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**CHILDREN'S ONCOLOGY GROUP**

**AEWS1031**

**A Phase III Randomized Trial of Adding Vincristine-topotecan-cyclophosphamide to Standard Chemotherapy in Initial Treatment of Non-metastatic Ewing Sarcoma**

**A Groupwide Phase III Study**

**This study is supported by the NCI Cancer Trials Support Unit (CTSU) (See [page # 2](#))**

**Endorsing Cooperative Groups**

**Group name**

Radiation Therapy Oncology Group (RTOG)



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**Institutions not aligned with COG will participate through the CTSU mechanism as outlined below and detailed in Appendix III- CTSU Participation Procedures.**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU members' side of the website located at <https://www.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU participation procedures (Appendix III) for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to Appendix III for specific instructions and forms to be submitted.
- Data management will be performed by COG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to COG unless otherwise directed by the protocol. Do not submit study data or case report forms to the CTSU Data Operations. Do not copy the CTSU on data submissions.
- **Data query and delinquency reports** will be available for viewing on the COG website. Query responses and delinquent data will be handled with COG via the SADD (Schedule and Delinquent Data) system. Sites should check this system regularly to view their site's information. Do not copy the CTSU Data Operations on any forms. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the COG data center.

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<b>AGENT</b>	<b>NSC#</b>	<b>IND#</b>
Vincristine	NSC #67574	Exempt
Doxorubicin	NSC #123127	Exempt
Cyclophosphamide	NSC #26271	Exempt
Topotecan	NSC #609699	Exempt
Ifosfamide	NSC #109724	Exempt
Etoposide	NSC #141540	Exempt
Mesna	NSC #113891	Exempt
Dexrazoxane	NSC# 169780	Exempt

SEE [SECTION 14.4.3](#) FOR SPECIMEN SHIPPING ADDRESSES



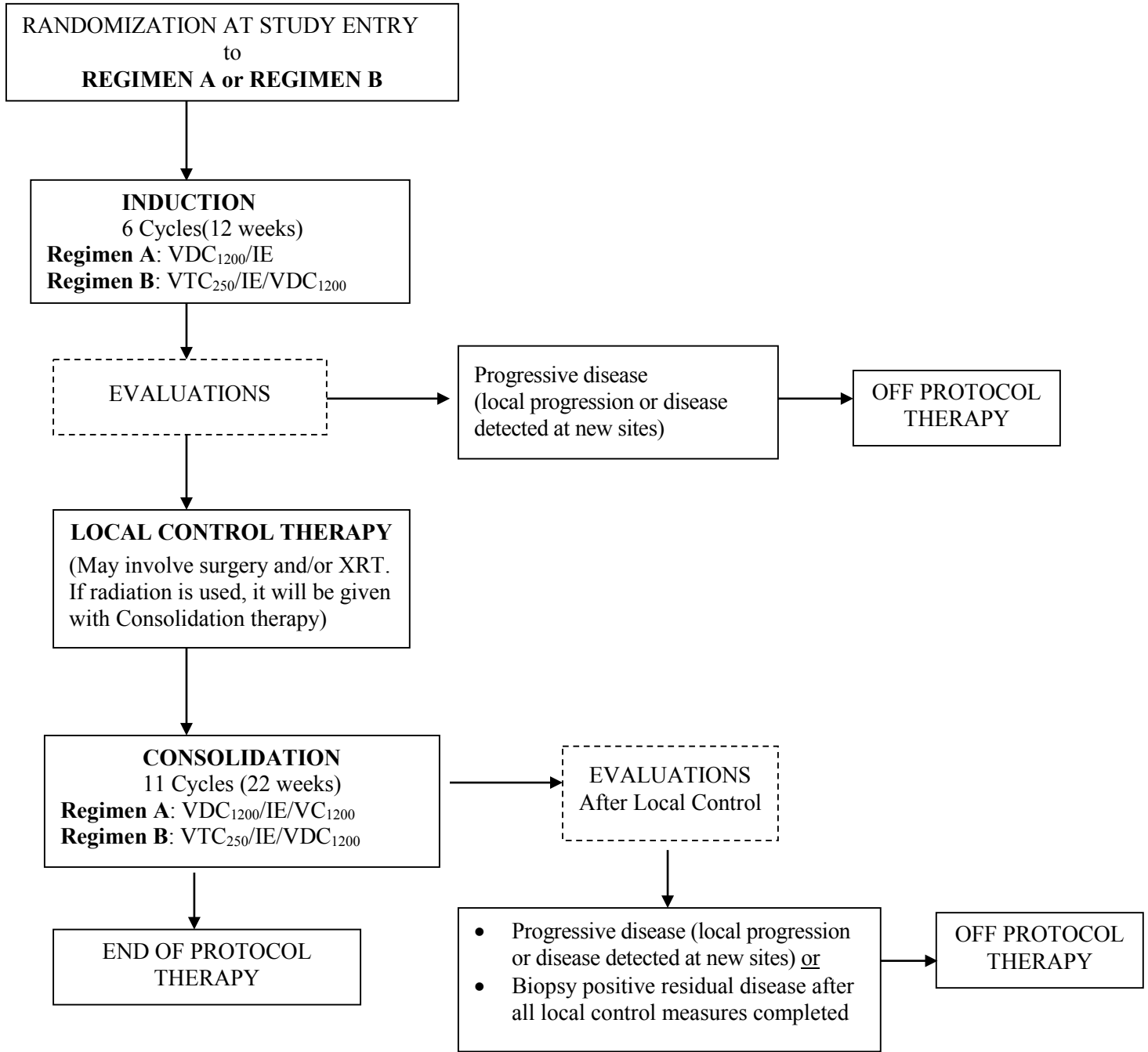
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## ABSTRACT

Intergroup Ewing sarcoma study INT-0091 (CCG 7881, POG 8850) demonstrated that a regimen of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide was superior to vincristine-doxorubicin-cyclophosphamide alone. AEWS0031 has demonstrated interval compression to be superior to standard timing. The five drug alternating combination using interval compression should be considered the North American standard therapy for localized Ewing sarcoma. Cyclophosphamide with topotecan has been demonstrated to be active in patients with recurrent and metastatic Ewing sarcoma. Vincristine has been shown to be synergistic with topotecan in xenograft models of rhabdomyosarcoma. This randomized Phase 3 trial will test the efficacy of adding vincristine-topotecan-cyclophosphamide to the interval compressed 5 drug backbone.

This study will also assess initial tumor volume, histologic response to induction chemotherapy and response measured by FDG-PET as prognostic factors for event free survival in patients with non-metastatic Ewing sarcoma.

**EXPERIMENTAL DESIGN SCHEMA**



VDC<sub>1200</sub>: vincristine-doxorubicin-cyclophosphamide<sub>1200</sub> mg  
 IE: ifosfamide-etoposide  
 VTC<sub>250</sub>: vincristine-topotecan-cyclophosphamide<sub>250</sub> mg  
 VC<sub>1200</sub>: vincristine-cyclophosphamide<sub>1200</sub> mg  
 XRT: radiation therapy

## 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

### 1.1 Primary Objective

Test the effect of the combination of vincristine, cyclophosphamide and topotecan added to the standard 5-drug chemotherapy interval compressed backbone on event-free and overall survival in children and young adults with Ewing sarcoma.

### 1.2 Correlative Science Objectives

#### 1.2.1

Evaluate initial volumetric tumor size as a prognostic factor for event free survival (EFS) in patients with localized Ewing tumors.

#### 1.2.2

Evaluate histologic response as a prognostic factor for EFS in patients with localized Ewing tumors.

#### 1.2.3

Continue evaluation of biologic markers both as related to prognosis and as eventual therapeutic targets via encouraging concurrent enrollment on a Ewing sarcoma specimen collection study.

#### 1.2.4

Evaluate imaging response by FDG-positron emission tomography (PET) as a prognostic factor for EFS.

#### 1.2.5

Evaluate the effects of the type of local therapy on EFS and overall survival.

#### 1.2.6

Evaluate the effect of local surgical margins in conjunction with histologic response on EFS in patients with localized Ewing tumors.

#### 1.2.7

Evaluate the effect of local therapy modality (surgery, radiotherapy or a combination) as well as the type of surgical reconstruction on musculoskeletal complications.

## 2.0 BACKGROUND

Intergroup Ewing sarcoma study INT-0091 (CCG 7881, POG 8850) demonstrated that a regimen of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide was superior to vincristine-doxorubicin-cyclophosphamide alone. Dactinomycin was substituted for doxorubicin once a cumulative doxorubicin dose of 375 mg/m<sup>2</sup> had been given. Patients received 17 courses of chemotherapy. Among the 398 patients with non-metastatic disease the mean five year event free survival in the experimental therapy group was 69% ± 3% (198 patients) as compared with 54% ± 4% (200 patients) in the standard therapy group.<sup>1</sup> The five drug alternating combination (without dactinomycin) became the North American standard therapy for Ewing sarcoma. The 5-year event-free survival (EFS) and overall survival rates for all eligible patients were 71.1% (95% CI, 67.7% to 75.0%) and 78.6% (95% CI, 74.6% to 82.1%), respectively. There was no significant difference (P = .57) in EFS between patients treated with the standard (5-year EFS, 72.1%; 95% CI, 65.8% to 77.5%) or intensified regimen (5-year EFS, 70.1%; 63.9% to 75%).<sup>2</sup>

The recently completed study for initially localized Ewing sarcoma, AEWS0031, tested dose intensification of all agents by interval compression. The compressed arm was demonstrated to be superior to the standard arm in event free survival: 76% versus 65% at 4 years (p=0.029), and overall survival: 91% versus 85% at 4 years (p=0.026).<sup>3</sup> This study established the five drug alternating chemotherapy combination using interval compression as the standard therapy for localized Ewing sarcoma.

The European collaborative study Euro-Ewing 99 uses six cycles of 4 drug induction (vincristine-ifosfamide-doxorubicin-etoposide or VIDE) based on results of EICESS 92 and UK ET-2 which demonstrated the importance of ifosfamide in induction. After induction therapy, the study includes two randomized comparisons: for patients with localized disease and a good response (< 10% viable tumor after VIDE), continuation therapy with either vincristine-dactinomycin with cyclophosphamide (VAC) versus ifosfamide (VAI); for patients with large tumors (>200 mL) or poor response (>10% viable tumor after VIDE) VAI versus Busulfan-Melphalan megatherapy.

Another strategy to potentially improve outcome for these patients would be the addition of new active drug combinations.

### 2.1 Rationale for cyclophosphamide, topotecan and vincristine in Ewing sarcoma

Cyclophosphamide in combination with topotecan has been studied in the pediatric Phase I setting, establishing a recommended dose of cyclophosphamide (250 mg/m<sup>2</sup>/dose) followed by topotecan (0.75 mg/m<sup>2</sup>/dose), each given as a 30-minute infusion, daily for 5 days, followed by G-CSF on Day 6. The Pediatric Oncology Group Phase II study showed activity in recurrent or refractory rhabdomyosarcoma, neuroblastoma and Ewing sarcoma. Responses were reported in 6/17 patients with Ewing sarcoma. Hematopoietic toxicities were common but only 11% of 307 courses were associated with Grade 3 or 4 infection.<sup>4</sup> Non-hematologic toxicities were rare. Additional experience in the window setting in patients with Ewing sarcoma that was metastatic at initial diagnosis (P9457) yielded 21 PR (57%), 15 SD and only 1 PD of 37 evaluable patients treated with one (the patient with PD) or two cycles of topotecan-cyclophosphamide. Again, the predominant toxicity was hematologic. Non-hematopoietic toxicities were rare. Recently reported data from Germany confirm a similar response rate in patients with recurrent Ewing sarcoma. Forty-four patients (37 in first relapse) received a median of 3 courses. Responses were observed in 18/44 (41%) including 5 CR and 13 PR.<sup>5</sup>

In xenografts representing rhabdomyosarcoma, neuroblastoma and brain tumors, the combination of topotecan and vincristine has greater than additive activity. The schedule used was topotecan IV daily for 5 days and vincristine IV every 7 days.<sup>6</sup> The combination of vincristine, topotecan and cyclophosphamide has been tolerable in the rhabdomyosarcoma intermediate risk study (D9803) and in patients with metastatic rhabdomyosarcoma.<sup>7</sup>

The combination of topotecan-cyclophosphamide with weekly vincristine is therefore a good candidate for testing in previously untreated patients with localized Ewing sarcoma.

## 2.2 Rationale for weekly vincristine schedule

The single agent activity of vincristine in Ewing sarcoma has been estimated at 50%.<sup>8</sup> Vincristine has been used in a once every 21- 28 day schedule in Ewing sarcoma with VDC and VAC courses in previous Ewing study group protocols. This is in contrast to the once every 7 day scheduling used in other tumors such as Wilms tumor and rhabdomyosarcoma. Specific information regarding the effect of vincristine scheduling in Ewing sarcoma is lacking. However, a study of 7 versus 21-day intervals in human rhabdomyosarcoma xenografts demonstrated clear superiority of every 7 day administration.<sup>9</sup> The xenograft study of vincristine with topotecan also includes every 7-day dosing of vincristine.<sup>6</sup> In order to maximize the effectiveness of vincristine, and appropriately parallel the xenograft model of vincristine-topotecan synergy, it is proposed to use vincristine in a weekly schedule during VDC and VTC courses in this study.

## 2.3 Dexrazoxane cardioprotection

Long term cardiotoxicity is a recognized complication of anthracycline-based chemotherapy. Clinical cardiotoxicity has been reported in up to 3% of patients treated for Ewing sarcoma.<sup>10</sup> Dexrazoxane has been shown to provide short- and medium-term protection from cardiotoxicity induced by anthracyclines in children with acute lymphoblastic leukemia<sup>11</sup> as well as pediatric sarcomas.<sup>12,13</sup> Dexrazoxane has also been included in pediatric trials for Hodgkin lymphoma, T cell ALL and osteosarcoma. The agent has been well tolerated, although there have been reported increases in neutropenia and neutropenic enteropathy in some series. Possible tumor protection was reported in one adult breast tumor study although the response rate in the control arm appeared to be unusually high.<sup>14</sup> Tumor protection has not been demonstrated in other studies including pediatric trials using dexrazoxane.<sup>15</sup> In adults, decreased cardiotoxicity has been observed when dexrazoxane has been used with later anthracycline containing courses.<sup>16</sup> Based on this it has been recommended that dexrazoxane be considered in adults receiving more than 300 mg/m<sup>2</sup> doxorubicin-based therapy.<sup>17</sup> No similar recommendations exist for pediatric oncology. We propose the addition of dexrazoxane to doxorubicin containing courses above a 225 mg/m<sup>2</sup> cumulative dose. Long term clinical toxicity will be evaluated in comparison to previous Ewing studies which have used the same agents and the same total doxorubicin dose.

In order to facilitate the use of dexrazoxane, doxorubicin will be administered as short, 15 minute infusions, rather than the 48- hour infusion used in CCG7942/POG 9354 and AEWS0031. Short infusion doxorubicin has been previously used in INT0091 (POG8850/CCG7881). The similar event free survivals for patients with non-metastatic Ewing tumors on the INT0091 and CCG7942/POG9354 suggest the use of short infusion will not affect EFS. Continuous infusion doxorubicin was initially reported as being associated with less cardiotoxicity.<sup>18,19</sup> However, recent publications suggest no benefit.<sup>20-22</sup> In addition patients receiving doxorubicin by continuous infusion as part of treatment for osteosarcoma on CCG7921/POG9351 were reported to have more mucositis than those who received divided bolus doses on the previous intergroup study. The use of short infusion/bolus doxorubicin will also decrease the hospitalization time necessary with 48-hour infusion doxorubicin.

## 2.4 Rationale for timing intensification

Dose intensification by escalating drug doses is limited by the toxicities of the agents used. The advantage of dose intensification via interval compression is that it provides a means of increasing the dose intensity of all drugs, without apparent increases in toxicity. Decreasing the chemotherapy interval from three weeks to two provides 33% dose intensification. Though this does not seem a huge increase, it may be therapeutically significant. This therapeutic effect and feasibility has been demonstrated in several adult breast and lung cancer studies.<sup>23-28</sup>

COG AEWS0031 (which closed to patient accrual in August 2005) investigated interval compression of the 5-drug combination vs. standard chemotherapy for localized Ewing sarcoma and showed comparable toxicity between both treatment regimens. Five hundred and sixty four eligible patients were randomized between the experimental every-2-week regimen and the standard every-3-week regimen. Preliminary results of this study reveal that patients treated with the experimental interval compressed 5-drug alternating combination had a superior EFS (4 year EFS: 76 vs. 65%,  $p=0.029$ ) and OS (4 year OS: 91 vs. 85%,  $p=0.026$ ) when compared to the standard 5-drug alternating combination administered every 3 weeks.<sup>3</sup> On the basis of this, the five drug alternating combination with interval compression has become the North American standard therapy for localized Ewing sarcoma.

### 2.5 Feasibility of administration of VDC-IE-VTC on a interval compressed schedule

The feasibility of administering the vincristine-topotecan-cyclophosphamide in combination with the five drug standard chemotherapy was tested in AEWS07P1. This study demonstrated that interval compression was possible with the mean time from start of therapy to surgery (after 6 cycles of chemotherapy) was 14.7 weeks. The mean time from start of therapy to the chemotherapy prior to local therapy was 12.62 weeks as compared to 11.5 weeks for subjects on AEWS0031 who were receiving the 5 drug standard combination. Toxicity appeared to be otherwise acceptable. It is suggested that this degree of interval compression demonstrated is acceptable for proceeding to test this combination in a phase 3 setting.<sup>29</sup>

### 2.6 Biologic prognostic factors

Biologic prognostic factors are being investigated as part of companion specimen studies. Investigation of these biologic factors will continue in parallel to AEWS1031, through enrollment on the current Ewing sarcoma biology study such as AEWS07B1 or on any successor biology study.

### 2.7 Tumor size and histologic response as prognostic Factors

The most prognostic risk factor in Ewing sarcoma is the presence of metastatic disease. In patients with localized disease at diagnosis, both initial tumor size and histologic response have been evaluated as risk factors. In patients treated according to CESS 86, 177/263 (67%) had tumors >100 mL and had a 10 yr EFS 0.51 as compared with 0.61 for patients with tumors <100 mL.<sup>30</sup> Sixty-nine of 118 (58%) patients treated on INT-0091 had tumors >100 mL and had a 5 yr EFS 0.6 as compared with 0.81 in patients with tumors <100 mL.<sup>31</sup> In patients treated according to CESS 86, 85/228 (37%) had tumors >200 mL and had a 10 yr EFS 0.36 as compared with 0.63 for patients with tumors < 200 mL.<sup>30</sup> Forty-one of 118 (35%) patients treated on INT-0091 had tumors >200 mL and had a 5 yr EFS 0.47 as compared with 0.8 in patients with tumors <200 mL.<sup>31</sup> Current data from EuroEwing 99 (AEWS0331), in which volumes are being used for treatment stratification suggest that about 50% (482/986) are >200 mL. The results of the recently completed CCG9354/POG7942 combined with the results from INT-0091 confirm these findings. One hundred seventeen of 381 (117/381) patients had tumors 200 mL or more in volume and had a 5 year EFS 0.55 as compared with patients having tumors < 200 mL who had an EFS 0.78. Although tumor volumes may be estimated as ellipses or cylinders, volume estimation as 200mL or more based on approximating tumor volume as an ellipse defined by three perpendicular tumor diameters ( $\text{volume in mm}^3 = \pi/6 (d_1 \cdot d_2 \cdot d_3)$ ) was the best discriminator of outcome. The calculations to derive the estimates of tumor volume were performed centrally, based on tumor dimensions supplied by the institution.<sup>31</sup>

Although data is accumulating regarding the prognostic value of tumor size for EFS, data regarding the influence of tumor volume and local control (LC) are mixed. In a recent report of patients with pelvic tumors treated on INT-0091, tumor size did not correlate with LC.<sup>32</sup> This is in contrast to a previous prospective study from St Jude Children's Research Hospital suggesting improved local control for tumors < 8cm (90% vs 52%,  $p = 0.054$ ). A retrospective update of the St. Jude experience focusing only on patients treated with definitive radiotherapy confirmed an association between tumor size and LC. LC for tumors <8cm was 89%, in contrast to only 54% in the larger tumors ( $p=.002$ ).<sup>33</sup> The majority of data evaluating the association between tumor size and local control in Ewing tumor has used 8cm as a cut-point for risk



determination, with tumors larger than 8cm in maximal diameter being at higher risk for local recurrence.<sup>34</sup> In the CESS studies, size > 100mL was associated with increased risk of local recurrence in definitive radiotherapy patients, but not in patients who received surgery as a component of local therapy.<sup>35</sup>

CESS 86 data demonstrated 10 year EFS 0.64 in patients with a good histologic response and 0.38 in patients with a poor response.<sup>30</sup> INT-0091 data suggests a 5 year EFS 0.56 if some viable tumor is present and 0.79 where no viable tumor is found.<sup>31</sup> It should be noted that patients treated on INT 0091 received 4 courses of chemotherapy prior to local therapy while patients receiving therapy on this trial will receive 6 cycles, as do patients receiving treatment on EuroEwing 99 (AEWS0331). This increase in treatment prior to local therapy may increase the proportion of patients having a good histologic response and change the utility of this response as prognostic factor for EFS.

Local control outcomes based on histologic response have been retrospectively reported based on outcomes in the (E1) CESS-Studies. In patients with wide surgical margins and favorable histologic response, only 1% experienced local relapse. Even with wide margins, 12% experienced local relapse with a poor histologic response, which was improved to 6% in the patients who received post-operative radiotherapy. Post-operative radiation was recommended for patients with narrow margins or poor histologic response but not always administered. LC was similar in patients with or without post-operative radiation after marginal resections (6%). However, patients who received post-operative radiotherapy were more likely to have a poor histologic response.<sup>36</sup>

Confirmation of these findings may allow future development of risk based treatment for patients with localized Ewing sarcoma.

## 2.8 Impact of local therapy decisions on local control

Although surgery is the preferred local therapy in patients with Ewing family tumors, there remain a significant portion of patients treated on COG studies who receive radiotherapy for local control either definitively (20%), or adjuvantly (15%) (Krailo, personal communication). Generally, definitive radiotherapy patients tend to have large axial tumors and complete surgical resection is felt to be impossible or associated with significant morbidity. However, improvements in surgical techniques have allowed previously unresectable tumors to be potentially resectable. A recent COG report of patients treated on INT-0091 suggests local control rates of 80-90% even for pelvic tumors, a historically poor-prognostic site, regardless of local therapy modality utilized. Although not significant, combined surgery and radiotherapy was associated with the lowest rates of local relapse (10.5% surgery + RT vs 25% for either surgery or RT alone).<sup>32</sup> These results mirror the local recurrence outcomes in the entire cohort of patients which was only 2% for patients receiving combined modality treatment (versus 5% for surgery and 9% for radiotherapy alone, p= NS).<sup>2</sup> Combined modality treatment has been favored in European studies with 63% of patients treated on EICESS 92 receiving combined surgery and radiation, and 19% and 18% receiving surgery or radiotherapy alone, respectively. This aggressive treatment strategy resulted in 95% LC for patients receiving surgery as a component of local therapy, compared to 75% for those receiving RT alone.<sup>36</sup>

Prospective, randomized data in adults with soft tissue sarcomas has demonstrated superiority of pre-operative RT over post-operative RT in terms of better local control, improved survival and smaller radiotherapy field sizes.<sup>37</sup> Thus, in patients with Ewing sarcoma felt to be at high risk for requiring adjuvant radiotherapy, there may be a role for pre-operative radiotherapy to allow for a lower-dose and more limited radiotherapy volume. In addition, if combined modality treatment is necessary, treating the intact tumor generally allows a more favorable geometry because normal tissues are displaced by the tumor. Post-operatively, adjacent normal structures, such as lung in the thorax and small bowel in the pelvis, are in closer proximity to the radiation target and thus receive higher radiation doses. The goal of pre-operative radiotherapy would be primarily to minimize morbidity in patients requiring combined modality therapy as

well as to improve the likelihood of necrosis at the margin thus preventing the need for a high-dose boost after surgery. The objective of preoperative radiotherapy is not to make an inoperable tumor operable.

There is little information regarding musculoskeletal complications related to type of local therapy (radiation versus surgery) and to type of surgical reconstruction when surgery is used as local control. In addition, the durability of local therapy modalities has not been well described. Failures may occur throughout the first decade. Surgical revisions may be required either as a result of fracture or dysfunction (usually loosening) or early vascular compromise.<sup>38</sup> Single institution reports suggest surgical revisions may be required in 25% of patients.<sup>39</sup> Although not possible to study long term outcomes within the context of this trial there is an opportunity to follow functional outcomes throughout study follow-up at 5 years post closure of the study to accrual. One report in adults suggests a revision rate of 17% for endoprostheses at 5 years<sup>40</sup> supporting the usefulness of this length of follow-up. Functional limitations or pain may be present. Although contemporary clinical trials have emphasized EFS and OS outcomes, better information regarding functional outcomes may influence early decisions regarding local therapy choices.

## 2.9 Radiologic Response and prognosis

### 2.9.1 Initial Staging And Prognosis

Presence of metastasis is the strongest prognostic factor in Ewing sarcoma. Conventional staging has generally included plain radiographs, MRI and CT of the primary site, CT of the chest, and bone scintigraphy. More recently, functional imaging such as FDG-PET have been increasingly available, and appear more sensitive at detecting metastatic disease.<sup>41</sup> A recent prospective, multi-institutional study compared effectiveness of conventional imaging modalities with that of PET in pediatric sarcoma patients in terms of tumor staging and treatment planning. FDG-PET was superior in detection of lymph node metastasis (sensitivity, 95% vs 25%) and osseous metastasis (sensitivity, 90% vs 57%). The sensitivity difference for detecting osseous metastasis was more significant in Ewing sarcoma, (sensitivity, 88% vs 37%). Treatment was modified in 30% of patients based on the additional data obtained from FDG PET. A study by Kniesl in Ewing and osteosarcoma patients revealed similar results. For Ewing sarcoma, FDG PET detected osseous metastases not evident on bone scintigraphy in 18% of cases which resulted in modification of treatment strategy.<sup>42</sup>

### 2.9.2 Imaging Response And Prognosis

The correlation of imaging response and EFS has not been completely evaluated in pediatric patients receiving treatment for Ewing tumor. The response in bone is difficult to evaluate using traditional radiologic tools. Response, in terms of disappearance of the soft tissue component has been evaluated only in small numbers of patients.<sup>43</sup> The radiology committee has recommended MRI, bone scan and functional imaging (thallium or FDG PET) as appropriate investigations at diagnosis and prior to local therapy, surgery or radiation. A small series using FDG PET in evaluation of a variety of non-bone sarcomas suggests this modality may be a useful predictor of histologic response and EFS.<sup>44</sup> Standardized uptake value (SUV) both prior to treatment and the change between pre-treatment and pre-local therapy were found to be important in prognosis. In a small series of Ewing sarcoma family tumors, FDG PET at diagnosis (SUV1) and at the time of local therapy (SUV2) was evaluated to assess the correlation with histologic response at the time of surgery as well as EFS. In this report SUV2 was correlated with histologic response in 68% of patients and was strongly correlated with EFS regardless of initial SUV. EFS at 4 years for patients with an SUV2 < 2.5 was 72%, compared to only 27% for patients with an SUV2 ≥ 2.5 (p.01).<sup>45</sup>

Functional imaging response (PET) and radiologic response may aid in prognostic stratification of patients with localized Ewing sarcoma and allow development of future risk based treatment strategies. In addition, future local control decisions may also be individualized as to guiding surgical resection, the utility of pre-operative or post-operative radiotherapy, and modified radiotherapy volumes based on local control correlations with functional imaging response.



### 3.0 STUDY ENROLLMENT 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 eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

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.

##### 3.1.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSUS) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSUS IRB Transmittal Sheet) and the IRB approval document(s). The CTSUS IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSUS forms can be located on the CTSUS web page (<https://www.ctsu.org>). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSUS Member's Website under the RSS Tab.

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

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

##### 3.1.3 Patient Registration

Prior to study enrollment, all patients must have been registered via the eRDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

##### 3.1.4 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

##### 3.1.5 Timing

Study enrollment must take place prior to beginning protocol therapy. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the

eligibility section below. All staging scans to evaluate for metastatic disease need to be done within 4 weeks of enrollment and adequate preoperative imaging of the primary site is required prior to unplanned excisions. Patients must be enrolled within 8 weeks (56 days) of diagnostic biopsy.

### 3.1.6 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study. To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

### 3.1.7 Randomization

Randomization will take place at the time a patient is enrolled on study. Patients will be assigned to either Regimen A (vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide) or Regimen B (vincristine/topotecan/cyclophosphamide, ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide). Randomization will be stratified according to age and primary tumor site. Age will be stratified as: (a) seventeen years or less at age at diagnosis; or (b) eighteen years of age or greater at diagnosis. Primary site will be stratified as: (a) pelvic primary; or (b) non-pelvic primary (c) extra-osseous site.

## 3.2 Patient 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.**

### 3.2.1 Age

Age less than or equal to 50 years.

Note:

- Patients of age 0-15 years are to be enrolled by pediatric oncology services. 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.
- Patients of age 16-50 years can be enrolled by both pediatric and adult oncology services.

### 3.2.2 Diagnosis

Patients with newly diagnosed, biopsy confirmed, extracranial, non-metastatic Ewing sarcoma or PNET of bone or soft tissue are eligible for this study.

Note:

- For the purpose of this study, chest wall tumors with ipsilateral pleural effusions, ipsilateral positive pleural fluid cytology or ipsilateral pleural based secondary tumor nodules will be considered localized disease.
- Patients with regional node involvement, based on clinical suspicion confirmed by pathologic documentation are considered to be non-metastatic.
- Patients with discontinuous osseous lesions within the same bone are considered to be non-metastatic.
- See [Section 3.2.6](#) for the protocol definition of pulmonary metastatic disease.
- Tumors arising in the bony skull (extra-dural) are considered to be extracranial.

### 3.2.3 Pathologic Criteria

Patient eligibility will be based on a diagnosis of Ewing sarcoma or PNET by institutional pathologist. (Note: Refer to [Section 14.0](#) for details of microscopy, immunohistochemistry, and molecular and cytogenetic studies.)

3.2.4 Prior Therapy

No prior chemotherapy or radiation therapy is allowed. 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 unplanned excision was attempted or accomplished as long as adequate imaging was obtained prior to surgery. (Note: Refer to [Section 4.1](#) for details on unplanned excision.)

3.2.5 Organ Function Requirements:

3.2.5.1 Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR  $\geq$  70mL/min/1.73 m<sup>2</sup> or
- A serum creatinine based on age/gender as follows:

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

### 3.2.5.2 Adequate liver function defined as:

- Total bilirubin < 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.

### 3.2.5.3 Adequate cardiac function defined as:

- Shortening fraction of  $\geq 27\%$  by echocardiogram, or
- Ejection fraction of  $\geq 50\%$  by radionuclide angiogram.

## EXCLUSION CRITERIA

### 3.2.6 Patients must have no evidence of metastatic disease

#### Metastatic disease:

- Are lesions which are discontinuous from the primary tumor, are not regional lymph nodes and do not share a body cavity with the primary tumor. If there is any doubt whether lesions are metastatic, a biopsy of those lesions should be taken.
- Skeletal lesions in adjacent bones (trans-articular). See [Section 4.1](#)
- Contralateral pleural effusion and 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 biopsied and negative for Ewings
  - Biopsies of solitary nodule  $\leq 0.5$  cm or multiple nodules  $\leq 0.3$  cm are not required but if performed and positive indicate metastatic disease.

3.2.7 Patients whose tumors arise in the dural and intra-dural soft tissues of the cranium and spine are not eligible.

### 3.2.8 Microscopy

Patients with pathologic diagnoses other than Ewing sarcoma as defined in [Section 14.0](#) will be excluded.

### 3.2.9 Second Malignant Neoplasms

Patients diagnosed with Ewing Sarcoma as a second malignant neoplasm are not eligible if they have received chemotherapy or radiation for the treatment of their primary malignancy.

### 3.2.10 Pregnancy and breast feeding

Pregnant women will not be entered on this study as fetal toxicities and teratogenic effects have been noted for several of the study drugs. Pregnancy tests must be obtained in female patients who are post-menarchal. Lactating females may not participate unless they have agreed not to breastfeed their infants. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of the study treatment.

### 3.2.11 Regulatory Criteria

#### 3.2.11.1

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

#### 3.2.11.2

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

## 4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 4.1 Overview of Treatment plan

Please note: Patients should not have planned or unplanned surgical resections prior to chemotherapy. If a patient has a (presumably small) soft tissue mass that was not expected to be malignant and was resected with negative margins, no further local therapy will be required, provided the primary tumor was not violated at the time of surgery and the cuff of normal tissue surrounding the soft tissue tumor was at least 2 cm wide on all surfaces. In the case of Ewing tumor within an encapsulated organ, no additional local treatment is required if the capsule was not breached by the tumor or violated at the time of surgery. If the primary tumor was violated at the time of surgery, prior to the initiation of chemotherapy or margins as defined in this paragraph are inadequate, then further local therapy (surgery, radiation or both) at the time of local control must be delivered. In this case the initial procedure would be considered a large biopsy. For osseous (“skip”) lesions within the same bone involved by the primary tumor, the intervening “normal” area should be included in the local control treatment plan.

#### 4.1.1

Protocol therapy will consist of Induction, Local control and Consolidation therapy. Local therapy planning with a surgical and radiation oncology team should be initiated at the time of diagnosis, to ensure appropriate imaging is obtained for surgical or radiotherapy treatment planning.

Protocol therapy must begin only after study enrollment and randomization. All patients, whether in Regimen A or Regimen B will receive a total of 17 cycles of chemotherapy; each cycle will be of 2 weeks duration. Induction consists of 6 cycles (12 weeks) of chemotherapy and will be delivered prior to local control therapy which may involve surgery and/or radiation therapy. Consolidation therapy will consist of 11 cycles (22 weeks) of chemotherapy.

##### 4.1.1.1

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. This is usually possible one to two weeks later. The passing of more than 6 weeks between chemotherapy cycles for reasons other than severe chemotherapy toxicity should be avoided.

##### 4.1.1.2

For patients who will have radiation alone or will be given radiation pre-operatively, Consolidation chemotherapy should be initiated concurrently with the radiation therapy, upon recovery from Induction chemotherapy. Administration of vinCRistine-topotecan-cyclophosphamide and ifosfamide-etoposide chemotherapy concurrently with radiation is allowed. Radiation may begin concurrently or immediately after Cycle 1 Consolidation 1(VDC) in Regimen A. 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. The objective of preoperative radiotherapy should not be an attempt to make an

inoperable tumor operable. Patients who are to be treated with planned lower dose (36 Gy) radiation followed by planned excision should be treated with radiation during Weeks 1 through 4 of Consolidation, and then proceed onto surgical resection of the tumor as soon as possible (ideally within 2 weeks). If post-operative radiotherapy boost is required, radiation therapy should be scheduled to start as soon as recovery from surgery permits. Following surgery, the next cycle of chemotherapy should be given as soon as possible post-operatively: this can be given concurrently with boost radiotherapy if necessary. The passing of more than 6 weeks between chemotherapy cycles for reasons other than severe chemotherapy toxicity should be avoided.

See [Section 4.3](#) for detailed information about local control and [Section 4.4](#) for the drug administration schedule and criteria to start chemotherapy cycles.

#### 4.1.1.3

Evaluations will occur prior to local therapy, post Cycle 5 Consolidation and at the end of therapy. See [Sections 7.1](#) and [16.0](#) for details.

#### 4.1.1.4

Blood count criteria for start of cycle are  $ANC \geq 750/\mu L$  and platelet count  $\geq 75,000/\mu L$  post nadir. The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq 750/\mu L$  after the nadir but then falls the next cycle should be given despite  $ANC < 750/\mu L$ .

4.1.2 Treatment schema

**Regimen A**

INDUCTION			CONSOLIDATION		
Cycle	Week	Drugs	Cycle	Week	Drugs
1	1	VDC <sub>1200</sub>	1	1	VD <sup>%</sup> C <sub>1200</sub>
	2	V		2	V
2	3	IE	2	3	IE
	4			4	
3	5	VDC <sub>1200</sub>	3	5	IE
	6	V		6	
4	7	IE	4	7	VC <sub>1200</sub>
	8			8	V
5	9	VDC <sub>1200</sub>	5	9	VD <sup>%</sup> C <sub>1200</sub>
	10	V		10	V
6	11	IE	6	11	IE
	12			12	
<b>Evaluations</b>	13		7	13	VC <sub>1200</sub>
<b>Local Control</b>	14			14	V
<p>V=VinCRIS<sup>t</sup>ine      C<sub>1200</sub>=Cyclophosphamide<sub>1200 mg</sub>                      I=Ifosfamide    E=Etoposide    D=DOXOrubicin</p> <p><b>NOTES:</b>                      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 consolidation Cycle 1 should start at the same time.</p> <p>%- Dexrazoxane 375 mg/m<sup>2</sup> (or 12.5mg/kg if &lt;10kg or &lt; 1yo) will be administered <b>ONLY</b> in the 4th and 5th VDC cycles (Cycles 1 and 5 of Consolidation), on Days 1 and 2 prior to DOXOrubicin.</p> <p>Myeloid growth factor support between cycles is required for interval compression (<b>GM-CSF excluded</b>).</p>			8	15	IE
				16	
			9	17	VC <sub>1200</sub>
				18	V
			10	19	IE
				20	
			11	21	VC <sub>1200</sub>
				22	V
			<b>End of Therapy</b>		

**Regimen B**

INDUCTION			CONSOLIDATION					
Cycle	Week	Drugs	Cycle	Week	Drugs			
1	1	VTC <sub>250</sub>	1	1	VTC <sub>250</sub>			
	2	V		2	V			
2	3	IE	2	3	IE			
	4			4				
3	5	VDC <sub>1200</sub>	3	5	IE			
	6	V		6				
4	7	IE	4	7	VTC <sub>250</sub>			
	8			8	V			
5	9	VTC <sub>250</sub>	5	9	VDC <sub>1200</sub>			
	10	V		10	V			
6	11	VDC <sub>1200</sub>	6	11	IE			
	12	V		12				
<b>Evaluations</b>	13		7	13	VD <sup>%</sup> C <sub>1200</sub>			
<b>Local Control</b>	14			14	V			
V=VinCRiStine T=TOPOtecan C <sub>1200</sub> =Cyclophosphamide <sub>1200 mg</sub> C <sub>250</sub> =Cyclophosphamide <sub>250 mg</sub> D=DOXOrubicin I=Ifosfamide E=Etoposide <b>NOTES:</b> 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 consolidation Cycle 1 should start at the same time.  %- Dexrazoxane 375 mg/m <sup>2</sup> or 12.5mg/kg if <10kg or < 1yo will be administered <b>ONLY</b> in the 4th and 5th VDC cycles (Cycles 7 and 10 of Consolidation), on Days 1 and 2 prior to DOXOrubicin.  Myeloid growth factor support between cycles is required for interval compression ( <b>GM-CSF excluded</b> ).			8	15	VTC <sub>250</sub>			
				16	V			
			9	17	IE			
				18				
			10	19	VD <sup>%</sup> C <sub>1200</sub>			
				20	V			
			11	21	IE			
				22				
						<b>End of Therapy</b>		

**4.2 Concomitant Medications**

4.2.1

No other cancer chemotherapy or immunomodulating agents (including steroids unless used as an antiemetic) will be used.

4.2.2

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 azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) and strong inducers include drug such as rifampin, phenytoin, phenobarbitol, carbamazepine, and St. John’s wort. 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 stimulators or inhibitors should be avoided or used with great caution. Aprepitant also interacts with CYP3A4 and should be used with caution with etoposide, ifosfamide, or vinCRiStine chemotherapy.



A more complete list of drugs that are metabolized by cytochrome P450 isoform is available via the link below. Drug names are hyperlinks to specific journal references:

<http://medicine.iupui.edu/clinpharm/ddis>

#### 4.2.3

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. For COG Supportive Care Guidelines see

[https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp)

### 4.3 **General Approach to Primary Tumor Treatment (Local Control)**

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. This will require careful consultation between the orthopedic or surgical oncologist and the radiation oncologist.

Recent experience indicates that most patients will be treated with surgical excision alone or surgical excision preceded or followed by radiation therapy.

#### 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 margins 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 treated with neo-adjuvant chemotherapy having complete resections (R0) with a clear margin (defined as no viable tumor at the cut surface) 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. Patients who have excisional biopsy of the tumor as a first procedure before the administration of chemotherapy require at least a 2 cm cuff of normal tissue completely surrounding the tumor to be considered a clear margin. In cases where the normal uninvolved tissue is less than 2 cm thick, the procedure will be considered as a large biopsy and additional surgery or radiation therapy will be required after the completion of induction chemotherapy. For encapsulated organs, complete excision of the organ prior to chemotherapy where the tumor has not been violated at the time of surgery and the capsule not breached by the tumor will be considered to have had adequate local therapy and no additional surgery and/or radiation is necessary.

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) after neo-adjuvant chemotherapy 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 the tumor is completely resected prior to administration of chemotherapy, the cuff of surrounding normal tissue must be at least 2 cm wide on all surfaces, otherwise additional local therapy will be needed following induction chemotherapy.

#### 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. While avoiding radiation completely with a wide (R0) excision decreases the risk of secondary sarcoma for example, a combined approach appears to be a reasonable alternative. Patients with apparently **resectable** tumors in some select sites such as pelvis, chest wall, axial tumors etc. can have a higher risk of positive microscopic margins following surgery and many orthopedic and surgical oncologists prefer to combine surgery with pre-operative radiation. In these cases, 36 Gy of radiation therapy may be considered prior to resection. The objective of preoperative radiotherapy should not be an attempt to make an inoperable tumor operable. This low dose should only be given when complete surgical excision is planned within 2 weeks following the completion of the last dose of radiation. If a possible outcome of surgery is an intralesional excision (R2), pre-operative radiotherapy as mandated in this study 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 hospital center.

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 usually within 2 weeks.

Patients with microscopic residual disease after planned pre-operative radiation therapy will receive additional radiation (see [Sections 17.2](#) and [17.7.2.1](#)).

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, once recovered from Induction chemotherapy. For details on radiotherapy, see [Section 17.0](#).

### 4.4 Chemotherapy Administration Schedule

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

#### 4.4.1 Administration Schedules for Regimen A

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

Criteria to start Induction: ANC  $\geq$  750/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L (without transfusion).

Criteria to start subsequent cycles: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls the next cycle should be given despite ANC  $<$  750/ $\mu$ L. 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 or weighing less than 10 kilograms, chemotherapy should be calculated by weight rather than by surface area. Dose/kilogram = dose/meter<sup>2</sup> divided by 30.

#### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

Day 1 of Weeks 1, 2, 5, 6, 9 and 10.

Dose: 1.5 mg/m<sup>2</sup>/dose. (Maximum dose is 2 mg.) For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.05 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. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

**DOXOrubicin: IV push/infusion over 1-15 minutes.** Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate.

Days: 1 and 2 of Weeks 1, 5 and 9.

Dose: 37.5 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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<sub>5</sub>W 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. The conventional and liposomal formulations are NOT interchangeable.

**Cyclophosphamide: IV over 30-60 minutes**

Day 1 of Weeks 1, 5 and 9

Dose is 1,200 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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

**Ifosfamide: IV, infuse the diluted solution over 1 hour**

Days 1-5 of Weeks 3, 7 and 11.

Dose: 1,800 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 1 year old, the dose is 60 mg/kg/dose.

Mesna must be administered in conjunction with ifosfamide (see below).

Suggested hydration: Administer 3,000 mL/m<sup>2</sup>/day (125 mL/m<sup>2</sup>/hour) using fluid containing D<sub>5</sub>W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of 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<sup>2</sup>/day. For patients < 10 kg or < 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<sup>2</sup>/day. For patients < 10 kg or < 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 oxazaphosphorine 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 with the oxazaphosphorine 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 ifosfamide/cyclophosphamide 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 oxazaphosphorine 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 oxazaphosphorine dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the oxazaphosphorine 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.

#### **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<sup>2</sup>/dose. For patients < 10 kg or < 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.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D<sub>5</sub>W. Avoid use of large volumes of D<sub>5</sub>W due to potential development of hyponatremia.

#### **Growth Factor Support** <sup>46-52</sup>

Begin myeloid growth factor support 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. If given daily, growth factor administration is to be continued in weeks where vinCRISTine is given alone, without regard to vinCRISTine administration.

**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 are provided in the following three pages. Local control will follow Induction. (see [Section 4.3](#) for details). See [Section 7.1](#) for observations prior to Local Control. See [Section 16.0](#) for imaging pre- and post- Local Control. Details of Consolidation chemotherapy for Regimen A are provided in [Section 4.4.1.2](#)

**Induction for Regimen A (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); a VDC cycle followed by an IE cycle.**

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
DOB

Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls, Cycle 2 should be given despite ANC  $<$  750/ $\mu$ L. 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	OBSERVATIONS
VinCRISStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or < 1 yo	1 and 8	\$- Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.1</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT, c. Urinalysis d. CBC, Plt, Diff*  * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or < 1 yo	1 and 2	&- Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.1.1</a> for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or < 1 yo	1	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	1	Administer with CPM, see <a href="#">Section 4.4.1.1</a>	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or < 1 yo	15 - 19	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	15 - 19	Administer with IFOS, see <a href="#">Section 4.4.1.1</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or < 1 yo	15 - 19	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.1.1</a> for details.	

Cycle 1: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 2: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day <sup>%</sup>	IFOS mg	MESNA (with IFOS) mg/day <sup>%</sup>	ETOP mg	Studies
<b>Enter calculated dose above and actual dose administered below</b>											
		1	1	_____ mg	_____ mg	_____ mg	_____ mg/day <sup>%</sup>				a, b, c, d,
			2		_____ mg						
			3-4 <sup>#</sup>	Growth factor used: _____			Dose: _____			Date of first dose: _____ Date of last dose: _____	
		2	8	_____ mg							d
			14								d*
		3	15					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	a, b, c, d
			16					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			17					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			18					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			19					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			20-21 <sup>#</sup>	Growth factor used: _____			Dose: _____			Date of first dose: _____ Date of last dose: _____	
		4	22								d
			28								d*

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

<sup>#</sup>- 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



**Induction for Regimen A 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); a VDC cycle followed by an IE cycle.**

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
DOB

Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls, Cycle 3 and 4 should be given despite ANC < 750/ $\mu$ L. 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	OBSERVATIONS
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	29 and 36	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.1</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT, c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	29 and 30	&- Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.1.1</a> for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	29	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	29	Administer with CPM, see <a href="#">Section 4.4.1.1</a>	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	43-47	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	43-47	Administer with IFOS, see <a href="#">Section 4.4.1.1</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	43-47	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.1.1</a> for details.	

Cycle 3 : Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 4: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day <sup>%</sup>	IFOS mg	MESNA (with IFOS) mg/day <sup>%</sup>	ETOP mg	Studies
<b>Enter calculated dose above and actual dose administered below</b>											
		5	29	_____ mg	_____ mg	_____ mg	_____ mg/day <sup>%</sup>				a, b, c, d
			30		_____ mg						
			31-32 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		6	36	_____ mg							d
			42								d*
		7	43					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	a, b, c, d
			44					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			45					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			46					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			47					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			48-49 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		8	50								d
			56								d*

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

<sup>#</sup>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

<p><b>Induction for Regimen A Continued</b>                  Induction consists of 6 two-week cycles (84 days in total).                  The therapy delivery map presents Induction therapy on 3 pages.  <b>This therapy delivery map relates to Cycles 5 and 6 (Weeks 9-12); a VDC cycle followed by an IE cycle.</b></p>	<p style="text-align: center;">_____ Patient name or initials</p> <p style="text-align: center;">_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls, Cycle 5 and 6 should be given despite ANC < 750/ $\mu$ L. 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	OBSERVATIONS
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or < 1 yo	57 and 64	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.1</a>	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT, c. Urinalysis d. CBC, Plt, Diff* e. ECG and ECHO or MUGA *See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
DOXOrubicin (DOXO)	IV push/infusion over 1-15 mins <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or < 1 yo	57 and 58	&- Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.1.1</a> for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or < 1 yo	57	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	57	Administer with CPM, see <a href="#">Section 4.4.1.1</a>	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or < 1 yo	71-75	See <a href="#">Section 4.4.1.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.1</a>	71-75	Administer with IFOS, see <a href="#">Section 4.4.1.1</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or < 1 yo	71-75	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.1.1</a> for details.	

Cycle 5: Ht				cm				Wt				kg				BSA				m <sup>2</sup>				Cycle 6: Ht				cm				Wt				kg				BSA				m <sup>2</sup>			
Date Due	Date Given	Week	Day	VCR mg	DOXO mg	CPM mg	MESNA (with CPM) mg/day%	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	Studies																																				
<b>Enter calculated dose above and actual dose administered below</b>																																															
		9	57	_____ mg	_____ mg	_____ mg	_____ mg/day%				a, b, c, d, e																																				
			58	_____ mg	_____ mg																																										
			59-60 <sup>#</sup>	Growth factor used: _____ Dose: _____				Date of first dose: _____ Date of last dose: _____																																							
		10	64	_____ mg							d																																				
			70								d*																																				
		11	71					_____ mg	_____ mg/day%	_____ mg	a, b, c, d																																				
			72					_____ mg	_____ mg/day%	_____ mg																																					
			73					_____ mg	_____ mg/day%	_____ mg																																					
			74					_____ mg	_____ mg/day%	_____ mg																																					
			75					_____ mg	_____ mg/day%	_____ mg																																					
			76-77 <sup>#</sup>	Growth factor used: _____ Dose: _____				Date of first dose: _____ Date of last dose: _____																																							
		12	78								d																																				
			84	<b>Local Control will follow Induction therapy. See <a href="#">Section 4.3</a> for Local Control options. See <a href="#">Section 7.1</a> for observations prior to Local Control.</b>																																											

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

<sup>#</sup>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 for Consolidation Therapy (Weeks 1-22) for 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.

Criteria to start Consolidation: ANC  $\geq$  750/ $\mu$ L and platelet  $\geq$  75,000/ $\mu$ L post nadir (without transfusion).  
Criteria to start subsequent cycles: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls the next cycle should be given despite ANC  $<$  750/ $\mu$ L. 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 or weighing less than 10 kilograms, chemotherapy should be calculated by weight rather than by surface area. Dose/kilogram = dose/meter<sup>2</sup> divided by 30.

#### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

Day 1 of Weeks 1, 2, 7, 8, 9, 10, 13, 14, 17, 18, 21 and 22.

Dose: 1.5 mg/m<sup>2</sup>/dose (Maximum dose is 2 mg). For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.05 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. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

#### **DOXOrubicin: IV push/infusion over 1-15 minutes**

Days: 1 and 2 of Weeks 1 and 9

Dose: 37.5 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  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<sub>5</sub>W 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. 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 9.

Dose: 375 mg/m<sup>2</sup>/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). For patients  $<$  10 kg or  $<$  1 year old, the dose is 12.5 mg/kg/dose.

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

#### **Cyclophosphamide: IV over 30-60 minutes**

Day 1 of Weeks 1, 7, 9, 13, 17 and 21

Dose: 1,200 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  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

**Ifosfamide: IV, infuse the diluted solution over 1 hour**

Days 1-5 of Weeks 3, 5, 11, 15 and 19

Dose: 1,800 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 1 year old, the dose is 60 mg/kg/dose.

Mesna must be administered in conjunction with IFOS (see below).

Suggested hydration: Administer 3,000 mL/m<sup>2</sup>/day (125 mL/m<sup>2</sup>/hour) using fluid containing D<sub>5</sub>W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of 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, 13, 17 and 21

Total IV Dose: 720 mg/m<sup>2</sup>/day. For patients < 10 kg or < 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, 15 and 19

Total IV Dose: 1,080 mg/m<sup>2</sup>/day. For patients < 10 kg or < 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 oxazaphosphorine 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 with the oxazaphosphorine 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**. 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 ifosfamide/cyclophosphamide 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 oxazaphosphorine 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 oxazaphosphorine dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the oxazaphosphorine 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.

**Etoposide: IV, infuse the diluted solution over at least 1-2 hours**

Days 1-5 of Weeks 3, 5, 11, 15 and 19

Dose: 100 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D<sub>5</sub>W. Avoid use of large volumes of D<sub>5</sub>W due to potential development of hyponatremia.

**Growth Factor Support**

Begin myeloid growth factor support at least 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC  $\geq 750/\mu\text{L}$  post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy. If given daily, growth factor administration is to be continued in weeks where vinCRISStine is given alone, without regard to vinCRISStine administration.

**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 are provided on the following 6 pages. See [Section 7.1](#) for observations required at end of therapy.

<p><b>Consolidation Chemotherapy for Regimen A</b></p> <p>Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages. <b>This page relates to Cycle 1 (Weeks 1 and 2) of Consolidation chemotherapy</b></p>	<p style="text-align: right;">_____ Patient name or initials</p> <p style="text-align: right;">_____</p> <p style="text-align: center;">DOB</p>
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Begin Consolidation when ANC  $\geq 750/\mu\text{L}$  and platelet count  $\geq 75,000/\mu\text{L}$  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 n Cycle 1 Consolidation should start at the same time.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	1 and 8	\$.-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.2</a> .	a. History and Physical Exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* e. Imaging per <a href="#">Section 16.0</a>  * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5-15 min)	375 mg/m <sup>2</sup> /dose OR 12.5 mg/kg/dose for pt < 10 kg or <1 yo	1 and 2	Administer immediately prior to DOXO. The combined infusion time for DXRZ + DOXO should be $\leq 30$ min. See <a href="#">Section 4.4.1.2</a> .	
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	1 and 2	See <a href="#">Section 4.4.1.2</a> for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	1	See <a href="#">Section 4.4.1.2</a> .	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	1	Administer with CPM, see <a href="#">Section 4.4.1.2</a>	

Cycle 1: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

%-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](#).

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

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.

<b>Consolidation Chemotherapy for Regimen A</b> Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages. <b>This page relates to Cycles 2 and 3 (Weeks 3 - 6) of Consolidation chemotherapy</b>	_____ Patient name or initials _____
	_____ DOB

Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after nadir but then falls, Cycles 2 and 3 should be given despite ANC < 750/ $\mu$ L. 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 <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	15-19 and 29-33	See <a href="#">Section 4.4.1.2</a> for details.	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	15-19 and 29-33	Administer with IFOS, see <a href="#">Section 4.4.1.2</a> .	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	15-19 and 29-33	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.1.2</a> .	

Cycle 2: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 3: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

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

% Enter total daily dose as mg/day by CI or intermittent infusion;    <sup>#</sup>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.

<b>Consolidation Chemotherapy for Regimen A</b> Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages. <b>This page relates to Cycles 4 and 5 (Weeks 7-10) of Consolidation chemotherapy</b>	_____ Patient name or initials
	_____ DOB

Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after nadir but then falls, Cycles 4 and 5 should be given despite ANC < 750/ $\mu$ L. 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 <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	43, 50, 57 and 64	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.2</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT, c. Urinalysis d. CBC, Plt, Diff* e. ECG and ECHO or MUGA* f. Imaging per <a href="#">Section 16.0</a> * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	43 and 57	See <a href="#">Section 4.4.1.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	43 and 57	Administer with CPM, see <a href="#">Section 4.4.1.2</a>	
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5 15min)	375 mg/m <sup>2</sup> /dose OR 12.5 mg/kg/dose for pt < 10 kg or <1 yo	57 and 58	Administer immediately prior to DOXO. The combined infusion time for DXRZ+ DOXO should be $\leq$ 30 min. See <a href="#">Section 4.4.1.2</a>	
DOXOrubicin (DOXO)	IV push over 1-15 mins	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	57 and 58	See <a href="#">Section 4.4.1.2</a> for details.	

Cycle 4: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 5: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	CPM mg	MESNA (with CPM) mg/day%	DXRZ mg	DOXO mg	Studies	Comments (Include any held doses, or dose modifications)	
<b>Enter calculated dose above and actual dose administered below</b>											
		7	43	mg	mg	mg/day%			a, b, c, d		
			44-45 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		8	50	mg					d		
			56						d*		
		9	57	mg	mg	mg/day%	mg	mg	a, b, c, d, e		
			58				mg	mg			
			59-60 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		10	64	mg					d		
			70						d*, f		

% Enter total daily dose as mg/day by CI or intermittent infusion; <sup>#</sup> 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.

<p><b>Consolidation Chemotherapy for Regimen A</b>                  Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).                  This Therapy Delivery Map is on 6 pages.  <b>This page relates to Cycles 6 and 7 (Weeks 11-14) of Consolidation chemotherapy.</b></p>	<p style="text-align: center;">_____ Patient name or initials</p> <p style="text-align: center;">_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after nadir but then falls, Cycles 6 and 7 should be given despite ANC < 750/ $\mu$ L 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 <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	71-75	See <a href="#">Section 4.4.1.2</a> for hydration guidelines.	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff*  * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	71-75	Administer with IFOS, see <a href="#">Section 4.4.1.2</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	71-75	Slow rate of administration if hypotension occurs.	
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	85 and 92	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg</b> See <a href="#">Section 4.4.1.2</a>	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	85	See <a href="#">Section 4.4.1.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	85	Administer with CPM, see <a href="#">Section 4.4.1.2</a>	

Cycle 6: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 7: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	VCR mg	CPM <sub>1200</sub> mg	MESNA (with CPM) mg/day%	Studies	
<b>Enter calculated dose above and actual dose administered below</b>											
		11	71	_____ mg	_____ mg/day%	_____ mg				a, b, c, d	
			72	_____ mg	_____ mg/day%	_____ mg					
			73	_____ mg	_____ mg/day%	_____ mg					
			74	_____ mg	_____ mg/day%	_____ mg					
			75	_____ mg	_____ mg/day%	_____ mg					
			76-77 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		12	78							d	
			84							d*	
		13	85				_____ mg	_____ mg	_____ mg/day%	a, b, c, d	
			86-87 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		14	92				_____ mg			d	
			98							d*	

%-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.



<p><b>Consolidation Chemotherapy for Regimen A</b>                  Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).                  This Therapy Delivery Map is on 6 pages.  <b>This page relates to Cycles 8 and 9 (Weeks 15-18) of Consolidation chemotherapy.</b></p>	<p>_____ Patient name or initials</p> <p>_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after nadir but then falls, Cycles 8 and 9 should be given despite ANC < 750/ $\mu$ L. 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 <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg OR <1 yo	99-103	See <a href="#">Section 4.4.1.2</a> for details.	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	99-103	Administer with IFOS, see <a href="#">Section 4.4.1.2</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg OR <1 yo	99-103	Slow rate of administration if hypotension occurs.	
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg OR <1 yo	113 and 120	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.2</a> for details.	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg OR <1 yo	113	See <a href="#">Section 4.4.1.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	113	Administer with CPM, see <a href="#">Section 4.4.1.2</a>	

Cycle 8: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 9: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	IFOS mg	MESNA (with IFOS) mg/day <sup>%</sup>	ETOP mg	VCR mg	CPM mg	MESNA (with CPM) mg/day <sup>%</sup>	Studies
<b>Enter calculated dose above and actual dose administered below</b>										
		15	99	_____ mg	_____ mg/day <sup>%</sup>	_____ mg				a, b, c, d
			100	_____ mg	_____ mg/day <sup>%</sup>	_____ mg				
			101	_____ mg	_____ mg/day <sup>%</sup>	_____ mg				
			102	_____ mg	_____ mg/day <sup>%</sup>	_____ mg				
			103	_____ mg	_____ mg/day <sup>%</sup>	_____ mg				
		104-105 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		16	106							d
			112							d*
		17	113				_____ mg	_____ mg	_____ mg/day <sup>%</sup>	a, b, c, d
		114-115 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____							
		18	120				_____ mg			d
			126							d*

<sup>%</sup>-Enter total daily dose as mg/day by CI or intermittent infusion; <sup>#</sup>- 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.



<p><b>Consolidation Chemotherapy for Regimen A</b>                  Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).                  This Therapy Delivery Map is on 6 pages.  <b>This therapy delivery map relates to Cycles 10 and 11 (Weeks 19-22) of Consolidation chemotherapy.</b></p>	<p style="text-align: center;">_____ Patient name or initials</p> <p style="text-align: center;">_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to  $\geq$  750/ $\mu$ L after nadir but then falls, Cycles 10 and 11 should be given despite ANC < 750/ $\mu$ L. 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 <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg OR <1 yo	127-131	See <a href="#">Section 4.4.1.2</a> for details..	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	127-131	Administer with IFOS, see <a href="#">Section 4.4.1.2</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg OR <1 yo	127-131	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.1.2</a>	
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg OR <1 yo	141 and 148	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.1.2</a> .	
Cyclophosphamide (CPM)	IV over 30-60 mins	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg OR <1 yo	141	See <a href="#">Section 4.4.1.2</a> for further details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.1.2</a>	141	Administer with CPM, see <a href="#">Section 4.4.1.2</a>	

Cycle 10: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg      BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 11: Ht \_\_\_\_\_ cm      Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

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	
<b>Enter calculated dose above and actual dose administered below</b>											
		19	127	_____ mg	_____ mg/day%	_____ mg				a, b, c, d	
			128	_____ mg	_____ mg/day%	_____ mg					
			129	_____ mg	_____ mg/day%	_____ mg					
			130	_____ mg	_____ mg/day%	_____ mg					
			131	_____ mg	_____ mg/day%	_____ mg					
		132-133 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		20	134							d	
			140							d*	
		21	141				_____ mg	_____ mg	_____ mg/day%	a, b, c, d	
		142-143 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		22	148				_____ mg			d	
			154	<b>End of Therapy. See <a href="#">Section 7.1</a> and <a href="#">Section 16.0</a> for required observations and imaging at end of therapy</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](#)  
 See [Section 5.0](#) for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

#### 4.4.2 Administration Schedules for Regimen B

##### 4.4.2.1 Administration Schedule for Induction Therapy (Weeks 1-12)

Criteria to start Induction: ANC  $\geq$  750/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L (without transfusion).

Criteria to start subsequent cycles: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls the next cycle should be given despite ANC  $<$  750/ $\mu$ L. 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 or weighing less than 10 kilograms, chemotherapy should be calculated by weight rather than by surface area. Dose/kilogram = dose/meter<sup>2</sup> divided by 30.

##### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

Day 1 of Weeks 1, 2, 5, 6, 9, 10, 11 and 12.

Dose: 1.5 mg/m<sup>2</sup>/dose (Maximum dose is 2 mg). For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.05 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. For intravenous use only- Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

##### **Topotecan: IV, infuse the diluted solution over 30 minutes**

Days 1-5 of Weeks 1 and 9.

Dose: 0.75 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.025 mg/kg/dose.

##### **Cyclophosphamide**

**Note that the VDC and the VTC combinations involve a different dose of CPM.**

##### **C<sub>250</sub> – dose administered during cycles of VTC: IV over 15-30 minutes**

Days 1-5 of Weeks 1 and 9.

C<sub>250</sub> dose is 250 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  1 year old, the dose is 8.3 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.

Hydrate per institutional guidelines

##### **C<sub>1200</sub> – dose administered during cycles of VDC: IV over 30-60 minutes**

Day 1 of Weeks 5 and 11.

C<sub>1200</sub> dose is 1,200 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  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 C<sub>1200</sub> (see below).

Hydrate per institutional guidelines

##### **Ifosfamide: IV, infuse the diluted solution over 1 hour**

Days 1-5 of Weeks 3 and 7.

Dose: 1,800 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  1 year old, the dose is 60 mg/kg/dose.

Mesna must be administered in conjunction with IFOS (see below).

**Suggested hydration:** Administer 3,000 mL/m<sup>2</sup>/day (125 mL/m<sup>2</sup>/hour) using fluid containing D<sub>5</sub>W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

### **Mesna with IFOS**

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

Total IV Dose: 1,080 mg/m<sup>2</sup>/day. For patients < 10 kg or < 1 year old, the IV dose is 36 mg/kg/day.

### **Mesna with C<sub>1200</sub>**

Administer mesna by IV infusion or IV/PO on Day 1 of Weeks 5 and 11.

Total IV Dose: 720 mg/m<sup>2</sup>/day. For patients < 10 kg or < 1 year old, the IV dose is 24 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 oxazaphosphorine 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 with the oxazaphosphorine 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**. 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 ifosfamide/cyclophosphamide 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 oxazaphosphorine 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 oxazaphosphorine dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the oxazaphosphorine 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.

**Etoposide: IV, infuse the diluted solution over at least 1-2 hours**

Days 1-5 of Weeks 3 and 7.

Dose: 100 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D<sub>5</sub>W. Avoid use of large volumes of D<sub>5</sub>W due to potential development of hyponatremia.

**DOXOrubicin: IV push/infusion over 1-15 minutes.** Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate.

Days 1 and 2 of Weeks 5 and 11.

Dose: 37.5 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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<sub>5</sub>W 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. The conventional and liposomal formulations are NOT interchangeable.

**Growth Factor Support**

Begin myeloid growth factor support 24-36 hours after the last dose of chemotherapy. If given daily then continue a minimum of 7 days and until ANC  $\geq$  750/ $\mu$ L post nadir and discontinue at least 24 hours prior to next cycle of chemotherapy. If given daily, growth factor administration is to be continued in weeks where vinCRISTine is given alone, without regard to vinCRISTine administration.

**Note: Use of GM-GCSF (sargramostim) is not permitted.**

See [Section 5.0](#) for Dose Modifications based on toxicities.

The therapy delivery maps for Induction are provided on the following 4 pages. Local control will follow Induction (see [Section 4.3](#) for details). See [Section 7.1](#) for observations prior to Local Control. See [Section 16.0](#) for imaging pre- and post- Local Control. Details of Consolidation chemotherapy for Regimen B are provided in [Section 4.4.2.2](#).

<p><b>Induction for Regimen B</b>                  Induction consists of 6 two-week cycles (84 days in total).                  The therapy delivery map presents Induction therapy on 3 pages.  <b>This therapy delivery map relates to Cycles 1 and 2 (Weeks 1-4): a VTC<sub>250</sub> cycle followed by an IE cycle.</b></p>	<p style="text-align: center;">_____</p> <p style="text-align: center;">Patient name or initials</p> <p style="text-align: center;">_____</p> <p style="text-align: center;">DOB</p>
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Criteria to start each cycle: ANC ≥ 750/μL and platelets ≥ 75,000/μL (without transfusion). If ANC has risen to ≥ 750/μL after nadir but then falls, Cycle 2 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
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	1 and 8	\$.-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.1</a> for further details.	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Topotecan (TOPO)	IV over 30 min	0.75 mg/m <sup>2</sup> /dose OR 0.025 mg/kg/dose for pt < 10 kg or <1 yo	1 - 5	See <a href="#">Section 4.4.2.1</a>	
Cyclophosphamide (CPM <sub>250</sub> )	IV over 15-30 min	250 mg/m <sup>2</sup> /dose OR 8.3 mg/kg/dose for pt < 10 kg or <1 yo	1 - 5	See <a href="#">Section 4.4.2.1</a> .	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	15 - 19	See <a href="#">Section 4.4.2.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.1</a>	15 - 19	Administer with IFOS, see <a href="#">Section 4.4.2.1</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	15 - 19	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.2.1</a>	

Cycle 1: Ht \_\_\_\_\_ cm    Wt \_\_\_\_\_ kg    BSA \_\_\_\_\_ m<sup>2</sup>                     
 Cycle 2: Ht \_\_\_\_\_ cm    Wt \_\_\_\_\_ kg    BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	TOPO mg	CPM <sub>250</sub> mg	IFOS mg	MESNA (with IFOS) mg/day <sup>%</sup>	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
<b>Enter calculated dose above and actual dose administered below</b>											
		1	1	mg	mg	mg				a, b, c, d	
			2		mg	mg					
			3		mg	mg					
			4		mg	mg					
			5		mg	mg					
		6-7 <sup>#</sup>	Growth factor used:		Dose:		Date of first dose:		Date of last dose:		
		2	8	mg						d	
			14							d*	
		3	15				mg	mg/day <sup>%</sup>	mg	a, b, c, d	
			16				mg	mg/day <sup>%</sup>	mg		
			17				mg	mg/day <sup>%</sup>	mg		
			18				mg	mg/day <sup>%</sup>	mg		
			19				mg	mg/day <sup>%</sup>	mg		
		20-21 <sup>#</sup>	Growth factor used:		Dose:		Date of first dose:		Date of last dose:		
		4	22							d	
			28							d*	

%- 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 maps for Induction continue on the next 2 pages.

SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE

**Induction for Regimen B**

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): a VDC<sub>1200</sub> cycle followed by an IE cycle.**

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
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 3 and 4 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
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	29 and 36	§-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.1</a>	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	29 and 30	&- Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.2.1</a> .	
Cyclophosphamide (CPM <sub>1200</sub> )	IV over 30-60 min	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	29	See <a href="#">Section 4.4.2.1</a> for further details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.1</a>	29	Administer with CPM, see <a href="#">Section 4.4.2.1</a>	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	43 - 47	See <a href="#">Section 4.4.2.1</a> for further details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.1</a>	43 - 47	Administer with IFOS, see <a href="#">Section 4.4.2.1</a>	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	43 - 47	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.2.1</a> .	

Cycle 3: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 4: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	DOXO mg	CPM <sub>1200</sub> mg	MESNA (with CPM <sub>1200</sub> ) mg/day <sup>%</sup>	IFOS mg	MESNA (with IFOS) mg/day <sup>%</sup>	ETOP mg	Studies
<b>Enter calculated dose above and actual dose administered below</b>											
		5	29	_____ mg	_____ mg	_____ mg	_____ mg/day <sup>%</sup>				a, b, c, d
			30		_____ mg						
			31-32 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____	
		6	36	_____ mg							d
			42								d*
		7	43					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	a, b, c, d
			44					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			45					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			46					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			47					_____ mg	_____ mg/day <sup>%</sup>	_____ mg	
			48-49 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____	
		8	50								d
			56								d*

%- 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 maps for Induction continue on the next page.

SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE



<p><b>Induction for Regimen B</b>                  Induction consists of 6 two-week cycles (84 days in total).                  The therapy delivery map presents Induction therapy on 3 pages.  <b>This therapy delivery map relates to Cycles 5 and 6 (Weeks 9-12): a VTC<sub>250</sub> cycle followed by a VDC<sub>1200</sub> cycle.</b></p>	<p>_____ Patient name or initials</p> <p>_____ DOB</p>
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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 5 and 6 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
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	57, 64, 71 and 78	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.1</a>	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff*  * See <a href="#">Section 7.1</a> for details.  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Topotecan (TOPO)	IV over 30 min	0.75 mg/m <sup>2</sup> /dose OR 0.025 mg/kg/dose for pt < 10 kg or <1 yo	57 - 61	See <a href="#">Section 4.4.2.1</a>	
Cyclophosphamide (CPM <sub>250</sub> )	IV over 15-30 min	250 mg/m <sup>2</sup> /dose OR 8.3 mg/kg/dose for pt < 10 kg or <1 yo	57 - 61	See <a href="#">Section 4.4.2.1</a> for r details.	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	71 and 72	&- Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.2.1</a> .	
Cyclophosphamide (CPM <sub>1200</sub> )	IV over 30-60 min	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	71	See <a href="#">Section 4.4.2.1</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.1</a> .	71	Administer with CPM <sub>1200</sub> , see <a href="#">Section 4.4.2.1</a> .	

Cycle 5: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 6: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	TOPO mg	CPM <sub>250</sub> mg	DOXO mg	CPM <sub>1200</sub> mg	MESNA (with CPM <sub>1200</sub> ) mg/day <sup>%</sup>	Studies	Comments (Include any held doses, or dose modifications)
<b>Enter calculated dose above and actual dose administered below</b>											
		9	57	_____ mg	_____ mg	_____ mg				a, b, c, d	
			58		_____ mg	_____ mg					
			59		_____ mg	_____ mg					
			60		_____ mg	_____ mg					
			61		_____ mg	_____ mg					
		62-63 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		10	64	_____ mg						d	
			70							d*	
		11	71	_____ mg			_____ mg	_____ mg	_____ mg/day <sup>%</sup>	a, b, c, d,	
			72				_____ mg				
		73-74 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____								
		12	78	_____ mg						d	
			84	Local Control will follow Induction therapy. See <a href="#">Section 4.3</a> for Local Control options. See <a href="#">Section 7.1</a> for observations prior to Local Control.							

<sup>%</sup>- Enter total daily dose as mg/day by CI or intermittent infusion; <sup>#</sup>- 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. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**



#### 4.4.2.2 Administration Schedule for Consolidation Therapy (Weeks 1-22) for Regimen B

Ensure adequate time for healing following surgical local control.

Criteria to start Consolidation: ANC  $\geq$  750/ $\mu$ L and platelet  $\geq$  75,000/ $\mu$ L post nadir (without transfusion).  
Criteria to start subsequent cycles: ANC  $\geq$  750/ $\mu$ L and platelet  $\geq$  75,000/ $\mu$ L post nadir (without transfusion).  
The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq$  750/ $\mu$ L after the nadir but then falls the next cycle should be given despite ANC  $<$  750/ $\mu$ L. If a cycle of chemotherapy is delayed due to toxicity, see [Section 5.0](#) for criteria to resume chemotherapy. For patients receiving radiation therapy for local control, radiation therapy should begin concomitantly with Week 1 of consolidation therapy. DOXOrubicin should not be administered concurrently with radiation therapy.

**Note:** for children less than 1 year of age or weighing less than 10 kilograms, chemotherapy should be calculated by weight rather than by surface area. Dose/kilogram = dose/meter<sup>2</sup> divided by 30.

#### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

Day 1 of Weeks 1, 2, 7-10, 13-16, 19 and 20.

Dose: 1.5 mg/m<sup>2</sup>/dose. (Maximum dose is 2 mg.) For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.05 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. For intravenous use only- Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable.

#### **Topotecan: IV, infuse the diluted solution over 30 minutes**

Days 1-5 of Weeks 1, 7 and 15.

Dose: 0.75 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  1 year old, the dose is 0.025 mg/kg/dose.

#### **Cyclophosphamide:**

**Note that the VDC and the VTC combinations involve a different dose of CPM.**

#### **C<sub>250</sub> – dose administered during cycles of VTC: IV over 15-30 minutes**

Days 1-5 of Weeks 1, 7 and 15.

C<sub>250</sub> dose is 250 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  1 year old, the dose is 8.3 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.

Hydrate per institutional guidelines

#### **C<sub>1200</sub> – dose administered during cycles of VDC: IV over 30-60 minutes**

Day 1 of Weeks 9, 13 and 19.

C<sub>1200</sub> dose is 1200 mg/m<sup>2</sup>/dose. For patients  $<$  10 kg or  $<$  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 C<sub>1200</sub> (see below).

Hydrate per institutional guidelines

**Ifosfamide: IV, infuse the diluted solution over 1 hour**

Days 1-5 of Weeks 3, 5, 11, 17, and 21.

Dose: 1800 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 1 year old, the dose is 60 mg/kg/dose.

Mesna must be administered in conjunction with IFOS (see below).

Suggested hydration: Administer 3,000 mL/m<sup>2</sup>/day (125 mL/m<sup>2</sup>/hour) using fluid containing D<sub>5</sub>W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

**Mesna with IFOS**

Administer mesna by IV infusion or IV/PO on Days 1-5 of Weeks 3, 5, 11, 17, and 21.

Total IV Dose: 1080 mg/m<sup>2</sup>/day. For patients < 10 kg or < 1 year old, the IV dose is 36 mg/kg/day.

**Mesna with C<sub>1200</sub>**

Administer mesna by IV infusion or IV/PO on Day 1 of Weeks 9, 13 and 19.

Total IV Dose: 720 mg/m<sup>2</sup>/day. For patients < 10 kg or < 1 year old, the IV dose is 24 mg/kg/day.

**Mesna with C<sub>250</sub>**

Mesna is **not** required with C<sub>250</sub> containing cycles but may be used at investigator discretion. Initial Dose if required: 150 mg/m<sup>2</sup>/day. For patients <10 kg or < 1 year old, the IV dose is 5 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 oxazaphosphorine 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 with the oxazaphosphorine 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**. 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 ifosfamide/cyclophosphamide 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 oxazaphosphorine 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 oxazaphosphorine dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the oxazaphosphorine 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.

**Etoposide: IV, infuse the diluted solution over at least 1-2 hours**

Days 1-5 of Weeks 3, 5, 11, 17, and 21.

Dose: 100 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D<sub>5</sub>W. Avoid use of large volumes of D<sub>5</sub>W due to potential development of hyponatremia.

**Dexrazoxane: Slow IV Push (eg, over 5-15 minutes) given immediately prior to DOXOrubicin**

Days 1 and 2 of Weeks 13 and 19.

Dose: 375 mg/m<sup>2</sup>/dose (ie, 10 mg of dexrazoxane for every mg of DOXOrubicin). For patients < 10 kg or < 1 year old, the dose is 12.5 mg/kg/dose.

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

**DOXOrubicin: IV push/infusion over 1-15 minutes.** Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate.

Days 1 and 2 of Weeks 9, 13\* and 19\*.

Dose: 37.5 mg/m<sup>2</sup>/dose. For patients < 10 kg or < 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<sub>5</sub>W or 0.9% NaCl and that it is infused into a large vein.

**Note:** \* Administration must not exceed 15 minutes for Weeks 13 and 19 where dexrazoxane is administered immediately prior to DOXOrubicin doses. Longer infusions must not be used when DOXOrubicin is administered post-dexrazoxane.

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

**Growth Factor Support**

Begin myeloid growth factor support 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. If given daily, growth factor administration is to be continued in weeks where vinCRISTine is given alone, without regard to vinCRISTine administration.

**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 are provided on the following 6 pages. See [Section 7.1](#) for observations required at end of therapy.

<p><b>Consolidation Chemotherapy for Regimen B</b></p> <p>Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages.</p> <p><b>This page relates to Cycle 1 (Weeks 1 and 2) of Consolidation chemotherapy</b></p>	<p style="text-align: center;">_____ Patient name or initials</p> <p style="text-align: center;">_____ DOB</p>
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Begin Consolidation when ANC  $\geq$  750/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L (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.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	1 and 8	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.2</a>	a. History and Physical Exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* e. Imaging per Section 16.0  * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Topotecan (TOPO)	IV over 30 min	0.75 mg/m <sup>2</sup> /dose OR 0.025 mg/kg/dose for pt < 10 kg or <1 yo	1 - 5		
Cyclophosphamide (CPM <sub>250</sub> )	IV over 15-30 min	250 mg/m <sup>2</sup> /dose or 8.3 mg/kg/dose for pt < 10 kg or <1 yo	1 - 5	See <a href="#">Section 4.4.2.2</a>	

Cycle 1: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	TOPO mg	CPM <sub>250</sub> mg	Studies	Comments (Include any held doses, or dose modifications)
				<b>Enter calculated dose above and actual dose administered below</b>				
		1	1	_____ mg	_____ mg	_____ mg	a, b, c, d, e*	
			2		_____ mg	_____ mg		
			3		_____ mg	_____ mg		
			4		_____ mg	_____ mg		
			5		_____ mg	_____ mg		
			6-7 <sup>#</sup>	Growth factor used: _____ Dose: _____		Date of first dose: _____ Date of last dose: _____		
		2	8	_____ mg			d	
			14				d*	

**# 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 maps for Consolidation continue on the next 5 pages.

**SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

<p><b>Consolidation Chemotherapy for Regimen B</b>                  Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).                  This Therapy Delivery Map is on 6 pages.  <b>This page relates to Cycles 2 and 3 (Weeks 3 - 6) of Consolidation chemotherapy</b></p>	<p>_____ Patient name or initials</p> <p>_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If the ANC has risen to  $>$ 750/ $\mu$ L after nadir, but then falls Cycles 2 and 3 should be given despite ANC  $<$  750/ $\mu$ L. 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 <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	15-19 and 29-33	See <a href="#">Section 4.4.2.2</a> details.	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a> .	15-19 and 29-33	Administer with IFOS, see <a href="#">Section 4.4.2.2</a> .	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	15-19 and 29-33	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.2.2</a> .	

Cycle 2: Ht _____ cm Wt _____ kg BSA _____ m <sup>2</sup>				Cycle 3: Ht _____ cm Wt _____ kg BSA _____ m <sup>2</sup>				
Date Due	Date Given	Week	Day	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
<b>Enter calculated dose above and actual dose administered below</b>								
		3	15	_____ mg	_____ mg/day%	_____ mg	a, b, c, d	
			16	_____ mg	_____ mg/day%	_____ mg		
			17	_____ mg	_____ mg/day%	_____ mg		
			18	_____ mg	_____ mg/day%	_____ mg		
			19	_____ mg	_____ mg/day%	_____ mg		
		20-21 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____					
		4	22				d	
			28				d*	
		5	29	_____ mg	_____ mg/day%	_____ mg	a, b, c, d	
			30	_____ mg	_____ mg/day%	_____ mg		
			31	_____ mg	_____ mg/day%	_____ mg		
			32	_____ mg	_____ mg/day%	_____ mg		
			33	_____ mg	_____ mg/day%	_____ mg		
		34-35 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____					
		6	36				d	
			42				d*	

%- 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 maps for Consolidation continue on the next 4 pages.

SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE

<p><b>Consolidation Chemotherapy for Regimen B</b>                  Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).                  This Therapy Delivery Map is on 6 pages.  <b>This page relates to Cycles 4 and 5 (Weeks 7 - 10) of Consolidation chemotherapy</b></p>	<p style="text-align: center;">_____ Patient name or initials</p> <p style="text-align: center;">_____ DOB</p>
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Criteria to start each cycle: ANC  $\geq$  750/ $\mu$ L and platelet count  $\geq$  75,000/ $\mu$ L post nadir (without transfusion). If the ANC has risen to  $>$ 750/ $\mu$ L after nadir, but then falls Cycles 4 and 5 should be given despite ANC  $<$  750/ $\mu$ L. 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
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	43, 50, 57 and 64	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.2</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* e. ECG and ECHO or MUGA f. Imaging per <a href="#">Section 16.0</a> * See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Topotecan (TOPO)	IV over 30 min	0.75 mg/m <sup>2</sup> /dose OR 0.025 mg/kg/dose for pt < 10 kg or <1 yo	43 - 47		
Cyclophosphamide (CPM <sub>250</sub> )	IV over 15-30 min	250 mg/m <sup>2</sup> /dose OR 8.3 mg/kg/dose for pt < 10 kg or <1 yo	43 - 47	See <a href="#">Section 4.4.2.2</a> .	
DOXOrubicin (DOXO)	IV push/infusion over 1-15min <sup>&amp;</sup>	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for patients < 10 kg or <1 yo	57 and 58	<b>&amp;</b> - Short infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. See <a href="#">Section 4.4.2.2</a>	
Cyclophosphamide (CPM <sub>1200</sub> )	IV over 30-60 min	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	57	See <a href="#">Section 4.4.2.2</a>	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	57	Administer with CPM <sub>1200</sub> , see <a href="#">Section 4.4.2.2</a>	

Cycle 4: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 5: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	VCR mg	TOPO mg	CPM <sub>250</sub> mg	DOXO mg	CPM <sub>1200</sub> mg	MESNA (with CPM <sub>1200</sub> ) mg/day <sup>%</sup>	Studies	Comments (Include any held doses, or dose modifications)
<b>Enter calculated dose above and actual dose administered below</b>											
		7	43	_____ mg	_____ mg	_____ mg				a, b, c, d	
			44		_____ mg	_____ mg					
			45		_____ mg	_____ mg					
			46		_____ mg	_____ mg					
			47		_____ mg	_____ mg					
		48-49 <sup>#</sup>	Growth factor used:			Dose:		Date of first dose:		Date of last dose:	
		8	50	_____ mg						d	
			56							d*	
		9	57	_____ mg			_____ mg	_____ mg	_____ mg/day <sup>%</sup>	a, b, c, d, e	
			58				_____ mg				
		59-60 <sup>#</sup>	Growth factor used:			Dose:		Date of first dose:		Date of last dose:	
		10	64	_____ mg						d	
			70							d*, f	

<sup>%</sup>- Enter total daily dose as mg/day by CI or intermittent infusion;      <sup>#</sup>- 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 maps for Consolidation continue on the next 3 pages.

**SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**



**Consolidation Chemotherapy for Regimen B**

Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total).

This Therapy Delivery Map is on 6 pages.

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

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

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	71-75	See <a href="#">Section 4.4.2.2</a> for details.	a. History and physical exam
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	71-75	Administer with IFOS, see <a href="#">Section 4.4.2.2</a>	b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	71-75	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.2.2</a>	c. Urinalysis
VinCRiStine (VCR)	IV push over 1 min <sup>5</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	85 and 92	\$-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.2</a> .	d. CBC, Plt, Diff*
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5-15 min)	375 mg/m <sup>2</sup> /dose OR 12.5 mg/kg/dose for pt < 10 kg or <1 yo	85 and 86	Administer immediately prior to DOXO. Combined infusion time for DXRZ + DOXO should be $\leq$ 30 min. See <a href="#">Section 4.4.2.2</a>	* See <a href="#">Section 7.1</a> for details.
DOXOrubicin (DOXO)	IV push over 1-15 min	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for patients < 10 kg or <1 yo	85 and 86	See <a href="#">Section 4.4.2.2</a>	<b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Cyclophosphamide (CPM <sub>1200</sub> )	IV over 30-60 min	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	85	See <a href="#">Section 4.4.2.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	85	Administer with CPM <sub>1200</sub> , see <a href="#">Section 4.4.2.2</a> .	

Cycle 6: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>      Cycle 7: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week	Day	IFOS _____ mg	MESNA (with IFOS) _____ mg/day%	ETOP _____ mg	VCR _____ mg	DXRZ _____ mg	DOXO _____ mg	CPM <sub>1200</sub> _____ mg	MESNA (with CPM <sub>1200</sub> ) _____ mg/day%	Studies
<b>Enter calculated dose above and actual dose administered below</b>												
		11	71	_____ mg	_____ mg/day%	_____ mg						a, b, c, d
			72	_____ mg	_____ mg/day%	_____ mg						
			73	_____ mg	_____ mg/day%	_____ mg						
			74	_____ mg	_____ mg/day%	_____ mg						
			75	_____ mg	_____ mg/day%	_____ mg						
		76-77 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____									
		12	78									d
			84									d*
		13	85				_____ mg	_____ mg	_____ mg	_____ mg	_____ mg/day%	a, b, c, d,
			86					_____ mg	_____ mg			
		87-88 <sup>#</sup>	Growth factor used: _____ Dose: _____ Date of first dose: _____ Date of last dose: _____									
		14	92				_____ mg					d
			98									d*

%- 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 maps for Consolidation continue on the next 2 pages.

SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE



<b>Consolidation Chemotherapy for Regimen B</b> Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages. <b>This page relates to Cycles 8 and 9 (Weeks 15 - 18) of Consolidation chemotherapy</b>	_____ Patient name or initials _____
	_____ DOB _____

Criteria to start each cycle: ANC ≥ 750/ $\mu$ L and platelet count ≥ 75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to ≥ 750/ $\mu$ L after nadir but then falls, Cycles 8 and 9 should be given despite ANC < 750/ $\mu$ L. 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
VinCRiStine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	99 and 106	\$-or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.2</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff*
Topotecan (TOPO)	IV over 30 min	0.75 mg/m <sup>2</sup> /dose OR 0.025 mg/kg/dose for pt < 10 kg or <1 yo	99-103		
Cyclophosphamide (CPM <sub>250</sub> )	IV over 15-30 min	250 mg/m <sup>2</sup> /dose OR 8.3 mg/kg/dose for pt < 10 kg or <1 yo	99-103	See <a href="#">Section 4.4.2.2</a> .	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	113-117	See <a href="#">Section 4.4.2.2</a> for details.	* See <a href="#">Section 7.1</a> for details.
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	113-117	Administer with IFOS, see <a href="#">Section 4.4.2.2</a> .	<b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	113-117	Slow rate of administration if hypotension occurs. See <a href="#">Section 4.4.2.2</a> .	

Cycle 8: Ht _____ cm Wt _____ kg BSA _____ m <sup>2</sup>				Cycle 9: Ht _____ cm Wt _____ kg BSA _____ m <sup>2</sup>				Studies	Comments (Include any held doses, or dose modifications)	
Date Due	Date Given	Week	Day	VCR mg	TOPO mg	CPM <sub>250</sub> mg	IFOS mg			MESNA (with IFOS) mg/day%
<b>Enter calculated dose above and actual dose administered below</b>										
		15	99	mg	mg	mg				a, b, c, d
			100		mg	mg				
			101		mg	mg				
			102		mg	mg				
			103		mg	mg				
			104-105 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____
		16	106	mg						d
			112							d*
		17	113				mg	mg/day%	mg	a, b, c, d
			114				mg	mg/day%	mg	
			115				mg	mg/day%	mg	
			116				mg	mg/day%	mg	
			117				mg	mg/day%	mg	
			118-119 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____
		18	120							d
			126							d*

%-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 PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE

<b>Consolidation Chemotherapy for Regimen B</b> Consolidation Chemotherapy consists of 11 two-week cycles (154 days in total). This Therapy Delivery Map is on 6 pages. <b>This page relates to Cycles 10 and 11 (Weeks 19 - 22) of Consolidation chemotherapy</b>	_____ Patient name or initials _____
	_____ DOB

Criteria to start each cycle: ANC ≥ 750/ $\mu$ L and platelet count ≥ 75,000/ $\mu$ L post nadir (without transfusion). If ANC has risen to ≥ 750/ $\mu$ L after nadir but then falls, Cycles 10 and 11 should be given despite ANC < 750/ $\mu$ L. 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
VinCRISTine (VCR)	IV push over 1 min <sup>s</sup>	1.5 mg/m <sup>2</sup> /dose OR 0.05 mg/kg/dose for pt < 10 kg or <1 yo	127 and 134	§-Or infusion via minibag as per institutional policy. <b>Maximum dose: 2 mg.</b> See <a href="#">Section 4.4.2.2</a> .	a. History and physical exam b. Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT c. Urinalysis d. CBC, Plt, Diff* e. ECG and ECHO or MUGA *See <a href="#">Section 7.1</a> for details. <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Dexrazoxane (DXRZ)	Slow IV push (eg, over 5-15 min)	375 mg/m <sup>2</sup> /dose OR 12.5 mg/kg/dose for pt < 10 kg or <1 yo	127 and 128	Administer immediately prior to DOXO. The combined infusion time for DXRZ + DOXO should be ≤ 30 min.	
DOXOrubicin (DOXO)	IV push over 1-15 min	37.5 mg/m <sup>2</sup> /dose OR 1.25 mg/kg/dose for pt < 10 kg or <1 yo	127 and 128	See <a href="#">Section 4.4.2.2</a> .	
Cyclophosphamide (CPM <sub>1200</sub> )	IV over 30-60 min	1200 mg/m <sup>2</sup> /dose OR 40 mg/kg/dose for pt < 10 kg or <1 yo	127	See <a href="#">Section 4.4.2.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	127	Administer with CPM <sub>1200</sub> , see <a href="#">Section 4.4.2.2</a> .	
Ifosfamide (IFOS)	IV over 1 hour	1800 mg/m <sup>2</sup> /dose OR 60 mg/kg/dose for pt < 10 kg or <1 yo	141-145	See <a href="#">Section 4.4.2.2</a> for details.	
Mesna (MESNA)	IV or IV/PO	See <a href="#">Section 4.4.2.2</a>	141-145	Administer with IFOS, see <a href="#">Section 4.4.2.2</a> .	
Etoposide (ETOP)	IV over 1-2 hours	100 mg/m <sup>2</sup> /dose OR 3.3 mg/kg/dose for pt < 10 kg or <1 yo	141-145	Slow rate of administration if hypotension occurs.	

Cycle 10: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>
 Cycle 11: Ht \_\_\_\_\_ cm Wt \_\_\_\_\_ kg BSA \_\_\_\_\_ m<sup>2</sup>

Date Due	Date Given	Week k	Day	VCR mg	DEXRA mg	DOXO mg	CPM <sub>1200</sub> mg	MESNA (with CPM <sub>1200</sub> ) mg/day%	IFOS mg	MESNA (with IFOS) mg/day%	ETOP mg	Studies
<b>Enter calculated dose above and actual dose administered below</b>												
		19	127	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg/day%				a, b, c, d, e
			128		_____ mg	_____ mg						
			129-130 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____		
		20	134	_____ mg								d
			140									d*
		21	141						_____ mg	_____ mg/day%	_____ mg	a, b, c, d
			142						_____ mg	_____ mg/day%	_____ mg	
			143						_____ mg	_____ mg/day%	_____ mg	
			144						_____ mg	_____ mg/day%	_____ mg	
			145						_____ mg	_____ mg/day%	_____ mg	
			146-147 <sup>#</sup>	Growth factor used: _____		Dose: _____		Date of first dose: _____		Date of last dose: _____		
		22	148									d
			154	<b>End of Therapy. See <a href="#">Section 7.1</a> and <a href="#">Section 16.0</a> for required observations and imaging at end of therapy</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](#)  
**SEE PROTOCOL [SECTION 5.0](#) FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE.**

## 5.0 DOSE MODIFICATIONS FOR TOXICITIES

### 5.1 Slow Blood Count Recovery

Recovery of absolute neutrophil count to  $\geq 750/\mu\text{L}$ , and platelet count to  $\geq 75,000/\mu\text{L}$  is required at the start of each myelosuppressive cycle. The ANC often falls after discontinuing myeloid growth factor support. If the ANC has risen to  $\geq 750/\mu\text{L}$  after the nadir but then falls the next cycle can be given despite ANC  $< 750/\mu\text{L}$ . If a cycle is delayed for more than 7 days, the next time the chemotherapy combination causing the delay is administered doses of myelosuppressive agents should be reduced by 25%. If cycles are still delayed, a further 25% reduction in dose may be made for a total of 50% reduction. Re-escalation should be attempted if subsequent cycles do not result in treatment delay. If a particular cycle is delayed for more than 14 days, the administered doses of the myelosuppressive agents for the following cycle of chemotherapy should be decreased by 25%. Doses may be re-escalated as tolerated for subsequent cycles. Only vinCRistine is not considered myelosuppressive. Vincristine doses at weeks where vincristine is given alone should be given regardless of blood counts.

### 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<sup>2</sup>, 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  $\leq 2$  mg/dL (or  $< 0.6$  mmol/L) without supplementation on measurements taken before the next ifosfamide cycle.

Modify therapy as follows:

**Delete ifosfamide from all subsequent cycles and substitute cyclophosphamide  $440$  mg/m<sup>2</sup> per day or  $15$  mg/kg/day for those  $< 10$  kg or  $< 1$  year old with mesna uroprotection (60% of the cyclophosphamide dose =  $265$  mg/m<sup>2</sup>/day or  $9$  mg/kg/day for those  $< 10$  kg or  $< 1$  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<sup>2</sup> give full dose, for CrCl of 15-50 mL/min/1.73m<sup>2</sup> give 75% of the dose (a 25% dose reduction). Etoposide should be held if CrCl < 15 mL/min/1.73m<sup>2</sup>.

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

### 5.2.4 Topotecan

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 > 40 mL/min/1.73 m<sup>2</sup> give full dose, for CrCl of 20-40 mL/min/1.73 m<sup>2</sup> give 50% of the dose (a 50% dose reduction). Topotecan should be held if CrCL <20 mL/min/1.73 m<sup>2</sup>

## 5.3 **Cardiac Toxicity**

### 5.3.1 Monitoring

Electrocardiogram for evaluation of QTc and echocardiogram with determination of shortening fraction or MUGA (radionuclide angiogram) for ejection fraction is to be obtained before treatment, prior to 3<sup>rd</sup> and 5<sup>th</sup> doxorubicin containing cycle, and at the completion of therapy. Use the same test each time for consistency in evaluation.

### 5.3.2 Abnormalities

If prolongation of the QTc interval (> 0.48 sec), a decrease in the ejection fraction to < 50%, or a decrease of 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, 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 dactinomycin containing chemotherapy courses should be administered on a 21 day cycle (and not 14 days) since interval compression is not possible when dactinomycin is administered. No changes 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

**Vincristine neurotoxicity may occur more frequently on this trial as a result of the increased exposure to vincristine.**

Grade 1 and 2 neurotoxicity requires no dose modification. For Grades 3 and 4 (interfering with activities of daily living) hold 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 ( $\leq$  Grade 2) may receive ifosfamide in subsequent cycles. If neurotoxicity > Grade 2 occurs or symptoms are prolonged, delete ifosfamide from all subsequent cycles and substitute cyclophosphamide 440 mg/m<sup>2</sup> per day with mesna uroprotection 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 such as 0.12% chlorhexidine gluconate should be considered. Medications include the following:

Glutamine: Oral swish-and-swallow glutamine suspension at 2 gram/m<sup>2</sup> 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 q.i.d. 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.

For Grade 3 or 4 mucositis which persists more than 15 days after a vincristine-topotecan-cyclophosphamide cycle, reduce the topotecan dose 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<sup>2</sup>/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<sup>2</sup>/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 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 until hematuria clears. When hematuria clears, restart at 50% of the previous cyclophosphamide/ifosfamide dose. Use hydration of 3500-4000 mL/m<sup>2</sup>/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. Reinstigate cyclophosphamide/ifosfamide at 50% of the initial dose, with hydration of 3500-4000 mL/m<sup>2</sup>/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 or until resolved to Grade 1	Delay 1 week or until resolved to Grade 1	Delay 1 week or until resolved to Grade 1

## 5.8 Dermatologic Toxicity

### 5.8.1 Nails

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

### 5.8.2 Palms and Soles

A few patients may 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 Any Other Grade 3 or 4 Toxicities

Delay therapy 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.

### 5.10 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.

## 6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group" at: [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp) under Standard Sections for Protocols.

## 7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).



**7.1 Required/Recommended Clinical, Laboratory and Disease Evaluations**

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

Observation	Study Entry	During Chemotherapy	Prior to Local Control	Post Local Control and post Cycle 5 Consolidation	Off protocol therapy/End of Therapy
History and Physical Exam	X	X <sup>1</sup>	X		X
Biopsy	X				
Electrolytes, creatinine, bicarbonate, phosphorus, calcium, bilirubin, AST, ALT	X	X <sup>1</sup>			
LDH	X Recommended				
Performance Status	X				
Urinalysis	X	X <sup>1</sup>	X		
CBC, Plt, Diff.	X	X <sup>2</sup>	X		
Bilateral Bone Marrow Biopsy and Aspirate	X <sup>5</sup>				
Whole Body Bone Scintigraphy	X <sup>3</sup>		X <sup>4</sup>		X <sup>#</sup>
PET Scan (See <a href="#">Section 16.0</a> ) <sup>5</sup>	X Recommended		X <sup>4</sup> Recommended		X <sup>#</sup>
Radiograph (2 views of primary site) <sup>6</sup>	X		X <sup>4</sup>	X <sup>#</sup>	X <sup>#</sup>
MRI with gadolinium (primary site) <sup>7</sup>	X <sup>3</sup>		X <sup>4</sup>	X <sup>8, #</sup>	X <sup>#</sup>
CT Scan of Chest <sup>9</sup>	X		X <sup>4</sup>	X <sup>#</sup>	X <sup>#</sup>
Chest X-Ray (PA and Lateral)	X Recommended				
ECG and ECHO or MUGA	X	X <sup>10</sup>			X
Pregnancy test <sup>11</sup>	X				
Orthopedic functional assessment <sup>12</sup>					X Recommended

- 1 Obtain prior to each cycle.
  - 2 Obtain on Day 1 and 8 of each cycle. Obtain blood counts every Monday, Wednesday and Friday (or 3 other non-consecutive days per week) after Day 12, until the criteria for starting the next cycle are satisfied
  - 3 Preferably pre-biopsy.
  - 4 Obtain within 4 weeks prior to primary tumor treatment (local control).
  - 5 Functional imaging with FDG- PET is recommended, if available at the institution. For patients having PET- SUV<sub>max</sub> will be reported and images submitted (see [Section 16.1](#))
  - 6 Obtain for bone tumors of extremity and pelvic sites at study entry.
  - 7 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 may be limited to plain radiographs. CT scan with contrast may be considered in place of MRI for post local control and end of therapy evaluation. For chest wall primaries –MRI is strongly encouraged to visualize soft tissue extent but not required. If MRI is not performed, the chest wall primary site should be adequately imaged by CT.
  - 8 MRI for patients having surgery as primary control may be done anytime between surgery and recovery from Consolidation Cycle 5. For patients receiving radiation as primary control obtain MRI at the end of Consolidation therapy.
  - 9 CT Scan of the chest should use spiral technique (if available) with a single breathhold, for patients able to cooperate.
  - 10 Electrocardiogram for evaluation of QTc and echocardiogram with determination of shortening fraction or MUGA (radionuclide angiogram) for ejection fraction is to be obtained prior to 3<sup>rd</sup> and 5<sup>th</sup> doxorubicin containing cycle. Use the same test each time for consistency in evaluation.
  - 11 Pregnancy test required prior to study enrollment for females of childbearing potential only.
  - 12 Regular assessment should include range of motion, limb length assessment, gait and pain assessment.
- \$ Unilateral bone marrow aspirate and biopsy is sufficient from the contralateral side for pelvic tumors that involve the ilium.
- # See [Section 16.0](#) for complete details of the required imaging and also recommended imaging.

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

## 7.2 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. Refer to COG Late Effects Guidelines for recommended post treatment follow-up at: <http://www.survivorshipguidelines.org/>.

### 7.2.1 Suggested Observations Following Completion of Protocol Therapy

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
CBC with diff, platelet count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest Radiograph (PA and Lateral)	X	X	X	X	X	X	X	X		X		X	X	X	X	X
CT Chest <sup>4</sup>																
Radiograph <sup>1</sup> (Primary site)	X	X	X	X	X	X	X	X		X		X	X	X	X	X
MRI or CT <sup>2</sup> (Primary Site)	X	X	X	X		X		X		X		X	X	X	X	X
Whole Body Bone Scintigraphy <sup>3</sup>																
FDG- PET <sup>3</sup>																
Electrolytes, creatinine, bicarbonate, phosphorus, calcium	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA				X				X				X		X		X

1 Obtain for bone tumors of extremity and pelvic sites at study entry

2 Obtain for non-bony, soft tissue tumor not readily assessed by physical examination or abnormal symptoms or abnormal imaging.

3 Recommended only in case of abnormal symptoms or abnormal imaging

4 Recommended if previous abnormalities, abnormal chest X-ray or symptoms

### 7.2.2 Relapse

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

**8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA**

**8.1 Criteria for Removal from Protocol Therapy**

- a) Progressive disease.
- b) Disease detected at new sites
- c) Biopsy positive residual disease after all local control measures completed
- 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 the date the patient was enrolled on the study.

**9.0 STATISTICAL CONSIDERATIONS**

**9.1 Patient Accrual and Expected Outcome and Expected Duration of Trial**

Based on past studies, COG institutions will enroll approximately 140 patients with localized Ewing Sarcoma annually. The sample size calculations are based on the model of Barthel [et al.](#)<sup>53</sup>

The aggregate EFS outcome of AEWS0031 current to March 2008 is summarized in the table below:

Time Since Enrollment (Years)	Estimated Aggregate Event-Free Survival	95% Confidence Interval
1	0.94	0.92-0.96
2	0.81	0.78-0.84
3	0.75	0.71-0.79
4	0.73	0.68-0.76
5	0.70	0.65-0.75

Patients will be enrolled for 54 months (4.5 years) and the last patient enrolled will be followed for an additional 1 year. This will provide approximately 630 patients with at least 1 year of follow-up for the last patient enrolled. We anticipate we will require at most 693 patients to account for a maximum ineligibility rate of 10%. The statistical characteristics associated with this design are provided below.

Randomization will be stratified according to age and primary tumor site. Age will be stratified as: (1) seventeen years or less at age at diagnosis; or (2) eighteen years of age or greater at diagnosis. Primary site will be stratified as: (1) pelvic primary; (2) non-pelvic primary; or (3) extra-osseous site.

## 9.2 Statistical Analysis Methods

### 9.2.1 Primary Outcome Comparisons

The primary endpoint will be event free survival (EFS). This is defined as the time from study enrollment to disease progression, appearance of disease at sites considered previously uninvolved, diagnosis of a second malignant neoplasm, death or last patient contact, whichever occurs first. Disease progression, appearance of disease at sites considered previously uninvolved, diagnosis of a second malignant neoplasm and death are considered analytic events for the purposes of comparing the two regimens with respect to EFS. In all other cases, the patient will be considered censored at last contact.

The endpoint for the comparison between the two regimens to address aim 1.2.1 will be survival from study enrollment. Survival is defined as the time from study enrollment to death or last patient contact, whichever occurs first. Death, regardless of cause, is considered an event for the purposes of comparing the two regimens with respect to survival. In all other cases, the patient will be considered censored at last contact.

The therapy containing topotecan will be considered the experimental regimen. This regimen has increased intensity when compared with the intensively timed non-VTC therapy ('standard therapy') used in this protocol. The experimental regimen will be identified as the one to carry forward only if that regimen reduces the risk for EFS-event significantly using a 1-sided test of size 0.05. Patients will be enrolled for 4.5 years and followed for an additional 1 year. This will provide approximately 630 patients with at least 1 year of follow-up for the last patient enrolled. With these accrual characteristics, we will be able to detect an increase from 70% to 80% long-term EFS with approximately 80% power. This corresponds to a relative hazard rate of 0.63 for a proportional hazards model for EFS. The primary analysis will include all eligible patients and outcome will be assigned to the patient's randomized regimen.

### 9.2.2 Interim Monitoring

We will monitor for emerging differences between the randomized treatments using the Lan and DeMets spending function approach. The test statistic used for this for interim monitoring will be:

$$\frac{\ln \{ \text{Hazard Ratio for EFS-event for Experimental: Standard Therapy} \}}{\sqrt{\text{Estimated Variance of the Hazard Ratio}}}$$

Where the hazard ratio is estimated from a proportional hazards regression stratified according to the factors by which randomization is stratified. The spending function will be  $\alpha(t)=at^2$ . We will monitor for differences in EFS across the regimens at the times shown below. The projected expected information times are presented in the tables as well.

Monitoring Time (Years Since Study Opening)	Expected Information Time	Lower Monitoring Boundary	Cumulative $\alpha$
2	0.21	-2.85	0.0022
3	0.43	-2.41	0.0071
4	0.65	-2.13	0.021
5.5 (Final Analysis)	1.0	-1.74	0.05

At each of the monitoring times above, we will calculate the conditional probability the log-rank test statistic will exceed 1.74 in absolute value at the projected final analysis time of the study. The model used for the EFS-failure time for all patients who have not experienced an EFS event by the time of analysis will be that associated with outcome table quoted above for those randomized to the experimental regimen and will be  $S(t) = [S_{\text{Standard}}(t)]^{0.63}$ , viz., the alternative as specified in [Section 9.2](#). If the conditional

probability of rejection of the null hypothesis is less than 5% at any monitoring time, the study will be identified for possible closure of accrual.

#### *Monitoring the Incidence of Second Malignant Neoplasms*

At the time of the next two planned interim monitoring occurrences, which will occur at 43% and 65% of the expected information, the aggregated SMN sub-distribution for AEWS1031 will be compared with the aggregated SMN sub-distribution for AEWS0031 using the methods proposed by Fine and Gray.<sup>54</sup> If the one-sided p-value is 0.05 or less for the test  $H_0$ : the relative sub-distribution hazard ratio (SHR) for SMN for AEWS1031 relative to AEWS0031 is 1 v. the alternative hypothesis  $H_1$ : the relative sub-distribution hazard ratio (SHR) for SMN for AEWS1031 relative to AEWS0031 is greater than 1, AEWS1031 will be considered for possible modification, including termination of enrollment to AEWS1031.

The dataset for AEWS0031 will be taken to be that used for the publication Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier E, Marcus K, Sailer S, Healey JH, Dormans JP and Weiss AR Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group. J Clin Oncol 30: 4148-54. The cumulative incidences of SMN for the two regimens that comprised AEWS0031 were very similar and, therefore, the aggregate cohort for AEWS0031 is an appropriate comparator for AEWS1031.

#### 9.2.3 Outcome Comparisons for Correlative Science Objectives

The relative risk for death and the naïve p-value associated with the null hypothesis  $H_0$ : relative risk for death is 1 will be estimated using the stratified partial likelihood for the relative risk regression model accounting for the factors used to stratify randomization at the time full information is obtained for the EFS comparison. The survival analysis comparison will be conducted again once the observed number of death-events reaches the expected number of EFS-events under the primary null hypothesis.

Event free survival after local control will be the endpoint for the analysis of the prognostic effect of histological response. Only patients who received surgery as part of local control will be considered for that endpoint, as described below. Event free survival after local control will be the endpoint for the analysis of the prognostic effect of PET-determined response. All patients who receive local control therapy, regardless of the modalities employed, will be considered for this analysis. Methods for censored survival data, including but not limited to log-rank comparisons and proportional hazards regression modeling will be used to assess prognostic significance.

*Assessment of the Prognostic Significance of Tumor Volume at Study Enrollment:* At enrollment, patients should have three tumor dimensions available, either by CT or MRI. Tumor volume will be calculated centrally using three perpendicular tumor dimensions according to the formula:

$$Volume\ in\ mm^3 = \frac{4\pi}{3} \frac{d_1}{2} \frac{d_2}{2} \frac{d_3}{2} = 0.52d_1d_2d_3$$

The same formula will be used for all tumor shapes.

Tumor volume will be calculated according to the formula above from tumor measurements provided by institutional investigators. Event-free survival will be used as the outcome measure. Data from INT-0091 indicated that the relative risk for EFS-event associated with tumors 200 ml or greater compared with tumors 199 ml or less is between two and three. The probabilities of identifying tumors of at least 200 ml as associated with increased risk using a two sided log-rank test of size 0.05 as a function of the percent of patients for whom measurements can be obtained are described below. For the table below, we assume conservatively that 35% of patients will have tumors of 200 ml or greater in estimated volume. The long-term EFS for patients with small tumors is assumed to be 80%, the target EFS for the experimental therapy. We plan to conduct the analysis concurrently with the final analysis for the primary study aim.

Probability of Identifying Tumors of 200 ml or Greater At Enrollment as Associated with Poor Prognosis As a Function of Percent of Patients With Three Tumor Dimensions Available and Relative Risk Associated with 'Large' Tumor Volume

Relative Risk	Percent of Patients For Whom Tumor Volume Can Be Determined			
	50	60	70	80
1.5	0.42	0.49	0.55	0.60
2.0	0.89	0.94	0.97	0.98
2.5	0.99	>0.99	>0.99	>0.99

*Assessment of the Prognostic Significance of Necrosis Grading after 'Induction' Chemotherapy:* Extent of tumor necrosis will be obtained at time of local therapy for patients who have surgical resection of their tumor. The necrosis grading will be correlated with risk for EFS-event. All patients who receive surgery as the only local control modality will be considered for this outcome. Also, patients who receive surgery and radiation therapy as local control therapy will be considered for this analysis, provided the radiation therapy has occurred after surgery. Event-free survival post local control will be used as the outcome measure. Data from INT-0154 indicates approximately 60% of patients will be included in this cohort of patients. The primary analysis will be to segregate patients into two groups according to 'good' necrosis grading (less than 10% viable tumor in the resection specimen) and 'standard' necrosis grading (10% or more viable tumor in the resection specimen). The long-term EFS for patients with good necrosis grading is assumed to be 80%, the target EFS for the experimental therapy. The probabilities of identifying patients with 'standard' necrosis grading as associated with increased risk using a two sided log-rank test of size 0.05 as a function of the percent of patients with 'standard' necrosis grading and its associated relative risk are described below.

Probability of Identifying Patients with 'Standard' Necrosis Grading as Having Poor Prognosis As a Function of Percent of Patients With 'Standard' Necrosis Grading and Relative Risk Associated with 'Standard' Necrosis Grading

Relative Risk	Percent of Patients with 'Good' Necrosis Grading			
	60	50	40	30
1.5	0.48	0.49	0.46	0.40
2.0	0.94	0.94	0.91	0.86
2.5	>0.99	>0.99	>0.99	0.99

*Assessment of the Prognostic Significance of Radiological Response by Positron Emission Tomography (PET) and Disappearance of Soft Tissue Mass:* Radiological data prior to treatment and prior to local therapy, including disappearance of soft tissue mass and PET characteristics (SUV prior to treatment and prior to local control therapy) will be collected and correlated with risk for EFS-event. Radiological response of soft tissue component of mass to induction chemotherapy will be obtained from institutional reports.

Institutions using clinical PET scanning as functional imaging in evaluation and response to treatment will be asked to submit data at start of therapy and prior to local treatment (prior to Week 13) as part of the patients scheduled evaluation. This will be an optional element and PET scanning will not be required for study entry. However, it is recognized as an acceptable evaluation tool being used by many institutions at this time and is expected to increase in use over the upcoming years. Guidelines for image acquisition and processing, as developed by ACRIN will be included for institutional use. Institutionally reported SUV values will be used. Electronic copies of images will be reviewed centrally for study purposes by study imaging representative. An interim evaluation of this objective will be performed and this objective deleted if it appears futile.



All patients who survive event free to the time of local control will be considered for this outcome. Event-free survival post local control will be used as the outcome measure. Data from INT-0154 indicate approximately 95% of patients will have conventional imaging study data available for the assessment of radiological response to induction therapy. We posit the long-term post-local-control EFS in the CR group of patients will be 80%. The primary analysis will be to segregate patients into two groups according to complete v. not complete soft tissue response. The probabilities of identifying patients with CR as associated with decreased risk for EFS-event when compared with patients with less-than-CR using a two sided log-rank test of size 0.05 as a function of the percent of patients with standard response and its associated relative risk are described below.

Probability of Identifying Patients with Less than CR as Having Poor Prognosis As a Function of Percent of Patients With Less than CR and Relative Risk Associated with Less than CR Radiographic Response

Relative Risk	Percent of Patients with Less than CR Radiographic Response			
	40	50	60	70
1.5	0.48	0.49	0.46	0.40
2.0	0.94	0.94	0.91	0.86
2.5	>0.99	>0.99	>0.99	0.99

Not all institutions will comply with the guidelines for PET because of availability of the requisite equipment or funding issues. We will monitor the number of patients who participate in the PET analysis each time an interim monitoring report is prepared. If there is evidence that significantly fewer than 34% of all patients enrolled will participate in the PET evaluation, that component of the trial will be considered for termination. If 34% of patients participate in the PET investigation (approximately 214 patients total), the power to detect an increase in risk for event associated with ‘standard’ response under a ‘favorable’ statistical configuration (50% of patients have a ‘standard’ response and the relative risk associated with a ‘standard’ response is 2.5) will be 0.95.

The analysis of the prognostic impact of  $SUV_{max}$  derived from PET scanning done at enrollment will be assessed on EFS and an analysis of the prognostic impact of  $SUV_{max}$  derived from PET scanning done prior to the local control phase will be carried out on EFS post local control therapy. The study population will be divided into two groups based on amount of uptake (high versus standard, generally as above v. at or below the median  $SUV_{max}$ ). These groups will be compared using the log-rank test. The expected statistical properties of this strategy are similar to those given in the tables given above.

*Assessment of the Prognostic Significance of Type of Local Control Therapy on Risk for EFS-Event:* All patients who survive event-free to the time of local control will be considered for this outcome. Event-free survival post local control will be used as the outcome measure. Data from INT-0154 indicate approximately 95% of patients will complete induction therapy. The primary analysis will be to segregate patients into three groups according to surgery only v. radiation therapy only v. surgery and radiation therapy as local control measures. Data from AEWS0031 indicate this will occur in the ratio of approximately 0.50:0.20:0.30. An omnibus log-rank test of size 0.05 will be used to assess whether there are differences associated with local control modality. Since site of tumor is related to both risk for EFS event and type of local control modality employed, the analysis will be stratified according to primary site of tumor as pelvis v. bone but not pelvis v. extra-osseous site. The analysis for this study goal will be conducted at the time of the analysis for the primary study aim. The probability the omnibus test of equality of risk across types of local control, as a function of the relative risks associated with each local control type, is provided below. The long-term EFS associated with the surgery-only group is assumed to be 80%.



Probability of Identifying A Pattern of Risk Significantly Different than Equal Risk Across Local Modality Types as a Function of the True Relative Risks of EFS-Event

Scenario Number	Type of Local Control	Relative Risk for EFS-Event	Power
1	Surgery Only	1	0.968
	Radiation Therapy Only	2	
	Surgery Plus Radiation Therapy	2	
2	Surgery Only	1	0.9189
	Radiation Therapy Only	1.5	
	Surgery Plus Radiation Therapy	2	
3	Surgery Only	1	0.507
	Radiation Therapy Only	1.5	
	Surgery Plus Radiation Therapy	1.5	

Evaluate the effect of local therapy modality (surgery, radiotherapy or a combination) as well as the type of surgical reconstruction on musculoskeletal complications: Any CTCAE version 4.0 Grade 2 or higher musculoskeletal events, or surgery required to treat a complication of local therapy that occur within three months of the date of the first local control procedure will be considered a musculoskeletal event (ME). Any patient who experiences a ME at any time during the three months following completion of local control therapy or does not experience an ME and completes three months of post-local-control therapy follow-up will be considered in the analysis of this outcome measure. The proportion of patients who experience any ME will be compared across the three regimens using logistic regression where the p-value to indicate a statistically significant relationship will be 0.05. Size of tumor at the time of local control may be a strong confounding variable, as it is related to the approach to local therapy and may be related to the occurrence of ME after surgery. The logistic analysis will be adjusted for size of the tumor after enrollment but before the first local control modality is executed. Both the longest dimension and size relative to initial measurement will be employed.

As with the analysis of risk of EFS-event according to local control type, we expect 95% of patients enrolled will contribute to the analysis of ME. The proportion of patients who will receive surgery only as local control therapy and who will experience an ME has not been investigated to date. The power characteristics of the proposed test of proportions is presented below using various ME rates associated with the types of local control considered.

Probability of Identifying A Pattern of Risk for ME Significantly Different From That of Equal Risk Across Local Modality Types as a Function of the True Probabilities of ME

Scenario Number	Type of Local Control	Relative Risk for EFS-Event	Power
1	Surgery Only	0.10	0.787
	Radiation Therapy Only	0.15	
	Surgery Plus Radiation Therapy	0.20	
2	Surgery Only	0.20	0.93
	Radiation Therapy Only	0.30	
	Surgery Plus Radiation Therapy	0.35	
3	Surgery Only	0.10	0.904
	Radiation Therapy Only	0.20	
	Surgery Plus Radiation Therapy	0.20	

### 9.3 Gender and Minority Accrual Estimates

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

<b>Accrual Targets</b>			
<b>Ethnic Category</b>	<b>Sex/Gender</b>		
	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	28	34	62
Not Hispanic or Latino	289	342	631
<b>Ethnic Category: Total of all subjects</b>	317	376	*693
<b>Racial Category</b>			
American Indian or Alaskan Native	3	3	6
Asian	8	7	15
Black or African American	8	12	20
Native Hawaiian or other Pacific Islander	7	2	9
White	291	352	643
<b>Racial Category: Total of all subjects</b>	317	376	*693

\* These totals must agree

This distribution was derived from AEWS0031.

## 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 web site ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)). Additionally, toxicities are to be reported on the appropriate data collection forms.

Please note: ‘CTCAE v4.0’ is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

### 10.2 Response Criteria for Patients with Solid Tumors

This study will use three dimensional measurements of the primary tumor rather than single dimension as used in RECIST. Regional nodal disease if present will be evaluated by single dimension measurement. The value of 3D volume measurement has already been substantiated in several studies.<sup>55-57</sup> In addition, bone tumors, which will constitute the majority of tumors on this trial, are considered non-measurable according to RECIST guidelines. The evaluation of response in multiple lesions as outlined in RECIST will not apply as this study is limited to patients with localized disease only.

#### 10.2.1 Primary Tumor Measurement

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

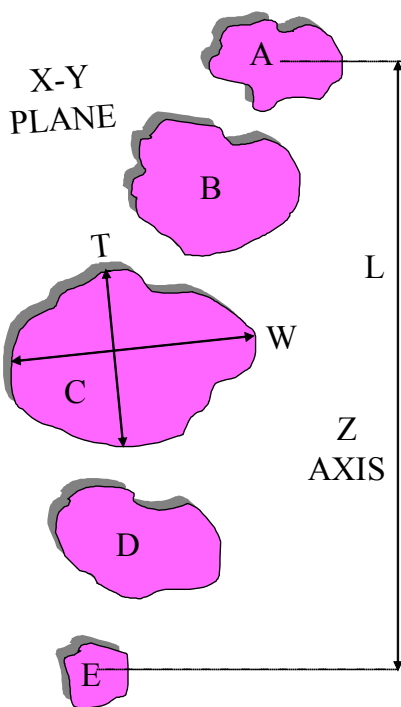
1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle).

2. CT slice thickness should be 5mm 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.

#### 10.2.1.2 Magnetic resonance imaging (MRI)

1. Axial images and at least one additional plane are acquired. At least two pulse sequences, such as T1, T2, STIR, or FLAIR-weighted, or in-phase/out-of-phase 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.
2. 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).

10.2.1.3 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  $\text{mm}^3 = \pi/6 \cdot (d_1 \cdot d_2 \cdot d_3) = (\text{AP} \times \text{transverse} \times \text{longitudinal}) \times 0.5$ . 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 =  $0.5 L \times W \times T$
- The same modality and measurement method used in the initial imaging should be used in follow ups

#### 10.2.2 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<sup>58</sup>:

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.

### 10.2.3 Local-regional Lymph Node Disease

**Pathologic lymph nodes:** Other than the primary tumor the only other lesions that will be followed radiographically are local-regional lymph nodes in which tumor involvement has been biopsy proven. Lymph nodes that can be accurately measured in the axial plane (do not use the longitudinal dimension, even though it may be the largest diameter) and whose longest diameter in the axial plane is  $\geq 1.0$  cm will be considered to be pathologic and will be followed. The local investigator will identify up to a total of 5 pathologic lymph nodes. If there are more than 5 total pathologic lymph nodes, then those that are the most easily measured and amenable to reliable, reproducible, follow-up measurement should be chosen. The nodes must be measured in 2 planes; the longest diameter and the axis perpendicular to it.

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

### 10.2.4 Response of pathologic lymph nodes:

The response of lymph nodes will be based on the report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas.<sup>59</sup>

Complete Response:

- 1) All nodes measure  $< 1.0$  cm OR
- 2) All lymph nodes with 1.5cm maximal transverse diameter must decrease to less than 1.5 cm, and all nodes 1.1-1.5 cm in maximal transverse diameter before treatment must decrease to 1.0 cm or less OR
- 3) More than 75% decrease in the sum of the products of the two dimensions for each node (SPD)

Partial Response:

At least 50% decrease in SPD

Stable Disease:

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest disease measurement since the treatment started

Progressive Disease:

At least 50% increase from nadir in the SPD

### 10.2.5 Overall response assessment

The overall response assessment takes into account response in the primary tumor, associated pathologic lymph nodes, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of the primary tumor, adenopathy and new lesions in the preceding columns.

<b>Primary tumor</b>	<b>Lymph nodes</b>	<b>New Lesions</b>	<b>Overall Response</b>
CR	CR	No	CR
CR	PR/SD	No	PR
PR	PR/SD	No	PR
SD	Non-PD	No	SD
PD	Any	Any*	PD
Any	PD	Any*	PD
Any	Any	Yes*	PD

\*Solitary, small (< 1cm) and osseous sites of suspected new disease should be biopsied

## 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

### 11.2 Determination of Reporting Requirements

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

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

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

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

### 11.3 Reporting of Adverse Events for Commercial Agents - AdEERS abbreviated pathway

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

- COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE

**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.**

**AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days<sup>1</sup>**

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

<sup>1</sup>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 AdEERS.

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.

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

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

**11.4 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 AdEERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. All events requiring AdEERS reporting also need to be reported on the AE CRF. In addition, for this study, routine reporting will include:

- Grade 2 and higher musculoskeletal adverse events occurring within 3 months of completion of local therapy.

**12.0 RECORDS AND REPORTING**

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

Any tumor that involves bone or is in contact with bone is classified as and should be reported as an osseous primary. All others should be reported as extra-osseous primaries.

## 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.

## 13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

COG member institutions are encouraged to enroll patients on a specimen collection study (such as AEWS07B1 or on any successor biology study). Surgeons, treating team and pathologists should review specimen requirements for tissue collection and handling for that study if applicable 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. 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. Tissue from 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.



### 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. Principles of biopsy should be followed. Imaging, in particular MRI, should be obtained prior to biopsy. 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 for Soft Tissue Tumors

Clinical and imaging evaluation of regional lymph nodes should be performed before therapy begins. Pathologic evaluation of clinically suspicious nodes should be performed. Regional node sampling in the absence of clinical or radiographic abnormality is not necessary, except in soft tissue primary tumors, which may prove to be rhabdomyosarcomas on detailed pathologic evaluation. 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. 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**

### 13.3.1

Tumors arising in the extremities are usually situated in recognized anatomical compartments.<sup>60,61</sup> 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. In some institutions, where available, a PET scan is indicated for evaluation. Furthermore, the extent of the lesions is usually dramatically reduced following induction chemotherapy, making lesions which 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.<sup>62,63</sup> 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 less 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.

#### 13.3.2 Patient Eligibility

Having completed the initial phase of chemotherapy, the effect of induction chemotherapy on the primary lesion will be evaluated by plain radiographs, bone scan, MRI and PET scan where available. 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 12 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/PNET to preoperative chemotherapy is usually 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.

At the end of Consolidation chemotherapy, the treatment team should review residual masses and consider surgical resection. If definitive radiation is to be used first, followed by "late" consideration of surgery, the delayed surgery should be done after the end of chemotherapy. 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 below knee amputation. 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. 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.

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, yet it is the site where removal of residual bulk disease may have the greatest impact relative to local control and survival. 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. Lesions which are more extensive or have a poorer response to chemotherapy may become resectable after radiation, and one should consider at the completion of consolidation chemotherapy. Surgical complication rates are high particularly when they follow high dose radiotherapy. Delays in resumption of chemotherapy may contribute to the poor prognosis of pelvic Ewing tumors. Radiotherapy planning can be difficult due to the proximity to vital organs such as bowel and bladder. During surgery expandable spacers can sometimes be inserted which when inflated can help push bladder and bowel out of the way. Ovaries can occasionally be transplanted out of the radiation field.

Lesions in the periacetabular area require careful consideration. There are no good reconstruction options for a resection at this site, but the therapeutic gain from resection of disease may outweigh sacrifice of some function. 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). At times, amputation or leaving the hip flail with an internal hemipelvectomy or a saddle prosthesis may be the best options.

Pelvic lesions which cross the sacroiliac joint 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 hemipelvectomy for large "unresectable" lesions of the pelvis is unclear. In most instances it is to be avoided unless it is the only means feasible to achieve adequate control in a non-metastatic patient.

#### 13.4.7 Spine

Patients with symptoms of spinal cord compression should be considered for emergency radiotherapy (see [Section 17.4](#)). 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 the lesions are localized and 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.

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.

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 are possible and offer good 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. If a patient has a (presumably small) soft tissue mass that was not expected to be malignant and was resected with negative margins no further local therapy will be required provided the primary tumor was not violated at the time of surgery and the cuff of normal tissue surrounding the soft tissue tumor was at least 2 cm wide on all surfaces. In the case of Ewing tumor within an encapsulated organ, margins are negative if the capsule was not surgically violated or breached by the tumor. If the primary tumor was violated at the time of surgery prior to the initiation of chemotherapy, then further local therapy (surgery, radiation or both) at the time of local control must be delivered. In this case the initial procedure would be considered a large biopsy. At the completion of induction chemotherapy, the patients should be re-staged with plain radiographs of the primary site, MRI, total body bone scan, and a chest CT and PET 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, it may be helpful to precede the resection with radiotherapy. 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.<sup>62,63</sup> 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 Reporting

The surgical checklist and AEWS1031 Local Control Checklist must be completed by the surgeon within one month of the definitive surgical procedure.

## 14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Central pathology retrospective review of definitive resection margins (post-chemotherapy) will be done. Submission of materials must be done within two months from the time of diagnostic biopsy and any surgical procedure done on study. COG member institutions are also encouraged to enroll patients on a Ewing sarcoma specimen collection study, such as AEWS07B1 or on any successor biology study. Please see the specimen collection study for directions for specimen preparation and shipment.

### 14.1 Biopsy Pathology Procedures

#### Gross

Surgeons should be encouraged to send fresh tissue in all biopsy and resection 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 when sufficient tissue is present and saved or processed for electron microscopy. 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 staining) consistent with a Ewing family tumor (Ewing sarcoma/peripheral primitive neuroectodermal tumor) of bone or soft tissue. In addition, there should be no immunohistochemical or ultrastructural evidence suggesting lymphoma or another sarcoma such as rhabdomyosarcoma. Patients with esthesioneuroblastoma will be ineligible.

#### 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 such as 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), as well as any 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.

#### Electron Microscopy

It is recommended that tissue should be saved for electron microscopy, and ultrastructural evaluation should be performed whenever necessary for diagnosis.

### **14.2 Molecular and Cytogenetic Studies for Initial Diagnosis**

#### 14.2.1 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 a EWS rearrangement consistent with a Ewing family tumor may be used as supporting evidence for a Ewing sarcoma/PNET diagnosis.

#### 14.2.2 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 cytogenetic 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 as 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.

In patients where surgical resection precedes neo-adjuvant therapy the cuff of normal tissue surrounding the soft tissue tumor should be least 2 cm wide on all surfaces. In the case of Ewing tumor within an encapsulated organ, margins are negative if the capsule was not surgically violated or breached by the 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](#) is required to grade the histologic response accurately. The institutional pathologist should assess the tumor’s pathologic response as follows:

- No viable tumor in specimen
- Viable tumor cells present, occupying < 10% of the original tumor bed
- Viable tumor occupies  $\geq$  10% of the original tumor bed

Unlike osteosarcoma, Ewing sarcoma does not produce a stromal framework, and as a result in some post-treatment specimens, tumor volume decreases significantly, complicating efforts to assess percentage necrosis.<sup>64</sup> In addition, many Ewing sarcomas have marked necrosis at diagnosis, prior to treatment. In general, post-treatment specimens that contain only isolated individual viable tumor cells would correspond with a response of < 10% viable tumor cells present and post-treatment specimens with larger nodules or sheets of viable tumor would correspond to a response of  $\geq$  10% viable tumor cells present.

#### 14.4 **Pathology Review Requirements**

The following material must be submitted to the COG Biopathology Center (BPC) (see address below) within 2 months of diagnostic biopsy and subsequent surgical procedures. Dr. Bruce Pawel, MD and Dr. Atif Ahmed, M.B.B.S are the COG reviewers for AEWS1031 specimens. Do NOT send specimens directly to them. Send all specimens to the Biopathology Center as specified below.

##### 14.4.1 Biopsy

Required materials for central review, within 2 months of initial diagnostic biopsy are:

- 2 representative H & E stained slides from the diagnostic biopsy with tumor
- A copy of the institutional pathology report(s)
- A copy of the institutional surgical report
- Specimen Transmittal Form

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed of each patient enrolled on AEWS1031 and to request that patients’ materials be forwarded to the Biopathology Center. The Biopathology Center and the review pathologist will not request materials.

##### 14.4.2 Resection/Amputation

Required materials for central review, within 2 months of the surgical resection/amputation are:

- Two blocks representing the closest margins from the resection specimen should be selected. From both blocks, 2 H&E stained slides and 5 unstained slides should be submitted. In specimens where there is no evidence of residual tumor or fibrosis or inflammation (the entire specimen composed of histologically unremarkable tissue), blocks and slides do not have to be submitted for central review.
- Grid diagram of resection specimen (MAP) denoting location of blocks obtained.
- A copy of the institutional pathology report(s) which includes measurement of the tumor in 2 dimensions, percent necrosis and margins of excision (mm)
- A copy of the institutional surgical report
- Institutional Radiology Report(s)]

- Photograph of the gross specimen (if available).
- Completed AEWS1031 Pathology checklist

It is the responsibility of the Principal Investigator enrolling a patient on this trial to request from the submitting pathologist that s/he send the appropriate set of forms, local pathology report including the schematic block map, and specimens to the Biopathology Center.

#### 14.4.3 Pathology Review Specimen Shipment

Pathology review materials can be shipped by regular mail or using your own courier account.

Please label pathology review materials with patient's COG Patient ID Number and the surgical pathology identification (SPID) number and block number from the corresponding pathology report.

Send specimens to:

Biopathology Center  
(Attn: Pathology Review AEWS1031)  
Nationwide Children's Hospital  
700 Children's Drive, Room WA1340\*  
Columbus, OH 43205  
Phone: (614) 722-2894  
FAX: (614) 722-2897  
For questions call: (800) 347-2486

\*The room number is required. Packages not listing the room number will be denied and returned to the sender.

#### 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.



Please note that materials sent to the reviewers for consultation will not be included in the Biopathology Center's Institutional Performance Monitoring System. The consultation is separate from a study submission.

#### 15.0 **SPECIAL STUDIES SPECIMEN REQUIREMENTS**

This protocol does not include correlative biology studies. However, COG member institutions are strongly encouraged to collect tumor specimens by enrolling patients onto one of the Ewing sarcoma biology studies for banking (such as AEWS07B1 or on any successor biology study).

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

**16.1 Primary site imaging**

MRI is the preferred method of primary site imaging prior to treatment and prior to local therapy. Plain radiographs of primary site should also be obtained.

Functional imaging with FDG-PET is recommended prior to treatment and prior to local therapy. If FDG-PET is used SUV<sub>max</sub> at those two time points will be reported by local institution and electronic copies of scan (PET and CT/MRI of involved area) as well as reports will be submitted to QARC for imaging committee review (see [Section 16.5](#)).

16.1.1

The primary tumor must be measured and reported in three dimensions prior to therapy and prior to local therapy. The three largest perpendicular measurements will be measured and reported in RDE. See [Section 10.2.1.3](#).

**16.2 Metastatic site imaging**

Total body bone scan, chest CT, and imaging of selected regional nodal sites by MRI or CT are required to exclude metastatic disease. Functional imaging with FDG-PET is strongly recommended as it has increased sensitivity for detection of osseous and lymphatic metastasis. Patients with metastatic disease at diagnosis, other than regional nodal spread, are not eligible for enrollment.

**16.3 Required and Recommended Imaging**

All imaging studies are required unless otherwise noted.

16.3.1 At Presentation and Prior to Local Control

Site	Anatomic Imaging	Functional Imaging	Timing
Primary	Frontal and lateral radiographs		Required at presentation and prior to local control for bone tumors of extremity and pelvic sites at study entry*
Primary	MRI with gadolinium		Required at presentation and prior to local control*
Chest	CT		Required at presentation and prior to local control*
Chest	Frontal and lateral radiographs		Recommended at presentation only
Whole body		MDP bone scintigraphy	Required at presentation and prior to local control*
Whole body		FDG-PET	Strongly recommended at presentation. Recommended prior to local control*, particularly if primary bone tumor positive on prior PET and negative on bone scintigraphy.

\*- The pre-local control image should be obtained within 4 weeks of local control

16.3.2 Surveillance on Consolidation Chemotherapy and End of Therapy Evaluations

Site	Anatomic Imaging	Functional Imaging	Timing
Primary	Frontal and lateral radiographs		Required for bone tumors of extremity and pelvic sites at study entry – After Cycle 5 consolidation and at end of cytotoxic chemotherapy
Chest	CT		Required – After Cycle 5 consolidation and at end of cytotoxic chemotherapy
Whole body		MDP bone scintigraphy	At end of cytotoxic chemotherapy (unless bone scintigraphy negative and FDG-PET positive at presentation) <u>Perform sooner if symptoms or abnormal imaging</u> (and surgical or other intervention contemplated AND primary tumor positive on prior bone scintigraphy)
Whole body		FDG-PET	Required – At end of cytotoxic chemotherapy if bone scintigraphy negative and FDG-PET positive on prior imaging Recommended – At end of cytotoxic chemotherapy (unless bone scintigraphy positive and FDG-PET negative at presentation) <u>Perform sooner if symptoms or abnormal imaging</u> (and surgical or other intervention contemplated AND positive on prior FDG-PET)
Primary	MRI with gadolinium or CT scan with IV contrast		Recommended if symptoms or abnormal imaging (and surgical intervention or radiation therapy contemplated)

16.3.3 Recommended Surveillance Post-Chemotherapy

Site	Anatomic Imaging	Functional Imaging	Timing
Primary	Frontal and lateral radiographs		Obtain for bone tumors of extremity and pelvic sites at study entry: q 3 months x 8, then q 6 months x 6, then q 12 months x 5
Chest	Frontal and lateral radiographs		q 3 months x 8, then q 6 months x 6, then q 12 months x 5
Chest	CT		If abnormal chest radiographs
Primary	MRI with gadolinium or CT scan with IV contrast		If symptoms or abnormal imaging (and surgical or other intervention contemplated)
Whole body		MDP bone scintigraphy	If symptoms or abnormal imaging (and primary tumor positive on prior bone scintigraphy AND surgical or other intervention contemplated)
Whole body		FDG-PET	If symptoms or abnormal imaging (and primary tumor positive on prior FDG-PET AND surgical or other intervention contemplated)

## 16.4 Technical Guidelines

### 16.4.1 CT and MRI

Technical guidelines for cross-sectional imaging are provided in [Section 10.2](#). Additional CT and MRI guidelines are available on the COG Member site at:

[https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp).

### 16.4.2 FDG-PET

FDG-PET scans may be performed according to local institutional standards. Guidelines are included institutions requiring them (Appendix I)

## 16.5 Submitting Imaging for Central Review

PET studies as well as MRI or CT scan images of the area involved with tumor obtained prior to study entry and those obtained prior to local control with the corresponding radiology reports will be submitted to QARC for central review.

Submission of diagnostic imaging data in digital format is required. Digital files must be in DiCOM format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicomcommunicator. Contact QARC at [Dicomcommunicator@QARC.org](mailto:Dicomcommunicator@QARC.org) for further information. Alternative electronic methods, e.g., sFTP are possible. Contact QARC for more information.

Please submit to:

Quality Assurance Review Center (QARC)  
Building A, Suite 201  
640 George Washington Highway,  
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 (per COG Administrative Policy 3.9) or at approved RTOG 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 per COG administrative Policy 5.14 (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 Ewing sarcoma.

#### 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.

##### 17.1.1.2 Required Benchmark and Questionnaires

All therapy units used on this protocol must have their calibrations verified by the Radiological Physics Center (RPC). RT using photons (either 3-D conformal [3-D CRT] or intensity modulated [IMRT]), electrons and protons, will be allowed in this study. Centers participating in this protocol using 3-D CRT are required to complete the 3-D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom (QARC or RPC) and those using protons must complete the proton benchmark and questionnaire. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center ([www.qarc.org](http://www.qarc.org)) and must be submitted before patients on this protocol can be evaluated. For information regarding the IMRT phantoms, please contact the RPC (<http://rpc.mdanderson.org/rpc>).

##### 17.1.1.3 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 [www.qarc.org](http://www.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.

##### 17.1.1.4 Guidelines and Requirements for the Use of Proton Beam Therapy

Investigators using proton beam therapy will be required to comply with the guidelines for the use of protons in National Cancer Institute sponsored cooperative group trials developed in 2007. These guidelines shall be available through [www.qarc.org](http://www.qarc.org). These guidelines specify the following for the participating institution: only passively or actively scattered proton beams will be used; the IAEA TRS 398 protocol shall be used for beam calibration; dose reporting will be in Cobalt Gy Equivalent (1 CGE = 1 proton Gy \* 1.1). Radiation doses shall be prescribed protocol specified definitions for gross (GTV) and clinical (CTV) target volumes. For set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis. The proton institution is required to participate in on-site and remote review according to COG guidelines.



**17.1.1.5 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 for conformal RT of residual disease in the operative bed of the primary tumor for select patients.

**17.2 Indications for Radiation Therapy**

See [Section 4.3](#) for a general discussion of local control.

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

\*Patients considered for pre-operative radiation (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.

**17.3 Timing of Radiotherapy**

**17.3.1**

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.

**17.3.2**

Patients treated with radiation as the primary local control measure, 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 4.0](#)).

The objective of preoperative radiotherapy should not be an attempt to make an inoperable tumor operable. Patients who are to be treated with planned lower dose (36 Gy) radiation followed by planned excision should be treated with radiation during Weeks 1 through 4 of Consolidation, and then proceed onto surgical resection of the tumor as soon as possible (ideally within 2 weeks). If post-operative radiotherapy boost is required, radiation therapy should be scheduled to start as soon as recovery from surgery permits, usually within 2 weeks. Following surgery, the next cycle of chemotherapy should be given as soon as possible post-operatively; this can be given concurrently with boost radiotherapy if necessary.

### 17.3.3

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. 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 (Week 14). 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. Ifosfamide/etoposide courses and vincristine-topotecan-cyclophosphamide courses may be given concurrently.

### 17.3.4 Mesna

In the past, mesna was held during radiation therapy. There is 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.

## 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  $\leq 10$  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 PTV 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 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.

Volumetric imaging for position verification may be in-room kV or MV cone beam or conventional CT imaging.

Imaging submission requirements:

- For 2D imaging, the portal and isocenter setup verification images should be submitted along with the DRRs from the treatment plan. Images should be sent in the form of screen captures or in hardcopy format.
- For volumetric imaging, submit representative axial slices showing the treatment scan registered to the planning scan and indicating correct positioning either by isocenter location or overlay of the isodoses.

## 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](http://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* is not the same as photons due to differences in beam penetration with movement and set up uncertainty. PTV varies with each individual field and coverage and will require additional adjustment to (1) the lateral margins, (2) smearing of compensator, (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 2-7 mm) will be based on the set up error determined for the particular body site at the individual proton institution. 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.

## 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 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 17.5](#).

### 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 extrasosseous 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 17.5](#).

### Special Presentations:

#### 1) Chest Wall Tumors with Ipsilateral Pleural Nodules and/or Isolated 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.

### 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. 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.

### 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 beam, the absorbed dose is specified in CGE, which is the same as ICRU 78 DRBE using a standard RBE of 1.10 with respect to water.

#### 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 malignant pleural effusion or pleural nodules

<b>Tumor Site and Presentation</b>	<b>PTV1</b>	<b>PTV2</b>
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
Preop RT	36 Gy	N/A
Postop RT after pre-op RT: microscopic residual, >90% necrosis	N/A	14.4 Gy
Postop RT after pre-op RT: microscopic residual, <90% necrosis	14.4 Gy	N/A
Postop RT after pre-op RT: gross residual	19.8 Gy	
Postop RT –microscopic residual, >90% necrosis	N/A	50.4 Gy
Postop RT – microscopic residual, <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

<b>Involved Lymph Nodes Doses</b>	<b>PTV1</b>	<b>PTV2</b>
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 pathologically involved pleural fluid

<b>Chest wall tumors with positive fluid cytology</b>			
Age	PTV1*	PTV2*	PTV3^
≤ 6	32.4 Gy	10.8 Gy	12 Gy
> 6	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 pleural nodules

<b>Chest wall tumor with secondary soft tissue only pleural nodules, radiographic PR</b>			
Age	PTV1*	PTV2*	PTV3^
≤ 6	23.4 Gy	19.8 Gy	12 Gy
> 6	21.6 Gy	19.8 Gy	15 Gy
<b>Chest wall tumor with secondary soft tissue only pleural nodules, radiographic CR</b>			
Age	PTV1*	PTV2*	PTV3^
≤ 6	37.8 Gy		12 Gy
> 6	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

17.7.3 Dose uniformity

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.

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, the heterogeneity correction algorithm must be approved by QARC. For questions about heterogeneity corrections or approved algorithms, please contact QARC ([www.QARC.org](http://www.QARC.org)).

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 (≥ 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) or IMRT 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. 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 apertures or proton-specific multileaf collimation.

### 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.

#### 17.8.4.2 Immobilization devices

Standard immobilization devices for the torso, extremities or head and neck are to be used. For IMRT 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.
- 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](#).

#### 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<sup>2</sup>, 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 bony 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

$$\text{Dose homogeneity index } HI = \frac{{}_{CTV}V_{100} - {}_{CTV}V_{150}}{{}_{CTV}V_{100}} \geq 0.80$$

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  $\geq 6$  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.

**17.9 Organs at Risk**

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 CGE).

**Table 17.9: Organs at risk dose recommendations**

<b>Organ</b>	<b>Volume (%)</b>	<b>Dose (cGy)</b>
<b>Single organs</b>		
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
<b>Paired organs</b>		
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 chestwall or pleura

## 17.10 Dose Calculations and Reporting

### 17.10.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be calculated and submitted using the RT-1/IMRT Dosimetry Summary Form. If IMRT is used, the monitor units generated by the IMRT 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 prescribed dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

### 17.10.2 Normal Tissue Dosimetry

The total 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 for the primary tumor, 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 17.10.2: 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
Chest	Thyroid
	Esophagus
Abdomen/Pelvis	Heart
	Left Lung
	Right Lung
	Bladder
	Left Kidney
All axial tumors	Liver
	Rectum
	Right Kidney
	Small Bowel (contour peritoneal cavity)
	Stomach
	Spinal Cord

## 17.11 Quality Assurance Documentation

### Key Points

- Data for the primary site only must be submitted for quality assurance review within 3 days of the start of treatment (see checklist).

**Institutions are required to submit the treatment plan in digital format.** An institution's treatment planning system must have the capability of exporting data in 1 of 2 formats:

- RTOG Data Exchange Format, Version 3.20 or later (specifications at [http://itc.wustl.edu/exchange\\_files/tapeexch400.htm](http://itc.wustl.edu/exchange_files/tapeexch400.htm)); or

- DICOM 3.0 in compliance with the Advanced Technology Consortium's (ATC) DICOM 3.0 Conformance Statement. A list of commercial systems that are known to have this capability are listed on the ATC Website ([http://atc.wustl.edu/credentialing/atc\\_compliant\\_tps.html](http://atc.wustl.edu/credentialing/atc_compliant_tps.html)).
- The data may be submitted on a CD or sent electronically via ftp to QARC. Instructions for digital submissions may be found on the QARC Website - [www.qarc.org](http://www.qarc.org), under Digital Data, RT Treatment Planning.

**Please submit the following for the Primary Site Target Volume:**

**External Beam Treatment Planning System**

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. When using IMRT, orthogonal isocenter images are sufficient.
- Isodose distributions for the composite treatment plan in the axial, sagittal and coronal planes at the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method must be clearly indicated.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in [Section 17.9](#). 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.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Beams-eye-view (BEV) of portals showing collimator, beam aperture, target volume and critical structures are required when not using IMRT.

**Digital Data**

- Submission of the treatment plan for the primary site in digital format is required. Please refer to [www.QARC.org](http://www.QARC.org) and click on "Digital Data" for guidelines regarding digital submission. All submissions, including those that are digital, require hard copy submission of the other items included in this list. If there are any problems with digital data submission, please contact QARC.

**Supportive Data**

- All diagnostic imaging used to plan the target volume. This includes CT or MRI PRIOR to attempted surgical resection of the primary tumor. Digital format is preferred.
- Documentation of an independent check of the calculated dose when IMRT is used.
- For protons, a description of the rationale for the PTV margins.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.
- If modifications are made for patients with age < 24 months, documentation should be provided.

**Forms**

- RT-1/IMRT 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 emergency RT is administered, documentation should be provided in the form of the RT-2 Total Dose Record Form and the radiotherapy record (treatment chart).
- Completed AEWS1031 Local Control Checklist

These data should be forwarded to:

Quality Assurance Review Center  
Building A, Suite 201  
640 George Washington Highway  
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  
Building A, Suite 201  
Quality Assurance Review Center  
640 George Washington Highway  
Lincoln, Rhode Island 02865-4207



**17.12 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
<b>Prescription Dose</b>		
External beam	Prescription dose is >5% but < 10% greater or less than protocol-specified dose	Prescription dose is > 10% greater or less than protocol-specified dose
Brachytherapy	Prescription dose is > 5% but < 10% greater or less than protocol-specified dose	Prescription dose is > 10% greater or less than protocol-specified dose
<b>Dose Uniformity</b>		
External beam	> 10% PTV receives > 110% of prescription dose <i>or</i> 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.
<b>Volume</b>	CTV or PTV margins are smaller than specified in the protocol.	The contoured GTV does not include imaging-visible residual tumor
<b>Organs at Risk</b>	Will be assessed at time of data review.	Will be assessed at time of data review.

**APPENDIX I: GUIDELINES FOR OPTIONAL FDG-PET IMAGING <sup>65</sup>**

**1 Pregnancy**

All female patients ≥ 10 years of age should be asked about their pregnancy potential prior to FDG injection. Patients who are sexually active and unsure of their pregnancy status should undergo a urine pregnancy test prior to FDG injection. Pregnant guardians should not be allowed in the FDG uptake room. The estimated maximum absorbed radiation dose for each patient based on weight is given in the table below. The lifetime risk of second malignancy from radiation exposure is estimated to be  $8 \times 10^{-4}$ /Rem.

**Radiation dose estimates for <sup>18</sup>F-FDG by intravenous injection**

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on recommended dose of 140 to 150 μCi/kg (minimum dose 1.0 mCi and maximum dose 12 mCi)	1.0	1.4	2.6	4.5	7.8	9.8
Effective Dose (ED) (rem)	0.86	0.49	0.56	0.63	0.86	0.88

**2 Technique**

Patients will be fasted for at least 4 hours before imaging. Total parenteral nutrition and intravenous fluids containing glucose should also be discontinued for at least 4 hours before the study. The patient should be well hydrated (oral or intravenous fluid administration) before administration of FDG. Fluids administered for hydration should not contain glucose.

If intravenous access is not already in place, this should be obtained, typically in the ante-cubital fossa, for patient hydration (if needed), determination of serum glucose and FDG administration.

It is recommended that blood glucose be measured and recorded just prior to injection of the FDG and must be ≤ 200 mg/dL. If the blood glucose concentration exceeds 200 mg/dL, the patient should not be injected and rescheduling of the study recommended.

In patients with tumors in the pelvis, placement of a Foley catheter is recommended. Patients in whom a Foley catheter is not placed should be asked to void prior to imaging in order to minimize bladder activity and to reduce their radiation exposure. Patients with bladder tumors should not undergo PET imaging for purposes of evaluating the primary tumor. PET-CT, however, may be useful in these patients if the tumor can be accurately localized on the co-registered CT images. The nuclear medicine physician should be consulted prior to planned imaging of bladder tumors to advise on modifying standard protocols.

**3 FDG Dosing and Injection**

0.15 mCi/kg (minimum: 2 mCi, maximum: 12 mCi) FDG will be administered intravenously followed by administration of 5-10 mL saline solution with the patient resting comfortably. The dose of FDG within the syringe used for injection must be measured immediately before administration. The injected dose must be +/- 10% of the prescribed dose for the patient. Should the dose not meet this requirement a decision will be made, by the physician who will interpret the PET scan, as to whether or not to proceed with the injection and imaging study. The postinjection syringe dose must be determined after the radioisotope is injected in order to calculate the actual injected dose as follows:

Injected dose = Pre-injection syringe dose - Post-injection syringe dose

The time of FDG injection must be recorded by the nuclear medicine technologist so that accurate standard uptake values ( $SUV_{max}$ ) can be determined (described in detail below). The clock in the FDG uptake room must be synchronized with the clock in the PET scanner in order to accurately determine the time after injection that the imaging is performed for purposes of SUV determination. The patient should remain supine, resting comfortably, until the time of imaging.

#### 4 PET Scanning Protocol

A whole-body PET scan covering the area from the vertex of the skull to the toes should be performed. The patient will be positioned supine, with arms either comfortably positioned above the head or at the side of the patient.

Patients can be imaged head-first or feet-first. However, individual patients must be imaged in the same manner each time (eg, if feet-first for the first scan, feet-first for all subsequent scans).

Transmission scanning matching the areas covered by the emission scan will need to be performed for attenuation correction of the emission scan. This will be done after injection of FDG. With a combined PET/CT scanner, attenuation correction should be done with CT data per manufacturer recommendations.

Emission scans are to be initiated  $60 \pm 10$  minutes after injection of FDG. The time that the emission scan is started must be recorded for accurate  $SUV_{max}$  calculation. In addition, the timing at which the scanning is initiated must be consistent for all scans of the same patient (eg, if the first scan is performed at 50 minutes after injection, all subsequent scans are to be performed on the same or similar machine and at 50 minutes post tracer administration).

Emission data must be collected for at least 5 minutes per bed position for BGO, LSO, and GSO systems operated in the 2-D mode; at least 3 minutes per bed position for BGO, LSO, and GSO systems operated in the 3-D mode. Images will be corrected for scatter, random events, and dead-time losses using manufacturer's software. Bed positions should be overlapped to avoid large changes in sensitivity at the joints between the bed positions.

#### 5 After Completion of the PET Scan

The patient must empty his or her urinary bladder as soon as possible after imaging. Image reconstruction will depend on the scanner manufacturer. We recommend an iterative reconstruction method with parameters chosen to yield 6-8 mm resolution in the reconstructed images.

#### 6 FDG Handling and Dose Documentation

FDG is to be synthesized by standard methods and tested for pyrogenicity and radiochemical purity on each production run, or purchased from nuclear pharmacies licensed to sell FDG. The radiochemical purity of the FDG should be  $> 90\%$ . The PET scans will be submitted electronically to QARC and stored in an electronic database. The scans will be used for visual interpretation.

## 7 PET Imaging Quality Control Standards

FDG-PET imaging will be performed using "state-of-the-art" equipment – a PET CT.

Daily and monthly steps will be taken to assure quantitative accuracy of PET imaging studies and reliable imaging results at all performance sites. Daily quality assurance includes a simplified chi-square test to assure consistent performance of the PET scanner. The calculation provides a quantitative means of monitoring drift of the scanner electronics with time. A blank scan is also performed daily for later attenuation correction. Either of these measurements may be viewed routinely as an additional measure of performance. A liquid-filled or standardized sealed-source cylinder phantom is used monthly to validate the quantitative accuracy of the images against a dose calibrator. The dose calibrator is itself calibrated daily against standards for constancy and annually for accuracy using NIST-traceable standards. Each month, fine gain calibration of all detectors in the PET system will be performed, followed by recalculation of the sensitivity normalization factors for the scanner.

Transmission scans will be obtained with CT data from a combined PET/CT scanner, in accordance with manufacturer's recommendations). An algorithm to correct for activity in the field of view should be used for processing of these postinjection transmission images, if provided by the vendor. Then the corresponding emission images, each at least 5 minutes per bed position for BGO, LSO and GSO systems operated in the 2-D mode; at least 3 minutes per bed position for BGO, LSO, and GSO systems operated in the 3-D mode. Alternatively, the individual emission and transmission scans may be acquired in alternating fashion. The PET images will be reconstructed by standard vendor-provided reconstruction algorithms, using either filtered back projection with a Hanning filter (frequency cutoff  $0.6 \times N_{\text{q}}$  [ $N_{\text{q}} = 0.3 \text{ cycle/pixel}$ ) or the manufacturer's recommended iterative reconstruction algorithm with an appropriate filter. Segmentation of transmission images should be used for attenuation correction. Emission data will be corrected for randoms, dead-time and scatter using vendor-provided algorithms. Multiple-bed position studies must be corrected for radioactive decay. The emission images will be reconstructed both with and without attenuation correction.

## 8 Standard Uptake Value

The local radiologist or internist assigned to this protocol will determine the FDG-PET standard uptake value (SUV) for each primary tumor. The SUV will be determined by manually drawing a region of interest over the area of FDG activity corresponding to the tumor in question. The SUV is a measure of the amount of tracer taken up in a particular tissue normalized by the dosage of tracer administered and the weight of the patient. The equation for calculation of the  $SUV_{\text{max}}$  is:

$$SUV = \frac{\text{radioactivity concentration [Bq cm}^{-3}\text{] in the region of interest}}{\text{Injected dose Bq/weight of patient}}$$

Factors that influence the magnitude of the SUV include patient size, imaging time, plasma glucose levels, partial volume effects, region-of-interest depth, and recovery coefficient effects. Factors that we can control are the region of interest size, injected dose and time to imaging. The region of interest size will vary depending on the size of the tumor because it will be manually drawn to include the entire area that demonstrates FDG activity. Therefore, in order to address differences in tumor size, we will record both the maximum SUV value for the entire area as well as the average intensity for all pixels within the area. The injected dose, as previously described, will be based on body weight as per local institutional protocol. The time to imaging will be kept to no longer than 2 hours after the injection of FDG. When a tumor

demonstrates no obvious FDG activity, the SUV measurement will not be attempted. To enable accurate and meaningful SUVs to be calculated, the following information must be recorded for each scan:

- ✓ *injection time*
- ✓ *injected tracer dosage (pre-injection syringe dose minus post-injection syringe dose)*
- ✓ *start-of-emission scan time*
- ✓ *emission scan duration*
- ✓ *patient height (to be measured on the day of scan)*
- ✓ *patient weight (to be measured on the day of scan)*

**APPENDIX II: YOUTH INFORMATION SHEETS****INFORMATION SHEET REGARDING RESEARCH STUDY – AEWS1031  
(for children from 8 - 12 years of age)**

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*(Intensive Multi-Drug Therapy for Patients with Localized Ewing Sarcoma)*

1. We have been talking with you about Ewing sarcoma. Ewing sarcoma is a type of cancer that grows in the bones or in the soft tissues around the bones. After doing tests, we have found that you have this type of cancer.
2. Now we want to ask you to take part in a research study because you have Ewing sarcoma. A research study is when doctors work together to try out new ways to treat people who are sick. In this study, we are trying to learn more about how to treat Ewing sarcoma. We will do this by adding another drug to the treatment often used for Ewing sarcoma. We do not know how well the new way will work in children. That is why we are doing this study.
3. Children who are part of this study will be randomly assigned to receive standard chemotherapy (anti-cancer drugs) or standard treatment plus another drug. This is called randomization. This is a lot like flipping a coin. A computer decides which treatment plan you will get and not your doctor. You 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 that you are able to get rid of the cancer but we don’t know for sure if there is any benefit of being part of this study.
5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” Being in this study may involve special risks, which your doctor will discuss with you. Other things may happen to you that we don’t know about yet.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. Please talk this over with your parents. Together you can decide if you want to take part in the study or not. 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.

**INFORMATION SHEET REGARDING RESEARCH STUDY – AEWS1031  
(for teens from 13 - 18 years of age)**

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*(Intensive Multi-Drug Therapy for Patients with Localized Ewing Sarcoma)*

1. We have been talking with you about Ewing sarcoma. Ewing sarcoma is a type of cancer that grows in the bones or in the soft tissues around the bones. 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 Ewing sarcoma. A research study is when doctors work together to try out new ways to treat people who are sick. In this study, we are trying to learn more about how to treat Ewing sarcoma. We will do this by seeing how well adding another chemotherapy (anti-cancer) drug called topotecan to the standard chemotherapy works in children and teens with Ewing sarcoma.
3. Children and teens who are part of this study will be randomly assigned to either Regimen A - standard treatment plan or Regimen B - standard treatment + topotecan. This is called randomization. This is a lot like flipping a coin. A computer will decide which treatment plan you will get and not your doctor. The reason for this is to make sure there are same numbers of people on both treatments. Studies like this are done to learn which type of treatment works best. We do not know if one treatment is better than another treatment plan. Your treatment will also include surgery and/or 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 that the treatment you get will help make your health better. If you get topotecan, we hope it will be better at getting rid of the cancer, but, we don’t know this for sure.
5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” Chemotherapy can cause side effects. For example, some types of chemotherapy cause changes in the blood cells. These changes can make a person feel tired or get an infection easier. Side effects can be increased when chemotherapy drugs are combined. If you receive topotecan, there is a chance that you will have more side effects. Being in this study may involve other special risks, which your doctor will discuss with you. Other things might happen to you that we don’t know about yet.
6. People who decide they don’t want to take part in the study can still get treatment for their cancer. This treatment would be chemotherapy (with the 5 standard drugs) and possibly surgery and/or radiation therapy.
7. Please talk this over with your parents. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you and your parents agree to withdraw from this study, you can do so and it will not affect your right to get other treatments and services. No one will be mad or upset with you.





**APPENDIX III CANCER TRIALS SUPPORT UNIT (CTSUS) PARTICIPATION PROCEDURES**

**CTSUS ADDRESS AND CONTACT INFORMATION**

<p><b>To submit site registration documents, contact:</b></p> <p>CTSUS Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSUS Fax – 215-569-0206</p>	<p><b>For patient enrollments, contact:</b></p> <p>CTSUS Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)</p> <p>[Registrations received after 5:00 PM ET will be handled the next business day. For CTSUS patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]</p>	<p><b>Submit study data directly to COG, unless otherwise specified in the protocol.</b></p> <p>All data submission will be via eRDES; access is available on the COG website. After patient enrollment, COG will provide the site with a username and password and assign two roles at the site, treating physician and CRA for data submission.</p> <p>Do not submit study data or forms to CTSUS Data Operations. Do not copy the CTSUS on data submissions.</p>
<p><b><u>For patient eligibility or treatment-related questions</u></b> contact the Study PI of the Coordinating Group.</p> <p><b><u>For questions unrelated to patient eligibility, treatment, or data submission</u></b> contact the CTSUS Help Desk by phone or e-mail: CTSUS General Information Line – 1-888-823-5923, or <a href="mailto:ctsuscontact@westat.com">ctsuscontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSUS representative.</p> <p><b><u>For detailed information on the regulatory and monitoring procedures for CTSUS sites</u></b> please review the CTSUS Regulatory and Monitoring Procedures policy located on the CTSUS members’ website <a href="https://www.ctsus.org">https://www.ctsus.org</a></p>		

**Registration/Randomization**

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSUS. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form

1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at <https://www.ctsu.org>; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU 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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' area at <https://www.ctsu.org>

All forms and documents associated with this study can be downloaded from the AEWS1031 Web page on the CTSU members' area of the website (<https://www.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

#### **Requirements for AEWS1031 Site Registration:**

- All therapy units used on this protocol must have their calibrations verified by the Radiological Physics Center (RPC). RT using photons (either 3-D conformal [3-D CRT] or intensity modulated [IMRT]), electrons and protons, will be allowed in this study. Centers participating in this protocol using 3-D CRT are required to complete the 3-D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom (QARC or RPC) and those using protons must complete the proton benchmark and questionnaire. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center ([www.qarc.org](http://www.qarc.org)) and must be submitted before patients on this protocol can be evaluated. For information regarding the IMRT phantoms, please contact the RPC (<http://rpc.mdanderson.org/rpc>).
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- IRB-approved consent form
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

#### **Pre-Study Requirements For Patient Enrollment On AEWS1031**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient and/or their parents or legal guardian has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and pre study evaluations performed within the time period specified in the protocol.

#### **CTSU Procedures for Patient Enrollment**

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms (all these below forms must be submitted with each enrollment):
  - CTSU Patient Enrollment Transmittal Form
  - AEWS1031 Eligibility Checklist
  - COG Patient Transfer Form
  - COG Roster Form
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the COG, to obtain a unique patient ID (to be used on all future forms and correspondence) and randomize the patient to one of two treatment arms. A Biopathology Center (BPC) number will also be assigned as part of the registration process  
  
The CTSU registrar will confirm registration/enrollment/random assignment by fax.
5. COG will provide CTSU sites with a unique username and password to access the COG website. An email from COG with this information will be sent to the site within 24 hours of enrollment, excluding weekends. COG will include the username and password and assign two roles at the site, treating physician and CRA for data submission.

The date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

#### **Data Submission And Reconciliation**

1. All case report forms (CRFs) associated with this study must be downloaded from the AEWS1031 Web page located on the CTSU members' area of the website (<https://www.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms) directly to the COG via eRDES [see [contacts table](#)].
3. The COG Statistics and Data Center (SDC) will have query notices and delinquency reports accessible via SADD for reconciliation (see contacts table). Please send query responses and delinquent data to the COG Statistics and Data Center (SDC) via SADD and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP IAM account contact information current**. This will ensure timely communication between the clinical site and the COG Statistics and Data Center.

**Special Materials or Sub-studies**

Required Pathology Review ([Section 14.0](#)) and Imaging Studies ([Section 16.0](#))

- Collect, prepare, and submit specimens and/or imaging data as outlined in the protocol.
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU
- For specific details, please read [Sections 14.0](#) and [16.0](#).

**SERIOUS Adverse Event (AE) Reporting ([Section 11.0](#))**

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU members' side of the website (<https://www.ctsu.org>) or by drilling down to the Adverse Event Reporting Forms link under the documents folder of the AEWS1031 Web page.
3. Do not send adverse event reports to the CTSU.

**Drug Procurement ([Section 6.0](#))**

Commercial agents: Cyclophosphamide, Vincristine, Doxorubicin, Topotecan, Ifosfamide, Etoposide

1. Information regarding the agents used in this trial can be found at:  
[https://members.childrensoncologygroup.org/\\_files/disc/Pharmacy/CommercialAgentsMonographs.pdf](https://members.childrensoncologygroup.org/_files/disc/Pharmacy/CommercialAgentsMonographs.pdf)
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center tree on the AEWS1031 Web page.

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