CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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

October 24, 2019

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

The study committee for **ANBL17P1,** *A Pilot Induction Regimen Incorporating Chimeric 14.18 Antibody (ch14.18, dinutuximab) (NSC# 764038) and Sargramostim (GM-CSF) for the Treatment of Newly Diagnosed High-Risk Neuroblastoma*, has provided Amendment 2 for CTEP review. This amendment is being submitted to remove aldesleukin from post-consolidation therapy as instructed in the ANBL17P1 safety memo posted on 08/23/2019.

The ANBL17P1 study committee looks forward to approval of this amendment. Please contact me with any questions or concerns.

Sincerely,

Edwin Ha, Protocol Coordinator (for)
Sara Federico, MD, ANBL17P1 Study Chair
Peter Adamson, MD, Children's Oncology Group Chair

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CIRB SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In response to CIRB stipulations, the following specific revision has been made to the protocol. Additions are in boldfaced font and deletions in strikethrough font.

#	Section	Page(s)	Change
1.	4.9.6	89	We have corrected the typographical error illustrated below: Enter Cycle # _____ (1 ~~, 3 or~~ - 5)

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

#	Section	Page(s)	Change
1.	Title Page & Throughout	1	The protocol version date and amendment number have been updated.
2.	Table of Contents	3-6	The table of contents has been updated and repaginated.
3.	Study Committee	9	The COG research coordinator and protocol coordinator have been updated.
4.	Study Committee	10	Removed aldesleukin from the list of agents for the study.
5.	Schema	12	The schema was revised based on the new post-consolidation regimen, which utilizes one treatment schedule for the first 5 cycles of post-consolidation. The previous cycles 2 and 4 of post-consolidation, which contained aldesleukin, has been removed.
6.	2.8	19-20	Background information and rationale has been provided regarding the removal of aldesleukin from post-consolidation therapy. All subsequent background sections were renumbered.
7.	4.1	35	The phrase "as per ANBL0032" was removed in reference to the post-consolidation regimen, as the updated Post-Consolidation regimen is not the same regimen as in ANBL0032.
8.	4.1.5	38	Minor administrative edits were made in the post-consolidation summary to reflect changes to the post-consolidation regimen.
9.	4.9.5	88	References to aldesleukin in the additional guidance for post-consolidation were removed.

#	Section	Page(s)	Change
10.	4.9.6	89	The following changes have been made to the Cycles 1 – 5 therapy delivery map: • The TDM was revised so the first 5 cycles of post-consolidation will now utilize one therapy delivery map. Cycles 2 and 4 will follow the same observation schedule as Cycle 5. • The duration of the first 5 cycles of post-consolidation have been extended from 24 days to 28 days for ease of scheduling. The additional 3 days (Days 25- 28) will be rest days. • Certain correlative study timepoints have been moved based on the changes to the post-consolidation regimen. • For the end of Cycle 3 disease evaluation, labs were removed from the evaluation so that only imaging and bone marrow biopsies are required.
11.	4.9.7	90	The days that the end of Cycle 3 disease evaluation could be performed was updated to reflect the 28-day cycle.
12.	4.10	93-95	The previous therapy delivery map for post-consolidation Cycles 2 and 4, which contained aldesleukin, has been removed from the protocol.
13.	4.10	93	Section numbers subsequent to 4.9 in the treatment section have been renumbered accordingly.
14.	5.3	98-100	Under renal toxicity dose modifications, in addition to nuclear medicine GFR and creatinine clearance, an estimated GFR is being added as an option to assess GFR, as serum creatinine increases of > 2x the baseline value can often occur.
15.	5.11 5.13	108-111 112-113	References to aldesleukin in the dose modification section were removed from the protocol. Other parts of the dose modifications were reworded for clarity.
16.	5.11	108-111	The term cytokines was replaced with the term sargramostim for specificity.
17.	Throughout Section 5.0	Throughout	Section numbers subsequent to 5.11 in the dose modification section have been renumbered accordingly based on the removal of the aldesleukin-containing dose modifications.
18.	5.13.2	113	We have included a statement which allows for institutional standards to be used for dose modifying dinutuximab and sargramostim in post-consolidation.

#	Section	Page(s)	Change
19.	6.2	122	The aldesleukin monograph was removed from the drug information section.
20.	Throughout Section 6.0	Throughout	Section numbers subsequent to 6.1 in the drug information section have been renumbered accordingly based on the removal of the aldesleukin monograph.
21.	15.1.3 15.1.6	188 192	Due to the changes in the post-consolidation regimen, the days for which optional specimens are being obtained are being altered slightly to match the change to the post-consolidation cycle lengths.
22.	Appendix IV	232	Aldesleukin has been removed from the possible drug interactions appendix.
23.	Appendix V	238	Based on the changes to Section 15, minor edits have been made for consistency in the summary of optional correlative studies table.
24.	Appendix VI	240	The term cytokines was replaced with the term sargramostim for specificity and references to aldesleukin were removed.

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Activated: 01/14/19 Version Date: 10/24/19
Closed: Amendment #2

CHILDREN'S ONCOLOGY GROUP

ANBL17P1

A Pilot Induction Regimen Incorporating Chimeric 14.18 Antibody (ch14.18, dinutuximab) (NSC# 764038) and Sargramostim (GM-CSF) for the Treatment of Newly Diagnosed High-Risk Neuroblastoma

NCI Supplied Agent: Chimeric 14.18 Antibody (ch.14.18, dinutuximab) (NSC#764038)
IND sponsor: DCTD, NCI

A Limited Institution Pilot Study. Participation is limited to the following COG institutions:

St. Jude Children's Research Hospital, Memphis, TN
Dana-Farber Cancer Institute, Boston, MA
Children's Hospital of Los Angeles, Los Angeles, CA
Primary Children's Hospital, Salt Lake City, UT
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA
Children's National Medical Center, Washington, DC
Columbia University/Herbert Irving Cancer Center, New York, NY
Starship Children's Hospital, Auckland, New Zealand
The Children's Hospital at Westmead, Westmead, NSW, Australia
Royal Children's Hospital, Parkville, VIC, Australia

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CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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 user log on with 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 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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AGENT	NSC #	Supplier
Ch14.18 (Dinutuximab)	764038	CTEP
Carboplatin	241240	Commercial
Cisplatin	119875	Commercial
Cyclophosphamide	26271	Commercial
Dexrazoxane	169780	Commercial
Doxorubicin	123127	Commercial
Etoposide	141540	Commercial
Filgrastim	614629	Commercial
Isotretinoin	329481	Commercial
Melphalan	8806	Commercial
Mesna	113891	Commercial
Pegfilgrastim	725961	Commercial
Sargramostim	613795	Commercial
Thiotepa	6396	Commercial
Topotecan	609699	Commercial
Vincristine	67574	Commercial

IND Sponsor: DCTD, NCI

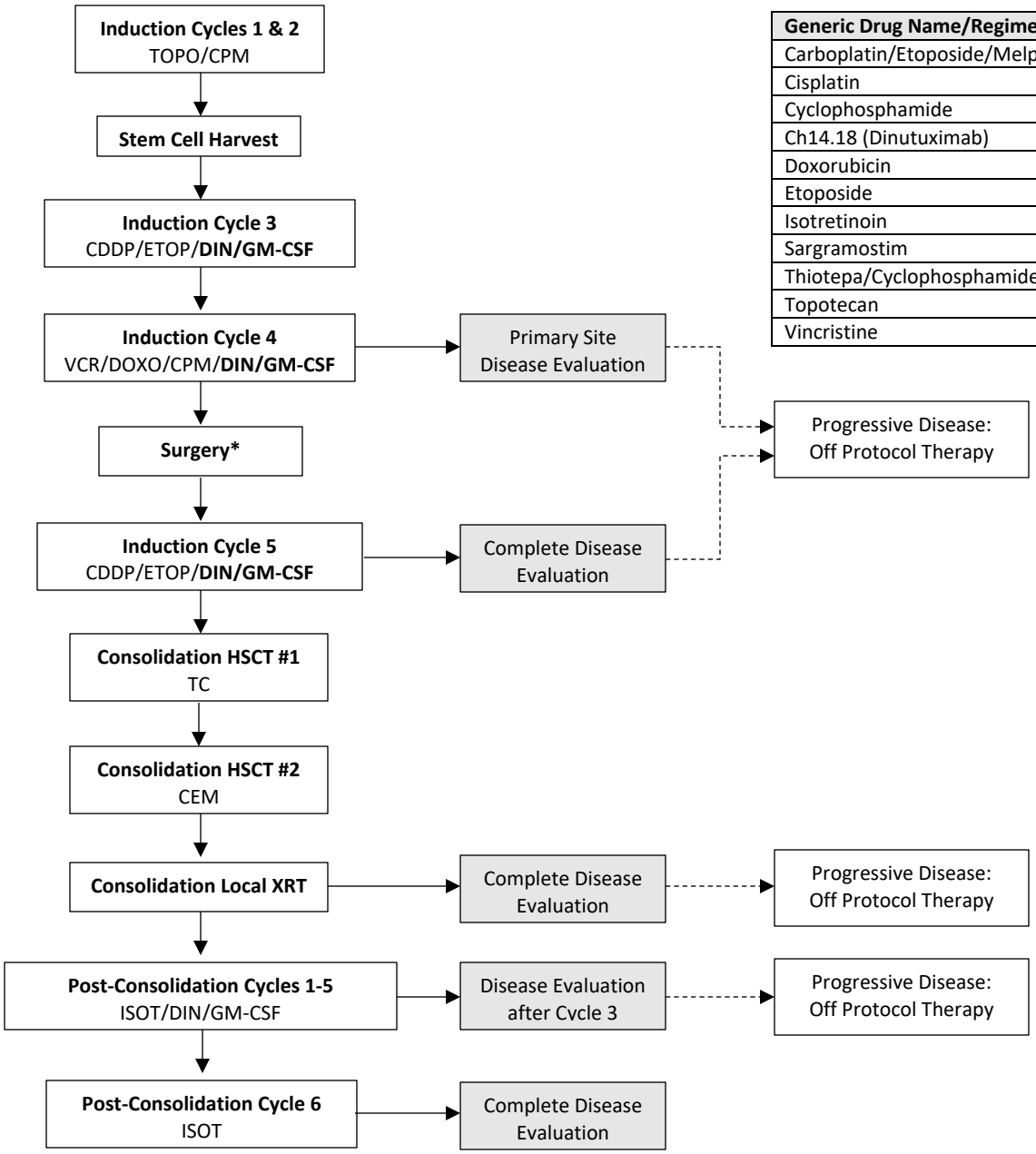
SEE SECTION 15.0 FOR SPECIMEN SHIPPING ADDRESSES

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

Intensification of Consolidation therapy with tandem autologous stem cell transplants and the addition of post-Consolidation immunotherapy targeting the disialoganglioside GD2 present on neuroblastoma cells have led to improved event-free survival rates for patients with high-risk neuroblastoma. However, a substantial number of children still experience disease progression during Induction therapy, show evidence of persistent metastatic disease, or relapse after completion of treatment. The need for innovative therapies for children with high-risk neuroblastoma remains critical. Recent studies conducted in patients with recurrent or refractory neuroblastoma have demonstrated objective clinical responses following treatment with the combination of an anti-GD2 monoclonal antibody (mAb) plus chemotherapy and GM-CSF. This protocol will evaluate whether the addition of the anti-GD2 mAb, ch14.18 (dinutuximab), and GM-CSF to standard Induction chemotherapy Cycles 3 to 5 for patients with newly-diagnosed neuroblastoma is safe and tolerable. Secondary endpoints will include disease response and survival. Embedded biologic correlative studies will further evaluate tumor and host response to the proposed therapy.

EXPERIMENTAL DESIGN SCHEMA



Generic Drug Name/Regimen	Abbreviation
Carboplatin/Etoposide/Melphalan	CEM
Cisplatin	CDDP
Cyclophosphamide	CPM
Ch14.18 (Dinutuximab)	DIN
Doxorubicin	DOXO
Etoposide	ETOP
Isotretinoin	ISOT
Sargramostim	GM-CSF
Thiotepa/Cyclophosphamide	TC
Topotecan	TOPO
Vincristine	VCR

*If clinically indicated, surgery may take place after the fifth cycle of Induction.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

1.1.1 To assess the feasibility and tolerability of administering ch14.18 (dinutuximab) and sargramostim (GM-CSF) in combination with a multi-agent chemotherapy regimen during Cycles 3-5 of the Induction phase for patients with newly-diagnosed high-risk neuroblastoma.

1.2 Secondary Aim

1.2.1 To describe the response rates, event-free survival (EFS) and overall survival (OS) for patients receiving the combination of standard Induction chemotherapy and ch14.18 (dinutuximab) followed by tandem transplant, radiation therapy, and post-Consolidation immunotherapy.

1.3 Exploratory Aims

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

1.3.2 To describe the clinical relevance of natural killer (NK) receptor NKp30 isoforms in patients receiving ch14.18 (dinutuximab).

1.3.3 To describe the association between host factors, including human anti-chimeric antibodies (HACA), and response to protocol therapy.

1.3.4 To describe the immune environment (gene expression; immune effector cells, activities and signaling molecules; immune target expression) during and following treatment.

1.3.5 To describe the association between levels of circulating GD2, and tumor cell GD2 expression with response to therapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

High-risk neuroblastoma

In spite of recent improvements in therapy, outcomes for patients with high-risk neuroblastoma remain poor. For patients enrolled on COG A3973, the estimated 5-year EFS was only 38%.[1] In COG ANBL0032, the addition of an anti-GD2 monoclonal antibody (dinutuximab) to the post-Consolidation phase of therapy was evaluated. In this study, patients with high-risk neuroblastoma who had not experienced disease progression during Induction or Consolidation therapy were randomized to receive either ch14.18 (dinutuximab) combined with cytokines and isotretinoin or isotretinoin alone. The patients that received immunotherapy plus isotretinoin had a 2-year post-randomization EFS of 66% (± 5%) versus 46% (± 5%) in those that received single agent isotretinoin.[2] In ANBL0532, Consolidation therapy was intensified; patients were randomized to receive either high-dose chemotherapy followed by autologous stem cell transplant (ASCT) or two sequential cycles of high dose chemotherapy with ASCT (tandem ASCT). Patients who received a tandem ASCT had a significantly improved 3-year post-randomization EFS of 63% (± 5%) compared to 49% (± 5%) for patients assigned to a single transplant.[3] While intensification of Consolidation therapy and the addition of post-Consolidation immunotherapy have both improved EFS for high-risk patients, a substantial number of children still experience disease progression during Induction therapy, show

evidence of persistent metastatic disease, or relapse after the completion of treatment. Thus, the need for innovative therapies for children with high-risk neuroblastoma remains critical.

This pilot study represents the culmination of decades of studies evaluating the role of GD2-directed therapy in patients with high-risk neuroblastoma. The trial will evaluate the feasibility and tolerability of administering concurrent anti-GD2 monoclonal antibody ch14.18 (dinutuximab) with GM-CSF and chemotherapy in Cycles 3-5 of the Induction phase of treatment for patients with newly-diagnosed high-risk neuroblastoma. If delivery of the combined therapy is feasible and results in improved outcomes, this pilot study will provide the basis for a definitive Phase 3 clinical trial to determine whether the addition of anti-GD2 immunotherapy during Induction improves survival in children with newly diagnosed high-risk neuroblastoma. If the results are positive, this could alter clinical practice by establishing a new Induction standard of care.

Importantly, the rate of development of HACA in patients treated with ch14.18 (dinutuximab) during Induction will also be studied during this pilot trial. These results will be instrumental in guiding the development of a future Phase 3 study. To aid in identification of patients most likely to benefit from the GD2-directed immunotherapy, potential biomarkers of response will also be evaluated. The exploratory work that will be completed during this trial could provide the basis for prospective validation of biomarkers in a larger Phase 3 clinical trial.

2.2 Rationale for GD2-directed Therapy

2.2.1 Pre-Clinical Studies

The disialoganglioside GD2 is expressed on neuroblastoma cells, but its expression in normal human tissues is restricted to neurons, skin melanocytes and peripheral pain fibers.[4-6] Because of this pattern of expression, anti-GD2 monoclonal antibodies are an attractive form of targeted immunotherapy for children with neuroblastoma. Over the past 3 decades, antibodies directed against GD2 have been studied extensively. Early studies were performed using the murine IgG3 monoclonal antibody 3F8[4,5] and murine IgG2a, 14G2a.[7,8] 3F8 has been shown to mediate very efficient antitumor antibody dependent cell-mediated cytotoxicity (ADCC) *in vitro* in the presence of GM-CSF.[9] However, murine antibody therapy can be accompanied by development of a human anti-mouse antibody response (HAMA), which results in the formation of neutralizing antibodies. This can be particularly problematic in patients who have not received high dose chemotherapy or undergone myeloablative treatment within 90 days preceding murine antibody treatment.[10] To address this challenge, alternative antibody constructs have been developed. Ch14.18 (dinutuximab) consists of the variable regions of murine IgG3 b 14.18 and the constant regions of human IgG1-κ. Pharmacokinetic and immunological studies have shown that ch14.18 (dinutuximab) has a longer plasma half-life and less immunogenicity when compared to the murine antibody, making it potentially more effective.[11,12] Preclinical studies performed both *in vitro* and *in vivo* indicate that its anti-neuroblastoma activity involves complement dependent cytotoxicity (CDC) and ADCC when ch14.18 (dinutuximab) is used alone[13] or in combination with GM-CSF.[14]

2.2.2 Clinical Studies using anti-GD2 Antibodies

The murine anti-GD2 antibody 3F8 was tested in a Phase 1 trial in patients with neuroblastoma, and in a Phase 2 trial in combination with GM-CSF. The 2 agent combination appeared to have efficacy, especially in patients with bone marrow

disease.[15] Phase 1 and 2 clinical trials of ch14.18 (dinutuximab) or 14G2a, alone or combined with cytokines such as GM-CSF or IL-2 respectively, also showed signals of activity in patients with neuroblastoma.[11,16] Subsequent clinical trials have demonstrated a significant decrease in risk of relapse and an improvement in survival for patients with high risk neuroblastoma who are in remission after initial multi-modality therapy. An early analysis of results from a German study of single agent ch14.18 (dinutuximab) administered to patients > 1 year of age with Stage 4 neuroblastoma showed no difference in the rate of recurrence when compared to patients who did not receive the antibody.[17] However, analysis of data with longer follow up time revealed a statistically significant improvement in EFS for those patients who received ch14.18 (dinutuximab).[18] A randomized Phase 3 study (COG ANBL0032) of Post-consolidation ch14.18 (dinutuximab) combined with GM-CSF, interleukin 2 and isotretinoin compared with single agent isotretinoin was stopped early because the EFS of patients treated with the antibody containing regimen was clearly superior to that of patients treated with isotretinoin alone.[19]

The clinical evaluation of various anti-GD2 monoclonal antibodies in children with neuroblastoma initially focused on treatment of minimal residual disease. However, several studies conducted in adults with cancer suggest that monoclonal antibodies can be effectively combined with chemotherapy to treat patients, including those with measurable disease.[20-27] These studies provided a rationale for the development of chemo-immunotherapy regimens for patients with neuroblastoma.

2.3 Rationale for GD2-directed Therapy Plus Chemotherapy

Preclinical studies

Preclinical studies show that anti-GD2 antibodies may enhance the effects of chemotherapy in small cell lung cancer cell lines and in a neuroblastoma cell line. Yoshida *et al*. demonstrated that an anti-GD2 monoclonal antibody enhanced apoptotic effects of specific chemotherapeutic agents against a small cell lung cancer cell line.[28] In a neuroblastoma cell line, Kowalczyk *et al*. demonstrated that the anti-GD2 monoclonal antibody (mAb), 14G2a, had additive cell killing when combined with carboplatin and synergistic cell killing when combined with doxorubicin and topotecan.[29] In addition to synergistic effects of anti-GD2 mAbs with chemotherapy, there is also evidence that the anti-GD2-specific antibodies can suppress tumor growth, independent of the immune system involvement by directly inducing apoptosis in lung cancer cells[30] and suppressing growth in melanoma xenografts[31] and a neuroblastoma cell line.[29]

Clinical studies

In the clinical setting, investigators have demonstrated that the addition of an anti-GD2 mAb plus chemotherapy is safe and feasible, and that this combination results in clinically meaningful responses. The St. Jude Children's Research Hospital pilot study GD2NK evaluated the combination of a humanized anti-GD2 mAb, hu14.18K322A, with cytokines and alternating chemotherapy combinations (cyclophosphamide plus topotecan, irinotecan plus temozolomide and ifosfamide plus carboplatin and etoposide) in patients with recurrent or refractory neuroblastoma.[32] Administration of this therapy in a cohort of 13 patients was feasible and well-tolerated. Moreover, 8 of 13 (63%) had an objective response and the time to progression was delayed compared to historical controls.[32]

Based on these data, a Phase 2 clinical trial, NB2012, was designed to evaluate the response of combined anti-GD2 mAb (hu14.18K322A) with cytokines during Induction and Consolidation chemotherapy for patients with newly-diagnosed high-risk disease. An interim analysis

(performed after the first 20 patients) confirmed that the delivery of combined Induction chemotherapy plus hu14.18K322A in newly diagnosed patients is feasible and well-tolerated.[33] Additional patients were therefore enrolled. As reported at ASCO 2017, of 42 evaluable patients with newly-diagnosed high-risk neuroblastoma treated on NB2012 who completed the first 2 courses of chemotherapy plus hu14.18K322A, 32 achieved a response of ≥ PR (76.2%; 95% C.I. 61.3 – 87.9%).[34] This nearly doubled the response rate following 2 cycles of Induction therapy achieved by a historical control group that received the same chemotherapy regimen without the addition of mAb (p=0.05).[33,35] Further, none of the patients treated on NB2012 developed disease progression during Induction compared with the 10-15% who experienced disease progression on recent COG high-risk neuroblastoma trials.[1,36,37] All of the patients on NB2012 were able to proceed to Consolidation therapy (with a single BuMel ASCT) and subsequently to post-Consolidation immunotherapy. Only five percent of the patients discontinued treatment due to personal choice, unrelated to toxicities attributable to therapy.

The COG trial ANBL1221 evaluated response in patients with recurrent or refractory neuroblastoma following treatment with the combination of ch14.18 (dinutuximab) and chemotherapy. This trial was a 2-arm "pick the winner" study in which patients were randomized to treatment with irinotecan and temozolomide combined with either temsirolimus or ch14.18 (dinutuximab) and GM-CSF. Among 18 patients randomized to receive irinotecan/temozolomide/temsirolimus, 1 PR was observed (5.6%, 95% confidence interval (CI): [0.0%, 16.1%]). Among 17 patients randomized to receive irinotecan/temozolomide/ ch14.18 (dinutuximab)/GM-CSF, 9 (53%, 95% CI: [29.2%, 76.7%]) had objective responses (4 PR, 5 CR) including responses in 5/10 patients with relapsed/progressive disease and 4/7 with refractory disease. The combination of irinotecan with temozolomide and ch14.18 (dinutuximab) met the protocol-defined criteria for selection as the combination meriting further study.[38] After a 53% response rate was noted in the initial cohort of 17 patients assigned to irinotecan/temozolomide/ch14.18 (dinutuximab)/GM-CSF on the randomized portion of the study, the study was amended to allow greater confidence in the response estimate. Preliminary data indicate an overall response rate (CR + PR) of ~40% (95% CI: [26.5%, 52.8%]) in an intention to treat analysis including all patients on the trial who were assigned to irinotecan, temozolomide and ch14.18 (dinutuximab). Of the 53 patients assigned to the regimen, 17 during the randomization and 36 during study expansion, 21 experienced objective responses, including 11 CR and 10 PR. Taken together, these data provide a compelling basis for further evaluation of the anti-GD2 monoclonal antibody, ch14.18 (dinutuximab), given with Induction chemotherapy in children with newly diagnosed high-risk neuroblastoma.

Rationale for concurrent administration of ch14.18 (dinutuximab) and chemotherapy

Collectively, the 3 clinical studies previously described provide evidence that an anti-GD2mAb can be safely administered with chemotherapy in patients with bulky neuroblastoma. As noted, in the recurrent setting, 13 patients (many with significant tumor burden) safely received chemotherapy plus hu14.18K322A on a trial conducted at St. Jude (GD2NK) and 51 patients safely received chemotherapy plus ch14.18 (dinutuximab) with expansion of the COG trial (ANBL1221). In patients with newly diagnosed high-risk neuroblastoma, more than 40 patients have safely received hu14.18K322A combined with 6 cycles of Induction chemotherapy. Importantly, all of these newly-diagnosed patients have been able to receive Consolidation and post-Consolidation therapy. In total, over 100 patients with neuroblastoma have safely received anti-GD2mAb plus GM-CSF and chemotherapy.

One concern regarding the administration of ch14.18 (dinutuximab) during Induction is the potential for the development of HACA, which could interfere with delivery of ch14.18 (dinutuximab) during post-Consolidation therapy. Therefore, development of HACA will be

closely monitored. Analysis of data from COG ANBL0032, in which patients received ch14.18 (dinutuximab) during post-Consolidation, revealed a low incidence of neutralizing HACA [only 4.4% among patients who received ch14.18 (dinutuximab)] in the post-Consolidation setting. In addition, in the preliminary analyses of data regarding patients receiving a similar anti-GD2 mAb (hu14.18K322A in the St. Jude NB2012 trial), no patients have developed a neutralizing human anti-human antibody (HAHA) at any point during therapy.

Unpublished data from NB2012 indicate that exposure to hu14.18K322A during Induction does not cause an increase in detectable HAHA responses. At an interim analysis, twenty-two patients on NB2012 had samples evaluated for all 6 Induction cycles and 20 of these also had samples evaluated for all post-Consolidation cycles. HAHA was documented in 1 patient after Cycle 4 Induction. However, serum levels of hu14.18K322A were also detectable, thereby arguing against the development of a neutralizing antibody. HAHA was undetectable for all subsequent evaluations of this patient, including during post-Consolidation therapy. No other patients had a detectable HAHA at any time during therapy. Thus, of 22 evaluable patients assayed during Induction, only 1 (5%) showed a HAHA response, and 0 (0%) had a neutralizing response. Furthermore, for the 20 patients assessed during post-Consolidation, 0 (0%) had a detectible HAHA response.

Hu14.18K322A is a humanized (rather than chimeric) antibody, and therefore may be less immunogenic than a chimeric antibody. Importantly, single agent administration of hu14.18K322A antibody to patients with relapsed or refractory neuroblastoma resulted in HAHA development (>0.7 O.D.) in 15 of 37 (40%) patients.[39] However, the identification of HAHA in only 5% of patients treated on NB2012 suggests that the concurrent administration of chemotherapy with anti-GD2 antibody may mitigate the risk of developing a neutralizing antibody. Indeed, it is possible that frontline chemo-immunotherapy may be "tolerizing" patients and may help to avoid neutralizing antibody responses. Since this is the first time ch14.18 (dinutuximab) will be given in conjunction with induction chemotherapy it is critical to determine the incidence of HACA development during the ANBL17P1 trial. Based on the results summarized above, we hypothesize that the ANBL17P1 regimen is unlikely to cause a meaningful increase in HACA (or neutralizing HACA) compared to that seen in ANBL0032. Collection of HACA data on the uniformly treated ANBL17P1 cohort will be necessary prior to evaluation of this treatment in a frontline Phase 3 trial.

2.4 Rationale for Standard Induction Chemotherapy

The Induction chemotherapeutic regimen and schedule used for this study are identical to the first 5 cycles administered in COG ANBL09P1 and ANBL12P1, as well as the planned 5-cycle Induction regimen that will be administered in ANBL1531. Patients in the POG 9340 series of trials who received 5 cycles of Induction had similar response rates compared to patients who received 7 cycles of Induction.[40] Investigators from Memorial Sloan Kettering Cancer Center compared the end-Induction complete response (CR) and very good partial response (VGPR) rates for patients receiving 5 or 7 cycles of Induction therapy. In both study groups, the response rates were approximately 80%.[41] Further, rates of stable or progressive disease were similar between the 2 groups and there was a decrease rate of secondary leukemia in patients receiving 5 rather than 7 cycles of Induction.[42] In ANBL12P1 the end-Induction response rate following 5 cycles of chemotherapy was 82%, which is similar to the end-Induction response rate of 80% following 6 cycles of chemotherapy on ANBL0532.[43] Therefore, this study will use a 5-cycle Induction regimen.

2.5 Rationale for ch14.18 (dinutuximab) Dosage and Schedule during Induction Therapy

Ch14.18 (dinutuximab) (17.5 mg/m^2/dose) will be administered during Induction Cycles 3-5. Similar to ongoing studies evaluating the concurrent administration of anti-GD2 mAb and chemotherapy, ch14.18 (dinutuximab) will be given on Days 2-5 of Cycles 3, 4, and 5. Standard pre-medications, as outlined below, will be administered to limit allergic reactions. The initial infusion of ch14.18 (dinutuximab) will start out slowly and the rate will be increased if the infusion is well tolerated. The infusion rate is identical to the infusion rate used in ANBL1221.[38]

Ch14.18 (dinutuximab) will not be given during Induction Cycles 1 and 2 to avoid excessive toxicity in patients with newly diagnosed high-risk disease who are frequently systemically ill and/or have pleural or peritoneal fluid collections that may complicate their ability to tolerate the known capillary leak syndrome that can accompany ch14.18 (dinutuximab).[19] In addition, a delay in initiation of ch14.18 (dinutuximab) until Induction Cycle 3 (the time point for peripheral blood stem cell collection for the majority of patients) will allow for immune reconstitution following myeloablative Consolidation chemotherapy with a stem cell product that is not primed for HACA response. This is expected to decrease the potential development of HACA that could preclude administration or decrease the effectiveness of ch14.18 (dinutuximab) during post-Consolidation therapy.

Throughout ANBL17P1, samples will be obtained to assess HACA formation, and results of this testing will be compared to data from ANBL0032. This information will be critical to planning future randomized clinical trials using chemo-immunotherapy.

2.6 Rationale for the Addition of Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) to Induction Cycles 3 – 5

GM-CSF (250 mcg/m^2/dose subQ) will replace G-CSF during Cycles 3-5 of Induction therapy. Administration of GM-CSF during Cycles 3-5 will serve two purposes. It will both decrease the duration of chemotherapy-induced neutropenia and will augment antibody-dependent cell mediated cytotoxicity (ADCC).[44-46] Unlike the administration schedule defined by ANBL0032, GM-CSF administration during Induction will start on Day 6 or 7, occurring after administration of ch14.18 (dinutuximab) and chemotherapy. This schedule and dose of GM-CSF has been used in three other clinical trials of chemo-immunotherapy for patients with high-risk or relapsed/refractory neuroblastoma (St. Jude trials GD2NK and NB2012; COG-ANBL1221). In all 3 trials, GM-CSF was initiated 24-48 hours after the completion of chemotherapy. The rationale for sequential delivery during Induction therapy is related to the concern that GM-CSF, when combined with simultaneous myelosuppressive chemotherapy, may potentiate additional myelosuppression by driving division of myeloid precursors and make them more sensitive to the cytotoxic agents.[47] Daily sub-cutaneous administration of GM-CSF will continue post-nadir until the absolute neutrophil count (ANC) is greater than or equal to 2000/mm^3 or until criteria have been met to begin the next cycle of therapy. GM-CSF will be stopped at least 24 hours prior to initiating the next cycle of chemotherapy.

2.7 Rationale for the Tandem ASCT

COG ANBL0532 was designed to test the hypothesis that intensification of the Consolidation phase of therapy using tandem cycles of myeloablative chemotherapy would improve 3-year EFS of children with high-risk NBL. The tandem regimen used on ANBL0532 was successfully piloted in the ANBL00P1 study.[36] This trial demonstrated the feasibility of administering thiotepa/cyclophosphamide (TC) followed by carboplatin/etoposide/melphalan (CEM) in the cooperative group setting. Among 41 eligible patients, 33 (80%) underwent the first cycle of

myeloablative therapy and 26 (63%) underwent both cycles. Stopping rules for transplant-related mortality were not met, and complications of therapy, including hematologic, gastrointestinal, and infectious toxicities, were as expected.[36] A total of 652 eligible patients were enrolled on ANBL0532; 355 underwent randomization to either single (CEM) or tandem (TC, CEM) ASCT.[43] As noted above, the 3-year EFS from time of randomization for patients assigned to CEM was 49% (± 5%) compared to 63% (± 5%) for patients assigned to tandem ASCT. The 3-year EFS from time of diagnosis was 51%. The proportion of patients that went on to immunotherapy did not differ between the two arms of the study, and the difference in 3 year EFS in the two groups remained significant among those treated with immunotherapy (55% ± 5% for single vs 74% ± 5% for tandem transplant).[43] In light of these data, tandem ASCT has been adopted as the COG recommended consolidation regimen for patients with high-risk neuroblastoma.

2.8 Removal of Aldesleukin from Post-Consolidation Therapy (post-Amendment 2)

Based on the landmark results of the COG ANBL0032 trial, post-consolidation therapy including dinutuximab together with granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin-2 (IL-2) combined with isotretinoin has been considered a component of standard frontline treatment for children with high-risk neuroblastoma.[2] The toxicities associated with this regimen have been attributed to the combination of dinutuximab and both cytokines, though capillary leak syndrome and serious allergic reactions have been noted to be more common during IL-2-containing cycles compared to GM-CSF containing cycles.[2]

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.[48] In an intention-to-treat analysis, no differences in 3-year event-free survival (EFS) or cumulative incidence of relapse/progression were detected between patients treated with or without IL-2, nor was a difference in 5-year overall survival (OS) detected.[48] 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.[48] 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.[49] Rates of Grade 3 or higher fever and pain were reported among patients assigned to the IL-2-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.[49]

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.[50]

In this study, rates of Grade 3 or higher fever, allergic reaction, hematological toxicity and neurotoxocity 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, personal communication)

While differences exist between administration of anti-GD2 antibody and IL-2 in COG and SIOPEN trials, the COG Neuroblastoma Committee has concluded that the available data demonstrate a lack of clear benefit of IL-2 and show a higher rate of toxicity associated with IL-2-containing regimens. Therefore, patients on ANBL17P1 will no longer receive IL-2 as a component of post-consolidation therapy. Instead, GM-CSF will be administered will all five dinutuximab-containing post-consolidation cycles. This change was implemented as part of an urgent groupwide memo posted on August 23, 2019.

2.9 Correlative and Exploratory Studies

The correlative studies included in this trial are critical to identify potential biomarkers of activity and toxicity that will warrant validation in the context of a subsequent, a larger Phase 3 trial. Historically, cytotoxic chemotherapeutic regimens are evaluated with pharmacokinetic (PK) and pharmacodynamic (PD) studies to determine how drugs affect and are processed by the body, with the goal to identify the most appropriate doses that maximize efficacy and minimize toxicity. For immunotherapy and chemoimmunotherapy, the toxicity, efficacy and selected doses are not solely informed by PK or PD studies. Instead, it is imperative to measure the immune response and identify immune markers that may permit optimization of chemoimmunotherapy treatment. Identification of immune markers may play a critical role in the future selection of patients who are more likely to respond to upfront chemoimmunotherapy. Findings from the proposed correlative studies may serve as a foundation for the development of integrated biomarker studies in a larger Phase 3 trial.

This is the first trial to evaluate these markers in patients with newly diagnosed high-risk neuroblastoma who will receive immunotherapy with Induction chemotherapy. The analyses of the relationships between immune markers and response will primarily be descriptive given the small sample size. Many of these studies are time sensitive and/or the analytes are unstable and must therefore be processed and performed directly by the investigator(s) conducting the studies. The scientific basis for the correlative studies is provided below.

2.9.1 Rationale for studying naturally occurring anti-glycan antibodies

Ch14.18 (dinutuximab) is produced in a rodent cell line that contains the glycans galactose alpha-1,3-galactose (alpha-gal) and Neu5Gc. These glycans are found in most mammals but are missing in humans. All humans have naturally occurring antibodies to non-human glycans, including anti-alpha-gal and anti-Neu5Gc.[51] When ch14.18 (dinutuximab) is administered to a patient, the patient may experience an allergic reaction. Levels of anti-alpha-gal have been correlated with allergic reactions to the drug cetuximab (Erbitux), a chimeric antibody against the EGF receptor that is extensively modified with the glycans alpha-gal and Neu5Gc.[52] Thus, it is possible that the presence and/or levels of antibodies to these non-human glycans may correlate with allergic reactions to ch14.18 (dinutuximab). Additionally, the levels of anti-glycan antibodies may increase after serial courses of ch14.18 (dinutuximab) have been

administered. The presence and/or level(s) of antibodies to non-human glycans may affect the blood levels of ch14.18 (dinutuximab) and ultimately impact the response to therapy.

Pre-treatment blood samples from patients treated with ch14.18 (dinutuximab) during post-Consolidation on ANBL0032 and ANBL0931 demonstrated high levels of anti-alpha-gal and anti-Neu5Gc antibodies. (Alice Yu, personal communication, 2018). These levels were measured over the course of treatment [continued exposure to ch14.18 (dinutuximab)] and were found to decrease over time. Notably, in patients who received ch14.18 (dinutuximab), lower levels of both anti-alpha-gal and anti-Neu5Gc antibodies at the end of therapy were significantly associated with an improved EFS.[53] In patients with recurrent/refractory neuroblastoma treated with chemo-immunotherapy on ANBL1221 (n=14), the anti-glycan levels measured at the beginning and end of therapy were stable, but were lower than those detected at the last time point of ANBL0032 (Day 118 of Course 5), (Alice Yu personal communication, 2018). The significance of this is unknown, but merits further study. There was no association between anti-glycan levels and EFS in patients treated on ANBL1221; however power was limited due to the small sample size.

ANBL17P1 represents a unique opportunity to evaluate antiglycan levels present in patients with newly diagnosed high-risk neuroblastoma and to evaluate the relationship between antiglycan levels and response to therapy. The predictive value of this biomarker may be dependent on the timing of ch14.18 (dinutuximab) delivery and/or the combination of ch14.18 (dinutuximab) with chemotherapy. Anti-alpha-gal and anti-Neu5Gc antibodies will be collected prior to treatment and at varying time points during Induction and post-Consolidation therapy; associations between anti-glycan levels, ch14.18 (dinutuximab) half-life, treatment response and toxicity will be evaluated.

2.9.2 Rationale for NK cell receptor NKp30 isoform

The natural killer (NK) cell receptor NKp30 is selectively expressed by all human NK-cells and plays an important role in triggering NK-mediated cytotoxicity. NKp30 is also involved in the cross-talk between NK and dendritic cells. The three NKp30 splice variants[54] have been shown to be of prognostic significance in gastrointestinal stromal tumor (GIST), a malignancy that expresses NKp30 ligands and is treated with NK-stimulatory KIT tyrosine kinase inhibitors. Healthy individuals and those with GIST show distinct transcriptional patterns of functionally different NKp30 isoforms. In patients with GIST, predominant expression of the immunosuppressive NKp30*c* isoform (compared to the immunostimulatory NKp30*a* and NKp30*b* isoforms) was associated with the following: 1) reduced survival, 2) decreased NKp30-dependent tumor necrosis factor-α (TNF-α), IL-10 and CD107a release, and 3) defective secretions of interferon-γ (IFN-γ) and interleukin-12 (IL-12) in the NK-DC cross-talk that could be restored by blocking IL-10.[55] A French study reported an association between high levels of the immunosuppressive Nkp30*c*-isoform and inferior outcome in patients with high-risk neuroblastoma, (PFS *p-value= 0.01*). No impact of the Nkp30*a*-isoform was noted.[56]

Since NK cytotoxicity plays a major role in tumor immunity and specifically in anti-GD2-mediated neuroblastoma cell kill, the impact of NKp30 isoforms may be more pronounced in patients receiving ch14.18 (dinutuximab). On ANBL1221, NKp30 isoforms were evaluated in 14 patients with refractory/recurrent neuroblastoma who

received chemoimmunotherapy. Three of the 14 patients evaluated had the immunosuppressive (NK*p*30*c*) isoform. This small sample size precluded correlative analysis. The prognostic significance of NKp30 isoforms is still unknown, but further study of NKp30c status may permit identification of patients who will or will not respond to chemoimmunotherapy. Therefore, patient samples obtained on ANBL17P1 will quantify NKp30 isoforms present during Induction and post-Consolidation. Results will be correlated with response.

2.9.3 Rationale for studying the association between host factors and response to protocol therapy

2.9.3.1 Rationale for KIR/KIR-L genotyping

Killer-Immunoglobulin-like Receptors (KIR) recognize specific HLA molecules, regulate function of human NK cells and control their self-tolerance. The interactions between KIR on donor NK cells and KIR ligands (KIR-L) on recipient tissues influence anti-tumor efficacy in the setting of allogeneic hematopoietic stem cell transplantation, and influence the antitumor effects of autologous transplantation. Since the genes encoding KIR and KIR-L are inherited independently, it is possible for an individual to be KIR-receptor ligand mismatched with oneself. In a COG Phase 2 study of 38 patients with relapsed/refractory neuroblastoma receiving *humanized* anti-GD2 linked to IL-2, 7 of 24 mismatched patients experienced either complete response or improvement in disease status after immunocytokine therapy, while there was no response or comparable improvement in disease status in 14 patients who were matched ($p = 0.03$).[57] In the larger Phase 3 ANBL0032 study, KIR status (including the "all KIR-ligands present" genotype, inhibitory KIR2DL2 with its ligand (HLA-C1) and inhibitory KIR3DL1 with its ligand (HLA-Bw4)) was associated with improved outcome if patients received immunotherapy.[58] Taken together, these data suggest that patients with KIR receptor-ligand mismatch may experience a better clinical response to immunotherapy with an anti-GD2 antibody than patients without a mismatch. Further investigation of KIR/KIR-ligand genotypes may clarify their role in cancer immunotherapy and may enable KIR-KIR-ligand genotyping to be used prospectively to identify patients who are likely to benefit from chemoimmunotherapy. Therefore, at a single timepoint, KIR and KIR-ligand genotyping will be performed on ANBL17P1.

2.9.3.2 Rationale for Fc receptor genotyping

In general, the anti-tumor activities of unconjugated monoclonal antibodies require the contribution of either complement or Fcγ receptor (FcγR)-expressing effector cells in order to achieve tumor cell killing. However, because most tumor cells, including neuroblastoma, express increased amounts of complement-inhibiting proteins that protect the cells against lysis by complement, antibody-dependent cell-mediated cytotoxicity (ADCC) is considered the key antitumor mechanism of therapeutic antibodies *in vivo*. Most natural killer (NK) cells, certain subpopulations of T lymphocytes, as well as monocytes and granulocytes are capable of mediating ADCC against antibody-coated targets via their expression of FcγR for IgG. The FcγR genes display polymorphisms that greatly influence the affinity of IgG for the Fcγ

receptor. NK cells bearing the FcγRIIIa-158V/V allele mediate ADCC more effectively than those with F/F allele. Similarly, for FcγRIIA, the high-affinity H allele at position 131 results in greater affinity of FcγRIIa for IgG, whereas the low-affinity R allele correlates with decreased binding. In patients with lymphoma, Fc receptor polymorphisms have been reported to influence the response to rituximab whereby patients with the high affinity alleles have a better outcome.[59,60] While not uniformly reported for all analyses, most studies of FcγR genotypes in clinical trials of mAbs that mediate ADCC have shown similar associations of better outcome for patients with the high affinity alleles (i.e. as for trastuzumab).[61]

In the setting of neuroblastoma, in a small COG Phase 2 study of 38 patients treated with hu14.18-IL-2 (an immunocytokine linking anti-GD2 mAb to IL-2), there was evidence for an association between FcγRIIA genotype and response was seen.[57] No association was seen for FcγRIIIA in that study. However, because only 2 patients had the high affinity genotype, there was inadequate statistical power to identify a significant association. Unpublished FcγR genotype analyses have been performed for 174 neuroblastoma patients treated on COG ANBL0032, a randomized Phase 3 trial of ch14.18 (dinutuximab) + GM-CSF and IL-2.[19] When analyzed separately, there was no significant association of outcome with FcγRIIA status, nor with FcγRIIIA status (Alice Yu and Mitchell Diccianni, personal communication, 2018). FcγR expressing cells were also measured in patients with relapsed/refractory neuroblastoma who were treated on a German Phase 2 trial of ch14.18 (dinutuximab)-beta, given as a 10 day continuous infusion with IL-2.[62] In that report, Seibert et al found no significant association between outcome between either FcγR2A or FcγRIIIA status individually. However, when an algorithm that included both genotypes together was used, the favorable combined genotype showed a significant association with outcome ($p = 0.008$).[62] Thus, there is a need to further evaluate the potential predictive nature of FcR genotype for neuroblastoma patients receiving anti-GD2-based immunotherapy.

More recently the FcγRIIc molecules have been shown to influence ADCC. Polymorphisms at this locus can influence expression vs. lack of expression (function vs. lack of function) of this FcγRIIc (expressed on NK cells, neutrophils and monocytes/macrophages) and can mediate ADCC. The Sondel lab has shown that an algorithm incorporating polymorphism data for FcγRIIa, FcγRIIIa and FcγRIIc is more powerful than analyses of individual FcR loci or than an algorithm that combines only FcγRIIa, FcγRIIIa.[63] Using this algorithm, the authors found an association between FcR genotype and therapeutic response in an IL-2 immunotherapy trial for adults with renal cell carcinoma.[64] Because ch14.18 (dinutuximab) is very effective in mediating ADCC, its efficacy in neuroblastoma may be associated with Fc receptor genotype.

In ANBL17P1 we hypothesize that the strength of the ADCC-immunologic effect of combining ch14.18 (dinutuximab) with chemotherapy will be greater than that observed during prior trials in which dinutuximab was administered without chemotherapy. Further, we hypothesize that the greater

immunotherapeutic effect will augment the ability to detect an association of FcR genotype with therapeutic response. Finally, the 3-gene algorithm, that includes FcγRIIc[63], will be used to test for an association with outcome (response and survival). This method has never been used to analyze data on neuroblastoma trials and may identify a potential biomarker of disease response.

2.9.3.3 Rationale for HACA and PATA testing

Human anti-chimeric antibody (HACA) can develop following exposure to ch14.18 (dinutuximab). The identification of a detectible HACA response is not necessarily of functional significance. In some studies, the presence of anti-therapeutic antibodies (such as HAMA or HACA) have been associated with clinical benefit. However, this is not uniformly demonstrated, and the mechanistic connection to this observation remains uncertain. Some studies have generated data suggesting that the presence of HAMA or HACA may be a marker (or potentially a factor in the process) of induction of an endogenous host anti-tumor immune response. Even so, most agree that the presence of a neutralizing HAMA or HACA is antagonistic to the desired *in vivo* function of the mAb. For this reason, we will seek to identify HACA levels that are neutralizing.

While many *in vitro* assays can detect whether a HACA+ specimen can neutralize an anti-GD2 mAb *in vitro*, their relevance *in vivo* remains unproven. For this reason, COG investigators have used an "*in vivo* neutralization" approach. Once a HACA response is detected, if subsequent courses of ch14.18 (dinutuximab) are associated with a peak ch14.18 (dinutuximab) level <10% of that predicted, then the HACA response is considered to demonstrate "*in vivo* neutralization". Of 136 COG patients evaluated in ANBL0032, only 11 had detectible HACA and only 6 (4.4%) showed evidence of *in vivo* neutralization. In ANBL17P1 we will determine the incidence of overall HACA and *in vivo* neutralizing HACA during Induction cycles (in which patients receive ch14.18 (dinutuximab) with chemotherapy), and during post-Consolidation therapy (in which patients receive ch14.18 (dinutuximab) with cytokines).

Analysis of samples from a Phase 1 trial of a *humanized* anti-GD2 antibody (hu14.18K322A) conducted at St. Jude Children's Research Hospital[39] has shown that sera obtained prior to therapy from 9 of 38 patients with relapsed or refractory neuroblastoma contained **P**re-existing **A**nti-**T**herapeutic **A**ntibodies (PATA) that reacted against the anti-GD2 antibody. Notably, these patients had no prior exposure to any monoclonal antibody. Initial analyses of the immunologic reactivity pattern of the sera from these 9 PATA+ patients revealed that these PATA are not anti-idiotypic antibodies against the therapeutic hu14.18K322A mAb. Unexpectedly, these PATA bound to other human IgG1 mAbs (rituximab, trastuzumab), pooled human IgG (Gammagard), and also to the anti-GD2 chimeric antibody ch14.18 (dinutuximab). However, they did not bind to the parental mouse anti-GD2 mAb (14.G2a). The presence of PATA may be linked to patient outcome. Of the 38 initially evaluable patients with relapsed or refractory disease, only 4 were known to be in remission or without progression 2.5 years following

treatment. All 4 of these patients were among the 9 found to have PATA (p= 0.002). (Paul Sondel, personal communication, 2017) This preliminary observation requires further study, however it suggests that these PATA recognize a shared IgG1 epitope (also known as an antibody-allotype[65] that is found on most human IgG1 antibodies, but is "foreign" to the 9 PATA+ patients who may have been immunized via exposure to allo-IgG1 in prior transfusions). PATA/anti-alloantibodies may augment the efficacy of tumor reactive therapeutic antibodies and may represent some of the antibody reactivity identified in prior "human anti-chimeric antibody (HACA)" assays. An understanding of the role of PATA/anti-allotype biology may aid in the selection of patients for GD2-directed immunotherapy. The association between results of testing for the presence HACA, anti-idiotype and PATA/anti-allotype antibody [not directed against the ch14.18 (dinutuximab) idiotype] with response to study therapy will be examined.

2.9.4 Rationale for studying the immune environment during and following treatment

2.9.4.1 Rationale for immune function studies

Understanding the state of the immune effector cells may be crucial to the design of future passive immunotherapies for cancer. Specifically, the number of NK and NK-T cells, T cell subsets and expression of NK activation and inhibitory receptors present in patient blood may have an association with clinical responses to immunotherapies, including ch14.18 (dinutuximab). In ANBL0032, a pre-immunotherapy expression of NK markers including KIR, CD161 and NKp44 was associated with outcome, suggesting that patients with NK populations expressing these markers may be most responsive to the actions of ch14.18 (dinutuximab). This raises the possibility that these NK markers may represent a predictive biomarker of response to ch14.18 (dinutuximab). However, the number of patient samples available for marker analysis in ANBL0032 was small, and it is not known whether marker levels prior to Induction will be predictive of outcome. Thus, samples will be obtained prior to Induction, and prior to Consolidation therapy on ANBL17P1 to further study these issues as part of the process of biomarker evaluation and development.

For children with neuroblastoma, cytokine levels and changes in these levels throughout treatment may correlate 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.[66] 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.[67,68] 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, IL1ra, IFN-ɣ, IL-10, TNFα, IL5, IL17A, CXCL9, IL15 and nitric oxide when compared to baseline levels. However, a low pretreatment (baseline) level of CXCL9 was the only cytokine level that was associated with an improved event free survival ($p = 0.05$). Therefore, samples will be obtained on ANBL17P1 to evaluate the

levels of CXCL9 at baseline and throughout treatment to determine if CXCL9 levels may be predictive of response. Additionally, since investigators identified that the *rs1800795* IL-6 promoter SNP is an independent prognostic factor for EFS and OS in high-risk neuroblastoma, and since *rs1800795 SNP* has been shown to correlate with the production on IL-6,[68] IL-6 levels will also be measured at baseline and throughout therapy, and correlation with response to therapy will be assessed.

2.9.4.2 Rationale for analysis of gene expression studies

Expression of immune response related genes may be predictive of ADCC and anti-tumor effect in patients treated with ch14.18 (dinutuximab) in combination with Induction chemotherapy. Deep sequencing analyses to identify alterations in expression of genes related to circulating immune cells may provide biological insights and identify biomarkers for response. RNA sequencing (RNASeq) will be performed on blood samples obtained at baseline and during treatment to evaluate the expression of a panel of genes related to immune function (including cell surface receptors, proteases, cytokines and cytokine receptors, cell cycle and protein kinases, etc.) and non-immune genes. New algorithms (e.g. CIBERSORT) have emerged that allow estimation of immune cell presence in tumor and blood through deconvolution of RNAseq expression profiles. This technology will be used to assess gene expression from whole blood in children being treated with chemo-immunotherapy.

2.9.5 Rationale for studying the association between, levels of circulating GD2, and GD2 tumor cell expression with response to therapy

The ganglioside composition of neuroblastoma cells was studied decades ago;[69] yet much remains unknown about the relationship between the presence of gangliosides on neuroblastoma cells (particularly GD2) and response to anti-GD2 based therapy. Because serial tumor sampling is not possible in young children receiving neuroblastoma therapy, methods for detection of GD2 shed from the surface of neuroblastoma cells have been developed. A high performance liquid chromatography (HPLC)/tandem mass spectrometry (MS/MS) assay for enhanced detection of GD2 in plasma and serum has been validated. Median circulating GD2 concentration in serum from 40 children with high-risk neuroblastoma was >30-fold higher than the median circulating GD2 concentration in 40 normal controls, and circulating GD2 was elevated in all 40 samples from patients with high-risk neuroblastoma. In ANBL17P1, circulating GD2 concentrations will be measured at baseline and throughout therapy; levels will be correlated with response and outcome.

Circulating GD2 could bind to ch14.18 (dinutuximab) and block its therapeutic effect. We will estimate the fraction of circulating ch14.18 (dinutuximab) that is bound to GD2 (r) based on the measured circulating GD2 concentration and the previously reported KA (association constant) for ch14.18 (dinutuximab) of 3.5 x 108 M-1. The r value will be compared in responders and non-responders to determine if antibody binding to circulating GD2 influences response. Demonstrating that circulating GD2 can serve as a clinical tumor biomarker for neuroblastoma and a surrogate clinical trial endpoint for future clinical trials could have a substantial impact on the care of children with neuroblastoma and the design, conduct and efficiency of future trials. GD2 expression in tumor samples will be evaluated

using immunocytochemical (IC) analysis of touch preps of tumors at diagnosis and relapse. Immunocytochemical touch preps of bone marrow biopsies and smear slides of bone marrow aspirates obtained at diagnosis and at disease evaluation time points will also be evaluated. The GD2 IC test will utilize both concurrent staining of Phox2b and GD2 to qualitatively assess GD2 expression. The assay has been successfully tested on formalin fixed specimens (S. Asgharzadeh, H. Shimada, personal communication, 2018).

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

ANBL17P1 will only be open to enrollment at the following 10 institutions:

- St. Jude Children's Research Hospital, Memphis, TN
- Dana-Farber Cancer Institute, Boston, MA
- Children's Hospital of Los Angeles, Los Angeles, CA
- Primary Children's Hospital, Salt Lake City, UT
- Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA
- Children's National Medical Center, Washington, DC
- Columbia University/Herbert Irving Cancer Center, New York, NY
- Starship Children's Hospital, Auckland, New Zealand
- The Children's Hospital at Westmead, Westmead, NSW, Australia
- Royal Children's Hospital, Parkville, VIC, Australia

While ANBL17P1 is open and accruing at these trial centers, patients at these centers should not enroll onto protocol ANBL1531 until ANBL17P1 is closed to accrual.

3.1.1 Patient Registration

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

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

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

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

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

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

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

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (ie, laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

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

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in 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 user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number 'RESERVE' a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions:
https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

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

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

3.1.5 Enrollment on APEC14B1 or ANBL00B1

Patients must be enrolled on APEC14B1 (if open for the classification of NBL patients) or ANBL00B1 prior to enrollment on ANBL17P1.

- **It is strongly recommended that sites submit tissue on APEC14B1 ((if open for the classification of NBL patients) or ANBL00B1 and commence the process of enrollment as soon as a diagnosis of high-risk neuroblastoma is suspected.**

3.1.6 Timing

Patients must be enrolled onto APEC14B1 (if open for the classification of NBL patients) or ANBL00B1 prior to the time of enrollment on ANBL17P1. Once enrolled on APEC14B1 or ANBL00B1, biology results will be entered by the Neuroblastoma Reference Lab when available for viewing by the institution. Shortly thereafter, the Neuroblastoma Tracking Center will perform the Risk Group Analysis based upon the age, stage, and biology results. Risk group assignment will then be made available to the institution. In emergency situations (or if in the opinion of the treating physician, it is in the patient's best interest) consent can be obtained and the patient can be enrolled on both APEC14B1 or ANBL00B1 and ANBL17P1 on the same day if the patient is considered to have high risk neuroblastoma by virtue of BOTH stage (INRG Stage M) and age (>547 days) prior to submission of biology results by the Neuroblastoma Reference Lab.

For the majority of patients on this study, age > 547 days and the presence of metastatic disease are the key criteria for eligibility. For such patients, enrollment is expected to take place **within 5 days** of starting therapy.

- For patients with localized disease for whom tumor *MYCN* status is required to determine eligibility, but in whom the index of suspicion for high risk disease is high and emergency therapy is clinically indicated, therapy as per ANBL17P1 may be initiated. However, consent for ANBL17P1 must be obtained prior to start of therapy. Enrollment must take place when *MYCN* amplification has been documented **and no later than fourteen (14) calendar days** from the beginning emergent ANBL17P1 protocol therapy.
- For clinically stable patients initially thought to have non-high risk disease but subsequently found to have *MYCN* amplified tumor, study enrollment must occur after recovery from a maximum of one (1) cycle of intermediate risk chemotherapy and prior to the start of ANBL17P1 protocol therapy.
- For clinically stable patients > 547 days of age who were initially diagnosed with INRG L1 or L2 disease but who progress to Stage M, enrollment must take place within 4 weeks of progression to Stage M and prior to the start of ANBL17P1 protocol therapy.
- Likewise, clinically stable patients initially diagnosed with *MYCN* amplified INRG L1 disease who develop progression to Stage M must be enrolled within 4 weeks of progression and prior to the start of ANBL17P1 therapy.

Patients ≤ 547 days in age with INRG Stage M disease and patients of any age with INRG L2 or MS disease will only be eligible for this study if documentation of *MYCN* amplification is entered via APEC14B1 or ANBL00B1. While tracking center confirmation of risk group assignment is not required prior to consent and enrollment on ANBL17P1, results of *MYCN* testing through APEC14B1 or ANBL00B1 are required for these patients.

When ANBL17P1 enrollment is completed prior to the start of protocol therapy, the date protocol therapy is projected to start must be **no later than five (5) calendar days** after enrollment. In the event that an investigator determines that emergency therapy is required, protocol therapy may start before enrollment on ANBL17P1. However, consent for ANBL17P1 must be obtained prior to start of therapy AND enrollment must take place as soon as possible.

All clinical and laboratory studies to determine eligibility must be performed within **7 days prior** to enrollment unless otherwise indicated in the eligibility section below. Timing of imaging and assessment of bone marrow status is also indicated in the eligibility section below.

3.2 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, with the exception of ^{123}I-MIBG or PET scans, and bone marrow aspirates/biopsies must be obtained within 2 weeks prior to start of protocol therapy (repeat if necessary).

Note: Baseline ^{123}I-MIBG scans (and PET scans if the subject is found to have MIBG non-avid disease) must be performed within 14 days prior to or within 14 days after of the start of Cycle 1. Baseline audiogram or BAER must also be obtained before the end of Cycle 2.

See Section 4.2 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Enrollment on ANBL00B1 or APEC14B1

Patients must be enrolled on ANBL00B1 or APEC14B1 prior to enrollment on ANBL17P1.

3.2.2 Age

≤ 30 years of age at the time of initial diagnosis.

3.2.3 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. The following disease groups are eligible:

- Patients with **INRG Stage M** disease are eligible if found to have either of the following features:
  a) *MYCN* amplification (> 4-fold increase in *MYCN* signals as compared to reference signals), regardless of age or additional biologic features; OR
  b) Age > 547 days regardless of biologic features;

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

- Patients with **INRG Stage L2** disease with *MYCN* amplification

- Patients > 547 days of age initially diagnosed with INRG Stage L1, L2 or MS disease who progress to Stage M without prior chemotherapy may enroll within 4 weeks of progression to Stage M.

- Patients ≥ 365 days of age initially diagnosed with *MYCN* amplified INRG Stage L1 disease who progress to Stage M without systemic therapy may enroll within 4 weeks of progression to Stage M.

See Appendix II for INRG Staging System.

3.2.4 Prior Therapy

Patients initially recognized to have high-risk disease must have had no prior systemic therapy (other than topotecan/cyclophosphamide initiated on an emergent basis and within allowed timing as described in Section 3.1.6).

Patients observed or 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 3.2.3 will also be eligible.

Patients who receive localized emergency radiation to sites of life-threatening or function-threatening disease prior to or immediately after establishment of the definitive diagnosis will be eligible.

3.2.5 Organ Function Requirements

3.2.5.1 Adequate renal function defined as:

Creatinine clearance (CrCl) or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or a serum creatinine based on age/sex as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[70] utilizing child length and stature data published by the CDC.

3.2.5.2 Adequate liver function defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) < 10 x ULN. For the purposes of this study, ULN for ALT is 45 IU / L.

3.2.5.3 Adequate cardiac function defined as:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by echocardiogram or radionuclide angiogram.

3.2.5.4 Ability to tolerate PBSC Collection

No known contraindication to PBSC collection. Examples of contraindications might be a weight or size less than the collecting institution finds feasible, or a physical condition that would limit the ability of the child to undergo apheresis catheter placement (if necessary) and/or the apheresis procedure.

3.2.6 Exclusion Criteria

3.2.6.1 Patients >18 months of age with INRG Stage L2, *MYCN* non-amplified, regardless of additional biologic features.

3.2.6.2 Patients with bone marrow failure syndromes.

3.2.6.3 Patients that are ≥ 12 and ≤ 18 months of age with INRG Stage M and all 3 favorable biologic features (i.e., non-amplified *MYCN*, favorable pathology, and DNA index > 1) are not eligible.

3.2.6.4 Patients on immunosuppressive medications (e.g. tacrolimus, cyclosporine, corticosteroids for reasons other than prevention/treatment of allergic reactions, adrenal replacement therapy, etc.) are not eligible.

3.2.6.5 Pregnancy and Breast Feeding

3.2.6.5.1 Female patients who are pregnant are ineligible 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.

3.2.6.5.2 Lactating females who plan to breastfeed their infants.

3.2.6.6 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method during study therapy and for two months after the last dose of ch14.18 (dinutuximab) are not eligible.

3.2.7 Regulatory Requirements

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

3.2.7.2 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 for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Patients with newly-diagnosed high-risk neuroblastoma will receive three standard phases of treatment including: Induction, Consolidation, and post-Consolidation therapy. The research portion of this study includes the addition of ch14.18 (dinutuximab) with sargramostim (GM-CSF) to Cycles 3-5 of the Induction phase of therapy. **The ch14.18 (dinutuximab) used throughout this protocol will be provided by CTEP under an IND. Do not use commercial supply.**

Induction therapy will consist of 5 cycles of chemotherapy, similar to treatment given on ANBL12P1 and ANBL1531. Following Induction Cycle 2 of chemotherapy (topotecan and cyclophosphamide), peripheral blood stem cells will be harvested. Patients will then receive the remaining 3 cycles of Induction chemotherapy with the addition of ch14.18 (dinutuximab) on Days 2-5 and sargramostim (GM-CSF) beginning 24 – 48 hours after the completion of ch14.18 (dinutuximab). Ch14.18 (dinutuximab) will be withheld from Induction until an adequate PBSC product (minimum of 4 x 10^6 CD34+ cells/kg) is obtained for Consolidation therapy. Induction chemotherapy Cycles 3 and 5 will include cisplatin and etoposide, Cycle 4 will include vincristine, doxorubicin, and cyclophosphamide. Surgical resection of the primary tumor will be undertaken after the fourth cycle of chemotherapy as on ANBL09P1, ANBL12P1 and ANBL1531. If clinically indicated (e.g. surgeon's preference), it is permissible for surgery to take place after the fifth cycle.

Patients with stable disease or better tumor response at the end of Induction will proceed to Consolidation. Consolidation therapy will consist of two sequential cycles of high dose chemotherapy with autologous stem cell rescue. Conditioning for the first cycle will consist of thiotepa and cyclophosphamide and the second will consist of modified CARBOplatin, etoposide, and melphalan as per ANBL0532. Upon recovery from the second cycle, patients will undergo external beam radiation to the primary tumor bed and sites of persistent metastatic disease detected at the end of Induction. Following a disease evaluation at the end of Consolidation, patients with stable disease or better will go on to receive ch14.18 (dinutuximab)-based post-Consolidation therapy (see Section 4.1.5).

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines under Standard Sections for Protocols.

4.1.1 General guidelines for therapy

4.1.1.1 Central line

All patients will have a central venous line placed to facilitate administration of Induction chemotherapy. Appropriate devices for peripheral blood stem cell harvest, delivery of high dose chemotherapy with stem cell rescue, and

administration of immunotherapy will be used per institutional standard practice.

Due to the requirement for multiple supportive care medications concurrent with ch14.18 (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. Due to compatibility issues, it is possible that additional (peripheral) access may be required in patients needing narcotics other than morphine (e.g. hydromorphone or fentanyl).

4.1.1.2 Stem cell harvest

Patients will undergo PBSC harvest after Induction Cycle 2 REGARDLESS of bone marrow status. See Section 18.0 for additional information. The PBSC product will not be manipulated prior to cryopreservation. All patients must have a PBSC collection that is sufficient for tandem autologous stem cell rescue.

The goal for stem cell collection is therefore 10 - 20 x 10^6 CD 34 + cells / kg divided into 3 separate aliquots. Ch14.18 (dinutuximab) should not be started prior to confirmation of adequate PBSC collection. See Section 18.2 for guidance regarding the approach to patients from whom adequate PBSC collection is not obtained after Cycle 2. Interventions to maximize PBSC harvest are **strongly recommended** given that ch14.18 (dinutuximab) will not be administered during Induction until an adequate PBSC collection is obtained.

4.1.1.3 Clinical disease progression during Cycles 1 and 2 of Induction

There is no required disease evaluation after Cycle 2 of therapy. All patients will proceed to Cycle 3 (cisplatin/etoposide/ch14.18 (dinutuximab)/ sargramostim) regardless of disease status, including patients with clinical disease progression during topotecan/cyclophosphamide. Disease progression during the first two cycles of therapy will be noted, but progressive disease (PD) will not be a cause for discontinuation of protocol therapy. Furthermore, this will NOT be considered an analytic event during evaluation of data relevant to the primary study objectives.

4.1.1.4 Resection of the primary tumor

Patients will undergo surgical resection of the primary tumor after Induction chemotherapy Cycle 4 (or Cycle 5 if medically necessary). Response of the primary tumor to therapy must be assessed prior to surgical resection. See Section 13.0 for further information regarding surgery. Post-operative chemotherapy should begin as soon as possible following surgery. Therapy should not be delayed by more than one week after surgery unless complications arise. If surgery cannot be scheduled after chemotherapy Cycle 4, it should occur after chemotherapy Cycle 5.

4.1.2 Concomitant Therapy

The following guidance regarding concomitant therapy pertains primarily to the Induction phase of treatment. Additional guidance relevant to Consolidation and post-Consolidation therapy is detailed in the treatment section for those phases of therapy.

4.1.2.1 Chemotherapy or Immunomodulating Agents

No other cancer chemotherapy or immunomodulating agents (including steroids) will be used. Exception: Dexamethasone may be used as an antiemetic for short periods of time around chemotherapy administration only if all other antiemetic regimens have been maximized and the patient continues to have refractory nausea and vomiting. However, dexamethasone should be avoided during Induction Cycles 3-5 (during ch14.18 (dinutuximab) therapy) and during post-Consolidation. Corticosteroid therapy is also permitted for treatment of increased intracranial pressure or spinal cord compression and for immediate treatment of transfusion reactions.

4.1.2.2 External Beam Radiation

External beam radiotherapy is only permitted in emergency situations during Induction. Emergency situations are those that have the potential to result in loss of function (spinal cord compression, optic nerve compression).

4.1.2.3 CYP3A4 active agents

See Appendix III for a list of CYP3A4 active agents. The potential for interaction between these agents and the following drugs must carefully considered:

VinCRIStine, DOXOrubicin, etoposide
Strong inducers or inhibitors of CYP3A4 should not be administered with vinCRIStine, DOXOrubicin and etoposide if reasonable alternatives exist.

4.1.2.4 Nephro- and ototoxic agents

Administration of loop diuretics (eg, ethacrynic acid, furosemide, and bumetanide) and/or aminoglycosides should be avoided if possible during CISplatin-containing cycles of chemotherapy. Concurrent usage may increase the risk of nephrotoxicity and ototoxicity.

4.1.2.5 Enzyme inducing anticonvulsants

Enzyme inducing anticonvulsants (e.g. phenytoin, phenobarbital, and carbamazepine) should not be given concurrent with administration of vinCRIStine. See Appendix IV.

4.1.3 Induction Therapy

Patients will receive 5 cycles of chemotherapy. Each chemotherapy cycle lasts 21 days (3 weeks). Chemotherapy cycles **EXCEPT** Cycle 1 may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after post-chemotherapy nadir. There are no hematologic criteria to begin Cycle 1. See Section 5.0 for specifics regarding criteria to begin Induction chemotherapy cycles in the setting of myelosuppression and for dose

modifications for toxicity. See Section 18.0 for details regarding the PBSC harvest that will occur after Induction Cycle 2, and Section 16.0 for details regarding imaging that will occur prior to surgical resection and at end of Induction. Refer to Section 13.0 for details regarding the surgical resection that will occur after Induction Chemotherapy Cycle 4 (or Cycle 5 if medically necessary). Institutional count recovery criteria for surgical resection should be followed.

4.1.4 Consolidation Therapy

Consolidation therapy includes tandem transplant therapy (Thiotepa/Cyclophosphamide and modified CARBOplatin/Etoposide/Melphalan; TC/CEM). For further information regarding drug doses, schedules and administration, please see the Treatment Details in Sections 4.7 and 4.8. It is recommended that Consolidation treatment begin between 4 and 6 weeks from the start date of Induction chemotherapy Cycle 5. For patients who have surgical resection delayed until after Induction chemotherapy Cycle 5, it is recommended that Consolidation start within 4 weeks from the date of surgery.

Patients with progressive disease at the end of Induction evaluation (after completion of Cycle 5) are NOT eligible to continue on to the Consolidation phase of protocol therapy. Other eligibility criteria that must be met prior to starting Consolidation are listed in Section 4.6.6.

Restaging will not be performed between transplant cycles. Patients who complete the prescribed transplant component of therapy will not be required to undergo a disease evaluation prior to radiation therapy unless clinically indicated OR unless > 5 sites of metastatic disease were seen on the end-Induction MIBG or PET scan. Such patients will undergo repeat imaging to direct radiation therapy. See Section 17.0 for further information about radiation decision making for this group of patients.

Following completion of transplant and recovery from transplant related acute toxicities, patients will receive 21.6 Gy external beam radiation therapy (EBRT) to the primary site regardless of presence or absence of residual primary tumor at end Induction.

Patients with residual MIBG (if MIBG avid disease) or PET (if MIBG non-avid disease) positive metastases detected on end-Induction disease evaluations will receive 21.6 Gy EBRT to address up to and including 5 metastatic sites of disease. Patients with > 5 sites of residual metastatic disease detectable on end-Induction MIBG or PET scans will undergo repeat MIBG or PET scans (using the same modality used previously) upon recovery from HSCT #2. See Section 17.5.2.2 for additional information regarding radiation for such patients.

Local radiation therapy will begin no earlier than Day +42 following HSCT #2.See Section 18.0 for details regarding HSCT and Section 17.0 for details regarding radiation therapy.

4.1.5 Post-Consolidation Summary

All patients will receive standard post-Consolidation therapy with ISOtretinoin (ISOT) for 6 cycles during post-Consolidation therapy. For the first 5 of those cycles, patients will also receive ch14.18 (dinutuximab) combined with sargramostim (GM-CSF).

4.2 Induction Cycle 1

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

Begin Cycle 1 of therapy regardless of blood counts. See Section 5.0 for dose modifications. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Cyclophosphamide (CPM)	IV over 15-30 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.2.3 BSA ≥ 0.6 m^2: 400 mg/m^2/dose	Days 1-5	
Topotecan (TOPO)	IV over 30 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.2.3 BSA ≥ 0.6 m^2: 1.2 mg/m^2/dose	Days 1-5	
Myeloid Growth Factor	Start myeloid growth factor support 24 – 48 hours after the final dose of chemotherapy: e.g., (1) filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir or until the ANC ≥ 750 if it is ≥ Day 21 of the cycle: **or, (2) pegfilgrastim (0.1 mg/kg SubQ once; maximum dose 6 mg)**. Filgrastim should be discontinued for at least 24 hours before the start of the Cycle 2. If pegfilgrastim is used, the next chemotherapy cycle should start at least 14 days after pegfilgrastim administration.			

Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	CPM ____mg	TOPO ____mg	Myeloid growth factor used: _____ Calc. dose _____		Studies
			Enter calculated dose above and actual dose administered below		Start Date	Stop Date	
		1	_____mg	_____mg			a-p
		2	_____mg	_____mg			
		3	_____mg	_____mg			
		4	_____mg	_____mg			
		5	_____mg	_____mg			
		6					p
		7					
		8					b, c
		15					b, c
		22	Begin Cycle 2 on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).				

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

4.2.2 Required Observations in Induction Cycle 1

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

a. Physical exam, height, weight
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine, magnesium, phosphorous
d. ALT, AST, total bilirubin
e. Free T4, TSH
f. Urinalysis
g. Pregnancy test (obtain for females of childbearing potential)
h. GFR or creatinine clearance (obtain if serum creatinine is above maximum for age and sex)
i. ECG
j. ECHO or MUGA
k. Audiogram or BAER (may be obtained during Cycle 1 or 2 of therapy)
l. Cross sectional tumor imaging (MRI or CT) (submit for central review)
m. ^{123}I-MIBG scan – may be obtained during the first or second week of Cycle 1 (submit for central review)
n. FDG-PET/CT or PET/MR scan for patients with ^{123}I-MIBG non-avid disease - may be obtained during the first or second week of Cycle 1. Submit for central review.
o. Bilateral bone marrow aspirates and biopsies
p. Specimens for correlative studies (see Section 15 and Appendix V for specimen requirements)

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

Comments
(Include any held doses, or dose modifications)

4.2.3 Treatment Details for Induction Cycle 1 (3 weeks = 1 cycle)

Cyclophosphamide: **IV over 15-30 minutes**
Days: 1-5
Dose: For BSA ≥ 0.6 m^2 the dose of cyclophosphamide is 400 mg/m^2/dose.

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

Cyclophosphamide	
BSA (m^2)	Dose
0.25-0.29	68 mg
0.3-0.34	100 mg
0.35-0.39	124 mg
0.4-0.44	148 mg
0.45-0.49	180 mg
0.5-0.54	200 mg
0.55-0.59	220 mg

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

Topotecan: **IV over 30 minutes**
Days: 1-5
Dose: For BSA ≥ 0.6 m^2 the dose of topotecan is 1.2 mg/m^2/dose.

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

Topotecan	
BSA (m^2)	Dose
0.25-0.29	0.32 mg
0.3-0.34	0.38 mg
0.35-0.39	0.44 mg
0.4-0.44	0.5 mg
0.45-0.49	0.56 mg
0.5-0.54	0.62 mg
0.55-0.59	0.68 mg

Myeloid Growth Factors:
During Induction Cycle 1, cytokine support can include filgrastim or biosimilar or pegfilgrastim. Filgrastim or biosimilar should be administered at a dose of 5 mcg/kg/dose SubQ once daily. Pegfilgrastim should be administered at a dose 0.1 mg/kg/dose (maximum dose 6 mg) SubQ ONCE according to institutional standard guidelines. Choice of myeloid growth factor must be recorded appropriately in the therapy delivery maps. Myeloid growth factors should be started 24 – 48 hours after the final dose of chemotherapy. If filgrastim or biosimilar is used, it should be continued until the ANC ≥ 2000/µL following the nadir. Discontinue filgrastim or biosimilar a minimum of 24 hours prior to

administration of the next chemotherapy cycle. If the ANC has recovered to ≥ 750/µL by Day 21, but has not yet reached ≥ 2000, discontinue filgrastim and proceed to Cycle 2. If pegfilgrastim is used, the next chemotherapy cycle should start at least 14 days after pegfilgrastim administration.

Following completion of this cycle, Cycle 2 starts on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). **See Section 5.0 for Dose Modifications for Toxicities.**

4.3 Induction Cycle 2

4.3.1 Therapy Delivery Map – INDUCTION CYCLE 2 Cycle 2 lasts 3 weeks (21 days).	_____ Patient COG ID number _____ DOB

Begin Cycle 2 on Day 22 of Induction Cycle 1 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). For instructions regarding discontinuation of myeloid growth factor see Section 4.3.3. See Section 5.0 for dose modifications and for modification in timing of therapy for patients with delayed count recovery. Peripheral blood stem cells will be harvested as counts recover after Cycle 2. See Section 18.0 for information regarding stem cell harvest. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Cyclophosphamide (CPM)	IV over 15-30 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.3.3 BSA ≥ 0.6 m^2: 400 mg/m^2/dose	Days 1-5	
Topotecan (TOPO)	IV over 30 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.3.3 BSA ≥ 0.6 m^2: 1.2 mg/m^2/dose	Days 1-5	
Myeloid Growth Factor	Start filgrastim or biosimilar 5-10 mcg/kg/dose SubQ daily 24 – 48 hours after the final dose of chemotherapy. Follow Section 18.2 and institutional guidelines for use of growth factors prior to stem cell apheresis. Filgrastim should be discontinued at least 24 hours before the start of the next cycle. **Do NOT administer pegfilgrastim during Cycle 2.**			

Ht _____ cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CPM ____mg	TOPO ____mg	Myeloid growth factor used: _____ Calc. dose_____		Studies
			Enter calculated dose above and actual dose administered below		Start Date	Stop Date	
		1	_____mg	_____mg			a-f
		2	_____mg	_____mg			
		3	_____mg	_____mg			
		4	_____mg	_____mg			
		5	_____mg	_____mg			
		8					b, c
		15	PBSC Harvest as counts recover See Section 18.3				b, c
		22	Begin Cycle 3 on Day 22 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).				

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

4.3.2 Required Observations in Induction Cycle 2

a. Physical exam, height, weight
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine
d. ALT, AST, total bilirubin
e. Urinalysis
f. Audiogram or BAER: If not obtained during Cycle 1. Must be obtained prior to Cycle 3.

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

Comments
(Include any held doses, or dose modifications)

4.3.3 Treatment Details for Induction Cycle 2 (3 weeks = 1 cycle)

Cyclophosphamide: **IV over 15-30 minutes**
Days: 1-5
Dose: For BSA ≥ 0.6 m^2 the dose of cyclophosphamide is 400 mg/m^2/dose.

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

Cyclophosphamide	
BSA (m^2)	Dose
0.25-0.29	68 mg
0.3-0.34	100 mg
0.35-0.39	124 mg
0.4-0.44	148 mg
0.45-0.49	180 mg
0.5-0.54	200 mg
0.55-0.59	220 mg

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

Topotecan: **IV over 30 minutes**
Days: 1-5
Dose: For BSA ≥ 0.6 m^2 the dose of topotecan is 1.2 mg/m^2/dose.

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

Topotecan	
BSA (m^2)	Dose
0.25-0.29	0.32 mg
0.3-0.34	0.38 mg
0.35-0.39	0.44 mg
0.4-0.44	0.5 mg
0.45-0.49	0.56 mg
0.5-0.54	0.62 mg
0.55-0.59	0.68 mg

Myeloid Growth Factors:
Start myeloid growth factor support once daily after myelosuppressive chemotherapy. Pegfilgrastim is NOT permitted during Induction Cycle 2. See Section 18 for recommendations regarding use of growth factors and stem cell harvest.

Cycle 2 chemotherapy is administered in the same manner as that administered in Cycle 1. However, the dose of filgrastim following Cycle 2 may be larger (5- 10 mcg/kg/day) in anticipation of apheresis, per institutional guidelines. As with Cycle 1, filgrastim will start 24-48 hours after the final dose of chemotherapy.

Peripheral blood stem cells are to be harvested as counts recover after Cycle 2. See Section 18.2 for additional details.

See Section 5.0 for Dose Modifications for Toxicities.

4.4 Induction Cycle 3

4.4.1 Induction Therapy Cycle 3: CISplatin, Etoposide, Ch14.18 (Dinutuximab), and Sargramostim (GM-CSF)

Cycle 3 lasts 3 weeks (21 days).

_____
COG Patient ID Number

_____
DOB

Start Cycle 3 once peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Drugs should be given in the order listed below (see Section 4.4.3 for a summary of the schedule). See Section 5.0 for dose modification for organ dysfunction. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
CISplatin (CDDP)	IV over 1 hour	BSA < 0.6 m^2: See Dosing Table in Section 4.4.3 BSA ≥ 0.6 m^2: 60 mg/m^2/dose	1-3	Avoid use of dexamethasone during Cycle 3 of Induction therapy. See Section 4.4.3 for hydration and antiemetic recommendations.
Etoposide (ETOP)	IV over 2 hours	BSA < 0.6 m^2: See Dosing Table in Section 4.4.3 BSA ≥ 0.6 m^2: 200 mg/m^2/dose	1-3	
Ch14.18 (Dinutuximab)	IV over 10 hrs† †The infusion duration may be extended up to 20 hours if needed.	17.5 mg/m^2/dose See admin guidelines in Section 4.4.3.	2-5	**Ch14.18 (dinutuximab) should not be started prior to confirmation of adequate PBSC collection** (see Section 18. 2. and 4.4.3). For premedication and supportive care, see Section 4.4.4. Prior to the first dose of ch14.18 (dinutuximab), patients should not have dyspnea at rest or an oxygen requirement (see Section 4.4.3).
Sargramostim (GM-CSF)	SubQ	250 micrograms/m^2/dose	6 or 7 - nadir	Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab). See Section 4.4.3 for more details. Sargramostim should not be started prior to confirmation of adequate PBSC collection (see Section 18.2 and 4.4.3). If sargramostim and ch14.18 (dinutuximab) are not administered, start myeloid growth factor as outlined in Section 4.4.3.

Ht____cm Wt____kg BSA____m^2

Due Date	Date Given	Day	CDDP ____mg	ETOP ____mg	Ch14.18 ____mg	GM-CSF ____mcg	Cycle 3 Studies
			Enter calculated dose above and actual dose administered below				
		1	_____mg	_____mg			a-d, e if indicated, f
		2	_____mg	_____mg	____mg		c*
		3	_____mg	_____mg	____mg		c*
		4			____mg		c*
		5			____mg		c*
		6				____mcg	b, f
		7				____mcg	
		8				____mcg	b, c
		9				____mcg	
		10				____mcg	
		11				____mcg	
		12				____mcg	
		13				____mcg	
		14				____mcg	
		15				____mcg	b, c
		16				____mcg	
		17				____mcg	
		18				____mcg	
		19				____mcg	
		20				____mcg	
		21				____mcg	
		22	Begin the next cycle on Day 22 or when starting criteria are met, whichever occurs later (see Section 4.5.1).				

*Only required on Days 2-5 if ch14.18 (dinutuximab) is administered. See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in Induction Cycle 3

a. Physical exam, height, weight
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine, magnesium, phosphorus
d. ALT, AST, total bilirubin
e. GFR or Creatinine Clearance (obtain if serum creatinine is above maximum for age/sex or if serum creatinine increases to > 2 x baseline)
f. Correlative studies (see Section 15 and Appendix V for specimen requirements)

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

Comments
(Include any held doses, or dose modifications)

4.4.3 Treatment Details for Induction Therapy for Cycle 3

Begin therapy as early in the day as possible.

A summary of drug administration schedule for Days 1-5 is below.
Day 1:

1. CISplatin will be administered following pre-hydration.
2. Etoposide will be administered immediately after CISplatin, during post-CISplatin hydration.

Days 2 & 3:

1. CISplatin will be administered first, followed by post-hydration.
2. Etoposide will be administered immediately after CISplatin, during post-CISplatin hydration.
3. The ch14.18 (dinutuximab) infusion will be started immediately after completion of etoposide, during post-CISplatin hydration.

Days 4 & 5:

1. The ch14.18 (dintuximab) infusion will be started approximately 24 hours after the start of the prior ch14.18 (dinutuximab) dose.

CISplatin: IV over 1 hour. Protect from light.
Days: 1-3
Dose: For BSA ≥ 0.6 m^2 the dose of CISplatin is 60 mg/m^2/dose.

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

CISplatin	
BSA (m^2)	Dose
0.25-0.29	10 mg
0.30-0.34	14 mg
0.35-0.39	18 mg
0.40-0.44	22 mg
0.45-0.49	26 mg
0.50-0.54	30 mg
0.55-0.59	34 mg

Special precautions: Avoid use of aluminum containing needles or administration sets, since aluminum interacts with CISplatin causing black precipitate formation and loss of potency. The infusion solution should include at least 0.2% sodium chloride. To avoid precipitation, CISplatin solutions should not be refrigerated. CISplatin is incompatible with sodium bicarbonate and alkaline solutions. Accidental extravasation with solutions that are > 0.5 mg/mL may result in significant tissue toxicity.

Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).

Antiemetics may be used as needed. Dexamethasone and other corticosteroids SHOULD NOT BE GIVEN unless clinically indicated. Since dexamethasone is

discouraged [due to administration of ch14.18 (dinutuximab)], recommend maximizing antiemetics as suggested below.

Refer to institutional standards or use the following recommended antiemetic regimen:
- Ondansetron 0.15 mg/kg IV q8hrs (max 8 mg/dose); may consider another 5HT3 antagonist
- Diphenhydramine 0.5 mg/kg – 1 mg/kg IV q8hr (max 50 mg/dose) – begin 4 hours after 1st dose of ondansetron
- Lorazepam 0.04 mg/kg IV q8hr (max 2 mg/dose)
- Aprepitant 3 mg/kg (max 125 mg/dose) 1 hour prior to chemotherapy on Day 1 then 2 mg/kg (max 80 mg/dose) on Days 2 and 3. Do not use in patients < 6 months of age and/or < 6 kg.

Cisplatin Hydration and Fluid Status Monitoring Recommendations
Patients may receive aggressive pre- and post-CISplatin hydration IV fluids per institutional guidelines. The following IV fluid rate(s) and fluid status monitoring are recommended. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

Day 1 Pre-Hydration:
- A pre-hydration rate of 125 mL/m^2/hr overnight (prior to Day 1) or a rapid pre-hydration rate of 150-200 mL/m^2/hr for at least 2 hours AND
- Urine output of at least 1.5 mL/kg/hr for patients weighing < 70 kg or
- Urine output of at least 100 mL/hr in patients who weigh ≥ 70 kg
- Continue fluid rate throughout the Day 1 CISplatin infusion.

Day 1 Post-Hydration:
- Following completion of Day 1 CISplatin, continue the fluid rate at 125 mL/m^2/hr
- Continue until 24 hours after the completion of the last (Day 3) CISplatin infusion.

Day 4 Post-Hydration (24 hours after the Day 3 CISplatin infusion):
- Decrease the IV fluid rate to 90 mL/m^2/hr
- Continue fluids at this rate until the completion of the final ch14.18 (dinutuximab) infusion.
- Hydration fluids may contain supplemental magnesium, calcium, and potassium to decrease acute electrolyte losses associated with CISplatin therapy.

Fluid Status Monitoring:
The patient's fluid status (intake and output) should be monitored closely while receiving therapy. Patients are at risk for capillary leak related to ch14.18 (dinutuximab). Patients have known decreased urine output during ch14.18 (dinutuximab) therapy. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

For post-CISplatin monitoring, it is recommended that electrolytes be monitored daily and urine output (UOP) of ≥ 1 mL/kg/hr for patients < 70 kg or ≥ 100 mL/hr for patients ≥ 70 kg until 24 hours after the last dose of CISplatin be maintained. If the UOP is < 1 mL/kg/hr, may administer a bolus of 10 mL/kg of 0.9% NaCl. If the UOP remains < 1 mL/kg/hr, a second bolus of 10 mL/kg of 0.9% NaCl is recommended. If the UOP remains low, check electrolytes BID and consider administering a dose of mannitol. Given the concerns with ototoxicity and nephrotoxicity associated with CISplatin and furosemide, exercise caution and check chemistries twice a day if furosemide is administered.

Etoposide: **IV over 2 hours**
Days: 1-3
Dose: For BSA ≥ 0.6 m^2 the dose of etoposide is 200 mg/m^2/dose.

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

Etoposide	
BSA (m^2)	Dose
0.25-0.29	34 mg
0.3-0.34	48 mg
0.35-0.39	60 mg
0.4-0.44	72 mg
0.45-0.49	88 mg
0.5-0.54	100 mg
0.55-0.59	112 mg

Infuse diluted solution (concentration ≤ 0.4 mg/mL) over 120 minutes; slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

Ch14.18 (dinutuximab): IV over 10 hours*
Days: 2 through 5
Dose: 17.5 mg/m^2/dose.

Ch14.18 (dinutuximab) should not be started prior to confirmation of adequate PBSC collection (see Section 18.2). If an adequate PBSC collection (minimum of 4 x 10^6 CD34+ cells/kg) has not been obtained, then ch14.18 (dinutuximab) and sargramostim should not be administered. Instead, myeloid growth factor will be given after the completion of CISplatin and etoposide as described in Cycle 2, see Sections 4.3.1 and 4.3.3.

Note: Due to the increased risk of capillary leak and respiratory compromise with ch14.18 (dinutuximab) administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of ch14.18 (dinutuximab). Every effort should be made to give ch14.18 (dinutuximab) as ordered. Treatment may be delayed for up to one week for patients who have developed a new requirement for supplemental oxygen (due to an intercurrent illness or the like) prior to the start of a cycle of ch14.18 (dinutuximab)-containing Induction therapy. If the patient continues to have clinically significant respiratory symptoms (such as dyspnea or hypoxemia) after the one week delay and the treating team feels that the patient is ready to start the next cycle of Induction therapy, then dinutuximab should be omitted from that cycle of Induction therapy. Close monitoring of patients with prior bulky thoracic disease, pleural effusions or concurrent upper respiratory viral infections is recommended as these patients are at risk of developing respiratory compromise. **Before starting ch14.18 (dinutuximab)**, please obtain a copy of management recommendations for anaphylaxis and hypotension (see Appendix VI) and the study training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms of respiratory compromise occur.

Refer to Section 4.4.4 for premedication and supportive care for the prevention of anticipated toxicities associated with ch14.18 (dinutuximab), and for monitoring during the ch14.18 (dinutuximab) infusion. Additional information can be found in Appendix VI.

On Day 2, start ch14.18 (dinutuximab) immediately following the completion of CISplatin and etoposide. Run the ch14.18 (dinutuximab) concurrently with post-hydration fluids as outlined above. On Days 2 and 3, ch14.18 (dinutuximab) will be administered concurrently with a higher rate of post-chemotherapy hydration fluids. Once the post-chemotherapy hydration fluids are complete, it is recommended that intravenous fluids (IVF) continue at a maintenance rate through the completion of the Day 5 ch14.18 (dinutuximab) infusion. The ch14.18 (dinutuximab) should be started at a rate of 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 ch14.18 (dinutuximab) infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of ch14.18 (dinutuximab) antibody has not been delivered. Ch14.18 (dinutuximab) administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection
Days: 6 or 7 through nadir until the ANC is ≥ 2000/μL or until counts have recovered for the next cycle of therapy
Dose: 250 micrograms/m^2/dose

Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab). The sargramostim start day may fall on Day 6 or Day 7 of therapy.

If ch14.18 (dinutuximab) is not administered, sargramostim will not be administered either. Instead, myeloid growth factor will be given as described in Cycle 2, see Sections 4.3.1 and 4.3.3.

Of note, the sargramostim dose will be held if the total white blood 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 blood cell count is less than 20,000/μL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications for Toxicities.

4.4.4 Premedication and Supportive Care for the prevention of anticipated toxicities associated with ch14.18 (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: Post-chemotherapy hydration IVF will run concurrently with ch14.18 (dinutuximab) on Days 2 and 3. When post-chemotherapy hydration fluids have finished, recommend decreasing IVF to maintenance rate. Continue IVF at maintenance rate with Days 4 and 5 ch14.18 (dinutuximab). Consider administering NS 20 mL/kg IV over 1 hour just prior to the ch14.18 (dinutuximab) infusion on Days 4 and 5.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q6h. Hydroxyzine PO may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each ch14.18 (dinutuximab) infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the ch14.18 (dinutuximab) infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the ch14.18 (dinutuximab) infusion without difficulty, may consider removing the continuous infusion rate in between ch14.18 (dinutuximab) doses (when ch14.18 (dinutuximab) is not infusing).
- Recommended starting dose of analgesics:
  - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of ch14.18 (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 ch14.18 (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 q15 minutes prn for pain.
- If fentanyl PCA is used, recommend fentanyl 1 microgram/kg 10 minutes prior to starting ch14.18 (dinutuximab) infusion. At the same time, start a continuous fentanyl infusion of 0.5 microgram/kg/hr with bolus doses of 0.25 microgram/kg/dose q10 minutes prn pain.
- Doses should be titrated as needed in accordance with institutional guidelines.

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

Have immediately available during the ch14.18 (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 ch14.18 (dinutuximab) infusion:
- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until ch14.18 (dinutuximab) infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.4.5 Additional guidance

- Capillary leak syndrome is an expected side effect of ch14.18 (dinutuximab) therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Given the concerns with ototoxicity and nephrotoxicity associated with CISplatin and furosemide, exercise caution and check chemistries twice a day if furosemide is administered.

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

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting ch14.18 (dinutuximab) treatment and 1 week after completing ch14.18 (dinutuximab) therapy.

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

4.5 Induction Cycle 4

4.5.1 Therapy Delivery Map –INDUCTION CYCLE 4 Cycle 4 lasts 3 weeks (21 days). This TDM is on 3 pages.	_____ Patient COG ID number _____ DOB

Begin Cycle 4 on Day 22 of the prior cycle or as soon as the peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later). Drugs should be given in the order listed below (see Section 4.5.3 for a summary of the schedule). See Section 5.0 for dose modification for organ dysfunction. Note that surgical resection will take place following recovery from Cycle 4 chemotherapy.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 minute or infusion via minibag per institutional policy.	BSA < 0.6 m^2: See Dosing Table Section 4.5.3 BSA ≥ 0.6 m^2: 2 mg/m^2/dose	1	**Maximum dose: 2 mg.**
Dexrazoxane (DXR)	Slow IV push or infusion over 5-15 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.5.3 BSA ≥ 0.6 m^2: 375 mg/m^2/dose	1-2	Administer immediately before DOXO
DOXOrubicin (DOXO)	Slow IV push or infusion over 1-15 minutes	BSA < 0.6 m^2: See Dosing Table in Section 4.5.3 BSA ≥ 0.6 m^2: 37.5 mg/m^2/dose	1-2	Administer within 30 minutes of beginning the dexrazoxane infusion
Mesna	IV (short or continuous infusion)	BSA < 0.6 m^2: See Section 4.5.3 BSA ≥ 0.6 m^2: 400 mg/m^2/dose x 5 doses / day	1-2	See Section 4.5.3. If given as a continuous infusion, please indicate in documentation.
Cyclophosphamide (CPM)	IV over 1 hour	BSA < 0.6 m^2: See Dosing Table in Section 4.5.3 BSA ≥ 0.6 m^2: 2000 mg/m^2/dose	1-2	
Ch14.18 (dinutuximab)	IV over 10 hrs† †The infusion duration may be extended up to 20 hours if needed.	17.5 mg/m^2/dose See admin guidelines in Section 4.5.3.	2-5	**Ch14.18 (dinutuximab) should not be started prior to confirmation of adequate PBSC collection** (see Section 18. 2. and 4.5.3). For premedication and supportive care, see Section 4.5.4. Patients should not have dyspnea at rest or an oxygen requirement (see Section 4.5.3).
Sargramostim (GM-CSF)	SubQ	250 micrograms/m^2/dose	6 or 7 - nadir	Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab) (see Section 4.5.3). Sargramostim should not be started prior to confirmation of adequate PBSC collection (see Section 18.2 and 4.5.3). If sargramostim and ch14.18 (dinutuximab) are not administered, start myeloid growth factor as outlined in Section 4.5.3.

This TDM is continued on the next page.

4.5.1 Therapy Delivery Map –INDUCTION CYCLE 4 - Continued Cycle 4 lasts 3 weeks (21 days). This TDM is on 3 pages.	_____ Patient COG ID number _____ DOB

Begin Cycle 4 on Day 22 of the prior cycle or as soon as the peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Drugs should be given in the order listed below (see Section 4.5.3 for a summary of the schedule). See Section 5.0 for dose modification for organ dysfunction. Note that surgical resection will take place following recovery from Cycle 4 chemotherapy.

Ht _____ cm Wt _____kg BSA _____m²

Date Due	Date Given	Day	VCR ____mg	DXR ____mg	DOXO ____mg	Mesna ___mg ___mg ___mg ___mg ___mg ___mg	CPM ____mg	Ch14.18 ____mg	GM-CSF ____mcg	Studies
			Enter calculated dose above and actual dose administered below							
		1	_____mg	_____mg	_____mg	___mg ___mg ___mg ___mg ___mg ___mg	_____mg			a-e, g
		2		_____mg	_____mg	___mg ___mg ___mg ___mg ___mg ___mg	_____mg	____mg		c*
		3						____mg		c*
		4						____mg		c*
		5						____mg		c*
		6							____mcg	b, g
		7							____mcg	
		8							____mcg	b, c
		9							____mcg	
		10							____mcg	
		11							____mcg	
		12							____mcg	
		13							____mcg	
		14							____mcg	
		15							____mcg	b, c, f, g
		16							____mcg	
		17							____mcg	
		18							____mcg	
		19							____mcg	
		20							____mcg	
		21							____mcg	
		22	Proceed to surgery after Cycle 4 and obtain correlative studies samples as per Appendix V. Begin Cycle 5 upon recovery from surgery. If surgery is delayed until after Cycle 5, begin Cycle 5 chemotherapy when counts recover (ANC ≥ 750/µL and platelets ≥ 75,000/µL) and obtain correlative studies samples pre- and post-surgery							

*Only required on Days 2-5 if ch14.18 (dinutuximab) is administered.

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

Induction Cycle 4

4.5.2 Required Observations in Induction Cycle 4

a. Physical exam, height, weight b. CBC with differential and platelets c. Electrolytes, BUN, creatinine d. ALT, AST, total bilirubin e. Urinalysis f. Cross sectional imaging of primary site (MRI or CT) – perform between Days 15 and 21 (pre-surgery). g. Correlative studies (see Section 15 and Appendix V)

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

Comments (Include any held doses, or dose modifications)

4.5.3 Treatment Details for Induction Cycle 4

Begin therapy as early in the day as possible.

A summary of drug administration schedule for Days 1 - 5 is below.

Day 1:

1. VinCRIStine should be administered first.
2. Dexrazoxane should then be administered, followed immediately by doxorubicin.
3. Doxorubicin should be administered within 30 minutes of beginning the dexrazoxane infusion.
4. Mesna should then be administered. The initial dose of mesna may be administered 15 minutes before or at the same time as cyclophosphamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of cyclophosphamide.
5. Cyclophosphamide should be administered over 1 hour.

Day 2:

1. Dexrazoxane should be administered first, followed immediately by doxorubicin.
2. Doxorubicin should be administered within 30 minutes of beginning the dexrazoxane infusion.
3. Mesna should then be administered. The initial dose of mesna may be administered 15 minutes before or at the same time as cyclophosphamide dose; subsequent mesna doses are given 3, 6, 9, and 12 hours after the start of cyclophosphamide.
4. Cyclophosphamide should be administered over 1 hour.
5. The ch14.18 (dinutuximab) infusion should be started immediately after cyclophosphamide is completed and should infuse concurrently with post-chemotherapy hydration.

Days 3 - 5:

1. The dintuximab infusion will be started approximately 24 hours after the start of the Day 2 ch14.18 (dinutuximab) dose. Intravenous fluids should continue at a maintenance rate throughout the duration of the ch14.18 (dinutuximab) infusion.

<u>VinCRIStine:</u> IV push over 1 minute or infusion via minibag as per institutional policy
Day: 1
Dose: For BSA ≥ 0.6 m^2 the dose of vinCRIStine is 2 mg/m^2/dose. **The max dose of vinCRIStine is 2 mg.**

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

VinCRIStine	
BSA (m^2)	Dose
0.25-0.29	0.32 mg
0.3-0.34	0.46 mg
0.35-0.39	0.6 mg
0.4-0.44	0.72 mg
0.45-0.49	0.85 mg
0.5-0.54	1 mg
0.55-0.59	1.1 mg

Administer vinCRIStine prior to dexrazoxane.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine.

<u>Dexrazoxane:</u> Slow IV push or IV given over 5-15 minutes immediately prior to administration of DOXOrubicin
Days: 1 and 2
Dose: For BSA ≥ 0.6 m^2 the dose of dexrazoxane is 375 mg/m^2/dose.

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

Dexrazoxane	
BSA (m^2)	Dose
0.25-0.29	66 mg
0.3-0.34	92 mg
0.35-0.39	120 mg
0.4-0.44	140 mg
0.45-0.49	160 mg
0.5-0.54	180 mg
0.55-0.59	200 mg

DOXOrubicin: IV Slow IV push or given over 1-15 minutes immediately after dexrazoxane administration.
Days: 1 and 2
Dose: For BSA ≥ 0.6 m^2 the dose of DOXOrubicin is 37.5 mg/m^2/dose.

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

DOXOrubicin	
BSA (m^2)	Dose
0.25-0.29	6.6 mg
0.3-0.34	9.2 mg
0.35-0.39	12 mg
0.4-0.44	14 mg
0.45-0.49	16 mg
0.5-0.54	18 mg
0.55-0.59	20 mg

IV push/short infusion: Administer after dexrazoxane at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 15 minutes. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Administer DOXOrubicin after completing the infusion of dexrazoxane but within 30 minutes of beginning the dexrazoxane infusion.

Mesna: IV (short or continuous infusion; start after completion of vinCRIStine, dexrazoxane, and DOXOrubicin)
Days: 1-2
Dose:
BSA < 0.6 m^2: Total dose of mesna per day is equal to the total daily cyclophosphamide dose divided into 5 equal doses given at the same time or 15 min prior to cyclophosphamide and again at 3, 6, 9, and 12 hours from the start of cyclophosphamide infusion.

BSA ≥ 0.6 m^2: 400 mg/m^2/dose x 5 doses per day given at the same time or 15 min prior to cyclophosphamide and again at 3, 6, 9, and 12 hours from the start of cyclophosphamide infusion.

IV short or continuous infusion: For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily cyclophosphamide dose. Mesna can be administered in 5 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as cyclophosphamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of cyclophosphamide.

For example: if cyclophosphamide dose is 1,000 mg, then the total daily mesna dose is 1,000 mg; 200 mg of mesna will be given 15 minutes before or with the cyclophosphamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 12 hours after the end of the cyclophosphamide infusion.

Cyclophosphamide: IV over 1 hour
Days: 1 and 2
Dose: For BSA ≥ 0.6 m^2 the dose of cyclophosphamide is 2000 mg/m^2/dose.

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

Cyclophosphamide	
BSA (m^2)	Dose
0.25-0.29	360 mg
0.3-0.34	480 mg
0.35-0.39	600 mg
0.4-0.44	720 mg
0.45-0.49	880 mg
0.5-0.54	1000 mg
0.55-0.59	1100 mg

Cyclophosphamide Hydration and Fluid Status Monitoring Recommendations:
Patients may receive pre- and post-cyclophosphamide hydration IV fluids per institutional guidelines. The following IV fluid rate(s) and fluid status monitoring are recommended. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

Day 1 Pre-Hydration:
- A pre-hydration rate of 125 mL/m^2/hr for a minimum of two hours AND
- Urine specific gravity ≤ 1.010 prior to the start of cyclophosphamide

Day 1 Post-Hydration:
- Following completion of Day 1 cyclophosphamide, continue the fluid rate at 125 mL/m^2/hr
- Continue until 24 hours after the completion of the last cyclophosphamide infusion.

Day 3 Post-Hydration (24 hours after the Day 2 cyclophosphamide infusion):
- Decrease the IV fluid rate to 90 mL/m^2/hr
- Continue fluids at this rate until the completion of the final ch14.18 (dinutuximab) infusion.

Fluid Status Monitoring:
The patient's fluid status (intake and output) should be monitored closely while receiving therapy. Patients are at risk for capillary leak related to ch14.18 (dinutuximab). Patients have known decreased urine output during ch14.18 (dinutuximab) therapy. The routine use of diuretics during Days 2-5 is

contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

For post-cyclophosphamide monitoring, it is recommended that electrolytes be monitored daily and urine output (UOP) of ≥ 1 mL/kg/hr for patients < 70 kg or ≥ 100 mL/hr for patients ≥ 70 kg until 24 hours after the last dose of cyclophosphamide be maintained. If the UOP is < 1 mL/kg/hr, may administer a bolus of 10 mL/kg of 0.9% NaCl. If the UOP remains < 1 mL/kg/hr, a second bolus of 10 mL/kg of 0.9% NaCl is recommended. If the UOP remains low, check electrolytes BID and consider administering a diuretic.

Ch14.18 (dinutuximab): IV over 10 hours*
Days: 2 through 5
Dose: 17.5 mg/m^2/dose.

Ch14.18 (dinutuximab) should not be started prior to confirmation of adequate PBSC collection (see Section 18.2). If an adequate PBSC collection (minimum of 4 x 10^6 CD34+ cells/kg) has not been obtained, then ch14.18 (dinutuximab) and sargramostim should not be administered. Instead, myeloid growth factor will be given after completion of vincristine, DOXOrubicin, cyclophosphamide therapy as described in Cycle 2, see Sections 4.3.1 and 4.3.3.

Note: Due to the increased risk of capillary leak and respiratory compromise with ch14.18 (dinutuximab) administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of ch14.18 (dinutuximab). Every effort should be made to give ch14.18 (dinutuximab) as ordered. Treatment may be delayed for up to one week for patients who have developed a new requirement for supplemental oxygen (due to an intercurrent illness or the like) prior to the start of a cycle of ch14.18 (dinutuximab)-containing Induction therapy. If the patient continues to have clinically significant respiratory symptoms (such as dyspnea or hypoxemia) after the one week delay and the treating team feels that the patient is ready to start the next cycle of Induction therapy, then dinutuximab should be omitted from that cycle of Induction therapy. Close monitoring of patients with prior bulky thoracic disease, pleural effusions or concurrent upper respiratory viral infections is recommended as these patients are at risk of developing respiratory compromise. **Before starting ch14.18 (dinutuximab)**, please obtain a copy of management recommendations for anaphylaxis and hypotension (See Appendix VI) and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms of respiratory compromise occur.

Refer to Section 4.5.4 for premedication and supportive care for the prevention of anticipated toxicities associated with ch14.18 (dinutuximab), and for monitoring during the ch14.18 (dinutuximab) infusion. Additional information can be found in Appendix VI.

Ch14.18 (dinutuximab) should be administered immediately after cyclophosphamide has been given, as early in the day as possible. Ch14.18 (dinutuximab) will be administered concurrently with a higher rate of post-chemotherapy hydration fluids on Day 2. Once post-chemotherapy hydration fluids are complete, it is recommended that intravenous fluids (IVF) continue at

a maintenance rate through the completion of the Day 5 ch14.18 (dinutuximab) infusion. The ch14.18 (dinutuximab) should be started at a rate of 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 ch14.18 (dinutuximab) infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of ch14.18 (dinutuximab) antibody has not been delivered. Ch14.18 (dinutuximab) administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim (GM-CSF): Subcutaneous injection
Days: 6 or 7 through nadir until the ANC is ≥ 2000/μL after the expected nadir or until Day 21. May discontinue if ANC >750 on Day 21.
Dose: 250 mcg/m^2/dose

Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab). The sargramostim start day may fall on Day 6 or Day 7 of therapy.

If ch14.18 (dinutuximab) is not administered, sargramostim will not be administered either. Instead, myeloid growth factor will be given as described in Cycle 2, see Sections 4.3.1 and 4.3.3.

Of note, the sargramostim dose will be held if the total white blood 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 blood cell count is less than 20,000/μL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

Following Cycle 4, patients will receive surgery followed by Induction Cycle 5. If clinically indicated, it is permissible for surgery to take place after the fifth cycle of Induction.

See Section 5.0 for Dose Modifications for Toxicities.

4.5.4 Premedication and Supportive Care for the prevention of anticipated toxicities associated with ch14.18 (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: Post-chemotherapy hydration IVF will run concurrently with Day 2 ch14.18 (dinutuximab). When post-chemotherapy hydration fluids have finished, recommend decreasing IVF to maintenance rate. Continue IVF at maintenance rate with Days 3, 4 and 5 ch14.18 (dinutuximab). Consider administering NS 20 mL/kg IV over 1 hour just prior to the ch14.18 (dinutuximab) infusion on Days 4 and 5.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q6h. Hydroxyzine PO may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each ch14.18 (dinutuximab) infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the ch14.18 (dinutuximab) infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the ch14.18 (dinutuximab) infusion without difficulty, may consider removing the continuous infusion rate in between ch14.18 (dinutuximab) doses [when ch14.18 (dinutuximab) is not infusing].
- Recommended starting dose of analgesics:
  - Morphine 0.1mg/kg/dose 20 minutes prior to initiation of ch14.18 (dinutuximab) infusion. At the same time, start a continuous morphine infusion of 0.02mg/kg/hr with bolus doses of 0.01mg/kg/dose q15 minutes prn for pain.
  - If hydromorphone PCA is used, recommend hydromorphone pre-infusion dose of 0.02 mg/kg/dose 20 minutes prior to starting the infusion of ch14.18 (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 ch14.18 (dinutuximab) infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
  - Doses should be titrated as needed in accordance with institutional guidelines.

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

<u>Have immediately available during the ch14.18 (dinutuximab) infusion</u>:

a. Albuterol and oxygen
b. Epinephrine

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

Monitoring during the ch14.18 (dinutuximab) infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until ch14.18 (dinutuximab) infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.5.5 Additional guidance

- Capillary leak syndrome is an expected side effect of ch14.18 (dinutuximab) therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Given the concerns with ototoxicity and nephrotoxicity associated with furosemide, exercise caution and check chemistries twice a day if furosemide is administered.

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

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting ch14.18 (dinutuximab) treatment and 1 week after completing ch14.18 (dinutuximab) therapy.

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

4.6 Induction Therapy Cycle 5

4.6.1 Induction Therapy Cycle 5: CISplatin, Etoposide, Ch14.18 (Dinutuximab), and Sargramostim (GM-CSF) This cycle lasts 3 weeks (21 days).	_____ COG Patient ID Number _____ DOB

Begin Cycle 5 when counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL AND upon recovery from surgery or Day 22 (whichever occurs later). Drugs should be given in the order listed below (see Section 4.6.3 for a summary of the schedule). See Section 5.0 for dose modification for organ dysfunction. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
CISplatin (CDDP)	IV over 1 hour	BSA < 0.6 m^2: See Dosing Table in Section 4.6.3 BSA ≥ 0.6 m^2: 60 mg/m^2/dose	1-3	Avoid use of dexamethasone during Cycle 5 of Induction therapy. See Section 4.6.3 for hydration and antiemetic recommendations.
Etoposide (ETOP)	IV over 2 hours	BSA < 0.6 m^2: See Dosing Table in Section 4.6.3 BSA ≥ 0.6 m^2: 200 mg/m^2/dose	1-3	
Ch14.18 (dinutuximab)	IV over 10 hrs† †The infusion duration may be extended up to 20 hours if needed.	17.5 mg/m^2/dose See admin guidelines in Section 4.6.3.	2 – 5	For premedication and supportive care, see Section 4.6.4. Prior to the first dose of ch14.18 (dinutuximab), patients should not have dyspnea at rest or an oxygen requirement (see Section 4.6.3).
Sargramostim (GM-CSF)	SubQ	250 micrograms/m^2/dose	6 or 7 - nadir	Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab) (see Section 4.6.3).

Ht____cm Wt____kg BSA____m^2

Due Date	Date Given	Day	CDDP ____mg	ETOP ____mg	Ch14.18 ____mg	GM-CSF ____mcg	Cycle 5 Studies
			Enter calculated dose above and actual dose administered below				
		1	mg	mg			a-d, e if indicated, n
		2	mg	mg	mg		c
		3	_____mg	_____mg	____mg		c
		4			____mg		c
		5			____mg		c
		6				____mcg	n
		7				____mcg	
		8				____mcg	b, c
		9				____mcg	
		10				____mcg	
		11				____mcg	
		12				____mcg	
		13				____mcg	
		14				____mcg	
		15				____mcg	b, c
		16				____mcg	
		17				____mcg	
		18				____mcg	
		19				____mcg	
		20				____mcg	
		21				____mcg	a - n
		22	Begin Consolidation when criteria in Section 4.6.6 are met.				

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

4.6.2 Required Observations in Induction Cycle 5

a. Physical exam, height, weight
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine, calcium, magnesium, phosphorous
d. ALT, AST, total bilirubin
e. GFR or creatinine clearance (due at end Induction for all patients; due at start of Cycle 5 if serum creatinine is above maximum for age/sex or if serum creatinine increases to > 2 x baseline)
f. Pregnancy test (obtain for females of childbearing potential)
g. ECG
h. ECHO or MUGA
i. Audiogram or BAER
j. Cross sectional tumor imaging (MRI or CT) (submit for central review)
k. ^{123}I-MIBG scan if MIBG-avid disease at baseline (submit for central review)
l. FDG-PET/CT or PET/MR scan if obtained and positive for disease at baseline (submit for central review)
m. Bilateral bone marrow aspirates and biopsies (submit for central review per Section 14.2)
n. Correlative studies (see Section 15 and Appendix V)

Disease evaluation may be performed after the completion of Induction therapy (chemotherapy and resection of the primary tumor), between Day 17 of Cycle 5 and prior to the start of Consolidation.

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

Comments
(Include any held doses, or dose modifications)

4.6.3 Treatment Details for Induction Therapy for Cycle 5

Begin therapy as early in the day as possible.

A summary of drug administration schedule for Days 1-5 is below.
Day 1:

1. CISplatin will be administered first following pre-hydration.
2. Etoposide will be administered immediately after CISplatin, during post-CISplatin hydration.

Days 2 & 3:

1. CISplatin will be administered first, followed by post-hydration.
2. Etoposide will be administered immediately after CISplatin, during post-CISplatin hydration.
3. The ch14.18 (dinutuximab) infusion will be started immediately after completion of etoposide, during post-CISplatin hydration.

Days 4 & 5:

1. The dintuximab infusion will be started approximately 24 hours after the start of the prior ch14.18 (dinutuximab) dose.

CISplatin: IV over 1 hour. Protect from light.
Days: 1-3
Dose: For BSA ≥ 0.6 m^2 the dose of CISplatin is 60 mg/m^2/dose.

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

CISplatin	
BSA (m^2)	Dose
0.25-0.29	10 mg
0.30-0.34	14 mg
0.35-0.39	18 mg
0.40-0.44	22 mg
0.45-0.49	26 mg
0.50-0.54	30 mg
0.55-0.59	34 mg

Special precautions: Avoid use of aluminum containing needles or administration sets, since aluminum interacts with CISplatin causing black precipitate formation and loss of potency. The infusion solution should include at least 0.2% sodium chloride. To avoid precipitation, CISplatin solutions should not be refrigerated. CISplatin is incompatible with sodium bicarbonate and alkaline solutions. Accidental extravasation with solutions that are > 0.5 mg/mL may result in significant tissue toxicity.

Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).

Antiemetics
Antiemetics may be used as needed. Dexamethasone and other corticosteroids SHOULD NOT BE GIVEN unless clinically indicated. Since dexamethasone is

discouraged [due to administration of ch14.18 (dinutuximab)], recommend maximizing antiemetics as suggested below.

Refer to institutional standards or use the following recommended antiemetic regimen:
- Ondansetron 0.15 mg/kg IV q8hrs (max 8 mg/dose); may consider other 5HT3 antagonist
- Diphenhydramine 0.5 mg/kg – 1 mg/kg IV q8hr (max dose 50 mg/dose) – begin 4 hours after 1st dose of ondansetron
- Lorazepam 0.04 mg/kg IV q8hr (max 2 mg/dose)
- Aprepitant 3 mg/kg (max 125 mg/dose) 1 hour prior to chemotherapy on Day 1 then 2 mg/kg (max 80 mg/dose) on Days 2 and 3. Do not use in patients < 6 months of age and/or < 6 kg

Cisplatin Hydration and Fluid Status Monitoring Recommendations
Patients may receive aggressive pre- and post-CISplatin hydration IV fluids per institutional guidelines. The following IV fluid rate(s) and fluid status monitoring are recommended. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

Day 1 Pre-Hydration:
- A pre-hydration rate of 125 mL/m^2/hr overnight (prior to Day 1) or a rapid pre-hydration rate of 150-200 mL/m^2/hr for at least 2 hours AND
- Urine output of at least 1.5 mL/kg/hr for patients weighing < 70 kg or
- Urine output of at least 100 mL/hr in patients who weigh ≥ 70 kg
- Continue fluid rate throughout the Day 1 CISplatin infusion.

Day 1 Post-Hydration:
- Following completion of Day 1 CISplatin, continue the fluid rate at 125 mL/m^2/hr
- Continue until 24 hours after the completion of the last (Day 3) CISplatin infusion.

Day 4 Post-Hydration (24 hours after the Day 3 CISplatin infusion):
- Decrease the IV fluid rate to 90 mL/m^2/hr
- Continue fluids at this rate until the completion of the final ch14.18 (dinutuximab) infusion.
- Hydration fluids may contain supplemental magnesium, calcium, and potassium to decrease acute electrolyte losses associated with CISplatin therapy.

Fluid Status Monitoring:
The patient's fluid status (intake and output) should be monitored closely while receiving therapy. Patients are at risk for capillary leak related to ch14.18 (dinutuximab). Patients have known decreased urine output during ch14.18 (dinutuximab) therapy. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise).

For post-CISplatin monitoring, it is recommended that electrolytes be monitored daily and urine output (UOP) of ≥ 1 mL/kg/hr for patients < 70 kg or ≥ 100 mL/hr for patients ≥ 70 kg until 24 hours after the last dose of CISplatin be maintained. If the UOP is < 1 mL/kg/hr, may administer a bolus of 10 mL/kg of 0.9% NaCl. If the UOP remains < 1 mL/kg/hr, a second bolus of 10 mL/kg of 0.9% NaCl is recommended. If the UOP remains low, check electrolytes BID and consider administering a dose of mannitol. Given the concerns with ototoxicity and nephrotoxicity associated with CISplatin and furosemide, exercise caution and check chemistries twice a day if furosemide is administered.

Etoposide: IV over 2 hours
Days: 1-3
Dose: For BSA ≥ 0.6 m^2 the dose of etoposide is 200 mg/m^2/dose.

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

Etoposide	
BSA (m^2)	Dose
0.25-0.29	34 mg
0.3-0.34	48 mg
0.35-0.39	60 mg
0.4-0.44	72 mg
0.45-0.49	88 mg
0.5-0.54	100 mg
0.55-0.59	112 mg

Infuse diluted solution (concentration ≤ 0.4 mg/mL) over 120 minutes; slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

Ch14.18 (dinutuximab): IV over 10 hours*
Days: 2 through 5
Dose: 17.5 mg/m^2/dose.

Note: Due to the increased risk of capillary leak and respiratory compromise with ch14.18 (dinutuximab) administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of ch14.18 (dinutuximab). Every effort should be made to give ch14.18 (dinutuximab) as ordered. Treatment may be delayed for up to one week for patients who have developed a new requirement for supplemental oxygen (due to an intercurrent

illness or the like) prior to the start of a cycle of ch14.18 (dinutuximab)-containing Induction therapy. If the patient continues to have clinically significant respiratory symptoms (such as dyspnea or hypoxemia) after the one week delay and the treating team feels that the patient is ready to start the next cycle of Induction therapy, then dinutuximab should be omitted from that cycle of Induction therapy. Close monitoring of patients with prior bulky thoracic disease, pleural effusions or concurrent upper respiratory viral infections is recommended as these patients are at risk of developing respiratory compromise. **Before starting ch14.18 (dinutuximab)**, please obtain a copy of management recommendations for anaphylaxis and hypotension (see Appendix VI) and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms of respiratory compromise occur.

Refer to Section 4.6.4 for premedication and supportive care for the prevention of anticipated toxicities associated with ch14.18 (dinutuximab), and for monitoring during the ch14.18 (dinutuximab) infusion. Additional information can be found in Appendix VI.

On Day 2, start ch14.18 (dinutuximab) immediately following the completion of CISplatin and etoposide. Run the ch14.18 (dinutuximab) concurrently with post-hydration fluids as outlined above. On Days 2 and 3, ch14.18 (dinutuximab) will be administered concurrently with a higher rate of post-chemotherapy hydration fluids on Days 2 and 3. Once the post-chemotherapy hydration fluids are complete, it is recommended that IVF continue at a maintenance rate through the completion of the Day 5 ch14.18 (dinutuximab) infusion. The ch14.18 (dinutuximab) should be started at a rate of 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 ch14.18 (dinutuximab) infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of ch14.18 (dinutuximab) antibody has not been delivered. Ch14.18 (dinutuximab) administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

Sargramostim: Subcutaneous injection
Days: 6 or 7 through nadir until the ANC is ≥ 2000/μL or until counts have recovered for the next cycle of therapy
Dose: 250mcg/m^2/dose

Start sargramostim 24-48 hours after the completion of Day 5 ch14.18 (dinutuximab). The sargramostim start day may fall on Day 6 or Day 7 of therapy.

Of note, the sargramostim dose will be held if the total white blood 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 blood cell count is less than 20,000/μL and then sargramostim will be resumed at 50% dose for the remainder of that cycle. Full dose sargramostim will be used for subsequent sargramostim cycles.

See Section 5.0 for Dose Modifications for Toxicities.

4.6.4 Premedication and Supportive Care for the prevention of anticipated toxicities associated with ch14.18 (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: Post-chemotherapy hydration IVF will run concurrently with ch14.18 (dinutuximab) on Days 2 and 3. When post-chemo hydration fluids have finished, recommend decreasing IVF to maintenance rate. Continue IVF at maintenance rate with Days 4 and 5 ch14.18 (dinutuximab). Consider administering NS 20 mL/kg IV over 1 hour just prior to the ch14.18 (dinutuximab) infusion on Days 4 and 5.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q6h. Hydroxyzine PO may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each ch14.18 (dinutuximab) infusion and scheduled q4-6h prn.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) or continuous opioid infusion during the ch14.18 (dinutuximab) infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the ch14.18 (dinutuximab) infusion without difficulty, may consider removing the continuous infusion rate in between ch14.18 (dinutuximab) doses (when ch14.18 (dinutuximab) is not infusing).
- Recommended starting dose of analgesics:
  - Morphine 0.1mg/kg/dose 20 minutes prior to initiation of ch14.18 (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 ch14.18 (dinutuximab). At the same time, start a continuous hydromorphone infusion of 0.004 mg/kg/hr (maximum initial rate: 0.2 mg/**h**our 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 ch14.18 (dinutuximab) infusion. At the same time, start a continuous fentanyl infusion of 0.5 mcg/kg/hr with bolus doses of 0.25 mcg/kg/dose q10 minutes prn pain.
- Doses should be titrated as needed in accordance with institutional guidelines.

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

Have immediately available during the ch14.18 (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 ch14.18 (dinutuximab) infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until ch14.18 (dinutuximab) infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.6.5 Additional guidance

- Capillary leak syndrome is an expected side effect of ch14.18 (dinutuximab) therapy. Complications of capillary leak syndrome can be mitigated if euvolemia is maintained. Close monitoring of heart rate and urine output is required, and fluids should be adjusted to compensate for third space losses. The routine use of diuretics during Days 2-5 is contraindicated unless clinically required (i.e. pulmonary capillary leak with respiratory compromise). Given the concerns with ototoxicity and nephrotoxicity associated with CISplatin and furosemide, exercise caution and check chemistries twice a day if furosemide is administered.

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

- The use of IVIG is discouraged. IVIG should not be given within 2 weeks of starting ch14.18 (dinutuximab) treatment and 1 week after completing ch14.18 (dinutuximab) therapy.

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

4.6.6 Criteria to Start Consolidation Therapy

It is recommended that Consolidation therapy should begin between 4 and 6 weeks after the start of Induction chemotherapy Cycle 5. In addition, patients must meet the criteria below:

- End of Induction disease evaluation demonstrating complete response (CR), partial response (PR), minor response (MR), or stable disease (SD) (see Section 10.2.3).
- Minimum number of frozen PBSCs remaining (with a back-up recommended but not required; see Section 18.3 for collection details).
  - Treatment requires that 2 bags of stem cells (each containing at least 2 x 10^6 CD34+ cells/kg based on weight at the start of Consolidation) remain available for each patient. A backup containing the same number of cells is strongly recommended but not required.
- ALT < 3 x ULN for age. For the purposes of this study, ULN for SGPT (ALT) is 45 IU/L
- Total bilirubin ≤ 1.5 x ULN for age; if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal
- Shortening fraction ≥ 27% **or** ejection fraction ≥ 50%, **and** no clinical evidence of congestive heart failure
- No evidence of dyspnea at rest and no requirement for supplemental oxygen
- GFR ≥ 60 mL/min/1.73m^2 assessed via nuclear blood sampling method or iothalamate clearance method
- No uncontrolled infection
- Recovery from acute toxicities of final cycle of Induction therapy

Patients unable to meet the criteria to begin Consolidation therapy within 12 weeks from the start of Cycle 5 of Induction therapy should undergo a disease re-evaluation before proceeding to Consolidation when criteria are met. If patients are unable to move to Consolidation within 16 weeks from the start of Cycle 5 Induction therapy, due to an inability to meet Consolidaton criteria, then they will be removed from protocol therapy.

4.7 Consolidation HSCT #1

4.7.1 Consolidation Therapy HSCT#1	_____ COG Patient ID Number _____ DOB

Begin HSCT#1 once criteria in Section 4.6.6 have been met. See TDM for Cycle 5 Induction for observations due at the end of Induction and prior to the start of Consolidation. See Section 4.7.3 for recommended anti-sinusoidal obstruction syndrome (SOS) prophylaxis. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Thiotepa (TEPA)	IV over 2 hours	300 mg/m^2/dose **or** If ≤ 12 kg: 10 mg/kg/dose Once daily	-7, -6 and -5	Thiotepa can cause significant skin toxicity, including sloughing of skin. See Section 6.15
Cyclophosphamide (CPM)	IV over 1 hour	1500 mg/m^2/dose **or** If ≤ 12 kg: 50 mg/kg/dose Once daily	-5, -4, -3, and -2	Suggested hydration at 3000 mL/m^2/day using fluid containing at least 0.45% NaCl. Suggest achieving urine specific gravity ≤ 1.010 prior to start of cyclophosphamide.
Mesna	IV (short or continuous infusion)	300 mg/m^2/dose **or** If ≤ 12 kg: 10 mg/kg/dose Given prior to the start of CPM and again 4 and 8 hours after the start of CPM	-5, -4, -3, and -2	See Section 4.7.3. If given as a continuous infusion, please indicate in documentation.
Filgrastim (G-CSF) or biosimilar	SubQ	5 micrograms/kg once daily until ANC recovery per institutional guidelines	Recommend beginning on Day 0 after stem cell infusion and continue per institutional guidelines	**Do not substitute** other colony stimulating factors (eg, pegfilgrastim or sargramostim).

Ht _____ cm Wt _____ kg BSA _____m^2

Date Due	Date Given	Day	TEPA ____mg	CPM ____mg	Mesna _____mg	G-CSF: _____mcg		Studies
			Enter calculated dose above and actual dose administered below			**Start Date**	**Stop Date**	
		-7	____mg					a-e
		-6	____mg					b, c
		-5	____mg	_____mg	____mg ____mg ____mg			b
		-4		_____mg	____mg ____mg ____mg			b, c
		-3		_____mg	____mg ____mg ____mg			b
		-2		_____mg	____mg ____mg ____mg			b, c
		-1	Rest					
		0	**PBSC Infusion (see Section 18.6)**					a, b (daily until neutrophil engraftment), c (every other day if stable) d (twice weekly)
		42	Proceed to HSCT#2 no less than 6 weeks and prior to 10 weeks from Day 0 of HSCT# 1					

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

4.7.2 Required Observations in Consolidation Therapy for HSCT #1

a. Physical exam, weight, and height to be obtained within 1 week prior to Day -7 b. CBC with differential and platelets c. Electrolytes, BUN, creatinine d. ALT, AST, total bilirubin e. Urinalysis

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

Comments (Include any held doses, or dose modifications)

4.7.3 Treatment Details for Consolidation HSCT#1

Thiotepa: IV over 2 hours
Days: -7 to -5
Dose: 300 mg/m^2/dose (or if ≤ 12 kg, 10 mg/kg/dose)

Thiotepa can cause significant skin toxicity, including sloughing of skin. Frequent bathing and linen changes should be done to avoid chemical skin burns. See Section 6.15.

Cyclophosphamide: IV over 1 hour
Days: -5 to -2
Dose: 1500 mg/m^2/dose (or if ≤ 12 kg, 50 mg/kg/dose)
Suggested hydration at 3000 mL/m^2/day using fluid containing at least 0.45% NaCl. Suggest achieving urine specific gravity ≤ 1.010 prior to start of cyclophosphamide.

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

Mesna: IV (short or continuous infusion)
Days: -5 to -2
Dose: Mesna 300 mg/m^2/dose (or if ≤ 12 kg, 10 mg/kg/dose) immediately prior to each cyclophosphamide dose and then 4 hours and 8 hours after the start of each cyclophosphamide dose.

Mesna can be administered in 3 divided doses by **short infusion (as above)** over 15 to 30 minutes. The initial bolus dose of mesna may be administered beginning 15-30 minutes before or at the same time as the cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide.

For example: If the cyclophosphamide dose is 1,500 mg, then the total daily mesna dose is 900 mg; 300 mg of mesna will be given 15-30 minutes before or with the cyclophosphamide dose. Two boluses of 300 mg each will be given at Hours 4 and 8 after the start of the cyclophosphamide dose.

Alternatively, mesna can be administered as a **continuous infusion (900 mg/m^2).** The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 12 hours after the end of the cyclophosphamide infusion.

For example: If the cyclophosphamide dose is 1,500 mg, then the total daily mesna dose is 900 mg; the 900 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the cyclophosphamide and be

completed no sooner than 12 hours after **the end** of the cyclophosphamide infusion.

Peripheral Blood Stem Cell (PBSC) infusion
Days: Day 0
Please see Section 18.6 for PBSC infusion details.

Filgrastim or biosimilar: SubQ
Days: Recommend beginning on Day 0 after stem cell infusion and continue per institutional guidelines
Dose: 5 micrograms/kg/dose (recommended starting dose)
Note: Do not substitute other colony stimulating factors (eg, pegfilgrastim or sargramostim).

Anti-sinusoidal obstruction syndrome (SOS) prophylaxis:
The use of ursodiol is strongly recommended during conditioning and through engraftment, with dosing per institutional guidelines. Suggested ursodiol dosing is 150 mg/m^2/dose PO, administered BID (up to 300 mg PO BID), beginning on Day -7 and continuing a minimum of 28 days post-transplant, or until the end of Consolidation. Defibrotide for SOS prophylaxis (or SOS therapy) may be used per institutional guidelines.

Please see COG endorsed supportive care guidelines (https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines) for suggested management of febrile neutropenia, mucositis, chemotherapy induced nausea and vomiting (CINV), and antifungal prophylaxis or manage per institutional guidelines. The use itraconazole, voriconazole, and posaconazole during chemotherapy conditioning should be avoided due to potential interaction with cyclophosphamide.

4.7.4 Criteria to Start Consolidation HSCT #2 (modified CEM)

No restaging will be performed between transplants unless clinically indicated. Patients will proceed to HSCT #2 (modified CEM) no less than 6 weeks and prior to 10 weeks from Day 0 of HSCT #1, provided they have recovered from acute toxicities of HSCT #1 and meet organ function criteria for HSCT #2.

All patients must have repeat GFR testing after hematologic recovery from HSCT #1 and prior to HSCT #2. GFR testing must be performed using direct measurement either with a nuclear blood sampling method or iothalamate clearance method. If the GFR is < 100 mL/min/1.73m^2, modified dosing is used as noted below. If the GFR is < 60 mL/min/1.73m^2, the patient is NOT eligible to receive HSCT #2.

Additional criteria to proceed to HSCT #2 include the following:

1. Resolution of acute pulmonary or cardiac toxicities developed during HSCT#1.
2. ALT < 3 x ULN. For the purposes of this study, ULN for ALT (SGPT) is 45 IU/L.
3. Total bilirubin ≤ Grade 1 (> ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal)

4. Shortening fraction ≥ 27%, or ejection fraction ≥ 50%, no clinical congestive heart failure
5. No evidence of dyspnea at rest and no requirement for supplemental oxygen
6. No uncontrolled infection
7. No prior history of severe liver dysfunction (such as CTC Grade 4 bilirubin) or sinusoidal obstruction syndrome (SOS) (formerly veno-occlusive disease (VOD)) during HSCT#1, defined as:
   CTCAE v5.0 Grade 4 SOS, or Grade 3 SOS **PLUS** a specific organ failure listed below:
   - CTC Grade 4 hepatic failure, OR
     Pulmonary dysfunction: Grade 3 hypoxia necessitating continuous oxygen support for >48 hours, ventilator support not clearly attributable to another cause, OR
   - Renal dysfunction: CTC Grade 3 creatinine, or the need for dialysis (CTC Grade 4 acute kidney injury), not clearly attributable to another cause.
8. A minimum of 2 x 10^6 CD34 cells/kg PBSCs must be available to proceed with HSCT #2
10. No clinical evidence of progressive disease as defined in Section 10.2.3; restaging studies between HSCT courses only as clinically indicated.
11. ANC recovery to ≥ 750/µL after HSCT #1
12. Platelet count > 20,000/µL (transfusion permitted)
13. Recovery from other acute toxicities related to HSCT#1

4.8 Consolidation HSCT #2

4.8.1 Consolidation HSCT #2.	_____ COG Patient ID Number _____ DOB

Start HSCT#2 once criteria in Section 4.7.4 have been met. See Section 4.8.3 for recommended anti-sinusoidal obstruction syndrome (SOS) prophylaxis. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Melphalan (MEL)	IV over 30 minutes	60 mg/m^2/dose **or** If ≤ 12 kg: 2 mg/kg/dose Once daily	Days -7, -6 and -5	See Section 4.8.3
Etoposide (ETOP)	IV over 24 hours	**GFR ≥ 100 mL/min/1.73m^2** 300 mg/m^2/dose **or** If ≤ 12 kg: 10 mg/kg/dose **GFR 60-99 mL/min/1.73m^2** 200 mg/m^2/dose **or** If ≤ 12 kg: 6.7 mg/kg/dose Once daily	Days -7, -6, -5 and -4	
CARBOplatin (CARBO)	IV over 24 hours	See Dosing Table in Section 4.8.3	Days -7, -6, -5 and -4	
Filgrastim (G-CSF) or biosimilar	SubQ	5 micrograms/kg once daily until recovery per institutional guidelines.	Recommend beginning on Day 0 after stem cell infusion and continue per institutional guidelines	Do not substitute other colony stimulating factors (eg, pegfilgrastim or sargramostim).

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	MEL ____mg	ETOP ____mg	CARBO ____mg	G-CSF: _____mcg		Studies
			Enter calculated dose above and actual dose administered below			Start Date	Stop Date	
		-7	mg	mg	mg			a-f
		-6	mg	mg	mg			b, c
		-5	mg	mg	mg			b
		-4		mg	mg			b, c
		-3						b
		-2						b, c
		-1	Rest					b
		0	**PBSC Infusion (See Section 18.6)**					a, b (daily until neutrophil engraftment), c (every other day if stable), d (twice weekly if stable)
		42	Begin radiation therapy no sooner than 42 days post-transplant, (see Section 17.0).					For patients with >5 persistently positive metastatic sites on end-Induction imaging, obtain MIBG or PET (as appropriate) for radiation planning purposes.

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

4.8.2 Required Observations in Consolidation Therapy for HSCT #2

a. Physical exam, weight, height to be obtained within one week prior to Day -7
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine
d. ALT, AST, total bilirubin
e. Urinalysis
f. GFR testing: must be performed using direct measurement either with a nuclear blood sampling method or iothalamate clearance method. See Section 4.7.4.

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

Comments
(Include any held doses, or dose modifications)

4.8.3 Treatment Details for Consolidation HSCT #2

As noted above, if the GFR is < 60 mL/min/1.73m^2, the patient is not eligible to receive HSCT #2 (see Section 4.7.4).

Melphalan: IV Infuse over 30 minutes.
Days: -7 to -5
Dose: 60 mg/m^2/dose (or if ≤ 12 kg, 2 mg/kg/dose, not adjusted for renal dysfunction) once daily

Stability: Melphalan stability is concentration-dependent once diluted for administration. The drug is most stable in NS. See Section 6.11 for agent specific preparation and stability information.

Etoposide: IV Infuse diluted solution (concentration ≤ 0.4 mg/mL) over 24 hours; slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested.
Days: -7 to -4
Dose (GFR ≥ 100 mL/min/1.73m^2): 300 mg/m^2/dose (or if ≤ 12 kg, 10 mg/kg/dose) continuous infusion once daily
Dose (GFR 60 to 99 mL/min/1.73m^2): 200 mg/m^2/dose (or if ≤ 12 kg, 6.7 mg/kg/dose) continuous infusion once daily

Special precautions: Etoposide can be mixed in 0.9% NaCl or D5W. Avoid use of large volumes of D5W due to potential development of hyponatremia.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

CARBOplatin: IV Administer each dose of CARBOplatin over 24 hours. Compatible with both saline- and dextrose-containing fluids. Prepare per institutional guidelines.
Days: -7 to -4
Dose: According to BSA and GFR per the tables below.

CARBOplatin daily dose				
BSA (m^2)	**GFR ≥100 mL/min/1.73 m^2**	**GFR 91-99 mL/min/1.73 m^2**	**GFR 76-90 mL/min/1.73 m^2**	**GFR 60-75 mL/min/1.73 m^2**
0.25-0.29	68 mg	54 mg	48 mg	40 mg
0.30-0.34	80 mg	64 mg	56 mg	48 mg
0.35-0.39	90 mg	72 mg	64 mg	54 mg
0.40-0.44	110 mg	90 mg	74 mg	66 mg
0.45-0.49	130 mg	100 mg	90 mg	80 mg
0.50-0.54	160 mg	130 mg	110 mg	100 mg
0.55-0.59	190 mg	150 mg	130 mg	120 mg

CARBOplatin daily dose				
BSA (m^2)	**GFR ≥ 100 mL/min/1.73 m^2**	**GFR 91-99 mL/min/1.73 m^2**	**GFR 76-90 mL/min/1.73 m^2**	**GFR 60-75 mL/min/1.73 m^2**
≥ 0.6	375 **mg/m^2**	300 **mg/m^2**	260 **mg/m^2**	230 **mg/m^2**

Patients with prior allergic reactions to platinum compounds may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose: 50 mg), ranitidine 1 mg/kg IV (maximum single dose: 50 mg) or equivalent H2 antagonist e.g., famotidine, and hydrocortisone 1-4 mg/kg IV.

Avoid use of aluminum containing needles or administration sets. **Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).**

Peripheral Blood Stem Cell (PBSC) infusion (Day 0). Please see Section 18.6 for PBSC infusion details.

Filgrastim or biosimilar: SubQ
Dose: 5 micrograms/kg/dose, (recommended starting dose)
Days: Recommend beginning on Day 0 after stem cell infusion and continue per institutional guidelines

Note: Do not substitute other colony stimulating factors (eg, pegfilgrastim or sargramostim).

Anti-sinusoidal obstruction syndrome (SOS) prophylaxis:
The use of ursodiol is strongly recommended during conditioning and through engraftment, with dosing per institutional guidelines. Suggested ursodiol dosing is 150 mg/m^2/dose PO, administered BID (up to 300 mg PO BID), beginning on Day -7 and continuing a minimum of 28 days post-transplant, or until the end of Consolidation. Defibrotide for SOS prophylaxis (or SOS therapy) may be used per institutional guidelines.

Please see COG endorsed supportive care guidelines (https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines) for suggested management of febrile neutropenia, mucositis, chemotherapy induced nausea and vomiting (CINV), and antifungal prophylaxis or manage per institutional guidelines.

Note: Upon recovery following HSCT #2, radiation therapy will begin. Please note that for patients with >5 persistent tracer-avid metastatic lesions at the end of Induction, imaging for radiation planning purposes should be performed after HSCT #2. See Section 17.0 for Radiation Therapy Guidelines. CBCs should be performed at least weekly for all patients during radiation therapy; additional testing may be performed as clinically indicated.

A disease evaluation will be performed after completion of radiation therapy, prior to the start of the post-Consolidation phase of treatment. See Appendix V for correlative study specimens to be obtained at the start of post-Consolidation therapy.

4.9 Post-Consolidation Therapy

Post-Consolidation therapy will be delivered after completion of external beam radiation as per Section 17.0.

4.9.1 Criteria to Start Post-Consolidation Therapy

To begin post-Consolidation therapy, at least 1 week must have elapsed since completion of external beam radiotherapy. Patients who do not undergo radiotherapy (those with unidentifiable primary tumors and no persistent metastatic disease) may begin post-Consolidation therapy upon recovery from ASCT. Prior to the start of post-Consolidation Therapy, patients will undergo a disease evaluation to consist of cross sectional tumor imaging (MRI or CT), an ^{123}I-MIBG or PET scan, and bilateral bone marrow aspirates and biopsies.

All patients must start post-Consolidation by Day 200 after HSCT #2 PBSC infusion (or HSCT #1 PBSC infusion if patient did not receive HSCT #2) and meet the following criteria to proceed, otherwise they will be removed from protocol therapy:

- Stable disease or better on complete disease re-evaluation (CNS imaging not required but recommended)
- No sooner than 1 week from completion of external beam radiotherapy
- ANC ≥ 500/µL
- Patients with a history of neuroblastoma metastatic to the central nervous system should receive platelet transfusion support to maintain platelet counts ≥ 50,000/µL. There is no platelet requirement for patients without a history of CNS metastases; platelets should be supported as per institutional standards for clinical care
- ALT < 10 x ULN for age. For the purposes of this protocol, the ULN for ALT is 45 IU/L.
- Total bilirubin ≤ 1.5 x ULN for age or > 1.0 – 1.5 x baseline if baseline was abnormal
- Renal function that meets criteria below
  - Creatinine clearance or radioisotope GFR ≥ 60 mL/min/1.73 m^2 or
  - A serum creatinine based on age/sex as follows:

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

- Cardiac function that meets criteria below
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by ECHO or radionuclide angiogram.
- Adequate respiratory function as reflected in absence of dyspnea at rest and no oxygen requirements. If PFTs are performed, FEV_1/FVC must be > 60%
- No uncontrolled infection
- Negative pregnancy test in females of childbearing potential
- Patients on immunosuppressive medications (e.g. tacrolimus, cyclosporine, corticosteroids for reasons other than prevention/treatment of allergic reactions, adrenal replacement therapy, etc) are not eligible.

4.9.2 Criteria to start Post-Consolidation Cycles 2-5:

a. ALT < 10x normal 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.
b. No evidence of serious infection, or infection under control with no active disease and negative blood culture
c. A serum creatinine based on age/sex as follows:

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

d. To proceed to post-Consolidation Cycle 4, patients must have no evidence of disease progression on the post-Cycle 3 evaluation. 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 bone marrow aspirates/biopsies as part of the post-Cycle 3 evaluation.

4.9.3 Criteria to Start ISOtretinoin in Each Cycle

- ALT ≤ 10 x ULN for age. For the purposes of this study, ULN for ALT is 45 IU/L
- Serum triglycerides < 500 mg/dL
- Serum creatinine below the upper limit of normal for age and sex per table above

Observations may be obtained within 7 days prior to start of ISOtretinoin.

4.9.4 Premedication and Supportive Care for the prevention of anticipated toxicities associated with ch14.18 (dinutuximab)

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

- IV hydration: Administer NS 20 mL/kg IV over 1 hour just prior to each ch14.18 (dinutuximab) infusion.
- Diphenhydramine 1 mg/kg/dose (maximum 50 mg) IV/PO 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q6h. Hydroxyzine PO may be used instead of diphenhydramine in patients for whom there is a specific indication.
- Ranitidine 1 mg/kg/dose (maximum 50 mg) IV 20 minutes prior to ch14.18 (dinutuximab) infusion and scheduled q8h or equivalent H2 antagonist e.g. famotidine IV.
- Acetaminophen PO/IV: 15 mg/kg/dose (maximum 1000 mg) 20 minutes prior to each ch14.18 (dinutuximab) infusion and scheduled q4-6h prn.

- May consider ibuprofen 10 mg/kg/dose (maximum 800 mg) PO scheduled q6 in patients with adequate platelets and adequate renal function as needed for control of persistent fever or pain.
- Consider use of cetirizine for patients with a history of allergic reactions
- Use of a patient controlled analgesia device (PCA) during the ch14.18 (dinutuximab) infusion is recommended. Morphine is the most commonly administered opioid. May use hydromorphone or fentanyl in patients with known indications for use of hydromorphone or fentanyl. If the patient tolerates the ch14.18 (dinutuximab) infusion without difficulty, may consider removing the continuous infusion rate.
- Recommended starting dose of analgesics is the maximum dose used for treatment of pain associated with previous ch14.18 (dinutuximab) cycles or the following:
  - Morphine 0.1 mg/kg/dose 20 minutes prior to initiation of ch14.18 (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 ch14.18 (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 micrograms/kg 10 minutes prior to starting dose of ch14.18 (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.
- To reduce opiate requirements during ch14.18 (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 ch14.18 (dinutuximab) administration. Dosing should follow institutional standards, however the following dosing may be considered:
  - Day 1: 5 mg/kg/dose (max 300 mg/dose) at bedtime
  - Day 2: 5 mg/kg/dose (max 300 mg/dose) BID
  - Day 3: 5 mg/kg/dose (max 300 mg/dose) TID – patients should be at this dose by the time of admission for the first cycle of ch14.18 (dinutuximab)
  - Gabapentin doses can be increased further if necessary; institutional guidelines should be followed

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.

Fluid shifts and increased insensible volume losses due to fever are commonly seen in patients receiving ch14.18 (dinutuximab). In addition to the IV saline bolus given immediately prior to the start of ch14.18 (dinutuximab) in patients with a prior history of hypotension-related to ch14.18 (dinutuximab), recommend administering IV fluids at maintenance rate while receiving the ch14.18 (dinutuximab). Fluids can be adjusted as needed based on intravascular volume status.

<u>Have immediately available during the ch14.18 (dinutuximab) infusion</u>:

a. Albuterol and oxygen

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

Monitoring during the ch14.18 (dinutuximab) infusion:

- Check vital signs every 15 minutes for the first hour; if stable check vitals hourly until ch14.18 (dinutuximab) infusion is complete
- Strict intake and output every 4 hours
- Call front line clinician for:
  a. Altered blood pressure (refer to baseline values for patient and normal values for age/sex/height of patient), tachycardia, tachypnea, fever
  b. Pain requiring an increase in narcotic infusion rate
  c. Urticaria, bronchospasm, peripheral/sensory neurotoxicity, new persistent cough

4.9.5 Additional guidance

- Capillary leak syndrome is an expected side effect of ch14.18 (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 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 tumors, bronchospasm or stridor unresponsive to other measures or life-threatening allergic reaction). Corticosteroids will impair the immune activation that is a critical part of the protocol therapy. **The use of steroids at any time during immunotherapy requires clear justification and documentation.**

- The use of IVIG during post-Consolidation therapy is discouraged. If necessary, IVIG may be given during the first 100 days post-ASCR because IVIG may interfere with ch14.18 (dinutuximab) dependent cellular cytotoxicity. IVIG should not be given within 2 weeks of starting ch14.18 (dinutuximab) treatment and 1 week after completing ch14.18 (dinutuximab) therapy; (i.e, if necessary, IVIG may be given on Days 14-17 and 42-45 of immunotherapy.

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

4.9.6 Post-Consolidation Therapy Cycles 1 - 5

4.9.6.1 Post Consolidation Therapy Cycles 1 - 5: Sargramostim (GM-CSF), Ch14.18 (Dinutuximab), and ISOtretinoin

Each cycle lasts 28 days.

_____
COG Patient ID Number

_____
DOB

Start Cycle 1 once criteria in Section 4.9.1 have been met. It is recommended that post-Consolidation cycles begin on a Wednesday or Thursday to allow for fresh specimen shipments. This TDM is on 2 pages.
Start Cycles 2 - 5 once criteria in Section 4.9.2 have been met.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Sargramostim (GM-CSF)	SubQ	250 micrograms/m^2/dose	1 – 14	Administer **prior to** ch14.18 (dinutuximab) administration. Follow GM-CSF with NS bolus (20 mL/kg) over 1 hour on Days 4-7. See guidelines in Section 4.9.8.
Ch14.18 (Dinutuximab)	IV over 10 hrs†	17.5 mg/m^2/dose **See admin guidelines in Section 4.9.8**	4 – 7	Start **1 hour after** GM-CSF administration (ie, immediately following NS bolus). † Start at 0.88 mg/m^2/hour x 0.5 hour, then 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 if needed.
ISOtretinoin (ISOT)	PO	BSA < 0.6 m^2: See Dosing Table in 4.9.8 BSA ≥ 0.6 m^2: 80 mg/m^2/dose BID	11–24	BID dosing. See additional starting criteria for ISOtretinoin in Section 4.9.3

Enter Cycle # _____ (1 - 5) Ht____cm Wt____kg BSA____m^2

Due Date	Date Given	Day	GM-CSF ____mcg	Ch14.18 ____mg	ISOT _____mg _____mg	Cycle 1 Studies	Cycles 2- 5 Studies
			Enter calculated dose above and actual dose administered below				
		Prior to start				a – m	a – d, m
		1	____mcg				
		2	____mcg				
		3	____mcg				
		4	____mcg	____mg		b, c, d, m	b, c, d Cycle 2 only: m
		5	____mcg	____mg		c	c
		6	____mcg	____mg		c	c
		7	____mcg	____mg		b, c, d, e, m	c, d, e, m
		8	____mcg				
		9	____mcg				
		10	____mcg				
		11	____mcg		_____mg _____mg		
		12	____mcg		_____mg _____mg		
		13	____mcg		_____mg _____mg		
		14	____mcg		_____mg _____mg		
		15			_____mg _____mg		
		16			_____mg _____mg		
		17			_____mg _____mg		
		18			_____mg _____mg		
		19			_____mg _____mg		
		20			_____mg _____mg		
		21			_____mg _____mg		
		22			_____mg _____mg		
		23			_____mg _____mg		
		24			_____mg _____mg		Cycle 3 only: g-j
		25-28	Rest Period				
		29	Begin the next cycle on Day 29 or when starting criteria are met, whichever occurs later (for Cycles 2 - 5 see Section 4.9.2; for Cycle 6 see Section 4.9.3).				

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

4.9.7 Required Observations in Post-Consolidation Cycles 1 – 5

a. Physical exam, height, weight
b. CBC with differential and platelets
c. Electrolytes, BUN, creatinine
d. ALT, AST, total bilirubin
e. Triglycerides, calcium
f. Free T4, TSH
g. Cross sectional tumor imaging (MRI or CT). This is required for all patients prior to start of post-Consolidation; only required after Cycle 3 for patients with residual disease detected at the start of post-Consolidation (only submit the scan obtained prior to the start of post-Consolidation for central review)
h. ^{123}I-MIBG scan (only submit the scan obtained prior to the start of post-Consolidation for central review)
i. FDG-PET/CT or PET/MR scan for patients with MIBG-non-avid disease (only submit the scan obtained prior to the start of post-Consolidation for central review)
j. Bilateral bone marrow aspirates and biopsies. This is required for all patients prior to start of post-Consolidation; only required after Cycle 3 for patients with detectable bone marrow involvement at the start of post-Consolidation (only submit the samples obtained prior to start of post-Consolidation for central review per Section 14.2)
k. ECHO
l. ECG
m. Correlative studies (see Section 15 and Appendix V)

Disease evaluation may be performed between Days 17 and 28 of Cycle 3

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

Comments
(Include any held doses, or dose modifications)

4.9.8 Treatment Details for Post-Consolidation Therapy for Cycles 1 – 5

If patient meets criteria for discontinuation of immunotherapy (see Section 5.13.3), treatment should be continued with ISOtretinoin unless organ function criteria do not permit ISOtretinoin administration.

See guidelines for management of toxicities in Appendix VI. Before starting immunotherapy, please obtain a copy of management recommendations for anaphylaxis and hypotension available in Appendix VI and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

See Section 5.0 for Dose Modifications for Toxicities. Information on management of toxicities is also included in Section 5.0.

Sargramostim: Subcutaneous injection
Days: 1 through 14
Dose: 250 micrograms/m²/dose.

NOTE: Sargramostim should be administered daily prior to ch14.18 (dinutuximab), around 8:00 – 9:00 AM. Follow sargramostim with 0.9% sodium chloride (NS) bolus (20 mL/kg) over 1 hour Days 4, 5, 6, and 7.

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

If criteria for holding sargramostim are met (e.g., see Sections 5.12 and 5.13), then ch14.18 (dinutuximab) should be administered daily without sargramostim.

Ch14.18 (dinutuximab): IV over 10* hours
Days: 4, 5, 6 and 7
Dose: 17.5 mg/m^2/dose.

Note: Due to the increased risk of capillary leak and respiratory compromise with ch14.18 (dinutuximab) administration, patients should not have dyspnea at rest or an oxygen requirement when starting the first dose of ch14.18 (dinutuximab). **Before starting ch14.18 (dinutuximab)**, please obtain a copy of management recommendations for anaphylaxis and hypotension (see Appendix VI) and the training module on the COG website. It is recommended that these be available on the inpatient unit to facilitate treatment decisions should these symptoms occur.

Refer to Section 4.9.4 for premedication and supportive care for the prevention of anticipated toxicities associated with ch14.18 (dinutuximab), and for monitoring during the ch14.18 (dinutuximab) infusion. Additional information can be found in Appendix VI.

Prior to ch14.18 (dinutuximab) administration (morning start recommended), administer an IV bolus of normal saline (20 mL/kg) over 1 hour. Begin antibody infusion one hour after

completion of sargramostim is administered (i.e. immediately following the bolus of normal saline [20 mL/kg]. Dose should start at 0.88 mg/m^2/hour x 0.5 hour, then gradually increase to 1.75 mg/m^2/hour for the remainder of the dose, if tolerated.

*The infusion duration may be extended up to 20 hours for anticipated toxicities (hypotension, tachypnea, etc.), not responding to other supportive measures, and the duration used should be recorded. In the setting of dose reductions described in Section 5.0, the infusion must be no longer than 20 hours, even if the full dose of ch14.18 (dinutuximab) antibody has not been delivered. Cytokine and antibody administration should not be given beyond the specified schedule regardless of whether doses were modified or held per guidelines in Section 5.0.

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours even if the total dose has not been administered in that timeframe. The total dose given in 20 hours should be recorded.

ISOtretinoin (ISOT): PO BID
Days: 11-24
Dose: For BSA ≥ 0.6 m^2 the dose of ISOtretinoin is 80 mg/m^2/dose 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	
BSA (m^2)	Dose (mg)
0.25-0.29	10 mg
0.3-0.39	20 mg
0.4-0.49	30 mg
0.5-0.59	40 mg

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 drug monograph). Administration via nasogastric tube or orally via syringe is not encouraged.

See Section 5.0 for Dose Modifications for Toxicities.

4.10 Post-Consolidation Therapy Cycle 6

4.10.1 **Post-Consolidation Therapy Cycle 6 – ISOtretinoin (ISOT)** This cycle lasts 28 days.	_____ COG Patient ID Number _____ DOB

Start Cycle 6 when criteria in Section 4.10.3 are met. This cycle lasts 28 days. The TDM for this cycle is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
ISOtretinoin (ISOT)	PO	BSA < 0.6 m^2: See Dosing Table in Section 4.10.3 BSA ≥ 0.6 m^2: 80 mg/m^2/dose BID	15-28	BID dosing.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	ISOT _____mg _____mg	Studies
			Enter calculated dose above and dose administered below	
		1-14	Rest Period	
		15	_____mg _____mg	a-f
		16	_____mg _____mg	
		17	_____mg _____mg	
		18	_____mg _____mg	
		19	_____mg _____mg	
		20	_____mg _____mg	
		21	_____mg _____mg	
		22	_____mg _____mg	
		23	_____mg _____mg	
		24	_____mg _____mg	
		25	_____mg _____mg	
		26	_____mg _____mg	
		27	_____mg _____mg	
		28	_____mg _____mg	
		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.		

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

4.10.2 Required Observations Post-Consolidation Therapy Cycle 6

a. Physical exam, height and weight
b. CBC with differential and platelets
c. ALT
d. Serum triglycerides
e. Serum creatinine
f. Correlative studies (see Section 15 and Appendix V)

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

Comments
(Include any held doses, or dose modifications)

4.10.3 Treatment Details for Post-Consolidation Therapy Cycle 6

Prior to beginning treatment on Day 15 of Cycle 6, a patient must have:

- ALT ≤ 10 x ULN for age. For the purposes of this study, ULN for ALT is 45 IU/L
- Serum triglycerides < 500 mg/dL
- Serum creatinine below the upper limit of normal for age and sex per the table below

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

See Section 5.0 for Dose Modification for Toxicities. Section 5.0 also includes information for management of toxicities.

ISOtretinoin (ISOT): PO BID
Days: 15-28
Dose: For BSA ≥ 0.6 m^2 the dose of ISOtretinoin is 80 mg/m^2/dose 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	
BSA (m^2)	Dose (mg)
0.25-0.29	10 mg
0.3-0.39	20 mg
0.4-0.49	30 mg
0.5-0.59	40 mg

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 teach child 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 drug monograph). Administration via nasogastric tube or orally via syringe is not encouraged.

See Section 7.1 for end of therapy evaluations to be conducted within 2 weeks of completion of Cycle 6.
See Section 5.0 for Dose Modifications for Toxicities.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

All toxicities should be graded according to the current version of the Common Terminology Criteria for Adverse Events. Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (ie, v5.02 and all subsequent iterations prior to version 6.0).

5.1 Hematologic Toxicities during Induction therapy

5.1.1 Hematopoietic Recovery Following Induction Cycle 1

If the ANC is <750/μL and/or the platelet count is <75,000/μL on Day 22 of Cycle 1, delay Cycle 2 by up to one week. If the ANC is <750/μL and/or the platelet count is <75,000/μL on Day 29 of Cycle 1 and the patient had marrow disease at diagnosis, proceed to Cycle 2 without further delay or dose modification.

If the ANC is <750/μL and/or the platelet count is <75,000/μL on Day 29 of Cycle 1 and the patient did not have marrow disease at diagnosis, delay chemotherapy, follow blood counts according to institutional standards, and proceed to Cycle 2 upon count recovery. The following dose adjustments should be made based upon time to recovery:

- If recovery occurs between Day 30-34, proceed to Cycle 2 with full dose topotecan and cyclophosphamide.
- If recovery occurs between Day 35-43, reduce the Cycle 2 topotecan and cyclophosphamide doses by 25%.
- If recovery occurs after Day 43 reduce the Cycle 2 topotecan and cyclophosphamide doses by 50%.

5.1.2 Hematopoietic Recovery Following Induction Cycle 2

If the patient has not met hematopoietic recovery criteria on or before Day 35 after Cycle 2, perform bone marrow aspirate and biopsy. If the marrow was positive for tumor at diagnosis and still contains ≥ 5% tumor at Day 35 of Cycle 2**,** proceed with the next cycle of chemotherapy without alteration in dose, regardless of ANC and platelets IF there is evidence of recovering hematopoiesis. If the marrow has <5% tumor and/or is severely hypocellular, delay the next cycle of therapy until ANC ≥ 750/μL and platelets ≥ 75,000/μL. **Full doses of Cycle 3 chemotherapy [cisplatin, etoposide, and ch14.18 (dinutuximab)] should be given upon count recovery**.

5.1.3 Hematopoietic Recovery Following Induction Cycle 3

If the patient has not met hematopoietic recovery criteria on or before Day 35 after Cycle 3 chemotherapy, perform bilateral bone marrow aspirates and biopsies. If the marrow was positive for tumor at diagnosis and still contains ≥ 5% tumor at Day 35 of Cycle 3, see Section 10.2.3 to determine if the definition of disease progression has been met. If the patient does not meet criteria for PD, proceed with the next cycle of chemotherapy without alteration in dose, regardless of ANC and platelets IF there is evidence of recovering hematopoiesis. If the marrow has <5% tumor and/or is severely hypocellular, delay the next cycle of therapy until ANC ≥ 750/μL and platelets ≥ 75,000/μL and reduce the doses of

doxorubicin/dexrazoxane and cyclophosphamide to be given in Cycle 4 by 25%. Full dose vincristine and ch14.18 (dinutuximab) should be administered.

5.1.4 Hematopoietic Recovery Following Induction Cycle 4

If the patient has not met hematopoietic recovery criteria on or before Day 35 after Cycle 4 chemotherapy, perform bilateral bone marrow aspirates and biopsies. If the marrow contains ≥ 5% tumor at Day 35 of Cycle 4, see Section 10.2.3 to determine if the definition of disease progression has been met. If the patient does not have progressive disease, proceed with the next cycle of chemotherapy without alteration in dose regardless of ANC and platelets IF there is evidence of recovering hematopoiesis. If the marrow has <5% tumor and/or is severely hypocellular, delay the next cycle of therapy until ANC ≥ 750/μL and platelets ≥ 75,000/μL and reduce doses of etoposide and cisplatin to be given in Cycle 5 by 25%. Full dose ch14.18 (dinutuximab) should be administered.

5.2 Hematuria during Induction therapy

5.2.1 Hematuria during Induction Cycle 1 or 2

- If transient microscopic hematuria (≥ 50 RBCs per high power field 1 or 2 times) is observed, increase the rate of post-hydration to 200 mL/m^2/hour and give for 8 hours.
- For persistent microscopic hematuria (≥ 50 RBCs per high power field ≥ 3 times) or for transient gross hematuria, increase the rate of post-hydration to 200 mL/m^2/hour and continue this for 8 hours. Also add mesna as a continuous infusion at 60% of the cyclophosphamide dose to run over 8 hours.
- For persistent gross hematuria (3 or more episodes during a cyclophosphamide-containing cycle of therapy) discontinue cyclophosphamide until urine clears to microscopic hematuria. When the urine clears, resume cyclophosphamide at 50% of the full dose with post-hydration for 24 hours and add mesna as a continuous infusion at 60% of the cyclophosphamide dose to be given over 8 hours. Escalate cyclophosphamide dose to 75% and 100% of full dose on consecutive remaining days of the chemotherapy cycle as tolerated. Consider urology consultation. If gross hematuria persists or recurs, discontinue cyclophosphamide for the remainder of induction therapy.
    - If 100% of full dose was delivered without recurrent hematuria by the end of Cycle 1, full dose cyclophosphamide may be administered at the start of Cycle 2, provided that there is no hematuria detected just prior to the start of Cycle 2 therapy. If microscopic hematuria is detected prior to the start of Cycle 2 therapy, follow guidance for persistent microscopic hematuria above. If gross hematuria is detected hold cyclophosphamide and consult urology.
    - If 75% of full dose cyclophosphamide was delivered without recurrent hematuria by the end of Cycle 1, 75% of full dose should be administered at the start of Cycle 2, provided that there is no hematuria detected just prior to the start of Cycle 2 therapy. Follow the guidance in the preceding bullet if hematuria is detected prior to initiation of Cycle 2. If no hematuria is detected after administration of 75% of full dose cyclophosphamide at

the start of Cycle 2, the dose can be increased to 100% of full dose. If hematuria recurs, follow instructions above.

5.2.2 Hematuria during Induction Cycle 4

- For patients with hematuria during Cycles 1 and/or 2, if Cycle 2 ended without cyclophosphamide dose reduction due to hematuria, begin Cycle 4 with full prescribed dose. If Cycle 2 ended with a cyclophosphamide dose reduction due to hematuria, begin Cycle 4 with the analogous dose reduction (e.g., 75% dose cyclophosphamide in Cycle 2 = 300 mg/m^2/dose would correspond to 1500 mg/m^2/dose in Cycle 4), prescribe continuous mesna for 12 hours at 100% equivalent cyclophosphamide dosing, and post-hydration with 200 mL/m2/hr for 24 hours.
- If new transient microscopic hematuria (≥ 50 RBCs per high power field 1 or 2 times) is observed in Cycle 4, increase the rate of post-hydration to 200 mL/m^2/hour and give for 8 hours. Also give mesna as a continuous infusion at 100% of the cyclophosphamide dose over 8 hours.
- For persistent microscopic hematuria (≥ 50 RBCs per high power field ≥ 3 times) or for transient gross hematuria, increase the rate of post-hydration to 200 mL/m^2/hour and continue this for 24 hours. Also give mesna as a continuous infusion at 100% of the cyclophosphamide dose over 24 hours. For persistent gross hematuria (3 or more episodes during a cyclophosphamide-containing cycle of therapy) discontinue cyclophosphamide if the infusion has not been completed. Consider urology consultation. If gross hematuria persists or recurs, do not give cyclophosphamide as a substitute for cisplatin/etoposide during Induction therapy.

5.3 Renal Toxicity during Induction Therapy

5.3.1 Cisplatin

No dose reductions in cisplatin will be made for a decrease in the baseline GFR or creatinine clearance as long as the value remains ≥ 60 mL/min/1.73m².

5.3.1.1 Renal Toxicity Prior to Cisplatin Cycles

If the serum creatinine increases by > 2 x the baseline value documented in the preceding cycle of therapy **prior to** a cycle of cisplatin-containing chemotherapy, **OR** increases to greater than maximum serum creatinine for age as listed in table below, obtain a nuclear medicine GFR, estimated GFR, or creatinine clearance.

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

If the GFR, estimated GFR, or creatinine clearance is < 60 mL/min/1.73 m² prior to a cisplatin/etoposide/ch14.18 (dinutuximab) cycle, substitute a vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) cycle for the cisplatin/etoposide/ch14.18 (dinutuximab) cycle and do not give ch14.18 (dinutuximab). Make a notation of substitution of chemotherapy and omission of ch14.18 (dinutuximab) on the data forms. The intent of Induction is to give a total of 2 cycles of cyclophosphamide and topotecan, 2 cycles of cisplatin/etoposide/ch14.18 (dinutuximab), and one cycle of cyclophosphamide/ doxorubicin/vincristine/ch14.18 (dinutuximab). Therefore if a substitution of cyclophosphamide/doxorubicin/vincristine/dinutuximab cycle is made for Cycle 3 cisplatin/etoposide/ch14.18 (dinutuximab), give the cisplatin/etoposide/ch14.18 (dinutuximab) cycle later in therapy. Again, do not give ch14.18 (dinutuximab) unless the GFR is > 60 mL/min/1.73 m². If GFR, estimated GFR or creatinine clearance remains < 60 mL/min/1.73 m² when a patient is due for a subsequent cycle of cisplatin/etoposide/ch14.18 (dinutuximab), replace this cycle with a cycle of cyclophosphamide/doxorubicin/vincristine so that the patient receives a total of 5 cycles of induction chemotherapy. If the patient has received 2 cycles of topotecan and cyclophosphamide and 2 cycles of vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab), and GFR, estimated GFR, or creatinine clearance remains < 60 mL/min/1.73 m², further cycles of cisplatin therapy will be omitted. In this case, an additional cycle of vincristine/doxorubicin/cyclophosphamide should be given. Note replacement therapy and/or omission on data forms.

5.3.1.2 Renal Toxicity during Cisplatin Cycles

If, during a cycle of cisplatin-containing chemotherapy, the serum creatinine increases to > 2x the baseline value documented at the beginning of the current cycle, or increases to greater than maximum serum creatinine for age as listed in table above, then hold remaining cisplatin and ch14.18 (dinutuximab) and obtain a nuclear medicine GFR, estimated GFR, or creatinine clearance. If the GFR is < 60 mL/min/1.73m² omit the remainder of the cisplatin and ch14.18 (dinutuximab) from that cycle. If the GFR is > 60 mL/min/1.73m², may resume cisplatin and ch14.18 (dinutuximab).

5.3.2 Etoposide

If GFR, estimated GFR, or creatinine clearance is < 60 mL/min/1.73 m² prior to cisplatin/etoposide/ch14.18 (dinutuximab) cycle, substitute a vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) cycle for the cisplatin/etoposide/ch14.18 (dinutuximab) cycle and do not give the ch14.18 (dinutuximab). Follow the instructions in the preceding section regarding additional substitutions for persistently decreased renal function.

5.3.3 Cyclophosphamide, Doxorubicin, Vincristine and Topotecan

No dose reductions in cyclophosphamide, doxorubicin, vincristine or topotecan are necessary for a decrease in creatinine clearance.

5.3.4 Ch14.18 (Dinutuximab)

Patients may have decreased urine output, develop peripheral edema, and elevated creatinine related to the effects of ch14.18 (dinutuximab). Since capillary leak is a common side effect related to ch14.18 (dinutuximab), consider the possibility of renal hypoperfusion and administer volume if appropriate.

If, during an Induction cycle of ch14.18 (dinutuximab)-containing therapy, the serum creatinine increases to > 2x the baseline value documented at the beginning of the current cycle, or increases to greater than maximum serum creatinine for age as listed in table above, then hold remaining ch14.18 (dinutuximab) and obtain a nuclear medicine GFR, estimated GFR, or creatinine clearance. If the GFR is < 60 mL/min/1.73m² omit the remainder of the ch14.18 (dinutuximab) from that cycle. If the GFR is > 60 mL/min/1.73m², may resume the ch14.18 (dinutuximab).

5.4 Cardiac Toxicity during Induction Therapy

5.4.1 Change in Ejection/Shortening Fraction

- If the patient has had a drop in SF/EF compared to his/her baseline but is not symptomatic from a cardiac perspective and has normal LV function (SF ≥ 27% or EF ≥ 50%), administer doxorubicin.
- If the patient is not symptomatic from a cardiac perspective and has SF < 27% or EF < 50%, delay the doxorubicin-containing cycle and repeat the echocardiogram in 1 week. If SF ≥ 27% or EF ≥ 50% on re-check, resume doxorubicin.
- For a persistent, asymptomatic decrease in LV function (SF < 27% or EF < 50%) that occurs prior to Cycle 4, substitute a cycle of cisplatin/etoposide/ch14.18 (dinutuximab) for doxorubicin-containing cycle, but do not give ch14.18 (dinutuximab). Make a notation of the substitution and omission on data forms. If a cycle of cisplatin/etoposide is substituted for a doxorubicin-containing cycle, give the cyclophosphamide/doxorubicin/vincristine/ch14.18 (dinutuximab) cycle in place of the next cisplatin/etoposide/ch14.18 (dinutuximab) if cardiac function improves (SF ≥ 27% or EF ≥ 50%). If cardiac function does not return to normal prior to rescheduled cyclophosphamide/doxorubicin/vincristine/ch14.18 (dinutuximab), omit the doxorubicin/dexrazoxane/ch14.18 (dinutuximab) and give cyclophosphamide/vincristine.
- If a patient becomes symptomatic, omit doxorubicin/dexrazoxane/ch14.18 (dinutuximab) from Cycle 4 and administer vincristine/cyclophosphamide.

5.4.2 Dysrhythmia

During Induction, if the patient develops Grade ≥ 2 cardiac dysrhythmia (other than sinus tachycardia or sinus bradycardia) as defined in the Common Toxicity Criteria, delay therapy and repeat the EKG in 1 week. If Grade ≥ 2 toxicity resolves

to ≤ Grade 1 toxicity, the patient may continue induction therapy without chemotherapy dose alterations.

If Grade ≥ 2 toxicity occurs prior to Cycle 4 and persists on the follow up EKG, substitute cisplatin/etoposide/ch14.18 (dinutuximab [but omit ch14.18 (dinutuximab)] for vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) until the dysrhythmia resolves. Make a notation of chemotherapy substitution/omission on the data form. The intent of Induction is to give a total of 1 cycle of vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) and 2 cycles of cisplatin/etoposide/ch14.18 (dinutuximab), therefore if a cisplatin/etoposide cycle is substituted for vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab), give the vincristine/ doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) cycle later in therapy. If dysrhythmia symptoms occur prior to re-scheduled vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab), proceed with cyclophosphamide/vincristine, but omit doxorubicin/dexrazoxane/ch14.18 (dinutuximab).

5.4.3 Hypertension

Hypertension due to neuroblastoma will NOT be considered a reason for removal from protocol therapy or alteration in chemotherapy doses.

5.4.4 Hypotension during Induction Ch14.18 (Dinutuximab) therapy

If severe hypotension is accompanied by poor perfusion, acidemia, or end organ dysfunction follow PALS guidelines and hold ch14.18 (dinutuximab).

- Moderate hypotension is defined as:
  i. Symptomatic; and/or
  ii. Systolic blood pressure <5th percentile for age/height/sex; and/or
  iii. Systolic or diastolic blood pressure decreased by >20% below baseline

- For patients with moderate hypotension in the absence of the above symptoms, the following steps should be taken:
  i. Immediately hold ch14.18 (dinutuximab)
  ii. Give normal saline bolus (20 mL/kg)
  iii. Decrease narcotic dose if possible

- If hypotension persists:
  i. Reassess perfusion, end organ function
  ii. Follow PALS algorithm if indicated
  iii. Repeat NS bolus OR:
    a. Consider use of albumin if serum albumin < 3.0 g/dL
    b. Consider use of RBCs if hemoglobin < 9 g/dL
    c. Consider use of platelets if count < 50,000
  iv. Consider PICU transfer
  v. If hypotension persists after 2 boluses, give additional bolus and prepare to give pressors (epinephrine or norepinephrine preferred over dopamine if possible)

If significant hypotension resolves:

- May resume ch14.18 (dinutuximab) infusion at 50% of the rate at which the reaction occurred
- Carefully assess volume status and consider adjusting fluids to ensure euvolemia if increased insensible losses or third spacing is suspected
- If blood pressure remains stable for 2 hours after resumption of the ch14.18 (dinutuximab), increase to the full ch14.18 (dinutuximab) rate at which the reaction occurred.
- If the hypotension has resolved and the patient is due for chemotherapy, may give chemotherapy as prescribed.

5.5 Liver Toxicities during Induction therapy

5.5.1 Hyperbilirubinemia during Induction

Bilirubin is evaluated as per CTCAE v5.0 using total bilirubin. For ≥ Grade 3 bilirubin (> 3 x ULN if baseline was normal or >3 x baseline if baseline was abnormal) prior to planned administration of an etoposide containing cycle, delay therapy for up to one week and repeat the bilirubin assessment. If the ≥ Grade 3 elevation persists, reduce the etoposide dose by 75% (eg, if the initial dose is 200 mg, reduce dose to 50 mg). May give full ch14.18 (dinutuximab) dose.

For ≥ Grade 3 bilirubin (> 3 x ULN if baseline was normal or >3 x baseline if baseline was abnormal) prior to planned administration of vincristine/doxorubicin/ cyclophosphamide/ch14.18 (dinutuximab), delay therapy for up to one week and repeat the bilirubin assessment. If the ≥ Grade 3 elevation persists, substitute cisplatin/etoposide/ch14.18 (dinutuximab) for a vincristine/doxorubicin/ cyclophosphamide/ch14.18 (dinutuximab) cycle and reduce the etoposide dose by 75% (eg, if the initial dose is 200 mg, reduce dose to 50 mg). May give full ch14.18 (dinutuximab) dose.

The intent of Induction is to give a total of 1 cycle of vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) and 2 cycles of cisplatin/etoposide/ch14.18 (dinutuximab), therefore if cisplatin/etoposide/ch14.18 (dinutuximab) cycle is substituted for vincristine/doxorubicin/ cyclophosphamide/ch14.18 (dinutuximab, give vincristine/doxorubicin/ cyclophosphamide/ch14.18 (dinutuximab) later in therapy. If ≥ Grade 3 elevation in bilirubin is detected prior to re-scheduled vincristine/doxorubicin/ cyclophosphamide/ch14.18 (dinutuximab) chemotherapy, omit doxorubicin/dexrazoxane and vincristine and give cyclophosphamide/ch14.18 (dinutuximab).

If Grade 2 bilirubin (> 1.5 but ≤ 3 x ULN if baseline was normal; > 1.5 – 3.0 x baseline if baseline was abnormal) is observed prior to Cycle 4 vincristine/doxorubicin/cyclophosphamide/ch14.18 (dinutuximab) chemotherapy, delay the cycle for one week and repeat the bilirubin. If the elevation persists, reduce doxorubicin and vincristine doses by 50%. If the doxorubicin dose is reduced, the dexrazoxane dose must also be reduced by the same percent such that the ratio of dexrazoxane to doxorubicin remains 10:1. Give the full dose of ch14.18 (dinutuximab).

5.5.2 Elevations in ALT during Induction therapy

If elevations in ALT 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 ch14.18 (dinutuximab) should be reduced by 25% for subsequent cycles (i.e. dose: 13.13 mg/m^2). For the purposes of this trial the ULN for ALT is defined as 45 U/L. If elevations of this magnitude recur despite the first dose reduction, the dose of ch14.18 (dinutuximab) should again be reduced by 25% for subsequent cycles (i.e. dose: 8.75 mg/m^2). If the dose limiting elevations of the same liver enzyme(s) recur despite the second dose reduction, then ch14.18 (dinutuximab) should be omitted from the remainder of Induction therapy. An elevation in ALT that causes a delay of ≥ 14 days between treatment cycles will also require a 25% reduction in the dose of ch14.18 (dinutuximab) for subsequent cycles (i.e. dose: 13.13 mg/m^2). If a delay of ≥ 14 days between treatment cycles recurs due to elevation in ALT despite the dose reduction, then ch14.18 (dinutuximab) should be omitted from the remainder of Induction therapy.

5.6 Other Gastrointestinal Toxicity during Cycles 1-5 of Induction Therapy

5.6.1 Mucositis

If the patient develops Grade 3 or 4 mucositis that resolves to < Grade 2 by Days 22-29 of a given cycle, no dose adjustments will be made in chemotherapy. If the patient develops Grade 3 or 4 mucositis that is NOT attributable to an infectious etiology AND recovery to < Grade 2 occurs between Days 30-43 for any cycle of Induction, reduce the dose of the suspected causative agent (doxorubicin/dexrazoxane or etoposide) in the next cycle of chemotherapy by 25% (eg, if the dose is 25 mg, reduce dose to 18.75 mg). If subsequent chemotherapy is tolerated without recurrence of Grade 3 or 4 mucositis, then resume full doses of chemotherapy agents in subsequent cycles of Induction that contain the suspected causative agent (if any). Ch14.18 (dinutuximab) dose will not be altered for mucositis.

If the patient develops Grade 3 or 4 mucositis that is NOT attributable to infectious etiology AND recovery to < Grade 2 occurs after Day 43 of any cycle, reduce the dose of the suspected causative agent (doxorubicin or etoposide) in the next cycle of chemotherapy that contains the suspected causative agent by 50% (eg, if the dose is 25 mg, reduce dose to 12.5 mg). If subsequent chemotherapy is tolerated without recurrence of Grade 3 or 4 mucositis, then escalate the dose of the previously reduced agent by 25% in subsequent cycles of Induction (eg, if the dose was reduced to 12.5 mg, increase dose to 18.75 mg). When the dose of doxorubicin is adjusted, the dexrazoxane dose should also be adjusted to maintain a dexrazoxane:doxorubicin ratio of 10:1.

If the patient develops mucositis that requires intubation for airway management, hold subsequent chemotherapy until toxicity resolves to < Grade 2. If the toxicity resolves to < Grade 2 by Day 43, proceed with next cycle of chemotherapy but reduce the dose of the suspected causative agent (doxorubicin or etoposide) in the next scheduled cycle of chemotherapy that contains that agent by 25% (eg, if the dose is 25 mg, reduce dose to 18.75 mg). If the doxorubicin dose is adjusted, the dexrazoxane dose

should be adjusted accordingly. If recovery to < Grade 2 occurs after Day 43 of any cycle, reduce the dose of the suspected causative agent (doxorubicin or etoposide) in the next cycle of chemotherapy by 50% (eg, if the dose is 25 mg, reduce dose to 12.5 mg). If subsequent chemotherapy is tolerated without recurrence of Grade 3 or 4 mucositis, then escalate the dose of the previously reduced agent by 25% in subsequent cycles of Induction that contain the suspected causative agent (eg, if the dose was reduced to 12.5 mg, increase dose to 18.75 mg). If the doxorubicin dose is adjusted, dexrazoxane dose must also be adjusted by the same percent such that the ratio of dexrazoxane to doxorubicin remains 10:1.

5.6.2 Diarrhea

If the patient develops severe diarrhea (Grade 3 or 4) attributable to chemotherapy, and not underlying infection (eg, C. difficile), that resolves by Days 22-29 of a given cycle, no dose adjustments will be made in chemotherapy. If recovery to < Grade 2 occurs between Days 30-43 for any cycle of Induction, reduce the dose of doxorubicin or etoposide in next cycle of chemotherapy by 25% (eg, if the dose is 25 mg, reduce dose to 18.75 mg). If subsequent chemotherapy is tolerated without recurrence of Grade 3 or 4 diarrhea, then resume full doses of chemotherapy agents in all subsequent cycles of Induction. If recovery to < Grade 2 occurs after Day 43 of any cycle, reduce the dose of doxorubicin or etoposide in the next cycle of chemotherapy by 50% (eg, if the dose is 25 mg, reduce dose to 12.5 mg). If subsequent chemotherapy is tolerated without recurrence of Grade 3 or 4 diarrhea, then escalate the dose of the previously modified agent by 25% in subsequent cycles of Induction (eg, if the dose was reduced to 12.5 mg, increase dose to 18.75 mg). If the doxorubicin dose is adjusted, the dexrazoxane dose must also be adjusted by the same percent such that the ratio of dexrazoxane to doxorubicin remains 10:1. Ch14.18 (dinutuximab) doses will not be modified for diarrhea.

5.6.3 Typhlitis

If a patient develops typhlitis (Grade 3 or 4), reduce the dose of doxorubicin or etoposide in the next cycle of Induction chemotherapy by 25%. If there is no recurrence of significant intestinal toxicity such as typhlitis, full dose doxorubicin or etoposide may be given in subsequent cycles. If the doxorubicin dose is adjusted, the dexrazoxane dose must also be adjusted by the same percent such that the ratio of dexrazoxane to doxorubicin remains 10:1.

5.7 Neurologic Toxicity during Induction Therapy

It is expected that the majority of patients will receive only a single dose of vincristine during induction. If other toxicities necessitate therapy substitution with another vincristine-containing cycle of therapy, then the following vincristine dose modifications apply. If ≥ Grade 3 peripheral neuropathy (vocal cord paralysis, inability to walk or perform usual motor functions) or ileus develops from vincristine, vincristine therapy should be held until the ileus resolves or the peripheral neuropathy improves. If vincristine is to be given with subsequent cycles of chemotherapy (substituted for cisplatin/etoposide cycles) restart vincristine at 50% of the calculated dose (eg, if the dose is 0.5 mg, restart at 0.25 mg,). If ≥ Grade 3 peripheral neuropathy recurs, do not give vincristine if another substituted cycle of vincristine/doxorubicin/cyclophosphamide is planned. If the ≥ Grade

3 peripheral neuropathy does not recur at the lower dose of vincristine, the same dose may be given during a subsequent substituted cycle.

If ≥ Grade 3 neuropathy develops following ch14.18 (dinutuximab) therapy, ch14.18 (dinutuximab) should be held until the neuropathy resolves to baseline prior to the next cycle of ch14.18 (dinutuximab)-containing therapy. If the abnormalities resolve when criteria to start the next cycle of ch14.18 (dinutuximab)-containing therapy are met, the dose of ch14.18 (dinutuximab) in the next ch14.18 (dinutuximab)-containing cycle should be reduced by 50%. If the reduced dose is tolerated, consider increasing dose to 100% with subsequent cycles. If symptoms recur following the reduced dose of ch14.18 (dinutuximab), further ch14.18 (dinutuximab) should be omitted from the induction regimen. If symptoms do not completely resolve when criteria to start the next cycle of ch14.18 (dinutuximab)-containing therapy are met, ch14.18 (dinutuximab) should be omitted from the next cycle of therapy.
Occasionally, ch14.18 (dinutuximab) may cause impaired accommodation and dilated pupils with a sluggish light reflex (with or without photophobia). These findings may last for weeks to months. If pupillary responsiveness improves by the time of the next scheduled cycle, ch14.18 (dinutuximab) can be resumed at full dose. If pupillary responsiveness does not improve in this time frame the dose of ch14.18 (dinutuximab) in the next cycle should be decreased by 50%. Full dose ch14.18 (dinutuximab) may be resumed in subsequent cycles if pupillary responsiveness improves. Dose reductions for changes in accommodation are not required.

5.8 Hypothyroidism during Induction Therapy

Dose modification is not required due to hypothyroidism, however replacement therapy should be initiated per institutional standards.

5.9 Allergic reactions during Induction Therapy

5.9.1 Etoposide

Etoposide allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum single dose: 50 mg), ranitidine 1 mg/kg IV (maximum single dose: 50 mg) or equivalent H2 antagonist e.g., famotidine IV, and hydrocortisone 1-4 mg/kg IV and by slowing the rate of the infusion. For those reactions that cannot be controlled with pre-medication and slowing of the rate of etoposide infusion, etoposide phosphate may be substituted in the same dose and at the same rate. Pre-medication for etoposide phosphate is recommended.

5.9.2 Cisplatin

Platinum compound allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose: 50 mg), ranitidine 1 mg/kg IV (maximum single dose: 50 mg) or equivalent H2 antagonist e.g., famotidine IV, and hydrocortisone 1-4 mg/kg IV. If a patient experiences a life threatening allergic reaction to cisplatin during Cycle 3 chemotherapy, a cycle of vincristine/doxorubicin/cyclophosphamide should be substituted for cisplatin/etoposide during Cycle 5.

5.9.3 Ch14.18 (Dinutuximab)

Note: Coughing may herald the onset of bronchospasm. If this occurs, the patient should be closely monitored.

- Mild allergic reactions: limited to rash, flushing, urticaria, mild dyspnea
  i. Decrease the rate of the ch14.18 (dinutuximab) infusion to 50% of the rate at which the symptoms began; monitor closely.
  ii. Give diphenhydramine 1-2 mg/kg/dose up to 50 mg/dose (if not already being given); consider scheduling every 4-6 hours
  iii. Give oral cetirizine (Less than 2 years: 2.5 mg daily, 2-5 years: 5 mg daily, > 6 years: 10 mg daily)
  iv. Consider ranitidine or equivalent if not already being given (IV or oral)
  v. Consider oral hydroxyzine (2 mg/kg/day divided every 8 hours)
  vi. When symptoms resolve resume the original infusion rate
  vii. If symptoms recur when original rate is resumed, decrease the infusion to half rate
  viii. Infusion must be stopped after 20 hours whether or not the full dose has been given
  ix. Document the amount of drug delivered

- More severe allergic reactions and anaphylaxis: Any of the following – symptomatic bronchospasm with or without urticaria, IV medications required for treatment, allergy-related edema/angioedema, OR anaphylaxis
  i. **Immediately hold** ch14.18 (dinutuximab) infusion
  ii. Assess airway, breathing and circulation
    a. For airway concerns:
      i. Administer oxygen and albuterol immediately for bronchospasm
      ii. Administer IV diphenhydramine (if not already being given)
      iii. Administer IM epinephrine immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
  iii. Administer antihistamines
    a. Give diphenhydramine (if not already being given); schedule q4-6 hours
    b. Give oral cetirizine (Less than 2 years: 2.5 mg daily, 2-5 years: 5 mg daily, > 6 years: 10 mg daily)
    c. Give ranitidine or equivalent if not already being given
    d. Give oral hydroxyzine (2 mg/kg/day divided every 8 hours)
  iv. Administer IV hydrocortisone (2 mg/kg) **for** any of the following:
    a. Patient has frank anaphylaxis with cardiorespiratory collapse
    b. Two or more doses of epinephrine are required
    c. Moderate to severe symptoms recur upon challenge with ch14.18 (dinutuximab) [see below regarding resumption of ch14.18 (dinutuximab) following allergic reactions]
  v. Permanently discontinue ch14.18 (dinutuximab) in patients who experienced **clinically significant angioedema or life-threatening bronchospasm**

- For patients with angioedema that does **not** affect the airway or patients with ≤ Grade 2 bronchospasm
  i. If symptoms fully resolve in < 2 hours with the interventions above without the need for hydrocortisone administration, ch14.18

(dinutuximab) can be resumed on the same day but at half of the rate at which the symptoms occurred and complete the following:
   a. Continue scheduled H1 and H2 blockers
   b. Monitor closely for additional symptoms
ii. If symptoms do not resolve rapidly, hold ch14.18 (dinutuximab) until complete resolution of symptoms or until the next day, whichever comes later
   a. When ch14.18 (dinutuximab) is resumed, administer at half of the rate at which symptoms occurred and monitor closely
   b. Continue scheduled H1 and H2 blockers
iii. If clinically significant symptoms recur when ch14.18 (dinutuximab) is resumed despite scheduled antihistamine administration, stop ch14.18 (dinutuximab) for the current cycle. May administer ch14.18 (dinutuximab) with the next cycle; but, must infuse at half of the rate at which the symptoms occurred.

- For hypotension in the setting of an allergic reaction
  i. Hold ch14.18 (dinutuximab) and give 20 mL/kg normal saline bolus
  ii. Stop or adjust doses of narcotics
  iii. For patients with hypotension that resolves with initial volume bolus and other allergic symptoms have resolved, resume ch14.18 (dinutuximab) at the same rate.
  iv. Consider additional volume resuscitation, ICU transfer and use of vasopressors if response is not adequate or hypotension recurs

5.9.4 Sargramostim

Mild allergic reactions (erythema around injection site) are not uncommon following sargramostim administration. It may be possible to decrease local site reactions by alternating sites of administration. Significant reactions are those that result in erythema (often with tenderness) that involves an extended area (eg entire thigh rather than area immediately around injection site). Hold the next scheduled sargramostim dose if this occurs and administer appropriate antihistamines. If the reaction resolves by the time the next scheduled dose is due, the dose should be given at an alternative site. If a significant reaction is seen again, sargramostim should be discontinued for the remainder of the course. Sargramostim should be discontinued if an anaphylactic reaction is observed.

Sargramostim will be held if the total white cell count is > 50,000/μL. This is not a toxicity of sargramostim but rather an expected outcome related to its use. The sargramostim will be held until the total white cell count is less than 20,000/μL and then sargramostim will be resumed at half dose for the remainder of that cycle of therapy. Full dose sargramostim will be used for subsequent sargramostim cycles. If patients develop Grade 3 or greater serum sickness during Induction therapy. Discontinue sargramostim.

5.10 Other toxicities associated with Induction therapy

5.10.1 Other toxicities associated with Induction chemotherapy

For any Grade 3 or 4 toxicity not mentioned above with the exception of cisplatin-associated hearing loss, the treatment should be withheld until patients recover to ≤ Grade 2 toxicity. No dose modification will be made for hearing loss; full dose cisplatin should be given.

- For any non-hematologic Grade 3 or 4 organ toxicity attributed to chemotherapy AND not related to underlying infection or metabolic derangement that is not discussed in Sections 5.1-5.10, and is not attributed to ch14.18 (dinutuximab), and resolves to < Grade 2 **by Day 43**, reduce the subsequent dose of that chemotherapy agent by 25% if that agent is to be given as part of a subsequent planned cycle of induction therapy.
- For any non-hematologic Grade 3 or 4 toxicity attributed to therapy AND not related to underlying infection or metabolic derangement that is not discussed in Sections 5.1-5.10, and is not attributed to ch14.18 (dinutuximab), and resolves to < Grade 2 **after Day 43**, reduce the subsequent dose of that chemotherapy by 50% (eg, if the dose is 25 mg, reduce dose to 12.5 mg) if that agent is to be given as part of a subsequent planned cycle of induction therapy.

5.10.2 Other toxicities associated with Induction ch14.18 (dinutuximab) therapy

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours, even if the total dose has not been administered in that timeframe.

Ch14.18 (dinutuximab) doses that are missed or held due to toxicity will not be made up.

Ch14.18 (dinutuximab) may cause fever, tachycardia, nausea, emesis, hyponatremia, hypokalemia, elevated transaminases and hypoalbuminemia. These toxicities are generally transient, and can be readily managed with supportive care. See Section 5.3.4 for guidance regarding management of renal dysfunction during ch14.18 (dinutuximab) containing cycles of Induction therapy.

5.11 Ch14.18 (dinutuximab)-associated toxicities during post-Consolidation

Please note the maximum infusion time from initiation of ch14.18 (dinutuximab) is 20 hours, even if the total dose has not been administered in that timeframe.

5.11.1 Treatment of Allergic Reactions and Anaphylaxis during post-Consolidation

Note: Coughing may herald the onset of bronchospasm. If this occurs, the patient should be closely monitored.

- Mild allergic reactions: limited to rash, flushing, urticaria, mild dyspnea
  During post-Consolidation, decrease the rate of the ch14.18 (dinutuximab) infusion to 50% of the rate at which the symptoms began; monitor closely
  i. Continue sargramostim
  ii. Give diphenhydramine (if not already being given); consider scheduling every 4-6 hours

iii. Give oral cetirizine (Less than 2 years: 2.5 mg daily, 2-5 years: 5 mg daily, > 6 years: 10 mg daily)
iv. Consider ranitidine or equivalent if not already being given (IV or oral)
v. Consider oral hydroxyzine (2 mg/kg/day divided every 8 hours)
vi. When symptoms resolve resume original infusion rate
vii. If symptoms recur when original rate is resumed, decrease the infusion to half rate
viii. Infusion must be stopped after 20 hours whether or not the full dose has been given
ix. Document the amount of drug delivered

- More severe allergic reactions and anaphylaxis: Any of the following – symptomatic bronchospasm with or without urticaria, IV medications required for treatment, allergy-related edema/angioedema, OR anaphylaxis
  i. **Immediately hold** ch14.18 (dinutuximab) infusion and sargramostim administration
  ii. Assess airway, breathing and circulation
    a. For airway concerns:
      i. Administer oxygen and albuterol immediately for bronchospasm
      ii. Administer IV diphenhydramine (if not already being given)
      iii. Administer IM epinephrine immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
  iii. Administer antihistamines
    a. Give diphenhydramine (if not already being given); schedule q4-6 hours
    b. Give oral cetirizine (Less than 2 years: 2.5 mg daily, 2-5 years: 5 mg daily, > 6 years: 10 mg daily)
    c. Give ranitidine or equivalent if not already being given
    d. Give oral hydroxyzine (2 mg/kg/day divided every 8 hours)
  iv. Administer IV hydrocortisone (2 mg/kg) **for** any of the following:
    a. Patient has frank anaphylaxis with cardiorespiratory collapse
    b. Two or more doses of epinephrine are required
    c. Moderate to severe symptoms recur upon challenge with ch14.18 (dinutuximab) or cytokine (see below regarding resumption of ch14.18 (dinutuximab) and cytokines following allergic reactions)
  v. Permanently discontinue ch14.18 (dinutuximab) or cytokines in patients who experienced **clinically significant angioedema or life-threatening bronchospasm**

- For patients with angioedema that does **not** affect the airway or patients with ≤ Grade 2 bronchospasm
  i. During post-Consolidation, if symptoms fully resolve in < 2 hours with the interventions above without the need for hydrocortisone administration, ch14.18 (dinutuximab) can be resumed on the same day but at half of the rate at which the symptoms occurred and complete the following:
    a. Continue scheduled H1 and H2 blockers
    b. Monitor closely for additional symptoms
    c. Do not resume sargramostim until the following day

ii. During post-Consolidation, if symptoms do not resolve rapidly, hold ch14.18 (dinutuximab) until complete resolution of symptoms or until the next day, whichever comes later
   a. When ch14.18 (dinutuximab) is resumed, administer at half of the rate at which symptoms occurred and monitor closely
   b. Continue scheduled H1 and H2 blockers
   c. If symptoms do not recur, resume sargramostim on the day following resumption of ch14.18 (dinutuximab)
iii. If clinically significant symptoms recur when ch14.18 (dinutuximab) or sargramostim is resumed despite scheduled antihistamine administration, stop ch14.18 (dinutuximab) and sargramostim for the current cycle

- For hypotension in the setting of an allergic reaction
  i. Hold ch14.18 (dinutuximab) and give 20 mL/kg normal saline bolus
  ii. Stop or adjust doses of narcotics
  iii. For patients with hypotension that resolves with initial volume bolus and other allergic symptoms have resolved, during post-Consolidation, resume ch14.18 (dinutuximab) at half of the rate at which the reaction occurred
  iv. Consider additional volume resuscitation, ICU transfer and use of vasopressors if response is not adequate or hypotension recurs

5.11.2 Treatment of Hypotension during ch14.18 (dinutuximab during post-Consolidation)

If severe hypotension is accompanied by poor perfusion, acidemia, or end organ dysfunction follow PALS guidelines and hold ch14.18 (dinutuximab) and sargramostim

- Moderate hypotension is defined as:
  i. Symptomatic; and/or
  ii. Systolic blood pressure <5th percentile for age/height/sex; and/or
  iii. Systolic or diastolic blood pressure decreased by >20% below baseline

- For patients with moderate hypotension in the absence of the above symptoms, the following steps should be taken:
  i. Immediately hold ch14.18 (dinutuximab) and sargramostim
  ii. Give normal saline bolus (20 mL/kg)
  iii. Decrease narcotic dose if possible
- If hypotension persists:
  i. Reassess perfusion, end organ function
  ii. Follow PALS algorithm if indicated
  iii. Repeat NS bolus OR:
     a. Consider use of albumin if serum albumin < 3.0 g/dL
     b. Consider use of RBCs if hemoglobin < 8 g/dL
     c. Consider use of platelets if count < 50,000
  iv. Consider PICU transfer
  v. If hypotension persists after 2 boluses, give additional bolus and prepare to give pressors (epinephrine or norepinephrine preferred over dopamine if possible)

- **If significant hypotension resolves**:
  i. May resume ch14.18 (dinutuximab) infusion at 50% of the rate at which the reaction occurred
  ii. Carefully assess volume status and consider adjusting fluids to ensure euvolemia if increased insensible losses or third spacing is suspected
  iii. During Cycles 1 – 5:
    a. If blood pressure remains stable for 2 hours after resumption of the ch14.18 (dinutuximab), increase to the full ch14.18 (dinutuximab) rate at which the reaction occurred
    b. If blood pressure remains stable for 2 hours thereafter, continue to increase the rate stepwise to full rate
    c. If IV sargramostim was being used prior to the hypotensive episode, do NOT resume IV administration; change to SC administration of sargramostim

5.11.3 Renal Side Effects associated with ch14.18 (dinutuximab) during post-Consolidation

Patients may have decreased urine output, develop peripheral edema, and elevated creatinine (1.5-2 x baseline). This may be due to decreased renal perfusion and intrinsic renal effects of ch14.18 (dinutuximab). The common manifestations of renal dysfunction in this setting are weight gain (1-10% of baseline body weight; due to fluid retention) and metabolic acidosis.

- Recheck creatinine the following day
  - If creatinine remains > 2 x baseline value at the start of the cycle, ch14.18 (dinutuximab) may be continued **if** parameters for renal function in Section 4.9 are met.
  - If creatinine is ≤ 2 x baseline value and criteria in Section 4.9 are met, continue ch14.18 (dinutuximab). Check creatinine daily and follow the same guidelines for discontinuation if the creatinine rises.

5.11.4 Other toxicities associated with ch14.18 (dinutuximab) during post-Consolidation

Ch14.18 (dinutuximab) may cause fever, tachycardia, nausea, emesis, hyponatremia, hypokalemia, elevated transaminases and hypoalbuminemia. These toxicities are generally transient, and can be readily managed with supportive care. See Section 5.11.3 for guidance regarding management of renal dysfunction during ch14.18 (dinutuximab) containing cycles of post-Consolidation therapy.

Occasionally, ch14.18 (dinutuximab) may cause impaired accommodation and dilated pupils with a sluggish light reflex (with or without photophobia). These findings may last for weeks to months. If pupillary responsiveness improves by the time of the next scheduled cycle, ch14.18 (dinutuximab) can be resumed at full dose. If pupillary responsiveness does not improve in this time frame the dose of ch14.18 (dinutuximab) in the next cycle should be decreased by 50%. Full dose ch14.18 (dinutuximab) may be resumed in subsequent cycles if pupillary responsiveness improves. Dose reductions for changes in accommodation are not required.

5.12 Sargramostim (GM-CSF)-associated toxicities during post-Consolidation therapy

If sargramostim related toxicities are observed during the sargramostim alone or during the ch14.18 (dinutuximab) infusion, the dose of sargramostim should be reduced by 50% or, if necessary, discontinued while maintaining the dose of ch14.18 (dinutuximab).

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

Mild allergic reactions (erythema around injection site) are not uncommon following sargramostim administration. It may be possible to decrease local site reactions by alternating sites of administration. Significant reactions are those that result in erythema (often with tenderness) that involves an extended area (eg entire thigh rather than area immediately around injection site). Hold the next scheduled sargramostim dose if this occurs and administer appropriate antihistamines. If the reaction resolves by the time the next scheduled dose is due, the dose should be given at an alternative site. If a significant reaction is seen again, sargramostim should be discontinued for the remainder of the course. Sargramostim should be discontinued if an anaphylactic reaction is observed.

5.13 Ch14.18 (dinutuximab + sargramostim-associated toxicities during post-Consolidation therapy

5.13.1 Expected toxicities that do not require ch14.18 (dinutuximab) dose modification.

The following expected toxicities will NOT require dose modification provided that these toxicities are judged to be tolerable by the responsible clinician, as well as the patient and family.

a. Grade 3 pain or pain requiring intravenous narcotics.
b. Grade 3 nausea, vomiting and diarrhea.
c. Grade 3 fever.
d. Grade 3 skin toxicity that remains stable and tolerable, or improves with treatment (e.g., antihistamines) within 24 hours.
e. Grade 3 electrolytes (especially hyponatremia in the absence of CNS symptoms and sequelae) that improve with treatment within 24 hours.
f. Grade 3 hepatic toxicity that returns to Grade 1 prior to the time for next ch14.18 (dinutuximab) treatment course.
g. Grade 3 neurotoxicity with subjective findings only (e.g., tingling, hot or cold hands, etc.).
h. Grade 4 hematologic toxicity, which improves to at least Grade 2 or baseline pre-therapy values within one week.
i. Decreased performance status (Karnofsky 30 – 50 or Lansky 30 – 50).
j. Impaired visual accommodation, correctable with eye glasses.
k. Altered taste.

5.13.2 Dose modification of ch14.18 (dinutuximab) + sargramostim

The following are recommended dose modification guidelines for dinutuximab and sargramostim. Since these agents are routinely used in the management of this patient population in the post-consolidation setting, institutional standards for dose modification may also be used.

a. Significant hypotension – see Section 5.11.2.
b. Grade 3 capillary leak syndrome (respiratory compromise or fluid support required) – see Section 4.9.5.
c. Allergic reaction and anaphylaxis – see Section 5.11.1.
d. Grade 3 infection during the period of administraton of ch14.18 (dinutuximab) + sargramostim: do not give additional planned doses of dinutuximab during the cycle. Missed doses will not be replaced. May proceed to the subsequent planned immunotherapy cycle when infection resolves or is under control (asymptomatic and negative blood culture). Administration of sargramostim is to continue if the patient completed at least one dose of dinutuximab.
e. Elevated creatinine – During sargramostim + ch14.18 (dinutuximab) cycles, if creatinine is > 2 x the baseline value at the start of the cycle and exceeds the maximum for age and sex as per Section 4.9, hold ch14.18 (dinutuximab) and repeat the creatinine the following day. If the creatinine is ≤ 2 x baseline value for that cycle and criteria in Section 4.9 are met, resume ch14.18 (dinutuximab). If the creatinine remains > 2 x the baseline value and exceeds the maximum for age and sex, hold the ch14.18 (dinutuximab) and repeat the creatinine the next day. If the elevation persists discontinue ch14.18 (dinutuximab) and sargramostim for the remainder of the cycle. If the creatinine is < 2 x baseline value for that cycle and criteria in Section 4.9 are met, resume ch14.18 (dinutuximab) but do not "make up" missed dose(s).

5.13.3 Criteria for stopping post-Consolidation ch14.18 (dinutuximab) + sargramostim:

Patients should be taken off immunotherapy if the following toxicities occur (please note that patients should remain on study, treated with isotretinoin).

a. True anaphylaxis, clinically significant angioedema, or significant bronchospasm as specified in Section 5.11.1.
b. Grade 3 or higher serum sickness*
c. Severe, unrelenting neuropathic pain unresponsive to appropriate doses of gabapentin (or equivalent), continuous infusion of narcotics and other adjuvant measures including lidocaine or ketamine infusions.
d. Neurotoxicity: 1) Grade 3 sensory changes interfering with daily activities > 2 weeks after completing a cycle of ch14.18 (dinutuximab) therapy; 2) ≥ Grade 3 peripheral motor neuropathy, 3) ≥ Grade 3 ataxia attributable to immunotherapy; 4) ≥ Grade 3 encephalopathy attributable to immunotherapy persisting > 4 days after completion of ch14.18 (dinutuximab); 5) ≥ Grade 3 decrease in vision per CTC v.5.0.
e. Grade 4 hyponatremia (< 120 mEq/L) despite appropriate fluid management.
f. Grade 4 skin toxicity.

* The following criteria based on timing and signs/symptoms will favor a diagnosis of serum sickness:

Timing:
Serum sickness develops 1-3 weeks after administration of the causative agent. Signs and symptoms developing later (1-3 weeks) favor the diagnosis of serum sickness. However, it can occur within 12-36 hours in individuals who have been previously sensitized through an antecedent exposure. Signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy, glomerulonephritis in the presence of persistent fevers and cutaneous eruptions favor the diagnosis of serum sickness.

5.14 Isotretinoin (ISOT)-associated toxicities during post-Consolidation therapy

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, and reduce the isotretinoin dose to 125 mg/m^2/day or 4 mg/kg/day if the child weighs ≤ 12 kg. An additional dose reduction to 100 mg/m^2/day (3.33 mg/kg/day if child weighs ≤ 12 kg) should occur if criteria are still not met one week after the due date for subsequent cycles.

Decrease isotretinoin dose to 125 mg/m^2/day (or 4 mg/kg/day if child weighs ≤ 12 kg) for subsequent cycles for the occurrence of any Grade 3 or 4 toxicities 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 (or 3.3 mg/kg/day if child weighs ≤ 12 kg). If the same toxicity recurs at 100 mg/m^2/day, discontinue the drug.

If serum creatinine increases is > 2x baseline value documented at the start of post-Consolidation therapy in any course of post-Consolidation treatment, a creatinine clearance (or nuclear medicine GFR) should be done prior to starting the next course. 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

For localized cheilitis, apply topical agents (eg Vitamin E) to lips for subsequent cycles. If this does not control symptoms sufficiently to allow oral intake, decrease dose to 125 mg/m^2/day (or 4 mg/kg/day if child weighs ≤ 12 kg).

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 (or 4 mg/kg/day if child weighs ≤ 12 kg) for subsequent cycles.

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

6.0 DRUG INFORMATION

6.1 CHIMERIC MONOCLONAL ANTIBODY 14.18

(dinutuximab, human/murine anti-G_{D2} monoclonal antibody; chimeric anti-G_{D2}; chimeric mAb 14.18; ch14.18, Unituxin®) NSC# 764038, **(02/14/19)**

Source and Pharmacology:
Chimeric MOAB 14.18 (ch14.18, dinutuximab) is an anti-G_{D2} monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.G2a and the human constant region genes for heavy chain IgG_1 and light chain kappa. Ch14.18 (dinutuximab) exerts its antitumor effect by binding specifically to the disialoganglioside G_{D2}, an antigen found in human tumors of neuroectodermal origin such as melanoma and neuroblastoma. This chimeric antibody has been shown to lyse melanoma and neuroblastoma cells through the process of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. By targeting the G_{D2} antigen on the cell surface, ch14.18 (dinutuximab) may also prevent attachment of circulating malignant cells to the extracellular matrix. Additionally, ch14.18 (dinutuximab) mediates lysis of several melanoma and neuroblastoma cell lines in a dose dependent manner in the presence of potent mediators of ch14.18 (dinutuximab)-dependent cytotoxicity, such as human peripheral blood mononuclear cells and granulocytes. This is most profound with neutrophils, especially in the presence of recombinant human granulocyte-macrophage colony-stimulating factor.

The PK profile of ch14.18 (dinutuximab) has been determined in adults with melanoma and children with neuroblastoma. Although the plasma clearance for both groups of patients follow a two-compartment model, circulating antibody is cleared from the plasma at a much faster rate in children than adults (mean $t_{½}\beta$ = 66.6 ± 27.4 hours in children versus 123 ± 29 hours and 181 ± 73 hours in two adult trials, respectively). Maturation of the hepatic and renal systems with age is thought to impact on drug metabolism and elimination and could account for these differences. In general, the mAb half-life following the first course of treatment was longer than the half-lives following subsequent courses in a given patient.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MoAb 14.18, chimeric (CH14.18, NSCs 623408 and 764038)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pd

f for further clarification. *Frequency is provided based on 359 patients.* Below is the CAEPR for MoAb 14.18, chimeric (CH14.18).

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

Version 2.9, January 10, 2019[71]

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 5.0 Term) [n= 359]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Disseminated intravascular coagulation		***Disseminated intravascular coagulation (Gr 2)***
		Hemolytic uremic syndrome[36]	
CARDIAC DISORDERS			
		Cardiac arrest	
		Sinus bradycardia	
	Sinus tachycardia		***Sinus tachycardia (Gr 3)***
EYE DISORDERS			
		Eye disorders - Other (eye disorders)[34]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fever			***Fever (Gr 3)***
	Generalized edema		
Pain			***Pain (Gr 3)***
		Sudden death NOS	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 3)***
		Anaphylaxis	
	Serum sickness		
INFECTIONS AND INFESTATIONS			
	Infection[34]		***Infection[34] (Gr 3)***
		Myelitis[34]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***

Adverse Events with Possible Relationship to MoAb 14.18, chimeric (CH14.18) (CTCAE 5.0 Term) [n= 359]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Investigations - Other (elevated c-reactive proteins)			***Investigations - Other (elevated c-reactive proteins) (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 3)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Neuralgia		***Neuralgia (Gr 2)***
		Peripheral motor neuropathy	
	Peripheral sensory neuropathy[37]		***Peripheral sensory neuropathy[37] (Gr 3)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (atonic urinary bladder)[6]	
	Urinary retention[37]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Bronchial obstruction		
Cough			***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 3)***
	Hypoxia		***Hypoxia (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 3)***
VASCULAR DISORDERS			
	Capillary leak syndrome		***Capillary leak syndrome (Gr 3)***
	Hypertension		
	Hypotension		***Hypotension (Gr 3)***

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

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

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

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

[5]Myelitis expressed as transverse myelitis has occurred in patients treated with chimeric MoAb 14.18. Symptoms may include weakness, paresthesia, sensory loss, or incontinence.

[6]Acute urinary retention occurs during therapy and is thought to be due to fluid shifts and narcotic administration that accompany ch14.18 administration. Atonic urinary bladder results in chronic urinary retention (CUR) that requires intermittent urethral catheterization days to weeks following chimeric MoAb 14.18 administration.

Adverse events reported on MoAb 14.18, chimeric (CH14.18) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MoAb 14.18, chimeric (CH14.18) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (thrombotic microangiopathy [e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]); Bone marrow hypocellular; Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Cardiac disorders - Other (gallop on exam); Cardiac disorders - Other (N-terminal BNP); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired
ENDOCRINE DISORDERS - Endocrine disorders - Other (transient hypoaldosteronism); Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Papilledema; Periorbital edema; Scleral disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Constipation; Duodenal obstruction; Dysphagia; Enterocolitis; Esophageal stenosis; Esophageal ulcer; Esophagitis; Gastrointestinal disorders - Other (bleeding, NOS); Gastrointestinal disorders - Other (esophageal stricture); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastroparesis; Hemorrhoidal hemorrhage; Ileus; Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Mucositis oral; Oral pain; Rectal hemorrhage; Stomach pain; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Edema trunk; Fatigue; General disorders and administration site conditions - Other (cold and clammy); General disorders and administration site conditions - Other (vascular leak syndrome); Hypothermia; Injection site reaction; Localized edema; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Cholesterol high; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Fibrinogen decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count increased; Urine output decreased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hypoglycemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Chest wall pain; Muscle weakness lower limb; Myalgia; Neck pain

NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Headache; Hydrocephalus; Meningismus; Movements involuntary; Nystagmus; Oculomotor nerve disorder; Paresthesia; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Delirium; Hallucinations; Insomnia; Irritability; Personality change; Restlessness
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Hematuria; Renal and urinary disorders - Other (acute renal insufficiency); Renal and urinary disorders - Other (urethritis); Renal hemorrhage
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Ovarian hemorrhage; Pelvic pain; Penile pain; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Atelectasis; Bronchospasm; Laryngeal edema; Laryngopharyngeal dysesthesia; Laryngospasm; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Stridor; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hyperhidrosis
VASCULAR DISORDERS - Flushing

Note: MoAb 14.18, chimeric in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Formulation and Stability:
Ch14.18 (dinutuximab) is provided as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM Histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8. Intact vials should be stored in the refrigerator (2ºC to 8ºC). Stability studies of the intact vials are ongoing.

Withdraw the required dose of ch14.18 (dinutuximab) from the vial(s) and inject the exact volume for the 17.5 mg/m^2/day dose into a bag containing 100 mL of 0.9% sodium chloride. The use of a filter during preparation is not required. The final prepared product of ch14.18 (dinutuximab) in NS is stable at room temperature for 24 hours when diluted to a concentration between 0.044 mg/mL and 0.56 mg/mL; however, the final dosage form should be prepared immediately prior to administration as there is a maximum infusion time of 20 hours. The minimum infusion time for the antibody infusion is 10 hours. There is no need to keep empty or partially used vials of ch14.18 (dinutuximab).

If a storage temperature excursion is identified, promptly return ch14.18 (dinutuximab) to the refrigerator temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

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

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

Patient Care Implications:
Pain is one of the most common adverse effects of ch14.18 (dinutuximab). It is predominately neuropathic and manifests as abdominal cramps or back and extremity pain. Prophylactic administration of morphine by

continuous infusion is required before and during the infusions of ch14.18 (dinutuximab). Other narcotics such as hydromorphone or fentanyl can be used. Gabapentin may be used in conjunction with other pain medications per institutional practice. Use of additional pain medications (lidocaine, ketamine) in extenuating circumstances should be undertaken in consultation with pediatric pain management specialists.

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

Human anti-mouse antibodies (HAMA) may block the effectiveness of therapy by prematurely clearing the treatment antibody and limiting further immunotherapy. HAMA responses may also be associated with immune-complex related adverse events such as serum sickness and anaphylaxis. HAMA responses were detected in over 50% of the patients tested. Although no increase in allergic reactions has been observed in patients treated with ch14.18 (dinutuximab) in the presence of HAMA, immune complex formation may have induced serum sickness in some patients.
Supplier: Manufactured by United Therapeutics and distributed by the CTEP, DCTD, NCI. **Do not use commercial supply.**

Agent Ordering:
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

No starter supplies will be provided. Sites may order supplies once an enrollment has been confirmed by PMB.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

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

Useful Links and Contacts

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

6.2 CARBOPLATIN

(Paraplatin®) NSC #241240 **(05/06/11)**

Source and Pharmacology:

The mechanism of action of carboplatin would appear to be similar to that of cisplatin. It binds to replicating DNA causing single strand breaks and interstrand cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The α $t_{½}$ is 1.1 to 2 hours and the β $t_{½}$ is 2.6 to 5.9 hours. Carboplatin is not protein bound. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages will require adjustment dependent on the glomerular filtration rate.

Toxicity:

	Common Happens to 21-100 out of every 100 children	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Hypersensitivity reactions[2] (anaphylaxis, bronchospasm, hypotension), constipation, diarrhea	Metallic taste, rash, mucositis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression[1] (anemia, neutropenia, leukopenia, thrombocytopenia), electrolyte abnormalities (↓ Na, K, Ca, Mg)	↑ LFTs (alkaline phosphatase, SGOT (AST)), abdominal pain, nephrotoxicity (↓ GFR, ↑ Cr and BUN), asthenia	↑ bilirubin
Delayed: Any time later during therapy		Ototoxicity (tinnitus, hearing loss)	Alopecia, temporary loss of vision to light and colors, peripheral neuropathy with mild paresthesias,

			diminished sense of vibration, light touch, pinprick, and joint position
Late: Any time after completion of treatment			Secondary leukemia
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of carboplatin have been noted in animals and may cause fetal harm when administered to pregnant women. It is unknown whether the drug is excreted in breast milk.		

[1] *Thrombocytopenia is more severe or dose limiting.*
[2] *Hypersensitivity reactions are seen more frequently with repeated courses of therapy (after six courses in adults).*

Formulation and Stability:
Carboplatin is available in 50 mg, 150 mg, 450 mg, and 600 mg vials. It is provided as a premixed aqueous solution or lyophilized powder for injection.

Aqueous Solution:
Carboplatin aqueous solution is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin in multidose vials. Unopened vials of carboplatin aqueous solution are stable to the date indicated on the package when stored at 25°C (77°F), excursions permitted from 15°-30°C (59°-86°F). Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25ºC following multiple needle entries.

Powder for Injection:
Carboplatin powder for injection is a sterile lyophilized white powder in single dose vials containing equal parts by weight of carboplatin and mannitol. Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F), excursions permitted from 15°-30°C (59°-86°F). Protect from light.

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

IV: Reconstitute lyophilized powder to concentration of 10 mg/mL with SWFI, D5W, or NS, or use the premixed 10 mg/mL aqueous solution. May further dilute in dextrose or sodium chloride containing solutions to a final concentration as low as 0.5 mg/mL. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature.

Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.

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

6.3 CISPLATIN

(Cis-diamminedichloroplatinum II, CDDP, cis-DDP, Platinol-AQ) NSC #119875

(11/17/17)

Source and Pharmacology:

Cisplatin is an inorganic, water-soluble complex containing a central platinum atom, 2 chlorine atoms, and 2 ammonia molecules. In aqueous solution, the chloride ions are slowly displaced by water generating a positively charged aquated complex. This activated complex is then available to react with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bi-functional covalent links, very similar to alkylating reactions. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Cisplatin has a rapid distribution phase of 25-80 minutes with a slower secondary elimination half-life of 60-70 hours. The platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Platinum is present in tissues for as long as 180 days after the last administration. Both cisplatin and platinum are excreted through the kidneys ranging from 10-50%. Fecal elimination is minimal. Cisplatin's penetration into the CNS is poor.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea (L), vomiting (L)	Metallic taste (L)	Anaphylactic reaction (facial edema, wheezing, tachycardia, and hypotension), phlebitis, extravasation (rare) but if occurs = local ulceration (only in concentration > 0.5 mg/mL)
Prompt: Within 2-3 weeks, prior to the next course	Anorexia (L), myelosuppression, hypomagnesemia (L), high frequency hearing loss (L), nephrotoxicity (↑ Cr, BUN, Uric Acid) (L)	Electrolyte disturbances (L) (hypocalcemia, natremia, kalemia, & phosphatemia) peripheral neuropathy, (paresthesias in a stocking-glove distribution) (L)	Vestibular dysfunction, tinnitus (L), rash, seizure (L), elevated liver function tests (L)
Delayed: Any time later during therapy		Hearing loss in the normal hearing range	Areflexia, loss of proprioception and vibratory sensation, (very rarely loss of motor function) (L), optic neuritis, papilledema, cerebral blindness, blurred vision and altered color perception (improvement or total recovery usually occurs after discontinuing), chronic renal failure, deafness
Late: Any time after completion of treatment			Secondary malignancy

Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cisplatin have been noted in animals and cisplatin can cause fetal harm in humans. Cisplatin is excreted into breast milk.

(L) Toxicity may also occur later

Formulation and Stability:
Available as an aqueous solution containing 1 mg/mL of cisplatin and 9 mg (1.54 mEq)/mL of sodium chloride in 50 mL, 100 mL, and 200 mL multi-dose non-preserved vials. Store at 15°-25°C (68º-77ºF). **Do not refrigerate**. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. Cisplatin removed from its amber container should be protected from light if not used within 6 hours.

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

Prior to infusion, dilute cisplatin in NS, D5$^1/_2$NS or D5NS. Do **NOT** dilute in D5W. The final infusion solution should contain ≥ 0.2% sodium chloride. Dextrose/saline/mannitol containing solutions, protected from light, are stable refrigerated or at room temperature for 24 to 72 hours, however, cisplatin solutions should not be stored in the refrigerator to avoid precipitation. Cisplatin is incompatible with sodium bicarbonate and alkaline solutions.

Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin causing precipitate formation and a loss of potency.

Accidental extravasation with solutions that are > 0.5 mg/mL may result in significant tissue toxicity.

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

6.4 CYCLOPHOSPHAMIDE INJECTION

(Cytoxan) NSC #26271 **(03/13/13)**

Source and Pharmacology:
Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, sex, and degree of pubertal development at time of treatment.*
[2] *Risk increased with pulmonary chest irradiation and higher doses.*
(L) Toxicity may also occur later.

Formulation and Stability:
Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

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

Cyclophosphamide for Injection:
If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be

further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

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

6.5 DEXRAZOXANE (11/17/17)

(ICRF-187, ADR-529, Zinecard®, Totect®) NSC #169780

Source and Pharmacology:
Dexrazoxane is a synthetic chemical, a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring opened chelating agent that interferes with iron mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy. The disposition kinetics of dexrazoxane are dose-dependent with administered doses from 60 to 900 mg/m^2. The plasma half-life is 2 to 2.5 hours. Qualitative metabolism studies have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. Metabolite levels were not measured in the pharmacokinetics studies. Urinary excretion plays an important role in the elimination of dexrazoxane: 42% of the drug (500 mg/m^2) was excreted in the urine. *In vitro* studies have shown that dexrazoxane is not bound to plasma proteins. The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic or renal insufficiency. There was no significant effect of dexrazoxane on the pharmacokinetics of doxorubicin (50 mg/m^2) or its predominant metabolite, doxorubicinol, in a crossover study in cancer patients.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Pain on injection, phlebitis, transient increases in triglycerides and amylase, increase in SGPT (ALT)/ SGOT (AST) and bilirubin, mild nausea, vomiting, diarrhea, increase in serum iron, decrease in serum zinc and calcium	Anorexia, malaise, extravasation (rare) but if occurs may = ulceration
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression		Prolongation of PT/PTT
Late: Any time after completion of treatment			Secondary malignancies (have been reported with oral razoxane; the racemic mixture, of which dexrazoxane is the S(+)-enantiomer)

Unknown and Frequency Timing:	Fetal toxicities and teratogenic effects have been noted in animals. Dexrazoxane was maternotoxic, embryotoxic, and teratogenic when given to pregnant rats and rabbits during the period of organogenesis. It is not known whether dexrazoxane is excreted in human milk.

Formulation and Stability:

Three products are available:

1. **Dexrazoxane for Injection (generic)**
   a. Available as a sterile, pyrogen-free lyophilized powder in the following strengths: 250 mg single dose vial packaged with a 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP,* and 500 mg single dose vial packaged with a 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*.
   b. Store protected from light at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

2. **Dexrazoxane (Zinecard®, Pfizer brand)**
   a. Available in as a sterile, pyrogen-free lyophilized powder in 250 mg and 500 mg single use vials. Hydrochloric Acid, NF is added to the vials for pH adjustment.
   b. Intact vials should be stored at 25°C (77°F); excursions are permitted to 15° to 30°C (59° to 86°F).

3. **Totect® (dexrazoxane for anthracycline extravasation only)**
   a. Totect is packaged as an emergency treatment carton for single patient use. Each carton contains 10 vials of Totect (dexrazoxane for injection) 500 mg and 10 vials of 50 mL diluent, which provides a complete three day treatment.

Reconstitution and dilution requirements and expiration dating vary based on the product used. Refer to package insert for additional details.

1. **Dexrazoxane (generic)**
   a. Dexrazoxane (250 mg or 500 mg vials) must be reconstituted with a sufficient quantity of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*, to a concentration of 10 mg dexrazoxane for each mL of sodium lactate.
   b. Further dilute solution in either D_5W or NS to a final concentration of 1.3 to 5 mg/mL.
   c. The final solution is stable for up to 6 hours at room temperature, 15°C to 30°C (59°F to 86°F), or under refrigeration, 2°C to 8°C (36°F to 46°F).

2. **Dexrazoxane (Zinecard®, Pfizer brand)**
   a. Reconstitute with Sterile Water for Injection, USP as follows:
      - For 250 mg vials, reconstitute with 25 mL.
      - For 500 mg vials, reconstitute with 50 mL.
      - The resultant reconstituted solutions will have a concentration of 10 mg/mL.
   b. Following initial reconstitution, Zinecard® is stable for 30 minutes at room temperature or up to 3 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).
   c. The pH of the resultant solution is 1.0 to 3.0. Further dilution with Lactated Ringer's Injection, USP is required to achieve a final concentration range of 1.3 to 3 mg/mL in intravenous infusion bags. The infusion solution has a pH of 3.5 to 5.5.
   d. The infusion solution is stable for one (1) hour at room temperature or if storage is necessary, up to 4 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).

3. **Totect® (dexrazoxane for anthracycline extravasation only)**
   a. Totect® must be reconstituted with supplied diluent to provide a final concentration of 10 mg/mL. The patient's dose of Totect® (based on body surface area) should be injected into a 1000 mL bag of NS for infusion.
   b. This solution is stable for 4 hours (begin infusion within 2 hours of preparation) when stored at temperatures < 25°C (< 77°F).
   c. Stability studies indicate that Totect® is chemically and physically stable after reconstitution with sterile water for injection and dilution in Lactated Ringer's Injection when stored in refrigerated conditions (2-8°C) for no more than 8 hours (email communication Cumberland Pharma).

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

For the prevention of anthracycline-induced cardiomyopathy, administer IV immediately prior to anthracycline dose. Administer the anthracycline after completing the infusion of dexrazoxane but within 30 minutes of beginning of the dexrazoxane infusion.

The first infusion of Totect® should be administered as soon as possible and within the first 6 hours following the extravasation.

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

6.6 DOXORUBICIN

(Adriamycin®) NSC #123127 **(05/09/11)**

Source and Pharmacology:
An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6

and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, 130incristin, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age.*
(L) Toxicity may also occur later.

Formulation and Stability:
Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1]vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1] *Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.*
[2] *Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.*

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

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

Administer IV through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

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

6.7 ETOPOSIDE – INJECTION

(Toposar®, Etopophos®,VP-16) NSC #141540 **(11/15/16)**

Source and Pharmacology:
A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial $t_{½}$ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100

Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Etoposide for Injection is available as a 20 mg/mL solution in sterile multiple dose vials (5 mL, 25 mL, or 50 mL each). The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen. Unopened vials of etoposide are stable until expiration date on package at controlled room temperature (20˚-25˚C or 68˚-77˚F).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate *USP*, and 300 mg dextran 40. Etoposide phosphate must be stored under refrigeration (2°- 8°C or 36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

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

Etoposide:
Dilute etoposide to a final concentration ≤ 0.4 mg/mL in D5W or NS. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL. Use in-line filter during infusion secondary to the risk of precipitate formation. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL. **Do not administer etoposide by rapid intravenous injection.** Slow rate of administration if hypotension occurs.

Leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags occurred with etoposide 0.4 mg/mL in NS. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy; glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used to minimize exposure to DEHP.

Etoposide Phosphate:
Reconstitute the 100 mg vial with 5 or 10 mL of Sterile Water for Injection, D5W, NS, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide equivalent (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. **Use diluents without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.**

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for up to 48 hours. Following reconstitution with SWFI, D5W, or NS store at controlled room temperature for up to 24 hours.

Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with D5W or NS. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

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

6.8 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®) NSC #614629 **(11/15/16)**

Source and Pharmacology:
Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 hours.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq): skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Neupogen® supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration.

Store refrigerated at 2º - 8ºC (36º - 46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours. Infusion must be completed within 24 hours of preparation. TBO-filgrastim may be removed from 2ºC – 8ºC (36ºF – 46ºF) storage for a single period of up to 5 days between 23ºC to 27ºC (73ºF to 81ºF). Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations >15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 mcg/mL and 15 mcg/mL. At concentrations below 15 mcg/mL,

human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º - 8ºC (36º - 46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

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

Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

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

6.9 ISOTRETINOIN

(13-cis-retinoic acid, RO-43,780, Accutane®, Amnesteem® Claravis®, Sotret®)
NSC#329481 **(10/13/17)**

Source and Pharmacology:
Isotretinoin is a naturally occurring analogue of Vitamin A. Retinoids are required for the maintenance of normal cell growth, differentiation, and loss within epithelial tissues. Various retinoids have been shown to suppress or reverse epithelial carcinogenesis and to prevent the development of invasive cancers in many animal systems. Retinoids act primarily in the post-carcinogen phases of promotion and progression, which makes them more useful for chemoprevention. However in certain malignancies (notably acute promyelocytic leukemia and neuroblastoma), high-doses of retinoids can have significant anti-tumor activity. The exact mechanism of RA-induced maturation of tumor cells is not known. The mechanism by which retinoids regulate the growth and differentiation of normal and malignant cells has not been completely elucidated, but it is thought that these effects result from the ability of retinoids to modulate the transcriptional regulatory activity of a set of nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs) belonging to the super family of thyroid/steroid hormone receptors.

Isotretinoin is highly lipophilic and 99.9% bound to plasma protein (almost entirely albumin) and has a half-life of 10-20 hours. Oral absorption of isotretinoin is enhanced when given with a high fat meal increasing both the peak plasma concentration and AUC by more than double. Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-*oxo*isotretinoin, retinoic acid (tretinoin-), and 4-*oxo*-retinoic acid (4-*oxo*-tretinoin). Retinoic acid and 13-*cis*-retinoic acid are geometric isomers and show reversible inter-conversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-tretinoin. All of these metabolites possess retinoid activity that is in some in vitro models more than that of the parent isotretinoin. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65-83%). In a study

comparing the pharmacokinetics of isotretinoin in pediatric and adult patients there were no statistically significant differences.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Nausea and vomiting	Anaphylaxis, bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Dry skin (L), dry mucosa (L), epistaxis, cheilitis, (L), photosensitivity, elevated ESR, back pain (L), arthralgias (L), triglyceride elevation (L), hypercalcemia (L)	Rash (L), conjunctivitis (L), headache (L), decrease in high density lipoproteins (L), cholesterol elevation (L), transaminase elevation (L), anemia (L)	Alopecia, appetite disturbances, hyperglycemia, hyper- or hypo-skin pigmentation, nail changes, eruptive xanthomas, seizures, dizziness, pseudotumor-cerebri (papilledema, headache, nausea, vomiting, visual disturbances), psychiatric disorders (depression, aggressive and/or violent behaviors, suicidal ideation, suicide, dream disturbances), insomnia, lethargy, malaise, nervousness, paresthesias, weight loss, myelosuppression, elevated platelet counts, agranulocytosis, allergic vasculitis (L), chest pain, pancreatitis (including very rarely fatal hemorrhagic pancreatitis), hearing impairment, inflammatory bowel disease, visual disturbances (decrease in night vision, corneal opacities which resolve on d/c, photophobia, color vision disturbances, cataracts), edema, inflammation of the gums, drying of respiratory tract with voice alteration, respiratory infections, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Delayed: Any time later during therapy, excluding the above conditions		Skeletal hyperostosis	Osteoporosis, bone fractures or delayed healing, premature epiphyseal closure, rhabdomyolysis, abnormal menses, renal disturbances (WBC in urine, proteinuria, hematuria, renal calculi), calcification of tendon and ligaments
Unknown frequency and timing:	Major human fetal abnormalities related to isotretinoin administration in females have been documented. There is an increased risk of spontaneous abortion. In addition, premature births have been reported. Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia and cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial		

	nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted. Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported. It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive isotretinoin.

(L) Toxicity may also occur later.

Formulation and Stability:
Isotretinoin, a retinoid, is available in 10 mg, 20 mg, 30 mg and 40 mg soft gelatin capsules for oral administration. Inactive ingredients vary depending on the manufacturer but capsule formulations may include the following inactive ingredients: beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, soybean oil and vitamin E. Gelatin capsules may contain glycerin and parabens (methyl and propyl), with the following dye systems: iron oxide (red and black) and titanium dioxide; FD&C Red No. 3 or 7, FD&C Blue No. 1 or 2, FD&C Yellow No. 6 or 10, propylene glycol, and shellac glaze.

Store at controlled room temperature (59°86°F, 15°30°C). Protect from light.

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

Give orally with food (ideally, high fat) or milk to enhance absorption. For children unable to swallow the capsules whole, the following options may be used:

Soften capsule (in warm water), bite, swallow, or suck out contents or place softened capsule in fatty food such as peanut butter and swallow. The method of softening the capsule and withdrawing contents with an oral syringe is not preferred as it is difficult to remove all of the drug from the capsule.

Squeeze out the entire contents of the capsule into a small medicine cup and give with fatty food, such as peanut butter. (If at all possible have the child suck on the empty capsule in hopes of getting more of the intended dose.)

The preferred method is to poke a hole in the capsule to allow the capsule to be chewed and embed the capsule in a food or candy enjoyed by the child.

Under no circumstances should isotretinoin be removed from the capsules for more than 1 hour prior to administering to the patient. It is NOT recommended to administer isotretinoin through a feeding tube (e.g., NG, ND, or NJ tube) as exposure to isotretinoin is suboptimal and may affect response.[72]

Note: Women of childbearing potential should wear gloves when handling isotretinoin capsules.

If the contents are withdrawn from the capsule and mixed with food or milk, administer as closely as possible to mixing to avoid oxidation or conversion by exposure to light to a more toxic and less potent product.

Isotretinoin is contraindicated in patients with paraben allergies as the capsule is preserved with the agent. Patients should be warned about enhanced photosensitivity; the use of sunscreen and avoidance of direct sunlight should be recommended. Patients should limit the intake of vitamin A.

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

SITES WITHIN THE UNITED STATES:
Isotretinoin MUST be prescribed under the Committed to Pregnancy Prevention Program (iPLEDGE). (*Physicians must complete a one-time registration with the program in order to be able to prescribe the drug. Each physician (or their office representative), dispensing pharmacy, and patient must be registered on line @ https://www.ipledgeprogram.com (or call 1-866-495-0654 to begin the registration process).*

UPON REGISTRATION YOU WILL RECEIVE ALL OF THE INFORMATION AND EDUCATIONAL MATERIALS NECESSARY TO PRESCRIBE ISOTRETINOIN.
Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE. Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Isotretinoin must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE. The iPLEDGE program is a computer-based risk management system that uses verifiable, trackable links between prescriber, patient, pharmacy, and wholesaler to control prescribing, using, dispensing and distribution of isotretinoin.

OVERVIEW: PROGRAM REQUIREMENTS
The iPLEDGE program has specific requirements for prescribers, patients, and pharmacists. One of the prescriber's main responsibilities is knowing and educating patients about these requirements. Note: The FDA has provided the following statement concerning the physician training aspects of the iPLEDGE site:

"FDA and the sponsors would like the oncology community who uses isotretinoin to enroll in iPLEDGE and to know that the "I know how to diagnose and treat the various presentations of acne," statement can be truthfully addressed by oncologists who "know how to diagnose and treat" suspected cases by referring these cases to dermatologists for management. All the sponsors and FDA agree on this interpretation."

Prescribers are responsible for registering every patient, who meets the program requirements, in the iPLEDGE program via the automated system. They are responsible for educating patients about the side effects of isotretinoin and the high risk of birth defects for female patients of childbearing potential while taking the drug. As part of this process, they are also responsible for counseling patients about the monthly steps they must follow to receive isotretinoin.

Prescribers can only write a patient's prescription for isotretinoin once a month, and then only up to a maximum of a 30-day supply. Patients must plan for monthly appointments to receive their prescriptions. At each of these appointments, the prescriber must counsel the

patient about the iPLEDGE program requirements and then confirm via the iPLEDGE automated system that this counseling occurred. They must also enter this information after the first appointment.

There are different program requirements for male patients and female patients who are not of childbearing potential and for female patients of childbearing potential. The prescriber must determine if a patient is a female patient of childbearing potential and document that she meets the specific requirements of the program. These include taking pregnancy tests (processed in a CLIA-certified laboratory) and using 2 forms of birth control consistently. Both of these requirements must be followed before, during, and after treatment, but are not necessary for patients the physician determines are not of childbearing potential. To receive monthly prescriptions, a female patient of childbearing potential must also address questions in the iPLEDGE system about the program requirements and pregnancy prevention. She must also enter the two forms of birth control she is using. In addition to the monthly counseling information, the prescriber must also enter into the system the patient's 2 forms of contraception and the results of the monthly pregnancy test obtained from a CLIA-certified laboratory. This information is the criteria the system uses to authorize a pharmacy to fill a prescription.

Requirements for Pharmacists

- Isotretinoin can only be obtained from pharmacies registered with and activated in the iPLEDGE program.
- Registered and activated pharmacies can obtain isotretinoin only from wholesalers registered with the iPLEDGE program.
- **The dispensing pharmacist must obtain authorization and a Risk Management Authorization (RMA) number** before filling and dispensing prescriptions.
- **Upon receiving authorization, the dispensing pharmacist can fill a prescription** for a maximum 30-day supply of isotretinoin.
- **Upon authorization, the iPLEDGE system** provides a Risk Management Authorization (RMA) number to the dispensing pharmacist. The pharmacist should record the RMA number directly on the prescription.
- **Upon authorization, the iPLEDGE system** provides a **"Do Not Dispense to Patient After"** date (7 days from office visit date) to the dispensing pharmacist. The pharmacist should record this date on the prescription bag sticker.

6.10 MELPHALAN

(L-phenylalanine mustard, phenylalanine mustard, L-PAM, L-sarcolysin, Alkeran®, Evomela®) NSC #008806 **(07/10/18)**

Source and Pharmacology:

Melphalan, a phenylalanine derivative of nitrogen mustard, is a bifunctional alkylating agent. Melphalan forms covalent cross-links with DNA or DNA protein complexes thereby resulting in cytotoxic, mutagenic, and carcinogenic effects. The end result of the alkylation process results in the misreading of the DNA code and the inhibition of DNA, RNA, and protein synthesis in rapidly proliferating tumor cells. It is cell cycle non-specific. After IV administration, melphalan plasma concentrations decline rapidly in a bi-exponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Plasma m**elphalan** levels are highly variable after oral

dosing, both with respect to the time of the first appearance of m**elphalan** in plasma (range approximately 0 to 6 hours) and to the peak plasma concentration achieved. These results may be due to incomplete intestinal absorption, a variable "first pass" hepatic metabolism, or to rapid hydrolysis. The oral dose averages 61% ± 26% of that following IV administration. The terminal elimination plasma half-life of oral melphalan is 1.5 ± 0.83 hours. The steady-state volume of distribution of m**elphalan** is 0.5 L/kg. The extent of m**elphalan** binding to plasma proteins ranges from 60-90%. **Melphalan** is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. The 24-hour urinary excretion of parent drug is approximately 10% suggesting that renal clearance is not a major route of elimination of parent drug. Penetration into CSF is low. Despite the fact that the contribution of renal elimination to melphalan clearance appears to be low, one pharmacokinetic study suggests dosage may need to be reduced in patients with renal impairment.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea, vomiting, hyponatremia (high dose)		Anaphylaxis, hypotension, diaphoresis, pruritus atrial fibrillation (high dose), extravasation (rare) but if occurs = local ulceration, SIADH, Seizures
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L), mucositis, diarrhea, alopecia		Abnormal liver function tests, jaundice, hepatitis
Delayed: Any time later during therapy, excluding the above conditions		Amenorrhea, testicular suppression	Bone marrow failure, hemolytic anemia, pulmonary fibrosis, interstitial pneumonitis
Late: Any time after completion of treatment		Sterility, primary ovarian failure	Secondary malignancy
Unknown Frequency and Timing:	Melphalan was embryolethal and teratogenic in rats following oral (6 to 18 mg/m^2/day for 10 days) and intraperitoneal (18 mg/m^2) administration. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly). It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later

Formulation and Stability:
Melphalan for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains **melphalan** hydrochloride equivalent to 50 mg **melphalan** and 20 mg povidone. Melphalan for Injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and SWFI to a total of 10 mL. Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light.

- Reconstitute to a concentration of 5 mg/mL by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear

solution is obtained. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.
- **Immediately** dilute the dose to be administered in NS to a final concentration not to exceed 2 mg/mL for IV central line administration or ≤ 0.45 mg/mL for peripheral IV administration.
- A precipitate forms if the reconstituted solution is stored at 5°C. Do not refrigerate the reconstituted product.

(*The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of melphalan with the sterile diluent for melphalan. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolyzes every 10 minutes.)*

Evomela brand of melphalan for injection is supplied as 50 mg, white to off-white lyophilized powder in single-dose vial for reconstitution (after reconstitution the solution is clear and colorless to light yellow). Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride and 2700 mg Betadex Sulfobutyl Ether Sodium, NF. Evomela is light sensitive. Retain in original carton until use. **Do not mix Evomela® with other melphalan hydrochloride for injection drug products.**

- Use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed) to reconstitute Evomela and make a 50 mg/10 mL (5 mg/ mL) nominal concentration of melphalan. The normal saline used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline. The reconstituted Evomela drug product is stable for 24 hours at refrigerated temperature (5°C) without any precipitation due to the high solubility. The reconstituted Evomela drug product is stable for 1 hour at room temperature.
- Calculate the required volume of Evomela needed for a patient's dose and withdraw that volume from the vial(s).
- Add the required volume of Evomela to the appropriate volume of 0.9% Sodium Chloride Injection, USP to a final concentration of 0.45 mg/mL. The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution.

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

Injection:
Administer by IV infusion through a peripheral or a central line. **The infusion must be completed within 60 minutes of product reconstitution.**

Evomela: Infuse over 30 minutes via an injection port or central venous catheter

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

6.11 MESNA – INJECTION

(sodium 2-mercaptoethane sulfonate, UCB 3983, Mesnex®) NSC #113891

(10/13/17)

Source and Pharmacology:
Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

After an 800 mg dose the half lives for mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours.

Toxicity[1]:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Nausea, vomiting, stomach pain, fatigue, headache	Facial flushing, fever, pain in arms, legs, and joints, rash, transient hypotension, tachycardia, dizziness, anxiety, confusion, periorbital swelling, anaphylaxis, coughing
Prompt: Within 2-3 weeks, prior to the next course		Diarrhea	
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well-controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk		

3 *All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension*

leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800 mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]

Formulation and Stability:
Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature 15º-25°C (68º77ºF). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna- as benzyl alcohol-preserved vials may be stored and used for 8 days.

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

For IV administration, dilute mesna to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Mesna may cause false positive test for urinary ketones.

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

6.12 PEGFILGRASTIM, PEGFILGRASTIM-JMDB, PEGFILGRASTIM-CBQV

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®, Fulphila®, Udenyca®)
NSC #725961 **(01/28/19)**

Source and Pharmacology:
Pegfilgrastim is the PEGylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

Toxicity:

Incidence	Toxicities
Common (>20% of patients)	• Bone pain
Occasional (4-20% of patients)	• Pain in extremity
Rare (≤3% of patients)	• Acute respiratory distress syndrome (ARDS) • Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing • Antibody development • Capillary leak syndrome • Glomerulonephritis • Injection site reaction • Leukocytosis • Sickle cell crisis • Splenic rupture, splenomegaly • Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis • Aortitis
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Adverse events were observed in some animal reproduction studies. It is unknown whether the drug is excreted in breast milk.

Formulation and Stability:
Pegfilgrastim (Neulasta®): Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe™ Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex).

Pegfilgrastim-jmdb (Fulphila®): Supplied as 6 mg/0.6 mL sterile, clear, colorless preservative-free solution (pH 4.0) containing acetate (0.7 mg), D-sorbitol (30 mg), polysorbate 20 (0.024 mg) and sodium (0.01 mg) in Water for Injection, USP. It is intended for subcutaneous use only and is supplied in a single-dose prefilled syringe with a 29 gauge, ½ inch needle, with UltraSafe Passive Plus™ Needle Guard. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).

Pegfilgrastim-cbqv (Udenyca®): Supplied as 6 mg/0.6 mL syringe in a sterile, clear, colorless, preservative- free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP. It is supplied in 0.6 mL prefilled single-dose syringes with an UltraSafe Passive™ Needle Guard for manual subcutaneous injection. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL). The needle cap of the prefilled syringe is not made with natural rubber latex.

Storage:
Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard Neulasta® and Udenyca® syringes if stored at room temperature for more than 48 hours. Fulphila™ syringes should be discarded if stored at room temperature for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

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

Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

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

6.13 SARGRAMOSTIM

(Granulocyte Macrophage Colony Stimulating Factor, rhu GM-CSF, rGM-CSF, GM-CSF, Leukine®) NSC #613795 **(11/27/17)**

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

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Headache, malaise, fatigue, rash, pruritus, bone pain, myalgia, arthralgia, fever, chills	Abdominal pain, weakness, anorexia, nausea, local injection reactions	Anaphylaxis, "first dose reaction" (hypoxia, dyspnea, hypotension, fever, tachycardia, diaphoresis, flushing, back pain), vomiting, diarrhea, phlebitis, SVT, pericardial effusion
Prompt: Within 2-3 weeks, prior to the next course		Weight gain	In high doses: capillary leak syndrome: (pleural effusion, peripheral edema, ascites, weight gain, hypotension), pneumonitis, peripheral edema, elevation of creatinine, bilirubin and hepatic enzymes in patients with pre-existing renal or hepatic dysfunction
Delayed: Any time later during therapy		Thrombocytopenia	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: It is not known whether sargramostim can cause fetal harm or affect reproduction capacity when administered to a pregnant woman. It is unknown whether the drug is excreted in breast milk.		

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

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

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

Use sargramostim for subcutaneous injection without further dilution. Perform dilution for IV infusion in NS. If the final concentration is < 10 mcg/mL, add albumin (human) at a final concentration of 0.1% to the saline prior to addition of sargramostim to prevent adsorption to the components of the drug delivery system. For a final concentration of 0.1% albumin (human), add 1 mg albumin (human) per 1 mL NS. For example, for a final volume of 50 mL NS, add 50 mg (or 1 mL) of 5% albumin [human]. Intravenous dilutions

are stable for up to 48 hours at room temperature or refrigerated but should be used within 6 hours due to microbiological concerns. Do not use an in-line membrane filter for IV infusion.

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

6.14 THIOTEPA

(Tepadina®, Tespa, Thiophosphamide, Triethylenethiophosphoramide Tspa, WR-45312)
NSC #6396 **(01/23/18)**

Source and Pharmacology:
Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines. Thiotepa is desulfurated by cytochrome P-450 enzymes such as 2B1 and 2C11 which catalyze the conversion of thiotepa to tepa. Tepa is less toxic than thiotepa and has been demonstrated to produce alkali-labile sites in DNA, rather than cross-links. These findings indicate that tepa reacts differently from thiotepa and produces monofunctional alkylation of DNA. A second metabolite of thiotepa, a mercapturic acid conjugate, is formed via glutathione conjugation. Monochloro tepa is the third metabolite found in the urine.

Following short intravenous infusion (less than 5 minutes), peak concentrations of thiotepa were measured within 5 minutes. At steady state, the volume of distribution was independent of dose and ranged from 0.3 to 1.6 liters per kilogram (L/kg).

Approximately 4.2% of the original dose is eliminated in the urine within 24 hours as tepa. The elimination half-life of thiotepa ranges from 2.3 to 2.4 hours. The half-life of tepa ranged from 3 to 21.1 hours in one study.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia, fatigue, weakness	Pain at the injection site, dizziness, headache, blurred vision, abdominal pain, contact dermatitis, rash	Anaphylaxis, laryngeal edema, wheezing, hives
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression; at higher doses in conditioning regimens for BMT: mucositis, esophagitis	At higher doses in conditioning regimens for BMT: encephalopathy (inappropriate behavior, confusion, somnolence), increased liver transaminases, increased bilirubin, hyperpigmentation of the skin (bronzing effect)	Febrile reaction, conjunctivitis, dysuria, urinary retention

Delayed: Anytime later during therapy, excluding the above conditions	Gonadal dysfunction/infertility, azoospermia, amenorrhea		Alopecia, secondary malignancy
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Carcinogenic and teratogenic effects of thiotepa have been noted in animal models at doses ≤ to those used in humans. It is not known if thiotepa is excreted into human breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:
Thiotepa for Injection *USP*, for single use only, is available in vials containing 15 mg of nonpyrogenic, sterile lyophilized powder. Store in a refrigerator at 2°-8°C (36°-46°F). **PROTECT FROM LIGHT AT ALL TIMES.**

Note: FDA is allowing temporary importation of a European thiotepa product (Tepadina®). Verify product, storage, and preparation instructions prior to dispensation and administration. Refer to specific product labeling for details.

Tepadina®: Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light; do not freeze. Reconstituted solution (10 mg/mL) is stable for 8 hours when stored at 2°C to 8°C (36°F to 46°F). Solution further diluted for infusion is stable for 24 hours when stored at 2°C to 8°C (36°F to 46°F), or for 4 hours when stored at 25°C (77°F).

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

Reconstitute Thiotepa for Injection with 1.5 mL of Sterile Water for Injection resulting in a drug concentration of approximately 10 mg/mL**.** (As per manufacturer's information: Actual content per vial 15.6 mg; withdrawable amount 14.7 mg/1.4 mL; approximate reconstituted concentration: 10.4 mg/mL). When reconstituted with Sterile Water for Injection, solutions of thiotepa should be stored at refrigerated temperatures 2°-8°C (36°-46°F) protected from light and used within 8 hours. The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% NaCl) prior to use. Thiotepa at a concentration of 1-5 mg/mL in 0.9% NaCl is stable for 24 hours at room temperature. At concentration of 0.5mg/mL it is stable for only one hour and stability decreases significantly at concentrations of less than 0.5mg/mL. Therefore, solutions diluted to 0.5mg/mL should be used immediately.

In order to eliminate haze, filter solutions through a 0.22 micron filter [Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®-GSFilter Unit)] prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

Tepadina®: Reconstitute each 15 mg vial with 1.5 mL SWFI, or each 100 mg vial with 10 mL SWFI, to a concentration of 10 mg/mL. Gently mix by repeated inversions. Solution may be clear or opalescent; do not use if particulate matter is present. Further dilute reconstituted solution for IV infusion in 500 mL NS (1,000 mL NS if dose > 500 mg). If dose is < 250 mg, dilute in an appropriate volume of NS to achieve a final concentration of 0.5 to 1 mg/mL.

When thiotepa is given in bone marrow transplant doses, bathe the patient and change linen frequently (≥ 2 baths/day) to avoid the contact dermatitis and discoloration of the skin that is seen with high dose.

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

6.15 TOPOTECAN

(SKF-104864, Hycamtin®) NSC #609699 **(06/03/13)**

Source and Pharmacology:
Topotecan hydrochloride is a semi-synthetic derivative of camptothecin (an alkaloid derived from the camptothecin tree which grows widely throughout Asia) and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks. Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤ 4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. *In vitro* studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway. Topotecan exhibits multi-exponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

In humans, about 30% of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination. In patients with mild renal impairment (Cl_{cr} of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Dosage adjustment is recommended for these patients. Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea (L), constipation, fever, pain (abdominal, skeletal, back pain)	Anorexia, headache, asthenia, rash (urticaria, pruritus, bullous eruption) (L), asymptomatic hypotension, dyspnea	Anaphylaxis, angioedema, chest pain, rigors
Prompt:	Myelosuppression, fatigue, febrile neutropenia	Stomatitis/mucositis, increased SGOT	Elevated bilirubin, paresthesias, myalgia,

Within 2-3 weeks, prior to next course		(AST)/SGPT (ALT)/alkaline phosphatase, sepsis	arthralgia, intratumoral bleeding
Delayed: Anytime later during therapy	Alopecia		Microscopic hematuria, increased creatinine, proteinuria
Unknown Frequency and Timing:	Teratogenic effects of topotecan have been noted in animal models at doses ≤ to those used in humans. It is not known if topotecan is excreted into human breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:
Topotecan is available as a lyophilized powder for reconstitution and as a solution concentrate. Each vial of lyophilized powder contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. Inactive ingredients are mannitol 48 mg, and tartaric acid 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. Topotecan concentrate solution for injection is supplied as a sterile, non-pyrogenic, clear, yellow to yellow-green solution at a topotecan free base concentration of 4 mg/4 mL (1 mg/mL) available in single use vials. Each mL of topotecan injection contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base, 5 mg tartaric acid, NF and water for injection, USP. Hydrochloric acid and/or sodium hydroxide may be used for pH adjustment. The pH of the solution is approximately 2.6 to 3.2; both products must be further diluted prior to administration in a minimum of 50 mL of compatible fluid for infusion. Both types of vials should be protected from light in the original cartons and stored at controlled room temperature between 20° and 25°C (68° and 77°F).

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

Reconstitute each topotecan 4 mg vial with 4 mL SWFI to concentration of 1 mg/mL. Further dilute in 50-250 mL D5W or NS. Reconstituted vials of topotecan diluted for infusion are stable at approximately 20°-25°C (68°-77°F) and ambient lighting conditions for 24 hours.

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

6.16 VINCRISTINE SULFATE

(Oncovin®, VCR, LCR) NSC #67574 **(08/16/12)**

Source and Pharmacology:
Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

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

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the

patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only – Fatal if given by other routes."

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

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 End of Therapy and Follow-up

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

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

STUDIES TO BE OBTAINED	End of Therapy	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	
Free T4, TSH	X		X		X		X	X		X		X		X	
ECHO	X				X			X		X		X		X	
Audiogram	X				X			X		X		X		X	
Cross sectional imaging of primary tumor site (MRI or CT)	X[1]		X		X		X	X		X					X[1]
^{123}I-MIBG scan if positive at baseline	X[1]	X	X		X		X	X		X					X[1]
FDG-PET/CT or PET/MR scan if positive at baseline	X[1]	X	X		X		X	X		X					X[1]
Bilateral bone marrow aspirates and biopsies	X[2]														X
Optional studies (see Appendix V)	X														X

[1] Submit for central review

[2] Submit for central review per Section 14.2

7.2 Research Studies for which Patient Participation is Optional

For full details, see Section 15.0. For a summary of samples, see Appendix V.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Repeat eligibility studies (if required) prior to the initiation of protocol therapy are outside the parameters required for eligibility (see Section 3.2)
b) Refusal of further protocol therapy by patient/parent/guardian
c) Lack of sufficient stem cells to support tandem transplant or inability to harvest stem cells prior to Consolidation (see Section 18.2)
d) Did not receive dinutuximab during Induction therapy
e) Progressive disease at any time from the end of Induction Cycle 4 until the end of protocol therapy. Patients with stable disease or better may remain on protocol therapy.
f) Completion of planned therapy
g) Physician determines it is in the patient's best interest
h) Delays in therapy that meet the criteria in Sections 4.6.6 and 4.9.1
i) Development of a second malignancy

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

Forty-two evaluable patients will be necessary to analyze the primary objective, assessing the tolerability and feasibility of ch14.18 (dinutuximab) administration during Induction. Enrollment of up to 45 patients may be required in order to generate the 42 evaluable patients. The additional 3 patients accounts for an estimated 3% of patients that may discontinue protocol therapy during the first 2 cycles of Induction [prior to the first dose of ch14.18 (dinutuximab], as reported on the previous COG high-risk neuroblastoma study ANBL0532, and losing an additional 5% for other reasons. The 42 eligible, evaluable patients will provide suitable operating characteristics to determine whether administration of ch14.18 (dinutuximab) and GM-CSF during Induction is tolerable and feasible for further study.

Conservative accrual estimates are based on the enrollment on ANBL0532, the previous COG high-risk neuroblastoma study. An estimated accrual rate of 18 patients per year was observed on ANBL0532 at 8 of the included institutions. The remaining two institutions, St. Jude Children's Research Hospital and Royal Children's Hospital, did not enroll patients on ANBL0532, but conservatively expect to accrue 4 and 7 patients per year respectively. Therefore, the total expected accrual for ANBL17P1 will be 29 patients per year. Thus, accrual of up to 45 patients should be completed in approximately 1.6 years. The study will require an additional 12 months for completion of therapy and toxicity evaluation for a total study duration of approximately 2.6 years.

The following institutions will participate in this limited-institution study:

Institutions	Average Annual Enrollment on ANBL0532
St. Jude Children's Research Hospital, Memphis TN	4.00*
Dana-Farber Cancer Institution, Boston, MA	4.68
Children's Hospital of Los Angeles, Los Angeles, CA	2.86
Primary Children's Hospital, Salt Lake City, UT	2.08
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA	2.60
Children's National Medical Center, Washington, DC	1.82
Columbia University/Herbert Irving Cancer Center, New York, NY	1.04
Starship Children's Hospital, Auckland, New Zealand	2.08
The Children's Hospital at Westmead, Westmead, NSW, Australia	1.04
Royal Children's Hospital, Parkville, VIC, Australia	7.00*

*Estimated rate; institution did not enroll any patients on ANBL0532

9.2 Study Design

This trial is a prospective, single arm, limited institution pilot study to assess the tolerability and feasibility of administering ch14.18 (dinutuximab) in combination with a multi-agent chemotherapy regimen during the Induction phase for patients with newly-diagnosed high-risk neuroblastoma. All patients will receive the same treatment. A stopping rule for tolerability will be used to closely monitor patients for the occurrence of toxicities deemed

unacceptable. In addition, we will monitor for the feasibility of administering the intended doses of ch14.18 (dinutuximab).

9.3 Methods of Analysis

9.3.1 Evaluability

Any eligible patient who receives at least one dose of ch14.18 (dinutuximab) during Induction will be evaluable for purposes of evaluating the tolerability and feasibility monitoring rules. Any eligible patient who receives at least one dose of ch14.18 (dinutuximab) during post-Consolidation will be evaluable for exploratory study objective 1.3.3 related to HACA development during post-Consolidation.

9.3.2 Primary Endpoint

9.3.2.1 Tolerability

The primary endpoints used to assess the tolerability aspect of the primary objective include:

a. the number of toxic deaths during Cycles 3-5 of Induction.
b. the number of patients with unacceptable toxicities (using CTCAE v.5.0 for toxicity assessment and grading) related to ch14.18 (dinutuximab) during Cycles 3–5 of Induction as defined below:
   i. Hypotension requiring the use of pressors for ≥ 24 hours, including Grade 4 capillary leak syndrome or Grade 3 and 4 hypotension requiring pressors.
   ii. Respiratory toxicity requiring ventilator support ≥ 24 hours, including Grade 4 respiratory toxicity.
   iii. Grade 4 neuropathy that does not resolve to baseline prior to the next cycle of therapy.
   iv. Grade ≥ 3 neuropathy that recurs following a 50% dose reduction.
   v. Failure to recover ANC to ≥ 750/mm^3 by Day 35 of a cycle.

A patient will be counted as having experienced an unacceptable toxicity if a toxic death or one of the unacceptable toxicities listed above occurs. Only toxicities designated as possibly, probably, or definitely attributed to ch14.18 (dinutuximab) during Cycles 3–5 of Induction will be considered.

9.3.2.2 Feasibility

The feasibility of delivering ch14.18 (dinutuximab) during Cycles 3-5 of Induction chemotherapy will be monitored in this trial. The primary endpoint used to assess the feasibility aspect of the primary objective will be the proportion of patients who are classified as a "failure". Feasibility "failures" are defined as patients that do not receive ≥ 75% of the planned ch14.18 (dinutuximab) doses during Induction. Any doses of ch14.18 (dinutuximab) held during Cycles 3-5 of Induction per protocol due to inability to harvest adequate stem cells will not count as planned/intended doses.

9.3.3 Secondary Endpoints

Response will be determined using the revised International Neuroblastoma Response Criteria (INRC).[73] Response rate will be calculated as the percentage of eligible patients with at least a partial response (PR) or better at the end of Induction and will also be considered in determining whether the regimen is worth further study. For event-free survival (EFS), time to event will be calculated from the time of study enrollment to the occurrence of disease relapse or progression, secondary malignancy, or death. For overall survival (OS), death will be the only event considered and time to death will be calculated from the time of study enrollment. Patients without an event or death will be censored at the time of last follow-up.

9.3.3.1 Power Calculations for HACA Development

With enrollment of up to 45 patients, an estimated 30 evaluable patients will be available for evaluation of exploratory study objective 1.3.3 related to HACA development during post-Consolidation. This accounts for an estimated 35% of patients going off protocol therapy prior to starting post-Consolidation ch14.18 (dinutuximab). The projected discontinuation from protocol therapy is less than was seen on the most recent COG high-risk neuroblastoma studies. Approximately 42% of patients treated on contemporaneous COG high-risk neuroblastoma protocols did not receive post-Consolidation ch14.18 (dinutuximab) on COG ANBL0032 due to inadequate disease response, organ toxicity, or family preference. However, in a current St. Jude Children's Research Hospital clinical trial (NB2012), the addition of a humanized anti-GD2 mAb to Induction therapy demonstrated improved response to Induction therapy, with 95% of patients moving on to receive Consolidation and post-Consolidation therapy. Five percent discontinued protocol therapy due to family preference. This suggests that, although only 58% percent of patients enrolled on COG high-risk neuroblastoma trials have completed all therapy, the percentage of patients who complete all therapy on this study may be higher based on the recent success of NB2012.

The 30 evaluable patients will provide suitable operating characteristics and power to evaluate HACA development during post-Consolidation. Analyses of data from patients treated with ch14.18 (dinutuximab)-based immunotherapy on COG ANBL0032 reported the incidence of neutralizing HACA was 4.4%. An increase in neutralizing HACA from 4.4% to >20% (i.e.: >9 of 45 patients during the Induction phase, or >6 of 30 during the post-Consolidation phase) would be a sufficiently large increase in a biologically meaningful HACA and may have a deleterious action on the desired effects of ch14.18 (dinutuximab) during post-Consolidation. With 45 enrolled patients [30 evaluable patients receiving post-Consolidation ch14.18 (dinutuximab)], there will be >96% power at the 5% significance level to detect an increase in the proportion of patients with a neutralizing HACA (from 4.4% to >20%) during Induction therapy and over 87% power during post-Consolidation using a one-sided exact test of proportion with binomial enumeration.

9.3.4 Monitoring

9.3.4.1 Tolerability

There may be cause to stop the trial early if the unacceptable toxicity rate appears too high. An unacceptable toxicity rate of 10% was observed at the interim analysis of the NB2012 study. However, these unacceptable toxicities were related to Consolidation therapy and were attributed to the Consolidation conditioning regimen (busulfan and melphalan). Since the evaluation period for the occurrence of toxicity during treatment is approximately 6 months, in order to avoid significant delays in accrual, the study will not be halted while the data are gathered for the assessment of the monitoring rule.

A one-sided Pocock group-sequential boundary with a sample size of 42 will be used to monitor the number of patients who experience at least one unacceptable toxicity during Cycle 3-5 of Induction (Section 9.3.2.1). Interim monitoring will be done after every sixth patient has been fully evaluated for the occurrence of unacceptable toxicity (Table 1). The upper bound on the number of unacceptable toxicity events needed to declare the therapy too toxic uses a cumulative alpha level of 0.13. The probability of declaring the regimen too toxic under the alternative hypothesis toxicity rates of 25% and 28% appears in Table 2. The average sample size when the unacceptable toxicity rate is 10%, 25%, and 28% is 39.22, 22.95, and 19.64, respectively.

Table 1. Interim monitoring plan and number of observed unacceptable toxicities needed to declare therapy too toxic.

Monitoring percent of total information	Number of patients fully evaluated for toxicity	Monitoring boundary	Number of observed unacceptable toxicities to declare too toxic
14.3%	6	1.9028 (p=0.02854)	≥ 3 (50%)
28.6%	12	1.8178 (p=0.03455)	≥ 4 (33%)
42.9%	18	1.7495 (p=0.04010)	≥ 5 (28%)
57.1%	24	1.6961 (p=0.04493)	≥ 6 (25%)
71.4%	30	1.6531 (p=0.04915)	≥ 7 (23%)
85.7%	36	1.6175 (p=0.05289)	≥ 8 (22%)
100.0%	42	1.5872 (p=0.05624)	≥ 8 (19%)

Table 2. Probability of detecting a difference under various alternative hypothesis unacceptable toxicity rates.

Monitoring percent of total information	Number of patients fully evaluated for toxicity	Power under a true unacceptable toxicity rate of 25%	Power under a true unacceptable toxicity rate of 28%
14.3%	6	0.1694	0.2196
28.6%	12	0.3512	0.4452
42.9%	18	0.4813	0.5968
57.1%	24	0.5778	0.7016
71.4%	30	0.6519	0.7762
85.7%	36	0.7103	0.8304
100.0%	42	0.8589	0.9334

If this monitoring rule for tolerability is triggered, CTEP and the study committee will review the data and discuss amending the study to reduce the dose of ch14.18 (dinutuximab) administered during Induction by 25%. If this were to occur, discussions related to further steps in accrual to the trial will include re-starting rather than resuming accrual, with up to 45 patients enrolling with the reduced dosing of ch14.18 (dinutuximab). Only the patients in the cohort enrolled after such an amendment would be included in the analysis of tolerability.

9.3.4.2 Feasibility

We will monitor for inability to administer the intended dose of ch14.18 (dinutuximab). On COG ANBL1221, 14/51 (27.5%) patients that received ch14.18 (dinutuximab) required a dose modification, however therapy was discontinued in only 8/51 (15.7%) cases. A feasibility “failure” rate of 25%, in between the two rates observed on ANBL1221, is expected on this trial. The study will not be halted while the data are gathered for the assessment of the monitoring rule.

A one-sided Pocock group-sequential boundary with a sample size of 42 will be used to monitor the number of patients deemed feasibility "failures" during Cycle 3-5 of Induction (section 9.3.2.2). Interim monitoring will be done after 1/3 and 2/3 of the planned number of patients have been fully evaluated as to receiving 75% or more of the intended ch14.18 (dinutuximab) doses (Table 3). The upper bound on the number of feasibility "failures" needed to declare the therapy not feasible uses a cumulative alpha level of 0.10. The probability of declaring the regimen not feasible under the alternative hypothesis feasibility "failure" rates of 45% and 48% appears in Table 4. The average sample size when the feasibility "failure" rate is 25%, 45%, and 48% is 40.30, 26.53, and 23.83, respectively.

Table 3. Interim monitoring plan and number of observed feasibility "failures" needed to declare therapy not feasible.

Monitoring percent of total information	Number of patients fully evaluated	Monitoring boundary	Number of observed feasibility "failures" to declare not feasible
33.3%	14	1.6924 (p=0.04528)	≥ 7 (50%)
66.7%	28	1.6477 (p=0.04971)	≥ 12 (43%)
100.0%	42	1.6107 (p=0.05362)	≥ 16 (38%)

Table 4. Probability of detecting a difference under various alternative hypothesis feasibility "failure" rates.

Monitoring percent of total information	Number of patients fully evaluated	Power under a true feasibility "failure" rate of 45%	Power under a true feasibility "failure" rate of 48%
33.3%	14	0.4539	0.5451
66.7%	28	0.6596	0.7678
100.0%	42	0.8544	0.9257

If this monitoring rule for feasibility is triggered, CTEP and the study committee will review the data and discuss amending the study to reduce the dose of ch14.18 (dinutuximab) administered during Induction by 25%. If this were to occur, discussions related to further steps in accrual to the trial will include re-starting rather than resuming accrual, with up to 45 patients enrolling with the reduced dosing of ch14.18 (dinutuximab). Only the patients in the cohort enrolled after such an amendment would be included in the analysis of feasibility.

The rate of completion of Consolidation and post-Consolidation therapy will also be descriptively monitored to determine the effect of administration of ch14.18 (dinutuximab) during Induction on subsequent treatment. Of the 378 patients that enrolled on ANBL0532 in 2010 and after (when randomization was halted on ANBL0032 and all patients were subsequently assigned to the ch14.18 (dinutuximab) arm), 100 were randomized to the tandem transplant arm. Of these patients, 75 (75%) went on to enroll on ANBL0032 (none enrolled on ANBL0931), indicating completion of Consolidation therapy. Sixty-five of the 75 patients completed all planned cycles of ch14.18 (dinutuximab) post-Consolidation therapy; therefore, 65% of the 100 patients randomized to the tandem transplant arm on ANBL0532 completed Consolidation and post-Consolidation therapy. Similar completion rates of Consolidation and post-Consolidation therapy are also expected on this study. Observed rates of completion and reasons for inability to complete therapy will be tabulated and reported to the data safety monitoring committee.

9.3.5 Assessment of Study Objectives

The primary study objective (1.1.1) related to tolerability will be assessed by the unacceptable toxicity monitoring rule (Section 9.3.4.1), and in addition, by estimation of the combined toxic death and unacceptable toxicity rate together with a 95% CI. The therapy will be deemed tolerable at the specified dose level if the tolerability monitoring rule is not triggered.

The primary study objective (1.1.1) related to feasibility will be assessed by the monitoring rule (Section 9.3.4.2), and in addition, by estimation of the feasibility "failure" rate together with a 95% CI. The therapy will be deemed feasible at the specified dose level if the feasibility monitoring rule is not triggered.

To address secondary objective 1.2.1, the response rate to treatment will be calculated, including placement of a 95% CI on the response rate. Kaplan-Meier curves of EFS and OS will also be generated.

To assess exploratory objective 1.3.1, the incidence of naturally occurring anti-glycan antibodies at different time points during Induction and post-Consolidation therapy will be calculated, including placement of a 95% CI on the incidence. In addition, anti-glycan levels prior to the start of Induction therapy and prior to the start of post-Consolidation therapy will be compared with Wilcoxon's signed-rank test for paired data.

Exploratory objective 1.3.2 will be assessed by calculating the incidence of NK receptor NKp30 isoforms, including placement of a 95% CI on the incidence.

To address exploratory objective 1.3.3, the relationship between response to treatment with $\geq$ PR at the end of induction and end of therapy (response vs. non-response) and naturally occurring anti-glycan antibodies, KIR/KIR-L genotyping, Fc receptor genotyping, and HACA will be explored with Fisher's exact test for categorical and Wilcoxon rank-sum test for continuous host factors. Both the presence/absence and level of naturally occurring anti-glycan antibodies will be considered. For the KIR/KIR-L analysis, patients will be categorized as either matched or mismatched. Patients will be grouped into one of the three genotype subgroups of Fc receptor genotyping for that analysis. The presence/absence of HACA, anti-idiotype, and PATA/anti-allotype antibody will be considered for the HACA analysis.

To assess exploratory objective 1.3.4, the incidence of NK receptor NKp30 isoforms will be calculated, including placement of a 95% CI on each incidence rate. Summary statistics will also be generated for serum cytokine (IL6, CXCL9) levels and gene expression of circulating immune function cells.

Exploratory objective 1.3.5 will be assessed by exploring the relationship between response to treatment with > PR (response vs. non- response) with circulating GD2 levels, and GD2 tumor cell expression following therapy with a Wilcoxon rank-sum test. Changes from baseline will also be analyzed.

9.4 Evaluability for Response

All eligible patients will be considered evaluable for response.

9.5 Evaluability for Toxicity

All eligible patients treated with at least one dose of study drug will be considered evaluable for toxicity. Any eligible patient who receives at least one dose of ch14.18 (dinutuximab) during Induction will be evaluable for purposes of evaluating the tolerability and feasibility monitoring rules (Section 9.3.4).

9.6 Gender and Minority Accrual Estimates

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

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	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	4	0	0	**6**
White	14	18	3	2	**37**
More Than One Race	0	0	0	0	**0**
Total	**17**	**23**	**3**	**2**	**45**

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.

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

10.2 Response Criteria

This study will use the revised International Neuroblastoma Response Criteria for disease assessment.[73] 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 toxicity: All eligible patients treated with at least one dose of study drug will be considered evaluable for toxicity. Any eligible patient who receives at least one dose of ch14.18 (dinutuximab) during Induction will be evaluable for purposes of evaluating the tolerability and feasibility monitoring rules (Section 9.3.4).

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

10.2.2 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.[74] 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/CT or PET/MR) 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 1.1 criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

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, 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/CT or PET/MR scans. Technetium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system. 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.).[75] 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/CT OR PET/MR[2]) IMAGING
Complete Response (CR)	• < 10 mm residual soft tissue at primary site, AND • complete resolution of MIBG or FDG-PET/CT or PET/MR 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/CT or PET/MR 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

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET/CT or PET/MR[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/CT or PET/MR 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) or ≥ 50% reduction in number of FDG-PET/CT or PET/MR 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/CT or PET/MR avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma; • Any new bone site that is MIBG avid; • A new bone site that is FDG-PET/CT or PET/MR 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[4]
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/CT or PET/MR uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[4]Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes but the same imaging methodology should be used for all evaluations.

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 >20% 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.
See Appendix VII for additional information regarding overall response assessment

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

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

11.2 Determination of Reporting Requirements

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

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

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

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

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

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not

considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

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

11.4 Special Situations for Expedited Reporting

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

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

11.4.2 Persistent or Significant Disabilities/Incapacities

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

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression"*** in the system organ class (SOC***) "General disorders and administration site conditions."***. Evidence that the death was a

manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

11.4.5 Second Malignancy

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

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other***

(pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions SOC.

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

11.4.6.2 **Pregnancy Loss (Fetal Death)**

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

11.4.6.3 **Death Neonatal**

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

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

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

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

11.5.2 Persistent AEs

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

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

11.5.3 Recurrent AEs

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

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

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

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

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

11.6.2 Special Situations as Exceptions to Expedited Reporting

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

11.7 Reporting Requirements - Investigator Responsibility

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

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

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical

company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.

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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

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

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

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

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

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

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

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

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

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

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

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

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

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

The following events do not need to be reported in CTEP-AERS, regardless of hospitalization.

- Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia) does not require expedited reporting unless associated with >3 week delays in the start of the next scheduled therapy.
- Grades 1-2 AST/ALT elevations do not require expedited reporting unless associated with >3 week delays in the start of the next scheduled therapy.
- Hospital admission/prolongation of hospitalization for Grade 3 febrile neutropenia does not require expedited reporting.
- Hospital admission/prolongation of hospitalization for Grade 3 infection does not require expedited reporting.
- Hospital admission/prolongation of hospitalization for Grade 3 sepsis does not require expedited reporting.
- Grades 1-3 irritability does not require expedited reporting
- Grades 1-3 urine output decrease does not require expedited reporting
- Grades 1-3 pain does not require expedited reporting
- Grades 1-3 capillary leak does not require expedited reporting
- Grades 1-2 vision decreased or Grade 3 vision decreased that resolve within 7 days of onset does not require expedited reporting

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

- All Grade 4 and 5 pulmonary complications
- All Grade 4 and 5 hepatic complications
- All Grade 4 and 5 cardiac complications
- All Grade 4 and 5 renal complications
- Grade 4 sinusoidal obstruction syndrome (SOS) or Grade 3 SOS PLUS a specific organ failure listed below:
  - CTC Grade 4 hepatic failure, OR
  - Pulmonary dysfunction: Continuous oxygen support for > 48 hours, ventilatory support not clearly attributable to another cause, OR
  - Renal dysfunction: serum creatinine > 3 times the ULN for age and sex (CTC Grade 3 creatinine), or the need for dialysis (CTC Grade 4 acute kidney injury), not clearly attributable to another cause.

11.11 Reporting of Adverse Events for Commercial Agents – CTEP-AERS Abbreviated Pathway

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

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

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

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

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.12 Routine Adverse Event Reporting

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

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and all Grade 3 and higher non-hematologic events in the Induction, Consolidation, and Post-Consolidation portions of therapy. The following Adverse Events will also be collected:

- During Cycles 3-5 of Induction therapy, any adverse event that results in drug doses being held or drug dose modification according to Section 5.0.

Delays of ≥ 2 weeks in the start of cycles of Induction therapy, initiation of Consolidation therapy ≥ 10 weeks from the start of Cycle 5 of Induction chemotherapy, and initiation of post-Consolidation therapy ≥ 14 weeks from Day 0 of the last stem cell transplant will be reported in COG case report forms. The reason for the delays must be documented.

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 CDUS

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

12.2 Data and Safety Monitoring Committee

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

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

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

12.3 CRADA/CTA

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

13.1 Surgical Rationale

The overall surgical goal in high-risk patients with neuroblastoma is the most complete tumor resection with as much preservation of full organ and neurologic function as possible. In addition, the surgeon is responsible for the preservation and delivery of an adequate surgical specimen to the local hospital laboratory for crucial biologic analyses.

Surgical resection of soft tissue disease will occur during Induction therapy. All patients will undergo attempt a complete surgical resection of primary tumor following Cycle 4 chemotherapy (or Cycle 5, if clinically necessary) during induction. Titanium clips should be placed around sites of gross residual disease.

13.2 Pre-Operative Management

Adequate pre-operative imaging of the primary tumor and sites of regional spread requires MRI, CT, or a combination of these modalities. For paraspinal and/or epidural lesions, pre-operative neurosurgical consultation is recommended, and a baseline neurologic assessment should be performed. The planned operation should be discussed with the attending pediatric oncologist, and discussion in the context of a multidisciplinary tumor board is strongly recommended. The goals of the surgery should be clearly understood by all involved services pre-operatively.

13.3 Specimen/Sampling Requirements at Diagnosis

In all patients, the primary purpose of the initial surgical procedure is to obtain enough tissue to establish the diagnosis, contribute to risk assignment, and secure enough properly preserved tumor for required biological studies.

Biopsy of the primary tumor or an accessible metastatic site is acceptable. An adequate biopsy to determine the diagnosis and assess biological variables such as histopathologic classification and *MYCN* amplification status is required. Usually at least 1 cubic centimeter of viable tissue is needed for these assays. Image-guided percutaneous biopsy, minimally invasive surgical biopsy, or open surgical biopsy are all appropriate options for obtaining tissue, as best determined by the surgeon, oncologist, and interventional radiologist. If percutaneous core biopsy is obtained, multiple cores (25-30) are required with a minimum recommended needle size of 16 gauge. It is important to note that a

significant portion of the tumor may be necrotic. Frozen section pathologic examination will verify that viable neuroblastoma is being biopsied.

Placement of the specimen in formalin should be avoided. Rather, the pathologist should be alerted and the specimen rapidly transferred from the operating room fresh and sterile. The surgeon and/or interventional radiologist should verify with the pathologist that viable tissue was sent and is being processed appropriately.

13.4 Specimen/Sampling Requirements at Definitive Surgery

13.4.1 The primary purpose of surgery after Induction cycle 4 chemotherapy is definitive resection of the primary tumor. However, the surgical specimen obtained will be used for important correlative studies, even if portions of the tumor are largely necrotic. Placement of the specimen in formalin should be avoided. The specimen should be rapidly transferred from the operating room to pathology, fresh and sterile.

13.5 Operative Management

13.5.1 Central Line Placement

Patients will require central venous access. It is usually feasible and efficient to place a vascular access device and obtain a bone marrow aspirate and biopsy during the same anesthetic. The appropriate catheter should be placed at the time of initiation of therapy.

Apheresis catheters for stem cell harvest: Medcomp or similar catheters are specifically designed as tunneled, permanent apheresis catheters. It may not be possible to draw at a sufficient rate from a non-apheresis catheter that is smaller than 10 Fr. If a smaller lumen must be placed, or if it is institutional practice to use a temporary catheter for pheresis, placement of the pheresis catheter may be deferred until Cycle 2.

13.5.2 Diagnostic Surgery

The great majority of high-risk patients will undergo initial diagnostic biopsy without resection. The surgeon should try to obtain at least 1 cm^3 of viable tumor tissue, if feasible, according to the surgeon's judgment. Complete excision of the primary tumor can occasionally be performed if the tumor is easily resectable without a lengthy procedure or extensive dissection. However, a resection should not be undertaken initially if a significant delay in the initiation of chemotherapy or significant morbidity would be associated with upfront resection.

13.5.3 Epidural Tumors with Intraspinal Extension

When the tumor approaches the spinal canal on imaging (see Section 16.1), a detailed physical examination must assess neurological function.

Laminectomy should not be performed in patients who are neurologically asymptomatic. Patients with symptomatic spinal cord compression secondary to epidural extension of neuroblastoma through a neural foramina may require laminectomy, or osteoplastic laminotomy at diagnosis to prevent permanent

paralysis. However, treatment with chemotherapy alone or chemotherapy and radiation therapy will frequently be sufficient to rapidly reverse symptoms of cord compression. Therapeutic decisions in neuroblastoma patients with spinal cord compression should be made with the multidisciplinary involvement of the attending pediatric oncologist, pediatric surgeon, and pediatric neurosurgeon.

If neurologic deterioration occurs during chemotherapy, neurosurgical evaluation should be sought and operative decompression strongly considered. Appropriate to the degree of neurological impairment, the treating physicians may decide that operative neurosurgical decompression is indicated under these circumstances. If feasible, the neurosurgeon should perform an osteoplastic laminotomy, with secure replacement of the laminae after decompression has been accomplished. Operative details will be recorded in the RAVE system.

13.5.4 Operative Management of Primary Tumors after Chemotherapy

The majority of patients will undergo resection of the primary tumor after 4 cycles of Induction chemotherapy. Surgical resection should be performed when the ANC > 500/µL and the patient is medically stable after chemotherapy Cycle 4 of Induction. Surgical resection may be performed later in Induction, if necessary, but MUST occur prior to Consolidation. Surgical scheduling **SHOULD AVOID DELAYS OF MORE THAN 6 WEEKS BETWEEN CHEMOTHERAPY CYCLES. THE SAME TIME FRAME SHOULD BE OBSERVED WHEN SURGERY OCCURS AFTER CYCLE 5.**

The goal of the definitive surgical procedure is gross total resection of residual tumor in the primary site as well as tumor in areas of regional dissemination (usually lymph nodes). Resection with microscopically negative margins may not be feasible because of proximity to major vascular structures and the spine. Instead, the surgeon should concentrate on removing, as completely as possible, all gross disease. It is acceptable, and often necessary, to incise the tumor and remove it in a segmental fashion. Titanium clips should be used to mark all areas of residual disease. All attempts should be made to preserve organs, especially the kidney. Rarely, nephrectomy may be necessary for complete tumor removal but this should only be planned if the involved kidney has greatly diminished function. **If a nephrectomy is being considered pre-operatively, then a differential GFR should be obtained to determine what the renal function will be in the remaining kidney, and consult with a nephrologist is recommended.** The COG Surgical Committee strongly recommends kidney preservation when feasible.

It is vital that the operating surgeon dictate a detailed operative note, which should include the following information:

- the completeness of resection,
- areas of residual disease,
- estimated blood loss, and
- any operative complication such as identification of injury to adjacent structures, removal of normal organs, renal injury, and vascular injury.

13.6 Management of Surgical Complications

Guidance regarding management of surgical complications is provided below. Surgical complications will be graded using the Clavien-Dindo scale.[76]

13.6.1 Intraoperative Complications

Intraoperative complications are site-dependent. Major hemorrhage from either venous or arterial structures is always possible with these infiltrative tumors. The principles of vascular surgery, including proximal and distal control, pertain. Appropriate intraoperative vascular consultation should be sought if necessary. Crucial vessels like the carotid, subclavian, hepatic, superior mesenteric or renal arteries should be repaired and flow restored even if bypass grafting is required. Nerve injuries may also be incurred and should be primarily repaired using magnification.

13.6.2 Post-Operative Complications

Acute and long-term complications and duration of complications will be prospectively monitored, including infectious complications, chylous leak (thoracic and abdominal); non-infectious diarrhea; bowel obstruction due to intussusception or post-surgical adhesions; and renal dysfunction and/or atrophy due to vascular injury.

Pulmonary Complications
Resection of large abdominal neuroblastoma tumors may result in significant third space losses and require vigorous fluid replacement intraoperatively and postoperatively. Because of this fluid requirement, patients may require significant periods of post-operative ventilation. The need for post-operative monitoring in an intensive care environment should be anticipated. Pneumonias or other pulmonary complications related to postoperative course (including intubation > 7 days) should be reported.

Bowel Obstruction
Small bowel obstruction may occur for many reasons, including injury, exposure, or blunt trauma during the resection, postoperative intussusception, formation of adhesions, or related to radiation injury. Obstruction may occur in the early postoperative period, or may occur months to years later.

Chylous Leak
Extensive dissection of the retroperitoneum or mediastinum may result in either frank disruption of chylous channels, or interruption causing intraluminal lymphatic hypertension and leak.

Renal Injury/Atrophy
Renal injury may manifest in many forms, related to the nature of the injury or insult. While nephrectomy is strongly discouraged, extensive perirenal dissection and kidney sparing surgery may still result in vascular occlusion, infarction, traumatic compression, or other injury mechanisms sufficient to cause long term dysfunction or atrophy. Additionally, radiation therapy may lead to kidney damage, again with the long term finding of atrophy.

Diarrhea
Extensive sympathetic denervation associated with aggressive retroperitoneal dissection may result in increased frequency of stooling or diarrhea.

13.7 Special Techniques

13.7.1 Nerve Stimulation

Nerve stimulation can be useful in detecting motor nerves in the brachial or lumbo-sacral plexus. This requires cooperation from the anesthesiologist as muscle relaxation must be allowed to wear off. Nerve stimulation should always be used with dissection along the pelvic sidewall or in the neck or thoracic inlet.

13.7.2 Thoracoscopy

Video-assisted thoracoscopy can be used to remove small posterior mediastinal or thoracic inlet tumors provided there is no vascular encasement. One-lung ventilation or low pressure insufflation is recommended.

13.7.3 Laparoscopy

Laparoscopic resection of small adrenal or pelvic primaries can be done. Extensive tumors or those with significant vascular encasement, or locoregional nodal spread can be more completely resected using standard open approaches.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

14.1 Rapid Central Pathology Review

A rapid review of histology (under COG APEC14B1/ANBL00B1) is required to confirm the diagnosis of neuroblastoma to determine eligibility of patients for this study. See APEC14B1/ANBL00B1 for complete details on specimen requirements. The Neuroblastoma Pathology Checklist must be completed by the institutional pathologist when tumor tissue is obtained at diagnosis.

As per APEC14B1/ANBL00B1, representative slides MUST be sent to the COG Biopathology Center via Federal Express for overnight delivery. The slides will then be forwarded to Dr. Hiroyuki Shimada, and Dr. Shimada and Dr. Jason Jarzembowski will determine the histologic diagnosis and notify the Neuroblastoma Biology Reference Laboratory. The Tracking Center will then determine risk status and will notify the treating institution of the results.

14.1.1 Neuroblastoma Tracking Center Activity

Institutions will first enroll patients on APEC14B1/ANBL00B1 once the patient's age, diagnosis and disease stage have been determined. The COG Statistical Office will notify the Tracking Center with the enrollment information. Results of *MYCN* testing will be sent to the Tracking Center and to the treating institution by the Neuroblastoma Biology Reference Laboratory as soon as the results are available.

14.1.2 Review Material Required at Diagnosis

Review materials are submitted through APEC14B1/ANBL00B1. Do not submit separate pathology review materials for this protocol. Please refer to APEC14B1/ANBL00B1 for submission details.

14.1.3 Review Material at Second Look or Definitive Surgery and/or Relapse

Pathology materials must be submitted through APEC14B1/ANBL00B1 at the time of second look surgery, whether this procedure is a biopsy, partial resection, or complete resection, and/also at the time of relapse. Please refer to APEC14B1/ANBL00B1 for specimen requirements.

14.1.4 Study Pathologist

Study Pathologist of record:
Hiroyuki Shimada, MD
Department of Pathology
Children's Hospital Los Angeles

14.2 Retrospective Central Review of Bone Marrow Samples

A retrospective central review of bilateral bone marrow aspirates and biopsies will be performed on this study to confirm response status to therapy. The results of the review will not be returned to the submitting institution.

14.2.1 Time points

Samples will be collected at the following time points.

- End of Induction, Cycle 5
- Prior to post-Consolidation, Cycle 1
- End of therapy

14.2.2 Review Materials Required and Shipping

At each time point listed above submit:

- Two H&E and 5 unstained slides from each biopsy block
- Representative stained slide(s) from each aspiration procedure.
- Pathology report for each procedure (biopsy and aspiration)
- Specimen Transmittal Form: Bone Marrow Central Review

Label slides and accompanying paperwork with:

- Patient's COG number
- Specimen type (bone marrow biopsy, clot or aspirate)
- Surgical Pathology ID (SPID) number from corresponding pathology report
- Note the course and day of therapy bone marrow was drawn and the collection dates on the transmittal form.

Complete the Specimen Transmittal Form: Bone Marrow Central Review in RAVE and include a printed copy with the bone marrow central review samples

and pathology report(s). Slides from all timepoints may be held and sent in one shipment. Send via regular mail or using the institution's courier account to:

Biopathology Center
Nationwide Children's Hospital
Protocol ANBL17P1
700 Children's Drive, Room 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.*

14.2.3 Central Review Pathologist

The BPC will forward the bone marrow samples for central review to:
Dr. Hiroyuki Shimada
Department of Pathology
Children's Hospital Los Angeles

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Optional Studies

Tumor obtained at diagnosis as part of APEC14B1 or ANBL00B1 may be used. **All other specimens described in the following section are to be obtained in addition to samples submitted as part of ANBL00B1 or APEC14B1.** Each of these correlative studies is optional, but **strongly encouraged**. All patients will be eligible for all optional studies on ANBL17P1.

A summary table of Optional Studies samples and time points is provided in Appendix V.

Every effort should be made to obtain samples from all time points, including the pre-therapy time point. However, if the baseline sample cannot be obtained, subsequent samples should still be collected as specified (see Appendix V).

The study committee recognizes that the blood volume requested for correlative studies at both the pre-treatment and prior to post-Consolidation time points is significant. If the requested samples exceed the maximum allowable blood draw for a given day, samples may be drawn on subsequent days as long as all blood draws are within 1 week prior to starting Induction or prior to post-Consolidation.

Study prioritization:
If blood volume obtainable is limited at a time point, please follow the priority list below. This list is written from highest to lowest priority. See the section numbers provided and Appendix V for sample details.

1. HACA/PATA Analysis (Section 15.1.3) / NK Marker Analysis and Genotyping (Section 15.1.4)

2. Anti-glycan Antibodies (Section 15.1.1)
3. NK Cell Receptor NKp30 Isoform (Section 15.1.2)
4. Gene Expression Studies: RNA Sequencing (Section 15.1.6)
5. Cytokine Analysis (Section 15.1.5)
6. GD2 Biomarkers (Section 15.1.7)

Biospecimen banking
If material is leftover after the correlative studies below are performed, it will be banked at the Biopathology Center if the patient consented to biobanking. Samples sent directly to outside labs will not be stored for biobanking.

15.1.1 Naturally occurring anti-glycan antibodies

15.1.1.1 Specimen Schedule and Requirements

At each time point, 7 to 10 mL of whole blood should be collected in an EDTA tube.

Samples are requested at the following time points:

- Pretreatment
- Induction Cycle 3, Day 1
- Induction Cycle 3, Day 6
- Induction Cycle 4, Day 1
- Induction Cycle 4, Day 6
- Prior to post-Consolidation, Cycle 1
- At first episode of disease progression or relapse.

15.1.1.2 Specimen Processing

No onsite processing is required for samples collected Monday to Thursday. Samples should be kept at room temperature before shipping. Do not store in the refrigerator. Samples must be sent to Dr. Alice Yu by next day courier, insulated to guard against extreme heat or cold.

For Weekend Collection: If the sample is collected on Friday, Saturday or Sunday, then spin the sample at 200-300 RCF for 15 minutes. Next, remove and freeze the top layer (plasma). The plasma is the sample that will be analyzed. Send the plasma and cell layer, at your earliest convenience, to Dr. Alice Yu's laboratory.

15.1.1.3 Specimen Labeling and Shipping

Tubes must be labeled with:

- The patient's COG ID number
- Specimen type (blood or plasma)
- Collection time point (i.e. Induction Cycle 3, Day 6)
- Date collected.

Samples must be sent by next day courier, insulated to guard against extreme heat or cold. For samples collected on the weekend, the plasma

and the cell layer can be sent at the earliest convenience, but must be shipped frozen on dry ice. Please contact Dr. Mitchell Diccianni prior to shipping to obtain a FedEx account number and provide the FedEx tracking number so that the samples can be tracked. Include specimen transmittal form with each shipment.

Send samples to:
Alice Yu, MD, PhD / Mitchell Diccianni, PhD
UCSD Medical Center
Clinical Teaching Facility, C-101
214 Dickinson Street
San Diego, CA 92103-8447
Lab Phone: (619)-543-2436
Lab FAX: (619)-543-5413
E-mail: yulab@ucsd.edu

Lab contact: Dr. Mitchell Diccianni
(619) 534-2436
mdiccianni@ucsd.edu

15.1.1.4 Methodology

Antiglycan antibodies will be assessed using an ELISA assay previously described and processed by Yu laboratory personnel. This work will be performed under the supervision of Dr. Mitchell Diccianni at Rady Children's Hospital- San Diego.

15.1.2 NK cell receptor NKp30 isoform

15.1.2.1 Specimen Schedule and Requirements

At each time point, 2.5 mL of whole blood should be collected in a PAXgene RNA tube. PAXgene RNA tubes will be provided by the Biopathology Center to sites in North America. To request PAXgene tubes, please access the BPC Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement/) and select "ANBL17P1" for the protocol.

Samples are requested at the following time points:

- Pretreatment; and
- Prior to post-Consolidation Cycle 1

See Section 15.2 for shipping instructions and address.

15.1.2.2 Specimen Processing

i. For samples collected in PAXgene RNA tubes, blood is placed immediately into the tube, which is then inverted 8 - 10 times to mix. Blood should be stored upright in a wire rack and placed in -20°C freezer until shipment. Do not freeze tubes upright in a

styrofoam tray as this may cause the tubes to crack. Please note that if tubes are to be kept at temperatures below -20°C, they must first be stored at -20°C for 24 hours before being transferred into a -70°C or -80°C freezer. Blood in PAXgene RNA tubes is stored frozen and it must be shipped on dry ice.

ii. PAXgene RNA tubes should be batched for each cycle and shipped prior to the next cycle. Please ship on dry ice overnight on a day that would permit delivery on a working day.

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

15.1.2.3 Specimen Labeling

Tubes must be labeled with:

- The patient's COG ID number
- BPC number
- Specimen type (blood)
- Date collected.

Specimens are shipped to the BPC. See Section 15.2 for shipping instructions and address.

15.1.2.4 BPC Handling

The BPC will batch transfer frozen PAXgene RNA tubes to the laboratory of Dr. Alice Yu at Rady Children's Hospital – San Diego.

15.1.2.5 Methodology

NKp30 expression will be performed under the supervision of Dr. Alice Yu at Rady Children's Hospital- San Diego.

15.1.3 Changes in Tumor Markers During Therapy – HACA / PATA analysis

15.1.3.1 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:

- Induction Cycle 5, Day 1
- Induction Cycle 5, Day 6
- Post-Consolidation Cycle 2, Day 1
- Post-Consolidation Cycle 2, Day 7
- Post-Consolidation Cycle 3, Day 1
- Post-Consolidation Cycle 3, Day 7
- Post-Consolidation Cycle 4, Day 7
- Post-Consolidation Cycle 5, Day 7

15.1.3.2 Specimen Processing

Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA. Centrifuge the blood at 200-300 RCF 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) and immediately freeze the vials upright in a -70ºC to -80ºC freezer. Retain frozen until ready for batch shipment.

15.1.3.3 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 Biopathology Center frozen on dry ice in batch shipments. See Section 15.2 for shipping address and additional shipping instructions.

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

15.1.3.4 Methodology

Plasma samples will be assayed for HACA using an ELISA test previously described. Analysis will be performed under the supervision of Dr. Paul Sondel at The University of Wisconsin Hospital and Clinics.

In addition to the specimens listed in Section 15.1.3.1, HACA/PATA analysis will also be performed on plasma obtained from the NK marker analysis (see Section 15.1.4). The Yu lab will share plasma with the Sondel lab for these studies; no additional samples need to be collected. For shared time points, see Appendix V.

15.1.4 Immune Function Profiling: NK marker analysis and genotyping for KIR/KIR ligands and FcR

15.1.4.1 Specimen Schedule and Requirements

At each time point, 7 mL of whole blood should be collected in an EDTA tube.

Samples are requested at the following time points:

- Pretreatment
- Induction Cycle 3, Day 1
- Induction Cycle 3, Day 6
- Induction Cycle 4, Day 1
- Induction Cycle 4, Day 6

- Prior to Post-Consolidation Cycle 1
- Post-Consolidation Cycle 1, Day 7
- Post-Consolidation Cycle 4, Day 1
- Post-Consolidation Cycle 5, Day 1
- Post-Consolidation Cycle 6, Day 15

15.1.4.2 Specimen Processing

No onsite processing is required. Samples should be kept at room temperature before shipping. Do not store in the refrigerator. Samples must be sent by next day courier, insulated to guard against extreme heat or cold.

For Weekend Collection: No onsite processing is required. If the sample is collected on Friday, Saturday or Sunday, the sample should be stored at room temperature and shipped immediately the next business day.

15.1.4.3 Specimen Labeling and Shipping

Tubes must be labeled with:

- The patient's COG ID number
- Specimen type (whole blood)
- Collection time point (i.e. Induction cycle 3, Day 6)
- Date collected.

Note: A copy of the CBC result with differential obtained on the day of the NK marker draw should accompany the specimen. For highest accuracy, obtain the CBC on the same draw as the NK marker sample.

Samples must be sent by next day courier, insulated to guard against extreme heat or cold. For samples collected on the weekend, the blood should be shipped immediately the next business day. Please contact Dr. Mitchell Diccianni prior to shipping to obtain a FedEx account number and provide the FedEx tracking number so that the samples can be tracked. Include specimen transmittal form with each shipment.

Send samples to:
Alice Yu, MD, PhD / Mitchell Diccianni, PhD
UCSD Medical Center
Clinical Teaching Facility, C-101
214 Dickinson Street
San Diego, CA 92103-8447
Lab Phone: (619)-543-2436
Lab FAX: (619)-543-5413
E-mail: yulab@ucsd.edu

Lab contact: Dr. Mitchell Diccianni
(619) 534-2436
mdiccianni@ucsd.edu

15.1.4.4 Methodology

Samples will be processed by the Yu laboratory personnel, and assays for immune cell subsets will be performed on site. Phenotyping will be performed by direct measurement of surface expression and quantified by flow cytometry. This work will be performed under the supervision of Dr. Alice Yu at Rady Children's Hospital- San Diego.

Yu laboratory personnel will then distribute components of the samples collected, specifically the plasma, to other co-investigators conducting correlative studies on ANBL17P1.

DNA from a granulocyte pellet for KIR/KIR ligand and Fc receptor genotyping as well as plasma for HACA testing will be sent from the Yu Lab to the Sondel laboratory at the University of Wisconsin. Serum to assess for GD2 will be sent to the Balis laboratory at the Children's Hospital of Philadelphia. Please see Appendix V for additional information.

15.1.5 Immune function studies: Cytokine analysis

15.1.5.1 Specimen Schedule and Requirements

At each time point, 3 mL of whole blood should be collected in a red-top tube.

Samples are requested at the following time points:

- Pretreatment
- Induction Cycle 3, Day 1
- Induction Cycle 3, Day 6
- Induction Cycle 4, Day 1
- Induction Cycle 4, Day 6
- Prior to Post-Consolidation Cycle 1
- At first episode of disease progression or relapse.

15.1.5.2 Specimen Processing

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

15.1.5.3 Specimen Labeling and Shipping

Tubes must be labeled with:

- The patient's COG ID number

- BPC number
- Specimen type (serum)
- Collection time point (i.e. Induction Cycle 3, Day 6)
- Date collected.

Specimens are shipped to the Biopathology Center. See Section 15.2 for the BPC shipping address and additional shipping instructions. For questions about sample processing and shipping, please contact the BPC directly.

15.1.5.4 BPC Handling

The BPC will ship the serum to the laboratory of Dr. Alice Yu at Rady Children's Hospital – San Diego.

15.1.5.5 Methodology

Serum samples will be assayed for cytokines using an ELISA test previously described. Cytokine analysis will be performed under the supervision of Dr. Alice Yu at Rady Children's Hospital- San Diego.

15.1.6 Analysis of Gene Expression Studies: RNA Sequencing

15.1.6.1 Specimen Schedule and Requirements: PAXgene RNA Sequencing Studies

PAXgene RNA tubes will be provided by the Biopathology Center to sites in North America participating in this trial at the start of the study. To request PAXgene tubes, please access the BPC Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement/) and select "ANBL17P1" for the protocol.

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:

- Pretreatment
- Induction Cycle 1, Day 6
- Induction Cycle 3, Day 1
- Induction Cycle 3, Day 6
- Induction Cycle 4, Day 1
- Induction Cycle 4, Day 6
- Induction Cycle 5, Day 1
- Induction Cycle 5, Day 6
- Induction Cycle 5, Day 21
- Prior to start of post-Consolidation
- Post-Consolidation Cycle 1, Day 4
- Post-Consolidation Cycle 1, Day 7
- Post-Consolidation Cycle 2, Day 4
- Post-Consolidation Cycle 2, Day 7

- Post-Consolidation Cycle 6, Day 15
- Relapse

15.1.6.2 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 for 2-72 hours and then freeze upright in a wire rack (not Styrofoam holder) for 24 hours at -20°C, then transfer to a -70 or -80°C freezer until batch shipment. Please note that if tubes are to be kept at temperatures below -20°C, they must first be stored at -20°C for 24 hours before being transferred into a -70°C or -80°C freezer.

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

15.1.6.3 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 frozen on dry ice in batch shipments. See Section 15.2 for shipping address and additional shipping instructions.

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

15.1.6.4 Methodology

The BPC will batch transfer frozen PAXgene RNA tubes to the laboratory of Dr. Shahab Asgharzadeh at Children's Hospital of Los Angeles. Samples will be processed and analyzed for alterations in the circulating immune cells using next generation sequencing.

15.1.7 GD2 Biomarkers

15.1.7.1 Specimen Schedule and Requirements

Blood:
At each time point, 1 mL of whole blood should be collected in a red-top tube and processed for serum.

Samples are requested at the following time points:

- Pretreatment

- Induction Cycle 4, Day 15
- Induction Cycle 5, Day 1
- Induction Cycle 5, Day 21
- End of therapy

Bone Marrow Slides:
At each time point, 3 air-dried smear slides (bone marrow aspirate) and 3 air-dried touchprep slides (bone marrow biopsy) from each site are required. Prior to the administration of the anticancer therapy described in this study, baseline bone marrow biopsy and bone marrow aspirate samples should be obtained. This can be obtained with pre-study labs within 7 days of starting therapy or on Day 1 of Cycle 1.

Samples are requested at the following time points:

- Pretreatment
- Induction Cycle 5, Day 21
- End of therapy
- Progression/relapse.

Tumor Tissue Slides:
Prior to the administration of the anticancer therapy described in this study, baseline tumor biopsy samples should be obtained. At each time point, 3 air-dried touchprep slides from each site are required.

Samples are requested at the following time points:

- Pretreatment
- Progression/relapse. Tumor from any site biopsied at this time point will be accepted.

15.1.7.2 Specimen Processing and Storage

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

Bone Marrow:

- Bone marrow biopsy: 3 air-dried touchprep slides.
- Bone marrow aspirate: 3 air-dried sample smears slides.

Tumor Tissue:
Tumor biopsy: 3 air-dried touchprep slides.

15.1.7.3 Specimen Labeling

Serum vials must be labeled with:

- The patient's COG ID number
- BPC number
- Specimen type (serum)
- Collection Time Point (i.e. Induction Cycle 4, Day 15)
- Collection date

Bone Marrow Slides must be labeled with:

- The patient's COG ID number
- BPC number
- Specimen type (bone marrow)
- Surgical pathology ID from Bone Marrow Report
- Time Point (i.e. End of Induction)
- Collection Date

Tissue Slides must be labeled with:

- The patient's COG ID number
- Specimen type (P for primary tissue or M for metastatic tissue)
- Surgical pathology ID
- Time Point (i.e. Pretreatment)
- Collection Date

Note: both the COG and BPC numbers must be included in labeling since extractions will be performed in a CLIA lab.

Specimens are shipped to the Biopathology Center. See Section 15.2 for the BPC shipping address and additional shipping instructions.

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

15.1.7.4 Methodology

For circulating GD2 studies, the BPC will transfer 0.5 ml of serum per subject to the laboratory of Dr. Frank Balis at The Children's Hospital of Philadelphia. A validated HPLC/MS/MS assay will be used for GD2 detection in samples from each time point.

For bone marrow and tissue studies, immunocytochemical (IC) analysis on touch preps of tumors at diagnosis and relapse, and touch preps of bone marrow biopsies and smear slides of bone marrow aspirates will utilize both concurrent staining of Phox2b and GD2 to qualitatively assess GD2 expression. The studies will be overseen by Dr. Shahab Asgharzadeh at Children's Hospital of Los Angeles.

15.2 Shipping Instructions for Specimens Submitted to the Biopathology Center

15.2.1 Blocks and slides

Formalin-fixed and paraffin embedded tumor material and associated pathology report(s) should be sent to the COG Biopathology Center (BPC) at room temperature using the submitting institution's courier account.

An ANBL17P1 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen. In addition, the corresponding pathology report must be included with the shipment.

Blocks and slides should not be shipped for Saturday delivery. See Section 15.2.4 for shipping address.

15.2.2 Frozen specimens (snap frozen tissue, PAXgene tube, serum, plasma)

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

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

An ANBL17P1 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen. When tissue or bone marrow slides are submitted, the corresponding pathology report must also be included in the shipment.

Specimen Procurement Kit Instructions for Frozen Specimens

1. Before frozen 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. When batch shipping frozen specimens, allow room for 5 lbs. of dry ice.
   a. Place the specimens in zip lock bags (one bag per specimen type/time point). Because specimens will be batch shipped from multiple time points, it is extremely important that all specimens be clearly labeled with the specimen type and time point.
   b. Place the zip lock bags in a biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope.
   c. Place the biohazard envelope inside a Tyvek envelope. Expel as much air as possible and seal the envelope.
2. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. Place the foam lid on top to insulate the specimens during shipment.
3. Place the transmittal form(s) and pathology report (when applicable) on top of the foam lid.

4. Close the outer lid of the specimen procurement kit and secure with filament or other durable sealing tape.
5. Sites in North American will print a shipping label via the BPC Kit Management application and attach to the top of the kit.
6. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.
7. Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355.

Ship frozen specimens on Monday through Thursday for a Tuesday through Friday delivery. See Section 15.2.4 for shipping address.

15.2.4 Shipping Address

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

Biopathology Center
Nationwide Children's Hospital
Protocol ANBL17P1
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.*

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and other 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 for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

Note: the guidelines below are recommendations only and are not intended to replace institutional guidelines.

16.1 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: (1) pre-treatment, (2) post Cycle 4 of Induction (prior to surgical resection), (3) at the end of Induction (pre-Consolidation), (4) prior to start of post-Consolidation therapy (5) after Cycle 3 of post-Consolidation, (6) at the end of therapy, and (7) at relapse. Submission of the MRI or CT scans for central review is requested at some of the above time points. See Section 16.6 for specific time points for submission of scans for retrospective central review.

16.1.1 MRI Scans

Typically MRI will be performed on 1.5 T or 3 T MRI units. 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.

16.1.2 CT Scans

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. 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.[77] 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.

16.2 ^{123}I-MIBG Scintigraphy

^{123}I-MIBG scintigraphy is required on this trial and is the preferred study for assessment of osteomedullary disease. 99m Technetium bone scans are no longer recommended. All patients will undergo a diagnostic quality ^{123}I–MIBG scan 14 days prior to or 14 days after the start of Cycle 1. Preferably, this scan will take place before therapy is initiated. This scan is for diagnostic and response evaluation purposes. For patients with MIBG avid disease, an MIBG scan is also required at the end of Induction, end of Consolidation (pre-immunotherapy/isotretinoin), after 3 cycles of post-Consolidation, at the end of post-Consolidation, and at relapse. Patients with > 5 MIBG positive metastatic sites on the end-Induction scan should also undergo an MIBG scan post-transplant to facilitate radiation therapy decision-making. This scan will usually be performed between Day +30 and Day +42, but should be performed with sufficient time to allow radiation to begin as described in Section 17.2.

See Table 16.6 for a summary of MIBG scan time points.

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

16.2.1 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 3 days. Dose is by weight; 1.2 mg iodine/kg (4 mg/drop).

16.2.2 ^{123}I-MIBG Scintigraphy Procedures

Dose: 10 mCi/1.7 m^2 body surface area (approximately 150 μCi/kg; maximum 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 proximal lower extremities are obtained for 10 minutes at approximately 24 hours after injection and may be done 48 hours after injection. Anterior views of the distal lower extremities are sufficient. A large field of view dual-head gamma camera with low-energy or medium-energy collimators is preferred.

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. For the time points required to be submitted for central review (see table 16.6) submit the CT file, the attenuation corrected (AC) SPECT file and a non-attenuation corrected (NAC) SPECT file. Do not submit screen capture images for the SPECT or CT.

16.3 [^{18}F]–Fluorodeoxyglucose (^{18}FDG)-PET Scintigraphy

^{18}FDG-PET/CT scan is indicated for patients whose tumors are not ^{123}I-MIBG avid. FDG-PET/CT is performed at the following time-points: (1) pre-treatment, (2) at the end of Induction (pre-Consolidation), (3) at the end of Consolidation (pre-immunotherapy/isotretinoin), (4) after 3 cycles of post-Consolidation therapy, (5) at the end of post-Consolidation therapy, (6) at relapse. It is recommended that the PET/CT 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. Patients with >5 FDG avid sites of metastatic disease detected on the end-Induction scan should have another PET/CT scan performed prior to local radiotherapy if patient exhibits > 5 sites of disease. This scan will usually be performed between Day +30 and Day +42, but should be performed with sufficient time to allow radiation to begin as described in Section 17.2.

The initial FDG-PET/CT scan should be performed prior to initiation of chemotherapy when possible, or as soon as possible after documentation of MIBG non-avid disease. 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 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. The attenuation correction CT should be acquired per local institutional guidelines using dose reduction techniques. PET/MR is also permissible at centers that routinely use this imaging modality.

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.

The FDG-PET/CT study is processed for display by an iterative reconstruction algorithm. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake value (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 should 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 or MRI) is performed from the top of the head through the toes with the patient breathing shallow, followed by emission imaging at 3-5 minutes per bed position. 2D acquisitions are acceptable in older PET/CT scanners that do not have 3D capability. Most acquisitions will be 3D. Data are reconstructed as described above.

16.4 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).

16.5 Curie Scoring

Curie scoring will be performed centrally using previously published techniques, in which the body is divided into 10 anatomic regions, 9 skeletal and 1 primary soft tissue, and each region individually scored based upon the extent of MIBG avidity within that region. A patient's final Curie score will be calculated as the sum of his/her scores over all individual regions. The date of scan acquisition is defined as the date of completion of the MIBG scan. The results of the central review will not be returned to the institution.

Curie scoring will be will be determined retrospectively by a central imaging committee using images from the following time points:
(1) initial diagnosis, (2) at the end of Induction, (3) prior to start of post-Consolidation therapy, (4) at the end of therapy, and (5) at relapse. Exception: Curie scoring will not be performed for patients who are found to have MIBG non-avid disease at diagnosis.

16.6 Submission of Scans for Central Review

Curie scoring will be performed centrally.

In addition, cross sectional tumor imaging scans (MRI or CT), FDG-PET/CT or PET/MR scans will be evaluated via central review for confirmation of response status. The results of the central review will not be returned to the institution.

Table 16.6: Time points mandated for cross sectional tumor imaging scans (MRI or CT), MIBG scans and FDG-PET scans

Time	MRI or CT	MIBG scan	FDG-PET scan[1]
Diagnosis	Yes	Yes	Yes
End-Induction	Yes	Yes	Yes
Prior to start of post-Consolidation therapy	Yes	Yes	Yes
End of therapy	Yes	Yes	Yes
Relapse/Progression	Yes	Yes	Yes

[1] For patients with MIBG non-avid disease.

Notes:

- For MIBG, submit planar, tomographic images, include SPECT/CT imaging when available (see Section 16.2.2)
- Patients with > 5 metastatic sites at end-Induction should undergo an MIBG scan post-transplant to assist in radiotherapy planning. See Section 16.2.

Submit the scans listed in Table 16.6 above together with their corresponding reports.

Imaging required for the radiation oncology review (see Section 17.10), and imaging central review only need to be submitted once.

Submission of Diagnostic Imaging data in DICOM format is required. Submission of the digital files and reports via TRIAD is preferred. Instructions for TRIAD set up are below.

Alternatively, the images and reports may be submitted via sFTP to IROC Rhode Island. Digital data submission instructions including instructions for obtaining a sFTP account, can be found at http://irocri.qarc.org. Follow the link labeled digital data. Sites using the Dicommunicator software to submit imaging may continue to use that application.

Please contact IROC RI for questions or more information: DataSubmission@QARC.org or 401-753-7600.

Digital RT Data Submission Using TRIAD (if TRIAD is available at your site):
TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure

method to transmit DICOM and DICOM RT files and other digital objects, such as reports. TRIAD de-identifies and validates the images as they are transferred.

TRIAD Access Requirements:

- Site staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site TRIAD user must be on the site roster and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

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

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

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

IROC Rhode Island (formerly QARC) will facilitate the central reviews.

17.0 RADIATION THERAPY GUIDELINES

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).

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities.

To view the ANBL17P1 Contouring Atlas, please visit www.qarc.org and under NCI Groups, select COG and follow the link titled "COG Contouring Atlases."

General Guidelines

The radiation therapy guidelines for this study were developed specifically for patients with high-risk neuroblastoma. The objective of radiation therapy is to improve event free and overall survival while preserving uninvolved organ function. Three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or proton therapy are required for patients treated on this protocol to minimize the risk of late-term normal tissue complications.

Radiation therapy will be delivered following 5 cycles of Induction chemotherapy and intensified consolidation therapy with autologous stem cell transplantation.

Credentialing Requirements

3D-CRT, IMRT and proton therapy will be the allowed treatment methods for this study. Patients may not receive intraoperative radiation therapy on this protocol. The credentialing requirements by treatment modality are summarized in the following table.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**			
	Treatment Modality			**Key Information**
	3D-CRT	IMRT	Proton	
Facility Questionnaire		**X**	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Credentialing Status Inquiry Form		**X**	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation		**X**	**X**	Sites treating with IMRT and not previously credentialed for its use must irradiate IROC Houston's head and neck phantom. Protons centers must complete all required phantom irradiations for IROC Houston credentialing. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site. (**http://irochouston.mdanderson.org**).
Motion Management (when used)		**X**	**X**	If treating with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**)
Credentialing Notification Issued to:				
Institution				Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

Guidelines and Requirements for the Use of IMRT
Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored (NCI) cooperative group trials. These guidelines are available at www.irocri.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the first treatment. Measurements in a QA phantom can suffice for a check as long as the patient plan can be directly applied to a phantom geometry.

Guidelines and Requirements for the Use of Proton Therapy
Proton therapy may be used to deliver radiation on this protocol. Allowed proton therapy methods include scattering, uniform scanning and pencil beam scanning depending on institutional availability, but the specific beamline in use must have been appropriately credentialed by the IROC Houston QA Center. Intensity modulated proton therapy (IMPT) is permitted for those centers that have IROC approval. Investigators using proton beam radiation must comply with current NCI proton therapy guidelines as outlined in the Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, available at http://rpc.mdanderson.org/RPC/home_page/Proton_guidelines.htm .

17.1 Indications for Radiation Therapy

17.1.1 Treatment Sites and Doses

All patients will be irradiated and volumetric targeting for radiation therapy planning should be priority.

Table 17.1.1

Site/Target	Dose
Primary tumor site and initially involved lymph nodes according to imaging criteria or documented by surgery (CTV/PTV*)	21.6 Gy delivered in 1.8 Gy fractions
Metastatic disease present after Induction (mCTVx /mPTVx*)	21.6 Gy delivered in 1.8 Gy fractions
Life or organ-threatening disease	Document and report to Study Coordinator
Hepatomegaly leading to respiratory distress	4.5 Gy delivered in 1.5 Gy fractions
*When proton therapy is used, the prescription target will be the CTV. When photon radiotherapy is used, the prescription target for coverage will be the PTV. In either case, dose reporting will reference the PTV in accordance with ICRU guidelines.	

17.2 Timing of Radiation Therapy

Radiation will be given after recovery from the last ASCT. Treatment volumes will be based on post-Induction imaging (MIBG, CT and/or MRI) and operative reports. Organ toxicity within the radiation field should have resolved. It is recommended that radiation therapy begin **no sooner than Day +42 and before Day +80** following ASCT.

17.2.1 Consideration for Radiation Delay

Please see Table 17.2.1 below for circumstances in which delay in radiation therapy should be considered based on the organ being irradiated.

Table 17.2.1

Organ in Radiation Field	**Considerations for Delay of Radiation Therapy**
Hematologic [Volume of potential marrow radiation exceeding 10% of total marrow (see Table 17.2.2)]	Persistent cytopenias, including absolute neutrophil count ≤ 500/μL (off G-CSF for ≥ 48 hours), and/or transfusion-refractory thrombocytopenia with platelet count < 40,000/ μL.
Liver	Active sinusoidal obstruction syndrome without sign of resolution*
Trachea	Grade 2 or higher airway edema that requires respiratory support
Abdomen	Refractory diarrhea, greater than CTCAE Grade 2
Kidneys**	Persistently elevated serum creatinine for age/sex (see Section 3.3.4) or 2 x the creatinine value obtained at the start of consolidation therapy
Bladder	Persistent hematuria

*Radiation involving the liver should be delayed for active sinusoidal obstruction syndrome (SOS) of any grade. Hepatomegaly and fluid accumulation may persist after SOS has begun to resolve, and radiation may be initiated providing that hyperbilirubinemia and pain are improving.

**Please refer to Section 17.8.1 for discussion of renal scintigraphy in the event that recommended kidney dose constraints are exceeded.

Table 17.2.2 Distribution of Marrow within the Bony Skeleton

Site	**% Total Marrow**
Skull	13%
Upper limb girdle	8%
Sternum	2%
Ribs	8%
Vertebrae	
Cervical	3%
Thoracic	14%
Lumbar	11%
Sacrum	14%
Lower limb girdle	26%
Adapted from Ellis RE, 1961.	

17.3 Emergency Radiation

Patients are allowed to have received emergent radiation at diagnosis to sites of life-threatening or function-threatening disease such as respiratory distress or vision loss (see Section 17.5.3). Generally, this treatment is used as a last resort when disease is causing symptoms not responding to chemotherapy. This must be reported to the study coordinator at the time of registration on study and will not be considered as part of the planned treatment

course to be delivered at a later time provided normal tissue dose constraints are met. Prior radiation therapy dose constraints are included as part of protocol eligibility criteria. Regarding further radiation of metastatic sites that received radiation emergently at the time of diagnosis, please see Section 17.5.2.1.

17.4 Equipment and Methods of Delivery and Verification

17.4.1 Modality

Equipment	Photons	IMRT	Protons	Electrons
Linear Accelerator	X	X		X
Proton Beam			X	

To avoid treatment delays resulting from unplanned equipment unavailability, photon therapy may be administered instead of proton therapy.

17.4.2 Treatment planning

CT (volumetric) based planning is required to optimize dose to the target volumes while protecting normal tissues. Organs at risk within the irradiated volume should be contoured including those required. A DVH is necessary to determine target coverage and evaluate dose to normal tissues. CT slice thickness should be ≤ 3 mm.

17.4.3 In-room Verification of Spatial Positioning

17.4.3.1 Portal Imaging

Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. If volumetric imaging is not available, orthogonal paired (AP and lateral) portal images (MV or kV) are required to verify that the isocenter is in correct alignment relative to the patient position. Beam's eye view imaging of each treatment port should be performed when feasible.

17.4.3.2 Volumetric Imaging

Volumetric imaging is allowed in this study. This includes in-room kV,MV cone beam or conventional CT imaging. Please prepare representative axial images for submission showing the isocenter and the correct alignment in relationship to the patients' position. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

17.4.4 Evaluation and Management of Target and Normal Tissue Motion and Setup Variations

17.4.4.1 Motion Management and 4D Simulation

Considering motion of target and normal tissue volumes is important. Evaluation of target and normal tissue motion is required for patients treated with proton therapy and suggested for patients treated with IMRT.

17.4.4.2 Simulation Guidelines

The following guidelines suggest a framework for achieving improved immobilization and targeting:

- Anesthesia: If general anesthesia is used for simulation, this should be continued through therapy unless the patient is re-simulated/re-planned.
- General Guidelines: For most cases, CT simulation supine, in neutral position, with arms over head and with adequate upper torso wing-board and/or vac-lock support out of the plane of treatment ports should be used.
- Simulation Marking: Two axial planes should be marked to enhance setup uncertainty even if CBCT is used to verify positioning. Markers approximating the anterior superior iliac spine and xiphoid process are suggested.
- Site Specific Guidelines:
    - Adrenal: Elevating the lower extremities with behind the knee blocks can flatten the lower spine against the treatment table to enhance immobilization and attempt to make most of the superior/inferior respiratory motion conform to a plane close to parallel with the treatment table. (This would not be considered useful for pelvic extension or mediastinal extension.)
    - Head and Neck: This site is variably imaged and often the setup for diagnostic imaging does not align with the treatment setup. In these cases, it is preferable to do a diagnostic CT in the anticipated treatment position prior to surgery. Close coordination with the surgical and oncology team is essential.
    - Paraspinal: There is frequent extension along spinal nerve roots. MRI imaging is recommended in these cases and these should be completed in the treatment position. 3D acquisition techniques such as MPRAGE or SPGR should be considered, or if not available, multi-plane (axial, sagittal) reconstructions are a reasonable substitute.

17.4.4.3 Motion Management Reporting

A description of the method used and evidence of the remaining tumor motion (e.g., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT or 4D MRI) should

be submitted on the Motion Management Reporting Form with the Quality Assurance documentation materials.

17.4.5 Calibration

All therapy units used for this protocol shall have their calibrations verified by the IROC Houston QA Center.

17.5 Target Volume Definitions

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study. Using the ICRU terminology, the gross tumor volume (GTV) is anatomically defined, the clinical target volume (CTV) is anatomically confined and the planning target volume (PTV) is comprised of two margins meant to account for physiologic changes in the CTV (IM=internal margin) and set-up uncertainty (SM=set-up margin). ICRU-62 conventions should also be considered by the treating radiation oncologist where organs at risk and target volume motion may compromise either preservation of normal tissue tolerances or target volume coverage, respectively.

While not expressly used as a target volume, the Gross Tumor Volume Post Chemotherapy, Pre-Surgery (GTV_PreSurgery) volume may be useful as a reference for delineating target volumes. The GTV_PreSurgery volume includes disease defined by CT, MR and MIBG imaging PRIOR to surgery. The GTV_PreSurgery includes radiographically or pathologically involved tumor and lymph nodes. (See Contouring Atlas, figure 2). The GTV_PreSurgery does NOT include the extent of disease PRIOR to chemotherapy. The GTV_PreSurgery does NOT include uninvolved draining lymph node regions. See Contouring Atlas.

17.5.1 Primary Site Volume Definitions

Gross Tumor Volume (GTV)

- The GTV is the volume of tissue representing the anatomical space confined by normal tissues which contain the highest concentration of residual tumor cells.
- The GTV is bounded superiorly and inferiorly by the GTV_PreSurgery volume but anatomically confined to the post-surgery space after adjusting for reduced mass effect on surrounding organs at risk. (See Contouring Atlas, figure 3)
- The GTV includes additional regions of tumor involvement defined intraoperatively that were not readily identified by imaging. Every effort should be made to correlate pathologic findings to the complete operative report. Discussion with the patient's surgeon is recommended.
- The GTV is corrected volumetrically to reflect the return of normal structures to their proper anatomic position after surgical resection.
- The GTV does NOT include the extent of disease PRIOR to chemotherapy.
- The GTV does NOT include uninvolved draining lymph node regions. Elective nodal treatment is not recommended.
- See Contouring Atlas for further details.

Special Circumstances (GTV)

- If the primary tumor was grossly resected at diagnosis, the GTV will be based on the initial diagnostic tumor volume. However, principles as outlined above should be applied – i.e. the GTV should be bounded by fixed organs at risk and not extend into adjacent organs/bone/etc. unless there is strong suspicion or evidence that the tumor infiltrated or invaded these regions.
- In cases where there is discrepancy between imaging studies or intraoperative findings, the larger volume will define GTV.
- When the primary tumor expands into a body cavity such as the lung or displaces a normal structure (such as the liver without infiltration) and following surgical resection the normal structure now occupies the space previously occupied by tumor, only the rim (< 3mm) of normal tissue that was in contact with the tumor volume should be included within the GTV.

Clinical Target Volume (CTV)

- The CTV is defined as the volume of tissue containing subclinical microscopic disease.
- The CTV margin should be an expansion of the GTV to encompass microscopic disease.
- The CTV for this protocol is the GTV with an anatomically confined margin of 1.0 cm.
    - To be anatomically defined means limiting the treated volume to encompass only the potential space with which the tumor came into contact. The volume may be adjusted to exclude the normal organs that fall back into place after the loss of tumor-related mass effect. When clear evidence of invasion of an adjacent organ is documented by imaging or in the operative report, the CTV should not be anatomically confined to the border of that adjacent organ and instead should extend into the region of the organ that is anticipated to likely reflect residual disease. In general, the intra-abdominal primary site CTV can be modified to exclude the kidney, liver and vertebral bodies (see Contouring Atlas, Figure 3). Cervico-thoracic, pelvic and head and neck sites should have their CTV's adjusted to exclude uninvolved bone.
- The superior and inferior extent of CTV should cover the extent to the superior and inferior extent of the GTV_PreSurgery volume.
- See Contouring Atlas for further details

Planning Target Volume (PTV)

- The PTV is a geometric concept that includes a margin surrounding the CTV.
- The PTV should account for physiologic motion in the CTV and set-up uncertainty.
- The PTV is defined as the CTV with a geometric margin of 0.3-0.8 cm.
    - Movement prone regions such as the region just under the diaphragm should be considered for a more generous PTV closer to 0.5-0.8 cm while anatomical sites more apt to rigid immobilization such as the head and neck should be considered for tighter margins of 0.3 cm.

- The PTV may vary according to immobilization and patient cooperation, although 0.3 cm is the minimum extent of the margin surrounding CTV to form PTV. See Contouring Atlas, figure 5 for reference.
- The PTV margin does not have to be uniform in all dimensions; especially if it compromises normal tissue volumes or if directional target or normal tissue motion is assessed and understood with 4D simulation techniques.
- See Contouring Atlas for further details on target delineation and vertebral body inclusion guidelines.

Table 17.5.1 Suggested PTV Margins

Primary Site	Non-CBCT	CBCT
Head and Neck	5 mm	3 mm
Upper Paraspinal	5 mm	3-5 mm
Intra-thoracic	5 mm	5 mm
Abdomen	5-8 mm	3-5 mm
Lower Paraspinal/Pelvic	5 mm	3-5 mm

Target Volume Definitions for Proton Therapy:

- GTV is the same for protons and photons.
- CTV is the same for protons and photons.
- PTV will be uniquely defined for proton therapy.

When passive scattering or uniform scanning methods are used, the boost planning target volume (PTV) for proton therapy will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment at the treating proton center. **The PTV will be used for dose reporting and not specifically for treatment planning.**

The goal of treatment planning will be CTV coverage at 100% with measures taken for each specific uncertainty. Specific adjustments will be made to (1) aperture margin definitions, (2) smearing of compensator (if applicable), (3) range of the individual beams (depth of penetration), and (4) modulation width of the SOBP. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator, set-up margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed below in Section 17.6.4.2.

Accounting for Motion of Target and Normal Tissue Volumes

- For a CTV susceptible to physiologic motion, a margin of 0.5 cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1.0 cm should be chosen.

17.5.2 Metastatic Sites

17.5.2.1 Criteria for Treatment of Metastases

While the primary site is always irradiated, radiation is only given to those metastatic sites with persistent active disease demonstrated at the time of evaluation prior to Consolidation based on persistent soft tissue mass

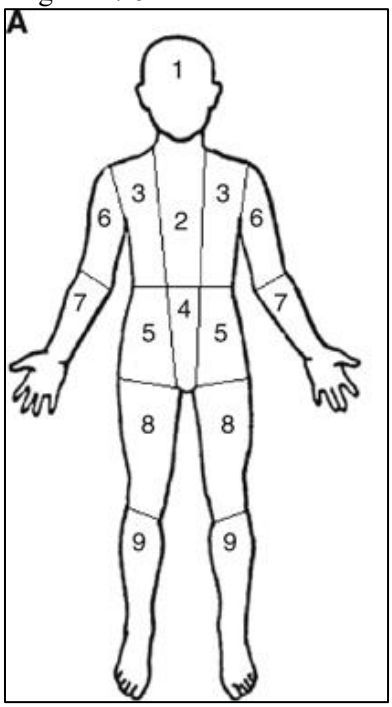
>1 cm^3 and/or MIBG (or FDG) uptake. Sites that are negative on imaging prior to Consolidation will NOT be irradiated, even if they had enhanced uptake on MIBG (or FDG-PET) at diagnosis. This remains the case for sites that received emergent radiation at the time of diagnosis – these sites will not receive further radiation providing they are negative on imaging prior to consolidation. If greater than 50% of the bone marrow would be irradiated using these criteria, treatment fields should be discussed or reviewed with the study coordinator prior to simulating the patient for radiation therapy (please see Table 17.2.2).

17.5.2.2 Patients with > 5 MIBG or PET avid metastatic sites prior to Consolidation

If the patient had > 5 persistently positive metastatic sites identified by MIBG (or PET), the appropriate scan should be repeated after stem cell transplant. Only sites remaining positive will then be irradiated. If there are still > 5 MIBG (or PET) positive sites, notify the study coordinator or chair.

In patients with > 5 persistent lesions that are MIBG (or PET) positive lesions prior to transplant and there are concerns regarding hematopoietic toxicity, consideration should be given to reserving a portion of the collected peripheral blood stem cell product to use as boost after radiation if leukocyte counts fall and fail to recover within 2-3 weeks after radiation is completed. Please notify study chair if "backup" stem cells are given.

Figure 17.5.2



17.5.2.3 Metastatic Site Volume Definitions

Metastasis Gross Tumor Volume (mGTVx)

- The mGTVx volume is the *post-Induction* chemotherapy MIBG avid disease prior to Consolidation visible on either CT, MRI, and/or MIBG scans.
- The "x" refers to the anatomical segment designated in the INRG 123I-MIBG Scoring system (see Figure 17.5.2).

Metastasis Clinical Tumor Volume (mCTVx)

- The "x" refers to the anatomical segment designated in the INRG ^{123}I-MIBG Scoring system (see Figure 17.5.2).
- The mCTVx is the mGTV1x volume expanded by 1 cm bounded by the mGTVx volume.
- See Table 17.5.2 suggestions for metastatic site CTV modification.

Table 17.5.2 Suggestions for Metastatic Site CTV Modifications

Treatment Site(s)	**Methods to anatomically confine CTV**
Calvarium	Adjust CTV to avoid extension into the cerebral cortex unless the lesion extends through the skull with suspected dural involvement. In cases where the entire calvarium needs to be treated, a brain sparing approach such as that used by Wolden et al (Pediatr Blood Cancer 2008) should be used.
Base of Skull	Adjust CTV to avoid extension beyond bony structures unless there is radiographic evidence of extension into brain tissue. T2-weighted imaging can be useful in delineating the target.
Limb	Adjust CTV to avoid circumferential limb treatment, growth plates & joint spaces (unless involved).
Spine	Adjust CTV to facilitate uniform dose to the entire vertebrae including the transverse and spinous process, vertebral body, and pedicles (regardless of if non-uniformly involved by disease) to minimize the risk of scoliosis. The entire vertebral body should receive >18 Gy if treatment is required.
Rib	The CTV should be adjusted such that CTV does not extend into the lung parenchyma unless there is strong evidence of parietal pleura involvement.

Metastasis Planning Tumor Volume (mPTVx)

- The "x" refers to the anatomical segment designated in the INRG ^{123}I-MIBG Scoring system (see Figure 17.5.2.1).
- The mPTVx is the mCTVx volume expanded by 0.5-0.8 cm depending on the anatomic site and immobilization.

17.5.3 Emergency Radiation Target Delineation

17.5.3.1 Emergency Radiation Indications

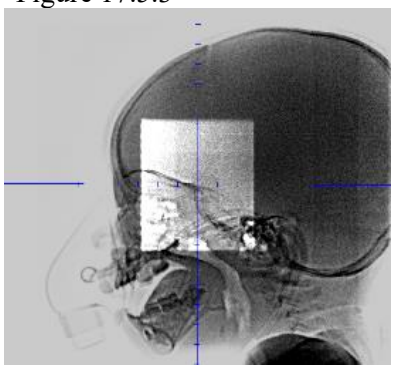
Respiratory Distress: In cases where respiratory distress is present at diagnosis secondary to liver disease, radiotherapy may be administered over three treatments at 1.5 Gy per fraction.

Vision Loss: In clear cases of vision loss or the development of visual field deficits, radiotherapy may be administered over 3 fractions at 1.5 Gy per fraction.

17.5.3.2 Emergency Radiation Field Design

Orbital/Optic Pathway Radiotherapy: In emergent situations when simulation is not possible, radiotherapy may be prescribed using a limited symmetrical field for several fractions (see Figure 17.5.3).
Liver Radiotherapy: In general, the entire extent of the liver need not be targeted and the bulk of the volume can be selected for treatment to minimize dose the abdomen and lungs.

Figure 17.5.3



17.6 Target Dose

17.6.1 Dose Definition and Specification

Photon dose is to be specified in Gray (Gy)-to-muscle. For proton beams, the absorbed dose, ICRU 78's D_{RBE}, is specified in Gy(RBE), using a standard RBE of 1.1 with respect to Cobalt-60.

17.6.2 Prescription Dose and Fractionation

The daily dose should be 1.8 Gy for the primary and metastatic sites. Sites of metastatic disease should be irradiated concurrently with the primary site.

Table 17.6.2

Nominal Dose by Site	Dose/fraction	Number of Fractions
Primary Site (CTV/PTV) 21.6 Gy	1.8 Gy	12
Metastatic Site(s) post-Induction therapy (mCTVx/mPTVx) 21.6 Gy	1.8 Gy	12
Hepatomegaly/Partial Liver	1.5 Gy	3
Craniospinal Dose	1.8 Gy	12

17.6.3 Tissue Heterogeneity

All dose calculations shall take into account the effects of tissue heterogeneities. When protons are used, tissue heterogeneity calculations should be performed with

the CT-based treatment planning system to generate dose distributions from the proton relative stopping power.

17.6.4 Dose Uniformity

17.6.4.1 Coverage Goals

For photons, at least 95% of the protocol-specified dose should encompass 100% of the PTV, no more than 10% of the PTV should receive greater than 110% of the prescription dose as evaluated by DVH. Wedges, compensators, and other methods of generating more uniform dose distributions are encouraged.

17.6.4.2 Proton Therapy Specific PTV definition

For protons, the PTV concept differs from photon therapy. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV Proton plans should be evaluated for adequate PTV coverage from the summation of all beams. For scattered and uniform scanning beams, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and setup and internal margins (SM and IM). These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the setup and internal margins (SM and IM). The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. Most proton centers use 3.5% of the maximum water-equivalent depth of the CTV to account for CT HU uncertainty and then add another 3 millimeters to account for uncertainties in beam range calibration and compensator fabrication. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should ensure proximal coverage of the target volume.

A PTV should be created by a uniform expansion from CTV for reporting purposes. The expansion margin should be consistent with SM and IM and is typically 3 mm for a static target volume when daily imaging is performed. With the planning guidelines provided herein, no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. In most cases, at least 95% of the protocol-specified dose should encompass 100% of the PTV. A potential exception is when the range margin is smaller than the PTV expansion (e.g., 3mm). As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

17.6.5 Interruptions and Delays

There will be no planned rests or breaks from treatment, once radiation therapy has been initiated. Blood product support should be instituted according to

institutional/protocol guidelines. If cytopenias are refractory to support and/or transfusion, a treatment interruption may be considered based on the specific clinical scenario. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

17.7 Treatment Technique

17.7.1 Beam Configuration

Every attempt should be made to minimize the dose to critical normal tissue volumes without compromising coverage of the target volume. If significant volumes of vertebral bodies are contained within the treated volume, the dose should be distributed homogeneously to the vertebral bodies to avoid growth asymmetry (see Figure 17.8.1).

17.7.2 Selection of Proton Beam Arrangements

The use of posterior or posterior oblique fields is strongly recommended as the majority of these tumors are posterior in location (adrenal or paraspinal) and it is advisable to avoid uncertainties introduced by tissue heterogeneity and organ motion. Any treatment plan including anterior, anterior oblique or lateral fields should be discussed with the radiation oncology protocol coordinators prior to treatment delivery. The use of a 4D CT is recommended for proton planning to evaluate for target volume and organ motion. Gating may be used during treatment.

17.7.3 Patient Position

Reproducible setups are critical and the use of immobilization devices is strongly encouraged. Use of anesthesia is encouraged if necessary for proper positioning.

17.7.4 Field Shaping

Field shaping for photons will be done with multileaf collimation. Field shaping for protons will be done with either customized brass apertures, proton-specific multileaf collimation, or through scanning.

17.7.5 Special Consideration for Patient Simulation for Protons

Patient set-up and immobilization will be determined prior to obtaining the planning CT scan. CT planning is required for proton therapy because the relative stopping power based on Hounsfield units must be defined. The type of immobilization will be determined by the anatomic location of the site to be treated. Most patients will be immobilized in the supine position for reproducibility and ease of anesthesia administration. The majority of neuroblastomas are located posterior (adrenal or para-spinal). Posterior-anterior or posterior oblique fields typically allow for improved normal tissue sparing and minimize uncertainties due to organ motion and tissue heterogeneity introduced by organ motion or filling (i.e. lung, bowel). Posterior field arrangements are strongly recommended and this should be taken into consideration at the time of simulation. 4-D CT is recommended to evaluate target volume and organ motion.

17.7.6 Special Site Considerations

Calvarial Metastases: Brain-sparing radiotherapy for skull metastases should be considered in cases where there is diffuse involvement of the calvarium and/or the skull base. Mixed photon and patched electron fields may be useful in cases with predominately calvarial involvement without base of skull extension.[78] In cases where there is extensive base of skull involvement, IMRT may be more appropriate to achieve sufficient coverage.

Brain Metastases: In cases where brain metastases are noted, the entire cranio-spinal axis should be treated as these cases are at high risk for distant CNS relapse with focal radiotherapy.[79]

17.8 Organs at Risk

Planning should be done to minimize dose to normal tissue volumes including those described in the table below. No attempt should be made to spare these structures when they intersect or are adjacent to the target volumes. To avoid exceeding the suggested dose constraints, the dose coverage may be adjusted provided the guidelines of the protocol are observed.

17.8.1 Normal Tissue Tolerances and Special Site Volume Considerations

Care must be taken to avoid a steep dose gradient that transverses the vertebral body. When any part of a vertebral body must be included in the PTV, the entire vertebrae (corpus, pedicles, transverse and spinous process) should receive at least 18 Gy. The target volume should not be modified to include the vertebral body, ; rather, the vertebral body should be contoured as an additional pseudo-target structure with a specified minimum dose of 18 Gy if any part of it is included in the PTV (see Figure 17.8.1.1).

Table 17.8.1

Organ	Dose Limit
Contralateral Kidney*	<25% > 18 Gy
Ipsilateral Kidney-whole*	<75% > 18 Gy <100% > 14.4 Gy Mean dose ≤ 18 Gy
Liver**	Mean dose < 15 Gy
Vertebrae (If vertebral body is included in PTV)	Minimum dose 18 Gy to entire vertebrae and pedicles (See Figure 17.8.1)
Bilateral lungs	<30% ≥ 20 Gy
Ipsilateral lung	<30% ≥ 20 Gy
Contralateral lung	<10% ≥ 20 Gy

*If kidney dose exceeds the constraints outlined, renal scintigraphy is recommended to ensure that both kidneys are functioning prior to beginning radiotherapy.

**If liver constraints are exceeded due to need to radiate a liver lesion, extra concern should be exercised for patients who are recovering from SOS.

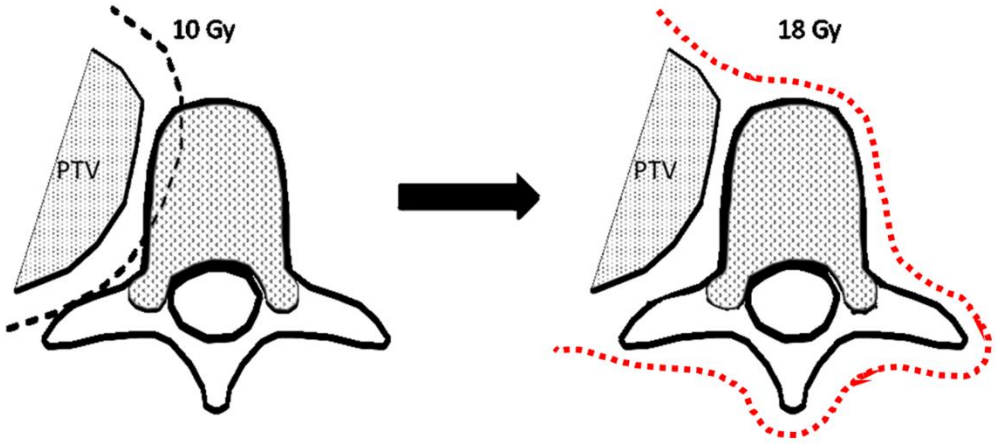


Figure 17.8.1 Vertebral Body Low Dose Spillage Adjustment

17.9 Dose Calculations and Reporting

Centers participating in this protocol must complete the appropriate credentialing outlined in Section 17.0.

17.9.1 Prescribed Dose

The dose prescription and fractionation shall be reported on the RT1/ Proton Dosimetry Summary Forms. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the first treatment. Measurements in a QA phantom can suffice for a check as long as the patient plan can be directly applied to a phantom geometry.

17.9.2 Delivered Dose

The total dose delivered shall be reported on the RT-2 Radiotherapy Total Dose Record Form.

17.9.3 Normal Tissues Dosimetry

The dose to the critical organs indicated should be calculated whenever they are included in the radiation field. For patients treated with volume-based techniques, the appropriate dose volume histograms should be submitted. If IMRT is used, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

Required normal tissue DVH data according to primary site of treatment:

Table 17.9.3

Treatment Area	Required DVH	Standard Names
Neck	Thyroid	Thyroid
	Spinal Cord	SpinalCord
Chest	Right Lung	Lung_R
	Left Lung	Lung_L
	Left and Right Lung	Lungs
	Heart	Heart
	Spinal Cord	SpinalCord
Abdomen	Liver	Liver
	Right Kidney	Kidney_R
	Left Kidney	Kidney_L
	Spinal Cord	SpinalCord

17.10 Quality Assurance Documentation

Key Points

- No on-treatment review will be required for this study.
- Within 1 week of the completion of radiotherapy.
  - Submit data for the primary site only (see checklist).
  - Primary site data submission must be in digital format.
  - Diagnostic imaging data must be in digital format.
- Only the RT-2 form and a copy of the treatment chart need to be submitted for metastatic sites.

17.10.1 Submission of Diagnostic Imaging Data

Copies of the diagnostic imaging used to determine the primary treatment volume (CT, MRI, and/or MIBG (PET-CT if MIBG negative) scans performed prior to surgical resection and after the end of Induction with corresponding diagnostic imaging reports; as well as the operative and pathology reports) should be submitted. Repeat MIBG (PET-CT) for cases with >5 positive sites after induction. Submission via TRIAD is preferred (see Section 16.6). Alternatively, imaging can be submitted via sFTP. Instructions for digital diagnostic submissions may be found on the IROC Rhode Island website - www.irocri.qarc.org, under Digital Data, Diagnostic. If images have been submitted to IROC Rhode Island for central imaging reviews (see Section 16.6), duplicate images do not need to be submitted.

17.10.2 Submission of Radiotherapy Data

Digital Submission:

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission via TRIAD is preferred (see Section 16.6), but alternatively sites may use sFTP. Instructions for data submission via sFTP are on the IROC Rhode Island web site at http://irocri.qarc.org under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the

digital RT data via TRIAD or sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

17.10.3 Primary Site Data Submission

Treatment Planning System Output:

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Submission of DRR's is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by IROC Rhode Island and the radiation oncologist.
- Proton therapy: Smearing radius of the compensator (if applicable), set-up margin (SM) and PTV margin for each treatment beam and a description of the rationale for the PTV margins.

Forms

- RT1 or Proton Dosimetry Summary Form
- RT-2 Radiotherapy Total Dose Record form
- Motion management reporting form, if applicable

17.10.4 Metastatic Site(s) Data Submission

- The RT-2 Radiotherapy Total Dose Record form.
- Copy of the patient radiotherapy record including prescription and daily and cumulative doses to all targeted volumes and critical organs.

These data can be uploaded to TRIAD, sFTP or emailed to:
DataSubmission@QARC.org

Questions regarding the dose calculations or documentation should be directed to:
COG Protocol Dosimetrist at physics@QARC.org or 401.753.7600

17.11 Definitions of Deviations in Protocol Performance

In the following table, the GTV, CTV and PTV descriptions and evaluations will applied for the primary site radiation treatment plan.

	DEVIATION	
	Variation Acceptable	**Deviation Unacceptable**
Prescription Dose		
	Difference in prescribed or computed dose is 6-10% of protocol specified dose	Difference in prescribed or computed dose is > 10% of protocol specified dose
Dose Uniformity		
	>10% PTV received > 110% of the prescription dose *or* <93% isodose covers 100% of PTV	<90% isodose covers 100% of PTV
Target Volume		
	CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	GTV does not encompass MR-visible residual tumor
Organs at Risk		
	OAR deviations will be assessed at the time of final review.	OAR deviations will be assessed at the time of final review.
Radiotherapy Timing		
	Radiation started more than 80 days after consolidation	Radiation started more than 120 days after consolidation

18.0 HEMATOPOIETIC TRANSPLANT GUIDELINES

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).

All transplants performed on COG trials must occur at FACT-accredited SCT programs.

18.1 Catheter Use

PBSC may be collected using a large bore double lumen central venous catheter that will allow the 1-2 mL/kg/min flow rates required for apheresis. Institutional preference for apheresis catheters may be used.

18.2 PBSC Mobilization

Institutional standard operating procedures (SOPs) will be used for mobilization and pheresis.

In the absence of institutional SOPs, the following suggested guidelines could be used: Patients should begin G-CSF starting one to three days after completing a cycle of chemotherapy. They should continue on G-CSF 5 mcg/kg/day while recovering from the cycle of chemotherapy until the post-nadir ANC > 500-1000/μL, at which point it is recommended to increase the dose of G-CSF to at least 10 mcg/kg/day per institutional policies.

Institutions that time collections using circulating CD34 cell counts will generally begin pheresis when the CD34 count is ≥ 10-20 cells/μL. Otherwise, the timing of collection is within 1-4 days of increasing the G-CSF dose to 10 mcg/kg, when WBC is > 2000 - 5000 (usually Day 14 from start of chemotherapy). It is critical that G-CSF be given daily until PBSC collection is complete. If peripheral WBC is > 60,000, decrease G-CSF dose to 5 mcg/kg/day. If more than one day of PBSC collection is required, adjust the G-CSF dose per institutional guidelines.

If patients are off G-CSF prior to planned PBSC harvest, they should receive G-CSF 10-16 mcg/kg/day for 3 days prior to the first day of scheduled PBSC harvest (per institutional policies), harvest on Day 4 of G-CSF treatment, and continue daily G-CSF until PBSC collections are completed.

TIMING: PBSC mobilization is strongly recommended following Cycle 2 REGARDLESS of disease status in the marrow. Documentation of clearance of tumor cells from the bone marrow is NOT REQUIRED because the rate of immunocytochemical (ICC) positivity is <1% even in the setting of marrow disease. However, if the patient's medical condition prohibits safe apheresis, it is appropriate to delay PBSC mobilization and harvest until after Cycle 3 of Induction therapy. If PBSC mobilization is inadequate, an additional harvest may be performed after Cycle 3. If PBSC mobilization is still inadequate after Cycle 3, an additional harvest may be performed after Cycle 4. Significant efforts should be made to collect an adequate PBSC product (minimum of 4 x 10^6 CD34+ cells/kg) following Cycle 2.

Ch14.18 (dinutuximab) should not be started prior to the PBSC collection. For patients who undergo PBSC collection after Cycle 3, the ch14.18 (dinutuximab) should be held during Cycle 3. For the rare patient whose stem cell collection is not complete until after Cycle 4, ch14.18 (dinutuximab) should be held during Cycles 3 and 4.

18.3 PBSC Collection Guidelines

18.3.1 Laboratory Studies

For patients < 25 kg, a type and cross for packed red blood cells (PRBC) should be performed one day prior to procedure to avoid apheresis delays.

18.3.2 Collection Goals

It is recommended that large volume apheresis be performed on all patients for each collection, per institutional guidelines.

Optimal collection goal (total for all collections) is 10-20 x 10^6 CD 34+ cells/kg for PBSC. The minimum collection is 4 x 10^6 CD 34+ cells/kg divided in 3 aliquots of at least 2 x 10^6 CD 34+ cells/kg per aliquot. Collections in excess of 20 million CD34/kg are allowed. If possible, collection of a 4th aliquot should be considered, the aliquot stored as a back-up. :

- Aliquot #1: 2-4x10^6 CD34+ cells/kg for PBSC support with HSCT #1 (Thiotepa/Cyclophosphamide)
- Aliquot #2: 2-4x10^6 CD34+ cells/kg for PBSC support with HSCT #2 (Carboplatin/Etoposide/Melphalan)
- Aliquot #3: (if possible): 2-4x10^6 CD34+ cells/kg as a backup for delayed engraftment, or for potential subsequent use.

CD34+ cell counts should be done at local institution for each daily collection as per institutional SOP. In the event that a patient's collection is just short of or just equal to 4 x 10^6 CD 34+ cells/kg, it is recommended that the patient undergo an additional day of pheresis. If the "additional" pheresis is unable to be performed on the subsequent day to the first pheresis, then apheresis may be performed following the next cycle of Induction chemotherapy.

18.4 PBSC Analyses

The following studies are recommended for each PBSC collection:

1) Culture for bacterial and fungal contamination,
2) Nucleated cell count and differential,
3) CD34+ cell enumeration

18.5 Cryopreservation of PBSC Products

Each aliquot (as detailed above) should be processed and cryopreserved on the day of collection as per Institutional SOPs. These SOPs include the use of 7.5-10% dimethyl sulfoxide (DMSO) final concentration in the cryopreservation medium, use of a monitored, controlled-rate freezer, and storage in liquid nitrogen with appropriate monitoring. The

goal is to have multiple aliquots cryopreserved separately to facilitate multiple infusions and to provide a potential backup.

18.6 Autologous Stem Cell Rescue

Institutional SOPs may be followed. **However, the PBSC product should NEVER be irradiated prior to infusion.**

18.6.1 Premedication

DMSO may cause a histamine-like reaction when infused into the patient. Therefore, premedication with an antihistamine and acetaminophen is recommended.

18.6.2 Thawing of PBSC

PBSC are thawed in a 37°C water bath. Only 1 bag of PBSC should be thawed at a time – when the infusion of 1 bag is completed, the next bag should be thawed.

Thawed PBSC should be infused as rapidly as tolerated through a central venous catheter. The unit may be infused by gravity, or the cells may be drawn up into a syringe and pushed by trained personnel. Microaggregate filters and leukodepletion filters MUST NOT be used for infusion of PBSC. If a thawed unit appears clumpy or stringy and these particles cannot be dispersed with gentle kneading, the PBSC product could be infused through a standard 170 micron blood filter.

18.6.3 Possible Symptoms during Infusion

Precipitating Factor	Possible Symptoms
hemolyzed red cells	fever, chills, hemoglobinuria
cellular clumps and debris	chest pain, hypoxia, hypertension
cold 10% DMSO	nausea, headache
microbial contamination	fever, chills, hypotension
plasma proteins	urticaria

18.6.4 Recommendations for Stem Cell Infusion

a. Institutional SOPs may be followed
b. Discontinue all other IV fluids if possible during stem cell infusion to avoid volume overload.
c. Consider anti-emetics prior to stem cell infusion to limit DMSO-induced nausea and vomiting.
d. Where the DMSO volume in the stem cell product would exceed accepted level for infusion within a 24-hour period, stem cell products may be infused over 2 days to meet this standard
e. Hydrate for 6-12 hours post stem cell infusion at 125 mL/m²/hr.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

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 (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

Additional information can be found 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).

Requirements For [insert study number] **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
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users 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, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX II: INTERNATIONAL NEUROBLASTOMA RISK GROUP (INRG) STAGING SYSTEM[80,81]

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.

* See Appendix VIII

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

APPENDIX III: 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
alfentanil[4,5] acalabrutinib[5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] ergotamine[4] erlotinib eplerenone[5] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

ivacaftor ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] telaprevir tamoxifen temsirolimus teniposide tetracycline 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 4.1.2.1 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 IV: 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.

Carboplatin

Drugs that may interact with carboplatin
• Antibiotics like gentamicin or tobramycin • Anti-seizure medications like fosphenytoin or phenytoin • Arthritis medications like leflunomide, tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like clozapine or natalizumab

Food and supplements that may interact with carboplatin
• Echinacea

Cisplatin

Drugs that may interact with cisplatin
• Antibiotics like gentamicin or tobramycin • Anti-seizure medications like fosphenytoin or phenytoin • Arthritis medications like leflunomide or tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like bumetanide, clozapine, furosemide, natalizumab

Food and supplements that may interact with cisplatin
• Echinacea

Cyclophosphamide

Drugs that may interact with cyclophosphamide
• Allopurinol • Amiodarone • Carbamazepine • Cyclosporine • Digoxin • Efavirenz • Etanercept • Hydrochlorothiazide • Lumacaftor • Mifepristone • Pentostatin • Rifampin • Ritonavir • Warfarin

Food and supplements that may interact with cyclophosphamide
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Doxorubicin

Drugs that may interact with doxorubicin*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Clozapine, fluoxetine, fluvoxamine, nefazodone, paroxetine
• Antibiotics and Antifungals
  • Fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Antiretrovirals and antivirals
  • Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir, zidovudine
• Anti-seizure medications
  • Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, diltiazem, dronedenarone, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
  • Ado-trastuzumab emtansine, bevacizumab, idelalisib, trastuzumab, taxane derivatives
• Many other drugs, including the following:
  • Aprepitant, cyclosporine, fosaprepitant, fosnetupitant, deferasirox, ivacaftor, mifepristone, natalizumab, netupitant

Food and supplements that may interact with doxorubicin
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Etoposide

Drugs that may interact with etoposide

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Clozapine, nefazodone
• Antifungals
  • Fluconazole, itraconazole, 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
• Anti-seizure medications
  • Carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Aprepitant, atovaquone, bosentan, deferasirox, ivacaftor, lomitapide, mifepristone, modafinil natalizumab, pimozide

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

Isotretinoin

Drugs that may interact with isotretinoin
• Aminiolevulinic 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

Melphalan

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

Food and supplements that may interact with melphalan
• Echinacea

Thiotepa

Drugs that may interact with thiotepa
• Arthritis medications like leflunomide or tofacitinib • Other medications like bupropion, clozapine, efavirenz, methadone, promethazine, or natalizumab

Food and supplements that may interact with thiotepa
• Echinacea

Topotecan

Drugs that may interact with topotecan

• Antibiotics and antifungals
  ○ Clarithromycin, erythromycin, itraconazole, ketoconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Antiretrovirals and antivirals
  ○ Lapatinib, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, velpatasvir, voxilaprevir
• Anti-seizure medications
  ○ Fosphenytoin, phenytoin
• Heart medications
  ○ Amiodarone, carvedilol, dronedenarone, propafenone, quinidine, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Clozapine, eltrombopag, ivacaftor, natalizumab, tolvaptan

Food and supplements that may interact with topotecan
• Echinacea

Vincristine

Drugs that may interact with vincristine

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

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

APPENDIX V: SUMMARY OF OPTIONAL CORRELATIVE STUDIES

Correlative Studies: Induction

	Time point	Sample Type	Volume per tube	Quantity	Tube Type / Sample Prep	Notes	Ship to	Section Number
CORRELATIVE STUDIES: INDUCTION	**Pre-Tx**	Blood	7 – 10 mL	2 tubes	EDTA	Ship immediately	Yu	15.1.1 15.1.4[1]
			2.5 mL	2 tubes	PAXgene RNA		BPC	15.1.2 15.1.6
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
			1 mL	1 tube	Red Top	Process for serum	BPC	15.1.7
		Tumor Tissue[2,3]		3	Air dried touchprep slides		BPC	15.1.7
		Bone Marrow		3 of each slide type	• Air-dried smear slides (aspirate) • Air-dried touchprep slides (biopsy)		BPC	15.1.7
	Cycle 1, Day 6	Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 3, Day 1	Blood	7 – 10 mL	2 tubes	EDTA	Ship immediately	Yu	15.1.1 15.1.4[1]
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 3, Day 6	Blood	7 – 10 mL	2 tubes	EDTA		Yu	15.1.1 15.1.4[1]
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 4, Day 1	Blood	7 – 10 mL	2 tubes	EDTA	Ship immediately	Yu	15.1.1 15.1.4[1]
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 4, Day 6	Blood	7 – 10 mL	2 tubes	EDTA	Ship immediately	Yu	15.1.1 15.1.4[1]
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 4, Day 15	Blood	1 mL	1 tube	Red Top	Process for serum	BPC	15.1.7
	Cycle 5, Day 1	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
		Blood	1 mL	1 tube	Red Top	Process for serum	BPC	15.1.7
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 5, Day 6	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3

		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 5, Day 21	Blood	1 mL	1 tube	Red top	Process for serum	BPC	15.1.7
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
		Bone Marrow		3 of each slide type	• Air-dried smear slides (aspirate) • Air-dried touchprep slides (biopsy)		BPC	15.1.7

[1] Samples collected on 15.1.4 (NK Marker Analysis) will be shared for use on 15.1.3 (HACA/PATA) and KIR/KIRL and Fc Receptor genotyping. Additional samples do not need to be collected at these shared time points. CBC results obtained on the day of the NK Marker Analysis specimen should accompany the specimen transmittal form.
[2.] Only collect if not submitted on APEC14B1 or ANBL00B1.
[3.] Paraffin embedded tissue block may be sent instead of slides.

Correlative Studies: Post-Consolidation

Time point		Sample Type	Volume per tube	Quantity	Tube Type / Sample Prep	Notes	Destination Lab	Section Number
CORRELATIVE STUDIES: POST-CONSOLIDATION	**Prior to post-Consolidation, Cycle 1**	Blood	7 – 10 mL	2 tubes	EDTA	Ship immediately	Yu	15.1.1 15.1.4[1]
			2.5 mL	2 tubes	PAXgene RNA		BPC	15.1.2 15.1.6
		Blood	3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
	Cycle 1, Day 4	Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 1, Day 7	Blood	7 mL	1 tube	EDTA		Yu	15.1.4[1]
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 2, Day 1	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
	Cycle 2, Day 4	Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 2, Day 7	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	Cycle 3, Day 1	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
	Cycle 3, Day 7	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
	Cycle 4, Day 1	Blood	7 mL	1 tube	EDTA	Ship immediately	Yu	15.1.4[1]
	Cycle 4, Day 7	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
	Cycle 5, Day 1	Blood	7 mL	1 tube	EDTA	Ship immediately	Yu	15.1.4[1]
	Cycle 5, Day 7	Blood	2 mL	1 tube	EDTA	Process for plasma	BPC	15.1.3
	Cycle 6, Day 15	Blood	7 mL	1 tube	EDTA	Ship immediately	Yu	15.1.4[1]

		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
	End of therapy	Blood	1 mL	1 tube	Red top	Process for serum	BPC	15.1.7
		Bone Marrow[2]		3 of each slide type	• Air-dried smear slides (aspirate) • Air-dried touchprep slides (biopsy)		BPC	15.1.7
	Relapse / Progression	Blood	7 – 10 mL	1 tube	EDTA	Ship immediately	Yu	15.1.1
			3 mL	1 tube	Red Top	Process for serum	BPC	15.1.5
		Blood	2.5 mL	1 tube	PAXgene RNA		BPC	15.1.6
		Bone Marrow		3 of each slide type	• Air-dried smear slides (aspirate) • Air-dried touchprep slides (biopsy)		BPC	15.1.7
		Tumor Tissue[3]		3	Air dried touchprep slides		BPC	15.1.7

[1] Samples collected on 15.1.4 (NK Marker Analysis) will be shared for use on 15.1.3 (HACA/PATA) and KIR/KIRL and Fc Receptor genotyping. Additional samples do not need to be collected at these shared time points. CBC results obtained on the day of the NK Marker Analysis specimen should accompany the specimen transmittal form.

[2.] Only collect if bone marrow was positive for tumor immediately prior to Post-Consolidation.

[3.] Only collect if not submitted on APEC14B1 or ANBL00B1.

APPENDIX VI: EMERGENCY MANAGEMENT OF CH14.18 (DINUTUXIMAB) TOXICITIES

This document is for rapid reference. See Section 5.11 for further information regarding management of acute toxicities during ch14.18 (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** ch14.18 (dinutuximab) infusion **and** sargramostim
- 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 ch14.18 (dinutuximab) and/or cytokine

For hypotension in setting of allergic reaction:

- Hold ch14.18 (dinutuximab) and sargramostim 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 ch14.18 (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, ch14.18 (dinutuximab) can be resumed at half rate with very close observation
- **Do not resume sargramostim until the next day**

Minimal criteria for resumption of ch14.18 (dinutuximab) infusion:

- Complete resolution of airway symptoms
- Complete resolution of hypotension

APPENDIX VII: 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
NI	PR	PR	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
SD	SD	NI	SD
SD	NI	NI	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 VIII: 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 IX: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ANBL17P1
(for children from 7 through 12 years of age)

A Study of a New Way to Treat Children with Neuroblastoma (NBL)

1. We have been talking with you about your illness, neuroblastoma (NBL). NBL is a kind of cancer that grows in the soft tissue in your body. It can grow in different parts of the body. After doing tests, we have found that you have high-risk NBL. It is called high-risk because your tumor is difficult to treat.

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.

3. All children who are part of this study will be treated with chemotherapy, surgery and x-ray treatment followed by additional chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment.

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

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatment may not work as well as other therapies. Also, the study treatment may cause more side effects than other therapies. Other things may happen to you that we do not know about yet. 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. 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 some extra blood and bone marrow. We will take the extra blood and bone marrow when other regular tests are done to avoid extra needle sticks. We are also asking your “okay” to collect any tumor tissue that is left over from any operations you have while you are part of this study. We want to see if there are ways to tell how the cancer will react to treatment. You can still take part in this study even if you do not allow us to collect the extra blood and bone marrow or save the leftover tumor tissue for research.

INFORMATION SHEET REGARDING RESEARCH STUDY ANBL17P1
(for teens from 13 through 17 years of age)

A Study of Ch14.18 (dinutuximab) Added to Standard Induction Therapy for Children with Newly Diagnosed 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 in your body. It can grow in different parts of the body. After doing tests, we have found that you have high-risk NBL. It is called high-risk because your tumor is difficult to treat..

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.

3. Children and teens who are part of this study will be treated with chemotherapy, surgery and x-ray treatment followed by additional chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. Study doctors would like to learn if your cancer responds to treatment.

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 extra blood and bone marrow. We will take blood and bone marrow samples when other regular tests are done to avoid extra needle sticks. We are also asking your permission to collect any tumor tissue that is left over from any surgeries you have while you are part of this study. We would like to use the blood, bone marrow, and tumor tissue to do tests to see if there are ways to tell how the cancer will respond to treatment. If there is any tumor tissue left over from these tests, we would like to save it for other research tests in the future. You can still be treated on this study even if you do not allow us to collect the extra blood and bone marrow or save the leftover tumor tissue for research.

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