progressive disease) is expected to be finalized by the end of 2012. Until that time, for patients on the current trial, data regarding each component of response (cross sectional imaging, functional imaging, marrow assessment) in the revised INRC will be collected to permit subsequent comparisons of response using the older and newer criteria.

2.8 Development Plans

The agent shown to be the most promising during this selection design study will be integrated into frontline therapy for patients with high-risk neuroblastoma in 1 of 2 ways. One option would be to integrate the entire cassette of irinotecan, temozolomide and the "winner" from this trial as salvage therapy for the treatment of patients with disease that is refractory to initial induction therapy. Recent analyses of end-induction MIBG scans for patients enrolled on COG A3973 indicate that 3 year event free survival for patients with Curie scores >5 following multi-agent chemotherapy was less than 10%.[87] Integration of a novel therapeutic cassette containing cytotoxics with either temsirolimus or ch14.18 (dinutuximab) may improve disease response for these patients prior to proceeding to myeloablative consolidation therapy.

Alternatively, the agent identified as the "winner" during this trial could be integrated into induction therapy for all patients with high-risk disease. While the 3-year EFS in patients with end-induction Curie scores > 5 is extremely poor, survival even among patients with better end-induction Curie scores (≤ 5) is still less than 50%[87] and 20% of patients will experience disease progression during induction therapy. Thus, there is considerable room for improvement among all patients with high-risk neuroblastoma. Toxicity data generated during the current trial will inform decision-making regarding the best approach to integrating the "winner" into upfront therapy. Given the known toxicity of high-risk neuroblastoma chemotherapy induction, a small pilot trial would need to be undertaken to ensure tolerability of combining the "winner" with induction therapy.

2.8.1 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. Temsirolimus and ch14.18 (dinutuximab) have shown activity against neuroblastoma in both *in vitro* and *in vivo* animal models, and have been shown to be safe and tolerable in pediatric Phase I trials. This will be the first attempt to move molecularly targeted agents in combination with chemotherapy into front-line therapy in this important pediatric disease. We expect that at least one of these agents will move forward to a randomized Phase III trial as part of induction therapy for high-risk neuroblastoma. Alternatively, one of these agents could be used in a regimen for patients refractory to initial induction therapy. Furthermore, this trial design will serve as a model for testing of molecularly targeted agents for integration into neuroblastoma therapy.

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 COG Registry system 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.

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

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to theCTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
E-mailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure 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 patients to this study.

CRAs/Site Investigators should refer to the COG website to determine if the study is currently open for accrual. 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 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions:
https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps above. Reservations may be obtained 24 hours a day through the OPEN system.

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. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN. 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.

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 **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II 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.

3.2 Patient Eligibility Criteria

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

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 and bone marrow examination must be obtained within 3 weeks prior to enrollment (repeat if necessary).

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

Patients of all ages are eligible for this study.

3.2.2 Disease Status

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 (ie, > 2 x 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. Patients must have ONE of the following:

1) First episode of recurrent disease following completion of aggressive multi-drug frontline therapy.
2) First episode of progressive disease during aggressive multi-drug frontline 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, etc.).

3.2.2.3 Documentation of Disease:

Patients must have at least ONE of the following:

1) Measurable tumor on MRI, CT scan obtained within 3 weeks prior to study entry. 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 scan obtained within 3 weeks prior to study entry 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 new site of soft tissue disease (radiographic evidence of disease progression) regardless of whether progression occurs while receiving therapy or after completion of therapy.

Note: Patients with elevated catecholamines (ie, > 2 x ULN) only or bone marrow disease 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
Patients must have received frontline therapy (including surgery, chemotherapy, autologous SCT +/- MIBG, immunotherapy, radiotherapy, and retinoids) but may NOT have received second line chemotherapy for resistant/refractory, relapsed disease or progressive disease.

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 agent): At least 7 days must have elapsed since the completion of therapy with a non-myelosuppressive biologic agent or retinoid.

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 is allowed to sites that will not be used to measure response during this study.

3.2.4.5 Stem Cell Transplants (SCT): Patients are eligible ≥ 6 weeks after autologous stem cell transplants or stem cell infusions 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: Subjects who have previously received anti-GD2 monoclonal antibodies for biologic therapy or for tumor imaging are eligible unless they have had progressive disease while receiving prior anti-GD2 therapy. Subjects who have received autologous marrow infusions or autologous stem cell infusions that were purged using monoclonal antibody linked to beads, but no other form of anti-GD2 monoclonal antibody, are eligible.

3.2.5 Concomitant Medications Restrictions

(Please see Section 4.1.1 for the concomitant therapy restrictions for patients *during* treatment.)

- Patients must not have received long-acting myeloid growth factors (eg, Neulasta) 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:

- 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 platelet count criteria are met but are not evaluable for hematological toxicity.

3.2.6.2 Adequate renal function defined as:

- Creatinine clearance or estimated radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine ≤ upper limit of normal (ULN) based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
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 (Schwartz et al. J. Peds, 106:522, 1985) 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 central nervous system function defined as:

- Patients with a history of CNS disease must have no clinical or radiological evidence of 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

3.2.6.5 Adequate cardiac function defined as:

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

3.2.6.6 Adequate coagulation defined as:

- PT ≤ 1.2 x upper limit of normal.

3.2.6.7 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.

Important Note: Eligibility criteria listed in Section 3.2 must be met at the time of enrollment AND at the start of protocol therapy. If there is a change in the patient's clinical condition between the time of study enrollment and the start of protocol therapy, relevant organ function studies should be repeated to determine whether the patient should receive protocol therapy. If there are questions regarding a patient with an evolving clinical status, please contact the study chair immediately to discuss the changing clinical scenario.

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 elevated catecholamines (ie, > 2 x ULN) only or bone marrow disease only 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.

3.2.7.4
Patients must not have received enzyme-inducing anticonvulsants including phenytoin, phenobarbital, valproic acid, or carbamazepine for at least 7 days prior to study enrollment. Patients receiving non-enzyme inducing anticonvulsants such as gabapentin or levetiracetam will be eligible.

3.2.7.5
Patients must not have been diagnosed with myelodysplastic syndrome or with any malignancy other than neuroblastoma.

3.2.7.6
Patients with symptoms of congestive heart failure are not eligible.

3.2.7.7
Patients must not have ≥ Grade 2 diarrhea

3.2.7.8
Patients must not have uncontrolled infection.

3.2.7.9
Patients with a history of Grade 4 allergic reactions to anti-GD2 antibodies or reactions that required discontinuation of the anti-GD2 therapy are not eligible.

3.2.7.10
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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

As of Amendment #5, patients will only be assigned to Regimen B therapy. Patients on Regimen B will receive irinotecan/temozolomide/ch14.18 (dinutuximab) followed by sargramostim (GM-CSF).

Treatment cycles will be repeated every 21 days (3 weeks). Tumor response will be assessed after Cycles 2, 4, 6 and every 4 cycles thereafter until the end of protocol therapy. Patients with CR, PR or SD may continue to receive the assigned therapy for a maximum of 17 cycles (approximately 1 year).

Regimens:

Regimen-B

Day 1	Day 2	Day 3	Day 4	Day 5	Days 6-12
TEMO	TEMO	TEMO	TEMO	TEMO	
IRIN	IRIN	IRIN	IRIN	IRIN	
	ch14.18 (dinutuximab)	ch14.18 (dinutuximab)	ch14.18 (dinutuximab)	ch14.18 (dinutuximab)	GMCSF

TEMO= Temozolomide 100 mg/m^2/dose PO daily on Days 1-5; given at least 1 hr prior to Irinotecan. For patients whose body surface area is <0.5m^2, temozolomide dosing is based on body weight in kg (see Appendix II). **Subsitution of IV Temozolomide is not permitted.**

IRIN = Irinotecan: 50 mg/m^2/dose IV daily on Days 1-5.
ch14.18 (dinutuximab) = ch14.18 (dinutuximab) IV at 17.5 mg/m^2/dose on Days 2-5.
GMCSF = sargramostim 250 mcg/m^2/dose SubQ on Days 6-12.

See the Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.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.

If there is a change in the patient's clinical condition between the time of study enrollment and the start of protocol therapy, relevant organ function studies should be repeated to determine whether the patient should receive protocol therapy. If there are questions regarding a patient with an evolving clinical status, please contact the study chair immediately to discuss the changing clinical scenario.

4.1.1 Concomitant Medications and Supportive Care

4.1.1.1 Diarrhea prophylaxis

Cefixime (8 mg/kg/day PO once daily) or an available equivalent oral cephalosporin (eg, cefpodoxime (Vantin™) 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.

4.1.1.2 Pneumocystis prophylaxis

Patients **must** receive pneumocystis prophylaxis during study therapy.

4.1.1.3 Other anti-cancer therapy

No other systemic anti-cancer therapy will be permitted. Radiotherapy to localized painful lesions is acceptable, provided at least one measurable/MIBG evaluable lesion is not irradiated. Lesions irradiated during protocol therapy will not be used to assess tumor response. Patients should be evaluated prior to radiotherapy with appropriate tumor imaging. If measurable or evaluable progressive disease is documented after enrollment then the patient should be taken off protocol therapy.

4.1.1.4 Corticosteroid therapy

Pharmacologic doses of systemic corticosteroids should be used ONLY for life-threatening conditions (ie, 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.**

4.1.1.5 Other supportive care

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary. Note: aprepitant (Emend) should not be used as an anti-emetic. The use of gabapentin as an adjunct for patients receiving ch14.18 (dinutuximab) should be considered.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.2 Patients on Regimen B: Irinotecan/Temozolomide with ch14.18 (dinutuximab)

Each chemotherapy cycle lasts 21 days (3 weeks). Patients will receive up to a maximum of 17 cycles of chemotherapy.

A cycle may be repeated every 21 days if the patient has stable disease or better, and has again met laboratory parameters as defined in the eligibility section (Section 3.2) except for the following repeat cycle modified starting criteria: ALT ≤ 5 x ULN provided that the usual causes of transaminitis such as infections, tumor progression, or drug toxicity are excluded by appropriate blood and imaging studies AND the transaminitis is stable if not improving.

Drug doses should be adjusted based on the BSA calculated from **height and weight obtained within one week** prior to the beginning of each cycle.

Temozolomide: PO
Days: 1-5
Dose: 100 mg/m^2/dose for patients ≥ 0.5m^2. The maximum dose to be administered is 200 mg. For patients whose body surface area is <0.5m^2, dosing is based on body weight in kg (see Appendix II).

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. Bedtime administration may decrease nausea and vomiting. For patients whose body surface area is ≥ 0.5m^2, the temozolomide dose should be rounded off to the nearest 5 mg (round 2.5 mg down, see Appendix II). For ease of swallowing, the capsule content may be mixed with applesauce or juice (see instructions in Appendix IV) or an oral suspension may be compounded (see drug monograph in Section 6.5). If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated.

Administration of PO temozolomide should be documented; missed doses should be noted on the 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 drug monograph for additional details and examples.

Irinotecan: IV over 90 minutes
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.

ch14.18 (dinutuximab): IV as detailed below
Days: 2-5
Dose: 17.5 mg/m^2/dose (regardless of BSA).

Sargramostim (GM-CSF): SubQ (preferred) or IV as detailed below
Days: 6-12
Dose: 250 mcg/m^2/dose (regardless of BSA)
Detailed administration guidelines for chemotherapy and ch4.18 and GM-CSF (Days 2-5) follow:

- 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 ch14.18 (dinutuximab) infusion (Days 2-5 of each cycle) start IVF bolus of normal saline (≥ 10 mL/kg) over one hour.
- At hour 2.5: on days patient is receiving ch14.18 (dinutuximab) infusion (Days 2-5 of each cycle), start ch14.18 (dinutuximab) infusion. Each daily dose of ch14.18 (dinutuximab) should be infused IV over approximately 10 hours, starting at 0.88 mg/m^2/hr x 0.5 hr, then increasing to 1.75 mg/m^2/hr for the remainder of the dose, if tolerated. The infusion duration may be extended up to 20 hours for anticipated toxicities (pain, fever, tachycardia, tachypnea, hypotension), not responding to other supportive measures, and the duration used should be recorded.
- The maximum infusion time is 20 hours; ch14.18 (dinutuximab) administration must be stopped after 20 hours even if the total dose has not been administered. The total dose given in 20 hours should be recorded.
- Recommended premedications include:
    - Hydroxyzine (0.5-1 mg/kg; max dose 50 mg) PO or diphenhydramine (0.5-1 mg/kg; max dose 50 mg) IV over 10 minutes to start approximately 20 minutes prior to ch14.18

(dinutuximab) infusion; may be repeated every 6 hours as needed during ch14.18 (dinutuximab) infusion. Note: intravenous hydroxyzine is NOT recommended.
    - Acetaminophen (10 mg/kg; max dose 650 mg) PO given approximately 20 minutes prior to ch14.18 (dinutuximab) infusion; may be repeated every 4-6 hours as needed for fever.
- Recommended pain management:
    - Morphine sulfate loading dose immediately prior to ch14.18 (dinutuximab) administration. A dose of 50 mcg/kg is recommended, though this may be adjusted based on a given patient's pain history.
    - Continue with morphine sulfate drip titrated to effect. The recommended dose range for the continuous infusion is 20-50 mcg/kg/hr to continue for 2 hours after completion of the ch14.18 (dinutuximab) infusion.
    - Other narcotics such as hydromorphone or fentanyl can be used.
    - Gabapentin may be used in conjunction with other pain medications per institutional practice.
    - The use of additional pain medications (lidocaine, ketamine) in extenuating circumstances should be undertaken in consultation with pediatric pain management specialists.
        - For example, a lidocaine infusion may be used in conjunction with IV bolus of morphine on prn basis. Suggested administration guidelines for a lidocaine infusion are shown below:
            - Give lidocaine IV bolus at 2 mg/kg in 50 mL NS over 30 min prior to the start of ch14.18 (dinutuximab) infusion.
            - At the beginning of ch14.18 (dinutuximab) infusion, start IV lidocaine infusion at 1 mg/kg/hr and continue until two hours after the completion of ch14.18 (dinutuximab) infusion.
            - May give morphine IV bolus 25-50 microgram/kg every 2h prn pain.
            - Patient should be monitored closely for sedation scale, EKG (rate and rhythm), HR, BP, RR, oxygen saturation (pulse oximeter) and pain score. If patient develops dizziness, perioral numbness, tinnitus attributable to lidocaine, then stop lidocaine infusion.
- Monitoring during ch14.18 (dinutuximab) infusion:
    - Vital signs should be assessed every 15 minutes for the first hour of the infusion, then hourly during the remainder of the infusion if stable after the first hour. More frequent assessment may be required based on the patient's clinical condition. Between antibody doses, vitals should be assessed every 4 hours.
    - Strict observation of intake and output is required on the days of ch14.18 (dinutuximab) administration.
    - Daily physical examination including a careful eye exam for pupillary reflexes and extraocular movements.
    - Patients should be weighed daily on the days of ch14.18 (dinutuximab) administration.

- Sargramostim (GM-CSF) administration is to begin on Day 6 of each cycle:
    - The standard route of administration is subcutaneous; use of an insuflon catheter is permitted.
    - In extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Cycle 1, the next cycle starts on Day 22 or when the patient has met the criteria for repeat cycles stated above.

The therapy delivery map (TDM) for Cycle 1 is on the next page (Section 4.2.1). The TDMs for therapy subsequent to Cycle 1 are provided in Section 4.2.2.

Patients who have stable disease or better following disease re-evaluations may continue on study for a total of 17 cycles (approximately 1 year), provided that there are no toxicities that preclude continuation of protocol therapy.

4.2.1 **Regimen B: Irinotecan and Temozolomide with ch14.18** (dinutuximab) - **Cycle 1** Three consecutive weeks (21 days) will constitute one cycle. This therapy delivery map relates to Cycle 1of TEMO+IRIN+ch14.18 (dinutuximab).	_____ Patient COG ID number _____ DOB

Criteria to start Cycle 1: patient met laboratory parameters as defined in the eligibility section (Section 3.2).
Each cycle lasts 21 days and this Therapy Delivery Map is on **1 page**. Dose calculations should be based on actual BSA except where noted for TEMO.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS (See Section 7.1 for Baseline studies)
Temozolomide (TEMO)	PO	For patients ≥0.5m^2: 100 mg/m^2/dose. Round off to the nearest 5 mg. For patients <0.5 m^2: dose on a per kg basis	1-5	Max dose= 200 mg **Administer at least one hour prior to IRIN administration.** See Dosing Table in Appendix II and admin. guidelines in Section 4.2.	a. History; ht, wt, BSA b. Physical exam with vital signs c. CBC, differential, platelets d. Electrolytes and creatinine e. ALT, total bilirubin, PO_4, Mg^{++} f. Optional biology studies OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE
Irinotecan (IRIN)	IV over 90 min	50 mg/m^2/dose	1-5	Administer at least 1 hour after temozolomide, see Section 4.2.	
Ch14.18 (dinutuximab) IND# 4308	IV over 10 hours**	17.5 mg/m^2/dose	2-5	** Infusion duration may be extended to 20 hours maximum, as detailed in Section 4.2. See Section 4.2 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	6-12	See Section 4.2 for detailed administration guidelines.	

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	TEMO _____mg	IRIN _____mg	Ch14.18 (dinutuximab) _____mg	GM-CSF _____mcg	Studies	Comments (Include any held doses, missed doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	_____ mg	_____ mg			a, b, c, d, e, f%	
		2	mg	mg	mg		d	
		3	mg	mg	mg		d	
		4	mg	mg	mg		d	
		5	_____ mg	_____ mg	_____ mg		d, f%	
		6				_____mcg		
		7				_____mcg		
		8				_____mcg	b, c#, d, e, f%	
		9				_____mcg		
		10				_____mcg		
		11				_____mcg		
		12				_____mcg		
		15					b, c#, d, e, f%	
		22	Begin next cycle on Day 22 or when criteria to begin cycle are met (whichever occurs later). See Section 4.2.2.					

\# If patients have Grade 4 neutropenia, CBCs should be checked at least twice per week until recovery to Grade 3.
% See Section 13.1 for details.

See Section 5.0 for Dose Modifications for Toxicities. For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

4.2.2 **Regimen B: Irinotecan and Temozolomide with ch14.18 (dinutuximab) - Therapy post Cycle 1**

This therapy delivery map relates to all cycles of TEMO+IRIN+ ch14.18 (dinutuximab) subsequent to Cycle 1. Three consecutive weeks (21 days) will constitute 1 cycle.
Use a copy of this page once for each cycle. *Please note cycle number below.*

_____
Patient COG ID number

_____
DOB

Criteria to start each cycle: patient meets laboratory parameters as defined in the eligibility section (Section 3.2) except for the following modified criteria: ALT ≤ 5 x ULN provided that the usual causes of transaminitis such as infections, tumor progression, or drug toxicity are excluded by appropriate blood and imaging studies AND the transaminitis is stable if not improving.
Each cycle lasts 21 days and this Therapy Delivery Map is on **1 page**. Dose calculations should be based on actual BSA except where noted for TEMO.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Temozolomide (TEMO)	PO	For patients ≥0.5m^2: 100 mg/m^2/dose. Round off to the nearest 5 mg. For patients <0.5 m^2: dose on a per kg basis	1-5	Max dose= 200 mg **Administer at least one hour prior to IRIN administration.** See Dosing Table in App. I and admin. guidelines in Section 4.2.	a. History; ht, wt, BSA; physical exam with vital signs; performance status b. CBC, differential, platelets c. Electrolytes and creatinine d. ALT, total bilirubin, PO_4, Mg^{++}, albumin e. HVA/VMA f. Imaging evaluation. See Section 7.1.1 for details. g. Bilateral bone marrow aspirates/biopsies h. Optional biology studies OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE
Irinotecan (IRIN)	IV over 90 min	50 mg/m^2/dose	1-5	Administer at least 1 hour after temozolomide, see Section 4.2.	
Ch14.18 (dinutuximab) IND# 4308	IV over 10 hours**	17.5 mg/m^2/dose	2-5	** Infusion duration may be extended to 20 hours maximum, as detailed in Section 4.2. See Section 4.2 for detailed admin guidelines, including premedications and monitoring during the infusion.	
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 mcg/m^2/dose	6-12	See Section 4.2 for detailed administration guidelines.	

Enter Cycle #: _____ **Ht** _____ **cm** **Wt** _____ **kg** **BSA** _____ **m^2**

Date Due	Date Given	Day	TEMO _____mg	IRIN _____mg	Ch14.18 (dinutuximab) _____mg	GM-CSF _____mcg	Studies	Comments (Include any held doses, missed doses, or dose mods)
			Enter calculated dose above and actual dose administered below					
		1	_____mg	_____mg			(a, b*,%, c, d, h$)^	
		2	_____mg	_____mg	_____mg		c	
		3	_____mg	_____mg	_____mg		c	
		4	_____mg	_____mg	_____mg		c	
		5	_____mg	_____mg	_____mg		c, h$	
		6				_____mcg		
		7				_____mcg		
		8				mcg	b*,%, h$	
		9				_____mcg		
		10				mcg		
		11				_____mcg		
		12				mcg		
		15					b*,%, h$	
		21					e#,+, f^,&, g&,@, h$	
		22	Begin next cycle on Day 22 or when criteria to begin cycle are met (whichever occurs later). See details above.					

^ Studies may be obtained within 3 days prior to the start of the cycle.
* If patients have Grade 4 neutropenia, CBCs should be 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 may be obtained at the start of subsequent cycles and as clinically indicated.
\# Obtain in patients who had elevated catecholamines (ie, > 2 x ULN) at initial diagnosis.
\+ End of Cycles 2, 4 and 6, then following every 4th cycle thereafter.
& May be performed within 1 week prior to the start of the next planned cycle of therapy.
@ End of Cycles 2, 4 and 6, then following every 4th cycle thereafter for patients with known marrow involvement. Marrow should be evaluated following Cycle 6 for all patients (even if no history of marrow disease).
$ See Section 13.1 for details.

See Section 5.0 for Dose Modifications for Toxicities. For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

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 irinotecan and temozolomide, this can be done as part of clinical care but will not be considered protocol therapy.

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 III). If patient experiences neutropenia that causes a delay of ≥ 14 days again 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 III). If patient experiences thrombocytopenia that causes a delay of ≥ 14 days again 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 4.2) within 21 days after the planned subsequent cycle start date (ie, 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.

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 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 (ie, irinotecan dose 37.5 mg/m^2).
- If Grade 4 therapy-associated diarrhea recurs despite reducing the dose of irinotecan by 25%, the ch14.18 (dinutuximab) dose should also be decreased by 25% for subsequent cycles (ie, ch14.18 (dinutuximab) dose 13.13 mg/m^2).
- 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 regimen-related nausea and vomiting recurs despite optimized anti-emetic usage, doses of irinotecan and temozolomide should be reduced by 25% for subsequent cycles (ie, irinotecan dose 37.5 mg/m^2; for temozolomide see dose reduction nomogram in Appendix III).
- 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 the preceding section 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 be reduced by 25% for subsequent cycles (ie, irinotecan dose is 37.5 mg/m^2; for temozolomide see dose reduction nomogram in Appendix III).
- 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 occur in patients receiving irinotecan, temozolomide, and ch14.18 (dinutuximab)/GM-CSF, the dose of ch14.18 (dinutuximab) should be reduced by 25% for subsequent cycles (ie, ch14.18 (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 ch14.18 (dinutuximab) should again be reduced by 25% for subsequent cycles (ie, ch14.18 (dinutuximab) dose: 8.75 mg/m^2). If the dose limiting elevations of the same liver enzyme(s) recur despite the second 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 ch14.18 (dinutuximab) for subsequent cycles (ie, ch14.18 (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 ch14.18 (dinutuximab)/GM-CSF specific dose modifications and toxicity management recommendations

5.2.5.1 Treatment of ch14.18 (dinutuximab) induced hypotension (without evidence of allergic reaction)

- If hypotension is severe and accompanied by poor perfusion, end organ dysfunction, or acidemia – Pediatric Advanced Life Support (PALS) guidelines should be followed and ch14.18 (dinutuximab) infusion should be discontinued.
- In the absence of poor perfusion, end organ dysfunction or acidemia, moderate hypotension is defined as
    - Symptomatic decreases in blood pressure and/or
    - Systolic blood pressure (SBP) < 80 mmHg for age > 12 years
    - SBP < 70 mmHg for age 1-12 years
    - SBP < 65 mmHg for age < 1 year OR
    - SBP or DBP decreased by > 15% below baseline
- If moderate hypotension is observed:
    - Immediately hold ch14.18 (dinutuximab)
    - 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
- If hypotension persists after the above measures have been taken:
  - Reassess perfusion and end organ function; follow PALS algorithm if needed
  - Repeat NS bolus
  - Consider use of albumin if albumin < 3 gm/dL
  - Consider use of PRBCs if Hb < 10 gm/dL
  - Consider transfer to intensive care setting
- If hypotension persists following 2 volume boluses, give an additional bolus and prepare to administer pressors
  - Epinephrine is preferred over dopamine if possible
- Resumption of ch14.18 (dinutuximab)
  - For patients whose hypotension resolves promptly and completely with limited volume resuscitation and without requirement for pressor support, ch14.8 may be restarted at 50% of the previous infusion rate. The ch14.18 (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 (eg, > 60 mL/kg) when ch14.18 (dinutuximab) is given at full rate but tolerates the 50% infusion rate, the remaining days' doses of ch14.18 (dinutuximab) should be given at the 50% rate of infusion. If > 20 hours have elapsed since the start of the infusion, restart ch14.18 (dinutuximab) the following day.
    - If blood pressures are stable for 2 hours after resumption of ch14.18 (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 ch14.18 (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 ch14.18 (dinutuximab) should be given at the 50% rate of infusion.
  - For patients who require multiple volume boluses for hemodynamic stabilization, ch14.18 (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 ch14.18 (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 ch14.18 (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 ch14.18 (dinutuximab) should be given at the 50% rate of infusion.
  - For patients who require pressors for treatment of hypotension, if blood pressure is stable off pressors for at least 6 hours, administration of ch14.18 (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. Ch14.18 (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 ch14.18 (dinutuximab) is resumed should discontinue protocol therapy.

5.2.5.2 Treatment of Allergic Reactions/Infusion Reactions

5.2.5.2.1 Mild allergic reactions/infusion reactions to ch14.18 (dinutuximab) infusion

- A mild allergic reaction is limited to rash, flushing, urticaria, mild dyspnea – Grade 1 or 2
- The following recommendations do NOT apply to Grade 3 or 4 allergic reactions, including anaphylaxis
- Management
    - Decrease rate of ch14.18 (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 ch14.18 (dinutuximab) has been administered or not); document total amount of drug given in the 20 hour time period

5.2.5.2.2 Moderate to severe allergic reactions/infusion reactions to ch14.18 (dinutuximab) infusion

- Moderate to severe reactions include any of the following: symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, or anaphylaxis – Grade 3 or 4
- The following recommendations do NOT apply to Grade 1 or 2 allergic reactions
- Management
    - **Immediately hold ch14.18 (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 ch14.18 (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, ch14.18 (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 ch14.18 (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 5.2.6.1 should be followed.

5.2.5.3 Management of capillary leak syndrome (≥ Grade 3)

- Hold ch14.18 (dinutuximab) infusion
- Provide oxygen, fluids as needed
- Diuretics should be used with caution and hypotension avoided
- **See Section 5.2.6.1 for management of hypotension, anemia and hypoalbuminemia**
- Do NOT resume ch14.18 (dinutuximab) therapy if symptoms of severe capillary leak syndrome persist on the same day or subsequent days of a given cycle. Only resume ch14.18 (dinutuximab) therapy when the capillary leak syndrome resolves or requires less significant intervention (Grade 2 or less).
- If capillary leak resolves, may resume ch14.18 (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 ch14.18 (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 ch14.18 (dinutuximab) at 50% rate. If renal function normalizes by the following day, ch14.18 (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 ch14.18 (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 ch14.18 (dinutuximab) is permitted

5.2.5.5 Management of hyponatremia (≥ Grade 3; Na < 130 mEq/L)

- 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 ch14.18 (dinutuximab) for the remainder of the cycle. Sodium should be monitored closely during the next cycle of therapy. Empiric dose reduction is not required at the start of the next cycle of therapy, though ch14.18 (dinutuximab) would again be discontinued if Grade 4 hyponatremia were to persist despite optimal fluid management. In such cases, no additional cycles of therapy would be given.

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 ch14.18 (dinutuximab) therapy should be given to patients who experience treatment related 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 pain requiring intravenous narcotics for ≥ 48 hours following completion of ch14.18 (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 ch14.18 (dinutuximab) therapy) recurs during a subsequent cycle despite this intervention, the patient should discontinue protocol therapy.

5.2.5.8 Management of visual changes

- Ch14.18 (dinutuximab) should be discontinued for patients who develop dilated pupils with sluggish light reflexes with or without photophobia during administration of the antibody. If papillary abnormalities remain stable or improve before the next immunotherapy course is due, the patient should receive ch14.18 (dinutuximab) at a dose that is 50% reduced compared to the prior dose. Full dose GM-CSF should be given. If the lower dose of ch14.18 (dinutuximab) is tolerated without worsening of ocular toxicity, full dose ch14.18 (dinutuximab) should be given in subsequent courses. If visual toxicity worsens, the patient should discontinue all immunotherapy.
- Dose reductions for changes in accommodation 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.
- Ch14.18 (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 ch14.18 (dinutuximab) (ie, ch14.18 (dinutuximab) dose: 8.75 mg/m^2). If symptoms do not completely resolve or recur with ch14.18 (dinutuximab) then the patient should discontinue protocol therapy.

5.2.6 Management of GM-CSF related toxicities

- Hold GM-CSF 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 GM-CSF are common, and GM-CSF 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 GM-CSF for the current cycle and discontinue GM-CSF 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 GM-CSF in a particular cycle. This syndrome generally resolves with symptomatic treatment and usually does not recur with subsequent doses of GM-CSF in the same cycle of treatment. For safety purposes in this study, if such a "first dose reaction" occurs, the GM-CSF dose will be reduced to 50% for the next dose (ie, GM-CSF dose 125 mcg/m^2). If a similar reaction occurs at the 50% dose, the GM-CSF 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 GM-CSF will be discontinued for subsequent cycles of therapy.

6.0 DRUG INFORMATION

Please see Appendix VI for drug interactions associated with the drugs used in this study.

6.1 CHIMERIC MONOCLONAL ANTIBODY 14.18 (05/12/17)

(Chimeric Monoclonal Antibody 14.18; human/murine anti-G_{D2} monoclonal antibody; chimeric anti-G_{D2}; chimeric mAb 14.18; ch14.18, dinutuximab, Unituxin®) NSC# 764038, IND# 4308

Source and Pharmacology:
Chimeric MOAB 14.18 (ch14.18, dinutuximab) 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. Ch14.18 (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, ch14.18 (dinutuximab) may also prevent attachment of circulating malignant cells to the extracellular matrix. Additionally, ch14.18 (dinutuximab) mediates lysis of several melanoma and neuroblastoma cell lines in a dose dependent manner in the presence of potent mediators of ch14.18 (dinutuximab)-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 ch14.18 (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 ± 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.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MoAb 14.18, chimeric (CH14.18, 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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 351 patients.* Below is the CAEPR for MoAb 14.18, chimeric (CH14.18).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 4.0 Term) [n= 351]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Disseminated intravascular coagulation		***Disseminated intravascular coagulation (Gr 2)***
		Hemolytic uremic syndrome[2]	
CARDIAC DISORDERS			
		Cardiac arrest	
		Sinus bradycardia	
	Sinus tachycardia		***Sinus tachycardia (Gr 3)***
EYE DISORDERS			
		Eye disorders - Other (eye disorders)[3]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fever			***Fever (Gr 3)***
		Infusion related reaction	
Pain			***Pain (Gr 3)***
		Sudden death NOS	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 3)***
		Anaphylaxis	
	Serum sickness		
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
Investigations - Other (elevated c-reactive proteins)			***Investigations - Other (elevated c-reactive proteins) (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 4.0 Term) [n= 351]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 3)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
		Myelitis[5]	
	Neuralgia		***Neuralgia (Gr 2)***
		Peripheral motor neuropathy	
	Peripheral sensory neuropathy[6]		***Peripheral sensory neuropathy[6] (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (atonic urinary bladder)[6]	
	Urinary retention[6]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Bronchial obstruction		
Cough			***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 3)***
	Hypoxia		***Hypoxia (Gr 3)***
	Stridor		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 3)***

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 4.0 Term) [n= 351]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
VASCULAR DISORDERS			
	Capillary leak syndrome		***Capillary leak syndrome (Gr 3)***
	Hypertension		
	Hypotension		***Hypotension (Gr 3)***

[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 chimeric MoAb 14.18. 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 ch14.18 administration. Atonic urinary bladder results in chronic urinary retention (CUR) that requires intermittent urethral catheterization days to weeks following chimeric MoAb 14.18 administration.

Adverse events reported on MoAb 14.18, chimeric (CH14.18) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MoAb 14.18, chimeric (CH14.18) 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 - Acute coronary syndrome; 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; Scleral disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Constipation; Duodenal obstruction; Dysphagia; Enterocolitis; Esophageal stenosis; Esophageal ulcer; Esophagitis;

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; Edema face; Edema trunk; Fatigue; General disorders and administration site conditions - Other (cold and clammy); Hypothermia; Injection site reaction; Irritability; 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; Investigations - Other (isolated glycosuria); 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; Personality change; Restlessness
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; 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); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hyperhidrosis; Periorbital edema
VASCULAR DISORDERS – Flushing

Note: MoAb 14.18, chimeric (CH14.18) 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:
Ch14.18 (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 (2ºC to 8ºC). Stability studies of the intact vials are ongoing.

Withdraw the required dose of ch14.18 (dinutuximab) from the vial(s) and inject the exact volume for the dose (17.5 mg/m^2/dose) into a bag containing 100 mL of 0.9% sodium chloride. The use of a filter during

preparation is not required. The final prepared product of ch14.18 (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. The minimum infusion time for the antibody infusion is 10 hours. There is no need to keep empty or partially used vials of ch14.18 (dinutuximab).

Lot number information will be collected on the NCI Drug Accountability Record Form (DARF) (see the Agent Accountability section below).

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

Patient Care Implications:
Pain is one of the most common adverse effects of ch14.18 (dinutuximab). It is predominately neuropathic and manifests as abdominal cramps or back and extremity pain. Prophylactic administration of morphine by continuous infusion is required before and during the infusions of ch14.18 (dinutuximab). Other narcotics such as hydromorphone or fentanyl can be used. Gabapentin may be used in conjunction with other pain medications per institutional practice. Use of additional pain medications (lidocaine, ketamine) in extenuating circumstances should be undertaken in consultation with pediatric pain management specialists.

Acute allergic or infusion reactions are common and may include hypotension, urticaria, hypoxia, and dyspnea. Premedication with antihistamines and acetaminophen are required for ch14.18 (dinutuximab) administration.

Human anti-mouse antibodies (HAMA) may block the effectiveness of therapy by prematurely clearing the treatment antibody and limiting further immunotherapy. HAMA responses may also be associated with immune-complex related adverse events such as serum sickness and anaphylaxis. HAMA responses were detected in over 50% of the patients tested. Although no increase in allergic reactions has been observed in patients treated with ch14.18 (dinutuximab) in the presence of HAMA, immune complex formation may have induced serum sickness in some patients.

Supplier:
Manufactured by United Therapeutics and distributed by the CTEP, DCTD, NCI. **Do not use commercial supply.**

Agent Ordering:
NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the

maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability:
Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Agent Returns:
Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/docs/return_form.pdf.

Investigator Brochure Availability:
The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.2 IRINOTECAN (05/09/11)

[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:

	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	Nausea, vomiting, anorexia, fever, asthenia, cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea)	Constipation, headache, diarrhea (L)	Anaphylaxis, dehydration with dizziness & hypotension, bradycardia, dyspnea and cough, disorientation/confusion, somnolence, pain at infusion site
Prompt: Within 2-3 weeks, prior to the next course	Neutropenia, alopecia, eosinophilia, elevations in transaminases, alkaline phosphatase, bilirubin, mucositis, infection	Anemia, rash, dyspepsia, thrombocytopenia	Colitis, renal failure (secondary to severe dehydration), thromboembolic events, ileus
Delayed: Any time later during therapy			Pneumonitis
Late: Any time after completion of treatment			
Unknown Frequency and Timing:	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.

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.

6.3 SARGRAMOSTIM (04/16/14)

(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, pruritis, 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: Any time later during therapy		Thrombocytopenia	
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 and as a sterile, preserved injectable solution in a 500 mcg/mL (2.8 million International Units/mL) 1 mL 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. The liquid formulation also contains 1.1% benzyl alcohol (11 mg/mL).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. Only sargramostim (yeast-derived recombinant human GM-CSF) will be used in this study. The *Escherichia coli*-derived product (molgramostim) will not be used.

CANADIAN SITES
Sargramostim is not commercially available in Canada. Sites may purchase and import the USA commercial supply of Liquid Leukine® (500 µg/1 mL) or Lyophylized Leukine® (250 µg/vial) manufactured by Genzyme USA via an International Distributor (Pharma Exports LLC; Contact: Pete Bigley, phone: 1-412-885-3700, fax: 1-412-885-8022, email: pharexp@aol.com or pbigley@pharma-whitehall.com) under the authority of the protocol's No Objection Letter (NOL).

Consult the product monograph for appropriate reconstitution and infusion preparation instructions.
The C17 Canadian Senior Medical Officer (SMO)'s office is responsible for coordinating the "Fax Back" for all lot numbers and expiry dates to Health Canada's Biologics and Genetic Therapies Directorate for approval for use in Canada on behalf of all Canadian sites. Canadian sites are notified by the SMO's Office of new lots as they are approved and a list of approved lot numbers is posted on www.c17.ca website under the protocol titled Sargramostim. If an unapproved lot is received from the distributor, quarantine the lot and contact the SMO's office immediately (Ellen Morrison ellen.morrison4@albertahealthservices.ca or 780-492-7064).

Canadian sites must keep a drug accountability log (DAL) recording, at a minimum, manufacturer, lot number and expiry date of all formats for all doses dispensed to any registered study patient.

Note: Sargramostim may have orders placed and Drug Accountability Logs maintained on a multiple protocol basis (Multiple Protocol—Imported Biologic) as long as each protocol has an NOL and the DAL clearly indicates which protocol the subject is registered on.

6.4 TEMOZOLOMIDE (06/30/14)

(Temodar®, Temodal®) NSC #362856

Source and Pharmacology:
An orally administered alkylating agent, a second generation imidazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. Exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the O^6-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13 hr (intraperitoneally) and 1.29 hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100 mL/min/m^2 and plasma elimination half-life is ~ 100 minutes.

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

Incidence	Toxicities
Common (>20% of patients)	Constipation, nausea, vomiting, diarrhea, anorexia, alopecia, alanine aminotransferase increased, aspartate aminotransferase increased, ataxia, anxiety, depression, insomnia, nervous system disorders – other: hemiparesis or paresis, dizziness, gait disturbance, amnesia, paresthesia, somnolence, headache, seizure, fatigue
Occasional (4-20% of patients)	Edema limbs, localized edema, rash maculopapular, dysphagia, mucositis oral, anemia, platelet count decreased, white blood cell count decreased, lymphocyte count decreased, aplastic anemia, blood bilirubin increased, urinary frequency, cough, upper respiratory infection, sinusitis

Incidence	Toxicities
Rare (≤ 3% of patients)	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hypercalcemia, lower gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, cholecystitis, alkaline phosphatase increased, myelodysplastic syndrome, leukemia secondary to oncology chemotherapy, infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatic failure
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 controlled room temperature.

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 is stable for 7 days at room temperature or 60 days in the refrigerator. 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. (Trissel LA, Yanping Z, Koontz SE. Temozolomide stability in extemporaneously compounded oral suspensions. *Int J Pharm Compounding* 10:396-9, 2006).

Alternatively, the capsules can be opened and mixed with apple sauce or juice (refer to Appendix IV).

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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. See Section 3.2 for eligibility requirements and for requirements to initiate protocol therapy, including the timing of imaging, clinical, and laboratory studies.

Obtain other studies prior to start of cycle unless otherwise indicated.

7.1.1 Required and optional studies for all patients

STUDIES TO BE OBTAINED	Baseline	During Cycle 1	Subsequent Cycles^
History	X	X	X
Physical Exam with vital signs	X	Weekly	X
Height, weight, BSA	X	X	X
Performance Status	X		X
CBC, differential, platelets	X	Weekly[1]	Weekly[1,2]
Electrolytes and Creatinine	X	Weekly through the cycle; daily during ch14.18 (dinutuximab) administration	Start of cycle and daily during ch14.18 (dinutuximab) administration
ALT, total bilirubin, PO_4, Mg^{++}	X	Weekly	X
Albumin	X		X
Pregnancy test[3]	X		
PT	X		
HVA/VMA	X		End of Cycles 2, 4 and 6, then following every 4th cycle thereafter[4]
Pulmonary Function Tests	X[5]		
ECHO or MUGA	X		
Imaging Evaluation[6]	X		End of Cycles 2, 4 and 6, then following every 4th cycle thereafter[7]
Bilateral bone marrow aspirates/biopsies	X		End of Cycles 2, 4 and 6, then following every 4th cycle thereafter for patients with known marrow involvement. Marrow should be evaluated following Cycle 6 for all patients (even if no history of marrow disease)[7]
Optional Biology studies: Peripheral Blood[8]		X[8]	X[8]
Optional Biology studies: Tissue[9]	X[9]		

^ Studies may be obtained within 3 days prior to the start of the subsequent cycle.

1 If patients have Grade 4 neutropenia, CBCs should be checked at least twice per week until recovery to Grade 3.

2 If patients remain on study for >4 cycles and cytopenias are not observed, CBCs may be obtained at the start of subsequent cycles and as clinically indicated.

3 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

4 Obtain in patients who had elevated catecholamines (ie, > 2 x ULN) at initial diagnosis.

5 Normal pulmonary function tests (including DLCO) if there is clinical indication for determination. For patients who do not have respiratory symptoms, full PFTs are NOT required.

6 For patients with measurable disease, the same modality (CT or MRI) should be used for serial disease evaluations. MIBG scans should be performed for all patients with MIBG avid disease, including those with disease also detectable by CT or MRI. **Note:** FDG-PET may be used to evaluate disease in patients whose tumors are MIBG non-avid.
7 Imaging and marrow aspirates/biopsies to assess disease burden may be performed within 1 week prior to the start of the next planned cycle of therapy.
8 See Section 13.1 for details. **Note:** Blood sample may be collected within 7 days prior to Day 1 of Cycle 1.
9 See Section 13.2 for details.

These tables only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 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.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Intolerance of study therapy as described in Section 5.
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of the maximum allowable number of cycles of therapy (see Section 4.1).
e) Physician determines it is in patient's best interest.
f) Second malignant neoplasm (SMN).
g) Patients who do not meet criteria to start the next treatment cycle within 21 days after the planned subsequent cycle start date (ie, there is a ≥ 3 week delay in start of next cycle).
h) 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 consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent.
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

Overview: This is a prospective, randomized Phase II selection design study to identify an agent that is sufficiently promising to be studied further in a Phase III trial.

Within each treatment regimen, we will concurrently conduct a 2-stage group sequential design ("Activity Design") per Simon. In addition, we will use the same data for a randomized, prospective, 2-stage "pick the winner" design ("Selection Design") per Steinberg and Venzon.[14] The advantage of the pick-the-winner design is that it allows for a mathematical specification of the error rates while allowing clinical considerations to play a part in the decision when appropriate. The within-regimen 2-stage designs are needed to test for a minimum acceptable level of activity.

The primary objective of the study was achieved when Regimen B (irinotecan/temozolomide/ dinutuximab) met the minimum acceptable level of activity required in Stage 1 of the Activity Design in order to be deemed worthy of additional study in patients with neuroblastoma. Regimen A (irinotecan/temozolomide/ temsirolimus) failed to do so, and randomization was halted. The "randomized portion of the trial" is the portion prior to Amendment #5 when patients were randomly assigned to Regimen A vs B. The "non-randomized portion of the trial" is the portion as of Amendment #5, when all newly enrolled patients are non-randomly assigned to Regimen B. The primary objective of the "non-randomized portion of the trial" is to determine the response rate of patients with relapsed, refractory or progressive neuroblastoma following treatment with irinotecan, temozolomide and dinutuximab and to compare this with the known response rate of patients treated with irinotecan and temozolomide alone.

9.1 Sample Size and Study Duration

Randomized portion of the trial
Enrollment of up to 37 patients per regimen (for a total of up to 74 patients) will be required in order to generate the 25 eligible, evaluable patients per regimen (50 total) that will be analyzed. Conservatively high estimates of ineligibility were used to arrive at the potential maximum enrollment. The 50 eligible evaluable patients will provide suitable operating characteristics to select the best agent for further study. If both agents are dropped at the first stage for insufficient activity, the study will require fewer patients (as few as 34, if all patients enrolled are eligible). At an accrual rate of 24 patients per year and accounting for accrual closures and re-openings to assess stopping rules, the accrual to this study can be completed within 4 years, and possibly within 2 years. With the addition of 6 months for treatment and follow-up, the total study duration will be 2.5-4.5 years.

A total of 36 patients, 35 of whom were eligible (1 patient ineligible in Regimen A), were enrolled (18 on Regimen A, 17 on Regimen B) during the randomized portion of the trial. In addition, 1 patient on Regimen B was not evaluable for toxicity and feasibility (see Section 9.2.2 for definition of evaluability). Prior to the suspension of randomization, annual accrual was about 20 patients per year.

Non-randomized portion of the trial
Enrollment of patients to the randomized portion of the trial was suspended in Fall 2015 when the COG Phase III Data and Safety Monitoring Committee released the interim study results demonstrating activity of Regimen B. To allow further study of feasibility and to more accurately estimate the response rate to this therapy, additional patients will be enrolled to Regimen B to permit accrual of a total of 50 eligible patients. This sample size will enable estimation of the response rate with a standard error of 0.07. This will require enrollment of up to an additional 40 patients on Regimen B in order to obtain the required 33 more eligible patients. Thus, enrollment may proceed up to a total of 76 patients, which includes the 36 patients that enrolled during the randomized portion of the study.

The accrual rate of 20 patients per year observed prior to the suspension of randomization is expected to be sustained or exceeded. Thus, accrual of the non-randomized patients should be completed within 2 years. With the addition of 6 months for treatment and follow-up, the total study duration will be 2.5 years.

9.2 Endpoints

9.2.1 Primary Endpoint

The primary study endpoint will be the proportion of patients who are responders. However, in the case that both treatment regimens have enough responders to meet the activity design response level, then other criteria (toxicity, feasibility, PFS) will be used to subjectively select the winner and answer the primary study objective. Responders are defined patients who achieve a ≥ PR, per the INRC,[88] as their best overall response. Patients with PD prior to attaining a ≥ PR will be considered failures for the analysis of response, and go off protocol therapy. In addition, patients who meet off protocol therapy criteria due to toxicity prior to attaining a ≥ PR will also be considered treatment failures. For a given patient, this primary endpoint is binary (responder, non-responder).

If a patient becomes a responder and later has progressive disease or later goes off protocol therapy due to toxicity or by choice, then the patient will be counted as a responder. It is possible that a patient's response to therapy may not occur until after many months of treatment. In order to prevent bias, the maximum duration of time/treatment over which a patient's response is to be assessed for determination of the best overall response is after the completion of the first 6 cycles. This limit of 6 cycles applies to the inclusion of response data for the assessments of the Activity and Selection Designs as well as the non-randomized portion of the trial for the primary objective.

9.2.2 Exploratory Endpoints

- Progression-free survival: For PFS, an event is defined as a relapse, progressive disease, or death attributable to tumor or treatment. Time to event for PFS will be calculated from the time of enrollment on the study until the occurrence of the first event or until the time of last contact if no event has occurred. Analysis of overall survival (event = death) will also be performed.
- Toxicity: The toxicity endpoint will be defined as the occurrence of unacceptable toxicity per the CTCAE v4.0 toxicity grading scale as defined below.
- Feasibility: Feasibility will be defined as the ability to maintain intended treatment with all agents (irinotecan, temozolomide and the experimental agent) without a dose reduction or going off protocol therapy for toxicity.
- Response rates: a) using current INRC and b) using recently proposed revised INRC. In recent years, major pediatric cooperative groups from around the world have made considerable efforts to develop standard approaches to neuroblastoma risk stratification and disease evaluation. There is an ongoing international collaboration to redefine standardized response criteria for neuroblastoma with the ultimate goal to improve our ability to compare response evaluations across clinical trials. While the response rate endpoint for the conduct of this study will be evaluated using traditional INRC criteria, response based upon the newly revised INRC will be calculated from the multiple imaging response components, and concordance of INRC and revised INRC response will be checked.

Evaluability

All eligible, randomized and non-randomized patients will be evaluable for inclusion in the analysis of the primary objective and response. All analyses of response will be conducted as intent-to-treat.

Any eligible patient who receives at least one dose of temsirolimus or ch14.18 (dinutuximab) on study will be considered evaluable for toxicity and feasibility.

9.3 Study Design and Interim Monitoring

We will first conduct a safety phase, whereby the first 6 patients treated on each regimen of the study will be closely monitored for toxicity. If the stopping rule in the safety phase is not triggered, we will move on to the efficacy phase (assessment of response using activity and selection rules), including the first 12 patients from the safety phase. Accrual to the study will be halted at the following times in order to gather data for assessment of the monitoring rules before continuing accrual on the next stage:
- Rule A, at the end of Stage 1 (the "safety phase") and Stage 2;
- Rule B, at the end of Stage 1;
- Activity design, at the end of Stage 1; and,
- Selection design, at the end of Stage 1.

Analysis of response will be intent-to-treat of eligible, randomized patients. The primary study objective and interim monitoring will be accomplished using 2 distinct 2-stage designs:

- A design within each treatment regimen. Each of these will determine that a given regimen meets the minimum level of activity. These designs will be referred to as the "activity" designs.
- A second design that compares the 2 treatment regimens. This design will be referred to as the "selection" design.

9.3.1 Randomization/Strata

Patients will be randomized 1:1 to Regimen-A (irinotecan/temozolomide/temsirolimus) or Regimen-B (irinotecan/temozolomide/ch14.18, dinutuximab), stratified by the extent of disease and prior therapy as well as *MYCN* status[89] (Strata 1-12).

Randomization will be stratified to ensure equal distribution of disease category, prior exposure to anti-GD2 antibody therapy , and *MYCN* amplification between the 2 treatment regimens. The study is not powered nor designed to evaluate each stratum separately.

The strata are:

Stratum 1: Patients whose disease is measurable with conventional CT and/or MRI, no prior anti-GD2 therapy; *MYCN* amplified tumor

Stratum 2: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, no prior anti-GD2 therapy; *MYCN* amplified tumor

Stratum 3: Patients whose disease is measurable with conventional CT and/or MRI, with prior anti-GD2 antibody therapy; *MYCN* amplified tumor

Stratum 4: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, with prior anti-GD2 therapy; *MYCN* amplified tumor

Stratum 5: Patients whose disease is measurable with conventional CT and/or MRI, no prior anti-GD2 therapy; *MYCN* non-amplified tumor

Stratum 6: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, no prior anti-GD2 therapy; *MYCN* non-amplified tumor**.**

Stratum 7: Patients whose disease is measurable with conventional CT and/or MRI, with prior anti-GD2 antibody therapy; *MYCN* non-amplified tumor

Stratum 8: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, with prior anti-GD2 therapy; *MYCN* non-amplified tumor

Stratum 9: Patients whose disease is measurable with conventional CT and/or MRI, no prior anti-GD2 therapy; *MYCN* unknown/unable to be determined

Stratum 10: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, no prior anti-GD2 therapy; *MYCN* unknown/unable to be determined**.**

Stratum 11: Patients whose disease is measurable with conventional CT and/or MRI, with prior anti-GD2 antibody therapy; *MYCN* unknown/unable to be determined

Stratum 12: Patients whose disease is detected by abnormal uptake at ≥ 1 site on MIBG scan, with prior anti-GD2 therapy. *MYCN* unknown/unable to be determined

Patients in Strata 2, 4, 6, 8, 10, and 12 may not have measurable disease on CT and/or MRI.

9.3.2 Safety Phase

The first 6 patients treated on each regimen of the study will be closely monitored for toxicity during a safety phase, and accrual will be halted after the enrollment of 6 patients per treatment regimen in order to make this assessment. The presence or absence of an unacceptable toxicity will be determined for each patient during the first 2 cycles of each regimen. Any patient who receives at least one dose of temsirolimus or ch14.18 (dinutuximab) on study will be considered evaluable for toxicity. If 3 or more patients out of 6 on a given regimen have at least one unacceptable toxicity, then that treatment regimen will be temporarily closed for DSMC review and reassessment of drug doses. Accelerated reporting of treatment data including toxicities will be required for the first 6 patients treated on each regimen. Reporting period data are to be completed on-line within 7 working days of the end of each cycle of therapy followed by routine toxicity reporting being completed on line within 10 working days of the end of each cycle. Toxicity data will be reviewed on a weekly basis by the study chair and study statistician.

9.3.3 Stopping Rule for Tolerability

Definition of unacceptable toxicity

Many of the toxicities that occur due to the therapy are not unexpected. However, we plan to consider a subset of the toxicities unacceptable. Those designated as unacceptable are listed below with the associated CTC v4 MeDRA code in parentheses:

1. Toxicity requiring the use of pressors for ≥ 24 hrs, including Grade 4 capillary leak syndrome (10007196), Grade 4 anaphylaxis/allergic reaction (10002218 or 10001718) or Grade 3 and 4 hypotension (10021097) requiring pressors.

2. Toxicity requiring ventilatory support for more than 24 hours, including Grade 4 respiratory toxicity such as ARDS (10001409), Grade 4 bronchospasm (10006482), Grade 4 dyspnea (10013963), Grade 4 hypoxia (10021143), Grade 4 anaphylaxis/allergic reaction (10002218 or 10001718), or Grade 4 respiratory failure (10038695) that requires intubation and mechanical ventilation.

3. Peripheral motor neuropathy Grade 4 or Grade 3 that does not resolve prior to start of next course of therapy (10034580).

4. Peripheral sensory neuropathy Grade 4 or Grade 3 that does not resolve prior to start of next course of therapy (10034620).

5. Grade 4 Cytokine Release Syndrome/Acute Infusion Reaction (10052015).

6. Toxic death.

Rule A - Stopping rule for tolerability

This is a 3-stage rule, and Stage 1 corresponds to the Safety Phase described above. This rule will be applied to each treatment regimen separately.

Stage 1 – Accrue 6 patients to a given treatment regimen. If 3 or more patients have at least one unacceptable toxicity, then the treatment regimen will be temporarily closed to new accrual to allow for DSMC review and reassessment of drug doses. If < 3 patients have an unacceptable toxicity, then continue to Stage 2.

Stage 2 – Accrue 11 more patients for a total of 17 in a given treatment regimen. If 4 or more patients have at least one unacceptable toxicity, then the DSMC and study committee will review the treatment for reassessment of drug doses. If < 4 patients have an unacceptable toxicity, then continue to Stage 3.

Stage 3 – Accrue 8 more patients for a total of 25 in a given treatment regimen. If 6 or more patients have at least one unacceptable toxicity, then the treatment regimen will be considered not sufficiently safe. If < 6 patients have an unacceptable toxicity, then the treatment regimen will be considered sufficiently tolerable for further study.

This rule has the following operating characteristics: The null hypothesis is that the toxicity rate is more than 32% and the alternative hypothesis is that the toxicity rate is less than 10%. This rule has > 90% power and alpha < 0.10. Under the null hypothesis, the expected sample size is 15.0, the probability of stopping after the first stage is 0.294, and the probability of stopping after the second stage is 0.847.

Non-randomized portion of the trial
There may be cause to stop the trial early if the unacceptable toxicity (as defined in Section 9.3.3) rate on Regimen B appears too high. The presence or absence of an unacceptable toxicity will be determined for each evaluable patient during the first 2 cycles of therapy. During the randomized portion of the trial, 1 unacceptable toxicity was observed, which will be counted in the monitoring rule below.

If at any time 8 or more patients have at least one unacceptable toxicity, then Regimen B will be considered not sufficiently safe. If 7 or less patients have an unacceptable toxicity, then Regimen B will be considered sufficiently tolerable for further study.

For this single-stage rule, with N=50 evaluable patients, there is a 0.90 probability of concluding the toxicity rate is unacceptable when the true rate is 23.8% and there is a 0.10 probability of concluding the toxicity rate is unacceptable when the true rate is 10% (i.e., uses a null hypothesis toxicity rate of 10%, 23.8% under the alternative, and has 90% power with a Type I error rate of 10%).

Rule B – Stopping Rule for Feasibility
We will monitor for inability to administer intended dose intensity of chemotherapy agents for the full protocol. This rule will be applied independently within each treatment regimen.

Stage 1 – Accrue 17 patients in a given treatment regimen. If 9 or more patients have at least one dose modification (including patients who are taken off protocol therapy due to toxicity), then the DSMC and the study committee will review the treatment regimen for reassessment of drug doses. If < 9 patients have a dose modification, then continue to Stage 2.

Stage 2 – Accrue 8 more patients for a total of 25 in a given treatment regimen. If 14 or more patients have at least one dose modification or are taken off protocol therapy due to toxicity, then the treatment regimen will be considered not sufficiently safe. If < 14 patients have a dose modification, then the treatment regimen will be considered sufficiently feasible for further study.

This rule has the following operating characteristics: The null hypothesis is that the dose modification rate is more than 60% and the alternative hypothesis is that the dose modification rate is less than 32%. This rule has > 90% power and alpha < 0.07. Under the null hypothesis, the expected sample size is 18.59, and the probability of early termination is 0.801.

Non-randomized portion of the trial
There may also be cause to stop the trial early if toxicity precludes the administration of the intended doses of irinotecan, temozolomide, and dinutuximab during the first 2 cycles of therapy. During the randomized portion of the trial, 3 patients on Regimen B had dose modifications >25% due to toxicity during the first 2 cycles of therapy or were taken off protocol therapy due to toxicity during the first 2 cycles of therapy. These will be counted in the monitoring rule below.

If at any time 21 or more patients have a modification of irinotecan, temozolomide or dinutuximab dose of >25% due to toxicity during the first 2 cycles of therapy or are taken off protocol therapy due to toxicity during the first 2 cycles of therapy, then Regimen B will be considered not sufficiently safe. If 20 or fewer patients have such dose modifications for toxicity, then Regimen B will be considered sufficiently feasible for further study. Dose modifications related to formulation issues or patient/family preference will not be counted during application of this rule.

For this single-stage rule, with N=50 evaluable patients, there is a 0.90 probability of concluding the dose modification rate due to toxicity is unacceptable when the true rate is 50.1% and there is a 0.10 probability of concluding the dose modification rate due to toxicity rate is unacceptable when the true rate is 32% (i.e., uses a null hypothesis toxicity rate of 32%, 50.1% under the alternative, and has 90% power with a Type I error rate of 10%).

Rule C: Stopping Rule for Toxic Death and Ventilator Support
If at any time either a) a toxic death occurs; or, b) a patient requires intubation or ventilator support for > 24 hours, the treatment regimen will be temporarily closed to new accrual to allow for DSMC review and reassessment of drug doses.

9.3.4 Efficacy Phase
For design descriptive purposes, designate the 2 agents being tested as X and Y.

Activity design
Within each regimen, the activity design will be used to determine if elimination of a regimen is necessary due to a given regimen not meeting the minimum level of activity.

Stage 1 of the activity design: Accrue 17 patients to each agent. Evaluate the following with each treatment regimen: If an agent has 3 or fewer responders, then there is insufficient evidence of activity of that agent. If an agent has 4 or more responders, then the trial may continue to Stage 2 for that agent.

Stage 2 of the activity design: Accrue 8 additional patients to the agent for a total of 25. If the agent has 6 or fewer responders, then there is insufficient evidence of activity of that agent. If the agent has 7 or more responders, then it is reasonable to conclude that the agent is worthy of consideration in the Selection Design.

This optimal two-stage design has 91.1% power to detect a 25% difference (15% under the null and 40% under the alternative hypothesis) and Type I error of 0.064. Furthermore, of interest is the probability that both regimens will be eliminated by application of the activity design rule; when the activity rate for both regimens is .15, this probability is equal to .88= (1-.064)(1-.064). The probability of both regimens meeting the activity criteria at the end of the study, when the true rate in both regimens is .4, is .83 = (.911*.911).

Selection design
The selection design is relevant only in the case where both agents have met the minimum level of activity at Stage 1 of the activity design. Stage 2 of the selection design is relevant only in the case where at least one agent has met the minimum level of activity at Stage 2 of the activity design. In other words, the

selection design will not be applied at all if one or both agents are eliminated at Stage 1 of the activity design; Stage 2 of the selection design will not be applied if both agents are eliminated by Stage 2 of the activity design.

Stage 1 of the selection design: Using the first 17 patients accrued to each agent,

a) Eliminate an inferior agent according to comparison of agents.
    i. Let agent Y be the agent with the most responders at Stage 1. If agent Y has 3 or more responders than agent X, then enrollment will stop on agent X regimen and Y will be declared the winner. In this case, we may conclude with high probability that Y is either superior to, or in the worst case, more or less equivalent to, X. Accrual to regimen Y will continue until we have determined if Y meets the minimum activity level in the activity design.
    ii. However, if neither agent has 3 or more responders than the other, then both regimens may continue to Stage 2.

If an agent has not been eliminated at Stage 1, accrual will continue to Stage 2.

Stage 2 of the selection design:

a) If neither X or Y was eliminated: Accrue 8 additional patients to each regimen.
    i. Let agent Y be the agent with the most responders at Stage 2. If agent Y has 3 or more responders than agent X, then Y will be declared the winner. In this case, we may conclude with high probability that Y is either superior to, or in the worst case, more or less equivalent to, X.
    ii. However, if neither agent has 3 or more responders than the other, (and both agents have enough responders to meet the activity design response level), then other criteria will be used to subjectively select the winner. The specifics of these criteria are listed in Section 9.4.
b) If one agent was eliminated at Stage 1: Accrue 8 additional patients to the remaining regimen for use in the activity design.

Table 1. Operating characteristics of the combined activity and selection designs, for hypothetical true response rates of agents X and Y for five possible scenarios.

Scenario	True response level of X	True response level of Y	Prob. Accept X	Prob. Accept Y	Both X and Y active, but neither selected	Both X and Y not active	Expected Sample Size
A	.15	.15	.057	.060	.0034	.8796	37.9
B	.15	.4	.0066	.891	.0245	.0779	42.7
C	.275	.275	.2955	.3000	.1834	.2211	44.8
D	.275	.4	.0602	.57	.234	.0404	45.4
E	.4	.4	.2919	.2902	.4094	.0089	46.8

Accrual will not be permitted to continue while Stage 1 is evaluated.

9.4 Methods to Address Study Objectives

To address primary objective 1.1.1, we will apply the activity and selection rules, as described above. The agent identified by the selection rule will be the optimal agent. In the case that both treatment regimens have enough responders to meet the activity design response level, and neither treatment regimen was identified by the selection rule, then the following criteria, in ranked order of importance, will be used to subjectively select the winner and answer the primary study objective:

1. Toxic death;

2. Unacceptable toxicity rate (see definition in Section 9.3.3);
3. PFS;
4. Feasibility (dose modifications, off protocol therapy due to toxicity, concomitant medication usage), and
5. Number of days hospitalized (overnight stays); number of overnight stays in the pediatric intensive care unit

In addition, we will perform a descriptive analysis of the response of patients who received more than 6 cycles of therapy.

To address primary objective 1.1.2, the response rate to treatment with irinotecan, temozolomide and dinutuximab will be calculated among the 50 eligible patients accrued, including placement of a 95% confidence interval on the response rate. If the lower bound of the confidence interval is above the objective response rate of 15% observed on ANBL0421, then the addition of dinutuximab will be considered to improve response over treatment with irinotecan and temozolomide alone.

To address exploratory objective 1.2.1, a Fisher's exact test will be used to test for a difference in the proportion of patients who are responders, for temsirolimus versus ch14.18 (dinutuximab). This proportion (RR) will be calculated for each treatment group as the number of responders divided by the total number of patients in that treatment group.

To address exploratory objective 1.2.2, Kaplan-Meier curves of PFS and OS will be generated by treatment group, and the curves will be compared using a log-rank test. The following factors have been shown to be prognostic of OS post-relapse in neuroblastoma patients: age at diagnosis, INSS stage, *MYCN* status, time from diagnosis to first relapse,[89] and prior treatment. To further characterize the outcome of patients on this study's treatments, and describe the treatment effect in context of known prognostic factors and prior treatment, Kaplan-Meier curves of PFS and OS will be generated for these factors, and log-rank tests performed.

To address exploratory objective 1.2.3, Stopping Rule A will be applied. In addition, a Fisher's exact test will be used to test for a difference in the proportion of patients who experience unacceptable toxicity, for temsirolimus versus ch14.18 (dinutuximab). This proportion will be calculated for each treatment group as the number of patients who experience unacceptable toxicity divided by the total number of patients in that treatment group. Also, the toxicities (Grade ≥ 3) for each treatment group will be descriptively summarized.

To address exploratory objective 1.2.4, Stopping Rule B will be applied. In addition, a Fisher's exact test will be used to test for a difference in the proportion of patients who required a dose modification, for temsirolimus versus ch14.18 (dinutuximab). This proportion will be calculated for each treatment group as the number of patients who required a dose modification divided by the total number of patients in that treatment group. Also, the dose modifications for each treatment group will be descriptively summarized.

To address exploratory objective 1.2.5, for each patient the overall response (CR, PR, SD, PD) will be determined per INRC and per the revised INRC. The relative degree of concordance will be presented using a weighted kappa statistic (± standard error), where higher values of kappa indicate greater agreement between the 2 systems. These analyses will be repeated within each treatment group. In addition, the overall response rate (RR) per INRC and per revised INRC will be calculated, and the degree of concordance will be tested using a McNemar's test.

To address exploratory objective 1.2.6, within the ch14.18 (dinutuximab) treatment group, the incidence of naturally occurring anti-glycan antibodies will be calculated, including the placement of a 95% confidence interval on the incidence.

To address exploratory objective 1.2.7, the incidence of NK receptor NKp30 isoforms will be calculated, including the placement of a 95% confidence interval on the incidence.

To address exploratory objective 1.2.8, the relationship between response to treatment with irinotecan, temozolomide, and dinutuximab (response vs. non-response) and naturally occurring anti-glycan antibodies, KIR/KIR-L genotyping, Fc receptor genotyping, and HACA will be explored with Fisher's exact test for categorical and Wilcoxon rank-sum test for continuous host factors. Both the presence/absence and level of naturally occurring anti-glycan antibodies will be considered. For the KIR/KIR-L analysis, patients will be categorized as either matched or mismatched. Patients will be grouped into one of the three genotype subgroups of Fc receptor genotyping for that analysis. The presence/absence of HACA, anti-idiotype and PATA/anti-allotype antibody will be considered for the HACA analysis.

To address exploratory objective 1.2.9, the incidence of NK receptor NKp30 isoforms, immune checkpoint proteins (CD274 (PDL1) and CD276 (B7H3)) expression, and expression of GD2 will be calculated, including placement of a 95% confidence interval on each incidence rate. Summary statistics will also be generated for serum cytokine (IL1, IL6, TNF-alpha, IFN-gamma, etc.) and infiltrating TIL (including TAMs) levels.

To address exploratory objective 1.2.10, the relationship between response to treatment with irinotecan, temozolomide, and dinutuximab (response vs. non-response) and NK receptor NKp30 isoforms, immune checkpoint proteins (CD274 (PDL1) and CD276 (B7H3)) expression, expression of GD2, serum cytokine levels (IL1, IL6, TNF-alpha, IFN-gamma, etc.), and infiltrating TILs (including TAMs) levels will be explored with Fisher's exact test for categorical and Wilcoxon rank-sum test for continuous tumor immune-microenvironment factors. Patients will be categorized as either present/absent for NK receptor NKp30 isoforms, immune checkpoint proteins expression, and expression of GD2 for these analyses. The levels of serum cytokines and infiltrating TILs will be considered.

To address exploratory objective 1.2.11, the relationship between response to treatment with irinotecan, temozolomide, and dinutuximab (response vs. non-response) and gene expression (CHGA, DCX, DDC, PHOX2B, and TH) and circulating GD2 levels following therapy will be explored with a Wilcoxon rank-sum test. Changes from baseline will also be analyzed.

9.5 Gender and Minority Accrual Estimates

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

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	29	41	70
Ethnic Category: Total of all subjects	32	44	*76
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	1	1	2
Black or African American	4	6	10
Native Hawaiian or other Pacific Islander	0	1	1
White	27	35	62
Racial Category: Total of all subjects	32	44	*76

* These totals must agree

This distribution was derived from ANBL0421 and ANBL00B1.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the NCI website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Additionally, toxicities are to be reported on the appropriate case report forms. Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria For Patients with CT/MRI Lesions

For CT/MRI lesions, response and progression will be evaluated in this study using the revised Response Evaluation Criteria In Solid Tumors (RECIST) guideline (version 1.1).[90] Key points are that a maximum of 5 target lesions are identified and that changes in the ***largest*** diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

10.2.1 Definition of Measurable (Evaluable) Disease on CT/MRI Scan

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm (CT scan slice thickness no greater than 5 mm). The investigator will identify up to 5 measurable lesions to be followed for response. Previously irradiated lesions must demonstrate clear evidence of progression to be considered measurable.

Serial measurements of lesions are to be done with CT or MRI. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

10.2.2 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

10.2.3 End-of-Cycle Response

a) Complete Response (CR)
Disappearance of all target and non-target lesions.

b) Very Good Partial Response (VGPR)
Greater than 90% decrease of the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry. Non-target CT/MRI lesions stable to smaller in size.

c) Partial Response (PR)
At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment. No new lesions or progression of any non-target measurable lesion.

d) Progressive Disease (PD)
At least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

e) Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

10.2.4 Overall Best Response Assessment
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined as described in Section 10.5.

10.3 Response Criteria for Morphologic Bone Marrow Disease

Note: patients with bone marrow as the ONLY site of disease are not eligible for this study. Response criteria in this section are intended to be used when assessing marrow involvement as a component of overall response.

Histologic analysis at the local institution of marrow tumor cell involvement is **required** for all patients pre-therapy (Cycle 1) at the end of Cycles 2, 4, and 6, and then after every 4th cycle thereafter for patients with known marrow involvement. Marrow should be evaluated following Cycle 6 for all patients (even if no history of marrow disease). Note: If progressive disease is documented by RECIST criteria using tumor measurements or by MIBG scan, then a repeat BM is not needed to confirm PD.

10.3.1 Bone Marrow Involvement
Bone Marrow response is determined by H&E staining of bilateral bone marrow biopsies and aspirates.

Complete Response
No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 3 weeks apart.

Progressive Disease
a) Patients who enroll without evidence of neuroblastoma in bone marrow will be defined as having progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 3 weeks apart.

b) Patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to ≥ 60%).

Stable Disease
Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

10.3.2 Overall Best Response Assessment
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined as described in Section 10.5.

10.4 Response Criteria for Patients with ^{123}I-MIBG Positive Lesions

Patients who have a positive ^{123}I-MIBG scan at the start of therapy will be evaluable for MIBG response. MIBG scans will be evaluated by both the treating institution (Section 10.4.1) and subsequently by a COG central review (Section 10.4.2). An Overall Response assessment (Section 10.5) will be determined, using the MIBG grade from the central review.

10.4.1 Critera for the Treating Institution
The following criteria will be used to report MIBG response by the treating institution on the Reporting Period forms:

Complete response: Complete resolution of all MIBG positive lesions
Partial response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions.
Stable disease: No change in MIBG scan in number of positive lesions.
Progressive disease: Development of new MIBG positive lesions.

The intensity of MIBG uptake is not to be considered in the above institutional evaluation.

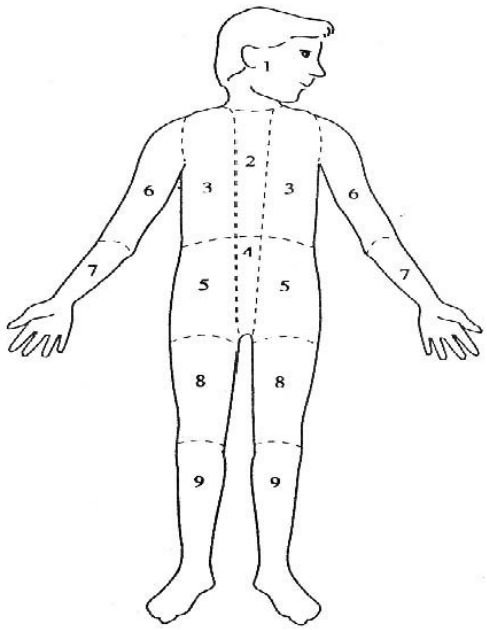
10.4.2 Critera for Central Review
MIBG disease will be assessed by central review using the Curie scale as outlined below for all patients with MIBG avid lesions at study entry who respond to therapy or have long term stable disease on protocol therapy (see Section 14.2).

NOTE: This scoring is NOT required to be done by the treating institution for end of cycle response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment
1 = 1 site per segment
2 = more than one site per segment
3 = massive involvement (> 50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1) **Complete response:** all areas of uptake on MIBG scan completely resolved.
2) **Partial response:** Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3) **Stable disease:** Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4) **Progressive disease:** New lesions on MIBG scan.

10.4.3 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined as described in Section 10.5.

10.5 Definition of Overall Response for Each Patient

The International Neuroblastoma Response Criteria (INRC) will be used to define overall response for this study. The response criteria integrate response at all sites defined as measurable in this study, including CT/MRI lesions which meet RECIST criteria, MIBG positive lesions, and bone marrow disease. These criteria will be used to define the overall response for the patient in all strata in the statistical analysis. The treating Institution should grade overall response using the INRC criteria, with MIBG grading as listed in Section 10.4.1. NOTE: The central review of MIBG scans will be used for the formal statistical evaluation of overall response.

10.5.1 Complete Response (CR)

Disappearance of all target lesions. No evidence of tumor at any site (chest, abdomen, liver, bone, bone marrow, nodes, etc.).

10.5.2 Very Good Partial Response (VGPR)

Greater than 90% decrease of the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; all pre-existing

bone lesions with CR by MIBG; MIBG scan can be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI. CR in bone marrow (by morphology criteria). No new sites of tumor.

10.5.3 Partial Response (PR)

At least a 30% decrease in the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry. Bone marrow with CR (by morphology response criteria in Section 10.3). MIBG with either PR/CR in bone lesions; MIBG may be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI. HVA/VMA may still be elevated.

10.5.4 Progressive Disease (PD)

Any one of the following:

a) At least a 20% increase in the disease measurement for CT/MRI target lesions, taking as reference the smallest disease measurement recorded since the start of treatment.
b) Appearance of one or more new lesions or new sites of tumor.
c) PD as defined above for either bone marrow or MIBG lesions.

10.5.5 Stable disease (SD)

The patient will be classified as stable disease for overall response if there is stable disease by either CT/MRI lesion, bone marrow, or MIBG criteria. No new lesions; no new sites of disease.

The overall response as assessed at any particular time point based on the various disease sites is summarized in the table below.

Table 10.5.1. Overall Response

Response by individual site				Overall response
CT/MRI lesions	MIBG lesions	Bone marrow	Catechols	
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
VGPR	CR in bone lesions; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Normal	VGPR
PR	PR/CR in bone lesions; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Any	PR
SD	SD/PR/CR	SD/CR	Any	SD
SD/PR/VGPR/CR	SD	SD/CR	Any	SD
SD/PR/VGPR/CR	SD/PR/CR	SD	Any	SD

The best response observed at any time point for each individual patient will be considered that patient's best overall response on this study.

10.6 Confirmation of Response Status Determined by MRI, CT, MIBG Scans or FDG-PET Scan by Central Review

Any patient that is scored by his or her local institution as showing long term SD or a CR, VGPR or PR based on improvement in CT, MRI or MIBG scanning (or FDG-PET if tumor is not MIBG avid) will have scans evaluated centrally by COG, after completion of therapy. For this study, long term stable disease is defined as SD lasting 6 cycles or greater (minimum 4 months). See Section 14.2 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 regimen, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which 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, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the NCI's CTEP Adeverse 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 which 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 a NCI 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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"*** under the system organ class (SOC) of the same name. 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 (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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 Pregnancy, Fetal Death, 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 301-230-0159. 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.

11.4.5.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which 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.

There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, **pregnancy in partners of men on study needs be reported and followed in the same manner as a patient pregnancy**.

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.

11.4.5.2 **Fetal Death**

Fetal death, defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation*", needs to be reported expeditiously, as **Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*"**. Do NOT report a fetal death as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.5.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"A disorder characterized by cessation of life occurring during the first 28 days of life*" needs to be reported expeditiously, as **Grade 4 "*General disorders and administration***

- *Other (neonatal loss)*" 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 (eg, 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

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as 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 descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at:
https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- 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 under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

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.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# 626-303-1768; 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 (NCI) **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 which 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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	**7 Calendar Days**			**24-Hour Notification 5 Calendar Days**
Not resulting in Hospitalization ≥ 24 hrs	**Not Required**		**7 Calendar Days**	

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

The following do not require expedited reporting:

For Regimen A:

- **Grade 1-2 dehydration or Grade 3 dehydration ≤ 3 days duration**
- **Grade 1-3 hypersomnia, or insomnia**
- **Grade 1-3 oliguria**

For Regimen B:

- **Grade 1-2 dehydration or Grade 3 dehydration ≤ 3 days duration**
- **Grade 1-3 irritability**
- **Grade 1-3 oliguria**
- **Grade 1-2 visual changes or Grade 3 visual changes that resolve within 7 days of onset**

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 which 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). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This 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 (eg, termination, dropping a regimen 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.

12.3 CRADA/CTA

NCI/DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

Participation in the optional biology studies listed below is strongly encouraged.

13.1 Optional Biology Studies: Peripheral Blood

If the patient consents, any specimens left over after the special studies listed below are performed will be banked at the Biopathology Center for future research studies.

13.1.1 Prioritization of Blood Samples to be Used for Biology Studies

If there is an inadequate amount of blood for all of the studies listed below, collection of the green top (heparinized) tubes should be prioritized.

13.1.2 Peripheral blood sample collection and schedule

Prior to the administration of the anticancer therapy described in this study, a baseline blood sample should be drawn. This can be obtained with pre-study labs within 7 days of starting therapy or on Day 1 of Cycle 1.

Peripheral blood sampling requirements are summarized in the tables below:

Children weighing ≥ 12 kg:

	Cycle 1				Cycle 2				Cycles 3, 4	After Cycles 4 and 6*
	Prior to start of therapy	Day 5 (post completion of dinutuximab)	Day 8 optional[#]	Day 15 optional[#]	Prior to start of therapy	Day 5	Day 8 optional	Day 15 optional	Prior to start of therapy	
Green top (heparin) tubes^ (See Sections 13.1.3 & 13.1.4)	5 mL				5 mL				5 mL	4 mL
Red top tubes (See Sections 13.1.3 & 13.1.4)	2 mL	2 mL			2 mL	2 mL				
PAX gene tubes (See Sections 13.1.6 & 13.1.7)	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL		

^ Samples collected in green top tubes should be drawn Monday through Thursday to allow for immediate shipping as they should NOT be stored over a weekend or holiday

[#] Even if the patient has consented to peripheral blood collection, samples collected on Days 8 and 15 of Cycles 1 and 2 are not mandatory, but strongly encouraged.

* Can be drawn on the days of disease evaluations or at any point prior to the start of Cycle 5 and Cycle 7 therapy

Children weighing <12 kg:

	Cycle 1				Cycle 2				Cycles 3, 4	After Cycles 4 and 6*
	Prior to start of therapy	Day 5 (post completion of dinutuximab)	Day 8 optional#	Day 15 optional#	Prior to start of therapy	Day 5	Day 8 optional	Day 15 optional	Prior to start of therapy	
Green top (heparin) tubes^ (See Sections 13.1.3 & 13.1.4)	5 mL				5 mL				5 mL	4 mL
Red top tubes (See Sections 13.1.3 & 13.1.4)	2 mL	2 mL			2 mL	2 mL				
PAX gene tubes (See Sections 13.1.6 & 13.1.7)	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL		

^ Samples collected in green top tubes should be drawn Monday through Thursday to allow for immediate shipping as they should NOT be stored over a weekend or holiday

Even if the patient has consented to peripheral blood collection, samples collected on Days 8 and 15 of Cycles 1 and 2 are not mandatory, but strongly encouraged.

* Can be drawn on the days of disease evaluations or at any point prior to the start of Cycle 5 and Cycle 7 therapy

13.1.3 Sample Processing: Green and Red Top Tubes

Green Top Tubes:

Samples in green top tubes should be collected Monday through Thursday and sent at the appropriate temperature by overnight carrier (see below). Do NOT batch the green top samples.

It is particularly important that the baseline blood sample be drawn on a Monday through Thursday and the green top tubes shipped immediately. Baseline blood samples should NOT be collected on Fridays, Saturdays, Sundays or national holidays. **Subsequent day green top** samples should also be collected Monday through Thursday and sent at the appropriate temperature.

Red Top Tubes:

After the blood in red top tubes has clotted, tubes should be centrifuged at 1,100-1,300 x *g* for 15 minutes at room temperature. Serum should be collected and transferred to a conical tube for mixing. Evenly dispense at least 0.5 mL of the serum into pre-labeled 1.8 mL screw-cap cryotubes. Cap the cryovial securely and freeze upright if possible. Storage in an ultra-cold freezer (≤ -70°C) or in liquid nitrogen is ideal; use of a non-cycling -20°C freezer is acceptable but should be avoided if possible. The serum should be shipped overnight (frozen) on the following Monday or the next day that would permit delivery on a working day. Batching of serum samples is acceptable.

13.1.4 Sample Labeling and Shipping: Green and Red Top Tubes

EACH sample should be labeled with:

1) Patient's COG registration number
2) Study number ANBL1221
3) Cycle and day of therapy blood was drawn

Each specimen must be sent with a completed Specimen Transmittal Form. In addition, details of CBC with differentials should be provided, if available.

As noted above, samples will be received Tuesday through Friday only.

Samples should be sent to the address below at the appropriate temperature via Federal Express Priority Overnight using the COG account number (refer to https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf). Green top tubes must be shipped with insulation or cold pack to avoid

freezing or over-heating respectively. Red top tubes should be batched and sent frozen)

Alice Yu, MD, PhD
UCSD Medical Center
Clinical Teaching Facility, B-114
212 Dickinson Street
San Diego, CA 92103-8447
Lab Phone: (619)-543-2438
Lab FAX: (619)-543-5413
E-mail: yulab@ucsd.edu

Lab contact: Jenna Mielke

13.1.5 Subsequent Processing by Dr. Yu's Lab

Samples will be processed by Yu laboratory personnel, and assays for antiglycan antibodies, cytokine levels, NK receptors and immune cell subsets will be performed on site. Yu laboratory personnel will distribute components of the samples collected to other investigators conducting correlative studies being performed using blood samples.

DNA for KIR/KIR ligand and Fc receptor genotyping as well as plasma for HACA testing will be sent to the Sondel laboratory at the University of Wisconsin and to the Chinnaiyan laboratory at the University of Michigan. Plasma will be sent to the Balis laboratory at the Children's Hospital of Philadelphia.

Remaining components of blood samples will be stored at the Biopathology Center for additional testing if necessary. If additional testing is not required, the sample will be banked for future research.

13.1.6 Sample Processing: PAX Gene Tubes

1) For samples collected in PAXgene tubes blood is placed immediately into the tube, which is then inverted 8 - 10 times to mix. Blood should be stored upright in a wire rack and placed in -20°C freezer until shipment. Do not freeze tubes upright in a styrofoam tray as this may cause the tubes to crack. Please note that if tubes are to be kept at temperatures below -20°C, they must first be stored at -20°C for 24 hours before being transferred into a -70°C or -80°C freezer. PAX Gene blood is stored frozen and it must be shipped on dry ice.

2) PAX gene tubes should be batched for each cycle and shipped prior to the next cycle. Please ship on dry ice overnight on a day that would permit delivery on a working day.

   Note: If the PAXgene tube is the only tube to be drawn, blood should be drawn into a "Discard Tube" prior to drawing blood into the PAXgene tube. Otherwise the PAXgene tube should be the last tube drawn.

13.1.7 Sample Labeling and Shipping: PAXgene Tubes

EACH sample should be labeled with:

1) Patient's COG registration number
2) Study number ANBL1221
3) Cycle and day of therapy blood was drawn

Each specimen must be sent with a completed Specimen Transmittal Form. In addition, details of CBC with differentials should be provided, if available.

Samples should be sent to the address below via Federal Express Priority Overnight using the COG

account number (refer to https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf).

Shahab Asgharzadeh, MD
Children's Hospital Los Angeles
Smith Research Tower, 515
4650 Sunset Boulevard
Los Angeles, CA 90024
Lab Phone: (323) 361-4503
Lab FAX: (323) 361-4902
Lab Contact: Rebekah Kennedy
E-mail: rekennedy@chla.usc.edu or shahab@chla.usc.edu

13.1.8 Subsequent Processing by Dr. Asgharzadeh's Lab
Samples will be processed by Asgharzadeh laboratory personnel, and assays for immune-related gene expression and the NB5 assay will be performed on site. Asgharzadeh laboratory personnel will distribute components of the samples collected to other investigators conducting correlative studies being performed using blood samples.

RNA for NKp30 testing will be sent to the Yu lab at the University of California San Diego.

13.2 Collection of Tumor Tissue and Bone Marrow-derived Tumor Cells
The importance of submitting tumor-containing specimens obtained at the time of disease progression or relapse cannot be overstated**.** Collection of tumor cells derived from involved marrow in patients with relapsed neuroblastoma is strongly encouraged as is collection of tumor tissue from biopsy samples (if biopsy is performed either for clinical reasons or to document disease as per eligibility requirements outlined in Section 3.2.2.3). For patients previously enrolled on ANBL00B1, please see Appendix IV of the ANBL00B1 protocol for specific information regarding sample collection, handling, and shipping.

13.3 Optional Biology Studies: Tumor Tissue
Tumor from the **time of initial diagnosis** is also requested for all patients (regardless of prior enrollment or submission on ANBL00B1) for analyses described in Section 2.7.7 and 2.7.10. See Section 13.3.1 for details.

Specimens collected on ANBL00B1 **at relapse** for patients enrolled on ANBL1221 will be flagged and used for correlative studies described in Sections 2.7.7 and 2.7.10.

For consenting patients who have not enrolled on or submitted tumor specimen at relapse on ANBL00B1 see Section 13.3.1 for specimen requirements.

13.3.1 Specimen Collection and Labeling
Tumor may be sent in the form of a paraffin block, or as tissue scrolls (10 scrolls 15µm thick) AND 10-25 unstained slides. Frozen tumor should also be sent if available. If scrolls AND slides are submitted, they should be cut sequentially from one representative block.

Specimens must be labeled with the COG patient ID, specimen type (P for primary or M for metastatic), the surgical pathology ID number and block number from the corresponding pathology report.

13.3.2 Specimen Shipment
A Single Chamber Specimen Procurement Kit for shipping frozen tumor tissue to the BPC are provided upon request. To request a Specimen Procurement Kit, click on the 'Biopathology Center Application' link

on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. Select 'ANBL1221' to order kits for the submission of frozen tumor tissue.

Blocks, slides and scrolls must be shipped in your own shipping container using the institution's courier account or by USPS.

Include a copy of the specimen transmittal form and the corresponding pathology report with each shipment.

Shipping Frozen Tumor in a Single Chamber Kit:

1. Before the frozen tissue is placed into the Specimen Procurement Kit, it must first be placed in three separate layers of packaging :
    a. Place the tissue in a zip-lock bag.
    b. Place the zip-lock bag in the plastic watertight biohazard diagnostic envelope and seal the envelope securely.
    c. Place the clear plastic biohazard diagnostic envelope inside the pressure-proof Tyvek diagnostic envelope and seal securely.
2. Place the tissue inside the kit compartment with dry ice. 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.
3. Place the transmittal form and corresponding pathology report inside the compartment.
4. Place the stryofoam lid on top to secure specimns during shipment.
5. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable tape.
6. Access the BPC Kit Management application to print a Federal Express shipping label. A blank adhesive label is provided in the Specimen Procurement Kit to use when printing the shipping label. Attach the shipping label to the top of the kit. Complete the dry ice label (UN 1845). Stick the dry ice and Exempt Human Specimen labels to the side of the kit
7. Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355.

Shipping Address:
Biopathology Center
700 Children's Drive, Room WA1340
Columbus, OH 43205
Telephone: (614) 722-2865 (include on all packages)
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

Specimens are to be shipped Monday through Thursday for delivery Tuesday through Friday. Weekend and holiday deliveries are not accepted. If tumor is obtained on a Friday, Saturday or on the day before a holiday, please ship on the next business day.

The Biopathology Center will distribute tumor samples to the Asgharzadeh laboratory at Children's Hospital Los Angeles and to the Chinnaiyan laboratory at the University of Michigan.

14.0 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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

14.1 Timing of Imaging

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

- within 3 weeks preceding enrollment into the study
- end of Cycles 2, 4 and 6, then following every 4th cycle thereafter

14.2 Imaging Required for Confirmation of Response Status

The pertinent imaging studies (CT/MRI and MIBG or FDG PET) of those patients who respond to therapy or have long term stable disease on protocol therapy will be centrally reviewed.

A retrospective central review will be performed by the Diagnostic Imaging Specialists of the Study Committee. They will review baseline scans and scans documenting best response for patients who are scored by their local institution as showing a CR, VGPR, PR or long term SD (≥ 6 cycles; minimum of 4 months) based on imaging studies (CT, MRI, MIBG or FDG PET). 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 through the first 6 cycles of therapy who show a CR, VGPR or PR, the following must be submitted for review:

Baseline and Best Response Scans:
- CT/MRI
- MIBG scan (see MIBG scan guidelines in Appendix VII)
- FDG PET scan if tumor is not MIBG avid
- Copies of the reports for the scans submitted

For any patient who achieves long-term stable disease (defined as SD for ≥ 6 cycles) or a patient who achieves a CR, VGPR or PR after the first 6 cycles of therapy, the following must also be submitted for review.

Baseline and Scans Documenting Long-Term Stable Disease and/or Overall Best Response:
- CT/MRI
- MIBG scan (see MIBG scan guidelines in Appendix VII)
- FDG PET scan if tumor is not MIBG avid
- Copies of the reports for the scans submitted

For PET scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of ^{18}F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found at the following link: http://imaging.cancer.gov/programsandresources/reportsandpublications/publications/clinical-trials-guidelines.[91]

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in Dicom format. These files can be burned to a CD and mailed to IROC Rhode Island (formerly QARC). Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicommunicator. Contact IROC Rhode Island at Dicommunicator@QARC.org for further information. Alternative electronic methods, eg, sFTP are possible. Contact IROC Rhode Island for more information.

Imaging and Radiation Oncology Core, Rhode Island
Building B, Suite 201
640 George Washington Highway,
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the ANBL1221 protocol page located on the CTSU members' website. 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 RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the COG link to expand, then select trial protocol ANBL1221
- Click on the Site Registration Documents link

Requirements for ANBL1221 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX II: 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:
Patient is 0.3 m^2 and weighs 5 kg. Patient administered dose = 5 kg x 3.3 mg/kg = 16.5 mg

Patient is 0.66 m^2. 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	105-114	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 III: 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

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	2.5mg/kg	2.5mg/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
1.97-2.00	148-152	150
> 2.0	> 152	155

APPENDIX IV: RECOMMENDATIONS FOR ADMINISTRATION OF TEMOZOLOMIDE

(Patients who are unable to swallow capsules and cannot obtain a suspension)

Temozolomide is an oral cancer medicine that your child will be taking for treatment of his/her cancer. If your child is unable to swallow capsules, the following instructions must be followed for safe administration of this medicine.

- Temozolomide must be kept in a dark container.
- Temozolomide should be taken the same time every day.
- If your child requires nausea medicine it should be taken prior to the temozolomide.
- If the dose of temozolomide is vomited (which is unusual) within the first 20 minutes after it is taken, the dose should be repeated. If your child vomits more than 20 minutes after the temozolomide has been taken, do not repeat the dose.
- If the person dispensing this medicine is pregnant, breastfeeding or suspects she is pregnant, she should not dispense this medicine.

Since temozolomide is an anti-cancer agent, special precautions must be taken when handling this medicine. There is potential hazard to anyone who handles this medicine once the protective capsule is opened. Since your child is unable to swallow the capsule you will be required to open the capsules and mix the contents of the capsule in apple sauce or apple juice. This process must be done according to the following guidelines to ensure safe administration of this medicine.

- Find a place that is free from drafts or wind and is not an area where food is stored or prepared.
- The work surface should be covered with an impermeable and disposable mat such as the one a pharmacy uses to reduce exposure to other members of the family.
- Temozolomide can be mixed in apple sauce or apple juice.
- Place the apple sauce or apple juice in a disposable container.
- Put on gloves, a mask and a pair of goggles (eye protection).
- Open each capsule required for the daily dose and place the powder in a medicine cup.
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup.
- If you need to have additional juice or apple sauce remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves.)
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce.
- Once all of the medicine is taken, throw away the following in a Ziploc-type plastic bag: Medicine cup, the container the medicine was mixed in, the covers/mats for the work surface, masks, gloves and anything else that has been in contact with the medicine.
- Once a course of medicine is completed bring the plastic bag with you to the clinic so it can be disposed of properly.

APPENDIX V: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Treatment of Diarrhea

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. The doses and schedules for loperamide included here are higher than the standard but consistent with COG protocols D9802, P9761, and ARST0121.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any 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 2 hours until your 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):

LOPERAMIDE DOSING RECOMMENDATIONS FOR LATE DIARRHEA (maximum dose of Loperamide for adults is 16 mg/day)	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL of the 1 mg/5 mL oral solution or one-half capsule or tablet) after the first loose bowel movement, followed by 1 mg (5 mL of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 1.0 mg (5 mL of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 6 mg per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (5 mL of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL of the 1 mg/5 mL oral solution or 1 caplet) every 4 hours. Do not exceed 8 mg per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL of the 1 mg/5 mL oral solution or 1 capsule or tablet) after the first loose bowel movement, followed by 1 mg (5 mL of the 1 mg/5 mL oral solution or one-half capsule or tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 4 hours. Do not exceed 12 mg per day.
Over 43 kg	Take 4 mg (20 mL of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL 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 (20 mL of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg per day.

APPENDIX VI: POSSIBLE DRUG INTERACTIONS

The lists below <u>do not</u> 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.

Temozolomide

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

Food and supplements that may interact with temozolomide**
• Echinacea

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Irinotecan

Drugs that may interact with irinotecan
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Citalopram, clozapine, desipramine, nefazodone, sertraline • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, dronedenarone, diltiazem, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Bosentan, sitaxentan, aprepitant, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, succinylcholine

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

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX VII: RECOMMENDED PROCEDURE FOR PERFORMING MIBG SCANS

MIBG (meta-iodobenzylguanidine) was developed by Dr. Donald Wieland of the University of Michigan in the late 1970's for scintigraphic imaging of neuroendocrine tumors, specifically pheochromocytomas and neuroblastomas. MIBG is an aralkylguanidine which bears structural similarity to the neurotransmitter and catecholamine hormone norepinephrine and the ganglionic blocking drug guanethidine. When MIBG is labeled with radioactive iodine, gamma camera imaging of patients injected with this compound produces images of the sites of the tumors and of the related structures of the sympathetic nervous system. The I-123 labeled form of this agent has been approved for use by the US Food and Drug Administration for the diagnostic imaging of neuroblastoma and pheochromocytoma, and this agent is commercially available as Adreview (GE). MIBG has considerably assisted the diagnostic evaluation of patients with known or suspected neuroblastoma, since it provides information about the tumor behavior all along the course of the disease from diagnosis to completion of therapy. Scores of publications from around the world have documented its utility in the diagnosis and monitoring of neuroblastoma. It alone is the single best imaging test for monitoring disease activity. MIBG imaging is performed routinely at many institutions. The following protocol is recommended, to assure high quality images are obtained at all institutions which participate in neuroblastoma evaluations.[92]

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Patients and/or parents are always asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

A. I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

1. Planar – Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

2. SPECT - Most patients receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Please refer to Section 14.0 for requirements of central review (including the time-points and address to submit the required reports).

APPENDIX VIII YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ANBL1221
(for children from 7 through 12 years of age)

A trial to compare 2 ways to treat children 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 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 using the drug "ch14.18" (also called dinutuximab). Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment with ch14.18.

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 ch14.18. We are asking your permission to collect extra blood and use the blood for research studies. We would take extra when we collect blood 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 ANBL1221
(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. Children and teens who are part of this study will be treated with chemotherapy using the drug ch14.18 (also called dinutuximab). Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment with ch14.18.

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 ch14.18. We are asking your permission to collect extra blood and use the blood for research studies. We would take extra when we collect blood 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.

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