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**CHILDREN'S ONCOLOGY GROUP**

*ARET0321*

**A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma**

**A Groupwide Phase III Study**

In Collaboration with

**GALOP - Grupo America Latina de Oncologia Pediatrica** (coordinating centers include **Hospital de Pediatria Juan P. Garrahan, Buenos Aires, Argentina; Instituto de Oncologia Pediatrica/GRAAC Sao Paulo, Brazil**)

and

**Children's Cancer Hospital, El Saida Zenab, Egypt 57357**

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**STUDY CHAIR**



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STUDY COMMITTEE

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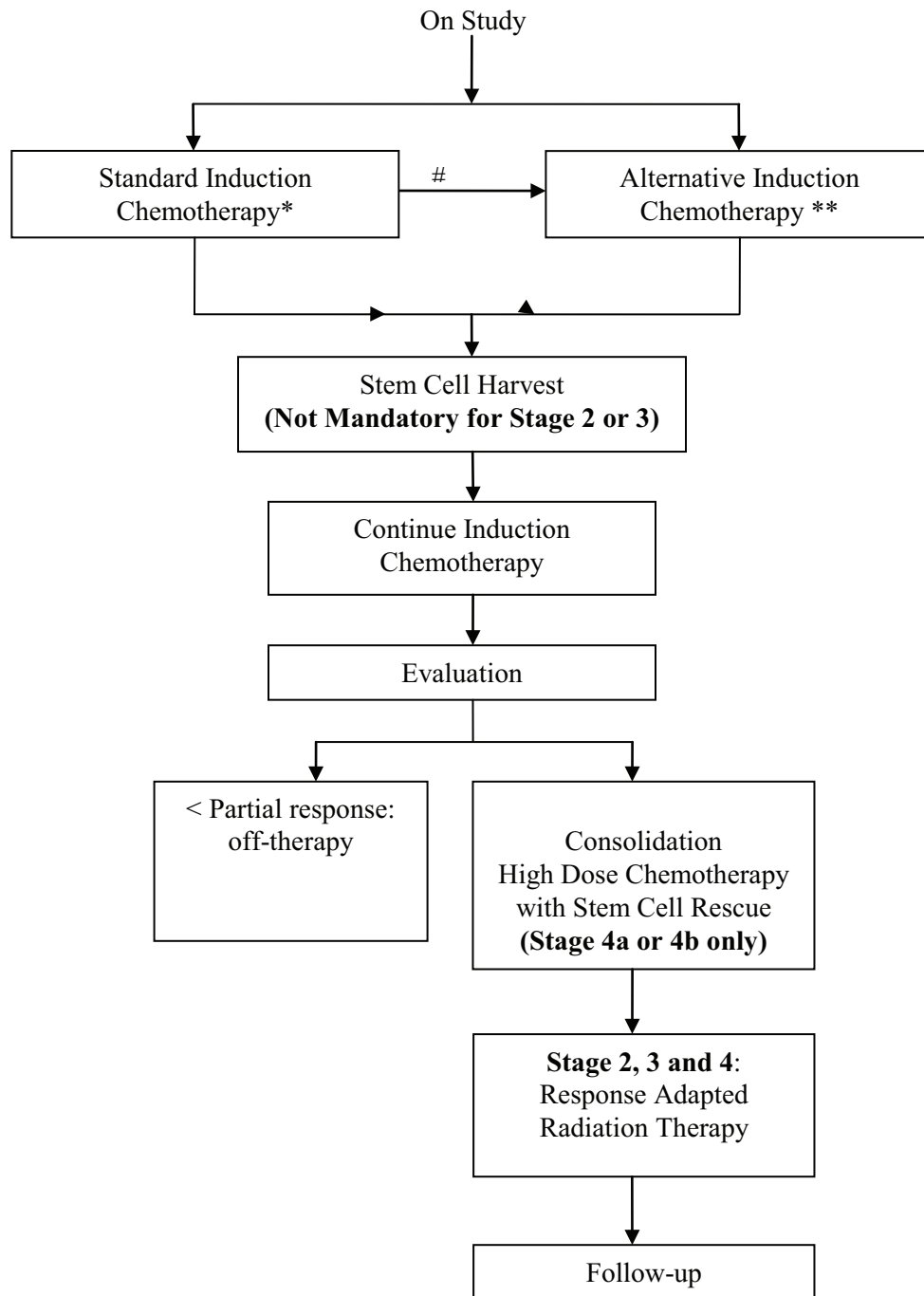
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## **ABSTRACT**

Intra-ocular retinoblastoma has been highly curable for many years using treatment modalities such as enucleation, external beam radiation therapy, chemotherapy and local therapies such as plaque brachytherapy, cryotherapy, and laser photocoagulation. Patients with regional disease (orbit, optic nerve margin positivity, regional nodal disease) appear to be curable with conventional chemotherapy and external beam radiation therapy, but only limited data have been reported. Survivors of disseminated metastatic disease have only anecdotally been reported following treatment with conventional chemotherapy and external beam radiation therapy. Recently, however, several groups in Europe and North America have noted that intensification of treatment with high-dose chemotherapy and stem cell rescue has been associated with improved survival.

This trial seeks to confirm that intensive multi-modality therapy including conventional chemotherapy, high-dose chemotherapy with stem cell rescue and external beam radiation therapy is associated with a better survival rate for patients with metastatic retinoblastoma as compared to historical experiences with conventional chemotherapy and external beam radiation therapy, and that conventional chemotherapy and external beam radiation therapy are sufficient for patients with regional extra-ocular disease. Response to therapy and toxicity of the regimens will also be assessed.

**EXPERIMENTAL DESIGN SCHEMA**



\*See Section 4.2.1 for details of Standard Induction regimen.  
 \*\*See Section 4.2.2 for details of Alternative Induction regimen.  
 #Patients with severe ototoxicity following cisplatin administration.

## **1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)**

1.1 To estimate the proportion of 3 groups of patients with extra-ocular retinoblastoma

- Stage 2 and 3: Regional extra-ocular disease
- Stage 4a: Disseminated metastatic disease not involving the CNS
- Stage 4b: Patients with CNS disease

who achieve long-term event-free survival after aggressive multimodality therapy as prescribed in this protocol.

1.2 To estimate the response rate to the induction phase of the regimen.

1.3 To evaluate the toxicities associated with this regimen.

## **2.0 BACKGROUND**

### **2.1 Introduction/Rationale for Development**

Intra-ocular retinoblastoma has been highly curable for many years using treatment modalities such as enucleation, external beam radiation therapy, plaque brachytherapy, cryotherapy, and laser photocoagulation, and more recently, chemotherapy, but patients with extra-ocular disease have had a much poorer prognosis. Recently significant improvements in survival have been reported for patients with extra-ocular disease. This protocol will seek to confirm that the majority of patients with regional extra-ocular disease can be successfully treated with conventional chemotherapy and external beam radiation therapy, and that patients with distant metastatic disease will benefit from the addition of high-dose chemotherapy with stem cell rescue.

### **2.2 Proposed International Staging System Classification**

Although intra-retinal retinoblastoma has long been staged presurgically according to the Reese-Ellsworth system, retinoblastoma differs from other pediatric neoplasms in never having had a widely accepted classification system that encompasses the entire spectrum of the disease. This prompted an international working group led by Dr. Guillermo Chantada (Buenos Aires, Argentina) to recently develop an international staging system proposal. Many of the members of that working group are COG retinoblastoma committee members (Ira Dunkel, Eric Grabowski, Carlos Rodríguez-Galindo, Anna Meadows) or likely international collaborators on this study (Guillermo Chantada, Francois Doz, Celia Antoneli, Richard Grundy, Maja Beck Popovic, Bernhard Kremens) and we have decided to use the new staging system in this study:

Stage 0 and 1 patients are not eligible for this study because they do not have extra-ocular disease.

Stage 2 includes patients who underwent enucleation but have microscopic residual disease. Included in this stage are patients with involvement of the optic nerve to the transection line and those with microscopic trans-scleral invasion.

Stage 3 includes patients with overt regional extension (orbital or lymph node involvement).

Stage 4 includes patients with hematogenous metastases not involving the CNS (Stage 4a) and those with CNS disease (Stage 4b).

Additional literature on details regarding the staging scheme is available.<sup>1</sup>



### 2.3 Regional Extra-Ocular Retinoblastoma (Stages 2 and 3) can be cured with conventional Therapy

Patients with isolated orbital disease had fared poorly when treated with surgery +/- radiation therapy.<sup>2</sup> Their prognosis improved considerably when conventional chemotherapy was added to the treatment regimen, with 1-year event-free survival of 40% reported following treatment with a variety of chemotherapy agents.<sup>3,4</sup>

Recent publications confirm that patients with regional extra-ocular disease (orbital and/or pre-auricular disease, optic nerve margin positivity) may be cured with conventional chemotherapy and external beam radiation therapy. Investigators in Argentina treated 15 patients with orbital or pre-auricular nodal disease on 2 consecutive protocols. Protocol 87 chemotherapy included vincristine (0.05 mg/kg), doxorubicin (0.67 mg/kg/day x 3 days), and cyclophosphamide (20-40 mg/kg). Protocol 94 chemotherapy included cycles of vincristine (0.05 mg/kg), idarubicin (10 mg/m<sup>2</sup>), and cyclophosphamide (65 mg/kg) followed by cycles of carboplatin (18.7 mg/kg/day or 560 mg/m<sup>2</sup>/day x 2 days) and etoposide (3.3 mg/kg/day or 100 mg/m<sup>2</sup>/day x 3 days). The external beam radiation therapy dose was 4500 cGy, administered up to the chiasm for patients with orbital disease and to the involved nodes in patients with pre-auricular adenopathy. The group achieved a 5-year event-free survival of 84%.<sup>5</sup> The Argentine and New York groups also reported the results of 12 patients with optic nerve margin positivity treated with the chemotherapy regimens above and orbital radiation therapy (4000 to 4500 cGy). All 12 were event-free survivors.<sup>6</sup>

Similarly, investigators in Brazil reported the results of 2 consecutive protocols. From 1987 to 1991, chemotherapy included cycles of vincristine (0.05 mg/kg), doxorubicin (2 mg/kg) and cyclophosphamide (30 mg/kg) alternating with cycles of cisplatin (90 mg/m<sup>2</sup>) and teniposide (100 mg/m<sup>2</sup>). From 1992 to 2000, chemotherapy included cycles of ifosfamide (1800 mg/m<sup>2</sup>/day x 5 days) and etoposide (100 mg/m<sup>2</sup>/day x 5 days) alternating with cycles of cisplatin (90 mg/m<sup>2</sup>) and teniposide (100 mg/m<sup>2</sup>). The external beam radiation therapy dose was 4000 to 5000 cGy to the orbit. Triple intrathecal therapy was also administered. Their therapy was successful in 20 of 32 patients (63%) with orbital disease and 22 of 29 (76%) with optic nerve margin positivity.<sup>7</sup>

Thus, available data suggest that patients with regional extra-ocular retinoblastoma can be cured with an appropriately intensive treatment that includes systemic chemotherapy and external beam radiation therapy.

**Alternative Induction regimen for patients with significant ototoxicity or expected visual impairment:** to avoid ototoxicity in patients with pre-existing ototoxicity or expected visual impairment, carboplatin will be used instead of cisplatin as the induction therapy. Carboplatin has been the single most commonly prescribed chemotherapy medication for retinoblastoma for about the past 15 years and has been successfully used in combination therapy.<sup>5,8,9</sup>

### 2.4 Patients with Metastatic Disease (Stage 4) Have a Poor Prognosis When Treated with Conventional Therapy

Older publications from several centers reported the results of trials utilizing conventional dose chemotherapy and radiation therapy for metastatic extra-ocular disease, most using vincristine, doxorubicin, cyclophosphamide, cisplatin, and etoposide. Despite occasional reports of long-term event-free survival,<sup>10,11</sup> the bulk of the evidence suggested that the prognosis remained grim with such an approach.<sup>12-14</sup>

Recent publications confirm the dismal prognosis. The Argentine investigators (using the regimens discussed above) noted that all 26 patients with distant metastases died.<sup>5</sup> Similarly, the Brazilian investigators noted that treatment with their regimens (discussed above) led to survival of only 1 of 14 patients (7%) with distant metastases.<sup>7</sup>

While trilateral retinoblastoma (bilateral retinoblastoma plus an intracranial third tumor focus, usually pineal or suprasellar) does not represent CNS metastatic disease, its prognosis has been comparably poor. Kivela's meta-analysis noted that only 5 of 89 patients (6%) with reasonable follow-up were event-free survivors, at 10, 30, 108, 132, and 168 months.<sup>15</sup>

## 2.5 Rationale for the Use of High-Dose Chemotherapy with Stem Cell Rescue for Patients with Metastatic Disease Not Involving the CNS (Stage 4a)

Case reports had suggested that the use of high-dose chemotherapy with autologous stem cell rescue (ASCR) might be beneficial for patients with metastatic retinoblastoma,<sup>16,17</sup> and subsequently, Institut Curie investigators reported the results of 25 patients with high-risk retinoblastoma treated with high-dose carboplatin, etoposide and cyclophosphamide followed by ASCR.<sup>8</sup> Five of eight patients with metastases not involving the CNS were event-free survivors 11 to 70 months after high-dose chemotherapy. Three had central nervous system relapses and died of disease 10 to 20 months after high-dose chemotherapy. Three other patients had disease that progressed during induction with conventional induction chemotherapy and never received high-dose chemotherapy. In total, then, 5 of 11 patients (45%) with metastatic disease not initially involving the central nervous system were event-free survivors.

Memorial Sloan-Kettering Cancer Center (MSKCC) investigators reported the results of 4 patients with metastatic retinoblastoma not involving the CNS. All had bone marrow metastases +/- bone, liver, and orbit disease and were treated with a high-dose carboplatin, thiotepa and etoposide with ASCR regimen.<sup>18</sup> All responded to a vincristine, platinum agent, cyclophosphamide and etoposide (plus doxorubicin in 1 case) induction regimen similar to that being proposed in this study. All 4 patients were event-free survivors from 46 to 80 months following diagnosis of metastatic disease. Updated data from New York presented at SIOP in September 2004 reveal that 7 of 10 patients with metastatic retinoblastoma not involving the CNS are event-free survivors at a median of 84 months.<sup>19</sup> Two relapsed in the CNS at 7 and 10 months after the diagnosis of metastatic disease (prior to high-dose chemotherapy). These 2 failures were associated with treatment delays due to fungal infection (n=1) and insurance denial (n=1) and the patients later died of progressive tumor. One patient relapsed in the CNS 16 months after the diagnosis of metastatic disease and later died of progressive tumor. The remaining 7 patients were failure free and alive at 16 to 130 months after the diagnosis of metastatic disease.

In 2003 two groups published promising results using high-dose chemotherapy to treat small series of patients. German investigators treated 5 patients, 3 of whom were distant metastatic CNS negative patients who received a regimen very similar to that used at MSKCC.<sup>20</sup> None of those 3 patients received radiation therapy and they were event-free survivors at 24, 69, and 124 months from diagnosis of metastatic disease. St. Jude investigators reported 4 patients treated with intensive therapy, including high-dose chemotherapy with stem cell rescue, but their regimens (carboplatin-etoposide, busulfan-cyclophosphamide-melphalan, cyclophosphamide-etoposide, cyclophosphamide-topotecan) did not include thiotepa.<sup>21</sup> Radiation therapy was used for bone metastases. Two of the 4 patients were long-term survivors.

CHLA investigators included 2 patients with metastatic disease not involving the CNS in their report regarding patients with extra-ocular disease.<sup>22</sup> One patient with orbit, bone and bone marrow disease

received high-dose cyclophosphamide, thiotepa and etoposide with stem cell rescue, but died of disease at 10 months. Another patient had an isolated bone metastasis and received high-dose carboplatin, etoposide and melphalan with stem cell rescue. He died at 23 months due to a secondary Ewing sarcoma.

Most recently, a Japanese report included 3 patients with bone and/or bone marrow disease treated with intensive therapy, including high-dose melphalan-based chemotherapy with stem cell rescue.<sup>23</sup> One of the 3 patients received radiation therapy. All 3 patients were event-free survivors at 38, 107, and 113 months.

The overall experiences suggest that addition of high-dose chemotherapy with stem cell rescue is associated with improved survival for patients with metastatic retinoblastoma not involving the CNS. The inclusion of thiotepa in the regimen may be associated with a lower risk of CNS recurrence (the most likely site of failure) due to the excellent CNS penetration of that agent.

## 2.6 Rationale for the Use of High-Dose Chemotherapy with Stem Cell Rescue for Patients with Metastatic Disease Involving the CNS (Stage 4b) or Trilateral Disease

Fewer data are available regarding the prognosis of patients with retinoblastoma involving the central nervous system disease treated with high-dose chemotherapy and stem cell rescue. The SFOP experience included 4 patients with CNS metastases who received high-dose carboplatin, etoposide and cyclophosphamide with stem cell rescue. Three died of CNS disease, and one was free of disease at 63 months.<sup>8</sup>

The CHLA report included 4 patients with CNS disease and 3 with trilateral disease.<sup>22</sup> The only survivor (trilateral retinoblastoma) was also the only one that had received high-dose chemotherapy (cyclophosphamide, etoposide and thiotepa) with stem cell rescue. It is unclear whether any of the others had been treated with the intention to include high-dose chemotherapy in the regimen even though none ultimately received such therapy.

The Japanese report included 2 patients with CNS disease.<sup>23</sup> Both died of disease.

Unpublished data from MSKCC reveals that 1 of 2 patients with trilateral retinoblastoma treated with high-dose chemotherapy and stem cell rescue is an event-free survivor at 29 months.

This paucity of data led us to perform a multi-center retrospective study. We asked large centers to contribute patients with retinoblastoma involving the central nervous system whose therapy was intended to include high-dose chemotherapy with stem cell rescue, regardless of whether it was ultimately administered. The following unpublished data were accepted for presentation at the International Retinoblastoma Symposium in Whistler, BC in September 2005. Fourteen patients with trilateral (n=9) or CNS metastatic (n=5) retinoblastoma were treated. Trilateral sites were pineal (n=7) and suprasellar (n=2); 5 had localized disease and 4 had leptomeningeal dissemination. All 5 CNS metastatic retinoblastoma patients had leptomeningeal dissemination. Eight patients had CNS retinoblastoma at original diagnosis; 6 had later onset (3 to 42 months). Induction chemotherapy generally included vincristine, cisplatin or carboplatin, cyclophosphamide, and etoposide. High-dose chemotherapy regimens were thiotepa-based (n=4), carboplatin, etoposide & cyclophosphamide (n=3), or melphalan & cyclophosphamide (n=2). Two patients died of toxicity (septicemia & multi-organ system failure) during induction and 3 had disease progression prior to high-dose chemotherapy. Nine patients received high-dose chemotherapy at a median of 5 months (range 4 to 9) post-diagnosis of CNS disease. Five of 9 trilateral patients survive event-free at 17, 34, 39, 59, & 67 months without radiation therapy. Two of 5 CNS metastatic patients survive event-free at 7 & 54 months; 1 received orbital RT. This experience indicates that intensive chemotherapy is effective for some patients with CNS retinoblastoma.

## 2.7 Toxicity Considerations

The proposed regimen is expected to be associated with severe toxicities, but the patients' guarded prognoses justify the intensive therapy. The induction regimen is very similar to that used recently in COG study 99703 for infants with malignant brain tumors. Dr. Cohen's 10-26-04 committee progress report noted that while there was a high incidence of grade 3 or 4 hematological or infectious toxicity, there was no unexpected toxicity. Eighty nine patients received 259 induction cycles and no toxic death due to induction chemotherapy was encountered.

The high-dose chemotherapy with stem cell rescue consolidation component of the protocol is expected to have severe acute toxicity, with severe mucositis requiring opioid infusions and total parenteral nutrition (TPN) being expected in addition to severe myelosuppression. While few children with retinoblastoma have received the high-dose carboplatin, thiotepa, and etoposide chemotherapy regimen, it has been used in many patients with malignant brain tumors and the risks and supportive care needs are well known.<sup>9,24</sup> Recent data suggest that the toxic mortality rate has declined significantly from the 8-13% rates seen in earlier studies, probably due to greater experience leading to improved supportive care, and to better patient selection (exclusion of older patients). Detailed toxicity data from the Head Start 2 protocol have not yet been published, but unpublished data shared by Head Start 2 investigators (personal communications from Drs. Jonathan Finlay, CHLA and Sharon Gardner, NYU) reveal that the toxic mortality rate associated with the carboplatin, thiotepa and etoposide regimen (same doses to be used in this study) was 2.2% (1 death in 46 patients treated). Additional preliminary and incomplete toxicity data reveal that 0/24 patients experienced AST elevation, and 2/26 experienced

Additionally, MSKCC investigators published their experience treating 21 patients with a similar regimen (carboplatin, thiotepa and topotecan).<sup>25</sup> No death due to toxicity was encountered. All patients experienced grade 4 mucositis and grade 3 or 4 skin toxicity. Two patients developed grade 3 (n=1) and grade 4 (n=1) hypertension. Two patients developed grade 3 or 4 hyperbilirubinemia and one patient developed sinusoidal obstruction syndrome (SOS) formerly known as veno-occlusive disease (VOD) of the liver (grade not specified). The authors noted that patients with normal or near-normal hearing at study entry developed grade 1 or 2 ototoxicity, while those with significantly impaired hearing at study entry were left with grade 3 or 4 deficits. Additional significant toxicities described included a pericardial effusion that required drainage (n=1), seizure (n=1), transient organic brain syndrome (n=2), unexplained hypotension that required dopamine treatment (n=4) and bacterial infections (n=3).

## 2.8 Rationale for the Use of External Beam Radiation Therapy for Stage 4 Patients

Because patients with metastatic disease have traditionally had such a poor prognosis and because external beam radiation therapy is very effective for intra-ocular retinoblastoma, it has often been included as part of the multi-modality approach for patients with metastatic disease that does not involve the central nervous system. For patients whose treatment includes high-dose chemotherapy (thiotepa and/or melphalan) with stem cell rescue, it is not clear that it is necessary, but it is important to recognize that the data summarized below regarding RT and event-free survival were not obtained in the context of randomized trials designed to assess the necessity of radiation therapy in these patients. Patients received treatment according to protocol, family preference and/or individual patient characteristics that could certainly bias the results (for example, if patients perceived to have a better prognosis were those not treated with radiation therapy).

<b>Group</b>	<b>RT (+) EFS</b>	<b>RT (-) EFS</b>	<b>Reference</b>
SFOP	1/4	4/4	15
MSKCC	5/5	2/3	17
Essen		3/3	18
St Jude	2/4		19
CHLA		0/2	20
Japan	1/1	2/2	21
<b>Total</b>	<b>9/14</b>	<b>11/14</b>	

Therefore, the role of external beam radiation therapy for patients with metastatic retinoblastoma who are treated with high-dose chemotherapy with stem cell rescue is unclear. In this study, Stage 4a and 4b patients who achieve a complete response following induction chemotherapy will not receive external beam radiation therapy while those who achieve a lesser response will receive external beam radiation therapy following consolidative high-dose chemotherapy with stem cell rescue.

### **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 (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (<https://www.ctsu.org>). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as

'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions, call the CTSU General Helpdesk at: 1-888-823-5923.

### 3.1.3 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 the online help in the Applications area of the COG website.

### 3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than *five (5)* calendar days after the date of study enrollment.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

### 3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

## 3.2 **Patient Eligibility Criteria**

**Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy). 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 which will serve as the source document for verification at the time of audit.**

### 3.2.1 Age

Patients must be no greater than 10 years of age at study enrollment.

### 3.2.2 Histologic Diagnosis

Patients must have histologic or cytologic verification of extra-ocular retinoblastoma. Extra-ocular disease includes orbital disease, optic nerve involvement at the surgical margin, regional nodal disease, and/or overt distant metastatic disease (at sites such as bone, bone marrow, liver and/or the central nervous system). Patients with trilateral retinoblastoma will also be included in this protocol.

Patients with a CNS lesion consistent with trilateral or Stage 4b disease may be enrolled without tissue confirmation if (1) unequivocal leptomeningeal disease is present on brain or spine MRI scan and/or (2) the primary tumor is at least 2 cm in diameter, predominantly solid, and demonstrates enhancement on the post-Gadolinium images. However, even in such cases surgery should be given serious consideration.

3.2.3 Performance Level (See [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp) under Standard Material for Protocols). Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients >16 years of age and Lansky for patients

### 3.2.4 Prior Therapy

No prior chemotherapy or radiotherapy for the extra-ocular retinoblastoma may have been administered prior to entering this study. Prior treatment (chemotherapy and/or radiation therapy) for intra-ocular retinoblastoma is permissible.

3.2.5 Organ Function Requirements

3.2.5.1 Adequate Bone Marrow Function Defined As

- Peripheral absolute neutrophil count (ANC)  $\geq 750/\mu\text{L}$
- Platelet count  $\geq 75\,000/\mu\text{L}$  (transfusion independent)
- If the ANC and/or platelet count are not adequate, but due to bone marrow metastatic disease, these criteria will be waived

3.2.5.2 Adequate Renal Function Defined As

- Creatinine clearance or radioisotope GFR  $\geq 70\text{ml/min}/1.73\text{ m}^2$  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
	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.

3.2.5.3 Adequate Liver Function Defined As

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

3.2.6 Regulatory

3.2.6.1

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

3.2.6.2

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).

### **Stratification**

Patients will be stratified into 3 groups hypothesized to have different prognoses and requiring different treatment.

Stage 2 or 3: Patients with orbital disease (including microscopic trans-scleral invasion seen on enucleation pathology), optic nerve margin (+), and/or regional nodal disease, but no other sites of metastases.

Stage 4a: Patients with overt distant metastatic disease (such as bone, bone marrow, and/or liver) but no detectable CNS involvement.

Stage 4b: Patients with overt CNS involvement (brain parenchyma, leptomeninges and CSF cytology). Patients with trilateral retinoblastoma will be included. Patients with extradural/dural disease, but without parenchymal or leptomeningeal disease should not be included and will be considered to be Stage 4a patients.

### **4.1 Overview of Treatment Plan**

Protocol therapy will consist of 3 reporting periods; Induction, Consolidation with Stem Cell Rescue and External Beam Radiation Therapy.

Stage 2 and 3 patients will receive Induction chemotherapy and External Beam Radiation Therapy, but will not receive Consolidation therapy (High-Dose Chemotherapy with Stem Cell Rescue).

Stage 4a and 4b patients will receive Induction chemotherapy, Stem Cell Harvesting, Consolidation with Stem Cell Rescue, and depending on response to Induction chemotherapy, possibly External Beam Radiation Therapy.

#### **4.1.1**

Induction consists of 4 cycles of chemotherapy; each cycle will be 3 weeks in duration. Induction therapy may be Standard Induction or Alternative Induction (for patients who have significant ototoxicity or pre-existing hearing and/or visual impairment). Consolidation therapy includes high dose chemotherapy with stem cell rescue using peripheral blood stem cells harvested during induction; Consolidation lasts 4 to 6 weeks. External Beam Radiation Therapy for Stage 2 and Stage 3 patients will begin after Cycle 4 of Induction chemotherapy. For Stage 4 patients who will receive External Beam Radiation Therapy, this will be after autologous stem cell infusion.

#### **4.1.2 Concomitant Medications Restrictions**



#### 4.1.2.1

Strong inhibitors of cytochrome P450 3A4 are known to alter vincristine metabolism, leading to increased vincristine neurotoxicity. Strong inhibitors of cytochrome P450 3A4, including azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) should all be avoided or used with great caution.

Additional inducers or inhibitors of CYP450 3A4 enzymes can be found at <http://medicine.iupui.edu/clinpharm/ddis>.

#### 4.1.2.2

PCP prophylaxis must be prescribed during induction chemotherapy and following consolidation. Cotrimoxazole (sulfamethoxazole/trimethoprim) should be the first consideration, but if that is not tolerated, pentamidine, dapsone, or other established PCP prophylactic regimens may be used. See the COG supportive care Guidelines at: [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp)

#### 4.1.2.3

Due to the significant risk of ototoxicity associated with the cisplatin and high-dose carboplatin used in this protocol, aminoglycoside antibiotics should be avoided if possible, or used with careful monitoring. While individual institutional practices regarding empiric antibiotic therapy for fever and neutropenia may be followed, it may be worth considering that the pilot patients treated at MSKCC usually received cefepime and ciprofloxacin.

#### 4.1.2.4

**Antiemetics:** (As per institutional guidelines). Aprepitant is a substrate, a weak to moderate (dose dependent) inhibitor, and a weak inducer of Cytochrome CYP450 3A4. Aprepitant is also a weak inducer of CYP450 2C9. Therefore, aprepitant can interact with many drugs including steroids and benzodiazepines. Aprepitant should be used with caution when administering with etoposide or vincristine.

#### 4.1.2.5

No other cancer chemotherapy, radiotherapy or immunomodulating agents will be used other than the regimen prescribed by the protocol. Corticosteroid therapy may be used for treatment of increased intracranial pressure in patients with CNS tumors. Due to theoretical concerns that dexamethasone may stabilize the blood-brain-barrier and decrease chemotherapy delivery to the central nervous system, dexamethasone should only be used with caution as an anti-emetic and the dose adjusted if used with aprepitant (see the COG supportive care Guidelines at:

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

#### 4.1.2.6

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary (for Supportive Care see Section VIII or the COG Supportive Care Guidelines at: [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp)).

## 4.2 Administration Schedules

### 4.2.1 Administration Schedule for a Reporting Period (Standard Induction-Cycles 1-4)

Note: An Alternative Induction scheme will be employed for patients with significant ototoxicity, pre-existing hearing impairment and/or expected visual impairment. See Section 4.2.2 for treatment details for Alternative Induction therapy.

Criteria to start cycle/course: ANC  $\geq 1500/\mu\text{L}$ , platelets  $\geq 100000/\mu\text{L}$

#### 4.2.1.1 VinCRISTine (VCR) - Administer by IV push over 1 minute or infusion via minibag as per institutional policy

Days 0, 7 and 14 of Cycles 1-4

0.05 mg/kg/day for patients < 36 months

1.5 mg/m<sup>2</sup>/day for patients  $\geq 36$  months (Maximum dose: 2 mg per dose)

Avoid extravasation. Administration through a central line is suggested.

**Medication errors have occurred due to confusion between vinCRISTine and vinBLASStine.**

#### 4.2.1.2 CISplatin (CDDP) - Administer by IV infusion over 6 hours

Day 0 of Cycles 1-4.

3.5 mg/kg/day for patients < 36 months

105 mg/m<sup>2</sup>/day for patients  $\geq 36$  months

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

Suggested hydration: Administer 3000 mL/m<sup>2</sup>/day (125 mL/m<sup>2</sup>/hour) using fluid containing at least 0.45% NaCl. Achieve urine specific gravity  $\geq 1.020$ . Urine should contain supplemental magnesium, calcium, and potassium to decrease acute electrolyte losses associated with cisplatin therapy.

Suggested hydration would be D<sub>5</sub>W 1/2NS +10 mEq KCl/L + 1-2 grams (8-16 mEq) magnesium sulfate/L at 125 mL/m<sup>2</sup>/hour. May add calcium gluconate 250 mg/L.

Use of mannitol: Cisplatin doses may require use of mannitol to augment diuresis.

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

#### 4.2.1.3 Cyclophosphamide (CPM) - Administer by IV infusion over 1 hour

Days 1 and 2 of Cycles 1-4.

65mg/kg/day for patients < 36 months

1950 mg/m<sup>2</sup>/day for patients  $\geq 36$  months

Mesna must be administered in conjunction with Cyclophosphamide (see Section 4.2.1.4)

#### 4.2.1.4 Mesna (MESNA)

When administered intravenously, the total daily mesna dose is equal to 60% of the daily cyclophosphamide dose and is 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 cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide. For example: if the cyclophosphamide dose is 1000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or with the cyclophosphamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8.

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

For example: if the cyclophosphamide dose is 1000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

Mesna can also be administered as a continuous IV infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of the cyclophosphamide infusion. For example: if the cyclophosphamide dose is 1000 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 cyclophosphamide and be completed no sooner than 8 hours after the end of the cyclophosphamide infusion. If cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

##### 4.2.1.4.1 Mesna with cyclophosphamide - Administer by IV infusion or IV/PO

Days 1 and 2 of Cycles 1-4.

40 mg/kg/day for patients < 36 months

1200 mg/m<sup>2</sup>/day for patients

##### 4.2.1.5 Etoposide (ETOP) - Administer by IV infusion over 1 hour

Days 1 and 2 of Cycles 1-4.

4 mg/kg/day for patients < 36 months

120 mg/m<sup>2</sup>/day for patients

Infuse diluted solution (concentration \_\_\_\_\_ 1 hour; slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested. 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.

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

**Patients with Stage 2 or Stage 3 disease should proceed from Standard Induction Chemotherapy to External Beam Radiation Therapy (see Section 4.2.5).**

**Patients with Stage 4a or 4b disease proceed to the Consolidation phase of therapy.**

**The therapy delivery maps for the first reporting period (Standard Induction) are on the following two (2) pages.**

**The modifications to induction therapy (Alternative Induction) for patients with significant ototoxicity or expected visual impairment follow in Section 4.2.2.**

4.2.1.6 <b>Standard Induction</b> (All Patients): Cycles 1-4 This Therapy Delivery Map relates to Cycles 1 and 2	Patient name or initials _____	DOB _____
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*This Therapy Delivery Map covers the first 2 cycles of Standard Induction Therapy and is on one (1) page. Each cycle lasts 3 weeks. Extensive treatment details are provided in Section 4.2.1 Begin therapy when ANC ≥ 750/μL and platelets ≥ 75 000/μL (without transfusion)*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRISTine (VCR)	IV push over 1 min*	Pts < 36 mos: 0.05 mg/kg/day Pts <sup>2</sup> /day	0, 7 and 14	*Or infusion via minibag as per institutional policy. <b>Maximum dose: 2mg per dose</b>	a. History <sup>1</sup> , Creatinine, CBC (Differential, Platelets). Total Bilirubin, ALT (SGPT), Audiogram. b. Creatinine Clearance or GFR c. Physical Exam (Ht, Wt, BSA), Performance Status. d. Bone Marrow Examinations e. Other Tumor Response Evaluations <sup>2</sup>  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
CISplatin (CDDP)	IV over 6 hours	Pts < 36 mos: 3.5 mg/kg/day Pts <sup>2</sup> /day	0	See Section 4.2.1.2 for administration guidelines	
Cyclophosphamide (CPM)**	IV over 1 hour.	Pts < 36 mos: 65 mg/kg/day Pts <sup>2</sup> /day	1 and 2	See Section 4.2.1.3 for hydration guidelines	
** Mesna administered with CPM. See Section 4.2.1.4 for details.					
Etoposide (ETOP)	IV over 1 hour.	Pts < 36 mos: 4 mg/kg/day Pts <sup>2</sup> /day	1 and 2	Slow rate of administration if hypotension occurs.	
Start filgrastim (G-CSF) 5mcg/kg/day SubQ on Day 3 of each cycle and continue until the ANC _____ post-nadir. <i>For any cycle in which peripheral blood stem cell harvest is anticipated to be performed at recovery, the G-CSF dose will be 10mcg/kg/day SubQ.</i> Discontinue at least 24 hours before the start of the next cycle.					

<sup>1</sup>See Section 7.1 for details on follow-up observation. <sup>2</sup>See Section 7.1 for details on baseline extent of disease evaluations.

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	Cycle	Day	VCR mg	CDDP mg	CPM mg	MESNA mg/ mg/ mg	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)	
Enter calculated dose above and actual dose administered below											
		1	0	_____ mg	_____ mg				(a, b, c, d, e) <sup>@</sup>		
			1			_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg			
			2			_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg			
			3	Filgrastim Dose: _____ mcg			Date of first dose: _____		Date of last dose: _____		
			7	_____ mg							
			14	_____ mg							
			15-21	<b>Rest Period- No Chemotherapy</b>						(a, b <sup>#</sup> , d <sup>^</sup> ) <sup>+</sup>	
		2	0	_____ mg	_____ mg						
			1			_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg			
			2			_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg			
			3	Filgrastim Dose: _____ mcg			Date of first dose: _____		Date of last dose: _____		
			7	_____ mg							
			14	_____ mg							
			15-21	<b>Rest Period- No Chemotherapy</b>						(a, b <sup>#</sup> , d <sup>^</sup> , e <sup>+</sup> ) <sup>+</sup>	

See Section 4.2.3 for guidelines on peripheral stem cell harvest during induction. The Therapy delivery Maps for Cycles 3 and 4 continue on the next page.

<sup>@</sup>-Baseline requirements;

<sup>#</sup> Obtain if serum creatinine increases by \_\_\_\_\_ over baseline

<sup>^</sup> If positive at baseline, repeat prior to each cycle till stem cell harvest is complete.

<sup>+</sup> Prior to next cycle.

\*Repeat studies should address each site present at baseline

SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES, SECTION 8 FOR SUPPORTIVE CARE GUIDELINES

4.2.1.7 <b>Standard Induction</b> (All Patients): Cycles 1-4 This Therapy Delivery Map relates to Cycles 3 and 4				Patient name or initials _____ DOB _____	
<i>This Therapy Delivery Map covers the last 2 cycles of Standard Induction therapy and is on one (1) page. Each cycle lasts 3 weeks. Extensive treatment details are provided in Section 4.2.1 Begin therapy when ANC ≥ 750/μL and platelets ≥ 75 000/μL (without transfusion)</i>					
DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vincristine (VCR)	IV push over 1 min*	Pts < 36 mos: 0.05 mg/kg/day Pts _____ <sup>2</sup> /day	0, 7 and 14	*Or infusion via minibag as per institutional policy. <b>Maximum dose: 2mg per dose</b>	a. History <sup>1</sup> , Creatinine, CBC (Differential, Platelets). Total Bilirubin, ALT (SGPT), Audiogram. b. Creatinine Clearance or GFR c. Physical Exam (Ht, Wt, BSA), Performance Status. d. Bone Marrow Examinations e. Other Tumor Response Evaluations <sup>2</sup> .
CISplatin (CDDP)	IV over 6 hours	Pts < 36 mos: 3.5 mg/kg/day Pts _____ <sup>2</sup> /day	0	See Section 4.2.1.2 for administration guidelines	
Cyclophosphamide (CPM)**	IV over 1 hour	Pts < 36 mos: 65 mg/kg/day Pts _____ <sup>2</sup> /day	1 and 2	See Section 4.2.1.3 for hydration guidelines	
Etoposide (ETOP)	IV over 1 hour	Pts < 36 mos: 4 mg/kg/day Pts _____ <sup>2</sup> /day	1 and 2	Slow rate of administration if hypotension occurs.	
** Mesna administered with CPM. See Section 4.2.1.4 for details.					
Start filgrastim (G-CSF) 5mcg/kg/day SubQ on Day 3 of each cycle and continue until the ANC _____ post-nadir. <b>For any cycle in which peripheral blood stem cell harvest is anticipated to be performed at recovery, the G-CSF dose will be 10mcg/kg/day SubQ.</b> Discontinue at least 24 hours before the start of the next cycle.					
<b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>					

<sup>1</sup>See Section 7.1 for details on follow-up observation.

<sup>2</sup>See Section 7.1 for details on baseline extent of disease evaluations.

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	Cycle	Day	VCR mg	CDDP mg	CPM mg	MESNA mg/ mg/ mg	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)	
				Enter calculated dose above and actual dose administered below							
		3	0	mg	mg						
			1			mg	mg/ mg/ mg	mg			
			2			mg	mg/ mg/ mg	mg			
			3	Filgrastim		Dose: mcg		Date of first dose:		Date of last dose:	
			7	mg							
			14	mg							
			15-21	<b>Rest Period- No Chemotherapy</b>						(a, b <sup>#</sup> , d <sup>^</sup> ) <sup>†</sup>	
		4	0	mg	mg						
			1			mg	mg/ mg/ mg	mg			
			2			mg	mg/ mg/ mg	mg			
			3	Filgrastim		Dose: mcg		Date of first dose:		Date of last dose:	
			7	mg							
			14	mg							
			15-21	<b>Rest Period- No Chemotherapy</b>						a, b, c, d, e*	

See Section 4.2.3 for guidelines on Peripheral Stem Cell Harvest during Induction. Stages 2 and 3 patients go on to External Beam Radiation Therapy (Section 4.2.5) while Stages 4a and 4b patients go on to have Consolidation with Stem Cell Rescue (Section 4.2.4). The Therapy delivery Maps for the next reporting period (Consolidation) continues on page 29.

<sup>#</sup> Obtain if serum creatinine increases by \_\_\_\_\_ above baseline

<sup>^</sup> If positive at baseline, repeat prior to each cycle till stem cell harvest is complete and prior to consolidation.

<sup>†</sup> Prior to next cycle.

\*Repeat studies (prior to consolidation or radiation therapy) should address each site present at baseline

SEE SECTION 5.0 FOR DOSE MODIFICATIONS FOR TOXICITIES, SECTION 8 FOR SUPPORTIVE CARE GUIDELINES



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 cyclophosphamide and be completed no sooner than 8 hours after the end of the cyclophosphamide infusion. If cyclophosphamide is administered over 1 hour and mesna is started 30 minutes before the cyclophosphamide infusion, the total mesna infusion will last at least 9 hours and 30 minutes.

#### 4.2.2.3.1 Mesna with CPM - Administer by IV infusion or IV/PO

Days 0 and 1 of Cycles 1 and 2.

40 mg/kg/day for patients < 36 months

1200 mg/m<sup>2</sup>/day for patients

#### 4.2.2.4 Etoposide (ETOP)

**Note that the dose and number of days given during Cycles 1 or 2 and Cycles 3 or 4 are different.**

##### 4.2.2.4.1 Etoposide dose administered during Cycle 1 or 2

**Administer by IV infusion over 1 hour**

Days 0 and 1 of Cycles 1 or 2

4 mg/kg/day for patients < 36 months

120 mg/m<sup>2</sup>/day for patients

Infuse diluted solution (concentration

hypotension occurs. The use of an in-line filter during the infusion is suggested. 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.

##### 4.2.2.4.2 Etoposide dose administered during Cycle 3 or 4

**Administer by IV infusion over 1 hour**

Days 0, 1 and 2 of Cycles 3 or 4

3.3 mg/kg/day for patients < 36 months

100 mg/m<sup>2</sup>/day for patients

Infuse diluted solution (concentration

hypotension occurs. The use of an in-line filter during the infusion is suggested. 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.

#### 4.2.2.5 CARBOplatin (CARBO) - Administer IV over 1 hour

Days 0 and 1 of Cycle 3 or 4

16.7 mg/kg for patients < 36 months

500 mg/m<sup>2</sup> for patients

Infuse the diluted solution to a concentration as low as 0.5 mg/mL. Avoid use of aluminum containing needles or administration sets.

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

**See Section 5.0 for Dose Modifications based on Toxicities.**



**Patients with Stage 2 or Stage 3 disease should proceed from Alternative Induction Chemotherapy to External Beam Radiation Therapy (see Section 4.2.5)**

**Patients with Stage 4a or 4b disease proceed to the Consolidation phase of therapy.**

**The therapy delivery maps for the first reporting period (Alternative Induction- Cycles 1 to 4) for patients with expected visual impairment are on the following two (2) pages.**

**See Section 4.2.3 for guidelines on peripheral stem cell harvest during alternative induction.**

**The second reporting period (Consolidation) follows in Section 4.2.4.**

4.2.2.6 <b>Alternative Induction (Patients with Expected Visual Impairment):</b> Cycles 1-4 This Therapy Delivery Map relates to Cycles 1 or 2	_____	_____
	Patient name or initials	DOB

*This Therapy Delivery Map covers the first 2 Cycles of Alternative Induction Therapy and is on one (1) page. Each Cycle lasts 3 weeks Extensive treatment details are provided in Section 4.2.2. Begin therapy when ANC ≥ 750/μL and platelets ≥ 75 000/μL (without transfusion)*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRISTine (VCR)	IV push over 1 min*	Pts < 36 mos: 0.05 mg/kg/day Pts _____ <sup>2</sup> /day	0, 7 and 14	* Or infusion via minibag as per institutional policy. <b>Maximum dose: 2mg per dose</b>	a. History <sup>1</sup> , Creatinine, CBC (Differential, Platelets). Total Bilirubin, ALT (SGPT), Audiogram. b. Creatinine Clearance or GFR c. Physical Exam (Ht, Wt, BSA), Performance Status. d. Bone Marrow Examinations e. Other Tumor Response Evaluations <sup>2</sup> .  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
Cyclophosphamide (CPM)**	IV over 1 hour	Pts < 36 mos: 65 mg/kg/day Pts _____ <sup>2</sup> /day	0 and 1	See Section 4.2.2.2 for hydration guidelines	
**Mesna administered with CPM. See Section 4.2.2.3 for details.					
Etoposide (ETOP)	IV over 1 hour	Pts < 36 mos: 4 mg/kg/day Pts _____ <sup>2</sup> 20 mg/m <sup>2</sup> /day	0 and 1	Slow rate of administration if hypotension occurs.	
Start filgrastim (G-CSF) 5mcg/kg/day SubQ on Day 3 of each cycle and continue until the ANC _____ post-nadir. <i>For any cycle in which peripheral blood stem cell harvest is anticipated to be performed at recovery, the G-CSF dose will be 10mcg/kg/day SubQ.</i> Discontinue at least 24 hours before the start of the next cycle.					

<sup>1</sup>See Section 7.1 for details on follow-up observation.

<sup>2</sup>See Section 7.1 for details on baseline extent of disease evaluations.

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	Cycles	Day	VCR mg	CPM mg	MESNA mg/ mg/ mg	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		1	0	_____ mg	_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg	(a, b, c, d, e) <sup>@</sup>	
			1		_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg		
			3	Filgrastim		Dose: _____ mcg	Date of first dose: _____		Date of last dose: _____
			7	_____ mg					
			14	_____ mg					
			15-21	<b>Rest Period- No Chemotherapy</b>				(a, b <sup>#</sup> , d <sup>^</sup> ) <sup>+</sup>	
		2	0	_____ mg	_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg		
			1		_____ mg	_____ mg/ _____ mg/ _____ mg	_____ mg		
			3	Filgrastim		Dose: _____ mcg	Date of first dose: _____		Date of last dose: _____
			7	_____ mg					
			14	_____ mg					
			15-21	<b>Rest Period- No Chemotherapy</b>				(a, b <sup>#</sup> , d <sup>^</sup> , e*) <sup>+</sup>	

See Section 4.2.3 for guidelines on peripheral stem cell harvest during alternative induction. The Therapy Delivery Maps for Cycles 3 or 4 follow on the next page.

<sup>@</sup>-Baseline requirements;

<sup>#</sup> Obtain if serum creatinine increases by

<sup>^</sup> If positive at baseline, repeat prior to each cycle till stem cell harvest is complete.

<sup>+</sup>Prior to next cycle.

\* Repeat studies should address each site present at baseline

See Section 5.0 for Dose Modifications for Toxicities, Section 8 and the COG website posted materials for Supportive Care Guidelines

4.2.2.7 <b>Alternative Induction (Patients with Expected Visual Impairment):</b> Cycles 1-4 This therapy delivery map relates to Cycles 3 or 4	_____	_____
	Patient name or initials	DOB

*This Therapy Delivery Map covers the last 2 Cycles of Alternative Induction therapy and is on one (1) page. Each Cycle lasts 3 weeks. Extensive treatment details are provided in Section 4.2.2. Begin therapy when ANC ≥ 750/μL and platelets ≥ 75 000/μL (without transfusion)*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Vincristine (VCR)	IV push over 1 min*	Pts < 36 mos: 0.05 mg/kg/day Pts <sup>2</sup> /day	0, 7 and 14	*Or infusion via minibag as per institutional policy. <b>Maximum dose: 2mg per dose</b>	a. History <sup>1</sup> , Creatinine, CBC (Differential, Platelets), Total Bilirubin, ALT (SGPT), Audiogram. b. Creatinine Clearance or GFR c. Physical Exam (Ht, Wt, BSA), Performance Status. d. Bone Marrow Examinations e. Other Tumor Response Evaluations <sup>2</sup> . <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
CARBOplatin (CARBO)	IV over 1 hour	Pts < 36 mos: 16.7 mg/kg /day Pts <sup>2</sup> /day	0 and 1		
Etoposide (ETOP)	IV over 1 hour	Pts < 36 mos: 3.3 mg/kg/day Pts <sup>2</sup> /day	0, 1 and 2	Slow rate of administration if hypotension occurs.	
Start filgrastim (G-CSF) 5mcg/kg/day SubQ on Day 3 of each cycle and continue until the ANC 2000/μL post-nadir. <b>For any cycle in which peripheral blood stem cell harvest is anticipated to be performed at recovery, the G-CSF dose will be 10mcg/kg/day SubQ.</b> Discontinue at least 24 hours before the start of the next cycle.					

<sup>1</sup>See Section 7.1 for details on follow-up observation.

<sup>2</sup>See Section 7.1 for details on baseline extent of disease evaluations.

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	Cycle	Day	VCR mg	CARBO mg	ETOP mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		3	0	mg	mg	mg		
			1		mg	mg		
			2			mg		
			3	Filgrastim		Dose: _____ mcg	Date of first dose: _____	Date of last dose: _____
			7	mg				
			14	mg				
			15-21	<b>Rest Period- No Chemotherapy</b>			(a, b <sup>#</sup> , d <sup>^</sup> ) <sup>+</sup>	
		4	0	mg	mg	mg		
			1		mg	mg		
			2			mg		
			3	Filgrastim		Dose: _____ mcg	Date of first dose: _____	Date of last dose: _____
			7	mg				
			14	mg				
			15-21	<b>Rest Period- No Chemotherapy</b>			a, b, c, d, e*	

See Section 4.2.3 for guidelines on peripheral stem cell harvest during Induction. The Therapy Delivery Maps for the next reporting period (Consolidation) continues on page 29.

<sup>#</sup> Obtain if serum creatinine increases by

<sup>^</sup> If positive at baseline, repeat prior to each cycle till stem cell harvest is complete and prior to consolidation.

\* Repeat studies (prior to consolidation or radiation therapy) should address each site present at baseline <sup>+</sup> Prior to next cycle

See section 5.0 for dose modifications for toxicities, section 8 the COG website posted materials for supportive care guidelines

#### 4.2.3 Peripheral Blood Stem Cell Harvesting (During Induction).

Peripheral blood stem cells will be the preferred source of hematopoietic stem cells on this protocol, but should the institutional clinicians deem bone marrow harvesting preferable, bone marrow may be used as a permissible alternative stem cell source. In such case, bone marrow harvesting should be performed according to institutional guidelines.

If the bone marrow was not involved at baseline, the harvest may be performed after any cycle of induction chemotherapy. However, many of the patients on this study will have bone marrow metastases at diagnosis and so appropriate timing of the stem cell harvest is important. The MSKCC experience suggests that administration of 2 additional cycles of induction chemotherapy following documentation of marrow clearance allows harvest of a product free of contaminating tumor. Therefore, on this protocol, stem cell harvesting will be performed 2 cycles post-marrow clearance. For example, if marrow disease is no longer detectable after Cycle 1, the stem cell harvest will be performed post-cycle 3. If the bone marrow was initially positive at baseline, bone marrow examinations should be performed after each cycle of chemotherapy prior to stem cell harvesting.

Institutional practices for the peripheral blood stem cell harvest may be followed as long as the target goal of stem cell product is achieved. The following are suggested guidelines only.

##### 4.2.3.1. Catheter Placement

Patients will need a double lumen apheresis catheter for the peripheral blood stem cell collection. If the patient has a mediport for use during the induction chemotherapy period, it will likely not be sufficient for the harvest and placement of a temporary femoral vein apheresis catheter for the harvest is recommended.

##### 4.2.3.2. Protocol for Peripheral Stem Cell Mobilization

When the ANC is  $> 1000/\mu\text{L}$  post nadir, plan harvest approximately 2 days later. Continue filgrastim until the harvest is complete and an adequate yield is documented.

##### 4.2.3.3. Procedure for Peripheral Stem Cell Collections

The goal of apheresis will be to collect 2 aliquots of  $(2.5 \times 10^6 \text{ CD34+ cells/kg})$  per aliquot. If less than a single aliquot of  $2.5 \times 10^6 \text{ CD34+ cells/kg}$  can be obtained the patient will not be allowed to proceed to consolidation and will be off protocol therapy (for Stage 4a and 4b patients). It is recommended that at least 3 blood volumes be processed per day.

#### 4.2.4 Administration Schedule for a Reporting Period (Consolidation) - High-Dose Chemotherapy with Stem Cell Rescue

**Only Patients With Stage 4a Or 4b Disease Receive the Consolidation Phase of Therapy. Patients with Stage 2 Or Stage 3 Disease Should Proceed From Induction Chemotherapy to External Beam Radiation Therapy.**

Criteria to proceed to Consolidation:

- Adequate stem cell yield
- Adequate remission status (complete response, very good partial response or partial response as defined in Section 11). Please note: for some patients with trilateral retinoblastoma, it may be difficult to distinguish between tumor necrosis and refractory tumor. Please consider second look surgery prior to Consolidation therapy should uncertainty arise as to whether an adequate response has been achieved.
- Creatinine clearance or nuclear medicine GFR > 60 mL/minute/1.73 m<sup>2</sup>
- Total bilirubin < 1.5 x upper limit of normal
- AST < 3 x upper limit of normal
- Echocardiogram or MUGA scan demonstrating normal cardiac function (normal ejection fraction or fractional shortening)
- No evidence of uncontrolled serious infection

##### 4.2.4.1 CARBOplatin (CARBO) - Administer IV over 4 hours

Days -8 to -6

AUC=7/day\* for patients < 36 months (Maximum 16.7 mg/kg)

AUC=7/day\* for patients <sup>2)</sup>

Infuse the diluted solution to a concentration as low as 0.5 mg/mL. Avoid use of aluminum containing needles or administration sets.

##### Modified Calvert Formula for calculating carboplatin dose

Dose (mg) = target AUC x [raw CrCl + (BSA x 15)] for patients ≥ 10 kg of body wt.

Dose (mg) = target AUC x [raw CrCl + (body weight in kg x 0.36)] for patients < 10 kg of body wt.<sup>26</sup>

Important note: The raw creatinine clearance is used in the formulas above, not the creatinine clearance corrected to 1.73 m<sup>2</sup>. The maximum daily dose of carboplatin will be 500 mg/m<sup>2</sup> for patients ≥ 36 months or 16.7 mg/kg for patients < 36 months (even if the calculated dose via the Calvert formula is higher than that). Repeat creatinine clearances should be obtained following the day -8 and day -7 carboplatin administration and will be used to determine the dose for the subsequent day of carboplatin.

Example:

For a patient ≥ 10 kg and ≥ 36 months:

If the GFR is reported as corrected GFR = 171 mL/min/1.73m<sup>2</sup>

BSA = 0.71 m<sup>2</sup> Weight = 17 kg Target AUC = 7 mg•min/mL

1. Convert corrected GFR to raw GFR  
 $171 \text{ mL/min/1.73 m}^2 \times 0.71 \text{ m}^2 = 70.2 \text{ mL/min/m}^2$
2. Insert above value into following formula:  
Dose in mg = 7 x [70.2 + (0.71 x 15)] = 566 mg

3. Compare to dose in  $\text{mg}/\text{m}^2$ :  
Dose in  $\text{mg}=500 \text{ mg}/\text{m}^2 \times 0.71\text{m}^2=355 \text{ mg}$ .

Use the lower dose =355 mg

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

#### 4.2.4.2 Thiotepa (TEPA) - Administer intermittent IV infusion over 3 hours

Days -5 to -3

10 mg/kg/day for patients < 36 months

300  $\text{mg}/\text{m}^2$ /day for patients

Frequent bathing and linen changes should be done to avoid chemical skin burns.

#### 4.2.4.3 Etoposide (ETOP) - Administer by IV infusion over 3 hours

Days -5 to -3.

8.3 mg/kg/day for patients < 36 months

250  $\text{mg}/\text{m}^2$ /day for patients

Fluid volumes may be prohibitive at a 0.4 mg/mL concentration; an alternative dilution of 0.6 mg/mL (8 hour stability) may be used. Infusion of undiluted etoposide has been associated with cracking of hard plastic in chemotherapy venting pins and infusion lines. For concentration > 0.4 mg/mL, use an in-line filter during infusion secondary to precipitate formation risk

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.

#### 4.2.4.4 Stem Cell Infusion - Administer IV

Day 0

Dose is  $5 \times 10^6$  CD34+cells/kg

At least 48 hours must elapse between completion of Consolidation chemotherapy infusion and infusion of the peripheral blood stem cells (PBSC). The dose of PBSC infused will be at least  $2.5 \times 10^6$  CD34+ cells/kg. If bone marrow is the source of stem cells, at least  $1.0 \times 10^8$  total nucleated cells/kg will be infused. The peripheral blood stem cells may be washed and placed in a bag for infusion.

Suggested pre-medications are acetaminophen and diphenhydramine, but institutional practice guidelines may be substituted.

**See Section 5.0 for Dose Modifications based on Toxicities.**

**The therapy delivery map for the second reporting period (Consolidation) is on the following one (1) page. The third reporting period (External Beam Radiation Therapy) will follow in Section 4.2.5**



### 4.3 Radiation Therapy Guidelines

Radiation therapy for patients on COG protocols can only be delivered at approved COG RT facilities (see Administrative Policy 3.9).

#### 4.3.0.1 General Guidelines

The radiation therapy guidelines for this study were developed specifically for patients with newly diagnosed extraocular retinoblastoma. The guidelines are meant to cover a broad range of indications and the use of a variety of treatment modalities. Because this study includes patients with metastatic disease who will be treated with curative intent, body site specific treatment recommendations have been included which parallel guidelines used in other COG solid tumor protocols.

#### 4.3.0.2 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 irradiate the RPC head and neck phantom and those using protons must complete the proton benchmark and questionnaire. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (QARC, [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>).

#### 4.3.0.3 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.

#### 4.3.0.4 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. These guidelines shall be available through [www.qarc.org](http://www.qarc.org).

#### 4.3.0.5 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.

### 4.3.1 Indications for Radiation Therapy

Stage 2 and 3 patients (orbital and/or regional involvement) will receive radiation therapy (RT) to sites that were initially involved. Stage 4a and 4b patients will receive RT to sites initially involved based on response. Stage 4a patients (hematogenous metastases not involving the CNS) who achieve a complete response to induction chemotherapy or with less than 5 mm of residual tumor at the time of planned irradiation, will not receive RT. RT will be omitted for stage 4b patients (CNS involvement) who achieve a complete response to induction chemotherapy.



**4.3.2 Timing**

4.3.2.1 All patients should be seen in consultation by a radiation oncologist at the time of study enrollment. 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.

4.3.2.2 For Stage 2 and 3 patients, RT should begin within 42 days after the start of cycle 4 of induction chemotherapy. For Stage 4a and 4b patients who will receive radiation therapy, treatment should start on approximately day +42 post-autologous stem cell infusion.

4.3.2.3 Multiple metastatic sites

Some patients will have multiple metastatic sites that require irradiation. When the number of lesions exceeds 3, the radiation oncologist must prioritize metastatic sites for treatment and may consider obviating or delaying treatment of certain sites. Factors to consider when choosing metastatic sites for irradiation when all cannot feasibly or safely be treated include: (1) sub-optimal response to chemotherapy, (2) sites which will be problematic in the event of disease progression, and (3) sites that can be imaged with sufficient accuracy for treatment.

4.3.3 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. The entire course of treatment does not need to be administered from the outset. Often symptoms may be alleviated after a few treatments. The treatment may then be discontinued and the doses and volumes appropriately incorporated into the definitive treatment.

4.3.4 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			
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.

4.3.4.1 Treatment planning

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 4.3.9). 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. CT section thickness should be  $\leq 5$ mm although 2-3mm is preferred.

4.3.4.2 In-room verification of spatial positioning

4.3.4.2.1 Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy.

Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

4.3.4.2.2 Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging. Please submit representative axial images showing the isocenter and the correct alignment in relationship to the patients' position. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

#### 4.3.5 Target Volumes

##### 4.3.5.1 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*.

##### 4.3.5.2 Protocol tumor and target volume definitions

###### 4.3.5.2.1 GTV

GTV 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. For patients with initial tumors that extend into body cavities (i.e., thorax, abdomen) the GTV may require modification. If the tumor has been resected or responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV excludes the volume which extends into the cavity. Examples include tumors which compress but not invade the brain, lung, intestine or bladder that radiographically return to normal anatomic position following surgery or chemotherapy. The GTV must include all infiltrative disease detected at initial presentation.

#### 4.3.5.2.2 CTV

If there are no sites that warrant irradiation for potential occult tumor, then the CTV is defined as the GTV plus 0.5cm (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 (see Section 4.3.5.4). When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.

#### 4.3.5.2.3 PTV

For external beam photon techniques, the PTV is defined as the CTV 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 CTV. The minimum margin is 0.5cm but does not have to be uniform in all dimensions. For proton planning, beam specific PTV expansions will be required.

#### 4.3.5.4 Site-specific modifications

##### *Extremity Sites*

The CTV should be modified at the discretion of the radiation oncologist to avoid circumferential irradiation of extremity lymphatics and treatment across a joint.

##### *Head and Neck Sites*

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, lid, lacrimal gland, and optic nerve.

##### *Orbital Sites*

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 Sites*

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 Sites*

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. In the event that whole abdomen radiotherapy is required (*i.e.*, for malignant ascites or diffuse peritoneal involvement), the dose will be 2400cGy at 150cGy per fraction with appropriate blocking of the kidneys and liver to keep them within normal tissue recommendations (see Section 4.3.8).

#### *Lymph Nodes*

For tumors with no evidence of nodal involvement ( $N_0$ ), the draining regional lymph nodes should not be irradiated. When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.

#### *Pulmonary Metastases*

Patients with single or multiple pulmonary metastases will receive bilateral whole lung irradiation to 1500cGy in 150cGy fractions. Patients 6 years of age and younger will receive 1200cGy at 150cGy per fraction. Gross disease may be boosted with a small targeted field to 4500cGy if the normal tissue recommendations can be followed. For patients with a single malignant pleural effusion, only the involved hemithorax will be irradiated to 1500cGy (1200cGy in patients 6 years and younger). Dose to the thoracic metastases when given concurrently with whole lung irradiation will be given at 150cGy per fraction. After the whole lung portion is completed, the primary tumor site cumulative dose should be brought to the intended dose using 180cGy per day fractionation.

#### *Metastatic Sites - General*

Radiation is recommended to all metastatic sites when feasible. Feasibility diminishes as the number of metastatic sites increases and will be determined by the treating radiation oncologist. Radiation is recommended to those metastatic sites not irradiated when directed if there remains a concern about disease control at that site and the patient can tolerate further radiotherapy without undue morbidity. Re-evaluation imaging will help the radiation oncologist determine if the various remaining sites are in need of further treatment and will consider the following: (1) sub-optimal response to chemotherapy by clinical or imaging criteria, (2) sites which will be problematic in the event of disease progression (*i.e.*, tumor in a weight bearing bone), and (3) sites that can be imaged with sufficient accuracy for treatment, and (4) expected tolerance and morbidity (*i.e.*, bone marrow tolerance). The GTV for metastatic sites is the area of residual tumor defined on CT, PET, and/or MRI (postchemotherapy/surgery). In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated.

#### 4.3.5.5 Targeting of metastases

The GTV for metastatic sites is the area of residual tumor defined on CT or MRI (post-chemotherapy/surgery). In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. A CTV is not required for the treatment of metastatic lesions. The appropriate PTV should be the GTV with a geometric margin of 1cm.

#### 4.3.6 Target Dose

Integrated boost radiotherapy plans are not permitted.

##### 4.3.6.1 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.

**4.3.6.2 Prescribed dose and fractionation**

The protocol-specified dose per fraction is 180cGy. The treatment should be limited to one fraction per day. At least two fractions should be given during the first week of treatment. 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 tolerance (*i.e.*, mucositis or diarrhea). Changes to the fractionation regimen should be noted in the treatment record and submitted information.

**Table 4.3.5.5.1: Target volumes and doses for patients with Stage 2 and 3 retinoblastoma**

Stage/Site	GTV	CTV	PTV	PTV Doses
Stage 2 Orbital Involvement	Residual Tumor	Orbit including GTV	CTV+5mm	45 Gy
Stage 3 Orbital and Regional Extraorbital Involvement	Residual Tumor and Regional Lymph Nodes after Induction	Orbit† including GTV and initially involved extraorbital and regional lymph nodes	CTV+5mm	45 Gy

Definitions: Orbit = internal bony orbit, optic foramen and optic nerve to chiasm; GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume

† Orbit may be omitted from the treatment volume for Stage 3 retinoblastoma when Stage 2 features are not present.

**Table 4.3.5.5.2: Target volumes and doses for patients with Stage 4a retinoblastoma**

	Irradiation Sites	GTVx	CTVx	PTVx	PTVx Doses
4a	≥ 5mm Pre-RT Residual	Pre-RT residual	GTV+5mm	CTV+5mm	36 Gy
	< 5mm Pre-RT Residual or CR	-	-	-	-

Definitions: GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; disease measurements are determined by MR or CT; x = denotes more than one metastatic site that requires irradiation and the nomenclature of GTVa, CTVa, PTVa; GTVb, CTVb, PTVb... is preferred with appropriate documentation for each target volume.

**Table 4.3.5.5.3: Target volume and doses for patients with Stage 4b retinoblastoma**

		CTV1	PTV1	GTV2x	CTV2x	PTV2x	PTV2x Doses
4b	< CR	CSI 23.4 Gy (Age 36.0Gy (Age > 60m):	CTV1 + 5mm	≥5mm and/or pineal	GTV +5mm and/or pineal +5mm	CTV2 +5mm	36 Gy (spine); 45 Gy (cranium); 50.4 Gy (pineal)
	CR	-	-	-	-	-	-

Definitions: GTV = gross tumor volume(s); CTV = clinical target volume; PTV = planning target volume; CSI = craniospinal irradiation of intracranial and spinal subarachnoid volume encompassed using standard techniques; Age = age in months at the start of radiation therapy; CTV1 and PTV1 are the clinical and planning target volumes for craniospinal irradiation; x = denotes more than one CNS site that requires irradiation and the nomenclature of GTV2a, CTV2a, PTV2a, GTV2b, CTV2b, PTV2 is preferred with appropriate documentation for each target volume.

#### 4.3.6.3 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.

#### 4.3.6.4 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)).

#### 4.3.6.5 Environment of care - Interruptions, delays and dose modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life-threatening infection or severe hematologic toxicity defined as ANC < 300/ $\mu$ L or platelets < 40 000/ $\mu$ L during the course of treatment. Under these circumstances, radiation therapy shall be delayed until the counts have recovered. Blood product support should be instituted according to institutional/protocol guidelines. There is no minimum hemoglobin level during radiation therapy. The reason for any interruptions greater than 5 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels.

#### 4.3.7 Treatment Technique

##### 4.3.7.1 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.

##### 4.3.7.2 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.

##### 4.3.7.3 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.

#### 4.3.7.4 Simulation including patient positioning and immobilization

##### 4.3.7.4.1 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.

##### 4.3.7.4.2 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.

##### 4.3.7.5 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

##### 4.3.7.6 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. The planning organ at risk volume (PRV) includes the organs at risk (OAR) surrounded by a margin to compensate for physiologic change in the target volume. If adequate clinical data do not exist to define the IM component of the PTV or the PRV margin, the following suggestions are provided:

- A margin of at least 0.5cm should be added to any OAR to form the PRV.
- 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 4.3.10.

##### 4.3.7.7 Brachytherapy

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.

The following guidelines may be considered in planning the implant:

A single plane implant is generally used for patients with microscopic residual disease. The target volume should include all sites of potential microscopic disease with at least 1.0cm margin on all sides. 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.

Multi-plane implants are generally used for patients with gross 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 3cm, external beam radiation therapy should be considered, but is not required.

Implants should be designed to meet the following dose uniformity criteria:

$${}_{CTV}D_{100}$$

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

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 for node negative patients; 3000cGy for node positive patients

Dose rate range: 40-100cGy/hour.

HDR brachytherapy

Total dose: 2100cGy for node negative patients; 2400cGy for node positive patients

Dose per fraction: 300cGy BID (separate fractions by )

Number of fractions: 7 for node negative patients; 8 for node positive patients

Brachytherapy should not begin until postoperative Day 5 to allow for wound healing.

**4.3.8 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. In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines. Normal tissue dose recommendations are the same for photons and protons (proton dose measured in CGE).

**Table 4.3.8: Organs at risk dose recommendations**

Organ	Volume (%)	Dose (cGy)
<b>Single organs</b>		
Bladder	100%	4500
Heart	100%	3000
Liver	100%	2340
	50%	3000
Rectum	100%	4500
Optic chiasm	100%	5400
Small Bowel	75%	4500



Organ	Volume (%)	Dose (cGy)
Spinal Cord	Any volume	4500
<b>Paired organs</b>		
Kidney (bilateral)	50%	2400
Kidney (bilateral)	100%	1440
Lung (bilateral)	20%	2000
Lung (bilateral)	100%	1500
Optic nerve	100%	5400

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 %.

#### 4.3.9 Dose Calculations and Reporting

##### 4.3.9.1 Prescribed Dose

The dose prescription and fractionation shall be reported on the RT-1/IMRT Dosimetry Summary Form. The total dose delivered shall be reported on the RT-2 Radiotherapy Total Dose Record. 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.

##### 4.3.9.2 Normal Tissue Dosimetry

The daily dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record form. The appropriate dose-volume histograms should 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 4.3.9.2: Required normal tissue DVH data according to primary treatment site(s)**

Treatment Area	Required DVH
Head	Optic Nerve
	Optic Chiasm
	Pituitary
	Right and Left Cochlea
Neck	Thyroid
Chest	Lung
	Heart
	Liver
Abdomen	Right and Left Kidney
	Bladder and rectum
Pelvis	Bladder and rectum
Spinal Cord	Spinal Cord

#### 4.3.10 **Quality Assurance Documentation**

##### Key Points

- Within 3 days of the initiation of treatment, please submit date for on treatment review (**orbital and craniospinal irradiation cases only**).
- Within 1 week of the completion of radiotherapy:
  - Submit data for the primary site only (see checklist);
  - It is required that primary site data submission be in digital format.
- Only the RT-2 form and a copy of the treatment chart need to be submitted for metastatic sites.

**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 4.3.8. 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 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.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- 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 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).

- 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 4.3.7).
- RT-2 Radiotherapy Total Dose Record Form.

**Please submit the following for Metastatic Sites:**

**Forms**

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

**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 the 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)

These data should be forwarded to:

Quality Assurance Review Center  
272 West Exchange St., Suite 101  
Providence, Rhode Island 02903-1025  
Phone: (401) 454-4301  
Fax: (401) 454 4683

Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist  
Quality Assurance Review Center  
272 West Exchange St., Suite 101  
Providence, Rhode Island 02903-1025

**4.3.11 Definition of Minor and Major Deviations**

Definitions of deviation in protocol performance will be applied to the treatment of the primary lesion only.

ARET0321	DEVIATION	
	Minor	Major
<b>Prescription Dose</b>		
External beam	Difference in prescription dose is 6%-10% of protocol-specified dose	Difference in prescription dose is > 10% of protocol-specified dose

Brachytherapy	Difference in prescription dose is 6%-10% of protocol-specified dose	Difference in prescription dose is >10% of protocol-specified dose
<b>Dose Uniformity</b>		
External beam	> 10% PTV receives > 110% of protocol 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 less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	GTV does not encompass MR-visible residual tumor

## **5.0 DOSE MODIFICATION FOR TOXICITY**

### **5.1 Drug Modifications for Induction**

#### **5.1.1 Infection**

No modification of subsequent induction chemotherapy cycles will be made for infection or fever following a previous cycle.

#### **5.1.2 Ototoxicity and Visual Impairment**

Ototoxicity is a particular concern in this study especially with the likelihood of visual impairment or blindness in some of these children. The goal of the induction therapy is to use intensive cyclophosphamide and platinum based therapy to rapidly induce a bone marrow remission to allow harvesting of peripheral blood stem cells free of tumor. If the child is expected to have normal vision in at least 1 eye (fovea free of tumor), the standard induction regimen (Section 4.2.1) should be used.

The following conditions may require treatment modification guidelines:

- If hearing loss following cisplatin administration is equal to or greater than 20 decibels at 500 - 4000 Hz in either ear, omit cisplatin. No modification of dose for hearing loss above 4000 Hz.
- If the patient is expected to have significant pre-existing visual impairment bilaterally (for example, neither fovea free of tumor).

An alternative induction scheme intended to still employ intensive cyclophosphamide and platinum may be used. In such cases, cisplatin may be omitted from the induction regimen for the first 2 cycles (administer vincristine, cyclophosphamide and etoposide only). In such case, cyclophosphamide and etoposide will be administered on Days 0 and 1 rather than on Days 1 and 2. Cycles 3 and 4 will consist of vincristine, carboplatin, and etoposide (see Section 4.2.2 for details).

#### **5.1.3 Nephrotoxicity**

If GFR is greater than 100 mL/min/1.73 m<sup>2</sup>, give full dose cisplatin. If 50 to 100 mL/min/1.73 m<sup>2</sup> give 2/3 dose; if less than 50 mL/min/1.73 m<sup>2</sup>, omit cisplatin.

If GFR is greater than 50 mL/min/1.73 m<sup>2</sup>, give full dose etoposide. If 10 to 50 mL/min/1.73 m<sup>2</sup> give 75% dose; if less than 10 mL/min/1.73 m<sup>2</sup>, give 50% dose of etoposide.

If GFR is greater than 50 mL/min/1.73 m<sup>2</sup>, give full dose cyclophosphamide. If 10 to 50 mL/min/1.73 m<sup>2</sup> give 75% dose; if less than 10 mL/min/1.73 m<sup>2</sup>, give 50% dose of cyclophosphamide.

#### 5.1.4 Hepatotoxicity

Doses of **etoposide** should be modified for an elevated bilirubin according to the following table:

Direct bilirubin	Recommended Dose
< 1.5 mg/dL (< 26 micromoles/L)	Give full dose
1.5-3 mg/dL (26-51 micromoles/L)	Give 50% of scheduled dose
> 3 mg/dL (>51 micromoles/L)	Hold dose

Doses of **vincristine** should be modified for an elevated direct bilirubin according to the following table:

Direct bilirubin	Recommended Dose
≤ 3 mg/dL (51 micromoles/L)	Give full dose
> 3 mg/dL (51 micromoles/L)	Give 50% of scheduled dose up to a MAX of 1 mg

If the AST is 60 to 180 units/L, administer 50% of the etoposide dose. If the AST is \_\_\_\_\_ units/L, hold etoposide.

#### 5.1.5 Neurological toxicity

If Grade 3 or 4 peripheral neuropathy (starting January 1<sup>st</sup>, 2011, it will include “**Peripheral motor neuropathy**” and/ or “**Peripheral Sensory neuropathy**” per CTCAE V4.0 terms) develops, defer vincristine until improvement occurs then resume at 50% dose and escalate as tolerated.

#### 5.1.6 Hemorrhagic cystitis

If microscopic or gross hematuria occurs after cyclophosphamide, consider (1) placement of a Foley catheter during cyclophosphamide infusion and for about 24 hours afterwards and (2) doubling the Mesna dose and/or extending the duration of Mesna therapy by 24 hours.

#### 5.1.7 Etoposide allergy

In the event of an allergic reaction to etoposide, etoposide phosphate may be substituted.

#### 5.1.8 Stage 2 & 3 patients

For Stage 2 & 3 patients only: for grade 4 neutropenia or thrombocytopenia that last for > 14 days, decrease the dose of cyclophosphamide by 25% in the next cycle.

## **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 noted 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 Clinical, Laboratory and Disease Evaluations**

STUDIES TO BE OBTAINED	Baseline	Prior to each induction cycle	Prior to consolidation	Prior to RT	Completion of therapy	During follow-up
History	X	X	X	X	X	X****
Physical Exam (Ht, Wt, BSA)	X		X	X	X	
Performance Status	X		X	X	X	
CBC, differential, platelets	X	X	X	X	X	
Creatinine	X	X	X	X	X	
Creatinine clearance or GFR	X	X*	X			
Total bilirubin, ALT	X	X	X	X	X	
Audiogram	X	X	X	X	X	
Bone marrow examinations	X	X**	X**			
Other tumor response evaluations	X <sup>o</sup>	Pre-cycle 3***	X***	X***	X***	

(<sup>o</sup>) Baseline extent of disease evaluations include Brain/Orbit MRI (with and without Gadolinium), lumbar puncture for CSF cytology, Abdominal CT (with IV contrast), and bone scan. If either the brain MRI or CSF cytology is (+), a total spine MRI (with and without Gadolinium) should be performed.

(\* ) Obtain if serum creatinine increases by

(\*\* ) If initially positive at baseline, repeat bone marrow examinations prior to each cycle until stem cell harvest is complete and prior to consolidation.

(\*\*\*) Repeat tumor response evaluations should address each site of disease present at baseline.

(\*\*\*\*) Report of the patient’s status should be made about every 3 months for the first year following completion of therapy, and then at least annually (until 10 years past the date on which the study is no longer open for accrual). Laboratory and radiological studies to be performed during follow-up will be at the treating physician’s discretion.

**7.2 Recommended Clinical, Laboratory and Disease Evaluations**

Prior to consolidation high-dose chemotherapy: As well as the mandated studies outlined above, institutional practices should apply. Many hematopoietic cell transplantation programs may require viral serologies, dental evaluation, and consideration of a chest CT if there is any suggestion of pulmonary disease.

### 7.3 Specimens Requested for Biologic Studies

Submission of primary intra-ocular tumor and/or metastatic tumor is not required for participation on this protocol, but is strongly encouraged to allow future biological studies regarding genetic alterations associated with the metastatic phenotype.

*Tissue:* Please submit any available tissue not required for diagnostic purposes at originating institution. If a tissue piece of at least 0.5 cm in diameter is available, then tissue should be equally divided between formalin-fixation and cryopreservation at  $-70^{\circ}\text{C}$ . **If less is available, please send frozen tissue as the priority.**

- 1) Frozen Tissue: Submit representative primary and metastatic tumor tissue at diagnosis. 20 to 50 mg of non-sterile tumor should be frozen as soon as possible after biopsy. Wrap in aluminum foil, freeze in liquid nitrogen or isopentane and then place in the plastic zip-lock bag provided in the Specimen Procurement Kit. Store at  $-70^{\circ}\text{C}$  until shipped to BPC.
- 2) Formalin Fixed Tissue: Submit a minimum of 1 representative formalin-fixed paraffin-embedded tissue block from primary and metastatic tumor. If a block is not available, submit primary and metastatic tissue in 10% buffered formalin. Store and ship at room temperature.
- 3) Slides: 20 tissue sections from formalin-fixed paraffin-embedded block. Sections should be 3-5 $\mu\text{m}$  in thickness and placed on coated slides for immunocytochemical studies. Store and ship at room temperature.

*Blood:* Collect 5 mL of blood in an EDTA (purple top) tube. Centrifuge sample and draw off plasma. Distribute plasma evenly among the 5 vials from the Specimen Procurement Kit. Store plasma at  $-70^{\circ}\text{C}$  to  $-80^{\circ}\text{C}$  until shipped. Plasma will be collected from all patients at diagnosis.

Additionally, on the days when bone marrow aspirates are performed, 2.5 mL of peripheral blood in PAXgene tube (Qiagen) should be obtained and submitted at room temperature.

*Bone marrow:* An additional aliquot of bone marrow (5 to 10 mL with 100 Units of heparin/mL of marrow) should be obtained when each bone marrow aspiration is performed and submitted at room temperature.

Label specimens for biologic studies with the BPC Number, collection date and specimen type.

### 7.4 Specimen Shipping

To facilitate collection of biologic samples, the Biopathology Center (BPC) will provide a Specimen Procurement Kit. The specimen procurement kit is constructed to allow shipment of frozen (on dry ice) and ambient temperature tissues in the same container. The kit provides specimen collection containers, instructions, a pre-printed Federal Express air bill and required biohazard and dry-ice labels. For further information, or to obtain kit, please contact the BPC at (800) 347-2486.

Dry ice may be placed in either compartment of the kit, but should not be put in both. Place the frozen tissue and plasma in one compartment of the kit along with 4 lbs. of dry ice. Place the fixed tissue and slides in the other compartment of the kit. All specimens should be shipped in three layers of packaging. Remember to package ambient and frozen specimens separately. First place the specimens in a zip-lock bag and seal securely. Next place the zip-lock bag into a Biohazard Secondary Shipping Envelope with absorbent material and seal securely. Then, place the Biohazard envelope into the Tyvek Diagnostic Envelope and seal securely. Always include a specimen transmittal form with each shipment.

Specimens should only be sent to the BPC Monday-Thursday for Tuesday-Friday delivery. If a specimen is obtained Friday through Sunday, please hold it under appropriate conditions (as described above) until the following Monday.

Send the Specimen Procurement Kit by Federal Express Priority Overnight. Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, be sure to give the account number on the pre-printed air-bill (1290-2562-0), but stress that pick-up is at your institutional address. Ship to the following address:

Biopathology Center  
Attention: ARET0321  
Nationwide Children's Hospital  
700 Children's Drive, WA 1340  
Columbus, OH 43205  
Phone: (614) 722-2865  
Fax: (614) 722-2897

## **8.0 SUPPORTIVE CARE**

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Reference may be made to the COG supportive care guidelines, at: [https://members.childrononcologygroup.org/prot/reference\\_materials.asp](https://members.childrononcologygroup.org/prot/reference_materials.asp)). The information provided below acts as a supplement to this document.

### **During Induction Therapy and Consolidation:**

#### **8.1 Filgrastim- Myeloid Growth Factor Support.**

Filgrastim SubQ 5 mcg/kg/day will begin on Day 3 of each cycle and continued until the post nadir ANC is  $\geq 1.5 \times 10^9 / \mu\text{L}$ . For any cycle in which peripheral blood stem cell harvest is anticipated to be performed at recovery, the filgrastim dose will be SubQ 10 mcg/kg/day. Filgrastim should be stopped at least 24 hours before the next chemotherapy cycle.

#### **8.2 Blood product support**

##### **8.2.1**

All blood products should be irradiated with at least 1500 cGy in order to prevent graft versus host disease. Up to 5000 cGy may be administered without any demonstrable adverse effects on red cell, neutrophil or platelet function.

##### **8.2.2**

All blood products should be obtained from CMV-seronegative blood donors if the recipient is CMV-seronegative. If CMV-negative blood products are unavailable, then all cellular blood products should be filtered through a leukodepletion filter.

##### **8.2.3**

Concentrated red cell transfusions should be given as per local institutional guidelines. It is recommended that hemoglobin be maintained at



#### 8.2.4

Platelet transfusions should be given as local institutional guidelines. It generally is recommended that platelet counts be kept  $> 20\,000/\mu\text{L}$ . Patients with CNS lesions or manifestations of bleeding despite a platelet count  $> 20\,000/\mu\text{L}$  should be managed more conservatively maintaining a platelet count  $> 50\,000/\mu\text{L}$ .

#### 8.3

Infectious complications may be managed as per local Institutional protocols, using the following suggested guidelines as considerations.

##### 8.3.1

Fever and neutropenia: Patients that develop fever need to be promptly evaluated, appropriate cultures taken and intravenous antibiotic coverage started. Broad spectrum coverage (2-drug) is recommended and should be continued until neutrophil engraftment. For persistent fever of undetermined cause of greater than 5 days duration empiric fungal coverage should be added

##### 8.3.2

Nephrotoxicity: Note that these patients have previously received nephrotoxic chemotherapeutic agents and caution must be taken when using aminoglycosides, Vancomycin or Amphotericin B deoxycholate. Careful monitoring of antibiotic levels and renal function (serum creatinine, urea and electrolytes) should be undertaken when using such agents. Abnormal renal function will also require modification of antibiotic doses and dose intervals, which can be most rationally determined by monitoring of peak and trough antibiotic levels in the blood.

##### 8.3.3

Anti-fungal prophylaxis: Fluconazole 6 mg/kg/day IV/PO daily is recommended, particularly during periods of neutropenia and during consolidation.

##### 8.3.4

PCP prophylaxis: During induction therapy, PCP prophylaxis should be administered as per institutional guidelines, preferably with trimethoprim-sulfamethoxazole unless the patient has a sulfa allergy.

#### **The Following Apply to the Consolidation Phase of Treatment Only:**

8.3.5 Protective isolation should be as per local institutional guidelines.

##### 8.3.6

HSV prophylaxis: For patients with a history or serologic evidence of previous oral HSC infection acyclovir ( $750\text{ mg}/\text{m}^2/24\text{ hrs}$  based on ideal body weight, divided q8h) from day -8 to day +30

##### 8.3.7

PCP prophylaxis: During consolidation therapy, trimethoprim-sulfamethoxazole (5 mg/kg/day in 2 divided doses orally) is recommended until Day -2 before the stem cell infusion, with re-initiation of trimethoprim-sulfamethoxazole on Day + 30 provided the ANC is  $> 750/\mu\text{L}$  on 3 consecutive measurements after transplant and continued until 6 months post transplant. In patients who are allergic to trimethoprim-sulfamethoxazole, aerosolized pentamidine 300 mg given upon admission for transplant, then every 4 weeks thereafter for 6 months is a reasonable substitute.

### 8.3.8

Intravenous immunoglobulin: IgG should be measured weekly and intravenous IgG should be given at a dose of 0.6 g/kg for levels < 5.0 g/L.

### 8.3.9

Skin care: Skin reactions following thiotepa administration are common. Frequent bathing/washing (at least 4 times daily) is recommended during and for at least 24 hours following administration. Sheet changes should be frequent.

## **9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA**

### **9.1 Criteria for Removal from Protocol Therapy**

- a. Progressive disease.
- b. Less than a partial response at the completion of 4 cycles of induction chemotherapy
- c. Second malignancy
- d. Refusal of further protocol therapy by patient/parent/guardian.
- e. Completion of protocol-prescribed therapy.
- f. Physician determines it is in patient's best interest.

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.

### **9.2 Off Study Criteria**

- a. Death.
- b. Lost to follow-up.
- c. Withdrawal of consent for any further data submission.
- d. Patient enrollment onto another COG study with tumor therapeutic intent (e.g. at recurrence).
- e. Tenth anniversary of study entry.

## **10.0 STATISTICAL CONSIDERATIONS**

### **10.1 Statistical Design**

The study involves a non-randomized assignment of CNS negative (stratum Stage 4a) and CNS positive (stratum Stage 4b) distant metastatic patients to receive a treatment regimen involving induction chemotherapy, stem cell harvesting, external beam radiation therapy, and consolidation therapy (high-dose chemotherapy with stem cell rescue). Patients with orbital, regional nodal disease and/or optic nerve margin positivity, but no other sites of metastases (stratum Stage 2 & 3), will be non-randomly assigned to receive the same treatment regimen without consolidation therapy. Observed event-free survival distributions will be compared to fixed, historical distributions separately for each stratum. An event is defined as relapse, second malignancy, or death from any cause.

### **10.2 Patient Accrual and Expected Duration of Trial**

The primary aim of the study is to compare the event-free survival rate between the current strata-specific strategies and historical experiences. The historical event-free survival rate at 1 year for patients with orbital

disease is 40% with very few failures after 1 year.<sup>4</sup> The 1-year historical event-free survival rate for distant metastatic patients treated with less intensive strategies is at most 20% for CNS negative patients and approximately 5% for CNS positive patients.<sup>15</sup> Multiple investigators have reported a near 0% event-free survival rate<sup>5,12-14</sup>, though anecdotal evidence has reported some event-free survivors. It is thought that the proposed treatment strategies will improve the 1-year event-free survival rates (EFS) to 70%, 70%, and 20% for orbital, distant metastatic CNS negative and distant metastatic CNS positive patients respectively.

The observed EFS distribution will be compared to historical experience separately for each group of patients because orbit patients will not receive the high dose chemotherapy with stem cell rescue, and the prognoses of CNS negative and CNS positive patients will likely be quite different (due to blood-brain barrier considerations). Although we hypothesize that both the CNS negative and CNS positive patients will experience a reduction in risk of failure under the proposed therapy, a 78% reduction and a 46% reduction, respectively based on an exponential survival model, the reduction in risk is expected to be lower in the CNS positive subgroup. So, estimation of a combined relative risk would result in a slight underestimate for the CNS negative patients and a slight overestimate for the CNS positive patients. Furthermore, the CNS negative and CNS positive patients have historically been summarized as separate cohorts in the literature, and therefore, there is interest in estimation of stratum-specific EFS. Clinically and scientifically, it is most logical to describe the event-free survival distribution separately for each of the patient strata.

### Sample Size

The estimated number of retinoblastoma cases per year in the USA is 300-350. About 5% of cases develop extraocular disease; therefore about 15 cases of metastatic disease per year occur in the United States. Survey of the COG retinoblastoma group attending the 4-01 meeting seemed to confirm that estimate. An equal number of CNS negative, CNS positive and orbital patients are expected. The retinoblastoma committee is interested in having this study be an international collaboration with appropriate European and South American centers and we have had promising initial discussions regarding this matter with international colleagues and Dr. Barry Anderson (CTEP). The proposed annual accrual of 15 patients across the 3 strata is based on North American accrual estimates and does not rely on international collaboration. Power was computed based on comparison to a binomial proportion using SAS Proc Power.

During the first two years of study activation, accrual was very slow with a total of 11 patients enrolled. However, the rate of enrollment has steadily increased to an estimated steady state of 12 patients per year. Based on these observations, it is anticipated that there will be a total of 60 patients enrolled at 6 years from the start of the study. Also, enrolled patients are split about equally in the three risk groups.

Stage 2 and 3 patients (regional disease patients): With 20 patients and assuming that the EFS rate from historical experience is 40% at 1 year, at a 1-sided alpha level of 0.05, the power to detect a true increase in the event-free survival rate of 30% (70%-40%) is 89%. A 1-sided alpha level was chosen as primary interest is in detecting an improvement in event-free survival rate under the more intensive therapy. The target sample size will result in a standard error of approximately 0.10 for the 12-month event-free survival rate, assuming a 12-month event-free survival rate of 0.7 under the proposed therapy.

Stage 4a patients (distant metastatic CNS negative patients): Twenty CNS negative distant metastatic patients will be accrued over the 6-year period required to address the orbital patient aim. Assuming that the event-free survival rate for the current therapy is 20% at 1 year, we will have greater than 95% power to detect a true increase in the EFS of 50% (70% - 20%). The target sample size will result in a standard error of approximately 0.10 for the 12-month EFS rate, assuming a 12-month EFS rate of 0.7 under the proposed therapy.

Stage 4b patients (distant metastatic CNS positive patients): Twenty CNS positive distant metastatic patients will be accrued over the 6-year period required for the orbital patient study. Assuming that the EFS rate for the current therapy is 5% at 1 year, we will have 80% power to detect a true increase in the EFS of 15% (20% - 5%) assuming a 1-sided alpha level of 0.05, an annual accrual of 5 patients, a 6 year accrual period. A 1-sided alpha level was chosen as primary interest is in detecting an improvement in event-free survival rate under the more intensive therapy. The target sample size will result in a standard error of approximately 0.09 for the 12-month EFS rate, assuming a 12-month EFS rate of 0.2 under the proposed therapy.

In summary, a total of 20 patients will be enrolled in each stratum. Enrollment in a particular stratum will stop after the 20 patient target has been met, even if the accrual targets in the other strata have not been met. It is estimated that patients will be accrued over a 6-year period, with an additional 1 year of follow-up on all patients, resulting in a total study duration of 7 years. These calculations do not include patients from international institutions mentioned above.

### 10.3 Statistical Analysis Methods

#### Primary Endpoint

We will assume that the failure-free survival (FFS) experience of each group of patients (distant metastatic CNS positive, distant metastatic CNS negative, and orbit patients) can be adequately modeled using the exponential cure model.<sup>27</sup> We will compare the observed survival experience to the expected distribution using a method adapted from Woolson.<sup>28</sup>

#### Interim Monitoring

The difference between the number of observed and expected failures is approximately normally distributed with independent increments and may be used for interim monitoring using standard group sequential boundaries. Based on data reported by Doz et al.,<sup>4</sup> we will assume a fixed null hypothesis model for the FFS probability over time of the historical patients as follows:

$$FFS(t) = 0.37 + 0.63[\exp(-1.8t)].$$

Outcome data for the regional disease (stratum stage 2 and 3) patients will be formally reviewed for increased harm relative to the historical experience, using the Lan-DeMets implementation of the O'Brien and Fleming group sequential boundaries, after 50% and 100% of the expected information is observed (after approximately every 6 failures under the null hypothesis). An alpha spending function of  $(\alpha * t)$  will be used to specify the monitoring boundaries, as it is of interest to detect early indications of increased harm relative to historical experience.<sup>29</sup> The critical values will be 1.64 and 1.44. Under this design, the study will be stopped for review with probability of 0.10 under the null long-term failure rate of 63% and with probability of 0.65 under a true long-term failure rate of 90%.

For the patients with distant metastatic CNS positive disease or distant metastatic CNS negative disease, the toxic death rate will be monitored as described below. No additional outcome monitoring will be performed, unless the toxic death rate appears to be higher than is acceptable based on historical experience, at which point we would like to know if there is lack of evidence of superiority given the increased risk of toxic death. In this case, the data will be monitored for lack of evidence of superiority under the proposed therapy relative to historical experience (futility). Otherwise, if there are no indications of increased risk of toxic death, we will not monitor for futility or increased harm because the historical outcome for these patients is so poor, we want to avoid acting on early failures when there

might be a delayed benefit, and we would like to continue to the target accrual in order to preserve estimation precision.

The study proposes to enroll a small number of subjects in each stratum and therefore, will not be monitored for early evidence of superior outcome in any stratum because halting the study accrual early would reduce the already limited precision of estimation.

The toxicity-associated death rate and the percentage of patients for whom an adequate yield of stem cells cannot be harvested will be monitored across all treatment groups collectively. Specifically, a 5% toxicity-associated death rate is acceptable, while a 10%-15% rate would be cause for concern. A continuous monitoring rule will be used where the study is stopped for review by the DSMB and study committee if at any point in time the probability of observing more than the current number of toxic deaths out of the number of accrued patients is less than 0.005 under the null hypothesis of a 5% event rate. Specifically, the following algorithm will be followed:

Stop the Study for Review if

Number of Events Observed	Number of Patients On Study
2	1-7
3	8-14
4	15-23
5	24-32
6	33-42
7	43-53
8	54-60

So, if for example, 5 toxic deaths are observed among the first 25 patients enrolled, the study will be stopped for review. Under the specified monitoring rule, the study will be stopped with probability of 0.84 under an event rate of 15%, with probability of 0.65 under an event rate of 12%, with probability of 0.48 under an event rate of 10%, and with probability of 0.09 under the null rate of 5%.

Also, it is expected that over 98% of the patients receiving autologous stem cell rescue (ASCR) will yield an adequate amount of stem cells, whereas if only 90% of the patients yield an adequate amount, this would be cause for concern. A continuous monitoring rule will be used where the study is stopped for review by the DSMB and study committee if at any point in time the probability of observing more than the current number of patients with an inadequate amount of stem cells out of the number of accrued patients is less than 0.01 under the null hypothesis of a 2% event rate. Specifically, the following algorithm will be followed:

Stop the Study for Review if

Number of Events Observed	Number of Patients On Study
2	2-22
3	23-42
4	43-60

So, if for example, 3 patients with an inadequate supply of stem cells are observed among the first 25 patients enrolled, the study will be stopped for review. Under the specified monitoring rule, the study will be stopped with probability of 0.91 under the alternative event rate of 10% and will be stopped with probability of 0.09 under the null rate of 2%.

The accrual rate will also be closely monitored. If fewer than 10 patients from all participating institutions are accrued per year on average across the 3 treatment strata, and more than a 9 year accrual period would be required to assess the event-free survival endpoints, and would therefore be cause for early termination review.

**Secondary Endpoints**

The response rate to the induction phase of the regimen will be estimated and a corresponding 95% confidence interval calculated for all strata combined. Toxicities will be descriptively summarized.

**10.4 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	2	1	3
Not Hispanic or Latino	29	28	57
<b>Ethnic Category: Total of all subjects</b>	31	29	*60
<b>Racial Category</b>			
American Indian or Alaskan Native	1	1	2
Asian	2	1	3
Black or African American	4	4	8
Native Hawaiian or other Pacific Islander	1	0	1
White	23	23	46
<b>Racial Category: Total of all subjects</b>	31	29	*60

\* These totals must agree

This distribution was derived from SEER data.<sup>30</sup>

## **11.0 EVALUATION CRITERIA**

### **11.1 Common Terminology Criteria for Adverse Events (CTCAE)**

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. **The descriptions and grading scales found in the revised CTCAE version 4.0 will be utilized for reporting beginning January 1st, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0, which can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).**

### **11.2 Response Criteria**

This study will use a modified version of the international criteria for neuroblastoma response.

Please note: for some patients with trilateral retinoblastoma, it may be difficult to distinguish between tumor necrosis and refractory tumor. Please consider second look surgery prior to consolidation therapy should uncertainty arise as to whether an adequate response has been achieved.

#### **11.2.1 Complete Response (CR)**

Resolution of the metastatic disease as defined by bone marrow examinations and relevant imaging studies (those that revealed an abnormality prior to enrollment on this study).

#### **11.2.2 Very Good Partial Response (VGPR)**

> 90% decrease in the sum of the 2-dimensional measurements of the tumor(s) on relevant (CT and/or MRI) imaging studies. No new lesions. Bone marrow free of tumor. Improved bone scan.

#### **11.2.3 Partial Response (PR)**

50-90% decrease in the sum of the 2-dimensional measurements of the tumor(s) on relevant (CT and/or MRI) imaging studies. No new lesions. Bone marrow free of tumor.

#### **11.2.4 Stable Disease (SD)**

< 50% decrease and < 25% increase in the sum of the 2-dimensional measurements of the tumor(s) on relevant (CT and/or MRI) imaging studies. No new lesions.

#### **11.2.5 Progressive Disease (PD)**

At least a 25% increase in the sum of the 2-dimensional measurements of the tumor(s) on relevant (CT and/or MRI) imaging studies, and/or a new lesion that unequivocally represents retinoblastoma.

#### **11.2.6 Response Assessment**

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described above.

## **12.0 ADVERSE EVENT REPORTING REQUIREMENTS**

### **12.1 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.

## 12.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event.

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.*

### 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 CTEP-AERS. Three options are available to describe the event:

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

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

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

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

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

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the 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.**

**CTEP-AERS 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			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
<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 that can be attributed (possibly, probably, or definitely) to the agent and is <u>not</u> due to cancer recurrence must be reported via CTEP-AERS.			

**12.4 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 CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 3 and higher Non-hematologic Adverse Events.

## **13.0 RECORDS AND REPORTING**

### **13.1 Categories of Research Records**

Research records for this study can be divided into 3 categories:

1. Non-computerized Information: Pathology Narrative Reports, Surgical Reports. These forms are submitted through the Document Imaging System in the eRDES.
2. Reference Labs' required records and QARC data. These data accompany submissions to these centers, which forward their review data electronically to the COG Research Data Center.
3. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) as provided in the data form packet.

See separate Data Form Packet which includes submission schedule.

### **13.2 CDUS**

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. 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.

### **13.3 CRADA/CTA**

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement

The agent(s) (hereinafter referred to as "Agent(s)"), used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between Company (or Companies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment, Diagnosis and Centers. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborators(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
  - a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

- b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialization its own investigational Agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), and not to other parties.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigator's (Group Chair for cooperative group studies, or PI for other studies) of Collaborators wish to contact them.
5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC, if there is a DMC for this clinical trial).
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to: The instructions in the box below will be included in each sample consent.

Regulatory Affairs Branch, CTEP, DCTDC, NCI  
Executive Plaza North, Room 7111  
Bethesda, Maryland 20892  
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

**APPENDIX I: YOUTH INFORMATION SHEET****INFORMATION SHEET REGARDING RESEARCH STUDY ARET0321  
(for children 7 - 12 years of age)**

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**A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma.  
(A Treatment Study of Retinoblastoma that has Spread Outside of the Eye)  
Distant Metastatic Disease-Stage 4a and 4b**

1. We have been talking with you about your cancer, called metastatic retinoblastoma. Metastatic means that the cancer has spread outside of the eye.
2. Now we would like to ask you to take part in a research study about treatment for metastatic retinoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat children with metastatic retinoblastoma.
3. We have been talking with your parent(s) about this study. We want to include you as we talk more about it. Being in this study may involve special risks, which the doctor will discuss with you.
4. In this study, doctors will use a new treatment for retinoblastoma that uses big doses of cancer fighting drugs (chemotherapy). The doctors also want to do something called a “stem cell rescue.” This is when special blood cells (called stem cells) are taken out of your blood and saved. Stem cells are like “parent cells” for all the cells in your blood. Later, the stem cells are put back into your blood. This is often done when patients get big quantities of chemotherapy which lower the number of your blood cells. It is done to help your body get better by giving your body back the parent cells it needs to grow new blood cells. Some children may also get high energy x-ray treatment (called external beam radiation therapy) which also helps to kill cancer cells.
5. This study is being done to see if this new treatment is better at getting rid of metastatic retinoblastoma for as long as possible; than the treatments used in the past. We do not know if the bigger amounts of chemotherapy and the stem cell rescue will help get rid of the cancer better than older treatments. We do not know which treatment is better. That is why we are doing this study.
6. If you take part in this study, you will get chemotherapy into something called a central line, which is often used for children getting this kind of chemotherapy. A central line is a special type of tubing that is put into a large vein in your chest. If you have a central line, you will not get to be pricked too many times to get chemotherapy or have blood samples taken.
7. While getting the first part of chemotherapy (called induction), your stem cells will be collected and saved. Chemotherapy given during induction may be with 4 drugs (called Standard Induction) or with 3-drugs (called Alternative Induction). If you have serious hearing and/or vision problems, you may get alternative induction to try to minimize the risk of more visual and/or hearing loss. You will get more chemotherapy after induction. This is called consolidation therapy. During consolidation, you will have your stem cells that were saved during induction, put back into your blood. Following the end of consolidation chemotherapy, some children may

also get external beam radiation therapy. Your doctors will let you know if you should have external beam radiation therapy or not.

8. After you get your chemotherapy, you will have regular check-ups to see how well the drugs are working.
9. Please talk this over with your parent(s). Together you can decide if you want to take part in this study. Please ask any questions that you can think of. If you have a question later, you can ask the next time you see me.
10. If you and your parent(s) decide not to be in this study, no one will be mad or upset with you. You will be able to receive treatment used in the past, or other experimental treatments if it is available.

**INFORMATION SHEET REGARDING RESEARCH STUDY ARET0321**  
**(for children 7 - 12 years of age)**

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**A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma.**  
**(A Treatment Study of Retinoblastoma that has Spread Outside of the Eye)**  
**Regional Metastatic Disease- Stage 2 and 3**

1. We have been talking with you about your cancer, called metastatic retinoblastoma. Metastatic means that the cancer has spread outside of the eye.
2. Now we would like to ask you to take part in a research study about treatment for metastatic retinoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat children with metastatic retinoblastoma.
3. We have been talking with your parent(s) about this study. We want to include you as we talk more about it. Being in this study may involve special risks, which the doctor will discuss with you.
4. In this study, doctors will use a new treatment for retinoblastoma that uses big doses of cancer fighting drugs (chemotherapy). Doctors also want to use high energy x-rays (called external beam radiation therapy) which also help kill cancer cells.
5. This study is being done to see if this new treatment is better at getting rid of metastatic retinoblastoma for as long as possible; than the treatments used in the past. We do not know if the bigger amounts of chemotherapy and the external beam radiation therapy will help get rid of the cancer better than older treatments. We do not know which treatment is better. That is why we are doing this study.
6. If you take part in this study, you will get chemotherapy into something called a central line, which is often used for children getting this kind of chemotherapy. A central line is a special type of tubing that is put into a large vein in your chest. If you have a central line, you will not get to be pricked too many times to get chemotherapy or have blood samples taken.
7. During the first part of treatment (called Induction), you will get chemotherapy. Chemotherapy given during induction may be with 4 drugs (called Standard Induction) or with 3-drugs (called Alternative Induction). If you have serious hearing and/or vision problems, you may get alternative induction to try to minimize the risk of more visual and/hearing loss. Following the end of induction, you will also get external beam radiation therapy as the second part of your treatment. Your doctors will explain to you what to expect with these treatments.
8. After you get your chemotherapy, you will have regular check-ups to see how well the drugs are working.
9. Please talk this over with your parent(s). Together you can decide if you want to take part in this study. Please ask any questions that you can think of. If you have a question later, you can ask the next time you see me.

If you and your parent(s) decide not to be in this study, no one will be mad or upset with you. You will be able to receive treatment used in the past, or other experimental treatments if it is available.

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