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The world's childhood cancer experts

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

November 16, 2020

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
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Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
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Dear Ms. Kruhm,

Enclosed please find Amendment #4B for protocol **ARST1431**, *A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, TORISEL, NSC# 683864) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)*, for CTEP review.

This amendment will:

- expand the permitted use of blood samples already being collected and stored at the Biopathology Center to include use of white blood cells for germline analysis
- reflect the completion of central FOXO1 fusion status testing
- clarify dose modification guidelines
- modify surgical guidelines to reflect the most up-to-date information
- and clarify use of filgrastim, pegfilgrastim, and their biosimilars.

Revisions to the protocol and consent documents are detailed in the pages below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked but not specified below.

Please contact me with any questions or concerns.

Sincerely,

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

Abha Gupta, MD, ARST1431 Study Chair
Rajkumar Venkatramani, MD, COG Soft Tissue Sarcoma Disease Chair
Douglas Hawkins, MD, Children's Oncology Group Chair

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

#	Section	Page(s)	Change
1.	Title Page & Throughout	Throughout	Version date and amendment number have been updated.
2.	Table of Contents	3-6	The table of contents has been updated and repaginated.
3.	Study committee	7-9	The study committee has been updated to reflect the current roster and contact information.
4.	1.3.3	13	Expanded Exploratory Aim 1.3.3 to allow the study team to examine patterns of tumor heterogeneity and evolution in ctDNA from multiple timepoints: "To estimate the frequency of patients with circulating tumor DNA (ctDNA) at diagnosis and subsequent time-points**, and explore whether tumor-specific somatic variants are detectable in the ctDNA**."
5.	3.1.2	30-31	IRB approval text was updated to match current CTSU template language.
6.	3.1.3 3.1.4	31 32-33	Reservation requirement and patient enrollment texts have been updated to match current CTSU template language.
7.	3.3.1 14.2.1	37 163	The test to determine the concordance rate between institutional and central *FOXO1* fusion status has been completed. These sections have been modified to reflect this update.
8.	4.1.2.2	42	Clarified that temsirolimus ~~should~~ **must** be held for 1 week following any minor surgical procedures (insertion of central venous catheters, gastrostomy tubes, biopsies) and 2 weeks prior to any major surgical procedures (tumor resection either initially or at DPE).
9.	4.1.3	43	Clarified concomitant use of aprepitant and fosaprepitant.
10.	4.2.1 4.2.4 4.2.7 4.3.1 4.3.4a 4.3.4b 4.3.7 4.5.1 Appendix VII	45 50 55 60 66 67 73 83 220	Modified myeloid growth factor support guidelines to allow the use of pegfilgrastim biosimilars.

#	Section	Page(s)	Change
11.	4.2.1 4.2.3.2 4.2.4 4.2.6.2 4.2.7 4.2.9.2 4.3.1 4.3.3.2 4.3.4a 4.3.4b 4.3.6.2 4.3.7 4.3.9.2 4.5.1 4.5.3.2 4.5.4 4.5.6.2	45 48 50 53 55 58 60 63 66 67 70 73 76 83 86 87 90	Clarified that dactinomycin could be administered by either slow IV push over 1-5 minutes **or IV infusion over 10-15 minutes**.
12.	4.2.2 4.2.5 4.2.8 4.3.2 4.3.5 4.3.8 4.4.2 4.5.2 4.5.5	46 51 56 61 68 74 80 84 88	The **total** bilirubin observation in the required observations table was clarified for protocol consistency.
13.	4.3.1 4.3.4a 4.3.4b 4.3.7 Appendix VII	60 66 67 73 220	Clarified that the use of filgrastim and biosmiliar may be continued without regard to VCR **or TORI**.
14.	4.4.3.2	82	• Provided site instructions for patients who vomit after or within 20 minutes of a dose of cyclophosphamide (tablet, capsule, and oral suspension). • For Canadian sites, provided high-level guidance with a reference to Appendix XII for splitting tablets if liquid formulation is not available.

#	Section	Page(s)	Change
15.	5.2	92	Clarified dose modification guidelines for temsirolimus during VAC/VI cycles: • "In the event of **any Grade ≥ 3 non-hematological** toxicity, the doses of temsirolimus will be adjusted according to the guidelines ~~shown in the Dose Modifications tables below~~ **described in Section 5.1**." • "**Dose levels will be as** shown in the ~~Dose Modifications~~ table~~s~~ below. No dose escalations are permitted after reductions for confirmed toxicity. ~~If an AE is not covered in the relevant table, doses may be reduced or held at the discretion of the investigator for the patient's safety.~~ Dose modifications for hematological toxicity are based on the blood counts obtained on the day of treatment." • "Patients with toxicities that are manageable with supportive therapy may not require dose reductions (e.g., hypertriglyceridemia or cholesterol high). ~~Patients requiring more than 2 dose reductions of temsirolimus will discontinue temsirolimus and remain on study and receive VAC/VI alone.~~ Patients requiring dose reductions will not have the dose re-escalated with subsequent treatments."
16.	5.4	98	Revised hematological dose modification guidelines to: • recommend the provision of myeloid support for prolonged neutropenia before a dose reduction of irinotecan • provide guidance if subsequent cycle is delayed.
17.	6.1	102-111	Updated Temsirolimus Monograph.
18.	6.5	116-118	Updated Filgrastim Monograph.
19.	6.9	123-124	Updated Pegfilgrastim Monograph.
20.	6.10	125-127	Updated Vincristine Sulfate Monograph.
21.	11.4.3 11.4.6	146 147	Updated reporting guidelines for adverse events to match current template.
22.	13.3 13.4.2 13.4.4 13.5.3 13.5.4 13.5.7	155 156-157 158 158 159 160-161	Surgical guidelines were modified based on a review of data regarding nodal sampling in paratesticular RMS.
23.	13.4 13.4.4	156 157	Provided guidance to sites that **amputations and other radical procedures are to be avoided whenever possible**.
24.	14.2.2	163	• Rearranged information on materials to send for readability • Updated the contact information for study pathologist Dr. Michael Arnold.

#	Section	Page(s)	Change
25.	15.0	164	Moved the list detailing how diagnostic pretreatment tumor tissue will be prioritized from Section 15.1.1 to 15.0. List was also rearranged so the ctDNA correlative is higher on the list of prioritization for patients who consented.
26.	15.1	164-165	• Removed panel for NOS-1 because it was not staining robustly: "Use of formalin-fixed, paraffin-embedded tissue sections for immunohistochemical staining including a panel for ~~four~~ **3** antibodies (myogenin, AP2b, ~~NOS-1,~~ and HMGA2). This will identify tumors which may harbor a fusion protein that does not include the FOXO1 gene, which would **not** be detected by institutional FISH or other molecular techniques." • Expanded the methodology to analyze variant gene fusion cases to include targeted sequencing panel: "Cases suspicious for variant gene fusions after immunohistochemical analysis, institutional FOXO1 results and PAX3/7 testing will be further analyzed by an indepth FISH **and/or targeted sequencing** panel to identify any of the currently known fusion variants implicated in RMS tumorigenesis."
27.	15.1.2	165	• Reduced the number of required unstained slides sent to Dr. Rudzinski to reflect the removal of the NOS-1 panel mentioned above: "For all cases enrolled, ~~four (4)~~ **three (3)** unstained slides will then be sent to Erin Rudzinski, MD at Seattle Children's Hospital for immunohistochemical staining with antibodies to AP2b, ~~NOS-1,~~ HMGA2, and myogenin." • Revised the number of unstained slides sites submit to the Biopathology Center for analysis of PAX3/7 by FISH to identify common fusion partners. All cases with ~~an institutional diagnosis of ARMS~~ **confirmed FOXO1 fusion** will be analyzed. • "For cases with a discrepancy between the immunohistochemical panel, FOXO1 fusion result or PAX3/7 fusion result, 6 additional unstained slides will be sent to Julia Bridge at the University of Nebraska Medical Center and/or the Translational Genomics Research Institute (TGen) for comprehensive ~~FISH~~ analysis of all fusion variants described in rhabdomyosarcoma."
28.	15.2.3	167	Clarified pre-treatment blood sample submission requirement.
29.	15.2.4	167	Listed information that must be labeled on Streck tubes to increase readability.

#	Section	Page(s)	Change
30.	15.2.5	168	• Expanded ctDNA correlative to the permit use of samples already collected for ctDNA analysis and are currently being stored at the BPC to include the use of white blood cells for germline analysis. • Expanded the methodology of the correlative to include the following: "**After the above aims have been completed, additional nucleic acids will then be subjected to deep next-generation sequencing (including but not restricted to whole-exome sequencing) to determine whether detection of a greater number of somatic single-nucleotide variants is better able to detect the presence of ctDNA and whether we can detect patterns of tumor heterogeneity and evolution in ctDNA from multiple timepoints.**"
31.	16.2.1	169-170	• Clarified that the Week 42 imaging timepoint is at the end of VAC/VI therapy **+/- temsirolimus** for Regimens A and B for internal consistency. • Baseline radiology submission requirements have been expanded to include both **scans and** reports.
32.	16.3	170	Clarified the pre-study image submission requirement for patients who were scanned with more than one imaging modality.
33.	16.4.3 Appendix XIII	173-175 234-237	• Removed link to ACRIN PET Standard Operating Procedures because it is no longer active and maintained. An appendix has been added with pediatric FDG PET/CT guidelines. • Updated ACR link to reflect most up-to-date information. • Made two minor revisions to provide clarifications: o "Prior to and following [18F]FDG injection", was added to the statement "the patient is kept at rest in a warm room until the time of imaging to minimize [18F]FDG uptake in activated brown adipose tissue or other physiologic [18F]FDG artifacts" to acknowledge that brown adipose tissue can be lessened by keeping the patient warm prior to injection. o The text "if needed to assist bladder emptying" was added to the statement "In patients with tumors in the pelvis, placement of a Foley catheter is recommended" as some patients may be able to empty their bladder sufficiently that a Foley catheter is not needed.
34.	17.7.2	186	Clarified the prescribed radiation dose instructions to note that patients with positive lymph nodes at diagnosis that were only sampled by biopsy are Clinical Group III and will receive 50.4 Gy **to the primary** while those that are completely resected will receive 41.4 Gy **to the primary**.
35.	17.12	200	Clarified the "End of ~~Therapy~~ **VAC/VI +/- temsirolimus**" image submission timepoint for the purposes of RT review.
36.	17.12.3	202	Text has been updated to match current CTSU template language.

#	Section	Page(s)	Change
37.	Appendix I	203-205	Appendix was updated to match revised CTSU language.
38.	Appendix XI	231	Removed the following sentence because it was a duplicate: "*~~Patients exceeding a BSA of 3.00 m^2 should have their cyclophosphamide doses calculated on actual BSA with no maximum dose.~~"
39.	Appendix XII	232-233	For Canadian sites, provided instructions for splitting tablets if liquid formulation is not available.

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Activated: 5/23/2016
Closed:

Version Date: 11/16/2020
Amendment: #4B

CHILDREN'S ONCOLOGY GROUP

ARST1431

A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

An Intergroup NCTN Phase 3 Study

NCI Supplied Agents: Temsirolimus (NSC# 683864)

IND sponsor for temsirolimus: DCTD, NCI

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ALLIANCE / Alliance for Clinical Trials in Oncology

ECOG-ACRIN / ECOG-ACRIN Cancer Research Group

NRG / NRG Oncology

SWOG / SWOG

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#	IND#
Temsirolimus	# 683864	
Cyclophosphomide	# 26271	Commercial
Dactinomycin	# 3053	Commercial
Irinotecan	# 616348	Commercial
Vincristine sulfate	# 67574	Commercial
Vinorelbine tartrate	# 608210	Commercial

IND sponsor: DCTD, NCI

SEE SECTION 14.0 AND 15.0 FOR SPECIMEN SHIPPING ADDRESSES.

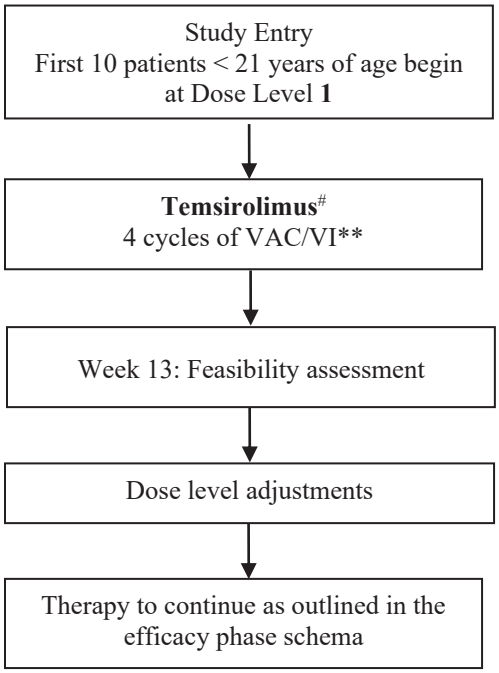
ABSTRACT

Unfortunately about 25% of patients with intermediate-risk (IR) embryonal rhabdomyosarcoma (ERMS) and 50% of those with IR alveolar rhabdomyosarcoma (ARMS) will experience disease recurrence with a resulting long-term event-free survival (EFS) of 65%. The mTOR pathway is important in RMS biology, and temsirolimus, an mTOR inhibitor, has demonstrated clinical activity in patients with relapsed RMS. In an attempt to improve long-term survival for patients with IR RMS, ARST1431 will compare the EFS of patients with newly diagnosed IR RMS randomly assigned to standard vincristine, dactinomycin, and cyclophosphamide (VAC) alternating with vincristine and irinotecan (VI) versus VAC/VI plus temsirolimus. Radiotherapy (RT) is planned to start at Week 13 of therapy for all patients, with RT to metastatic sites at the end of VAC/VI therapy. **Beginning with Amendment #3,** all patients will also be receiving maintenance chemotherapy with low dose oral cyclophosphamide and IV vinorelbine following the completion of the initial 42 weeks of VAC/VI therapy. Correlative biology studies will be performed including a determination of the FOXO1 gene fusion status in the tumor, and measurement of cell free tumor DNA.

EXPERIMENTAL DESIGN SCHEMA: FEASIBILITY PHASE

The feasibility phase is complete, effective with Amendment #1.

During the feasibility (dose-finding) phase, patients will be non-randomly assigned to treatment with VAC/VI plus temsirolimus.



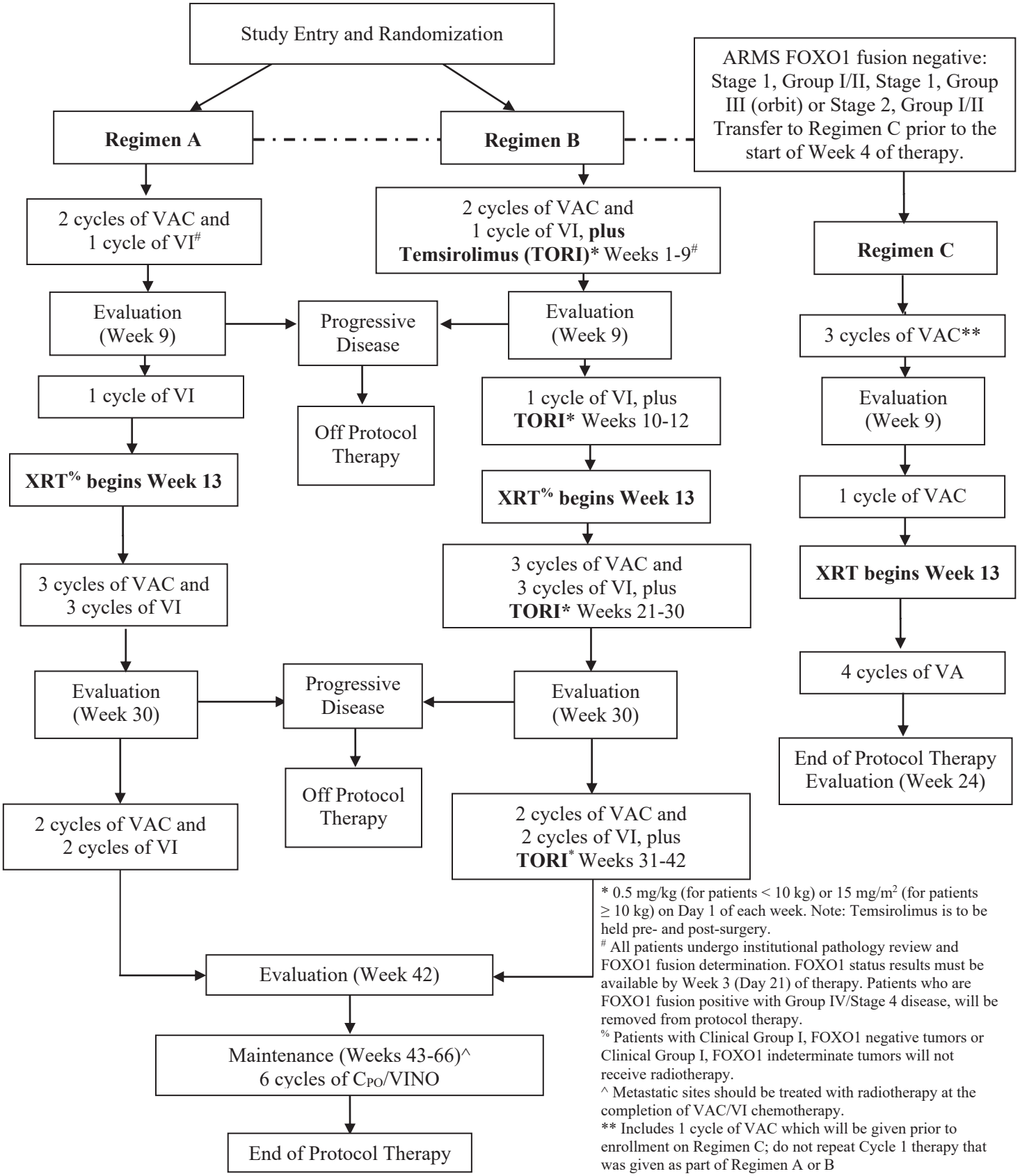
#Temsirolimus

Dose Level	Temsirolimus Dose
1	15 mg/m^2 IV, Days 1, 8 and 15 of each cycle
0	10 mg/m^2 IV, Days 1, 8 and 15 of each cycle
-1	10 mg/m^2 IV, Days 1 and 8 of each cycle

	Drug	Age	Dose
V	VINCristine	< 0.6 m^2 BSA	BSA-based dosing, see dosing table (Section 4.2.3.2)
		≥ 0.6 m^2 BSA	1.5 mg/m^2 IV Days 1, 8 & 15 (maximum dose 2 mg)
A	Dactinomycin	< 14 kg	Weight-based dosing, see dosing table (Section 4.2.3.2)
		≥ 14 kg	0.05 mg/kg IV Day 1 (maximum dose 2.5 mg)
C	Cyclophosphamide	< 0.6 m^2 BSA	BSA-based dosing, see dosing table (Section 4.2.3.2)
		≥ 0.6 m^2 BSA	1200 mg/m^2 IV Day 1
I	Irinotecan	< 0.6 m^2 BSA	BSA-based dosing, see dosing table (Section 4.2.3.2)
		≥ 0.6 m^2 BSA	50 mg/m^2 IV Days 1-5 (maximum dose 100 mg)

** All patients undergo institutional pathology review and FOXO1 fusion determination. FOXO1 status results must be available by Week 3 (Day 21) of therapy. Patients who are FOXO1 fusion positive with Group IV/Stage 4 disease, will be removed from protocol therapy. Patients who are ARMS FOXO1 fusion negative and Stage 1, Group I/II, Stage 1, Group III (orbit) or Stage 2, Group I/II are eligible for Regimen C (as shown in the Feasibility schema above). Transfer to Regimen C prior to the start of Week 4 of therapy (see Section 3.1.8 for call back details).

EXPERIMENTAL DESIGN SCHEMA: EFFICACY PHASE



* 0.5 mg/kg (for patients < 10 kg) or 15 mg/m^2 (for patients ≥ 10 kg) on Day 1 of each week. Note: Temsirolimus is to be held pre- and post-surgery.

All patients undergo institutional pathology review and FOXO1 fusion determination. FOXO1 status results must be available by Week 3 (Day 21) of therapy. Patients who are FOXO1 fusion positive with Group IV/Stage 4 disease, will be removed from protocol therapy.

% Patients with Clinical Group I, FOXO1 negative tumors or Clinical Group I, FOXO1 indeterminate tumors will not receive radiotherapy.

^ Metastatic sites should be treated with radiotherapy at the completion of VAC/VI chemotherapy.

** Includes 1 cycle of VAC which will be given prior to enrollment on Regimen C; do not repeat Cycle 1 therapy that was given as part of Regimen A or B

V = VinCRIStine; A = DACTINomycin;
C = Cyclophosphamide (IV); I = Irinotecan;
CPO = Cyclophosphamide (oral); VINO = Vinorelbine
Each cycle of VAC, VI, or VA lasts 21 days (3 weeks).
Each cycle of maintenance therapy lasts 28 days (4 weeks).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To compare the event-free survival (EFS) of patients with IR RMS treated with surgery, radiotherapy, and VAC alternating with VI (VAC/VI) with maintenance to that of patients treated with surgery, radiotherapy and VAC/VI plus temsirolimus with maintenance.

1.2 Secondary Aims

1.2.1 To compare the overall survival (OS) of patients with IR RMS treated with surgery, radiotherapy, and VAC alternating with VI with maintenance to that of patients treated with surgery, radiotherapy and VAC/VI plus temsirolimus with maintenance.

1.3 Exploratory Aims

1.3.1 To compare the outcome of patients based on their FOXO1 fusion gene partner, by evaluating PAX3 vs. PAX7 in all patients found to be FOXO1 fusion positive.

1.3.2 To compare the outcome of patients based on their [F^{18}]-fluorodeoxy-D-glucose-positron emission tomography (FDG-PET) response at Week 9 (positive or negative), as assessed by Deauville Criteria (5-point).

1.3.3 To estimate the frequency of patients with circulating tumor DNA (ctDNA) at diagnosis and subsequent time-points, and explore whether tumor-specific somatic variants are detectable in the ctDNA.

1.3.4 To compare the outcome of patients (VAC/VI with or without temsirolimus) who have received maintenance therapy on ARST1431 to those who received VAC/VI on ARST0531.

2.0 BACKGROUND

2.1 Introduction and Rationale for Development

The three most recent COG IR RMS studies (IRS-IV, D9803, and ARST0531) each tested the addition of one or more traditional cytotoxic chemotherapeutic agents to VAC and failed to improve outcome compared to VAC.[1-3] As an alternative strategy, the current study will explore the addition of a biologically targeted agent, temsirolimus to a backbone of VAC alternating with VI in a randomized, phase 3 design, with a primary goal of comparing EFS and secondary objective of comparing OS between the two arms.

2.1.1 Intermediate Risk Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents with approximately 350 new diagnoses annually in the United States.[4] Despite cooperative group trial efforts, about 25% of patients with IR ERMS tumors and 50% of those with IR ARMS tumors will experience disease recurrence[5,6] and only a small fraction of the patients who relapse can be cured.[7] Patients with an estimated 3-yr EFS of 50-75% are considered to be IR and comprise almost 50% of all patients with RMS.[3] Historically, this group was comprised of patients with unresected, non-metastatic ARMS at all primary sites

and ERMS arising in unfavorable sites and unresected.[3,8] However, recent COG low-risk (ARST0331) and high-risk (ARST0431) RMS clinical trials support shifting some RMS populations into IR. First, patients < 10 years of age with metastatic ERMS have previously been treated on both high risk (ARST0431) and IR (D9803) protocols. In this trial these patients will be classified as IR as they had a 60% 3-yr EFS (n=20) with intensive, interval compressed seven-drug chemotherapy on COG ARST0431[9] and a 60% 4-yr EFS (n=47) with VAC (with or without topotecan) on COG D9803.[3] In addition, patients with ERMS who were either Stage 1 (favorable site); Group III (unresected); non-orbit or Stage 3 (unfavorable site); or Group I/II (resected) on ARST0331, who were considered as low-risk subset had a 3-yr EFS of only 64% after a 4.8 g/m^2 cumulative dose of cyclophosphamide.[10] When these patients were treated with 28 g/m^2 of cyclophosphamide on D9602, 5-yr EFS was 85%.[11] Thus, this latter group of patients will also be re-classified as "intermediate" risk in the current trial which will give a moderate cumulative dose of cyclophosphamide (8.4 g/m^2) to all enrolled subjects.

2.1.2 Age of Eligibility: Adolescents and Young Adults

To address the problem of trial accrual among young adults and encourage uniform treatment of adults with 'pediatric-type' RMS, previous RMS studies permitted enrolment up to age 50 years. However, two subsequent analyses have demonstrated that adolescents and young adults experience greater neurotoxicity and nausea compared to younger children.[12,13] Despite the increased age of eligibility, accrual of adults was poor on ARST0531. In the current study, we will still hope to accrue young adults, but will limit accrual to below age 40 years, which coincides with the NCI definition of a young adult. Moreover, adults with RMS older than age 40 years are much more likely to have the pleomorphic subtype of the disease which is biologically and clinically distinct from, and unresponsive to chemotherapy compared with, ARMS and ERMS.[14]

2.1.3 Defining RMS Using Fusion Status Rather than Histology

Patients who are newly diagnosed with biopsy proven RMS of any histologic type except adult-type pleomorphic (based upon institutional histology) will be eligible for enrollment. ARST1431 will use FOXO1 fusion status rather than histology for study eligibility because it is more predictive of outcome as demonstrated by two independent analyses.[15,16] FOXO1 fusion status will be performed within the first 3 weeks of study enrollment. Patients with ERMS who have distant metastases and are found to be FOXO1 positive will be deemed ineligible and removed from study.

2.1.4 Translocation Negative ARMS: 'Low Risk' Patients to Receive Only VAC/VA

Approximately 20% of histologically defined ARMS are negative for FOXO1 fusion (nARMS). These patients will be considered IR, and continue on protocol therapy as randomized unless they are Stage 1/2, Group I-II (completely resected) or orbital primary site (Group I-III). This molecularly defined low risk population will receive 24 weeks of VAC/VA therapy as per ARST0331 instead of the randomized arm of therapy. On D9803, these low risk nARMS patients had 100% EFS but at the cost of a high cumulative cyclophosphamide dose (30.8 g/m^2).[15] Although the rarity of low risk nARMS will limit the ability to

draw strong statistical conclusions, ARST1431 will be the only opportunity to estimate the success of reduced intensity therapy for low risk nARMS.

2.1.5 Reduced Staging Investigations for Patients with Translocation Negative Disease

In an effort to simplify the staging evaluations in patients with RMS, a recent analysis of ERMS and ARMS patients demonstrated that patients with ERMS who have tumors that are less than 5 cm and non-invasive (T1), without nodal disease, had a 0% chance of having bone or bone marrow metastases.[17] Based on the staging algorithm proposed in this analysis, patients in ARST1431 who have ERMS without nodal or lung metastases, will not require bone scans or bone marrow evaluations.

2.2 Rationale for Investigation of an mTOR inhibitor in Children with Newly Diagnosed RMS: Temsirolimus (Torisel®)

Results of COG ARST0921, a randomized phase 2 selection design study in relapsed RMS that compared bevacizumab (BEV) to temsirolimus, both administered in combination with cyclophosphamide and vinorelbine, showed that the temsirolimus arm had a superior 6-month EFS (65%, 95% CI: 44%, 79%) compared to the bevacizumab arm (50%, 95% CI: 32%, 66%, $p = 0.0031$).[18] There was also a higher proportion of partial responses on the temsirolimus arm (33%) versus the BEV arm (18%). Furthermore, the complete response (CR) + partial response (PR) rate for the temsirolimus arm was 47% compared with 28% for the BEV arm. Based upon this clinical evidence of activity in heavily pre-treated patients with RMS, temsirolimus is a high priority agent to evaluate in a large phase 3 study.

2.2.1 Mammalian Target of Rapamycin

Mammalian target of rapamycin (mTOR) is a 289-kDa serine/threonine kinase that exists in the cytoplasm and plays a role in several tumor-promoting intracellular signaling pathways. Regulation of the mTOR pathway is highly complex and is mediated through a series of interactions linking growth factor receptor signaling and other cell stimuli as well as phosphatidylinositol 3-kinase and the Akt/protein kinase B pathway activation. This process leads to production of hypoxia inducible factor–1α that regulates transcription of genes that stimulate cell growth and angiogenesis including vascular endothelial growth factor (VEGF). Other effects of mTOR activation include stimulation of increased mRNA translation that encodes cell cycle regulators such as c-myc, cyclin D1, and ornithine decarboxylase resulting in increased cell division and survival.[19] Thus, targeting the mTOR pathway is a relevant strategy to inhibit cancer.

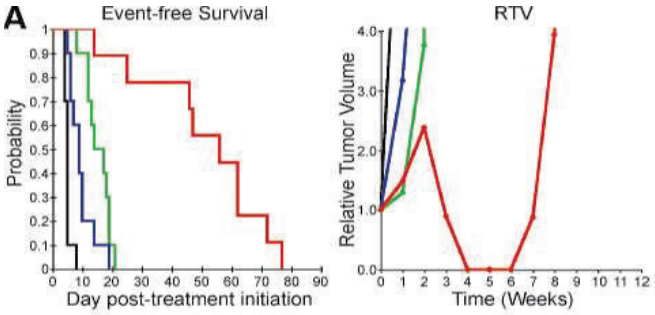
2.2.2 Preclinical Data for mTOR in RMS

Temsirolimus is a soluble ester prodrug of sirolimus, which is a natural product initially developed as an antifungal drug and then as an immunosuppressive agent and forms a complex with FK506-binding protein and prohibits the activation of mTOR.[19] ARMS cell lines are highly sensitive to the growth-inhibitory effects of sirolimus, and RMS cell line sensitivity was likely due to sirolimus inhibition of insulin-like growth factor 1 receptor-mediated signaling.[20] Temsirolimus has been shown to inhibit the growth of RMS xenografts.[21] The Pediatric Preclinical Testing Program (PPTP) reported on single agent activity of

sirolimus against its models.[22] Six RMS xenografts were tested. Two (Rh18 and Rh10) had partial responses to sirolimus. Of the remaining four tested, two had their times to event more than doubled by sirolimus compared to controls. These data suggest that mTOR inhibition by sirolimus has an *in vivo* effect on RMS xenografts.

2.2.3 Rationale for combining mTOR inhibitor with VAC/VI

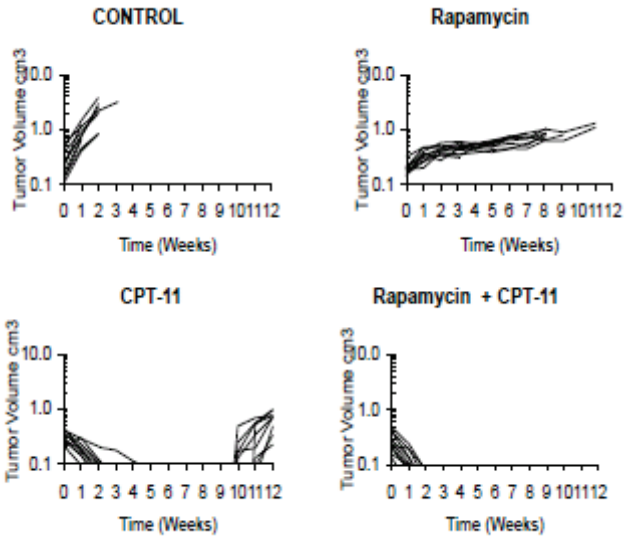
PPTP xenograft experiments also demonstrate a synergistic effect of mTOR inhibition in combination with cyclophosphamide, vincristine or irinotecan. Xenografts demonstrated the combination of sirolimus with either cyclophosphamide (Rh30) or vincristine (Rh18) was significantly more effective than the respective standard agents used alone at their maximum tolerated doses.[23] Vincristine was found to be supra-additive and cyclophosphamide additive in combination with sirolimus. Similar results were seen with irinotecan in combination with sirolimus (unpublished observation, Peter Houghton).



RAPAMYCIN + VINCRISTINE

RAPAMYCIN + CYCLOPHOSPHAMIDE

A synergistic anti-tumor effect was observed in Rh30 xenograft mice following treatment with vincristine or cyclophosphamide ± rapamycin



Synergistic activity was also observed with irinotecan plus sirolimus in the Rh30 mouse xenograft model

2.2.4 Experience with Temsirolimus Alone and in Combination with Irinotecan in Patients with Solid Tumors

A summary of relevant clinical experience with temsirolimus is provided in a table below. A pediatric phase 1 study of temsirolimus (n = 19) demonstrated dose limiting toxicities (DLTs) at 150 mg/m^2 including thrombocytopenia, anorexia, anemia, neutropenia and transaminitis. The recommended phase 2 dose (RP2D) was 75 mg/m^2 weekly IV, although *in vivo* Akt inhibition was demonstrated by decreases in pAKT, pS6, and p4EBP1 in peripheral blood mononuclear cells at all dose levels, including 10 and 25 mg/m^2 IV weekly.[24] As a single agent, Grade 1 hematological toxicity was seen at a temsirolimus dose of 10 or 25 mg/m^2 (see table below).

A pediatric phase 1 trial of temsirolimus plus oral irinotecan and temozolomide investigated many different dose combinations.[25] The RP2D was temsirolimus 35 mg/m^2 IV weekly, with oral irinotecan 90 mg/m^2 (Days 1-5) and oral temozolomide 125 mg/m^2 orally on (Days 1–5). With this dose of temsirolimus, there were frequent Grade 1 and 2 non-hematologic toxicities and frequent ≥ Grade 3 hematological toxicity.

ARST0921, a phase 2 study of temsirolimus plus vinorelbine (25 mg/m^2) and cyclophosphamide (1.2 g/m^2) in relapsed RMS confirmed the feasibility of adding temsirolimus to cyclophosphamide (1.2 g/m^2) and a vinca alkaloid.[18] Temsirolimus was administered at a dose of 15 mg/m^2 weekly, which was associated with frequent episodes of febrile neutropenia (FN) in this heavily pre-treated cohort as demonstrated by an incidence of 26% in the first 6 weeks (reporting period 1 of therapy). In comparison, the rate of FN on ARST0531 with VAC/VI was 10.5% in the first 15 weeks of therapy.

	Phase 1 temsirolimus in children[24]		Phase 1 temsirolimus plus oral Irino plus Temodal[25]		Phase 2 temsirolimus plus VC[18]		Phase 1 temsirolimus plus Irino (adult sarcoma)[26]		Phase 2 temsirolimus plus Irino (adult colon CA)[27]	
Dose	temsirolimus 25 mg/m^2 d1,8,15 q21d		temsirolimus 35 mg/m^2 d 1,8,15 q21d Oral Irinotecan 90 mg/m^2 d 1-5 Oral Temodal 125 mg/m^2		temsirolimus 15 mg/m^2 d 1,8,15 q21d Vinorelbine 24 mg/m^2 d1,8 Cyclophosphamide 1.2 g/m^2 d1		temsirolimus 20 mg IV d1,8,15 q28d Irinotecan 80 mg/m^2 IV d1,8,15		temsirolimus 25 mg IV weekly Irinotecan 180 mg/m^2 IV q2 weeks	
Selected Toxicities	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4*	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Anemia	0	0	6/6	0	NR	0	3/8	0	NR	NR
Neutropenia	2/5	2	2/6	4	NR	3/42	1/8	1	6/64	2
Thrombocytopenia	2/5	0	2/6	4	NR	1/42	2/8	0	17/64	5
Diarrhea	1/5	0	3/6	0	NR	0	3/8	0	29/64	3
Nausea	1/5	0	5/6	0	NR	0/42	2/8	0	25/64	2
Vomiting	1/5	0	4/6	2	NR	0	1/8	0	NR	NR
Elevated LFTs	2/4 2/5	0	3/6	1	NR	2/42	1/8	0	NR	NR
Mucositis	1/5	0	2/6	0	NR	5/42	0	0	33/64	1
Fatigue	NR	NR	2/6	0	NR	1/42	1/8	0	NR	NR
Hyperglycemia	3/5	0	5/6	0	NR	0	0	0	15/64	5
Hyperlipidemia	3/5	0	4/6	0	NR	4/42	NR	NR	35/64	4
Hypercholesterolemia	2/5	0	3/6	0	NR	1/42	NR	NR	NR	NR
Fever	NR	NR	0	0	NR	11/42	0	0	18/64	5

NR: not reported; *denotes only reporting period 1

2.3 Vincristine, Dactinomycin and Cyclophosphomide (VAC) with Vincristine and Irinotecan (VI)

Irinotecan was discovered to have substantial activity in preclinical models of RMS.[28] Subsequently, various schedules were explored in children with RMS, as summarized below. Due to a favorable toxicity profile and convenient schedule, irinotecan 50 mg/m^2 IV Days 1-5 in combination with vincristine every 21 days was selected for further study.

Regimen	RMS Patient Population	n	Response Rate	Reference
Irinotecan [(dx5)2]	Relapsed	4	75%	[29]
Irinotecan q 3 weeks	Relapsed/refractory	34	11.4%	[30]
Irinotecan (dx5)	Relapsed	18	5.5%	[31]
Irinotecan [(dx5)2]	Untreated metastatic	19	42%	[32]
Vincristine and Irinotecan [(dx5)2]	Untreated metastatic	50	70%	
Vincristine and Irinotecan (dx5)	Refractory/initial relapse	47	36%	[33]
Vincristine and Irinotecan [(dx5)2]	Refractory/initial relapse	42	26%	

The recently completed study ARST0531 randomized patients with IR RMS to VAC versus VAC alternating with VI. For the current study VAC alternating with VI was selected as the standard backbone rather than VAC. The reasons for choosing VAC/VI are: 1) VAC and VAC/VI had similar outcomes on ARST0531; 2) VAC/VI had significantly less hematologic toxicity and less Grade 3 or 4 febrile neutropenia[1]; and 3) VAC/VI has the potential for less infertility in both males and females due to lower cumulative cyclophosphamide dose (8.4 g/m^2 versus 16.8 g/m^2).[1]

2.3.1 Previous Experience with VAC/VI

Due to the results from ARST0531, VAC/VI has now been selected as the new standard chemotherapy for IR RMS. In previous sequential studies from IRS-III to IRS-IV to D9803, the cumulative dose of cyclophosphamide had increased significantly.[2,34,35] The dose per course of cyclophosphamide was increased from approximately 0.9 g/m^2 during IRS-III to 2.2 g/m^2 during IRS-IV in order to achieve equivalent hematologic toxicity with the ifosfamide-containing arms, VAI and VIE.[2] The same cyclophosphamide dose per course was maintained during D9803. However, there was no improvement in outcome for either IR ERMS (3 year EFS on IRS-III, 74% versus IRS-IV, 75%, p = 0.47) or IR ARMS (3 year EFS on IRS-III, 70% versus IRS-IV, 64%, p=0.35), despite the escalation of cyclophosphamide cumulative dose.[2,35] The IRS-IV/D9803 dose of cyclophosphamide contributed to acute and chronic toxicity, especially infertility. For these reasons, the control VAC arm was changed to 1.2 g/m^2, which represents an intermediate dose intensity of cyclophosphamide between IRS-III and IRS-IV/D9803. This is the dose that has been used on the most recent RMS studies examining patients with low (ARST0331), intermediate (ARST0531), high (ARST0431) or relapsed (ARST08P1) disease.

ARST0531 randomized patients with IR RMS to receive either VAC alone or VAC alternating with VI. The outcome was similar between the 2 arms, with no difference among patients with either ERMS or ARMS.[1]

	4-year EFS (95% CI)			**4-year OS (95% CI)**		
Patient Category	VAC	VAC/VI	*P*	VAC	VAC/VI	*P*
All patients (n = 448)	63% (55-70%)	59% (51-66%)	0.51*	73% (66-79%)	72% (65-79%)	0.80*
ARMS only (n = 196)	58% (48-69%)	51% (39-62%)	0.25	68% (58-78%)	66% (55-77%)	0.59
ERMS/NOS/other (n = 252)	66% (57-76%)	64% (54-73%)	0.85	77% (69-86%)	76% (68-84%)	0.96

* Adjusted p-value after including randomization stratum (on the basis of central reviewed data, with 24 patients excluded for not belonging to any of the 3 strata) as a covariate in a Cox regression model. Eight and 16 of the 24 patients were categorized by the enrolling institution as having ARMS, stage II/III and group 2/3, and ERMS, stage II/III and group 3, respectively.

Myelosuppression was substantially lower in the VAC/VI arm (see table below). Additionally, we hypothesize that the overall cost of VAC/VI will be lower due to fewer admissions for FN and blood product transfusion, and that there is a potential for a decreased risk of infertility given the total lower cumulative dose of cyclophosphamide (8.4 g/m^2 versus 16.8 g/m^2).

Grade 3 or 4 Toxicity	Week 1-15		Week 16-30		Week 31-43	
	VAC	VAC/VI	VAC	VAC/VI	VAC	VAC/VI
Diarrhea	4.8%	15.7%	2.5%	11.1%	0.5%	2.2%
Oral mucositis	10.1%	18.3%	2.0%	2.5%	0.5%	1.1%
Febrile neutropenia	13.6%	10.5%	17.8%	8.1%	8.6%	4.4%
Anemia	24.1%	18.3%	27.2%	8.1%	26.2%	9.3%
Thrombocytopenia	11.4%	5.2%	31.7%	12.1%	29.9%	6.6%

2.4 Initial Safety Phase Prior to Randomization

A short safety phase in the first 10 subjects who enrolled was conducted. This phase was limited to patients < 21 years of age. These subjects received temsirolimus, 15 mg/m^2 IV weekly, along with VAC/VI. Accrual was suspended until this cohort of patients completed the first 12 weeks of treatment. If fewer than 4 patients had dose limiting toxicity (DLT – see Section 5.1), and the median time to complete the first 12 weeks of prescribed therapy was < 16 weeks, the study would proceed to the randomization component of the trial (VAC/VI ± temsirolimus, 15 mg/m^2). If 4 or more experienced a DLT or the median time to complete the first 12 weeks of prescribed therapy was ≥ 16 weeks, a second cohort of 10 patients would be enrolled to receive 10 mg/m^2 temsirolimus. Again, accrual would be suspended until patients completed 12 weeks of prescribed therapy. If fewer than 4 patients experienced DLT and time to complete 12 weeks of planned therapy was < 16 weeks, this would be the temsirolimus dose for patients randomized to receive VAC/VI + temsirolimus. If this dose was also intolerable, patients would be offered 10 mg/m^2 temsirolimus on Days 1 and 8 only. If greater than 4 patients experienced DLT or time to complete 12 weeks of planned therapy was greater than or equal to 16 weeks, the study would be closed.

The first 10 eligible patients (excluding 1 low-risk Regimen C transfer) enrolled in the feasibility phase received VAC/VI with temsirolimus at 15 mg/m^2 on Days 1, 8 and 15 of each cycle. Criteria to determine feasibility as outlined in Section 4.1.1 "Proceed to Efficacy Phase if < than 4/10 subjects experience a non-hematological DLT, and the median duration of the first 12 weeks of therapy is < 16 weeks, otherwise, proceed to dose level 0" were evaluated. Two patients experienced protocol-defined non-hematological DLTs: one patient experienced oral mucositis and subsequently was removed from the protocol therapy due to physician determination that it was in the patient's best interest, and one patient experienced oral mucositis and lung infection. The median duration of the first 12 weeks of therapy was 12 weeks. Based on the review of toxicities and treatment duration, the feasibility phase has been completed and Dose Level 1 (15 mg/m^2) is the dose of temsirolimus established for the efficacy phase.

2.5 Local Control Recommendations

2.5.1 Improving Local Control: Rationale for Delayed Primary Excision and Increasing Boost Dose to Residual

Local control of RMS may be attained through surgery, definitive RT, individually or in combination. A combined modality approach may optimize local control yet minimize the potential morbidity associated with each individual

modality. RT can be associated with significant late effects, particularly in young children.[36-40] Surgery also can be associated with significant late effects, particularly if organs are sacrificed.[41] In an effort to minimize RT toxicity, many European RMS trials have utilized RT selectively.[42,43] In D9803, the RT dose was adjusted by the amount of residual tumor present following 12 weeks of induction chemotherapy: no evidence of disease (NED) 36 Gy, microscopic residual (MR) 41.4 Gy, and gross residual disease (GRD) 50.4 Gy. With this local control strategy for patients with Group III disease, the overall failure rate was 30%, with 19% including a component of local failure with the first progression. The rate of local failure did not vary by histology or regional nodal status and was similar to historical studies.

Local Failure Pattern Among Patients with Group III Disease

Patient subsets	**IRS-III**	**IRS-IV**	**D9803**
All patients	19%	13%	19%
Embryonal RMS	19%		20%
Alveolar RMS (and undifferentiated sarcoma for IRS-III)	17%		17%
Parameningeal	19%	16%	19%
Extremity	17%	7%	15%
Bladder/prostate	14%	19%	14%
N0	16%		19%
N1	32%		17%
≤ 5 cm	16%		10%*
> 5 cm	21%		25%*

*p=0.0004

The only significant predictor of local failure was initial tumor size > 5 cm (25% vs 10%).[44] Therefore, in the current study, we will explore two strategies to reduce the rate of local failure and also potentially minimize long term toxicity. These include: 1) delayed primary excision (DPE) and 2) increasing the boost dose of XRT to patients with tumors > 5 cm (at diagnosis) and residual disease.

2.5.2 Delayed Primary Excision

To minimize RT toxicity, local tumor control may be achieved with reduced dose RT in conjunction with DPE following Week 9 evaluation in select patients. This local control paradigm may have potential benefit to the patient since patients who have DPE may be able to receive decreased RT dosing, although this strategy has not been shown to improve outcome. Patients may be considered for DPE for select non-parameningeal (PM) primary sites when gross total resection

(GTR) can be easily performed with minimal morbidity or loss of function and with minimal disruption to the overall treatment scheme. Adequate margins of uninvolved tissue are required unless this involves sacrifice of normal tissue that would result in an unacceptable loss of function, form or is not technically feasible. **Debulking operations are absolutely discouraged as they may cause harm, and will not result in reduction of RT dose.** Heroic attempted R0 resections are also discouraged, as all patients will undergo planned RT; delay in the initiation of RT is associated with increased risk of local recurrence.

In D9803, reduction of RT dose based upon the completeness of surgical resection of the primary tumor prior to chemotherapy did not compromise nor did it improve local control, failure free survival (FFS), or OS compared to historical controls.[45] A total of 161 Group III patients were evaluated (24 bladder dome, 63 extremity, and 74 trunk). Seventy-three patients (45%) underwent DPE which achieved removal of all gross disease in 61 (84%) who were then eligible for reduced RT dose (43/73 received 36 Gy, 19/73 received 41.4 Gy). The local 5-year failure rate (0% for bladder dome, 7% for extremity and 20% for trunk) was similar to IRS-IV, which did not encourage DPE and did not allow for DPE adapted RT dose reduction.

In the current protocol, we will allow the paradigm of DPE and modulated RT dose for those patients who have easily resectable masses after 9 weeks of prescribed chemotherapy with a plan for GTR (not debulking) if such can be achieved without loss of form/function or a significant delay in overall protocol treatment. A similar strategy was used on CWS-81,[46] resulting in a local failure rate of 18% for Stage 2-3 patients.

2.5.3 Increasing RT Dose to Tumors > 5 cm

The analysis shown in the table above (in Section 2.5.1) demonstrates that a tumor size > 5 cm was a significant predictor of increased local failure. Thus, in ARST1431, we propose to increase the total dose of RT following induction chemotherapy to 59.4 Gy for primary sites > 5 cm at diagnosis for those patients who will not be undergoing DPE or those who have imaging evidence of gross residual disease after DPE, a situation we hope to avoid. We do not anticipate a greater risk of radiation toxicity because of significant advances in imaging and radiation delivery. ARST1431 will use smaller margins for uncertainty based on current standards of improved immobilization, planning and daily on-treatment imaging. All patients will undergo 3-dimensional conformal RT and the vast majority will receive intensity modulated radiation or proton radiotherapy. The original tumor at the time of diagnosis will be treated to 36 Gy, with the extra dose being given to residual tumor volume based on imaging done at Week 9. For patients undergoing DPE, an additional CT or MRI scan will be necessary post-operatively to confirm GTR or to indicate any gross residual disease requiring a boost to 50.4 Gy or 59.4 Gy depending upon the initial tumor size.

Previously, IRS-IV randomized patients to conventional RT of 50.4 Gy or to hyperfractionated RT of 59.4 Gy. While the results of that study showed no statistically significant difference with respect to EFS, OS, and local control between the 2 groups, the cumulative local control at 5 years was 85-88%, the highest achieved on any IRS studies. Thus, we are hopeful that the current

proposed RT dose escalation will result in improved local control for several reasons. First, IRS-IV used small fraction sizes of 1.1 Gy BID to give 59.4 Gy. This is a lower biologically effective dose than 59.4 Gy in 1.8 Gy fractions as proposed in this study. Also, in IRS-IV, all patients were randomized which could have potentially diluted a benefit to those with higher risk tumors, such as those of large size, who fail to achieve a CR to induction chemotherapy. In ARST1431, only those with tumors at highest risk of local failure (> 5 cm at diagnosis with a PR following 9 weeks of induction chemotherapy) will receive the higher radiation dose.

Patients who have large tumors (> 5 cm at diagnosis) who achieve a CR will not require higher dose RT. The definition of a CR that will warrant avoidance of a higher dose RT will include a radiological CR by cross sectional imaging (no visible tumor) **AND any** one of the following: 1) negative PET; or 2) biopsy that shows NO residual tumor, including rhabdomyoblasts. Furthermore, patients who achieve GTR with DPE (imaging to confirm no visible tumor left by surgeon and a pathology report with no more than microscopic residual tumor) will also not require higher dose RT. These definitions are applicable to the local control guidelines and are separate from the RECIST response definitions in Section 10.2.

2.5.4 Timing of Radiotherapy

Loco-regional failure remains the most common pattern of initial disease progression in RMS. On D9803, the 4-yr local, regional, and distant failure rates were 17.5%, 4.6%, and 12.3%, respectively.[3] Moreover, > 50% of IR RMS patients have a PM primary site, which was associated with a local failure rate of 19% on D9803. The timing of RT differed in three sequential completed RMS studies: IRS-IV (Week 10), D9803 (Week 13), ARST0531 (Week 4). Furthermore, in IRS-IV, PM RMS patients with high-risk features were irradiated as close after study enrollment as possible. There was no difference in local failure rate among PM RMS patients with or without high risk features on IRS-IV (19%) or D9803 (19%).[47] We have therefore chosen to return RT delivery to Week 13. This strategy will permit the feasibility evaluation of temsirolimus with VAC/VI prior to introducing RT, provide sufficient time for complex RT planning, and will allow DPE in selected patients for which DPE is feasible after initial response to chemotherapy. RT should be initiated as soon as possible, once there is evidence of adequate wound healing.

Occasionally patients present with function-limiting disease such as spinal cord compression or cranial nerve palsies. Chemotherapy may be as effective as RT to reduce tumor-related symptoms;[48] thus, emergency RT may not be necessary. Patients for whom emergency RT (prior to Week 13) is planned should not enroll on ARST1431. The use of steroids in this regard is permissible.

2.5.5 Nodal Disease Assessment at Diagnosis

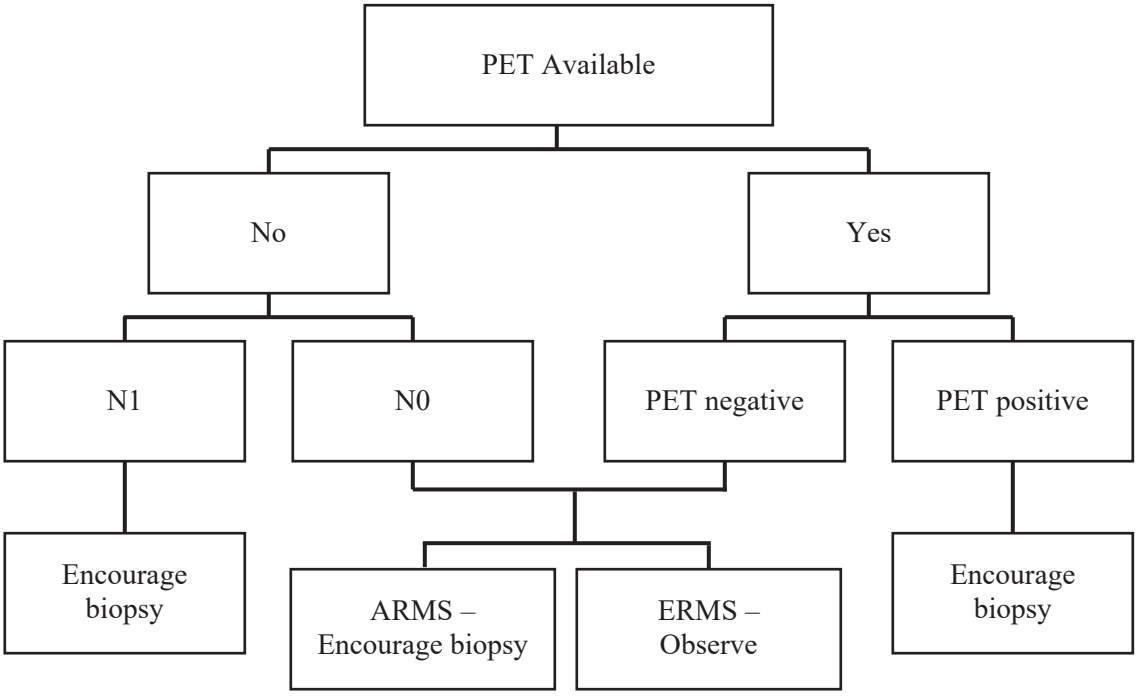
To reduce loco-regional failure, systematic lymph node sampling (preferably using the sentinel node approach) is recommended. Until now, surgical lymph node staging has only been required for study eligibility for patients with extremity tumors or males > 10 years with paratesticular RMS; ARST0531 also recommended biopsy of clinically enlarged nodes. A recent analysis of the

Surveillance, Epidemiology, and End Results database demonstrated the survival benefit with the use of lymph node dissection in paratesticular RMS, although the benefit was restricted to those > 10 years old (86% 5 year survival rate with dissection versus 64% without, $p < 0.009$),[49] further supporting the importance of adequate evaluation of regional lymph nodes in selected patients. On IRS-IV, 23% of patients had regional lymph node disease (N1), which was an independent prognostic factor in patients with ARMS but not in ERMS.[50] N1 status was more common in older patients, those with ARMS, large tumors, and tumors at certain anatomic sites (including perineum, retroperitoneum, extremity, bladder/prostate, PM, and paratesticular). These data illustrate the importance of nodal disease in ARMS. Furthermore, in certain sites such as extremity and body wall, clinical positivity of nodal disease underestimated pathological nodal involvement. Thus, more attention to nodal disease is warranted.

[F^{18}]-fluorodeoxy-D-glucose-positron emission tomography (FDG-PET) imaging could provide a non-invasive alternative to surgical lymph node sampling, although the sensitivity of FDG-PET imaging compared to surgical lymph node sampling is unknown. ARST1431 will collect FDG-PET assessment of regional lymph nodes and pathologic data from surgical lymph node sampling to define FDG-PET false negative rate and for refinement of study guidelines in the future. Therefore, in addition to the previous requirements and recommendations for regional lymph node evaluation, pathological evaluation of clinically uninvolved nodes for all patients with ARMS and for all those with clinically involved nodes (regardless of histology) is recommended. The definition of "clinically involved" nodes is those including the following features: 1) > 1 cm on CT or MRI; OR 2) FDG avid. Imaging of all potential sites of nodal disease, either by FDG-PET or cross sectional imaging, is strongly encouraged since RT is mandatory for nodal disease. If nodes are clinically involved, we strongly encourage biopsy in order to be confident that RT in fact is warranted. If nodes are clinically involved and not biopsied, RT will be delivered to those areas.

For non-paratesticular primary sites, the preferred method of sampling would be to use the sentinel technique in order to identify the most likely drainage basin for the tumor. If this is not available, random regional nodal sampling should be performed. Nodes should either be sampled using excisional biopsy or core needle biopsy. Fine needle aspirates are discouraged due to the potential for false negatives.

In the current study, the following algorithm will be followed. **Note: Nodal sampling is MANDATORY for patients with paratesticular disease (if age ≥ 10 years) and for patients of any age with extremity tumors, regardless of histology.**



2.6 FDG-PET Definitions and Its Utility to Assess Outcome in RMS

Defining positive versus negative scans remains a challenge, however, assessing interim PET using the Deauville criteria (5 point scale)[51] have gained validity in adults with Hodgkin lymphoma.[52,53] In ARST1431, the Deauville criteria will be used to define a 'positive' scan using the primary site of disease. The limitations of using FDG-PET to identify at-risk lymph nodes are well appreciated, nonetheless, the more data available to help determine whether nodal disease should be biopsied is important for this study. Notably, institutional review will be used for decision making as central imaging review for decision making will not be performed on ARST1431.

Response to therapy of the primary tumor as defined by change in tumor size, does not predict outcome in RMS.[54,55] After 8-12 weeks of chemotherapy (with or without RT), 15-23% of patients with Group III RMS have no response (stable disease). Surprisingly, patients with no response after initial therapy have a similar outcome as those with complete or partial response. Response at the completion of therapy also fails to predict outcome.[56] As an alternative to anatomic imaging to define response, changes in metabolic activity could be more predictive of outcome. FDG-PET response predicts failure-free survival in non-RMS soft tissue sarcoma,[57] Ewing sarcoma,[58] and osteosarcoma.[59] Memorial Sloan-Kettering Cancer Center (MSKCC) studied 94 patients with RMS who received varying chemotherapy protocols. RT was delivered at a median of 15 weeks after initiation of chemotherapy. With 3-year median follow-up, local relapse-free survival was improved among post-radiation PET-negative vs PET-positive patients: 94% vs 75%, p=0.02.[60] A follow up analysis from MSKCC confirmed these findings in a larger cohort of RMS patients showing that metabolic response by ^{18}F-FDG PET/CT accurately predicted EFS, overall survival, and local control with statistical significance.[61] However, these results are limited by the relatively small study population, heterogeneous treatment, and inclusion of localized and metastatic patients. ARST1431

will determine whether response of the primary tumor at Week 9 on FDG-PET correlates with EFS within the context of uniform therapy, risk grouping, and a larger prospective study.

In ARST0531, FDG-PET was encouraged but not required prior to chemotherapy, Week 4, and Week 15 (following RT). Only 25 patients had FDG-PET performed at Week 4, precluding a statistical analysis. There was no association with PET response at Week 15 and outcome. However, all Week 15 PET evaluations were after RT, and it is possible that PET has limited utility following RT. In ARST1431, we will assess PET response at Week 9 following chemotherapy but prior to RT, with the potential for better correlation with outcome.

2.7 Fusion Status

2.7.1 Fusion Status to Confirm Eligibility

Patients who are newly diagnosed with biopsy proven RMS of any histologic type, except adult-type pleomorphic, are eligible for enrollment on ARST1431. ARST1431 will use FOXO1 fusion status rather than histology for study eligibility because it is more predictive of outcome as demonstrated by two independent analyses.[15,16] FOXO1 fusion status must be performed at local institutions within the first 3 weeks of study enrollment to confirm eligibility and for patients to remain on study. To confirm the anticipated high concordance rate between institutional and central *FOXO1* fusion status, the first 150 patients enrolled on ARST1431 will have *FOXO1* fusion status determined by FISH at the Biopathology Center (BPC). Patients with ERMS who have distant metastases and are found to be FOXO1 positive will be deemed inevaluable and removed from study.

Patients with ARMS without distant metastases are eligible if FOXO1 fusion positivity is confirmed. Approximately 20% of histologically defined ARMS are negative for FOXO1 fusion (nARMS). These patients will continue on protocol therapy as randomized unless they are Stage 1/2, Group I-II (completely resected) or orbital primary site (Group I-III). This molecularly defined low risk population will receive 24 weeks of VAC/VA therapy as per ARST0331 instead of the randomized arm of therapy (see Appendix III). On D9803, these low risk nARMS patients had 100% EFS but at the cost of a high cumulative cyclophosphamide dose (30.8 g/m^2).[15] Although the rarity of low risk nARMS will limit the ability to draw strong statistical conclusions, ARST1431 will be the only opportunity to estimate the success of reduced intensity therapy for low risk nARMS.

If institutions are not able to comply with local fusion testing, the patient will be removed from protocol therapy (but remain on study) for failure to comply with protocol requirement. If fusion study is performed but is an indeterminant result, the patient will remain on therapy. Finally, if an ARMS patient turns out to be FOXO1 fusion negative and low-risk, he/she will be transferred to VAC/VA arm (and stop temsirolimus if previously on arm B); we anticipate that 50% of the VAC/VA patients will have received 1-3 doses of temsirolimus.

In FISH testing of 417 COG ARMS cases, 315 were translocated or positive (79% of 398 evaluable cases), 82 were negative (21% of evaluable cases), 4 were

equivocal (1% of all cases), and 15 failed hybridization (3.6% of all cases).[62] The accuracy and reportable ranges were established by comparison to RT-PCR results. Of 109 cases deemed positive by RT-PCR, 105 (96%) were also positive by FISH and the others were equivocal by FISH (4%). Of 63 cases called negative by RT-PCR, 59 (94%) were negative by FISH, 3 (5%) were equivocal by FISH, and 1 case was positive by FISH (likely due to a variant translocation partner).

2.8 Maintenance Therapy (Implemented with Amendment #3)

The duration of therapy has been of interest in the treatment of children with RMS. Recently, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) completed a randomized phase 3 trial, with an objective to determine whether the addition of maintenance therapy following standard induction therapy and local control improves outcome. In EpSSG RMS 2005, patients with disease profiles that are similar to how COG defines IR RMS (including patients with non-metastatic alveolar and locally advanced embryonal disease) who achieved complete remission following induction chemotherapy (with ifosfamide, actinomycin, vincristine, doxorubicin) were randomized to receive an additional 6 months of maintenance therapy (n=185) versus no maintenance (n = 186).[63] Maintenance therapy consisted of continuous daily low dose oral cyclophosphamide (CPM) plus weekly IV vinorelbine (on Days 1, 8, and 15 of each 28-day cycle). The results as presented at ASCO 2018 are described in the table below. Addition of maintenance therapy was associated with a statistically significant improvement in overall survival.

	No Maintenance	Maintenance	*p*
3-year EFS (95% CI)	72.3% (65.0-78.3%)	78.4% (71.5-83.8%)	0.061
3-year OS (95% CI)	77.4% (70.1-83.1%)	87.3% (81.2-91.6%)	0.011

Although there are differences between the EpSSG and COG approaches to RMS including differences in backbone therapy and in the precise definitions of 'IR RMS,' the overall conclusions are important and relevant for all patients with RMS. Additionally, the specific question of benefit of maintenance therapy will not be again tested in a randomized study.

Furthermore, a recent comparison of similar cohorts of patients showed a lower EFS on ARST0531 (CPM = 1.2 g/m^2/dose; total cumulative dose = 8.4 g/m^2 on VAC/VI therapy) compared to D9803 (CPM = 2.2 g/m^2/dose; total cumulative dose = 30.8 g/m^2 on VAC therapy). The reason for the inferior outcome on ARST0531 compared to D9803 is uncertain, but may be related to lower cumulative CPM dose.[1] A summary of the EFS/OS outcome comparison by clinical risk groups is presented below:

Clinical stratum	4 year EFS		Log rank p-value	4 year OS		Log rank p-value
	ARST0531	D9803		ARST0531	D9803	
ERMS, Stage 2/3, Group III	65% (55-72%)	73% (67-78%)	**0.028**	77% (71-83%)	79% (74-84%)	0.21
ARMS, Stage 1 or Group I	69% (55-84%)	76% (65-87%)	0.51	85% (74-97%)	90% (82-97%)	0.77
ARMS, Stage 2/3 and Group II/III	51% (42-60%)	58% (50-66%)	0.14	62% (53-71%)	71% (63-78%)	0.13

The COG STS Committee has given serious consideration to these two observations. There is substantive limitation to the retrospective non-randomized comparison of D9803 to ARST0531, and it remains uncertain whether the difference in outcomes seen on D9803 and ARST0531 is indeed due solely to the higher cumulative CPM dose. Moreover, increased frequency of events on ARST0531 is predominantly local recurrence and is most pronounced in patients with tumors > 5 cm at diagnosis.

The STS Committee has taken into consideration the following: 1) the role of temsirolimus in intermediate risk RMS remains an important question to answer; 2) patients with tumors > 5 cm will receive a higher dose of radiation on ARST1431 compared to ARST0531 (59.4 vs 50.4 Gy); 3) there is significantly increased acute and long-term toxicities associated with higher dose CPM (as used in D9803); and 4) maintenance chemotherapy as used by EpSSG offers a more modest increase in cumulative CPM exposure (4.2 g/m^2) and has been shown to improve overall survival in a similar population of patients with RMS.

Taking all the above into account, ARST1431 will incorporate maintenance chemotherapy as a strategy to improve outcome without exposing all intermediate risk patients to a substantially higher cumulative CPM dose. Patients who receive either VAC/VI alone or VAC/VI plus temsirolimus will continue to receive an additional 6 months of maintenance therapy beginning with Amendment #3.

The toxicity observed in EpSSG RMS 2005 with maintenance therapy was minimal and treatment was delivered in an ambulatory setting.

Patients on Regimen C will not receive maintenance therapy.

2.9 Biological Correlatives

2.9.1 Comparing Outcome Among Patients with Translocation Positive Disease: PAX3 vs. PAX7

The vast majority of ARMS cases are *PAX3-FOXO1* or *PAX7-FOXO1* translocation positive.[16,64] Previous reports suggest that for patients with metastatic disease, presence of a *PAX7-FOXO1* fusion transcript may confer a more favorable prognosis than a *PAX3-FOXO1* transcript. Conflicting reports exist, however, and there is currently insufficient data to base risk stratification on specific fusion type. We will compare the outcome of patients based on their

FOXO1 partner, by evaluating PAX3 vs. PAX7 in all submitted tumor specimens found to be FOXO1 fusion positive.

Rare cases of fusion positive ARMS involve variant gene partners, ie. PAX3-NCOA1, PAX3-NCOA2, PAX3-FOXO4 (AFX), and FGFR1-FOXO1. Fusion negative ARMS will be further examined for the presence of one of these variant gene fusions using a combination of IHC and in depth fluorescence in situ hybridization (FISH) analysis. Of note, if a patient with fusion negative ARMS is found to have one of these uncommon translocations, that patient will be considered a fusion negative case since the results will not be available in real-time.

2.9.2 Assessing Circulating Tumor DNA in Patients with Intermediate Risk RMS

Radiographic response to therapy is unable to predict outcome in RMS, and so, alternative approaches to performing response-based stratification are needed. One appealing alternative includes minimal residual disease testing by detection, quantification, and serial tracking of circulating tumor DNA (ctDNA), also known as liquid biopsy, obtained from peripheral blood draws. ctDNA technologies have demonstrated superior rates of detection and quantification compared to assays for circulating tumor cells.[65] Furthermore, ctDNA can be reliably extracted from plasma using commercially available kits.

ctDNA from patients with solid tumors has been used to assess disease burden, track disease response to therapy, identify clonal evolution, and predict relapse after remission.[65,66] However, the application of ctDNA technologies has yet to be applied prospectively in pediatric RMS. In ARST1431, we will collect serial plasma samples from patients to quantify ctDNA at diagnosis and during therapy. No prior data regarding frequency of ctDNA in patients with RMS at diagnosis is available. Further, no prior information on change in ctDNA is available from prior studies to assess response to therapy, and the timecourse of decline in ctDNA in response to therapy is unknown.

Since FOXO1 translocations are never present in the germline, detection of any FOXO1 in plasma guarantees that it represents tumor DNA. FOXO1 negative RMS, in contrast, are driven by oncogenic single-nucleotide variants in a number of genes participating in tyrosine kinase signaling cascades.[67] Approaches to developing a liquid biopsy assay for FOXO1 fusion negative RMS require the survey of several proto-oncogenes, distinguishing somatic from germline variants, and/or detecting somatic copy number changes that are frequent in these tumors.[67] In this study, multiple approaches will be applied to detect ctDNA from blood samples of patients with FOXO1 translocated tumors as well as patients with FOXO1 fusion negative disease.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once

authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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

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

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

3.1.2 IRB Approval

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

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

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the

Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

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

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

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

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

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

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

3.1.3 Reservation Requirements

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

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

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

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
   https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.1.4 Patient Enrollment

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

Requirements for OPEN access:

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

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

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

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

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

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

3.1.5 Timing

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

Patients must start protocol therapy within 42 days from the date of collection of the material that establishes the diagnosis of RMS. Patients who fail to begin therapy within 42 days of the procedure which establishes diagnosis will be removed from protocol therapy per Section 8.1.

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.

IMPORTANT: If the patient has consented to ctDNA study, tubes should be ordered via the BPC Kit Management system as soon as possible after patient enrollment to allow time for tubes to be shipped by ground transportation. Shipping will take 3-5 business days.

The Kit Management System can be accessed via the following link: https://ricapps.nationwidechildrens.org/KitManagement/Auth/Login.
You must select ARST1431 as the protocol when ordering Streck tubes for ARST1431 patients.

3.1.6 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.1.7 Randomization

Randomization will take place at the time a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

3.1.8 Callback

Following randomization, if a patient is found to be eligible for Regimen C (see Section 3.3.2) they will require consent and callback. Callback, performed in OPEN as a Step 2 Registration, should be submitted for eligible subjects who consent to a new treatment regimen after initial randomization.

3.1.9 Emergent RT Therapy

Patients for whom emergency RT (prior to Week 13) is planned should not enroll on ARST1431. The use of steroids in this regard is permissible.

3.2 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 4 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 4.0 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

Feasibility Phase: Patients must be < 21 years of age at the time of enrollment.
Please note: the feasibility phase is complete, effective with Amendment #1.

Efficacy Phase: Patients must be ≤ 40 years of age at the time of enrollment.

3.2.2 Diagnosis

Patients with newly diagnosed RMS of any subtype, except adult-type pleomorphic, based upon institutional histopathologic classification, are eligible to enroll on the study based upon Stage, Group, and age, as below.

RMS types included under ERMS include those classified in the 1995 International Classification of Rhabdomyosarcoma (ICR) as ERMS (classic, spindle cell, and botryoid variants), which are reclassified in the 2013 WHO Classification as ERMS (classic, dense and botryoid variants) and spindle cell / sclerosing RMS (encompassing the historical spindle cell ERMS variant and the newly recognized sclerosing RMS variant). Classification of

ARMS in the 2013 WHO Classification is the same as in the ICR and includes classic and solid variants.

- ERMS
  - Stage 1, Group III (non-orbit)
  - Stage 3, Group I/II
  - Stage 2/3, Group III
  - Stage 4, Group IV, < 10 years old

- ARMS: Stages 1-3, Groups I-III

3.2.3 Specimen Submission

Patients must have sufficient tissue available for the **required** biology study (see Section 15.0).

3.2.4 Performance Level

Lansky performance status score ≥ 50 for patients ≤ 16 years of age.
Karnofsky performance status score ≥ 50 for patients >16 years of age.

3.2.5 Organ Function Requirements

3.2.5.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/μL
- Platelet count ≥ 75,000/μL

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[68] utilizing child length and stature data published by the CDC.

Patients with an elevated serum creatinine due to obstructive hydronephrosis secondary to tumor are still eligible. However, patients with urinary tract obstruction by tumor must have unimpeded urinary flow established via diversion (ie. percutaneous nephrostomies or ureteric stents) of the urinary tract.

3.2.5.3 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

3.2.6 Exclusion Criteria

3.2.6.1 Patients who have previously received temsirolimus, another mTOR inhibitor, or any other investigational agent.

3.2.6.2 Patients who have received any chemotherapy (excluding steroids) and/or RT prior to this enrollment.

3.2.6.3 Patients with uncontrolled hyperglycemia

3.2.6.4 Patients with uncontrolled hyperlipidemia.

3.2.6.5 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for at least 3 months after treatment is completed.

3.2.6.6 Female patients who are pregnant are not eligible since fetal toxicities or teratogenic effects have been noted for several of the study drugs.
Note: A pregnancy test is required for female patients of childbearing potential prior to study entry.

3.2.6.7 Lactating females who plan to breastfeed their infants are not eligible.

Please see Section 4.1.3 for the concomitant therapy restrictions for patients during treatment.

3.2.7 Regulatory Requirements

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

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

3.3 FOXO1 Fusion Status

3.3.1 All patients will undergo institutional pathology review and FOXO1 fusion determination regardless of histology. If institutions are not able to comply with local fusion testing, the patient will be removed from protocol therapy (but remain on study) for failure to comply with protocol requirement. If fusion study is performed but the result is indeterminant, the patient will remain on therapy.

FOXO1 status results must be available by Week 3 (Day 21) of therapy.
Every effort should be made to **SUBMIT** FOXO1 results as an upload to RAVE soon as they are available.

Patients will be eligible to remain on protocol therapy based upon Stage, Group, and age: (See Appendix III and Appendix IV for Stage and Grouping)

- FOXO1 fusion negative:
  - Stage 1, Group III (non-orbit)
  - Stage 3, Group I/II
  - Stage 2/3, Group III
  - Stage 4, Group IV, < 10 years old
- FOXO1 fusion positive: Stage 1-3, Group I-III

Note: FOXO1 fusion status must be performed at local institutions. To confirm the anticipated high concordance rate between institutional and central *FOXO1* fusion status, the first 150 patients enrolled on ARST1431 were to have *FOXO1* fusion status determined by FISH at the Biopathology Center. Centrally determined *FOXO1* fusion status results will not be returned to the institution.

As of August 24, 2019, 92 evaluable specimens have been analyzed at the Biopathology Center (BPC), of which 91 had concordant *FOXO1* fusion status determined by FISH with local institutions, for an overall concordance rate of 98.9%. We will no longer be evaluating *FOXO1* fusion status at the BPC as of Amendment #4. PAX3 and PAX7 evaluations will continue.

3.3.2 Patients with institutional histologic classification of ARMS but FOXO1 fusion negative with the following Stage and Group can remain on study but will receive VAC/VA therapy on Regimen C instead of the previously assigned treatment regimen. Patient consent is required to transfer to Regimen C. See Section 3.1.8 for callback details:

- Stage 1, Group I/II
- Stage 1, Group III (orbit)
- Stage 2, Group I/II

4.0 TREATMENT PLAN

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

4.1 Overview of Treatment Plan

Prior to randomization, a feasibility phase will be conducted where all patients will be non-randomly assigned to receive VAC/VI plus temsirolimus. Once the appropriate dose is selected, the study will be amended and all subsequent patients will be randomized at study entry to receive either VAC/VI alone (Regimen A) or VAC/VI plus temsirolimus (Regimen B). Patients who had received the appropriate dose selected in the feasibility phase will be included in the analysis of the efficacy phase. **The feasibility phase is complete, effective with Amendment #1A.** Dose Level 1 (temsirolimus 15 mg/m^2/day on Days 1, 8, 15) was found to be the safe dose.

NOTE: **REGIMEN C:** Patients with an institutional histopathologic classification of ARMS that is FOXO1 fusion negative with the following Stage and Group as outlined below will receive **VAC/VA** therapy on Regimen C instead of the previously assigned treatment arm. If an eligible patient refuses treatment on Regimen C they will be removed from protocol therapy.

- Stage 1, Group I/II
- Stage 1, Group III (orbit)
- Stage 2, Group I/II

Transfer to Regimen C requires consent and callback (see Section 3.1.8). Eligible patients should be transferred as soon as the FOXO1 fusion result is obtained and prior to the start of Week 4 of therapy (see Section 4.5 for Regimen C treatment details).

Prior to Amendment #3, the treatment duration was 42 weeks (VAC/VI with or without temsirolimus) for both Regimens A and B, with RT delivered at Week 13. **Beginning with Amendment #3**, the treatment duration will be extended to 66 weeks for both Regimens A and B (42 weeks of VAC/VI with or without temsirolimus, and 24 weeks of maintenance), with RT delivered at Week 13. The treatment duration for Regimen C will not change.

For patients on Regimen B, temsirolimus will be held during and for 2 weeks following RT. A higher dose of boost RT will be given to patients with a large tumor at diagnosis (> 5 cm) who are not in CR at Week 9. Delayed primary excision (DPE) will be permitted in selected non-parameningeal patients with the potential to achieve gross total resection with minimal morbidity and without loss of function. In order to permit enough time for local control decision making, imaging assessment of CR will be made at Week 9.

Note: Multi-disciplinary consultation and discussion with radiation and surgical oncology is required for all patients prior to initiating any chemotherapy and again following Week 9 evaluations.

FOXO1 Fusion Status

All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 3 (Day 21) of therapy.** Failure to obtain FOXO1 status by Day 21 of therapy will result in removal from protocol therapy. Patients with FOXO1 fusion positive and Group IV/Stage 4 disease will be removed from protocol therapy. **Institutional PAX3 vs. PAX7 determination is not required.**

Special Note for Patients ≤ 24 Months Old

The long-term morbidity of RT or aggressive surgery for very young (≤ 24 months old) children makes appropriate local control challenging. Many clinicians are unwilling to follow standard local control guidelines for very young children. We strongly encourage adherence to standard local control guidelines for children ≤ 24 months old but administered dose is at the discretion of the local radiation oncologist. **Documentation of rationale for dose and field of RT must be documented if different than protocol guidelines.**

Week 9 Evaluation: Assessment of CR

TWO methods of defining CR are required to confirm CR at Week 9 that will warrant a dose reduction in RT. At Week 9, CR must be present on cross sectional imaging (CT or MRI) that has NO measurable tumor, **AND** the patient must have one of the following: 1) negative FDG-PET or 2) biopsy of residual disease to confirm no viable tumor. FDG-PET is strongly encouraged, but not mandatory, prior to starting therapy and at Week 9 and will be utilized for assessing nodal involvement, response to induction chemotherapy and determination of RT fields. (See Section 17.0 for details.) **For those in whom FDG-PET is not performed at diagnosis and Week 9, a BIOPSY of residual disease/tumor bed is required to confirm CR at Week 9.** Central imaging review will not be conducted.

Please note: Lymph node (LN) sampling is required for all patients with extremity primaries (preferably using the sentinel node technique) and males ≥ 10 years of age with paratesticular primaries, irrespective of whether the nodes are clinically involved or not and regardless of histology/FOXO1 status. Note that tumors arising in the shoulder and hip girdle are considered to be extremity tumors and are required to have LN sampling. LN sampling is also strongly encouraged in all patients with ARMS and in those with ERMS and clinically suspicious nodes on imaging.

Delayed Primary Excision (DPE)

Following the first evaluation at Week 9, patients may be considered for DPE for select non-PM primary sites when GTR can be easily performed with minimal morbidity or loss of function and with minimal disruption to the overall treatment scheme. If DPE is being considered, discussions with radiation and surgical oncology should be started immediately following Week 9 evaluation. Adequate margins of uninvolved tissue are required unless this involves sacrifice of normal tissue that would result in an unacceptable loss of function, form, or is not technically feasible. **Debulking operations are absolutely discouraged as they may cause harm, and will not result in reduction of RT dose.** Additional CT or MRI imaging will be necessary as soon as possible

following DPE to confirm GTR or to indicate residual disease that would require a full dose radiotherapy boost to 50.4 Gy or 59.4 Gy based on initial tumor size. For patients who do achieve GTR and are in CR, the dose of RT will be reduced. (See Section 17.0 for details.)

DPE should be planned as soon as possible following Week 9 evaluation to avoid potential delays to RT. For those considering DPE, hold chemotherapy and resume where you left off. If doses of specific agents (ie. temsirolimus) need to be held in the best interest of the patient, they will be omitted, and not made up at later dates. For those enrolled on Regimen B, temsirolimus must be held 2 weeks prior to and 1 week following DPE.

Sperm Banking and Fertility Consult
Sperm cryopreservation discussions with all post-pubertal boys receiving RMS therapy are strongly encouraged as per the ASCO guidelines.[69]

4.1.1 Feasibility Phase

The feasibility phase is complete, effective with Amendment #1A. Dose Level 1 (temsirolimus 15 mg/m^2/day on Days 1, 8, 15) was found to be the safe dose. The feasibility of combining temsirolimus with VAC/VI will be assessed prior to expanding to the efficacy phase. Initially, 10 eligible patients < 21 years of age will be non-randomly assigned to receive VAC/VI plus temsirolimus. Feasibility will be assessed during treatment Weeks 1-12. Accrual will be suspended during the assessment to determine feasibility (see table below and Section 9.0).

Dose Level	Temsirolimus Dose and Schedule		
Dose 1	15 mg/m^2 IV Days 1,8,15 of each cycle	Enroll 10 patients to complete Weeks 1-12. Suspend accrual until all 10 patients evaluated.	Proceed to Efficacy Phase if < than 4/10 subjects experience a non-hematological DLT, and the median duration of the first 12 weeks of therapy is < 16 weeks, otherwise, proceed to dose level 0
Dose 0	10 mg/m^2 IV Days 1,8,15 of each cycle	Enroll 10 patients to complete Weeks 1-12. Suspend accrual until all 10 patients evaluated.	Proceed to Efficacy Phase if < than 4/10 subjects experience a non-hematological DLT, and the median duration of the first 12 weeks of therapy is < 16 weeks, otherwise, proceed to dose level -1
Dose -1	10 mg/m^2 IV Days 1, 8 of each cycle	Enroll 10 patients to complete Weeks 1-12. Suspend accrual until all 10 patients evaluated.	Proceed to Efficacy Phase if < than 4/10 subjects experience a non-hematological DLT, and the median duration of the first 12 weeks of therapy is < 16 weeks, otherwise the study is not feasible.

Note: See Section 5.1 for DLT definition.

4.1.2 Efficacy Phase

Patients will be randomly assigned to Regimen A or B in which the only difference is the addition of temsirolimus. **With Amendment #3**, following completion of 42 weeks of therapy, all patients in Regimen A or B will receive 24 weeks of maintenance therapy. See Section 4.1 regarding Regimen C.

4.1.2.1 Regimen A

Patients will receive VAC/VI only for a total of 42 weeks, with primary site RT at Week 13, followed by 24 weeks of maintenance therapy. Metastatic site RT will occur at Week 43.

Cycle	1			2			3				4		
Week	1%	2	3	4%	5	6	7%	8	9**		10	11	12&
	VAC	V	V	VI	V	V	VAC	V	V	Eval.	VI	V	V

Cycle	5			6			7			8			9			10		
Week	13	14	15	16	17	18	19%	20	21	22	23	24	25	26	27	28	29	30
	VAC			VI	V		VI	V		VAC	V	V	VI	V		VAC		Eval.
	Radiation Therapy***																	

Cycle	11			12			13			14		
Week	31	32	33	34	35	36	37	38	39	40	41	42%
	VI	V	V	VAC			VI	V		VAC		Eval.

Cycle	M1				M2				M3			
Week	43^	44	45	46	47	48	49	50	51	52	53	54
	VINO	VINO	VINO		VINO	VINO	VINO		VINO	VINO	VINO	Eval.
	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO

Cycle	M4				M5				M6				
Week	55	56	57	58	59	60	61	62	63	64	65	66	67%
	VINO	VINO	VINO		VINO	VINO	VINO		VINO	VINO	VINO		End of therapy eval.
	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	

% ctDNA sample, see Section 15.2
**Consideration of DPE, if applicable
& For patients who undergo DPE, post-operative CT or MRI is required prior to RT
***See Section 17.0 for RT guidelines. Patients with Clinical Group I, FOXO1 negative tumors or Clinical Group I, FOXO1 indeterminate tumors will not receive radiotherapy.
^ Metastatic sites should be treated with radiotherapy at the completion of VAC/VI chemotherapy. See Section 17.0.

	Drug	Dosing Parameter	Dose
VAC/VI			
V	VinCRIStine	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	1.5 mg/m^2 IV (maximum dose 2 mg) See TDMs for days given
A	DACTINomycin	< 14 kg	Weight-based dosing, see dosing table
		≥ 14 kg	0.05 mg/kg IV Day 1 (maximum dose 2.5 mg)
C	Cyclophosphamide (IV)	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	1200 mg/m^2 IV Day 1
I	Irinotecan	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	50 mg/m^2 IV Days 1-5 (maximum dose 100 mg)
Maintenance (implemented with Amendment #3)			
VINO	Vinorelbine	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	25 mg/m^2 IV Days 1, 8, 15

C_{PO}	Cyclophosphamide (oral)		25 mg/m^2 PO once daily Days 1-28
Mesna and fluids will be used with IV Cyclophosphamide			
Neutrophil growth factor will be used with VAC. See Appendix VII (Supportive Care) for specific directions.			
If there is an age change during treatment, use the new appropriate age dosing in the next cycle			

4.1.2.2 Regimen B

Patients will receive VAC/VI plus temsirolimus for a total of 42 weeks, with primary site RT at Week 13, followed by 24 weeks of maintenance therapy. Metastatic site RT will occur at Week 43. Temsirolimus will be held during RT and restarted 2 weeks following completion of RT and once mucositis has resolved to ≤ Grade 1. The dose of RT will be the same in Regimen A and Regimen B.

Temsirolimus must be held for 1 week following any minor surgical procedures (insertion of central venous catheters, gastrostomy tubes, biopsies) and 2 weeks prior to any major surgical procedures (tumor resection either initially or at DPE). Temsirolimus should be held for a minimum of 1 week following major surgery and may be reinitiated after a surgical procedure at the discretion of the treating physician/surgeon (all wound and surgical complications should not be greater than Grade 1 according to CTCAE version 5.0).

Cycle	1			2			3				4		
Week	1%	2	3	4%	5	6	7%	8	9**		10	11	12&
	VAC	V	V	VI	V	V	VAC	V	V	Eval	VI	V	V
	T	T	T	T	T	T	T	T	T		T	T	T

Cycle	5			6			7			8			9			10		
Week	13	14	15	16	17	18	19%	20	21	22	23	24	25	26	27	28	29	30
	VAC			VI	V		VI	V		VAC	V	V	VI	V		VAC		Eval.
									T	T	T	T	T	T	T	T	T	T
	Radiation Therapy***																	

Cycle	11			12			13			14		
Week	31	32	33	34	35	36	37	38	39	40	41	42%
	VI	V	V	VAC			VI	V		VAC		Eval.
	T	T	T	T	T	T	T	T	T	T	T	T

Cycle	M1				M2				M3			
Week	43^	44	45	46	47	48	49	50	51	52	53	54
	VINO	VINO	VINO		VINO	VINO	VINO		VINO	VINO	VINO	Eval.
	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}

Cycle	M4				M5				M6				
Week	55	56	57	58	59	60	61	62	63	64	65	66	67%
	VINO	VINO	VINO		VINO	VINO	VINO		VINO	VINO	VINO		End of therapy eval.
	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	C_{PO}	

%ctDNA sample, see Section 15.2
**Consideration of DPE, if applicable

& For patients who undergo DPE, post-operative CT or MRI is required prior to RT
***See Section 17.0 for RT guidelines. Patients with Clinical Group I, FOXO1 negative tumors or Clinical Group I, FOXO1 indeterminate tumors will not receive radiotherapy.
^ Metastatic sites should be treated with radiotherapy at the completion of VAC/VI chemotherapy. See Section 17.0.

Please note: The schema above represents temsirolimus Dose Levels 1 and 0 only, Dose Level -1 is administered on Days 1 and 8 only, not on Day 15 (see Section 5.2).

	Drug	Dosing Parameters	Dose
VAC/VI			
V	VinCRIStine	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	1.5 mg/m^2 IV (maximum dose 2 mg), see TDMs for days given
A	DACTINomycin	< 14 kg	Weight-based dosing, see dosing table
		≥ 14 kg	0.05 mg/kg IV Day 1 (maximum dose 2.5 mg)
C	Cyclophosphamide (IV)	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	1200 mg/m^2 IV Day 1
I	Irinotecan	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	50 mg/m^2 IV Days 1-5 (maximum dose 100 mg)
T	Temsirolimus	< 10 kg	0.5 mg/kg IV Day 1 of each week during Weeks 1-12 and Weeks 21-42 No temsirolimus is administered during RT and for 2 weeks after (see Section 4.1.2.2)
		≥ 10 kg	15 mg/m^2 IV (maximum dose 25 mg) Day 1 of each week during Weeks 1-12 and Weeks 21-42 No temsirolimus is administered during RT and for 2 weeks after (see Section 4.1.2.2)
Maintenance (implemented with Amendment #3)			
VINO	Vinorelbine	< 0.6 m^2 BSA	BSA-based dosing, see dosing table
		≥ 0.6 m^2 BSA	25 mg/m^2 IV Days 1, 8, 15
C_{PO}	Cyclophosphamide (oral)		25 mg/m^2 PO once daily Days 1-28
Mesna and fluids will be used with IV Cyclophosphamide			
Neutrophil growth factor will be used with VAC. See Appendix VII for specific directions.			
If there is an age change during treatment, use the new appropriate age dosing in the next cycle			

4.1.3 Concomitant Therapy

Temsirolimus, vinCRIStine, vinorelbine, and irinotecan are sensitive substrates of CYP450 3A4 isozyme. The use of moderate to strong CYP3A4 inhibitors and inducers should be avoided within 7 days of study initiation and for the duration of the study (see Appendix VIII for more information on CYP3A4 inducers and inihibitors; please consult frequently updated medical references for a full list of CYP3A4 inducers and inhibitors). The use of systemic corticosteroids (eg., dexamethasone) is allowed on this study. Single aprepitant or fosaprepitant doses do not substantially inhibit CYP3A4 and are permitted on this study. Longer multi-day apprepitant regimens may cause moderate CYP3A4 inhibition and should be avoided.

In addition, temsirolimus and irinotecan are substrates for P-glycoprotein (p-gp). The use of p-gp inhibitors (eg, amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone,

quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, verapamil) or inducers (eg, carbamazepine, rifampin, saquinavir, tipranavir) should be avoided for the duration of the study.

Concomitant use of temsirolimus and angiotensin-converting enzyme inhibitors (ACEIs) and/or calcium channel blockers (eg. amlodipine) may increase the risk of angioedema. Concurrent therapy with ACEIs and calcium channel blockers should be avoided in patients receiving temsirolimus.

4.1.4 Supportive Care Guidelines

Please see Appendix VII for protocol-specific supportive care guidelines. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

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

4.2 Regimen A (VAC/VI Only)

4.2.1 ARST1431 Regimen A Cycles 1-4

This therapy delivery map (TDM) relates to Cycles 1-4 of therapy (Weeks 1-12). Each cycle lasts 21 days (3 weeks).

_____ Patient COG ID number

_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1.5 **mg/m^2/dose**	Day 1 of each week.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 1 and 7.	Maximum dose: 2.5 mg
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1200 **mg/m^2/dose**	Day 1 of Weeks 1 and 7.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 50 **mg/m^2/dose**	Days 1 through 5 of Weeks 4 and 10.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle. See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.				

Cycle 1 (Week 1): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 2 (Week 4): Ht_____cm Wt_____kg BSA_____m^2**

Cycle 3 (Week 7): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 4 (Week 10): Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Cycle	Week	Day	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
					Enter calculated dose above and actual dose administered below					Start date	Stop date	
		1	1	1	____mg	____mg	____mg		____mg ____mg ____mg			a-p
			2	1	____mg							b
			3	1	____mg							b
		2	4	1	____mg			____mg				a-c, p
				2				____mg				
				3				____mg				
				4				____mg				
				5				____mg				
			5	1	____mg							b
			6	1	____mg							b
		3	7	1	____mg	____mg	____mg		____mg ____mg ____mg			a-c, p
			8	1	____mg							b
			9	1	____mg							a, b, f-i
		4	10	1	____mg			____mg				a-c
				2				____mg				
				3				____mg				
				4				____mg				
				5				____mg				
			11	1	____mg							b
			12	1	____mg							b, f
					Continue to Cycle 5 (Week 13) therapy if all criteria to start the next cycle have been met.							

4.2.2 Required Observations Prior to and During Cycles 1-4

NOTE: All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 3 (Day 21) of therapy and submitted as an upload to RAVE as soon as possible.** If patients FOXO1 status is FOXO1 fusion positive with Group IV/Stage 4 disease, they will be removed from protocol therapy (for example, a patient greater than 10 years of age with metastatic disease who is found to be FOXO1 fusion positive). Patients eligible to transfer to Regimen C must do so prior to the start of Week 4 of therapy (see Section 4.1).

All baseline radiology reports should be submitted to IROC Rhode Island at the time of study enrollment (see Section 16.2.1).

a. Physical exam/weight /height.
b. CBC/diff/platelets
c. Total bilirubin, ALT, creatinine.
d. Bilateral bone marrow biopsy (not required for patients with ERMS and clinically uninvolved nodes, and no lung or bone metastases). Repeat bone marrow examinations are only required in patients who had positive bone marrow disease at diagnosis.
e. Cerebrospinal fluid cytology for parameningeal tumors, including orbital site with parameningeal extension and paraspinal tumors with dural involvement.
f. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0. CT may be used for regional nodes. Post-operative imaging is required at Week 12 (prior to RT) only for patients who undergo DPE.
g. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat staging CT chest is required at Week 9 only for those patients who had lung metastases at diagnosis. See Section 16.0.
h. FDG-PET with diagnostic quality CT. For patients who consented to the FDG-PET part of the study. See Section 16.0.
i. Bone scan. May be omitted if PET-CT is performed. May be omitted for patients with ERMS and clinically uninvolved nodes and no lung metastases. Only needs to be repeated at Week 9 in those patients who had bone metastases at diagnosis. See Section 16.0.
j. CT or MRI of regional nodal basin. Week 9. May omit if PET-CT is done. Perform in those patients who had clinically involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
k. Lymph node biopsy. See Section 13.4.2 for details. **Mandatory** for extremity tumors, paratesticular tumors in patients ≥ 10 years of age regardless of histology; **strongly recommended** in *all* patients with alveolar histology (particularly if FOXO1 fusion positive) and in those with *clinically involved* nodes regardless of histology or fusion status).
l. Performance status. Use the Lansky performance score if < 16 years of age and the Karnofsky performance scale if ≥ 16 years of age.
m. Tissue submission for biology studies. Identification of fusion partners and variant gene fusions in RMS (Required). See Section 15.0.
n. Sperm banking. Recommended for post-pubertal males.
o. Fertility consult. Recommended for patients with abdominal/pelvic disease.
p. Circulating tumor DNA. Patient Consent required. Samples must be drawn within 7 days prior to starting therapy (Day 1); Week 4 and 7 (prior to chemotherapy on that day). See Section 15.2.

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

Comments

4.2.3 Regimen A (VAC/VI Only) Administration Details for Cycles 1-4

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days). For those considering DPE, hold chemotherapy and resume where you left off. If doses of specific agents (ie. temsirolimus) need to be held in the best interest of the patient, they will be omitted, and not made up at later dates.

All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 3 (Day 21) of therapy and submitted as soon as possible.** If patients FOXO1 status is FOXO1 fusion positive with Group IV/Stage 4 disease, they will be removed from protocol therapy (for example, a patient greater than 10 years of age with metastatic disease who is found to be FOXO1 fusion positive). Patients eligible to transfer to Regimen C must do so prior to the start of Week 4 of therapy (see Section 4.1).

4.2.3.1 Criteria to Start Each Cycle

4.2.3.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to >750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.2.3.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.2.3.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 1 through Week 12.
Dose: BSA-based dosing:

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.3-0.34	0.34 mg
0.35-0.39	0.44 mg
0.4-0.44	0.55 mg
0.45-0.49	0.65 mg
0.5-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Give before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 1 and 7.
Dose: **Weight-based** dosing:

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10 – 11.2	0.4 mg
11.3 –12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 1 and 7.
Dose: BSA-based dosing:

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes daily
Days: 1 through 5 of Weeks 4 and 10.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.2.3.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this course, the next course starts on Day 1 of Week 13 or when starting criteria are met, whichever occurs later.

Regimen A (VAC/VI Only) Cycles 1-4

4.2.4 ARST1431 Regimen A Cycles 5-10

This therapy delivery map (TDM) relates to Cycles 5-10 of therapy (Weeks 13-30). Each cycle lasts 21 days (3 weeks).

_____ _____
Patient COG ID number DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/μL and platelets ≥ 75,000/μL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages. See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1.5 **mg/m^2/dose**	Day 1 of Weeks 13, 16, 17, 19, 20, 22-26 and 28.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 13, 22 and 28.	Maximum dose: 2.5 mg. **Give the Week 13 dose of DACT before beginning radiation therapy.** For patients receiving liver irradiation, see Section 4.2.6.2.
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1200 **mg/m^2/dose**	Day 1 of Weeks 13, 22 and 28.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 50 **mg/m^2/dose**	Days 1 through 5 of Weeks 16, 19 and 25.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/μL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle.				

Cycle 5 (Week 13): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 6 (Week 16): Ht_____cm Wt_____kg BSA_____m^2** **Cycle 7 (Week 19): Ht_____cm Wt_____kg BSA_____m^2**

Cycle 8 (Week 22): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 9 (Week 25): Ht_____cm Wt_____kg BSA_____m^2** **Cycle 10 (Week 28): Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Cycle	Week	Day	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
					Enter calculated dose above and actual dose administered below					Start date	Stop date	
		5	13	1	mg	mg	mg		mg mg mg			a-c
		6	16	1	mg			mg				a-c
				2				mg				
				3				mg				
				4				mg				
				5				mg				
			17	1	mg							b
		7	19	1	mg			mg				a-c, h
				2				mg				
				3				mg				
				4				mg				
				5				mg				
			20	1	mg							b
		8	22	1	mg	mg	mg		mg mg mg			a-c
			23	1	mg							b
			24	1	mg							b
		9	25	1	mg			mg				a-c
				2				mg				
				3				mg				
				4				mg				
				5				mg				
			26	1	mg							b
		10	28	1	mg	mg	mg		mg mg mg			a-c
			30									b, d-g
					Continue to Cycle 11 (Week 31) therapy if all criteria to start the next cycle have been met.							

4.2.5 Required Observations Prior to and During Cycles 5-10

a. Physical exam/weight /height.
b. CBC/diff/platelets
c. Total bilirubin, ALT, creatinine.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
f. Bone scan or PET-CT. Only needs to be repeated in those patients who had bone metastases at diagnosis. See Section 16.0.
g. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
h. Circulating tumor DNA. Patient Consent required. Sample must be drawn at Week 19. See Section 15.2.

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

Comments

4.2.6 Regimen A (VAC/VI Only) Administration Details for Cycles 5-10

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 18 weeks (126 days).

4.2.6.1 Criteria to Start Each Cycle

4.2.6.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to > 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.2.6.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.2.6.2 Treatment

Radiotherapy

RT begins at Cycle 5 (Week 13) and may last up to 6.5 weeks for all patients. See Section 17.0 for radiotherapy guidelines.

Give the Week 13 dose of dactinomycin before beginning RT.

Note: For patients receiving liver irradiation, reduce the dactinomycin dose by 50% for the next cycle (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose reduction) and increase by 25% (for example, if the 50% dose is 0.7-0.8 mg, then administer 0.9-1 mg to increase the dosage by 25%), if tolerated, up to full dose for subsequent cycles. No reductions of vincristine or cyclophosphamide are needed unless total bilirubin is elevated (see Section 5.3.1).

Chemotherapy

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy)
Day: 1 of Week 13, 16, 17, 19, 20, 22-26, and 28.
Dose: BSA-based dosing:

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Administer before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 13, 22 and 28.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 13, 22, and 28.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes
Days: 1 through 5 of Weeks: 16, 19, and 25.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.2.6.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

See Section 16.0 for Week 30 evaluations.

Following completion of this course, the next course starts on Day 1 of Week 31 or when start criteria are met, whichever occurs later.

Regimen A (VAC/VI Only) Cycles 5-10

4.2.7 ARST1431 Regimen A Cycles 11-14 This therapy delivery map (TDM) relates to Cycles 11-14 of therapy (Weeks 31-42). Each cycle lasts 21 days (3 weeks).	_____ Patient COG ID number	_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1.5 **mg/m^2/dose**	Day 1 of Weeks 31-34, 37, 38 and 40.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 34 and 40.	Maximum dose: 2.5 mg
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1200 **mg/m^2/dose**	Day 1 of Weeks 34 and 40.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 50 **mg/m^2/dose**	Days 1 through 5 of Weeks 31 and 37.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle. See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.				

Cycle 11 (Week 31): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 12 (Week 34): Ht_____cm Wt_____kg BSA_____m^2**

Cycle 13 (Week 37): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 14 (Week 40): Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Cycle	Week	Day	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
					Enter calculated dose above and actual dose administered below					Start date	Stop date	
		11	31	1	____mg			____mg				a-c
				2				____mg				
				3				____mg				
				4				____mg				
				5				____mg				
			32	1	____mg							b
			33	1	____mg							b
		12	34	1	____mg	____mg	____mg		____mg ____mg ____mg			a-c
		13	37	1	____mg			____mg				a-c
				2				____mg				
				3				____mg				
				4				____mg				
				5				____mg				
			38	1	____mg							b
		14	40	1	____mg	____mg	____mg		____mg ____mg ____mg			a-c
			42									d-h
			43		Continue to Cycle 1 of Maintenance (Week 43) if all criteria to start have been met (see Section 4.4).							

4.2.8 Required Observations Prior to and During Cycles 11-14

a. Physical exam/weight /height.
b. CBC/diff/platelets
c. Total bilirubin, ALT, creatinine.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
f. Bone scan or PET-CT. Only needs to be repeated in those patients who had bone metastases at diagnosis. See Section 16.0.
g. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
h. Circulating tumor DNA. Patient Consent required. Sample must be drawn at Week 42. See Section 15.2.

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

Comments

4.2.9 Regimen A (VAC/VI Only) Administration Details for Cycles 11-14

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days).

4.2.9.1 Criteria to Start Each Cycle

4.2.9.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to > 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.2.9.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.2.9.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 31-34, 37, 38, and 40.
Dose: BSA-based dosing

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Administer before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 34 and 40.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 34 and 40.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes daily
Days: 1 through 5 of Weeks: 31 and 37.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose (mg)**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.2.9.3 Supportive Care
Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor

support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this course, Maintenance starts on Day 1 of Week 43 or when starting criteria are met, whichever occurs later (see Section 4.4).

In patients with metastatic disease, relevant metastatic sites should be treated with RT at the completion of VAC/VI chemotherapy. See Section 17.0.

4.3 Regimen B (VAC/VI Plus Temsirolimus)

4.3.1 ARST1431 Regimen B Cycles 1-4

This therapy delivery map (TDM) relates to Cycles 1-4 of therapy (Weeks 1-12). Each cycle lasts 21 days (3 weeks).

_____ Patient COG ID number _____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages. Please review Mucositis Management Guidelines in Appendix VII.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temsirolimus (TORI)* **Do not use commercial supply** -	IV over 30-60 minutes	15 **mg/m²/dose** OR 0.5 **mg/kg/dose** for pt < 10 kg	Day 1 of each week.	Maximum dose: 25 mg. *Premedicate with diphenhydramine IV approx. 30 min prior to TORI. See Section 4.3.3.2 for administration guidelines.
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1.5 **mg/m²/dose**	Day 1 of each week.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 1 and 7.	Maximum dose: 2.5 mg
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1200 **mg/m²/dose**	Day 1 of Weeks 1 and 7.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²:50 **mg/m²/dose**	Days 1 through 5 of Weeks 4 and 10.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR or TORI. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle. See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.				

Cycle 1 (Week 1): Ht_____cm Wt_____kg BSA_____m² **Cycle 2 (Week 4): Ht_____cm Wt_____kg BSA_____m²**

Cycle 3 (Week 7): Ht_____cm Wt_____kg BSA_____m² **Cycle 4 (Week 10): Ht_____cm Wt_____kg BSA_____m²**

Date Due	Date Given	Cycle	Week	Day	TORI _____mg	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
						Enter calculated dose above and actual dose administered below					Start date	Stop date	
		1	1	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-p
			2	1	____mg	____mg							b
			3	1	____mg	____mg							b
		2	4	1	____mg	____mg			____mg				a-c, p
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			5	1	____mg	____mg							b
			6	1	____mg	____mg							b
		3	7	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-c, p
			8	1	____mg	____mg							b
			9	1	____mg	____mg							a, b, f-j
		4	10	1	____mg	____mg			____mg				a-c
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			11	1	____mg	____mg							b
			12	1	____mg	____mg							b, f
					Continue to Cycle 5 (Week 13) therapy if all criteria to start the next cycle have been met.								

4.3.2 Required Observations Prior to and During Cycles 1-4

NOTE: All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 3 (Day 21) of therapy and submitted as an upload to RAVE as soon as possible.** If patients FOXO1 status is FOXO1 fusion positive with Group IV/Stage 4 disease, they will be removed from protocol therapy (for example, a patient greater than 10 years of age with metastatic disease who is found to be FOXO1 fusion positive). Patients eligible to transfer to Regimen C must do so prior to the start of Week 4 of therapy (see Section 4.1).

All baseline radiology reports should be submitted to IROC Rhode Island at the time of study enrollment (see Section 16.2.1).

a. Physical exam/weight /height.
b. CBC/diff/platelets.
c. Total bilirubin, ALT, creatinine, calcium, phosphorus, triglycerides, cholesterol, urinalysis. If triglycerides or cholesterol levels are elevated, repeat with fasting.
d. Bilateral bone marrow biopsy (not required for patients with ERMS and clinically uninvolved nodes, and no lung or bone metastases). Repeat bone marrow examinations are only required in patients who had positive bone marrow disease at diagnosis.
e. Cerebrospinal fluid cytology for parameningeal tumors, including orbital site with parameningeal extension and paraspinal tumors with dural involvement.
f. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0. Post-operative imaging is required at Week 12 (prior to RT) only for patients who undergo DPE.
g. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required at Week 9 only for those patients who had lung metastases at diagnosis. See Section 16.0.
h. FDG-PET with diagnostic quality CT. Patients must have consented to the FDG-PET part of the study. Week 9. PET scans must be performed no sooner than **4 days following temsirolimus infusion**. See Section 16.0.
i. Bone scan. May be omitted if PET-CT is performed. May be omitted for patients with ERMS and clinically uninvolved nodes and no lung metastases. Only needs to be repeated at Week 9 in those patients who had bone metastases at diagnosis. See Section 16.0.
j. CT or MRI of regional nodal basin. Week 9. May omit if PET-CT is done. Perform in those patients who had clinically involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
k. Lymph node biopsy. See Section 13.4.2 for details. **Mandatory** for extremity tumors, paratesticular tumors in patients ≥ 10 years of age regardless of histology; **strongly recommended** in *all* patients with alveolar histology (particularly if FOXO1 fusion positive) and in those with *clinically involved* nodes regardless of histology or fusion status).
l. Performance status. Use the Lansky performance score if < 16 years of age and the Karnofsky performance scale if ≥ 16 years of age.
m. Tissue submission for biology studies. Identification of fusion partners and variant gene fusions in RMS (Required). See Section 15.0.
n. Sperm banking. Recommended for post-pubertal males.
o. Fertility consult. Recommended for patients with abdominal/pelvic disease.
p. Circulating tumor DNA. Patient Consent required. Samples must be drawn within 7 days prior to starting therapy (Day 1) and Weeks 4 and 7 prior to chemotherapy. See Section 15.2.

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

Comments

4.3.3 Regimen B (VAC/VI Plus Temsirolimus) Administration Details for Cycles 1-4

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days). For those considering DPE, hold chemotherapy and resume where you left off. If doses of specific agents (ie. temsirolimus) need to be held in the best interest of the patient, they will be omitted, and not made up at later dates. In those considering DPE, temsirolimus must be held 2 weeks prior to and 1 week following DPE.

All patients will undergo institutional pathology review and FOXO1 fusion determination. **FOXO1 status results must be available by Week 3 (Day 21) of therapy and submitted as soon as possible.** If patients FOXO1 status is FOXO1 fusion positive with Group IV/Stage 4 disease, they will be removed from protocol therapy (for example, a patient greater than 10 years of age with metastatic disease who is found to be FOXO1 fusion positive). Patients eligible to transfer to Regimen C must do so prior to the start of Week 4 of therapy (see Section 4.1).

4.3.3.1 Criteria to Start Each Cycle

4.3.3.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/μL
- Platelet count ≥ 75,000/μL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to >750/μL after nadir but then falls to < 750/μL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/μL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.3.3.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.3.3.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

Temsirolimus (Dose Level 1): IV over 30-60 minutes once weekly
Day: 1 of Week 1 through Week 12.
Dose: For patients < 10 kg, the dose is 0.5 mg/kg/dose.
For patients ≥ 10 kg, the dose is 15 mg/m^2/dose (maximum dose: 25 mg).

Because of idiosyncratic infusion-related reactions, all patients receiving temsirolimus will be pre-medicated with **diphenhydramine** (0.5-1 mg/kg; maximum dose: 50 mg)**, approximately 30 minutes before the start of each temsirolimus infusion**. If the patient begins to develop a reaction despite pretreatment with diphenhydramine, the

infusion should be stopped for at least 30-60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H2-receptor antagonist (ie, ranitidine or famotidine) approximately 30 minutes before restarting the temsirolimus. The rate of temsirolimus infusion may also be slowed (decreased by 50% or slower). All patients should be monitored while receiving temsirolimus and health care personnel must be readily available to respond to infusion-related reactions. Infusion-related reactions are not considered dose limiting, see Section 5.2.2 for detailed instructions.

Temsirolimus is distributed by NCI. Do not use commercial supply.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 1 through Week 12.
Dose: BSA-based dosing:

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Administer before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 1 and 7.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 1and 7.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes daily
Days: 1 through 5 of Weeks 4 and 10.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.3.3.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.3.3.4 Concomitant Therapy Restrictions

The use of moderate to strong CYP3A4 and p-gp inducers and inhibitors should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy, if reasonable alternatives exist. See Appendix VIII for a list of CYP3A4 inducers and inhibitors. See Section 4.1.3 for examples of p-gp inducers/inhibitors. Corticosteroids are permitted.

St. John's Wort may decrease temsirolimus plasma concentrations unpredictably and should be avoided. Grapefruit juice may increase plasma concentrations of sirolimus and should be avoided as well.

The combination of temsirolimus and angiotensin converting enzyme inhibitors (ACEIs) or calcium channel blockers (eg. amlodipine) has resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). During temsirolimus treatment, the coadministration of ACEIs or calcium channel blockers is not permitted.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this course, the next course starts on Day 1 of Week 13 or when starting criteria are met, whichever occurs later.

Regimen B (VAC/VI Plus TORI) Cycles 1-4

4.3.4a ARST1431 Regimen B Cycles 5-10

This therapy delivery map (TDM) relates to Cycles 5-10 of therapy (Weeks 13-30). Each cycle lasts 21 days (3 weeks).
TEMSIROLIMUS TO BE HELD DURING AND FOR 2 WEEKS FOLLOWING RT.

_____ Patient COG ID number

_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **three** pages. Please review Mucositis Management Guidelines in Appendix VII.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temsirolimus (TORI)* **Do not use commercial suppy -**	IV over 30-60 minutes	15 **mg/m²/dose** OR 0.5 **mg/kg/dose** for pt < 10 kg	Day 1 of Weeks 21-30.	Maximum dose: 25 mg. *Premedicate with diphenhydramine IV approx 30 min prior to TORI. See Section 4.3.6.2 for administration guidelines.
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1.5 **mg/m²/dose**	Day 1 of Weeks 13, 16, 17, 19, 20, 22-26 and 28.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 13, 22 and 28.	Maximum dose: 2.5 mg. **Give the Week 13 dose of DACT before beginning radiation therapy.** For patients receiving liver irradiation, see Section 4.3.6.2.
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1200 **mg/m²/dose**	Day 1 of Weeks 13, 22 and 28.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 50 **mg/m²/dose**	Days 1 through 5 of Weeks 16, 19 and 25.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR or TORI. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle.				

Cycle 5 (Week 13): Ht_____cm Wt_____kg BSA_____m² **Cycle 6 (Week 16): Ht_____cm Wt_____kg BSA_____m²** **Cycle 7 (Week 19): Ht_____cm Wt_____kg BSA_____m²**

Date Due	Date Given	Cycle	Week	Day	TORI _____mg	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
						Enter calculated dose above and actual dose administered below					**Start date**	**Stop date**	
		5	13	1		____mg	____mg	____mg		____mg ____mg ____mg			a-c
			14										b
			15										b
		6	16	1		____mg			____mg				a-c
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			17	1		____mg							b
			18										b
		7	19	1		____mg			____mg				a-c, h
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			20	1		____mg							a, b
			21	1	____mg								b
					The therapy delivery map for Cycles 5-10 continues on the next page.								

See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.

4.3.4b ARST1431 Regimen B Cycles 5-10

This therapy delivery map (TDM) relates to Cycles 5-10 of therapy (Weeks 13-30). Each cycle lasts 21 days (3 weeks).

_____ Patient COG ID number

_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **three** pages. Please review Mucositis Management Guidelines in Appendix VII.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temsirolimus (TORI)* **Do not use commercial supply** -	IV over 30-60 minutes	15 **mg/m²/dose** OR 0.5 **mg/kg/dose** for pt < 10 kg	Day 1 of Weeks 22-30.	Maximum dose: 25 mg. *Premedicate with diphenhydramine IV approx 30 min prior to TORI. See Section 4.3.6.2 for administration guidelines.
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1.5 **mg/m²/dose**	Day 1 of Weeks 13, 16, 17, 19, 20, 22-26 and 28.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 13, 22 and 28.	Maximum dose: 2.5 mg For patients receiving liver irradiation, see Section 4.3.6.2.
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1200 **mg/m²/dose**	Day 1 of Weeks 13, 22 and 28.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 50 **mg/m²/dose**	Days 1 through 5 of Weeks 16, 19 and 25.	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR or TORI. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle.				

Cycle 8 (Week 22): Ht_____cm Wt_____kg BSA_____m² **Cycle 9 (Week 25): Ht_____cm Wt_____kg BSA_____m²** **Cycle 10 (Week 28): Ht_____cm Wt_____kg BSA_____m²**

Date Due	Date Given	Cycle	Week	Day	TORI _____mg	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
						Enter calculated dose above and actual dose administered below					Start date	Stop date	
		8	22	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-c
			23	1	____mg	____mg							b
			24	1	____mg	____mg							b
		9	25	1	____mg	____mg			____mg				a-c
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			26	1	____mg	____mg							b
			27	1	____mg								b
		10	28	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-c
			29	1	____mg								b
			30	1	____mg								b, d-g
					Continue to Cycle 11 (Week 31) therapy if all criteria to start the next cycle have been met.								

See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.

4.3.5 Required Observations Prior to and During Cycles 5-10

a. Physical exam/weight /height.
b. CBC/diff/platelets.
c. Total bilirubin, ALT, creatinine, calcium, phosphorus, triglycerides, cholesterol, urinalysis. If triglycerides or cholesterol levels are elevated, repeat with fasting.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
f. Bone scan or PET-CT. Only needs to be repeated in those patients who had bone metastases at diagnosis. See Section 16.0.
g. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
h. Circulating tumor DNA. Patient Consent required. Sample must be drawn prior to chemotherapy at Week 19. See Section 15.2.

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

Comments

4.3.6 Regimen B (VAC/VI Plus Temsirolimus) Administration Details for Cycles 5-10

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 18 weeks (126 days).

4.3.6.1 Criteria to Start Each Cycle

4.3.6.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to >750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.3.6.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.3.6.2 Treatment

Radiotherapy

RT begins at Cycle 5 (Week 13) and may last up to 6.5 weeks. See Section 17.0 for radiotherapy guidelines.

Give the Week 13 dose of dactinomycin before beginning RT.

Note: For patients receiving liver irradiation, reduce the dactinomycin dose by 50% for the next cycle (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose reduction) and increase by 25% (for example, if the 50% dose is 0.7-0.8 mg, then administer 0.9-1 mg to increase the dosage by 25%), if tolerated, up to full dose for subsequent cycles. No reductions of vincristine or cyclophosphamide are needed unless total bilirubin is elevated (see Section 5.3.1).

Chemotherapy

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

Temsirolimus (Dose Level 1): IV over 30-60 minutes once weekly
Day: 1 of Week 21-30.
Dose: For patients < 10 kg, the dose is 0.5 mg/kg/dose.
For patients ≥ 10 kg, the dose is 15 mg/m^2/dose (maximum dose: 25 mg).

Temsirolimus will be held during RT and restarted 2 weeks following completion of RT and once mucositis has resolved to ≤ Grade 1.
Because of idiosyncratic infusion-related reactions, all patients

receiving temsirolimus will be pre-medicated with **diphenhydramine,** (0.5-1 mg/kg; maximum dose: 50 mg) **approximately 30 minutes before the start of each temsirolimus infusion**. If the patient begins to develop an infusion-related reaction despite pretreatment with diphenhydramine, the infusion should be stopped for at least 30-60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H2-receptor antagonist (ie, ranitidine or famotidine) approximately 30 minutes before restarting the temsirolimus. The rate of temsirolimus infusion may also be slowed (decreased by 50% or slower). All patients should be monitored while receiving temsirolimus and health care personnel must be readily available to respond to infusion-related reactions. Infusion-related reactions are not considered dose limiting, see Section 5.2.2 for detailed instructions.

Temsirolimus is distributed by NCI. Do not use commercial supply.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 13, 16, 17, 19, 20, 22-26, and 28.
Dose: BSA-based dosing:

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Administer before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 13, 22 and 28.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 13, 22, and 28.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes daily
Days: 1 through 5 of Weeks: 16, 19, and 25.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.3.6.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.3.6.4 Concomitant Therapy Restrictions

The use of moderate to strong CYP3A4 and p-gp inducers and inhibitors should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy, if reasonable alternatives exist. See Appendix VIII for a list of CYP3A4 inducers and inhibitors. See Section 4.1.3 for examples of p-gp inducers/inhibitors. Corticosteroids are permitted.

St. John's Wort may decrease temsirolimus plasma concentrations unpredictably and should be avoided. Grapefruit juice may increase plasma concentrations of sirolimus and should be avoided as well.

The combination of temsirolimus and angiotensin converting enzyme inhibitors (ACEIs) or calcium channel blockers (eg. amlodipine) has resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). During temsirolimus treatment, the coadministration of ACEIs or calcium channel blockers is not permitted.

See Section 5.0 for Dose Modifications based on Toxicities.

See Section 16.0 for Week 30 evaluations.

Following completion of this course, the next course starts on Day 1 of Week 31 or when start criteria are met, whichever occurs later.

4.3.7 ARST1431 Regimen B Cycles 11-14

This therapy delivery map (TDM) relates to Cycles 11-14 of therapy (Weeks 31-42). Each cycle lasts 21 days (3 weeks).

_____ Patient COG ID number

_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age.

This course lasts 84 days and the TDM is described on **two** pages. Please review Mucositis Management Guidelines in Appendix VII.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Temsirolimus (TORI)* **Do not use commercial supply -**	IV over 30-60 minutes	15 **mg/m²/dose** OR 0.5 **mg/kg/dose** for pt < 10 kg	Day 1 of each week.	Maximum dose: 25 mg. *Premedicate with diphenhydramine IV approx 30 min prior to TORI. See Section 4.3.9.2 for administration guidelines.
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1.5 **mg/m²/dose**	Day 1 of Weeks 31-34, 37, 38 and 40.	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg. Administer before Irinotecan on days when both drugs are given.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 34 and 40.	Maximum dose: 2.5 mg
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²: 1200 **mg/m²/dose**	Day 1 of Weeks 34 and 40.	
Irinotecan (IRIN)	IV over 90 minutes	BSA < 0.6 m²: BSA-based dosing, see dosing table BSA ≥ 0.6 m²:50 **mg/m²/dose**	Days 1 through 5 of Weeks 31 and 37	Maximum dose: 100 mg/day
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR or TORI. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle. See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.				

Cycle 11 (Week 31): Ht_____cm Wt_____kg BSA_____m² **Cycle 12 (Week 34): Ht_____cm Wt_____kg BSA_____m²**

Cycle 13 (Week 37): Ht_____cm Wt_____kg BSA_____m² **Cycle 14 (Week 40): Ht_____cm Wt_____kg BSA_____m²**

Date Due	Date Given	Cycle	Week	Day	TORI _____mg	VCR _____mg	DACT _____mg	CPM _____mg	IRIN _____mg	MESNA _____mg	Myeloid growth factor used: _____ Calc. dose_____mcg		Studies
					Enter calculated dose above and actual dose administered below						Start date	Stop date	
		11	31	1	____mg	____mg			____mg				a-c
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			32	1	____mg	____mg							B
			33	1	____mg	____mg							B
		12	34	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-c
			35	1	____mg								B
			36	1	____mg								B
		13	37	1	____mg	____mg			____mg				a-c
				2					____mg				
				3					____mg				
				4					____mg				
				5					____mg				
			38	1	____mg	____mg							b
			39	1	____mg								b
		14	40	1	____mg	____mg	____mg	____mg		____mg ____mg ____mg			a-c
			41	1	____mg								b
			42	1	____mg								b, d-h
			43		Continue to Cycle 1 of Maintenance (Week 43) if all criteria to start have been met (see Section 4.4).								

4.3.8 Required Observations Prior to and During Cycles 11-14

a. Physical exam/weight /height.
b. CBC/diff/platelets.
c. Total bilirubin, ALT, creatinine, calcium, phosphorus, triglycerides, cholesterol, urinalysis. If triglycerides or cholesterol levels are elevated, repeat with fasting.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
f. Bone scan or PET-CT. Only needs to be repeated in those patients who had bone metastases at diagnosis. See Section 16.0.
g. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
h. Circulating tumor DNA. Patient Consent required. Sample must be drawn at Week 42. See Section 15.2.

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

Comments

4.3.9 Regimen B (VAC/VI Plus Temsirolimus) Administration Details for Cycles 11-14

Each VAC/VI cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days).

4.3.9.1 Criteria to Start Each Cycle

4.3.9.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to > 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.3.9.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.3.9.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

Temsirolimus (Dose Level 1): IV over 30-60 minutes weekly
Day: 1 of Week 31-42.
Dose: For patients < 10 kg, the dose is 0.5 mg/kg/dose.
For patients ≥ 10 kg, the dose is 15 mg/m^2/dose (maximum dose: 25 mg).

Because of idiosyncratic infusion-related reactions, all patients receiving temsirolimus will be pre-medicated with **diphenhydramine,** (0.5-1 mg/kg; maximum dose: 50 mg) **approximately 30 minutes before the start of each temsirolimus infusion**. If the patient begins to develop an infusion-related reaction despite pretreatment with diphenhydramine, the infusion should be stopped for at least 30-60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H2-receptor antagonist (ie, ranitidine or famotidine) approximately 30 minutes before restarting the temsirolimus. The rate of temsirolimus infusion may also be slowed (decreased by 50% or slower). All patients should be monitored while receiving temsirolimus and health care personnel must be readily available to respond to infusion-related reactions. Infusion-related reactions are not considered dose limiting, see Section 5.2.2 for detailed instructions.

Temsirolimus is distributed by NCI. Do not use commercial supply.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 31-34, 37, 38, and 40.
Dose: BSA-based dosing

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

NOTE: Administer before Irinotecan on days when both drugs are to be given.

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 34 and 40.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 34 and 40.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

Irinotecan: IV over 90 minutes daily
Days: 1 through 5 of Weeks: 31 and 37.
Dose: BSA-based dosing

IRINOTECAN	
BSA (m^2)	**Dose**
0.25-0.29	8 mg
0.3-0.34	12 mg
0.35-0.39	15 mg
0.4-0.44	18 mg
0.45-0.49	22 mg
0.5-0.54	24 mg
0.55-0.59	28 mg
≥ 0.6	50 mg/m^2 (maximum 100 mg)

4.3.9.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna, myeloid growth factor support during VAC cycles, and antibiotics for prevention of irinotecan-induced diarrhea.

Please see Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea. In addition, for COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.3.9.4 Concomitant Therapy Restrictions

The use of moderate to strong CYP3A4 and p-gp inducers and inhibitors should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy, if reasonable alternatives exist. See Appendix VIII for a list of CYP3A4 inducers and inhibitors. See Section 4.1.3 for examples of p-gp inducers/inhibitors. Corticosteroids are permitted.

St. John's Wort may decrease temsirolimus plasma concentrations unpredictably and should be avoided. Grapefruit juice may increase plasma concentrations of sirolimus and should be avoided as well.

The combination of temsirolimus and angiotensin converting enzyme inhibitors (ACEIs) or calcium channel blockers (eg. amlodipine) has resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). During temsirolimus treatment, the coadministration of ACEIs or calcium channel blockers are not permitted.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this course, Maintenance starts on Day 1 of Week 43 or when starting criteria are met, whichever occurs later (see Section 4.4).

In patients with metastatic disease, relevant metastatic sites should be treated with RT at the completion of VAC/VI chemotherapy. See Section 17.0.

4.4 Regimens A & B – Maintenance

4.4.1 ARST1431 Regimens A & B – Maintenance Cycles 1-6

This therapy delivery map (TDM) relates to Cycles 1-6 of maintenance therapy (Weeks 43-66). Each cycle lasts 28 days (4 weeks). Use a copy of this page once for each cycle. Please note cycle number below.

_____
Patient COG ID number

_____
DOB

Criteria to start each cycle of therapy: Maintenance chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. This TDM is described on **two** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Vinorelbine (VINO)	IV push over 6-10 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 25 mg/m^2	Days 1, 8, 15.	Flush vinorelbine injection site with 75-125 mL of a compatible IV fluid for 15-60 minutes after administration to prevent burning at the injection site.
Cyclophosphamide (CPM)	PO	25 mg/m^2 once daily	Days 1-28.	See Section 4.4.3 for dose rounding and administration details.

Enter Cycle #: _____ Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VINO _____mg	CPM _____mg	Studies
			Enter calculated dose above and actual dose administered below		
		1	____mg	____mg	a-c
		2		____mg	
		3		____mg	
		4		____mg	
		5		____mg	
		6		____mg	
		7		____mg	
		8	____mg	____mg	B
		9		____mg	
		10		mg	
		11		mg	
		12		mg	
		13		mg	
		14		____mg	
		15	____mg	____mg	b
		16		____mg	
		17		____mg	
		18		____mg	
		19		____mg	
		20		____mg	
		21		____mg	
		22		____mg	
		23		____mg	
		24		____mg	
		25		mg	
		26		mg	
		27		____mg	
		28		____mg	
		29	Continue to next maintenance cycle if all criteria to start the next cycle have been met. See Section 7.0 for end of therapy evaluations.		(d-g)*, h^

* at end of Cycle 3 and end of protocol therapy
^ at end of protocol therapy

4.4.2 Required Observations Prior to and During Maintenance Cycles 1-6

a. Physical exam/weight /height.
b. CBC/diff/platelets.
c. Total bilirubin.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
f. Bone scan or PET-CT. Only needs to be repeated in those patients who had bone metastases at diagnosis. See Section 16.0.
g. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
h. Circulating tumor DNA. Patient Consent required. Sample must be drawn at end of protocol therapy. See Section 15.2.

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

Comments

4.4.3 Regimens A & B Maintenance Administration Details for Cycles 1-6

Maintenance therapy has been implemented with Amendment #3. Each cycle of maintenance lasts 4 weeks (28 days). Maintenance consists of 6 cycles and will take a total of 24 weeks. One cycle of maintenance is described below.

In patients with metastatic disease, relevant metastatic sites should be treated with RT at the completion of VAC/VI chemotherapy (Week 43). See Section 17.0.

4.4.3.1 Criteria to Start Each Cycle

4.3.3.1.1 Adequate bone marrow function defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

4.4.3.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

Vinorelbine: IV push over 6-10 minutes
Days: 1, 8, and 15.
Dose: BSA-based dosing

VINORELBINE 25 mg/m^2/dose	
BSA (m^2)	**Dose**
0.25-0.29	4 mg
0.30-0.34	6 mg
0.35-0.39	7.5 mg
0.40-0.44	9 mg
0.45-0.49	11 mg
0.50-0.54	12 mg
0.55-0.59	14 mg
≥ 0.6	25 mg/m^2

Infuse the diluted solution into the side port of a rapidly infusing solution of D5W or 0.9% NaCl. Consider flushing the vinorelbine injection site with 75-125 mL of a compatible IV fluid for 15-60 minutes after administration to prevent burning at the injection site.

Special precautions: FATAL IF GIVEN INTRATHECALLY.
The container or the syringe containing vinORELBine should be labeled with the following statement: "WARNING - FOR IV USE ONLY. FATAL IF GIVEN INTRATHECALLY."

Cyclophosphamide: PO
Days: 1-28.
Dose: 25 mg/m^2/dose once daily

It is advised to administer cyclophosphamide early in the morning to decrease the amount of drug remaining in the bladder overnight. During the treatment, an adequate fluid intake (e.g., 1 L/m^2) is recommended.

If a patient vomits within 20 minutes after a cyclophosphamide tablet or capsule is administered, the dose can be repeated once. Otherwise the dose should be skipped. The next dose should be administered at the regularly scheduled time.

Dose Rounding Recommendations:
US sites: Doses should be rounded to the nearest 25 mg capsule [see dosing table in Appendix XI].
Canadian sites: Dose should be rounded to the nearest 12.5 mg (1/2 tablet) [see dosing table in Appendix XI]. If liquid is unavailable and splitting a tablet is necessary follow institutional recommendations for safe handling of cytotoxic agents. Please refer to Appendix XII for safe handling, preparation, administration and disposal of cyclophosphamide tablets information for patients and families.
AU/NZ sites: Doses should be rounded to the nearest 50 mg tablet [see dosing table in Appendix XI].

Cyclophosphamide oral solution can be prepared using IV formulation (see Section 6.3). When using cyclophosphamide oral solution, doses should be rounded to the nearest 1 mg if using 10 mg/mL solution or 2 mg if using 20 mg/mL solution. If a patient vomits after taking cyclophosphamide oral solution, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

4.4.3.3 Supportive Care

Please see Appendix VII for protocol-specific supportive care guidelines.

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

4.4.3.4 Concomitant Therapy Restrictions

The use of moderate to strong CYP3A4 inducers and inhibitors should be avoided during maintenance therapy, if reasonable alternatives exist. See Appendix VIII for a list of CYP3A4 inducers and inhibitors. Corticosteroids are permitted.

See Section 5.0 for Dose Modifications based on Toxicities.

The next cycle of maintenance starts on Day 29 or when starting criteria are met, whichever occurs later.

See Section 7.0 for end of therapy evaluations.

4.5 Regimen C (VAC/VA Only)

4.5.1 ARST1431 Regimen C Cycles 1-4 (VAC)

This therapy delivery map (TDM) relates to Cycles 1-4 of therapy (Weeks 1-12). Each cycle lasts 21 days (3 weeks).

Weeks 1-3 may have been given on Regimen A or B. DO NOT REPEAT Week 1-3 therapy if already given on Regimen A or B.

_____ Patient COG ID number

_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1.5 **mg/m^2/dose**	Day 1 of Weeks 1-10	* Or infusion via minibag as per institutional policy Maximum dose: 2 mg.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 1, 4, 7 and 10.	Maximum dose: 2.5 mg.
**Mesna and fluids will be used with CPM. See Appendix VII for specific directions.				
Cyclophosphamide (CPM)**	IV over 60 minutes	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1200 **mg/m^2/dose**	Day 1 of Weeks 1, 4, 7 and 10.	
Start myeloid growth factor support (for example, filgrastim or biosimilar **5 mcg/kg/dose SubQ daily** until the ANC is ≥ 2000/µL after the expected nadir **or pegfilgrastim or biosimilar 0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose or per institutional standards**) 24 hours after myelosuppressive chemotherapy (VAC cycles only). Filgrastim or biosimilar may be continued without regard to VCR. Discontinue filgrastim or biosimilar at least 24 hours before the start of the next cycle.				

Cycle 1 (Week 1): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 2 (Week 4): Ht_____cm Wt_____kg BSA_____m^2**

Cycle 3 (Week 7): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 4 (Week 10): Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Cycle	Week	Day	VCR _____mg	DACT _____mg	CPM _____mg	MESNA _____mg	Myeloid growth factor used:_____ Calc. dose_____mcg		Studies
					Enter calculated dose above and actual dose administered below				**Start date**	**Stop date**	
		1	1	1	____mg	____mg	____mg	____mg ____mg ____mg			a-p
			2	1	____mg						b
			3	1	____mg						b
		2	4	1	____mg	____mg	____mg	____mg ____mg ____mg			a-c, p
			5	1	____mg						b
			6	1	____mg						b
		3	7	1	____mg	____mg	____mg	____mg ____mg ____mg			a-c, p
			8	1	____mg						b
			9	1	____mg						a, b, f-j
		4	10	1	____mg	____mg	____mg	____mg ____mg ____mg			a-c
			11								b
			12								b, f
					Continue to Cycle 5 (Week 13) therapy if all criteria to start the next cycle have been met.						

See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.

4.5.2 Required Observations Prior to and During Cycles 1-4

NOTE: **All baseline radiology reports should be submitted to IROC Rhode Island at the time of study enrollment (see Section 16.2.1).**

a. Physical exam/weight /height.
b. CBC/diff/platelets
c. Total bilirubin, ALT, creatinine.
d. Bilateral bone marrow biopsy (not required for patients with ERMS and clinically uninvolved nodes, and no lung or bone metastases). Repeat bone marrow examinations are only required in patients who had positive bone marrow disease at diagnosis.
e. Cerebrospinal fluid cytology for parameningeal tumors, including orbital site with parameningeal extension and paraspinal tumors with dural involvement.
f. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0. CT may be used for regional nodes. Post-operative imaging is required at Week 12 (prior to RT) only for patients who undergo DPE.
g. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. Repeat CT chest is required only for those patients who had lung metastases at diagnosis. See Section 16.0.
h. FDG-PET with diagnostic quality CT. Patients must have consented to the FDG-PET part of the study. See Section 16.0.
i. Bone scan. May be omitted if PET-CT is performed. May be omitted for patients with ERMS and clinically uninvolved nodes and no lung metastases. Only needs to be repeated at Week 9 in those patients who had bone metastases at diagnosis. See Section 16.0.
j. CT or MRI of regional nodal basin. Week 9. May omit if PET-CT is done. Perform in those patients who had clinically involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
k. Lymph node biopsy. See Section 13.4.2 for details. **Mandatory** for extremity tumors, paratesticular tumors in patients ≥ 10 years of age regardless of histology; **strongly recommended** in *all* patients with alveolar histology (particularly if FOXO1 fusion positive) and in those with *clinically involved* nodes regardless of histology or fusion status).
l. Performance status. Use the Lansky performance score if < 16 years of age and the Karnofsky performance scale if ≥ 16 years of age.
m. Tissue submission for biology studies. Identification of fusion partners and variant gene fusions in RMS (Required). See Section 15.0.
n. Sperm banking. Recommended for post-pubertal males.
o. Fertility consult. Recommended for patients with abdominal/pelvic disease.
p. Circulating tumor DNA. Patient Consent required. Samples must be drawn within 7 days prior to starting therapy (Day 1), Week 4, and 7 prior to chemotherapy on that day. See Section 15.2.

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

Comments

4.5.3 Regimen C (VAC/**VA** Only) Administration Details for Cycles 1-4

ARMS FOXO1 fusion negative patients with the following Stage and Group are eligible to receive VAC/VA therapy on Regimen C instead of the previously assigned treatment regimen:

- Stage 1, Group I/II
- Stage 1, Group III (orbit)
- Stage 2, Group I/II

Patient consent is required to transfer to Regimen C and transfer must occur prior to Week 4 of protocol therapy.

Each cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days).

4.5.3.1 Criteria to Start Each Cycle

4.5.3.1.1 Adequate bone marrow function defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to > 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.5.3.1.2 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.5.3.2 Treatment

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 1 through Week 10.
Dose: BSA-based dosing

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 1, 4, 7 and 10.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

Cyclophosphamide: IV over 60 minutes
Day: 1 of Weeks 1, 4, 7 and 10.
Dose: BSA-based dosing

CYCLOPHOSPHAMIDE	
BSA (m^2)	**Dose**
0.25-0.29	220 mg
0.3-0.34	280 mg
0.35-0.39	360 mg
0.4-0.44	440 mg
0.45-0.49	520 mg
0.5-0.54	600 mg
0.55-0.59	660 mg
≥ 0.6	1200 mg/m^2

Note: Mesna and fluids will be used with cyclophosphamide. See Appendix VII for specific directions.

4.5.3.3 Supportive Care
Please see Appendix VII for protocol-specific supportive care guidelines, including administration of mesna and myeloid growth factor support during VAC cycles. In addition, for COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

Following the Week 9 evaluations and the completion of Cycle 4, select patients may be considered for delayed primary excision for non-PM primary sites when GTR can be easily performed with minimal morbidity or loss of function and with minimal disruption to the overall treatment scheme. Surgical intervention where gross tumor is left behind is absolutely discouraged. For patients who achieve GTR confirmed by postoperative CT or MRI scan, the dose of RT will be reduced (see Section 17.0 for details).

4.5.4 ARST1431 Regimen C Cycles 5-8 (VA) This therapy delivery map (TDM) relates to Cycles 5-8 of therapy (Weeks 13-24). Each cycle lasts 21 days (3 weeks).	_____ Patient COG ID number	_____ DOB

Criteria to start each cycle of therapy: Chemotherapy cycles may begin when the ANC ≥ 750/µL and platelets ≥ 75,000/µL after nadir. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age. This course lasts 84 days and the TDM is described on **two** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
VinCRIStine (VCR)	IV Push over 1 minute*	BSA < 0.6 m^2: BSA-based dosing, see dosing table BSA ≥ 0.6 m^2: 1.5 **mg/m^2/dose**	Day 1 of Weeks 13-22	*Or infusion via minibag as per institutional policy Maximum dose: 2 mg.
DACTINomycin (DACT)	Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes	Weight < 14 kg: Weight-based dosing, see dosing table Weight ≥ 14 kg: 0.05 **mg/kg/dose**	Day 1 of Weeks 13, 16, 19 and 22.	Maximum dose: 2.5 mg. **Give the Week 13 dose of DACT before beginning radiation therapy. Omit Week 16 DACT during radiation therapy. Omit Week 19 DACT only if radiation therapy continues into Week 19.** For patients receiving liver irradiation, see Section 4.7.3.2.

Cycle 5 (Week 13): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 6 (Week 16): Ht_____cm Wt_____kg BSA_____m^2**

Cycle 7 (Week 19): Ht_____cm Wt_____kg BSA_____m^2 **Cycle 8 (Week 22): Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Cycle	Week	Day	VCR _____mg	DACT _____mg	Studies
					Enter calculated dose above and actual dose administered below		
		5	13	1	_____mg	_____mg	a-c
			14	1	_____mg		b
			15	1	_____mg		b
		6	16	1	_____mg	_____mg	a-c
			17	1	_____mg		b
			18	1	_____mg		b
		7	19	1	_____mg	_____mg	a-c, g
			20	1	_____mg		a, b
			21	1	_____mg		b
		8	22	1	_____mg	_____mg	a-c
			24				a, b, d-g

See Section 5.0 for Dose Modifications for Toxicities and Appendix VII for Supportive Care Guidelines.

4.5.5 Required Observations Prior to and During Cycles 5-8

a. Physical exam/weight /height.
b. CBC/diff/platelets.
c. Total bilirubin, ALT & creatinine.
d. MR primary site and regional nodal basin, CT may be considered for intra-abdominal primary. See Section 16.0.
e. CT chest. May be omitted if FDG-PET is performed with diagnostic quality CT. May be omitted for patients with ERMS and clinically uninvolved nodes. See Section 16.0.
f. CT or MRI of regional nodal basin. May omit if PET-CT is done. Perform in those patients who had clinical involved nodes at diagnosis and in all patients with extremity tumors and those with paratesticular tumors who are ≥ 10 years of age. See Section 16.0.
g. Circulating tumor DNA. Patient Consent required. Sample must be drawn at Week 19 and end of protocol therapy. See Section 15.2.

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

Comments

4.5.6 Regimen C (VAC/**VA** Only) Administration Details for Cycles 5-8

Each cycle in ARST1431 is a minimum of 3 weeks (21 days) duration. This course will take a minimum of 12 weeks (84 days).

4.5.6.1 Criteria to Start Each Cycle

4.5.6.1.1 Adequate bone marrow function defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL

NOTE: The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to > 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.

4.5.6.1.2 Adequate liver function defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age

4.5.6.2 Treatment

Radiotherapy (RT)

RT begins at Cycle 5 (Week 13) and may last up to 6.5 weeks for all patients. See Section 17.0 for RT guidelines.

Give the Week 13 dose of dactinomycin before beginning RT. Omit Week 16 dactinomycin during RT. Omit Week 19 dactinomycin only if RT continues into Week 19.

Note: For patients receiving liver RT, reduce the dactinomycin dose by 50% for the next cycle (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose reduction) and increase by 25% (for example, if the 50% dose is 0.7-0.8 mg, then administer 0.9-1 mg to increase the dosage by 25%), if tolerated, up to full dose for subsequent cycles. No reductions of vincristine or cyclophosphamide are needed unless total bilirubin is elevated (see Section 5.3.1).

Chemotherapy

The dose should be calculated on Day 1 of each cycle and not adjusted solely for weight during the cycle.

VinCRIStine: IV Push over 1 minute (or infusion via minibag as per institutional policy) weekly
Day: 1 of Week 13 through Week 22.
Dose: BSA-based dosing

VINCRISTINE	
BSA (m^2)	**Dose**
0.25-0.29	0.24 mg
0.30-0.34	0.34 mg
0.35-0.39	0.44 mg
0.40-0.44	0.55 mg
0.45-0.49	0.65 mg
0.50-0.54	0.74 mg
0.55-0.59	0.8 mg
≥ 0.6	1.5 mg/m^2 (maximum 2 mg)

DACTINomycin: Slow IV Push over 1-5 minutes or IV infusion over 10-15 minutes
Day: 1 of Weeks 13, 16, 19 and 22.
Dose: **Weight-based** dosing

DACTINOMYCIN	
Weight (kg)	**Dose**
3 – 4.5	0.09 mg
4.6 – 6	0.14 mg
6.1 – 7.3	0.21 mg
7.4 – 8.6	0.26 mg
8.7 – 9.9	0.33 mg
10- 11.2	0.4 mg
11.3 -12.5	0.5 mg
12.6 – 13.9	0.6 mg
≥ 14	0.05 mg/kg (maximum 2.5 mg)

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

See Section 5.0 for Dose Modifications based on Toxicities.

Regimen C (VAC/VA Only) Cycles 5-8

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Limiting Toxicity for Temsirolimus

The following will be considered non-hematological dose limiting toxicities (DLTs) and will be monitored in real time via AERS reporting:

- Grade ≥ 3 mucositis
- Grade ≥ 3 pulmonary events
- Grade 3 hyperglycemia (requiring hospitalization for control)
- Grade ≥ 4 hyperglycemia
- Grade ≥ 4 cholesterol high (hypercholesterolemia) or hypertriglyceridemia that does not return to ≤ Grade 2 levels with appropriate medical management within 35 days
- Grade ≥ 3 proteinuria

Patients who experience pulmonary events, hyperglycemia, or proteinuria as described above will be dose-modified as follows:

- If toxicity resolves to baseline or Grade 1 before the next cycle of therapy, then temsirolimus will resume at 100% (full) dose in subsequent cycles unless otherwise specified.
- Patients who are receiving temsirolimus on Days 1, 8, and 15 who experience the same non-hematological DLT for a second time will reduce the dose by one dose level (see Section 5.2). Patients who experience the same DLT again (3rd time) will change the temsirolimus schedule to Days 1 and 8 only (see Section 5.2) and maintain this new schedule for all subsequent therapy. Patients who experience the same DLT again (4th time) will remain on study but will discontinue temsirolimus and receive VAC/VI only.
- If toxicity does not resolve by the next cycle, then the temsirolimus dose should also be reduced to the next dose level (see Section 5.2).

In all cases, temsirolimus will be held until toxicity resolves to baseline or Grade 1, but the rest of chemotherapy (VAC or VI or V) will continue as planned. The dose of temsirolimus to restart is as described above.

See Section 5.2.4 below for dose modifications for mucositis and Section 5.2.6 below for dose modifications for hypercholesterolemia and hypertriglyceridemia.

All other non-hematological toxicities attributable to temsirolimus must resolve to ≤ Grade 1 or baseline to resume temsirolimus. Dose modifications for temsirolimus are as per the guidelines above.

5.1.1 Additional Important Dose Limiting Toxicities for Temsirolimus

In subjects that are receiving temsirolimus, the following adverse events (AEs) will also be considered dose-limiting irrespective of their attribution to temsirolimus and will be monitored in real time via AERS reporting. If any of these AEs occur, temsirolimus will be discontinued and VAC/VI chemotherapy will resume when the patient is clinically well enough to start and counts have recovered as outlined under criteria to start each cycle in the relevant treatment section.

- Any visceral perforation including fistula or leak (gastrointestinal or any other organ)
- Any intra-abdominal abscess/infection
- Grade ≥ 2 wound dehiscence
- Grade ≥ 3 wound infection - requiring IV antibiotics

5.2 Dose Modifications for Temsirolimus on Regimen B during VAC/VI Cycles

The anticipated toxic effects of temsirolimus include: pancytopenia, hypertension, hypotension, fatigue, fever, rash/desquamation, pruritis, acne/acne-like rash, urticaria, nail disorder, anorexia, nausea, diarrhea, stomatitis/pharyngitis, vomiting, dysgeusia, infection without neutropenia, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hypophosphatemia, conjunctivitis, chest pain (non-cardiac, non-pleuritic), headache, abdominal pain, back pain, pneumonitis, pulmonary infiltrates, cough, alveolitis, dyspnea, and respiratory failure.

In the event of any Grade ≥ 3 non-hematological toxicity, the doses of temsirolimus will be adjusted according to the guidelines described in Section 5.1.

Dose levels will be as shown in the table below. No dose escalations are permitted after reductions for confirmed toxicity. Dose modifications for hematological toxicity are based on the blood counts obtained on the day of treatment.

Patients with toxicities that are manageable with supportive therapy may not require dose reductions (e.g., hypertriglyceridemia or cholesterol high). Patients requiring dose reductions will not have the dose re-escalated with subsequent treatments.

Dose reductions will be made based on the following schema:

Patients < 10 kg:

Dose Level	Temsirolimus Dose
1	0.5 mg/kg IV, Days 1, 8 and 15 of each cycle
0	0.33 mg/kg IV, Days 1, 8 and 15 of each cycle
-1	0.33 mg/kg IV, Days 1 and 8 of each cycle

Patients ≥ 10 kg:

Dose Level	Temsirolimus Dose
1	15 mg/m^2 IV, Days 1, 8 and 15 of each cycle
0	10 mg/m^2 IV, Days 1, 8 and 15 of each cycle
-1	10 mg/m^2 IV, Days 1 and 8 of each cycle

5.2.1 Hematological Toxicity – Regimen B

Day 1 only

Recovery of ANC to ≥ 750/µL and platelets ≥ 75,000/µL is required at the start of each cycle (VAC or VI). If a cycle is delayed more than 14 days*, HOLD temsirolimus for 1 cycle and resume temsirolimus at Dose Level 0. If a subsequent cycle is delayed more than 14 days*, discontinue temsirolimus. Patient will remain on study and receive VAC/VI alone.

*Note: The rule of 14 days applies **only** to hematological toxicity. For non-hematological toxicity, please refer to the guidelines in Section 5.1.

Days 8, 15
Give temsirolimus regardless of ANC or platelet count.

5.2.2 Idiosyncratic Infusion-Related Reactions

Reactions to temsirolimus that begin shortly after the start of the infusion and end after stopping the infusion have been reported but are NOT considered dose limiting. Signs and symptoms include flushing of the face and neck (sometimes also the extremities and trunk); descriptions of feeling hot, uncomfortable, and/or anxious; chest pain/tightness; shortness of breath; decrease in oxygen saturation and cyanosis; hypotension; lightheadedness; periorbital puffiness; descriptions of feeling like the head is swelling; nausea; back pain; numbness and tingling of hands/feet/face; and difficulty speaking.

Because of these idiosyncratic reactions, patients will receive diphenhydramine IV approximately 30 minutes before the start of the temsirolimus infusion.

Patients who experience Grade 1 or 2 infusion-related reaction to temsirolimus, may resume drug as deemed safe by treating physician. Patients who experience ≥ Grade 3 or life-threatening infusion-related reaction should discontinue temsirolimus and will remain on study and receive VAC/VI alone. Infusion-related reactions of any grade are not considered a DLT and dose of temsirolimus will not be reduced.

Grade of Infusional Reaction	Action
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated or **Grade 2** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	If a patient develops an infusion-related reaction despite diphenhydramine pretreatment, stop infusion, wait 30-60 minutes (depending upon the reaction severity). At physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Suggest: famotidine 0.5 mg/kg IV (max. 20 mg). If famotidine unavailable, administer ranitidine 1-2 mg/kg IV (max. 50 mg). Re-attempt infusion at a slower rate, possibly over 60 minutes. If Grade 1-2 infusion reactions recur with subsequent dose, add dexamethasone 0.2 mg/kg (max 10 mg) IV or equivalent to premedications above. (Only dose interruption/discontinuation, but not dose reduction, is required for allergic/infusional reactions)

Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Stop infusion immediately. Administer dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Patient should discontinue temsirolimus. Patient should stay on study and receive VAC/VI alone.
Grade 4 Life-threatening consequences; urgent intervention indicated	Stop infusion immediately. Administer dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Patient should discontinue temsirolimus. Patient should stay on study and receive VAC/VI alone.

5.2.3 Pneumonitis/Pulmonary Infiltrates on Temsirolimus

Pneumonitis/pulmonary infiltrates and alveolitis have been reported among cancer patients receiving temsirolimus. Some patients have been asymptomatic with pneumonitis detected incidentally on CT scan or chest x-ray, while others have had symptoms of dyspnea, cough, and fever. In this situation, temsirolimus is discontinued and patients are treated with steroids and/or antibiotics. If a patient experiences these symptoms, temsirolimus will be discontinued, and the patient will remain on study and receive VAC/VI alone.

5.2.4 Mucositis

The development of mucositis in patients receiving temsirolimus plus VAC/VI is of greatest concern. Special attention is required to prevent mucositis and treat it aggressively when it occurs in order to avoid treatment delays, dose reduction, and morbidity. (See Appendix VII for mucositis management guidelines.)

Grade	Action
Grade 1 – mild, asymptomatic	Continue full dose temsirolimus. Use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
Grade 2 - Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Continue full dose temsirolimus. Topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate tetracaine hydrochloride, menthol, or phenol) may be used with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®). Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers and should not be used. Ensure good nutritional support.
Grade 3/4 - Severe pain; interfering with oral intake	Hold temsirolimus until resolves to < Grade 1. Restart temsirolimus at next lower dose. If Grade 3/4 mucositis recurs at lower dose, discontinue temsirolimus.

Please note the following:

- If fungal or viral infections are suspected, appropriate mouth swabs should be obtained. Empiric treatment of these infections with systemic agents should be avoided unless infection is documented.

- Systemic imidazole antifungal agents (ketoconoazole, fluconazole, itraconazole, etc.) should be avoided due to their strong inhibition of temsirolimus metabolism, therefore leading to higher temsirolimus exposure. Echinocandins are preferred if an infection is diagnosed.[70]
- Acyclovir can be added if HSV or CMV is confirmed.

5.2.5 Hyperglycemia

Grade of Hyperglycemia	Action
Grade 2 Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Initiate oral antiglycemic agent.*
Grade 3 Insulin therapy initiated; hospitalization indicated	Initiate insulin therapy. Hold temsirolimus until ≤ Grade 1 and the patient is judged to be suitable for retreatment. Resume temsirolimus at same dose IF patient is asymptomatic, AND fasting serum glucose is ≤ Grade 1 and recovery takes ≤ 7 days. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving temsirolimus. If Grade 3/4 hyperglycemia recurs, then patient will discontinue temsirolimus and remain on study and receive VAC/VI alone.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue temsirolimus.

*Recommended guidelines for use of oral diabetic agents:

- Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist. Metformin may be used per local endocrinologist's recommendations.
- Other oral anti-hyperglycemic agents may be used.
- Insulin therapy should be directed by specialists in pediatric diabetes with the goal of normal fasting blood sugars < 126 mg/dL and HgbA1C < 8%.

5.2.6 Cholesterol High and Hypertriglyceridemia

Cholesterol high	
Grade	**Action**
Grade 1 cholesterol high > ULN - 300 mg/dL; > ULN - 7.75 mmol/L	No change.
Grade 2 cholesterol high > 300 - 400 mg/dL; > 7.75 - 10.34 mmol/L	Continue temsirolimus; consider treatment with a cholesterol lowering agent depending upon recommendations of institutional consultants.
Grade 3 cholesterol high > 400 - 500 mg/dL; > 10.34 - 12.92 mmol/L	Continue temsirolimus; A cholesterol lowering agent should be started, and dosages adjusted based upon recommendations of institutional consultants. It is expected that optimal effects of the lipid lowering medication will be observed 2-4 weeks after its initiation. Treatment with temsirolimus can continue during this time provided that hypercholesterolemia remains ≤ Grade 3.

Grade 4 cholesterol high > 500 mg/dL; > 12.92 mmol/L	Hold temsirolimus; A cholesterol lowering agent should be started, and dosages should be adjusted based upon recommendations from institutional consultants. It is expected that optimal effect of the lipid lowering medication will be observed 2-4 weeks after initiation. Temsirolimus is to be resumed at the same dose when recovery to ≤ Grade 3 fasting cholesterol is observed. Upon retreatment with temsirolimus concurrent with a lipid lowering agent if Grade 4 elevations recurs, temsirolimus should be held until recovery to ≤ Grade 3. Further lipid lowering medication options should be discussed with institutional consultants. Upon recovery to ≤ Grade 3 fasting cholesterol, temsirolimus should be resumed at next lower dose level. If the toxicity recurs, hold temsirolimus while continuing cholesterol lowering agent until fasting cholesterol is ≤ Grade 3 and then resume temsirolimus at next lower dose level. If Grade 4 hypercholesterolemia recurs following this dose adjustment, discontinue temsirolimus and patient will remain on study to receive VAC/VI only.
Hypertriglyceridemia	
Grade	**Action**
Grade 2 hypertriglyceridemia > 300 mg/dL – 500 mg/dL; > 3.42 mmol/L - 5.7 mmol/L	Continue temsirolimus; consider treatment with a triglyceride lowering agent depending upon recommendations of institutional consultants.
Grade 3 hypertriglyceridemia > 500 mg/dL – 1000 mg/dL; > 5.7 mmol/L - 11.4 mmol/L OR **Grade 4** hypertriglyceridemia > 1000 mg/dL; > 11.4 mmol/L; life-threatening consequences	Hold temsirolimus until recovery to ≤ Grade 2; A triglyceride lowering agent should be started, and dosages should be adjusted based upon recommendations from institutional consultants. Upon retreatment at the same dose level, if Grade 3 or 4 toxicity recurs, lipid lowering medication should be adjusted in consultation with institutional consultants. Temsirolimus should be held until recovery to ≤ Grade 2 and resumed at next lower dose level. Upon retreatment with temsirolimus concurrent with a triglyceride lowering agent if Grade 3 or 4 elevations recur, temsirolimus should be held until recovery to ≤ Grade 2 and the triglyceride lowering agents continued. Upon recovery to ≤ Grade 2, temsirolimus should be resumed at next lower dose level. If Grade 3 or 4 hypertriglyceridemia recurs, discontinue temsirolimus and patient will remain on study to receive VAC/VI only.

5.2.7 Wound Dehiscence

mTOR inhibitors directly inhibit wound healing,[71] and thus if a patient experiences wound dehiscence (≥ Grade 2), there is little likelihood that the wound will close while still receiving the drug. Therefore, in patients with ≥ Grade 2 wound dehiscence, temsirolimus should be held until the wound is completely closed and healed. Temsirolimus can be restarted at the same dose once the wound is healed. If wound re-opens (≥ Grade 1), discontinue temsirolimus and continue VAC/VI alone.

5.2.8 Wound Infection

If a superficial wound infection occurs (Grade 2), hold temsirolimus until resolves, then restart at full dose. If infection recurs, hold until it resolves and

resume at next lower dose level. If infection again recurs, patient will discontinue temsirolimus, and remain on study to receive VAC/VI alone.

5.2.9 Hyperbilirubinemia

In patients with mild hepatic impairment (total bilirubin > 1 to 1.5 x ULN) decrease temsirolimus dose by 40% (e.g., 9 mg/m^2/dose up to a max of 15 mg/dose for Dose Level 1).

If total bilirubin is > 1.5 × ULN prior to chemotherapy, omit temsirolimus dose. If temsirolimus dose is omitted because of hyperbilirubinemia, subsequent doses should be based on above criteria, i.e., if bilirubin returns to normal the full dose of temsirolimus is to be given.

5.2.10 Interstitial Lung Disease

Consider withholding temsirolimus for clinically significant respiratory symptoms until after recovery of symptoms or radiographic improvement.

5.3 Non-Hematological Dose Modifications for VAC/VI Cycles

Toxicity	Dose Modification
Hematuria	Transient microscopic hematuria (≥ 50 rbc/hpf 1 or 2 times): double rate of post-hydration; give mesna as continuous infusion at 60% of the cyclophosphamide dose over 8 hours. Persistent microscopic hematuria: (≥ 50 rbc/hpf ≥ 3 times): double rate of post-hydration, continue for 24 h, and give mesna as 100% of the cyclophosphamide dose over 24 h. Transient gross hematuria: as per persistent microscopic hematuria. Persistent gross hematuria: discontinue cyclophosphamide until urine clears to microscopic hematuria; resume at 50% of full dose with post-hydration and mesna as for persistent microscopic hematuria; escalate dose to 75% and 100% of full dose as tolerated. Consider urology consultation. Consider continuous infusion of mesna for subsequent cycles (see Appendix VII).
Neurotoxicity	See Section 5.8 for vincristine dose modifications. No dose reduction for dactinomycin, irinotecan.
Jaw Pain	No dose reduction; offer analgesia.
Grade ≥ 3 Mucositis	Hold dactinomycin and cyclophosphamide until resolves to < Grade 1. No dose reduction for vincristine, irinotecan. Review mucositis guidelines in Appendix VII.
Creatinine clearance < 10 mL/min/1.73 m^2	Reduce cyclophosphamide by 25%. No dose reduction for vincristine, dactinomycin, irinotecan.
Grade ≥ 3 diarrhea related to irinotecan despite antibiotic prophylaxis	Reduce dose of irinotecan by 30%

5.4 Hematological Dose Modifications for VAC/VI Cycles – Regimen A

Note: recovery of ANC to ≥ 750/µL and platelets ≥ 75,000/µL is required at the start of each cycle (VAC or VI).

Day 1 ANC < 750/uL	Delay chemotherapy by 1 week. If recovered, proceed at full dose. If ANC recovery is delayed by > 1 week following VAC cycle, reduce the dose of dactinomycin and cyclophosphamide by 25% during next cycle of VAC. If If ANC recovery is delayed by > 1 week following VI cycle, add myeloid growth factor support (filgrastim, pegfilgrastim or biosimilars) prior to subsequent VI cycles. Do not reduce dose of irinotecan. If subsequent cycle is also delayed, reduce dose of chemotherapy (except vincristine) by 30% for next cycle. For example, if preceding cycle is VAC, dose reduce cyclophosphamide and dactiomycin by an additional 30% each in the next VAC cycle. If preceding cycle was VI, reduce irinotecan by 30% for next VI.
Day 1 Platelets < 75,000/µL	Delay chemotherapy by 1 week. If recovered, proceed at full dose. If platelets not recovered, reduce dose of dactinomycin and cyclophosphamide by 25% or irinotecan by 30% for next cycle for which the same drug is due. ie. if preceding cycle is VAC, dose reduce next VAC. If preceding cycle was VI, reduce irinotecan for next VI. .

Please note the following:

- Weekly vincristine doses should be given regardless of blood counts.
- The ANC frequently falls after discontinuing myeloid growth factor support (secondary neutrophil nadir). If the ANC recovers to ≥ 750/µL after nadir but then falls to < 750/µL after the myeloid growth factor is stopped, the next cycle of therapy can be given despite ANC < 750/µL if all other criteria for the next cycle of chemotherapy are met. No dose modification should be made under these circumstances.
- See Section 17.7.10 for guidelines for radiation treatment modifications due to low blood counts.

5.5 Dose Modifications for Vincristine, Dactinomycin, and Irinotecan in Patients with Hyperbilirubinemia Secondary to Biliary Obstruction due to Tumor and Other Situations with Elevated Bilirubin

Please note: Cyclophosphamide dose is not adjusted for hepatic dysfunction.

Direct bilirubin [mg/dL]	Direct bilirubin [micromole/L]	Dose to give
≤ 3.0	< 53	Full dose
3.1 – 5.0	54-85	50% of calculated dose
5.1 – 6.0	86-102	25% of calculated dose
> 6.0	> 102	Omit dose

Note: If bilirubin falls prior to subsequent cycles, increase the dose as indicated above in next cycle.

5.6 Dose Modifications for Patients who Receive Liver Irradiation

After completion of liver irradiation, reduce the dactinomycin dose by 50% for the next cycle (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose reduction) and increase by 25% (for example, if the 50% dose is 0.7-0.8 mg, then administer 0.9-1 mg to increase the dosage by 25%), if tolerated, up to full dose for subsequent cycles. No reductions of vincristine or cyclophosphamide are needed unless total bilirubin is elevated (see Section 5.5).

5.7 Dose Modifications for Hepatopathy

It appears that hepatopathy is closely related to the administration of VAC. Patients of young age appear to be at increased risk. A prior persistent or slow recovery of thrombocytopenia may be an indicator of hepatopathy.

5.7.1 Criteria for Diagnosis of Hepatopathy

Pathologic confirmation by liver biopsy OR
Reversal of portal venous flow by ultrasound OR
Two or more of the following: 1. Bilirubin > 1.4 mg/dL. 2. Unexplained weight gain greater than 10% of baseline weight or ascites. 3. Hepatomegaly or RUQ pain without other explanation.

5.7.2 Grading Criteria for Hepatopathy

Mild Hepatopathy	Total bilirubin ≤ 6 mg/dL Weight gain of ≤ 5% of baseline of non-cardiac origin Reversible hepatic dysfunction
Moderate Hepatopathy	Total bilirubin > 6 mg/dL and < 20 mg/dL Weight gain > 5% of baseline of non-cardiac origin Clinical or image documented ascites Reversible hepatic dysfunction
Severe Hepatopathy	Total bilirubin > 20 mg/dL and/or Ascites compromising respiratory function and/or Renal deterioration and/or Hepatic encephalopathy which may or may not be reversible

5.7.3 Therapy Modification for Hepatopathy

Since hepatopathy most likely results from a combination of factors including dactinomycin, cyclophosphamide and vincristine, the following therapy modifications should be taken in the presence of this complication.

Mild Hepatopathy	Half drug dose of dactinomycin and cyclophosphamide (age adjusted per Section 4.2.3.2) for the next course (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.8 mg for a half-dose; and if the full cyclophosphamide dose is 1200 mg, then administer 600 mg for a half-dose) and then resume full doses per course if tolerated.
Moderate Hepatopathy	Discontinue VAC. Patient will be removed from protocol therapy.
Severe Hepatopathy	Discontinue VAC. Patient will be removed from protocol therapy.

5.8 Neurotoxicity Secondary to Vincristine

5.8.1 Neuropathy: (see grading scale below)

- Grade 2 motor or sensory neuropathies (see neuropathy grading scale below): give 50% of full dose; increase to 75% of full dose when signs and symptoms improve to Grade 1 or resolve; increase dose to 100% after 2 additional doses of vincristine if signs and symptoms remain at Grade 1 or resolve. Hold the dose if symptoms worsen.
- Grade 3 neuropathies (see neuropathy grading scale below): omit doses until signs and symptoms improve to Grade 2, then resume at 50% of full dose and manage as above.
- Constipation: Give 50% dose if stimulant laxatives (e.g. senna) do not preserve bowel motility; omit dose if manual disimpaction is required or if ileus occurs.
- Jaw pain: Avoid dose modifications; try chewing gum, gabapentin, and/or pain medication instead.

5.8.2 Neuropathy grading:

Motor neuropathy:

- Grade 1: Subjective weakness, but no deficits on neurological exam
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis

Sensory neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that is controlled by non-narcotic medications, or alter (without causing loss of function) fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, *without abrogating ability* to perform these tasks.
- Grade 3: Paresthesias or pain that is controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation or pain that is not controlled by narcotics

5.9 Dose Modifications for Maintenance Therapy – Regimens A & B

5.9.1 Hematological Toxicity

CBC needs to be checked weekly during maintenance therapy. Hold oral cyclophosphamide if ANC < 750/μL or platelets < 75,000/μL. Resume cyclophosphamide once counts have recovered.

If cyclophosphamide is held for > 7 consecutive days during any cycle, hold 3rd dose of vinorelbine (Day 15) for next cycle only.

If vinorelbine dose was held during a prior cycle and needs to be held a second time, reduce the dose of vinorelbine to 75% of calculated dose for all subsequent cycles and omit 3rd dose of vinorelbine (Day 15) for all subsequent cycles.

5.9.2 Dose Modifications for Vinorelbine in Patients with Hyperbilirubinemia Secondary to Biliary Obstruction due to Tumor and Other Situations with Elevated Bilirubin

Please note: Cyclophosphamide dose is not adjusted for hepatic dysfunction.

Direct bilirubin [mg/dL]	Direct bilirubin [micromole/L]	Dose to give
≤ 3.0	< 53	Full dose
3.1 – 5.0	54-85	50% of calculated dose
5.1 – 6.0	86-102	25% of calculated dose
> 6.0	> 102	Omit dose

Note: If bilirubin falls prior to subsequent cycles, increase the dose as indicated above in next cycle.

5.9.3 Neurotoxicity Secondary to Vinorelbine

See neuropathy grading in Section 5.8.2. Vinorelbine should be dose modified only for incapacitating peripheral neurotoxicity (e.g. ≥ Grade 3 neurological toxicity [interferes with activities of daily living] or ≥ Grade 3 constipation), as follows:

- Grade 3 or higher neurological toxicity: Hold vinorelbine; resume at 75% of full dose when the symptoms have improved to Grade 1 toxicity or completely resolved. If ≥ Grade 3 toxicity recurs, no further vinorelbine will be given.
- Grade 3 or higher constipation: Hold vinorelbine; resume at 75% of full dose when the symptoms have improved to Grade 1 toxicity or completely resolved. Omit dose if manual disimpaction is required or if ileus occurs.

6.0 DRUG INFORMATION

6.1 TEMSIROLIMUS (02/07/20)

(Torisel®, CCI-779, rapamycin analog, WAY-130779) NSC# 683864

Source and Pharmacology: Temsirolimus is an ester of the immunosuppressive compound sirolimus (rapamicin). Its chemical name is rapamycin 42-[2,2-bis(hydroxymethyl)propionate]. Temsirolimus is a specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. Temsirolimus binds to an intracellular protein FK506 binding protein (FKBP) 12 and the protein-drug complex inhibits the activity of mTOR and controls cell division. Inhibition of mTOR prevents progression from G_1 to S phase of the cell cycle. *In vitro* studies show that inhibition of the activity of mTOR resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha and VEGF.

Pharmacokinetic studies of a single IV dose of temsirolimus in adults showed that over a dose range of 1 mg to 25 mg, the drug exposure increased with increasing doses in a less than proportional fashion. After a single 25 mg IV dose, the volume of distribution was large (172 L) with preferential partitioning into blood, the mean clearance was 16.2 L/h, and the terminal half-life was 17.3 hours.

The pharmacokinetics of temsirolimus was assessed in 19 pediatric subjects with relapsed or refractory advanced solid tumors. The typical subject was an 11-year-old male child, with a body weight of 44.4 kg and a body surface area of 1.38 m^2. Subjects received doses of 10, 25, 75, and 150 mg/m^2 once weekly. Comparisons of exposure with adult subjects show that temsirolimus C_{max} and AUC_{sum} (sum of temsirolimus and sirolimus area under the concentration vs time curve) in the pediatric subjects was comparable to adult subjects, while temsirolimus AUC was higher in the pediatric subjects. This greater exposure to parent drug in the pediatric population was balanced by the shorter half-lives of sirolimus metabolite and corresponding lower AUCs.

The safety and pharmacokinetics of temsirolimus were evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin > 1.5 × upper limit of normal (ULN) experienced greater toxicity than patients with baseline bilirubin ≤ 1.5 × ULN when treated with temsirolimus. The overall frequency of ≥ Grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin > 1.5 × ULN due to increased risk of death. Caution should be used when treating patients with hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Temsirolimus is contraindicated in patients with bilirubin > 1.5 x ULN.

Temsirolimus is metabolized extensively in the liver mainly by the isoenzyme cytochrome (CYP) P450 3A4. The main active metabolite is sirolimus and the other four metabolites account for less than 10% of the parent drug. The activity of temsirolimus is dictated both by the parent drug and by the equipotent metabolite sirolimus. Sirolimus half life is longer (54.6 hours) and after a single 25 mg IV dose its AUC is 2.7-fold that of temsirolimus AUC due to mainly the longer half-life of sirolimus. Temsirolimus elimination occurs primarily in the liver with only minor amounts of drug-related products eliminated in the urine. Multiple doses of 25 mg administered once weekly exhibited little or no substantial accumulation.

Since the primary oxidative metabolism of temsirolimus is via CYP3A4, inhibitors and inducers of the CYP3A4 enzyme system may alter the metabolism of temsirolimus; however, temsirolimus does not induce CYP3A4. Temsirolimus may inhibit the metabolic clearance of substrates of CYP3A4/5 or CYP2D6, but not CYP2C9 or CYP2C8. Caution should be used when administering strong CYP3A4 inhibitors or strong CYP3A4/5 inducers with temsirolimus IV. In phase 1 drug interaction studies, co-administration of IV temsirolimus with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus, but increased the major metabolite sirolimus exposure. Co-administration of temsirolimus with rifampin, a potent CYP3A4 inducer, had no significant effect on temsirolimus, but decreased sirolimus exposure.

In vitro studies showed that temsirolimus is subject to P-gp-mediated efflux; additionally temsirolimus inhibited the transport of digoxin, a P-gp substrate. These results indicate that temsirolimus has the potential to alter the transport of agents that are P-gp substrates as well as to be altered by P-gp inhibitors. Clinical implications related to concomitant administration of P-gp substrates are unknown and dose modifications for co-administration with P-gp substrates or inhibitors are not provided in the drug package insert.

The combination of temsirolimus and angiotensin converting enzyme inhibitors (ACEIs) and/or calcium channel blockers (eg., amlodipine) resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). Co-administration of sunitinib and temsirolimus resulted in increased toxicity. During temsirolimus treatment, the co-administration of sunitinib, ACEIs or calcium channel blockers should be avoided. Prothrombin time and INR should be monitored if warfarin is added or discontinued.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Temsirolimus (CCI-779, NSC 683864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1927 patients.* Below is the CAEPR for temsirolimus (CCI-779).

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

Version 2.6, August 19, 2018[1]

Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
ENDOCRINE DISORDERS			
	Testosterone deficiency		***Testosterone deficiency (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis[2]		***Anal mucositis[2] (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
		Gastrointestinal fistula[3]	
		Gastrointestinal perforation[4]	***Gastrointestinal perforation[4] (Gr 4)***
Mucositis oral[2]			***Mucositis oral[2] (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis[2]		***Rectal mucositis[2] (Gr 2)***
	Small intestinal mucositis[2]		***Small intestinal mucositis[2] (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		***Edema face (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[5]		***Allergic reaction[5] (Gr 2)***
INFECTIONS AND INFESTATIONS[6]			
	Infection[7]		***Infection[7] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound dehiscence[8]		***Wound dehiscence[8] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
Cholesterol high[9]			***Cholesterol high[9] (Gr 4)***
	Creatinine increased		***Creatinine increased (Gr 3)***
	Fibrinogen decreased		***Fibrinogen decreased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***

Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased[10]			***Platelet count decreased[10] (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 2)***
Anorexia			***Anorexia (Gr 3)***
	Glucose intolerance[11]		***Glucose intolerance[11] (Gr 2)***
	Hyperglycemia[11]		***Hyperglycemia[11] (Gr 3)***
	Hyperlipidemia[9]		***Hyperlipidemia[9] (Gr 4)***
	Hypertriglyceridemia[9]		***Hypertriglyceridemia[9] (Gr 4)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hypophosphatemia		***Hypophosphatemia (Gr 4)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		***Depressed level of consciousness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
PSYCHIATRIC DISORDERS			
	Depression		***Depression (Gr 2)***
	Insomnia		***Insomnia (Gr 2)***
	Libido decreased		***Libido decreased (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury[12]	
		Nephrotic syndrome	
		Proteinuria	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Erectile dysfunction		***Erectile dysfunction (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
	Laryngeal mucositis[2]		***Laryngeal mucositis[2] (Gr 2)***
	Pharyngeal mucositis[2]		***Pharyngeal mucositis[2] (Gr 2)***
	Pleural effusion		***Pleural effusion (Gr 3)***
	Pneumonitis[13]		***Pneumonitis[13] (Gr 3)***
	Sinus disorder		***Sinus disorder (Gr 2)***
	Tracheal mucositis[2]		***Tracheal mucositis[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry skin		***Dry skin (Gr 2)***
	Nail changes[14]		***Nail changes[14] (Gr 1)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
	Hypotension		***Hypotension (Gr 3)***
		Thromboembolic event	***Thromboembolic event (Gr 4)***

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

[2]Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

[5]Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

[6]Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

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

[8]Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

[9]Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

[10]Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

[11]Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.

[12]Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

[13]Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

[14]Nail Changes includes Nail discoloration, Nail loss, and Nail ridging under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

[15]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

Adverse events reported on temsirolimus (CCI-779) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that temsirolimus (CCI-779) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (coagulopathy); Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (Cushing's syndrome); Endocrine disorders - Other (diabetes mellitus)
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Eye disorders - Other (diplopia); Eye pain; Flashing lights; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Anal fissure; Anal pain; Anal ulcer; Ascites; Bloating; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[15]; Hemorrhoids; Ileus; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Rectal pain; Small intestinal obstruction; Stomach pain; Typhlitis; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Facial pain; Gait disturbance; Injection site reaction; Localized edema; Malaise; Multi-organ failure; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fracture; Postoperative hemorrhage; Vascular access complication; Wound complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CD4 lymphocytes decreased; INR increased (potential interaction with Coumadin); Investigations - Other (BUN increased); Lipase increased; Lymphocyte count increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (albuminuria); Metabolism and nutrition disorders - Other (blood urea increased); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle cramp; Muscle weakness lower limb; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoma of the lung); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lymphoma); Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Hydrocephalus; Lethargy; Neuralgia; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Spasticity; Stroke; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Mania; Psychiatric disorders - Other (bipolar disorder); Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Cystitis noninfective; Hematuria; Hemoglobinuria; Renal hemorrhage; Urinary frequency; Urinary retention; Urinary tract pain; Urinary urgency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Irregular menstruation; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Reproductive system and breast disorders - Other (female genital tract fistula); Spermatic cord hemorrhage; Testicular disorder; Testicular hemorrhage; Testicular pain; Uterine hemorrhage; Vaginal discharge; Vaginal dryness; Vaginal fistula; Vaginal hemorrhage; Vaginal inflammation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (angioneurotic edema); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Phlebitis; Superficial thrombophlebitis

Note: Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus (CCI-779).

Note: Temsirolimus (CCI-779) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Effect in pregnancy:
Temsirolimus can cause fetal harm. Female of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for three months after temsirolimus

therapy has stopped. Male with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for three months after the last dose of temsirolimus.

Formulation and Stability:
Temsirolimus (Torisel®) is supplied as the commercially labeled kit consisting of a concentration solution and a diluent. The kit components are:

- Temsirolimus injection (25 mg/mL), 1.2 mL
- DILUENT vial that includes a deliverable volume of 1.8 mL.

Temsirolimus injection 25 mg/mL is a clear, colorless to light yellow, non-aqueous, ethanolic, sterile solution. The inactive ingredients include dehydrated alcohol (39.5% w/v), *dl*-alpha-tocopherol, propylene glycol, and anhydrous citric acid. The diluent is a sterile, non-aqueous solution that includes polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v) and dehydrated alcohol (19.9% w/v). After the temsirolimus injection vial has been diluted with the provided diluent, the solution contains 35.2% alcohol. The two-vial kit must be stored at 2°-8°C (36°-46°F) protected from light.

If a storage temperature excursion is identified, promptly return temsirolimus to 2° – 8° C temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

During handling and preparation of admixtures, temsirolimus should be protected from excessive room light and sunlight. In order to minimize the patient exposure to the plasticizer di-2-ethylhexyl phthalate (DEHP) which may be leached from polyvinyl chloride (PVC) infusion bags, the final temsirolimus dilution for infusion should be prepared in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin). The preparation of the solution for administration requires two-step dilution process in an aseptic manner. These mixing instructions apply to the commercial Torisel® kit that is provided for this study.

Step 1:

- The temsirolimus injection vial contains 30 mg temsirolimus in 1.2 mL (25 mg/mL).
- Inject 1.8 mL of the provided diluent into the vial of temsirolimus injection (25 mg/mL). The resulting drug concentration is 10 mg/mL and the total volume is 3 mL.
- Mix well by inversion of the vial. DO NOT SHAKE. Allow sufficient time for air bubbles to subside. The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates.
- The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

Step 2:

- Withdraw the amount of temsirolimus required for the dose from the 10 mg/mL drug solution/diluent mixture prepared in Step 1.
- For doses less than 10 mg, filter the concentrate/diluents mixture using a syringe filter unit before measuring required volume.

- Further dilute with 0.9% sodium chloride injection immediately in non-DEHP container (see above) to a final concentration between 0.04 mg/mL and 1 mg/mL.
- Mix by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.
- The diluted solution for administration is stable at controlled room temperature for up to six hours from the time of the final dilution. Protect the bag/bottle from light.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Route of Administration: Intravenous with an appropriate in-line filter (i.e. 0.2 to 5 micron) for all temsirolimus doses equal to or greater than 10 mg. To avoid drug loss, prepare doses less than 10 mg by filtering the concentrate/diluent mixture as noted previously in the Formulation and Stability section Steps 1 and 2 using a syringe filter unit.

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

To prevent hypersensitivity reaction, an H_1 antihistamine (eg, diphenhydramine) should be administered before the start of the temsirolimus infusion. Administration of final diluted solution should be completed within 6 hours of preparation.

Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)pthalate (DEHP) to prevent DEHP leaching. Store diluted temsirolimus solutions in bottles (glass) or plastic bags (polyolefin or polypropylene). Infusion sets containing polyvinyl chloride should not be used to administer temsirolimus to avoid leaching of plasticizer.

The following are examples of in-line filters that are compatible with temsirolimus:
- IV 6200 Disposable I.V. Filter 0.2 micron by EPS®, Inc
- IV 6120 Disposable I.V. Filter 1.2 micron by EPS®, Inc
- LV 5000 Large Volume 5 micron Conical Filter by B. Braun
- Baxter Paclitaxel Set with 0.22 micron filter
- Codan 5 micron monofilter

Other polyethersulfone filters may be used.

Supplier: Supplied by Pfizer and distributed by the NCI DTCD. **Do not use commercially available drug.**

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

agents for the study should be ordered under the name of one lead participating investigator at that institution.

Subjects must be enrolled and assigned to the Regimen B treatment arm prior to submitting the agent request to PMB.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

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

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

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

6.2 CYCLOPHOSPHAMIDE INJECTION (Cytoxan) NSC #26271 (03/13/13)

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

Toxicity:

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

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

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

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

Cyclophosphamide for Injection:
If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

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

6.3 CYCLOPHOSPHAMIDE - ORAL (10/31/18)
(Cytoxan) NSC #26271

Source and Pharmacology:
Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. Cyclophosphamide is well absorbed orally with a bioavailability greater than 75%. The plasma half-life ranges from 4.1 to 16 hours after IV administration and 1.3 to 6.8 hours after oral administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression

Delayed: Any time later during therapy, excluding the above conditions	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

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

Formulation and Stability:
US: Available as 25 mg and 50 mg capsules. Inactive ingredients vary depending on manufacturer.
Canada: Available as 25 mg and 50 mg tablets. Inactive ingredients vary depending on manufacturer.
Australia/New Zealand: Available as 50 mg tablets. Inactive ingredients vary depending on manufacturer.

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

Cyclophosphamide injection for oral administration:

1. The reconstituted cyclophosphamide injection (20 mg/mL) repackaged into polypropylene syringes is stable under refrigeration (4°C) for four weeks. (Kirk B, Melia CD, Wilson JV, et al. Chemical stability of cyclophosphamide injection. Br J Parenter Ther 1984;5:90 7).
2. The reconstituted injection can also be used for the preparation of cyclophosphamide suspension. To prepare, reconstitute a vial of cyclophosphamide 2000 mg with 100 mL of NS to a final concentration of 20 mg/mL. Measure 100 mL of Ora-Plus (or simple syrup) and pour into an 8 ounce or larger amber bottle. Add the reconstituted cyclophosphamide (100 mL of a 20 mg/mL solution) to achieve a final volume of 200 mL. Shake well to disperse evenly. The cyclophosphamide suspension concentration would be 10 mg/mL. Draw up individual doses into amber syringes for oral use. Store the syringes in the refrigerator (4°C), protected from light. The suspension is stable in amber syringes in a dark, refrigerated environment, for up to 56 days. (Kennedy R, Groepper D, Tagen M et al. Stability of cyclophosphamide in extemporaneous oral suspensions. Ann Pharmacother 2010;44:295-301).

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

6.4 DACTINOMYCIN (05/09/11)

(Actinomycin-D, Cosmegen®) NSC #3053

Source and Pharmacology:

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

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Anaphylaxis, abdominal pain, extravasation (rare) but if occurs = local ulceration
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression, alopecia (L)	Diarrhea, mucositis, cheilitis, radiation recall reactions, fatigue, lethargy, malaise	Elevated LFTs, hepatitis, hepatomegaly, sinusoidal obstruction syndrome (SOS, formerly VOD) (L), proctitis, acne, skin eruptions, hypocalcemia, fever, ulcerative stomatitis, esophagitis and/or enteritis, myalgia
Delayed: Any time later during therapy			Growth retardation, pneumonitis
Late: Any time after completion of treatment			Secondary malignancies
Unknown frequency and timing:	Fetal toxicities of dactinomycin have been noted in animal models. It is not known if dactinomycin is excreted into breast milk		

(L) Toxicity may also occur later.

Formulation and Stability:

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

Reconstitute with 1.1 mL of sterile water without preservative to give a final concentration of 500 mcg/mL (0.5 mg/mL). The resulting solution should be clear to gold colored. Preservatives may cause precipitation. Stable at room temperature, 25°C (77°F) protected from light for up to 24 hours.

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

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

6.5 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ, FILGRASTIM-AAFI

(05/13/19)

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®, Grastofil®, Nivestym®) NSC #614629

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

Toxicity:

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

Formulation and Stability:
Neupogen®, Granix® and Nivestym® are supplied as a clear solution of 300 mcg/1 mL or 480 mcg/1.6 mL preservative-free single use vials. Discard unused portions of open vials.

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

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

For IV use, dilute filgrastim (Neupogen®), tbo-filgrastim (Granix®), and filgrastim-aafi (Nivestym®) in D5W only to concentrations > 15 mcg/mL. Filgrastim-sndz (Zarxio®) and filgrastim-aafi (Nivestym®) may be diluted in D5W to concentrations between 5 mcg/mL to 15 mcg/mL. At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 4 products (communication on file from Teva Pharmaceuticals USA). Filgrastim, filgrastim-sndz and filgrastim-aafi dilutions to a concentrations of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted

filgrastim biosimilar products should be stored at 2º-8ºC (36º-46ºF) and used within 24 hours. Do not shake.

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

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

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

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

CANADIAN SITES:
Grastofil® brand of filgrastim biosimilar is available in Canada. See package insert for further information.

6.6 IRINOTECAN (03/07/17)

[CPT-11, Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348

Source and Pharmacology:
Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from *Camptotheca acuminata)*. Irinotecan is a prodrug that requires conversion, by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN-38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

Toxicity:

Incidence	Toxicities
Common (>20% of patients)	• Anemia • Thrombocytopenia • Neutrophil count decreased • White blood cell count decreased • Nausea • Vomiting • Constipation • Anorexia • Fever • Asthenia • Cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and diarrhea) • Alopecia • Bilirubin increased • Mucositis • Dyspnea • Cough • Weight loss • Pain
Occasional (4-20% of patients)	• Abdominal fullness • Flatulence • Vasodilation • Hypotension • Dehydration • Edema • AST increased • Alkaline phosphatase increased • Ascites • Jaundice • Febrile neutropenia • Infection • Headache • Dizziness • Chills • Insomnia • Rash • Dyspepsia • Somnolence • Thromboembolic events • Pneumonia
Rare (≤ 3% of patients)	• Anaphylaxis • Bradycardia • Disorientation/confusion • Colitis

	• Renal failure (secondary to severe dehydration) • Ileus • Pancreatitis • Pneumonitis (L)
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.

(L) Toxicity may also occur later.

Formulation & Stability:
Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL),100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL). Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.
IV administration: Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in D5W, (preferred) or NS to a final concentration range of 0.12-2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in D5W and stored at refrigerated temperatures (approximately 2°-8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using NS is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

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

6.7 MESNA – INJECTION (10/13/17)
(sodium 2-mercaptoethane sulfonate, UCB 3983, Mesnex®) NSC #113891

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

studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

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

Toxicity[1]:

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

[1]*All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800 mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]*

Formulation and Stability:
Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature 15º-25°C (68º-77ºF). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

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

For IV administration, dilute mesna to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for

administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Mesna may cause false positive test for urinary ketones.

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

6.8 **MESNA – ORAL** **(11/27/17)**
(sodium 2-mercaptoethane sulfonate,UCB 3983, Mesnex®) NSC #113891

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

After an 800 mg dose the half lives for mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

Toxicity[1]:

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

[1]All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid .In

pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]

Formulation and Stability:
Mesna is available as scored 400 mg oral tablets. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature, 15°-25°C (68-77ºF). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

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

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

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

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

Mesna may cause false positive test for urinary ketones.

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

6.9 PEGFILGRASTIM, PEGFILGRASTIM-JMDB, PEGFILGRASTIM-CBQV

(01/28/19)

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

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific

colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

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

Toxicity:

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

Formulation and Stability:

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

Pegfilgrastim-jmdb (Fulphila®): Supplied as 6 mg/0.6 mL sterile, clear, colorless preservative-free solution (pH 4.0) containing acetate (0.7 mg), D-sorbitol (30 mg), polysorbate 20 (0.024 mg) and sodium (0.01 mg) in Water for Injection, USP. It is intended for subcutaneous use only and is supplied in a single-dose prefilled syringe with

a 29 gauge, ½ inch needle, with UltraSafe Passive Plus™ Needle Guard. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).

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

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

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

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

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

6.10 VINCRISTINE SULFATE (08/20/20)

(Oncovin®, VCR, LCR) NSC #67574

Source and Pharmacology:
Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

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

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via a minibag is **preferred** for COG protocols. Slow IV push vincristine administration is permissible. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the

vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

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

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

6.11 VINORELBINE TARTRATE (05/10/11)

(Navelbine®) NSC #608210

Source and Pharmacology:
Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca++-transport ATPase activity, 3) cellular respiration. Vinorelbine may be selective to mitotic microtubules vs. axonal microtubules as compared to other vinca alkaloids. This selectivity possibly limits neurotoxicity compared to other vincas.

Following IV administration, vinorelbine plasma concentration decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg. Steady-state volume of distribution values range from 25.4 to 40.1 L/kg. Vinorelbine demonstrates high binding to human platelets and lymphocytes. Plasma binding ranged from 79.6% to 91.2%. Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration. 10-12% of vinorelbine is recovered unchanged in the urine. Two metabolites have been identified: vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine is the primary metabolite of vinorelbine and has been shown to possess antitumor activity similar to vinorelbine. Metabolism of vinca alkaloids are mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Injection site reactions (erythema, pain, vein discoloration), nausea, vomiting	Muscle weakness, phlebitis, diarrhea	Fever, hypersensitivity (anaphylaxis, SOB, bronchospasm, hypotension), hypertension, pulmonary edema, dyspnea, chest pain (usually with pre-existing cardiac or pulmonary disease), extravasation (rare) but if occurs = local ulceration
Prompt: Within 2-3 weeks, prior to next course	Granulocytopenia, leukopenia, anemia, fatigue, constipation, elevated SGOT (AST)	Thrombocytopenia neuropathy (paresthesias, hypesthesia) (related to cumulative dose), anorexia, abdominal pain, stomatitis, elevated bilirubin, alopecia	Rash, myocardial infarction , hepatoxicity, loss of deep tendon reflex, gait disturbances, myalgia, erythema and skin desquamation in palms & soles, auditory deficits, headache, jaw pain, hemorrhagic cystitis, pancreatitis, ARDS (interstitial pulmonary changes), thromboembolic events (pulmonary embolism, DVT, SCV thrombosis with IV catheters), paralytic ileus & intestinal obstruction with necrosis
Delayed: Any time later during therapy			SIADH, radiation recall (dermatitis, esophagitis)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Fetal toxicities and teratogenic effects of vinorelbine have been noted in animals at 1/3rd and 1/6th of the usual human dose. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Available as 10 mg/mL injection in 1 mL and 5 mL vials in SWFI. Contains no preservatives or other additives. Store vials under refrigeration at 2°-8°C (36°-46°F) in the carton. Unopened vials are stable at room temperature up to 25°C (77°F) for up to 72 hours. Protect from light. Do not freeze.

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

Vinorelbine injection must be diluted in D5W or NS for bolus administration by syringe or short IV infusion. For syringe administration, dilute vinorelbine to a concentration of 1.5 to 3 mg/mL. For infusion administration dilute to a concentration of 0.5 to 2 mg/mL. The diluted vinorelbine should be administered into the side port of a free-flowing IV **closest to the IV bag** followed by flushing with at least 75 to 125 mL of dextrose or saline containing solution. Care should be taken to avoid extravasation; the use of a central line is suggested.

Syringes containing vinorelbine should be labeled: "WARNING - FOR IV USE ONLY. FATAL IF GIVEN INTRATHECALLY."

Vinorelbine may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5°-30°C (41°-86°F).

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

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 Recommended End of Therapy & Follow-up

General Follow-Up, All Patients	
Years off therapy	**Evaluation**
First year	-PE every 3 months -CBC, Platelets, creatinine as clinically indicated -CXR every 3 months -Imaging of primary site and nodal basin every 3 months -Other indicated imaging studies as clinically indicated every 3 to 6 months
Second and third years	-PE every 4 months -CXR every 4 months -Imaging of primary site and nodal basin every 4 months -Other indicated imaging studies as clinically indicated every 4 to 6 months
Fourth year	-PE every 6 months -CXR every 6 months -Imaging of primary site and nodal basin every 6 months
Five to ten years	-Annual visit for PE
After ten years	-Maintain annual visit or phone contact if possible. -Record any offspring. -Report any second malignancy.
Additional General Follow-Up for Children	
Height and weight at 6 months to 1 year intervals. Any child showing a growth deceleration of 20-25 percentile units on standard growth charts from the pretreatment height, should be evaluated for thyroid and pituitary function.	
Annual Tanner Staging for girls and boys until maturity (Tanner Stage 5). If there is delayed appearance of secondary sexual maturation, the patient warrants evaluation of gonadal hormone values, i.e., at 10-12 years in girls (FSH, LH and estradiol) and 12-14 years in boys (FSH, LH and testosterone). Consider referral to pediatric endocrinologist. Males: Surveillance of testicular growth in boys at annual visits and initial screening of gonadal hormone values at 14 years of age (FSH, LH and testosterone). Adult values for these hormones are expected at 16-17 years of age. High FSH values suggest damage to the germinal epithelium. Semen analysis can be done in post-pubertal males if requested by the patient or if the patient is receptive to the suggestion by the physician.	
Record annual measurement of testicular size in boys using volume measured by Prader orchidometer if possible. All patients on this study will receive alkylating agents and may accrue damage to the germinal epithelium of the testis.	
Record the onset of menses in girls and regularity of periods. Because of local radiotherapy or alkylating agent therapy, acute ovarian failure may occur in some patients. In cases of delayed menses, referral to a pediatric	

endocrinologist is warranted.
History should include school performance and behavioral disturbances so that early intervention can be made for recognized problems.

Additional follow-up for patients with:	
Head and Neck primaries	1. Annual growth measurements plotted on standard growth curves for all patients 2. Annual ophthalmologic exam by an ophthalmologist if eye was in radiotherapy field. 3. Annual dental exam if maxillary/mandibular sites were in radiotherapy field. 4. If radiotherapy was given to the primary site, get bone x-rays of the primary site every 1-2 years until maturity. Include opposing normal side for comparison of degree of bone hypoplasia. 5. Consider TSH, growth hormone, FSH, LH if clinically indicated
Trunk primaries	1. If radiotherapy was given to primary tumors of the chest take history for exercise intolerance or shortness of breath. 2. Consider echocardiograms every 5 years for potential RT scatter to heart
Abdominal/pelvic primaries	1. Studies appropriate to investigate problems following abdominal/pelvic irradiation, which may include bowel obstruction, chronic diarrhea, inadequate absorption, rectal stenosis, and sphincter problems. 2. Kidney function should be followed in patients receiving para-aortic node irradiation or other abdominal sites encroaching on the kidneys. Annual UA, creatinine, and imaging studies if indicated. 3. If radiotherapy port included the upper femurs/hip joints, slipped capital femoral epiphyses or avascular necrosis may occur several years after therapy. Symptoms are limp or pain. Strongly consider referral to gynecologist/fertility specialist at age 18 years for ovarian function assessment in females who received abdominal/pelvic RT
Genito-urinary primaries	Ongoing follow-up with a pediatric urologist is recommended. 1. Patients without a bladder and with various types of urinary diversion should have kidney function evaluated with imaging studies every 1-2 years for hydronephrosis, evidence of pyelonephritis and renal function. Contrast studies of ileal loops may be necessary to detect kinking, stenosis or reflux of the ureters. 2. Females with uterine or vaginal tumors should be followed for sexual maturation and ovarian failure 3. If radiotherapy was given to the bladder, the volume and function should be assessed by voiding cysto-urethrograms or other imaging studies if indicated. 4. History in post pubescent males should include questions of normal ejaculatory function, particularly in patients with bladder/prostate of paratesticular primaries. 5. Semen analysis
Extremity primaries	1. If radiotherapy was given, appropriate bilateral limb length measurements should be done annually. 2. X-rays of primary sites for bone growth/abnormalities should be done as indicated. Get normal side for comparison. 3. History should address limp, evidence of pain, and other dysfunction of the involved extremity. 4. Pain in the primary site 5-10 years after therapy warrants investigation for the development of secondary bone tumors. This is applicable to all radiation sites.

Second Malignant Neoplasms – the development of a second malignant neoplasm, either leukemia, lymphoma, or solid tumor, should be reported immediately via the eRDE system and CTEP-AERS.

- Known risk familial factors for SMN in RMS include history of neurofibromatosis and Li-Fraumeni – germline p53 mutation.
- All tumors and leukemias should have chromosome analysis on fresh tissue performed at the local institution if possible. Please freeze fresh specimens for additional molecular biology studies.

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

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

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease or relapse.
b) Unacceptable toxicity due to protocol therapy (see Section 5.0).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of planned therapy.
e) Physician determines it is in patient's best interest.
f) Development of a second malignancy.
g) Repeat eligibility studies (if required) prior to the initiation of protocol therapy are outside the parameters required for eligibility (see Section 3.2).
h) Pregnancy.
i) FOXO1 fusion positive with Group IV/Stage 4 disease.
j) Refusal to transfer to Regimen C for patients meeting eligibility requirements for Regimen C.
k) FOXO1 fusion status not determined by the institution by Day 21.
Note: FOXO1 fusion that yield indeterminate or equivocal results will not lead to removal from protocol therapy.
l) Patient's start date of protocol therapy is greater than 42 days from the date of the collection of the material that established the diagnosis of RMS.

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

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Patient Accrual and Expected Duration of Trial

Based on the prior enrollment experience of D9803 and ARST0531, we expect an annual accrual of about 100 patients (including the patients with metastatic FOXO1 fusion negative disease and < 10 years of age and the "low-risk", subset 2 patients, who were previously treated on high- or low-risk studies, respectively).

The sample size for ARST1431 is driven by the primary comparison of event-free survival (EFS: time from study enrollment to the first occurrence of progression, relapse, second malignant neoplasm, or death as a first event). The expected EFS outcome for patients randomized to VAC/VI is a 3-year EFS rate of 60% with a long-term EFS plateau at about 55%. The study is designed to have power of 0.84 (testing at a 1-sided 0.05 Type I level; only improvement with the addition of temsirolimus is of interest) to detect an overall increase in the 3-year EFS from 60% to 74%, an absolute difference in the 3-year EFS of 14%, or a relative risk of failure of 0.59 for comparing VAC/VI with temsirolimus to VAC/VI only. A total of 282 patients and 101 observed events are required to attain the power of 0.84 to detect a relative risk of 0.59:1.00 assuming the property of proportional hazards holds. The sample size of 282 also allows detecting an increase in the overall survival (OS: time from study enrollment to death from any cause) by 10% at 3-year and an OS hazard ratio of 0.47. The power analysis was conducted using software STATA 15 with methods proposed by Lakatos.[84] **Prior to Amendment #3,** we planned to enroll up to 307 patients to Regimens A and B (including 10 initially non-randomly assigned to treatment with temsirolimus in the feasibility phase), to allow for the possibility of an ineligibility rate and the loss to follow-up prior to observing an event of interest of up to 5%.

Patients with institutional histologic classification of ARMS but FOXO1 fusion negative with the following Stage and Group (Stage 1, Group I/II, OR Stage 1, Group III (orbit), OR Stage 2, Group I/II) will remain on study but will receive VAC/VA therapy as per ARST0331. Enrollment of about 5-10 such eligible patients per year is expected (approximately 30 patients in total).

We anticipate that 60 randomized patients will be considered inevaluable because they have completed the 14 cycles of VAC/VI therapy with or without temsirolimus [Regimen A or B] before Amendment #3 to add maintenance therapy is approved. **Thus total enrollment is expected to be up to 397 patients.** We expect the enrollment will complete after about 6 years because the study has been temporarily closed for about 2 years for feasibility evaluation and study amendments. Full information for the randomized comparison is expected to be available about 9 years after enrollment begins.

9.2 Statistical Analysis Methods

Patient subset not eligible for randomization (feasibility phase):
The first ten (10) evaluable patients will be non-randomly assigned to treatment with temsirolimus and enrollment then suspended while these subjects are monitored through protocol Week 12 for adverse events (AEs). The dose of temsirolimus will start at 15 mg/m^2 on Days 1, 8 and 15 of each cycle. The focus will be on evaluating AEs reasonably associated with the addition of temsirolimus. The study will be suspended until these feasibility phase patients have completed the first 12 weeks of treatment; their AE experience will be qualitatively assessed. Should it be determined that the AE

experience is acceptable, randomization will begin. Certain specific protocol defined temsirolimus-associated AEs (see Section 11.10.1) will be monitored in real time via AERs reporting. If the 10 mg/m^2 temsirolimus dose is also found not to be feasible, we will consider discontinuous temsirolimus dosing (Day 1 and 8; omit Day 15) depending upon the observed toxicity profile. **The feasibility phase is complete, effective with Amendment #1A. Dose Level 1 (temsirolimus 15 mg/m^2/day on Days 1, 8, 15) was found to be the safe dose.**

Patient subset eligible for feasibility phase and randomization phase:
Randomization on a 1:1 basis will be stratified by:
1) ERMS Stage 3, Group I/II or Stage 1, Group III (non-orbit)
2) ERMS Stage 2/3, Group III
3) ARMS Stage 1-3, Group I-III
4) ERMS Stage 4, Group IV < 10 years old

The patient AE experience will continue to be monitored during the randomization phase. Study team conference calls will be held after the enrollment of approximately every 50 patients to compare the AE experience of the experimental regimen to that of standard therapy.

The EFS and OS distributions will be estimated using the Kaplan-Meier method and will be compared between the randomized treatment groups using the log-rank test. The primary analysis will be performed when 100% of the expected information (101 observed events) is observed.

Interim efficacy monitoring of outcome for the randomized patients will begin after at least 50 protocol events (50% information) have been observed and then subsequently after 75 (75% information) events have been observed. Efficacy will be monitored using the O'Brien-Fleming-type cumulative error spending function.[85] The table below lists the p-value boundaries for rejecting the null hypothesis (H_0: no improvement in 3-year EFS with the addition of temsirolimus) when the one-sided Type I error rate is 0.05 and power is 0.84. The final analysis will be performed at the 0.0427 significance level.

Efficacy Monitoring	Cumulative Observed Events	Information Content	Significance Level
1	50	50%	0.00557
3	75	75%	0.0219

Interim inefficacy monitoring of the primary EFS outcome for the randomized patients will begin when 50 protocol events (50% information) have been observed.[82] Study termination or treatment modification will be considered if the observed log hazard ratio exceeds zero.

The central pathology review diagnosis and FOXO1 fusion testing (when performed) will be used in all descriptive and outcome analyses in cases where there is discordance between institutional and central pathology review diagnosis. Patients may be excluded from the outcome analyses based upon the central pathology review. Possible scenarios include 1) histologic diagnosis other than RMS or 2) if patients received inappropriate therapy based on institutional FOXO1 testing – ie. Patients with stage 4 disease FOXO1 negative by institution and positive by central review, and received therapy on

ARST1431. In either example, the patient will be excluded from the analytic dataset. Patients who completed the first 14 cycles of therapy before the maintenance therapy is made available will also be considered as inevaluable and will be excluded in the outcome analysis.

Patient subset eligible for non-randomized treatment with VAC/VA therapy as per ARST0331:

ARMS, FOXO1 fusion negative:
1) Stage 1, Group I/II, III (orbit)
2) Stage 2, Group I/II

These patients are expected to have a long-term event-free survival (EFS) of about 85% (what is seen for patients with embryonal histology tumors with these characteristics). With 30 patients, a total of 4.5 failures are expected. The outcome for these patients will be monitored comparing the observed EFS to a fixed outcome which is that expected for similar patients with embryonal histology tumors, namely:

$S(t) = 0.85 + 0.15 * \exp(-t)$

A one sample log-rank test will be used to assess the outcome for these patients. Testing at the 20% level of statistical significance, we will have power of 0.8 to detect a doubling of the risk of failure (long-term EFS 72%). We will perform an analysis when 4 events are observed. Under the null hypothesis, this would be expected to be observed after all patients have been enrolled and follow-up is about complete. Should the true long-term EFS be 72%, more than 8 events total would be expected and the analysis would be expected to be performed about half-way into the planned study.

Exploratory aims
The exploratory aims are primarily descriptive. The aims are:

1. *To estimate the frequency of circulating tumor DNA (ctDNA) at diagnosis and subsequent time-points for patients.*
   We will determine the frequency with which of ctDNA is detected in patients with IR RMS at diagnosis and how these levels change over time with. In addition, the level of ctDNA as a percent of total cell-free DNA will be summarized by reporting the median and range. Since no prior data are available on the rate of positivity nor the change over time, the analysis will be purely descriptive. Changes over time will be plotted to visually determine and compare the trajectories of ctDNA during the early and late stages of therapy.

2. *To compare the outcome of patients based on their FOXO1 partner, by evaluating PAX3 vs. PAX7 in all patients found to be FOXO1 fusion positive.*
   A total of 282 eligible patients are expected to be randomized. Approximately 55% (n~155) are expected to be ERMS. The remaining 45% (n~127) will be ARMS. Ten percent (n~13) of these ARMS will not be evaluated for translocation status; of those remaining, about 85% (n~97) will be fusion positive. Based on Missiaglia 2012, we expect 75% of the fusion positive to be PAX3 (n~73) and 25% to be PAX7 (n~24).[16] The power to detect a difference in 3-year EFS of 20% (PAX3: 50%, PAX7: 70%, based on ARST0531) is 0.83 with

97 FOX01+ cases (~3:1, PAX3 (73) vs PAX7 (24)) and one-sided Type I error rate of 0.15. The power analysis was conducted using software PASS 2008 with methods proposed by Lakatos.[84]

3. *To compare the outcome of patients based on their [F18]-fluorodeoxy-D-glucose-positron emission tomography (FDG-PET) response at Week 9 (positive or negative), as assessed by Deauville Criteria (5-point).*
   Based on Casey 2014, we anticipate that approximately 40% of patients will have a negative PET at Week 9. We expect to compare the median EFS and EFS rates of the 186 FDG-PET responders and 124 non-responders.[61]

4. *To compare the outcome of patients (VAC/VI with or without temsirolimus) who have received maintenance therapy on ARST1431 to those who received VAC/VI on ARST0531.*
   The two-sample log-rank test will be performed.

9.3 Gender and Minority Accrual Estimates

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

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	2			**4**
Asian	4	11			**15**
Native Hawaiian or Other Pacific Islander					
Black or African American	33	26	1	1	**61**
White	125	149	18	25	**317**
More Than One Race					
Total	**164**	**188**	**19**	**26**	**397**

This distribution was derived from ARST0531. All gender and minority groups are included from enrollment, but some of the groups are unlikely to be represented based on the ARST0531 enrollment.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

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

10.2 Response Criteria

For the purposes of this study, patients should have imaging performed at baseline and be re-evaluated for response at Week 9, Week 30*, Week 42*, Week 54*, and end of protocol therapy. (*for patients on Regimens A and B only)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[86]

10.2.1 Definitions

The COG guideline (see diagram below) will be used for measurement of the primary tumor on cross-sectional imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]).

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first response period will also be considered evaluable.)

Evaluable non-target disease response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.2.2 Disease Parameters

10.2.2.1 Measurable disease: Measurable lesions are defined as those that are ≥ 10 mm with CT or MRI. For masses that are smaller than 10 mm, a measurable mass has to be at least twice the slice thickness (< 5 mm) used. All tumor measurements must be recorded in millimeters or decimal fractions of centimeters. The maximal perpendicular diameters in all three planes are recorded.

10.2.2.2 Malignant lymph nodes: To be considered clinically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm) or MRI. At baseline and in follow-up, only the short axis will be measured and followed. (The long axis (craniocaudal) in lymph nodes may be >15 mm but not reflect clinical enlargement.)

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

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

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

10.2.2.4 Target lesions: Target lesion must include the primary site for all non Group I/II patients. Three dimensions must be recorded from cross sectional imaging (CT or MRI) in cm to 1 decimal place or mm.

10.2.2.5 Non-target lesions: Non-target lesions should include lymph nodes for those who have nodal disease. All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required in 3 dimensions (in cm or mm).

10.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations must be obtained within 4 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is required. Evaluation by clinical examination for the purpose of reporting is not acceptable.

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

10.2.3.2 Chest x-ray: Lesions seen on chest x-ray must be confirmed by CT.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible. The utility and potential of diffusion-weighted imaging (DWI) in soft tissue sarcoma diagnosis and therapy response is unknown. Its utility is encouraged.

10.2.3.4 FDG-PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not of optimal diagnostic CT quality for use with RECIST measurements. Thus, the site must document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (**with IV and oral contrast**), in order to use the CT portion of the PET-CT for diagnostic staging and RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

10.2.3.5 Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified

by ultrasound in the course of the study, confirmation by CT or MRI is required.

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

10.2.4 Response Criteria

10.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

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

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

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

10.2.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

10.2.4.3 Response Criteria Using [^{18}F]-FDG-PET:

FDG-PET scans will be evaluated locally using the 5-point Deauville criteria.[51] The use of FDG-PET-MRI can be used instead of FDG-PET-CT, when appropriate.

Score 1	No uptake
Score 2	Uptake ≤ mediastinum
Score 3	Uptake > mediastinum but ≤ liver
Score 4	Moderately increased uptake > liver
Score 5	Markedly increased uptake > liver and/or new lesions

Response will be assessed by the table below:

Baseline Score	**Week 9 Score**	**Response**
1 or 2	1 or 2	SD
1 or 2	> 3	PD
3	> 4	PD
3	1	CR
3	2	PR
4	5	PD
> 3	1 or 2	CR
4	3	PR
5	3 or 4	PR

Patients who have a PET-CT (or FDG PET-MRI) must also have a diagnostic quality CT/MRI with IV/oral contrast. **Overall response must therefore suit both Deauville and RECIST criteria.**

10.2.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Non-Metastatic Patients with Measurable Disease (i.e., Target Disease)

Target Lesion (Primary Tumor)	Non-Target Lesions	New Lesions	PET response (if done)	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	PR or CR	CR	
CR	Non-CR/Non-PD	No	PR	PR	
CR	Not evaluated	No	PR or CR	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR or CR	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD, PR, or CR	SD	
PD	Any	Yes or No	SD or PD	PD	no prior SD, PR or CR
Any	PD**	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
	*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.				

Metastatic Patients with Measurable Disease (i.e., Target Disease)

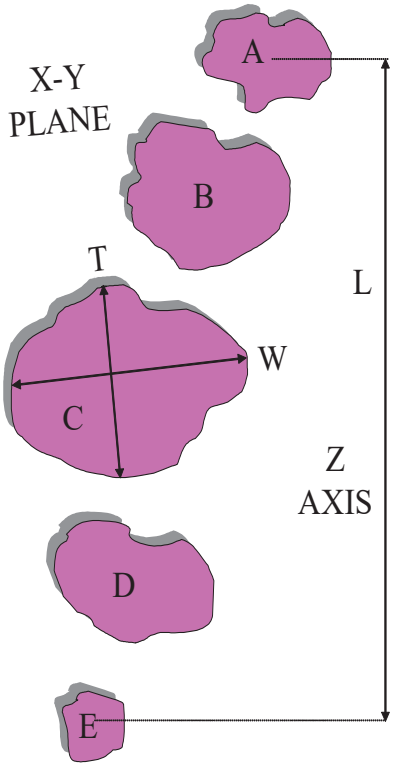
Target Lesion (Primary Tumor)	Target Lesion (Metastatic Site)	Non-Target Lesions	New Lesions	Pet Response (if done)	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	CR	No	PR or CR	CR	
CR	CR	Non-CR/Non-	No	PR or CR	PR	
CR	PR	Not	No	PR or CR	PR	
PR	CR or PR	Non-CR/Non-PD/not	No	PR or CR	PR	
SD	SD	Non-CR/Non-PD/not	No	SD, PR, or CR	SD	
PD	Any	Any	Yes or No	Any	PD	no prior SD, PR or CR
Any	PD	Any	Yes or No	Any	PD	
Any	Any	PD**	Yes or No	Any	PD	
Any	Any	Any	Yes	Any	PD	
	*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.					

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

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

RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")

	Diameter, 2R	Product, (2R)2	Volume, 4/3pR3
Response	**Decrease**	**Decrease**	**Decrease**
	30%	50%	65%
	50%	75%	87%
Disease Progression	**Increase**	**Increase**	**Increase**
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%



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

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

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

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

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

Target lesions at baseline must measure greater than 1 cm; if these target lesions decrease in size to below 1 cm, care should be taken in measuring and inadvertently progressing a patient due to minimal changes in measurement from a nadir value below 1 cm, which may be within measurement error. When multiple primary or metastatic masses are present, all masses will be described. However, up to 5 target masses should be measured, using the same method in subsequent follow up

TECHNICAL GUIDELINES FOR CROSS-SECTIONAL IMAGING COMPUTED TOMOGRAPHY (CT)

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

MAGNETIC RESONANCE IMAGING (MRI)

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

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in

combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-

AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease progression*" in the system organ class (SOC) "*General disorders and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

11.4.5 Second Malignancy

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

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the **"*Pregnancy, puerperium and perinatal conditions*"** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero.*" Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4, "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE

terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI

Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

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

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	**7 Calendar Days**			**24-Hour Notification 5 Calendar Days**
Not resulting in Hospitalization ≥ 24 hrs	**Not Required**		**7 Calendar Days**	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 Protocol Specific Additional Instructions

11.10.1 The following require expedited reporting for patients on **Regimen B**:

- Grade ≥ 3 mucositis
- Grade ≥ 3 pulmonary events
- Grade 3 hyperglycemia (requiring hospitalization for control)
- Grade ≥ 4 hyperglycemia

- Grade ≥ 4 cholesterol high (hypercholesterolemia) or hypertriglyceridemia that does not return to ≤ Grade 2 levels with appropriate medical management within 35 days
- Grade ≥ 3 proteinuria
- Any visceral perforation including fistula or leak (gastrointestinal or any other organ)
- Any intra-abdominal abscess/infection
- Grade ≥ 2 wound dehiscence
- Grade ≥ 3 wound infection - requiring IV antibiotics

11.11 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

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

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

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

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

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 2 and higher Adverse Events.

12.0 RECORDS AND REPORTING

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

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol-and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website (http://ctep.cancer.gov/reporting/cdus.html).

12.2 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the

Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0 SURGICAL GUIDELINES

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

13.1 Data Submission

The Surgical Committee of the STS Committee will evaluate the pretreatment stage assigned, the Clinical Group assignment, the anatomic site designation, and the adherence by the surgeon(s) to these surgical guidelines for quality assurance reporting.

See Section 16.2.1 for instructions regarding the submission of baseline radiology reports to be used for central surgical review. Results from central review will not be returned to the originating institution.

13.2 Pretreatment Clinical Staging

This is a modification of the UICC-TNM staging system and is based on site, size, clinical regional nodal status, and distant spread. The staging is CLINICAL and should be done BY THE RESPONSIBLE PHYSICIAN based on PREOPERATIVE imaging and physical findings. Intraoperative and/or pathologic results should not affect the stage (but will affect Clinical Group).

Size should reflect actual physical examination or imaging measurements. Site designation alters stage and, therefore, treatment assignment. Careful evaluation of clinical and/or imaging findings should precede multidisciplinary site assignment. THE SURGEON IS GENERALLY BEST ABLE to designate site when choice is difficult. See Appendices III, IV, V and VI for Staging/Clinical Grouping Criteria and Site Classification.

13.3 Surgical-Pathologic (Clinical) Group

Clinical Group assignment is based on intraoperative findings and post-operative pathologic status and must include final pathologic verification of margins, residual disease, node involvement, and cytological examination of pleural and peritoneal fluid, and CSF, when applicable. See Appendix IV for Clinical Grouping Criteria.

***It is important to note that the Clinical Group designation is assigned prior to the initiation of chemotherapy and reflect best surgical outcome based on initial operative procedure and any other pre-treatment excision (PRE) but remains unchanged, regardless of any delayed primary excision that may be performed, after the initiation of chemotherapy. Upfront resection should only be considered when there is no loss of function or organ and is not recommended in certain sites including parameningeal tumors.**

13.4 Surgical Principles

The basic principles of wide and complete resection of the primary tumor with a surrounding envelope of normal tissue should be followed at the initial and/or subsequent operations wherever possible and reasonable. Adequate margins of uninvolved tissue are required unless this involves sacrifice of normal tissue that would result in an unacceptable loss of function, form or is not technically feasible. IN OTHER WORDS THE INTENT OF EACH OPERATION SHOULD BE THE COMPLETE EXCISION OF DISEASE WITH NEGATIVE MARGINS UNLESS THIS WOULD RESULT IN UNACCEPTABLE LOSS OF FUNCTION OR FORM. Amputations and other radical procedures are to be avoided whenever possible.

Debulking or partial resection of primary tumors have equivalent outcomes to patients that just have a biopsy and therefore should not be performed. When the neoplasm arises from a somatic muscle, excision of the entire muscle of origin or the entire compartment may not be necessary. However, adequate margins of normal tissue are preferable to leaving gross or microscopic tumor. Any tumor that is removed piecemeal is considered to have microscopic residual disease and should be classified as Clinical Group II.

13.4.1 Margins

The surgeon should mark all margins and orient the specimen at the operative field, so that margin evaluation is precise. Narrow margins are unavoidable in some sites such as in the head and neck. In these situations, the surgeon should take a number of separate biopsies of the “normal” tissue around the margins of resection and these should be marked and submitted separately for pathologic review. Communication with the pathologist is mandatory to assure accuracy of margin examination. The tumor should not be bisected or cut into separate specimens prior to this discussion. Any suspected microscopic or gross residual tumor should be marked in the tumor bed with small titanium clips to aid radiotherapy simulation. Again, any tumor that is removed piecemeal is considered to have microscopic residual disease and should be classified as Clinical Group II.

13.4.2 Node Sampling or Node Dissection

Clinical and/or imaging evaluation of regional lymph nodes should be performed pretreatment and preoperatively by the responsible surgeon and is an important part of pretreatment staging. In those patients with clinically/radiographically enlarged nodes, treatment with chemotherapy and RT is required. However, it is preferable to avoid the need for RT. Therefore, clinically or radiographically enlarged node(s) should be evaluated histologically; patients with no tumor in the node(s) will not require radiation of the regional nodal bed. Failure to obtain pathologic confirmation of nodal disease will necessitate nodal RT for clinically positive nodes. In general, prophylactic radical node dissection, as employed for some other malignancies, is not necessary in childhood RMS. Nodal evaluation by open biopsy is recommended, preferably using sentinel node technique, however core needle biopsy may be appropriate. Identification of the sentinel node by injection of methylene blue dye and technetium 99m at the site of the primary tumor is optimal for nodal evaluation and is strongly recommended as the preferred method for nodal evaluation. If sentinel node evaluation is not

available at your institution then random regional lymph node sampling is the next most appropriate method of surgical evaluation for most sites.

Pathologic evaluation of clinically uninvolved regional nodes is site specific; it is **required** in extremity sites and in boys ≥ 10 years with paratesticular primaries. Radical bilateral regional node dissection, as employed for some other testicular malignancies, is not necessary nor appropriate in childhood paratesticular RMS. However, staging ipsilateral template nerve-sparing retroperitoneal lymph node dissection (SIRPLND) (see description Appendix IV) or ipsilateral infra-renal lymph node sampling of a minimum 7-12 nodes is required for all boys 10 years of age and older with paratesticular RMS and for patients < 10 yrs with positive nodes on CT exam. Data demonstrate that patients with FOXO1 fusion positive RMS and positive nodal disease have a worse prognosis. Therefore, pathologic nodal evaluation of clinically uninvolved nodes in FOXO1 fusion positive patients is strongly encouraged but is not required.[45]

In summary, nodal evaluation is required for all patients with extremity primary tumors and patients with paratesticular primary tumors who are ≥ 10 years of age, and is strongly encouraged for patients with ARMS or clinically involved lymph nodes (regardless of histology). The preferred method of nodal evaluation is sentinel node biopsy whenever available.

13.4.3 Pretreatment Re-excision (PRE)

The initial surgical procedure may have been performed prior to establishing the diagnosis and/or the involvement of the oncology team and may result in a situation in which there is: 1) gross residual tumor, 2) microscopically involved margins, or 3) uncertainty as to margins or residual. This applies even if the microscopic margin is thought to be clear, if the operation and pathologic study were not done as an oncologic procedure as described in Section 13.4.1.

Under these circumstances the concept of Pretreatment Re-excision (PRE) is permissible and should be applied wherever feasible. This means wide re-excision of the previous operative site, including an adequate "envelope" of normal tissue, with careful marking and examination of all margins. This approach is particularly applicable to extremity and trunk lesions although it should be applied wherever possible. In order for this to effect Clinical Group, and therefore prognosis this procedure must be done prior to administration of chemotherapy or RT. Clinical Group assignment will be determined on the basis of pathology from the definitive operation prior to the start of multimodal therapy. The prior procedure(s) will be considered as an excisional biopsy. The conclusion that PRE is not advisable or feasible must be reached by multidisciplinary discussion and the reasons are to be listed on the surgical check sheet.

13.4.4 Delayed Primary Excision (DPE)

Delayed primary excision (DPE) is the term used to describe resection of the primary tumor after the initiation of chemotherapy. In this protocol patients that were not resectable prior to the initiation of chemotherapy may be assessed to determine the feasibility of complete resection of the primary tumor at **Week 9**.

The same principles should be applied as previously described. The intent of each operation should be the complete excision of disease with negative margins unless this would result in unacceptable loss of function or form. Amputations and other radical procedures are to be avoided whenever possible. Debulking operations are absolutely discouraged as they may cause harm and will not result in reduction of RT dose. DPE may be utilized at any site provided this guideline is followed. The benefit of DPE is that it may allow a decreased dose of RT (36-41.4 Gy) to be administered depending on the completeness of disease resection. Recent data demonstrate that local control is equivalent using this paradigm of DPE and reduced dose RT compared to historical controls who received 50.4 Gy radiotherapy alone.[45]

***It is important to note that the Clinical Group designation assigned at the time of enrollment on study remains unchanged regardless of any delayed primary excisions that may be performed.**

13.5 Specific Anatomic Sites

There are pathologic and biologic differences between tumors found in different sites that lead to differences in surgical management.

13.5.1 Head and Neck (Superficial)

Wide excision is appropriate, when feasible, but the possibility of achieving wide margins is generally restricted to those patients with relatively superficial lesions. Cosmetic and functional factors should always be considered.

13.5.2 Orbit

Rhabdomyosarcomas of this site are, in many respects, quite different from those arising in other head and neck sites. The prognosis is better, and non-excisional therapy has become standard. Biopsy generally is followed by chemotherapy and radiation as outlined elsewhere for Stage 1, Clinical Group III disease.

13.5.3 Head and Neck (Parameningeal)

Wide excision is appropriate when feasible, but the possibility of achieving wide margins is generally restricted to those patients with relatively superficial lesions. Cosmetic and functional factors should always be considered.

Delayed primary excision is rarely applicable in these sites. However, craniofacial or skull base resection for anterior skull-base tumors of the nasal areas, paranasal sinuses, temporal fossa, and other such sites should be reserved to those surgical teams expert in its performance and to secondary procedures when tumor persists after initial chemo- and RT.
Node management: See Section 13.4.2

13.5.4 Extremity

Children with extremity rhabdomyosarcoma have a relatively higher incidence of nodal and distant spread and a greater frequency of lesions with unfavorable histology, compared to those with head and neck sites. This observation should

encourage more extensive pretreatment assessment for regional, in-transit, and metastatic disease in these children.

Local resection: Extremity tumors may be amenable to GTR while sparing the involved limb. Radical soft tissue or compartmental excision generally will provide a wide margin of resection that is sufficient for local tumor control. Excision of an entire muscle from origin to insertion or resection of the entire compartment may not be required, depending on the size and invasiveness of the specific tumor.

The high rate of recurrence in extremity lesions is predominantly in the group of children with Group III disease. The definitive pre-treatment operation should be designed to remove all tumor. If there is suspicion or knowledge of residual tumor after the initial resection, PRE may be considered if can be performed with functional preservation; otherwise, DPE may be considered.

Lymph Node Evaluation: Regional node evaluation is an integral part of the staging of patients with extremity RMS and should be performed in each patient (See Section 13.4.2).

Clinically negative nodes: Sentinel node biopsy should be used whenever possible. Otherwise, random inguinal or axillary lymph node sampling is required even when there are no palpable involved nodes. Femoral triangle node sampling, rather than a formal node dissection, is recommended for lower extremity lesions. Lymph node mapping (See Section 13.4.2, above) should be done when feasible.

NOTE: Removal of digits and distal portions of the hand or foot is regarded as a wide local excision, with the Clinical Group determined by the usual criteria.

13.5.5 Chest Wall

An initial biopsy should be performed on chest wall sites since many of these are sarcomas of the Ewing or PNET type and not rhabdomyosarcoma. The proper protocol is determined by histology. The biopsy should always be performed in the long axis of the tumor, i.e., parallel to the ribs. Once a diagnosis is established then definitive resection should be performed is possible. A wide excision should be accomplished, removing the full thickness of the chest wall, including the previous biopsy site, all involved chest wall muscles, and involved ribs. This may require wedge excision of underlying lung. Thoracoscopy is sometimes beneficial to determine the pleural extent of the tumor and the presence of attachments to the underlying lung. It is not necessary to remove the entire rib, but a wide margin should be accomplished, preferably 2 cm. It is not always necessary to remove the rib above and the rib below if a wide margin can be accomplished without so doing. Sometimes, removal of the periosteum of the rib above and the rib below will allow adequate margins while preserving the rib. If necessary, the rib above and rib below can be removed. Reconstruction can be accomplished with mesh. Sometimes, bone struts are necessary, using homografts, rib from the contralateral side, or titanium rib implants.

13.5.6 Genitourinary: Vulva/Vagina/Uterus/Cervix

Complete gross removal of vaginal tumors prior to chemotherapy is frequently impossible when adhering to the surgical treatment paradigm outlined previously. However, the response of vaginal and vulvar tumors to primary chemotherapy is impressive and generally precludes the need for radical surgery, i.e., pelvic exenteration.

Most vaginal tumors should be treated by chemotherapy and local control with RT utilizing brachytherapy whenever feasible. Primary uterine tumors may be less responsive to chemotherapy than those in vaginal sites. For uterine lesions the same surgical treatment guidelines and indications of primary resection, PRE, and DPE should be utilized. For uterine lesions treated by hysterectomy where fertility preservation is generally infeasible, preservation of the distal vagina and ovaries is usually possible. Some polypoid uterine tumors primary in the cervix may be removed without hysterectomy. Oophorectomy is not indicated unless there is gross ovarian involvement with tumor.

Pelvic exenteration or total cystectomy is usually not required for patients with tumors in any of these sites but, if needed, anterior exenteration can usually encompass the tumor.

13.5.7 Paratesticular

Lesions adjacent to the testis or spermatic cord should be removed by orchidectomy and resection of the entire spermatic cord. This requires an inguinal incision and proximal spermatic cord control. Open biopsy or tumor spillage of any kind should be avoided since inguinal recurrence may follow. If biopsy is felt to be necessary prior to orchidectomy, the following should be performed: 1) atraumatic high spermatic cord control; 2) the mobilized testis and cord should be carefully isolated from the operative field with non-permeable drapes; 3) the biopsy site should be closed and the testis covered with a non-permeable dressing (e.g. placed in a sterile baggy) awaiting frozen section report 4) instruments used for the biopsy, gowns and gloves should be discarded from the field; 5) if the biopsy report is positive, the testis and the entire cord including the atraumatic clamp should be immediately removed without removing the protective dressing (baggy or the atraumatic clamp); 6) the field should be thoroughly irrigated. Any unprotected spillage should be considered Clinical Group IIa. Tumor invasion of the scrotum should be treated with hemiscrotectomy during resection of the primary tumor. However, previous transcrotal biopsy or resection does not require hemiscrotectomy.

Nodal Management
All patients with paratesticular primary tumors should have thin cut (< 10 yr. 5 mm, ≥ 10 yr. 7 mm) abdominal and pelvic CT scans with double contrast to evaluate for evidence of nodal involvement. Regional lymph nodes are the ipsilateral iliac and retroperitoneal nodes up to the hilum of the ipsilateral kidney.

For patients who are less than 10 years of age and whose CT scans show no evidence of lymph node enlargement, retroperitoneal node dissection is not necessary. Patients > 10 years old or with positive nodes on CT scan, regardless

of age, should have surgical assessment of retroperitoneal nodes; a minimum of 7-12 nodes are required to adequately determine the presence or absence of nodal pathology. This number of nodes may be obtained either by nodal sampling of the ipsilateral infrarenal nodes, especially by the renal vein, or by a nerve sparing template dissection. The dissection recommended is an ipsilateral nerve sparing resection of the spermatic vessels and associated node-bearing tissue to the level of the renal vein using an abdominal or laparoscopic approach. Complete bilateral dissection has the disadvantage of the significant sequellae of bilateral sympathetic nerve resection and is not required. The "top" node of the dissection, i.e., at the level of the renal vein, should be marked for the pathologist. Alternatively, sentinel node resection to ensure removal of the sentinel node and then further sampling is acceptable. Any positive node(s) on CT scan not completely removed places the patient in Clinical Group III.

These lesions rarely involve inguinal lymph nodes, except when there is scrotal invasion by the tumor. In this instance, i.e., with scrotal involvement, inguinal nodes should be biopsied. They are, however, not considered regional lymph nodes and the patient would be in Clinical Group IV, if they were positive.

13.5.8 Genitourinary: Bladder/Prostate

Tumors in these sites will be surgically managed as per the general principles outlined and receive subsequent therapy based on Stage and Clinical Group. Rarely, the tumor can (and should) be completely removed at presentation with preservation of bladder and urethral function. The initial operative procedure in most patients consists of a biopsy, which is usually performed endoscopically, perineally, or suprapubically, but may be by laparotomy. Pretreatment staging requires determination of the extent and size of the tumor by CT or MRI. If laparotomy is performed, iliac and paraaortic node sampling should be included, as well as biopsy of any other clinically involved nodes. Partial cystectomy, when applicable, has resulted in a similar survival rate and a higher rate of functional bladders when compared to other treatment options. This is usually applied to dome-of-bladder tumors but may occasionally be applicable to the more distal bladder and may require ureteral reimplantation or bladder augmentation. This technique should be used whenever appropriate and feasible, even in patients with distant spread. Timing can be either before chemotherapy (Clinical Group I or II) or as DPE. Bladder salvage is an important goal of therapy for tumors arising in this site and can be anticipated in 50-60% of patients. Complete response to non-operative therapy may not be rapid and, as long as there is partial response, radical resection procedures (e.g. pelvic exenteration) should be delayed.

Urinary tract obstruction: Should obstructive uropathy occur prior to or during therapy, percutaneous, endoscopic or open decompression should not be delayed.

Prostatectomy: Adequate but incomplete response of prostatic tumors to therapy may allow prostatectomy to be performed with complete gross and/or microscopic tumor removal and preservation of the urethra and bladder. This is rare.

13.5.9 Other sites

Paraspinal/perineal/intrathoracic/retroperitoneum/abdominal wall:
Rhabdomyosarcoma at these sites are usually large cannot be completely removed because of their close association with other vital structures. Regardless tumors at these sites follow the same principles of surgical intervention outlined previously. The intent of each operation (initial resection, PRE, DPE) should be the complete excision of disease with negative margins unless this would result in unacceptable loss of function or form. Debulking or partial resection of primary tumors have equivalent outcomes to patients that just have a biopsy and therefore are discouraged.

Biliary tract:
Tumors at this site respond relatively well with multimodal therapy without aggressive surgery. The primary role of surgery is for diagnosis and staging. Relief of biliary obstruction is likely to occur in response to chemotherapy: therefore attempts to establish bile drainage with aggressive surgery are unnecessary and are likely to result in an increase in morbidity. Likewise, external drainage of the biliary tract while the patient is immunosuppressed on chemotherapy appears to be associated with a high incidence of sepsis and should be avoided if possible. Most of these patients will have gross residual tumor.

13.5.10 Tissue Handling

The pathologist should be immediately notified and will deal with the specimen as defined in the Pathology Guidelines (See Section 14.0).

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

14.1 Tissue Specimens/Pathology Review at Time of Diagnosis, Delayed Primary Excision, Relapse and Autopsy

All patients enrolling on this protocol require institutional histological confirmation of RMS and institutional molecular confirmation of fusion status at the time of original diagnosis. **Patients are required to submit tumor samples collected at original diagnosis and are encouraged to submit tumor samples at DPE, relapse, or autopsy.**

14.1.1 Suggested Minimal Histologic Sampling:

a. Incisional biopsy material - If practical, all tissues should be processed. Needle biopsy specimens are the least desirable for classification of primary tumors. If needle biopsies are obtained, it is helpful to divide the tissue into multiple cassettes (one to two cores per cassette) for optimum conservation of tissue.

b. Tumor excision – Representative tissue blocks are needed from various regions of the mass for tumor classification. Adequate sampling requires approximately 1 section per cm diameter of tumor. The narrowest tissue margins should be blocked to satisfy the examiner of complete or incomplete tumor excision.

14.2 Pathology Review Requirements

14.2.1 Retrospective Central Review of Diagnostic Samples

All patients enrolling on this protocol will undergo a non-rapid, retrospective pathology review to confirm histologic classification.

Note: As of Amendment #4, the test to determine the concordance rate between institutional and central *FOXO1* fusion status has been completed. To confirm the anticipated high concordance rate between institutional and central *FOXO1* fusion status, the first 150 patients enrolled on ARST1431 will have *FOXO1* fusion status determined by FISH at the Biopathology Center. Centrally determined *FOXO1* fusion status and results of the pathology review will NOT be returned to the referring institution.

14.2.2 Retrospective Central Review at Time of DPE, Relapse, or Autopsy

A pathology review will be performed on DPE, relapse, or autopsy specimens submitted for review. This is also a non-rapid, retrospective review and results will not be returned to the referring institution.

Materials to send:

Send at the time of study entry, DPE, relapse, or autopsy: **Representative formalin-fixed paraffin blocks, and H&E stained slides:** • 1 H&E section of all available blocks **and** • 1-2 representative FFPE block(s). If blocks absolutely cannot be sent, then submit 20 plus-charged (polarized) unstained sections (4 micron section thickness) from 1-2 representative blocks in addition to the H&E stained slides listed above. The unstained slides from each block must be cut sequentially and will be used for immunoperoxidase and other special studies. Paraffin blocks will only be returned upon request. **Documentation including:** Institutional Final Pathology Report Institutional Cytogenetics/Molecular Report Institutional Operative Report (even for biopsy only) COG Specimen Transmittal Form	**All reports must be labeled with the patient's COG patient identification number. Blocks or slides for central review must be labeled with the COG patient identification number, surgical pathology ID, and block number from the corresponding pathology report and specimen type (primary or metastatic).** Label the parcel, as applicable, with "Diagnostic Sample Review", "Delayed Primary Excision Review", "Relapse Review" or "Autopsy Review". Please use the phone number listed below on all packages shipped to the Biopathology Center. **Send all pathology central review materials via regular mail or using the institution's courier account to:** Biopathology Center Nationwide Children's Hospital 700 Children's Drive WA1340 Columbus, OH 43205 **Phone: (614) 722-2865** FAX: (614) 722-2897 Email: BPCParaffinTeam@nationwidechildrens.org

The study review pathologists are:
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15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

Use of diagnostic pretreatment tumor tissue will be prioritized in the following order:

1) H&E stained slide for central pathology review
2) Myogenin immunohistochemistry and additional immunohistochemical staining for fusion variants
3) PAX3/7 fusion testing (in FOXO1 fusion positive cases)
4) Correlation with circulating tumor DNA (if patient consented)
5) Deeper analysis of fusion variants by FISH and /or targeted sequencing

15.1 Identification of Fusion Partners and Variant Gene Fusions in RMS

We aim to identify fusion variant RMS cases to determine their clinicopathologic characteristics compared to traditional fusion negative and FOXO1 fusion positive tumors. There are four components to this correlative study:

i) Central pathology review will confirm the pathologic diagnosis and identify histologic features unique to fusion type.
ii) Use of formalin-fixed, paraffin-embedded tissue sections for immunohistochemical staining including a panel for 3 antibodies (myogenin, AP2b, and HMGA2). This will identify tumors which may harbor a fusion protein that does not include the FOXO1 gene, which would be detected by institutional FISH or other molecular techniques.
iii) All FOXO1 fusion positive cases will undergo PAX3 and PAX7 testing by FISH to identify common fusion partners.
iv) Cases suspicious for variant gene fusions after immunohistochemical analysis, institutional FOXO1 results and PAX3/7 testing will be further analyzed by an

indepth FISH and/or targeted sequencing panel to identify any of the currently known fusion variants implicated in RMS tumorigenesis.

15.1.1 Sample Collection and Processing

See Section 14.2 for required samples and shipping instructions.

Note: The availability of adequate tumor tissue (pretreatment paraffin-embedded tumor material (block) or unstained slides) as defined in Section 14.2.2 is required for study entry.

COG sites: if adequate representative blocks or stained and unstained slides have been submitted already on APEC14B1 (Project:EveryChild), additional tissue may not be required. If blocks or slides submitted via APEC14B1 are to be used for ARST1431 then you MUST communicate that to the BPC either through documentation on the APEC14B1 transmittal form or by email to bpcbank@nationwidechildrens.org. If the material submitted for APEC14B1 does not meet the requirements for ARST1431, then the Biopathology Center will request additional material for ARST1431.

15.1.2 Identification of Fusion Positive RMS

The following workflow will be used:

Prospective cases collected on ARST1431 will be processed, as material is received at the BPC, for fusion variants implicated in RMS tumorigenesis.

Unstained slides will be processed at the BPC.
For all cases enrolled, if an H&E slide is not submitted, one unstained slide will be stained with hematoxylin and eosin for routine histologic examination on subsequent central review.

For all cases enrolled, three (3) unstained slides will be sent to Erin Rudzinski, MD at Seattle Children's Hospital for immunohistochemical staining with antibodies to AP2b, HMGA2, and myogenin. Myogenin staining is essential for both central pathology review as well as an integral component of the immunohistochemical surrogate fusion panel.

For all cases with confirmed FOXO1 fusion, two to four (2-4) unstained slides will be used by the Biopathology Center for analysis of PAX3/7 by FISH to identify common fusion partners.

For cases with a discrepancy between the immunohistochemical panel, FOXO1 fusion result or PAX3/7 fusion result, 6 additional unstained slides will be sent to Julia Bridge at the University of Nebraska Medical Center and/or the Translational Genomics Research Institute (TGen) for comprehensive analysis of all fusion variants described in rhabdomyosarcoma. For all cases, immunohistochemical and molecular data will be returned to the COG Statistics and Data Center (SDC).

15.1.3 Banking of Leftover Specimens

If the patient consents, any specimens leftover after the required studies described above in Section 15.1 have been performed will be banked at the BPC for future research studies.

15.2 Circulating Tumor DNA (ctDNA)

Patient consent is required for participation in this correlative study.

15.2.1 Streck Cell-Free DNA BCT Tube Ordering

IMPORTANT: Streck Cell-Free DNA BCT tubes can be ordered via the BPC Kit Management system. These tubes are provided to sites in North America who have patients who have consented to the ctDNA study. Funding for these tubes is specific to ARST1431, so they must be used only for patients enrolled on ARST1431. The Kit Management System can be accessed via the following link: https://ricapps.nationwidechildrens.org/KitManagement/Auth/Login. You must select ARST1431 as the protocol when ordering Streck tubes for ARST1431 patients. Tubes are shipped ground, so please allow 3-5 business days for receipt.

15.2.2 Specimen Collection

- 2 of the unstained pretreatment tumor slides submitted as detailed in Section 14.2 will be used for this study.
- Peripheral blood samples should be obtained as follows:
  - Blood should be collected in Streck Cell-Free DNA BCT tubes
  - For patients > 25 kg: Collect 20 mL (10 mL per tube x 2 tubes)
  - For patients > 2 kg but < 25 kg: Collect 10 mL (one tube)
  - For patients < 2 kg: Research samples will not be collected

In all cases, blood draw volumes should strictly adhere to institutional limitations, taking other blood draws into consideration. However, if a reduction in volume is required, samples should be collected in 10 mL increments (ie. 0, 10, or 20 mL should be collected such that each Streck Cell-Free DNA BCT is completely filled). After collection, blood samples in Streck tubes should be stored and shipped at **room temperature**, never on ice or refrigerated.

15.2.3 Time Points for ctDNA Blood Sample Collection

If patient consents for this biology study, peripheral blood will be required at the following time points:

- Pre-Treatment (within 7 days prior to treatment start)*
- Weeks 4, 7, and 19 prior to the delivery of chemotherapy on that day
- Week 42 evaluation (within 1 week of CT/MRI evaluation; only for Regimens A and B)
- End of protocol therapy evaluation (within 1 week of CT/MRI evaluation; for all patients including Regimen C)
- At relapse/progression

*All patients should submit one pretreatment blood sample collected in a Streck tube.

- If the patient also consented to Part A of APEC14B1, then the pretreatment sample must be submitted under APEC14B1 rather than ARST1431.
- If the patient did not consent to Part A of APEC14B1, then the pretreatment sample is submitted through ARST1431.

Only one pretreatment specimen should be collected per patient so if a pretreatment blood sample was already collected in a Streck tube and submitted under APEC14B1 prior to enrollment on ARST1431, then an additional pretreatment blood sample should not be collected. If the pretreatment blood sample is missed, samples should still be collected for all subsequent timepoints.

Note: If treatment is delayed or held, please collect the blood on the day that treatment was scheduled to be given and not the day when treatment is actually delivered.

Established institutional guideline should be followed for blood collection via vascular access devices. Heparin should be avoided in pre-collection flush procedures. In patients with heparinized central lines, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

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

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

15.2.4 Specimen Labeling and Shipment

Streck tubes must be labeled:

- COG patient ID number
- BPC number
- Specimen type (blood)
- Collection date.

Streck tubes should be shipped by FedEx Priority Overnight at room temperature to the COG Biopathology Center for immediate separation, extraction, and storage of plasma and cellular DNA. Samples should be shipped from Monday through Friday for Tuesday through Saturday delivery. If blood is collected in the Streck tube over the weekend or on the day before a holiday, the sample can be stored at room temperature until shipped on the next business day.

North American sites will access the Kit Management application to print a FedEx shipping label for shipping blood in Streck tubes. A ctDNA Specimen Transmittal form must be included with each shipment. The time point listed on the transmittal form must be written on the transmittal form exactly as listed above.

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol ARST1431
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865

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

For questions about this correlative study, please contact the study chair, Dr. Gupta. For questions about sample processing and shipping, please contact the BPC directly.

15.2.5 Methodology

Tumor tissue (consisting of a minimum of 2 unstained slides) or extracted nucleic acids, plasma and extracted germline DNA will be sent from the BPC to Dr. Crompton at Dana-Farber Cancer Institute. Extracted nucleic acids from these samples will be subjected to hybrid capture sequencing and low coverage whole-genome sequencing (WGS) to identify the patient-specific somatic variants in the tumors and detect the presence of circulating tumor DNA (ctDNA) in the plasma.[87] For fusion positive or MYOD1 positive samples, data from paneled sequencing and the remaining nucleic acids from the tumor and plasma will be shared with Dr. Shukla at Memorial Sloan-Kettering Cancer Center (MSKCC) for the development of patient-specific digital PCR primers and detection of ctDNA. For fusion negative, MYOD1 negative samples, remaining tumor, plasma and germline nucleic acid material will be shared with Dr. Avanthi Shah at UCSF to identify somatic point mutations by CAPP-Seq to detect the presence of ctDNA in the plasma.[88]

Sensitivity of each assay (hybrid capture sequencing, low-passage WGS, CAPP-Seq and ddPCR) will be determined for plasma samples obtained at diagnosis (prior to the initiation of therapy) and for samples serially collected during therapy. After the above aims have been completed, additional nucleic acids will then be subjected to deep next-generation sequencing (including but not restricted to whole-exome sequencing) to determine whether detection of a greater number of somatic single-nucleotide variants is better able to detect the presence of ctDNA and whether we can detect patterns of tumor heterogeneity and evolution in ctDNA from multiple timepoints.

15.2.6 Banking of Leftover Specimens

If the patient consents, any specimens leftover after the research studies described above in Section 15.2 have been performed will be banked at the BPC for future research studies.

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

16.1 Goals of Diagnostic Imaging

Routine diagnostic imaging will be performed at diagnosis, during treatment and follow-up, and at the time of suspected tumor progression/recurrence to detect and characterize sites of disease involvement.

Full body FDG PET-CT (FDG PET-MRI) is optional (study consent is required). Central review of imaging studies will not be performed for decision making in this study.

16.2 Timing of Diagnostic Imaging

16.2.1 Required Imaging Time Points

- Regimens A and B:
  - At study enrollment*
  - At Week 9
  - Immediately post-operatively (only in cases undergoing DPE)
  - At Week 30
  - At Week 42 (end of VAC/VI therapy +/- temsirolimus)
  - At Week 54 (end of maintenance Cycle 3)
  - At end of protocol therapy
  - At the time of suspected tumor progression/recurrence
  - At the time of diagnosis of a second malignant neoplasm

- Regimen C:
  - At study enrollment*
  - At Week 9
  - Immediately post-operatively (only in cases undergoing DPE)
  - At end of protocol therapy
  - At the time of suspected tumor progression/recurrence
  - At the time of diagnosis of a second malignant neoplasm

Central review of diagnostic imaging studies will not be obtained at the above time points.

***Note:** All baseline radiology scans and reports should be submitted to IROC Rhode Island at the time of study enrollment. These scans and reports will be made available to the central surgical reviewers; results will not be returned to

the institution. Scans and reports can be uploaded via TRIAD, sFTP, or emailed to DataSubmission@qarc.org. Please label all materials with protocol & case #.

16.2.2 Recommended Imaging Time Points Post-Treatment

Please see Section 7.1 for required imaging following completion of therapy.

16.3 **Required Imaging Studies**

- Primary tumor – To be evaluated at the time points specified in using:
  - CT imaging *or* MR imaging *or* FDG-PET with diagnostic quality CT/MRI.

NOTE: If more than one imaging modality was acquired, please submit all available pre-study images.

In order to standardize target volume definition using better tumor and soft tissue definition, an MRI of the primary site is highly preferred unless a patient has contraindications to MRI (e.g., implanted pacemaker, neurostimulator, aneurysm clips, metallic foreign objects, or other contra-indications).

- Metastatic sites
  - CT or MR imaging of the draining lymph node bed. At study enrollment and at the time of suspected tumor progression/recurrence; repeat at each follow-up visit only if adenopathy identified on baseline study.
  - Chest CT - At the time points specified in Section 16.2.1
  - Other imaging studies - Any imaging studies in patients other than the above that identify sites of disease that were not detected on other scans should be repeated at the time points specified in Section 16.2.1.

Note: the same imaging modality should be used at each evaluation. If possible, patients should be imaged on the same scanner for the baseline and follow-up studies.

16.4 **Diagnostic Imaging Guidelines**

For PET scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of 18F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found in the consensus statement by Shankar and colleagues (http://jnm.snmjournals.org/content/47/6/1059.long).

Note: the guidelines below are recommendations only and are not intended to replace institutional guidelines.

Assessment of the size and features of rhabdomyosarcoma requires cross-sectional imaging such as computed tomography (CT) and/or magnetic resonance (MR) imaging. The optimal imaging modality is selected based on the anatomic site of involvement, with the goal of evaluating the tumor volume and assessing tissue characteristics of the lesion [such as x-ray attenuation or density (CT) or signal intensity (MR)]. Usually, direct

axial (rarely coronal) images are obtained on CT imaging, and images are acquired in 2 or more planes perpendicular to each other on MR imaging.

In general, MR imaging is superior in evaluating tumors located in the soft tissues of the trunk and extremities, and may also be useful in retroperitoneal and pelvic sites. CT imaging is preferred for evaluation of pulmonary nodules and may be helpful for intraabdominal and pelvic tumors. The same modality should be used at study enrollment and at each follow up visit to allow fair comparisons to be made. [^{18}F]FDG imaging is optional but is encouraged to allow an assessment of the value of this modality in identifying sites of disease and measuring tumor response.

16.4.1 CT Imaging

Breath-hold technique should be used in cooperative patients to reduce motion artifact and spatial misregistration from respiration. In patients incapable of immobilization, conscious sedation should be considered when clinically feasible to minimize image degradation from patient motion.

Use of Contrast Medium

Whether intravenous or enteral (oral and rectal) contrast medium is used is determined by the location and density of the lesion and the surrounding normal tissues. Vascular opacification helps to identify vascular encasement, displacement, and tumor margin. Tumor enhancement is absent in areas of necrosis or cystic degeneration before or after treatment. Enteral contrast helps to differentiate tumor from the surrounding opacified bowel. A dose of 2 mL/kg of ionic or non-ionic contrast is usually given intravenously. The amount of enteral contrast varies with patient's age and tolerance to oral (or nasogastric) or rectal administration.

Technical Guidelines

Technical parameters for CT scans should be chosen to achieve the best compromise between image quality, scan time, and patient radiation dose, and may vary based on the imaging equipment and expertise available at each institution. Image acquisition parameters include beam collimation, detector size configuration, table increment per detector rotation (pitch), gantry rotation time, reconstructed image thickness and spacing, contrast dose, contrast injection rate, image acquisition timing relative to contrast administration, and radiation exposure factors (kVp and tube current). Image display parameters include field-of-view, window width and level, and hardcopy or softcopy format (e.g., film or computer workstation monitors). Follow-up studies should be performed and interpreted with parameters as close as possible to the baseline study. For example, lesions should be measured at the same window width and level settings and reconstruction intervals.

The selection of optimal slice thickness is influenced by the patient's size. The use of thinner sections to increase spatial resolution may be valuable in certain settings, such as the evaluation of questionable small lesions, but incurs the expense of increased radiation dose and should be used judiciously. As a general guideline, radiation dose can be minimized and scan coverage maximized with helical/spiral CT by increasing pitch. For single detector CT (SDCT), pitch values in the range of 1.4 - 2.0 are usually optimal, with

degradation of longitudinal axis resolution limiting the use of higher values. For multiple detector CT (MDCT), a more complex relationship between pitch and radiation dose exists and the optimal value will vary with the type of scanner. Reconstruction intervals generally should be set to equal the slice thickness, although overlapping reconstructions with small interscan spacing may be used to increase lesion conspicuity in selected circumstances, such as in the evaluation of small lesions that would otherwise be obscured by volume averaging. The gantry rotation time of scanners can vary from 0.42-1.0 second, and the more rapid rotation times should be chosen in pediatric patients to reduce scan time and motion artifact. Most pediatric body CT is performed with tube voltage in the range of 80-120 kVp. To keep radiation dose as low as reasonably achievable, the tube current (mA) and gantry rotation time should be set as low as possible while maintaining lesion conspicuity for diagnostic quality images. In general, the smaller and younger the patient, the lower the mAs should be set. The specific settings should be decided for the encountered range of patient sizes and ages at each institution based upon experience with the available CT scanning equipment and published recommendations.

16.4.2 MR Imaging

MR imaging allows a better evaluation of soft tissues than CT imaging by identifying differences in T1, T2, and proton density between normal tissues and tumor tissue. The signal amplitude detected is also affected by the presence of motion (such as flow), system noise, and pulse sequence used. The most commonly used pulse sequences in clinical MRI imaging include T1- and T2-weighted, and fat-suppressed short-tau inversion recovery (STIR) pulse sequences. Fat- suppressed T1-weighted pulse sequence is used in cases where the tumor is surrounded by fat (such as in subcutaneous tissues). The cellularity of a tumor, which may vary with the type of tumor and change in response to therapy, can be studied with diffusion-weighted imaging (optional).

Breathhold techniques can be used for patients who are old enough to cooperate and this technique can reduce the scan time. In patients incapable of immobilization, conscious sedation should be considered when clinically feasible to minimize image degradation from patient motion. Initial and follow-up studies should use the same pulse sequences, scanning plane, and IV contrast.

Use of Contrast Medium

The use of intravenous contrast agent (0.1 mmol/kg body weight gadolinium-DTPA) may or may not enhance the differentiation of tumor from the surrounding normal tissues. However, IV contrast is required for MRI scans of the primary tumor obtained at study enrollment and at Weeks 13 and 43). IV contrast is required in these settings to enable an accurate assessment of tumor necrosis (and therefore tumor response). In this study, necrosis is defined as the absence of contrast enhancement.

16.4.3 Recommendations for FDG-PET and Diffuse-Weighted MR Imaging Studies

[^{18}F]–2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) Positron Emission Tomography (FDG-PET) imaging is optional and requires consent but is encouraged. Please refer to Appendix XIII for pediatric FDG-PET/CT guidelines.

The following generally accepted FDG-PET issues and items should be adhered to as much as possible in this clinical trial to allow for uniformity of inter- and intra-patient FDG-PET imaging and analysis needed for this study:

Summary of Definite Requirements

1) Patients should be fasted for at least 4 hours before [^{18}F]FDG administration.
2) PET imaging should begin at 60 ± 10 min after injection of [^{18}F]FDG.
3) Maximum recommended dose of [^{18}F]FDG for children is 12 mCi and 20 mCi for adults or as per institutional guidelines.
4) For follow-up PET imaging of the same patient, all attempts should be made to image the patient on the same PET/CT (PET/MRI) scanner.
5) The following PET parameters should be recorded for each imaging session:
   a. Patient's weight and height
   b. [^{18}F]FDG dose and time of administration
   c. Start time of PET imaging
   d. Serum glucose level (or verify that level is less than 200 mg/dL)
   e. Use of low-dose propranolol or fentanyl for pharmacologic suppression of activated brown adipose tissue
   f. Time (in days) from last infusion of temsirolimus for patients on Regimen B.
6) Institutional radiologist or nuclear medicine physician assessment and report of the PET scan for qualitative visual classification (5-point Deauville criteria) and anatomical location of the primary tumor site only.
   a. This visual PET criteria are scored according to uptake in the primary tumor site: (1) no uptake, (2) uptake ≤ mediastinal blood pool, (3) > mediastinal blood pool but ≤ liver, (4) moderately increased uptake > liver, or (5) markedly increased uptake > liver and/or new lesions. Physiologic [^{18}F]FDG liver uptake is used as a reference with score of 1 to 3 regarded as PET negative and 4 or 5 as positive.
7) Temsirolimus is an inhibitor of GLUT1 and other glucose transporters into cells.[81] An FDG-PET scan taken shortly after temsirolimus infusion could demonstrate decreased [^{18}F]FDG uptake, as a pharmacodynamic effect of the mTOR inhibitor, separate from any anti-tumor activity. Since temsirolimus has a half-life of 17.3 hours, FDG-PET scans should not be performed within 4 days after infusion of the drug.

Summary of Other Optional Recommendations

1) State some type of annual scanner QC/QA.
   Recommend either:
   - American College of Radiology (ACR) - Nuclear Medicine/PET accreditation Program

(https://www.acraccreditation.org/Modalities/Nuclear-Medicine-and-PET) or

- Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) PET accreditation (http://www.icanl.org/icanl/index.htm)

a) If either of these PET QC/QA are not used in your facility, please provide your PET scanner QC/QA accreditation.

2) [^{18}F]FDG dosing requirements
   a) Confirm dosing in recommended dosing is in the range of 0.10-0.14 mCi/kg for children.
   b) Confirm dosing in recommended dosing is in the range of 5-20 mCi or per institutional guidelines for adults.
   c) If recommended dose range is not used, state institutional pediatric PET dosing formula or schema.

3) Prior to and following [^{18}F]FDG injection, the patient is kept at rest in a warm room until the time of imaging to minimize [^{18}F]FDG uptake in activated brown adipose tissue or other physiologic [^{18}F]FDG artifacts.

Pregnancy

All female patients ≥ 10 years of age should be asked about their pregnancy potential prior to [^{18}F]FDG injection. Patients who are pregnant or breast feeding will only be injected if the FDG-PET scan is deemed necessary for clinical management by the patients' primary physician and the patient agrees to the study. Patients who are sexually active and unsure of their pregnancy status should undergo a urine or serum pregnancy test prior to [^{18}F]FDG injection. Pregnant guardians should not be allowed in the [^{18}F]FDG uptake room.

Recommended Technique

Patients should be fasted for at least 4 hours before imaging, except for water and non calorie containing beverages. If the patient is going to receive sedation, then sedation/anesthesia guidelines may be more stringent. Total parenteral nutrition and intravenous fluids containing glucose should also be discontinued for at least 4 hours before the study. The patient should be well hydrated (oral or intravenous fluid administration) before administration of [^{18}F]FDG. Fluids administered for hydration should not contain glucose.

It is suggested that the patient's measured height and weight on the day of the FDG-PET scan be recorded for each imaging session.

If intravenous access is not already in place, this should be obtained, typically in the antecubital fossa, for patient hydration (if needed), determination of serum glucose and [^{18}F]FDG administration. Good hydration is required as the primary route of [^{18}F]FDG excretion is renal. The patient should drink water or receive intravenous fluids after injection to promote urinary [^{18}F]FDG excretion.

Venous serum blood glucose will be measured and recorded just prior to injection of the [^{18}F]FDG and should be ≤ 200 mg/dL.

Diabetic patients should be scheduled in the morning after an overnight fast before the first meal, and dose of insulin should be titrated appropriately in consultation with the patient's referring physician to keep the serum glucose ≤ 200 mg/dL at the time of scheduled [^{18}F]FDG injection. If the serum glucose is significantly elevated (> 200 mg/dL) then the test should be rescheduled if at all possible with better glucose control or, if necessary, insulin can be used to achieve normoglycemia. After regular insulin the patient should wait 2-4 hours (with ultra short acting insulin 1-2 hours) prior to administration of [^{18}F]FDG in order to minimize physiologic skeletal muscle and myocardial [^{18}F]FDG uptake.

In patients with tumors in the pelvis, placement of a Foley catheter is recommended if needed to assist bladder emptying. Patients in whom a Foley catheter is not placed should be asked to void immediately prior to imaging in order to minimize bladder activity and to reduce their radiation exposure.

[^{18}F]FDG Dosing and Injection

Children: [^{18}F]FDG is administered intravenously at a dose of 0.10-0.14 mCi/kg with a minimum dose of 1.0 mCi and maximum dose of 12 mCi.

Adults: [^{18}F]FDG is administered intravenously at a dose of 5 - 20 mCi or per institutional guidelines.

After injection, the patient is kept at rest in a warm room until imaging. After voiding the bladder, whole-body imaging should begin at 60 ± 10 min after injection of [^{18}F]FDG. For serial scans of the same patient it is important to start the PET scan with the same delay time after injection of the [^{18}F]FDG radiotracer. Therefore, it is recommended that all subsequent PET scans have approximately the same delay time (± 10 min) as the baseline scan. The use of low-dose propranolol or fentanyl for pharmacologic suppression of [^{18}F]FDG uptake in activated brown adipose tissue can be applied as per institutional protocol and recorded.

The net injected [^{18}F]FDG dose and time of injection should be recorded. The peripheral IV or central line injection site location should also be recorded.

PET Scanning Protocol

A whole body FDG-PET imaging protocol is utilized, covering the area from the base of skull/top of the ears to the proximal/mid-thigh, just below the pubis. If there is suspicion of involvement in the lower extremities, skull, or skull contents, the volume that is imaged may be expanded. The patient will be positioned supine, with arms comfortably positioned above the head if at all possible (to limit attenuation of the thorax), or at the side of the patient if necessary. Scans should proceed upward from the pelvis to diminish the effects of accumulation of [^{18}F]FDG activity in the bladder.

CT scanning matching the areas covered by the emission scan will need to be performed for attenuation correction of the emission scan. This will be done after injection of [^{18}F]FDG. The CT can be performed either with or without intravenous contrast. It is recommended that the COG institution adjust the CT dose used for attenuation correction to limit the CT radiation dose to the patient

without significantly affecting PET quality or anatomic correlation to CT. Please refer to protocol recommendations from the Image Gently website (http://www.imagegently.org/Home.aspx).

The 511 KeV-annihilation photons, produced by interaction of positrons with electrons, are imaged. Because of the short physical half-life of ^{18}F of 1.8 hours and the high photon energy of 511 KeV, FDG-PET imaging may follow bone or gallium scintigraphy, or a MUGA study on the same day (that use lower energy photons) or FDG-PET imaging may be performed on the day preceding any of these other nuclear medicine studies.

The following acquisition parameters should be recorded: start time of emission scan and type of transmission scan.

The PET images should be reconstructed with and without attenuation correction. For serial scans of the same patient, image reconstruction techniques and parameters be consistent across all scans, including filters and application of the attenuation map.

After Completion of the PET Scan

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

[^{18}F]FDG Handling and Dose Documentation

[^{18}F]FDG is most often purchased from nuclear pharmacies licensed to sell [^{18}F]FDG or, less commonly, synthesized by standard methods and tested for pyrogenicity and radiochemical purity on each production run. The radiochemical purity of the [^{18}F]FDG should be > 90%.

PET Imaging Quality Control Standards

FDG-PET imaging will be performed using PET/CT.

Daily and monthly steps will be taken to assure quantitative accuracy of FDG-PET imaging studies and reliable imaging results at all performance sites, with recommended clinical standards described above under “Summary of Other Optional Requirements” under “State some type of annual scanner QC/QA”.

The level of tumor uptake is assessed subjectively by visual inspection as described in the Evaluation Criteria (see Section 10). **Semi-quantitative assessment of response by determination of standardized uptake values (SUV) is not utilized in this protocol response criteria, however SUV parameters can be provided as per routine clinical practice.** Deauville score assessment should be performed utilizing coronal attenuation corrected FDG-PET images rather than MIP or fused images.

17.0 RADIATION THERAPY GUIDELINES

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

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

17.1 General Guidelines

The RT guidelines for this study were developed specifically for patients with newly diagnosed intermediate-risk RMS defined by protocol criteria. All patients should plan to receive radiotherapy to the primary tumor at Week 13.

In select cases where delayed primary excision (DPE) is performed, post-operative CT or MRI imaging must be done to confirm gross total resection (GTR) or to define any gross residual disease requiring a boost. In these cases, post-operative RT should begin as soon as possible after allowing for post-operative imaging and adequate wound healing.

For patients on Regimen B, temsirolimus will be held during RT.

17.1.1 Special Note for Patients ≤ 24 Months Old

The long-term morbidity of RT or aggressive surgery for very young (≤ 24 months old) children makes appropriate local control challenging. Many clinicians are unwilling to follow standard local control guidelines for very young children. ARST1431 encourages adherence to standard local control guidelines for children > 24 months old but permits deviations at the discretion of the treating clinicians only for children ≤ 24 months who are **FOXO1 negative**. Deviation from protocol-mandated radiotherapy must be included in the QA documentation submitted to IROC RI. **For children ≤ 24 months of age with FOXO1 positive disease, deviations from standard local control guidelines will be considered a protocol violation.** Only for patients ≤ 24 months with FOXO1 negative disease, deviations from the standard local control guidelines will not be considered protocol violations.

17.1.2 Credentialing

- All therapy units used on this protocol must have their calibrations verified by IROC Houston. The table in Section 17.5 indicates allowable modes of treatment delivery.
- IMRT: Institutions treating with IMRT and not previously credentialed for use of IMRT in COG trials must irradiate IROC Houston's head and neck phantom. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.

- Proton Therapy: Each beam line used to treat patients on this study must be credentialed for clinical trial use by IROC Houston. See Section 17.1.3 below.
- Motion Management: If patients are treated with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Thorax-Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion.
- Stereotactic Body RT (SBRT): Use of SBRT is encouraged but not mandatory for treatment of bone metastases < 5 cm (based upon maximal dimension at diagnosis), but credentialing is required for its use. SBRT credentialing includes the following three components: (1) completion of the Motion Management Questionnaire (2), irradiation of IROC Houston's Spine Phantom and (3) approval of the institution's IGRT process. See http://irocri.qarc.org/ for the Motion Management Questionnaire and a description of IGRT credentialing requirements.

NOTE:

- SBRT is not to be used for sites other than bone metastases.
- COG will accept SBRT credentialing through NRG provided that the credentialing included irradiation of IROC Houston's Spine Phantom (RTOG 0631).

17.1.3 Guidelines and Requirements for the Use of Proton Beam Therapy

Proton therapy may be used to deliver RT on this protocol. The proton therapy method will be limited to scattering, uniform scanning, and pencil beam scanning depending on institutional availability. Investigators using proton beam radiation must comply with current NCI proton therapy guidelines as outlined in the Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, available at http://rpc.mdanderson.org/RPC/home_page/Proton_guidelines.htm.

17.1.4 Guidelines and Requirements for the Use of Brachytherapy or Intraoperative Irradiation

Brachytherapy, using either high dose rate or low dose rate radioactive sources may be used on this protocol. Typically, brachytherapy or intraoperative RT will be used for conformal RT of residual disease in the operative bed of the primary tumor for select patients.

17.2 Treatment of Metastatic Disease

17.2.1 Metastatic Disease

All patients should have all local and distant disease addressed with an appropriate local control modality after the completion of VAC/VI chemotherapy (Week 43). Definitive local therapy (surgery, SBRT, EBRT) is recommended to all metastatic sites documented at the time of diagnosis. SBRT is recommended to all bone metastatic sites < 5 cm in maximal dimension (based upon maximal dimension at diagnosis) if not treated surgically. Optimal local control will be determined by the treating institution and should involve input from pediatric oncology, surgery, and radiation oncology. **The pediatric radiation oncologist should be involved at the**

time of diagnosis to assess if imaging is adequate for local therapy and to ensure that all required credentialing tests for SBRT have been met. It is expected that the majority of patients will receive RT to the often multiple sites of metastatic disease.

Because of the option of SBRT for bone metastatic sites, RT guidelines follow for treatment of primary site and then separately for treatment of metastatic sites. **Note**: SBRT is not to be used for sites other than bone metastases.

RT for Metastatic Sites

Definitive RT	Unresected tumor > 5 cm
Definitive SBRT	Unresected/post-operative gross disease in bone mets that were < 5 cm at diagnosis
Post-operative RT	(1) Post-operative gross or microscopic residual tumor (2) Intra-operative spill
Special presentations	(1) Pulmonary metastases (2) Pathologically involved lymph nodes

RT is not indicated for the following conditions: bone marrow lesions with no evidence of bone involvement or sites not assessable clinically or by imaging and radiation that would exceed normal marrow tolerance.

17.3 Timing

17.3.1 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 risk classification and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning.

17.3.2 Patients will have RT delivered to the primary site and any involved regional lymph nodes with a goal to begin at Week 13. **It is strongly recommended that the patient be evaluated by the radiation oncologist at the time of study entry (prior to any study therapy).** This will allow adequate time for simulation and planning prior to Week 13. The radiation oncologist will review the adequacy of the initial diagnostic imaging studies for subsequent RT planning. In patients who are undergoing DPE, post-operative imaging must be obtained to assess completeness of resection. RT should be initiated as soon as possible once this imaging has been performed and there is evidence of adequate wound healing.

Metastatic sites will be treated at the completion of VAC/VI chemotherapy (Week 43).

17.3.3 Vincristine, cyclophosphamide, or irinotecan chemotherapy may be given concurrent with radiotherapy. Dactinomycin should be withheld during RT and re-instituted after completion of RT. Dactinomycin can be given at Week 13 prior to starting RT. For those on Regimen B, Temsirolimus will be held during and for 2 weeks following RT.

17.4 Emergency Radiation Therapy

Patients for whom emergency RT is planned should not be enrolled on this study.

17.5 Equipment and Methods of RT Delivery and Verification

Equipment	Photons (any energy)	Electrons (any energy)	IMRT (4-10MV)	Protons	Brachytherapy*
Linear Accelerator**	X	X	X		
Proton Beam				X	
Intraoperative RT	X	X			X
Brachytherapy – high or low dose rate					X

*Permanent radioactive implants are *not allowed* on this protocol.
**For tumors adjacent or included in lung tissue, photon beam energy should be ≤ 10 MV.

17.5.1 Treatment Planning

CT-treatment planning: All patients will undergo CT treatment planning for this protocol. Slices no more than 0.5cm thick (0.2-0.3cm is recommended) shall be taken throughout the extent of the irradiated volume.

CT (volumetric)-based planning is required to optimize dose to the planning target volume (PTV) while protecting normal tissues. Organs within the irradiated volume should be contoured including those required by treatment site (see Table 17.10.1). A DVH is necessary to determine target coverage and evaluate dose to normal tissues. In the event that a patient must start emergently with a non-volumetric treatment plan, a volumetric plan will be accomplished as soon as is reasonably possible and the previously utilized beams must be incorporated into the composite plan.

17.5.2 In-Room Verification of Spatial Positioning

Two-dimensional or volumetric imaging may be used to verify correct patient positioning. Portal imaging using EPIDs is the most common two-dimensional method, particularly when the target volume possesses a fixed spatial relationship with visualized bony anatomy. Film is discouraged but is acceptable. For IMRT and 3-D CRT treatments, a pair of images (usually orthogonal AP and lateral) is required to verify that the isocenter is in correct alignment relative to the treatment plan; these may be MV or kV images. When proton radiation is employed, daily image guidance with either 2-D or volumetric imaging is required.

Volumetric imaging for position verification may be in-room kV or MV cone beam or conventional CT imaging. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

17.6 Target Volumes

17.6.1 Standard Tumor and Target Volume Definitions

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study. Treatment planning will be based on the following definitions and applies only to the primary tumor site.

Photons

- *Gross tumor volume (GTV)* is the volume occupied at diagnosis by visible disease.
- *Clinical target volume (CTV)* includes the GTV and sites with potential occult tumor involvement including lymph nodes adjacent to the GTV that may be clinically involved.
- *Planning target volume (PTV*) is the CTV surrounded by a geometric margin to account for variability in set-up, breathing or motion during treatment.

Protons

- *GTV* is the same for protons and photons.
- *CTV* is the same for protons and photons.
- *PTV* will be uniquely defined for proton therapy.
  The planning target volume (PTV) for proton therapy will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center.

  When proton therapy is used, the PTV will be used for dose reporting and not specifically for treatment planning. The goal of treatment planning will be CTV coverage at 100% with measures taken for each specific uncertainty.

  The PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator (if applicable), (3) range of beam (depth of penetration), and (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 3-15 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator, set-up margin (SM), and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 17.7.3.

Brachytherapy

- *GTV* is the same as for photons.
- *CTV* is the same as for photons.
- *PTV* is equal to *CTV*.

17.6.2 Protocol Tumor and Target Volume Definition

Treatment will be prescribed to the PTV, which will be derived from the GTV and CTV.

17.6.2.1 GTV1

GTV1 is defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET scan) prior to any surgical debulking or chemotherapy. 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 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. For select patients undergoing delayed primary excisions (DPE), GTV will also be defined by the initial extent of tumor and will encompass the post-operative surgical bed.

17.6.2.2 CTV1 – RT to Nodal Disease

If there are no sites that warrant irradiation for potential occult tumor, then the CTV1 is defined as GTV1 + 1 cm (but not extending outside of the patient). It also includes regional lymph node chains for clinically or pathologically involved nodes. For tumors with no evidence of nodal involvement (N_0), the draining regional lymph nodes are not irradiated. For some sites, the definition of CTV is modified to account for specific anatomic barriers to tumor spread. **When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.** The definition of "clinically involved" nodes will be clarified as those including the following features: 1) > 1 cm on CT or MRI; OR 2) FDG avid on PET-CT; OR 3) pathologically confirmed to have microscopic disease. **RT to the nodal basin will be required for clinically involved nodes, unless they are biopsied and deemed pathologically negative.**

17.6.2.3 PTV1

For external beam photon techniques, the PTV1 is defined as the CTV1 plus an institutional specified margin to account for day-to-day setup variation related to the ability to immobilize the patient and physiologic motion of the CTV1. The minimum margin is 0.3 cm but does not have to be uniform in all dimensions. For proton planning, beam specific PTV expansions will be required.

17.6.3 Target Dose

On this study, patients with tumors > 5 cm **at the time of diagnosis** will receive an additional boost to a total of 59.4 Gy. For those patients who have a CR at Week 9 evaluation defined by CR on cross sectional imaging of tumor on CT/MRI AND 1) negative FDG-PET OR 2) radiological CR with biopsy confirmed no evidence of disease will receive a dose reduction regardless of the size at diagnosis. (See Section 17.7) If a patient undergoes DPE for a tumor that initially measured > 5 cm, any gross residual disease after DPE will be boosted to 59.4 Gy. For this reason, we discourage DPE that cannot easily achieve a gross total resection in patients with initial tumors > 5 cm.

17.6.4 Volume Reduction / Boost

For patients whose total dose will be 36 Gy, the PTV1 should not be modified unless the normal tissue dose recommendations will be exceeded (Table 17.9.7). Volume reduction is permitted for patients whose total dose will be 41.4-59.4 Gy. In cases where there is a decrease in tumor size following chemotherapy, a cone-down should be performed after 36 Gy. This is encouraged for tumors with "pushing" rather than invasive margins when significant normal tissue sparing will result from a volume reduction. Examples include tumors that displace the lung, intestine, or bladder that show clear return to a more normal anatomic position. Volume reduction is not recommended for invasive tumors. If there is no measurable reduction in tumor size by Week 9, no volume reduction is required and the initial PTV1 may be maintained for the entire treatment.

17.6.4.1 GTV2

GTV2 is defined as residual visible or palpable tumor as assessed by CT, MRI, PET scan or physical exam following induction chemotherapy. If DPE is performed and gross residual disease is detected on mandatory postoperative imaging, that residual disease will represent GTV2.

17.6.4.2 CTV2

CTV2 is defined as the GTV2 + 1 cm (but not extending outside the patient) and areas at risk for microscopic disease and modified to account for specific anatomic barriers to tumor spread.

17.6.4.3 PTV2

PTV2 is defined as the CTV2 with an institution and modality specific margin (minimum 0.3 cm) to account for day to day setup variation and physiologic motion of the CTV2. For proton planning, beam specific PTV expansions will be required.

17.6.5 Site-Specific Modifications

Extremity Tumors
The CTV can be modified at the discretion of the Radiation Oncologist to avoid circumferential irradiation of extremity lymphatics and treatment across a joint.

Orbit
For orbit primaries, the CTV will not extend outside of the bony orbit, providing there is no bone erosion of the orbit. The entire orbit does not need to be irradiated, only the tumor volume with margins (PTV). Every attempt should be made to shield the lens, cornea, and lacrimal gland appropriately (see Table 17.9.5).

Head and Neck Tumors
Many of these tumors may be considered unresectable due to close proximity to critical structures and surgical risks contributing to functional or cosmetic deficits. Every attempt should be made to minimize dose to the brain, cochlea, optic chiasm and orbit including eye, lacrimal gland, and optic nerve.

Chest Wall/Intrathoracic Tumors
Tumors which have displaced a significant amount of lung parenchyma which has subsequently returned to normal anatomic position following surgery or chemotherapy will have the GTV defined as the preoperative (pre-chemotherapy) tumor volume excluding the intrathoracic tumor which was removed by surgery or decreased in size by chemotherapy. All areas of pleural involvement will be included in the GTV regardless of whether the radiation is delivered pre- or postoperatively.

Intra-abdominal/Retroperitoneal/Pelvic Tumors
Tumors which have displaced a significant amount of bowel which has 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 intrapelvic 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 postoperatively. In the event that whole abdomen radiotherapy is required (*i.e.*, for malignant ascites or diffuse peritoneal involvement), the dose will be 24 Gy at 1.5 Gy per fraction with appropriate blocking of the kidneys and liver to keep them within normal tissue recommendations.

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. For example, the entire ipsilateral neck is treated for a jugular lymph node metastasis. Clinically enlarged nodes which are biopsied and do not contain tumor do not need to be irradiated. At the time of RT, any areas of potential microscopic nodal disease should receive 36 Gy while areas of residual gross nodal disease should be boosted to 50.4 Gy.

Vaginal Tumors
Brachytherapy is strongly encouraged for patients with vaginal primary tumors.

Pulmonary Metastases and Malignant Pleural Effusions (CTV3, PTV3)
These patients will require bilateral whole-lung radiation. Whole lung volume is designated CTV3. PTV3 is an expansion of CTV3 to account for organ motion during respiration as well as a 0.5-1 cm geometric expansion to account for day

to day set-up uncertainty. Organ motion can be determined with a 4D simulation, fluoroscopy, or lateral chest radiograph at full inspiration to document diaphragmatic excursion.
IMRT is allowed for whole lung radiation.

Non-Pulmonary Metastases
Radiation is recommended to all non-marrow metastatic sites. Bone marrow deposits of tumor must have bone disruption/erosion to qualify as bone disease. CT may be useful to determine bone involvement. However, feasibility of delivering metastatic site radiation diminishes as the number of metastatic sites increases and will be determined by the treating radiation oncologist. SBRT has been introduced to improve the feasibility of treating multiple metastatic sites. If the treating radiation oncologist does not feel treatment of all sites is feasible, radiation is recommended to those metastatic sites if there remains a concern about disease control at that site and the patient can tolerate further radiotherapy without undue morbidity. Re-evaluation imaging at the completion of therapy will help the radiation oncologist determine if the various remaining sites are in need of further treatment and will consider the following: (1) sub-optimal response to chemotherapy by clinical or imaging criteria; (2) sites which will be problematic in the event of disease progression (*i.e.*, tumor in a weight bearing bone); (3) sites that can be imaged with sufficient accuracy for treatment; and (4) expected tolerance and morbidity (i.e., bone marrow tolerance).

Treated with Standard RT (not SBRT)
The GTV2 for metastatic sites is the area of residual tumor defined on CT or MRI (post-chemotherapy/surgery) and involved bone. In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. To minimize irradiated volume, no GTV1 will be defined for metastatic sites. CTV2 is defined as GTV2 plus an additional 1.0 cm margin to account for sub-clinical areas of residual disease but confined by anatomic boundaries. PTV2 is the CTV2 volume with an additional margin of approximately 0.5 cm.

Bone Metastases Treated with SBRT
The GTV2, CTV2 and PTV2 for metastatic sites is the area of residual tumor defined on MRI and/or CT (post-chemotherapy/surgery) and involved bone. In cases where there is a discrepancy in volume between the scans, the larger volume will be irradiated. To minimize irradiated volume, no GTV1 will be defined for metastatic sites. For SBRT, modifications to CTV2 and PTV2 are as follows:
CTV2=GTV2+1cm expansion for microscopic disease but limited by anatomic constraints such as bone cortex PTV2=CTV2+2mm expansion for setup error, but can be limited to avoid critical normal structures such as spinal canal.

Definitive local therapy (surgery, SBRT, EBRT) is recommended to all bone metastatic sites documented at the time of diagnosis. SBRT is recommended to all bone metastatic sites < 5 cm in maximal dimension (based upon maximal dimension at diagnosis). Bone marrow deposits of tumor must have bone disruption/erosion to qualify as bone disease. CT may be useful to determine bone involvement. SBRT has been introduced to improve the feasibility of treating multiple metastatic sites. If the treating radiation oncologist does not feel

treatment of all sites is feasible, radiation is recommended to those metastatic sites if there remains a concern about disease control at that site and the patient can tolerate further radiotherapy without undue morbidity. Re-evaluation imaging at the completion of therapy will help the radiation oncologist determine if the various remaining sites are in need of further treatment and will consider the following: (1) sub-optimal response to chemotherapy by clinical or imaging criteria; (2) sites which will be problematic in the event of disease progression (*i.e.*, tumor in a weight bearing bone); and (3) sites that can be imaged with sufficient accuracy for treatment; and (4) expected tolerance and morbidity (i.e., bone marrow tolerance).

17.7 Target Dose

Integrated boost radiotherapy plans are not permitted.

17.7.1 Dose Definition

Photon dose is specified in Gray (Gy)-to-muscle. For proton beams, the absorbed dose, ICRU 78's D_{RBE}, is specified in Gy(RBE), using a standard RBE of 1.1 with respect to Cobalt-60.

17.7.2 Prescribed Dose and Fractionation

The protocol-specified dose per fraction is 1.8 Gy. The treatment should be limited to one fraction per day. Five fractions should be given per week. There may be an exception if a department is closed on a major holiday but an effort should be made to minimize days missed. The dose per fractionation may be reduced from 1.8 Gy to 1.5 Gy 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.

The primary site and any involved nodal regions should be treated concurrently though the total dose to the primary site and nodal region may differ depending upon the surgical status of each site. NOTE: Patients with positive lymph nodes at diagnosis that were only sampled by biopsy are Clinical Group III and will receive 50.4 Gy to the primary while those that are completely resected will receive 41.4 Gy to the primary.

17.7.3 Radiation dose according to FOXO1 fusion status, clinical group, and site. Patients with metastatic disease (Clinical Group IV) will have primary site radiotherapy according to the staging of the primary site. Patients with Clinical Group I, FOXO1 negative tumors or Clinical Group I, FOXO1 indeterminate tumors will not receive radiotherapy.

	Total Dose - Gy		**post DPE - Dose Gy**		
Clinical Group	if no CR at Week 9**	if CR at Week 9**	if GTR post DPE with negative margin	if GTR post DPE with microscopic margin	if post DPE, gross residual disease
I, FOXO1 neg	0	0	N/A	N/A	N/A
I, FOXO1 indeterminate	0	0	N/A	N/A	N/A
I, FOXO1 +	36	36	N/A	N/A	N/A
II	36	36	N/A	N/A	N/A
III, ≤ 5 cm*	50.4	36	36	41.4	50.4
III, > 5 cm*	59.4	36	36	41.4	59.4
*Based on size at diagnosis **CR defined as Radiological CR by CT/MRI (no visible tumor) (see Section 10.2.4.3) and 1) CR by FDG-PET; **or** 2) biopsy that shows no residual viable tumor.					

17.7.4 Radiation Dose Guidelines for Patients with Lung Metastases or Malignant Pleural Effusion

All patients with any lung metastasis(es) or malignant pleural effusion should receive bilateral whole lung radiotherapy. The dose will be 15 Gy in 10 fractions of 1.5 Gy.

17.7.5 Standard (Non-SBRT) Radiation Dose Guidelines for Individual Metastatic Lesions (all non-bone sites, all non-lung sites and bone sites > 5 cm)

	Dose (Gy)
Sites of initial metastases in CR	40 in 20 fractions
Lesions which are SD or PR	50 in 25 fractions

17.7.6 SBRT Dose Guidelines for Lesions that are SD or PR at Completion of VAC/VI Chemotherapy

	Dose/fraction (Gy)	**Dose (Gy)**
PTV2 = GTV2	7.0	35
PTV1= CTV2 + 2mm	6.0	30
After 15Gy whole lung		
PTV2 = GTV2	6.0	30
PTV1 = CTV2+2mm	5.0	25

17.7.7 SBRT Dose Guidelines for Lesions that are CR at Completion of VAC/VI Chemotherapy

PTV2 = GTV2	6.0	30
PTV1= CTV2 + 2mm	5.0	25
After 15Gy whole lung		
PTV2 = GTV2	5.0	30
PTV1 = CTV2+2mm	4.0	20

17.7.8 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 protocol-specified dose. Wedges, compensators, and other methods of generating more uniform dose distributions are encouraged.

Proton Specific Guidelines: For protons, the PTV concept differs from photon therapy. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV. Proton plans should be evaluated for adequate PTV coverage from the summation of all beams. For scattered and uniform scanning beams, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and setup and internal margins (SM and IM). These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the setup and internal margins (SM and IM). The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. Most proton centers use 3.5% of the maximum water-equivalent depth of the CTV to account for CT HU uncertainty and then add another 3 millimeters to account for uncertainties in beam range calibration and compensator fabrication. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should ensure proximal coverage of the target volume.

A PTV should be created by a uniform expansion from CTV for reporting purposes. The expansion margin should be consistent with SM and IM and is typically 3 mm for a static target volume when daily imaging is performed. With the planning guidelines provided herein, no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. In most cases, at least 95% of the protocol-specified dose should encompass 100% of the PTV. A potential exception is when the range margin is smaller than the PTV expansion (e.g., 3 mm). As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

17.7.9 Tissue Heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When IMRT is used in lung, planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. When protons are used, tissue heterogeneity calculations should be performed with the CT-based treatment planning system to generate dose distributions from the proton relative stopping power. Proton therapy should be

used with extreme caution when any of the treatment beams traverse normal lung parenchyma.

17.7.10 Environment of Care – Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once RT has been initiated, treatment will not be interrupted.

The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels. In the unusual case of a prolonged interruption, patients will have their treatment regimen modified according to the schedule noted below.

17.7.10.a Modifications in treatment regimen due to delays – Patients prescribed 36 Gy

Timing	Fx Size (Gy)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	20	36.0	4 – 6 wks
2-3 wk split	1.8	21	37.8	6 - 7 wks
> 3 wk split	1.8	22	39.6	> 7 wks

17.7.10.b Modifications in treatment regimen due to delays – Patients prescribed 41.4 Gy

Timing	Fx Size (Gy)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	23	41.4	4.6 – 6.5 wks
2-3 wk split	1.8	24	43.2	6.6 – 7.6 wks
> 3 wk split	1.8	25	45.0	> 7.6 wks

17.7.10.c Modifications in treatment regimen due to delays – Patients prescribed 50.4 Gy

Timing	Fx Size (Gy)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	28	50.4	5.4 - 7.3 wks
2-3 wk split	1.8	29	52.2	7.4 - 8.4 wks
> 3 wk split	1.8	30	54.0	>8.4 wks

17.7.10.d Modifications in treatment regimen due to delays – Patients prescribed 59.4 Gy

Timing	Fx Size (Gy)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	31	59.4	6.2-8.2 wks
2-3 wk split	1.8	32	57.6	8.3-9.3 wks
> 3 wk split	1.8	33	59.4	>9.3 wks

17.8 Treatment Technique

17.8.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissue.

17.8.2 Selection of Proton Beam Arrangements

There are uncertainties (0.1-0.3 cm) in the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in a critical organ will not be allowed. Individual proton beams which are a component of a multi-field proton beam, which stop within such an organ, will be allowed.

17.8.3 Field Shaping

Field shaping for photons will be done with either customized cerrobend blocking or multileaf collimation. The field shaping for protons will be done with either brass or cerrobend apertures or proton-specific multileaf collimation for scattered and uniform scanning beams. Pencil beam scanning does not require additional accessories for field shaping.

17.8.4 Simulation including Patient Positioning and Immobilization

17.8.4.1 Patient Positioning

Reproducible setups are critical and the use of immobilization devices is strongly encouraged.

The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

17.8.4.2 Immobilization Devices

Standard immobilization devices for the torso, extremities, or head and neck are to be used.

For IMRT and proton delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the beam location relative to the target volume location with the patient in the treatment position.

17.8.5 Special Considerations

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

17.8.6 Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the 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 organ 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 0.5 cm should be added to any OAR to form the PRV.
- For a CTV susceptible to physiologic motion, a margin of at least 0.5 cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1 cm 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.
- A description of the method used and evidence (*i.e.*, observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT) of the remaining tumor motion should be submitted on the Motion Management Reporting Form as noted in Section 17.12.

17.8.7 Brachytherapy

Sources used shall have assay directly traceable to NIST.

CT or MRI planning shall be used for post-implant 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 0.5-1 cm margin on all sides. If the area to be implanted is larger than 50 cm^2, external beam RT should be considered. Catheters should be parallel and positioned 1 cm apart. To ensure sufficient coverage the catheters should be placed with the distal end of the catheter projecting 1-2 cm 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 0.5 cm margin on all sides. If the thickness of tissue to be implanted is larger than 3 cm, external beam RT should be considered, but is not required.

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

$_{CTV}D_{100} \geq 95\%$ of the prescribed dose

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

where $_{CTV}D_{100}$ is the dose received by 100% of the CTV, $_{CTV}V_{100}$ is the fraction of the CTV receiving the prescribed dose, and $_{CTV}V_{150}$ is the fraction of the CTV receiving 150% of the prescribed dose.

It is recognized that the dose distribution from brachytherapy implants is inherently non-uniform and that for some implant geometries the above criteria for dose homogeneity index may be difficult to meet.

When a brachytherapy implant is used, the isodose distribution shall be calculated in descriptive planes (3 perpendicular planes passing through the target center and in two transverse planes 2 cm from the ends of the implant). CT based planning shall be used.

Total dose/fractionation and dose rate

In the rare circumstance that post-operative brachytherapy is used instead of external beam radiation, then the following recommendations apply:

LDR brachytherapy
Total dose: 26 Gy Dose rate range: 0.40-1.00 Gy/hour.
HDR brachytherapy
Total dose: 21 Gy Dose per fraction: 3.00 Gy BID (separate fractions by ≥ 6 hours)
Number of fractions: 7

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

When brachytherapy is used for the treatment of gross disease, a dose and fractionation schedule should be determined that is biologically equivalent to the corresponding external beam dose of 50.4 Gy in 28 fractions (assuming tumor is < 5 cm).

17.9 SBRT Guidelines

This study uses SBRT directed to sites of bone metastasis < 5 cm (based upon maximal dimension at diagnosis). For the purposes of this study, bone metastases are defined radiographically as lesions causing disruption of bone on anatomic imaging.
All sites treating with SBRT to sites of bone metastasis must be credentialed. COG will accept SBRT credentialing through NRG. See Section 17.1.2.

SBRT is not to be used for sites other than bone metastases.

17.9.1 Localization

Stereotactic radiation requires meticulous definition of the target, normal tissue structures, and visualization for localization during treatment delivery. Although CT is superior for evaluating bone changes due to tumor involvement, the extent of intramedullary involvement is difficult to determine on CT. Thus MRI within 4 weeks of treatment is required for planning for lesions treated with SBRT. This can either be in the form of treatment planning MRI or an MRI fused for treatment planning. A separate PET-CT is optional but can be used for treatment planning with fusion—this study would be done identically if the patient were having standard fractionated radiation. These studies can assist with delineation of the target and visualization for stereotactic treatment.

Patients will be positioned in a reproducible treatment position with an appropriate immobilization device custom-made for each patient and specific to treatment site. A variety of immobilization systems can be used on study such as stereotactic frames which surround the patient on three sides or large rigid pillows that reference to a stereotactic coordinate system. For cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device should be used. Patient immobilization must be reliable enough to achieve the accuracy requirement of image-guidance.

17.9.2 Simulation

CT simulation will be performed. The simulation study must include the target and all organs at risk for treatment planning. Simulation scan length should be 5-10 cm superior and inferior to the target. All organs at risk within the scan length should be contoured for dose - volume histogram analysis. For stereotactic treatment, tomographic slice thickness of 1-3 mm through the target is recommended.

Special consideration should be given to the analysis of internal organ motion if the target lesion is located in a site subject to motion such as the chest wall. Techniques to image moving targets such as active breath-hold techniques, accelerator gating with respiratory cycle, tumor tracking, 4D CT scan acquisition in conjunction with maximum intensity projection (MIP), will be considered acceptable maneuvers to account for organ motion. All systems used to account for internal organ motion must be accredited by the Study Committee. If the target cannot be visualized or localized on the planning imaging modality as a result of motion or metal artifact, stereotactic treatment should not be used.

The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed with a diagnostic radiologist on sequential axial computed tomography images. A radiosurgical treatment plan will be developed based on tumor geometry and location.

17.9.3 OAR Dose Constraints for SBRT

Accurate contouring of normal structures is critical in SBRT (please see Tables 17.9.4, 17.9.5, and 17.9.6 for a list of normal tissue dose constraints to be used on protocol as well as constraints for high and low-dose spillage). **OAR dose constraints are primary planning priority in SBRT treatment planning.** Tumor coverage is secondary. Patients in whom optimal tumor coverage is not possible while meeting planning constraints should not receive SBRT and instead should be treated with standard fractionation EBRT. The following are examples of contouring requirements for bone lesions near these critical structures:

Spinal Cord
The spinal cord is the visualized spinal cord based on image fusion with T2-weighted MRI, T1-weighted MRI with contrast. Because of curvature in the spine that is dependent on position and immobilization, MRI in the treatment position is ideal but not required. The spinal cord should be drawn of every slice of simulation CT (ie not interpolated). Spinal cord volume will be defined as 5-6 mm above and below the radiosurgery target volume.

Thecal Sac
The spinal cord can move within the thecal sac. The thecal sac will be contoured based on T2 MRI or bony limit of spinal canal and will serve as a PRV (planning organ at risk volume) for the spinal cord. Thecal sac volume will be defined as 6 mm above and below the radiosurgery target volume.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. The skin is essentially a rind of 0.5 cm enveloping the entire body in axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations. Ribs within 5 cm of the PTV should be contoured by outlining bone and bone marrow. The intercostal spaces should not be included as part of the ribs.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and muscular layers. The esophagus should be defined starting at least 10 cm above the superior extent of the target volume and continuing on every CT slice to at least 10 cm below the inferior extent of the target volume.

Larynx and Pharynx
The larynx and pharynx will be contoured to the mucosa, submucosa, cartilages and airway channels associated with these structures.

Trachea and Airway
The trachea and airway adjacent to the spines will be contoured including the mucosa, submucosa, cartilage rings and airway channels.

Lung
Both the right and left lungs should be contoured using pulmonary windows. All inflated and collapsed lung should be contoured; however, paraspinal gross tumor, if any, should not be included in this structure.

Kidney
Both the right and left kidneys should be contoured. Paraspinal gross tumor as defined above should not be included in this structure.

OAR dose constraints are primary planning priority in SBRT treatment planning. Tumor coverage is secondary (see Section 17.12 for assessment of deviations). Patients in whom optimal tumor coverage is not possible while meeting planning constraints should not receive SBRT and instead should be treated with standard fractionation EBRT. The main criteria for dose prescription for tumors of or in proximity to the spine will be the achievement of the spinal cord dose constraint (see table below).

17.9.4 Spinal Cord DVH Parameters for Spinal Cord

Normal Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	Myelitis

For tumors distant from the spinal cord, the main criteria for dose prescription will be OAR as per Table 17.9.5.

17.9.5 Organs at Risk – SBRT

Dose Constraints for Five Fractions – Based upon the AAPM Report TG 101 reduced by 10% for prior systemic chemotherapy

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥ Grade 3)
Optic Pathway	<0.2 cc	18 Gy (3.6 Gy/fx)	22.5 Gy (4.5 Gy/fx)	neuritis
Cochlea			24.7 Gy (4.95 Gy/fx)	hearing loss
Brainstem	<1 cc	23.4 Gy (4.68 Gy/fx)	31 Gy (6.2 Gy/fx)	cranial neuropathy
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	20.2 Gy (4.05 Gy/fx) 15 Gy (3 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Cauda Equina	<5 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuritis
Sacral Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Rib	<1 cc	31.5 Gy (6.3 Gy/fx)	38.7 Gy (7.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	24.7 Gy (4.95 Gy/fx)	31.5 Gy (6.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	28.8 Gy (5.76 Gy/fx)	34.2 Gy (6.84 Gy/fx)	pericarditis
Great vessels	<10 cc	42.3 Gy (8.46 Gy/fx)	47.7 Gy (9.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	16.2 Gy (3.24 Gy/fx)	34.2 Gy (6.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Stomach	<10 cc	25.2 Gy (5.04 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	16.2 Gy (3.24 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	17.5 Gy (3.51 Gy/fx)	31.5 Gy (6.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	colitis/fistula
Rectum*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	proctitis/fistula
Bladder wall	<15 cc	16.4 Gy (3.28 Gy/fx)	34.2 Gy (6.84 Gy/fx)	cystitis/fistula
Penile Bulb	<3 cc	27 Gy (5.4 Gy/fx)	45 Gy (9 Gy/fx)	impotence
Femoral Heads (Right & Left)	<10 cc	27 Gy (5.4 Gy/fx)		necrosis
Renal hilum/ vascular trunk	<2/3 volume	20.7 Gy (4.14 Gy/fx)		malignant hypertension
Parallel Tissue	**Volume**	**Critical Volume Dose**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Liver	700 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15.7 Gy (3.15 Gy/fx)		Basic renal function

*** Avoid circumferential irradiation**

For patients with prior whole lung RT, Table 17.9.6 lists the OAR constraints to be used.

17.9.6 Organs at Risk – SBRT after Whole Lung RT

Dose Constraints for Five Fractions – Based upon the AAPM Report TG 101 reduced for prior chemotherapy and 15 Gy whole lung RT

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	18.2 Gy (3.64 Gy/fx) 10.9 Gy (2.18 Gy/fx)	20.2 Gy (4.05 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	18.2 Gy (3.64 Gy/fx) 13.5 Gy (2.7 Gy/fx)	25 Gy (5 Gy/fx)	myelitis
Rib	<1 cc	26.5 Gy (5.3 Gy/fx)	33.7 Gy (6.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	19.7 Gy (3.94 Gy/fx)	26.5 Gy (5.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	23.8 Gy (4.76 Gy/fx)	29.2 Gy (5.84 Gy/fx)	pericarditis
Great vessels	<10 cc	37.3 Gy (7.46 Gy/fx)	42.7 Gy (8.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	11.2 Gy (2.24 Gy/fx)	29.2 Gy (5.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Stomach	<10 cc	20.2 Gy (4.04 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	11.2 Gy (2.24 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	12.5 Gy (2.51 Gy/fx)	26.5 Gy (5.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	17.5 Gy (3.5 Gy/fx)	29.2 Gy (5.84 Gy/fx)	colitis/fistula
Parallel Tissue	**Volume**	**Critical Volume Dose**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	300 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Lung (Right & Left)+	35%	20 Gy		Pneumonitis
Liver	200 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Liver+	50%	30 Gy		Basic Liver Function

*** Avoid circumferential irradiation**

Patients treated with SBRT will receive a prescribed dose of 40 Gy in 5 fractions to cover at least 90% of the defined target volume. The minimum, mean, and maximum dose to the PTV will be reported. Only ≤ 1 cc or ≤ 1-5% of unspecified tissue outside of the PTV can receive ≥ 100-110% of the prescribed dose.

Guidelines for Spillage

High Dose Spillage:

1. Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the

cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should not be more than 15% of the PTV volume.

2. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

Low Dose Spillage:

1. The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
   a. The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below.
2. The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given. See Table below.
3. Respect all critical organ dose-volume limits listed above.

17.9.7 Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, R50%		Maximum dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D2cm (Gy)		Percent of Lung Receiving 20 Gy Total or More, V20 (%)	
	Goal	Acceptable	Goal	Acceptable	Goal	Acceptable	Goal	Acceptable
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	≤91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	≤94.0	<10	<15

Treatment/Localization

Within four weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. This protocol allows conventional linear accelerators and specialized linear accelerators with image guidance (e.g. Novalis, Trilogy, Synergy, Artiste) capable of conformal dose delivery and IMRT. Specialized accelerators (e.g. Cyberknife or Tomotherapy) are also allowed provided that institutions have satisfied all credentialing requirements.

SBRT is an image-guided procedure. In-room imaging technology allowing imaging of the target bone should be used. Coordinate systems between imaging system and delivery system should be aligned for SBRT.

During treatment, real time cone beam CT images or orthogonal kilovoltage images of the patient's body site of interest will be obtained. Cone beam CT scan or kilovoltage orthogonal images will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment, is within 2 mm. Imaging should be performed during and at the end of treatment to ensure maintenance of patient positioning throughout treatment.

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments. Anesthesia will be delivered by a dedicated pediatric anesthesiologist.

17.10 Organs at Risk for Fractionated Targets (Not SBRT)

The organs at risk (OAR) guidelines in this section are recommendations. If the recommended doses to the OAR 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 tolerance is the same for photons and protons (proton dose measured in CGE).

17.10.1 Organs at Risk Dose Recommendations

Organ	Volume (%)	Dose (Gy)
Single organs		
Bladder	100%	45
Heart	100%	30
Liver	100%	23.4
	50%	30
Rectum	100/%	45
Optic chiasm	100%	54
Small Bowel	50%	45
Spinal Cord	Any volume	45
Paired organs		
Kidney (bilateral)	50%	24
Kidney (bilateral)	100%	14.4
Lung (bilateral)	20%	20
Lung (bilateral)	100%	15
Optic nerve	100%	54
Lens	100%	14.4
Lacrimal Gland/Cornea	100%	41.4

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 %.

17.11 Dose Calculations and Reporting

17.11.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

17.11.2 Normal Tissue Dosimetry

The daily dose to the critical organs indicated should be calculated whenever any beam traverses the structure. 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, 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.

17.11.3 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
Abdomen	Liver
	Right and Left Kidney
Pelvis	Bladder
	Rectum
Spinal Cord	Spinal Cord

17.12 Quality Assurance Documentation

Within three days of the start of RT, detailed treatment data for the primary site shall be submitted for on treatment review. Data for metastatic sites may be submitted at the end of treatment.

Digital Submission:
Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission of these files by TRIAD is preferred. Instructions for TRIAD setup are in Section 17.12.3 below. Alternatively, sites

may use sFTP. Instructions for data submission via sFTP are on the IROC Rhode Island web site at http://irocri.qarc.org/ under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via TRIAD or sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following for All Radiated Sites:

External Beam Treatment Planning System

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. DRR's are not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- All diagnostic imaging used to plan the target volume, including CT/MR/PET/Bone Scan images done at Pre-study and at Week 9 when applicable for planning volume reduction/boost volumes.
    - For metastatic sites, submit the End of VAC/VI +/- temsirolimus CT/MR images. For SBRT, include treatment planning MR images (within 4 weeks prior to start of RT).
    - For DPE patients, include the CT/MR done post-op prior to RT. Digital Imaging files can be submitted via TRIAD or sFTP with the DICOM RT submission.
- Copies of all radiology reports corresponding to the diagnostic studies noted above. Copies of operative, pathology, and cytology reports.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC RI 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 Dosimetry Summary or Proton Reporting Form.
- Motion Management Reporting Form (if applicable, see Section 17.8.6).
- RT-2 Radiotherapy Total Dose Record Form.

Please submit the following additional 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 additional information for intra-operative RT:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk
- Physician's note describing the procedure, dose calculation and description of the applicator along with any relevant dosimetric characteristics (i.e. percent depth dose for the prescribed energy)

Within 1 week of the completion of radiotherapy submit the following items:

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

These data can be submitted via TRIAD or sFTP, or e-mailed to DataSubmission@QARC.org.

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

COG Protocol Dosimetrist
IROC Rhode Island QA Center
Email: physics@qarc.org
Phone: (401) 753-7600

17.12.1 Definition of Deviations

	Deviation	
	Variation Acceptable	**Deviation Unacceptable**
Prescription Dose		
External beam	Difference in prescribed or computed dose is 6-10% of protocol-specified dose	Difference in prescribed or computed dose is > 10% of protocol-specified dose
Brachytherapy	Difference in prescribed or computed dose is 6-10% of protocol-specified dose	Difference in prescribed or computed dose is > 10% of protocol-specified dose
Dose Uniformity		
External beam	10% PTV receives > 110% of protocol-specified dose *or* 95% isodose covers < 90% of the PTV or < 100% but > 90% of the CTV	95% isodose covers < 90% of CTV
Brachytherapy	95% isodose covers < 100% of CTV	90% isodose covers < 100% of CTV
Volume	Margins for CTV/PTV less than specified or excessively large	A portion of the GTV or potentially tumor bearing area (CTV) is not included in the treated volume
Organs at Risk	Will be assessed at time of data review	Will be assessed at time of data review

17.12.2 Evaluation of SBRT Plans for Deviations

Evaluation of SBRT plans will be performed for feasibility analysis. In the context of this feasibility study, deviations will be recorded and institutions will receive feedback but deviations will not affect institutional performance scores.

	Deviation	
Dose	**Variation Acceptable**	**Deviation Unacceptable**
SBRT	90% isodose covers < 90% but > 80% of the CTV	90% isodose covers < 80% of CTV
Volume	CTV or PTV margins are smaller than specified in the protocol.	The contoured GTV does not include imaging-visible residual tumor or bone abnormality
Organs at Risk	Will be assessed at time of data review.	Exceeding max point dose for OAR as per Sections 17.9.4, 17.9.5, 17.9.6

17.12.3 Digital Radiation Therapy Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:
To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and

NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

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

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

CTSU REGISTRATION PROCEDURES

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

Downloading Site Registration Documents:
Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *COG*, and protocol number (*insert study number*).
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Requirements for ARST1431 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations,

though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

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

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

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

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

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

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail

from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.
To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

APPENDIX II: YOUTH INFORMATION SHEETS
(for children from 7 through 12 years of age)

A study to compare 2 treatments for a type of cancer called Intermediate-Risk RMS

1. We have been talking with you about rhabdomyosarcoma (RMS). RMS is a type of cancer that occurs in the soft tissues of the body like the muscles. After doing tests, we have found that you have RMS.

2. We are asking you to take part in a research study because you have intermediate-risk (IR) RMS. 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 IR RMS. One standard treatment for IR RMS is a combination of 4 anti-cancer drugs called "VAC/VI" therapy. This study will compare VAC/VI therapy to VAC/VI plus a new drug called temsirolimus. This study will also look at giving treatment for longer than the standard treatment usually lasts. We do not know how well the study treatment will work in children. That is why we are doing this study.

3. Children and teens who are part of this study will be randomly assigned to either Regimen A with VAC/VI or Regimen B with VAC/VI plus temsirolimus. A computer decides which treatment plan you will get and not your doctor. It is a lot like flipping a coin and this is done so that we have an equal number of patients in each regimen. You will also have surgery and/or receive radiation therapy. Radiation therapy is the use of high energy X-rays to kill cancer cells. After the treatment with VAC/VI or VAC/VI plus temsirolimus, you will get 6 additional months of treatment with 2 standard anti-cancer drugs.

   Your doctor is doing more tests on your tumor. Based on test results that may come back a few weeks after you start the study, your doctor may find that you have low-risk RMS. If you have low-risk RMS, you will get a different treatment called "VAC/VA" instead of the treatment you were assigned to. VAC/VA therapy is a combination of 3 standard anti-cancer drugs. You will also have surgery and/or receive radiation therapy.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." Being in this study may involve special risks, which your doctor will discuss with you. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood for special tests. These tests will help us better understand RMS. The blood draws would be taken when other standard blood tests are being performed. We would also like to save any leftover samples for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood samples or save the leftover samples for research.

YOUTH INFORMATION SHEETS
(for teens from 13 through 17 years of age)

A study to compare treatments with and without temsirolimus for Intermediate-Risk RMS

1. We have been talking with you about rhabdomyosarcoma. Rhabdomyosarcoma (RMS) is a type of cancer that occurs in the soft tissues of the body like the muscles. After doing tests, we have found that you have intermediate-risk RMS. That means there is about a 1 in 3 chance that your tumor will come back after treatment.

2. We are asking you to take part in a research study because you have intermediate-risk (IR) RMS. 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 IR RMS. We will do this by adding another drug to one of the standard treatments for IR RMS. A standard treatment for IR RMS is a combination of 4 anti-cancer drugs called "VAC/VI" therapy. This study will compare VAC/VI therapy to VAC/VI plus a new drug called temsirolimus. This study will also look at extending the standard treatment to include a treatment phase called maintenance therapy. We do not know how well the study treatment will work in children. That is why we are doing this study.

3. Children and teens who are part of this study will be randomly assigned to either Regimen A- VAC/VI chemotherapy (anti-cancer drugs) or Regimen B- VAC/VI plus temsirolimus. This is called randomization. This is a lot like flipping a coin. A computer decides which treatment plan you will get and not your doctor. You will also have surgery and/or receive radiation therapy. Radiation therapy is the use of high energy X-rays to kill cancer cells. You will also get 6 months of maintenance therapy after treatment with VAC/VI or VAC/VI plus temsirolimus. Maintenance therapy uses 2 standard anti-cancer drugs.

   Your doctor is doing additional testing on your tumor and the results may not be available until a few weeks after you join the study. Based on the test results, your doctor may find that you have a type of RMS that is low-risk. If you have low-risk RMS, you will stop getting the assigned treatment (VAC/VI or VAC/VI plus temsirolimus), and you will get a different treatment called "VAC/VA" therapy (a combination of 3 standard anti-cancer drugs). You will also have surgery and/or receive radiation therapy. You will not get maintenance therapy after VAC/VA therapy.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the treatment you get will help make your health better. If you get temsirolimus, we hope it will be better at getting rid of the cancer, but, we don't know this for sure.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." Chemotherapy can cause side effects. For example, some types of chemotherapy cause changes in the blood cells. These changes can make a person feel tired or get an infection easier. Side effects can be increased when chemotherapy drugs are combined. If you receive temsirolimus, there is a chance that you will have more side effects. Being in this study may involve other special risks, which your doctor will discuss with you. Other things might happen to you that we don't know about yet.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood for special tests. These tests will help us better understand RMS. The blood draws would be taken when other standard blood tests are being performed. We would also like to save any leftover samples for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood samples or save the leftover samples for research.

APPENDIX III: TNM PRE-TREATMENT STAGING CLASSIFICATION

Staging prior to treatment requires thorough clinical examination, laboratory and imaging examinations. Biopsy is required to establish the histologic diagnosis. Pre-treatment size is determined by external measurement or MRI or CT depending on the anatomic location. For less accessible primary sites, CT will be employed as a means of lymph node assessment as well. Metastatic sites will require some form of imaging (but not histologic confirmation, except for bone marrow examination) confirmation.

Stage	Sites	T	Size	N	M
1	Orbit Head and neck (excluding parameningeal) GU – non-bladder/ non-prostate Biliary Tract/Liver	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Bladder/Prostate Extremity, Cranial Parameningeal, Other (includes trunk, retroperitoneum, etc.) Except Biliary tract/Liver	T_1 or T_2	a	N_0 or N_x	M_0
3	Bladder/Prostate Extremity Cranial Parameningeal, Other (includes trunk, retroperitoneum, etc.) Except Biliary tract/Liver	T_1 or T_2	a b	N_1 N_0 or N_1 or N_x	M_0 M_0
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

Definitions – See Appendix V for anatomic definitions of parameningeal, orbit and other head and neck sites

Tumor –

$T(site)_1$ – confined to anatomic site of origin

a. ≤ 5 cm in diameter in size
b. > 5 cm in diameter in size

$T(site)_2$ – extension and/or fixative to surrounding tissue

a. ≤ 5 cm in diameter in size
b. > 5 cm in diameter in size

Regional Nodes –

N_0 regional nodes not clinically involved

N_1 regional nodes clinically involved by neoplasm defined as 1) > 1 cm by CT or MRI OR 2) ^{18}FDG avid

N_x clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation

Metastasis –

M_0 no distant metastasis
M_1 distant metastasis present

Note: The presence of positive cytology in pleural fluid, abdominal fluid, or CSF and the presence of implants on pleural or peritoneal are considered evidence of metastasis.

APPENDIX IV: STS CLINICAL GROUPING CLASSIFICATION

Clinical Group I: Localized disease, completely resected

(Regional nodes not involved – lymph node biopsy or sampling is highly advised, except for head and neck lesions)

a. Confined to muscle or organ of origin
b. Contiguous involvement – infiltration outside the muscle or organ of origin, as through fascial planes.

Notation: This includes both gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative. If the latter should be involved microscopically, then the patient is placed in the Clinical Group IIb or IIc (See Below).

Clinical Group II: Total gross resection with evidence of regional spread

a. Grossly resected tumor with microscopic residual disease

(Surgeon believes that he has removed all of the tumor, but the pathologist finds tumor at the margin of resection and additional resection to achieve clean margin is not reasonable). No evidence of gross residual tumor. No evidence of regional node involvement. Once radiotherapy and/or chemotherapy have been started, re-exploration and removal of the area of microscopic residual does not change the patient's group.

b. Regional disease with involved nodes, completely resected with no microscopic residual.

Notation: Complete resection with microscopic confirmation of no residual disease makes this different from Clinical Groups IIa and IIc. Additionally, in contrast to Clinical Group IIa, regional nodes (which are completely resected, however) are involved, but the most distal node is histologically negative.

c. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.

Clinical Group III: Incomplete resection with gross residual disease

a. After biopsy only
b. After gross major resection of the primary (>50%)

Clinical Group IV: Distant Metastatic disease present at onset
(Lung, liver, bones, bone marrow, brain, and distant muscle and nodes)

Notation: The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favorable grouping (as noted above under Group II).

The following are also considered evidence of metastatic disease and place the patient in Group IV:
1. The presence of positive cytology in CSF,

2. Positive cytology in pleural or abdominal fluids
3. The presence of implants on pleural or peritoneal surfaces

NOTE: The presence of a pleural effusion or ascites without positive cytologic evaluation is not considered evidence of metastatic disease and the patient will not be considered to have Group IV disease.

REGIONAL NODAL BASINS FOR RHABDOMYOSARCOMA

Extremity
Lower Extremity –inguinal, femoral, popliteal nodes (rarely involved)
Upper extremity – axillary, brachial, epitrochlear, infraclavicular nodes (infraclavicular)

Genitourinary
Bladder/Prostate – pelvic, retroperitoneal nodes at renal artery level or below
Cervix and Uterus– pelvic, retroperitoneal nodes at renal artery level or below
Paratesticular – pelvic, retroperitoneal nodes at renal artery level or below
Vagina – retroperitoneal, pelvic nodes at or below common iliacs inguinal nodes
Vulva – inguinal nodes

Head and Neck
Head/Neck – ipsilateral cervical, jugular, preauricular, occipital, supraclavicular nodes for laterally placed tumors (excluding scalp); may have bilateral adenopathy with centrally placed tumors
Orbit/Eyelid – ipsilateral jugular, preauricular, cervical nodes

Intrathoracic
Internal mammary, mediastinal nodes

Retroperitoneum/Pelvis –
Pelvic, retroperitoneal nodes

Trunk
Abdominal Wall – inguinal, femoral nodes
Chest Wall – axillary, internal mammary, infraclavicular nodes

OTHER
Biliary/Liver – liver hilar nodes
Perianal/Perineal – inguinal, pelvic nodes; may be bilateral

NOTES
Any tumor – involved node other than those listed above signifies distant metastasis (Stage 4/Group IV). Examples: perineal primary with nodes above the pelvis; thigh primary with iliac or periaortic nodes; intrathoracic primary with subdiaphragmatic nodes; paratestis primary with inguinal nodes with or without transscrotal biopsy or scrotal involvement.

APPENDIX V: ANATOMIC DEFINITIONS OF PARAMENINGEAL, ORBIT AND OTHER HEAD AND NECK SITES FOR USE IN PRE-TREATMENT STAGING

Introduction
There are three groupings of sites in the head and neck: parameningeal; orbit; and all others ("head and neck")

PARAMENINGEAL

1. Middle Ear
   This refers to a primary that begins medial to the tympanic membrane. This tumor is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the "middle ear" designation should be picked as it implies the more aggressive therapy required.
2. Nasal Cavity and Paranasal Sinuses
   The three paranasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity and primary in one will frequently extend to another. It can be difficult to determine the exact site of origin but the choice is academic as the randomization is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumor arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and paranasal sinus is unclear, the site selected should be paranasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx. Again the choice of site is academic as the therapy is not different.
3. Nasopharynx
   This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.
4. Infratemporal Fossa/Pterygopalatine and Parapharyngeal Area
   This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumors in this region may extend through the parotid gland and present as a mass of the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term "infratemporal". The distinction between this and the "parapharyngeal" area is academic.

ORBIT

1. Eyelid
   This site is sometimes erroneously designated as "eye". Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.
2. Orbit
   This refers to the bony cavity which contains the globe, nerve and vessels, and the extra ocular muscles. Tumor in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumor which is clearly adjacent to the skull base and it meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of the bone.

HEAD AND NECK

1. Scalp
   This site includes primaries arising apparently in or just below the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose and forehead, but not the eyelids or cheek.
2. Parotid Region
   The parotid gland lies just in front of and under the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. Tumors in the parotid region may not arise in the parotid gland itself. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid region primary should not, on radiographic studies, reveal a mass in the infratemporal fossa.
3. Oral Cavity
   This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, and the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek but the distinction is academic. This would also include those lesions arising in and near the lips.
4. Larynx
   This refers to the primaries arising in the subglottic, glottic, or supraglottic tissues. Tumors of the aryepiglottic folds can be difficult to distinguish from the hypopharynx but the distinction is academic.
5. Oropharynx
   This includes tumors arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumors arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumor as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.
6. Cheek
   This refers to the soft tissues of the face that surround the oral cavity. Tumors arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.
7. Hypopharynx
   This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic with regard to randomization.
8. Thyroid and Parathyroid
   Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the trachea.
9. Neck
   This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately this site overlaps with the designation “paraspinal” included under the site group “trunk”. Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space.

APPENDIX VI: DESIGNATION OF THE PRIMARY SITE FOR USE IN PRE-TREATMENT STAGING (SELECTION OF "SITE CATEGORY" FOR PATIENT ENTRY)

NOTE: This will extend to other areas the guidelines prepared to aid in the identification of head and neck sites (Appendix V). Some of the distinctions made below are largely semantic. Although they do not change therapy they may be important in reviewing results for specific sites. Others are vital as they would make a change in stage and therapy. It is astonishing how frequently data forms on the same patient from the same institution list quite different primary sites. This can only be determined in retrospect, but it should make one cautious regarding accepting a confusing or illogical site designation at the time of registration.

I. Comment on the Terms Used to Designate Primary Site for RMS

The Dictated Operative Note

If the patient has undergone an initial major operative procedure, the "post-operative diagnosis: listed on the operative note that should be dictated following the procedure will ordinarily include reference to site. In such cases, this is usually the most accurate source document for site designation.

Larger Site Categories

Most of the terms used follow common usage. As you are aware, we consider an "extremity" to include the total forequarter or total hindquarter. This extends the extremity area on the posterior, but not the anterior, aspect of the body. The muscles over the scapula are include in the upper extremity and the muscles making up the buttocks in the lower extremity. This confines the trunk area posteriorly to that which is paraspinal and chest wall; and anteriorly, chest wall and abdominal wall. The retroperitoneal and perineal sites are listed separately in the IRS.

Primary Site vs. Areas of Extension

Primary site rather than areas of extension ordinarily determines the site category. In the case of the parameningeal tumors, however, the primary site is incidental, and the approach to the meninges is the important factor in site determination in the IRS.

Large Tumors Involving Multiple Organs and/or Structure

Our aim in these cases is to attempt to select the most likely site of original involvement or origin. The terms "abdominal", "thoracic" and "unknown" are the least helpful in analysis.

"Bones"

When the designated site on the institutional forms is a word indicating a bone, i.e. "tibia", "scapula", etc., try for something more accurate or at least make it an adjective.

II. Specific Sites Within Major Categories

The following is a glossary of site designations. They are almost entirely taken from IRS I-III forms reviewed by the Committee. Some of them should not be used and others would appear to need definition. In some cases we have simply provided an explanation of what a surgeon would ordinarily mean by a given term. Site designations in data collection sheets and even operative notes may be worded in terms that are not inaccurate but not appropriate for site designation in the IRS, where consistency is required.

1. Abdominal Wall

This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and iliac crests to the paraspinal region. From a practical point of view, this posterior extension is so narrow in a child that it is probably insignificant as a primary site.

2. Arm
   Refers to the area from the shoulder joint to the elbow joint.
3. Biliary Tract/Liver
   Biliary tract tumors might also be called "choledochus" or "bile duct". Tumors in the liver are believed to arise from intrahepatic bile ducts. Biliary tract represents the preferred primary site designation for these tumors. Localized biliary tract/liver tumors are considered Stage 1.
4. Bladder
   Our criteria for identifying the bladder as a primary site has included the appearance of tumor within the bladder cavity, which can be biopsied through an endoscope or occasionally at laparotomy. We do not recognize as primary bladder tumors those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic sites, unless otherwise specified.
5. Bladder/Prostate
   In approximately 20% of males with bladder or prostatic tumors, the precise site cannot be determined even at autopsy. This histologic features are similar. Although it is desirable to have an indication of the "most probable: site from the institution, and one should strive to get this, it may not be possible.
6. Buttocks - These are extremity lesions.
7. Inguinal Canal
   See paratesticular
8. Paraspinal
   When tumors are described as adjacent to the vertebral column, this designation is preferable to "truck" or "neck".
9. Paratesticular (testicular)
   Rhabdomyosarcomas rarely arise from testicular tissue. These tumors are almost always "paratesticular" arising either adjacent to the testes within the scrotum or in the inguinal canal, i.e., "groin" or lower abdominal wall. In either case they are classified in the G. U. major site category and called paratesticular.
10. Pelvis
    This site must be distinguished from the previously designated "special pelvic" category used in prior IRS studies. It may be regarded as a tumor within the pelvis when no more specific site is appropriate.
11. Perianal (often called "anus" or "rectum")
    These sites are ordinarily "perirectal" or "perianal". They are distinguished with difficulty from perineal and vulval sites; but the latter distinction is important.
12. Perineum
    This should include the sites which appear anterior to the anus and posterior to the scrotum in males and posterior to the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and vaginal sites.
13. Peritoneum
    This primary site is imprecise as it extends from the diaphragm to the pelvis. One should try for specific site.
14. Prostate
    See Bladder/Prostate
15. Retroperitoneal (often called "psoas muscle")
    We reserve the term retroperitoneal for those posteriorly situated abdominal tumors in which there does not seem to be a more specific site. If the tumor arose in an abdominal viscus, such as the pancreas, etc., this would be a preferable site designation, to "retroperitoneal". Tumors in a retroperitoneal site are in the posterior aspect of the abdomen and/or pelvis. The term "psoas" as a

site is not very specific, as this muscle extends through the posterior lower abdomen, pelvis, and into the leg.

16. Shoulder
The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

17. Testes
See Paratesticular

18. Uterus
A tumor in this primary site may be difficult to differentiate from a primary vaginal site, because a tumor originating in the uterus may fill the vagina. After a therapeutic response the distinction is usually clear. In general there is wide separation of age ranges between these two groups with the vaginal cases occurring in infancy or early childhood and the uterine primaries in adolescents or young adults. One should be skeptical regarding a patient with a designated "vaginal" site who is over five years of age, or a patient with a designated uterine site in a patient who is under 10 years of age. Fortunately, this is not a therapy-related distinction.

19 Vagina
For the purpose of our study the patient with a primary vaginal lesion must have evidence of a visible tumor on the vaginal surface which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

20. Vulva
Primary lesions in this site arise in the labial minor or majora, and these terms are often used, and are acceptable.

APPENDIX VII: SUPPORTIVE CARE GUIDELINES

These supportive care guidelines are provided for institutional consideration but are not intended to supplant institutional practices. Investigator discretion should be used, and certain clinical situations and institutional guidelines may suggest other approaches. Investigators may wish to refer to Supportive Care of Children with Cancer, Arthur Ablin ed., 2004, for further recommendations.

Sperm Banking and Fertility Consult

The total dose of cyclophosphamide on both Regimen A and B is 8.4 g/m^2. The effect of this dose on male fertility is unknown. Furthermore, the impact of mTOR inhibition on male fertility is unknown. We therefore **strongly encourage** sperm cryopreservation be discussed with all post-pubertal boys receiving RMS therapy.

For males and females of all ages with primary disease in the abdomen/pelvis, RT to the gonads is almost a certainty. Due to the sterilizing effects of RT on both male and female gonads, disclosure regarding infertility is strongly encouraged, especially for children and adolescents with abdominal/pelvic disease. Egg cryopreservation is no longer considered experimental, and can be discussed with post-pubertal females who are planned to receive pelvic RT when appropriate.

Mouthcare and Mucositis Management

Temsirolimus is commonly associated with mucositis, which can be persistent and often result in treatment delay. In adults receiving mTOR inhibitors, mouth lesions can appear as discrete, ovoid, superficial, well demarcated ulcers with a grayish-white pseudomembrane.[90] Alternative presentations include clustering of lesions (such as seen with herpetic lesions) and also larger ulcers similar in appearance to those observed in patients with major aphthous stomatitis. Lesions are often confined to the nonkeratinized, movable mucosa, such as the inner aspect of the lips, the ventral and lateral surfaces of the tongue, and the soft palate. An aggressive regimen is strongly recommended to help manage mucositis especially in patients receiving temsirolimus, but can be offered to all patients.

- Xyloxylin (1:1:1 ratio) (diphenhydramine, Maalox, lidocaine) 10 mL swish/swallow QID prn
- Caphosol (saliva substitute) 15 mL swish/spit Q 4 hours prn
- Biotene mouth wash Q 4 hours prn
- Sucralfate 1 Gm/10 mL 10 mL swish/swallow or spit QID prn

Irinotecan-Induced Diarrhea Prophylaxis

Cefixime or an available equivalent antibiotic is recommended as a diarrhea prophylaxis in Regimens A and B during VI or VI + temsirolimus cycles, respectively. Initiation of antibiotic treatment two days prior to the start of irinotecan is recommended, and should continue during, and for 3 days after the last dose of irinotecan for a total of 10 days. This antibiotic therapy will continue throughout protocol therapy. Cefixime will be dosed at 8 mg/kg PO once daily (max: 400 mg/day). If cefixime is not available, cefpodoxime can be used as an alternative at 5 mg/kg/dose PO twice daily (10 mg/kg/day in two divided doses; max: 200 mg/dose). In countries where cefiixime or cefpodoxime are not available, other equivalent antibiotics can be used instead.

See Appendix X for loperamide dosing in the treatment of irinotecan-induced diarrhea.

Central Venous Access

Central venous access is recommended for all patients.

Dental Consultation

Dental consultation is recommended prior to initiation of therapy for patients with head/neck tumors. Removal of braces prior to initiation of therapy is recommended.

Supplemental Nutrition

Supplemental parenteral nutrition should be considered for patients who have lost ≥ 10% of their body weight or have persistent hypoalbuminemia of < 3 g/dl. Patients with nasopharyngeal primary tumors often experience significant mucosal reactions during radiation. Early placement of nasogastric or gastrostomy tube for supplemental feeding, prior to beginning irradiation, may be indicated.

***Pneumocystis Jirovecii* Pneumonia Prophylaxis**

Trimethoprim (TMP)/sulfamethoxazole prophylaxis is not required but may be strongly considered as per treating physician, especially in children less than 5 years of age and in those on Regimen B. Suggest TMP 5 mg/kg/day divided bid, two-three consecutive days per week. If allergic or intolerant, use pentamidine or dapsone.

Hemorrhagic cystitis prophylaxis

Mesna and fluids will be used with Intravenous Cyclophosphamide

- Recommended pre-hydration 0.9% NaCl, 750 mL/m^2 IV over 1 hour.
- Continuing hydration: 0.45% NaCl, 100 mL/m^2/h IV until last mesna dose is finished. **There is no need to measure urine specific gravity**.
- IV Mesna Dose: 20% of cyclophosphamide dose IV over 15-30 minutes immediately before (or mixed with) cyclophosphamide infusion, and again 4 and 8 hours after the start of cyclophosphamide infusion.
- PO Mesna Dose: The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6.
- Alternative Mesna regimen (institutional choice): 60% of cyclophosphamide dose as 8-hour continuous infusion, beginning when cyclophosphamide infusion starts.

Myeloid growth factor support: (for VAC cycles only)

Filgrastim (G-CSF) or biosimilar **5 mcg/kg/day SubQ** starting a minimum of 24 hours after the last dose of VAC chemotherapy. Continue until the ANC ≥ 2000/μL after the expected nadir. Myeloid growth factor support may be continued without regard to vinCRIStine or temsirolimus. Discontinue myeloid growth factor support a minimum of 24 hours prior to administration of the next chemotherapy cycle. Note: ANC ≥ 2000 prior to the nadir of a cycle is **not** sufficient for discontinuing growth factor support, as the ANC may rise before the nadir and then fall. Pegfilgrastim or biosimilar **0.1 mg/kg/dose (for patients < 45 kg) or 6 mg/dose (for patients ≥ 45 kg) SubQ x 1 dose** or per institutional standards may be used starting 24 hours after the last dose of chemotherapy.

Older patients can occasionally complain of bone pain associated with filgastrim. In this case, the drug can be discontinued early and will not be considered a protocol violation.

APPENDIX VIII: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5]	atazanavir	aprepitant	barbiturates	bosentan
alfentanil[4,5]	boceprevir	conivaptan	carbamazepine	dabrafenib
amiodarone[4]	clarithromycin	crizotinib	enzalutamide	efavirenz
aprepitant/fosaprepitant	cobicistat	diltiazem	fosphenytoin	etravirine
atorvastatin	darunavir	dronedarone	phenobarbital	modafinil
axitinib	delavirdine	erythromycin	phenytoin	nafcillin
bortezomib	grapefruit[3]	fluconazole	primidone	rifapentin
bosutinib[5]	grapefruit juice[3]	fosamprenavir	rifampin	
budesonide[5]	idelalisib	grapefruit[3]	St. John's wort	
buspirone[5]	indinavir	grapefruit juice[3]		
cabozantinib	itraconazole	imatinib		
calcium channel blockers	ketoconazole	isavuconazole		
cisapride	lopinavir/ritonavir	mifepristone		
citalopram/escitalopram	nefazodone	nilotinib		
cobimetinib[5]	nelfinavir	verapamil		
conivaptan[5]	posaconazole			
copanlisib	ritonavir			
crizotinib	saquinavir			
cyclosporine[4]	telaprevir			
dabrafenib	telithromycin			
dapsone	voriconazole			
darifenacin[5]				
darunavir[5]				
dasatinib[5]				
dexamethasone[2]				
diazepam				
dihydroergotamine				
docetaxel				
doxorubicin				
dronedarone[5]				
eletriptan[5]				
eplerenone[5]				
ergotamine[4]				
erlotinib				
estrogens				
etoposide				
everolimus[5]				
fentanyl[4]				
gefitinib				
haloperidol				
ibrutinib[5]				
idelalisib				
imatinib				
indinavir[5]				
irinotecan				
isavuconazole[5]				
itraconazole				
ivacaftor				

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Refer to Section 4.1.3 regarding use of corticosteroids. The use of corticosteroids is permitted on the study.
[3] The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4] Narrow therapeutic range substrates
[5] Sensitive substrates (drugs that demonstrate an increase in AUC of ≥ 5-fold with strong inhibitors)

APPENDIX IX: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, **temsirolimus**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Temsirolimus interacts with certain specific enzymes in your liver* and certain transport proteins that help move drugs in and out of cells**.

- *The enzyme in question is **CYP3A4 isoenzyme**. Temsirolimus is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
- **The protein in question is **P-glycoprotein**. Temsirolimus is moved in and out of cells/organs by this transport protein.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Temsirolimus may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Temsirolimus must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **moderate to strong inducers/inhibitors of CYP3A4 isoenzyme or P-glycoprotein**.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain

ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Examples include certain heart and blood pressure medications (eg., amiodarone, dronedarone, propafenone, quinidine, ranolazine, carvedilol, verapamil), antibiotics (eg., clarithromycin, erythromycin, rifampin), antifungals (eg., itraconazole, voriconazole), anti-seizure medications (eg., carbamazepine, phenytoin, phenobarbital), antiretrovirals (eg., lapatinib, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir), and herbal supplements (eg., St. John's wart, grapefruit or grapefruit juice).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **temsirolimus.** This clinical trial is sponsored by the NCI. **Temsirolimus** may interact with drugs that are **processed by your liver, or use certain transport proteins in your body**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Temsirolimus interacts with a **specific liver enzyme called CYP3A4 and a transport protein called P-glycoprotein**, and must be used very carefully with other medicines that interact with this enzyme and/or transporter.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **moderate to strong inducers/inhibitors of CYP3A4, or P-glycoprotein.**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

POSSIBLE DRUG INTERACTIONS

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

Some drugs, food, and supplements may interact with temsirolimus. Examples include:

Drugs that may interact with temsirolimus

• Antibiotics
  ○ Clarithromycin, erythromycin, metronidazole, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Clozapine, desvenlafaxine, nefazodone
• Antidiabetic agents
• Antifungals
  ○ Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine, sirolimus, tacrolimus
• Antiretrovirals and antivirals
  ○ Atazanavir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lapatinib, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, telaprevir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart and blood pressure medications
  ○ Accupril, amiodarone, amlodipine, captopril, carvedilol, diltiazem, dronedarone, enalapril, felodipine, isradipine, lisinopril, nicardipine, nifedipine, nimodipine, propafenone, quinidine, ranolazine, ramipril, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, bosentan, conivaptan, cobicistat, deferasirox, ivacaftor, mifepristone, natalizumab, tocilizumab

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

Some drugs, food, and supplements may interact with cyclophosphamide. Examples include:

Drugs that may interact with cyclophosphamide
• Allopurinol • Amiodarone • Carbamazepine • Cyclosporine • Digoxin • Efavirenz • Etanercept • Hydrochlorothiazide • Lumacaftor • Mifepristone • Pentostatin • Rifampin • Ritonavir • Warfarin

Food and supplements that may interact with cyclophosphamide
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Some drugs, food, and supplements may interact with dactinomycin. Examples include:

Drugs that may interact with dactinomycin
• Clozapine, leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with dactinomycin
• Echinacea

Some drugs, food, and supplements may interact with irinotecan. Examples include:

Drugs that may interact with irinotecan

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Clozapine, nefazodone
• Antifungals
  ○ Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib

- Anti-rejection medications
  - Cyclosporine
- Antiretrovirals and antivirals
  - Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, carvedilol, dronedenarone, diltiazem, propafenone, quinidine, ranolazine, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Aprepitant, bosentan, cobicistat, conivaptan, ivacaftor, mifepristone, modafinil, natalizumab

Food and supplements that may interact with irinotecan

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with <u>vincristine</u>. Examples include:

Drugs that may interact with vincristine

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

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

Some drugs, food, and supplements may interact with vinorelbine. Examples include:

Drugs that may interact with vinorelbine
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin • Antidepressants and antipsychotics o Clozapine, nefazodone • Antifungals o Fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Antiretrovirals and antivirals o Atazanavir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir • Anti-seizure medications o Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, diltiazem, dronedarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, bosentan, cobicistat, conivapatan, deferasirox, fosnetupitant, ivacaftor, lomitapide, mifepristone, modafinil natalizumab, netupitant

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

APPENDIX X: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

***NOTE**: Institutional practice may be used in place of these guidelines.*

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

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

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

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

Please follow these directions carefully, using dosing guidelines below:

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

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

APPENDIX XI: CYCLOPHOSPHAMIDE DOSING GUIDELINES DURING MAINTENANCE

Cyclophosphamide 25 mg/m^2 PO daily

Body Surface Area (m^2)*	US sites Suggested Daily Dose (d) over 7 days (1 capsule = 25 mg)	Canadian sites Suggested Daily Dose (d) over 7 days (1 tablet = 25 mg)	Cumulative Weekly Dose
0.32-0.38	use liquid formulation	1/2 tab / d x 5	62.5 mg/wk
0.39-0.46	use liquid formulation	1/2 tab / d x 6	75 mg/wk
0.47-0.53	use liquid formulation	1/2 tab /d x 7	87.5 mg/wk
0.54-0.60	use liquid formulation	1 tab / d x 2; 1/2 tab / d x 4	100 mg/wk
0.61-0.64	use liquid formulation	1 tab / d x 2; 1/2 tab / d x 5	112.5 mg/wk
0.65 - 0.78	1 cap / d x 5	1 tab / d x 3; 1/2 tab / d x 4	125 mg/wk
0.79 - 0.92	1 cap / d x 6	1 tab / d x 6	150 mg/wk
0.93 – 1.07	1 cap / d x 7	1 tab / d x 7	175 mg/wk
1.08 – 1.21	2 cap / d x 1; 1 cap / d x 6	2 tab / d x 1; 1 tab / d x 6	200 mg/wk
1.22 – 1.35	2 cap / d x 2; 1 cap / d x 5	2 tab / d x 2; 1 tab / d x 5	225 mg/wk
1.36 – 1.49	2 cap / d x 3; 1 cap / d x 4	2 tab / d x 3; 1 tab / d x 4	250 mg/wk
1.50 – 1.64	2 cap / d x 4; 1 cap / d x 3	2 tab / d x 4; 1 tab / d x 3	275 mg/wk
1.65 – 1.78	2 cap / d x 5; 1 cap / d x 2	2 tab / d x 5; 1 tab / d x 2	300 mg/wk
1.79 – 1.92	2 cap / d x 6; 1 cap / d x 1	2 tab / d x 6; 1 tab / d x 1	325 mg/wk
1.93 – 2.07	2 cap / d x 7	2 tab / d x 7	350 mg/wk
2.08 – 2.21	3 cap / d x 1; 2 cap / d x 6	3 tab / d x 1; 2 tab / d x 6	375 mg/wk
2.22 - 2.35	3 cap / d x 2; 2 cap / d x 5	3 tab / d x 2; 2 tab / d x 5	400 mg/wk
2.36 – 2.49	3 cap / d x 3; 2 cap / d x 4	3 tab / d x 3; 2 tab / d x 4	425 mg/wk
2.50 – 2.64	3 cap / d x 4; 2 cap / d x 3	3 tab / d x 4; 2 tab / d x 3	450 mg/wk
2.65 – 2.78	3 cap / d x 5; 2 cap / d x 2	3 tab / d x 5; 2 tab / d x 2	475 mg/wk
2.79 – 2.92	3 cap / d x 6; 2 cap / d x 1	3 tab / d x 6; 2 tab / d x 1	500 mg/wk
2.93 – 3.00*	3 cap / d x 7	3 tab / d x 7	525 mg/wk

Body Surface Area (m^2)*	Australia/New Zealand sites Suggested Daily Dose (d) over 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
< 1.3	use liquid formulation	
1.3 – 1.57	1 tab / d x 5	250 mg/wk
1.58 – 1.85	1 tab / d x 6	300 mg/wk
1.86 – 2.14	1 tab / d x 7	350 mg/wk
2.15 - 2.42	2 tab / d x 1; 1 tab / d x 6	400 mg/wk
2.43 – 2.71	2 tab / d x 2; 1 tab / d x 5	450 mg/wk
2.72 – 3*	2 tab / d x 3; 1 tab / d x 4	500 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their cyclophosphamide doses calculated on actual BSA with no maximum dose.*

APPENDIX XII: INSTRUCTIONS FOR CYCLOPHOSPHAMIDE TABLETS PREPARATION, ADMINISTRATION AND SAFE HANDLING (CANADIAN SITES)

Patient Name: _____ Cycle#: _____ Date Range: _____

Cyclophosphamide is an oral medicine for the treatment of cancer. This information sheet will help you prepare, administer, store, and dispose of the medicine. Please read the information before preparing and giving the medicine. If you have any questions, please contact:_____

WHAT DO I NEED?

You should use the following number of tablets for each dose): 25 mg is a full tablet and 12.5 mg is half a tablet:

_____

Give each dose by mouth on time each morning for the number of days per week that your doctor tells you to give cyclophosphamide to your child.

You should give the cyclophosphamide on the following days of the week:_____

Supplies:

Cyclophosphamide tablets as above

Disposable pad or paper towels

Disposable gloves and mask

A pair of goggles (eye protection)

Gown or designated shirt used for chemotherapy medication only

Disposable medicine cup

Tablet splitter used for chemotherapy medication only

Tweezers used for chemotherapy medications only

Oral syringe(s) with caps, if using liquid to dissolve drug

Disposable clear plastic bag

A container to collect waste (zip top plastic bag or medical waste bag or container)

HOW DO I STORE THE MEDICINE AND WASTE?

Store the medication in the original bottle away from food and out of the reach of children or pets. Store the waste container out of the reach of children or pets.

WHAT SAFETY MEASURES SHOULD I TAKE?

If the medicine gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. If you spilled the medicine on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention if the skin becomes red, irritated, or if you are concerned. Call your doctor or nurse immediately at:_____

HOW DO I PREPARE AND GIVE THE MEDICINE?

CAUTION: If you are pregnant, could become pregnant, or are breast-feeding, DO NOT prepare or administer this medicine.

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Wash your hands with soap and water; dry them well.
4. Put on a gown. If you do not have a gown select a designated shirt to wear when preparing this medication and wash separately.
5. Put on disposable mask, a pair of goggles or eye protection and then your disposable gloves.
6. Place a disposable pad or paper towel on the clean working space and place all supplies on the pad or paper towel.
7. Do not crush the tablets.
8. If you need to split the tablets in half to obtain the correct dose for your child please do it immediately before your child's dose is due.
9. Use a pair of tweezers to place tablet in the splitter and to remove the split tablet piece.
10. Gently lower the lid of the splitter and ensure the tablet splits into two equal halves.
11. Discard any remaining piece of tablet in waste collection container. Do not put back in the medicine bottle/container.
12. If your child cannot swallow the tablet whole, dissolve the tablet in water as follows:
    - *a.* Put water in a medicine cup. Do not use other drinks such as juice or a soft drink.
    - *b.* Remove the plunger of the syringe.
    - *c.* With tweezers, place the required number of tablets (including part tablets) into the barrel of the oral syringe.
    - *d.* Replace the plunger and push in until it touches the tablets within. Cap the syringe.
    - *e.* Hold the syringe so that the plunger will not move (thumb on plunger) and place in a clear plastic bag. Gently tap on the absorbent pad surface to break up the tablets.
    - *f.* Place the medicine cup with water into a plastic bag and draw up 5 mL (one teaspoon) to 7.5 mL (one and 1/2 teaspoons) of water. Cap the syringe.
    - *g.* Gently rock syringe back and forth to mix.
    - *h.* The dose should be given as soon as the tablet breaks apart (2 to 5 minutes). Note that you may see small particles floating in the water. It is fine to give the medicine like this to your child.
    - *i.* After the dose has been given, draw up another 5 mL (one teaspoon) of water into the same syringe. Give this to your child to ensure there is no medicine left in the syringe.

ADDITIONAL INFORMATION ON HOW TO CARE FOR YOUR CHILD TAKING CYCLOPHOSPHAMIDE

- Take/give an anti-nausea medicine 30-60 minutes before the cyclophosphamide only if instructed to do so by your doctor.
- Take/give cyclophosphamide at around the same time each morning with or without food.
- Have your child drink lots of fluid the day before and on the day he/she takes cyclophosphamide. Your doctor or nurse will tell you how much fluid your child should drink each day.
- Try to get your child to empty their bladder every 2 hours while awake and at bedtime.
- If your child is able to swallow cyclophosphamide tablets whole and the dose is vomited within 20 minutes, the dose can be repeated once. Otherwise the dose should be skipped. If the dose is vomited after taking cyclophosphamide liquid, do not repeat the dose. The next dose should be administered at the regularly scheduled time.
- If your child is unable to take a dose, or a dose is accidentally missed, place the remaining medicine from this dose in the waste container, seal, and contact your doctor or nurse for instructions.

HOW SHOULD I DISPOSE OF CHEMOTHERAPY-RELATED WASTE?

- Remove disposable gloves without touching the outside where the residual medication may linger (turn inside out). If using reusable gloves, wash the outside with soap and water and dry with paper towel before removing.
- Then remove your gown/shirt followed by your mask and goggles. Wash your hands with soap and water and dry thoroughly.
- When you are finished, place all used disposable supplies in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- Wash and dry all non-disposable items thoroughly and separately from other items such as dishes. Store reusable supplies away from other similar items; a marked plastic container would be ideal.
- Wash and dry preparation area well.
- Ask your nurse where you should dispose of your chemotherapy related waste.

APPENDIX XIII: PEDIATRIC FDG PET/CT GUIDELINES FOR ARST1431

FDG-PET/CT imaging is strongly recommended as part of staging and response evaluation in all eligible pediatric patients. Many institutions will have standard guidelines for acquisition of pediatric FDG-PET/CT. For the purposes of performing pediatric [^{18}F]-FDG PET in ARST1431 individual investigators must use this standard operating procedure as a minimum standard. An approach is outlined below which is designed to optimize acquisition.[91-97]

Patient preparation

The indication/appropriateness for PET CT exam and preparation required for the patient should be reviewed in advance. The height and weight of the patient should be measured and recorded within one week prior to the study.

Patients should be fasting for 4-6 hours before [^{18}F]-FDG injection to decrease serum glucose level and to maintain a low insulin level. Fasting should be continued during the uptake phase. If sedation is to be used the patient must be NPO for 4-6 hours. If the patient is not NPO in preparation for general anesthesia or sedation, then drinking only plain, unflavored water is permitted for example, 15 mL/kg during the 2 hours prior to injection and the patient is also encouraged to increase hydration and excretion of radiotracer. Patients must not drink liquids containing sugar. Glucose-containing IV fluids and parenteral nutrition must be discontinued and replaced by saline IV fluid at least 4 hours prior to injection. The serum glucose level should be measured before the radiotracer administration. The glucose level should be below 200 mg/dL (11.1 mmol/L). If the blood glucose level is found to be more than 200 mg/dL (11.1 mmol/L), the referring physician should be notified and the study should be rescheduled, if possible, when better glucose control is achieved. If anesthesia/sedation is needed for a high quality study, then NPO guidelines (minimum 4 hours) or per local regulations will apply. If clear liquids are permissible within 4 hours prior to injection, liquids must not contain glucose or other carbohydrates. Tests for pregnancy will be performed in females who have reached puberty per institutional protocol. If positive, the study will be deferred until the risks vs benefits of the scan are discussed with the referring physician and with the patient/legal guardian/parent.

The patient should be sitting in a chair or lying on a bed in a quiet, dimly lit, warm room for [^{18}F]-FDG injection and during the uptake phase. Patients should avoid exercising or chewing immediately before and after [^{18}F]-FDG is administered. Vigorous exercise should be avoided for 24 hours before the examination to avoid increased muscle uptake. To minimize the patient's distress and muscle tension, a peripheral IV access should be obtained in advance. Anesthetic cream or other distraction methods can be used to minimize pain. If a central line is used for tracer injection the line should be flushed with a sufficient amount of normal saline solution.

To reduce brown fat uptake, the uptake room should be warm (minimum 25°C) both before and after injection. Pharmacologic methods to reduce brown fat uptake include, oral propranolol, oral diazepam, or intravenous fentanyl, and may be employed per institutional protocols.

Recommended FDG-PET/CT Imaging Sequence and Details

Intravenous administration of FDG

Dose:
Please use 0.1 to 0.14 mCi/kg, minimum of 0.7 mCi, maximum of 12 mCi. This applies to pediatric patients from newborns to 21 years of age. The dose may be influenced by the characteristics of the PET CT scanner. Modern scanners have higher sensitivity than older scanners and require less activity for high quality images than do older scanners.

The North American Guidelines for Pediatric Nuclear Medicine for high-quality images at low radiation dose can be found at "http://snmmi.files.cms-plus.com/docs/GoWithGuidelines_files/ImageGentlyPoster_2017.pdf

Uptake period:
Patient should remain at rest in a warm, quiet, dimly light uptake room for the uptake period. Patients should empty their bladder immediately prior to imaging. Imaging must begin 60 minutes +/- 10 minutes after FDG injection. Follow-up PET CT scans should match the technique of the baseline PET CT when possible (including same machine and software level when able).

Imaging should include the base of skull through thighs at a minimum. Some trial protocols may require total body imaging on all patients. For children and short adolescents imaging of the entire body is preferred.

Imaging typically begins with CT acquisition. CT parameters will vary depending on institutional protocols and the quality of CT desired. CT options available include, but are not limited to:

1. C-CT (non-contrast enhanced CT) for CTAC (CT for attenuation correction and lesion localization) of the entire body is used at the majority of centers in the US in 2020. Arms may be placed by the patient's side or raised. The side position may be more comfortable for longer duration PET CT scans and is preferred for head and neck tumors. Here, the CT is not intended for diagnostic purposes. Acquisition parameters will vary among institutions. In general, acquisition parameters for the low-dose CT scan for attenuation correction should be approximately as follows: kV = 80-120; effective mAs = 10-80 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed width = 3-5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; with or without iodinated contrast.
2. Some centers will acquire a fully diagnostic C+CT (or contrast-enhanced CT in place of the non-contrast enhanced CTAC) with breath-hold, intravenous and/or oral contrast depending on the location of the primary tumor. The axial extent of the fully diagnostic CT vary and might be restricted to those regions of the body that require high anatomic detail, such as the lungs, or other areas of tumor location. Use of the diagnostic CT for attenuation correction may result in slightly lower overall radiation exposure compared to obtaining a PET/CT and diagnostic CT separately.

   The use of CT contrast during the time of PET may vary by institution protocol as this is not routinely performed in the US at this time (late 2020). If IV or iodine containing oral

contrast is used, please also follow institutional guidelines for consent and patient safety regarding possible contrast allergy and renal function guidelines.

- The axial field of view of the CT scan for attenuation correction should match that of the PET acquisition and will likely range from the skull base to mid thighs at a minimum and in some cases will be full body, like the PET study - top of the head through the toes. Arm positioning will be the same as for the PET scan.
- The CT scan will be performed during the patient's normal breathing for a non-diagnostic, C-CT attenuation correction only exam. Respiratory gating is not routine in this circumstance. After the CT scan, a PET scan covering the same axial field of view should be performed. Most often PET imaging will start at the head and proceed inferiorly. The number of bed positions and the acquisition time per bed position will be patient and scanner specific. Typical parameters are 6 bed positions and an acquisition of 2 to 5 minutes per bed position.
- Additional diagnostic-quality CT of the neck or other areas should be performed with contrast if needed to fulfill requirements for anatomic post-treatment imaging.

FDG-PET/CT Image Reconstruction

The PET/CT data will be corrected for dead time, scatter, random coincidence events detected, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck or other views, a post-filter with a full-width at half maximum (FWHM) in the range of 5 mm is recommended.

Specific details of the CT and PET acquisitions will vary per machine and local customs. KvP, mA, kernel, slice thickness, rotation speed, patient feed (mm/sec), window and levels can all be varied at CT. For PET, various iterations, zooms, filters, colors can be applied per institution and manufacturer preferences.

For output, please include:

- PET MIP
- Soft tissue (and where appropriate lung, bone, and/or brain windows) reconstructions in the axial, sagittal, and coronal planes for CT. Please also reconstruct PET in these same planes and also provide fused images in these planes.
- Attenuation and non-attenuation corrected PET image sets should be provided in these planes
- A final set of key images (with comparison to prior exams) is not required, although many find this helpful for final review and image sharing
- Please include CTDI vol and DLP (for CT) whenever possible. This might be required in some locations, where reporting of these is required by law.

Image analysis and interpretation: PET CT images should be relayed to a PACS (picture archiving and communication system) and/or nuclear medicine workstation for analysis and data storage. Report should include description of findings such as location, extent, and intensity of any abnormal [^{18}F]-FDG activity, and relevant CT morphologic findings related to PET abnormalities on CT images. The intensity of [^{18}F]-FDG activity can be described as mild,

moderate, or intense. It can alternatively or additionally be described semi-quantitatively as the SUV (usually SUV_{max}). The intensity of [^{18}F]-FDG activity can be also compared with the blood pool and liver background activity. The Deauville score may be applicable in certain protocols, particularly lymphomas. As some protocols will also require SUV comparison to a normal appearing portion of the liver, please include this value in reports. Any incidental finding on either PET or CT should be reported. The findings should be compared with the previous relevant studies. The limitations, if any (e.g. previous G-CSF use and limited bone marrow evaluation, patient motion, altered biodistribution of radiotracer, etc.), and how they may affect the results of the study should be reported. Structured reports may be incorporated per institutional preference.

PET/MRI may be used if available. The MRI serves as the basis for attenuation correction. MRI sequences should be obtained per local institutional preferences. At institutions where both PET/CT and PET/MRI are available, it is recommended that whichever technology is used initially be used for subsequent evaluations.

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