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The world's childhood cancer experts

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

May 1, 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 **AEWS1221**, *Randomized Phase 3 Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479, NSC# 750008, IND#) to Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma*, has provided Amendment 6 for CTEP review.

This amendment is submitted in response to FDA comments from Dr. Julie Rhie dated April 11, 2019 and a Request for Rapid Amendment (RRA) from Dr. Helen Chu dated April 23, 2019. In this amendment, the protocol provides guidance to investigators for managing suspected cases of pneumonitis, the addition of oxygen saturation in follow-up vital sign assessments for patients who have previously received whole lung radiotherapy, and the revised CAEPR for ganitumab (Version 2.1, March 26, 2019). This study was closed to patient accrual on March 20, 2019. The risk information in the informed consent document has been updated to include the risk of pneumonitis. Additional administrative updates have been made to the protocol. Revisions to the protocol and consent documents are detailed in the pages below.

The AEWS1221 study committee looks forward to approval of this amendment. Please contact me with any questions or concerns.

Sincerely,

Tiffany Liu, MS, MA, Protocol Coordinator (for)

Steven DuBois, MD, AEWS1221 Study Chair
Peter Adamson, MD, Children's Oncology Group Chair

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	• Updated version date and amendment number. • Inserted study closure date.
2.	Table of Contents	3-5	Updated to reflect current pagination and headings.
3.	Study Committee	7	Updated study committee member's contact information
4.	Experimental Design Schema	10	Added the following statement: "**NOTE: As of March 20, 2019, the study closed to accrual and institutions were instructed to immediately discontinue ganitumab for patients on Regimen B.**"
5.	2.16	23	Provided background information for why study is being amended. This information was communicated to sites in an investigator memo dated March 20, 2019.
6.	4.1.1	31-33	• Added/modified text to reflect that study has closed to accrual and that institutions were instructed to immediately discontinue ganitumab for Regimen B patients. • Updated Treatment and Regimen B Consolidation Schemas to indicate that ganitumab administration has been discontinued.
7.	4.1.1.1	33-34	• Modified text to reflect the discontinuation of ganitumab for Regimen B patients. • Added a statement that the sequence of Consolidation cycles may be adjusted at the physician's discretion to avoid resuming doxorubicin shortly after completing a course of radiation.
8.	4.1.1.2 4.1.1.3	34-35 36	Modified text to reflect the discontinuation of ganitumab for Regimen B patients.
9.	4.2.2 4.2.3	36 36	• Removed corticosteroid therapy information because it pertained to ganitumab administration, which has been discontinued. • Renumbered to reflect the removal of the original Section 4.2.2
10.	4.4.1.1 4.4.1.2 4.4.2.1 4.4.2.2	43 50 60 68	Clarified that both filgrastim and pegfilgrastim biosimilar products are permitted: "Begin myeloid growth factor support (filgrastim ~~biosimilar products~~ or pegfilgrastim **or biosimilar products** according to institutional standards for patients receiving interval compressed chemotherapy) at least 24-36 hours after the last dose of chemotherapy."

#	Section	Page(s)	Change
11.	4.4.1.1 4.4.1.3 4.4.2.1 4.4.2.3	44-46 54-56 62-64 72-74	Removed fasting metabolic labs from Therapy Delivery Maps due to discontinuation of ganitumab. Re-lettered required observations to reflect change.
12.	4.4.2	57	Added/modified text to reflect that institutions were instructed to immediately discontinue ganitumab for Regimen B patients.
13.	4.4.2.1 4.4.2.2 4.4.2.3	62-64 72-74 74	Removed ganitumab information from Therapy Delivery Maps and Administration Schedule instructions. Maintenance was removed in its entirety. Re-numbered to reflect removal of the Therapy Delivery Map for Maintenance.
14.	4.4.2.3	69	Added the following End of Therapy instructions for Regimen B patients: "**Following completion of Metastatic Site Radiation, patients on Regimen B will have completed all prescribed protocol therapy. See Sections 7.1.3 for observations due at End of Therapy and Section 7.3 for recommended observations during follow-up.**"
15.	5.1.1 5.1.2 5.3.2 5.5 5.7 5.7.1 5.10	75 75 77 78 80 80 81	Removed dose modification information specific to ganitumab-related toxicities.
16.	5.10	81	Added new Section 5.10 with additional guidance for patients who develop pneumonitis.

#	Section	Page(s)	Change

17.	6.1	82-84	Inserted revised CAEPR for ganitumab (Version 2.1, March 26, 2019) to replace Version 2.0. Specific changes are as follows:
			
			• Added New Risk:
			  • Also Reported on Ganitumab Trials But With Insufficient Evidence for Attribution: Agitation; Alkaline phosphatase increased; Anal fistula; Anal mucositis; Atrial fibrillation; Back pain; Bone pain; Blood and lymphatic system disorders - Other (pancytopenia); Cardiac disorders - Other (diastolic dysfunction); Constipation; Cough; Creatinine increased; Dysphagia; Ejection fraction decreased; Epistaxis; Esophagitis; Febrile neutropenia; Heart failure; Hematoma; Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (jaundice cholestatic); Hyperkalemia; Hypocalcemia; Hypophosphatemia; Hypoxia; Infections and infestations - Other (pneumococcal infection); Investigations - Other (electrocardiogram abnormal); Malaise; Myelitis; Oral pain; Palmar-plantar erythrodysesthesia syndrome; Pleural effusion; Rectal fistula; Rectal hemorrhage; Skin infection; Skin ulceration; Soft tissue infection; Syncope; Tremor; Typhlitis; Urinary tract infection; Urinary tract obstruction; Vascular access complication; Weight loss
			
			• Increase in Risk Attribution:
			  • Changed to Likely from Less Likely: Fatigue
			  • Changed to Less Likely from Also Reported on Ganitumab Trials But With Insufficient Evidence for Attribution: Lymphocyte count decreased; Myalgia
			  • Changed to Rare But Serious from Also Reported on Ganitumab Trials But With Insufficient Evidence for Attribution: Pneumonitis
			
			• Provided Further Clarification:
			  • Footnote #4 has been added: “The rate and severity of radiation-associated pneumonitis may be increased in patients who receive ganitumab shortly before or after radiation to the lungs.”
			  • Enterocolitis (*CTCAE 4.0 language*) is now reported as Gastrointestinal disorders - Other (enteritis).
			  • Nervous system disorders - Other (sciatica) (*CTCAE 4.0 language*) is now reported as Radiculitis.
			  • Dyspnea has been deleted and is now reported as part of footnote #3.

18.	6.11	102-103	Monograph has been updated.

#	Section	Page(s)	Change
19.	7.1.1	106-107	Removed fasting metabolic labs, including its respective footnote, from the list of studies to be obtained due to discontinuation of ganitumab.
20.	7.1.2 7.1.3	108-109 110	• Removed Table 7.1.3 that contained evaluations during Metastatic Site Radiation and Maintenance. Table 7.1.2 now includes evaluations during Metastatic Site Radiation. • Removed fasting metabolic labs, including its respective footnote, from the list of studies to be obtained due to discontinuation of ganitumab. • Removed information pertaining to Maintenance. • Added the following footnote: ○ "**13 Submission of imaging demonstrating the first episode of disease progression/suspected relapse is required for central review (see Section 16.3). For times other than suspected relapse, follow recommended disease evaluation schedule for all patients in Regimens A and B in Section 7.3 timed from end-Consolidation. This includes disease restaging 3 months and 6 months from end-Consolidation.**"
21.	7.3	111-112	• Added oxygen saturation by pulse oximetry to the list of follow-up observations and included the following new footnote 1: "**For patients treated with whole lung radiation.**" • Renumbered footnotes to reflect the addition of the above footnote.
22.	11.10 11.11	148 149	Modified CTEP-AERS reporting instructions: "CTEP-AERS 24-hour Notification is required for ≥ Grade ~~2~~ **1** pneumonitis."
23.	15.4	169	Modified bone marrow collection and delivery information: "Material must arrive fresh in the laboratory. Marrow samples collected on Monday ~~Friday~~ **Thursday** are eligible for submission such that samples arrive in the laboratory Tuesday ~~Saturday~~ **Friday**. ~~Weekday deliveries are preferred, if possible.~~ **For patients undergoing clinical biopsies on a Friday, do not submit marrow samples from that biopsy for this correlative study.**"

Activated: 12/8/14
Closed: 03/20/2019

Version Date: 05/01/2019
Amendment: 6

CHILDREN'S ONCOLOGY GROUP

AEWS1221

Randomized Phase 3 Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479, NSC# 750008, IND#) to Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma

An Intergroup NCTN Phase 3 Study

NCI Supplied Agent: Ganitumab (NSC# 750008, IND#)
IND sponsor for ganitumab: DCTD, NCI

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NRG / NRG Oncology

ALLIANCE / Alliance for Clinical Trials in Oncology

ECOG-ACRIN / ECOG-ACRIN Cancer Research Group

SWOG / SWOG

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
NCI Supplied Agent: Ganitumab, NSC# 750008
Other Agents: Vincristine, NSC# 67574, Commercial
Doxorubicin, NSC# 123127, Commercial
Cyclophosphamide, NSC# 26271, Commercial
Ifosfamide, NSC# 109724, Commercial
Etoposide, NSC# 141540, Commercial
Dexrazoxane, NSC# 169780, Commercial
MESNA, NSC# 113891, Commercial
IND#:
IND sponsor for Ganitumab: DCTD/NCI

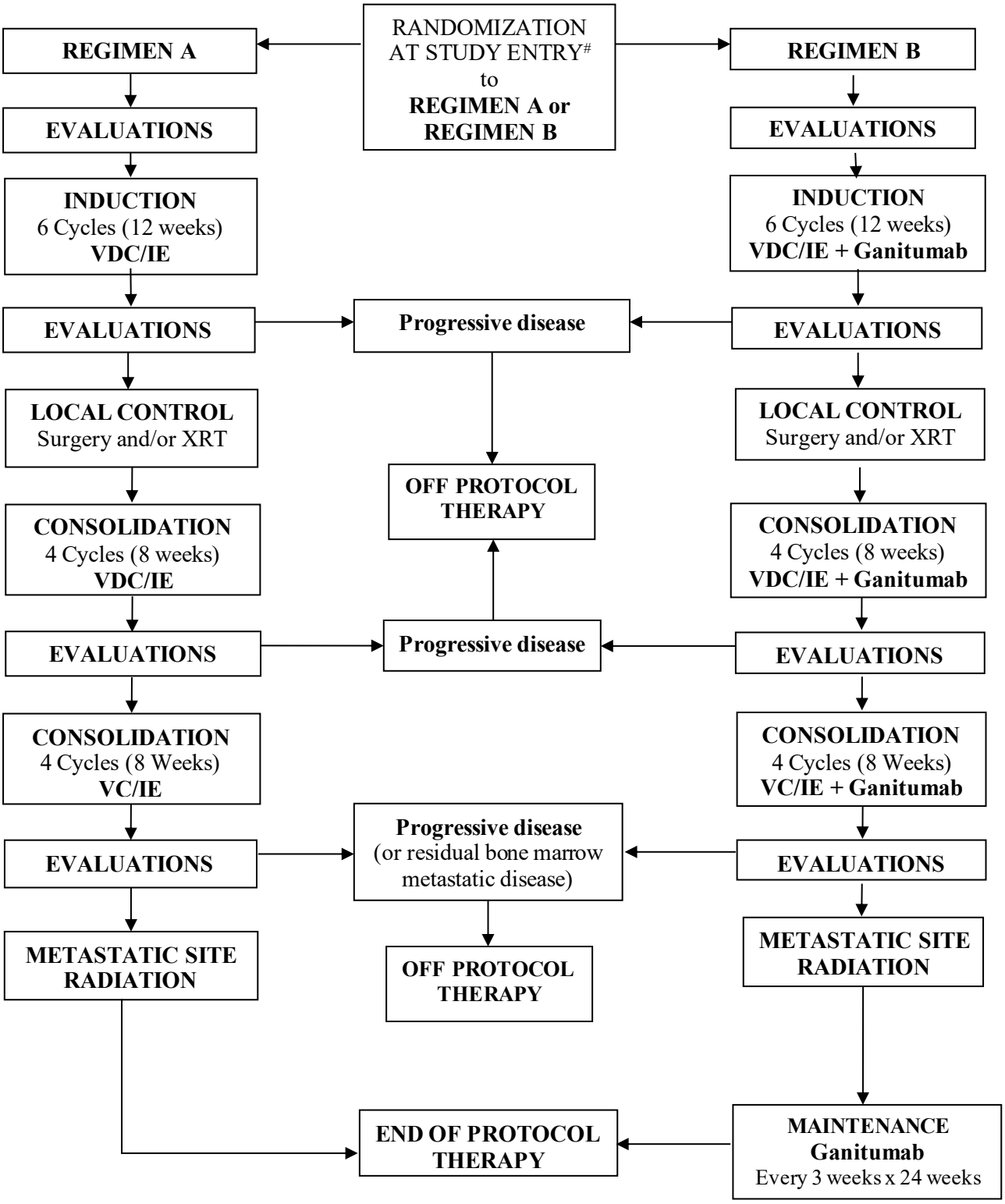
SEE SECTION 15.0 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Despite improvements in outcomes for patients with localized Ewing sarcoma, patients with newly diagnosed metastatic Ewing sarcoma continue to have poor outcomes with standard multiagent chemotherapy. A large body of preclinical data supports a role for IGF-1R inhibition in the treatment of Ewing sarcoma. More recently, clinical trials of IGF-1R monoclonal antibodies have demonstrated single-agent activity in patients with relapsed Ewing sarcoma. Ganitumab is a fully human monoclonal antibody directed against IGF-1R. In this phase 3 randomized trial, patients with newly diagnosed metastatic Ewing sarcoma are randomized at study entry to the comparator arm with interval compressed multiagent chemotherapy or to the experimental arm with interval compressed multiagent chemotherapy and the addition of ganitumab. The primary endpoint is event-free survival. Feasibility of this approach and evaluation of stereotactic body radiotherapy to sites of bone metastasis are additional clinical objectives. 300 eligible and evaluable patients will enroll. A series of correlative biology studies will explore markers of response to IGF-1R inhibition. These studies include serum markers of the IGF-1 pathway, IGF-1R expression on bone marrow micrometastatic tumor cells, and polymorphisms in *EGFR* as a potential resistance mechanism.

EXPERIMENTAL DESIGN SCHEMA

NOTE: As of March 20, 2019, the study closed to accrual and institutions were instructed to immediately discontinue ganitumab for patients on Regimen B.



Patients will be randomized at study entry to receive either Regimen A or Regimen B. The first 10 patients < 21 years old randomized to Regimen B will submit mandatory trough serum samples for ganitumab concentrations (completed as of July 2015).

VDC: vincristine-doxorubicin-cyclophosphamide
IE: ifosfamide-etoposide
Ganitumab: IGF-1R monoclonal antibody
XRT: radiation therapy

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objective

To determine if event-free survival (EFS) in patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy is improved with the addition of ganitumab (AMG 479).

1.2 Secondary Objective

1.2.1 To describe the toxicity of the addition of ganitumab to multimodality therapy for patients with newly diagnosed metastatic Ewing sarcoma.

1.2.2 To compare overall survival in patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of ganitumab.

1.3 Exploratory Objectives

1.3.1 To compare bone marrow response rates in patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of ganitumab.

1.3.2 To describe the toxicity of 6 months of ganitumab monotherapy as Maintenance therapy following multimodality therapy in patients with newly diagnosed metastatic Ewing sarcoma.

1.3.3 To describe trough levels of ganitumab in a cohort of patients with Ewing sarcoma < 21 years of age treated with 18 mg/kg.

1.3.4 To describe the feasibility of and local failure rates following hypofractionated stereotactic body radiotherapy (SBRT) directed at bone metastases in patients with newly diagnosed metastatic Ewing sarcoma.

1.3.5 To determine if EFS, overall survival, bone marrow response rates, and toxicity differ based on serum markers of the IGF-1 pathway in patients with newly diagnosed metastatic Ewing sarcoma treated with interval compressed chemotherapy with and without the addition of ganitumab.

1.3.6 To determine if EFS, overall survival, and bone marrow response rates differ based on protein, DNA, and RNA markers in patients with newly diagnosed metastatic Ewing sarcoma treated with interval compressed chemotherapy with and without the addition of ganitumab.

1.3.7 To evaluate bone marrow micrometastatic disease and tumor cell surface IGF-1R expression at diagnosis and after 3 and 6 cycles of study therapy in patients with newly diagnosed metastatic Ewing sarcoma.

1.3.8 To determine if the presence of germline polymorphisms in *EGFR* correlate with response to multiagent therapy with and without ganitumab.

1.3.9 To investigate the ability of FDG-PET to augment conventional response assessment of primary Ewing sarcoma tumors by MRI.

1.3.10 To explore FDG-PET response at the primary tumor as a prognostic marker and as a predictive biomarker of clinical activity of IGF-1R inhibition in patients with newly diagnosed metastatic Ewing sarcoma.

1.3.11 To collect data on institutional testing for *EWSR1* translocation status in patients enrolling on study.

1.3.12 To explore the capacity of plasma cell-free DNA analysis to detect tumor-specific genetic changes at initial diagnosis and after initiation of protocol therapy.

1.3.13 To collect a population of bone marrow metastatic tumor cells by flow cytometry for genomic profiling.

2.0 BACKGROUND

2.1 Metastatic Ewing Sarcoma

There has been considerable improvement in the outcome of patients with localized Ewing sarcoma over the last two decades. In contrast, the overall survival for patients with initially metastatic disease continues to be less than 30% across multiple studies.[1-5] Some groups have reported that patients with isolated lung metastases have a better outcome than patients with bone and/or bone marrow metastases.[4,5]

2.2 Interval Compressed Chemotherapy in Ewing Sarcoma

Standard therapy for Ewing sarcoma in COG protocols includes alternating cycles of vincristine/doxorubicin/cyclophosphamide (VDC) with ifosfamide/etoposide (IE).[6] With the positive results of COG protocol AEWS0031, the new standard remains VDC alternating with IE, with cycles now given on an interval-compressed basis every 2 weeks for a total of 14 cycles.[7] Of note, the standard arm of AEWS1031 includes a total of 17 cycles of chemotherapy in order to maintain uniformity in treatment length with the experimental arm of that study. The effect of the addition of 3 cycles on outcomes is not clear and therefore 14 cycles of therapy per the interval compressed arm of AEWS0031 has been chosen for the chemotherapy backbone of this study.

Sub-analysis of AEWS0031 demonstrated that older patients were able to receive interval-compressed chemotherapy as prescribed. Specifically, the median cycle length for patients ≥ 18 years of age was 15 days compared to 15 days for patients < 18 years of age (R. Womer, personal communication).

AEWS0031 only included patients with localized Ewing sarcoma. Therefore, the tolerability and activity of interval-compressed VDC/IE in patients with metastatic disease remains unclear. This issue will be addressed in this study.

2.3 Role of IGF-1R Inhibition in Ewing Sarcoma

Several lines of evidence indicate that targeting the insulin like growth factor receptor-1 (IGF-1R) will be an effective strategy in the treatment of Ewing sarcoma. All but one Ewing sarcoma cell line evaluated in 2 early studies demonstrated expression of both IGF-1 and IGF-1R.[8,9] In contrast to wild-type fibroblasts, fibroblasts lacking the IGF-1R were not transformed after transfection with *EWS/FLI1*.[10] *EWS/FLI1* appears to repress expression of IGF binding protein-3 (IGF-BP3), an endogenous inhibitor of the IGF-1 pathway.[11] Several small molecule inhibitors of IGF-1R have demonstrated activity in preclinical models of Ewing sarcoma.[12-14] In one study, Ewing sarcoma was among the solid tumor histologies most sensitive to inhibition by one such inhibitor, GSK1904529A.[14]

Early studies demonstrated that a neutralizing antibody against the IGF-1R inhibited the growth of all Ewing sarcoma cell lines tested.[8,9,15] This effect was also observed in Ewing sarcoma mouse xenografts.[16] Compared to 43% of control-treated mice, no antibody-treated mice developed lung metastases. The Pediatric Preclinical Testing Program (PPTP) has evaluated two IGF-1R monoclonal antibodies (SCH 717454 and IMC-A12) in a panel of Ewing sarcoma cell lines and xenografts[17,18] SCH 717454 demonstrated little *in vitro* activity. In contrast, 2 of 5 Ewing sarcoma xenografts demonstrated significant prolongation of time to event and significant inhibition of tumor growth after treatment with SCH 717454. One of these xenografts showed tumor regression in response to SCH 717454 and met criteria for "high" level activity.[18] IMC-A12 demonstrated both *in vitro*

and *in vivo* activity. Two of 4 Ewing sarcoma cell lines demonstrated more than 50% reduction in cell growth. Two of 5 Ewing sarcoma xenografts showed reductions in tumor size and 3 of 5 showed prolongation in time to event.[17] Ganitumab has also been evaluated in preclinical models of Ewing sarcoma, with demonstrated activity both as a single agent and in combination with rapamycin.[19]

2.4 Clinical Experience with IGF-1R Monoclonal Antibodies in Patients with Ewing Sarcoma

Based on these promising preclinical studies, several groups have evaluated anti-IGF-1R monoclonal antibodies in patients with relapsed or refractory Ewing sarcoma. A phase 2 study of ganitumab included 18 patients with Ewing sarcoma treated with 12 mg/kg IV every two weeks. One patient had a confirmed partial response (6% response rate).[20] Closer evaluation of the data demonstrated that 6/18 (33%) patients had regressions of at least 10%. A phase 2 study of R1507 included 115 patients with relapsed or refractory Ewing sarcoma and demonstrated an objective response rate of 10%.[21] In COG protocol ADVL0712, one of 10 patients with Ewing sarcoma treated with IMC-A12 at the 6 mg/kg dose level had a confirmed partial response and 4 additional patients had stable disease for at least 3 cycles.[22] At the 9 mg/kg dose level, 2 of 20 patients had RECIST partial responses.[23] Of 16 patients with Ewing sarcoma treated on a phase 1 study of figitumumab (20 mg/kg IV every 3-4 weeks), one patient had a complete response, one patient had a partial response, and 6 patients had stable disease for more than 4 months (12.5% response rate).[24] A phase 2 study of figitumumab in 106 patients with relapsed or refractory Ewing sarcoma recently demonstrated a 14% response rate.[25] A phase 1 study of MK-0646 included 6 patients with Ewing sarcoma, one of whom had a mixed response.[26] These studies indicate that IGF-1R monoclonal antibodies have single agent activity in patients with relapsed or refractory Ewing sarcoma, with objective response rates of approximately 10%.

2.5 Rationale for Combining IGF-1R Inhibition and Chemotherapy in Ewing Sarcoma

Several preclinical studies have evaluated the strategy of IGF-1R inhibition in combination with chemotherapy. These studies have demonstrated that treatment with an IGF-1R inhibitor increases the sensitivity of Ewing sarcoma cells to the effects of chemotherapy. In one study, the addition of an IGF-1R monoclonal antibody enhanced the cytotoxic effects of doxorubicin (synergistic effect) or vincristine (additive effect) on Ewing sarcoma cells.[27] This effect was observed when cells were treated with IGF-1R monoclonal antibody with concomitant or sequential chemotherapy. Synergistic and additive antiproliferative effects in *in vitro* and *in vivo* Ewing sarcoma studies have also been reported with the combination of chemotherapy and small molecule IGF-1R inhibitors[13,28] or with an IGF-1R dominant negative construct.[29]

IGF-1R monoclonal antibodies have started to undergo evaluation in combination with chemotherapy in adults and children. COG protocol ARST08P1 is evaluating intensive chemotherapy with and without the addition of IMC-A12 in children and young adults with newly diagnosed high-risk rhabdomyosarcoma. The chemotherapy backbone in ARST08P1 is similar to the chemotherapy backbone of this study, including cycles of VDC alternating every two weeks with IE. Toxicity has been consistent with the expected toxicity during intensive chemotherapy alone, though 3 cases of sinusoidal obstruction syndrome (SOS) at the highest dose level of IMC-A12 prompted dose reduction to the equivalent of the adult recommended phase 2 dose (Doug Hawkins, personal

communication). With regard to risk of cardiac toxicity, 1 of 20 patients treated with IMC-A12 at a dose of 3 mg/kg developed Grade 3 congestive heart failure and 1 of 19 patients treated without IMC-A12 developed Grade 3 or 4 left ventricular systolic dysfunction. None of the 13 patients treated with IMC-A12 at a dose of 6 mg/kg has developed Grade 3 or 4 cardiac toxicity. Detailed data on Grade 1 and 2 toxicities are not collected on ARST08P1. The addition of IMC-A12 has not impacted the ability to administer interval compressed chemotherapy cycles. The median duration of each reporting period has been similar for patients on ARST08P1 treated with and without IMC-A12 (J. Anderson/S. Malempati, personal communication).

IMC-A12 has been evaluated in combination with doxorubicin in adults with soft tissue sarcoma (median age 64 years with range 29-80 years).[30] In this phase 1 study, 2 dose-limiting toxicities (mucositis and hyperglycemia) were seen among 13 patients treated with 3 mg/kg IMC-A12. The dose was escalated to the maximum planned dose of 6 mg/kg IMC-A12 in 10 evaluable patients, none with dose-limiting toxicity. Two of 13 patients treated with 3 mg/kg IMC-A12 developed Grade 3 left ventricular systolic dysfunction after a minimum of 4 courses of combination therapy.

Figitumumab has also been evaluated in combination with cytotoxic chemotherapy in patients with non-small cell lung cancer. Patients in a phase 1 study were treated with paclitaxel, carboplatin, and escalating doses of figitumumab.[31] A maximum tolerated dose was not identified. A phase 2 study randomized 156 patients to paclitaxel and carboplatin, with or without figitumumab.[32] The response rate was higher in patients randomized to receive figitumumab. The combination was tolerable, with the rates of Grade 3 or 4 neutropenia and hyperglycemia somewhat higher in patients receiving figitumumab. With this experience, a phase 3 trial was initiated in patients with newly diagnosed advanced NSCLC.[33] Patients were randomized to receive paclitaxel and carboplatin either with or without figitumumab. The study was discontinued early when a planned interim analysis met futility limits.

2.6 Clinical Experience with Ganitumab

Ganitumab is a fully human monoclonal antibody directed against IGF-1R. The drug has high affinity for IGF-1R, with a K_D of 0.3 nM (Ganitumab Investigator's Brochure; October 4, 2011). The drug inhibits binding of IGF-1 and IGF-2 to the extracellular domain of IGF-1R. The IC_{50} for blocking IGF-1R phosphorylation in the presence of IGF-1 or IGF-2 is 0.6 nM.

A phase 1 study included 53 patients with advanced solid cancers treated twice weekly.[34] A maximum tolerated dose was not reached and 20 mg/kg IV every 2 weeks was deemed tolerable, though biochemical blockade was achieved at levels of 12 mg/kg IV every 2 weeks. Four of 23 patients treated at the 20 mg/kg dose level developed Grade 3 thrombocytopenia. The only other Grade 3 toxicities noted across dose levels were arthralgia (n=1); diarrhea (n=1); and fatigue (n=1).

Aside from the aforementioned study of single agent ganitumab in Ewing sarcoma (and desmoplastic small round cell tumor or DSRCT), most phase 2 studies of this agent have focused on combination approaches. Preliminary reports have demonstrated the tolerability of ganitumab at doses $\geq$ 12 mg/kg IV every 2 weeks when used in combination with erlotinib, sorafenib, AMG 655, and gemcitabine.[35-37] The combination of ganitumab (12 mg/kg IV every 2 weeks) to gemcitabine improved 6-month overall survival in patients

with advanced pancreatic cancer in a phase 2 trial,[36] though a randomized phase 3 trial testing this combination in advanced pancreatic cancer was stopped early when futility stopping rules were met.

The pharmacokinetic profile of ganitumab appears to differ somewhat between adult patients with various solid tumors and adult patients with Ewing sarcoma and DSRCT treated on a phase 2 trial.[20] Specifically, patients on this phase 2 trial treated with 12 mg/kg every 2 weeks had lower trough concentrations after their first and third doses of ganitumab compared to patients with relapsed solid tumors treated on 2 other studies with this same dose and schedule. The mean ± SD trough concentration after Cycle 1 was 17.5 ± 8.52 µg/mL for EWS/DSRCT vs. 22 ± 11 µg/mL and 26.1 ± 12.5 µg/mL for other solid tumors. The mean ± SD trough concentration after Cycle 3 was 15.9 ± 33.6 µg/mL for EWS/DSRCT vs. 27 ± 15.9 µg/mL and 42.2 ± 18.5 µg/mL for other solid tumors (Ganitumab Investigator's Brochure; October 4, 2011). 22 of 29 patients (75%) with EWS/DSRCT had ganitumab trough concentrations $\geq$ 10 µg/mL after a single dose of 12 mg/kg.[20]

While a pediatric phase 1 clinical trial of ganitumab has not been performed, several points suggest that proceeding with the proposed pediatric and adult study based on the adult experience with this drug is reasonable. First, IGF-1R monoclonal antibodies as a class have been well tolerated in both adults and children. Second, of the compounds in this class in which adult and pediatric phase 1 studies have been performed, the recommended pediatric dose has not been lower than the adult dose. For example, the recommended pediatric phase 2 dose of IMC-A12 is 9 mg/kg weekly,[23] which compares favorably to the adult recommended phase 2 dose of 6 mg/kg weekly.[38] Likewise, for dalotuzumab, the recommended pediatric phase 2 dose (900 mg/m^2 IV every 3 weeks) was similar to the recommended adult phase 2 dose.[39] Third, the dose used in this study is below the maximum dose evaluated and deemed tolerable in the adult single agent phase 1 study. Fourth, the study includes a pharmacokinetics cohort to confirm that pediatric patients achieve adequate serum levels of ganitumab with the planned starting dose of 18 mg/kg (see Section 2.7).

2.7 Rationale for Proposed Ganitumab Starting Dose and Pharmacokinetic Evaluation

The starting dose of ganitumab for this study will be 18 mg/kg. This dose was selected for several reasons. First, biochemical blockade of IGF-1R signaling is observed at serum concentrations $\geq$ 10 µg/mL.[40] Blockade of IGF-1R epitope binding on neutrophils also begins to saturate at serum concentrations of 10 µg/mL (Ganitumab Investigator's Brochure; October 4, 2011). Trough serum concentrations in excess of this target trough concentration value of 10 µg/mL are anticipated using 18 mg/kg, extrapolating from the experience from the phase 2 trial of young adults with relapsed Ewing sarcoma treated with 12 mg/kg (see above). These trough serum concentrations compare favorably with the IC_{50} of ganitumab in 2 Ewing sarcoma cell lines of 1.6 and 3.7 nanomolar (0.54 µg/mL and 0.23 µg/mL).[19] In *in vivo* studies of ganitumab against mouse Ewing sarcoma xenografts, activity was noted at doses of ganitumab that yield steady state serum concentrations of 4.7 µg/mL.[19] Second, experience with ganitumab and other IGF-1R monoclonal antibodies have demonstrated clinical activity in patients with Ewing sarcoma at doses below maximal evaluated dose levels of 20 mg/kg.[23,41] For example, the phase 2 trial of ganitumab in patients with relapsed Ewing sarcoma used 12 mg/kg IV every 2 weeks.[41] Third, combination studies have evaluated doses of 12-20 mg/kg every 2 weeks.[36] Fourth, given the risk of thrombocytopenia that has been observed with IGF-1R monoclonal

antibodies,[21,23,34] use of maximal studied doses of ganitumab (20 mg/kg) may not be feasible in combination with interval compressed chemotherapy used for patients with Ewing sarcoma.

Ganitumab has not been formally studied in children. Based on the phase 2 experience with ganitumab in Ewing sarcoma, it appears as though adults with Ewing sarcoma have higher clearance compared to adults with other solid tumors. While the starting dose of ganitumab has been increased to 18 mg/kg to account for this possibility, it is nevertheless possible that younger patients will not meet the goal trough concentration of 10 µg/mL. In order to assess this possibility, the first 10 patients < 21 years of age randomized to receive ganitumab in Regimen B provided trough serum samples for pharmacokinetics of ganitumab in Induction and Maintenance. These data demonstrated trough levels of ganitumab given at 18 mg/kg every 2 or 3 weeks appear to be adequate.

2.8 Rationale for Open-Label Study Design

The study committee considered the possibility of a double-blind placebo-controlled study design. Such a design might have the advantage of reducing bias in the assessment of toxicity associated with protocol therapy. Another potential benefit of a placebo-controlled design might be reduction in early withdrawal of patients randomized to receive chemotherapy alone.

However, it is not clear that these general benefits of a placebo-control apply to this specific clinical context. First, the toxicity assessments of greatest interest (depth and duration of myelosuppression; reduction in left ventricular systolic function) are objective test measures rather than subjective symptom-based toxicities. Likewise, the ascertainment of the primary study endpoint (disease progression) is typically clear in this patient population and therefore less likely to be influenced by bias compared to more subjective endpoints. Second, patients who are randomized to receive chemotherapy alone will receive a chemotherapy regimen that has become standard in the community outside of a clinical trial. Importantly, the effect of interval compression on outcomes in metastatic Ewing sarcoma has not been studied. It is therefore possible that patients randomized to receive chemotherapy alone will have superior outcomes compared to patients treated with previous regimens solely as a result of interval compression. Moreover, the study committee is not aware of a competing trial for patients with newly diagnosed metastatic Ewing sarcoma who have already started chemotherapy and have not had disease progression. Third, the investigator blind associated with a placebo control would be threatened by anticipated hyperglycemia following ganitumab. For all of these reasons, the added cost and complexity associated with adding a placebo control does not appear justified and this study will utilize an open label design.

2.9 Rationale for Maintenance Phase with Ganitumab

Several pieces of data suggest that use of single-agent ganitumab as Maintenance therapy may be beneficial in patients with advanced Ewing sarcoma. First, preclinical data indicate that IGF-1R inhibition reduces formation of bone metastases in an experimental metastasis xenograft model of Ewing sarcoma.[12] These findings have implications for using ganitumab to slow the progression of minimal residual disease. Second, as described above, ganitumab has single-agent preclinical and clinical activity in Ewing sarcoma.[19,41] Third, the strategy of using biological therapy to eradicate minimal residual disease has been used successfully in the treatment of patients with high-risk neuroblastoma.[42,43] This strategy

has not previously been used in the treatment of metastatic Ewing sarcoma and the current trial provides an opportunity to evaluate this approach in this high-risk population. Based on pharmacokinetic modeling in adults with solid tumors, use of ganitumab at a dose of 18 mg/kg given every 3 weeks is anticipated to yield adequate trough serum concentrations (Ganitumab Investigator Brochure; October 4, 2011) and this protocol includes an assessment of trough concentrations with this dosing schedule.

2.10 Rationale for FDG-PET Imaging of Bone Metastases

Previous COG trials for patients with metastatic Ewing sarcoma have relied upon technetium-based radionuclide whole body bone scans to detect and evaluate bone metastases. Since the inception of those previous trials, multiple studies have been published that detail the superior performance of FDG-PET scans for the diagnosis and evaluation of bone metastases in patients with Ewing sarcoma.[44-49] For example, one report noted sensitivity and specificity for identifying bone metastases in Ewing sarcoma as 100% and 96% for FDG-PET vs. 68% and 87% for bone scan.[45] Results were more striking in another analysis of 17 patients with Ewing sarcoma and paired bone scans and FDG-PET scans.[48] The sensitivity for detecting bone metastases was 88% for FDG-PET and only 37% for bone scan.

Therefore, the current trial will utilize FDG-PET imaging to detect bone metastasis. A collateral benefit of this change is that FDG-PET allows detection of soft tissue sites of metastasis[48], provides information about response at the primary tumor (see below), and may serve as a biomarker of response to IGF-1R inhibition (see below).

2.11 Rationale for Imaging Aims

FDG-PET in addition to MRI to evaluate primary tumor response

Conventional response assessment of primary Ewing sarcoma tumors involves anatomic imaging, most commonly with MRI. For those patients undergoing surgical local control, histologic response to neoadjuvant chemotherapy can also be assessed. Recent reports have raised concern that response by MRI may not correlate with histologic response to neoadjuvant chemotherapy in patients with Ewing sarcoma. For example, one report noted similar changes in tumor volume by MRI between patients with good histologic response and patients without a good histologic response.[50] Another study reached the same conclusion using tumor cross-sectional area by MRI.[51]

FDG-PET imaging has been shown to be a useful tool for monitoring the response to neoadjuvant chemotherapy in patients with newly diagnosed Ewing sarcoma. Several reports have noted that response by FDG-PET correlates with histologic response at the time of definitive surgical resection of the primary Ewing sarcoma tumor.[44,50-53] Moreover, at least one report observed that favorable response by FDG-PET after neoadjuvant chemotherapy correlated with improved progression-free survival.[53]

However, it is important to note that the majority of patients in these previous studies had localized Ewing sarcoma. The ability of FDG-PET to aid in primary tumor response assessment in patients with metastatic disease has been less well studied and differences in FDG-PET imaging may exist between these 2 populations. Indeed, one group has reported that baseline primary tumor standardized uptake values (SUVs) are higher in patients with metastatic Ewing sarcoma compared to localized Ewing sarcoma.[54]

Since patients will undergo serial whole body FDG-PET imaging to evaluate their metastatic disease, this study provides an opportunity to evaluate the utility of FDG-PET imaging in assessing primary tumor response in metastatic Ewing sarcoma. Non-invasive measures of tumor response are particularly important in this patient population given lower rates of surgical local control.

FDG-PET as a potential biomarker of response to IGF-1R inhibition
Agents that inhibit the IGF-1R pathway may result in hyperglycemia due to impairments in cellular uptake of glucose. Not surprisingly, then, FDG-PET imaging has been explored as a potential biomarker of response to IGF-1R inhibition. In preclinical studies of a small molecule IGF-1R/insulin receptor inhibitor, drug exposure impeded FDG uptake in cells expressing IGF-1R, but not in cells that lack IGF-1R expression.[55] This effect also correlated with direct measures of IGF-1R pathway inhibition, including lower phospho-AKT levels. A similar effect on FDG uptake was observed in a preclinical study following treatment with an antibody directed against IGF-1 and IGF-2 ligand.[56] Finally, in a phase 1 trial of IMC-A12 plus temsirolimus for adults with advanced solid tumors, change in SUV showed a suggestive correlation with clinical benefit from that drug combination.[57]

2.12 Rationale for Evaluation of Hypofractionated Stereotactic Body Radiotherapy (SBRT) for Bone Metastases

Conventional external beam radiotherapy (EBRT) for Ewing sarcoma requires 31 daily treatments totaling 55.8 Gy. Bone metastases are currently recommended to receive the same dose and fractionation using EBRT, with some evidence of efficacy of this approach.[58,59] Because of the volume of bone marrow in the radiation field and concerns about ability to complete chemotherapy, treatment of the metastatic sites is often delayed until after treatment of the primary site and often at the end of therapy. Local control after radiotherapy to metastatic sites is largely unknown, as many patients with multiple or extensive sites of disease are often treated with palliative doses of radiation which are not expected to provide long-term durable tumor control.

Hypofractionated stereotactic radiation therapy has been shown to be a highly effective treatment for brain metastases in both the adult and pediatrics population.[60,61] Intracranial stereotactic radiation treatments are often complete in 1 to 5 fractions with similar or improved local control outcomes as conventional fractionation and the benefit of minimal interruption to systemic therapy treatments and smaller irradiated volumes. Until recently, treatment of extracranial sites with radiosurgery has not been possible due to inadequate immobilization and image-guidance to safely administer large doses of highly-targeted radiotherapy.[62] Recent technologic advances including full-body immobilization devices, robotic treatment tables, and stereotactic image-guidance are now available and have been used to treat extracranial metastases with stereotactic radiotherapy in adults.[63] Doses range from 18-30 Gy in a single fraction to 24-60 Gy in 5 fractions. Local control rates in excess of 75-90% have been reported using extracranial SBRT for metastatic tumors of the spine[64], lung and liver, which is significantly higher than conventional moderate dose radiation in these locations.[65] Toxicity has been minimal in these reports despite the use of very high biological equivalent doses and now over 10 years of experience with this technology.[66,67]

SBRT has a particularly strong rationale for application in pediatrics given that high biologically effective doses have been shown to increase local control in more radioresistant histologies, such as sarcomas.[68,69] With stereotactic radiation therapy techniques, both patient immobilization and rapid dose fall-off result in a reduction in

normal tissue dose surrounding the target lesion of interest and may result in lower toxicity.[65] Reduction in irradiated volumes may also facilitate earlier administration of local control. In addition, the convenience of a 5-fraction treatment course is expected to improve compliance with the recommendation for definitive radiotherapy at known sites of disease. We hypothesize that aggressive treatment of bone metastases with SBRT will be possible within the context of a COG groupwide study and may improve outcomes by preventing progression at known sites of disease compared with standard EBRT.

2.13 Rationale for Dexrazoxane Cardioprotection

IGF-1 appears to protect cardiac myocytes from doxorubicin-induced apoptosis.[70,71] At least part of this effect involves signaling through the PI3-kinase/AKT pathway.[72] IGFBP-3, which sequesters IGF-1, promotes doxorubicin-induced apoptosis in cardiac myocytes.[73] Therefore, a theoretical risk of increased cardiac toxicity exists with the combination of an IGF-1R monoclonal antibody and doxorubicin-based chemotherapy.

Dexrazoxane is a cardioprotectant that is recommended for use in adult patients receiving > 300 mg/m^2 cumulative doxorubicin doses.[74] Several studies in children and adults with sarcoma have demonstrated a role for dexrazoxane in reducing the risk of anthracycline-induced cardiomyopathy.[75-79] In COG protocol AEWS1031 for patients with newly diagnosed localized Ewing, dexrazoxane is used as a cardioprotectant during the last 2 courses of doxorubicin-based therapy. In COG trials of agents that may increase the risk of doxorubicin-induced cardiomyopathy (AOST0121 with trastuzumab for osteosarcoma; ARST08P1 with IMC-A12 for rhabdomyosarcoma), dexrazoxane has been utilized from the start of doxorubicin-based chemotherapy. The addition of dexrazoxane in these studies has not appeared to impact the ability to deliver intensive multi-agent chemotherapy, including a similar chemotherapy regimen in ARST08P1 to the regimen used in the current protocol.

Patients in both arms of the trial will receive dexrazoxane cardioprotection prior to each dose of doxorubicin. This therapy will be administered to patients randomized to chemotherapy alone in order to standardize the therapy received by both treatment groups and also due to the anticipated high rates of whole lung radiation to be employed in the treatment of this patient population.

2.14 Rationale for Correlative Biology Studies

2.14.1 Serum Markers of IGF-1 Pathway as Predictors of Response to IGF-1R Inhibition

Given the heterogeneous response to IGF-1R monoclonal antibodies in patients with relapsed Ewing sarcoma, identifying predictive biomarkers of response is critical in the development of these agents for patients with Ewing sarcoma. Peripheral blood markers of the IGF-1 pathway are among the most promising putative response biomarkers in adults with carcinoma treated with IGF-1R monoclonal antibodies. For example, preliminary data suggest that patients with non-small cell lung cancer and elevated serum free IGF-1 levels have reduced toxicity and increased survival when treated with figitumumab.[80] Similarly, patients with advanced pancreatic cancer and elevated total IGF-1 blood levels appeared to have improved outcomes when treated with ganitumab.[81]

Recent data have emerged that also support an association between IGF-1 levels and outcome after anti-IGF-1R therapy in patients with relapsed Ewing sarcoma.

These studies demonstrated that elevated baseline and Week 6 total serum IGF-1 as well as higher relative increase in serum IGF-1 correlated with outcomes in patients with relapsed Ewing sarcoma treated with R1507.[21] Total and free serum IGF-1 levels also correlated with outcomes in patients with relapsed Ewing sarcoma treated with figitumumab.[25] Increases in growth hormone, insulin, and IGFBP3 have also been reported in patients with Ewing sarcoma treated with IGF-1R monoclonal antibodies, though the impact of these changes on outcomes have not yet been reported.[23,25] In preclinical studies, upregulation of IGF-2 expression has been described as a mechanism of resistance to IGF-1R inhibition in Ewing sarcoma, though not yet evaluated as a potential biomarker of resistance in clinical studies.[82]

These results were obtained from uncontrolled trials in patients with relapsed Ewing sarcoma. These results may therefore indicate a role for IGF-1 levels as a prognostic factor rather than a predictive biomarker of response to anti-IGF-1R therapy. Moreover, the extent to which these findings will apply to patients with newly diagnosed Ewing sarcoma remains to be established.

2.14.2 Tumor IGF-1R Expression as Predictor of Response to IGF-1R Inhibition

Preclinical data from the PPTP suggest that Ewing sarcoma xenograft tumors with higher IGF-1R expression may be more likely to respond to an IGF-1R monoclonal antibody.[18] A cohort of 16 patients with Ewing sarcoma treated with an IGF-1R monoclonal antibody had tumor IGF-1R levels measured.[23] There was no association between tumor IGF-1R expression and response to IGF-1R inhibition in this small cohort. In contrast, in a cohort of 37 patients with non-small cell lung cancer, higher tumor IGF-1R expression correlated with higher response rate to therapy that included an IGF-1R monoclonal antibody.[83] The association between markers of tumor IGF-1R activation and clinical response to IGF-1R inhibitors has not been evaluated. Therapeutic IGF-1R monoclonal antibodies both inhibit IGF-1R function and reduce levels of IGF-1R protein present at the cell surface.[84] As such, clearance of cell surface IGF-1R would be anticipated to serve as a pharmacodynamic marker of IGF-1R effect, but also potentially as a predictive biomarker of response to IGF-1R monoclonal antibody treatment.

A flow cytometry approach for detecting occult Ewing sarcoma cells amidst a background of hematopoietic cells has been developed and depends upon the CD99-postive / CD45-negative (CD99+CD45-) immunophenotype of these cells.[85] Among 42 patients with newly diagnosed Ewing sarcoma and no clinical evidence of bone marrow metastases, 45% of patients had CD99+CD45- bone marrow cell levels greater than observed in controls. In the current study, flow cytometric evaluation of occult bone marrow tumor cells will be evaluated as a possible early marker of minimal residual disease in patients with metastatic Ewing sarcoma. Moreover, bone marrow micrometastatic cell IGF-1R co-expression will be evaluated as a potential biomarker of response to ganitumab therapy. This assay provides an ideal platform for evaluating tumor IGF-1R expression, activation, and clearance as markers of response to ganitumab.

The current study will utilize this flow cytometry assay as well as evaluation of paraffin-embedded diagnostic tumor material to quantify IGF-1R expression at diagnosis and following initiation of protocol therapy.

2.14.3 EGFR Expression and Germline *EGFR* Promoter Polymorphism as Predictors of Response to IGF-1R Inhibition

Increased EGFR pathway signaling may represent one mechanism of resistance to the anticancer effects of IGF-1R inhibitors.[86] In head and neck cancer, IGF-induced signaling is enhanced by EGFR activation and/or EGFR/IGF-1R scaffolding.[87] Reciprocal activation of EGFR and IGF-1R has been reported after inhibition of either receptor.[88] Inducible signaling through EGFR in response to IGF-1R inhibition has been observed in hepatocellular carcinoma.[89] In cell lines resistant to a small molecule inhibitor of IGF-1R (BMS-536924), EGFR is constitutively over-expressed. Additive activity was observed for BMS-536924 used in combination with gefitinib, a small molecule inhibitor of EGFR, in the Rh26 rhabdomyosarcoma cell line.[90]

Preclinical studies have demonstrated that the presence of a germline polymorphism (G/G) at site -216 in the *EGFR* promoter has been associated with Induction of *EGFR* gene expression in response to IGF-1R inhibition (E. Anders Kolb, personal communication). The presence of the G/G genotype at this locus correlated with resistance to IGF-1R inhibition in a panel of Ewing sarcoma xenografts. Whether this promoter polymorphism correlates with *EGFR* expression and response to IGF-1R inhibition has not been studied in patients treated with IGF-1R monoclonal antibodies. This protocol includes a correlative study to test the hypothesis that the presence of this polymorphism is associated with resistance to IGF-1R directed therapy.

2.14.4 Evaluation of *EWSR1* and Other Translocations

As detailed above, Ewing sarcoma appears to be particularly sensitive to IGF-1R inhibition and there is a link between the *EWSR1* translocation and increased IGF-1R signaling. Recently, Ewing-like sarcomas have been described that are characterized by translocations involving genes other than *EWSR1*.[91,92] It is not known to what extent these other sarcomas will be sensitive to IGF-1R inhibition. It is also not known what proportion of patients enrolling to clinical trials for Ewing sarcoma harbor alternative translocations.

Two aims will help to address these gaps in our knowledge. First, data on clinical testing performed to assess for the presence of an *EWSR1* translocation will be collected in patients enrolling to this study. Second, new technology has emerged that enables detection of tumor-specific genetic aberrations in cell free DNA collected from the plasma. This technology enables detection of a range of potential translocations of interest, as well as other potential mutations of interest in this disease (eg. *STAG2* and *TP53*).[93-95] This testing will be explored on a research basis to assess for *EWSR1* translocations, other translocations, and other potential tumor-specific genetic changes of interest at the time of study enrollment and in response to therapy.

Expansion of plasma cell free DNA assessment with Amendment #3C: Preliminary data from other groups suggest that circulating tumor DNA may clear rapidly after treatment.[96,97] In order to more fully characterize the dynamics of ctDNA clearance in this population, additional timepoints have been added with Amendment #3C. In addition, emerging data suggest that EDTA may not be the

optimal collection tube for evaluation of plasma cell free DNA in the context of a multicenter clinical trial. With Amendment #3C, blood for this aspect of the study will be collected in specialized Streck tubes.[98]

2.14.5 Genomic Testing of Tumor Cells

The flow cytometry approach described above (Section 2.14.2) provides the potential to isolate bone marrow metastatic tumor cells for potential future testing. As proof of principle, fluorescent activated cell sorting using the CD99+CD45- immunophenotype has been used to isolate and then test bone marrow metastatic tumor cells for the presence of the characteristic *EWSR1* translocation by fluorescent in situ hybridization (FISH). On both samples tested, the presence of this translocation was detected in ≥ 88% of the isolated cells. It is not known to what extent the genomic profile of metastatic Ewing sarcoma mirrors that of localized Ewing sarcoma. The current protocol provides an ideal opportunity to assess the genomic profile of metastatic Ewing sarcoma by using bone marrow metastatic tumor cells as the source of DNA for detailed genomic analysis.

With Amendment #3C, tumor DNA and RNA sequencing via next generation sequencing methods is being added as an optional study to expand the number of somatic markers evaluated as part of Aim 1.3.6. Sequencing data will provide an opportunity to explore potential relationships between key somatic mutations described in a subset of Ewing sarcoma tumors (e.g., *STAG2* and *TP53*) and clinical outcome.[93-95] Moreover, the RNA sequencing data will provide an opportunity to explore potential relationships between expression of key genes of interest (e.g., genes encoding IGF-1R, IGFBP3, PTEN, insulin receptors) and clinical outcome as well as potential relationships between gene expression profiles and clinical outcome. Finally, the RNA sequencing data will allow orthogonal ascertainment of translocation status, with determination of both gene partners involved in the translocation.

2.15 Rationale for Amendment #2

AEWS1221 was originally designed as a phase 2 randomized screening trial. This design was chosen over a definitive phase 3 trial due to concerns about the potential to complete a definitive phase 3 trial in a timely manner. Specifically, 3.5 patients/month were expected to be available. In the context of a screening trial requiring 126 patients, 3 years of accrual were expected. Moreover, at the time the study was designed, it was not clear that sufficient ganitumab would be available to support a larger trial.

AEWS1221 activated to enrollment in December 2014 and there have been no suspensions to enrollment. As of May 6, 2016, 96 patients have enrolled over 17 months for an average monthly accrual rate of 5.6 patients/month. Since the study was activated, an additional supply of ganitumab has become available.

Given the strong interest in this trial and its underlying rationale along with increased drug supply, the study committee has amended the trial to determine definitively the role of IGF-1R inhibition in this patient population. The study committee is not aware of competing trials in development that would impact interest in this trial.

2.16 Rationale for Amendment #6

The COG DSMC reviewed outcomes to date as of March 2019. The DSMC recommended closure to accrual and discontinuation of ganitumab for all patients on Regimen B on active therapy. These recommendations were based upon lack of significant benefit of the addition of ganitumab to interval compressed chemotherapy in this population as well as the potential for increased risk of toxicity in patients on Regimen B. Specifically, an imbalance between Regimen A and Regimen B was observed in the number of patients with pneumonitis (1 case on Regimen A and 6 cases on Regimen B).

The changes recommended by DSMC were implemented via an urgent COG groupwide memo dated March 20, 2019. Amendment #6 now makes these changes to the protocol and adds guidance for the diagnosis and management of pneumonitis.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

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

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)* or 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 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 (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

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

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

3.1.4 Study Enrollment

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

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

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

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

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

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

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on this study prior to study enrollment will be considered ineligible**.

3.1.6 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.1.7 Participation in Biology Studies.

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child. In order to minimize the potential for non-compliance once enrolled, patients/guardians must be made aware that a number of the biology research studies are mandatory and understand that a significant number of non-standard blood samples will be required.

3.1.8 Randomization and Treatment Assignment

Randomization will take place at the time a patient is enrolled via OPEN. Patients will be assigned to either the comparator arm (Regimen A) with the interval compressed VDC/IE, or the experimental arm (Regimen B) with VDC/IE and ganitumab.

Randomization will be stratified according to age at date of enrollment (< 21 years vs. ≥ 21 years) and extent of metastatic disease (lung only vs. any other metastatic site).

The first 10 patients < 21 years of age at study entry assigned to Regimen B will submit required ganitumab trough serum samples in Induction and Maintenance (see Section 15.5). Note: enrollment to this cohort completed as of July 2015.

3.2 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory

evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging, bone marrow and ECHO/MUGA must be performed within 4 weeks prior to start of protocol therapy (repeat if necessary).

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

INCLUSION CRITERIA

3.2.1 Age

Patients ≤ 50 years of age at enrollment will be eligible for this study.

Note:

- Infants and small children are eligible for this study, however, the treating physicians and family must be prepared to deliver adequate local control as required in this study (see Section 13.0 and 17.0).

3.2.2 Diagnosis

Patients with histologic diagnosis (by institutional pathologist) of newly diagnosed Ewing sarcoma or peripheral primitive neuroectodermal tumor (PNET) arising from bone or soft tissue and with metastatic disease involving lung, bone, bone marrow, or other metastatic site.

For the purpose of this study, metastatic disease is defined as one or more of the following:

- Lesions which are discontinuous from the primary tumor, are not regional lymph nodes, and do not share a bone or body cavity with the primary tumor. Skip lesions in the same bone as the primary tumor do not constitute metastatic disease. Skip lesions in an adjacent bone are considered bone metastases. If there is any doubt whether lesions are metastatic, a biopsy of those lesions should be performed.
- Contralateral pleural effusion and/or contralateral pleural nodules.
- Distant lymph node involvement.
- Patients with pulmonary nodules are considered to have metastatic disease if the patient has:
    - Solitary nodule ≥ 0.5 cm or multiple nodules of ≥ 0.3 cm unless lesion is biopsied and negative for tumor;
    - Patients with solitary nodule < 0.5 cm or multiple nodules < 0.3 cm are not considered to have lung metastasis unless biopsy documents tumor.
- Bone marrow metastatic disease is based on morphologic evidence of Ewing sarcoma based on H&E stains. In the absence of morphologic evidence of marrow involvement on H&E, patients with bone marrow involvement detected ONLY by flow cytometry, RT-PCR, FISH, or immunohistochemistry will NOT be considered to have clinical bone marrow involvement for the purposes of this study.

This study requires bilateral bone marrow biopsies at study entry. The suggested approach for patients with large pelvic tumors in which a posterior iliac crest bone marrow biopsy would track through the tumor is to instead undergo 2 marrow biopsies on the contralateral side (either 2 posterior biopsies or one posterior and one anterior biopsy).

- Bone metastasis: This study utilizes whole body FDG-PET scans to screen patients for bone metastases. Areas suspicious for bone metastasis based on FDG-PET scans require confirmatory anatomic imaging with either MRI or CT (whole body FDG-PET/CT or FDG-PET/MR scan acceptable). Whole body technetium bone scans may be performed at the discretion of the investigator and are not required. For patients without other sites of metastatic disease whose sole metastatic site to qualify for study entry is a single area suspicious for bone metastasis identified by FDG-PET, confirmatory biopsy or anatomic imaging evidence of an associated soft tissue mass at that site is required for study entry.

3.2.3 Adequate Tumor Tissue for Submission

Patients must have adequate tumor tissue to meet the minimum requirement for submission (see Section 15.2).

Enrolling institutions are reminded that submission of pre-treatment serum, tumor tissue and whole blood according to Sections 15.1, 15.2, and 15.3 is required.

3.2.4 Prior Therapy: Surgery

Patients should only have had a biopsy of the primary tumor without an attempt at complete or partial resection. Patients will still be eligible if excision was attempted or accomplished as long as adequate anatomic imaging (MRI for most primary tumor sites) was obtained prior to surgery.

3.2.5 Organ Function Requirements

3.2.5.1 Adequate Renal Function Defined As:

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

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
< 6 months	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[99] (Schwartz et al. J. Peds, 106:522, 1985) 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) < 3 x upper limit of normal (ULN) for age (except for patients with liver metastasis who may enroll if ALT < 5 times ULN for age).

3.2.5.3 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% or
- Ejection fraction of ≥ 50%

3.2.5.4 Normal blood glucose for age
Patients must have a normal blood sugar level for age to participate. If an initial random draw (ie. non-fasting) blood glucose value is out of range, it is acceptable to repeat this test as a fasting draw.

3.2.6 Exclusion Criteria

3.2.6.1 Patients with regional node involvement as their only site of disease beyond the primary tumor will not be eligible.

3.2.6.2 Patients whose primary tumors arise in the intra-dural soft tissue (eg. brain and spinal cord) are not eligible.

3.2.6.3 Patients who have received prior chemotherapy or radiation therapy are not eligible.

3.2.6.4 Pregnancy and Breast Feeding
Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained. Lactating females are not eligible unless they have agreed not to breastfeed their infants for the duration of protocol therapy. Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of protocol therapy.

3.2.6.5 Patients with known pre-existing diabetes mellitus will be excluded from study.

3.2.6.6 Concomitant Medications Restrictions
(Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.)

Patients receiving chronic pharmacologic doses of corticosteroids are not eligible. For the purposes of eligibility, chronic exposure is defined as anticipated exposure of > 3 weeks, including the sum of both pre-enrollment and anticipated post-enrollment dosing. Patients on acute corticosteroid therapy (≤ 3 weeks of total planned exposure) must still meet the normal blood glucose requirement in Section 3.2.5.4. Patients receiving chronic inhaled corticosteroids or chronic physiologic replacement doses of corticosteroids are 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 PROGRAM

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

4.1 Overview of Treatment Plan

4.1.1 Overview

NOTE: As of March 20, 2019, the study closed to accrual and institutions were instructed to immediately discontinue ganitumab for patients on Regimen B.

At study entry, patients will be randomized to Regimen A (VDC/IE) or Regimen B (VDC/IE + ganitumab).

Treatment will consist of 4 phases of therapy: Induction; Local Control; Consolidation; and Metastatic Site Irradiation. (Originally a 5th phase of therapy, Maintenance was administered to patients on Regimen B only. However, Maintenance therapy was discontinued effective March 20, 2019.) The chemotherapy backbone for this study is based on the interval compressed arm of AEWS0031. All patients will first receive a total of 14 cycles of chemotherapy; each cycle will be of 2 weeks duration. Induction consists of 6 cycles (12 weeks) of chemotherapy. Induction will be delivered prior to local control therapy, which may involve surgery and/or radiation therapy. Consolidation therapy will consist of 8 cycles (16 weeks) of chemotherapy.

Patients randomized to Regimen A will receive Induction, Local Control, Consolidation, and Metastatic Site Irradiation. These patients will then enter follow-up after completion of Metastatic Site Irradiation.

Prior to March 20, 2019, patients randomized to Regimen B received this same therapy with the addition of ganitumab 18 mg/kg/dose IV every 2 weeks for a total of 6 doses during Induction and for a total of 5 doses during Consolidation. In order to avoid jeopardizing local control measures, ganitumab was not to be given immediately prior to, during, or immediately after local control. After completion of Metastatic Site Irradiation, patients in Regimen B received an additional 8 doses of ganitumab 18 mg/kg given every 3 weeks as monotherapy during Maintenance. These patients then entered follow-up after completion of Maintenance.

Post March 20, 2019: patients on Regimen B discontinued ganitumab and instead receive the same therapy as patients on Regimen A.

Given theoretical concerns of possible additive cardiac toxicity of IGF-1R inhibition with doxorubicin, dexrazoxane will be given with each dose of doxorubicin in both regimens. Evaluation of cardiac function will be obtained at baseline, after cumulative doxorubicin dose of 150 mg/m^2, and then prior to each doxorubicin cycle. See also Section 7.0 for required time points.

The first 10 patients < 21 years of age at study entry assigned to Regimen B will submit required ganitumab trough serum samples in Induction and Maintenance (see Section 15.5). Registering sites will be notified of the need to obtain these samples at the time of randomization. (Enrollment to this cohort completed as of July 2015; for patients previously assigned to this cohort, continue to collect samples as detailed in Section 15.5.)

Treatment Schema

	Drugs	Dose
V	VinCRIStine	2 mg/m^2/day IV x 1 day **(max dose 2 mg)**
D	Doxorubicin	37.5 mg/m^2/day x 2 days IV (**with dexrazoxane for all doses**)
C	Cyclophosphamide	1200 mg/m^2/day IV x 1 day
I	Ifosfamide	1800 mg/m^2/day IV x 5 days
E	Etoposide	100 mg/m^2/day IV x 5 days
G	Ganitumab	18 mg/kg IV x 1 day **(Only in Regimen B)***

* As of March 20, 2019, institutions were instructed to immediately discontinue ganitumab for patients on Regimen B.

Regimen A

Induction

Cycle	1		2		3		4		5		6	
Week	1	2	3	4	5	6	7	8	9	10	11	12
	VDC		IE		VDC		IE		VDC		IE	

Post-Induction Local Control: See Sections 4.3, 13.0 and 17.0.

Consolidation

Cycle	1		2		3		4		5		6		7		8	
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	VDC		IE		IE		VDC		VC		IE		VC		IE	

Post-Consolidation Metastatic Site Radiation
See Sections 4.1.1.2 and 17.0. No systemic therapy is given during this phase of therapy.

Maintenance: Patients in Regimen A do not receive Maintenance therapy.

Regimen B
NOTE: As of March 20, 2019, the study closed to accrual and institutions were instructed to immediately discontinue ganitumab for patients on Regimen B. This led to the removal of Maintenance therapy.

Induction

Cycle	1		2		3		4		5		6	
Week	1	2	3	4	5	6	7	8	9	10	11	12
	VDC		IE		VDC		IE		VDC		IE	
	G		G		G		G		G		G	

Post-Induction Local Control: See Sections 4.3, 13.0 and 17.0.

Consolidation

Cycle	1		2		3		4		5		6		7		8	
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	VDC		IE		IE		VDC		VC		IE		VC		IE	
							G		G		G		G		G	

Post-Consolidation Metastatic Site Radiation
See Sections 4.1.1.2 and 17.0. No systemic therapy is given during this phase of therapy.

4.1.1.1 Local Control

Local control will take place once patients have recovered from Induction chemotherapy. If surgery is the primary local control, it should be scheduled at the time of recovery from the sixth cycle of Induction chemotherapy- usually at chronological Week 13. When surgery is performed, the next cycle of chemotherapy should be given as soon as possible post-operatively. The passing of more than 6 weeks between

chemotherapy cycles for reasons other than surgical complications and/or severe chemotherapy toxicity should be avoided.

Note: If logistical issues (such as surgeon availability) prevent surgery from taking place after completion of the sixth cycle of Induction, then the first cycle of Consolidation chemotherapy should be administered while awaiting surgery

For patients who will have radiation alone, Consolidation chemotherapy should be initiated concurrently with the radiation therapy, upon recovery from Induction chemotherapy. Administration of ifosfamide-etoposide chemotherapy concurrently with radiation is allowed and the schedule of chemotherapy in Consolidation is designed to accommodate primary site radiotherapy during the first part of Consolidation. If radiation to the primary tumor must occur at a different time for a compelling clinical indication, then the sequence of chemotherapy cycles should be adjusted to account for this change and to avoid concomitant doxorubicin and radiation administration. For example, if radiation is ongoing at the time Cycle 4 of Consolidation is due, Cycles 4 and 5 should be swapped. Likewise, the sequence of chemotherapy cycles may be adjusted at investigator discretion to avoid resuming doxorubicin shortly after a course of radiation completes.

Radiation may begin concurrently or immediately after Cycle 1 of Consolidation (VDC). Otherwise, doxorubicin should not be given during radiation treatment.

If radiation therapy is to follow surgery, radiation therapy should be scheduled to start as soon as recovery from surgery permits.

4.1.1.2 Metastatic Site Radiation

Patients with lung metastases at diagnosis will receive whole lung irradiation in 1.5 Gy daily fractions after the completion of Consolidation chemotherapy. Bone metastatic sites will also be radiated during this time. The recommended form of radiotherapy will be SBRT (40 Gy in 5 fractions over 5 days) rather than standard EBRT.

Metastatic site radiation will begin once patients have recovered from the last cycle of Consolidation chemotherapy, but no earlier than 3 weeks from the start of Week 15 of Consolidation.

In rare scenarios, whole lung radiation might occur early due to overlapping fields. If whole lung radiation will occur at the time of primary site radiation due to overlapping fields, then the timing of local control and sequence of Consolidation cycles should be modified to avoid receipt of doxorubicin after whole lung radiation. Consolidation Cycle 4 should be moved to Week 1 Consolidation and radiation delayed by two weeks. When radiation begins, a VDC cycle can be given at the start of radiation followed by two IE cycles (original Consolidation Cycles 1, 2, and 3).

Post-radiation, patients can resume chemotherapy with Cycle 5 Consolidation.

4.1.1.3 Evaluations

Patients will undergo full disease evaluation with MRI or CT of primary tumor site, chest CT, FDG-PET scan, and bilateral bone marrow aspirates and biopsies at study entry. If whole body PET/CT is obtained with thin cuts through chest, this scan may also substitute for required chest CT scan (see Section 10.3.2.1). The suggested approach for patients with large pelvic tumors in which a posterior iliac crest bone marrow biopsy would track through the tumor is to instead undergo 2 marrow biopsies on the contralateral side (either 2 posterior biopsies or one posterior and one anterior biopsy). Tumors with associated soft-tissue mass are recommended to undergo evaluation with MRI as MRI is superior at delineating soft-tissue extent. Chest CT to evaluate for lung metastasis should NOT be omitted for patients who undergo thoracic MRI as part of evaluation of the primary tumor. Patients with primary bone tumors are also recommended to undergo plain film of the primary tumor site at study entry as part of good clinical care. Sites suspicious for bone or soft tissue metastasis identified by FDG-PET scan at study entry should be imaged further with MRI or CT (whole body CT obtained as part of PET/CT scan is acceptable). For patients without other sites of metastatic disease whose sole metastatic site to qualify for study entry is a single area suspicious for bone metastasis identified by FDG-PET, confirmatory biopsy or anatomic imaging evidence of an associated soft tissue mass at that site is required for study entry.

All patients will undergo MRI or CT of primary tumor site (ideally with the same modality used at study entry), chest CT, and FDG-PET (or PET/CT) scan at the end of Induction prior to local control. Tumors with associated soft-tissue mass, including chest wall tumors are recommended to undergo evaluation with MRI as MRI is superior at delineating soft-tissue extent. Previous sites of bone or soft tissue metastasis and any new sites of concern for bone or soft tissue metastasis based on FDG-PET should be imaged further with MRI or CT (whole body CT obtained as part of PET/CT scan is acceptable).

All patients will undergo MRI or CT of primary tumor site, chest CT, and FDG-PET (or PET/CT) scan before Week 9 of Consolidation and at the end of Consolidation chemotherapy. Tumors with associated soft-tissue mass, including chest wall tumors, are recommended to undergo evaluation with MRI as MRI is superior at delineating soft-tissue extent. Plain film of the primary tumor site may be substituted for MRI or CT for patients who have undergone surgical resection with metallic implants though modern MRI techniques may still allow adequate imaging even in the presence of metallic implants. Previous sites of bone or soft tissue metastasis and any new sites of concern for bone or soft tissue metastasis based on FDG-PET should be imaged further with MRI or CT (whole body CT obtained as part of PET/CT scan is acceptable).

Following completion of Consolidation chemotherapy, patients in both arms of the study are recommended to undergo MRI or CT of primary tumor site, chest CT, and FDG-PET (or PET/CT) every 3 months following the schedule in Section 7.3. This schedule applies to patients in Regimen B who received Maintenance ganitumab. Previous sites of bone or soft tissue metastasis and any new sites of concern for bone or soft tissue metastasis based on FDG-PET should be imaged further with MRI or CT (whole body CT obtained as part of PET/CT scan is acceptable).

Patients with clinical evidence of bone marrow involvement at study entry (per Section 3.2.2) will undergo repeat bilateral bone marrow aspirates and biopsies after 3 cycles of Induction chemotherapy. For patients with clinically evident persistent bone marrow metastatic disease, repeat bilateral bone marrow aspirates and biopsies will be performed prior to local control and then every 4 cycles until clear. See Sections 10.3.4 and 10.4 for definitions of marrow response and note off-protocol therapy criteria for residual bone marrow involvement at end of Consolidation). Once clear and in the absence of clinical concern for relapsed disease, no repeat bone marrow aspirates / biopsies are required until these patients undergo their disease evaluations at the end of Consolidation chemotherapy.

Please see Section 15.4 for submission instructions for the recommended bone marrow correlative biology study.

4.1.2 Dose Adjustment for Obesity

There will be no dose adjustments for obese patients.

4.2 Concomitant Medications

No other cancer chemotherapy or immunomodulating agents will be used.

4.2.1 Cytochrome P450 drug interaction

Clinically significant drug interactions have been reported when using vincristine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors of cytochrome P450 3A4 include specific azole antifungals (such as voriconazole, itraconazole, ketoconazole) and strong inducers include drug such as rifampin, phenytoin, phenobarbitol, carbamazepine, and St. John's wort (see Appendix V for list of agents). These drugs should be avoided with vincristine.

The clinical outcome and significance of CYP450 interactions with cyclophosphamide, doxorubicin, etoposide and ifosfamide are less clear. CYP450 3A4 inducers or inhibitors should be avoided or used with great caution. Multi-day aprepitant regimen also interacts with CYP3A4 and should be used with caution with etoposide, ifosfamide, or vincristine chemotherapy.

4.2.2 Other supportive care

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

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

4.3 General Approach to Local Control of the Primary Tumor

This study requires definitive treatment of the primary tumor with complete surgical excision, a combination of surgical excision and radiation therapy for microscopic residual disease, or full-dose radiation therapy. A multidisciplinary approach to primary tumor treatment involving the oncologist, the radiation oncologist, and the surgeon is indispensable, and planning should begin immediately upon diagnosis.

The guiding principle for local control should be to eradicate the primary tumor and avoid local recurrence with the least amount of functional loss, while minimizing delays in systemic therapy in this metastatic patient population. This will require careful consultation between the oncologist, the orthopedic or surgical oncologist, and the radiation oncologist.

Even for patients anticipated to undergo surgical local control of the primary tumor, early radiation oncology referral is recommended to facilitate planning for metastatic site radiation, including the need for institutional credentialing to administer SBRT to bone metastases (see Section 17.1.2).

4.3.1 Primary Tumor Treatment Modalities

4.3.1.1 Surgery

Surgical excision should be considered for all tumors which respond to Induction chemotherapy. Surgery is the local therapy modality of choice if the lesion can be resected with negative microscopic margins (R0) and a reasonable functional result. If surgical expertise is not available at a given institution, it is strongly suggested that consultation be made with an experienced orthopedic or surgical oncologist at another institution. Patients with unresectable lesions or inadequate margins after surgery will receive radiation therapy.

The aim of surgery is to achieve a wide (R0) surgical excision which leaves a clear margin of normal tissue surrounding the lesion. Patients with complete resections (R0) with a clear margin (defined in next section) will not require radiation therapy. Currently there is no reliable way to assess tumor responsiveness non-invasively. Therefore, in most cases, a wide cuff of normal tissue will surround the tumor consistent with the planned reconstruction. In rare cases, the margin may be closer if an important structure such as a major growth plate, a joint or a structure such as the acetabulum can be preserved. A marginal (R1) excision leaves inflammatory tissue containing residual tumor cells. The pathologic margin is microscopic. The patient requires post operative radiation therapy.

Intralesional or debulking (R2) operations leaves gross residual tumor. This type of surgical procedure is never indicated. Recovery from complicated surgical procedures will delay the resumption of chemotherapy. Since gross residual tumor remains, the patient will require full dose radiation therapy (the same dose as if no surgical procedure was

performed). Radiation will be less effective in the hypoxic post surgical bed and the radiation field size will be larger than if surgery was not attempted.

For details on the surgical approach to the biopsy and excision, see Section 13.0.

4.3.1.2 Margins

At the time of resection, the surgeon should mark all margins and orient the specimen at the operative field, so that margin evaluation is precise. Narrow margins are unavoidable in some areas. In these situations, the surgeon should take a number of separate biopsies of the "normal" tissue around the margins of resection and these should be marked and submitted separately for pathologic review. Communication with the pathologist is mandatory to assure accuracy of margin examination. Consideration should be given to having the pathologist inspect the specimen in the operating theatre to help with orientation. The tumor should not be bisected or cut into separate specimens prior to this discussion.

The aim of surgery is to achieve a wide (R0) surgical excision which leaves a clear margin of normal tissue surrounding the lesion. Patients with complete resections (R0) with a clear margin (defined as no viable tumor at the cut surface) will not require radiation therapy. In most instances this will be normal non-reactive tissue. In some instances when resected tumors have greater than 90% overall necrosis, the tissue at the margin may be bland scar or loose fibrous tissue. This will be considered a clear margin and no postoperative radiation therapy will be required. If specimens with greater than 90% overall necrosis have inflammatory tissue or coagulative tumor necrosis at the margin, (the cytoarchitecture of the tumor cells is preserved) the margin will be considered microscopically positive and require post operative radiation therapy. If the tumor specimen has less than 90% overall necrosis, the cut surface of the resected tumor must be normal non-reactive tissue in order to be considered pathologically negative. If there is ambiguity about the margin status, investigators should strongly consider post-operative radiotherapy.

4.3.1.3 Surgery plus Radiation Therapy

Most patients will have either surgery alone, surgery with radiation therapy for positive microscopic margins, or radiation therapy alone.

When surgery is done first, followed by radiation therapy, surgery should occur as soon as possible after recovery from Induction Cycle 6 chemotherapy and radiation therapy should begin as soon as feasible thereafter.

Pre-operative radiotherapy is **not** indicated. This approach may result in considerable delays in chemotherapy: thus the benefits must be weighed against risk in each patient. The final decision regarding the best treatment is dependent on patient and tumor characteristics and is left to the consultants at the patient's institution.

In patients with **unresectable** tumors treated with definitive radiation, delayed excision is not typically indicated and therefore discouraged.

For details on the surgical approach to the biopsy and excision, see Section 13.0. For details on radiotherapy, see Section 17.0.

4.3.1.4 Radiation Therapy Only

Candidates for radiotherapy alone will include patients with bulky lesions in surgically difficult sites such as the spine, skull and periacetabular pelvis, patients with a poor response to Induction chemotherapy, or those patients in whom surgery would result in unacceptable functional results. Sites which, if removed, would result in significant impairment of function include the skull, facial bones, vertebrae and pelvic bones about the acetabulum. In some cases, resection even in these sites may be feasible in combination with radiation therapy, and decisions regarding a specific patient must be individualized.

Patients who are to be treated with radiotherapy alone should be treated with radiotherapy at the start of Consolidation Week 1 chemotherapy. Proton therapy is allowed as part of this study. For details regarding radiotherapy, see Section 17.0.

4.4 Chemotherapy Administration Schedule

Chemotherapy will be administered on an interval-compressed schedule every 2 weeks, as allowed by recovery from previous cycles. Recommended guidelines for administering interval-compressed chemotherapy include checking a CBC with differential on Day 1 and 8 of each cycle and then every Monday, Wednesday and Friday (or 3 other nonconsecutive days per week) after Day 12, until the criteria for starting the next cycle are satisfied.

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

4.4.1 Administration Schedules for Induction and Consolidation in Regimen A

Patients in Regimen A do not receive ganitumab.

Patients in Regimen A do not receive a Maintenance phase.

4.4.1.1 Administration Schedule: Induction (Weeks 1-12) Regimen A

Criteria to start Induction: No count criteria are required to start Induction Week 1 therapy.

Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen

to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/ µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as the patient meets count recovery criteria, regardless of myeloid growth factor utilized.

See Section 5.1 for exceptions in Weeks 1 and 3 for patients with bone marrow metastatic disease.

If a cycle of chemotherapy is delayed due to toxicity, see Section 5.0 for criteria to resume chemotherapy.

Note: for children less than 1 year of age, chemotherapy should be calculated by weight rather than by surface area. Dose/kg = dose/m^2 divided by 30 kg/m^2. Example: If patient is less than 1 year of age and weight is 15 kg and dose of Etoposide is 100 mg/m^2, then the dose of Etoposide is based on mg/kg = 100 mg/m^2 divided by 30 kg/m^2 = 3.3 mg/kg x15 kg = 49.5 mg.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 of Weeks 1, 5 and 9
Dose: 2 mg/m^2/dose. (Maximum dose is 2 mg.) **For patients < 1 year old, the dose is 0.067 mg/kg/dose.**

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. Fatal if given by other routes. For intravenous use only."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexrazoxane: Slow IV Push (eg, over 5-15 minutes) given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1, 5 and 9
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). **For patients < 1 year old, the dose is 12.5 mg/kg/dose.**
Note: Administer DOXOrubicin after completing the infusion of dexrazoxane and every effort should be made to keep the total combined infusion time for dexrazoxane and doxorubicin to ≤ 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 1, 5 and 9
Dose: 37.5 mg/m^2/dose. **For patients < 1 year old, the dose is 1.25 mg/kg/dose.**

Administer at a concentration not to exceed 2 mg/mL. 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.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 30-60 minutes
Day 1 of Weeks 1, 5 and 9
Dose: 1,200 mg/m^2/dose. **For patients < 1 year old, the dose is 40 mg/kg/dose.**
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

Mesna must be administered in conjunction with cyclophosphamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Ifosfamide: IV, infuse the diluted solution over 1 hour
Days: 1-5 of Weeks 3, 7 and 11
Dose: 1,800 mg/m^2/dose. **For patients < 1 year old, the dose is 60 mg/kg/dose.**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for cyclophosphamide/ifosfamide: Administer 3,000 mL/m^2/day (125 mL/m^2/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of cyclophosphamide/ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Cyclophosphamide
Administer MESNA by IV infusion or IV/PO on Day 1 of Weeks 1, 5 and 9.
Total IV Dose: 720 mg/m^2/day. **For patients < 1 year old, the IV dose is 24 mg/kg/day.**

Mesna with Ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-5 of Weeks 3, 7 and 11.
Total IV Dose: 1,080 mg/m^2/day. **For patients < 1 year old, the IV dose is 36 mg/kg/day.**

Mesna IV short or continuous infusion:

For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily ifosfamide/cyclophosphamide dose. Mesna can be administered in 3 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 the ifosfamide/cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of ifosfamide/cyclophosphamide).

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or at the start of the cyclophosphamide/ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8.

This total daily dose of mesna can also be administered as IV **continuous infusion (CI)**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide/cyclophosphamide and finished no sooner than 8 hours after the end of the ifosfamide/cyclophosphamide infusion.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide and be completed no sooner than 8 hours after **the end** of the ifosfamide/cyclophosphamide infusion. If ifosfamide/cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide/ifosfamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the ifosfamide/cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide/ifosfamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parental solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within

2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Etoposide: IV, infuse the diluted solution over at least 1-2 hours
Days: 1-5 of Weeks 3, 7 and 11
Dose: 100 mg/m^2/dose. **For patients < 1 year old, the dose is 3.3 mg/kg/dose.**
Infuse diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested for prolonged infusion due to risk of precipitation.

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.

Growth Factor Support [100-106]
Begin myeloid growth factor support (filgrastim or pegfilgrastim or biosimilar products according to institutional standards for patients receiving interval compressed chemotherapy) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC ≥ 750/μL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.
Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Induction in Regimen A are provided in the following 3 pages. Local Control will follow Induction (see Section 4.3 for details). See Section 7.1.1 for observations prior to Local Control.

Details of Consolidation chemotherapy in Regimen A are provided in Section 4.4.1.2.

AEWS1221 Regimen A: Induction (Weeks 1-12)
Induction consists of 6 two-week cycles (84 days in total). The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 1 and 2 (Weeks 1-4); one VDC cycle followed by one IE cycle.

_____ Patient ID

_____ DOB

No count criteria are required to start Induction Week 1 therapy. Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt < 1 yo	1	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.1.
Dexrazoxane (DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	1 and 2	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.1.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt < 1 yo	1 and 2	See Section 4.4.1.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt < 1 yo	1	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	1	Administer with CPM, see Section 4.4.1.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for < 1 yo	15 - 19	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	15 - 19	Administer with IFOS, see Section 4.4.1.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	15 - 19	Slow rate of administration if hypotension occurs. See Section 4.4.1.1 for details.

OBSERVATIONS
a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin
e. Albumin, EKG, Urine pregnancy test*
f. ECHO* or MUGA*
g. Plain film primary tumor (bone tumors only)
h. MRI or CT of primary tumor, Chest CT, FDG-PET scan. (See Sections 7.1.1 & 16.0)
i. MRI or CT and FDG-PET submission*
j. Required BMA aspirates and biopsies
k. Unstained slides*
l. Required baseline blood samples*
m. Optional BMA submission*
n. Optional sample in Streck*

*See Section 7.1.1

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 1: Ht cm Wt kg BSA m^2 Cycle 2: Ht cm Wt kg BSA m^2

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day[%]	IFOS mg	MESNA (with IFOS) mg/day[%]	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below									
		1	1	mg	mg	mg	mg	mg/day[%]				a – n	
			2		mg	mg							
			3-4[#]		Growth factor used:		Dose:	Date of first dose:		Date of last dose:			
		2	8									b*	
		3	15						mg	mg/day[%]	mg	a – d, n	
			16						mg	mg/day[%]	mg		
			17						mg	mg/day[%]	mg		
			18						mg	mg/day[%]	mg		
			19						mg	mg/day[%]	mg		
			20-21[#]		Growth factor used:		Dose:	Date of first dose:		Date of last dose:			
		4	22									b*	
			28									b*	

[%] **Enter total daily dose as mg/day by CI or intermittent infusion.** [#] **Begin myeloid growth factor support at least 24 - 36 hours after the last dose of chemotherapy. See Section 4.4.1.1.**

The therapy delivery map for Induction continues on the next 2 pages. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

AEWS1221 Regimen A: Induction Continued
Induction consists of 6 two-week cycles (84 days in total). The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 3 and 4 (Weeks 5-8); one VDC cycle followed by one IE cycle.

_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). If ANC has risen to ≥ 750/μL after the nadir but then falls, Cycle 3 and 4 should be given despite ANC < 750/μL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt < 1 yo	29	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.1.
Dexrazoxane (DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	29 and 30	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.1.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose OR 1.25 mg/kg/dose for pt < 1 yo	29 and 30	See Section 4.4.1.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt < 1 yo	29	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	29	Administer with CPM, see Section 4.4.1.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt or < 1 yo	43-47	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	43-47	Administer with IFOS, see Section 4.4.1.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	43-47	Slow rate of administration if hypotension occurs. See Section 4.4.1.1 for details.

OBSERVATIONS
a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin
e. Required BMA and biopsies if marrow involved at baseline*
f. Optional bone marrow aspirate submission*
g. Required serum sample*
h. Optional sample in Streck*

* See Section 7.1.1 for details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 3: Ht _____ cm Wt _____ kg BSA _____ m^2 **Cycle 4: Ht _____ cm Wt _____ kg BSA _____ m^2**

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day%	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below									
		5	29	_____mg	_____mg	_____mg	_____mg	_____mg/day%				a – d, g, h	
			30		_____mg	_____mg							
			31-32#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		6	36									b*	
		7	43						_____mg	_____mg/day%	_____mg	a – f	
			44						_____mg	_____mg/day%	_____mg		
			45						_____mg	_____mg/day%	_____mg		
			46						_____mg	_____mg/day%	_____mg		
			47						_____mg	_____mg/day%	_____mg		
			48-49#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		8	50									b*	
			56									b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **#Begin myeloid growth factor support at least 24 - 36 hours after the last dose of chemotherapy. See Section 4.4.1.1**

The therapy delivery map for Induction continues on the next page. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

AEWS1221 Regimen A: Induction Continued
Induction consists of 6 two-week cycles (84 days in total).
The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 5 and 6 (Weeks 9-12); one VDC cycle followed by one IE cycle.

_____
Patient ID

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after the nadir but then falls, Cycle 5 and 6 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	57	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.1
Dexrazoxane(DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	57 and 58	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.1.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt < 1 yo	57 and 58	See Section 4.4.1.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt < 1 yo	57	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	57	Administer with CPM, see Section 4.4.1.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt < 1 yo	71-75	See Section 4.4.1.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	71-75	Administer with IFOS, see Section 4.4.1.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	71-75	Slow rate of administration if hypotension occurs. See Section 4.4.1.1 for details.

OBSERVATIONS

a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++},
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin
e. ECHO/MUGA (prior to Week 9 chemotherapy).
f. MRI or CT of primary tumor, chest CT, FDG-PET scan. (See Sections 7.1.1 & 16.0)
g. MRI or CT and FDG-PET submission*
h. Required BMA and biopsies if marrow still positive at last eval *
i. Optional BMA submission*
j. Optional sample in Streck*

*See Section 7.1.1 for details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 5: Ht _____cm Wt _____kg BSA_____m^2 **Cycle 6: Ht _____cm Wt _____kg BSA_____m^2**

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day[%]	IFOS mg	MESNA (with IFOS) mg/day[%]	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below									
		9	57	mg	mg	mg	mg	mg/day%				a - e	
			58		mg	mg							
			59-60[#]		Growth factor used:			Dose:	Date of first dose:		Date of last dose:		
		10	64									b*	
		11	71						mg	mg/day[%]	mg	a – d	
			72						mg	mg/day[%]	mg		
			73						mg	mg/day[%]	mg		
			74						mg	mg/day[%]	mg		
			75						mg	mg/day[%]	mg		
			76-77[#]		Growth factor used:			Dose:	Date of first dose:		Date of last dose:		
		12	78									b*	
			84		**Local Control will follow Induction therapy. See Section 4.3 for Local Control options. See Section 7.1 for observations prior to Local Control.**							a, b, f – j	

% Enter total daily dose as mg/day by CI or intermittent infusion. **[#]Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.1.1**

SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES AND THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINE

4.4.1.2 Administration Schedule: Consolidation Therapy (Weeks 1-16) Regimen A

Ensure adequate time for healing following surgical local control. Consolidation will not begin until 2 weeks post-operatively. For patients receiving radiation therapy for local control, radiation therapy should begin concomitantly with Week 1 of Consolidation therapy. DOXOrubicin may be administered concurrently with radiation therapy only at Week 1 of Consolidation chemotherapy.

See Section 4.1.1.2 for modifying order of Consolidation for patients who receive early whole lung radiation due to overlapping radiation fields with the primary tumor.

Criteria to start Consolidation: ANC ≥ 750/µL and platelet ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as the patient meets count recovery criteria, regardless of myeloid growth factor utilized.

Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as the patient meets count recovery criteria, regardless of myeloid growth factor utilized.

If a cycle of chemotherapy is delayed due to toxicity, see Section 5.0 for criteria to resume chemotherapy.

Note: for children less than 1 year of age chemotherapy should be calculated by weight rather than by surface area. Dose/kg = dose/m^2 divided by 30 kg/m^2. Example: If patient is less than 1 year of age and weight is 15 kg and dose of Etoposide is 100mg/m^2, then the dose of Etoposide is based on mg/kg = 100mg/m^2 divided by 30 kg/m^2 = 3.3 mg/kg x15 kg = 49.5 mg.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 of Weeks 1, 7, 9, and 13
Dose: 2 mg/m^2/dose (Maximum dose is 2 mg). **For patients < 1 year old, the dose is 0.067 mg/kg/dose.**

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. Fatal if given by other routes. For intravenous use only."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexrazoxane: Slow IV Push (eg, over 5-15 minutes) given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1 and 7
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). **For patients < 1 year old, the dose is 12.5 mg/kg/dose.**
Note: Administer DOXOrubicin after completing the infusion of dexrazoxane and every effort should be made to keep the total combined infusion time for dexrazoxane and doxorubicin to ≤ 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days: 1 and 2 of Weeks 1 and 7
Dose: 37.5 mg/m^2/dose. **For patients < 1 year old, the dose is 1.25 mg/kg/dose.**

Administer at a concentration not to exceed 2 mg/mL. 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.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 30-60 minutes
Day 1 of Weeks 1, 7, 9 and 13
Dose: 1,200 mg/m^2/dose. **For patients < 1 year old, the dose is 40 mg/kg/dose.**
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

Mesna must be administered in conjunction with Cyclophosphamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Ifosfamide: IV, infuse the diluted solution over 1 hour
Days 1-5 of Weeks 3, 5, 11 and 15
Dose: 1,800 mg/m^2/dose. **For patients < 1 year old, the dose is 60 mg/kg/dose.**
Mesna must be administered in conjunction with IFOS (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for cyclophosphamide/ifosfamide: Administer 3,000 mL/m²/day (125 mL/m²/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of cyclophosphamide/ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with cyclophosphamide
Administer MESNA by IV infusion or IV/PO on Day 1 of Weeks 1, 7, 9 and 13.
Total IV Dose: 720 mg/m²/day. **For patients < 1 year old, the IV dose is 24 mg/kg/day.**

Mesna with ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-5 of Weeks 3, 5, 11 and 15.
Total IV Dose: 1,080 mg/m²/day. **For patients < 1 year old, the IV dose is 36 mg/kg/day.**

Mesna IV short or continuous infusion:
For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily ifosfamide/cyclophosphamide dose. Mesna can be administered in 3 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 the ifosfamide/cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of ifosfamide/cyclophosphamide).

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or at the start of the cyclophosphamide/ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8.

This total daily dose of mesna can also be administered as IV **continuous infusion (CI)**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide/cyclophosphamide and finished no sooner than 8 hours after the end of the ifosfamide/cyclophosphamide infusion. **For example:** if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide and be completed no sooner than 8 hours after **the end** of the ifosfamide/cyclophosphamide infusion. If ifosfamide/cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide/ifosfamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and

8) orally at 40% of the ifosfamide/cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide/ifosfamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parental solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within 2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Etoposide: IV, infuse the diluted solution over at least 1-2 hours
Days 1-5 of Weeks 3, 5, 11 and 15
Dose: 100 mg/m^2/dose. **For patients < 1 year old, the dose is 3.3 mg/kg/dose.**
Infuse diluted solution (concentration $\leq$ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested for prolonged infusion due to risk of precipitation.

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.

Growth Factor Support
Begin myeloid growth factor support (filgrastim or pegfilgrastim or biosimilar products according to institutional standards for patients receiving interval compressed chemotherapy) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC $\geq$ 750/µL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.
Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Consolidation in Regimen A are provided on the following 5 pages. See Section 7.1.2 for observations required during Consolidation.

Following recovery from Consolidation chemotherapy and no earlier than 3 weeks from start of Week 15 of Consolidation, patients proceed to Metastatic Site Radiation (see Section 17.0). No systemic therapy is given during Metastatic Site Radiation.

4.4.1.3 End of Therapy for Patients on Regimen A

Following completion of Metastatic Site Radiation, patients on Regimen A will have completed all prescribed protocol therapy. See Sections 7.1.3 for observations due at End of Therapy and Section 7.3 for recommended observations during follow-up.

AEWS1221 Regimen A: Consolidation Chemotherapy Consolidation chemotherapy consists of 8 two-week cycles (112 days in total). This Therapy Delivery Map is on 5 pages. **This page relates to Cycle 1 (Weeks 1 and 2) of Consolidation chemotherapy**	_____Patient ID _____ DOB

Begin Consolidation when ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of a chemotherapy cycle. If radiation is the primary local control measure or will be given pre-operatively then Consolidation chemotherapy should be initiated concurrently with the radiation therapy, i.e. both radiation and Cycle 1 Consolidation should start at the same time. DOXOrubicin may be administered concurrently with radiation therapy only at Week 1 of Consolidation chemotherapy.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	1	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.2.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA (prior to DOXOrubicin)* f. Unstained slides if surgical local control* g. Submission of percent tumor necrosis if surgical local control *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5-15 min)	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt <1 yo	1 and 2	Administer immediately prior to DOXO. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.1.2.	
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt <1 yo	1 and 2	See Section 4.4.1.2.for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt <1 yo	1	See Section 4.4.1.2.	
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	1	Administer with CPM, see Section 4.4.1.2.	

Cycle 1: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	VCR _____mg	DXRZ _____mg	DOXO _____mg	CPM _____mg	MESNA (with CPM) _____mg/day[%]	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						
		1	1	mg	mg	mg	mg	mg/day[%]	a – g	
			2		mg	mg				
			3-4#	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____						
		2	8						b*	
			9							
			14						b*	

%Enter total daily dose as mg/day by CI or intermittent infusion. **[#]Begin myeloid growth factor support at least 24-36 hours after the last dose of chemotherapy. See Section 4.4.1.2.**

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen A: Consolidation Chemotherapy Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total). This Therapy Delivery Map is on 5 pages. **This page relates to Cycles 2 and 3 (Weeks 3 - 6) of Consolidation chemotherapy**	_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 2 and 3 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt < 1 yo	15–19 and 29-33	See Section 4.4.1.2. for details.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	15–19 and 29-33	Administer with IFOS, see Section 4.4.1.2.	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	15–19 and 29-33	Slow rate of administration if hypotension occurs. See Section 4.4.1.2.	

Cycle 2: Ht_____cm Wt_____kg BSA_____m^2 **Cycle 3: Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	ETOP _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		3	15	_____mg	_____mg/day%	_____mg	a – d	
			16	_____mg	_____mg/day%	_____mg		
			17	_____mg	_____mg/day%	_____mg		
			18	_____mg	_____mg/day%	_____mg		
			19	_____mg	_____mg/day%	_____mg		
			20-21#	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____				
		4	22				b*	
		5	29	_____mg	_____mg/day%	_____mg	a – d	
			30	_____mg	_____mg/day%	_____mg		
			31	_____mg	_____mg/day%	_____mg		
			32	_____mg	_____mg/day%	_____mg		
			33	_____mg	_____mg/day%	_____mg		
			34-35#	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____				
		6	36				b*	
			42				b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **#Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.1.2.**

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen A: Consolidation Chemotherapy

Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total).

This Therapy Delivery Map is on 5 pages.

This page relates to Cycles 4 and 5 (Weeks 7-10) of Consolidation chemotherapy

_____ Patient ID

_____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 4 and 5 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	43 and 57	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.2.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA (prior to Wk 7 DOXOrubicin)* f. MRI or CT Scan of primary tumor, Chest CT, FDG PET scan (prior to Wk 9 chemotherapy). See Sections 7.1.2 & 16.0. g. Bilat. BMA and biopsies (prior to Wk 9 therapy) if marrow still positive at last eval * h. Optional marrow aspirate submission* i. Optional sample in Streck* * **See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5 15min)	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt <1 yo	43 and 44	Administer immediately prior to DOXO. The combined infusion time for DXRZ+ DOXO should be ≤ 30 min. See Section 4.4.1.2.	
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt <1 yo	43 and 44	See Section 4.4.1.2 for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose OR 40 mg/kg/dose for pt < 1 yo	43 and 57	See Section 4.4.1.2 for details.	
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	43 and 57	Administer with CPM, see Section 4.4.1.2.	

Cycle 4: Ht_____cm Wt_____kg BSA_____m^2 **Cycle 5: Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Week	Day	VCR _____mg	DXRZ _____mg	DOXO _____mg	CPM _____mg	MESNA (with CPM) _____mg/day[%]	Studies	Comments (Include any held doses, or dose modifications)
		7	43	_____mg	_____mg	_____mg	_____mg	_____mg/day[%]	a - e	
			44		_____mg	_____mg				
			45-46[#]		Growth factor used: _____ Dose: _____		Date of first dose: _____		Date of last dose: : _____	
		8	50						b*	
		9	57	_____mg			_____mg	_____mg/day[%]	a – d, f – i	
			58-59[#]		Growth factor used: _____ Dose: _____		Date of first dose: _____		Date of last dose: : _____	
		10	64						b*	
			70						b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **[#] Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy**. See Section 4.4.1.2.

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen A: Consolidation Chemotherapy

Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total).

This Therapy Delivery Map is on 5 pages.

This page relates to Cycles 6 and 7 (Weeks 11-14) of Consolidation chemotherapy.

_____ Patient ID

_____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 6 and 7 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt <1 yo	71-75	See Section 4.4.1.2 for hydration guidelines.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA * *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	71-75	Administer with IFOS, see Section 4.4.1.2	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt <1 yo	71-75	Slow rate of administration if hypotension occurs.	
VinCRIStine (VCR)	IV push over 1 min$	2.mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	85	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg** See Section 4.4.1.2	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt <1 yo	85	See Section 4.4.1.2 for details.	
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	85	Administer with CPM, see Section 4.4.1.2	

Cycle 6: Ht _____cm Wt _____kg BSA_____m^2 **Cycle 7: Ht _____cm Wt _____kg BSA_____m^2**

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	ETOP _____mg	VCR _____mg	CPM _____mg	MESNA (with CPM) _____mg/day%	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below							
		11	71	mg	_____mg/day%	mg				a – e	
			72	mg	_____mg/day%	mg					
			73	mg	_____mg/day%	mg					
			74	mg	_____mg/day%	mg					
			75	mg	_____mg/day%	mg					
			76-77#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____						
		12	78							b*	
		13	85				_____mg	_____mg	_____mg/day%	a – d	
			86-87#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____						
		14	92							b*	
			98							b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. # Begin myeloid growth factor support at least 24-36 hours after the last dose of chemotherapy. See Section 4.4.1.2.

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen A: Consolidation Chemotherapy

Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total).

This Therapy Delivery Map is on 5 pages.

This page relates to Cycle 8 (Weeks 15 and 16) of Consolidation chemotherapy.

_____
Patient ID

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 8 and 9 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt <1 yo	99-103	See Section 4.4.1.2 for details.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA* f. MRI or CT of primary tumor, chest CT, FDG-PET scan (See Sections 7.1.2 & 16.0) g. Bilateral BMA and biopsies (end-Consolidation for all patients if positive at study entry)* h. Optional bone marrow aspirate submission* i. Unstained slides (if late surgical resection)* j. Pulmonary function test (if lung mets at study entry)* k. Optional sample in Streck* l. Required end Consolidation serum sample* *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	99-103	Administer with IFOS, see Section 4.4.1.2	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt <1 yo	99-103	Slow rate of administration if hypotension occurs.	

Cycle 8: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		15	99	_____mg	_____mg/day%	_____mg	a – d	
			100	_____mg	_____mg/day%	_____mg		
			101	_____mg	_____mg/day%	_____mg		
			102	mg	_____mg/day%	mg		
			103	mg	_____mg/day%	mg		
			104-105#	Growth factor used: _____ Dose: _____	Date of first dose: _____	Date of last dose: _____		
		16	106				b*	
			112				(a – l)‡	

% Enter total daily dose as mg/day by CI or intermittent infusion.

‡ End of Consolidation/Pre-Metastatic Site Radiation

 # Begin myeloid growth factor support at least 24-36 hours after the last dose of chemotherapy. See Section 4.4.1.2.

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

4.4.2 Administration Schedules for Induction and Consolidation in Regimen B

NOTE: As of March 20, 2019, institutions were instructed to immediately discontinue ganitumab for patients on Regimen B.

Prior to March 20, 2019: Patients in Regimen B received ganitumab in Induction, Consolidation, and Maintenance.

The first 10 patients < 21 years of age at study entry randomized to Regimen B must submit required serum samples for measurement of ganitumab trough concentrations in Induction and Maintenance. Registering sites will be notified of the need to obtain these samples at the time of randomization. (Enrollment to this cohort completed as of July 2015; for patients previously assigned to this cohort, continue to collect samples as detailed in Section 15.5.)

4.4.2.1 Administration Schedule: Induction (Weeks 1-12) Regimen B

Criteria to start Induction: No count criteria are required to start Induction Week 1 therapy.

Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as the patient meets count recovery criteria, regardless of myeloid growth factor utilized.

See Section 5.1 for exceptions in Weeks 1 and 3 for patients with bone marrow metastatic disease.

If a cycle of chemotherapy is delayed due to toxicity, see Section 5.0 for criteria to resume chemotherapy.

Note: for children less than 1 year of age, chemotherapy should be calculated by weight rather than by surface area. Dose/kg = dose/m^2 divided by 30 kg/m^2. Example: If patient is less than 1 year of age and weight is 15 kg and dose of Etoposide is 100 mg/m^2, then the dose of Etoposide is based on mg/kg = 100 mg/m^2 divided by 30 kg/m^2 = 3.3 mg/kg x15 kg = 49.5 mg.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 of Weeks 1, 5 and 9
Dose: 2 mg/m^2/dose. (Maximum dose is 2 mg.) **For patients < 1 year old, the dose is 0.067 mg/kg/dose.**

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. Fatal if given by other routes. For intravenous use only."
Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexrazoxane: Slow IV Push (eg, over 5-15 minutes) given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1, 5 and 9
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). **For patients < 1 year old, the dose is 12.5 mg/kg/dose.**
Note: Administer DOXOrubicin after completing the infusion of dexrazoxane and every effort should be made to keep the total combined infusion time for dexrazoxane and doxorubicin to ≤ 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes.
Days: 1 and 2 of Weeks 1, 5 and 9
Dose: 37.5 mg/m^2/dose. **For patients < 1 year old, the dose is 1.25 mg/kg/dose.**
Administer at a concentration not to exceed 2 mg/mL. 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.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 30-60 minutes
Day 1 of Weeks 1, 5 and 9
Dose: 1,200 mg/m^2/dose. **For patients < 1 year old, the dose is 40 mg/kg/dose.**
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

Mesna must be administered in conjunction with cyclophosphamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Ifosfamide: IV, infuse the diluted solution over 1 hour
Days: 1-5 of Weeks 3, 7 and 11
Dose: 1,800 mg/m^2/dose. **For patients < 1 year old, the dose is 60 mg/kg/dose.**

Mesna must be administered in conjunction with ifosfamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for cyclophosphamide/ifosfamide: Administer 3,000 mL/m²/day (125 mL/m²/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of cyclophosphamide/ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with Cyclophosphamide

Administer MESNA by IV infusion or IV/PO on Day 1 of Weeks 1, 5 and 9.

Total IV Dose: 720 mg/m²/day. **For patients < 1 year old, the IV dose is 24 mg/kg/day.**

Mesna with Ifosfamide

Administer MESNA by IV infusion or IV/PO on Days 1-5 of Weeks 3, 7 and 11.

Total IV Dose: 1,080 mg/m²/day. **For patients < 1 year old, the IV dose is 36 mg/kg/day.**

Mesna IV short or continuous infusion:

For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily ifosfamide/cyclophosphamide dose. Mesna can be administered in 3 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 the ifosfamide/cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of ifosfamide/cyclophosphamide).

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or at the start of the cyclophosphamide/ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8.

This total daily dose of mesna can also be administered as IV **continuous infusion (CI)**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide/cyclophosphamide and finished no sooner than 8 hours after the end of the ifosfamide/cyclophosphamide infusion.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide and be completed no sooner than 8 hours after **the end** of the ifosfamide/cyclophosphamide infusion. If ifosfamide/cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide/ifosfamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

Use of oral mesna:

The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and

8) orally at 40% of the ifosfamide/cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide/ifosfamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parental solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within 2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Etoposide: IV, infuse the diluted solution over at least 1-2 hours
Days: 1-5 of Weeks 3, 7 and 11
Dose: 100 mg/m^2/dose. **For patients < 1 year old, the dose is 3.3 mg/kg/dose.**
Infuse diluted solution (concentration $\leq$ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested for prolonged infusion due to risk of precipitation.

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.

Growth Factor Support
Begin myeloid growth factor support (filgrastim or pegfilgrastim or biosimilar products according to institutional standards for patients receiving interval compressed chemotherapy) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC $\geq$ 750/µL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.
Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Induction in Regimen B are provided in the following 3 pages. Local Control will follow Induction (see Section 4.3 for details). See Section 7.1.1 for observations prior to Local Control.

Details of Consolidation chemotherapy in Regimen B are provided in Section 4.4.2.2.

AEWS1221 Regimen B: Induction (Weeks 1-12)
Induction consists of 6 two-week cycles (84 days in total). The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 1 and 2 (Weeks 1-4)

_____ Patient ID _____ DOB

No count criteria are required to start Induction Week 1 therapy. Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt < 1 yo	1	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.1.1.
Dexrazoxane (DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	1 and 2	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.2.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt < 1 yo	1 and 2	See Section 4.4.2.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt < 1 yo	1	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	1	Administer with CPM, see Section 4.4.2.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for < 1 yo	15 - 19	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	15 - 19	Administer with IFOS, see Section 4.4.2.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	15 - 19	Slow rate of administration if hypotension occurs. See Section 4.4.2.1 for details.

OBSERVATIONS

a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin,
e. Albumin, EKG, Urine pregnancy test*
f. ECHO* or MUGA*
g. Plain film primary tumor (bone tumors only)
h. MRI or CT of primary tumor, Chest CT, FDG-PET scan. (See Sections 7.1.1 & 16.0)
i. MRI or CT and FDG-PET submission*
j. Required BMA aspirates and biopsies
k. Unstained slides*
l. Required baseline blood samples*
m. Optional BMA submission*
n. PK blood sample (**ONLY** for 1st 10 patients < 21 yo; see Section 15.5)
o. Optional Sample in Streck*

***See Section 7.1.1**

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 1: Ht_____cm Wt_____kg BSA_____m^2 Cycle 2: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day[%]	IFOS mg	MESNA (with IFOS) mg/day[%]	ETOP mg		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below										
		1	1	____mg	_____mg	____mg	____mg	_____mg/day[%]					a – o	
			2		mg	mg								
			3-4[#]		Growth factor used:			Dose:		Date of first dose:		Date of last dose:		
		2	8										b*	
		3	15						mg	mg/day[%]	mg		a - d, n, o	
			16						mg	mg/day[%]	mg			
			17						mg	mg/day[%]	mg			
			18						mg	mg/day[%]	mg			
			19						mg	mg/day[%]	mg			
			20-21[#]		Growth factor used:			Dose:		Date of first dose:		Date of last dose:		
		4	22										b*	
			28										b*	

[%] Enter total daily dose as mg/day by CI or intermittent infusion. **[#]Begin myeloid growth factor support at least 24 - 36 hours after the last dose of chemotherapy. See Section 4.4.2.1.**

The therapy delivery map for Induction continues on the next 2 pages. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

AEWS1221 Regimen B: Induction Continued
Induction consists of 6 two-week cycles (84 days in total). The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 3 and 4 (Weeks 5-8)

_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after the nadir but then falls, Cycle 3 and 4 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt < 1 yo	29	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.2.1.
Dexrazoxane (DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	29 and 30	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.2.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose OR 1.25 mg/kg/dose for pt < 1 yo	29 and 30	See Section 4.4.2.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt < 1 yo	29	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	29	Administer with CPM, see Section 4.4.2.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt or < 1 yo	43-47	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	43-47	Administer with IFOS, see Section 4.4.2.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	43-47	Slow rate of administration if hypotension occurs. See Section 4.4.2.1 for details.

OBSERVATIONS
a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin,
e. Required BMA and biopsies if marrow involved at baseline*
f. Optional bone marrow aspirate submission*
g. Required serum sample*
h. PK blood sample (**ONLY** for 1st 10 patients < 21 yo; see Section 15.5)
i. Optional sample in Streck*

* See Section 7.1.1 for details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 3: Ht_____cm Wt_____kg BSA_____m^2 **Cycle 4: Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day%	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below										
		5	29	___mg	___mg	___mg	___mg	_____mg/day%					a – d, g, h, i	
			30		___mg	___mg								
			31-32[#]		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____									
		6	36										b*	
		7	43						___mg	_____mg/day%	___mg		a – f	
			44						___mg	_____mg/day%	___mg			
			45						___mg	_____mg/day%	___mg			
			46						___mg	_____mg/day%	___mg			
			47						___mg	_____mg/day%	___mg			
			48-49[#]		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____									
		8	50										b*	
			56										b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **[#]Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.2.1.**

The therapy delivery map for Induction continues on the next page. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

AEWS1221 Regimen B: Induction Continued
Induction consists of 6 two-week cycles (84 days in total).
The therapy delivery map presents Induction therapy on 3 pages.
This therapy delivery map relates to Cycles 5 and 6 (Weeks 9-12)

_____
Patient ID

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after the nadir but then falls, Cycle 5 and 6 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next chemotherapy cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose OR 0.067 mg/kg/dose for pt <1 yo	57	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.2.1
Dexrazoxane (DXRZ)	Slow IV push over 5-15 mins[‡]	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt < 1 yo	57 and 58	‡ Given immediately prior to DOXOrubicin. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.2.1.
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins	37.5 mg/m^2/dose OR 1.25 mg/kg/dose for pt < 1 yo	57 and 58	See Section 4.4.2.1 for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose OR 40 mg/kg/dose for pt < 1 yo	57	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	57	Administer with CPM, see Section 4.4.2.1
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose OR 60 mg/kg/dose for pt < 1 yo	71-75	See Section 4.4.2.1 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	71-75	Administer with IFOS, see Section 4.4.2.1
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose OR 3.3 mg/kg/dose for pt < 1 yo	71-75	Slow rate of administration if hypotension occurs. See Section 4.4.2.1 for details.

OBSERVATIONS

a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++},
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin
e. ECHO/MUGA (prior to Week 9 chemotherapy).
f. MRI or CT of primary tumor, chest CT, FDG-PET scan. (See Sections 7.1.1 & 16.0)
g. MRI or CT and FDG-PET submission*
h. Required BMA and biopsies if marrow still positive at last eval *
i. Optional BMA submission*
j. PK blood sample (**ONLY** for 1st 10 patients < 21 yo; see Section 15.5)
k. Optional sample in Streck*

*See Section 7.1.1 for details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 5: Ht **cm Wt** **kg BSA** **m^2** **Cycle 6: Ht** **cm Wt** **kg BSA** **m^2**

Date Due	Date Given	Week	Day	VCR mg	DXRZ mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day%	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below										
		9	57	mg	mg	mg	mg	mg/day%					a - e	
			58		mg	mg								
			59-60[#]		Growth factor used:			Dose:		Date of first dose:		Date of last dose:		
		10	64										b*	
		11	71						mg	mg/day%	mg		a – d, j	
			72						mg	mg/day%	mg			
			73						mg	mg/day%	mg			
			74						mg	mg/day%	mg			
			75						mg	mg/day%	mg			
			76-77[#]		Growth factor used:			Dose:		Date of first dose:		Date of last dose:		
		12	78										b*	
			84	**Local Control will follow Induction therapy. See Section 4.3 for Local Control options. See Section 7.1 for observations prior to Local Control.**									a, b, f – i, k	

% Enter total daily dose as mg/day by CI or intermittent infusion. **[#]Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.2.1**

SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES AND THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINE

4.4.2.2 Administration Schedule: Consolidation Therapy (Weeks 1-16) Regimen B

Ensure adequate time for healing following surgical local control. Consolidation will not begin until 2 weeks post-operatively. For patients receiving radiation therapy for local control, radiation therapy should begin concomitantly with Week 1 of Consolidation therapy. DOXOrubicin may be administered concurrently with radiation therapy only at Week 1 of Consolidation chemotherapy.

See Section 4.1.1.2 for modifying order of Consolidation for patients who receive early whole lung radiation due to overlapping radiation fields with the primary tumor.

Criteria to start Consolidation: ANC ≥ 750/µL and platelet ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as the patient meets count recovery criteria, regardless of myeloid growth factor utilized.

Criteria to start subsequent cycles: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle should be given despite ANC < 750/µL. To maintain dose intensity, administration of subsequent cycles of chemotherapy should not be delayed as along as patient meets count recovery criteria, regardless of myeloid growth factor utilized.

If a cycle of chemotherapy is delayed due to toxicity, see Section 5.0 for criteria to resume chemotherapy.

Note: for children less than 1 year of age chemotherapy should be calculated by weight rather than by surface area. Dose/kg = dose/m^2 divided by 30 kg/m^2. Example: If patient is less than 1 year of age and weight is 15 kg and dose of Etoposide is 100mg/m^2, then the dose of Etoposide is based on mg/kg = 100mg/m^2 divided by 30 kg/m^2 = 3.3 mg/kg x15 kg = 49.5 mg.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1 of Weeks 1, 7, 9 and 13
Dose: 2 mg/m^2/dose (Maximum dose is 2 mg). **For patients < 1 year old, the dose is 0.067 mg/kg/dose.**

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. Fatal if given by other routes. For intravenous use only."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexrazoxane: Slow IV Push (eg, over 5-15 minutes) given immediately prior to DOXOrubicin
Days: 1 and 2 of Weeks 1 and 7
Dose: 375 mg/m^2/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). **For patients < 1 year old, the dose is 12.5 mg/kg/dose.**
Note: Administer DOXOrubicin after completing the infusion of dexrazoxane and every effort should be made to keep the total combined infusion time for dexrazoxane and doxorubicin to ≤ 30 minutes.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days: 1 and 2 of Weeks 1 and 7
Dose: 37.5 mg/m^2/dose. **For patients < 1 year old, the dose is 1.25 mg/kg/dose.**

Administer at a concentration not to exceed 2 mg/mL. 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.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 30-60 minutes
Day 1 of Weeks 1, 7, 9 and 13
Dose: 1,200 mg/m^2/dose. **For patients < 1 year old, the dose is 40 mg/kg/dose.**
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

Mesna must be administered in conjunction with Cyclophosphamide (see below). Hydrate per institutional guidelines or according to recommendations below.

Ifosfamide: IV, infuse the diluted solution over 1 hour
Days 1-5 of Weeks 3, 5, 11 and 15
Dose: 1,800 mg/m^2/dose. **For patients < 1 year old, the dose is 60 mg/kg/dose.**
Mesna must be administered in conjunction with IFOS (see below). Hydrate per institutional guidelines or according to recommendations below.

Suggested hydration for cyclophosphamide/ifosfamide: Administer 3,000 mL/m²/day (125 mL/m²/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of cyclophosphamide/ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna with cyclophosphamide
Administer MESNA by IV infusion or IV/PO on Day 1 of Weeks 1, 7, 9 and 13
Total IV Dose: 720 mg/m²/day. **For patients < 1 year old, the IV dose is 24 mg/kg/day.**

Mesna with ifosfamide
Administer MESNA by IV infusion or IV/PO on Days 1-5 of Weeks 3, 5, 11 and 15
Total IV Dose: 1,080 mg/m²/day. **For patients < 1 year old, the IV dose is 36 mg/kg/day.**

Mesna IV short or continuous infusion:
For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily ifosfamide/cyclophosphamide dose. Mesna can be administered in 3 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 the ifosfamide/cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of ifosfamide/cyclophosphamide).

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or at the start of the cyclophosphamide/ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8.

This total daily dose of mesna can also be administered as IV **continuous infusion (CI)**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide/cyclophosphamide and finished no sooner than 8 hours after the end of the ifosfamide/cyclophosphamide infusion.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide and be completed no sooner than 8 hours after **the end** of the ifosfamide/cyclophosphamide infusion. If ifosfamide/cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide/ifosfamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the ifosfamide/cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6.

For example: if the cyclophosphamide/ifosfamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide/ifosfamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parental solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200 mg. Administer doses on a schedule as determined by timing of cyclophosphamide/ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within 2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Etoposide: IV, infuse the diluted solution over at least 1-2 hours
Days 1-5 of Weeks 3, 5, 11 and 15
Dose: 100 mg/m^2/dose. **For patients < 1 year old, the dose is 3.3 mg/kg/dose.**
Infuse diluted solution (concentration $\leq$ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested for prolonged infusion due to risk of precipitation.

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.

Growth Factor Support
Begin myeloid growth factor support (filgrastim or pegfilgrastim or biosimilar products according to institutional standards for patients receiving interval compressed chemotherapy) at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC $\geq$ 750/µL post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy.
Note: Use of GM-CSF (sargramostim) is not permitted.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery maps for Consolidation in Regimen B are provided on the following 5 pages. See Section 7.1.2 for observations required during Consolidation.

Following recovery from Consolidation chemotherapy and no earlier than 3 weeks from start of Week 15 of Consolidation, patients proceed to Metastatic Site Radiation (see Section 17.0). No systemic therapy is given during Metastatic Site Radiation.

4.4.2.3 End of Therapy for Patients on Regimen B

Following completion of Metastatic Site Radiation, patients on Regimen B will have completed all prescribed protocol therapy. See Sections 7.1.3 for observations due at End of Therapy and Section 7.3 for recommended observations during follow-up.

AEWS1221 Regimen B: Consolidation Chemotherapy Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total). This Therapy Delivery Map is on 5 pages. **This page relates to Cycle 1 (Weeks 1 and 2) of Consolidation chemotherapy**	_____Patient ID _____ DOB

Begin Consolidation when ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of a chemotherapy cycle. If radiation is the primary local control measure or will be given pre-operatively then Consolidation chemotherapy should be initiated concurrently with the radiation therapy, i.e. both radiation and Cycle 1 Consolidation should start at the same time. DOXOrubicin may be administered concurrently with radiation therapy only at Week 1 of Consolidation chemotherapy.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min$	2 mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	1	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.2.2.	a. History and physical exam height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA (prior to DOXOrubicin)* f. Unstained slides if surgical local control* g. Submission of percent tumor necrosis if surgical local control *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5-15 min)	375 mg/m^2/dose **OR** 12.5 mg/kg/dose for pt <1 yo	1 and 2	Administer immediately prior to DOXO. The combined infusion time for DXRZ + DOXO should be ≤ 30 min. See Section 4.4.2.2.	
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m^2/dose **OR** 1.25 mg/kg/dose for pt <1 yo	1 and 2	See Section 4.4.2.2.for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose **OR** 40 mg/kg/dose for pt <1 yo	1	See Section 4.4.2.2.	
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	1	Administer with CPM, see Section 4.4.2.2.	

Cycle 1: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	VCR _____mg	DXRZ _____mg	DOXO _____mg	CPM _____mg	MESNA (with CPM) _____mg/day%	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						
		1	1	mg	mg	mg	mg	mg/day%	a – g	
			2		mg	mg				
			3-4#	Growth factor used:_____ Dose:_____ Date of first dose:_____ Date of last dose:_____						
		2	8						b*	
			9							
			14						b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. # Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.2.2.

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen B: Consolidation Chemotherapy
Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total).
This Therapy Delivery Map is on 5 pages.
This page relates to Cycles 2 and 3 (Weeks 3 - 6) of Consolidation chemotherapy

_____
Patient ID

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 2 and 3 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose **OR** 60 mg/kg/dose for pt < 1 yo	15–19 and 29-33	See Section 4.4.2.2. for details.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	15–19 and 29-33	Administer with IFOS, see Section 4.4.2.2.	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt < 1 yo	15–19 and 29-33	Slow rate of administration if hypotension occurs. See Section 4.4.2.2.	

Cycle 2: Ht_____cm Wt_____kg BSA_____m^2 Cycle 3: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS _____ mg	MESNA (with IFOS) _____ mg/day%	ETOP _____ mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		3	15	_____mg	_____mg/day%	_____mg	a – d	
			16	_____mg	_____mg/day%	_____mg		
			17	_____mg	_____mg/day%	_____mg		
			18	_____mg	_____mg/day%	_____mg		
			19	_____mg	_____mg/day%	_____mg		
			20-21#	Growth factor used: _____ Dose: _____	Date of first dose: _____		Date of last dose: _____	
		4	22				b*	
		5	29	_____mg	_____mg/day%	_____mg	a – d	
			30	_____mg	_____mg/day%	_____mg		
			31	_____mg	_____mg/day%	_____mg		
			32	_____mg	_____mg/day%	_____mg		
			33	_____mg	_____mg/day%	_____mg		
			34-35#	Growth factor used: _____ Dose: _____	Date of first dose: _____		Date of last dose: _____	
		6	36				b*	
			42				b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. # Begin myeloid growth factor support at least 24 - 36 hours after the last dose of chemotherapy. See Section 4.4.2.2.

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen B: Consolidation Chemotherapy

Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total).

This Therapy Delivery Map is on 5 pages.

This page relates to Cycles 4 and 5 (Weeks 7-10) of Consolidation chemotherapy

_____
Patient ID

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 4 and 5 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to the administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV push over 1 min[$]	2 mg/m^2/dose OR 0.067 mg/kg/dose for pt <1 yo	43 and 57	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg.** See Section 4.4.2.2.
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5 15min)	375 mg/m^2/dose OR 12.5 mg/kg/dose for pt <1 yo	43 and 44	Administer immediately prior to DOXO. The combined infusion time for DXRZ+ DOXO should be ≤ 30 min. See Section 4.4.2.2.
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m^2/dose OR 1.25 mg/kg/dose for pt <1 yo	43 and 44	See Section 4.4.2.2.for details.
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose OR 40 mg/kg/dose for pt < 1 yo	43 and 57	See Section 4.4.2.2 for details.
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	43 and 57	Administer with CPM, see Section 4.4.2.2.

OBSERVATIONS

a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin ECHO or MUGA (prior to Wk 7 DOXOrubicin)*
e. MRI or CT Scan of primary tumor, Chest CT, FDG PET scan (prior to Wk 9 chemotherapy). See Sections 7.1.2 & 16.0.
f. Bilat. BMA and biopsies (prior to Wk 9 therapy) if marrow still positive at last eval *
g. Optional marrow aspirate submission*
h. Optional sample in Streck*

* **See Section 7.1.2 for details.**

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 4: Ht_____cm Wt_____kg BSA_____m^2 **Cycle 5: Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Week	Day	VCR _____mg	DXRZ _____mg	DOXO _____mg	CPM _____mg	MESNA (with CPM) _____mg/day[%]		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below							
		7	43	_____mg	_____mg	_____mg	_____mg	_____mg/day[%]		a - e	
			44		_____mg	_____mg					
			45-46[#]		Growth factor used: _____ Dose: _____			Date of first dose: _____	Date of last dose: : _____		
		8	50							b*	
		9	57	_____mg			_____mg	_____mg/day[%]		a – d, f – h	
			58-59[#]		Growth factor used:		Dose:	Date of first dose:	Date of last dose:		
		10	64							b*	
			70							b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **[#] Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy**. See Section 4.4.2.2. The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen B: Consolidation Chemotherapy
Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total). This Therapy Delivery Map is on 5 pages.
This page relates to Cycles 6 and 7 (Weeks 11-14) of Consolidation chemotherapy.

_____ Patient ID _____ DOB

Criteria to start each cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL post nadir (without transfusion). If ANC has risen to ≥ 750/μL after nadir but then falls, Cycles 6 and 7 should be given despite ANC < 750/μL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose OR 60 mg/kg/dose for pt <1 yo	71-75	See Section 4.4.2.2 for hydration guidelines.	a. History and physical exam, height, weight, BSA b. CBC, differential, platelets* c. Electrolytes, including Ca^{++}, PO_4, Mg^{++} d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin e. ECHO or MUGA* *** See Section 7.1.2 for details.** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	71-75	Administer with IFOS, see Section 4.4.2.2	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose **OR** 3.3 mg/kg/dose for pt <1 yo	71-75	Slow rate of administration if hypotension occurs.	
VinCRIStine (VCR)	IV push over 1 min$^{\$}$	2.mg/m^2/dose **OR** 0.067 mg/kg/dose for pt <1 yo	85	$ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg** See Section 4.4.2.2	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m^2/dose OR 40 mg/kg/dose for pt <1 yo	85	See Section 4.4.2.2 for details.	
Mesna (MESNA)	IV or IV/PO	Total IV dose: 720 mg/m^2/day **OR** 24 mg/kg/day for pt < 1 yo	85	Administer with CPM, see Section 4.4.2.2	

Cycle 6: Ht _____cm Wt _____kg BSA_____m^2 **Cycle 7: Ht _____cm Wt _____kg BSA_____m^2**

Date Due	Date Given	Week	Day	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	VCR mg	CPM mg	MESNA (with CPM) mg/day%		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below								
		11	71	mg	mg/day%	mg					a – e	
			72	mg	mg/day%	mg						
			73	mg	mg/day%	mg						
			74	mg	mg/day%	mg						
			75	mg	mg/day%	mg						
			76-77#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		12	78								b*	
		13	85				mg	mg	mg/day%		a – d	
			86-87#		Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		14	92								b*	
			98								b*	

% Enter total daily dose as mg/day by CI or intermittent infusion. **# Begin myeloid growth factor support at least 24- 36 hours after the last dose of chemotherapy. See Section 4.4.2.2.**

The therapy delivery map for Consolidation continues on the next page.

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

AEWS1221 Regimen B: Consolidation Chemotherapy
Consolidation Chemotherapy consists of 8 two-week cycles (112 days in total). This Therapy Delivery Map is on 5 pages. **This page relates to Cycle 8 (Weeks 15 and 16) of Consolidation chemotherapy.**

_____ PatientID _____ DOB

Criteria to start each cycle: ANC ≥ 750/µL and platelet count ≥ 75,000/µL post nadir (without transfusion). If ANC has risen to ≥ 750/µL after nadir but then falls, Cycles 8 and 9 should be given despite ANC < 750/µL. Myeloid growth factor support should be stopped a minimum of 24 hours prior to administration of the next cycle.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m^2/dose OR 60 mg/kg/dose for pt <1 yo	99-103	See Section 4.4.2.2 for details.
Mesna (MESNA)	IV or IV/PO	Total IV Dose: 1,080 mg/m^2/day **OR** 36 mg/kg/day for pt < 1 yo	99-103	Administer with IFOS, see Section 4.4.2.2
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m^2/dose OR 3.3 mg/kg/dose for pt <1 yo	99-103	Slow rate of administration if hypotension occurs.

OBSERVATIONS

a. History and physical exam, height, weight, BSA
b. CBC, differential, platelets*
c. Electrolytes, including Ca^{++}, PO_4, Mg^{++}
d. Urinalysis, Creatinine, SGPT (ALT), Total bilirubin
e. ECHO or MUGA*
f. MRI or CT of primary tumor, chest CT, FDG-PET scan (See Sections 7.1.2 & 16.0)
g. Bilateral BMA and biopsies (end-Consolidation for all patients if positive at study entry)*
h. Optional bone marrow aspirate submission*
i. Unstained slides (if late surgical resection)*
j. Pulmonary function test (if lung mets at study entry)*
k. Optional sample in Streck*
l. Required end Consolidation serum sample*

*** See Section 7.1.2 for details.**

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle 8: Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	IFOS _____mg	MESNA (with IFOS) _____mg/day%	ETOP _____mg		Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		15	99	_____mg	_____mg/day%	_____mg		a – d	
			100	_____mg	_____mg/day%	_____mg			
			101	_____mg	_____mg/day%	_____mg			
			102	mg	mg/day%	mg			
			103	mg	mg/day%	mg			
			104-105#	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____					
		16	106					b*	
			112					(a – l)‡	

% Enter total daily dose as mg/day by CI or intermittent infusion. # Begin myeloid growth factor support at least 24-36 hours after the last dose of chemotherapy. See Section 4.4.2.2.
‡ End of Consolidation/Pre-Metastatic Site Radiation

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

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Slow Blood Count Recovery

This section includes separate instructions for modifying myelosuppressive chemotherapy (Section 5.1.1), for modifying ganitumab during induction and consolidation (Section 5.1.2), and for modifying ganitumab during maintenance (Section 5.1.3) in the setting of slow blood count recovery.

5.1.1 Chemotherapy Dose Modifications for Slow Blood Count Recovery

Recovery of absolute neutrophil count to ≥ 750/µL, and platelet count to ≥ 75,000/µL is required at the start of each myelosuppressive chemotherapy cycle. The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to ≥ 750/µL after the nadir but then falls the next cycle can be given despite ANC < 750/µL. If a cycle is delayed for more than 7 days, the next time the chemotherapy combination causing the delay is administered doses of myelosuppressive chemotherapy agents (doxorubicin/cyclophosphamide and ifosfamide/etoposide) should be reduced by 25%. Vincristine does not require dose modification for slow blood count recovery.

For patients who have chemotherapy dose reduction, re-escalation in chemotherapy dose in 25% increments should be attempted if the next cycle with the chemotherapy combination causing the initial delay is administered at reduced dose and does not result in treatment delay.

If the bone marrow is involved at diagnosis, the above guidelines for ANC and platelet counts do not apply during the first 2 cycles of chemotherapy. In patients who have bone marrow involvement at the time of initial diagnosis and in whom chemotherapy has been delayed for more than 14 days due to persistent neutropenia or thrombocytopenia, obtain a bone marrow aspirate and biopsy. If bone marrow shows persistent tumor, proceed with next scheduled cycle of chemotherapy regardless of counts. Repeat bone marrow aspirate after this cycle to rule out progressive marrow involvement. Also, if a patient had achieved a complete response in the bone marrow and presents with prolonged myelosuppression, early repeat bone marrow aspirate and biopsy should be considered. If marrow had previously cleared and then becomes positive, the patient is considered to have progressive disease and should be removed from protocol therapy.

5.2 Renal Toxicity

5.2.1 Ifosfamide

Renal toxicity is the primary, long-term dose-limiting side effect of ifosfamide. Available information indicates that the renal injury produced by ifosfamide may be permanent, and in some cases progressive. Renal irradiation, young age (< 3 years of age), and absence of one kidney are risk factors for severe renal toxicity. The elements below define incomplete and significant Fanconi's syndrome for the purposes of this study. In the event a patient appears to have evidence of Fanconi's syndrome, the investigator may consider evaluation as detailed below and consider modifying therapy as detailed below.

Elements of Fanconi Syndrome include:

1. Renal phosphorus wasting with hypophosphatemia. (serum phosphate < 2.5 mg/dL = 0.8 mmol/L).
2. Renal bicarbonate wasting with acidosis (Bicarbonate < 16).
3. Renal potassium wasting with hypokalemia (< 3.0 mEq/L).
4. 1+ glycosuria with serum glucose < 150 mg/dL.
5. Proteinuria: a ratio of urine protein: urine creatinine > 0.2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection.

Incomplete Fanconi Syndrome, with only one or a few of these elements, is common. Over time, these abnormalities may resolve, remain static, or progress.

For the purposes of this study, significant Fanconi Syndrome will be defined as:

1. GFR is < 50 mL/min/1.73 m^2, not due to other causes such as aminoglycoside toxicity, amphotericin B, etc., in the presence of mineral/electrolyte wasting, OR
2. The GFR is any level, but there is significant evidence of persistent Renal Tubular Acidosis (RTA) as evidenced by serum bicarbonate less than 16 mmol/L and serum phosphate ≤ 2 mg/dL (or < 0.6 mmol/L) without supplementation on measurements taken before the next ifosfamide cycle.

Modify therapy for significant Fanconi syndrome as follows:
Delete ifosfamide from all subsequent cycles and substitute cyclophosphamide 440 mg/m^2/day or 15 mg/kg/day for those < 1 year old with Mesna uroprotection (60% of the cyclophosphamide dose = 265 mg/m^2/day or 9 mg/kg/day for those < 1 year old) for 5 days to be given together with 5 days of etoposide. This schedule of fractionated cyclophosphamide has previously been used in National Wilms Tumor Trial V, Regimen I.

5.2.2 Etoposide

If Grade 2 or greater renal toxicity (creatinine > 1.5 X ULN) occurs, nephrotoxic agents should be discontinued, chemotherapy held and renal function tests repeated in one week. If toxicity persists a GFR or creatinine clearance should be obtained. The following initial dose modification should be considered based on measured creatinine clearance: for CrCl > 50 mL/min/1.73 m^2 give full dose, for CrCl of 15-50 mL/min/1.73m^2 give 75% of the dose (a 25% dose reduction). Etoposide should be held if CrCl < 15 mL/min/1.73 m^2.

5.2.3 Cyclophosphamide

If Grade 2 or greater renal toxicity (creatinine >1.5 X ULN) occurs, nephrotoxic agents should be discontinued. Cyclophosphamide, since it is subject to renal clearance, should be held and renal function repeated in one week. If estimated creatinine clearance (eGFR) drops by ≥ 33% (1/3) from the eGFR at study baseline or if the eGFR drops into the abnormal range, cyclophosphamide will require dose modifications. Prior to dose adjustment the local investigator should confirm the subject was well-hydrated when renal chemistries were obtained and a validated 24-hour creatinine clearance or a radionuclide GFR should be obtained.

The following initial dose modification should be instituted:

Renal function	Cyclophosphamide dose
If drop in eGFR < 33% AND CrCl > 40 mL/min/1.73m^2	Full dose

If drop in eGFR > 33% **BUT** CrCl > 40 mL/min/1.73m^2	90% dose
If drop in eGFR > 33% **BUT** CrCl < 40 but > 10 mL/min/1.73m^2	50% dose
If CrCL < 10 mL/min/1.73m^2	Withhold until toxicity resolves

5.3 Cardiac Toxicity

Dexrazoxane will be used as a cardioprotecant prior to each dose of doxorubicin.

5.3.1 Monitoring

An electrocardiogram and echocardiogram with determination of shortening fraction, or radionuclide angiogram for ejection fraction should be performed before treatment and then according to the schedule in Section 7.0. Use the same test each time for consistency in evaluation.

5.3.2 Management

If prolongation of the QTc interval (> 0.48 sec), a decrease in the ejection fraction to < 50%, or a decrease in the left ventricular shortening fraction to < 27%, the doxorubicin-containing chemotherapy should be postponed 1 week, any existing electrolyte or micronutrient deficiencies corrected and the tests repeated. If the abnormalities persist during that 1 week delay or at any time patients have Grade ≥ 3 (symptomatic) left ventricular systolic dysfunction, doxorubicin should be PERMANENTLY DISCONTINUED. Substitute dactinomycin 0.045 mg/kg/day (max dose 2.5 mg) for 1 day, IV slow push on Day 1 only of the VDC cycle. The chemotherapy cycle administered following dactinomycin-contianing cycles should be administered after 21-days (and not 14 days) since interval compression is not possible when dactinomycin is administered (a 2-week interval may still be maintained following I/E cycles). No change in doxorubicin dosing is recommended for an asymptomatic decrease in cardiac ejection or shortening fraction provided they remain at or above 50% and 27% respectively.

5.4 Neurological Toxicity

Neurological toxicity can result from two of the agents used in this study, vincristine and ifosfamide.

5.4.1 Vincristine Neuropathy

Grade 1 and 2 neuropathy requires no dose modification. For Grades 3 and 4 (interfering with activities of daily living) hold indefinitely until symptoms decrease to Grade 1 (present on exam/testing but not symptomatic) or less and resume at 50% dose. Increases to 75% and full dose should be considered at the start of each vincristine containing cycle based on patient's symptoms.

Anticipate autonomic neuropathy resulting in constipation. Laxatives and/or stool softeners should be used preemptively during vincristine containing cycles. If severe paralytic ileus occurs vincristine should be stopped until normal bowel movements are re-established and then resumed at 50% dose. Mild to moderate constipation (< 4 days) is not an indication for interrupting vincristine.

5.4.2 Ifosfamide Neurotoxicity

This is an organic brain syndrome that ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses. If symptoms are mild and transient cycle may

continue with strict avoidance of potentially aggravating co-administered medications such as sedatives and anticholinergic drugs. If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue.

Patients who have experienced mild symptoms (≤ Grade 2) may receive ifosfamide in subsequent cycles. If patients with ≤ Grade 2 neurotoxicity are to be re-treated, the ifosfamide infusion may be prolonged at the investigator's discretion. If neurotoxicity > Grade 2 occurs or symptoms are prolonged, delete ifosfamide from all subsequent cycles and substitute cyclophosphamide 440 mg/m^2 per day with Mesna uroprotection (60% of the cyclophosphamide dose = 265 mg/m^2/day or 9 mg/kg/day for those < 1 year old) for 5 days, with 5 days of etoposide. This schedule of fractionated cyclophosphamide has previously been used in National Wilms Tumor Trial V, Regimen I.

5.5 Mucositis

A few simple remedies for mucositis are available, and all should be pursued before doses are reduced. The incidence and severity of mucositis have been related to degree of pre-existing mucosal disease and oral hygiene. Good mouth care, including use of mouth rinses should be considered. Medications include the following:

Glutamine: Oral swish-and-swallow glutamine suspension at 2 gram/m^2 swish-and-swallow twice daily has been shown to reduce the severity and duration of mucositis associated with chemotherapy and radiotherapy in a randomized controlled trial.

Sucralfate: Though its effectiveness is controversial, sucralfate suspension 1 gram/10 mL (40-80 mg/kg/day, max 1 gram per dose) swish-and-swallow 4 times daily may reduce the symptoms or severity of mucositis from chemotherapy and radiation therapy.

Chemotherapy doses should not be reduced for mucositis unless all supportive care remedies outlined above have been exhausted.

For Grade 3 or 4 mucositis (mouth or throat pain interfering with ability to hydrate or aliment adequately or diarrhea resulting in incontinence and interfering with daily activities) which persists more than 15 days after a vincristine-doxorubicin-cyclophosphamide cycle, and is unresponsive to the measures described, decrease the doxorubicin dose by 25% in subsequent cycles. Do not decrease the doses of the other drugs.

For Grade 3 or 4 mucositis which persists more than 15 days after an ifosfamide-etoposide cycle, reduce both the ifosfamide and etoposide doses by 25% in subsequent cycles. Re-escalation should be attempted if mucosal toxicity > Grade 2 does not recur.

5.6 Hematuria or Hemorrhagic Cystitis

5.6.1 Microscopic Hematuria

For treatment modifications, microscopic hematuria is a count defined as > 50 RBCs/HPF without visible blood in the urine.

For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), do not modify the cyclophosphamide/ifosfamide dose. Administer with increased hydration (3500-4000 mL/m^2/day) using a total daily mesna dose equal to 60% of the daily cyclophosphamide/ifosfamide dose as a continuous infusion over at least 9 hrs. For example, if the full cyclophosphamide dose is 1200 mg, then administer at least 720 mg of mesna by continuous infusion.

For persistent microscopic hematuria (more than 2 abnormal urinalyses during a cycle of therapy), do not modify the cyclophosphamide/etoposide dose. Administer with increased hydration (3500-4000 mL/m^2/day) using a total daily mesna dose equal to 100% of the daily cyclophosphamide/ifosfamide dose as a continuous infusion over at least 9 hrs.

5.6.2 Gross Hematuria

Gross hematuria is defined as visible blood in the urine.

All episodes of gross hematuria should be evaluated in conjunction with a pediatric surgical or urologic consult. Further testing, such as cystoscopy, urine culture, excretory urogram, and voiding cystogram should be considered based on good clinical judgment.

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during or following a cycle of therapy, hold cyclophosphamide/ifosfamide indefinitely until hematuria clears. When hematuria clears, restart at 50% of the previous cyclophosphamide/ifosfamide dose. Use hydration of 3500-4000 mL/m^2/day and mesna at 100% of the cyclophosphamide/ifosfamide dose as a continuous infusion over 24 hrs/day. The cyclophosphamide/ifosfamide dose may be escalated back to 100% if tolerated.

For persistent gross hematuria after completion of a cycle of therapy, hold subsequent cyclophosphamide/ifosfamide doses until the urine clears to less than gross hematuria. Reinstitute cyclophosphamide/ifosfamide at 50% of the initial dose, with hydration of 3500-4000 mL/m^2/day and the mesna at 100% of the cyclophosphamide/ifosfamide dose given as a continuous infusion over 24 hours. If this regimen is tolerated, the cyclophosphamide/ifosfamide dose may be escalated back to the original dose (100%). For persistent or recurrent gross hematuria on the mesna continuous infusion regimen, discontinue cyclophosphamide/ifosfamide.

5.7 Hepatotoxicity

Hepatotoxicity is not expected to occur frequently on this study and if observed, causes should be investigated. However, abnormal liver function may be associated with increased vincristine and doxorubicin toxicity. Dose adjustments for vincristine, doxorubicin and etoposide should be made based on the level of direct bilirubin. Vincristine doses omitted due to toxicity will not be replaced.

Hepatotoxicity	Vincristine adjustment	Doxorubicin adjustment	Etoposide adjustment
Grade 1 (Direct bilirubin < 1.5 X ULN)	Full Dose	Full Dose	Full Dose
Grade 2 (Direct bilirubin 1.5-3 X ULN)	Delay 1 week. Full dose if resolved to Grade 1 or less. 50% if still Grade 2.	Delay 1 week. Full dose if resolved to Grade 1 or less. 50% if still Grade 2.	Delay 1 week. Full dose if resolved to Grade 1 or less. 50% if still Grade 2.
Grade 3, 4	Delay 1 week and until resolved to Grade 1, then resume at full dose.	Delay 1 week and until resolved to Grade 1, then resume at full dose.	Delay 1 week and until resolved to Grade 1, then resume at full dose.

5.7.1 Sinusoidal Obstruction Syndrome (SOS, Formerly Known as Veno-occlusive Disease [VOD]) of the Liver (Hepatopathy)

Treating physicians are advised to monitor closely for signs of SOS.

Criteria for diagnosis of sinusoidal obstruction syndrome of the liver
a. Pathologic confirmation by liver biopsy OR
b. Reversal of portal venous flow by ultrasound OR
c. Two or more of the following:

- Serum Total Bilirubin > 2.0 mg/dL
- Unexplained weight gain greater than 10% of baseline weight or ascites
- Hepatomegaly or RUQ pain without other explanation

SOS is graded as below.

	MILD	**MODERATE**	**SEVERE**
Total Bilirubin	≤ 6 mg/dL	> 6 and < 20 mg/dL	≥ 20 mg/dL
Weight Gain	≤ 5% of baseline of noncardiac origin	> 5% of baseline of noncardiac origin	
Ascites	None	Clinical or radiologic documentation	Compromising respiratory function
Hepatic Dysfunction	Reversible	Reversible	Hepatic encephalopathy

For any SOS (mild, moderate, or severe), a CTEP-AERS report must be filed per Section 11.10 and 11.11.

5.8 Dermatologic Toxicity

5.8.1 Nails

Patients receiving interval compressed chemotherapy may rarely slough their fingernails. This is painless and reversible, and no countermeasures are indicated.

5.8.2 Palms and Soles

Patients may rarely experience painful inflammation and desquamation of the palms and soles, more often after ifosfamide-etoposide cycles. If this occurs, allow a 21-day interval in the next cycle, and attempt a 14-day cycle again subsequently.

5.9 Allergy to Etoposide

Pre-medication (such as diphenhydramine, +/- ranitidine and +/- hydrocortisone) and slowing of the rate of infusion with etoposide can be tried. Substitution with etoposide phosphate should be considered if a patient develops a reaction that would put him/her at risk if further etoposide were given. Etoposide phosphate may be substituted for etoposide with pre-medication and administered given at the same dose and rate.

5.10 Pneumonitis

Thoracic radiation may be used in this patient population for management of primary tumor (e.g., chest wall primary site) or for management of metastatic disease (e.g., whole lung radiation for patients with lung metastasis). The extent to which ganitumab may increase the risk or severity of pneumonitis is not known, though an interim analysis in March 2019 showed a higher number of cases of pneumonitis in patients treated with ganitumab.

Investigators should be vigilant for development of pneumonitis in patients treated with or without ganitumab. Oxygen saturation evaluation at time of protocol mandated physical examinations is required for patients who have been treated with whole lung radiation. Investigators should consider additional evaluations in patients who have been treated with whole lung radiation who present with unexplained cough, dyspnea, or physical exam findings on lung auscultation.

Pneumonitis will be managed according to local practice, individualized to each patient's clinical scenario:

Grade 1: Patients with Grade 1 pneumonitis (asymptomatic) should be monitored according to local practice for potential worsening to higher grade pneumonitis (symptomatic).

Grade 2 or higher: A typical approach to Grade 2 and higher radiation pneumonitis includes a protracted course (2-4 weeks) of high dose corticosteroids (prednisone) followed by a slow taper over 3 to 12 weeks. Prophylaxis for pneumocystis pneumonia (PCP) is required for patients receiving > 20 mg prednisone daily. Consultation with pulmonology is strongly encouraged. For questions about radiation pneumonitis, sites may reach out to the study chair (Steven DuBois), vice-chair (Julia Glade-Bender), and lead radiation oncologist (Nadia Laack).

Sites are to report pneumonitis of any grade in an expedited manner via CTEP-AERS and through routine reporting (see Section 11).

5.11 Any Other Grade 3 or 4 Toxicities

Delay chemotherapy until toxicity has resolved to Grade 1. Dose reduction of 25% may be considered at investigator's discretion. Attempts should be made to re-escalate dose if toxicity does not recur.

6.0 DRUG INFORMATION

6.1 GANITUMAB

(AMG 479) IND #, NSC 750008 (04/25/19)

Source and Pharmacology:

Ganitumab is a fully human recombinant IgG1 monoclonal antibody against human IGF-1R. Ganitumab exerts its anti-tumor activity by blocking ligand binding (IGF-1 and IGF-2) and inducing receptor internalization and degradation without cross-reacting with the insulin receptor. Ganitumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Ganitumab is a heterotetramer composed of 2 heavy chains of the IgG1 subclass and 2 light chains of the kappa subclass. The molecule contains 12 intramolecular and 4 intermolecular disulfide bonds and has a typical bi-antennary glycosylation pattern in the Fc portion of the heavy chain. Each heavy chain, with its 4 predicted intramolecular disulfides, contains 449 amino acids. The heavy chain contains an N-linked glycan. Each light chain contains 219 amino acids, with 2 putative intramolecular disulfides. The molecular weight is approximately 146 kilodaltons (kD).

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Ganitumab (AMG 479, NSC 750008)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 334 patients.* Below is the CAEPR for Ganitumab (AMG 479).

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 2.1, March 26, 2019[1]

Adverse Events with Possible Relationship to Ganitumab (AMG 479) (CTCAE 5.0 Term) [n= 334]			**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)***
EAR AND LABYRINTH DISORDERS			
		Hearing impaired[2]	
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***

Adverse Events with Possible Relationship to Ganitumab (AMG 479) (CTCAE 5.0 Term) [n= 334]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Infusion related reaction[3]			***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis[4]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[5]		***Rash[5] (Gr 2)***

[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]Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

[3]Infusional reactions may include chills, fever, hypotension, dyspnea, arthralgia, joint swelling, headache, dizziness, and cardiac arrhythmia (e.g., atrial fibrillation, tachycardia).

[4]The rate and severity of radiation-associated pneumonitis may be increased in patients who receive ganitumab shortly before or after radiation to the lungs.

[5]Rash includes rash, rash acneiform, rash maculo-papular, skin lesions, and pruritus.

Adverse events reported on ganitumab (AMG 479) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ganitumab (AMG 479) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (diastolic dysfunction); Heart failure; Myocardial infarction
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Cataract; Keratitis
GASTROINTESTINAL DISORDERS - Abdominal pain; Anal fistula; Anal mucositis; Constipation; Dysphagia; Esophagitis; Gastrointestinal disorders - Other (enteritis); Mucositis oral; Oral pain; Pancreatitis; Rectal fistula; Rectal hemorrhage; Small intestinal obstruction; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (jaundice cholestatic)
INFECTIONS AND INFESTATIONS - Anorectal infections; Infections and infestations - Other (pneumococcal infection); Lung infection; Myelitis; Sepsis; Skin infection; Soft tissue infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Vascular access complication
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; Ejection fraction decreased; Investigations - Other (electrocardiogram abnormal); Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Radiculitis; Reversible posterior leukoencephalopathy syndrome; Seizure; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Agitation
RENAL AND URINARY DISORDERS - Acute kidney injury; Urinary tract obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Cough; Epistaxis; Hypoxia; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (respiratory hemorrhage)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Palmar-plantar erythrodysesthesia syndrome; Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypertension; Thromboembolic event (venous)

Note: Ganitumab (AMG 479) 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:
Ganitumab will be supplied as a sterile, clear, colorless liquid with 70 mg/mL (210 mg/3 mL or 700 mg/10 mL) vial of ganitumab. The single-use vials also contain the following excipients; 10 mM sodium acetate, 5% w/v sorbitol, 0.004% w/v polysorbate 20, pH 5.2. Sites participating in Canada will utilize the 210 mg vial size. All other participating sites will use the 700 mg vial size.

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

Preparation:
The final concentration of ganitumab for administration should be between 3 mg/mL to 20 mg/mL in 0.9% sodium chloride (NS). Gently invert the infusion bag to mix. DO NOT SHAKE. Protect from light.

Storage**:** Store refrigerated between 2°C to 8°C. Do not shake or freeze. Protect from light.

Stability:
Once the ganitumab is injected into the infusion bag, the infusion must be completed within 8 hours. The total time between removal of ganituamb intact vials from the refrigerator and completion of infusion must not exceed 24 hours.

Vials contain no preservatives and any solution remaining in the vials after the dose is prepared should be discarded.

Route of Administration: Intravenous infusion

Administration:
The infusion line should be thoroughly flushed with saline before and after administration of ganitumab to avoid mixing with other drug products or IV solutions.

The first dose should be administered over 60 minutes without premedication. If well tolerated over 60 minutes, subsequent infusions may be administered over 30 minutes, at the investigator's discretion. Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion.

Doses over 2100 mg should be infused over 120 minutes. If well tolerated over 120 minutes, subsequent infusions may be administered over 60 minutes at the investigator's discretion.

Supplier:
Ganitumab will be supplied by NantBio and distributed by the PMB, CTEP, NCI.

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.

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, and 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 PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record Form (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 Registration and IAM account help: RCRHelpDesk@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 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, gender, 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.

6.3 DACTINOMYCIN

(Actinomycin-D, Cosmegen®) NSC #3053 (05/09/11)

Source and Pharmacology:

Dactinomycin is a member of a class of antibiotic compounds isolated from *Streptomyces parvullus*. Dactinomycin is composed of a planar tricyclic ring chromophore (phenoxazone) to which two identical cyclic polypeptides are attached. The compound binds to DNA by intercalation, depending on a specific interaction between the polypeptide chains and deoxyguanosine. This interaction blocks the ability of DNA to act as a template for RNA and DNA synthesis in a concentration-dependent manner. Low drug concentrations inhibit RNA synthesis more than higher drug concentrations, which block both RNA and DNA syntheses. Dactinomycin can also cause topoisomerase-mediated single-strand breaks in DNA. Dactinomycin is minimally metabolized and is concentrated in nucleated red blood cells with very little diffusion into the CNS. After an IV bolus, dactinomycin has a very short initial distribution half-life of about 1-minute but a prolonged terminal plasma half-life of 36 hours. Dactinomycin is primarily eliminated by renal and biliary excretion. Approximately 30% of the dose is recovered in urine and feces in one week.

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	Anaphylaxis, abdominal pain, extravasation (rare) but if occurs = local ulceration
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression, alopecia (L)	Diarrhea, mucositis, cheilitis, radiation recall reactions, fatigue, lethargy, malaise	Elevated LFTs, hepatitis, hepatomegaly, sinusoidal obstruction syndrome (SOS, formerly VOD) (L), proctitis, acne, skin eruptions, hypocalcemia, fever, ulcerative stomatitis, esophagitis and/or enteritis, myalgia
Delayed: Any time later during therapy			Growth retardation, pneumonitis
Late: Any time after completion of treatment			Secondary malignancies
Unknown frequency and timing:	Fetal toxicities of dactinomycin have been noted in animal models. It is not known if dactinomycin is excreted into breast milk		

(L) Toxicity may also occur later.

Formulation and Stability:

Lyophilized powder, in vials containing 500 mcg of dactinomycin, with 20 mg of mannitol. Store at controlled room temperature, 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and humidity.

Reconstitute with 1.1 mL of sterile water without preservative to give a final concentration of 500 mcg/mL (0.5 mg/mL). The resulting solution should be clear to gold colored.

Preservatives may cause precipitation. Stable at room temperature, 25°C (77°F) protected from light for up to 24 hours.

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

Dactinomycin can be injected directly into the vein or preferably administered through the tubing of a rapidly infusing solution of D5W or NS. The line should be flushed thoroughly at the end of the dactinomycin infusion. Significant binding of dactinomycin by cellulose ester membrane filters used in some intravenous in-line filters has been reported.

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

6.4 DEXRAZOXANE

(ICRF-187, ADR-529, ZINECARD®, Totect®) NSC #169780 (11/17/17)

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 Frequency and 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.

CANADIAN SITES
In Canada, Pfizer brand of Zinecard® is the only product commercially available and now has the same reconstitution, dilution, and expiration dating as the USA Pfizer Zinecard® above.

6.5 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 t½ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t½ 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, urticaria, 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 Modification 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.

6.6 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 Modification 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.

CANADIAN SITES
Etoposide for Injection is available as 20 mg/mL solution.

Etopophos® (etoposide phosphate) is not commercially available in Canada. Sites may purchase and import the USA commercial supply from Bristol Laboratories via an International Distributor (Pharma Exports LLC, phone: 1-412-885-3700, fax: 1-412-885-8022, email: pharexp@aol.com) under the authority of the protocol's No Objection Letter (NOL). Drug Accountability Record (DAL) must record Lot #'s and expiry dates of shipments received and doses dispensed. Sites may use their own DAL as long as it complies with all elements of ICH GCP and Division 5 of the Food and Drugs Act. Each site is responsible for the procurement (import +/- purchase) of Etoposide Phosphate (Etopophos). Sites may import and manage a single clinical trial supply for multiple protocols as long as each protocol has an NOL and the protocol the patient is registered on is recorded on the DAL.

6.7 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® is 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 2°C-8°C (36°F-46°F) storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). 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.

6.8 IFOSFAMIDE

(Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 (05/09/11)

Source and Pharmacology:
Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramide mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4 g/m² to 3.8-5 g/m², respectively. At 1.6-2.4 g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5 g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (< 10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

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 (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt:	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia,	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with

Within 2-3 weeks, prior to next course		asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	macroscopic hematuria, dysuria, cystitis and urinary frequency (< 5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconi-like syndrome gonadal dysfunction, ovarian failure[1] (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
(L) Toxicity may also occur later.

Formulation and Stability:
Ifosfamide is available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives and as a 50 mg/mL solution in 20 mL and 60 mL vials.

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

Reconstitute ifosfamide lyophilized powder with sterile water for injection or bacteriostatic water for injection(use 20 mL for the 1 g vial and 60 mL for the 3 g vial) to produce a final concentration of 50 mg/mL. **Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.** Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unreconstituted vials at room temperature 20°-25°C (68°-77°F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35°C.

Reconstituted solutions of ifosfamide or ifosfamide solution should be diluted further to concentrations of 0.6 to 20 mg/mL in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination.

Mesna must always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Refer to the Chemotherapy Administration Guidelines for additional information.

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

6.9 MESNA - INJECTION (10/13/17)

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

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		

[1] *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 (68º-77ºF). 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.

6.10 MESNA - ORAL (11/27/17)

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

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. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

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	Bad taste with oral use	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		

[1] *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 1800mg/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 is available as scored 400 mg oral tablets. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

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, 15°-25°C (68-77ºF). 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.

The oral dose of mesna is **twice** the IV dose.

Oral tablets:
Administer tablets or diluted parenteral solution. Mesna tablets are scored and doses can be rounded to half a tablet (200mg).

Injection for oral use:
Dilute the mesna parental solution before oral administration to decrease the sulfur odor associated with the product. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice.

Mesna may cause false positive test for urinary ketones.

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

6.11 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 manufacturers do 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.

6.12 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 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. **Obtain other studies prior to start of phase unless otherwise indicated.**

7.1.1 Required and Optional Clinical, Laboratory and Disease Evaluations at Study Entry, during Induction and at the end of Induction

STUDIES TO BE OBTAINED	Baseline	During Chemotherapy	End of Induction / Pre-Local Control
History and Physical Exam	X	X[1]	X
Height, Weight, BSA	X	X[1]	
CBC, differential, platelets	X	X[1, 2]	X
Urinalysis	X	X[1]	
Urine or serum pregnancy test	X[8]		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X[1]	
Creatinine, SGPT (ALT), Total bilirubin	X	X[1]	
Albumin	X		
EKG	X		
Echocardiogram or MUGA	X	X[4]	
Plain film of primary tumor (Recommended at baseline for bone tumors only)	X		
MRI or CT of primary tumor[6]	X		X
Chest CT[7]	X		X
FDG-PET scan, including primary tumor SUV	X[10]		X[10, 13]
Anatomic imaging of bone and soft tissue metastases	X[10]		X[10]
MRI or CT and FDG-PET scans submitted for imaging aims[12]	X		X
Bilateral bone marrow aspirates and biopsies	X	X[5]	X[5]
Serum for ganitumab pharmacokinetics (only for first 10 patients < 21 years of age in Regimen B)	X[11] (prior to ganitumab)	X[11] (Days 15, 29 and 71)	
Submission of bone marrow aspirate (optional)[9]	X	X	X
Peripheral blood in red top tube (required)[9]	X	Prior to Week 5 Chemotherapy	
Peripheral blood in Streck tube for ctDNA study (optional, patients enrolling with Amendment #1 and beyond)[9]	X	Prior to Week 3[14] and Week 5 Chemotherapy	X[14]
Unstained slides/block (required at study entry)[9]	X		
Peripheral blood in EDTA tube (required at study entry)[9]	X		

1 Obtain prior to each cycle.

2 Obtain additional CBCs as needed for good patient care. Recommended guidelines for administering interval-compressed chemotherapy include checking CBC with differential on

Day 1 and 8 of each cycle and then every Monday, Wednesday and Friday (or 3 other nonconsecutive days per week) after Day 12, until the criteria for starting the next cycle are satisfied.

4 Determination of shortening fraction or ejection fraction is to be obtained prior to Week 9 doxorubicin. Use the same test each time for consistency in evaluation.

5 For patients with clinical evidence of bone marrow metastatic disease at study entry, repeat bilateral bone marrow aspirates and biopsies after Cycle 3 of Induction chemotherapy. If still positive, repeat at time of other end-Induction disease evaluations. See Sections 10.3.4 and 10.4 for definitions of marrow response. See Section 15.0 for recommended bone marrow aspirate submission.

6 MRI preferred for most primary tumor sites.

7 CT scan of the chest should use spiral technique (if available) with a single breathhold, for patients able to cooperate. If whole body PET/CT obtained with thin cuts through chest, this scan may substitute for required chest CT scan otherwise a dedicated chest CT is required.

8 Pregnancy test required prior to study enrollment for females of childbearing potential only.

9 See Section 15.0 and Appendix II for specimen submission for required and optional studies.

10 Sites suspicious for bone or soft tissue metastasis by FDG-PET scan at study entry should be imaged further with MRI or CT (whole body CT as part of PET/CT is acceptable) at study entry and at end-Induction.

11 Serum samples for ganitumab concentrations are required for the first 10 patients < 21 years of age in Regimen B. See Section 15.5 for specimen requirements. (Enrollment to this required cohort completed as of July 2015 and all induction samples have been collected for this cohort)

12 See Section 16.3 for instructions on submitting CT or MRI and FDG-PET images for imaging correlative aims.

13 If an FDG-PET is obtained prior to the scan required at end-Induction, data on SUV at the primary tumor site should also be submitted.

14. This time point is for patients who consented to Amendment #3C and beyond.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

7.1.2 Required and Optional Clinical, Laboratory and Disease Evaluations during Local Control, Consolidation, and Metastatic Site Radiation

STUDIES TO BE OBTAINED	Prior to Resuming Consolidation Chemotherapy	During Chemotherapy	End of Consolidation / Pre-Metastatic Site Radiation	Metastatic Site Radiation
History and Physical Exam, including O_2 saturation for patients receiving whole lung radiation	X	X[1]	X	Weekly and within 30 days of completion of whole lung radiation
Height, Weight, BSA	X	X[1]		
CBC, differential, platelets	X	X[1, 2]	X	Weekly
Urinalysis	X	X[1]	X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X[1]	X	
Creatinine, SGPT (ALT), Total bilirubin	X	X[1]	X	
Echocardiogram or MUGA	X[4]	X[4]	X[4]	
Pulmonary Function Testing			X[8]	
MRI or CT of primary tumor[6]		Prior to Week 9	X	Any time for suspected relapse[13]
Chest CT[7]		Prior to Week 9	X	Any time for suspected relapse[13]
FDG-PET scan		Prior to Week 9[10]	X[10]	Any time for suspected relapse[13]
Anatomic imaging of bone and soft tissue metastases		Prior to Week 9[10]	X[10]	
Bilateral bone marrow aspirates and biopsies		X[5]	X[5]	Any time for suspected relapse[13]
Peripheral blood in red top tube (required)[9]			X[12]	
Submission of bone marrow aspirate (optional)[9]		X	X	
Unstained slides/block from patients undergoing surgical local control (optional)[9]	X		X	
Peripheral blood in Streck tube for ctDNA study (optional for patients enrolling with Amendment #1 and beyond)[9]		Prior to Week 9[12]	X	
Percent tumor necrosis for patients undergoing surgical local control[11]	X			

1 Obtain prior to each cycle.

2 Obtain additional CBCs as needed for good patient care. Recommended guidelines for administering interval-compressed chemotherapy include checking CBC with differential on Day 1 and 8 of each cycle and then every Monday, Wednesday and Friday (or 3 other nonconsecutive days per week) after Day 12, until the criteria for

starting the next cycle are satisfied.

4 Echocardiogram or MUGA (radionuclide angiogram) is to be obtained prior to each doxorubicin-containing cycle of Consolidation, prior to Week 11 Consolidation and again at end-Consolidation (at time of disease re-staging studies that take place at end-Consolidation). More frequent monitoring may be indicated as part of good clinical care. Use the same test each time for consistency in evaluation.

5 For patients with clinical evidence of bone marrow metastatic disease at end-Induction evaluation, repeat bilateral bone marrow aspirates and biopsies prior to Week 9. All patients with clinical evidence of bone marrow metastatic disease at study entry will undergo repeat bilateral bone marrow aspirates and biopsies at end-Consolidation. See Sections 10.3.4 and 10.4 for definitions of marrow response. See Section 15.0 for recommended bone marrow aspirate submission.

6 MRI preferred for most primary tumor sites. Note that MRI may not be interpretable if the patient has undergone resection of the primary bony site of disease with placement of a massive metallic prosthesis. Imaging of the primary site following such procedures may be limited to plain radiographs and/or CT scan with contrast.

7 CT scan of the chest should use spiral technique (if available) with a single breathhold, for patients able to cooperate. If whole body PET/CT obtained with thin cuts through chest, this scan may substitute for required chest CT scan otherwise a dedicated chest CT is required.

8 For all patients with lung metastases at study entry who receive whole lung radiotherapy during Metastatic Site Radiation.

9 See Section 15.0 for specimen submission for optional recommended biology studies. Submission of unstained slides is requested for patients undergoing surgical local control during Local Control phase or as part of a delayed resection of a residual primary tumor or metastatic deposit.

10 Sites of bone or soft tissue metastasis identified at study entry and any new sites of concern for bone or soft tissue metastasis based on FDG-PET should be imaged further with MRI or CT (whole body CT as part of PET/CT is acceptable) at each time point.

11 See Section 14.3.3.

12 This time point is for patients who consented to Amendment #3 C and beyond.

13 Submission of imaging demonstrating the first episode of disease progression/suspected relapse is required for central review (see Section 16.3). For times other than suspected relapse, follow recommended disease evaluation schedule for all patients in Regimens A and B in Section 7.3 timed from end-Consolidation. This includes disease restaging 3 months and 6 months from end-Consolidation.

This table only includes evaluations necessary to answer the study aims. Obtain other studies as indicated for good clinical care.

7.2 Correlative Biology Studies

The correlative biology studies include both required and strongly recommended samples for all patients in both Regimen A and Regimen B of the study. These studies are critical to improve our understanding of metastatic Ewing sarcoma and response to IGF-1R inhibition. Any time a tumor is resected or biopsied in a patient who has consented to optional tissue collection on this study, tumor material should be submitted to support correlative biology studies.

In addition to the correlative biology studies embedded within this clinical trial, all patients should be offered co-enrollment on the COG Ewing sarcoma biology study, AEWS07B1 or APEC14B1.

See Section 15.0 for detailed specimen requirements and Appendix II for a summary.

7.3 Follow-up

General follow-up should occur as per local institutional standards and as appropriate for individual patient care and known long term toxicities of agents received. See COG Late Effects Guidelines for recommended post treatment follow-up at: http://www.survivorshipguidelines.org/.

7.3.1 Suggested Clinical, Laboratory and Disease Evaluations during Follow-up

Note that evaluations are timed from the end of Consolidation therapy for patients in both Regimen A and in Regimen B.

Observation	3 Months	6 Months	9 Months	1 Year	1.25 Years	1.5 Years	1.75 Years	2 Years	2.25 Years	2.5 Years	2.75 Years	3 Years	3.5 Years	4 Years	4.5 Years	5 Years
History and Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen Saturation by Pulse Oximetry[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT Chest[2,5]	X	X	X	X	If Relapse Suspected											
Chest Radiograph[5]					X	X	X	X		X		X	X	X	X	X
MRI or CT[3,5] (Primary Site)	X	X	X	X	If Relapse Suspected											
Plain film primary site and sites of bone metastasis[5]					X	X	X	X		X		X	X	X	X	X
FDG-PET scan[4,5]	X	X	X	X	If Relapse Suspected											
Bilateral bone marrow aspirates and biopsies	If Relapse Suspected															
Echocardiogram or MUGA				X				X				X		X		X

1 For patients treated with whole lung radiation.

2 CT Scan of the chest should use spiral technique (if available) with a single breathhold, for patients able to cooperate. May be omitted if FDG-PET scan includes diagnostic quality chest CT otherwise a dedicated chest CT is required. If residual abnormalities on chest CT, ongoing chest CT should replace chest radiograph during year 2 following completion of Consdolidation chemotherapy.

3 MRI preferred for most primary tumor sites. Note that MRI may not be interpretable if the patient has undergone resection of the primary bony site of disease with placement of a massive metallic prosthesis. Imaging of the primary site following such procedures may be limited to plain radiographs and/or CT scan with contrast.

4 Sites of bone or soft tissue metastasis identified at study entry and any new sites of concern for bone or soft tissue metastasis based on FDG-PET should be imaged further with MRI or CT (whole body CT as part of PET/CT is acceptable) at each time point FDG-PET scan required.

5 Submission of the imaging demonstrating the first episode of disease progression/suspected relapse is required for central review (see Section 16.3).

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

7.3.2 Evaluations at time of suspected relapse

Biopsy confirmation of suspected recurrence is recommended in most cases when feasible. In case of local relapse, metastatic work-up is required for confirmation of extent of recurrence.

See Section 15.0 for submission of follow-up bone marrow aspirate material and/or unstained slides/tissue block and/or blood sample in Streck tubes obtained at the time of relapse.

See Section 16.3 for submission of scans obtained at the time of first episode of relapse or disease progression.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease according to Section 10.3.
b) Biopsy positive residual bone marrow metastatic disease by routine morphology at end-Consolidation (Section 10.4.1).
c) Biopsy positive viable tumor after completion of Metastatic Site Radiation (Section 10.4.3).
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Completion of planned therapy.
f) Physician determines it is in patient's best interest.
g) Development of a second malignant neoplasm.

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

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of patient's entry to the study.
f) Patients initially enrolled and randomized with a diagnosis of Ewing sarcoma or PNET for whom the initial enrolling diagnosis is changed to a diagnosis other than Ewing sarcoma or PNET.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

9.1.1 Randomization

The purpose of this study is to evaluate the role of ganitumab in the treatment of newly-diagnosed metastatic Ewing sarcoma. All patients enrolled on AEWS1221 will be randomized at the time of enrollment, after confirmation of eligibility.

Randomization will be done in the ratio of 1:1 to the non-ganitumab containing therapy ('comparator regimen') *v.* the ganitumab containing therapy ('experimental regimen'). Randomization will be stratified according to age at enrollment (< 21 years vs. ≥ 21 years) and extent of disease (lung only vs. any other metastatic site): (1) stratum 1 – patients < 21 years with metastatic disease in one or both lungs only; (2) stratum 2 – patients < 21 years with any extra-pulmonary metastases; (3) stratum 3 – patients ≥ 21 years with metastatic disease in one or both lungs only; and (4) stratum 4 – patients ≥ 21 years with any extra-pulmonary metastases.

9.1.2 Primary Endpoint and Hypothesis

The primary outcome measured on each participant will be time to adverse analytic event (EFS), defined to be disease-related event, diagnosis of a second malignant neoplasm, or death. A disease-related event will be: (1) disease progression as defined in Section 10.1-10.3; (2) persistent disease in bone marrow at the end of Consolidation therapy as defined in Section 10.4.1; or (3) biopsy-proven viable tumor after radiation of metastatic disease is completed, as described in Section 10.4.2.

The primary analysis will entail estimation of the relative risk of adverse analytic event for patients on the experimental therapy compared with that for the standard therapy. The primary statistical null hypothesis is H_0: The relative risk of an EFS-event associated with the ganitumab containing therapy is 1 and the statistical alternative hypothesis is H_1: The relative risk of an EFS-event associated with the ganitumab containing therapy is 0.67.

9.2 Patient Accrual and Expected Duration of Trial

Under the statistical null hypothesis we expect to observe 218 events in the study population at the time of analysis for the primary study goal (Table 2B). This will entail 5 years enrollment plus 1.5 years of follow-up of 300 randomized patients. With one-sided test of size 0.025, we will achieve 81% power under the alternative hypothesis.

Table 1A. Aggregate EFS from previous COG studies of newly diagnosed metastatic Ewing sarcoma.

Time Since Start Treatment (Years)	Estimated Proportion Event-Free	95% Confidence Interval
1	0.66	0.60-0.72
2	0.36	0.30-0.42
3	0.24	0.22-0.34
4	0.23	0.19-0.30

Based on this historical result, we estimate the survivor function for EFS for patients randomized to the comparator arm as the piecewise exponential survivor function with the times since enrollment and probabilities of remaining event-free given in Table 1B:

Table 1B: EFS from Enrollment Expected for Patients Enrolled to the Comparator Therapy

Time in Months Since Enrollment	Proportion Analytic Event Free
6	0.881
12	0.664
18	0.457
24	0.357
30	0.308
36	0.280
42	0.265
48	0.244
54	0.240
60	0.238
66	0.235
72	0.234
78	0.233

The enrollment experience as of June 2016 to AEWS1221 indicates we can expect approximately 5 patients per month (60 per year) to be enrolled. The study design will require the enrollment of 300 eligible patients with 1.5 years of follow-up after the last enrollment. We will enroll up to 330 patients to account for ineligible patients. The study will be open for accrual for approximately 5 years if 300 patients are required. In summary, the study will require 6.5 years to obtain sufficient data to address the primary study goal (5 years of enrollment plus 1.5 years of follow-up after the last patient is enrolled).

Design Summary

The two regimens will be compared using the relative risk regression model with strata representing those used for randomization. Each patient's outcome will be associated with that individual's assigned regimen regardless of received therapy. A log-partial-likelihood one-sided test of size 0.025 will be used to compare the two regimens. This level of α-error is commonly utilized in superiority designs intended to collect substantive evidence for a new treatment, particularly in a rare indication in which multiple definitive trials are not feasible. A one-sided comparison is used because the experimental regimen will be identified as the preferred therapy only if it is judged to be superior to the comparator regimen according to the statistical criteria described above. If the statistical alternative hypothesis is true, the experimental regimen will be identified for further development with probability 0.81. This probability was calculated using the method of Barthel et al,[107] as illustrated in the evaluations of the statistical properties of the proposed design presented below:

Table 2A: Characteristics of the Proposed Design If the Alternative Hypothesis is True

```
ART - ANALYSIS OF RESOURCES FOR TRIALS       (version 1.1.0, 10 December 2013)
-------------------------------------------------------------------------------
A sample size program by Abdel G Babiker, Patrick Royston & Friederike
Barthel,MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.
-------------------------------------------------------------------------------
Type of trial                              Superiority - time-to-event outcome
Statistical test assumed                   Unweighted logrank test (local)
Number of groups                           2
Allocation ratio                           Equal group sizes

Total number of periods                    13
Length of each period                      6 months

Survival probs per period (group 1[1])      0.881 0.664 0.457 0.357 0.308 0.280
                                            0.265 0.244 0.240 0.238 0.235 0.234
                                            0.233
Survival probs per period (group 2[2])      0.919 0.761 0.593 0.503 0.456 0.428
                                            0.413 0.390 0.386 0.384 0.381 0.380
                                            0.379
Number of recruitment periods              10
Number of follow-up periods                3
Method of accrual                          Uniform
Recruitment period-weights                 1 1 1 1 1 1 1 1 1 1 0 0 0

Hazard ratios as entered (groups 1,2)      1, .666666666667
Alpha                                      0.025 (one-sided)
Power (calculated)                         0.809

Total sample size (designed)               300
Expected total number of events            196
```

[1] Group 1- Comparator Regimen (Regimen A): The median EFS occurs at 16.6 months
[2] Group 2- Experimental Regimen (Regimen B): The median EFS occurs at 24.4 months

Table 2B: Projected Number of Events Observed at Various Time Points After the Start of Enrollment If the Null Hypothesis is True

Number of Elapsed Six Month Periods Since Study Opening	Expected Cumulative Number of Patients Enrolled	Expected Cumulative Number of Events – Comparator Regimen	Expected Cumulative Number of Events – Experimental Regimen
1	30	1	1
2	60	5	5
3	90	12	12
4	120	21	21
5	150	31	31
6	180	41	41
7	210	52	52
8	240	63	63
9	270	75	75
10	300	86	86
11	300	97	97
12	300	105	105
13	300	109	109

Table 2C: Projected Number of Events Observed at Various Time Points After the Start of Enrollment If the Alternative Hypothesis is True

Number of Elapsed Six Month Periods Since Study Opening	Expected Cumulative Number of Patients Enrolled	Expected Cumulative Number of Events – Comparator Regimen	Expected Cumulative Number of Events – Experimental Regimen
1	30	1	1
2	60	5	3
3	90	12	8
4	120	21	14
5	150	31	22
6	180	41	31
7	210	52	40
8	240	63	49
9	270	75	57
10	300	86	67
11	300	97	75
12	300	105	82
13	300	109	87

We expect many of the instances of disease progression will be identified at the time of regularly scheduled follow-up visits. This can lead to underestimation of the true relative risk associated with experimental regimen when relapse times are treated as exact.[108] Various solutions have been proposed.[108,109] To assess the effect of this possible bias we will use the methodology proposed by Whitehead.[110] Briefly, if all recurrences are detected at a scheduled screening time at the end of a reporting or follow-up period, we will apply Method 2 proposed by Whitehead.[110] That is, the data will be treated as a discrete time survival process with the effect of treatment acting multiplicatively on the conditional probability of relapse. If some recurrences are detected at times other than scheduled screen times, we will adopt Method 4 proposed by Whitehead.[110] That is, we will fit a parametric model that treats disease progressions identified at routine visits as interval censored observations with the left censoring time as the date of the last screening prior to the identification of the relapse and other relapse times as being know exactly. Initially we will fit generalized Gamma model for the exact time of relapse and use the Weibull model if this provides adequate fit.

Interim Monitoring of Primary Endpoint

The study will be monitored for evidence of reduction in EFS-event risk associated with ganitumab at 3 times after the start of randomization and prior to the final analysis. The flexible α-spending function approach will be used with the function $\alpha(t)=\alpha t^2$. Each of these analyses will occur at the first report preparation date where the information fraction identified in Table 3A has been met or exceeded. Given the model for the outcome for the comparator arm delineated in Table 2B above, the calendar timing of these analyses will be approximately 2.5 years, 3.5 years and 4.5 years after the study is opened. The boundaries for the test statistic that will result in identifying the study to the DSMC for possible closure are summarized in Table 3A.

The planned time for the final analysis is that time at which 218 EFS-events have been observed (Table 2B). If the enrollment rate and the EFS-event rate for the comparator arm are as predicted, and study enrollment is not terminated because of interim monitoring or futility monitoring, this will occur with 5 years of accrual and 1.5 years of follow-up after the last patient is enrolled.

Table 3A. Summary of Interim Monitoring for Evidence of EFS-Risk Reduction

Expected Number of Years of Enrollment of Randomized Patients	Total Expected Number of EFS-events Given the Null Hypothesis	Expected Information	Log-rank Test Statistic Boundary	Typical Value of $e^{\hat{\beta}}$ * at the Cutoff Value	Cumulative α
2.5	61	28%	-2.88	0.481177	0.00196
3.5	104	48%	-2.61	0.613302	0.00576
4.5	149	68%	-2.39	0.676864	0.0116
5 + 1.5 Years of Follow-up	218	100%	-2.07	0.755484	0.025

* $\hat{\beta}$ is the estimate of the log-hazard ratio and $e^{\hat{\beta}}$ is the estimated relative hazard rate for the EFS-event rates of $\frac{Experimental}{Comparator}$ regimens from the relative risk regression model.

Assessing inefficacy of ganitumab will be done following the methodology of Freidlin *et al*.[111] The table below provides a summary of the time point at which each evaluation is done, the statistic used for the comparison and the boundary where, if the statistic is greater than or equal to the boundary, the study will be identified to the COG DSMC for possible termination because of inefficacy of ganitumab.

Table 3B: Monitoring for Inefficacy of the Experimental Regimen

Expected Number of Years of Enrollment of Randomized Patients	Total Expected Number of EFS-events Given the Null Hypothesis	Expected Information	Statistic Considered	Boundary
2.5	61	28%	$\frac{\hat{\beta}}{s.d.\left(\hat{\beta}\right)}+$	1.96
3.5	104	48%	$e^{\hat{\beta}}$	1
4.5	149	68%	$e^{\hat{\beta}}$	0.97

+ $\hat{\beta}$ is the estimate of the log-hazard ratio, $e^{\hat{\beta}}$ is the estimated relative hazard rate for the EFS-event rates of $\frac{Experimental}{Comparator}$ regimens and $s.d.(\hat{\beta})$ is the estimated standard error of $\hat{\beta}$ from the relative risk regression model. Ten thousand simulated experiments were conducted under the null and alternative hypotheses to assess the frequency properties of the statistical design rules. The data for the comparator arm were generated using the survival distribution based on Table 1B, identified as $S_C(t)$ subsequently. The survivor function for the experimental regimen is identified as $S_E(t)$.

Null Hypothesis - $S_E(t) = S_C(t)$

Time Point in Proportion of Expected Information	Recommendation	Probability Recommendation Will be Made Assuming Null Hypothesis is True
28%	Experimental Arm Considered Superior	0.0015
	Insufficient Efficacy of the Experimental Arm	0.021
48%	Experimental Arm Considered Superior	0.0039
	Insufficient Efficacy of the Experimental Arm	0.4716
68%	Experimental Arm Considered Superior	0.0058
	Insufficient Efficacy of the Experimental Arm	0.1315
100%	Experimental Arm Considered Superior	0.0108
	Experimental Arm is Not Considered Superior	0.3539

The estimated size of the testing procedure is 0.022

Alternative Hypothesis - $S_E(t) = \left(S_C(t)\right)^{\frac{2}{3}}$

Time Point in Proportion of Expected Information	Recommendation	Probability Recommendation Will be Made Assuming Alternative Hypothesis is True
28%	Experimental Arm Considered Superior	0.0644
	Insufficient Efficacy of the Experimental Arm	0.0007
48%	Experimental Arm Considered Superior	0.1789
	Insufficient Efficacy of the Experimental Arm	0.0029
68%	Experimental Arm Considered Superior	0.2372
	Insufficient Efficacy of the Experimental Arm	0.0059
100%	Experimental Arm Considered Superior	0.2977
	Experimental Arm is Not Considered Superior	0.1862

The estimated power of the test procedure is 0.78.

Overall Toxicity of the Addition of Ganitumab to VDC/IE Chemotherapy
Patients who receive treatment during: (1) Induction; or (2) Consolidation phases will be considered in this analysis. Any of these phases in which a patient receives all planned chemotherapy, has an adverse experience that requires termination of protocol therapy or stops protocol therapy because of a disease related event will be considered in this analysis. A phase where a patient experiences a Grade 4 non-hematological toxicity, Grade 3 left ventricular systolic dysfunction, or terminates protocol therapy because of a CTC codeable adverse experience will be considered a phase with a toxicity-event. The frequency of toxicity-events for each of the two phases will be modeled according to the formula:

$$\Pr\left(Toxicity-event \mid \underline{x}_i\right) = \frac{e^{\beta_o + \sum_{j=1}^{k} \beta_{ij} x_{ij}}}{1 + e^{\beta_o + \sum_{j=1}^{k} \beta_{ij} x_{ij}}};$$

Where: $\underline{x}_i$ *are the reporting period characteristics*

β_0 *is the baseline toxicity – event coefficient*

β_i *are the coefficients associated with the characteristics*

The phase characteristics are indicator variables including the randomized regimen as well as the local control modalities used on the primary tumor site. The null hypothesis $\beta_{randomized}$

$_{regimen} = 0$ will be tested using a one-sided test against the alternative that the experimental regimen has an increased frequency of toxicity-events for each of the phases each time the study progress report is prepared for this trial. If this is significant at the 0.05 level, the study committee will alert the COG DSMC and CTEP that the experimental regimen has an increased toxicity-event rate. The committee will consult with the DSMC and CTEP to determine whether the experimental regimen should be modified. No adjustment will be made for multiple testing, since this is the most conservative approach to monitoring. For the Induction phase, where we expect 150 patients on each regimen to contribute to the analysis, the method proposed will identify the experimental regimen as having increased toxicity-event rate with at least probability 0.80 when the experimental regimen's toxicity-event rate is 33.2% and the comparator regimen's toxicity-event rate is 20%. At the time of the preparation of each study progress report, we will construct the 95% confidence interval for the toxicity-event rate for each phase noted above for patients enrolled on the comparator therapy. If this lower bound of this confidence interval exceeds 33.2%, the committee will consult with the DSMC and CTEP to determine whether the study treatments should be modified. This analysis will be presented only to the COG DSMC except when consultation as described above is required.

Sinusoidal Obstructive Disease (SOS) Associated with the Addition of Ganitumab to VDC/IE

Patients who receive treatment during: (1) Induction; or (2) Consolidation phases will be considered in this analysis. Any of these phases in which a patient receives all planned chemotherapy, has an adverse experience that requires termination of protocol therapy or stops protocol therapy because of a disease related event will be considered in this analysis.

Each phase will be evaluated for the occurrence of SOS according to the definition in Section 5.7.1.

A phase where a patient experiences any SOS will be considered a phase with an SOS toxicity-event. The relative frequency of toxicity-events for each of the two phases will be modeled according to the formula:

$$\Pr\left(Toxicity-event \mid x_i\right)=\frac{e^{\beta_o+\beta_1 x_i}}{1+e^{\beta_o+\beta_1 x_i}};$$

$$Where: x_i \text{ is } 1 \text{ if the patient is randomized to ganitumab; } 0 \text{ otherwise}$$

$$\beta_0 \text{ is the baseline toxicity}-\text{event coefficient}$$

$$\beta_1 \text{ is the coefficient associated with the randomized regimen}$$

The null hypothesis $\beta_1 = 0$ will be tested using a one-sided test against the alternative that the experimental regimen has an increased frequency of SOS toxicity-events for each of the phases each time the study progress report is prepared for this trial. For this analysis, initially all patient-phases will be considered as independent analytic units.

If the exact conditional test of the hypothesis $\beta_1 = 0$ is significant at the 0.10 level (one-sided), the study committee will alert the COG DSMC and CTEP that the experimental regimen has an increased SOS toxicity-event rate. The committee will consult with the DSMC and CTEP to determine whether the experimental regimen should be modified. No adjustment will be made for multiple testing, since this is the most conservative approach

to monitoring. At the time of the primary analysis, under the null hypothesis and given the historical EFS experience, we expect 286 patient-phases to be accumulated for each regimen. The method proposed will identify the experimental regimen as having increased toxicity-event rate with at least probability 0.80 when the experimental regimen's SOS toxicity-event rate is 5.7% and the comparator regimen's SOS toxicity-event rate is 2% during each of the Induction and Consolidation phases.

We will explore the effect of possible correlations between analytic units that arises because some analytic units are contributed by the same individual. We will employ a random effects binomial model where a Normally distributed random effect with 0 mean and unknown variance σ^2 is contributed by each unit in a pair of analytic units that arise from the same individual. The results with respect to estimated regimen coefficient and p-value for the null hypothesis for the two analytic approaches (completely independent *v.* random effects) $\beta_1 = 0$ will be compared.

A separate rule will monitor risk of SOS during the Maintenance phase. Because the experimental therapy has a Maintenance component that is not present in the comparator regimen, monitoring the incidence of SOS during Maintenance will be restricted to patients who are randomized to the experimental therapy and start the Maintenance phase of the protocol. A Maintenance phase in which a patient receives all planned ganitumab as prescribed by the protocol, has an adverse experience that requires termination of protocol therapy or stops protocol therapy because of a disease related event will be considered in this analysis. Each phase considered in the analysis will be evaluated for the occurrence of SOS according to the definition in Section 5.7.1. A phase where a patient experiences any SOS will be considered a phase with an SOS toxicity-event. All evaluable Maintenance phases will be aggregated and the statistical hypothesis:

$$H_0 : \Pr(\text{SOS Toxicity-Event is observed during maintenance}) = 0.02$$

will be tested using a one sided exact binomial test of size 0.10. Evaluation of COG experience with the treatment of newly-diagnosed metastatic Ewing sarcoma indicates at least 90% of patients will remain event-free through Induction and Consolidation. We expect, therefore, to have approximately 135 phases available for evaluation per regimen. If 5 or fewer patients experience SOS the treatment will be considered to have an acceptable rate of SOS during Maintenance. If the true probability of SOS during Maintenance is 2%, the probability of declaring that Maintenance is associated with an excessive SOS rate is 0.055. If the true SOS toxicity probability is 5.8%, the method proposed will identify the Maintenance phase SOS toxicity rate as elevated with probability 0.80. If the number of phases available for analysis differs from 135, we will adjust the cutoff values for the binomial test to maintain a type I error rate of at most 10% and a type II error rate of at most 20%, if possible.

The above-noted analyses will be presented only to the COG DSMC except when consultation as described above is required. Further, if an incident of severe SOS is identified, a report describing the incident will be prepared by the AEWS1221 study committee and presented to the COG DSMC within one month of the reporting of such an incident.

In an effort to capture and monitor for potentially undiagnosed cases of SOS, the study committee will tabulate all episodes of Grade $\geq$ 3 AST, ALT, and bilirubin according to randomized regimen twice yearly for review by the sponsor and COG DSMC.

Comparing Risk for Death

The two randomized regimens will be compared with respect to risk of death. The outcome measure for this secondary aim will be overall survival (OS) defined as the time from enrollment to death regardless of cause or last patient contact. A patient who is alive at last contact will be censored at that time for the purposes of this analysis; otherwise the patient will be considered to have experienced an event for the analysis described below.

Based on this historical result, we estimate the survivor function for OS for patients randomized to the comparator arm as the piecewise exponential survivor function with the times since enrollment and probabilities of remaining event-free given in Table 1B:

Table 4A: OS from Enrollment Expected for Patients Enrolled to the Comparator Therapy

Time in Months Since Enrollment	Proportion Alive
6	0.975
12	0.853
18	0.696
24	0.578
30	0.503
36	0.464
42	0.436
48	0.417
54	0.380
60	0.368
66	0.340
72	0.333
78	0.333

We will use a relative risk regression model with strata representing those used for randomization. Each patient's outcome will be associated with that individual's assigned regimen regardless of received therapy. A log-partial-likelihood one-sided test of size 0.05 will be used to compare the two regimens for this secondary analysis. A one-sided comparison is used because the experimental regimen will be identified as the preferred therapy only if it is judged to be superior to the comparator regimen according to the statistical criteria described above. One analysis will be conducted at the time the analysis utilizing the primary outcome measure (EFS) is done. The statistical alternative hypothesis for the OS endpoint is quantified as the hazard ratio for death for Regimen B relative to Regimen A is 0.67 or lower. If the statistical alternative hypothesis is true, the experimental regimen will be identified for further development with probability 0.796. This probability was calculated using the method of Barthel et al,[107] as illustrated in the evaluations of the statistical properties of the proposed design presented below:

```
ART - ANALYSIS OF RESOURCES FOR TRIALS       (version 1.1.0, 10 December 2013)
-------------------------------------------------------------------------------
A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel,
MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.
-------------------------------------------------------------------------------
Type of trial                           Superiority - time-to-event outcome
Statistical test assumed                Unweighted logrank test (local)
Number of groups                        2
Allocation ratio                        Equal group sizes

Total number of periods                 13
Length of each period                   6 months

Survival probs per period (group 1)[1]   0.975 0.853 0.696 0.578 0.503 0.464
                                         0.436 0.417 0.380 0.368 0.340 0.333
                                         0.333
Survival probs per period (group 2)[2]   0.984 0.899 0.785 0.694 0.632 0.600
                                         0.575 0.558 0.525 0.513 0.487 0.480
                                         0.480
Number of recruitment periods           10
Number of follow-up periods             3
Method of accrual                       Uniform
Recruitment period-weights              1 1 1 1 1 1 1 1 1 1 0 0 0

Hazard ratios as entered (groups 1,2)   1, .666666666667
Alpha                                   0.050 (one-sided)
Power (calculated)                      0.796

Total sample size (designed)            300
Expected total number of events         150
-------------------------------------------------------------------------------

[1] Group 1 - Comparator Regimen (Regimen A): The median OS occurs at 30.4
    months
[2] Group 2 - Experimental Regimen (Regimen B): The median OS occurs at 63
    months
```

Comparing Bone Marrow Response Rates

All eligible randomized patients who are enrolled on the trial with clinical evidence of bone marrow metastatic disease and who receive at least one dose of protocol chemotherapy will be considered for the evaluation of this endpoint. Each bone marrow evaluable patient will be assessed for the presence or absence of bone marrow metastatic disease over the interval between enrollment and the time of first local control measure or the end of the Induction reporting period, whichever comes first. Only one evaluation of best response will be used to classify the patient as complete responder (no evidence of marrow disease) or incomplete responder (residual marrow disease or progression according to Sections 10.3.4 and 10.4). We will provide an estimate of the proportion of patients who achieve complete bone marrow response and an associated 95% confidence interval.

We expect approximately 20% of the 300 randomized patients to have bone marrow disease detected at enrollment. Since the assignment to ganitumab is done through randomization, we expect approximately half of such patients will be assigned to the experimental regimen, providing approximately 30 patients for the evaluation of this endpoint for each treatment arm. The maximum expected confidence interval will occur if 50% of patients achieve a bone marrow CR, and the expected interval is 0.31-0.69.

Tolerability of Maintenance with Ganitumab

Each patient who receives ganitumab Maintenance will be evaluated for toxicity-event as described above. At the time each study progress report is prepared, the toxicity-event rate will be calculated and the one-sided test of size 0.05 of the null hypothesis that the toxicity-

event rate is 25% will be performed. No adjustment for multiple testing will be made. If the true toxicity-event rate is 35% and 135 patients are evaluable for Maintenance toxicity, the therapy will be identified as associated with an elevated toxicity-event rate with probability 0.80.

Ganitumab Pharmacokinetics

The first 10 patients < 21 years of age at enrollment ('younger patients') assigned to Regimen B will be considered in the evaluation of dosing adequacy for younger patients. These patients will be required to submit samples for pharmacokinetic (PK) testing in Induction as described in Section 15.5. The proportion of patients achieving a trough serum concentration ≥ 10 µg/mL prior to the second dose of ganitumab in Induction will be obtained. If 7 or more of these 10 patients achieve this trough concentration, then the dose of 18 mg/kg will be deemed adequate in younger patients and randomization will continue for this age group. If < 7 patients achieve this trough concentration, the study committee will discuss the PK results with CTEP in order to determine if protocol modification is required prior to continuing the randomization for younger patients. Randomization will continue without interruption while PK data from these first 10 patients are analyzed and reviewed, up to 3 months from Induction Day 29 of the 10th patient < 21 years of age at enrollment. If the true proportion of patients with trough levels that are ≥ 10 µg/mL is 0.45, the dose will be identified for modification with probability 0.90. If the true proportion of patients with trough levels that are ≥ 10 µg/mL is 0.81, the dose will be identified as providing sufficient trough levels with probability 0.90. Additional trough levels in Induction will allow for estimation of accumulation, half-life, and steady state clearance of ganitumab.

The first 10 patients < 21 years of age assigned to Regimen B will be required to submit samples for PK testing in Maintenance as described in Section 15.5. Results of this PK testing will be reported descriptively, with an emphasis on the proportion of patients achieving a trough serum ganitumab concentration ≥ 10 µg/mL at a dose of 18 mg/kg IV every 3 weeks. Additional trough levels in Maintenance will allow for estimation of accumulation, half-life, and steady state clearance of ganitumab.

Feasibility and Efficacy of SBRT for Bone Metastases

Based on data obtained from INT-0091, we expect approximately 45% of patients with newly-diagnosed metastatic Ewing sarcoma to present with bone metastases as a component of their metastatic disease burden. We expect at least half of these patients will receive SBRT, acknowledging there may be selection bias with respect to which patients receive SBRT. Compliance with protocol recommendations for SBRT timing (during local control vs. after completion of chemotherapy), dose and fractionation, and sites treated will be assessed in collaboration with IROC Rhode Island (formerly QARC). A patient will be considered an SBRT-feasibility-success if that individual has SBRT planned for at least one site, starts the treatment of metastatic disease phase of the protocol and has at least 85% of tumor sites planned to be treated with SBRT receive successful SBRT. Patients who are removed from protocol therapy prior to the planned start date of radiation to metastatic sites will not be considered in this evaluation. Successful treatment delivery is defined as a treatment plan that is acceptable or has only minor variation as assessed by IROC Rhode Island (formerly QARC) (see Section 17.14). In addition to this feasibility assessment, efficacy will be evaluated by comparing the failure rate at irradiated bone metastases with SBRT and EBRT, recognizing selection bias between patients treated with SBRT or EBRT. Failure at a radiated bone metastasis will be defined according to Section

10.3.3. The cumulative incidence of local failure as a function of time will be estimated using cumulative incidence methods as described by Kalbfleisch and Prentice.[112] Finally, the rates and grades of soft tissue ulceration and compression/insufficiency fractures at sites of SBRT will be reported descriptively.

Association between Serum IGF Pathway Components and Tissue Markers and Outcome
We will conduct exploratory analyses of initial IGF-1 level as well as other serum IGF-1 pathway components as well as tissue protein, DNA, and RNA markers. One of the analyses that will be conducted will be to segregate the population into groups according the median value of the particular biological characteristic. Given the current aggregate outcome, a plausible long-term EFS for one of the median groups is 35% and for the other is 21%; this corresponds to a 1.5-fold increase in risk. If such a difference is present, we will identify the median division in initial IGF-1 levels as prognostic for outcome with probability of greater than 86% when using a test of size 0.10 when 90% of patients submit evaluable samples.

It is of interest to compare the effect of each of the biological markers across groups defined by randomized treatment assignment. This will be done using the proportional hazards regression model:

$$\lambda(t;z,f) = \lambda_0(t)e^{\beta_1 z+\beta_2 f+\beta_3 z\times f} \quad \cdots \text{ [9.2.1]}$$

Where:

z takes on the value 0 if the patient is enrolled on the comparator arm and 1 otherwise; and

f takes on the value 0 if the patient's biological characteristic is at the median or below and 1 otherwise. A formal statistical of $H_0 : \beta_3 = 0$ will be conducted and a two-sided p-value of 0.20 or less will be considered suggestive of an interaction between the assigned treatment and the biological characteristic.

Linear trend in EFS-risk will be investigated by segregating the marker level according to quartiles. For bone marrow response rate analyses, Fisher's exact test will be used to compare the objective bone marrow response rate (complete response vs. incomplete response) at start of local control between patients with biomarker levels above and below the group median. In addition, exploratory analyses will be performed using marker divided according to quartile of IGF-1 level. These analyses will be repeated for other serum and tissue markers.

Evaluation of Bone Marrow Micrometastatic Disease and Tumor Cell Surface IGF-1R Expression
The percentage of patients with detectable bone marrow micrometastatic disease at baseline who clear their bone marrow micrometastatic disease after three and six cycles of study therapy will be reported descriptively according to treatment arm. Extent of tumor cell IGF-1R co-expression will also be reported. Moreover, the change in tumor cell IGF-1R co-expression in patients treated with and without ganitumab will be reported descriptively.

Germline Polymorphisms in EGFR
Patients will undergo genotyping for EGFR promoter polymorphism at -216. EFS will be compared between patients with and without the presence of the minor allele using the log rank test. We will use a two sided test of size 0.10 for this exploratory analysis. Power calculations are provided below for various participation rates for genotyping and allele frequency for the entire population:

Proportion Participation	Proportion with G/G Absent	Long-Term EFS with G/G Absent	Relative Risk for EFS-Event with G/G Absent	Power
1.0	0.50	0.35	1.5	0.89
0.75	0.50	0.35	1.5	0.81
0.50	0.50	0.35	1.5	0.66
1.0	0.25	0.35	1.5	0.79
0.75	0.25	0.35	1.5	0.69
0.50	0.25	0.35	1.5	0.53

The presence of the promoter polymorphism may have different prognostic implications depending on treatment assignment. We will fit the model specified by equation [9.2.1] and test for an interaction between polymorphism status and treatment regimen. A formal statistical of $H_0 : \beta_3 = 0$ will be conducted and a two-sided p-value of 0.20 or less will be considered suggestive of an interaction between the assigned treatment and polymorphism status. EFS also will be compared between patients with and without the presence of the minor allele using the log rank test within groups defined assigned treatment.

Additional analyses will compare overall survival and objective bone marrow response rate prior to local control as clinical outcomes of interest. Association between the number of copies of the minor allele and these clinical endpoints will be evaluated.

Aim 1.3.11: The institutional result of *EWS* tumor testing will be categorized as translocation detected (yes *v.* no) and the type of translocation detected will also be recorded. From previous experience, we expect translocation testing will be done for at least 80% of patients. The proportion of patients with a particular *EWS* translocation variant will be tabulated.

Risk for EFS-event will be compared across groups defined by translocation positivity using the log rank test. The power associated with such comparisons, as a function of patients evaluated for translocations and frequency of translocation positivity, can be obtained from the table above for *Germline Polymorphisms in EGFR*. The prognostic significance of each particular type of translocation, and any modifying effect of treatment assignment, will be assessed using a proportional hazards regression with indicator variables for the presence of each particular type of translocation and an indicator variable for treatment assignment. Since this is an exploratory exercise, a two-sided p-value of 0.10 or less will identify any particular coefficient as of interest for further exploration.

Aim 1.3.12: The results of ctDNA testing will be used to provide planning data for future trials. We expect baseline plasma samples obtained from the required EDTA baseline sample will be available from at least 250 patients (those who consented to future research for leftover samples prior to Amendment #1 and those who consent to the ctDNA

correlative study with Amendment #1 and beyond). With Amendment #1, we will also collect serial samples and expect that serial testing will be accomplished in at least 75 patients. The proportion of patients with detectable *EWSR1* translocations and key somatic mutations such as *STAG2* and *TP53*, along with the allelic frequency for these mutations will be reported along with the proportion of patients with these characteristics from samples done at later time points. For patients who are evaluated serially, we will report the proportion of patients that have a change in translocation result associated with ctDNA testing across time periods.

Aim 1.3.13: The results of serial genomic profiling from cells identified by flow cytometry will be used to provide planning data for future trials. We expect such testing will be accomplished in at least 50 patients, though the proportion of patients with insufficient bone marrow tumor cells to support genomic testing will be described. The profiles will be presented graphically, and samples obtained from different sites of tumor within the same individual will also be presented.

Statistical Considerations for Imaging Correlative Studies
Aim 1.3.9: This analysis will be conducted using modeling *via* the proportional hazards regression model. The outcome measure for this aim will be the event-free survival post Induction therapy. Analytic events include disease progression, disease recurrence, diagnosis of a second malignant neoplasm or death. Any patient who completes Induction chemotherapy without an analytic event and has received a PET scan at both start of therapy and end of Induction will be considered in this analysis. The change in average SUV (ΔS) between start of therapy and end of Induction and randomized treatment assignment will be independent variables in this analysis. Below, the variable z_i will be used to represent variously ΔS, including a categorical variable which takes on the value 0 if ΔS is below the median ΔS and 1 otherwise; ΔS categorized in tertiles; Z, where Z is 1 if all PET signal disappears and 0 otherwise; and actual ΔS. RECIST response is represented by the variable R_i below.

The proportional hazards regression model:

$$\lambda\left(t; z_i, t_i\right) = \lambda_0\left(t\right) e^{\beta_1 z_i + \beta_2 R_i}$$

The partial likelihood ratio test of H_0: $\beta_1 = 0$ will be conducted with R present in the relative risk regression model. A significance level of 0.10 will be considered suggestive of an augmentation of the predictive value of RECIST response in this population. We expect approximately 70% of patients will have the initial PET scan and of these, approximately 95% will complete Induction chemotherapy. Thus we expect 200 patients will be available for this analysis, fifty percent of whom will be randomized to ganitumab. The power for test noted above depends the correlation between Z, the characterization of ΔS and R_i, as seen in the following table for the variable Z which takes on the value 0 if ΔS is below the median ΔS and 1 otherwise:

Relative Hazard Rate Associated with Z = 1	Correlation between Z and R	Probability the Variable Z will be Identified as Of Interest According to the Criteria Above
2.2	0	0.80
2.5	0.5	0.80

Aim 1.3.10: This analysis will be conducted using modeling *via* the proportional hazards regression model. The outcome measure for this aim will be the event-free survival post Induction therapy. Analytic events include disease progression, disease recurrence, diagnosis of a second malignant neoplasm or death. Any patient who completes Induction chemotherapy without an analytic event and has received a PET scan at both start of therapy and end of induction will be considered in this analysis. The change in average SUV (ΔS) between start of therapy and end of Induction and randomized treatment assignment will be independent variables in this analysis. Below, the variable $\underline{a}_i$ will be used to represent variously ΔS, including a categorical variable which takes on the value 0 if ΔS is below the median ΔS and 1 otherwise; ΔS categorized in tertiles: 1 if all PET signal disappears and 0 otherwise; and actual ΔS. The randomized treatment assignment, b_i, will be included if there is evidence of a treatment effect.

The proportional hazards regression model:

$$\lambda\left(t;\underline{a}_i,b_i\right)=\lambda_0\left(t\right)e^{\underline{\beta}_1\underline{a}_i+\beta_2 b_i}$$

will be fitted to the data at the time of analysis for the primary study analysis. We will test H_0: $\beta_1 = 0$, a measure of effect of ΔS. A p-value less than 0.15 will be indicative of a possible relationship in this exploratory analysis. Estimated relative risks and 85% confidence intervals associated with the various characterizations of ΔS will be constructed from the proportional hazards regression model with all significant (as defined above) terms included. We expect approximately 70% of patients will have the initial PET scan and of these, approximately 95% will complete Induction chemotherapy. Thus we expect 200 patients will be available for this exploratory analysis.

The correlation between ΔS and percent necrosis in the resection specimen from the primary site of disease will be estimated. The correlation will be estimated treating the data as arising from a bivariate normal distribution. Any patient who completes Induction chemotherapy without an analytic event, has ΔS calculated and has the primary tumor site resected prior to the administration of primary site radiation treatment will be considered for this analysis. Of the 200 patients we expected will be available for the exploratory PET analysis described in the first paragraph of this section, we expect at least 50% of these individuals will also have resection of the primary disease site. With 100 patients, a test of size 0.10 of the null hypothesis of zero correlation between the results will be rejected with probability 0.80 if the true correlation is 0.245 or greater.

9.3 Gender and Minority Accrual Estimates

If 330 patients are required to complete the study, the gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	15	15	30
Not Hispanic or Latino	137	163	300
Ethnic Category: Total of all subjects	152	178	330
Racial Category			
American Indian or Alaskan Native	3	3	6
Asian	3	3	6
Black or African American	3	5	8
Native Hawaiian or other Pacific Islander	3	0	3
White	140	167	307
Racial Category: Total of all subjects	152	178	330

This distribution was derived from AEWS1031.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the 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 v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

10.2 Disease Assessment Requirements and Definitions

See Section 7.0 for required disease staging at study entry, after initiation of protocol therapy, and during follow-up.

10.2.1 Definitions

Evaluable for event-free survival: All eligible patients will be evaluable for the event-free survival primary endpoint from the time of randomization (intent-to-treat analysis).

Evaluable for overall survival: All eligible patients will be evaluable for the overall survival secondary endpoint from the time of randomization (intent-to-treat analysis).

Evaluable for bone marrow metastatic disease response: Patients with morphologic evidence of Ewing sarcoma bone marrow involvement based on H&E stains at study entry will be will be evaluable for the bone marrow response secondary endpoint. In the absence of morphologic evidence of marrow involvement on H&E, patients with bone marrow involvement detected ONLY by flow cytometry, RT-PCR, or immunohistochemistry will not be considered to have clinical bone marrow involvement for the purposes of this study.

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with protocol therapy.

10.2.2 Event-free Survival

The following will constitute an event for the purposes of the primary study endpoint:

- Death from any cause;
- Development of a second malignant neoplasm other than non-melanoma skin cancer (see Section 11 for reporting requirements);
- Disease progression according to Section 10.3.

10.3 Disease Response Criteria

Disease progression will be defined according to site of disease involvement and will be based upon local investigator assessment. Progression at any site of previous or existing disease involvement will constitute disease progression. Development of disease involvement at a previously uninvolved site by imaging and/or biopsy will also constitute disease progression.

10.3.1 Disease Assessment of Primary Bone Tumors

This study will use three-dimensional measurements of primary bone tumors (not metastatic bone lesions) rather than single dimension as used in RECIST. The value of 3D volume measurement has already been substantiated in several studies.[113-115] Moreover, bone tumors are considered non-measurable according to RECIST guidelines.

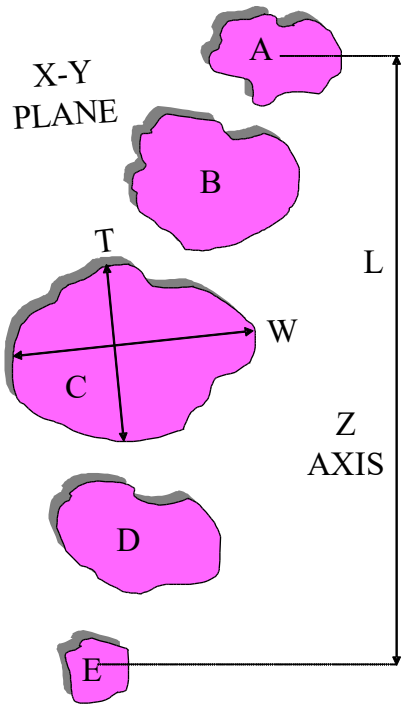
10.3.1.1 Magnetic resonance imaging (MRI)

MRI is the preferred imaging modality for primary bone tumors. Axial images and at least one additional plane are acquired. At least two pulse sequences, such as T1, T2, and STIR images are obtained. Post-contrast images are obtained if appropriate. Measurements should be made using the same sequence best showing the tumor in follow up for comparisons. Only axial images will be used for measurement. The cranio-caudal diameter is represented by the distance between the most cranial and caudal slice positions *plus* one *slice* thickness (or [slice thickness + gap] x number of slices showing the tumor *minus* one *gap* distance).

10.3.1.2 Technical guidelines for cross-sectional imaging computed tomography (CT)

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle).
2. CT slice thickness should be 5 mm or less.
3. The diameter of a "measurable" mass should be at least twice the reconstructed slice thickness. Smaller masses are considered detectable, but will be counted as "non-measurable."
4. Edge-enhanced lung windows, liver, and bone windows should be photographed, if recorded in hard copies. Digital images are submitted either electronically or in CD using DICOM format.

10.3.1.3 The primary tumor will be measured in the largest anterior-posterior, transverse and longitudinal dimensions. Reporting of these three dimensions will be required. These dimensions will be used for central estimation of tumor volume using the formula for a prolate ellipsoid: volume in $mm^3 = \pi/6\ (d_1 \cdot d_2 \cdot d_3)$ = (AP x transverse x longitudinal) x 0.5. Measurements should be obtained as described in the figure below.



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor

W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area

Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor *plus* one *slice* thickness), or [b] the product of ([slice thickness + gap] and the number of slices showing the tumor) *minus* one *gap* distance

- WHO criteria: TxW is used
- RECIST: the larger of the two (T & W) is used (W in this example)
- Elliptical model volume=0.5 LxWxT
- The same modality and measurement method used in the initial imaging should be used in follow ups

10.3.1.4 Response of the Primary tumor

Based on previously published data correlating tridimensional measurements to bi-directional and unidirectional measurements the following response criteria for the primary tumor will be used[116]:

Complete Response (CR): Complete disappearance of the tumor.

Partial Response (PR): At least 64% decrease in volume compared to the baseline.

Progressive Disease (PD): At least 40% increase in tumor volume compared to the smallest measurement obtained since the beginning of therapy.

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

10.3.2 Disease Assessment of Soft Tissue Primary Tumors and Metastatic Lesions

Assessment of soft tissue primary tumors and soft tissue metastatic lesions (including lung and node metastasis) will follow revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[117] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

10.3.2.1 Methods for Evaluation of Measurable Soft Tissue Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

MRI is widely available, has excellent contrast, spatial, and temporal resolution and should be used as the modality of choice for staging of most primary tumors, except some chest wall tumors. MRI is also evolving as a radiation-free imaging modality for whole body staging. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: Modern PET/CT scanners allow one to obtain a diagnostic, low dose CT scan, which can be both used for diagnostic purposes and for attenuation correction of PET data. In addition to reconstructing the whole body CT data in a soft tissue algorithm, the chest CT scan should be reconstructed in the lung algorithm. Most sites would be expected to be able to obtain such a combined scan in order to avoid duplicate irradiation of the patient. If a diagnostic CT (with IV contrast) is acquired as part of a PET-CT, then the CT portion of the PET-CT can be used for evaluation of pulmonary nodules and RECIST measurements.

However, some centers with older scanners may not be able to generate diagnostic CT quality for use with RECIST measurements and may have to obtain an additional, diagnostic CT scan on a separate CT scanner as a separate imaging procedure, and use this scan for RECIST measurements. This would be considered suboptimal based on ALARA guidelines.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate

between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at a site at baseline, with a positive FDG-PET at follow-up is concerning for progressive disease based on development of a new lesion. For the purposes of this study, confirmatory imaging with CT scan or MRI scan is required. Biopsy is strongly encouraged, but not required to confirm new site of bone metastasis. See Section 15.0 for submission of biopsy material at time of relapse in patients consenting to correlative biology studies.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, MRI or biopsy, this is progressive disease. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, MRI, or biopsy, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.3.2.2 Evaluation of Target Soft Tissue Lesions

Complete Response (CR): Disappearance of all target lesions. Any

pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.3.2.3 Evaluation of Non-Target Soft Tissue Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.3.2.4 Evaluation of Best Overall Response for Soft Tissue Lesions

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

For Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

For Patients with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

10.3.3 Disease Assessment of Bone Metastases

Radiographic assessment of bone metastasis can be difficult as remodeling bone may lead to residual abnormalities on bone scan, CT scan, and MRI scan. For the purposes of the current protocol, response at bone metastasis will be graded as follows:

Complete response (CR) = FDG-PET negative at all previous sites of bone metastasis.

Progressive disease (PD) = Any of the following will constitute PD:

- Development of new bone metastasis at a previously uninvolved site. FDG-PET imaging may NOT be the only study to document development of a new bone metastasis. Confirmatory imaging with bone scan, CT scan, or MRI scan is required. Biopsy is strongly encouraged, but not required to confirm new site of bone metastasis. See Section 15.0 for submission of biopsy material at time of relapse in patients consenting to correlative biology studies.

- Development of a new soft tissue mass ≥ 1 cm in maximum axial dimension at a previous site of bone metastasis without a soft tissue component or with a soft tissue component < 1 cm in maximum axial dimension on previous evaluations.

- For bone metastasis with a soft tissue component ≥ 1 cm in maximum axial dimension on previous evaluations, an increase in the longest axial diameter of the soft tissue component by > 20%.

- A previous bone metastasis that was positive on FDG-PET, became negative with protocol therapy, and then becomes positive again should prompt concern for progression at that site. Confirmatory testing is required to document progression at a previous site of bone metastasis. Together with return of FDG-PET uptake, MRI scan with documentation of an enhancing bone lesion will constitute adequate evidence to support progression at that site. Biopsy is strongly encouraged, but not required to confirm progression at a previous site of bone metastasis. See Section 15.0 for submission of biopsy material at time of relapse in patients consenting to correlative biology studies.
- Biopsy evidence of viable Ewing sarcoma at a previously radiated bone metastasis, at least 8 weeks after completion of treatment.

Stable disease (SD) = Patients not meeting either CR or PD criteria.

10.3.4 Disease Assessment of Bone Marrow Metastatic Disease

Since disease involvement can be patchy, bilateral bone marrow aspirates and biopsies are recommended for assessing bone marrow metastatic involvement. Bone marrow metastatic status is based solely on standard morphologic review of H&E stained bone marrow aspirate and biopsy material. For the purposes of this study, flow cytometry, FISH, RT-PCR for *EWSR1* fusion transcripts, and immunohistochemistry for CD99 are considered investigational for assessing bone marrow metastatic status.

The suggested approach for patients with large pelvic tumors in which a posterior iliac crest bone marrow biopsy would track through the tumor is to instead undergo two marrow biopsies on the contralateral side (either two posterior biopsies or one posterior and one anterior biopsy).

Bone marrow metastatic response will be graded as follows:

Complete response (CR) = No morphologic evidence of Ewing sarcoma

Progressive disease (PD) = Development of new marrow involvement in a patient without previous marrow involvement or in a patient who had previously achieved bone marrow CR. For patients in the latter category with < 10% bone marrow involvement, a confirmatory biopsy should be performed 2-4 weeks after initial biopsy showing recurrent marrow involvement.

Stable disease (SD) = Patients not meeting either CR or PD criteria.

10.4 Demonstration of Residual Viable Tumor

In addition to the above definitions of disease progression, the following criteria will constitute failure of protocol therapy to clear disease sufficiently at benchmark timepoints for the patient to continue on protocol therapy. Patients meeting these criteria will be

considered to have had an analytic event for the purposes of the primary study endpoint, even in the absence of disease progression as defined above.

10.4.1 Residual bone marrow metastatic disease by end-Consolidation
Patients who have not achieve a bone marrow CR as defined in Section 10.3.4 by the end of the Consolidation phase of therapy will constitute failure of protocol therapy to eradicate disease and patients will be removed from protocol therapy at that time.

10.4.2 Biopsy-proven residual tumor at any site after completion of Metastatic Site Radiation Phase
Patients with biopsy proven residual Ewing sarcoma following completion of the Metastatic Site Radiation phase of therapy and at least 8 weeks after completion of radiation treatment (if applicable) will constitute failure of protocol therapy to eradicate disease and patients will be removed from protocol therapy at that time. Biopsy is not mandated or recommended at this timepoint. Note that this criterion applies to patients in both Regimen A and Regimen B. This criterion also applies to radiated sites or non-radiated sites. This criterion applies to primary tumor sites and metastatic sites.

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 which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the NCI's CTEP 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 which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

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

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

11.4.2 Persistent or Significant Disabilities/Incapacities

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

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: 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 (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy
  Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 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 which may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions***" SOC.

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

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

11.4.6.2 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 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 which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

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

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

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

Expedited AE reporting timelines are defined as:

"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.

"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

- **CTEP-AERS 24-hour Notification is required for any degree of clinical sinusoidal obstruction syndrome (SOS), from mild to severe (see protocol Section 5.7.1).**
- **CTEP-AERS 24-hour Notification is required for ≥ Grade 1 pneumonitis.**
- **CTEP-AERS 24-hour Notification is required for ≥ Grade 2 decreased ejection fraction.**

The following adverse events do NOT require expedited CTEP-AERS reporting for this protocol:

- **Grades 1- 4 myelosuppression do not require expedited reporting.**
- **Hospital admission/prolongation of hospitalization for Grade 3 febrile neutropenia does not require expedited reporting unless unexpected.**
- **Hospital admission/prolongation of hospitalization for Grade 3 infection does not require expedited reporting unless unexpected.**

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

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

Commercial reporting requirements are provided in Table B.

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

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

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

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

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

Additional Instructions for CTEP-AERS Expedited Reporting Requirements for Commercial Agents:

- **CTEP-AERS 24-hour Notification is required for any degree of clinical sinusoidal obstruction syndrome (SOS), from mild to severe (see protocol Section 5.7.1).**
- **CTEP-AERS 24-hour Notification is required for ≥ Grade 1 pneumonitis.**
- **CTEP-AERS 24-hour Notification is required for ≥ Grade 2 decreased ejection fraction.**

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 all patients in this study, routine reporting requirements differ depending upon phase of therapy in which the adverse event occurs:

- During Induction and Consolidation, routine reporting will include all toxicities reported via CTEP-AERS expedited reporting system, all Grade 3 and higher non-hematologic Adverse Events, all Grade 4 and higher hematologic Adverse Events, and any toxicity that requires termination of protocol therapy.
- During Metastatic Site Radiation, routine reporting will include all toxicities reported via CTEP-AERS expedited reporting system, all Grade 3 and higher Adverse Events (hematologic and non-hematologic), and any toxicity that requires termination of protocol therapy.
- During Maintenance, routine reporting for patients who started Maintenance prior to activation of Amendment #3C will include all toxicities reported via CTEP-AERS expedited reporting system, all Grade 3 and higher Adverse Events (hematologic and non-hematologic), and any toxicity that requires termination of protocol therapy. Routine reporting for patients who started Maintenance after activation of Amendment #3C will include all grade adverse events.

In addition, any patient who receives radiation to a bone metastasis (SBRT or standard external beam radiation) will have Grade 2 or higher skin ulceration or Grade 2 or higher fracture at the site of bone radiation reported. Please specify on the AE form the type of radiation received.

12.0 STUDY REPORTING AND MONITORING

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

12.1 CDUS

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

12.2 Data and Safety Monitoring Committee

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

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

The DSMC approves major study modifications proposed by the study committee prior to implementation (eg, termination, dropping 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

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

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13.0 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 (except where explicitly prohibited within the protocol).

COG member institutions are encouraged to enroll patients on a specimen collection study (such as AEWS07B1 or APEC14B1). In addition, patients are encouraged to participate in the embedded correlative biology studies in this trial (see Section 15.0). Submission of material from initial tumor biopsy is required for participation in this study and this requirement should be considered when planning the initial biopsy. Surgeons, treating team and pathologists should review specimen requirements for tissue collection and handling for these studies prior to biopsy and definitive surgery.

13.1 Surgical Guidelines for Biopsy

13.1.1 Technique

Open, incisional biopsy of the primary is recommended to allow procurement of enough tissue for all biologic studies. Consultation with a surgical and/or orthopedic oncologist prior to open or needle biopsy is strongly recommended as the approach used for the initial biopsy may impact the future surgical approach. A move to performing open biopsy may be against the current practice in many institutions where a needle biopsy provides adequate tissue for diagnosis. Biologic studies are becoming increasingly important and may lead to changes in therapeutic approach. Multiple passes with a needle may not provide enough aggregate tissue for all of the studies currently done. A minimum of 1 cubic centimeter of tissue is required for special studies. An additional amount of fresh tissue must be obtained for diagnostic studies. Most children require a general anesthetic for needle biopsy, and often a venous access device can be inserted at the time of biopsy. Changing the practice to doing open biopsies therefore should not result in increased morbidity for the patients.

In most instances the diagnosis can be made from the surrounding involved soft tissues avoiding the need for obtaining bone. Creation of a bone defect during biopsy significantly weakens the bone thus increasing the risk of pathologic fracture. This risk is markedly increased if radiotherapy is later given as the definitive local therapy. A bone biopsy will also preclude the possibility of performing a frozen section to determine the adequacy of material for diagnosis.

13.1.2 Specimen Quality

Biopsy material should be sent to pathology in a fresh state in normal saline or tissue culture medium. Ewing sarcomas are often necrotic, therefore intra-operative frozen section or touch preparations should be done to be certain that the tissue obtained is adequate and sufficient for diagnosis. It is strongly recommended

that adequate tissue be obtained for biologic studies (AEWS07B1 and Section 15.0 of the current trial). The specimen should be handled in an expeditious manner and not left on the back table for more than a few minutes as substantial degradation begins immediately ex vivo.[118]

13.1.3 Specimen Quantity and Handling

Proper handling of biopsy tissue requires knowledge of the objectives to be studied. A minimum of 3-5 grams of fresh, viable, non-necrotic tumor tissue should be sent immediately to the Pathology Department. Material must be obtained for multiple analyses (routine histopathology, cytology, touch preparations, electron microscopy, tissue culture, flow cytometry, cytogenetics, etc.) to permit full evaluation for diagnosis and cancer biology studies.

13.1.4 Therapeutic Considerations

Future surgical excision and radiation therapy must be borne in mind during the biopsy. Imaging, in particular MRI, should be obtained prior to biopsy. Principles of biopsy should be followed. These include: longitudinal incisions; the ability to remove the biopsy tract with the lesion at the time of surgical excision; avoidance of neurovascular structures; and a direct route to the tumor through muscles rather than retracting them. If appropriate management of the tumor requires a compartmental resection, one should be able to proceed after biopsy and neoadjuvant chemotherapy without significantly extending the margins beyond those previously planned. If one is unfamiliar with the suspected extension of the lesion and the three dimensional compartmental anatomy of the extremity, a simple error on incision orientation and placement or injudicious exposure of a major neurovascular structure could result in the need for amputation. Postoperative hematoma formation can render a previously resectable lesion unresectable. Techniques that will diminish the likelihood of hematoma formation and dissection could include the use of a tourniquet (after gravity exsanguination), thrombogenic agents (activated thrombin, Oxygel, Avitene), and a hemostatic subarticular closure. The tourniquet if used at all should be deflated prior to closure in order to assure absolute hemostasis. Anatomic structures and planes dissected by hematoma should be considered contaminated and may have to be included in the subsequent definitive surgical margins. If a drain is left in place, it should exit in line with the longitudinal biopsy incision and close to the margin of the incision.

13.1.5 Regional Lymph Node Evaluation

Soft tissue Ewing sarcoma has higher rates of regional lymph node involvement compared to bone Ewing sarcoma. For patients with soft tissue primary tumors, clinical and imaging evaluation of regional lymph nodes must be performed before therapy begins. Pathologic evaluation of clinically suspicious nodes in patients with bone or soft tissue primary tumors should be performed. Regional node debulking or resection is not recommended. Open biopsy of the involved node is recommended, but needle biopsy or fine needle aspiration may be appropriate based on the surgeon's judgment and pathologist's recommendations. Sentinel node techniques may be used if lymph node sampling is planned.

13.2 Surgical Guidelines for Consideration of Amputation at Diagnosis

While the role of amputation in the management of the extremity primary in Ewing sarcoma is controversial, in certain clinical situations amputation may be the best

alternative. In compliance with the objectives of the study, if necessary, amputation should be done after the completion of neo-adjuvant chemotherapy. In the case of pathologic fracture, in most instances it is preferable to attempt to splint, cast or brace the extremity for the Induction neo-adjuvant phase of chemotherapy before resorting to amputation. Large destructive lower extremity lesions in children less than the age of 10, where considerable limb length inequality will be anticipated, may be the best managed by amputation though definitive radiotherapy remains a viable option, particularly in this high-risk patient population. Consultation with an experienced orthopedic or surgical oncologist is encouraged, because newer methods of limb length equalization, the use of growth plate sparing operations (especially for diaphyseal lesions) and "expandable" prosthesis may make amputation unnecessary.

13.3 Surgical Guidelines for Primary Bone Lesions

Tumors arising in the extremities are usually situated in recognized anatomical compartments.[119,120] Utilizing standard radiographic techniques (e.g., plain films, bone scan, MRI and at times CT or CT angiography), the precise anatomic location of the lesion should be defined prior to biopsy and the studies repeated prior to resection. Furthermore, the extent of the lesions is usually dramatically reduced following Induction chemotherapy, rendering lesions that are huge at diagnosis smaller and more "resectable" after chemotherapy. A surgical staging system for extremity musculoskeletal sarcomas which incorporates histopathological grading has been extensively tested and devised, whereby the histologic grade (high or low) and the extent of the disease (compartments involved, presence or absence of metastases) can be linked to the type of surgical procedure.[121,122] The procedures are defined based upon the margins they achieve relative to the tumor and its pseudocapsule. In the setting of pre-operative chemotherapy the aim of surgery should generally be to achieve a wide (R0) surgical margin of normal tissue around the lesion. The second surgical margin that may be acceptable is a marginal (R1) excision. In this surgery there are microscopically positive cells at the cut surface of the tumor which remain in the patient and must be treated by radiotherapy. The histologic response of the tumor to chemotherapy is also important but there is no means of making this assessment prior to resection.

For the purpose of this study, viable tumor at the cut surface of the specimen is considered a positive margin and requires radiotherapy. The plane of dissection should be through non-inflamed, non-edematous tissue to avoid leaving tumor cells in this tumor reactive zone.

Pre-resection consultation with a radiation oncologist is recommended, even if it seems likely a wide excision with a clear margin will be achieved. If a lesion is considered inoperable, that is, gross residual tumor would be left behind (an intralesional R2 excision), surgery should not be attempted. A partially removed tumor leaves the patient with a worse situation since full dose radiotherapy will be needed. The field size will be considerably larger since all of the surgical wound would have to be irradiated rather than the original tumor volume with a small margin. The post surgery tumor bed will be more anoxic rendering radiation less effective.

13.3.1 Eligibility for Local Control

Following Induction chemotherapy, patients will undergo disease restaging according to Section 7.0. It is recommended that all patients with a good clinical/radiologic response be considered for surgical resection with negative margins (i.e., "de-

bulking" R2 excision is not an acceptable term or procedure). If initial surgical excision is elected, using the criteria defined below, the procedure should be performed following recovery from Week 11 Induction chemotherapy and prior to Consolidation therapy.

13.4 Anatomic Guidelines for Resectability

The choice of local treatment will be left to the treating physicians, and may include: radiation alone, radiation followed by resection, resection followed by radiation, or surgical resection alone. The trend for local management of Ewing sarcoma has changed recently toward surgical resection whenever possible for non-metastatic disease. The guidelines for determining "resectability" and "adequate margins" are still being defined and require considerable judgement on the part of the entire treatment team. In general, the goal should be to remove the entire tumor and involved bone with a cuff of normal tissue around the tumor (a wide excision). Since the response of Ewing sarcoma to preoperative chemotherapy is often dramatic, the soft tissue extent of the tumor is frequently much less than at diagnosis. The exact thickness of the "cuff" of normal tissue oncologically "safe" (with respect to local recurrence) is not known, and probably depends upon the type of tissue forming the cuff. Fascia, periosteum and intermuscular septae are good barriers to tumor spread. On the other hand, fat and muscle are relatively poor barriers and require a thicker cuff. *If* margins are deemed "positive" after review of the treatment team (see Section 4.3.1.2), or if there is intra-operative tumor spill or cut through, then post-operative radiotherapy is indicated. Otherwise wide surgical resection alone is the goal when feasible.

The decision about whether a given patient is "resectable" should be made by the treatment team which should include an experienced orthopedic/surgical oncologist, radiation oncologist and oncologist. Consideration must be given at each site to the neurovascular structures, uninvolved muscles, the adjacent joint(s) and the growth centers. Not every tumor is resectable, nor should this necessarily be a goal. Experience and wisdom are needed to make this decision for an individual patient. Some specific guidelines by site are as follows:

13.4.1 Tibia

Proximal tibial lesions must be evaluated for the status of the adjacent knee joint. If it is free of tumor involvement, an intra-articular resection may be employed, followed by reconstruction in using osteo-articular allografts or metallic prostheses. An estimation of growth remaining should be made and plans for limb length equalization considered. Lesions with joint involvement will require an extra-articular resection and reconstruction with an arthrodesis or metallic prosthesis or rotationplasty.

Tibial lesions of the diaphysis may be treated by resection and diaphyseal reconstruction using allograft bone, autografts or metallic spacers. If it is possible to preserve the joint and growth plates at either end, near normal function can be expected. The posterior neurovascular bundle is often protected by the deep posterior compartment muscles.

Distal tibial lesions (supramalleolar) are probably best managed by definitive radiation. Rarely are lesions suitable for resection and intercalary reconstruction or ankle arthrodesis.

13.4.2 Femur

Proximal femoral lesions may be resected if there has been a good response to Induction chemotherapy. At times it is possible to preserve the femoral head and neck and perform an intercalary reconstruction. If an intra-articular resection is necessary, reconstruction with a metallic prosthesis, or allograft-prosthesis composite is indicated. Extra-articular resections can be achieved if the joint is involved and reconstruction carried out by means of an arthrodesis using allograft and/or autograft bone, or at times a modified total hip replacement or rotationplasty.

Diaphyseal lesions are frequently resectable using the vastus intermedius as a muscle cuff around the tumor. Intercalary reconstructions with allograft, autografts or - metallic spacers are possible with good functional results if the adjacent joints and growth plates are possible to preserve. As in the tibia, if a growth plate must be sacrificed to achieve an adequate margin, plans should be considered for limb length equalization after the completion of the drug protocol.

Distal femoral lesions may be resected either as an intra-articular procedure or an extra-articular procedure (depending upon the analysis of the staging studies with regard to joint involvement) if the neurovascular bundle is free. Intra-articular resections can be reconstructed with osteoarticular allograft or metallic prostheses, whereas extra-articular resections will require arthrodesis, metallic prostheses or allograft prosthesis composites. In skeletally immature patients less than age of 10, or in those with strong athletic inclinations, a rotationplasty may be considered.

13.4.3 Bones of the Hands and Feet

Lesions involving the digits, metacarpals, and metatarsals may be managed by ray amputation or resection, depending upon the degree of soft tissue and joint involvement following Induction chemotherapy. If surgically managed, the aim should be for complete resection with negative margins. Selected lesions may be managed by radiotherapy. Large destructive lesions of the hind portion of the foot may not be suited for either radiation or resection (due to the degree of destruction and lack of reconstruction options). Below-knee amputation is frequently the treatment of choice for these sites.

13.4.4 Fibula

The proximal fibula can be resected if the response to Induction chemotherapy is good. Soft tissue involvement noted at operation may be more extensive than that anticipated by pre-operative staging studies, therefore one should plan to take a wide cuff of tissue around the lesion. Extra-articular excision of the proximal tibial fibular joint can be done if there is epiphyseal involvement. MRI is the best imaging study from which to judge the extent of bony and soft tissue involvement. Reconstruction is not necessary as long as the distal 6-8 cm of fibula near the ankle can be preserved. The peroneal nerve may need to be sacrificed, but a posterior tibial tendon transfer or ankle foot orthosis compensates for its loss reasonably well. In some cases the soft tissue extent mandates that the toe and foot extensor muscles be removed with the tumor. Attention to varys instability should also be assessed. If present, the surgeon should consider lateral collateral ligament reconstruction.

Lesions involving the distal fibula may also be resected. Ideally, the lateral malleolus should be preserved, but if it is resected, adequate ankle function can be achieved by soft tissue reconstruction long term, bracing or, at times, an ankle arthrodesis. Occasionally a reconstruction is done with the uninvolved proximal fibular moved distally.

13.4.5 Ankle Region

For lesions located in the distal tibia, calcaneus and hindfoot a below knee amputation at the classical level is usually the best alternative (radiotherapy may be an alternative). Very small lesions might be managed by resection, but these are extremely unusual.

13.4.6 Pelvis

The pelvis is one of the most difficult areas for surgical resection. All pelvic lesions should be carefully studied by MRI with or without CT (and, at times CT or MR angiography) at the completion of Induction chemotherapy to decide if a resection is possible. Smaller lesions limited to the iliac wing, ischium or pubis, with good response, should be resected. Surgical complication rates are high particularly when they follow high dose radiotherapy. In this patient population, surgical resection is generally not indicated after a patient has received definitive radiation. Delays in resumption of chemotherapy may contribute to the poor prognosis of pelvic Ewing tumors.

Lesions confined exclusively to the iliac wing (Zone I) are generally resectable without imparting significant morbidity. The surgeon should reconstruct the abductor mechanism as best as possible.

Lesions in the periacetabular area (Zone II) require careful consideration. There are no good reconstruction options for a resection at this site. The decision will be individualized and require consultation with an experienced Orthopedic oncologist and radiotherapist, and full discussion of the local management options with the patient and his or her family. Possible reconstruction options include allografts (with or without hip joint prostheses), metallic implants, or arthrodesis (ilio-femoral or ischio-femoral). Definitive radiation may be the best option in this population with metastatic disease. For pubo-ischial lesions (Zone III), the difficulty of resection depends on the extent of interior pubic-ischial involvement. Reconstruction is generally not necessary.

Pelvic lesions which cross the sacroiliac joint (Zone IV) to reach the sacrum also require careful consideration. Most of these lesions will be managed by radiation alone. The ability to perform a resection will depend upon the extent of the lesion within the sacrum and the expected neurologic deficits (including possible loss of bowel and bladder function) which would remain following a resection. A combined radiotherapy/surgical approach may be appropriate if the improvement in disease control outweighs the functional loss.

The role of complete hemipelvectomy (Zone I-III +/-IV) for large "unresectable" lesions of the pelvis is unclear. In most instances it is to be avoided in favor of definitive radiotherapy.

13.4.7 Spine

Patients with symptoms of spinal cord compression should be considered for emergency radiotherapy (see Section 17.3.2). In many cases chemotherapy will relieve the cord compression and destabilizing laminectomies should be avoided. Surgical resection of primary lesions arising in the vertebrae may be indicated when there has been a good response to Induction chemotherapy. There are a variety of spine implants and bone grafts that are available for reconstruction following wide excision. Consultation could be made with a local orthopaedic spine surgeon. Radiation dose is limited at this site due to the sensitivity of the spinal cord. Special techniques can be used such as proton therapy (see Section 17.0), for protection of spinal cord and adjacent structures. The final decision regarding local management is ideally made after the response to Induction chemotherapy is assessed. It is expected that patients with vertebral and/or paraspinal tumors will most likely require radiation therapy. Before attempting local control with surgery only, the plan should be discussed with the treatment team.

13.4.8 Ribs

Initial resection is strongly discouraged. Patients should receive Induction chemotherapy prior to resection. Defining the extent of the rib involvement is difficult due to the curvature of the chest wall. MRI is the best modality for documenting extent around the curvature of the chest. Consideration can be made to marking the extent of involvement by a metallic marker inserted at the margins with pre-operative CT. The rib with a cuff of surrounding normal tissue should be resected en bloc. Generally the resection has included one normal rib above and one below the lesion. The depth of the resection should include at least the full thickness of the musculoskeletal chest wall with pleura, and wide resection of any areas of attachment to underlying lung parenchyma, pericardium or diaphragm. More conservative procedures may also yield good oncologic results and eliminate a need of chest wall reconstruction. Half of the circumference of the uninvolved rib above and below can be excised with all of the soft tissues on the adjacent upper and lower ribs. Limiting factors for effective resection are lesions encroaching on vertebrae, great vessels, and brachial plexus. Resection of posterior rib lesions may necessitate consultation with a surgeon with expertise in spine / paraspinal surgery.

Primary radiotherapy is an alternative to resection if resection is unreasonable, and post-operative radiotherapy is indicated if the margins are microscopic. If gross residual tumor is the expected outcome, surgery should not be attempted.

13.4.9 Scapula

Lesions presenting in the body of the scapula which do not invade the chest wall or glenoid can be resected without significant impairment of shoulder function. Primary lesions which involve the glenoid are possible to resect but reconstruction options are limited and there will be some loss of function (shoulder abduction active rotation strength). If the arm and brachial plexus can be preserved, resection may be attempted, even if it requires total scapulectomy. Reconstruction options include soft tissue repairs and fascial or artificial ligament slings to stabilize the proximal humerus to the chest wall. Metallic prostheses for the scapula and allografts have been attempted, but the functional results are as yet not well established.

13.4.10 Sternum and Medial One-fifth of Clavicle

Most lesions of this site are resectable if there is a reasonable response to pre-operative chemotherapy, but there is risk to the underlying normal structures in this area. Great care must be exercised regarding the heart, great vessels, trachea, esophagus, pleura and nerves. No reconstruction is necessary.

13.4.11 Clavicle (Lateral four-fifths)

A surgical resection should be considered unless this is precluded by the extent of the soft tissue involvement. The clavicle can be readily resected without appreciable loss of function.

13.4.12 Humerus

The proximal one third of the humerus may be resected in either an intra or extra-articular fashion, along with surrounding soft tissues (deltoid). A reduction in abduction arc and power is almost a certainty. Reconstructions employing allografts or vascularized fibula grafts for arthrodeses (extra-articular resections including the deltoid and rotator cuff) or as osteoarticular implants (if the rotator cuff can be preserved at time of an intra-articular resection), or employing metallic implants are possible. Clavicula pro humero is also an attractive and viable option.

The diaphyseal region of the humerus frequently lends itself to resection if the adjacent shoulder and elbow joint can be preserved and the neurovascular structures are free. Reconstruction of the intercalary defect with allograft or VFG autograft bone, or metallic implants is possible and offer excellent functional results.

The distal humerus (elbow) is a rare site of occurrence, and decisions relative to resection will depend on the size of the lesion and its relationship to the adjacent neurovascular structures. Reconstructions at this site are not commonly performed and require innovation depending upon the exact clinical situation. Radiotherapy may be a superior option at this site.

13.4.13 Radius and Ulna

Small lesions localized to one of the two bones may be considered for resection if there has been a good response to chemotherapy. Lesions which lend themselves to intercalary resections of one of the bones are ideal, as are lesions of the distal ulna which can be sacrificed without reconstruction. The distal radius can be resected as well, and reconstructed with auto- or allografts to re-create the radiocarpal joint or to establish an arthrodesis. Radiotherapy is an alternative.

13.4.14 Wrist

Fortunately, tumors arising in the small bones of the carpus are rare. Small well-localized lesions may be managed by radiation or resection; however, a below elbow amputation may be required.

13.4.15 Skull and Mandible

Tumors in these locations are beyond the scope of these guidelines. Consultation with a surgical oncologist or neurosurgeon experienced in tumors of these sites should be made. Resections are sometimes feasible, again with the aim of complete tumor excision with negative margins, but radiotherapy is usually required alone or as an adjunct for tumors in these locations.

13.4.16 Soft Tissue Ewing/PNET

In general, soft tissue lesions should be staged and treated along the same guidelines as those for bone tumors. At the completion of Induction chemotherapy, the site of the primary tumor should be re-imaged, usually with MRI scan.

In most cases, an enbloc resection of the lesion, the biopsy tract and a cuff of normal tissue surrounding the lesion en bloc should be attempted. If the lesion is adjacent to a major neurovascular structure or bone, definitive radiotherapy may be the best option. It is not necessary to resect the entire muscle compartment of involvement if the staging studies indicate lesser involvement, but in all cases the goal should be to achieve a wide or marginal excision as defined by Enneking.[121,122] Once transected a muscle is non-functional so generous margins of the muscle can be removed with the tumor.

If the adjacent bone is clearly involved by tumor, treatment principles for bone tumors should be employed. In most cases, lesions adjacent to bone with no recognizable involvement by CT or MRI can be resected without removing the bone; periosteum should be taken as a margin in these cases. When postoperative radiation therapy is required, the denuded bone is more susceptible to late pathologic fracture.

Major nerves should be preserved when feasible. If they are directly involved by tumor, a combined radiotherapy and surgical approach or radiation alone may be necessary. Similar guidelines apply to major vascular structures, but resection with vascular reconstruction is an alternative for involved vessels.

Most major muscle groups can be sacrificed without much loss in function. Local muscle transfers to restore function, achieve soft tissue coverage or to prevent dead space are sometimes necessary either at the time of resection or at completion of therapy. Some surgeons recommend tendon transfers at the time of resection.

13.5 Resection of Residual Lung Metastases

The role of resection of residual lung metastasis remains unclear in Ewing sarcoma. In general, lung metastases resolve completely during the course of chemotherapy. Resection of lung metastases remaining at the completion of Consolidation therapy is allowable. If performed, resection should take place prior to planned whole lung radiotherapy. See Section 15.0 for submission of resection specimens for correlative biology studies.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Central pathology review will not be done. Submission of specimens for required and optional correlative biology studies is detailed in Section 15.0. Submission of tumor material from initial biopsy is required for study participation and this requirement should be considered in planning biopsy and tissue triage.

COG member institutions are also encouraged to enroll patients on a Ewing sarcoma specimen collection study, such as AEWS07B1 or APEC14B1. Please see the specimen collection study for directions for specimen preparation and shipment.

14.1 Biopsy Specimen

Gross

Surgeons and interventional radiologists should be encouraged to send fresh tissue from all biopsy procedures.

Every effort should be made to obtain viable, undistorted tissue for study. Fixation and processing in a manner with which the laboratory routinely obtains good results (e.g., 10% neutral buffered formalin) is satisfactory. Whenever the amount of tissue is sufficient, fresh and frozen tissue should be obtained for cytogenetics and diagnostic biologic studies. A 1 mm slice from the cut surface of the tumor should be placed in buffered glutaraldehyde or other electron microscopy (EM) fixative and saved or processed for electron microscopy, if sufficient tissue is present. Touch preparations should be made for cytologic screening. Institutions are strongly encouraged to perform cytogenetics on fresh specimens when sufficient tissue is available and when this service is available.

Microscopy

The tumor must have a light microscopic appearance [by hematoxylin and eosin (H&E) staining] consistent with a Ewing family tumor [Ewing sarcoma/peripheral primitive neuroectodermal tumor (PNET)] of bone or soft tissue. In addition, there should be no immunohistochemical or ultrastructural evidence suggesting lymphoma or another sarcoma such as rhabdomyosarcoma.

Immunohistochemistry

In addition to routine H&E staining, it is recommended that institutional pathologists perform immunohistochemistry (IHC) using a panel of antibodies to aid in the diagnosis and exclude entities other than Ewing sarcoma/PNET. A suggested panel would include: CD99 (MIC2, 12E7, O13) to support a diagnosis of Ewing sarcoma/PNET; myogenic markers (desmin, muscle-specific actin, myogenin and MyoD1) to rule out rhabdomyosarcoma; antibodies for detecting lymphoid antigens (CD45, TdT, and additional B and T cell markers); and other exclusionary antibodies as indicated by a particular case. While CD99 (MIC2; 12E7, O13) positivity suggests Ewing sarcoma/PNET, CD99 positivity alone is not sufficient for a diagnosis of Ewing sarcoma/PNET, as lymphomas, synovial sarcoma, and alveolar rhabdomyosarcoma, among other tumors, may express this antigen.

14.2 Molecular and Cytogenetic Studies for Initial Diagnosis

Molecular studies

The most common cytogenetic abnormalities in EWS/PNET include t(11;22) and t(21;22); other, less common translocations have also been described. It is strongly recommended that tissue be obtained for molecular biologic study of these and other abnormalities by reverse transcriptase polymerase chain reaction (RT-PCR) and/or fluorescence in situ hybridization (FISH) using probes for the involved regions of chromosomes 11, 21, and 22. Evidence of an EWS rearrangement consistent with a Ewing family tumor may be used as supporting evidence for a Ewing sarcoma/PNET diagnosis.

Cytogenetic Studies

If sufficient tumor is available after submission of tumor for molecular studies, it is suggested that tumor cytogenetics be done at the home institution, if available. Fresh, sterile, unfixed tumor tissue should be submitted as specified by the local institution's cytogenetics laboratory.

14.3 Specimen from Surgical Resection

Gross

Resection margins must be marked with India ink or other color indicator. Description of the specimen, including measurements, should be recorded. Gross assessment of the completeness of resection should be made. A specimen radiograph (when facilities are available) should be made prior to taking sections. A single slice through the largest axis of the tumor should be fixed, decalcified if necessary, and entirely submitted for processing, with the location of blocks clearly marked on a photograph or diagram of the gross specimen. These sections will then be used for assessment of histologic response to chemotherapy. Additional sections of primary tumor, extraosseous tumor, any grossly or radiographically abnormal areas and margins of bone and/or soft tissue should be obtained. If viable tumor is grossly recognizable, obtain tissue for cytogenetics, flow cytometry, biologic studies, and EM as described in Section 14.1.

14.3.1 Surgical margins

Completeness of resection and the status of the margins should be assessed. A positive margin will be any margin in which either viable tumor or tumor displaying coagulative necrosis is present at the inked surface. The presence of bland scar or loose fibrous tissue, in the absence of coagulative tumoral necrosis at the margin (where the cytoarchitecture of tumor cells is preserved) will not be considered as a positive margin, provided that there is 90% or greater overall tumor necrosis. In tumors with less than 90% overall necrosis, the presence of abnormal fibrosis or reactive inflammatory tissue at the margin (indicative of treated tumor bed) will be considered a positive margin. The distance of the tumor from the margins should be measured in millimeters, and positive margins should be described as going through a solid nodule of viable tumor, going through individual viable infiltrating tumor cells, or going through necrotic tumor.

14.3.2 Histologic Response

Following definitive surgery the tumor should be examined to determine "histologic response." Since the effect of the preoperative chemotherapy may not be uniform throughout the tumor, adequate sampling as described in Section 14.3.3 is required to grade the histologic response accurately. The institutional pathologist should assess the tumor's pathologic response using the method for quantitation of necrosis described in Section 14.3.3 and utilizing the grading system below as a guideline.

Pathologic response

Grade	Percent Necrosis
I	Less than 50% necrosis
II	50%-89% necrosis
III	90%-99% necrosis
IV	100% necrosis

14.3.3 Procedure for Quantitation of Necrosis

Quantitation of necrosis is performed on the sections prepared from a single slice through the largest axis of the tumor. Only the areas representing tumor (viable

and necrotic) should be included in the quantitation. Areas representing normal tissue should not be included in the quantitation.

In some cases, the amount of residual viable tumor is obvious (e.g., less than 50% necrosis or 100% necrosis). In these instances, one can assign response to the appropriate grade listed in Section 14.3. For problematic (non-obvious) cases, the total area occupied by tumor (both viable and necrotic) should be outlined using a marking pen on each glass slide containing tumor. Using a different color marking pen, the area occupied by viable tumor should be demarcated on the same slides. Lightly cross-hatching the demarcated viable areas may improve the ease of subsequent quantitation. Graph paper with 2 mm squares can be photocopied (actual size) on to acetate sheets for overhead projection. These sheets can then be cut into rectangles and fixed over the cover slip using transparent double-sided tape. The total area occupied by tumor (viable and necrotic) and the area occupied by viable tumor can thus be quantified, and the per cent necrosis can be quantified using the following formula:

% Necrosis = 100 x [1 - (Area occupied by viable tumor/total area occupied by tumor)].

Quantitation of necrosis should not be performed by adding the estimated per cent necrosis on each slide and dividing by the number of slides containing tumor. This method does not take into account differences in the total area occupied by tumor on each slide and may result in inaccurate assessment of the amount of necrosis.

Special attention to quantitation is essential, as one of the secondary aims is to compare the histologic response with the response as determined by MRI and FDG-PET.

14.4 Pathology Specimen Requirements

Submission of materials from the diagnostic biopsy and resection/amputation specimens for pathology central review is not required for this study, though biopsy material must be submitted for the biology studies in Section 15.0. Submission of specimens for the required and optional correlative biology studies is detailed in Section 15.0. Dr. Lisa Teot, MD, is the COG pathologist for AEWS1221 and can be contacted as listed below for questions regarding handling of either the biopsy or resection/amputation specimen.

14.5 Consultation

If a consultation for a difficult case is desired this would be on a consultation basis only and a fee may be charged. If a consultation is desired, the institution should send pathology materials (all slides, a block or unstained slides, and surgical pathology report) to the consultant of their choice. Ship consultation materials using your own courier account.

Study Pathologist:

Lisa A. Teot, M.D.
Boston Children's Hospital
Department of Pathology
Bader 110
Boston, MA 02115
Tel: (857) 218-4962

Fax: (617) 730-0207
email: lisa.teot@childrens.harvard.edu

Please note that materials sent to a reviewer for consultation are separate from a study submission

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

Any time a tumor is resected or biopsied in a patient who has consented to optional tissue collection on this study, tumor material should be submitted to support correlative biology studies.

Submission of pretreatment blood, serum, and paraffin-embedded tumor material or unstained slides according to Sections 15.1, 15.2, and 15.3 is mandatory for enrollment and required of all patients. Submission of serum prior to Week 5 chemotherapy is also required.

Submission of serum samples for ganitumab pharmacokinetic (PK) testing in Induction and Maintenance is also required from the first 10 patients < 21 years of age randomized to Regimen B (see Section 15.5). Enrollment to this cohort completed as of July 2015.

Submission of bone marrow samples and all other follow-up samples from patients who provide additional consent is strongly encouraged of all patients (see Section 15.4).

Submission of samples for plasma cell-free DNA analysis from patients who provide additional consent is strongly encouraged of all patients (see Section 15.6). Note that these samples are to be submitted in Streck Cell-Free DNA BCT tubes, which should be requested from the Biopathology Center (BPC) once a potential patient is identified for this study.

See Appendix II for a reference guide to required and recommended correlative studies.

In addition to the strongly recommended studies embedded within this clinical trial, all patients should be offered co-enrollment on AEWS07B1 or APEC14B1. Specimen requirements for AEWS1221 are independent of specimen requirements for AEWS07B1 or APEC14B1.

Laboratories performing the correlative biology studies will be blinded to randomized treatment arm.

15.1 Serum Markers of IGF-1R Pathway

15.1.1 Specimen Schedule and Requirements

Collection of serum is mandatory at study entry (pretreatment), and just prior to the start of Week 5 Induction chemotherapy, and at the completion of Consolidation. Draw 10 mL of blood into a red top tube at each time point.
For patients on Regimen B (ganitumab arm), who have consented to specimen banking, draw an additional 5 mL of blood (for a total of 15 mL) into a red top tube at each time point.

15.1.2 Specimen Processing

Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum (top, straw-colored layer)

from the red blood cells (bottom, red layer). Dispense (aliquot) the serum into cryovials labeled according to the directions in 15.1.3. Aliquot serum into 0.5 – 1 mL aliquots, with a minimum of 2 mL pretreatment serum required. Cap the vials securely. Immediately **freeze the serum in an upright position** in a -70°C to -80°C freezer.

15.1.3 Specimen Labeling and Shipment

All tubes must be labeled with AEWS1221, the patient's COG patient ID number, specimen type (serum), and collection date.

The Biopathology Center (BPC) will provide a specimen procurement kit upon request. Kits are ordered via the BPC Kit Management system accessed using the following link: https://ricapps.nationwidechildrens.org/KitManagement.

All tubes should be sent to the COG BPC frozen on dry ice by FedEx Priority overnight. Ship to the COG BPC using a FedEx shipping label obtained through the BPC Kit Management system. See above for instructions. Serum may be shipped on Monday through Thursday for a Tuesday through Friday delivery. Do not ship frozen specimens to the BPC on a Friday or the day before a holiday.

Samples may be batch shipped.

Specimens must be accompanied by the completed AEWS1221 BPC specimen transmittal form printed out from the RAVE system and sent to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol AEWS1221
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

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

For questions about this correlative study, please contact the study chair, Dr. DuBois. For questions about sample processing and shipping, please contact the BPC directly.

15.1.4 Methodology

Serum will be analyzed by a commercial laboratory, such as ARUP Laboratory, for a panel of IGF-related proteins, including but not limited to: IGF-1; IGF-2; growth hormone; IGFBP-3 and related proteins using clinically-validated assays. Additional serum from consenting patients on Regimen B (ganitumab arm) will be banked for future tests that may include pharmacokinetic testing, novel biomarker testing, and/or immunogenicity studies, depending upon needs determined at the conclusion of the trial.

15.2 Tissue Markers

15.2.1 Specimen Schedule and Requirements

Pretreatment tumor material is mandatory for study entry for all patients. For patients who provide additional consent for follow-up samples, tumor material should also be submitted any time the patient undergoes resection or biopsy of tumor for any reason (including local control or confirmation of relapse/disease progression). If no viable tumor is seen from a follow-up sample, submission of that follow-up time point may be omitted.

Either a paraffin-embedded tissue block (preferred) or unstained slides should be submitted. If unstained slides are submitted, a minimum of 10 slides are required and optimally, 25 unstained slides should be submitted at each time point. Unstained slides should be standard sections of 3 to 4 µM thickness.

Submission of slides cut sequentially from the same block is strongly preferred. However, if the minimum 10 slides are not available from a single block, submission of slides from multiple blocks is acceptable.

15.2.2 Specimen Processing

No additional on-site processing is required.

15.2.3 Specimen Labeling and Shipment

All tumor material being shipped to the BPC must be labeled with the patient's COG patient ID number, BPC Number, specimen type (primary or metastatic), collection date, surgical pathology ID and block number from the corresponding pathology report.

For blocks and unstained standard slides, tumor material and associated pathology report(s) for that sample should be sent to the COG Biopathology Center (BPC) at room temperature by regular mail or by the submitting institution's courier account. In addition to the pathology report, an AEWS1221 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol AEWS1221
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

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

For questions about this correlative study, please contact the study chair, Dr. DuBois. For questions about shipping the slides, please contact the BPC directly.

15.2.4 Methodology

Immunohistochemistry:
For all patients, tumor material will be used to quantify IGF-1R, AKT, EGFR, ERK, and related proteins using immunohistochemistry.

Quantitative Proteomics Analysis (NantOmics):
For patients who enroll with Amendment #3C and beyond, proteomic analysis of baseline samples by NantOmics will be performed for each patient with an available baseline tissue block. For patients who provide additional consent for follow-up samples, proteomic analysis of follow-up samples by NantOmics will also be performed.

For patients who submit a tissue block, the BPC will cut an additional two (2) 10 micron sections per time point to be placed onto DIRECTOR® slides (provided by NantOmics). Sections along with one (1) H+E slide will then be transferred to NantOmics.

NantOmics will perform protein extraction and quanitification of IGF-1R pathway proteins using a mass spectrometry method. Proteomic analysis will be performed in batches. All efforts will be made to perform proteomic analysis should samples not meet the above specifications.

Whole Genome DNA and RNA Sequencing (NantOmics):
For patients who enroll with Amendment #3C and beyond, DNA and RNA sequencing of baseline samples by NantOmics will be mandatory. For patients who provide additional consent for follow-up samples, DNA and RNA sequencing of follow-up samples by NantOmics will also be performed. The BPC will perform co-extraction of tumor DNA and RNA using established methodology. The following materials (per sample time point) will be batch transferred by the BPC to NantOmics:

- 500 ng of tumor DNA at 5 ng/microliter (minimum acceptable: 50 ng at 1 ng/microliter)
- 1 microgram of tumor RNA at 50 ng/microliter (minimum acceptable: 250 ng at 25 ng/microliter)
- 500 ng of germline DNA at 5 ng/microliter (extracted by BPC as described in Section 15.3).

NantOmics will perform whole genome DNA and RNA sequencing of tumor (and germline to enable designation of aberrations as somatic events) using next generation sequencing methods. Sequencing will be performed in batches. All efforts will be made to perform DNA and RNA sequencing should samples not meet the above specifications.

15.3 *EGFR* Promoter Polymorphisms

15.3.1 Specimen Schedule and Requirements

A single pretreatment sample is mandatory. A single 5-10 mL of peripheral blood in EDTA (purple top tube) could be collected any time prior to initiating systemic chemotherapy.

15.3.2 Specimen Processing

Tubes should be gently inverted 3-4 times after sample collection. No other on-site processing is required. Sample should be kept in a refrigerator (4° C), until shipped.

15.3.3 Specimen Labeling and Shipment

Tubes must be labeled with the patient's COG patient ID number, BPC Number, specimen type (blood), and collection date.

Each sample should be sent on the day the sample was obtained. Do not collect and ship until after the patient is enrolled on AEWS1221. Sample should be shipped cold but not frozen by shipping along with a cold pack, taking care to keep the tube out of direct contact with the cold pack. (Do not use a cold pack when shipping during winter months or the specimen will freeze.) Ship to the COG Biopathology Center (BPC) using a Federal Express shipping label obtained through the BPC Kit Management application. See Section 15.1.3 for instructions on accessing the BPC Kit Management application. Blood may be shipped on Monday through Friday for a Tuesday through Saturday delivery.

An AEWS1221 BPC specimen transmittal form must be completed in RAVE, printed and sent with the specimen to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol AEWS1221
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865

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

For questions about this correlative study, please contact Dr. E. Anders Kolb at eakolb@nemours.org or (302) 651-5567. For questions about sample processing and shipping, please contact the BPC directly.

15.3.4 Methodology

The BPC will process DNA from blood samples using standard methodology. Plasma will be frozen to support the study described in Section 15.6 for patients meeting criteria for inclusion in that study. A discrete 689 bp region of the *EGFR* gene containing the promoter and a portion of exon 1 will be amplified by polymerase chain reaction using primers CCATTATCCGACGCTGGCTCTA and GCATCGCTGCTCCCCGAAGA. PCR will be performed on a Stratagene Robocycler for 35 cycles (30 sec at 95°C, 30 sec at 61°C, and 1 min at 72°C). PCR products will be purified with Qiaquick PCR Purification Kit (Qiagen). Sequencing reaction will be performed using the ABI BigDye Terminator Cycle Sequencing Ready Reaction kit v 3.1 in a 10 µL reaction and cleaned with Edge Bio Performa DTR columns. Sequencing reactions will be analyzed on the ABI3130XL Genetic Analyzer. Paraffin-embedded tumor material collected as in Section 15.2 will also be used to quantify EGFR protein expression.

15.4 Bone Marrow Micrometastatic Disease

Since samples must arrive fresh in the laboratory, this correlative study applies only to sites in the United States and Canada.

15.4.1 Specimen Schedule and Requirements

For patients who provide additional consent, bone marrow aspirate material should be submitted anytime patients have a diagnostic bone marrow evaluation, including study entry.

5-10 mL of aspirated marrow should be placed into an EDTA (purple top) tube and gently inverted several times to prevent clotting. Unilateral samples are adequate as are samples pooled from bilateral bone marrow aspiration. Samples should be kept at room temperature and shipped at room temperature.

Material must arrive fresh in the laboratory. Marrow samples collected on Monday-Thursday are eligible for submission such that samples arrive in the laboratory Tuesday-Friday. For patients undergoing clinical biopsies on a Friday, do not submit marrow samples from that biopsy for this correlative study. The study chair and the TransLab at Dana-Farber/Boston Children's must be notified prior to shipment by emailing: steven_dubois@dfci.harvard.edu and myriam.armant@childrens.harvard.edu.

15.4.2 Specimen Processing

No additional on-site processing is required.

15.4.3 Specimen Labeling and Shipment

Samples should be labeled with AEWS1221, COG patient ID number (NOT BPC number), Bone Marrow, and sample collection date.

Samples must arrive fresh in the laboratory. Each sample should be sent on the day the sample was obtained (or within a maximum of 24 hours from sample acquisition). Sample should be shipped at room temperature. Tubes should be sent to the reference laboratory by Federal Express overnight to arrive the next morning. For these specimen shipments only, Federal Express account number: 361615042 should be used. Be sure to also provide reference number 9618307.
A bone marrow specimen transmittal form should be completed in RAVE, printed and sent with the specimen to the following address to arrive the next morning:

ATTN: Myriam Armant, TransLab
Boston Children's Hospital
61 Binney Street
ENDERS Room 428
Boston, MA 02115
(617) 713-8085
Email: myriam.armant@childrens.harvard.edu

For questions about this correlative study, please contact the study chair Dr. DuBois or Myriam Armant in the reference laboratory at myriam.armant@childrens.harvard.edu or (617) 713-8085.

15.4.4 Methodology

Bone marrow mononuclear cells will be isolated on a Ficoll gradient. One to five million bone marrow mononuclear cells will be prepared for staining using standard methods and then stained with commercially available flow cytometry monoclonal antibodies against CD99, CD45, and IGF-1R. Cells will then be washed and one to five million cells will be assayed and collected on a BD FACS Aria flow cytometer. The proportion of CD99+CD45- cells will be quantified. Among CD99+CD45- cells, the intensity of IGF-1R co-expression as well as the percentage of tumor cells co-expressing IGF-1R will be determined. Additional analytes may be assessed as new information emerges.

Samples with sufficient CD99+CD45- cell burden will undergo fluorescent activated cell sorting to isolate CD99+CD45- cells to support Aim 1.3.13. DNA will be isolated from these cells followed by next-generation sequencing to identify primary oncogenic translocations, mutations in *TP53* and *STAG2*, and extent of somatic heterogeneity in tumor cells. When available, primary tumor material will be tested to allow comparison between paired primary and metastatic tumors.

15.5 Ganitumab Pharmacokinetic Study

The first 10 patients < 21 years of age assigned to Regimen B are **required** to provide serial blood samples for the assessment of ganitumab serum concentrations in Induction and Maintenance. Enrollment to this cohort completed as of July 2015. For patients previously assigned to this cohort, continue to collect samples as detailed in the following sections.

15.5.1 Specimen Requirements

Note: The samples for ganitumab pharmacokinetics can be drawn from a central line, including a central line used to administer ganitumab.

Induction

Serum samples are to be obtained:

- Prior to first dose of ganitumab
- Just prior to the second dose of ganitumab on Induction Day 15
- Just prior to the third dose of ganitumab on Induction Day 29
- Just prior to the sixth dose of ganitumab on Induction Day 71

If the second dose of ganitumab is delayed due to toxicity, serum should still be obtained on Induction Day 15 even if the patient will not receive ganitumab that day.

If the third and/or sixth dose of ganitumab is delayed beyond Induction Days 29 and/or 71 due to toxicity, serum should be obtained 14 days after the second and/or fifth dose of ganitumab.

At each time point, 2 mL of blood should be drawn into a serum separator tube without any added anticoagulant. After collection, the tubes should be gently inverted 5 times and held at room temperature for 30-60 minutes before processing according to Section 15.5.2. Samples should not sit for longer than 60 minutes before processing.

Maintenance
Serum samples are to be obtained:

- Prior to first Maintenance dose of ganitumab
- Just prior to the third Maintenance dose of ganitumab at Week 7
- Just prior to the fourth Maintenance dose of ganitumab at Week 10
- Just prior to the sixth Maintenance dose of ganitumab at Week 16

At each time point, 2 mL of blood should be drawn into a serum separator tube without any added anticoagulant. After collection, the tubes should be gently inverted 5 times and held at room temperature for 30-60 minutes before processing according to Section 15.5.2. Samples should not sit for longer than 60 minutes before processing.

15.5.2 Specimen Processing

Centrifuge tubes 1500 x g for 15 minutes at room temperature (if you have a temperature controlled centrifuge, set it to 20°C). With a pipette, remove serum from the top of the tube without disturbing the blood cells and transfer an ***equal volume*** (ideally 0.5 mL each) into labeled 2 mL cryovials (recommended vials: Sarstedt screw cap micro tube, self standing external thread, Catalog number 72.694.005, 2.0 mL capacity). If there is an inadequate amount of serum for 0.5 mL per cryovial, then split the available serum volume equally into all cryovials. Immediately place the labeled 2 mL cryovials containing the serum sample in a -70°C or colder freezer. If a -70°C freezer is unavailable, alternatively samples can be stored in a -20°C freezer for up to 3 months. If a -70°C or a -20°C freezer is unavailable, then freeze on dry ice and ship frozen to PPD on the day of collection.

Each serum sample must be frozen within 2 hours of blood collection.

15.5.3 Specimen Labeling and Shipment

Each cryovial should be labeled with:

- COG Patient ID number
- "AEWS1221"
- Date
- Time

Ship frozen cryovials on dry ice to PPD by overnight courier using the COG Federal Express account number provided in the link below: https://www.cogmembers.org/_files/reference/FEDEXmemo.pdf. Samples should be shipped Monday-Thursday for weekday first morning arrival at PPD. A study-specific paper PK transmittal form (provided in the CRF packet on the protocol webpage) must be submitted with the samples to the following address:

Sample Management
PPD Bioanalytical Lab
2246 Dabney Road
Richmond, VA 23230
Phone: (804) 977-8017
Fax: (804) 977-8104

In addition, a copy of the completed PK transmittal form must be uploaded into RAVE.

The first 3 Induction samples (prior to the first, second and third doses of ganitumab) should be batch shipped within 3 days of collection of the Day 29 samples. Do not wait until the remaining samples are available for a patient before shipping the first 3 Induction samples. The remaining Induction and Maintenance samples can be batch shipped after the Week 16 Maintenance samples have been obtained.

For questions about the pharmacokinetic study, please contact the study chair, Dr. DuBois. For questions about shipping samples, please contact PPD directly.

15.5.4 Methodology

Serum will be used to quantify ganitumab concentrations as previously described.[34] The primary data to be evaluated is trough concentrations.

15.6 Circulating Tumor DNA Analysis

15.6.1 Streck Cell-Free DNA BCT Tube Ordering

IMPORTANT: If the patient has consented to ctDNA study, tubes should be ordered via the BPC Kit Management system as soon as possible after patient enrollment to allow time for tubes to be shipped. When ordering the first set of Streck tubes for a patient for AEWS1221, please select "Overnight" for FedEx Shipping Type. In "Shipping Comment" please document "Overnight Shipping Exception per AEWS1221 instructions" and include the patient registration number. All other shipments will be sent by ground transportation and shipping will take 3-5 business days. The Kit Management System can be accessed via the following link: https://ricapps.nationwidechildrens.org/KitManagement.
You must select AEWS1221 as the protocol and Streck Cell-Free DNA Tube as the kit when ordering Streck tubes for AEWS1221 patients.

15.6.2 Specimen Schedule and Requirements

For patients who provide additional consent for this study of circulating tumor DNA (with Amendment #1 and beyond), 10 mL of blood in a Streck Cell-Free DNA BCT tube should be collected at the following time points:

- Baseline (prior to initiation of protocol therapy)
- Just prior to the start of Week 3 Induction
- Just prior to the start of Week 5 Induction
- End-Induction (at time of disease restaging)
- Mid-Consolidation (at time of disease restaging prior to Week 9 Consolidation)
- End Consolidation (at time of disease restaging)
- At time of relapse/progression.

15.6.3 Specimen Processing

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

15.6.4 Specimen Labeling and Shipment

The tube must be labeled with the patient's COG patient ID number, BPC Number, specimen type (blood), and collection date.

Each sample should be sent on the day the sample was obtained. Sample should be **SHIPPED AT ROOM TEMPERATURE**. Ship to the COG Biopathology Center (BPC) using a Federal Express shipping label obtained through the BPC Kit Management application. See Section 15.1.3 for instructions on accessing the BPC Kit Management application. Blood may be shipped on Monday through Friday for a Tuesday through Saturday delivery. Do not ship blood the day before a holiday. In cold months, add insulating material to keep the blood from freezing.

A BPC specimen transmittal form should be completed in RAVE, printed and sent with the specimen to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol AEWS1221
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865

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

For questions about this correlative study, please contact the study chair, Dr. DuBois. For questions about sample processing and shipping, please contact the BPC directly.

15.6.5 Methodology

The cohort will include patients enrolled prior to Amendment #1 who consented to use of leftover material as well as patients who enrolled with Amendment #1 and beyond who consent to serial sample collection to support this aim.

A capture NGS sequencing approach will be used to detect relevant translocations and mutations from cell free DNA extracted from approximately 2 milliliters of plasma for each patient using a commercial kit. After extraction, capture sequencing of cell free DNA will be performed utilizing oligonucleotides complementary to the genomic regions of interest. Sequencing of the captured cell free DNA and data analysis will be preformed by the Center for Cancer Genome Discovery (CCGD) at Dana-Farber Cancer Institute to identify genomic rearrangements in the intronic regions of the *EWSR1*, *FUS*, *CIC*, and *BCOR* genes as well as the coding regions of the *STAG2* and *TP53*.

15.7 **Additional correlative studies**

If the patient consented to banking of material for future research then blood, bone marrow, and paraffin-embedded material or unstained slides remaining after the studies detailed in Sections 15.1-15.4 have been completed may be used for future research exploring the biology of Ewing sarcoma or other diseases. Assays to be performed include sequencing (including whole exome or whole genome sequencing) and creation of cell lines. If used

for such additional biologic research, specimens would be de-identified prior to use. If biologic studies required linkage to treatment / outcome data (e.g., immunogenicity assays on banked serum) such linkage would be performed by an honest broker as is typical for this type of study.

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

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

16.1 Imaging Guidelines

CT and MRI guidelines are available on the COG Member site at: https://www.cogmembers.org/_files/reference/RefMaterial/DiagnosticImagingGuidelines_MRICT.pdf.

For PET scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of ^{18}F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found in the consensus statement by Shankar and colleagues.[123]

See also Section 10 for overview of response assessment and preferred imaging studies.

For local staging, MRI scans are preferred in the vast majority of cases. CT is also useful in assessing cortical changes and for chest wall tumors. MRI for local staging should be performed at field strength of 1-3 Tesla, using dedicated surface coils for the anatomical area of interest, and should always include axial fat-saturated T2-weighted sequences and contrast-enhanced T1-weighted sequences in a second plane, among other site-specific sequences. Diffusion-weighted scans and ADC maps are desirable. Gadolinium-chelates may be used in patients with an eGFR of > 60. Tumor measurement in three dimensions will be requested (see separate data forms packet).

Metastatic disease should be evaluated by FDG-PET scan and CT scan of the lungs. For FDG-PET scans, ^{18}F-FDG should be injected intravenously 45–60 min prior to image acquisition, and patients should be asked to void their urine immediately before the scan. For centers with PET/CT capability, a diagnostic quality chest CT with slice thickness of 5 mm or less is required of all patients. Diagnostic CT data will be reconstructed using soft tissue and lung algorithms. The same CT data can be used for attenuation correction of the PET emission data. PET and CT images will be merged and reconstructed in the transaxial, coronal and sagittal planes.

Sites suspicious for bone or soft tissue metastasis should be imaged further with MRI or CT (whole body CT or MRI obtained as part of PET/CT or PET/MRI scan is acceptable)

at study entry. Confirmed sites of bone or soft tissue metastatic involvement at study entry should have repeat MRI or CT at each follow-up re-staging evaluation.

For patients having a separate dedicated chest CT for metastatic staging, helical CT of the lungs should be obtained in low dose mode with a slice thickness of 5 mm or less. Contrast agent injection is optional and might be favored in case of a chest wall primary tumor and/or clinical suspicion for mediastinal or pleural disease.

While some centers may utilize whole body MRI scans to evaluate for metastatic disease, these scans are optional and should not replace required imaging studies. Whole body MR images can be obtained using whole body surface coils and STIR and/or diffusion weighted sequences. Data sets obtained at different bed positions will be post-processed to generate "whole body" scans.

The study radiologist is available for consultation for questions related to diagnostic imaging.

16.2 Correlative Imaging Aims

As part of routine clinical care, patients will undergo MRI (less commonly CT) of the primary tumor as well as whole-body FDG-PET scans. Scans from study entry and end-Induction will be submitted to IROC Rhode Island (formerly QARC) for batched central review and fusion of PET and MRI images by the study radiologist. MRI (or CT) data will be used to obtain the largest anterior-posterior, transverse and longitudinal dimensions. Reporting of these three dimensions will be required. These dimensions will be used for central estimation of tumor volume using the formula for a prolate ellipsoid: volume in $mm^3 = \pi/6 \cdot (d_1 \cdot d_2 \cdot d_3)$ = (AP x transverse x longitudinal) x 0.5.

Institutions will also report primary tumor FDG-PET standardized uptake value from the primary tumor at study entry and again at end-Induction.

16.3 Instructions for Submitting Imaging for Correlative Imaging Aims

Anatomic imaging (MRI or CT) and FDG-PET scans from study entry, end-Induction, and first episode of disease progression / relapse will be submitted to IROC Rhode Island as follows to support the correlative imaging aims 1.3.4, 1.3.9 and 1.3.10. If images already submitted to IROC Rhode Island as part of radiation oncology review, duplicate images do not need to be submitted to support these aims.

The corresponding radiology reports will also be submitted to IROC Rhode Island.

Submission of diagnostic imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information to obtain an sFTP account and submission instructions can be found at http://irocri.qarc.org/. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC Rhode Island. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD.

Please submit to:

IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201

Lincoln, RI 02865-4207
Phone: 401-753-7600
Fax: 401-753-7601

17.0 RADIATION THERAPY GUIDELINES

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities.

> 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).

17.1 General Guidelines

The radiation therapy guidelines for this study were developed specifically for patients with newly diagnosed, metastatic Ewing sarcoma. These guidelines apply to patients who require radiation therapy as a component of treatment of the primary tumor during the Local Control phase of therapy and also to patients who require radiation to metastatic sites during the Metastatic Site Radiation phase of therapy.

17.1.1 Special Note for Very Young Children

The long-term morbidity of RT or aggressive surgery for very young children makes appropriate local control challenging. Many clinicians are unwilling to follow standardized local control guidelines for very young children. This study encourages adherence to standardized local control guidelines for all children regardless of age. Consult with study surgeons and radiation oncologists as appropriate for a specific case.

17.1.2 Credentialing

- All therapy units used on this protocol must have their calibrations verified by IROC Houston (RPC). The table in Section 17.5 indicates allowable modes of treatment delivery.
- IMRT: Institutions treating with IMRT and not previously credentialed for use of IMRT in COG trials must irradiate IROC Houston's head and neck phantom. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.
- Proton Therapy: The Proton Questionnaire (available at http://irochouston.mdanderson.org) must be completed. Each beam line used to treat patients on this study must be credentialed for clinical trial use by IROC Houston. See Section 17.1.4 below.
- Motion Management: If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion.
- SBRT: Use of SBRT is encouraged for treatment of bone metastases <5 cm (based upon maximal dimension at diagnosis), but credentialing is

required for its use. SBRT credentialing includes the following three components: (1) completion of the Motion Management Questionnaire (2), irradiation of IROC Houston's Spine Phantom and (3) approval of the institution's IGRT process. See http://irocri.qarc.org/for the Motion Management Questionnaire and a description of IGRT credentialing requirements.

NOTE:

- SBRT is not to be used for sites other than bone metastases.
- COG will accept SBRT credentialing through NRG provided that the credentialing included irradiation of IROC Houston's Spine Phantom (RTOG 0631).

17.1.3 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 cooperative group trials. These guidelines are available through http://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.

17.1.4 Guidelines and Requirements for the Use of Proton Beam Therapy

Proton therapy may be used to deliver radiation therapy on this protocol. The proton therapy method will be limited to scattering, uniform scanning and pencil beam scanning depending on institutional availability. 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.

17.1.5 Guidelines and Requirements for the Use of Brachytherapy or Intraoperative Radiation Therapy

Brachytherapy, using either high dose rate or low dose rate radioactive sources may be used on this protocol. Typically, brachytherapy or intraoperative radiation therapy will be used to deliver focal RT to residual disease in the operative bed of the primary tumor for select patients.

17.1.6 Institutional Requirements to Offer SBRT

All sites treating with SBRT to sites of bone metastasis must be credentialed. COG will accept SBRT credentialing through NRG (see Section 17.1.2). As radiotherapy for metastatic sites is not performed until the completion of therapy, sites that are not credentialed at the initiation of therapy should have adequate time to obtain SBRT credentialing prior to its use. The pediatric radiation oncologist should be involved at the time of diagnosis to assess if imaging is adequate for local therapy and to ensure that all required credentialing tests for SBRT have been met.

17.2 Indications for Radiation Therapy

All patients should have all local and distant disease addressed with an appropriate local control modality. Definitive local therapy (surgery, SBRT, EBRT) is recommended to all metastatic sites documented at the time of diagnosis. SBRT is recommended to all bone metastatic sites < 5 cm in maximal dimension (based upon maximal dimension at diagnosis) if not treated surgically. Optimal local control will be determined by the treating institution and should involve input from pediatric oncology, surgery, and radiation oncology. **The pediatric radiation oncologist should be involved at the time of diagnosis to assess if imaging is adequate for local therapy and to ensure that all required credentialing tests for SBRT have been met.** It is expected that the majority of patients will receive radiotherapy to the often multiple sites of metastatic disease. Because of the option of SBRT for metastatic sites, RT guidelines follow for treatment of primary site and then separately for treatment of metastatic sites.

Note: SBRT is not to be used for sites other than bone metastases.

See Section 4.3 for a general discussion of local control.

RT for Primary Site

Definitive radiation therapy	Unresected tumor
Pre-operative radiation therapy	Resectable tumor*
Post-operative radiation therapy	(1) Post-operative gross or microscopic residual tumor (2) Intra-operative spill
Special presentations	(1) Chest wall tumor with ipsilateral pleural-based secondary tumor nodules or positive pleural fluid cytology (2) Pathologically involved lymph nodes

RT for Metastatic Sites

Definitive radiation therapy	Unresected tumor > 5cm
Definitive SBRT	Unresected/post-operative gross disease in bone mets that were <5 cm at diagnosis
Post-operative radiation therapy	(1) Post-operative gross or microscopic residual tumor (2) Intra-operative spill
Special presentations	(1) Pulmonary metastases (2) Pathologically involved lymph nodes

*Pre-operative radiotherapy is generally not indicated in this patient population (see Section 4.3.1.3).

Patients having microscopic or gross residual disease after planned pre-operative radiation therapy will receive additional radiation therapy (see table Section 17.7.2.1).

Patients who have had a complete surgical excision of the involved area of bone and/or soft tissue mass with adequate surgical margins (see Sections 4.3.1, 14.3.1 and 17.7.2.1) will not receive postoperative radiation.

Radiation is not indicated for the following conditions: bone marrow lesions with no evidence of bone involvement or sites not assessable clinically or by imaging and radiation that would exceed normal marrow tolerance.

17.3 Timing of Radiotherapy

17.3.1 Radiation Oncology Consultation

All patients should be seen in consultation by a radiation oncologist as early as possible if RT may be indicated according to the protocol. The purpose of the consultation is to participate in staging and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning, as well as to discuss and plan for potential use of various radiation modalities (SBRT, proton therapy).

Patients treated with radiation as the local control measure to the primary site, or preoperatively or postoperatively, will have radiotherapy delivered beginning concurrently with the beginning of Consolidation chemotherapy. If wound healing is incomplete, the possibility of a delay in initiation of radiation should be discussed with the protocol radiation oncologist. Ifosfamide and etoposide chemotherapy may be given concurrently with radiotherapy (See Section 4.1.1.1).

If radiation is used for metastatic sites, radiotherapy should be given at the end of Consolidation chemotherapy during the Metastatic Site Radiation phase of therapy. An exception may be made for treatment of limited lesions immediately adjacent to the primary site which may be difficult to treat without overlap of radiation volumes if treated at a later date. These metastatic sites will be treated concurrently with the primary tumor site. See Section 4.1.1.2 for modifying order of Consolidation for patients who receive early whole lung radiation due to overlapping radiation fields with the primary tumor.

17.3.2 Timing of Emergency/Urgent Radiation Therapy

Patients who require emergency radiotherapy, such as patients with spinal cord compression, may receive radiotherapy to their emergency site on Day 1 if deemed necessary by the treating physician. This is expected to be a rare event, since most patients will respond quickly and dramatically to chemotherapy. In addition, early therapy intensity appears to be associated with improved outcomes in this disease. The entire course of the emergency radiotherapy should be administered starting Day 1, rather than splitting the treatment and concluding the course at the beginning of Consolidation.

In cases requiring urgent or emergency radiotherapy, notify the study radiation oncologist. Note that doxorubicin courses must not be given during radiation with the exception of Consolidation Cycle 1 where concurrent start of chemotherapy and radiation is allowed. If emergency radiotherapy is required during Induction the order of the six planned chemotherapy cycles may be altered in order to avoid concurrent administration of doxorubicin with radiation (except Days 1 and 2 of doxorubicin in week 1 Induction, which may be given at the start of emergent radiation). Ifosfamide/etoposide courses may be given concurrently. Ganitumab must not be given concomitantly with radiation and therefore the schedule of ganitumab administration must also be altered while administering a total of 11 doses of ganitumab across Induction and Consolidation for patients in Regimen B.

17.3.3 Mesna

In the past, mesna was held during radiation therapy. There are no data to suggest that mesna is a radioprotector. Mesna will therefore not be held during radiation.

17.4 Emergency Radiation Therapy

Radiation therapy may be delivered on an emergent basis to patients with spinal cord compression, loss of vision or other function-threatening conditions. The decision to irradiate emergently should be made by the treating physicians. If emergent radiation is initiated, the entire course of the radiotherapy for that site should be delivered using the protocol specified doses, rather than waiting until the protocol specified times for irradiation. Doxorubicin should be withheld if patients receive emergency radiation therapy (except Days 1 and 2 of doxorubicin in week 1 Induction, which may be given at the start of emergent radiation). Ifosfamide/etoposide courses may be given concurrently. Ganitumab must not be given concomitantly with radiation and therefore the schedule of ganitumab administration must also be altered while administering a total of 11 doses of ganitumab across Induction and Consolidation for patients in Regimen B.

17.5 Equipment and Methods of Delivery and Verification

Equipment	Photons** (any energy)	Electrons (any energy)	IMRT (4-10MV)	Protons	Brachytherapy*
Linear Accelerator	X	X	X		
Proton Beam				X	
Intraoperative Radiation Therapy	X	X			X
Brachytherapy - high or low dose rate					X

* Permanent radioactive implants are *not allowed* on this protocol.

** For tumors adjacent or included in lung tissue, photon beam energy should be ≤ 10 MV.

17.5.1 Treatment planning

CT-treatment planning: All patients will undergo CT treatment planning for this protocol. Slices no more than 0.5cm thick (0.2-0.3cm is recommended) shall be taken throughout the extent of the irradiated volume.

CT (volumetric) based planning is required to optimize dose to the target volumes while protecting normal tissues. Organs within the irradiated volume should be contoured including those required by treatment site (Section 17.10). A DVH is necessary to determine target coverage and evaluate dose to normal tissues. In the event that a patient must start radiation emergently with a non-volumetric treatment plan, a volumetric plan will be accomplished as soon as is reasonably possible and the previously utilized beams must be incorporated into the composite plan.

17.5.2 In-room verification of spatial positioning

Two-dimensional or volumetric imaging may be used to verify correct patient positioning. Portal imaging using EPIDs is the most common two-dimensional method, particularly when the target volume possesses a fixed spatial relationship with visualized bony anatomy. Film is discouraged but is acceptable. For IMRT

and 3-D CRT treatments, a pair of images (usually orthogonal AP and lateral) is required to verify that the isocenter is in correct alignment relative to the treatment plan; these may be MV or kV images. When proton radiation is employed, daily image guidance with either 2-D or volumetric imaging is required.

Volumetric imaging for position verification may be in-room kV or MV cone beam or conventional CT imaging. 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.

17.6 Target Volumes

17.6.1 Standard tumor and 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. Treatment planning will be based on the following definitions and applies only to the primary tumor site:

Photons

- *Gross tumor volume (GTV)* is the volume occupied at diagnosis by visible or palpable disease.
- *Clinical target volume (CTV)* includes the GTV and sites with potential occult tumor involvement including lymph nodes adjacent to the GTV that may be clinically involved.
- *Planning target volume (PTV*) is the CTV surrounded by a geometric margin to account for variability in set-up, breathing or motion during treatment.

Protons

- *GTV* is the same for protons and photons.
- *CTV* is the same for protons and photons.
- *PTV* will be uniquely defined for proton therapy.
  The 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 (scattered versus scanning) at the treating proton center.

  When proton therapy is used, 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.

  The PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator (if applicable), (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 3-15 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error

determined for the particular body site at the individual proton institution. 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 in Section 17.7.3.

Brachytherapy

- *GTV* is the same as for photons.
- *CTV* is the same as for photons.
- *PTV* is equal to *CTV*.

17.6.2 Initial tumor and target volume definitions

The definitions for GTV1, CTV1 and PTV1 apply to all definitive, preoperative and postoperative treatment scenarios for which radiation therapy is indicated. Treatment will be prescribed to the PTV, which will be derived from the GTV and CTV

17.6.2.1 GTV1

GTV1 is defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET scan) prior to any surgical debulking or chemotherapy. It also includes enlarged but unresected, regional lymph nodes. For patients who undergo initial surgery, operative notes and pathology reports may be helpful. GTV1 may require modification for initial tumors that exhibit a "pushing margin" into body cavities (ie, thorax, abdomen). If the tumor has responded to chemotherapy and normal tissues have returned to their natural position, GTV1 excludes the pre-chemotherapy volume where that volume extends into the cavity. Examples include tumors that indent the lung, intestine or bladder that clearly return to a more normal anatomic position following chemotherapy. The modified GTV1 includes initially infiltrative disease which has responded to chemotherapy.

17.6.2.2 CTV1

If there are no sites that warrant irradiation for potential occult tumor, then the CTV1 is defined as the GTV1 plus 1 cm (but not extending outside of the patient). It also includes regional lymph node chains for clinically or pathologically involved nodes. For tumors with no evidence of nodal involvement (N_0), the draining regional lymph nodes are not irradiated. For some sites, the definition of CTV is modified to account for specific anatomic barriers to tumor spread. When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.

17.6.2.3 PTV1

For external beam photon techniques, the PTV1 is defined as the CTV1 plus an institutional specified margin to account for day-to-day setup variation related to the ability to immobilize the patient and physiologic motion of the CTV1. The minimum margin is 0.5 cm without daily image guidance but does not have to be uniform in all dimensions. Institutions with daily image-guidance may be able to reduce PTV based on institution-specific guidelines.

For proton planning, beam specific PTV expansions will be required as described in Section 17.6.1.

Motion of the target volume in three dimensions (cranial, caudal, anterior to posterior, and lateral) may be determined by 4-dimensional CT, respiratory gated CT, or other accepted techniques. An ITV (internal target volume) may be created to account for internal motion if average CT based planning is employed using the guidelines outlined in 17.8.6.

17.6.3 Volume reduction tumor and target volume definitions

The definitions for GTV2, CTV2, and PTV2 apply to all definitive, preoperative, and postoperative treatment scenarios for which radiation therapy is indicated.

17.6.3.1 GTV2

GTV2 is defined as residual visible or palpable tumor as assessed by CT, MRI, PET scan or physical exam following Induction chemotherapy with or without surgery. For unresected tumors, GTV2 includes the pre-treatment abnormalities in bone and the gross residual tumor in soft tissue after Induction chemotherapy. For partially resected tumors, GTV2 includes residual abnormalities in bone and the gross residual tumor in soft tissue and the tumor bed harboring microscopic residual tumor. For tumors with microscopic residual and >90% necrosis, this is the post-induction chemotherapy target volumes determined on pre-operative imaging.

Special Considerations: In the case of extraosseous primaries with a complete response to chemotherapy or with intra-operative spill, there is only a single GTV (GTV1=GTV2).

17.6.3.2 CTV2

CTV2 is defined as the GTV2 + 1 cm (but not extending outside the patient) and areas at risk for microscopic disease and modified to account for specific anatomic barriers to tumor spread. CTV2 includes lymph nodes adjacent to the GTV when appropriate. CTV2 should not extend outside of the patient.

17.6.3.3 PTV2

PTV2 is defined as the CTV2 with an institution and modality specific margin (minimum: 0.5 cm) to account for day to day setup variation and physiologic motion of the CTV2. For proton planning, beam

specific PTV expansions will be required as described in Section 17.6.1.

Special Presentations:

1) Chest Wall Tumors with Ipsilateral Pleural Nodules and/or Pleural Fluid Involvement (CTV3, PTV3)
These patients will require irradiation of the ipsilateral hemithorax followed by irradiation to the primary site, and if applicable, pleural based nodules. Target volumes for ipsilateral hemithorax irradiation are designated CTV3, PTV3 and will be irradiated first. Irradiation of the primary site or pleural based disease will follow. The GTV1, CTV1, PTV1 and GTV2, CTV2, and PTV2 for the primary are defined and treated as outlined in previous sections after completion of hemithorax irradiation. If the primary has been resected with adequate margins, and irradiation of the primary site is not indicated, the primary will not be treated and radiation will be administered only to PTV3. For ipsilateral or bilateral lung irradiation, the lung and pleural cavity is defined as the CTV3. PTV3 is an expansion of CTV3 to account for organ motion during respiration as well as a 0.5-1 cm geometric expansion to account for day to day set-up uncertainty. Organ motion can be determined with a 4D simulation, fluoroscopy, or lateral chest radiograph at full inspiration to document diaphragmatic excursion. The GTV1 and GTV2 for the primary and for the pleural based metastases are defined and treated as outlined in previous sections, however, there will be no GTV2 assigned to pleural based metastases having complete response to chemotherapy. The CTV1 and CTV2 of the primary and the CTV1 and CTV2 for the pleural based metastases respectively, may be combined if they can be treated in a single field based on the judgment of the radiation oncologist. Similarly a composite for the CTV3 including the pleural surfaces of the entire hemithorax and including the primary site and the pleural based metastases may be created to simplify treatment planning as long as dose requirements to these regions are met.

2) Pathologically Involved Lymph Nodes
Nodal target volumes are included in the definitions of GTV1, CTV1, PTV1. Nodal target volumes are included in the definitions of GTV2, CTV2, and PTV2 with some modifications:

In the case of a primary tumor which is resected with adequate margins, the nodal PTV should be drawn without the primary site and will be the only volume treated. The GTV for the primary site and GTV for the lymph nodes should initially be determined independently. If the volumes are contiguous the treating radiation oncologist should consider combining the volumes (especially after CTV and PTV expansions). The doses for the primary site and lymph nodes should be determined independently.

GTV2 is only defined for unresected lymph nodes and includes the nodal volume after chemotherapy. GTV2 cannot be defined

for resected lymph nodes or when there has been a complete response to chemotherapy.

CTV2 is only defined for unresected lymph nodes and its definition depends on the response to chemotherapy. CTV2 is defined as the original involved nodal region for unresected lymph nodes that have had a complete response to chemotherapy. CTV2 is defined as the original involved nodal region with an additional margin of 1.0 cm surrounding GTV2 for unresected lymph nodes after a partial response to chemotherapy.

PTV2 is only defined for unresected lymph nodes and includes an additional margin of 0.5-1.0 cm surrounding CTV2. When proton radiotherapy is employed, beam-specific PTV2 should be determined as described in Section 17.6.1.

Vertebral Body Tumors

The GTV1 and GTV2 are defined as outlined in previous sections. At a minimum, CTV1 is defined as the entire vertebral body. PTV1 is the CTV1 volume with an institution specific margin of approximately 0.5 cm to account for day to day variation in set-up and physiologic motion. For the field-reduction boost, CTV2 is defined as GTV2 plus an additional 0.5-1.0 cm margin to account for sub-clinical areas of residual disease but confined by anatomic boundaries (e.g. does not enter the spinal canal if initial disease did not enter the canal). PTV2 is the CTV2 volume with an additional margin of approximately 0.5 cm to account for day to day variation in set-up and physiologic motion. Again, this may be further adjusted and beam-specific when protons are utilized. Institutions with daily image-guidance may be able to reduce PTV based on institution-specific guidelines.

Extremity Tumors

The CTV should be modified at the discretion of the radiation oncologist to avoid circumferential irradiation of extremity lymphatics and treatment across a joint unless absolutely necessary for tumor coverage. A strip of tissue must be provided for extremity tumors, so that lymphatic obstruction and unacceptable morbidity can be avoided. If any of the treatment margins necessitates irradiating the epiphysis of an adjacent bone and there is no extension across the joint space, a smaller margin may be considered so that the adjacent epiphysis can be excluded. If the patient has a diaphyseal lesion, every attempt should be made to exclude at least one epiphysis (or both) of the affected bone. The most active growing epiphyses are those about the knee in the lower extremity and those in the shoulder and wrist area of the upper extremity. The gross tumor volume (GTV) should be treated to the prescribed dose whenever possible.

Head and Neck Tumors

Many of these tumors may be considered unresectable due to close proximity to critical structures and surgical risks contributing to

functional or cosmetic deficits. Every attempt should be made to minimize dose to the brain, cochlea, optic chiasm and orbit including eye, lacrimal gland, and optic nerve.

Orbital Tumors
For orbit primaries, the CTV will not extend outside of the bony orbit, providing there is no bone erosion of the orbit.

Chest Wall/Intrathoracic Tumors
Tumors which have displaced a significant amount of lung parenchyma then returned to normal anatomic position following surgery or chemotherapy will have the GTV defined as the preoperative (prechemotherapy) tumor volume excluding the component of intrathoracic tumor which was removed by surgery or decreased in size by chemotherapy. All areas of pleural involvement will be included in the GTV regardless of whether the radiation is delivered pre or postoperatively.

Intra-abdominal/Retroperitoneal/Pelvic Tumors
Tumors which have displaced a significant amount of bowel then returned to normal anatomic position following surgery or chemotherapy will have the GTV defined as the preoperative (prechemotherapy) tumor volume excluding the component of intra-abdominal or intra-pelvic tumor which was removed by surgery or decreased in size by chemotherapy. All areas of peritoneal or mesenteric involvement will be included in the GTV regardless of whether the radiation is delivered pre- or post-operatively. Whole abdomen RT is indicated for malignant ascites or diffuse peritoneal involvement. In such cases the entire peritoneal cavity is considered the CTV.

Pulmonary Metastases and Pleural Effusions (CTV3, PTV3)
These patients will require bilateral whole-lung radiation. Whole lung volume is designated CTV3. PTV3 is an expansion of CTV3 to account for organ motion during respiration as well as a 0.5-1 cm geometric expansion to account for day to day set-up uncertainty. Organ motion can be determined with a 4D simulation, fluoroscopy, or lateral chest radiograph at full inspiration to document diaphragmatic excursion.
Note: IMRT is not allowed for whole lung radiation.

Surgical management of residual pulmonary tumors after Consolidation chemotherapy is allowed. If the lung metastases are resected with adequate margins, boost irradiation is not indicated, and radiation will be administered only to PTV3.

If metastatectomy of residual lung lesions is not performed, a field reduction boost will be administered based on a volume designated GTV2. *As the post-chemotherapy volume (GTV2) is used, there will be no GTV1 in these patients.* GTV2, CTV2, and PTV2 for the residual

lung lesions are defined and treated as outlined in previous sections and treated at the completion of whole lung irradiation.

Non-Pulmonary Metastases Treated with Standard RT (not SBRT)
The GTV2 for metastatic sites is the area of residual tumor defined on CT or MRI (post-chemotherapy/surgery) and involved bone. In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. To minimize irradiated volume, no GTV1 will be defined for metastatic sites. CTV2 is defined as GTV2 plus an additional 1.0 cm margin to account for sub-clinical areas of residual disease but confined by anatomic boundaries. PTV2 is the CTV2 volume with an additional margin of approximately 0.5 cm.

Radiation is recommended to all non-marrow metastatic sites. Bone marrow deposits of tumor must have bone disruption/erosion to qualify as bone disease. CT may be useful to determine bone involvement. However, feasibility of delivering metastatic site radiation diminishes as the number of metastatic sites increases and will be determined by the treating radiation oncologist. SBRT has been introduced to improve the feasibility of treating multiple metastatic sites. If the treating radiation oncologist does not feel treatment of all sites is feasible, radiation is recommended to those metastatic sites if there remains a concern about disease control at that site and the patient can tolerate further radiotherapy without undue morbidity. Re-evaluation imaging at the completion of therapy will help the radiation oncologist determine if the various remaining sites are in need of further treatment and will consider the following: (1) sub-optimal response to chemotherapy by clinical or imaging criteria, (2) sites which will be problematic in the event of disease progression (*i.e.*, tumor in a weight bearing bone), and (3) sites that can be imaged with sufficient accuracy for treatment, and (4) expected tolerance and morbidity (i.e., bone marrow tolerance). Surgical resection of metastases can be considered if it can be done with reasonably low or acceptable morbidity.

Bone Metastases Treated with SBRT
The GTV2, CTV2 and PTV2 for metastatic sites is the area of residual tumor defined on MRI and/or CT (post-chemotherapy/surgery) and pre-treatment abnormalities in bone (see Section 17.6.3.1). In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. To minimize irradiated volume, no GTV1 will be defined for metastatic sites.

For SBRT, modifications to CTV2 and PTV2 are as follows:
CTV2=GTV2+1cm expansion for microscopic disease but limited by anatomic constraints such as bone cortex

PTV2=CTV2+2mm expansion for setup error, but can be limited to avoid critical normal structures such as spinal canal

Definitive local therapy (surgery, SBRT, EBRT) is recommended to all bone metastatic sites documented at the time of diagnosis. SBRT is recommended to all bone metastatic sites < 5 cm in maximal dimension (based upon maximal dimension at diagnosis) if not treated surgically. Bone marrow deposits of tumor must have bone disruption/erosion to qualify as bone disease. CT may be useful to determine bone involvement. SBRT has been introduced to improve the feasibility of treating multiple metastatic sites. If the treating radiation oncologist does not feel treatment of all sites is feasible, radiation is recommended to those metastatic sites if there remains a concern about disease control at that site and the patient can tolerate further radiotherapy without undue morbidity. Re-evaluation imaging at the completion of therapy will help the radiation oncologist determine if the various remaining sites are in need of further treatment and will consider the following: (1) sub-optimal response to chemotherapy by clinical or imaging criteria, (2) sites which will be problematic in the event of disease progression (*i.e.*, tumor in a weight bearing bone), and (3) sites that can be imaged with sufficient accuracy for treatment, and (4) expected tolerance and morbidity (i.e., bone marrow tolerance).

17.7 Target Dose

Integrated boost radiotherapy plans are not permitted.

17.7.1 Dose Definition

Photon dose is to be specified in centigray (cGy)-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.

17.7.2 Prescribed dose and fractionation

Dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied. The protocol-specified dose per fraction is 180cGy. The treatment should be limited to one fraction per day. The dose per fractionation may be reduced from 180cGy to 150cGy when large volumes are treated (*i.e.*, whole abdomen and pelvis) or when tolerance is poor (i.e., mucositis or diarrhea). Changes to the fractionation regimen should be noted in the treatment record and submitted information.

17.7.2.1 Radiation dose guidelines for all targeted volumes, excluding lymph nodes, and chest wall tumors with involved plueral fluid or nodules.

All doses are described in Gy; however, equivalent doses should be prescribed in Gy (RBE)when proton therapy is utilized.

Tumor Site and Presentation	PTV1	PTV2
Definitive RT	45 Gy	10.8 Gy
Definitive RT – vertebral bony lesion	45 Gy	5.4 Gy
Definitive RT – extraosseous ESFT without bony involvement with CR to Chemotherapy	50.4 Gy	N/A
Postop RT – microscopic positive margin and >90% necrosis	N/A	50.4 Gy
Postop RT – microscopic positive margin and <90% necrosis	50.4 Gy	N/A
Postop RT – gross residual	45 Gy	10.8 Gy

17.7.2.2 Radiation dose guidelines for pathologically involved lymph nodes

Involved Lymph Nodes Doses	**PTV1**	**PTV2**
LN resected – separate from primary site	50.4 Gy	
LN resected – contiguous with primary site	50.4 Gy	
LN unresected - primary adequately resected	45 Gy	10.8 Gy
LN unresected - primary inadequately resected (microscopic residual)	45 Gy	10.8 Gy
Whole abdomen RT for malignant ascites or diffuse peritoneal involvement	24 Gy*	

*Whole abdomen RT will be administered at 1.5 Gy per fraction

17.7.2.3 Radiation dose guidelines for chest wall tumors with pathologically involved pleural fluid

Chest wall tumors with positive fluid cytology			
Age	PTV1*	PTV2*	PTV3^
≤ 6 years	32.4 Gy	10.8 Gy	12 Gy
> 6 years	30.6 Gy	9 Gy	15 Gy

*PTV1 and PTV2 - 1.8 Gy per fraction
^PTV3 - 1.5 Gy per fraction
Note: Heterogeneity correction must be used for lung irradiation

17.7.2.4 Radiation dose guidelines for chest wall tumors with pleural nodules

Chest wall tumor with secondary soft tissue only pleural nodules, radiographic PR			
Age	PTV1*	PTV2*	PTV3^
≤ 6 years	23.4 Gy	19.8 Gy	12 Gy
> 6 years	21.6 Gy	19.8 Gy	15 Gy
Chest wall tumor with secondary soft tissue only pleural nodules, chest wall radiographic PR, pleural nodules radiographic CR			
Age	PTV1*chestwall	PTV2*chestwall	PTV3^
≤ 6 years	23.4 Gy	19.8 Gy	12 Gy
> 6 years	21.6 Gy	19.8 Gy	15 Gy
Age	PTV1*pleural nodules	PTV2*	PTV3^
≤ 6 years	37.8 Gy		12 Gy
> 6 years	36 Gy		15 Gy
Dose for soft tissue only (no bone involvement) chest wall primary and pleural nodules, chest wall radiographic PR and pleural nodules radiographic CR			
Age	PTV1*	PTV2*	PTV3^
≤ 6 years	37.8 Gy		12 Gy
> 6 years	36 Gy		15 Gy

*PTV1 and PTV2 - 1.8 Gy per fraction
^PTV3 - 1.5 Gy per fraction
Note: Heterogeneity correction must be used for lung irradiation

17.7.2.5 Radiation dose guidelines for pulmonary metastases and pleural effusions without chest wall tumor

Pulmonary metastasis or malignant pleural effusion (not chest wall tumor)^

Age	PTV1*	PTV2*	PTV3
≤ 6 years	0	36 Gy	12 Gy
> 6 years	0	34.2 Gy	15 Gy

**PTV2 - 1.8 Gy per fraction
^PTV3 - 1.5 Gy per fraction
Note: Heterogeneity correction must be used for lung irradiation

17.7.2.6 Standard (non-SBRT) radiation dose guidelines for individual metastatic lesions requiring irradiation (all non-bone sites, all non-lung sites and bone sites >5cm).

	Dose (cGy)
Total recommended dose for gross disease	5580
If resected with microscopic residual	5040
Non-osseous, complete response to chemotherapy	5040
If resected with no microscopic residual	0

17.7.2.7 SBRT Dose Guidelines

	Dose/fraction (cGy)	**Dose (cGy)**
PTV2 =GTV2	800	4000
PTV1= CTV2 + 2mm	700	3500
After 15Gy whole lung		
PTV2 = GTV2	700	3500
PTV1 = CTV2+2mm	600	3000

17.7.3 Dose uniformity – Conventional fractionation

At least 95% of the protocol-specified dose should encompass 100% of the PTV1/PTV2 and no more than 10% of PTV1 (PTV2 for patients with a volume reduction) should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the prescribed dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

Proton Specific Guidelines: 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.

17.7.4 Tissue heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When IMRT is used in lung, planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. 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. Proton therapy should be used with extreme caution when any of the treatment beams traverse normal lung parenchyma. Please see explicit planning guidelines for this situation in Section 17.9.1.1.

17.7.5 Environment of care - Interruptions, delays and dose modifications

There will be no planned rests or breaks from treatment. Once radiation therapy has been initiated, treatment will not be interrupted except for severe myelosuppression associated with complications which in the opinion of the treating physicians preclude administration of RT. Blood product support should be instituted according to institutional/protocol guidelines. Side effects that require treatment interruption include significant stomatitis or mucositis ($\geq$ Grade 3). The reason for any interruptions greater than three treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. When interruptions or delays occur, the total number of fractions or cumulative dose should not be modified.

17.8 **Treatment Technique**

17.8.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) IMRT or proton therapy are required to minimize dose to normal tissues.

17.8.2 Selection of proton beam arrangements

There are uncertainties (1-3 mm) in the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in a critical organ will not be allowed. Critical organs include, but are not limited to, spinal cord, brainstem, trachea, and mainstem bronchus. Individual proton beams which are a component of a multi-field proton beam, which stop within such an organ, will be allowed.

17.8.3 Field Shaping

Field shaping for photons will be done with either customized cerrobend blocking or multileaf collimation. The field shaping for protons will be done with either brass or cerrobend apertures or proton-specific multileaf collimation for scattered and uniform scanning beams. Pencil beam scanning does not require additional accessories for field shaping.

17.8.4 Simulation including patient positioning and immobilization

17.8.4.1 Patient positioning

Reproducible setups are critical and the use of immobilization devices is strongly encouraged.

The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

Immobilization devices

Standard immobilization devices for the torso, extremities or head and neck are to be used.

For IMRT and proton delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

17.8.5 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

17.8.6 Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the internal motion (IM) component of the PTV and is meant to account for potential motion of the CTV. If adequate clinical data do not exist to define the IM component of the PTV margin, the following suggestions are provided:

- For a CTV susceptible to physiologic motion, a margin of at least 0.5cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1.0cm should be chosen.
- For tumors of the thorax or abdomen, an assessment should be made to determine the extent of motion present. PTV margins should include this motion as a component.
- IMRT may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be limited to 0.5cm in any direction. If required to achieve this goal, techniques for managing or suppressing tumor motion shall be applied.
- Protons may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be limited to 0.5 cm in any direction. Motion should be accounted for in an ITV determined by 4-dimensional CT, respiratory gated CT, or other accepted techniques.
- A description of the method used and evidence (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4-D CT) of the remaining tumor motion should be submitted on the Motion Management Reporting Form with the Quality Assurance Documentation materials as noted in Section 17.11.
  NOTE: For patients treated with IMRT, use of gating or tracking methods to compensate for respiratory motion requires irradiation of IROC Houston's Thorax-Lung Phantom with accompanying reciprocating platform to simulate motion. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.

17.8.7 Brachytherapy

Single Plane Implant

It is expected that most patients will be treated by a single plane implant to the tumor bed after gross resection with microscopic residual disease or in the case of less than minimal margins. The target volume should include all sites of potential microscopic disease with at least 1.0 cm margin on all sides. A template, mesh or applicator can be used to keep the catheters parallel. If the area to be implanted is larger than 50cm^2, external beam radiation therapy should be considered. Catheters should be parallel and positioned 1cm apart. To ensure sufficient coverage the catheters should be placed with the distal end of the catheter projecting 1-2cm beyond the target volume.

Double or Multiple Plane Implant

A double plane implant will be performed for unresectable tumors less than 2 cm thick. A larger tumor may require a volume (multiplane) implant. These techniques should not be used for patients with unresected boney disease. The target volume should include the entire palpable or post chemotherapy tumor volume with at least a 0.5cm margin on all sides. If the thickness of tissue to be implanted is larger than 3 cm, external beam radiation therapy should be considered, but is not required. Catheters are to be implanted 1 cm apart throughout the tumor volume for these cases. The target volume is the entire palpable or post chemotherapy tumor with at least a 0.5 cm margin on all sides.

Brachytherapy Dosimetry

CT planning shall be used for post-implant dosimetry. The GTV, CTV, and PTV shall be outlined on the CT. DVHs for the GTV, CTV, and PTV shall be calculated and submitted for review.

Sources used shall have assay directly traceable to NIST.

CT or MRI planning shall be used for postimplant dosimetry. The GTV and CTV shall be outlined on the CT or MRI. The PTV is identical to the CTV for purposes of brachytherapy planning. DVHs for the GTV, CTV, and PTV shall be calculated and submitted for review.

Implants should be designed to meet the following dose uniformity criteria:

$_{CTV}D_{100} \geq 95\%$ of the prescribed dose

Dose homogeneity index $HI = \frac{{}_{CTV}V_{100} - {}_{CTV}V_{150}}{{}_{CTV}V_{100}} \geq 0.80$

Where $_{CTV}D_{100}$ is the dose received by 100% of the CTV, $_{CTV}V_{100}$ is the fraction of the CTV receiving the prescribed dose, and $_{CTV}V_{150}$ is the fraction of the CTV receiving 150% of the prescribed dose.

It is recognized that the dose distribution from brachytherapy implants is inherently non-uniform and that for some implant geometries the above criteria for dose homogeneity index may be difficult to meet.

When a brachytherapy implant is used, the isodose distribution shall be calculated in descriptive planes (3 perpendicular planes passing through the target center and in two transverse planes 2cm from the ends of the implant). CT-based planning shall be used.

Total dose/fractionation and dose rate

In the rare circumstance that postoperative brachytherapy is used instead of external beam radiation, then the following recommendations apply:

LDR brachytherapy
- Total dose: 2600cGy
- Dose rate range: 40-100cGy/hour.

HDR brachytherapy
- Total dose: 2100cGy
- Dose per fraction: 300cGy BID (separate fractions by ≥ 6 hours)
- Number of fractions: 7

Brachytherapy should not begin until postoperative Day 5 to allow for wound healing.

In the rare circumstance that brachytherapy is used instead of external beam radiation for an unresectable tumor, the following recommendations apply:

LDR brachytherapy
- Total dose: 5000 cGy
- Dose rate range: 40-100cGy/hour.

17.8.8 SBRT Guidelines

This study includes a secondary objective focused on evaluating the role of SBRT directed to sites of bone metastasis < 5 cm (based upon maximal dimension at diagnosis). For the purposes of this study, bone metastases are defined radiographically as lesions causing disruption of bone on anatomic imaging.

All sites treating with SBRT to sites of bone metastasis must be credentialed. COG will accept SBRT credentialing through NRG. See Section 17.1.2 for full details of the credentialing process.

Note: SBRT is not to be used for sites other than bone metastases.

17.8.8.1 Localization

Stereotactic radiation requires meticulous definition of the target, normal tissue structures, and visualization for localization during treatment delivery. Although CT is superior for evaluating bone changes due to tumor involvement, the extent of intramedullary involvement is difficult to determine on CT. Thus MRI within 4 weeks of treatment is required for planning for lesions treated with SBRT. This can either be in the form of treatment planning MRI or an MRI fused for treatment planning. A separate PET-CT is optional but can be used for treatment planning with fusion -- this study would be done identically if the patient were having standard fractionated radiation. These studies can assist with delineation of the target and visualization for stereotactic treatment.

Patients will be positioned in a reproducible treatment position with an appropriate immobilization device custom-made for each patient and specific to treatment site. A variety of immobilization systems can be used on study such as stereotactic frames which surround the patient on three sides or large rigid pillows that reference to a stereotactic coordinate system. For cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device should be used. Patient immobilization must be reliable enough to achieve the accuracy requirement of image-guidance.

17.8.8.2 Simulation

CT simulation will be performed. The simulation study must include the target and all organs at risk for treatment planning. Simulation scan length should be 5-10 cm superior and inferior to the target. All organs at risk within the scan length should be contoured for dose-volume histogram analysis. For stereotactic treatment, tomographic slice thickness of 1-3 mm through the target is recommended.

Special consideration should be given to the analysis of internal organ motion if the target lesion is located in a site subject to motion such as the chest wall. Techniques to image moving targets such as active breath-hold techniques, accelerator gating with respiratory cycle, tumor tracking, 4D CT scan acquisition in conjunction with maximum

intensity projection (MIP), will be considered acceptable maneuvers to account for organ motion. All systems used to account for internal organ motion must be accredited by the Study Committee. If the target cannot be visualized or localized on the planning imaging modality as a result of motion or metal artifact, stereotactic treatment should not be used.

The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed with a diagnostic radiologist on sequential axial computed tomography images. A radiosurgical treatment plan will be developed based on tumor geometry and location.

Accurate contouring of normal structures is critical in SBRT (please see Table 17.10 for a list of normal tissue dose constraints to be used on protocol as well as constraints for high and low-dose spillage). **OAR dose constraints are primary planning priority in SBRT treatment planning.** Tumor coverage is secondary. Patients in whom optimal tumor coverage is not possible while meeting planning constraints should not receive SBRT and instead should be treated with standard fractionation EBRT. The following are examples of contouring requirements for bone lesions near these critical structures:

Spinal Cord
The spinal cord is the visualized spinal cord based on image fusion with T2-weighted MRI, T1-weighted MRI with contrast, or CT myelogram. Because of curvature in the spine that is dependent on position and immobilization, MRI in the treatment position is ideal but not required. The spinal cord should be drawn of every slice of simulation CT (ie not interpolated). Spinal cord volume will be defined as 5-6 mm above and below the radiosurgery target volume.

Thecal Sac
The spinal cord can move within the thecal sac. The thecal sac will be contoured based on T2 MRI or bony limit of spinal canal and will serve as a PRV (planning organ at risk volume) for the spinal cord. Thecal sac volume will be defined as 6 mm above and below the radiosurgery target volume.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. The skin is essentially a rind of 0.5 cm enveloping the entire body in axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations. Ribs within 5 cm of the PTV should be contoured by outlining bone and bone marrow. The intercostal spaces should not be included as part of the ribs.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and muscular layers. The

esophagus should be defined starting at least 10 cm above the superior extent of the target volume and continuing on every CT slice to at least 10 cm below the inferior extent of the target volume.

Larynx and Pharynx
The larynx and pharynx will be contoured to the mucosa, submucosa, cartilages and airway channels associated with these structures.

Trachea and Airway
The trachea and airway adjacent to the spines will be contoured including the mucosa, submucosa, cartilage rings and airway channels.

Lung
Both the right and left lungs should be contoured using pulmonary windows. All inflated and collapsed lung should be contoured; however, paraspinal gross tumor, if any, should not be included in this structure.

Kidney
Both the right and left kidneys should be contoured. Paraspinal gross tumor as defined above should not be included in this structure.

17.8.8.3 Treatment Planning

OAR dose constraints are primary planning priority in SBRT treatment planning. Tumor coverage is secondary (See Section 17.14 for assessment of deviations). Patients in whom optimal tumor coverage is not possible while meeting planning constraints should not receive SBRT and instead should be treated with standard fractionation EBRT. The main criteria for dose prescription for tumors of or in proximity to the spine will be the achievement of the spinal cord dose constraint (see table below):

Normal Tissue	Volume	Volume Max (cGy)	Max Point Dose (cGy)	Endpoint (≥Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	Myelitis

For tumors distant from the spinal cord, the main criteria for dose prescription will be OAR as per table 17.10.

Patients treated with SBRT will receive a prescribed dose of 40 Gy in 5 fractions to cover at least 90% of the defined target volume. The minimum, mean, and maximum dose to the PTV will be reported. Only ≤ 1 cc or ≤ 1-5% of unspecified tissue outside of the PTV can receive ≥ 100-110% of the prescribed dose.

17.8.8.4 Treatment/Localization

Within four weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. This protocol allows conventional linear accelerators and specialized linear

accelerators with image guidance (e.g. Novalis, Trilogy, Synergy, Artiste) capable of conformal dose delivery and IMRT. Specialized accelerators (e.g. Cyberknife or Tomotherapy) are also allowed provided that institutions have satisfied all credentialing requirements.

SBRT is an image-guided procedure. In-room imaging technology allowing imaging of the target bone should be used. Coordinate systems between imaging system and delivery system should be aligned for SBRT.

During treatment, real time cone beam CT images or orthogonal kilovoltage images of the patient's body site of interest will be obtained. Cone beam CT scan or kilovoltage orthogonal images will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment, is within 2 mm. Imaging should be performed during and at the end of treatment to ensure maintenance of patient positioning throughout treatment.

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments. Anesthesia will be delivered by a dedicated pediatric anesthesiologist.

17.9 Organs at Risk – Conventional Fractionation

The organs at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. Normal tissue dose recommendations are the same for photons and protons (proton dose measured in Gy(RBE)).

17.9.1 Use of Proton Therapy in Treatment of Thoracic Tumors

During treatment of thoracic tumors, or tumors in locations that require beams to traverse normal lung tissue, proton therapy should be used with extreme caution. The following specific constraints will apply in this situation:

- When considering the total lung volume less the PTV:
  - The volume of lung receiving 20 Gy (V20) should be less than 20%
  - The volume of lung receiving 5 Gy (V5) should be less than 60%
  - The mean lung dose should be less than 20 Gy
- When considering the spinal cord:
  - The maximum dose should be 45 Gy
  - A structure called PAR-Cord should be created, and consist of the contoured spinal cord plus a 5 mm expansion. The maximum dose to the PAR-Cord structure should be 50 Gy.
- Additionally, the distal end of the bragg peak of a single beam should not stop in a critical structure, such as the spinal cord, trachea, or mainstem bronchus due to uncertainty with regard to dose deposition at the distal end

of the beam. Individual proton beams which are a component of a multi-field proton beam, which stop within such an organ, will be allowed.

Table 17.9: Organs at risk dose recommendations for Conventional Fractionation

Organ	Volume (%)	Dose (cGy)
Single organs		
Bladder	100%	4500
Esophagus	50%	4000
Heart	100%	3000
Liver	100%	2340
	50%	3000
Rectum	100%	4500
Optic chiasm	100%	5400
Small Bowel	75%	4500
Spinal Cord#	Any volume	5040
Paired organs		
Kidney (bilateral)	50%	2400
Kidney (bilateral)	100%	1440
Lung (bilateral)^	20%	2000
Lung (bilateral) ‡,$	35%	2000
Lung (bilateral)	100%	1500
Optic nerve	100%	5400
Eye	100%	4500
Lens	100%	600
Cochlea	100%	4000

Paired organs - % refers to **one** of the paired organs unless specified as bilateral (kidney, lung) in which **both** of the paired organs are included in the %.
^ V20 of 20% applies to patients not requiring hemithorax RT
‡ V20 of 35% applies to patients who require hemithorax RT and boost treatment of the chest wall or pleura
# Please see additional spinal cord constraints for patients receiving thoracic proton therapy (Section 17.9.1).
$ Please see additional lung constraints for patients receiving thoracic proton therapy (Section 17.9.1).

17.10 Organs at Risk – SBRT

Table 17.10a: Organs at Risk – SBRT
Dose Constraints for Five Fractions – Based upon the AAPM Report TG 101[32] reduced by 10% for prior systemic chemotherapy

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	18 Gy (3.6 Gy/fx)	22.5 Gy (4.5 Gy/fx)	neuritis
Cochlea			24.7 Gy (4.95 Gy/fx)	hearing loss
Brainstem	<1 cc	23.4 Gy (4.68 Gy/fx)	31 Gy (6.2 Gy/fx)	cranial neuropathy
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	20.2 Gy (4.05 Gy/fx) 15 Gy (3 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Cauda Equina	<5 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuritis
Sacral Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Rib	<1 cc	31.5 Gy (6.3 Gy/fx)	38.7 Gy (7.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	24.7 Gy (4.95 Gy/fx)	31.5 Gy (6.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	28.8 Gy (5.76 Gy/fx)	34.2 Gy (6.84 Gy/fx)	pericarditis
Great vessels	<10 cc	42.3 Gy (8.46 Gy/fx)	47.7 Gy (9.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	16.2 Gy (3.24 Gy/fx)	34.2 Gy (6.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Stomach	<10 cc	25.2 Gy (5.04 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	16.2 Gy (3.24 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	17.5 Gy (3.51 Gy/fx)	31.5 Gy (6.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	colitis/fistula
Rectum*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	proctitis/fistula
Bladder wall	<15 cc	16.4 Gy (3.28 Gy/fx)	34.2 Gy (6.84 Gy/fx)	cystitis/fistula
Penile Bulb	<3 cc	27 Gy (5.4 Gy/fx)	45 Gy (9 Gy/fx)	impotence
Femoral Heads (Right & Left)	<10 cc	27 Gy (5.4 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	20.7 Gy (4.14 Gy/fx)		malignant hypertension
Parallel Tissue	**Volume**	**Critical Volume Dose**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Liver	700 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15.7 Gy (3.15 Gy/fx)		Basic renal function

***Avoid circumferential irradiation**

Table 17.10b: Organs at Risk – SBRT after Whole Lung RT
Dose Constraints for Five Fractions – Based upon the AAPM Report TG 101[32] reduced for prior chemotherapy and 15Gy whole lung RT

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	18.2 Gy (3.64 Gy/fx) 10.9 Gy (2.18 Gy/fx)	20.2 Gy (4.05 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	18.2 Gy (3.64 Gy/fx) 13.5 Gy (2.7 Gy/fx)	25 Gy (5 Gy/fx)	myelitis
Rib	<1 cc	26.5 Gy (5.3 Gy/fx)	33.7 Gy (6.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	19.7 Gy (3.94 Gy/fx)	26.5 Gy (5.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	23.8 Gy (4.76 Gy/fx)	29.2 Gy (5.84 Gy/fx)	pericarditis
Great vessels	<10 cc	37.3 Gy (7.46 Gy/fx)	42.7 Gy (8.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	11.2 Gy (2.24 Gy/fx)	29.2 Gy (5.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Stomach	<10 cc	20.2 Gy (4.04 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	11.2 Gy (2.24 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	12.5 Gy (2.51 Gy/fx)	26.5 Gy (5.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	17.5 Gy (3.5 Gy/fx)	29.2 Gy (5.84 Gy/fx)	colitis/fistula
Parallel Tissue	Volume	**Critical Volume Dose**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	300 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Lung (Right & Left)+	35%	20 Gy		Pneumonitis
Liver	200 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Liver+	50%	30 Gy		Basic Liver Function

***Avoid circumferential irradiation**
+ Cumulative dose including 15 Gy whole lung RT

Guidelines for Spillage

High Dose Spillage:

1. Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should not be more than 15% of the PTV volume.
2. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

Low Dose Spillage

1. The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
   a. The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below.
2. The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given. See Table below.
3. Respect all critical organ dose-volume limits listed above

Table 17.10.1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, R50%		Maximum dose (in% of dose prescribed) @ 2 cm from PTV in Any Direction, D2cm (Gy)		Percent of Lung Receiving 20 Gy Total or More, V20 (%)	
	Goal	Acceptable	Goal	Acceptable	Goal	Acceptable	Goal	Acceptable
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	≤91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	≤94.0	<10	<15

17.11 Dose Calculations and Reporting

17.11.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

17.11.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The dose shall be reported on the RT-2 Radiotherapy Total Dose Record form and the appropriate dose-volume histograms shall 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.

Table 17.11.2: Required normal tissue DVH data according to primary treatment site(s)

Treatment Area	Required DVH
Head	Brain
	Chiasm
	Cochlea
	Eyes (contour each separately)
	Lenses
	Optic nerves (contour each separately)
Neck	Esophagus
	Thyroid
Chest	Esophagus
	Heart
	Left Lung
	Right Lung
Abdomen/Pelvis	Bladder
	Left Kidney
	Liver
	Rectum
	Right Kidney
	Small Bowel (contour peritoneal cavity)
	Stomach
All axial tumors	Spinal Cord
Proton therapy	PAR-Cord (spinal cord expanded by 5 mm)

17.12 Quality Assurance Documentation

Key Points

- Data for the primary site only must be submitted for on treatment review within 3 days of the start of treatment (see checklist). Data for metastatic sites may be submitted at the end of treatment.

Digital Submission:

Submission of treatment plans in digital format DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the IROC Rhode Island (formerly QARC) 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 sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following for All Radiated Sites:

External Beam Treatment Planning System

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.

- Digitally reconstructed radiographs (DRR) for each treatment field. DRR's are 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

- All diagnostic imaging used to plan the target volume. Digital format is preferred. Imaging scans previously submitted to IROC Rhode Island for secondary aims central review (Section 16.3) do not need to be resubmitted.
- Copies of reports (radiology, operative, pathology, cytology) and any other information used in defining the target volumes.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC Rhode Island and the radiation oncology reviewers.
- If modifications are made for patients with age < 24 months, documentation should be provided.
- Documentation of any emergency RT administered prior to the protocol prescribed course of RT. Documentation should be provided in the form of the radiotherapy record (treatment chart).

Forms

- RT-1 Dosimetry Summary Form.
- Proton Reporting Form (if applicable).
- Motion Management Reporting Form (if applicable, see Section 17.8.6).

Please submit the following additional primary site information for brachytherapy:

- Treatment planning CT used for post-implant dosimetry
- Computer printouts of the isodose distribution and associated CT-based calculations.
- Dose volume histograms for each GTV, CTV, and PTV.
- A completed Brachytherapy Physics Reporting Form.
- A copy of the written directive.

Please submit the following information for intra-operative radiation therapy:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk
- Physician's note describing the procedure, dose calculation and description of the applicator along with any relevant dosimetric characteristics (i.e., percent depth dose for the prescribed energy)

Within 1 week of the completion of radiotherapy submit the following items:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- RT-2 Radiotherapy Total Dose Record Form.
- If SBRT is used, setup images for the first fraction taken before and after treatment. Depending on the IGRT system capabilities, submission may include cone beam CT and/or kV imaging in DICOM format, DICOM spatial registration file, screen capture of shifts needed for correct alignment, or screen captures showing the image registration.

These data should be forwarded to:

IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753 7601

Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist
Imaging and Radiation Oncology Core, Rhode Island
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207
physics@qarc.org

17.13 Definition of Minor and Major Deviations

Definitions of deviation in protocol performance will be applied to the treatment of the primary lesion only.

	DEVIATION	
	Minor	**Major**
Prescription Dose		
External beam	Prescription dose differs from protocol-specified dose by >5% but <10%	Prescription dose differs from protocol-specified dose by >10%
Brachytherapy	Prescription dose differs from protocol-specified dose by >5% but <10%	Prescription dose differs from protocol-specified dose by >10%
Dose Uniformity		
External beam	>10% PTV receives >110% of prescription dose *or* 95% isodose covers <90% of the PTV or <100% but >90% of the CTV	95% isodose covers <90% of CTV.
Brachytherapy	95% isodose covers <100% of CTV	90% isodose covers <100% of CTV.
Volume	CTV or PTV margins are smaller than specified in the protocol.	The contoured GTV does not include imaging-visible residual tumor
Organs at Risk	Will be assessed at time of data review.	Will be assessed at time of data review.

17.14 Evaluation of SBRT Plans For Deviations

Evaluation of SBRT plans will be performed for feasibility analysis. In the context of this feasibility study, deviations will be recorded and institutions will receive feedback but deviations will not affect institutional performance scores.

	DEVIATION	
	Minor	**Major**
Dose		
SBRT	90% isodose covers < 90% but > 80% of the CTV	90% isodose covers < 80% of CTV
Volume	CTV or PTV margins are smaller than specified in the protocol.	The contoured GTV does not include imaging-visible residual tumor or bone abnormality
Organs at Risk	Will be assessed at time of data review.	Exceeding max point dose for OAR as per Section 17.10 .

Treatment Delivery Compliance

Setup images (obtained from the IGRT system) will be compared to corresponding reference images to identify any potential deviation. The institution's IGRT systems must demonstrate < 2mm agreement between simulation/planning and treatment, as well as at the end of treatment.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all 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 AEWS1221 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.

Delegation of Task Log (DTL)

Each site must complete a protocol-specific DTL. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. The DTL application is located on the CTSU members' website at www.ctsu.org. Any individual at the enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the DTL application.

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: REFERENCE GUIDE FOR REQUIRED AND RECOMMENDED CORRELATIVE STUDIES

	Study Entry	Induction	Local Control	Consolidation	Maintenance	Suspected Relapse
Serum Markers (Section 15.1)	10 mL blood *(15 mL if Regimen B and consent for banking)*** in RTT*	10 mL blood *(15 mL if Regimen B and consent for banking)*** in RTT prior to start of Week 5*		10 mL blood *(15 mL if Regimen B and consent for banking)*** in RTT at end Consolidation*		
Tissue Markers (Section 15.2)	25 unstained slides or block*,$		25 unstained slides or block^,$ (if surgical local control)	25 unstained slides or block^,$ (if delayed surgery or metastectomy)		25 unstained slides or block^,$ (if biopsy to confirm relapse)
***EGFR* Study (Section 15.3)**	5-10 mL blood in EDTA*					
Bone Marrow Studies (Section 15.4)	5-10 mL marrow in EDTA^	5-10 mL marrow in EDTA^,&		5-10 mL marrow in EDTA^,&	5-10 mL marrow in EDTA^ (if relapse suspected)	
Ganitumab PK# (Section 15.5)		Blood draws prior to Ganitumab on Days 1, 15, 29 and 71			Blood draws prior to Ganitumab in Weeks 1, 7, 10 and 16	
ctDNA Study (Section 15.6)	10 mL blood in Streck tube	10 mL blood in Streck tube prior to start of Week 3, Week 5, and at end Induction		10 mL blood in Streck tube prior to Week 9 and at end Consolidation		10 mL blood in Streck tube
Imaging Aims (Section 16)	1. Baseline SUV of primary tumor* 2. Baseline PET and MRI/CT of primary tumor*	1. End Induction SUV of primary tumor* 2. End Induction PET and MRI/CT of primary tumor*	Institutional report of primary tumor percent necrosis (if surgical local control)			Imaging documenting first episode of relapse or progression

* Required of all patients.
** 10 mL required for all patients at both time points. For patients randomized to ganitumab arm (Arm B) and consented to specimen banking, obtain an additional 5 mL at each timepoint for a total of 15 mL.
^ Recommended (option for participation embedded in main study consent).
$ 25 unstained slides is optimal. If limited tissue, a minimum of 10 unstained slides may be submitted.
& Patients with documented marrow disease at study entry undergo repeat marrow evaluations after Cycle 3 of Induction and at end of Consolidation. Additional marrows are to be obtained according to Section

7.0 if not clear after Cycle 3 of Induction. Submit marrows from consenting patients to Dana-Farber whenever obtained for clinical evaluation of bone marrow disease.

Required of the first 10 patients < 21 years old assigned to Regimen B.

RTT = Red top tube

APPENDIX III: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AEWS1221
(for children from 7 through 12 years of age)

A trial of a new drug, called ganitumab, to treat patients with EWS cancer that has spread

1. We have been talking with you about your illness, Ewing Sarcoma (EWS). EWS is a type of cancer that grows in the bones. After doing tests, we have found that you have this type of cancer and it has spread into other areas of your body.

2. We are asking you to take part in a research study because you have EWS that has spread to other areas of your body. A research study is when doctors work together to try out new ways to help people who are sick. We will do this by adding a new drug to the treatment often used for the type of cancer you have. This new drug is called ganitumab and it is an experimental drug.

   Some children in this study will get the new drug and some children will not. We do not know how well the new drug will work in children. That is why we are doing this study.

3. All children who are part of this study will be treated with chemotherapy (anti-cancer drugs) on 1 of 2 treatment plans. Children on one plan will get the drug ganitumab and children on the other plan will not get ganitumab.

   Children who are part of this study will be given either:
   - Chemotherapy or
   - Chemotherapy + ganitumab

   All children who are part of this study will also have surgery and/or receive radiation therapy. Radiation therapy is the use of high energy X-rays to kill cancer cells.

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 to 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." One risk to you from this study is that the study treatment may not work as well as other therapies. Also, the study treatment may cause more side effects than other therapies. Your doctors will watch you for signs of any side effects.

6. We want to see if there are ways to tell how the cancer will respond to treatment. To do this, we will collect extra blood and tumor samples from you for research tests. These samples would be taken when other standard blood draws or tumor surgery are being performed, so there would be no extra procedures.

7. 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.

8. We also would like your permission to collect extra bone marrow when you have standard bone marrow tests. We want to look for small amounts of cancer cells in your bone marrow. We will not perform an extra bone marrow test just to collect bone marrow for research. We would also like your permission to save any leftover samples. You can still take part in this study even if you don't allow us to collect the extra bone marrow for research or let us save any leftover samples.

INFORMATION SHEET REGARDING RESEARCH STUDY AEWS1221
(for teens from 13 through 17 years of age)

A trial of a new drug, called ganitumab, to treat patients with EWS cancer that has spread

1. We have been talking with you about your illness, metastatic Ewing Sarcoma (EWS). EWS is a type of cancer that grows in the bones. Metastatic means the cancer has spread into other areas of your body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have metastatic EWS. A research study is when doctors work together to try out new ways to help people who are sick. We will do this by adding a new experimental drug called ganitumab to the treatment often used for metastatic EWS. Some people in this study will get ganitumab and some will not. We do not know how well ganitumab will work in children and teens with metastatic EWS. That is why we are doing this study.

3. Children and teens who are part of this study will be treated with chemotherapy (anti-cancer drugs) on 1 of 2 treatment plans. People on one plan will get the experimental drug "ganitumab" and people on the other plan will not get ganitumab.

   A computer decides which treatment plan you will get and not your doctor. The reason for this is to make sure there is same number of people on both treatments. You have an equal chance of getting ganitumab or not getting ganitumab.

   Children and teens who are part of this study will be randomly assigned to receive either:

   Chemotherapy; or
   Chemotherapy + ganitumab

   All children and teens who are part of this study will also have surgery and/or receive radiation therapy. Radiation therapy is the use of high energy X-rays to kill cancer cells.

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." One risk to you from this study is that the study treatments may be less effective than other therapy options. If you receive ganitumab, there is a chance that you will have more side effects. 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. We want to see if there are ways to tell how the cancer will respond to treatment. To do this, we will collect extra blood and tumor samples from you for research tests. These samples would be taken when other standard blood draws or tumor surgery are being performed, so there would be no extra procedures.

7. 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.

8. We also would like your permission to collect extra bone marrow when you have standard bone marrow tests. We want to look for small amounts of cancer cells in your bone marrow. We will not perform an extra bone marrow test just to collect bone marrow for research. We would also like your permission to save any leftover samples. You can still take part in this study even if you don't allow us to collect the extra bone marrow for research or let us save any leftover samples.

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.

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

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, dronedarone, proprafenone, 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

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

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"

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

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"

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

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

Food and supplements that may interact with dactinomycin
• Echinacea

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

Drugs that may interact with ifosfamide

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

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

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

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, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, dronedarone, 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

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

Drugs that may interact with dexrazoxane
• Clozapine • Deferiprone • Dimethyl sulfoxide (DMSO)

Food and supplements that may interact with dexrazoxane
• Unknown

APPENDIX V: 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
acalabrutinib[5] alfentanil[4,5] 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] eplerenone[5] ergotamine[4] 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] tamoxifen telaprevir 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 CYP3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Refer to Section 4.2.2 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)

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