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CHILDREN'S ONCOLOGY GROUP

ANBL19P1

A Pilot Study of Dinutuximab, Sargramostim (GM-CSF), and Isotretinoin in Combination with Irinotecan and Temozolomide in the Post-Consolidation Setting for High-Risk Neuroblastoma

A COG Groupwide Pilot Study

[redacted]

CONTACT INFORMATION

For Regulatory Requirements	For Regulatory Requirements	For Regulatory Requirements
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

For clinical questions (i.e. patient eligibility or treatment-related)
Contact the Study PI of the Lead Protocol Organization.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

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STUDY COMMITTEE

[redacted]

[redacted]

AGENT	NSC#	Supplier
Dinutuximab	764038	Commercial
Irinotecan	616348	Commercial
Isotretinoin	329481	Commercial
Sargramostim	613795	Commercial
Temozolomide	362856	Commercial

[redacted]

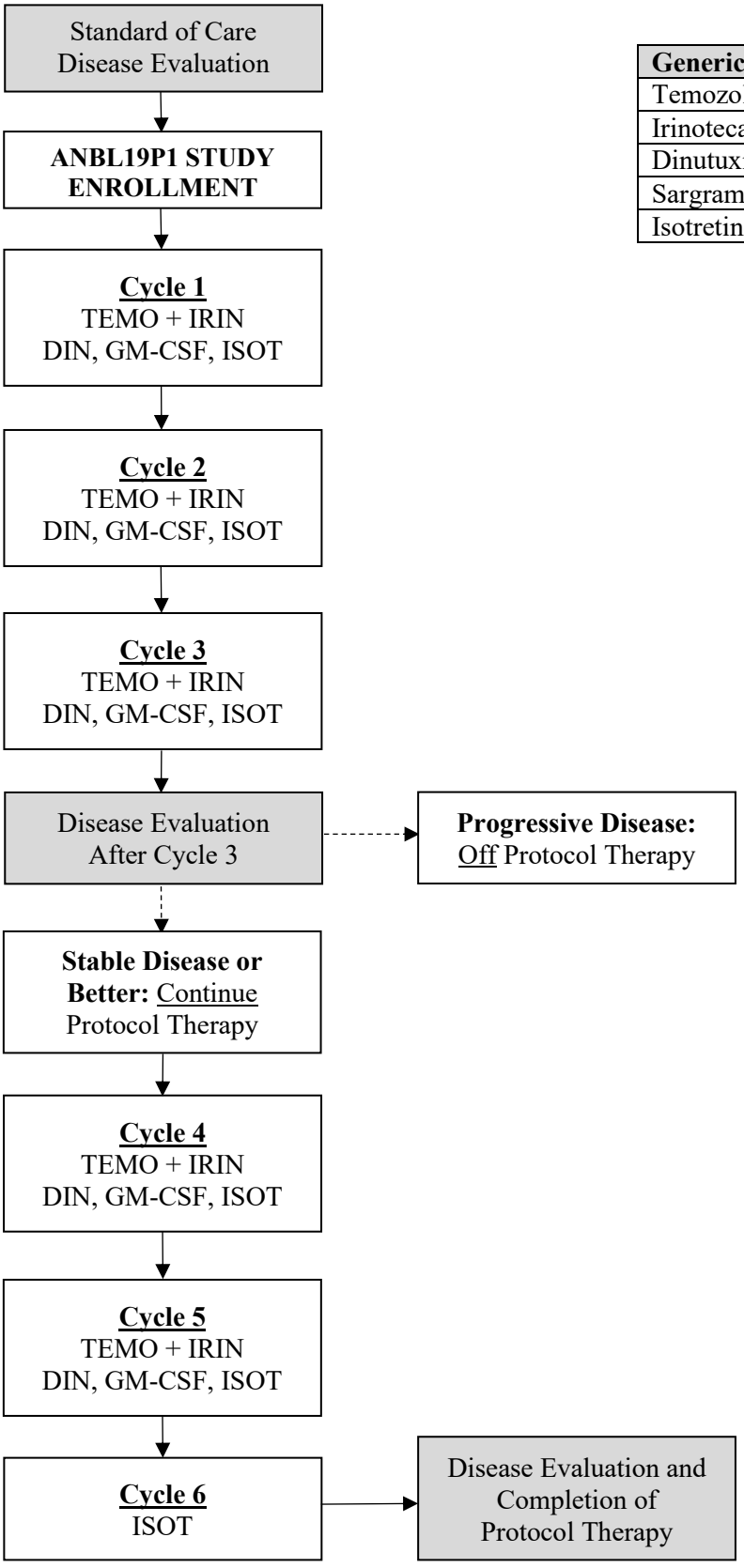
SEE SECTION 14.0 FOR SPECIMEN SHIPPING ADDRESSES

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.
The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

Post-Consolidation therapy consisting of the chimeric anti-G_{D2} monoclonal antibody dinutuximab in conjunction with the cytokines sargramostim (GM-CSF) and aldesleukin (IL-2) and the differentiating agent isotretinoin has improved survival for newly diagnosed patients with high-risk neuroblastoma. Nevertheless, 25-35% of children will still experience recurrence, and their long-term survival is dismal More effective approaches to eliminate minimal residual disease in the Post-Consolidation setting are needed to prevent recurrence in children with high-risk neuroblastoma. Data from the Children's Oncology Group (COG) Phase 2 study ANBL1221 indicate that the combination of irinotecan and temozolomide with dinutuximab and GM-CSF is active in the relapsed/refractory disease setting, with a response rate of approximately 40%. While ANBL1221 has demonstrated a role for chemo-immunotherapy in this context, planned administration of myelosuppressive chemotherapy shortly after recovery from autologous stem cell transplant has not been attempted in a COG neuroblastoma trial. Therefore, this pilot study will assess the feasibility of administering chemo-immunotherapy in the frontline, Post-Consolidation setting in patients with high-risk neuroblastoma. If the current trial demonstrates that delivery of chemo-immunotherapy is feasible in relatively close proximity to stem cell transplant, future trials may test the hypothesis that dinutuximab in combination with chemotherapy will be superior to standard Post-Consolidation immunotherapy.

EXPERIMENTAL DESIGN SCHEMA



Generic Drug Name	Abbreviation
Temozolomide	TEMO
Irinotecan	IRIN
Dinutuximab	DIN
Sargramostim	GM-CSF
Isotretinoin	ISOT

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the feasibility of administering dinutuximab, GM-CSF, and isotretinoin in combination with irinotecan and temozolomide in the frontline Post-Consolidation setting in patients with high-risk neuroblastoma who have undergone Induction and Consolidation therapy with tandem high-dose chemotherapy with stem cell rescue (ASCT).

1.2 Secondary Aims

1.2.1 To describe the toxicity profile of dinutuximab, GM-CSF, and isotretinoin in combination with irinotecan and temozolomide in the Post-Consolidation setting.

1.2.2 To describe the event-free survival and overall survival of patients who receive dinutuximab in combination with irinotecan and temozolomide, GM-CSF and isotretinoin in the Post-Consolidation setting.

1.3 Exploratory Aims

1.3.1 To describe the toxicity profiles associated with chemo-immunotherapy in the Post-Consolidation setting according to the type of prior therapy.

1.3.2 To describe response to chemo-immunotherapy in the Post-Consolidation setting using the revised International Neuroblastoma Risk Classification (INRC) in patients with evaluable or measurable disease at study entry.

1.3.3 To characterize immune and cytokine profiles in patients receiving Post-Consolidation chemo-immunotherapy.

1.3.4 To bank serial blood samples to investigate the relationship between factors related to the tumor, host, and immune environment and clinical outcomes in patients treated with chemo-immunotherapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Post-Consolidation therapy consisting of the chimeric anti-G_{D2} monoclonal antibody, dinutuximab, in conjunction with the cytokines sargramostim (GM-CSF) and aldesleukin (IL-2) and the differentiating agent isotretinoin has improved survival for newly diagnosed patients with high-risk neuroblastoma.[1] However, approximately 25-35% of children treated with multi-modality Induction, high-dose Consolidation chemotherapy and autologous stem cell transplant and this Post-Consolidation immunotherapy will experience recurrence[1,2] and their long-term survival is dismal.[3]

Data from the Children's Oncology Group (COG) Phase 2 study ANBL1221 indicate that the combination of irinotecan and temozolomide with dinutuximab and GM-CSF is active in the relapsed/refractory disease setting, with a response rate of approximately 40% in the full cohort of patients treated.[4,5] The high response rates observed in patients with

refractory or relapsed disease in ANBL1221 support the hypothesis that augmentation of Post-Consolidation immunotherapy with a chemo-immunotherapy approach may further improve outcome for children with high risk neuroblastoma. Hematologic toxicities were tolerable on ANBL1221. However, the toxicities associated with this regimen administered shortly following autologous stem cell transplant (ASCT) are unknown and have not been assessed in the context of a clinical trial. This pilot study will evaluate the feasibility of delivering dinutuximab in combination with irinotecan and temozolomide + GM-CSF (chemo-immunotherapy) in children with high-risk neuroblastoma who have received Consolidation therapy that includes tandem myeloablative chemotherapy and ASCT in the frontline setting. We hypothesize that the administration of dinutuximab in combination with chemotherapy (temozolomide and irinotecan) will be feasible in the Post-Consolidation setting. If the current trial demonstrates that delivery of chemo-immunotherapy is feasible in relatively close proximity to stem cell transplant, future trials may test the hypothesis that dinutuximab in combination with chemotherapy is superior to standard immunotherapy.

2.2 Current COG Standard Immunotherapy in the Post-Consolidation Setting for High-Risk Neuroblastoma

The current standard immunotherapy regimen recommended by the COG Neuroblastoma Committee includes dinutuximab, GM-CSF, and isotretinoin. The results of the randomized Phase 3 COG study ANBL0032 support this approach, as patients with at least a partial response to Induction therapy who were randomized to receive immunotherapy during Post-Consolidation with dinutuximab + cytokines + isotretinoin (n=113) had a significantly higher event-free survival (EFS) and overall survival (OS) at 2 years compared to patients randomized to isotretinoin alone (n=113), with EFS 66±5% vs. 46±5% (p=0.01) and OS 86±4% vs. 75±5% (p=0.02), respectively. Twenty-five patients with biopsy-proven persistent disease after ASCT were non-randomly assigned to immunotherapy with dinutuximab + cytokines + isotretinoin. The estimated 2-year EFS and OS rates for this cohort were 36±10% and 76±9%, respectively.[1] This seminal study led to a new COG standard-of-care for high-risk neuroblastoma, with administration of immunotherapy with dinutuximab plus cytokines and isotretinoin following ASCT. Common toxicities of the immunotherapy regimen include pain, fever, nausea, emesis, diarrhea, urticaria, mild elevation of hepatic transaminases, capillary leak syndrome, and hypotension.[1,6] Based on the results of ANBL0032, the FDA approved dinutuximab in combination with GM-CSF, IL-2, and isotretinoin for patients with high-risk neuroblastoma who have had at least a partial response to prior multimodality frontline therapy.[7,8]

While the addition of dinutuximab-based Post-Consolidation therapy clearly improved outcomes for children with newly diagnosed high-risk neuroblastoma, approximately one-third of patients who were eligible for randomization on ANBL0032 relapsed, and outcomes for those with biopsy proven disease following Consolidation remain unacceptable. There is a critical need to develop more effective Post-Consolidation therapy that will improve survival for all high-risk patients, including those with persistent disease following ASCT.

It is clear that the use of IL-2 as a component of Post-Consolidation therapy is associated with toxicity. To evaluate the contribution of IL-2 to survival outcomes and toxicity, the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) group conducted a trial in which patients were randomized to receive either dinutuximab derived from Chinese hamster ovary cells (dinutuximab beta) alone or dinutuximab beta with

subcutaneous IL-2.[9] In an intention-to-treat analysis, no differences in 3-year EFS or cumulative incidence of relapse/progression were detected between patients treated with or without IL-2, nor was a difference in 5-year OS detected.[9] Patients assigned to receive IL-2 had higher rates of fever, pain, allergic reaction, capillary leak syndrome, hematologic toxicity, neurotoxicity, and GI toxicity. Only 62% of patients randomized to the IL-2 + dinutuximab beta arm received the planned therapy while 87% of patients assigned to dinutuximab beta alone received the planned therapy.[9] Therefore, while the results raised questions regarding the relative contribution of IL-2 to this Post-Consolidation regimen, concern regarding the lack of receipt of assigned therapy suggested that further study of IL-2 as a component of Post-Consolidation therapy was necessary.

SIOPEN subsequently conducted a trial designed to reduce treatment-related toxicity overall so that a larger portion of patients would be expected to receive planned therapy. Dinutuximab beta (10 mg/m^2/day) was delivered over 10 days as a continuous infusion to all patients. For those assigned to the IL-2-containing arm, a reduced dose of subcutaneous IL-2 (3 million IU/m^2/day) was administered. During this trial, similar portions of patients on each arm completed therapy.[10] Rates of Grade 3 or higher fever and pain were reported among patients assigned to the IL2-containing therapy. Among evaluable patients, response rates and 2-year EFS/OS in the two arms did not differ significantly. Based on these results, SIOPEN has made the determination to eliminate IL-2 from standard Post-Consolidation therapy.[10]

Additional data also support the removal of IL-2 from dinutuximab beta-containing therapy. SIOPEN demonstrated in a randomized Phase 2 trial in patients with relapsed/refractory neuroblastoma that response rate, EFS and OS were similar among patients assigned to dinutuximab beta as a long-term infusion with or without the addition of subcutaneous IL-2.[11] In this study, rates of Grade 3 or higher fever, allergic reaction, hematological toxicity and neurotoxicity were higher in patients randomized to the IL-2-containing arm.

In addition, unpublished data suggest that treatment with dinutuximab and GM-CSF may result in elevation of soluble IL-2 receptor levels in the absence of IL-2 administration, potentially obviating the need for IL-2 administration to activate NK cells and promote antibody dependent cellular cytotoxicity (Paul Sondel, MD, PhD, personal communication).

Based upon these data, the COG Neuroblastoma Committee has concluded that there is a lack of clear benefit associated with IL-2, and the higher rate of toxicity associated with IL-2-containing regimens is cause for concern. Therefore, patients on frontline COG neuroblastoma trials no longer receive IL-2 as a component of standard Post-Consolidation therapy. Instead, GM-CSF is administered with all five dinutuximab-containing Post-Consolidation cycles.

2.3 Chemo-Immunotherapy for High-Risk Neuroblastoma

ANBL1221 evaluated response in patients with relapsed or refractory neuroblastoma following treatment with irinotecan and temozolomide in combination with either dinutuximab + GM-CSF or temsirolimus. The rationale for combining chemotherapy with immunotherapy in this study was based on pre-clinical data in small cell lung cancer and neuroblastoma that indicate that anti-G_{D2} antibodies augment the effect of chemotherapy through enhanced cytotoxicity.[12,13] Further, the use of monoclonal antibodies in combination with chemotherapy is supported by adult studies conducted for malignancies

such as breast and colon cancer. Trastuzumab has been combined with doxorubicin and cyclophosphamide for women with HER-2 positive breast cancer, and use of the combination has been associated with improved progression-free and overall survival.[14] Cetuximab in combination with irinotecan has been approved for EGFR-expressing metastatic colon cancer refractory to irinotecan-based therapy.[15]

Irinotecan/temozolomide was chosen as the chemotherapy backbone in ANBL1221 based on data regarding pre-clinical[16] as well as clinical activity in neuroblastoma.[17,18] Thirty-five patients were enrolled on the randomized portion of ANBL1221; 18 patients were randomized to Arm A (temsirolimus + irinotecan and temozolomide) and 17 patients were randomized to Arm B (dinutuximab + GM-CSF + irinotecan and temozolomide). Randomization was stratified based on prior therapy and *MYCN* status. Nine out of 17 patients (53%) on Arm B (dinutuximab + irinotecan and temozolomide) were found to have an objective response, defined as a complete response (CR, n=5) or partial response (PR, n=4), whereas only one patient (5%) on Arm A had a PR. One-year progression-free survival (PFS) among those who received dinutuximab + GM-CSF + irinotecan and temozolomide (Arm B) was 76.5% (95% CI, 56.3–96.7). In contrast, PFS among those who received temsirolimus + irinotecan and temozolomide (Arm A) was 24.7% (95% CI, 0.4–49.0).[4]

ANBL1221 reopened to continue accrual on Arm B to increase the precision around the point estimate of response rate. Objective responses were reported in 13 of 36 patients (36.1%, 95% CI [20.4%, 51.8%]) in this expansion cohort. In total (randomized patients and expansion cohort), 22/53 patients had objective responses (41.5%, 95% CI [28.2%, 54.8%]). This response rate exceeds the benchmark of 15% for irinotecan and temozolomide in this population[18] and the response rate reported for other regimens commonly used in the treatment of patients with relapsed neuroblastoma (e.g., ^{131}I-MIBG).[19]

Of the 16 patients randomized to the dinutuximab + GM-CSF + irinotecan and temozolomide arm who were evaluable for toxicity, the following CTCAE v4.0 ≥ Grade 3 hematologic toxicities were noted: neutropenia (4/16; 25%), thrombocytopenia (4/16; 25%), and anemia (4/16; 25%). Only 1 of 16 patients had CTCAE v4.0 Grade 3 diarrhea. Additional CTCAE v4.0 Grade 3 toxicities included pain (7/16; 44%), hypokalemia (6/16; 38%), fever and infection (4/16; 25%), and hypoxia (4/16; 25%); one patient had Grade 4 hypoxia related to therapy. Ten patients on the dinutuximab + GM-CSF + irinotecan and temozolomide arm required dose modifications; 4/16 patients required temozolomide dose modifications and 6/16 patients required dinutuximab dose modifications. Hematologic toxicity was defined as neutropenia or thrombocytopenia that caused a delay of ≥ 14 days between treatment cycles. Only two required dose modifications for hematologic toxicity (neutropenia, n=1; thrombocytopenia, n=1). Thus, hematologic toxicity was manageable on the dinutuximab + GM-CSF + irinotecan and temozolomide arm.[4]

Of the 35 patients evaluable for toxicity in the expansion cohort, the following CTCAE v4.0 ≥ Grade 3 hematologic toxicities were noted: thrombocytopenia (1/35; 2.9%) and neutropenia (12/35; 34.3%). Among the 51 patients evaluable for toxicity in the full cohort treated with this combination (randomized patients and patients in the expansion cohort), the most common ≥ Grade 3 toxicities were fever/infection (18/51; 35.3%), neutropenia (17/51; 33.3%), pain (15/51; 29.4%), and diarrhea (10/51; 19.6%). Grade 3 or higher thrombocytopenia was noted in 9.8% (5/51) of patients in the full cohort. Overall,

the hematologic as well as non-hematologic toxicities were tolerable in the expansion cohort (Rochelle Bagatell, MD, personal communication).[5]

The mechanism for the high level of anti-neuroblastoma activity observed in patients treated with the chemo-immunotherapy regimen has not yet been elucidated. Analysis of correlative biology samples collected during the ANBL1221 study is ongoing. It is possible that one or both chemotherapy agents may be altering the tumor microenvironment and/or inducing changes in tumor cell immunogenicity. The combination of irinotecan and temozolomide has been demonstrated to be well tolerated.[18] Therefore, both chemotherapeutic agents are included as part of the regimen for this study.

2.4 Dosing Rationale

In this pilot study, irinotecan and temozolomide will be administered using the same doses shown to be tolerable in ANBL1221. Isotretinoin, which has been shown to improve EFS following Consolidation therapy[20] and was incorporated with dinutuximab and cytokines in ANBL0032,[1] will be included in each cycle at standard dosing (80 mg/m^2/dose BID). Based on *in vitro* data indicating that isotretinoin reduces the activity of cytotoxic chemotherapeutic agents in neuroblastoma cell lines,[21] a break between the completion of isotretinoin and the start of the next cycle of therapy has been incorporated into the treatment schema. This schedule mirrors the administration of isotretinoin delivered in ANBL0032.[1]

2.5 Rationale for Correlative Studies

An understanding of the baseline Post-Consolidation immune status and changes in immune effector cells in response to immune modulating drugs will be important for the design of future passive immunotherapy regimens for patients with neuroblastoma. Key immune assessments of interest in this context include evaluation of the number of NK and NK-T cells, evaluation of T cell subsets and assessment of expression of NK activation and inhibitory receptors. For example, in ANBL0032, pre-immunotherapy expression of NK markers, including KIR, CD161 and NKp44, was associated with outcome (ANR 2018, Abstract 376), suggesting that patients with NK populations expressing these markers may be most responsive to dinutuximab. The importance of these markers in the context of chemo-immunotherapy rather than conventional Post-Consolidation immunotherapy as per ANBL0032 is not known, and ANBL19P1 provides an ideal context in which to obtain these data. In addition, this work will also improve our understanding of the potential impact of early chemo-immunotherapy on immune reconstitution following autologous stem cell transplant. A retrospective study of 39 patients with high-risk neuroblastoma demonstrated that most patients do not have full immune reconstitution at the start of immunotherapy after ASCT. Further, in this study, patients who remained in remission were noted to have higher white blood cell counts and absolute lymphocyte counts 3 months after completion of therapy, implying that tumor immune surveillance may impact outcomes.[22] Data regarding T-cell function in the peripheral blood of newly diagnosed children with neuroblastoma indicate that T-cell proliferative capacity is limited.[23] Additional studies in children with neuroblastoma and other solid tumors suggest that systemic immune dysfunction may also vary over time (David Barrett, MD, PhD, personal communication). There are ongoing efforts to collect data on immune and cytokine during frontline high-risk neuroblastoma therapy on the Phase 3 study, ANBL1531. As a result, an opportunity exists to compare immune profiles in those patients receiving standard immunotherapy on ANBL1531 versus chemo-immunotherapy on this pilot trial.

For children with neuroblastoma, cytokine levels and changes in these levels throughout treatment may be associated with therapeutic response to immunotherapy. Cytokines can be released by cancer cells or by cells of the tumor microenvironment and have a multitude of effects that either promote tumor cell growth or potentiate the effect of immunotherapy.[24] Cytokines have been associated with outcome in patients with cancer. In particular, elevated IL-6 levels at diagnosis have been associated with poor outcome in numerous cancers, including neuroblastoma.[25,26] In ANBL0931, a study of Post-Consolidation immunotherapy in patients with high-risk neuroblastoma, 15 cytokines/chemokines were measured throughout treatment. Samples were obtained during each cycle of immunotherapy. Results showed that patients developed significant increases ($p < 0.001$) in serum levels of IL-6, IL-1ra, IFN-ɣ, IL-10, TNFα, IL-5, IL-17A, CXCL9, IL-15 and nitric oxide compared to baseline levels (ANR 2018, Abstract 378). However, only a low pretreatment (baseline) level of CXCL9 was associated with an improved event free survival ($p = 0.05$) in patients receiving standard immunotherapy. Therefore, samples will be obtained on ANBL19P1 to evaluate the levels of these cytokines at baseline and during therapy to evaluate the effect of chemo-immunotherapy during therapy.

Importantly, samples and testing for immune profiling and cytokine analysis from this study parallel those being collected from patients in first relapse or with refractory neuroblastoma receiving identical chemo-immunotherapy on the Phase 2 trial ANBL1821 (Arm A). Thus, there is an opportunity to examine the differences in immune profiles both prior to and following chemo-immunotherapy across COG studies in patients in the frontline Post-Consolidative and relapsed/refractory setting.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

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

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

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

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site

registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

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

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

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

3.1.3 Reservation Requirements

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

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

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

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM username 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: www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (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.

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

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 enrollment.

- Enrollment must occur after completion of external beam radiotherapy, if given, and after completion of the standard Post-Consolidation disease assessment. The standard Post-Consolidation disease assessment must occur after completion of radiotherapy, if given, and must occur within 21 days prior to enrollment (repeat if out of window).
- Patients who do not undergo radiotherapy (those with unidentifiable primary tumors and no persistent metastatic disease) may enroll upon recovery from the last dose of high-dose chemotherapy and ASCT and completion of disease evaluations.

3.2 Patient Eligibility Criteria

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

Laboratory Studies
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if > 7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to *enrollment* (repeat if necessary).

Disease/Staging Imaging
Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to *enrollment* (repeat if necessary).

Inclusion Criteria

3.2.1 Age
Patients must be < 31 years of age at the time of enrollment.

3.2.2 Diagnosis
Patients must have a diagnosis of neuroblastoma or ganglioneuroblastoma (nodular) [verified by tumor pathology analysis or demonstration of clumps of tumor cells in bone marrow with elevated urinary catecholamine metabolites at the

time of diagnosis] and have been designated as having high-risk disease based on COG risk classification. The following disease groups are eligible:

- Patients with **INRG Stage M** disease with any of the following features:
  a) *MYCN* amplification (> 4-fold increase in *MYCN* signals as compared to reference signals), regardless of additional biologic features; OR
  b) Age > 547 days at the time of diagnosis regardless of biologic features; OR
  c) Age 365-547 days at the time of diagnosis with tumors with unfavorable histology and/or DNA index = 1.

- Patients with **INRG Stage MS** disease with *MYCN* amplification

- Patients with **INRG Stage L2** disease with either of the following features:
  a) *MYCN* amplification (> 4-fold increase in *MYCN* signals as compared to reference signals), regardless of additional biologic features; OR
  b) Age > 547 days at the time of diagnosis with *MYCN* non-amplified tumors with unfavorable histology.

Note**:** Patients observed or patients treated with a single cycle of chemotherapy per a low or intermediate risk neuroblastoma regimen (e.g., as per ANBL0531, ANBL1232 or similar) for what initially appeared to be non-high-risk disease but subsequently found to meet the criteria in Section 3.2.2 will also be eligible.

See Appendix II for INRG Staging System.

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 (Appendix III).

3.2.4 Prior Therapy

- All patients must have completed high-risk Induction therapy with 4-6 cycles of chemotherapy
- After completion of Induction therapy, patients may have received no more than 4 cycles of bridging chemotherapy or chemo-immunotherapy prior to ASCT.
- Patients cannot have previously progressed on immunotherapy with dinutuximab or other anti-G_{D2} monoclonal antibody.
- All patients must have had undergone surgical resection of their primary tumor as part of frontline therapy. Exceptions to this requirement include patients who had a complete response to Induction chemotherapy, patients with no identifiable primary tumor, and patients for whom the institutional surgical team determined that potential risks outweighed potential benefits of resection.
- All patients must have undergone tandem high-dose chemotherapy with ASCT as part of Consolidation.
- Patients must enroll between Day +56 and Day +200 from the peripheral blood stem cell (PBSC) infusion following the last dose of high-dose chemotherapy during Consolidation.
- All patients must have undergone external beam radiation therapy. Exceptions to this requirement include patients who had no identifiable primary tumor and

no persistent metastatic disease at the end of Induction. For patients who received radiotherapy, at least 7 days must have elapsed between completion of radiotherapy and enrollment on this study.

3.2.5 Concomitant Medications Restrictions

Please see Section 4.3 for the concomitant therapy restrictions for patients during treatment.

Patients must not have received long-acting myeloid growth factors (e.g., Neulesta) 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 ≥ 50,000/μL (transfusion independent for ≥ 7 days)

3.2.6.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2, or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
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[27] utilizing child length and stature data published by the CDC.

Note: Patients with history of transplant associated-thrombotic microangiopathy (TA-TMA) must have a creatinine clearance or radioisotope GFR at baseline to assess renal function and must meet the above criteria.

3.2.6.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) ≤ 5.0 x ULN for age (≤ 225 U/L)

Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L.

3.2.6.4 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or

- Ejection fraction of ≥ 50% by echocardiogram or radionuclide angiogram

3.2.6.5 Adequate Pulmonary Function Defined As:
- Absence of dyspnea at rest
- If pulmonary function tests (PFTs) are performed, FEV_1/FVC must be > 60%

3.2.6.6 Central Nervous System Function Defined As:
- No clinical evidence of active CNS disease at the time of study enrollment.
- Patients with seizure disorder may be enrolled if on non-enzyme-inducing anticonvulsants and well controlled.
- CNS toxicity from prior therapy ≤ Grade 2.

Exclusion Criteria

3.2.7 Patients must not have had progressive disease (PD) per the revised International Neuroblastoma Risk Criteria (INRC)[28] since the initial diagnosis of high-risk neuroblastoma.
Exception: Progressive disease within the first 2 cycles of Induction chemotherapy consisting of cyclophosphamide and topotecan is allowed. Patients with progression subsequent to initial cyclophosphamide and topotecan cycles are excluded.

3.2.8 Patients may not have received additional systemic cancer-directed therapy following completion of the last planned high-dose chemotherapy with ASCT prior to enrollment on this trial.

3.2.9 Patients may not have received ^{131}I-MIBG therapy at any time prior to enrollment on this trial.

3.2.10 Patients who received single (rather than tandem) high-dose chemotherapy with ASCT are excluded.

3.2.11 Patients cannot be receiving other ongoing anticancer therapy.

3.2.12 Patients who were enrolled onto ANBL1531 AND underwent arm assignment are not eligible. Patients who enrolled onto ANBL1531 who declined second consent may be eligible for ANBL19P1 if all other criteria are met.

3.2.13 Patients enrolled onto ANBL17P1 are not eligible.

3.2.14 Systemic Steroids and Immunosuppressive Medications

3.2.14.1 Patients must have been off pharmacologic doses of systemic steroids for at least 7 days prior to enrollment.

3.2.14.2 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.

Note: 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.

3.2.14.3 Patients on any other immunosuppressive medications (e.g., cyclosporine, tacrolimus) are not eligible. However, prior or planned concomitant treatment with eculizumab is permitted (e.g., treatment of TA-TMA).

3.2.15 Patients must not have received enzyme-inducing anticonvulsants including phenytoin, phenobarbital, valproic acid, or carbamazepine for at least 7 days prior to study enrollment.

Note: Patients receiving non-enzyme inducing anticonvulsants such as gabapentin or levetiracetam are eligible. (See Appendix IV for additional enzyme-inducing anticonvulsants and acceptable alternative options.)

3.2.16 Patients must not have received drugs that are strong inducers or inhibitors of CYP3A4 within 7 days prior to study enrollment. (See Appendix VII for a list of CYP3A4 active agents.)

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

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

3.2.19 Patients with moderate or large pericardial effusions are not eligible.

3.2.20 Patients must not have ≥ Grade 2 diarrhea.

3.2.21 Patients must not have uncontrolled infection.

3.2.22 Patients with a history of Grade 4 allergic reactions to anti-G_{D2} antibodies or reactions that required discontinuation of the anti-G_{D2} therapy are not eligible.

3.2.23 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.

3.2.24 Pregnancy and Breastfeeding

3.2.24.1 Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

3.2.24.2 Lactating females who plan to breastfeed their infants.

3.2.24.3 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.25 Regulatory Requirements

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

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

4.0 TREATMENT PLAN

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

4.1 Overview of Treatment Plan

This is a single-arm pilot study of dinutuximab in combination with irinotecan, temozolomide, sargramostim (GM-CSF), and isotretinoin in the Post-Consolidation setting for patients receiving frontline therapy for high-risk neuroblastoma.

Each cycle of therapy will be 28 days in length. During Cycles 1-5 (Table 1), patients will receive irinotecan and temozolomide (Days 1-5), dinutuximab (Days 2-5), GM-CSF (Days 6-12) and ISOtretinoin (Days 8-21). Cycle 6 (Table 2) will consist of isotretinoin alone (Days 8-21).

Disease evaluations will occur at baseline (within 21 days prior to study enrollment), after Cycle 3, and after completion of Cycle 6 (end of therapy). [Note: Patients who discontinue isotretinoin prior to Cycle 6 must complete full disease evaluations and end of protocol therapy requirements at the end of Cycle 5.] Imaging evaluations are to be performed during follow-up as detailed in Section 7.1.

Table 1. Post-Consolidation Cycles 1-5

Days	1	2	3	4	5	6-12	13-21	22-28
Temozolomide	X	X	X	X	X			
Irinotecan	X	X	X	X	X			
Dinutuximab		X	X	X	X			
GM-CSF						X		
ISOtretinoin						(D8-12)	X	

Table 2. Post-Consolidation Cycle 6

Days	1-7	8-21	22-28
ISOtretinoin		X	

4.2 General Guidelines for Therapy

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

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

4.2.1 Diarrhea Prophylaxis

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

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

4.2.2 Pneumocystis Jiroveci Pneumonia (PJP) Prophylaxis

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

4.2.3 Other Supportive Care

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary. To reduce opiate requirements during dinutuximab therapy, gabapentin use is recommended. Dosing should follow institutional standards; however, dosing guidance is provided in Section 4.4.3.

Note: Steroids (dexamethasone) may not be used as an anti-emetic. A multiple day aprepitant regimen may result in moderate CYP3A4 inhibition and should be avoided if reasonable alternatives exist. A single dose of aprepitant or fosaprepitant does not substantially inhibit CYP3A4 and can be utilized.

4.3 Concomitant Therapy

4.3.1 Chemotherapy or Immunomodulating Agents

No other systemic anti-cancer or immunomodulatory therapy (including steroids) will be permitted. Pharmacologic doses of systemic corticosteroids should be used ONLY for life-threatening conditions (i.e. life-threatening allergic reactions and anaphylaxis such as bronchospasm, stridor) unresponsive to other measures. **The use of dexamethasone as an anti-emetic is not permitted.** Corticosteroid therapy can be used as a premedication for transfusion in patients known to have a history of transfusion reactions or for treatment of an unexpected transfusion reaction (hydrocortisone 2 mg/kg or less or an equivalent dose of an alternative corticosteroid). Physiologic doses of steroid for patients with known adrenal insufficiency is acceptable. **The use of steroids during protocol therapy requires clear justification and documentation.** See Appendix VI for possible drug interactions.

4.3.2 External Beam Radiotherapy

Radiotherapy to localized painful lesions is not permitted on study.

4.3.3 Cytokines or Growth Factors

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

4.3.4 CYP3A4 Active Agents

See Appendix VII for a list of CYP3A4 active agents.

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

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

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

4.4 Cycle 1

4.4.1 Criteria to Start Immunotherapy – Cycle 1

Laboratory parameters must be within the range defined under eligibility (Section 3.2.6).

4.4.2 Criteria to Start ISOtretinoin – Cycle 1

- ALT < 10 x ULN for age. For the purposes of this study, ULN for ALT is 45 U/L.
- Serum triglycerides < 500 mg/dL.
- A serum creatinine based on age/gender as described in Section 3.2.6.2.

Note: Observations may be obtained within 4 days prior to start of ISOtretinoin (i.e., Days 5-8 of protocol therapy).

As per Section 5.2.8 *Management of Concurrent Transplant Associated-Thrombotic Microangiopathy (TA-TMA*), ISOtretinoin may be dose-reduced or omitted per institutional practice in patients with TA-TMA.

4.4.3 Premedication and Supportive Care Recommended for the Prevention of Anticipated Toxicities Associated with Dinutuximab

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

- IV hydration: Administer NS 10-20 mL/kg IV over 60-90 minutes just prior to each dinutuximab infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.
- H2 antagonist (e.g., famotidine IV dose: 0.25 mg/kg/dose every 12 hours; maximum dose: 20 mg/dose)
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 650 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- **To reduce opiate requirements during dinutuximab therapy, gabapentin dosing is recommended**. To optimize the effect of gabapentin, it should be initiated 1 week prior to expected start of antibody so that it can be increased to full dose by the start of dinutuximab administration. Dosing should follow institutional standards; however, the following dosing may be considered:
  - First day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) at bedtime
  - Second day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) BID
  - Third day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) TID – patients should be at this dose by the time of admission for Cycle 1 dinutuximab
  - Gabapentin doses can be increased further if necessary; institutional guidelines should be followed.
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. Hydromorphone or fentanyl may be

used in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without pain/discomfort, consider removing the continuous opioid infusion rate during periods when dinutuximab is not infusing.

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

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

Fluid shifts and increased insensible volume losses due to fever are commonly seen in patients receiving dinutuximab. In addition to the IV saline bolus given immediately prior to the start of dinutuximab, the administration of maintenance IV fluids should be considered. Fluids can be adjusted as needed based on intravascular volume status.

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

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

<u>Monitoring during the dinutuximab infusion</u>:

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

c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.4.4 Additional Guidance

- Due to the requirement for multiple supportive care medications concurrent with dinutuximab administration, the number of lumens available for venous access should be carefully considered. Many centers use 2 central lumens routinely; institutional standards should be followed.

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. Use of furosemide or other diuretics is indicated in cases of pulmonary capillary leak but is not required routinely.

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

- The use of intravenous immunoglobulin (IVIG) during Post-Consolidation therapy is discouraged. If necessary, its use should be limited to the first 100 days post-ASCT because IVIG may interfere with antibody (dinutuximab) dependent cellular cytotoxicity. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

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

Following completion of this cycle, Cycle 2 starts on Day 29 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 50,000/µL (whichever occurs later). **Please refer to Section 4.5.1 for additional criteria to start next cycle.**

Cycle 1

4.4.5 Therapy Delivery Map – Cycle 1

Cycle 1 is 4 weeks (28 days) in length.	_____ Patient COG ID number	_____ DOB

Start Cycle 1 once criteria in Section 4.4.1 have been met.
This TDM is on three (3) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temozolomide (TEMO)	PO (preferred) or via enteral tube	BSA ≥ 0.6 m^2: 100 mg/m^2/dose BSA < 0.6 m^2: See Dosing Table in 4.4.7. See Dosing Nomogram for Full Dosing in Appendix VIII Dosing Nomogram for Reduced Dosing is in Appendix IX	1 - 5	**Maximum dose = 200 mg** See treatment details in Section 4.4.7 for dose rounding instructions. For patients unable to tolerate enteral TEMO, IV TEMO may be substituted for enteral TEMO at the same dose (Section 5.3). **Administer enteral doses at least 1 hour prior to IRIN administration.**
Irinotecan (IRIN)	IV over 90 minutes	BSA ≥ 0.6 m^2: 50 mg/m^2/dose BSA < 0.6 m^2: See Dosing Table in 4.4.7	1 - 5	Administer IRIN at least 1 hour after the completion of enteral TEMO, see Section 4.4.7. IRIN may be administered immediately after the completion of IV TEMO.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	2 - 5	*Infusion duration may be extended up to 20 hours if needed. Infusions should not extend beyond 20 hours, even if the full dose has not been administered. Start immediately after completion of NS bolus and IRIN infusion. See Section 4.4.7 for detailed DIN administration guidelines, and Section 4.4.3 for premedications and monitoring during the infusion.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 micrograms/m^2/dose	6 - 12	See Section 4.4.7 for GM-CSF administration guidelines.
ISOtretinoin (ISOT)	PO	BSA ≥ 0.6 m^2: 80 mg/m^2/dose BID BSA < 0.6 m^2: See Dosing Table in 4.4.7	8 - 21	BID dosing. See additional starting criteria for ISOT in Section 4.4.7. Round doses to nearest 10 mg to accommodate capsule strength.

Continue to the next page for the therapy log.

Cycle 1

Cycle 1 is 4 weeks (28 days) in length.	_____ Patient COG ID number _____ DOB

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	TEMO _____ mg	IRIN _____ mg	DIN _____ mg	GM-CSF _____ micrograms	ISOT _____ mg _____ mg	Studies
			Enter calculated dose above and actual dose administered below					
		Prior to start						a – m
		1	_____ mg	_____ mg				
		2	_____ mg	_____ mg	_____ mg			d, e
		3	_____ mg	_____ mg	_____ mg			e
		4	_____ mg	_____ mg	_____ mg			e
		5	_____ mg	_____ mg	_____ mg			e
		6				_____ mcg		d, e, f*, g*, m*
		7				_____ mcg		
		8				_____ mcg	_____ mg _____ mg	
		9				_____ mcg	_____ mg _____ mg	
		10				_____ mcg	_____ mg _____ mg	
		11				_____ mcg	_____ mg _____ mg	d
		12				_____ mcg	_____ mg _____ mg	
		13					_____ mg _____ mg	
		14					_____ mg _____ mg	
		15					_____ mg _____ mg	d, e, f
		16					_____ mg _____ mg	
		17					_____ mg _____ mg	
		18					_____ mg _____ mg	
		19					_____ mg _____ mg	
		20					_____ mg _____ mg	
		21					_____ mg _____ mg	d, e, f
		29	Begin Cycle 2 on Day 29 or when starting criteria are met, whichever occurs later (see Section 4.5.1).					

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

Cycle 1

4.4.6 Required Observations – Cycle 1

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

a. History, physical exam with vital signs
b. Height, weight, BSA
c. Performance status
d. CBC with differential and platelets (patients who experience Grade 4 neutropenia or thrombocytopenia should have CBCs checked at least twice per week until recovery to Grade 3)
e. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus
f. ALT, AST, total bilirubin, albumin*
g. Triglycerides*
h. Pregnancy test (obtain for females of childbearing potential)
i. GFR or Creatinine Clearance (only required for patients with TA-TMA)
j. ECHO or MUGA
k. Tumor Imaging Evaluation (Cross sectional tumor imaging [MRI or CT]; and ^{123}I-MIBG or alternatively FDG-PET scan for patients with MIBG non-avid disease at diagnosis)
l. Bilateral bone marrow aspirates and biopsies
m. Specimens for correlative studies. Post-dinutuximab specimen should be collected at a single time point between Day 5 (post-dinutuximab) and Day 8 (pre-ISOtretinoin). See Section 14.0 and Appendix X for details.*

*Observations may be obtained between Days 5-8 (pre-ISOtretinoin)

This listing only includes evaluations necessary to answer the study aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

Cycle 1

4.4.7 Treatment Details – Cycle 1

Drug doses should be calculated based on the height and weight obtained within 1 week prior to beginning Cycle 1.

Suggested administration schedule for chemotherapy (Days 1-5; temozolomide and irinotecan) and dinutuximab (Days 2-5):

- At hour 0: patient should receive oral temozolomide.
- At hour 1: start IV irinotecan over 90 minutes. On days the patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 60-90 minutes.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5), start dinutuximab infusion.
- Note: Irinotecan must be administered at least 1 hour AFTER enteral temozolomide.

Temozolomide: PO daily (NG or G-tube administration is allowed)
Days: 1-5
Dose: For BSA ≥ 0.6 m^2, the dose for temozolomide is 100 mg/m^2/dose
MAXIMUM dose = 200 mg

For patients receiving capsule formulation, see dosing nomogram in Appendix VIII and reduced dosing nomogram in Appendix IX (if dose modification is required).

For patients receiving oral liquid formulation, round according to institutional standard.

For BSA < 0.6 m^2, please see the table below. The dose of temozolomide in the table is expressed as final dose in **mg** to be administered regardless of formulation used.

TEMOZOLOMIDE Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	15 mg
0.30-0.34	20 mg
0.35-0.39	30 mg
0.40-0.44	35 mg
0.45-0.49	40 mg
0.50-0.54	50 mg
0.55-0.59	55 mg

Note: For patients unable to tolerate enteral temozolomide, IV temozolomide may be administered. Please refer to Section 5.3 for guidance on IV temozolomide administration.

Sequencing: Enteral temozolomide must be administered at least 1 hour PRIOR to irinotecan.

Cycle 1

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended 30-60 minutes prior to each dose to prevent nausea and vomiting. When using temozolomide capsules, dose according to Temozolomide Dosing Nomogram in Appendix VIII. For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist. If emesis occurs within 20 minutes of taking a dose of temozolomide, the dose should be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated.

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

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See hyperlink to the drug monograph provided in Section 6.0 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: For BSA ≥ 0.6 m^2, the dose of irinotecan is 50 mg/m^2/dose.

For BSA < 0.6 m^2, please see the table below. The dose of irinotecan in the table is expressed as final dose in **mg** to be administered.

IRINOTECAN Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg

Note: Irinotecan should be administered at least 1 hour after enteral temozolomide has been given.

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

Cycle 1

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

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

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

Refer to Section 4.4.3 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 60-90 minutes. Bolus should be given concurrently with irinotecan infusion. On Day 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

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

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

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

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

Sargramostim dose will be held if the total white cell count is > 50,000/µL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/µL

Cycle 1

and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

ISOtretinoin: PO BID
Days: 8-21 **See additional starting criteria for ISOT in Section 4.4.2.**
Dose: For BSA ≥ 0.6 m^2, the dose of ISOtretinoin is 80 mg/m^2/dose BID, rounded to nearest 10 mg to accommodate capsule strength.

For BSA < 0.6 m^2, please see table below. The dose of ISOtretinoin in the table is expressed as final dose in **mg** to be administered.

NOTE: dose BID. For example, if BSA ≥ 0.6 m^2, administer 80 mg/m^2/dose BID. The total daily dose is 160 mg/m^2/day.

ISOtretinoin Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	10 mg BID
0.3-0.39	20 mg BID
0.4-0.49	30 mg BID
0.5-0.59	40 mg BID

Note: Capsules can be cut and the contents squeezed into a high fat food such as ice cream or peanut butter immediately prior to administration. Capsules can be chewed (best absorbed if chewed with high fat food) or the child taught to swallow entire capsules, which is feasible and to be encouraged. Under no circumstances should ISOtretinoin be removed from the capsules for more than 1 hour prior to administering to the patient (see hyperlink to the drug monograph provided in Section 6.0). Administration via nasogastric tube or orally via syringe is discouraged.

Missed doses of isotretinoin should **NOT** be made up during the one week break between the scheduled end of isotretinoin therapy and the start of chemotherapy in the subsequent cycle to avoid delays in therapy. A duration of one week between the scheduled end of isotretinoin (day 21) and the start of chemotherapy in the subsequent cycle should be maintained (e.g., last dose of isotretinoin is on day 21 regardless of start date or missed doses and the subsequent cycle starts on day 29 if all other criteria are met).

See Section 5.0 for Dose Modifications based on Toxicities.

Cycle 1

4.5 Cycles 2-5

4.5.1 Criteria to Start Immunotherapy – Cycles 2-5

a. ANC ≥ 750/μL and platelet count ≥ 50,000/μL (transfusion independent for ≥ 7 days).
b. ALT ≤ 5 x ULN for age 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. For the purposes of this study, ULN for ALT is 45 U/L.
c. Total bilirubin ≤ 1.5 x ULN for age
d. No evidence of serious infection, or infection under control (e.g., negative blood culture).
e. A serum creatinine based on age/sex as described in Section 3.2.6.2.
f. Any diarrhea from preceding cycle improved to CTCAEv5.0 Grade 1 or better.
g. All other non-hematologic toxicities not otherwise specified from the previous cycle must improve to CTCAEv5.0 Grade 2 or better
h. To proceed to Cycle 4, patients must have no evidence of disease progression on the post-Cycle 3 evaluation. For patients with no evidence of residual soft tissue disease at the start of Post-Consolidation, cross sectional imaging (CT or MRI) may be omitted from the post-Cycle 3 evaluation; all other patients should undergo cross sectional imaging. For patients with no evidence of marrow disease at the start of Post-Consolidation therapy, bone marrow aspirates and biopsies may be omitted from the post-Cycle 3 evaluation. Patients with marrow involvement at the start of Post-Consolidation therapy should undergo bilateral bone marrow aspirates/biopsies as part of the post-Cycle 3 evaluation.

4.5.2 Criteria to Start ISOtretinoin – Cycles 2-5

- ALT < 10 x ULN for age. For the purposes of this study, ULN for ALT is 45 U/L.
- Serum triglycerides < 500 mg/dL.
- A serum creatinine based on age/gender a described in Section 3.2.6.2.

Note: Observations may be obtained within 4 days prior to start of ISOtretinoin (i.e., Days 5-8 of protocol therapy).

As per Section 5.2.8 *Management of Concurrent Transplant Associated-Thrombotic Microangiopathy (TA-TMA)*, ISOtretinoin may be dose-reduced or omitted per institutional practice in patients with TA-TMA.

4.5.3 Premedication and Supportive Care Recommended for the Prevention of Anticipated Toxicities Associated with Dinutuximab

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

- IV hydration: Administer NS 10-20 mL/kg IV over 60-90 minutes just prior to each dinutuximab infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to dinutuximab infusion and scheduled q6h. Hydroxyzine PO (0.5-1.0 mg/kg; max dose 50 mg) may be used instead of diphenhydramine in patients for whom there is a specific indication.

Cycles 2-5

- H2 antagonist (e.g., famotidine IV dose: 0.25 mg/kg/dose every 12 hours; maximum dose: 20 mg/dose)
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 650 mg) 20 minutes prior to each dinutuximab infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- **To reduce opiate requirements during dinutuximab therapy, gabapentin dosing is recommended.** To optimize the effect of gabapentin, it should be initiated 1 week prior to expected start of antibody so that it can be increased to full dose by the start of dinutuximab administration. Dosing should follow institutional standards; however, the following dosing may be considered:
  - First day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) at bedtime
  - Second day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) BID
  - Third day of gabapentin: 5 mg/kg/dose (max 300 mg/dose) TID – patients should be at this dose by the time of admission for Cycle 1 dinutuximab
  - Gabapentin doses can be increased further if necessary; institutional guidelines should be followed.
- Use of a patient-controlled analgesia device (PCA) or continuous opioid infusion during the dinutuximab infusion is recommended. Morphine is the most commonly administered opioid. Hydromorphone or fentanyl may be used in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the dinutuximab infusion without pain/discomfort, consider removing the continuous opioid infusion rate during periods when dinutuximab is not infusing.
- Recommended starting dose of analgesics:
  - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of dinutuximab infusion. At the same time, start a continuous morphine infusion of 0.02 mg/kg/hr with bolus doses of 0.01 mg/kg/dose q15 minutes prn for pain.
  - If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of dinutuximab. At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/hour for opioid naïve patients) with bolus doses of 0.002 mg/kg/dose q15 minutes prn for pain.
  - If fentanyl PCA is used, recommend fentanyl 1 mcg/kg 10 minutes prior to starting dinutuximab infusion. At the same time, start a continuous fentanyl infusion of 0.5 micrograms/kg/hr with bolus doses of 0.25 micrograms/kg/dose q10 minutes prn pain.
  - Doses should be titrated as needed in accordance with institutional guidelines.

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

Cycles 2-5

Fluid shifts and increased insensible volume losses due to fever are commonly seen in patients receiving dinutuximab. In addition to the IV saline bolus given immediately prior to the start of dinutuximab, the administration of maintenance IV fluids should be considered. Fluids can be adjusted as needed based on intravascular volume status.

Have immediately available during the dinutuximab infusion:

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

Monitoring during the dinutuximab infusion:

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

4.5.4 Additional Guidance

- Due to the requirement for multiple supportive care medications concurrent with dinutuximab administration, the number of lumens available for venous access should be carefully considered. Many centers use 2 central lumens routinely; institutional standards should be followed.

- Capillary leak syndrome is an expected side effect of dinutuximab therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. Use of furosemide or other diuretics is indicated in cases of pulmonary capillary leak but is not required routinely.

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

- The use of Intravenous Immunoglobulin (IVIG) during Post-Consolidation therapy is discouraged. If necessary, its use should be limited to the first 100 days post-ASCT because IVIG may interfere with antibody (dinutuximab) dependent cellular cytotoxicity. IVIG should not be given within 2 weeks of starting dinutuximab treatment and 1 week after completing dinutuximab therapy.

Cycles 2-5

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

Following completion of each cycle, the subsequent cycle starts on Day 29 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 50,000/µL (whichever occurs later). **Please refer to Section 4.5.1 for criteria to start next cycle (for Cycles 3-5) or see Section 4.6.1 for criteria to start Cycle 6.**

Cycles 2-5

Cycles 2-5

4.5.5 Therapy Delivery Map - Cycles 2-5

Cycles 2 to 5 are each 4 weeks (28 days) in length.	_____ Patient COG ID number	_____ DOB

Treatment details and criteria to start are in Section 4.5.1.
This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temozolomide (TEMO)	PO (preferred) or via enteral tube	BSA ≥ 0.6 m^2: 100 mg/m^2/dose BSA < 0.6 m^2: See Dosing Table in 4.5.7. See Dosing Nomogram for Full Dosing in Appendix VIII. Dosing Nomogram for Reduced Dosing is in Appendix IX.	1 - 5	**Max dose = 200 mg** See treatment details in Section 4.5.7 for dose rounding instructions. For patients unable to tolerate enteral TEMO, IV TEMO may be substituted for enteral TEMO at the same dose (Section 5.3). **Administer enteral doses at least 1 hour prior to IRIN administration.**
Irinotecan (IRIN)	IV over 90 minutes	BSA ≥ 0.6 m^2: 50 mg/m^2/dose BSA < 0.6 m^2: See Dosing Table in 4.5.7	1 - 5	Administer IRIN at least 1 hour after the completion of enteral TEMO, see Section 4.5.7. IRIN may be administered immediately after the completion of IV TEMO.
Dinutuximab (DIN)	IV over 10 hours*	17.5 mg/m^2/dose	2 - 5	*Infusion duration may be extended up to 20 hours if needed. Infusions should not extend beyond 20 hours, even if the full dose has not been administered. Start immediately after completion of NS bolus and IRIN infusion. See Section 4.5.7 for detailed DIN administration guidelines, and Section 4.5.3 for premedications and monitoring during the infusion.
Sargramostim (GM-CSF)	SubQ (preferred) or IV over 2 hours	250 micrograms/m^2/dose	6 - 12	See Section 4.5.7 for GM-CSF administration guidelines.
ISOtretinoin (ISOT)	PO	BSA ≥ 0.6 m^2: 80 mg/m^2/dose BID BSA < 0.6 m^2: See Dosing Table in 4.5.7	8 - 21	BID dosing. See additional starting criteria for ISOT in Section 4.5.2. Round doses to nearest 10 mg to accommodate capsule strength.

Continue to the next page for the therapy log.

Cycles 2 to 5 are each 4 weeks (28 days) in length.	_____ Patient COG ID number _____ DOB

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	TEMO _____ mg	IRIN _____ mg	DIN _____ mg	GM-CSF _____ micrograms	ISOT _____ mg _____ mg	Cycles 2, 4, and 5 Studies	Cycle 3 Studies
			Enter calculated dose above and actual dose administered below						
		1	_____ mg	_____ mg				a – e, g, j	a – e, g, j
		2	_____ mg	_____ mg	_____ mg			c, d	c, d
		3	_____ mg	_____ mg	_____ mg			d	d
		4	_____ mg	_____ mg	_____ mg			d	d
		5	_____ mg	_____ mg	_____ mg			d	d
		6				_____ mcg		c, d, e*, f*	c, d, e*, f*
		7				_____ mcg			
		8				_____ mcg	_____ mg _____ mg		
		9				_____ mcg	_____ mg _____ mg		
		10				_____ mcg	_____ mg _____ mg		
		11				_____ mcg	_____ mg _____ mg	c	c
		12				_____ mcg	_____ mg _____ mg		
		13					_____ mg _____ mg		
		14					_____ mg _____ mg		
		15					_____ mg _____ mg	c, d, e	c, d, e
		16					_____ mg _____ mg		
		17					_____ mg _____ mg		
		18					_____ mg _____ mg		
		19					_____ mg _____ mg		
		20					_____ mg _____ mg		
		21					_____ mg _____ mg	c, d, e	c, d, e
									h, i
		29	Begin the next cycle on Day 29 or when starting criteria are met, whichever occurs later (for Cycles 3-5 see Section 4.5.1; for Cycle 6 see Section 4.6.1).						

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

Cycles 2-5

4.5.6 Required Observations – Cycles 2-5

a. History, physical exam with vital signs
b. Height, weight, BSA
c. CBC with differential and platelets (patients who experience Grade 4 neutropenia or thrombocytopenia should have CBCs checked at least twice per week until recovery to Grade 3)
d. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus
e. ALT, AST, total bilirubin, albumin*
f. Triglycerides*
g. Pregnancy test (obtain for females of childbearing potential)
h. Tumor Imaging Evaluation: ^{123}I-MIBG or alternatively FDG-PET scan for patients with MIBG non-avid disease at diagnosis. Cross sectional tumor imaging (MRI or CT) is only required after Cycle 3 for patients with residual soft tissue disease detected at the start of Post-Consolidation
i. Bilateral bone marrow aspirates and biopsies are only required after Cycle 3 for patients with detectable bone marrow involvement at the start of Post-Consolidation
j. Specimens for correlative studies. See Section 14.0 and Appendix X for details.**

*Observations may be obtained between Days 5-8 (pre-ISOtretinoin)
** Collect for Cycles 2 and 3 only.

Disease evaluations may be performed between Days 22 and 28 of Cycle 3.

This listing only includes evaluations necessary to answer the study aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

Cycles 2-5

4.5.7 Treatment Details – Cycles 2-5

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

Suggested administration schedule for chemotherapy (Days 1-5; temozolomide and irinotecan) and dinutuximab (Days 2-5):

- At hour 0: patient should receive oral temozolomide.
- At hour 1: start IV irinotecan over 90 minutes. On days the patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline (10-20 mL/kg) over 60-90 minutes.
- At hour 2.5: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.
- Note: Irinotecan must be administered at least 1 hour AFTER enteral temozolomide.

Temozolomide: PO daily (NG or G-tube administration is allowed)
Days: 1-5
Dose: For BSA ≥ 0.6 m^2, the dose for temozolomide is 100 mg/m^2/dose
MAXIMUM dose = 200 mg

For patients receiving capsule formulation, see dosing nomogram in Appendix VIII and reduced dosing nomogram in Appendix IX (if dose modification is required).

For patients receiving oral liquid formulation, round according to institutional standard.

For BSA < 0.6 m^2, please see the table below. The dose of temozolomide in the table is expressed as final dose in **mg** to be administered regardless of formulation used.

TEMOZOLOMIDE Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	15 mg
0.30-0.34	20 mg
0.35-0.39	30 mg
0.40-0.44	35 mg
0.45-0.49	40 mg
0.50-0.54	50 mg
0.55-0.59	55 mg

Note: For patients unable to tolerate enteral temozolomide, IV temozolomide may be administered. Please refer to Section 5.3 for guidance on IV temozolomide administration.

Sequencing: Enteral temozolomide must be administered at least 1 hour PRIOR to irinotecan

Cycles 2-5

Absorption is affected by food and therefore, consistency of administration with respect to food is suggested. Preferably, administer on an empty stomach (at least 1 hour before or 2 hours after food) to decrease nausea and vomiting and improve absorption. The whole dose, even if comprised of several capsule sizes, should be taken at one time at approximately the same time each day. Antiemetics are recommended 30-60 minutes prior to each dose to prevent nausea and vomiting. When using temozolomide capsules, dose according to Temozolomide Dosing Nomogram in Appendix VIII. For ease of swallowing, the capsule content may be mixed with applesauce or apple juice. An oral suspension may also be compounded by a pharmacist. If emesis occurs within 20 minutes of taking a dose of temozolomide, then the dose should be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated.

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

Special precautions: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See hyperlink to the drug monograph provided in Section 6.0 for additional details and examples.

Irinotecan: IV over 90 minutes daily
Days: 1-5
Dose: For BSA ≥ 0.6 m^2, the dose of irinotecan is 50 mg/m^2/dose.

For BSA < 0.6 m^2, please see the table below. The dose of irinotecan in the table is expressed as final dose in **mg** to be administered.

IRINOTECAN Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg

Note: Irinotecan should be administered at least 1 hour after enteral temozolomide has been given.

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

Cycles 2-5

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

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

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

Refer to Section 4.5.3 for premedication and supportive care for the prevention of anticipated toxicities associated with dinutuximab, and for monitoring during the dinutuximab infusion. Additional information can be found in Appendix XI.

Prior to dinutuximab administration (morning start recommended), administer IV bolus of normal saline (10-20 mL/kg) over 60-90 minutes. Bolus should be given concurrently with irinotecan infusion. On Day 2-5, start dinutuximab immediately following the completion of normal saline bolus and irinotecan infusion. Dinutuximab dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

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

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

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

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

Sargramostim dose will be held if the total white cell count is > 50,000/µL. This is not a toxicity of sargramostim but rather a possible outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/µL

Cycles 2-5

and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

ISOtretinoin: PO BID
Days: 8-21 **See additional starting criteria for ISOT in Section 4.5.2.**
Dose: For BSA ≥ 0.6 m^2, the dose of ISOtretinoin is 80 mg/m^2/dose BID, rounded to nearest 10 mg to accommodate capsule strength.

For BSA < 0.6 m^2, please see table below. The dose of ISOtretinoin in the table is expressed as final dose in **mg** to be administered.

NOTE: dose BID. For example, if BSA ≥ 0.6 m^2, administer 80 mg/m^2/dose BID. The total daily dose is 160 mg/m^2/day.

ISOtretinoin Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	10 mg BID
0.3-0.39	20 mg BID
0.4-0.49	30 mg BID
0.5-0.59	40 mg BID

Note: Capsules can be cut and the contents squeezed into a high fat food such as ice cream or peanut butter immediately prior to administration. Capsules can be chewed (best absorbed if chewed with high fat food) or the child taught to swallow entire capsules, which is feasible and to be encouraged. Under no circumstances should ISOtretinoin be removed from the capsules for more than 1 hour prior to administering to the patient (see hyperlink to the drug monograph provided in Section 6.0). Administration via nasogastric tube or orally via syringe is discouraged.

Missed doses of isotretinoin should **NOT** be made up during the one week break between the scheduled end of isotretinoin therapy and the start of chemotherapy in the subsequent cycle to avoid delays in therapy. A duration of one week between the scheduled end of isotretinoin (day 21) and the start of chemotherapy in the subsequent cycle should be maintained (e.g., last dose of isotretinoin is on day 21 regardless of start date or missed doses and the subsequent cycle starts on day 29 if all other criteria are met).

Note: Patients who discontinue ISOtretinoin prior to Cycle 6 must complete full disease evaluations and end of protocol therapy requirements (Section 7.1) within two weeks of the end of Cycle 5.

See Section 5.0 for Dose Modifications based on Toxicities.

Cycles 2-5

4.6 Cycle 6

4.6.1 Criteria to Start ISOtretinoin – Cycle 6

- ALT < 10 x ULN for age. For the purposes of this study, ULN for ALT is 45 U/L.
- Serum triglycerides < 500 mg/dL.
- A serum creatinine based on age/gender a described in Section 3.2.6.2.

Note: Observations may be obtained within 4 days prior to start of ISOtretinoin (i.e., Days 5-8 of protocol therapy).

As per Section 5.2.8 *Management of Concurrent Transplant Associated-Thrombotic Microangiopathy (TA-TMA)*, ISOtretinoin may be dose-reduced or omitted per institutional practice in patients with TA-TMA.

Cycle 6

4.6.2 Therapy Delivery Map – Cycle 6

Cycle 6 lasts 4 weeks (28 days) in length.	_____ Patient COG ID number _____ DOB

Start Cycle 6 once criteria in Section 4.6.1 have been met. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
ISOtretinoin (ISOT)	PO	BSA ≥ 0.6 m^2: 80 mg/m^2/dose BID BSA < 0.6 m^2: See Dosing Table in 4.6.4	8 - 21	BID dosing. See additional starting criteria for ISOT in Section 4.6.4. Round doses to nearest 10 mg to accommodate capsule strength.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	ISOT _____ mg _____ mg	Studies
			Enter calculated dose above and actual dose administered below	
		1		
		2		
		3		
		4		
		5		
		6		
		7		
		8	_____ mg _____ mg	a – h
		9	_____ mg _____ mg	
		10	_____ mg _____ mg	
		11	_____ mg _____ mg	
		12	_____ mg _____ mg	
		13	_____ mg _____ mg	
		14	_____ mg _____ mg	
		15	_____ mg _____ mg	
		16	_____ mg _____ mg	
		17	_____ mg _____ mg	
		18	_____ mg _____ mg	
		19	_____ mg _____ mg	
		20	_____ mg _____ mg	
		21	_____ mg _____ mg	
		29	Upon completion of Cycle 6, protocol therapy is complete. For required observations to be obtained within 2 weeks of end of therapy, see Section 7.1.	h

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

Cycle 6

4.6.3 Required Observations – Cycle 6

a. History, physical exam with vital signs b. Height, weight, BSA c. CBC with differential and platelets (patients who experience Grade 4 neutropenia or thrombocytopenia should have CBCs checked at least twice per week until recovery to Grade 3) d. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus e. ALT, AST, total bilirubin, albumin f. Triglycerides g. Pregnancy test (obtain for females of childbearing potential) h. Correlative studies sample (see Appendix X) Day 8 observations may be obtained within 4 days prior to start of ISOtretinoin (i.e., Days 5-8 of protocol therapy).

This listing only includes evaluations necessary to answer the study aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

Cycle 6

4.6.4 Treatment Details – Cycle 6

ISOtretinoin: PO BID
Days: 8-21
Dose: For BSA ≥ 0.6 m^2, the dose of ISOtretinoin is 80 mg/m^2/dose BID, rounded to nearest 10 mg to accommodate capsule strength.

For BSA < 0.6 m^2, please see table below. The dose of ISOtretinoin in the table is expressed as final dose in **mg** to be administered.

NOTE: dose BID. For example, if BSA ≥ 0.6 m^2, administer 80 mg/m^2/dose BID. The total daily dose is 160 mg/m^2/day.

ISOtretinoin Dosing If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	10 mg BID
0.3-0.39	20 mg BID
0.4-0.49	30 mg BID
0.5-0.59	40 mg BID

Note: Capsules can be cut and the contents squeezed into a high fat food such as ice cream or peanut butter immediately prior to administration. Capsules can be chewed (best absorbed if chewed with high fat food) or the child taught to swallow entire capsules, which is feasible and to be encouraged. Under no circumstances should ISOtretinoin be removed from the capsules for more than 1 hour prior to administering to the patient (see hyperlink to the drug monograph provided in Section 6.0). Administration via nasogastric tube or orally via syringe is not encouraged.

See Section 7.1 for end of therapy evaluations to be conducted within two weeks of completion of Cycle 6.

See Section 5.0 for Dose Modifications based on Toxicities.

Cycle 6

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, in general all protocol therapy should be discontinued and the patient would be taken off protocol therapy. However, if a patient requires permanent discontinuation of isotretinoin, the patient may continue on protocol therapy and receive the other therapy components (e.g., irinotecan, temozolomide, dinutuximab, GM-CSF).

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 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 IX). If patient experiences neutropenia that causes a delay of ≥ 14 days between treatment cycles despite this dose reduction, protocol therapy must be discontinued and patient must be removed from protocol therapy.

5.1.2 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 IX). If patient experiences thrombocytopenia that causes a delay of ≥ 14 days between treatment cycles despite this dose reduction, protocol therapy must be discontinued.

5.1.3 Delayed Recovery of Platelets and Neutrophils

Patients who do not meet criteria to start the next treatment cycle (see Section 4.5.1 or Section 4.6.1) within 28 days after the planned subsequent cycle start date (i.e. there is a ≥ 4 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. Section 4.5.1 and Section 4.6.1 describe criteria to be met prior to starting subsequent cycles.

5.2.1 Dose Modifications for Diarrhea

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

- If Grade 4 therapy-associated diarrhea is experienced by a patient with no evidence of infectious etiology and despite maximal use of anti-diarrheal medications (Appendix V) and appropriate use of prophylactic antibiotics

(Section 4.2.1), the dose of irinotecan should be reduced by 25% for subsequent cycles (i.e., irinotecan dose 37.5 mg/m^2/dose for patients with BSA $\geq$ 0.6 m^2).

- If Grade 4 therapy-associated diarrhea recurs without an infectious etiology despite reducing the dose of irinotecan by 25%, the dinutuximab dose should also be decreased by 25% for subsequent cycles (i.e. dinutuximab dose 13 mg/m^2/day).
- If Grade 4 diarrhea recurs despite maximal use of anti-diarrheals, prophylactic antibiotics, and these dose reductions, the patient must come off protocol therapy.

5.2.2 Dose Modifications for Nausea and Vomiting

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

5.2.3 Dose Modifications for Dehydration

- If dehydration is related to diarrhea or nausea/vomiting, the guidance in Section 5.2.1 or Section 5.2.2 should be followed.
- If regimen-related $\geq$ Grade 3 dehydration persists for > 3 days in the absence of significant diarrhea or nausea/vomiting, doses of irinotecan and temozolomide should both be reduced by 25% for subsequent cycles (i.e. irinotecan dose is 37.5 mg/m^2 for patients with BSA $\geq$ 0.6 m^2; for temozolomide see dose reduction nomogram in Appendix IX).
- If $\geq$ Grade 3 regimen-related dehydration recurs and persists for > 3 days despite the dose reduction, the patient must come off protocol therapy.

5.2.4 Dose Modifications for Elevations in ALT, AST, or GGT

- If elevations in ALT, AST or GGT occur such that values are > 20x ULN for any duration of time OR > 10x ULN but < 20x ULN and persisting for > 7 days, the dose of dinutuximab should be reduced by 25% for subsequent cycles (i.e. dinutuximab dose 13 mg/m^2/day). 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 in dinutuximab, the dose of temozolomide should be reduced by 25% for subsequent cycles (i.e. for temozolomide see dose reduction nomogram in Appendix IX). If the dose limiting elevations of the same liver enzyme(s) recur despite the temozolomide dose reduction, the patient must come off protocol therapy.
- An elevation in ALT that causes a delay of $\geq$ 14 days between treatment cycles will also require a 25% reduction in the dose of dinutuximab for all subsequent

cycles (i.e. dinutuximab dose 13 mg/m^2/day). 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.

- For hepatic function parameters to begin isotretinoin during each cycle, please refer to treatment guidelines (Cycle 1 see Section 4.4.2; Cycles 2-5 see Section 4.5.2; Cycle 6 see Section 4.6.1). Refer to Section 5.2.7 for isotretinoin-specific dose modifications if hepatic function abnormalities are attributed to isotretinoin.

5.2.5 Dinutuximab Specific Dose Modifications and Toxicity Management Recommendations

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

a. If hypotension is severe and accompanied by poor perfusion, end organ dysfunction, or acidemia – Pediatric Advanced Life Support (PALS) guidelines should be followed and dinutuximab infusion should be discontinued.

b. Treatment of **moderate hypotension** (without poor perfusion, end organ dysfunction or acidemia):

i. Immediately hold dinutuximab
ii. Give normal saline bolus (20 mL/kg as rapidly as possible)
iii. Stop or adjust doses of narcotics and sedating H1 blockers
iv. Consider use of Trendelenberg position

If hypotension persists after the above measures have been taken:

v. Reassess perfusion and end organ function
vi. Follow PALS algorithm if indicated
vii. Repeat NS bolus OR
viii. Consider use of albumin if albumin < 3 gm/dL
ix. Consider use of PRBCs if Hb < 8 gm/dL
x. Consider use of platelets if count <50,000/µL
xi. Consider transfer to the intensive care setting

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

Note: Moderate Hypotension is defined as:

i. Symptomatic decreases in blood pressure (BP) and/or
ii. Systolic BP < 5th percentile based on age and height and baseline BPs OR
iii. Systolic or diastolic BP decreased by > 20% below baseline

c. Resumption of dinutuximab

i. For patients whose hypotension resolves promptly and completely with limited volume resuscitation (≤ 40 mL/kg) and without requirement for pressor support, dinutuximab may be restarted at 50% of the previous infusion rate.

Restart on the same day within 20 hours of the start of the day's infusion, if possible. If blood pressures are stable for 2 hours, the infusion may be given at full rate for the remainder of that day and subsequent days. If the patient again experiences hypotension requiring multiple volume boluses (e.g., > 40 mL/kg) when dinutuximab is given at full rate, but the patient tolerates the 50% infusion rate, then the remaining dinutuximab dose for that day and subsequent days should be given at 50% rate of the initial infusion rate. Do not continue an infusion for >20 hours. If the patient's hypotension has resolved, a newly formulated dose should be started on the calendar day following the day on which the patient experienced the hypotensive reaction, with the dose given at 50% of the initial infusion rate.

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

ii. For patients who require multiple volume boluses for hemodynamic stabilization, dinutuximab should be resumed the following day at 50% of the initial infusion rate.

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

remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

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

5.2.5.2 Treatment of allergic reactions/infusion reactions

a. Mild allergic reactions/infusion reactions to dinutuximab infusion

i. A mild allergic reaction is limited to rash, flushing, urticaria, mild dyspnea – Grade 1 or 2

ii. The following recommendations do NOT apply to Grade 3 or 4 allergic reactions, including anaphylaxis

iii. Management

- Decrease rate of dinutuximab to 50% of full rate
- Perform serial exams at bedside
- Administer H1 blocker (diphenhydramine, cetirizine recommended)
- Administer H2 blocker
- When symptoms resolve, resume original infusion rate
- If symptoms recur when original rate is resumed, decrease to 50% rate again
- Infusion must be stopped after 20 hours (whether the full dose of dinutuximab has been administered or not); document total amount of drug given in the 20 hour time period.

b. Moderate to severe allergic reactions/infusion reactions to dinutuximab infusion

i. Moderate to severe reactions include any of the following: symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, or anaphylaxis – Grade 3 or 4

ii. The following recommendations do NOT apply to Grade 1 or 2 allergic reactions

iii. Management

- **Immediately hold dinutuximab**
- Assess airway, breathing and circulation
- Follow institutional guidelines for rapid response team notification if clinically indicated
- For airway concerns

- Administer oxygen and albuterol immediately for bronchospasm
- Administer IV diphenhydramine
- Administer epinephrine (1:1000 IM recommended) immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
- Administer IV hydrocortisone (1-2 mg/kg) if the patient has frank anaphylaxis with cardiorespiratory collapse OR if ≥ 2 doses of epinephrine are required OR if moderate to severe symptoms recur upon rechallenge with dinutuximab

- For hypotension in the setting of allergic reaction
  - Give normal saline bolus (20 mL/kg as rapidly as possible)
  - Stop or adjust doses of narcotics and sedating H1 blockers
  - Consider use of Trendelenberg position
  - See previous section for management of persistent hypotension
- For patients with mild bronchospasm or angioedema that does not impact breathing, completely resolves without the use of epinephrine and hydrocortisone and for patients whose hypotension resolves following volume bolus, dinutuximab may be resumed at 50% of the previous rate of infusion on the same day as the reaction occurred. If symptomatic angioedema or asymptomatic bronchospasm recurs when the dinutuximab is restarted, discontinue immunotherapy for that day and if symptoms/signs resolve completely that day, resume the next day with additional pre-medication of hydrocortisone 1-2 mg/kg IV. For this re-challenge, the infusion should be given in an ICU setting.
- For patients whose bronchospasm or angioedema requires the use of systemic epinephrine, protocol therapy must be discontinued.
- For patients with bronchospasm or angioedema that does not require systemic epinephrine but whose hypotension requires more extensive volume resuscitation, guidance in Section 5.2.5.1 should be followed.

5.2.5.3 Management of capillary leak syndrome (≥ Grade 3)

- Hold dinutuximab infusion
- Provide oxygen, fluids as needed
- Diuretics should be used with caution and hypotension avoided
- **See Section 5.2.5.1 for management of hypotension, anemia and hypoalbuminemia.**

- Do NOT resume dinutuximab therapy if symptoms of severe capillary leak syndrome persist on the same day or subsequent days of a given cycle. Only resume dinutuximab therapy when the capillary leak syndrome resolves or requires less significant intervention (Grade 2 or less).
- If capillary leak resolves, may resume dinutuximab infusion at 50% rate the same day and for subsequent doses during a given cycle. The infusion may be given at the full rate at the start of subsequent cycles.
- If mechanical ventilation (any duration) or pressor support for ≥ 24 hours is required due to therapy-related capillary leak syndrome, the patient must discontinue protocol therapy.

5.2.5.4 Management of renal insufficiency (unrelated to hypotension)

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

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

- Change hypotonic fluids to isotonic fluids as compatibilities permit
- Avoid administration of oral free water
- Correct fluid losses due to diarrhea
- 3% saline is only indicated in the following settings:
  - hyponatremia leading to seizure
  - drop in sodium level > 10 points in 6 hours or less
  - sodium level < 117 mEq/L
- If Grade 4 hyponatremia persists despite optimal fluid management, discontinue dinutuximab for the remainder of the cycle. Sodium should be monitored closely during the next cycle of therapy. If hyponatremia improves to Grade 2 or better, or baseline, empiric dose reduction is not required at the start of the next cycle of therapy, though dinutuximab would again be discontinued if Grade 4 hyponatremia were to persist despite optimal fluid management. In such cases, patient must discontinue protocol therapy.

5.2.5.6 Management of fever in the absence of hypotension

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

5.2.5.7 Management of treatment-related pain

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

5.2.5.8 Management of visual changes

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

5.2.5.9 Management of serum sickness

- Identification of serum sickness – signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy, glomerulonephritis in the presence of persistent fevers, cutaneous eruptions.
- Serum sickness typically develops 1 to 3 weeks after administration of the causative agent, but can develop within 12-36 hours in patients who have previously been sensitized to the causative agent.
- Patients with ≥ Grade 3 serum sickness must discontinue protocol therapy.
- For Grade 2 serum sickness, antihistamines should be prescribed.

5.2.5.10 Management of neurotoxicity

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

5.2.6 Management of Sargramostim Related Toxicities

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

5.2.7 Isotretinoin Specific Dose Modifications

If criteria to begin a 14-day course of isotretinoin are not met by the date the therapy is due to begin, delay therapy for one week. If criteria are still not met, hold therapy until criteria are met. If an observed toxicity is possibly, probably or definitely due to isotretinoin, reduce the isotretinoin dose to 125 mg/m^2/day divided BID for patients with BSA ≥ 0.6 m^2 (for patients < 0.6 m^2 BSA see suggested Dose Reduction 1 in the table below). An additional dose reduction to 100 mg/m^2/day divided BID for patients with BSA ≥ 0.6 m^2 (for patients < 0.6 m^2 BSA see suggested Dose Reduction 2 in the table below) should occur if criteria are still not met one week after the due date for subsequent cycles and the toxicity is possibly, probably or definitely due to isotretinoin.

Note: If there is a delay in beginning isotretinoin, patients need to maintain at least one week off isotretinoin before starting the next cycle of protocol therapy). Missed doses of isotretinoin should **NOT** be made up during the one week break between the scheduled end of isotretinoin therapy and the start of chemotherapy in the subsequent cycle to avoid delays in therapy.

SUGGESTED ISOTRETINOIN DOSE REDUCTION		
BSA (m^2)	Dose Reduction 1	Dose Reduction 2
0.25-0.29	10 mg PO BID x 4 days/wk and 10 mg PO once daily x 3 days/wk	10 mg PO daily x 6 days/wk and 10 mg PO BID x 1 day/wk
0.3-0.39	20 mg PO BID x 4 days/wk and 10 mg PO BID x 3 days/wk	10 mg PO BID x 6 days/wk and 20 mg PO BID x 1 day/wk
0.4-0.49	20 mg PO BID x 5 days/wk and 30 mg PO BID x 2 days/wk	20 mg PO BID x 5 days/wk, 10 mg PO BID x 2 days/wk
0.5-0.59	30 mg PO BID	20 mg PO BID

Decrease isotretinoin dose to 125 mg/m^2/day (see suggested Dose Reduction 1 in the table above for patients with BSA < 0.6 m^2 or reduce dose by ~25%) for subsequent cycles for the occurrence of any Grade 3 or 4 toxicities possibly, probably, or definitely attributable to isotretinoin EXCLUDING:

- Grade 3 or 4 hematologic toxicities
- Grade 3 hepatic toxicity
- Grade 3 nausea and vomiting
- Grade 3 fever

If the same Grade 3 or 4 toxicity recurs at 125 mg/m^2/day, decrease dose to 100 mg/m^2/day (see suggested Dose Reduction 2 in the table above for patients with BSA < 0.6 m^2 or reduce dose by ~25%). If the same toxicity recurs at 100 mg/m^2/day (Dose Reduction 2), discontinue isotretinoin. Patients can continue to receive protocol therapy with irinotecan, temozolomide, dinutuximab, and GM-CSF, and isotretinoin will be omitted from the remaining cycles of protocol therapy.

If serum creatinine at the time of the planned start of isotretinoin during Cycles 2-6 is > 2x baseline value documented at the start of Post-Consolidation therapy, a creatinine clearance (or nuclear medicine GFR) should be done prior to starting isotretinoin. If the creatinine clearance and/or GFR are < 50 mL/min/1.73 m^2, decrease the isotretinoin dose by 50%, and monitor serum creatinine twice per week. If the patient develops worsening hematuria, and/or proteinuria, hypertension, and/or a further increase in creatinine, hold isotretinoin until these parameters return to baseline levels.

If the patient develops > Grade 1 hematuria, > Grade 1 proteinuria, and/or > Grade 1 hypertension during any cycle of therapy, hold isotretinoin until these symptoms resolve or return to baseline. Please refer to Section 5.2.8 for isotretinoin administration in the setting of TA-TMA.

For localized cheilitis, topical agents (e.g., Vitamin E) may be applied to lips for subsequent cycles. If this does not control symptoms sufficiently to allow oral intake, decrease the isotretinoin dose to 125 mg/m^2/day for patients with BSA

≥ 0.6 m^2 (for patients < 0.6 m^2 BSA see suggested Dose Reduction 1 in the table above or reduce dose by ~25%).

If fasting serum triglycerides are > 500 mg/dL when isotretinoin is due to begin, hold isotretinoin and repeat fasting triglyceride level. If triglycerides remain > 500 mg/dL, start medical therapy for serum triglyceride reduction and begin isotretinoin (full dose) when triglycerides are ≤ 500 mg/dL. If triglycerides are still > 500 mg/dL by the time the next cycle of isotretinoin is due, then reduce dose to 125 mg/m^2/day for patients with BSA ≥ 0.6 m^2 (for patients < 0.6 m^2 BSA see suggested Dose Reduction 1 in the table above or reduce dose by ~25%) for subsequent cycles.

Isotretinoin has been associated with pseudotumor cerebri. This drug should be discontinued in patients who are found to have papilledema.

5.2.8 Management of Concurrent Transplant Associated-Thrombotic Microangiopathy (TA-TMA)

Isotretinoin may be dose-reduced or omitted per institutional practice in patients with TA-TMA.

5.2.9 Other Non-Hematologic Toxicities

The above sections cover dose modifications for most anticipated adverse events with this regimen. For Grade 3 or higher non-hematologic toxicities not specified above or for non-hematologic toxicities not specified above that prolong the start of subsequent cycles by ≥ 14 days, the doses of both irinotecan and temozolomide should be reduced by 25% in the subsequent cycle. If Grade 3 or higher non-hematologic toxicity recurs or cycles are again delayed by ≥ 14 days, the patient should be removed from protocol therapy.

5.2.10 Prolonged Non-Hematologic Toxicity

Patients who do not meet criteria to start the next treatment cycle (see Section 4.5.1 or Section 4.6.1) within 28 days after the planned subsequent cycle start date (i.e. there is a ≥ 4 week delay in start of next cycle) due to any ongoing non-hematologic toxicity must be removed from protocol therapy.

5.3 Inability to Tolerate Enteral Temozolomide

For patients unable to tolerate PO temozolomide (i.e., due to nausea, vomiting), IV temozolomide may be administered.

Suggested administration schedule for chemotherapy (Days 1-5; IV temozolomide and irinotecan) and dinutuximab (Days 2-5):

- At hour 0: patient should receive IV temozolomide over 90 minutes.
- At hour 1.5 patient should start IV irinotecan over 90 minutes. On days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start IVF bolus of normal saline saline (10-20 mL/kg) over 60-90 minutes.
- At hour 3: on days patient is receiving dinutuximab infusion (Days 2-5 of each cycle), start dinutuximab infusion.
- Note: Irinotecan may be administered immediately after the completion of IV temozolomide.

Temozolomide: IV over 90 minutes daily
Days: 1-5
Dose for IV infusion: IV temozolomide may be substituted at the same dose for patients unable to tolerate enteral dosage forms. The line must be flushed before and after administration.

Sequencing: IV temozolomide may be administered immediately prior to irinotecan.

Special Precautions: IV temozolomide contains polysorbate 80, which may increase the risk of infusion or allergic reactions. If reaction occurs, premedication with diphenhydramine 1 mg/kg (maximum dose 50 mg) and hydrocortisone 2 mg/kg (maximum dose 200 mg) may be considered. Re-challenging with enteral temozolomide is also an acceptable alternative as it does not contain polysorbate 80. May be administered through the same IV line as NS. Do not administer other medications through the same IV line.

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the Commercial Agent Monographs (https://www.cogmembers.org/_files/disc/pharmacy/CommercialAgentsMonographs.pdf).

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 End of Therapy & Follow-up

STUDIES TO BE OBTAINED	End of Therapy[1]	Time from End of Therapy (Months)													At Relapse
		3	6	9	12	15	18	24	30	36	42	48	54	60	
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam with VS (including BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ht, Wt, BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, differential, platelets	X	X	X	X	X		X	X		X		X		X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X	X	X	X		X	X		X		X		X	
Creatinine, ALT, bilirubin	X	X	X	X	X		X	X		X		X		X	
ECHO	X				X			X		X		X		X	
Cross sectional imaging of primary tumor site (MRI or CT)	X		X		X		X	X		X					X
^{123}I-MIBG scan[2]	X	X	X		X		X	X		X					X
FDG-PET scan[2]	X	X	X		X		X	X		X					X
Bilateral bone marrow aspirates and biopsies	X														X
Biologic correlative studies (see Section 14.0 & Appendix X)	X														X

[1]Obtain within 2 weeks of completing Cycle 6, or Cycle 5 for patients that discontinue isotretinoin.
[2]FDG-PET only in patients with MIBG non-avid disease at diagnosis who are followed by FDG-PET in place of ^{123}I-MIBG scan.

Note: If enrolled in APEC14B1/ANBL00B1 and consented to optional cell banking, submit PB and BM specimens if relapse occurs.

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.

7.2 Research Studies for which Patient Participation is Optional

See Section 14.0 for Special Studies requirements. Required studies are detailed in Section 14.1 and optional studies are detailed in Section 14.2.

A summary of specimens to be collected is provided in Appendix X. Every effort should be made to obtain samples from all time points, including the pre-therapy time point. However, if the pre-ANBL19P1 therapy sample cannot be obtained, subsequent samples should still be collected as specified.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Completion of planned therapy.
d) Physician determines it is in patient's best interest.
e) Unacceptable toxicity due to protocol therapy or delays in therapy that meet the criteria in Section 5.0.
f) Development of a second malignancy.
g) Repeat eligibility studies (if required) prior to the initiation of protocol therapy are outside the parameters required for eligibility (see Section 3.2).
h) Pregnancy

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

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG anti-cancer therapeutic study (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) Fifth anniversary of the date the patient was enrolled on this study.
f) Patient never received protocol therapy.

9.0 STATISTICAL CONSIDERATIONS

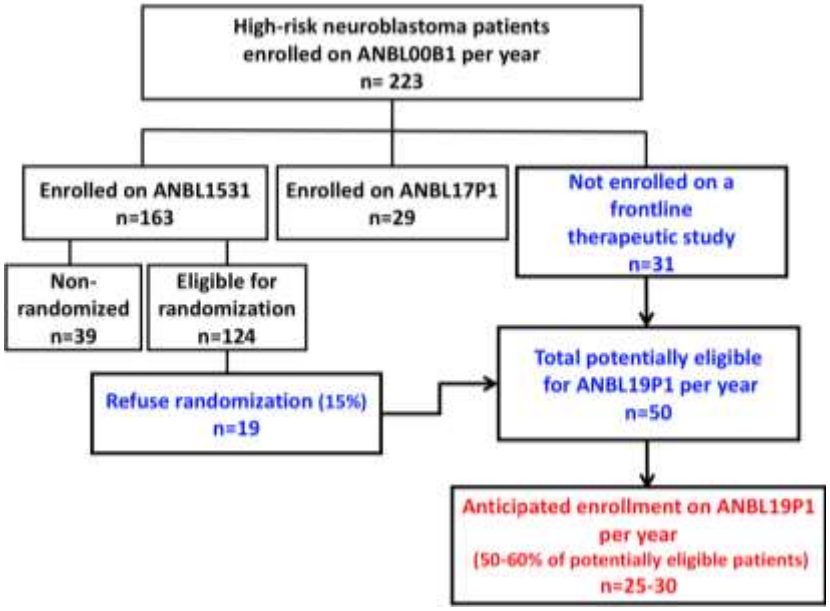
9.1 Sample Size and Study Duration

Forty eligible and evaluable patients will be necessary to analyze the primary objective, assessing the feasibility of dinutuximab, GM-CSF, and isotretinoin administration in combination with irinotecan and temozolomide during Post-Consolidation for patients with prior tandem ASCT. Enrollment of up to 45 patients will be required in order to generate the 40 eligible and evaluable patients that will be analyzed for the feasibility primary objective, accounting for potential ineligible patients. With 40 eligible and evaluable patients with prior tandem ASCT, the estimate of feasibility will have a standard error of at most 0.0791.

Approximately 223 patients/year enrolled on ANBL00B1 have high-risk neuroblastoma. Estimated accrual on high-risk neuroblastoma frontline therapeutic trials ANBL1531 and ANBL17P1 is 163 patients/year and 29 patients/year, respectively. Therefore, approximately 31 patients/year with high-risk neuroblastoma will not enroll on a frontline therapeutic trial and will be potentially eligible for the proposed study (Figure 1). Of the patients enrolled on ANBL1531 (163 patients/year), 124 patients/year are expected to be eligible for randomization and, if they proceed with randomization, will not be eligible for this study. Patients assigned to a treatment arm and not eligible for randomization (i.e., patients with MIBG non-avid disease [Arm D] or tumors demonstrating an ALK aberration [Arm E]) will also not be eligible for our pilot study. We predict that 15% of those eligible for randomization on ANBL1531 will refuse randomization and will be eligible for the proposed study (19 patients/year). Therefore, we anticipate that approximately 50 patients/year will be potentially eligible to enroll on ANBL19P1. If we assume 50-60% of the potentially eligible patients choose to enroll on this study and meet eligibility criteria, our expected accrual is 25-30 patients/year.

We estimate an accrual duration of approximately 1.5-2 years and an additional 6 months for completion of therapy and feasibility evaluation, for a total study duration of approximately 2.5 years.

Figure 1. Accrual Diagram



9.2 Study Design

This trial is a prospective, single arm pilot study to assess the feasibility of administering dinutuximab in combination with irinotecan, temozolomide, and GM-CSF in the frontline, Post-Consolidation setting in patients with high-risk neuroblastoma who have received prior tandem transplant. All patients will receive the same treatment on this trial. A stopping rule for feasibility will be used to monitor patients for early indication of inability to successfully administer all intended cycles of therapy. In addition, patients will be monitored for the occurrence of excessive toxicities.

9.3 Methods of Analysis

9.3.1 Primary Endpoint

The primary objective of the study is to determine the feasibility of administering 5 cycles of dinutuximab + GM-CSF and isotretinoin in combination with chemotherapy (irinotecan and temozolomide) in patients with high-risk neuroblastoma in the front-line setting following Consolidation with tandem transplant. In the absence of treatment delays, each cycle of dinutuximab-containing therapy will be completed in approximately 4 weeks, and there are 5 cycles of dinutuximab/chemotherapy-containing therapy included on this trial. Patients with disease progression detected at any time during protocol therapy or who meet pre-specified toxicity criteria will discontinue protocol-specified treatment and count against the feasibility of protocol therapy. The primary endpoint is the proportion of patients who complete 5 cycles of dinutuximab + chemotherapy without progressive disease within 30 weeks from the date of first treatment among patients who start protocol therapy.

Of the 108 patients randomized to tandem transplant on ANBL0532 that enrolled on ANBL0032 after randomization was halted, 87 (80.6%) completed at least 5 cycles of dinutuximab without progressive disease within 30 weeks. A feasibility therapy completion rate of 75% will be targeted on this study. With a sample size of 40 eligible and evaluable patients, at the 5% significance level, there will be

80% and 90% power, respectively, to detect a reduction in the therapy completion rate from target of 75% to 55.0% and 51.5%. This therapy will be declared feasible if a 95% Wilson confidence interval (CI) placed on the percentage of patients that complete at least 5 cycles of dinutuximab + chemotherapy without PD within 30 weeks contains 75% and the interim monitoring rules for feasibility and excessive toxicity (see Section 9.3.3) are not triggered. Using the closed-form formula for a 95% Wilson CI and resolving, the probability of this CI covering the value 75% when the true feasibility therapy completion rate is 50% or 60% is 0.0769 and 0.4402, respectively.

Patients who have dose modifications but remain on therapy and are able to complete the 5 cycles without PD within 30 weeks will not count against feasibility. Patients who meet off protocol criteria due to toxicity (i.e., require greater than one dose modification for irinotecan or temozolomide, or meet off protocol criteria for dinutuximab per Section 5.0) or other criteria for removal from protocol therapy (see Section 8.1) before completion of 5 cycles will count against feasibility. Any eligible patient with prior tandem ASCT who receives at least one dose of protocol therapy will be considered evaluable for the primary endpoint.

Note: Discontinuation of isotretinoin will not count against the feasibility endpoint on this study.

9.3.2 Secondary Endpoints

For event-free survival, time to event will be calculated from the time of start of protocol therapy to the occurrence of disease relapse or progression, secondary malignancy, or death. For overall survival, death will be the only event considered and time to death will be calculated from the time of start of protocol therapy. Patients without an event or death will be censored at the time of last follow-up.

9.3.3 Monitoring

Any eligible patient who receives at least one dose of protocol therapy will be considered evaluable for the monitoring rules. The study will not be halted while the data are gathered for the assessment of the monitoring rules.

9.3.3.1 Feasibility

We will monitor for early indication of inability to administer all 5 intended cycles of dinutuximab + chemotherapy without PD within 30 weeks. Of the 108 patients randomized to tandem transplant on ANBL0532 that enrolled on ANBL0032 after randomization was halted, 89 (82.4%) completed at least 3 cycles of dinutuximab without progressive disease within 18 weeks. This feasibility monitoring rule will monitor that ≥75% of patients will complete at least 3 cycles of dinutuximab + chemotherapy without PD within 18 weeks among patients who start protocol therapy. Patients who have dose modifications but remain on therapy and are able to complete the cycles without PD within the specified time frame above will not count against the feasibility monitoring rule.

A one-sided Pocock group-sequential boundary with a sample size of 40 will be used to monitor the number of patients that fail to receive at least 3 cycles of chemo-immunotherapy without progressive disease within

18 weeks. Interim monitoring will be done after 1/4 and 1/2 of patients have been evaluated for completion of at least 3 cycles of protocol therapy without PD (Table 3). The upper bound on the number of patients not receiving at least 3 cycles of protocol therapy without PD within 18 weeks that are needed to declare the therapy not feasible uses a cumulative alpha level of 0.125. The probability of declaring the regimen not feasible under the alternative hypothesis non-completion rates of 45% and 50% appears in Table 4. The average sample size when the non-completion rate is 25%, 45%, and 50% is 38.00, 25.32, and 20.86, respectively.

Table 3. Interim monitoring plan and number of observed patients that do not complete at least 3 cycles of chemo-immunotherapy without PD within 18 weeks needed to declare therapy not feasible.

Monitoring percent of total information	Number of patients evaluated for therapy completion	Monitoring boundary	Number of observed non-completions to declare not feasible
25%	10	1.6989 (p=0.04467)	≥ 6 (60%)
50%	20	1.6276 (p=0.05180)	≥ 9 (45%)

Table 4. Probability of detecting regimen not feasible under various alternative hypothesis therapy non-completion rates.

Monitoring percent of total information	Number of patients evaluated for therapy completion	Power under a true non-completion rate of 45%	Power under a true non-completion rate of 50%
25%	10	0.2616	0.3770
50%	20	0.5857	0.7483

9.3.3.2 Excessive Toxicity

Many of the toxicities that occur due to the therapy are expected. However, we plan to consider a subset of the toxicities unacceptable. Those designated as unacceptable are listed below with the associated CTCAE v5.0 MedDRA code in parentheses:

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

2. Toxicity requiring ventilatory support ≥ 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 cycle of therapy (10034580).

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

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

6. Toxic death.

7. Grade 4 documented infection [(infections and infestations-other, specify); 10021881].

8. Grade 4 diarrhea (10012727) that persists despite supportive care as detailed in Section 4.2.1 and Appendix V.

The unacceptable toxicities parallel those listed in ANBL1221 (#1-6) with the addition of documented infection (#7), as this regimen is given in the immediate Post-Consolidation setting, and diarrhea (#8) since irinotecan is included in this Post-Consolidation regimen.

There may be cause to stop the trial early if the unacceptable toxicity rate appears too high. An unacceptable toxicity rate statistically significantly >10% would be considered excessive on this trial. Of the 104 patients treated on ANBL0931 (Cycles 1, 3, 5- dinutuximab + GM-CSF + isotretinoin), the cumulative unacceptable toxicity rate for Grade ≥4 infection (n=3) and diarrhea (n=0) was 2.9%. Among patients who received irinotecan, temozolomide and dinutuximab on ANBL1221, one had an unacceptable toxicity (Grade 4 hypoxia possibly related to therapy).

A patient will be counted as having experienced an unacceptable toxicity if at least one of the unacceptable toxicities listed above occurs during protocol therapy. Only toxicities designated as possibly, probably, or definitely attributed to dinutuximab, chemotherapy, or isotretinoin will be considered.

A one-sided Pocock group-sequential boundary with a sample size of 40 will be used to monitor the number of patients who experience at least one unacceptable toxicity. Interim monitoring will be done after 1/4 and 1/2 of patients have been evaluated for the occurrence of unacceptable toxicity, with a final analysis at full information (Table 5). The upper bound on the number of unacceptable toxicity events needed to declare the therapy too toxic uses a cumulative alpha level of 0.155.

Table 5. Interim monitoring plan and number of observed unacceptable toxicities needed to declare therapy too toxic.

Monitoring percent of total information	Number of patients evaluated for toxicity	Monitoring boundary	Number of observed unacceptable toxicities to declare too toxic
25%	10	1.5947 (p=0.05539)	≥ 4 (40%)
50%	20	1.5072 (p=0.06588)	≥ 5 (25%)
100% (final analysis)	40	1.2752 (p=0.10112)	≥ 7 (17.5%)

After the first 5 patients have completed at least one cycle of protocol therapy, the study committee will prepare an early safety-briefing document for review by the DSMC and CTEP. The document will include a tabulation of Grade ≥3 non-hematologic toxicities, specifically targeting hematologic and gastrointestinal toxicities. Time to recovery from the first cycle of therapy will be documented as part of this initial safety evaluation. During preparation of this safety-briefing document, enrollment on the study will continue.

9.3.4 Assessment of Study Objectives

The primary study objective (Aim 1.1.1) related to feasibility will be assessed by estimation of the feasibility therapy completion rate together with a 95% Wilson CI. The therapy will be deemed feasible if the 95% CI placed on the percentage of patients that complete at least 5 cycles of dinutuximab + chemotherapy without PD within 30 weeks contains 75% and the interim monitoring rules for feasibility and excessive toxicity (Section 9.3.3) are not triggered.

To address Secondary Aim 1.2.1, adverse events (Grade ≥3) experienced by patients evaluable for toxicity will be descriptively summarized.

To assess Secondary Aim 1.2.2, EFS and OS Kaplan-Meier curves and estimates will be generated.

Exploratory Aim 1.3.1 will be assessed by a descriptive comparison of adverse events (Grade ≥3) experienced by patients evaluable for toxicity according to prior anti-GD2 directed therapy (yes vs. no) status.

To address Exploratory Aim 1.3.2, response will be assessed by the revised INRC[28] and descriptively summarized among those evaluable for response (see Section 9.4).

To address Exploratory Aim 1.3.3, immune and cytokine profiles will be described at baseline and the change in immune and cytokine profiles from baseline will be descriptively summarized. There will be a descriptive comparison of the immune and cytokine profiles of those receiving chemo-immunotherapy on this pilot in the frontline setting and those receiving chemo-immunotherapy (Arm A) in the relapsed/refractory setting on ANBL1821. There will also be a descriptive comparison of immune profiles at the start and end of Post-Consolidation therapy between those who receive chemo-immunotherapy on this pilot versus standard immunotherapy on ANBL1531 (Arm A) to assess the impact of these regimens on immune reconstitution.

9.4 Evaluability for Response

All eligible patients with evaluable or measurable disease at study entry and received at least one dose of irinotecan or temozolomide will be considered evaluable for response.

9.5 Evaluability for Toxicity

All eligible patients treated with at least one dose of irinotecan or temozolomide will be considered evaluable for toxicity.

9.6 Evaluability of No Treatment

If an eligible patient is "off protocol therapy" prior to treatment initiation, that patient remains eligible for the trial but will be inevaluable for feasibility and toxicity assessments.

9.7 Gender and Minority Accrual Estimates

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

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian / Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	4	0	0	6
White	11	15	3	2	31
More Than One Race	0	0	0	0	0
Total	**13**	**20**	**3**	**2**	**38**

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian / Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	3	4	0	0	7
More Than One Race	0	0	0	0	0
Total	**3**	**4**	**0**	**0**	**7**

This distribution was derived from ANBL0532.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

Note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria

This study will use the revised International Neuroblastoma Response Criteria for disease assessment.[28] The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do **not** include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

10.2.1 Definitions

Evaluable for response: All eligible patients with evaluable or measurable disease at study entry and received at least one dose of irintoecan or temozolomide will be considered evaluable for response.

Evaluable for toxicity: All eligible patients treated with at least one dose of irinotecan or temozolomide will be considered evaluable for toxicity.

10.2.2 Key Sites and Terms

10.2.2.1 **Primary site**: The primary site will be identified as a measurable lesion ≥ 10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation.[29] In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

Tracer avidity (^{123}I-MIBG or FDG-PET) in the primary site will be recorded at baseline. The scan appropriate for serial disease assessments should be used at each disease re-evaluation time point (e.g., ^{123}I-MIBG avid primary lesions should be followed using ^{123}I-MIBG scans during therapy).

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

For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases.

10.2.2.3 **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, and ascites, pleural/pericardial effusions are considered non-measurable.

10.2.2.4 **Bone lesions**: Osteomedullary disease will be assessed using ^{123}I-MIBG scans or FDG-PET scans. Technitium bone scans are no longer used as part of the revised INRC and are not included as part of disease

reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system (see Appendix XII for worksheet). SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

10.2.2.5 **Bone marrow disease**: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment time points. The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[30] The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

10.2.3 Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

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

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

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES[4]

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

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

Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following:
	  • Non-target lesions may be stable or smaller in size AND
	  • No new lesions AND
	  • ≥ 50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥ 0.1 to ≤ 0.5 using as reference the absolute score for bone lesions from time of enrollment[5]) or ≥ 50% reduction in number of FDG-PET avid bone lesions[3,4]

Progressive Disease (PD)	Any of the following: • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma; • Any bone site that is MIBG avid and that was not seen on the immediate prior scan or on the scan performed at the time of enrollment; • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma; • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions; • Relative MIBG score ≥ 1.2 using as reference the lowest absolute score for bone lesions since enrollment.[6]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions

[1] Used for MIBG non-avid tumors

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

[3] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[4]Criteria for soft tissue metastasis not applicable if the patient has only bone metastasis; criteria for bone metastasis not applicable if the patient has only soft tissue metastasis.

[5]Relative Curie score when assessing patient for partial response: [Current Curie score for bone sites] / [Curie score for bone sites at enrollment].
[6]Relative Curie score when assessing patient for progressive disease: [Current Curie score for bone sites] / [Lowest Curie score for bone sites since enrollment].

BONE MARROW RESPONSE

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

[1]Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

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

NI = Not involved, site not involved at study entry and remains not involved
MD = Minimal Disease, for bone marrow assessment only
*Patients who enroll with marrow only disease who have a marrow response of Minimal Disease will also be considered to have an overall response of Stable Disease.

See Appendix XIII for additional information regarding overall response assessment

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event 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.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

11.2.1 Secondary Malignancy

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

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

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

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

11.2.2 Second Malignancy

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

11.3 Reporting of Adverse Events for Commercial Agents – via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://ctepcore.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted within 7 calendar days of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

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

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

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

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

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

11.4 Protocol Specific Additional Instructions and Reporting Exceptions

For all patients, the following events require CTEP-AERS reports and submission of the AE Case Report Form:

- Toxic Death
- Pulmonary Complications
  - Grade 4 respiratory failure requiring intubation and mechanical ventilation
  - Grade 3 or 4 ARDS requiring ventilatory support >24 hours
  - Grade 4 bronchospasm requiring ventilatory support >24 hours
  - Grade 4 dyspnea requiring ventilatory support >24 hours
  - Grade 4 hypoxia requiring ventilatory support >24 hours

- Immune
  - Grade 4 anaphylaxis/allergic reaction requiring pressors >24 hours or requiring ventilatory support >24 hours
  - Grade 4 Cytokine Release Syndrome/Acute Infusion Reaction
- Cardiovascular
  - Grade 3 or 4 hypotension requiring pressors >24 hours
  - Grade 4 capillary leak syndrome requiring pressors >24 hours
- Hepatic Complications:
  - Grade 3 and 4 liver failure
  - Grade 3 and 4 sinusoidal obstruction syndrome
- Neurologic
  - Grade 4 peripheral motor or sensory neuropathy
  - Grade 3 peripheral motor or sensory neuropathy that does not resolve prior to the next course of therapy
- Infectious
  - All Grade 4 documented infections (infections and infestations-other, specify)
- All Grade 4 diarrhea that is persistent despite supportive care detailed in protocol (Section 4.2.1, Appendix V)

11.5 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.

The NCI defines both routine and expedited AE 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, Grade 3 and higher non-hematologic Adverse Events, and Grade 4 and higher hematologic Adverse Events.

11.6 Syndrome Reporting

Unless otherwise specified in this protocol, syndromes should be reported as a single event using the CTCAE term for the composite syndrome, and not as the individual events that make up the syndrome. For example, Tumor Lysis Syndrome should be reported under the composite definition rather than reporting the component events (hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) separately.

Transplant-Associated Thrombotic Microangiopathy (TA-TMA) will be defined by (1) lactate dehydrogenase (LDH) elevated above the upper limit of normal for age; (2) de novo thrombocytopenia with a platelet count $<50 \times 10^9$/L or a ≥50% decrease in the platelet count (from post-transplant recovery baseline, discuss with transplant physician); (3) de novo anemia with a hemoglobin below the lower limit of normal or anemia requiring transfusion support; (4) microangiopathic changes defined as the presence of schistocytes in the peripheral blood or histologic evidence of microangiopathy on a tissue specimen; and (5) absence of a coagulopathy and a negative Coombs test. All laboratory criteria must occur concurrently, and criteria 1 to 4 must be documented on at least 2 consecutive tests to be classified as positive. TA-TMA will be reported as CTCAE term "blood and lymphatic system disorder – other" and will be specified as TA-TMA in the free text.

12.0 RECORDS AND REPORTING

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

12.1 Demography Monitoring

Required submission of patient demographic data to NCI for this study will be submitted automatically via OPEN.

13.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

No pathology review is planned for this study. Bone marrow aspirates and biopsies will be performed and reviewed at participating institutions.

14.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

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

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

Study prioritization:
If blood volumes approach maximum allowance per institutional standards for small children at a time point, please follow the priority list below. The list is written from highest to lowest priority. See the section numbers provided and Appendix X for sample details.

1. Required samples: Immune Phenotyping (Section 14.1.1) and Cytokine Analysis (Section 14.1.2)
2. Whole Blood Collection for Plasma (EDTA tube) (Section 14.2.1.1)
3. Whole Blood Collection (Streck Cell Free DNA tube) (Section 14.2.1.2)
4. Whole Blood Collection (PAXgene RNA tube) (Section 14.2.1.3)

14.1 Required Studies

All patients will be eligible for all required special studies on ANBL19P1.

For Australia and New Zealand sites, please do not collect or send the immune phenotyping samples as these samples should not be refrigerated or frozen and would not be viable for testing by the time they are delivered to the CCTDC at Emory University.

14.1.1 Immune Profiling: Immune Phenotyping

14.1.1.1 Specimen Schedule and Requirements

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

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)

- Cycle 1, post-completion of dinutuximab (collect a single sample between Day 5 and Day 8, pre-isotretinoin)
- Cycle 2, Day 1 (prior to initiation of Cycle 2 therapy)
- End of therapy
- Relapse/Progression

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

14.1.1.2 Specimen Processing

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

14.1.1.3 Specimen Labeling

Tubes must be labeled with:

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

14.1.1.4 Specimen Shipping

These specimens will be shipped fresh (do NOT batch) by FedEx Priority Overnight delivery directly to the Emory University Children's Clinical and Translational Discovery Core (CCTDC).

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

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

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

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

Emory University Children's Clinical and Translational Discovery Core (CCTDC)
[redacted]
Health Sciences Research Building – E264
1760 Haygood Drive
Atlanta, GA 30322

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

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

14.1.1.5 Methodology

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

Flow cytometry panel:

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

14.1.2 Immune Profiling: Cytokine Analysis

14.1.2.1 Specimen Schedule and Requirements

At each time point, collect 5 mL of peripheral blood in a sodium heparin (green top) tube and process for plasma. If patient blood volumes require reduction, can reduce to 2.5 mL.

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 1, post-completion of dinutuximab (collect a single sample between Day 5 and Day 8, pre-isotretinoin)
- Cycle 2, Day 1 (prior to initiation of Cycle 2 therapy)
- End of therapy
- Relapse/Progression

14.1.2.2 Specimen Processing

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

14.1.2.3 Specimen Labeling and Shipping

Each cryovial must be labeled with:

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

Plasma for cytokine analysis can be batched and shipped on dry ice to the Emory University Children's Clinical and Translational Discovery Core (CCTDC) after the Cycle 4, Day 1 sample is drawn and processed.

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

14.1.2.4 Methodology

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

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

Single-plex: sIL6-R

14.2 Optional Studies

14.2.1 Specimens for Biobanking

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

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

14.2.1.1 Whole Blood Collection for Plasma (EDTA tube collection) for potential future studies, such as HACA

Specimen Schedule and Requirements

At each time point, 2 mL of whole blood will be collected in an EDTA tube

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 3, Day 1 (pre-treatment)
- Cycle 6, Day 8 (pre-treatment)

Specimen Processing
Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA. Centrifuge the blood at 1200xg for 15 minutes at 4ºC (preferred) or room temperature to separate the plasma (top layer) from the red blood cells (bottom, red layer). Remove the top, straw-colored layer (plasma), evenly dispense (aliquot) the plasma into pre-labeled cryoprotective 2 mL vials (minimum of 0.25 mL into each) and cap the vials securely. Immediately freeze the vials upright in a -70ºC to -80ºC freezer. Retain frozen until ready for batch shipment.

Specimen Labeling
Tubes must be labeled with:

- The patient's COG ID number
- BPC number
- Specimen type (plasma)
- Time point (cycle number and day)
- Date collected

Tubes should be sent to the BPC frozen on dry ice in batch shipments. See Section 14.3 for shipping address and additional shipping instructions.

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

14.2.1.2 Whole Blood Collection (Streck Cell Free DNA tube collection) for future studies, such as circulating tumor (ct)DNA studies

Specimen Schedule and Requirements
Streck Cell-Free DNA BCT Tubes will be provided to sites in North America, upon request. If the patient has consented to optional banking studies, then tubes should be ordered via the BPC Kit Management system as soon as possible to allow time for tubes to be shipped. Shipments will be sent by ground transportation and shipping will take 3-5 business days.

For all time points, please refer to the instructions in Section 14.2.1.3 to order a kit containing both Streck and PAXgene tubes so that the blood can be sent in one shipment.

At each time point, 10 mL of whole blood will be collected in one tube. If blood volumes require reduction, minimum of 5 mL can be submitted. Obtain as much as feasible, not to exceed 10 mL.

Samples are requested at the following time points:

- Pre-therapy (between study enrollment and start of therapy)
- Cycle 2, Day 1 (pre-treatment)
- Cycle 3, Day 1 (pre-treatment)
- End of therapy
- Relapse/progression

Established institutional guidelines should be followed for blood collection via vascular access devices. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, venipuncture is recommended as a first choice collection method. If a Streck Cell-Free DNA BCT tube immediately follows a heparin tube in the draw order, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

For patients who do not have indwelling catheters, blood should be collected via venipuncture. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
- Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Fill tube completely.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- Store blood in Streck tube at **room temperature** until shipment.

Specimen Processing

Blood should be drawn directly into the Streck tube. The tube should be completely inverted 8-10 times after sample collection. No other on-site processing is required. Sample should be kept **at room temperature** until shipped.

Specimen Labeling and Shipment

Tubes must be labeled with:

- The patient's COG ID number
- BPC number
- Specimen type (blood)
- Time point (cycle number and day)
- Date collected

Each sample should be sent on the day the sample was obtained. Sample should be **SHIPPED AT ROOM TEMPERATURE**. Ship to the BPC using a Federal Express shipping label obtained through the BPC Kit Management application. See Section 14.3.2 for instructions on accessing the BPC Kit Management application. Blood may be

shipped on Monday through Friday for a Tuesday through Saturday delivery. Do not ship blood the day before a holiday.

14.2.1.3 Whole Blood Collection (PAXgene RNA tube collection) for potential future studies, such as gene expression/sequencing studies

Specimen Schedule and Requirements
PAXgene RNA tubes will be provided by the BPC to sites in North America. **Since all PAXgene collection timepoints correspond to a collection time point for blood in Streck Cell-Free DNA, one ambient shipper with both a Streck and a PAXgene tube will be provided for each of the collection time points below.** Please only order kits for one or two time points per patient at a time as the PAXgene tubes have a short shelf life.

To request Streck/PAXgene tube kits, please access the BPC Kit Management system (https://kits.bpc-apps.nchri.org/) and select ANBL19P1 for the protocol and **Streck Cell Free DNA/PAXgene Tubes** for the kit type.

At each time point, 2.5 mL of peripheral blood in a PAXgene RNA tube should be collected.

Samples are requested at the following time points:
- Pre-therapy (between study enrollment and start of therapy)
- Cycle 2, Day 1 (pre-treatment)
- Cycle 3, Day 1 (pre-treatment)
- End of Therapy
- Relapse/Progression

Specimen Processing
Once blood is collected in the PAXgene RNA tube, the tube should be gently inverted 8-10 times to mix. Keep the tube at room temperature until shipment.

Specimen Labeling
Tubes must be labeled with:
- The patient's COG ID number
- BPC number
- Specimen type (blood)
- Collection time point (i.e. Pretreatment, End of Induction)
- Collection date

Tubes should be sent to the BPC at room temperature in an ambient shipper. See Section 14.3 for shipping address and additional shipping instructions.

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

14.2.1.4 Future Studies with Banked Biospecimens

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

14.3 Shipping Instructions for Specimens Submitted to the Biopathology Center

14.3.1 Ambient Blood

Ship to the COG BPC using a Federal Express shipping label obtained through the BPC Kit Management application.

Streck and PAXgene tubes must be kept at room temperature both prior to and during shipment. Tubes should be shipped in an ambient shipper with a SAF-T-Temp Pak to maintain an ambient temperature. Instructions for packaging the blood are provided in the kit.

An ANBL19P1 BPC specimen transmittal form must be completed in RAVE, saved and then printed and sent with the specimens.

Blood may be shipped on Monday through Friday for a Tuesday through Saturday delivery. See Section 14.3.3 for shipping address.

14.3.2 Frozen Plasma

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

Ordering a Kit for the submission of frozen specimens:
The BPC will provide a specimen procurement kit upon request to institutions in North America for batch shipments of frozen specimens.
Kits are ordered via the BPC Kit Management application (https://kits.bpc-apps.nchri.org/).

An ANBL19P1 BPC specimen transmittal form must be completed in RAVE, saved and then printed and sent with the specimen.

Specimen Procurement Kit Instructions

1. Before specimens are placed into the specimen procurement kit, they first need to be placed in three separate layers of packaging. A set of biohazard and Tyvek diagnostic envelopes are provided in the kit for this purpose.
   a. Place the specimens in zip lock bags (**one bag per specimen type/time point**). Because specimens will be batch shipped from multiple time points, it is extremely important that all specimens be clearly labeled with the specimen type and time point.
   b. Place the zip lock bags in a biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope.

c. Place the biohazard envelope inside a Tyvek envelope. Expel as much air as possible and seal the envelope.

2. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. Place the foam lid on top to insulate the specimens during shipment.
3. Place the transmittal form(s) on top of the foam lid.
4. Close the outer lid of the specimen procurement kit and secure with filament or other durable sealing tape.
5. Sites in North American will print a shipping label via the BPC Kit Management application and attach to the top of the kit.
6. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.
7. Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355.

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

14.3.3 Shipping Address

Specimens that are designated to be shipped to the COG BPC should be shipped to the following address:

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

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

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

15.1 Cross Sectional Imaging Studies

MRI or CT will be utilized for optimum visualization of all areas of bulk tumor (primary and metastases). This imaging is required for patients with measurable disease at enrollment: (1) pre-treatment, (2) after Cycle 3 of Post-Consolidation,* (3) at the end of therapy, (4) every 6 months x 4, (5) every year x 1, and (6) at relapse.

*Cross sectional tumor imaging (MRI or CT) is only required after Cycle 3 for patients with residual soft tissue disease detected at the start of Post-Consolidation

15.1.1 MRI Scans

Typically, MRI will be performed on 1.5 T or 3 T MRI units per institutional standard. Axial and at least 1 additional plane (coronal or sagittal) of the primary tumor will be performed using at least 2 pulse sequences (T1, T2, STIR, FLAIR, in/out phase, post contrast). The radiologist performing the study will determine the appropriateness of the use of intravenous gadolinium (0.2 mL/kg). Slice thickness will be determined by patient size and region covered, but should be less than 7 mm. The smallest appropriate coil should be used. The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation.

15.1.2 CT Scans

Axial imaging of the site of the primary tumor will be performed using low-dose technique according to the ALARA (As Low As Reasonably Achievable) concept. The studies will be performed using current-generation single or multi-detector systems. CT slice thickness should be 5 mm or less. Imaging will be performed during the administration of intravenous contrast, whenever possible, generally at 2 mL/kg. The use of oral contrast will be determined by the individual radiologist performing the study, but may be helpful in abdominal imaging. Images will be reconstructed in soft tissue and edge-enhanced bone/lung and liver algorithms. Coronal and sagittal multiplanar reconstructions may be helpful. As noted in the preceding section, serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation.

MRI is superior to CT in characterizing epidural tumor extension or leptomeningeal disease, and is the preferred imaging modality in such cases (neck, chest, nonadrenal retroperitoneum) with spinal cord or canal encroachment.[31] It may also be useful in evaluating an MIBG-avid focus detected in the skeleton or soft tissues. With the exceptions noted above, the choice of MRI or CT will be left to the referring pediatric radiologist.

15.2 ^{123}I-MIBG Scintigraphy

^{123}I-MIBG scintigraphy is required for this trial and is the preferred study for assessment of osteomedullary disease. Technitium bone scans are no longer recommended. All patients will undergo a diagnostic quality ^{123}I–MIBG scan within 21 days from enrollment. For patients with MIBG avid disease, an MIBG scan is also required: (1) pre-treatment, (2) after Cycle 3 of Post-Consolidation, (3) at the end of therapy, (4) every 3 months x 2, (5) every 6 months x 3, (6) every year x1, and (7) at relapse.

Patients with MIBG non-avid disease at diagnosis are not required to undergo subsequent diagnostic MIBG scans. In such circumstances, PET scans should be substituted for MIBG scans, at the same required time points.

15.2.1 Thyroid Blockade

Potassium iodide will be administered to reduce thyroid accumulation of free radioiodine. A *recommended* regimen is 13% KI (100 mg iodide/mL) to be administered daily beginning on the day prior to radionuclide injection, and continuing daily for a total of 5 days. Dose is by weight; 1.2 mg iodine/kg (4 mg/drop).

15.2.2 ^{123}I-MIBG Scintigraphy Procedures

Dose: 5.2 MBq/kg or 0.14 mCi/kg; maximum 370MBq[32] or 10 mCi

Scintigraphy: Performed to obtain both planar and tomographic images. For planar imaging, anterior and posterior spot views from the top of the head to the distal lower extremities are obtained for 10 minutes each at approximately 24 hours after injection and may be done 48 hours after injection. A large field of view dual-head gamma camera with medium-energy collimators is preferred. A whole body planar acquisition can be performed with a suggested scan rate of 5 cm/s. Additional orthogonal spot views of the head are recommended.

SPECT imaging with ^{123}I-MIBG is recommended when available, and should be performed approximately 24 hours after injection using a single or multiheaded camera with low-energy collimator. Institutional guidelines regarding data acquisition and reconstruction should be followed. MIBG-SPECT or MIBG-SPECT/CT may be used, however the same imaging methodology should be used for all evaluations other than the post-therapy scan that follow ^{131}I-MIBG treatment.

15.3 [^{18}F]–Fluorodeoxyglucose (^{18}FDG)-PET Scintigraphy

^{18}FDG-PET scan is indicated for patients whose tumors are not ^{123}I-MIBG avid. FDG-PET is performed at the following time-points: (1) pre-treatment, (2) after Cycle 3 of Post-Consolidation, (3) at the end of therapy, (4) every 3 months x 2, (5) every 6 months x 3, (6) every year x1, and (7) at relapse.

It is recommended that the PET scan be performed following count recovery if possible in order to minimize the likelihood that augmented marrow signal is related to colony stimulating factor effect/marrow recovery.

The patient should be fasted for at least 4 hours prior to injection of FDG. Plasma glucose should be checked and, if the patient is substantially hyperglycemic, the study should be rescheduled when adequate glucose control has been established. FDG is administered

intravenously per institutional guidelines. Good hydration is required as the primary route of FDG excretion is renal. The patient should drink water or receive intravenous fluids after injection to promote urinary FDG excretion. After injection, the patient is kept at rest for 45-60 minutes and imaging is then performed. The FDG dose range for a PET/CT scan is 3.7-5.2 MBq/kg (0.1-0.14 mCi/kg) and for a PET/MR scan is 2.59 -3.7 MBq (0.07 to 0.1 mCi/kg). The patient should void his/her bladder immediately prior to imaging if he/she is continent of urine. Whole body imaging (including extremities) should be obtained using institutional techniques.

Because of the short physical half-life of 1.8 hours and the high photon energy of 511 keV, FDG imaging may follow MIBG (either I-123 or I-131) or a MUGA study on the same day. If needed, the FDG imaging may be performed on the day preceding the MUGA.

Imaging with a dedicated PET/CT or PET/MR camera is preferred, but imaging with a stand-alone PET scanner is acceptable.

The FDG-PET study is processed for display by an iterative reconstruction algorithm. FDG activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of SUV. Uptake time, glucose levels, and partial volume effects influence both methods. The SUV method is also dependent on body weight and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. Small lesions may have underestimated SUVs due to partial volume averaging effects. To calculate the SUV, a region of interest (ROI) should be carefully drawn around the area of elevated FDG uptake in the lesion to minimize partial volume effects. The SUV should be calculated as SUV_{BSA}=ROI activity concentration (nCi/cc) X BSA / injected activity (nCi). The BSA is calculated from body mass (kg) and height (cm) using an appropriate algorithm. The SUV_{BSA} for each measured lesion should be recorded and the technique for assessing SUV_{BSA} should be consistent on follow-up studies. SUV measurements are directly available on almost all PET/CT display programs using simple ROIs.

PET may be performed in combination with CT on dual modality PET/CT scanners or in combination with MRI on dual modality PET/MR scanners. Typically attenuation correction imaging (low-dose, non-contrast-enhanced CT, contrast-enhanced CT) is performed from the neck through the pelvis with the patient breathing shallow, followed by emission imaging at 3-5 minutes per bed position PET/MR simultaneous scanner or PET/MR sequential scanner attenuation correction will be performed using MR based attenuation correction techniques. Data are reconstructed as described above. Non attenuation corrected and attenuation corrected PET data should be submitted for both PET/CT and PET/MR. For PET/CT, CT images should be submitted. For PET/MR, 3D T1 and axial T2 images should be submitted. Coronal fluid sensitive sequences can also be submitted if acquired.

15.4 Tumor Measurement

Tumors will be measured according to the COG Radiology Group guidelines. Diameter of a “measurable mass” must be at least twice the reconstructed slice thickness. Target lesions at baseline must be greater than 1 cm. When multiple or metastatic masses are present, all

masses will be described, and up to 5 target masses will be measured using the same method in subsequent follow-ups. See response evaluation section for information regarding measurement of soft tissue masses in accordance with revised INRC criteria (Section 10.2).

15.5 Curie Scoring

Curie scoring (Appendix XII) will be mandated for all patients at each time point that an MIBG scan is obtained. At all time points, Curie scoring will be determined by local institutions.

Exception: Curie scoring will not be performed for patients who are found to have MIBG non-avid disease at diagnosis.

16.0 RADIATION THERAPY GUIDELINES

No radiation therapy is planned for this study.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

Protocol Specific Requirements For ANBL19P1 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form– this form is submitted to IROC to verify credentialing status or to begin a new modality credentialing process.

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Your Site's Registration Status

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

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

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

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

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

Rave role requirements:

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

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

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

APPENDIX II: INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG) STAGING SYSTEM[33,34]

INRG Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors* and confined to one body compartment.
L2	Locoregional tumor with presence of one or more image-defined risk factors.*
M	Distant metastatic disease (except Ms).
Ms	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow (bone marrow involvement should be limited to < 10% of total nucleated cells on smears or biopsy). Primary tumor may be L1 or L2 as defined above.

Bone marrow disease is determined by morphology on smears and aspirates.

*INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG) IMAGE DEFINED RISK FACTORS

Risk factors related to localization:

1) Neck:
   - Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
   - Tumor extending to base of skull
   - Tumor compressing the trachea

2) Cervico-thoracic junction:
   - Tumor encasing brachial plexus roots
   - Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
   - Tumor compressing the trachea

3) Thorax:
   - Tumor encasing the aorta and/or major branches
   - Tumor compressing the trachea and/or principal bronchi
   - Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12

4) Thoraco-abdominal:
   - Tumor encasing the aorta and/or vena cava

5) Abdomen/Pelvis:
   - Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
   - Tumor encasing branches of the superior mesenteric artery at the mesenteric root
   - Tumor encasing the origin of the celiac axis, and/or of the superior mesenteric artery
   - Tumor invading one or both renal pedicles

- Tumor encasing the aorta and/or vena cava
- Tumor encasing the iliac vessels
- Pelvic tumor crossing the sciatic notch

6) Dumbbell tumors with or without symptoms of spinal cord compression:
   - Whatever the localization

7) Infiltration of adjacent organs/structures:
   - Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

APPENDIX III: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky***	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

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

Recommended Non-enzyme inducing anticonvulsants
Brivaracetam
Clonazepam
Diazepam
Ethosuximide
Fenfluramine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Methsuximide
Midazolam
Perampanel
Pregabalin
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Carbamazepine
Clobazam*
Eslicarbazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine*

*Denotes weak inducer of CYP3A4 isozyme. Therapy with this agent can be continued if the risk of switching to an alternative anticonvulsant outweighs the benefit of avoiding a possible drug interaction

APPENDIX V: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

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

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

Late diarrhea (more than 24 hours after the administration of the first dose of irinotecan)
Each family will be instructed to have antidiarrheal medication available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

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

Please follow these directions carefully, using dosing guidelines below:

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

LOPERAMIDE DOSING RECOMMENDATIONS (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [1 teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

APPENDIX VI: POSSIBLE DRUG INTERACTIONS

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

Irinotecan

Drugs that may interact with irinotecan

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

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

Temozolomide

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

Food and supplements that may interact with temozolomide
• Echinacea

Isotretinoin

Drugs that may interact with isotretinoin
• Aminolevulinic acid • Carbamazepine • Some oral contraceptives • Some antibiotics, like doxycycline, tetracycline, and tigecycline

Food and supplements that may interact with isotretinoin
• St. John's Wort • Vitamin A supplements or multivitamins that contain vitamin A

APPENDIX VII: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

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

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

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

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

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

dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] ebastine[5] eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] felodipine[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib lomitapide[5] lorlatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil naloxegol[5] nefazodone nilotinib nisoldipine[5] olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib				

pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen tadalafil[5] telaprevir temsirolimus teniposide tetracycline ticagrelor[5] tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

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

APPENDIX VIII: TEMOZOLOMIDE CAPSULE DOSING (100 MG/M^2) NOMOGRAM

Use this nomogram for patients whose BSA is at least 0.6 m^2 receiving capsule formulation. For patients with BSA <0.6 m^2, please see dosing table in the treatment section of the protocol.

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

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.6-0.62	58-62	60
0.63-0.67	63-67	65
0.68-0.72	68-72	70
0.73-0.77	73-77	75
0.78-0.82	78-82	80
0.83-0.87	83-87	85
0.88-0.92	88-92	90
0.93-0.97	93-97	95
0.98-1.0	98-100	100
1.01-1.05	100-105	105
1.06-1.14	106-114	110
1.15-1.24	115-124	120
1.25-1.34	125-134	130
1.35-1.44	135-144	140
1.45-1.54	145-154	150
1.55-1.64	155-164	160
1.65-1.74	165-174	170
1.75-1.84	175-184	180
1.85-1.94	185-194	190
1.95-2.00	195-200	200
> 2.0	> 200	200

APPENDIX IX: TEMOZOLOMIDE REDUCED (75 MG/M^2) DOSING NOMOGRAMS

For patients with BSA < 0.6 m^2 who require a dose reduction, use the table below.

The dose of temozolomide in the table is expressed as final dose in **mg** to be administered.

TEMOZOLOMIDE Dose Reduction If BSA < 0.6 m^2	
BSA (m^2)	Dose
0.25-0.29	10 mg
0.30-0.34	15 mg
0.35-0.39	20 mg
0.40-0.44	25 mg
0.45-0.49	30 mg
0.50-0.54	35 mg
0.55-0.59	40 mg

Use the nomogram below for patients whose BSA is at least 0.6 m^2 receiving capsule formulation.

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

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.6-0.63	43-47	45
0.64-0.70	48-52	50
0.71-0.76	53-57	55
0.77-0.83	58-62	60
0.84-0.90	63-67	65
0.91-0.96	68-72	70
0.97-1.03	73-77	75
1.04-1.10	78-82	80
1.11-1.16	83-87	85
1.17-1.23	88-92	90
1.24-1.30	93-97	95
1.31-1.36	98-102	100
1.37-1.43	103-107	105
1.44-1.50	108-112	110
1.51-1.56	113-117	115
1.57-1.63	118-122	120
1.64-1.70	123-127	125
1.71-1.76	128-132	130
1.77-1.83	133-137	135
1.84-1.90	138-142	140
1.91-1.96	143-147	145
≥ 1.97	148	150

APPENDIX X: SUMMARY OF BIOLOGIC CORRELATIVE LAB STUDIES

	Time point	Sample Type[b]	Volume per tube[c]	Quantity	Tube Type / Sample Prep	Notes	Destination Lab	Section Number
CORRELATIVE STUDIES: POST-CONSOLIDATION	**Pre-therapy**	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
			5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
			2 mL	1 tube	EDTA	Process for plasma Batch ship	BPC	14.2.1.1
			10 mL	1 tube	Streck Cell Free DNA tube[a]	Ship same day	BPC	14.2.1.2
			2.5 mL	1 tube	PAXgene RNA tube[a]	Ship same day	BPC	14.2.1.3
	Cycle 1, post completion of dinutuximab (collect single sample between Day 5-Day 8)	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
			5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
	Cycle 2, Day 1	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
			5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
			10 mL	1 tube	Streck Cell Free DNA tube[a]	Ship same day	BPC	14.2.1.2
			2.5 mL	1 tube	PAXgene RNA tube[a]	Ship same day	BPC	14.2.1.3
	Cycle 3, Day 1	Blood	2 mL	1 tube	EDTA	Process for plasma Batch ship	BPC	14.2.1.1
			10 mL	1 tube	Streck Cell Free DNA tube[a]	Ship same day	BPC	14.2.1.2
			2.5 mL	1 tube	PAXgene RNA tube[a]	Ship same day	BPC	14.2.1.3
	Cycle 6, Day 8	Blood	2 mL	1 tube	EDTA	Process for plasma Batch Ship	BPC	14.2.1.1
	End of therapy	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
		Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2
		Blood	10 mL	1 tube	Streck Cell Free DNA tube[a]	Ship same day	BPC	14.2.1.2
		Blood	2.5 mL	1 tube	PAXgene RNA tube[a]	Ship same day	BPC	14.2.1.3
	Relapse / Progression	Blood	5 mL	2 tubes	Sodium heparin (Green top) tube	REQUIRED; Ship same day *Immune Phenotyping*	Emory	14.1.1
		Blood	5 mL	1 tube	Sodium heparin (Green top) tube	REQUIRED; Process for plasma *Cytokine Analysis*	Emory	14.1.2

		Blood	10 mL	1 tube	Streck Cell Free DNA tube[a]	Ship same day	BPC	14.2.1.2
		Blood	2.5 mL	1 tube	PAXgene RNA tube[a]	Ship same day	BPC	14.2.1.3

a. If the patient has consented to optional banking studies, both PAXgene RNA tubes and Streck Cell Free DNA BCT tubes should be ordered via the BPC Kit Management system as soon as possible after patient enrollment to allow time for tubes to be shipped. Please see Section 14.2.1.2 for contact information.
b. Please refer to appropriate section regarding blood volume adjustments if applicable.
c. Prioritization of samples if blood volumes approach maximum allowance per institutional standards for small children.
    1. Required samples (sodium heparin [Green top] tubes)
    2. EDTA tube
    3. Streck Cell Free DNA tube
    4. PAXgene RNA tube

Please refer to appropriate section regarding blood volume adjustments if applicable.

APPENDIX XI: EMERGENCY MANAGEMENT OF DINUTUXIMAB TOXICITIES

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

Severe Allergic Reaction

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

Treatment:

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

For airway concerns:

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

For hypotension in setting of allergic reaction:

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

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

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

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

Minimal criteria for resumption of dinutuximab infusion:

- Complete resolution of airway symptoms
- Complete resolution of hypotension

APPENDIX XII: CURIE SCORING SUMMARY SHEET

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

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

Scan time point (circle 1): Baseline End of Cycle 3 End of therapy

Off therapy Surveillance (months from end of therapy):
3 6 12 18 24 36

Relapse/Progression

Other (specify):

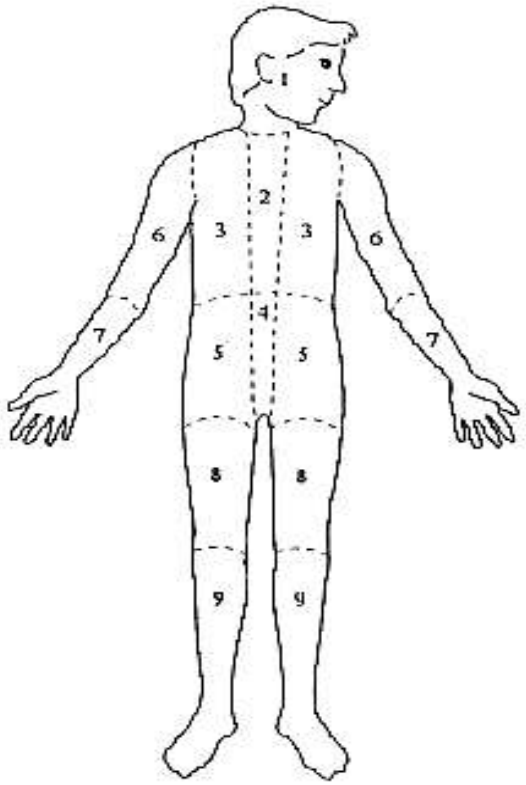
Table 1a. Scoring skeletal disease

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

Table 1b. Scoring soft tissue disease

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

Region	Site	Curie score
1	Head / Neck	
2	Cervico-Thoracic spine	
3	Ribs / Sternum / Clavicles/ Chest	
4	Lumbar / Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	
10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	



APPENDIX XIII: OVERALL RESPONSE CRITERIA

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

CR: Complete Response; MD: Minimal Disease; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive disease; NI: not involved; site not involved at study entry and remains not involved.

APPENDIX XIV: YOUTH INFORMATION SHEETS

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

A Study of a New Treatment for People with High-Risk Neuroblastoma (NBL)

1. We have been talking with you about your illness, neuroblastoma (NBL). NBL is a type of cancer that grows in the soft tissue of your body. It can grow in different parts of the body. You have had some treatment for this cancer already but more treatment is needed.

2. We are asking you to take part in a research study because you have high-risk NBL. A research study is when doctors work together to try out new ways to help people who are sick. This research wants to learn what effects a new treatment has on your cancer.

3. Children who are part of this study will be treated with two types of medicine at the same time. These medicines work in different ways to help get rid of cancer cells. The children in this study will be given the drug, dinutuximab. This drug has been shown to help treat NBL in children like you. They will also be given other drugs, irinotecan and temozolomide, which are commonly used to treat NBL. Study doctors would like to learn if your cancer stays away better with these two types of medicines given together.

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 have more side effects and might not work as well as other treatments. Other things may happen to you that we don’t yet know about. 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 are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

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

Treatment with Dinutuximab in combination with Irinotecan and Temozolomide for People with High-Risk Neuroblastoma (NBL)

1. We have been talking with you about your illness, neuroblastoma (NBL). NBL is a type of cancer that grows in the soft tissue of your body. It can grow in different parts of the body. You have had some treatment for this cancer already and this study takes place during the last part of treatment.

2. We are asking you to take part in a research study because you have high-risk NBL. A research study is when doctors work together to try out new ways to help people who are sick. This research study wants to learn what effects a new combination of therapy has on your cancer.

3. Children and teens who are part of this study will be treated with immunotherapy and chemotherapy. Both immunotherapy and chemotherapy are types of medicine that help get rid of cancer cells. The children and teens in this study will be given the immunotherapy drug dinutuximab which has been shown to help treat NBL in children and teens like you. They will also be given chemotherapy drugs, irinotecan and temozolomide. Study doctors would like to learn if your cancer stays away better with this combination of therapy.

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 are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

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