CureSearch
Children's Oncology Group

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CHILDREN'S ONCOLOGY GROUP
APPENDIX FOR

AOST0331
A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histological Response to Pre-Operative Chemotherapy ([redacted]

A Phase III Intergroup Study

Statistics and Data Center Contact: https://members.childrensoncologygroup.org

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[redacted]

For Group Operations (GOC) and
Statistics and Data Center (SDC) contacts see:
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AGENT NSC# [redacted]
Doxorubicin #123127
Cisplatin # 119875
Methotrexate #000740
Ifosfamide #109724
Etoposide #141540
Pegylated interferon alfa-2b # 720033 [redacted]

SEE SECTION 15.0 FOR SPECIMEN SHIPPING ADDRESSES

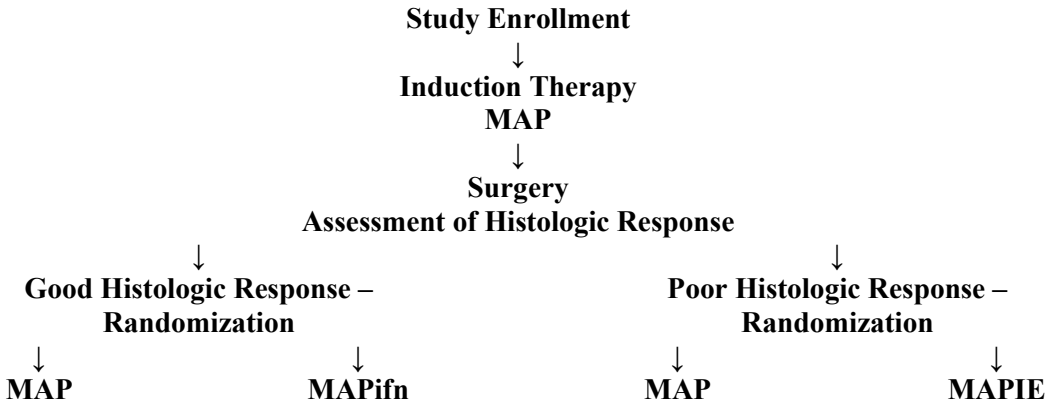
The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others

ABSTRACT

EURAMOS 1 is a joint protocol of four of the world‟s leading multi-institutional osteosarcoma groups (COG, COSS, EORTC/MRC, SSG). The collaboration‟s main aim is to optimize the treatment of patients suffering from osteosarcoma. The EURAMOS 1 trial is open for all patients with resectable high-grade osteosarcoma of the limbs or axial skeleton, whether the tumor is localized or primarily metastatic, who are considered suitable for neo-adjuvant chemotherapy. The trial takes into account the strong prognostic value of tumor response to preoperative chemotherapy and divides patients accordingly. All patients registered will receive a standard three-drug induction regimen consisting of 2 cycles of cisplatin and doxorubicin along with four cycles of methotrexate (**MAP**). After recovery from chemotherapy, patients then proceed to surgical resection. Post-operative therapy is determined by the histological response of the tumor. Good responders (< 10% viable tumor) will be randomized to continue with **MAP**, or receive pegylated interferon alfa-2b as maintenance therapy after MAP (**MAPifn**). Poor responders (≥ 10% viable tumor) will be randomized to continue with **MAP** or to receive the same regimen with the addition of ifosfamide and etoposide (**MAPIE**). Event-free survival is the primary endpoint.

EXPERIMENTAL DESIGN SCHEMA



MAP = doxorubicin, cisplatin, methotrexate
MAPIE = doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide
MAPifn = doxorubicin, cisplatin, methotrexate, pegylated interferon alfa-2b

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Primary:

1.1
In a randomized setting, to examine whether the addition of ifosfamide and etoposide (IE) to post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival for patients with resectable osteosarcoma and a poor histological response to 10 weeks of pre-operative chemotherapy.

1.2
In a randomized setting, to examine whether the addition of pegylated interferon alfa-2b as maintenance therapy after post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival for patients with resectable osteosarcoma and a good histological response to 10 weeks of pre-operative chemotherapy.

Secondary:

1.3
To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of Peg-Intron as maintenance therapy for good responders, leads to an improvement in the following outcomes:

a. Overall survival
b. Short-term toxicity
c. Long-term toxicity
d. Quality of life

1.4
To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of Peg-Intron as maintenance therapy for good responders, leads to an improvement in event-free and overall survival in patients with localized osteosarcoma at entry.

1.5
To investigate whether biological or clinical correlates to histological response and outcome can be identified by encouraging enrollment on a COG osteosarcoma specimen collection study.

1.6
To examine the outcome of the entire cohort of patients.

2.0 BACKGROUND

Please see EURAMOS 1 protocol document for complete background and references.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has

been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

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

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

3.1.2 IRB Approval

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

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

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

3.1.3 Study Enrollment

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

3.1.4 Timing

Study enrollment must take place within five calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than five (5) calendar days after enrollment.

3.1.5 Bilingual Services

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

3.1.6 Post-Surgical Randomization

Patients will be randomized based on local institutional assessment of histologic response in primary tumor following definitive surgery. Institutions are also required to submit surgical specimens for central review within 21 days of surgical procedure. Randomization to one of the treatment arms after induction therapy and evaluation must be performed within 35 days from date of definitive surgery. Treatment will be allocated using permuted tables, stratified by group, site of primary tumor and presence of metastases. Patients with a good histologic response to pre-operative therapy will be randomized to either continuing MAP (cisplatin, doxorubicin and methotrexate) or MAP plus Pegylated interferon alfa-2b. Patients with a poor histologic response will be randomized to continuing MAP or MAP plus ifosfamide and etoposide.

Patients must fulfill the following criteria for post-surgical randomization to occur:

3.1.6.1
Local institutional assessment of histologic response in the primary tumor following definitive surgery.

3.1.6.2
The combination of cisplatin and doxorubicin must have been administered exactly twice before surgery.

3.1.6.3
Methotrexate must have been administered at least twice but no more than six times before surgery.

3.1.6.4
Recovery from prior therapy allowing administration of chemotherapy as detailed in the protocol.

3.1.6.5
No evidence of disease progression as defined in section 11.2.5

3.1.6.5.1
No definite progression of metastatic disease and no evidence of new metastatic disease.

3.1.6.5.2
If local disease progression has resulted in surgery being performed prior to the administration of chemotherapy as required in Sections 3.1.6.2 and 3.1.6.3, the patient is off protocol therapy and will not be randomized (see Section 9.1).

3.1.6.6
Macroscopically complete surgical resection of the primary tumor

3.1.6.7
In patients with metastatic disease, complete removal of all metastases or complete removal planned and deemed feasible.

3.2 Patient Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy 7.2). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

3.2.1 Age
Patients must be ≥ 5 years and ≤ 40 years on date of diagnostic biopsy.

3.2.2 Diagnosis

3.2.2.1
Patients must have high grade osteosarcoma. This includes second malignancies.

3.2.2.2
Submission of diagnostic biopsy for rapid central review of diagnostic biopsy materials is required on this study.

3.2.2.3
The site of the primary tumor must be in:

Long bone of upper limb, scapula (C40.0)
Short bone of upper limb (C40.1)
Long bone of lower limb (C40.2)
Short bone of lower limb (C40.3)
Vertebral column (C41.2)
Ribs, sternum, clavicle (C41.3)
Pelvic bones, sacrum, coccyx (C41.4)

Craniofacial osteosarcoma is NOT included.

3.2.2.4
All tumor (primary, metastatic, or both) is resectable or is expected to become resectable after the initial chemotherapy.

3.2.3 Performance Level
Patients must have a Karnofsky score ≥ 50 or WHO/ECOG ≥ 2 for patients age ≥ 16, Lansky score ≥ 50 for patients age < 16 (for Performance Status Scales Scoring see https://members.childrensoncologygroup.org/prot/reference_materials.asp under **Standard Sections for Protocols**). Patients whose performance status is adversely affected by a pathologic fracture but who are able to undergo treatment are eligible.

3.2.4 Prior Therapy:
No previous treatment for osteosarcoma or previous chemotherapy for any disease. Previous radiotherapy for a prior cancer (other than osteosarcoma) is permitted.

3.2.5 Organ Function Requirements:

3.2.5.1 Adequate Renal Function Defined As:
- Creatinine clearance or radioisotope GFR ≥ 70ml/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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

See Also Appendix A.3 of the Intergroup document (AOST0331_euramos.pdf).

3.2.5.2 Adequate cardiac function defined as:
- Shortening fraction of ≥ 28% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.5.3 Adequate hematologic function defined as:

- Neutrophils $\geq 1.5 \times 10^9$/L (or WBC $\geq 3 \times 10^9$/L if neutrophils are not available) and platelet count $\geq 100 \times 10^9$/L

3.2.5.4 Adequate liver function defined as:

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

3.2.6 Other criteria

3.2.6.1
Female patients must have a negative pregnancy test.

3.2.6.2
Female patients who are lactating must agree to stop breast-feeding.

3.2.6.3
Patients must not be known to be HIV positive. Testing for HIV is not mandatory.

3.2.6.4
Sexually active patients of childbearing potential must agree to use effective contraception.

3.2.6.5
Patients must be able to cooperate fully with all planned protocol therapy.

3.2.7 Regulatory

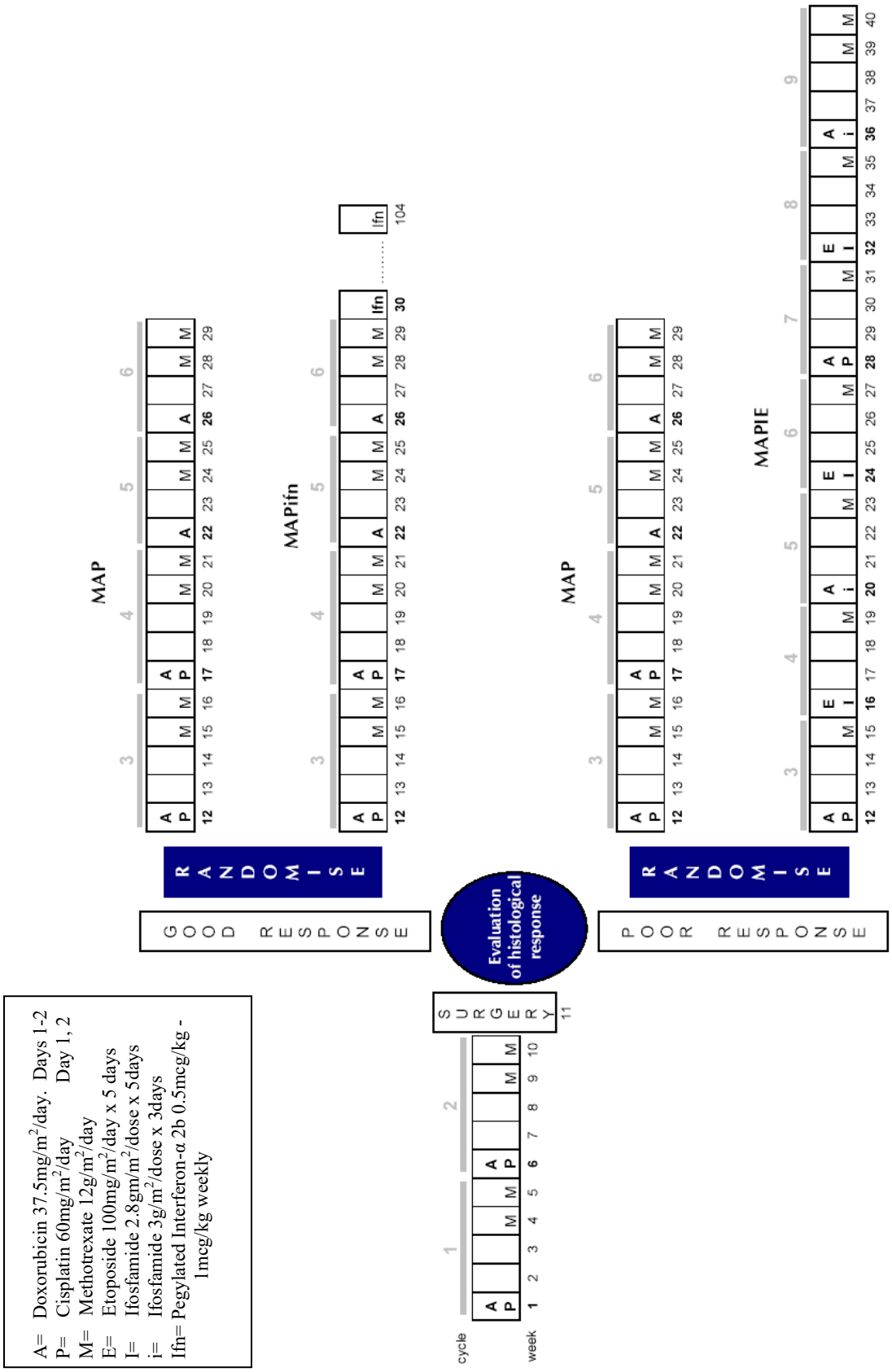
3.2.7.1
All patients and/or their parents or legal guardians must sign a written informed consent.

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

4.0 TREATMENT PLAN

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

TREATMENT SCHEMA



4.1 General Treatment Information

4.1.1 Induction – MAP Therapy- All Patients

Induction therapy lasts 10 weeks and consists of two cycles of MAP (doxorubicin-cisplatin and high dose methotrexate therapy). If administrative issues preclude surgical resection at Week 10, patients may receive up to two additional cycles of high dose methotrexate (maximum of 6 cycles of methotrexate) before surgical resection/amputation. In addition, if a patient develops mucositis or transaminase elevations precluding administration of back-to-back methotrexate cycles, the patient may receive only 2 cycles of high dose methotrexate (instead of four) before the surgical procedure.

Drug administration instructions should be followed except when they vary from institutional chemotherapy standards developed for purposes of promoting medication safety, and approved by the institutional Therapeutic Standards Committee or equivalent body.

4.1.2 Local Control

At Week 11 surgery will be done (see Section 14.0 for complete surgical directions). An evaluation of histologic response is essential (see Section 15.0 for information about this evaluation).

Please note: All chemotherapy doses should be calculated using pre-surgery body surface area with no adjustment for limb loss.

Radiation therapy is not recommended for patients on this study. However, if treating physicians must use radiation therapy for compelling clinical reasons, COG radiation therapy guidelines have been provided in Section 18.

At randomization, the institutional assessment of histologic response will be used in determining whether the criteria for randomization have been met. Institutions are also required to submit the surgical specimen for central review. See Section 15.0 for further details.

4.1.3 Treatment assignment after induction

Patients must fulfill the following criteria for randomization after surgery:

- Local institutional assessment of histological response in primary tumor following definitive surgery
- Exactly two courses of cisplatin and doxorubicin must have been administered before surgery
- At least two courses and no more than six courses of methotrexate must have been administered before surgery
- No severe toxicity precluding post-operative treatment
- No progression of metastatic disease or new metastatic disease
- No progression of localized tumor (see Section 9.1)
- Macroscopically complete surgical resection of the primary tumor
- In patients with metastatic disease, complete removal of all metastases or complete removal planned and deemed feasible
- Essential data for eligibility, chemotherapy, surgery, and pathology provided to SDC
- Written consent to undergo randomization obtained

4.1.3.1

Patients with good histologic response after induction therapy will be randomized to receive either therapy with MAP (29 total weeks of therapy) or with MAP plus pegylated interferon alfa-2b (104 total weeks of therapy). Week 12 and Week 15 MAP therapy may be started before randomization assignment is made, if the patient meets criteria to begin treatment but the pathology on the definitive surgical specimen has not yet been obtained.

4.1.3.2
Patients with poor histologic response after induction therapy will be randomized to receive either therapy with MAP (29 total weeks of therapy) or with MAP plus ifosfamide and etoposide (40 total weeks of therapy). Week 12 and Week 15 MAP therapy may be started before randomization assignment is made, if the patient meets criteria to begin treatment but the pathology on the definitive surgical specimen has not yet been obtained.

4.1.3.3
Patients who did not receive sufficient chemotherapy to allow randomization are recommended to receive post-operative chemotherapy with MAP. Patients who experience tumor progression during pre-operative treatment are recommended to receive post-operative treatment with MAPIE. Patients who are not eligible for randomization because macroscopically complete surgical resection could not be done should receive radiotherapy and/or other experimental treatments as determined at the treating institution.

All patients enrolled on AOST0331 will remain on-study for follow-up information until the conditions in Section 9.2 are met.

For imaging guidelines while on study and at end of therapy and during follow-up see Section 17.0. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp, under standard sections for protocols.

4.2 Administration schedule for MAP Cycles 1-2, All Patients

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 1 and 6.
Dose: 37.5 mg/m²/Daily dose (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1and 2 of Weeks 1 and 6, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

CISplatin: IV over 4 hours
Days: 1 and 2 of Weeks 1 and 6.
Dose: 60 mg/ m²/dose

Methotrexate: IV over 4 hours
Days: 1 of Weeks 4, 5, 9, and 10.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**

Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).

Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

If administrative issues preclude surgical resection at Week 11, patients may receive up to two additional cycles of high dose methotrexate (maximum of 6 cycles of methotrexate) before surgical resection/amputation. When additional cycles of high dose methotrexate are planned, give one week off after the last scheduled methotrexate and then give one or two extra doses weekly depending on when resection can be scheduled. In addition, if a patient develops mucositis or transaminase elevations precluding administration of back-to-back methotrexate cycles, the patient may receive only 2 cycles of high dose methotrexate (instead of four) before the surgical procedure.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAP Cycles 1 and 2 is on the next page.

Following completion of Cycle 2 MAP, surgery and assessment of histologic response in primary tumor will occur. Upon evaluation of histological response, patients will be randomized to receive MAP, MAPIE, or MAPifn therapy beginning at Week 12. See Section 4.1.3 for randomization information.

For Good and Poor responders randomized to receive MAP – see Section 4.3
For Good responders randomized to receive MAPifn –see Section 4.5
For Poor responders randomized to receive MAPIE –see Section 4.8

4.2.1 **MAP Cycles 1-2, All patients** Each cycle lasts 5 weeks. This therapy delivery map relates to Weeks 1-5 and Weeks 6-10 of MAP therapy.	_____ Patient name or initials _____ DOB

This therapy delivery Map is on one (1) page. Treatment details are provided in Section 4.2. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. Methotrexate at Weeks 4, 5, 9 and 10 can be administered as long as ANC is at least 250/µL and platelets at least 50 000/µL.

DRUG	**ROUTE**	**DOSAGE**	**DAYS**	**IMPORTANT NOTES**	**OBSERVATIONS (See Section 7.1 for baseline observations)**
DOXOrubicin* (DOXO)	IV over 48 hours	37.5 mg/m²/Daily dose*	1-2 of Weeks 1 and 6	*Total dose: 75 mg/m²/48 hours. Avoid extravasation. See Section 4.2 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including Ca^{++}, PO_4, Mg^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) GFR f) QOL assessment See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
CISplatin (CDDP)	IV over 4 hours	60 mg/ m²/dose	1 and 2 of Weeks 1 and 6		
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 4, 5, 9 and 10	**Maximum dose 20 g** See Section 4.2.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 4, 5, 9 and 10	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.2 and 19.3 for details.	

Cycle *(circle one)*: 1 2 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Date Due	Date Given	Week	Day	DOXO _____ mg	CDDP _____ mg	MTX _____g	LCV _____ mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		1 or 6	1	_____ mg	_____ mg			a, b, c, d, e@	
			2	_____ mg	_____ mg			a$	
		4 or 9	1			_____ g		a$	
			2				_____ mg		_____(date of last LCV dose)%
		5 or 10	1			_____ g		a$	
			2				_____ mg		_____(date of last LCV dose)%
			7					f ^	
				See Sections 4.1.2 and 4.1.3 for details on local control and randomization following Cycle 2. For patients randomized to receive MAP - see Section 4.3 For patients randomized to receive MAPifn –see Section 4.5 For patients randomized to receive MAPIE –see Section 4.8					

@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/cisplatin.
^ - End of Cycle 1 (after second MTX) and prior to start of Cycle 2. (see Section 16.3 for details).
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$M) (see Section 19.3 for details)

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.3 Administration Schedule for Good Responders and Poor Responders Randomized to MAP Therapy (Cycles 3-4)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 12 and 17.
Dose: 37.5 mg/m²/dose/ Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1and 2 of Weeks 12 and 17, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

CISplatin: IV over 4 hours
Days: 1 and 2 of Weeks 12 and 17.
Dose: 60 mg/ m²/dose.

Methotrexate: IV over 4 hours
Days: 1 of Weeks 15, 16, 20 and 21.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAP Cycles 3- 4 is on the next page. Following completion of MAP Cycle 4, begin MAP Cycles 5 (see Section 4.4).

4.3.1 **Good Responders and Poor Responders Randomized to MAP (Cycles 3-4)** Each cycle lasts 5 weeks. This therapy delivery map relates to Weeks 12-16 and Weeks 17-21 of MAP therapy.	_____ Patient name or initials _____ DOB

This therapy delivery Map is on one (1) page. Treatment details are provided in Section 4.3. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 15, 16, 20 and 21 can be administered as long as ANC is at least 250/µL and platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV over 48 hours	37.5mg/m²/Daily dose*	1 - 2 of Weeks 12 and 17	*Total dose: 75 mg/m²/48 hours Avoid extravasation. See Section 4.3 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urine Analysis d) Electrolytes including Ca^{++}, PO_4, Mg^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) Audiogram g) GFR See Section 17.0 for imaging requirements. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
CISplatin (CDDP)	IV over 4 hours	60 mg/ m²/dose	1 and 2 of Weeks 12 and 17		
Methotrexate+ (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 15, 16, 20 and 21	**Maximum dose 20 g.** See Section 4.3.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 15, 16, 20 and 21	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.3 and 19.3 for details.	

Cycle *(circle one)*: 3 4 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO ____mg	CDDP ____mg	MTX ____g	LCV ___mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		12 or 17	1	____mg	____mg			a, b, c, d, e+, f^, g@	
			2	____mg	____mg			a$	
		15 or 20	1			____g		a$	
			2				___mg		_____ (date of last LCV dose)%
		16 or 21	1			____g		a$	
			2				___mg		_____ (date of last LCV dose)%
				For Cycle 5 MAP (see Section 4.4). Begin next cycle ANC ≥ 750/µL and platelets ≥ 75 000/µL post nadir.					

+ - Prior to Cycle 3.
^ - Prior to Cycles 3 and 4.
@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/cisplatin.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (see Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.4 Administration Schedule for Good Responders and Poor Responders Randomized to MAP Therapy (Cycles 5 – 6)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 22 and 26.
Dose: 37.5 mg/m²/ Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 and 2 of Weeks 22 and 26, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

Methotrexate: IV over 4 hours
Days: 1 of Weeks 24, 25, 28 and 29.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L (1x10^{-7} M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L (1x10^{-7} M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L (1x10^{-7} M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAP Cycles 5-6 is on the next page. Therapy ends after MAP Cycle 6 for patients randomized to receive MAP therapy.

See Section 7.1 for required observations at the end of therapy and Section 17.0 for imaging studies required at the end of therapy.

4.4.1 **Good Responders and Poor Responders Randomized to MAP (Cycles 5 - 6)** Each cycle lasts 4 weeks. This therapy delivery map relates to Weeks 22-25 and Weeks 26-29 of MAP therapy.	_____ Patient name or initials _____ DOB

This therapy delivery Map is on one (1) page. Treatment details are provided in Section 4.4. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 24, 25, 28 and 29 can be administered as long as the ANC is at least 250/µL and platelets at least 50,000/µL

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV, over 48 hours	37.5 mg/m²/Daily dose*	1 - 2 of Weeks 22 and 26	*Total dose: 75 mg/m²/48 hours Avoid extravasation. See Section 4.4 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) QOL assessment g) GFR See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 24, 25, 28, and 29	**Maximum dose: 20 g.** See Section 4.4.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 24, 25, 28, and 29	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.4 and 19.3 for details.	

Cycle *(circle one)*: 5 6 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation.

Date Due	Date Given	Week	Day	DOXO _____mg	MTX _____g	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		22 or 26	1	_____mg			a, b, c, d, e+, g@	
			2	_____mg			a$	
		24 or 28	1		_____g		a$, f^	
			2			_____mg		_____ (date of last LCV dose)%
		25 or 29	1		_____g		a$	
			2			_____mg		_____ (date of last LCV dose)%
				Therapy ends after completion of Cycle 6 for patients on MAP. See Section 7.1 for required observations at end of therapy.				

+ - Prior to Cycle 5 and Cycle 6.
@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin.
^- After recovery from doxorubicin of Week 22/Cycle 5 and prior to methotrexate of Week 24/Cycle 5.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (see Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.5 Administration Schedule for Good Responders Randomized to MAPifn Therapy (Cycles 3-4)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf)

ANC must be ≥ 750/μL and platelets ≥ 75,000/μL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 12 and 17.
Dose: 37.5 mg/m²/Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 and 2 of Weeks 12 and 17, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

CISplatin: IV over 4 hours
Days: 1 and 2 of Weeks 12 and 17.
Dose: 60 mg/ m²/dose

Methotrexate: IV over 4 hours
Days: 1 of Weeks 15, 16, 20 and 21.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 μmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 μmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 μmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/μL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAPifn Cycles 3-4 is on the next page. Following completion of MAPifn Cycle 4, begin MAPifn Cycle 5 (see Section 4.6).

4.5.1 **Good Responders Randomized to MAPifn (Cycles 3-4)** Each cycle lasts 5 weeks. This therapy delivery map relates to Weeks 12-16 and Weeks 17-21 of MAPifn therapy.	_____ Patient name or initials _____ DOB

This therapy delivery map is on one (1) page. Treatment details are provided in Section 4.5. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 15, 16, 20 and 21 can be administered as long as the ANC is at least 250/µL and platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV, over 48 hours	37.5mg/m²/Daily dose*	1 - 2 of Weeks 12 and 17	*Total dose: 75 mg/m²/48 hours Avoid extravasation. See Section 4.5 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) Audiogram g) GFR See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
CISplatin (CDDP)	IV over 4 hours	60 mg/ m²/dose	1 and 2 of Weeks 12 and 17	See Section 4.5	
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 15, 16, 20 and 21	**Maximum dose 20 g.** See Section 4.5	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 15, 16, 20 and 21	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.5 and 19.3 for details.	

Cycle *(circle one)*: 3 4 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO _____mg	CDDP _____mg	MTX _____g	LEUC _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		12 or 17	1	_____mg	_____mg			a, b, c, d, e+, f^, g@	
			2	_____mg	_____mg			a$	
		15 or 20	1			_____g		a$	
			2				_____mg		_____(date of last LCV dose)%
		16 or 21	1			_____g		a$	
			2				_____mg		_____(date of last LCV dose)%
				For Cycle 5 MAPifn (see Section 4.6). Begin next cycle when ANC ≥ 750/µL and platelets ≥ 75000/µL post nadir.					

\+ - Prior to Cycle 3.
^ - Prior to Cycles 3 and 4.
@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/cisplatin.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (see Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.6 Administration Schedule for Good Responders Randomized to MAPifn Therapy (Cycles 5-6)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf)

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 22 and 26.
Dose: 37.5 mg/m²/ Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 and 2 of Weeks 22 and 26, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion and within 30 minutes after the beginning of dexrazoxane infusion).

Methotrexate: IV over 4 hours
Days: 1 of Weeks 24, 25, 28 and 29.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAPifn Cycles 5- 6 is on the next page. Patients on MAPifn therapy will start pegylated interferon alfa-2b after completion of Cycle 6 MAPifn (see Section 4.7).

4.6.1 **Good Responders Randomized to MAPifn (Cycles 5- 6)** Each cycle lasts 4 weeks. This therapy delivery map relates to Weeks 22-25 and Weeks 26-29 of MAPifn therapy.	_____ Patient name or initials _____ DOB

This therapy delivery map is on one (1) page. Treatment details are provided in Section 4.6.ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 24, 25, 28 and 29 can be administered as long as the ANC is at least 250/µL and platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV, over 48 hours	37.5mg/m²/Daily dose*	1 - 2 of Weeks 22 and 26	*Total dose: 75 mg/m²/48 hours. Avoid extravasation. See Section 4.6 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) QOL assessment g) GFR See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 24, 25, 28 and 29	**Maximum dose 20 g.** See Section 4.6.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 24, 25, 28 and 29	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.6 and 19.3 for details.	

Cycle *(circle one)*: 5 6 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO _____mg	MTX _____g	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below				
		22 or 26	1	_____mg			a, b, c, d, e^+, g@	
			2	_____mg			a$	
		24 or 28	1		_____g		a$, f^	
			2			_____mg		_____(date of last LCV dose)%
		25 or 29	1		_____g		a$	
			2			_____mg		_____(date of last LCV dose)%
				Patients on MAPifn will start pegylated interferon alfa-2b after completion of Cycle 6 MAPifn. (See Section 4.7).				

+ - Prior to Cycle 5 and Cycle 6.
@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin.
^ - After recovery from doxorubicin of Week 22/Cycle 5 and prior to methotrexate of Week 24/Cycle 5.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (see Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.7 Administration Schedule for Pegylated Interferon alfa-2b Therapy for Good Responders Randomized to MAPifn, (Weeks 30-104)

See also Section 9.1.8.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf)

Criteria for beginning pegylated interferon alfa-2b therapy:

- Bilirubin ≤ 1.5 x ULN and SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- Baseline ophthalmologic evaluation WNL.
- Triglycerides WNL , Amylase WNL and Pancreatic fraction amylase or lipase WNL.
- Hemoglobin ≥ 8 g/dL; ANC ≥ 750/µL or WBC ≥ 2000/ µL and platelets ≥ 75,000/µL.
- Creatinine ≤ 1.5 x ULN.
- Karnofsky ≥ 60 (age ≥ 16) or Lansky ≥ 60 (age < 16).

Pegylated interferon alfa-2b: SubQ

Starting Dose
Days: 1 of Week 30, 31, 32, and 33.
Dose: 0.5 microgram/kg/dose **(Maximum dose 50 microgram).**
If well tolerated (no more than Grade 2 flu-like symptoms with no other toxicity more than Grade 1) during first 4 weeks of therapy, escalate dose.

Escalated Dose
Days: 1 of Weeks 34-104.
Dose: 1 microgram/kg/dose **(Maximum dose 100 microgram).**

NOTE: Pretreatment with acetaminophen/paracetamol (10-15mg/kg/dose, maximum dose 1000 mg) given 30-60 minutes before each dose of pegylated interferon alfa-2b is recommended.

Autoimmune hepatitis is a contraindication for drug administration. Any AST/ALT elevation > Grade 3 would preclude administration of interferon. Decompensated liver disease is a contraindication for use of interferon.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for MAPifn Weeks 30-104 is on the next 2 pages.

Patients randomized to receive MAPifn therapy will complete their therapy at the end of Week 104.

See Section 17.0 for imaging requirements and Section 7.1 for required observations at the end of therapy.

4.7.1 **Pegylated interferon alfa-2b Therapy for Good Responders Randomized to MAPifn (Weeks 30-104)** This therapy delivery map relates to 75 weeks of pegylated interferon alpha- 2b therapy and is on two (2) pages.	_____ Patient name or initials _____ DOB

Criteria for beginning pegylated interferon alfa-2b therapy:

- Bilirubin ≤ 1.5 x ULN and SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- Baseline ophthalmologic evaluation WNL.
- Triglycerides WNL, Amylase WNL and Pancreatic fraction amylase or lipase WNL.
- Hemoglobin ≥ 8 g/dL; ANC ≥ 750/µL or WBC ≥ 2000/ µL and platelets ≥ 75,000/µL.
- Creatinine ≤ 1.5 x ULN
- Karnofsky ≥ 60 (age ≥ 16) or Lansky ≥ 60 (age < 16).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Pegylated interferon alpha-2b [redacted]	SubQ	Starting dose: 0.5 microgram/kg* Dose escalation: to 1 microgram/kg **	1 of Weeks 30--104	***Maximum starting dose: 50 microgram.** If starting dose is well-tolerated, escalate dose at Week 34 % ****Maximum escalated dose: 100 microgram.** Pretreat with acetaminophen/paracetamol. See Section 4.7.	a) CBC/Diff/Platelets& b) H & P, PS& c) (Electrolytes/CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos)& d) Evaluation of liver function & e) Triglyceride level& f) Thyroid function& g) Ophthalmologic evaluation h) QOL assessment &- Obtain weekly for first 8 weeks, and if stable, monthly during subsequent therapy. See Section 17.0 for imaging requirements. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Use this record of doses for the entire 75 weeks or until Pegylated interferon alfa-2b is stopped, whichever occurs first.

Note Patient's starting weight: _____kg Starting Dose: _____ microgram Escalated Dose: _____ microgram **Note Patient's weight at start of increased dose: _____kg (Weight may change over these 75 weeks).**									Comments (Include any held doses, or dose modifications)
Week	30$	31	32	33	34%	35	36	37	
Date									
Dose									
Week	38	39	40	41	42	43	44	45	
Date									
Dose									
Week	46	47	48	49	50	51	52	53	
Date									
Dose									
Week	54	55	56	57	58	59	60	61	
Date									
Dose									
Week	62	63	64	65	66	67	68	69	
Date									
Dose									

$- Obtain observations **a- g** prior to the first dose of pegylated interferon alfa-2b

% - Dose escalates at Week 34 if no more than Grade 2 flu-like symptoms with no other toxicity more than Grade 1 during the first 4 weeks.

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

The therapy delivery map for Pegylated interferon alpha-2b therapy (Weeks 70-104) is continued on next page.

4.7.1 **Pegylated interferon alfa-2b Therapy for Good Responders Randomized to MAPifn (Weeks 30-104)** This therapy delivery map relates to 75 weeks of pegylated interferon alpha- 2b therapy and is on 2 pages.	_____ Patient name or initials _____ DOB

Criteria for beginning pegylated interferon alfa-2b therapy:

- Bilirubin ≤ 1.5 x ULN and SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- Baseline ophthalmologic evaluation WNL
- Triglycerides WNL , Amylase WNL and Pancreatic fraction amylase or lipase WNL
- Hemoglobin ≥ 8 g/dL; ANC ≥ 750/µL or WBC ≥ 2000/ µL and platelets ≥ 75,000/µL.
- Creatinine ≤ 1.5 x ULN
- Karnofsky ≥ 60 (age ≥ 16) or Lansky ≥ 60 (age < 16).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Pegylated interferon alpha-2b [redacted]	SubQ	Starting dose: 0.5 microgram/kg * Dose escalation: to 1 microgram/kg**	1 of Weeks 30--104	***Maximum starting dose: 50 microgram.** If starting dose is well-tolerated, escalate dose at Week 34 ****Maximum escalated dose: 100 microgram.** Pretreat with acetaminophen/paracetamol. See Section 4.7.	a) CBC/Diff/Platelets& b) H & P, PS c) (Electrolytes/CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos)& d) Evaluation of liver function& e) Triglyceride level& f) Thyroid function & g) Ophthalmologic evaluation h) QOL assessment &- Obtain weekly for first 8 weeks, and if stable, monthly during subsequent therapy. See Section 17.0 for imaging requirements. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Use this record of doses for the entire 75 weeks or until Pegylated interferon alfa-2b is stopped, whichever occurs first.

Note Patient's starting weight: _____kg Starting Dose: _____ microgram Escalated Dose: _____ microgram **Note Patient's weight at start of increased dose: _____kg (Weight may change over these 75 weeks).**									Comments (Include any held doses, or dose modifications)
Week	70	71	72#	73	74	75	76	77	
Date									
Dose									
Week	78	79	80	81	82	83	84	85	
Date									
Dose									
Week	86	87	88	89	90	91	92	93	
Date									
Dose									
Week	94	95	96	97	98	99	100	101	
Date									
Dose									
Week	102	103	104						
Date									
Dose									
	Therapy ends after completion of Week 104 for patients on MAPifn. See Section 7.1 for required observations at end of therapy.								

#- QOL assessment at Week 72 from start of therapy (+/– 4 weeks). (See Section 16.3 for details.)

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.8 Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycles 3 and 7)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Weeks 12 and 28.
Dose: 37.5 mg/m²/Daily dose (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 & 2 of Weeks 12 & 28, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

CISplatin: IV over 4 hours
Days: 1 and 2 of Weeks 12 and 28.
Dose: 60 mg/ m²/dose.

Methotrexate: IV over 4 hours
Days: 1 of Weeks 15 and 31.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

Growth factor:
Myeloid growth factor support is recommended when a previous doxorubicin/cisplatin cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (> 7 days). Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map for MAPIE Cycles 3 and 7 is on the next page.
Following completion of Cycle 3 MAPIE, begin Cycle 4 MAPIE (see section 4.9).
Following completion of Cycle 7 MAPIE, begin Cycle 8 MAPIE (see section 4.9).

4.8.1 **Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycles 3 and 7)** Each cycle lasts 4 weeks. This therapy delivery map relates to Weeks 12-15 and Weeks 28-31of MAPIE therapy.	_____ Patient name or initials _____ DOB

This Therapy delivery Map is on one (1) page. Treatment details are provided in Section 4.8. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 15 and 31 can be administered as long as the ANC is at least 250/µL and platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV, over 48 hours	37.5 mg/m²/Daily dose*	1 - 2 of Weeks 12 and 28	*Total dose: 75 mg/m²/48 hours. Avoid extravasation. See Section 4.8 for dosing with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including CA^{++}, PO_4, MG^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) Audiogram g) GFR See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
CISplatin (CDDP)	IV over 4 hours	60 mg/ m²/dose	1 and 2 of Weeks 12 and 28		
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 15 and 31	**Maximum dose 20 g.** See Section 4.8.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 15 and 31	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.8 and 19.3 for details.	

Cycle *(circle one)*: 3 7 *(use this map twice)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO _____mg	CDDP _____mg	MTX _____g	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		12 or 28	1	____mg	____mg			a, b, c, d, e^+, f^+, $g^@$	
			2	____mg	____mg			$a^\$$	
		15 or 31	1			____g		$a^\$$	
			2				____mg		____(date of last LCV dose)%
				For Cycle 4 and Cycle 8 MAPIE (see Section 4.9) Begin next cycle when ANC ≥ 750/µL and platelets ≥ 75,000/µL post nadir.					

+ - Prior to Cycle 3 and Cycle 7.
@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/cisplatin.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (See Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.9 Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycles 4, 6 and 8)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

Ifosfamide: IV over 4 hours
Days: 1-5 of Weeks 16, 24 and 32.
Dose: 2.8 g/m²/dose.

Etoposide: IV over 1 hour
Days: 1-5 of Weeks 16, 24 and 32.
Dose: 100 mg/m²/dose.

Growth factor:
Myeloid growth factor support is recommended after all ifosfamide/etoposide cycles. Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

Mesna: IV over 24 hours
Days: 1-5 of Weeks 16, 24 and 32.
Dose: 2.8 g/m²/24 hours.
Alternatively, mesna may be administered in 3-4 divided doses; administer until at least 12 hours following completion of ifosfamide dose.

Methotrexate: IV over 4 hours
Days: 1 of Weeks 19, 27 and 35
Dose: 12 g/m²/dose (**Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for MAPIE Cycles 4, 6 and 8 is on the next page.

Following completion of Cycle 4 MAPIE, begin Cycle 5 MAPIE (see Section 4.10).
Following completion of Cycle 6 MAPIE, begin Cycle 7 MAPIE (see Section 4.8).
Following completion of Cycle 8 MAPIE, begin Cycle 9 MAPIE (see Section 4.11).

4.9.1 **Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycles 4, 6 and 8)** Each cycle lasts 4 weeks. This therapy delivery map relates to Weeks 16-19, Weeks 24-27 and Weeks 32-35 of MAPIE therapy.	_____ Patient name or initials _____ DOB

This Therapy delivery Map is on one (1) page. Treatment details are provided in Section 4.9. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 19, 27 and 35 can be administered as long as the ANC is at least 250/µL and the platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 4 hours	2.8 g/m²/dose	1-5 of Weeks 16, 24 and 32	See Section 4.9	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including CA^{++}, PO_4, MG^{++}; bicarbonate, creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) GFR See Section 17.0 for imaging requirements. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Etoposide (ETOP)	IV over 1 hour	100 mg/m²/dose	1-5 of Weeks 16, 24 and 32	Slow rate of administration if hypotension occurs. See Section 4.9.	
MESNA*	IV over 24 hours*	2.8 g/m²/dose	1-5 of Weeks 16, 24 and 32	*Dose may be divided into 3 or 4 doses and administered until at least 12 hours after start of ifosfamide dose. See Section 4.9	
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 19, 27 and 35	**Maximum dose: 20 g.** See Section 4.9	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 19, 27 and 35	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.9 and 19.3 for details.	

Cycle *(circle one)*: 4 6 8 *(use this map three times)* Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	IFOS _____g	ETOP _____mg	MESNA _____g	MTX _____g	LCV ____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						
		16 or 24 or 32	1	_____g	_____mg	_____g			a, b, c, d ,e@	
			2	_____g	_____mg	_____g			a$	
			3	_____g	_____mg	_____g				
			4	_____g	_____mg	_____g				
			5	_____g	_____mg	_____g				
		19 or 27 or 35	1				_____g		a$	
			2					____mg		_____(date of last LCV dose)%
			For Cycle 5 MAPIE (see Section 4.10). For Cycle 7 MAPIE (see to Section 4.8). For Cycle 9 MAPIE (see Section 4.11). Begin next cycle when ANC ≥ 750/µL and platelets ≥ 75,000/µL post nadir.						

@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after ifosfamide/etoposide.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (See Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.10 Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycle 5)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Week 20.
Dose: 37.5 mg/m²/ Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 & 2 of Week 20, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

Ifosfamide: IV over 4 hours
Days: 1, 2 and 3 of Week 20.
Dose: 3 g/m²/dose.

Growth factor:
Myeloid growth factor support after all doxorubicin/ifosfamide cycles is recommended. Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

Mesna: IV over 24 hours
Days: 1, 2 and 3 of Week 20
Dose: 3 g/m²/24 hours.
Alternatively, may be administered in 3-4 divided doses. Administer until at least 12 hours following completion of ifosfamide dose.

Methotrexate: IV over 4 hours
Days: 1 of Week 23.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) or delayed excretion criteria is reached. See Section 19.3 for details.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for MAPIE Cycle 5 is on the next page. Following completion of MAPIE Cycle 5, patients will begin MAPIE Cycle 6 (see Section 4.9).

4.10.1 **Administration Schedule for Poor Responders Randomized to MAPIE (Cycle 5)** This cycle lasts 4 weeks. This therapy delivery map relates to Weeks 20-23.	_____ Patient name or initials _____ DOB

This Therapy Delivery Map is on one (1) page. Treatment details are provided in Section 4.10.ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Week 23 can be administered as long as the ANC is at least 250/µL and the platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV over 48 hours	37.5mg/m²/Daily dose*	1-2 of Week 20	*Total dose: 75 mg/m²/48 hours. Avoid extravasation. See Section 4.10 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including Ca^{++}, PO_4, Mg^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) GFR f) QOL assessment See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Ifosfamide (IFOS)	IV over 4 hours	3 g/m²/dose	1, 2, 3 of Week 20	See Section 4.10.	
MESNA*	IV over 24 hours	3 g/m²/dose	1, 2, 3 of Week 20	*Dose may be divided into 3 or 4 doses and administered until at least 12 hours after start of ifosfamide dose. See Section 4.10.	
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Week 23	**Maximum dose 20 g** See Section 4.10	
Leucovorin^{+} (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Week 23	$^{+}$Leucovorin rescue must begin 24 hours after start of MTX infusion. See Section 4.10 and Section 19.3 for details	

Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO _____mg	IFOS _____g	MESNA _____g	MTX _____g	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						
		20	1	_____mg	_____g	_____g			a, b, c, d, e[@]	
			2	_____mg	_____g	_____g			a[$]	
			3		_____g	_____g			a[$]	
		23	1				_____g		a[$], f^	
			2					_____mg		_____ (date of last LCVdose)[%]
			For Cycle 6 MAPIE (See Section 4.9). Begin next cycle when ANC ≥ 750/µL and platelets ≥ 75,000/µL post nadir.							

@- Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/ifosfamide.
^ - After recovery from Week 20 doxorubicin/ifosfamide and prior to methotrexate at Week 23.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$ M) (See Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

4.11 Administration Schedule for Poor Responders Randomized to MAPIE Therapy (Cycle 9)

See also Appendix B.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy.

DOXOrubicin: IV over 48 hours
Days: 1-2 of Week 36.
Dose: 37.5 mg/m²/Daily dose. (Total dose is 75 mg/m²/48 hour infusion).
Avoid extravasation.
Hydration: 3000 mL/m^2/day.
Cardioprotection: Dexrazoxane may be used if a 10% fall in LVEF or similar fall within the normal range of SF occurs. If cardioprotection is used, 37.5 mg/m^2 of doxorubicin will be given as a 15 minute infusion on days 1 and 2 of Week 36, immediately following dexrazoxane (Start DOXOrubicin infusion after completion of dexrazoxane infusion but within 30 minutes of beginning of the dexrazoxane infusion).

Ifosfamide: IV over 4 hours
Days: 1, 2 and 3 of Week 36.
Dose: 3 g/m²/dose.

Growth factor:
Myeloid growth factor support after all doxorubicin/ifosfamide cycles is recommended. Begin myeloid growth factor support at least 24 hours after completion of chemotherapy. If given daily then continue until WBC ≥ 5000/µL after nadir and discontinue at least 2 days prior to next cycle of chemotherapy.

Mesna: IV over 24 hours
Days: 1, 2 and 3 of Week 36.
Dose: 3 g/m²/24 hours.
Alternatively, may be administered in 3-4 divided doses, until at least 12 hours following completion of ifosfamide dose.

Methotrexate: IV over 4 hours
Days: 1 of Weeks 39 and 40.
Dose: 12 g/m²/dose **(Maximum dose 20 g).**
Hydration: Adequate fluid with electrolytes and bicarbonate must be given to maintain a urine output > 80 % of the fluid intake, measured every four hours and alkalinization. This should be maintained until serum methotrexate level is < 0.1 µmol/L (1x10^{-7}M).
Urine pH: A urinary pH > 7 must be achieved before starting methotrexate infusion and maintained until serum methotrexate level is < 0.1 µmol/L (1x10^{-7}M).
Leucovorin rescue must begin 24 hours after start of methotrexate infusion and be continued until serum methotrexate level is < 0.1 µmol/L (1x10^{-7}M) or delayed excretion criteria is reached. See Section 19.3 for details.

See Section 5.0 for Dose Modifications based on Toxicities.
The Therapy Delivery Map for MAPIE Cycle 9 is on the next page. Therapy ends after Cycle 9 for patients randomized to receive MAPIE.

See Section 7.1 for required observations at end of therapy and Section 17.0 for imaging studies to be performed at end of therapy.

4.11.1 Administration Schedule for Poor Responders Randomized to MAPIE (Cycle 9) This cycle lasts 5 weeks. This therapy delivery map relates to Weeks 36-40.	_____ Patient name or initials _____ DOB

This Therapy Delivery Map is on one (1) page. Treatment details are provided in Section 4.11. ANC must be ≥ 750/µL and platelets ≥ 75,000/µL to start a cycle of therapy. MTX at Weeks 39 and 40 can be administered as long as the ANC is at least 250/µL and the platelets at least 50,000/µL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
DOXOrubicin (DOXO)	IV over 48 hours	37.5 mg/m²/Daily dose*	1-2 of Week 36	*Total dose: 75 mg/m²/48 hours. Avoid extravasation. See Section 4.11 for administration with dexrazoxane.	a) CBC/Diff/Platelets b) H & P, PS c) Urinalysis d) Electrolytes including Ca^{++}, PO_4, Mg^{++}, bicarbonate; creatinine, BUN, SGOT, SGPT, bilirubin, alk phos e) ECHO or MUGA f) GFR See Section 17.0 for imaging requirements **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Ifosfamide (IFOS)	IV over 4 hours	3 g/m²/dose	1, 2, 3 of Week 36	See Section 4.11.	
MESNA*	IV over 24 hours	3 g/m²/dose	1, 2, 3 of Week 36	*Dose may be divided into 3 or 4 doses and administered until at least 12 hours after start of IFOS dose. See section 4.11.	
Methotrexate (MTX)	IV over 4 hours	12 g/m²/dose	1 of Weeks 39 and 40	**Maximum dose: 20 g**. See Section 4.11.	
Leucovorin+ (LCV)	PO or IV	Varies according to MTX excretion levels.	2 of Weeks 39 and 40	+Leucovorin rescue must begin 24 hours after start of MTX infusion. See Sections 4.11 and 19.3 for details.	

Ht_____cm Wt____kg BSA____m^2

Do not attempt to correct BSA for amputation

Date Due	Date Given	Week	Day	DOXO _____mg	IFOS _____g	MESNA _____g	MTX _____g	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		36	1	_____mg	_____g	_____g			a, b, c, d, e, f@	
			2	_____mg	_____g	_____g			a$	
			3		_____g	_____g				
		39	1				_____g		a$	
			2					_____mg		_____ (date of last LCV dose)%
		40	1				_____g		a$	
			2					_____mg		_____ (date of last LCV dose)%
				Therapy ends after completion of Cycle 9 for patients on MAPIE. See Section 7.1 for required observations at end of therapy.						

@ - Calculated or measured GFR (see Appendix A.3 of the Intergroup document).
$ - Weekly after methotrexate and twice weekly after doxorubicin/ifosfamide.
% - Continue until serum methotrexate level is < 0.1 µmol/L ($1x10^{-7}$M) (see Section 19.3 for details).

See Section 5.0 for Dose Modifications for Toxicities. See Section 8.0 for Supportive Care.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Modifications for Doxorubicin/Cisplatin

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC < 0.75 x 10^9/L Plts < 75 x 10^9/L	Delay and repeat within 3-4 days until criteria are met Retreat at full dose unless previous dose reduction For repeated delay (>7 days) use growth factor support starting at least 24 hours post chemotherapy and continuing until WBC >5,000/uL post nadir. If delayed >7 days in spite of growth factor support reduce cisplatin by 25%.
Febrile Neutropenia		Febrile neutropenia accompanied by either sepsis or a microbiologically documented infection should prompt administration of growth factor support starting at least 24 hours after chemotherapy and continuing until WBC >5,000/µL post-nadir. Further episodes of febrile neutropenia accompanied by either sepsis or a microbiologically documented infection requiring prolonged hospitalizations should result in cisplatin dosage reduction by 25%. Investigators can consider the same dose reduction if there are persistent delays >7 days in therapy administration despite GCSF
Mucositis , Severe abdominal pain, Diarrhea, Typhlitis	Grade 4 mucositis or typhlitis or repeated Grade 3 mucositis	Delay until resolved & decrease subsequent doxorubicin to 60 mg/m^2/cycle
Audiology	> 30 dB at ≤ 2kHz	Discontinue cisplatin
Cardiotoxicity	LVEF < 50% or SF ≤ 28%	Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin
Renal Toxicity	Serum creatinine > 2 x baseline or GFR < 70 mL/min/1.73 m^2	Delay for one week If renal function does not improve, omit cisplatin and give doxorubicin alone Resume cisplatin at future courses if GFR ≥ 70 mL/min/1.73 m^2
Hepatic Toxicity	Raised Total Bilirubin	Reduce doxorubicin as follows: **Concentration** — **% Dose** 0 – 21 µmol/L (0 -1.24 mg/dL) 100% 22 – 35 µmol/L (1.25-2.09 mg/dL) 75% 36 – 52 µmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 µmol/L (3.06-5.0 mg/dL) 25% > 87 µmol/L (> 5.0 mg/dL) 0%
Peripheral neurotoxicity	Grade 2 ≥ Grade 3	Reduce cisplatin by 25% for all future courses Omit cisplatin for all future courses

An attempt to give any omitted doxorubicin/cisplatin cycles should be made after the end of scheduled protocol chemotherapy, if the patient fulfills the necessary organ function requirements. Patients scheduled to receive pegylated interferon alfa-2b should complete all standard cytotoxic chemotherapy and have a 7-day interval prior to beginning pegylated alfa interferon.

5.2 Dose Modifications for Methotrexate

Note that no dose reductions will apply. See Section 19.0 for MTX/leucovorin management.

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC $< 0.25 \times 10^9$/L Or WBC $< 1.0 \times 10^9$/L Plt $< 50 \times 10^9$/L	Delay until recovery according to group practice (see appendix B.6)
Mucositis, Severe abdominal pain, Diarrhea	Grade 3-4 mucositis or diarrhea after MTX If persists for >1 Week & is present in Week 4 of MAP cycle	Consider Leucovorin Rescue Adjustment. Reminder: exclude drugs interfering with excretion Omit Day 29 methotrexate (of this cycle only) & proceed to next cycle (or surgery)
Renal Toxicity	GFR < 70 mL/min/1.73m^2	Delay until recovery. If renal function does not improve within 1 week, omit MTX & proceed to next possible cycle. If renal function subsequently improves, MTX can be resumed (Patients receiving DOXO alone may continue to receive the drug)
Abnormal LFTs	<u>Not MTX induced</u> LFTs elevated <u>Probably MTX induced i.e. up to 3 weeks after MTX</u> Bilirubin > 1.5 x N	Delay one week. Give if ALT < x10 N It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia for longer than three weeks will result in discontinuation of MTX

An attempt to give any omitted MTX doses should be made after the end of scheduled protocol chemotherapy, if the patient fulfills the necessary organ function requirements.

5.3 Dose Modifications for Ifosfamide/Etoposide

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC $< 0.75 \times 10^9$/L Or WBC $< 2.0 \times 10^9$/L Plt $< 75 \times 10^9$/L	Delay and repeat within 3-4 days; retreat at full dose unless previous dose reduction. Consider reduction if cycle is delayed >7 days in spite of growth factor support (20% dose reduction by omitting the last day of the cycle).
Febrile neutropenia after previous IFOS/ETOP	Consider for grade 3 All Grade 4	Doses should be reduced in patients who experience febrile neutropenia with clinically significant or microbiologically documented infection. Reduce both drugs by 20% i.e. omit last day of cycle. If a second episode occurs, omit ETOP.
Mucositis, severe abdominal pain, diarrhea, typhlitis	Grade 4 mucositis after previous IFOS/ETOP Repeated Grade 3 mucositis	Reduce ETOP by 50%
Renal Toxicity – glomerular	Serum Creatinine 1.5 x baseline or GFR < 70 mL/min/1.73 m^2 GFR 10-50 mL/min GFR < 10 mL/min	Delay for one week. If renal function does not improve, discontinue IFOS, confirm GFR and consider substituting cyclophosphamide and MESNA, both 500mg/m^2 x 5 days Decrease dose ETOP by 25% Decrease dose ETOP by 50%
Renal Toxicity – tubular (based on GFR, serum bicarbonate, need for electrolyte replacement, or TmP/GFR)	Grade 1	No change
	Grade 2	Consider reduction of IFOS by 20% i.e. omit last day
	Grade 3 or 4	No further IFOS. Consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days
Hematuria (exclude vaginal bleeding and if microscopic, confirm where possible by microscopy)	Dipstick positive prior to IFOS	Give additional MESNA bolus of 600 mg/m^2 then continuous infusion at double dose
	Microscopic during IFOS ≥ 2 occasions (>50 RBC/HPF)	No further IFOS. If hematuria resolves completely, ifosfamide with double dose MESNA could be considered for the next ifosfamide containing cycle. Investigators could also consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days
	≥ Grade 2 Exclude other causes; double MESNA dose +/- increase hydration.	Discontinue IFOS, continue double dose MESNA and hydration for 24 hours after IFOS; consider cystoscopy; In subsequent IFOS containing cycles, consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days
Neurological toxicity – confusion or depressed level of consciousness	Grade2	No change unless persistent and distressing. Then decrease IFOS by 20% (omit last day"s dose). If persists, reduce by a further 20%
	Grade 3	Stop IFOS for this cycle. Decrease IFOS by 20% (omit last day"s dose) during the next cycle. If persists, reduce by a further 20%
	Grade 4	If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg (maximum dose 50 mg) on the day this occurs. The dose may be repeated at 4 hours and 8 hours after, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Investigators should consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days. Hypersensitivity, renal impairment and G-6PD deficiency are contraindications to administer methylene blue.
Table continued on next page		

Toxicity	Grade	Action
Neurological toxicity - seizures	Grade 2	Consider anticonvulsants (benzodiazepines preferred) and/or stopping IFOS for this cycle. Continue future cycles at same dose.
	Grade 3	Stop IFOS for this cycle. Consider future cycles at same dose with anticonvulsant coverage
	Grade 4	If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg (maximum dose 50 mg) on the day this occurs. The dose may be repeated at 4 hours and 8 hours after, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Investigators should consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days. Hypersensitivity, renal impairment and G-6PD deficiency are contraindications to administer methylene blue.
Neurological toxicity – peripheral neuropathy (exclude other causes)	≥ Grade 2	Omit further IFOS. Consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days

An attempt to give any omitted ifosfamide/etoposide cycles should be made after the end of scheduled protocol chemotherapy, if the patient fulfills the necessary organ function requirements. Patients scheduled to receive pegylated interferon alfa-2b should complete all standard cytotoxic chemotherapy and have a 7-day interval prior to beginning pegylated interferon alfa-2b.

5.4 Dose Modifications for Doxorubicin/Ifosfamide

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle, ANC <750/μL and platelets < 75,000/μL	Delay and repeat within 3-4 days. Retreat at full dose unless previous dose reduction. For repeated delay Investigators can consider reducing IFOS dose to 6 g/m² by eliminating the last day of the Cycle.
Febrile Neutropenia after previous DOXO/IFOS	All Grade 4, consider for Grade 3	If despite GCSF, reduce ifosfamide to total 6 g/m^2 by eliminating the last day of the cycle
Mucositis, Severe abdominal pain, Diarrhea, Typhlitis	Grade 4 mucositis after DOXO/ CDDP or repeated Grade 3 mucositis	Delay until resolved & decrease subsequent doxorubicin to 60 mg/m^2/cycle; Note: if previous DOXO dose reductions other than for cardiotoxicity or Grade 4 mucositis, decrease doxorubicin to 50 mg/m^2/cycle and ifosfamide to 6 g/m^2 by eliminating the last day of the cycle
Cardiotoxicity	LVEF < 50% or SF ≤ 28%	Repeat echo or MUGA in one week; If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further DOXO
Hepatic Toxicity	Elevated Total Bilirubin	Reduce doxorubicin as follows: Concentration — % Dose 0 – 21 μmol/L (0 -1.24 mg/dL) 100% 22 – 35 μmol/L (1.25-2.09 mg/dL) 75% 36 – 52 μmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 μmol/L (3.06-5.0 mg/dL) 25% > 87 μmol/L (> 5.0 mg/dL) 0%
Renal Toxicity – glomerular	Serum Creatinine 1.5 x baseline or GFR < 70 mL/min/1.73 m^2	Delay for one week. If renal function does not improve, omit IFOS, confirm GFR and consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 3 days for future cycles
Renal Toxicity – tubular (based on GFR, serum Bi, electrolyte replacement, TmP/GFR)	Grade 1	No change
	Grade 2	Reduce IFOS to 6 g/m^2 (by eliminating last day)
	Grade 3/4	No further IFOS
Hematuria (exclude vaginal bleeding and if microscopic, confirm where possible by microscopy)	Dipstick positive prior to IFOS	Exclude other causes; double MESNA dose +/- increase hydration.
	Microscopic during IFOS ≥ 2 occasions (>50 RBC/HPF)	Give additional 600 mg/m² MESNA bolus then continuous infusion at double dose. If persists, discontinue IFOS . If hematuria resolves completely, ifosfamide with double dose MESNA could be considered for the next ifosfamide containing cycle. Investigators could also consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days
	≥ Grade 2	Discontinue ifosfamide, continue double dose MESNA and hydration for 24 hours after ifosfamide; consider cystoscopy; For the next ifosfamide containing cycle, consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 5 days
Neurological toxicity – confusion or depressed level of consciousness	Grade2	No change unless persistent and distressing. For further cycles decrease ifosfamide to 6 g/m^2. (eliminating last day of cycle) If persists further, omit ifosfamide. Consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 3 days
	Grade 3	Decrease ifosfamide to 6 g/m^2 (eliminating last day of cycle). If persists further, omit ifosfamide. Consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 3 days
	Grade 4	If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg (maximum dose 50 mg) on the day this occurs. The dose may be repeated at 4 hours and 8 hours after, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Investigators should consider substituting cyclophosphamide and MESNA, both 500 mg/m² x 5 days. Hypersensitivity, renal impairment and G-6PD deficiency are contraindications to administer methylene blue.
Table continued-next page		

Toxicity	Grade	Action
Neurological toxicity - seizures	Grade 2	Consider anticonvulsants (benzodiazepines preferred) and/or stopping IFOS for this cycle. Continue future cycles at same dose.
	Grade 3	Stop IFOS for this cycle. Consider future cycles at same dose with anticonvulsant coverage
	Grade 4	If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg (maximum dose 50 mg) on the day this occurs. The dose may be repeated at 4 hours and 8 hours after, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Investigators should consider substituting cyclophosphamide and MESNA, both 500 mg/m² x 5 days. Hypersensitivity, renal impairment and G-6PD deficiency are contraindications to administer methylene blue.
Neurological toxicity – peripheral neuropathy (exclude other causes)	≥ Grade 2	Omit further IFOS. Consider substituting cyclophosphamide and MESNA, both 500 mg/m^2 x 3 days

An attempt to give any omitted doxorubicin/ifosfamide cycles should be made after the end of scheduled protocol chemotherapy, if the patient fulfills the necessary organ function requirements. Patients scheduled to receive pegylated interferon alfa-2b should complete all standard cytotoxic chemotherapy and have a 7-day interval prior to beginning pegylated interferon alfa-2b.

5.5 Dose Modifications for Pegylated interferon alfa-2b

Toxicity	Grade	Action
Fever, chills, fatigue, headache etc	Any	May improve with continued treatment. May be decreased with bedtime administration. Treat with paracetamol/acetaminophen and if severe, NSAID providing platelet count is maintained. Dose reduction appropriate only if sustained and not relieved by above. Hyperglycemia not controlled by drugs – discontinue ifn. Triglycerides persistently > 1000 associated with symptoms of potential pancreatitis or pancreatitis, hold ifn until resolution. Restart at lower dose level. If recurs, discontinue ifn.
Hemoglobin	Grade 3-4	Persistent and symptomatic Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn.
Leucopenia	Grade 3	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If resolves to ≤ grade 2, resume the previous dose level and, if at the starting dose level (0.5 mcg/kg/week), the planned dose escalation 4 weeks later. If no resolution within 4 weeks, stop ifn until resolved to ≤ Grade 2, then resume at reduced dose level (starting dose level 0.5 mcg/kg/week, or, at 25% below the starting dose level if toxicity was encountered at starting dose level). If toxicity recurs, stop ifn.
	Grade 4	Stop ifn until toxicity has resolved to ≤ Grade 2, then resume ifn at starting dose level (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If grade 3 or greater toxicity recurs, stop ifn.
Neutrophils	Grade 3	Reduce dose by 25% (if patient receiving 0.5 mcg/kg/week) or to starting dose (if patient receiving 1 mcg/kg/week). If toxicity resolves to ≤ grade 2 and patient reduced to starting dose attempt escalation to 1 mcg/kg/week after 4 weeks. If toxicity resolves to ≤ grade 2 and patient at 25% dose reduction, then attempt escalation to starting dose. If toxicity recurs after dose escalation, drop dose by 25% (if patient at 0.5 mcg/kg/week) or to starting dose (if patient at 1 mcg/kg/week) and wait for resolution to ≤ grade 2. Do not attempt further escalation and continue ifn at reduced dose (starting dose or 25% dose reduction). If no resolution of grade 3 neutropenia within 4 weeks of dropping dose (starting dose or 25% dose reduction) hold ifn until resolved to ≤ Grade 2, then resume ifn at starting dose level (if patient receiving 1 mcg/kg/week) or at 25% dose reduction (if patient receiving 0.5 mcg/kg/week). If patient tolerates dose reduction x 4 weeks without toxicity attempt escalation to starting dose level (0.5 mcg/kg/week) or if at starting dose level to 1 mcg/kg/week. If toxicity recurs after dose escalation, decrease dose to starting dose (if patient receiving 1 mcg/kg/week) or to 25% dose reduction (if patient receiving 0.5 mcg/kg/week). Do not attempt further dose escalation.
	Grade 4	**Grade 4 neutropenia:** Hold ifn until toxicity has resolved to ≤ Grade 2, then resume ifn at starting dose level (if patient receiving 1 mcg/kg/week) or at 25% dose reduction (if patient receiving 0.5 mcg/kg/week). If patient tolerates dose reduction x 4 weeks without toxicity attempt escalation to starting dose level (0.5 mcg/kg/week) or if at starting dose level to 1 mcg/kg/week. If toxicity recurs after dose escalation, decrease dose to starting dose (if patient receiving 1 mcg/kg/week) or to 25% dose reduction (if patient receiving 0.5 mcg/kg/week). Do not attempt further dose escalation. If grade 3 or greater toxicity recurs after resuming ifn at reduced dose, then hold ifn until toxicity has resolved to ≤ Grade 2, then resume ifn at starting dose level (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If grade 3 or greater toxicity recurs, permanently discontinue ifn.

Platelets	Grade 2 Grade 3-4	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%.. If resolves to ≤ grade 1, resume the previous dose level and, if at the starting dose level (0.5 mcg/kg/week), the planned dose escalation 4 weeks later. If no resolution within 4 weeks, stop ifn until resolved to ≤ Grade 1, then resume at reduced dose level (starting dose level 0.5 mcg/kg/week, or, at 25% below the starting dose level if toxicity was encountered at starting dose level). If toxicity recurs, stop ifn. Stop ifn until toxicity has resolved to ≤ Grade 1, then resume ifn at starting dose level (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If grade 2 or greater toxicity recurs, stop ifn.
Renal toxicity – raised creatinine	Grade 2 Grade 3-4	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.
Neurotoxicity incl. Mood disturbance	Grade 2 or greater Any mood disturbance	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn. Undertake psychiatric assessment. Consider discontinuation.
Cardiotoxicity e.g. arrhythmia	Grade 2 Grade 3-4	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.
Pancreatitis		Elevated triglycerides can result in pancreatitis. PEG-intron should be discontinued in patients who develop pancreatitis.
Hepatic Toxicity -raised bilirubin	Grade 3 Grade 4	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.
Table continued on next page		
Toxicity	**Grade**	**Action**
Gastro-intestinal e.g. vomiting or diarrhea	Grade 2 for > 2 weeks or ≥ grade 3	Reduce to starting dose (0.5 mcg/kg/week), or, if at starting dose level, decrease by 25%. If no resolution within 4 weeks, stop ifn.
Thyroid dysfunction	Any	Assess and treat thyroid as appropriate. Continue ifn unless not controlled.
Triglycerides	>8.5 ULN	Stop ifn until triglycerides <8.5 ULN.

6.0 DRUG INFORMATION

6.1 **DOXORUBICIN** (Adriamycin®) NSC #123127 (03/25/08)

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

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

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

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

Formulation and Stability:
Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1], 150 mg[2] vials and a preservative free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 75 mg[1], 200 mg[2] vials.
[1]: Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben 1 mg per each 10 mg of doxorubicin to enhance dissolution.
[2] Multiple dose vial contains lactose, 0.9%NS, HCl to adjust pH to 3.

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

Powder for Injection: Store unreconstituted vial at room temperature 15° - 30°C (59° - 86°F). Retain in carton until contents are used. Reconstitute with preservative-free normal saline to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light (100 footcandles) and 15 days under refrigeration 2°- 8°C (36° -46°F). Protect from exposure to sunlight. Doxorubicin may be further diluted in 0.9%NaCl or dextrose containing solutions and administered by infusion.

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

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

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

6.2 **CISPLATIN** (Cis-diamminedichloroplatinum II, CDDP, cis-DDP, Platinol-AQ) NSC #119875 (04/12/10)

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

Toxicities:

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

(L) Toxicity may also occur later.

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

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

Cisplatin may be further diluted in dextrose and saline solutions provided the solution contains ≥ 0.2% sodium chloride. Dextrose/saline/mannitol containing solutions, protected from light, are stable refrigerated or at room temperature for 24 to 72 hours, however, cisplatin solutions should not be stored in the refrigerator to avoid precipitation. Cisplatin is incompatible with sodium bicarbonate and alkaline solutions.

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

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

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

6.3 **METHOTREXATE** (MTX, amethopterin, Trexall®) NSC #000740 (10/15/08)

Source and Pharmacology:

A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

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	Transaminase elevations	Nausea, vomiting, anorexia,	Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritis, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures[1], photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity[1] (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability[1] (L)	Pneumonitis, pulmonary fibrosis(L), hepatic fibrosis (L), osteonecrosis (L), leukoencephalopathy[1] (L), pericarditis, pericardial effusions, hyperpigmentation of the nails,
Late: Any time after the completion of therapy			Progressive CNS deterioration[1]
Unknown Frequency and Timing:	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations.		

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(L) Toxicity may also occur later.

Formulation and Stability: Methotrexate for Injection is available as a lyophilized powder for injection in 20 mg and 1 g vials. The powder for injection contains approximately 0.14 mEq sodium in the 20 mg vial; 7 mEq sodium in the 1 g vial. Methotrexate for Injection is also available as a 25mg/mL solution in 2,4,8,10,20 and 40ml preservative free vials and 2 and 10mL vials with preservative. The 2, 4, 8, 10, 20,

and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, 4.3, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative and **must not be used for intrathecal or high dose therapy.**

Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º- 86 Fº). Protect from light

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

For IM/IV use: Powder for injection: Dilute 1 gm vial with 19.4 ml of non-preserved SWFI, Dextrose 5% in Water or 0.9% Sodium Chloride Injection for a 50mg/mL concentration. Dilute the 20mg vial to a concentration ≤ 25 mg/mL with above diluents. The powder for injection may be further diluted in 0.9% sodium chloride or dextrose containing solutions to a concentration of ≤25mg/mL for IV use.

The 25mg/mL solution may be given directly for IM administration or further diluted in Saline or Dextrose containing solutions for IV use. **Do not use the preserved solution due to risk of benzyl alcohol toxicity**. Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

High dose Methotrexate requires alkalinization of the urine, adequate hydration and leucovorin rescue. Avoid probenecid, penicillins, cephalosporins, aspirin, and NSAIDS as renal excretion of MTX is inhibited by these agents.

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

6.4 IFOSFAMIDE

(Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 (03/30/09)

Source and Pharmacology:

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

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea & vomiting (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia, asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis, and urinary frequency (<5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction : azoospermia or oligospermia (prolonged or permanent)[1] (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconi-like syndrome gonadal dysfunction, ovarian failure[1] (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

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

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

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

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

Mesna must always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide.

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

6.5 ETOPOSIDE

(VePesid®, Etopophos®,VP-16) NSC #141540 (03/30/09)

Source and Pharmacology: A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non renal clearance of etoposide.

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

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

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
UnknownFrequency and Timing:	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:

Etoposide for Injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

Unopened vials of etoposide are stable until expiration date on package at controlled room temperature (20°-25°C or 68°-77°F).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

Etoposide phosphate must be stored under refrigeration 2°-8°C or 36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

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

Etoposide:
Dilute etoposide to a final concentration ≤ 0.4 mg/mL in 5% Dextrose Injection, *USP* or 0.9% Sodium Chloride Injection, *USP*. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2mg/ml; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4mg/mL. Use in-line filter during infusion secondary to precipitate formation risk. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL. **Do not administer etoposide by rapid intravenous injection**. Slow rate of administration if hypotension occurs.

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

Etoposide Phosphate:
Dilute the 100 mg vial with 5 or 10 mL of Sterile Water for Injection, *USP*; 5% Dextrose Injection, *USP*; 0.9% Sodium Chloride Injection, *USP*; Bacteriostatic Water for Injection with Benzyl Alcohol; or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. **Use diluents without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.**

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for up to 48 hours. Following reconstitution with Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, store at controlled room temperature for up to 24 hours.

Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

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

CANADIAN SITES
Etopophos® (etoposide phosphate) is not commercially available in Canada. Sites may purchase and import the USA commercial supply from Bristol Laboratories via an International Distributor (Pharma Exports LLC, phone: 1-412-885-3700, fax: 1-412-885-8022, email: pharexp@aol.com) under the authority of the protocol‟s No Objection Letter (NOL). A "Fax Notification" of the lot number and expiry date of each lot received in a Canadian pharmacy must be faxed to Health Canada, Clinical Trials Quality Division, Bureau of Pharmaceutical Sciences at 613-954-8867, Attention: Michael Bourdon or designee by the site pharmacist. A lot must not be used until Health Canada has been notified by fax. Note: Etopophos® may have orders placed and Drug Accountability Logs maintained on a multiple protocol basis (Multiple Protocol - Imported Therapeutic) as long as each protocol has a NOL.

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6.7 **MESNA** (sodium 2-mercaptoethane sulfonate,UCB 3983, Mesnex®) NSC #113891 (03/30/09)

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 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 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.
Mesna non-preserved ampoules are no longer provided by Bristol-Myer Squibb Company.

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

For IV administration, dilute 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). Carefully expel air in syringes prepacked for use to avoid oxidation to dimesna.

Mesna may cause false positive test for urinary ketones.

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

CANADIAN SITES
Preservative-free Mesna is commercially available in Canada from Baxter Corporation (Urometixan®); supplied as 100mg/mL solution which contains edentate disodium and sodium hydroxide for pH adjustment, 4mL and 10mL single-use ampoules.

6.8 LEUCOVORIN CALCIUM (LCV, Wellcovorin®, citrovorum factor, folinic acid)
NSC #003590 (03/25/09)

Source and Pharmacology:
Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)- l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer (the biologically active form) but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

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			Anaphylaxis, urticaria, seizure
Unknown Frequency and timing: Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk.			

Formulation and Stability: Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F) protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, 350 mg and 500 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses >10 mg/m² or in infants < 2 years of age or patients with allergy to benzyl alcohol**. When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with sterile water, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

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

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral leucovorin should be spaced evenly (e.g.: every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

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

6.9 **DEXRAZOXANE** (ICRF-187, ADR-529, ZINECARD®) NSC #169780 (03/25/09)

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

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of		Pain on injection, phlebitis transient increases in triglycerides and amylase, increase in SGPT	Anorexia, malaise, extravasation (rare) but if

receiving drug		(ALT)/SGOT (AST) and bilirubin, mild nausea, vomiting, diarrhea, increase in serum iron, decrease in serum zinc and calcium	occurs may = ulceration
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression		Prolongation of PT/PTT
Late: Any time after completion of treatment			Secondary malignancies (have been reported with oral razoxane; the racemic mixture, of which dexrazoxane is the S(+)-enantiomer)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects have been noted in animals. Dexrazoxane was maternotoxic, embryotoxic and teratogenic when given to pregnant rats and rabbits during the period of organogenesis. It is not known whether dexrazoxane is excreted in human milk.		

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

Dexrazoxane must be reconstituted with 0.167 Molar (M/6) Sodium Lactate Injection, *USP*, to give a concentration of 10 mg dexrazoxane for each mL of sodium lactate. Reconstituted dexrazoxane, when transferred to an empty infusion bag, is stable for 6 hours from the time of reconstitution when stored at controlled room temperature, 15°-30°C (59°-86°F) or under refrigeration, 2°-8°C (36°-46°F).

The reconstituted dexrazoxane solution may be further diluted with either 0.9% Sodium Chloride Injection, *USP* or 5.0% Dextrose Injection, *USP* to a concentration range of 1.3 to 5.0 mg/mL in intravenous infusion bags. The resultant solutions are stable for 6 hours when stored at controlled room temperature, 15°-30°C (59°-86°F) or under refrigeration, 2°-8°C (36°-46°F).

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

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

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

7.1 Required and Suggested Observations

All entry/eligibility hematologic and biochemical studies must be performed within 1 week prior to entry onto the trial (unless otherwise specified). Imaging studies are required within 1 month prior to study entry. Rapid central review of biopsy and surgical specimens is required. Enrollment on an osteosarcoma specimen collection study is strongly encouraged.

STUDIES TO BE OBTAINED	Study Entry	Twice weekly	Before each Cycle	Post-op	Prior to PEG-Intron	End of Therapy	During Follow-up
History	X		X			X	Suggested
Physical Exam (Ht, Wt, BSA, VS)	X		X			X	Suggested
Performance Status	X		X			X	Suggested
CBC, differential, platelets	X	X[1]	X			X	Suggested
Urinalysis	X		X			X	Suggested
Urine phosphate and creatinine	X		---			X	Suggested
Electrolytes including Ca++, PO_4, Mg++, bicarbonate	X		X			X	Suggested
Creatinine, BUN, SGOT, SGPT, bilirubin, alk phos	X		X			X	Suggested
Evaluation for liver function					X		
Total protein/albumin	X					X	Suggested
Coagulation profile	X						Suggested
Glomerular Filtration Rate [2]	X		X			X	Suggested
Left ventricular function (Echo or MUGA)	X		X[3]				Suggested
Audiogram	X		X[4]			X	Suggested
Ophthalmologic evaluation					X		
Triglyceride level					X		
Thyroid function					X		
Quality of Life assessment (*see Section 16.3 for specific time points; also see administration guidelines)			X*	X*			X*
Specimen submission (see Section 15.0)	X			X			
Pregnancy Test	X						
Sperm banking recommended	X						
Imaging Requirements (#see Section 17.0 for specific time points)	X		X#	X#		X	Suggested

[1] Weekly during methotrexate cycles
[2] There must be some measure of renal function via calculated or measured GFR (see Appendix A.3)
[3] Every other doxorubicin containing cycle until 4 administered doxorubicin doses, then before every doxorubicin containing cycle.
[4] Before 3rd and 4th Doxorubicin/Cisplatin cycle
[5] At least once a year; more frequently if clinically indicated

7. 2 **Disease-related follow-up after completion of chemotherapy**

General follow-up after completion of chemotherapy should occur as per local institutional standards and as appropriate for individual patient care and known long-term toxicities of agents received. Refer to COG Late Effects Guidelines for recommended post treatment follow-up at:
http://www.childrensoncologygroup.org/disc/LE/default.htm

7. 2.1. Schedule

Participating institutions will follow all patients for 10 years after the patient is enrolled on the study, for relapse and survival, regardless of protocol violation. The date of relapse will be defined as the date on which evidence of relapse is confirmed, whether radiologically or clinically. If relapse is detected at any site, a complete diagnostic investigation (chest CT scan, bone scan, imaging of primary tumor site) is suggested. Refer to Section 17.0 for an overview of suggested imaging studies during follow-up.

7. 2.2. Clinic visits after end of chemotherapy

The following are minimum guidelines for timing of follow-up visits to ensure consistency in the detection of relapse or progression.

Years 1-2	every 6 weeks-3 months
Years 3-4	every 2-4 months
Years 5-10	every 6 months
Thereafter	every 6-12 months according to local practice

7. 2.3 Toxicity/Late – Effects Related Follow-Up

Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory, and reproductive function, orthopedic problems and other late effects including secondary malignancies. Appropriate additional investigations are suggested in order to ensure optimal patient care. Cardiac toxicity, renal toxicity and ototoxicity are of particular interest in this study. Refer to the COG form packet for follow-up requirements. .

8.0 SUPPORTIVE CARE GUIDELINES

8.1 Venous Access

The presence of a double lumen central venous access device (VAD) is recommended but not required.

8.2 Antiemetics

All patients must be treated with appropriate antiemetics according to institutional practice.

8.3 Neutropenia

8.3.1 Neutropenic fever

Antibiotic coverage is at the discretion of the investigator. Broad spectrum antibiotics should be chosen in consideration of local microbials. Since nephrotoxic agents are used in this therapy, aminoglycosides should be used with caution.

8.3.2

Growth factor support: Since treatment intensity is important, myeloid growth factor support is preferable to dose reduction and should begin at least 24 hours after completion of chemotherapy. If given daily then continue until WBC $\geq$ 5000/µL after nadir. The recommended dose indicated in the package insert should be used. Chemotherapy should not be given until a patient has been off myeloid growth factor support for 2 days.

8.4 Anemia and thrombocytopenia

8.4.1
Transfuse to maintain hemoglobin levels according to institutional practice. Erythropoietin is not recommended as standard therapy but may be used at the discretion of the investigator e.g. for patients who refuse transfusion on religious grounds.

8.4.2
Suggested platelet transfusions for bleeding associated with thrombocytopenia. Give platelet transfusions prophylactically when counts drop below 10,000/µl. Some institutions may use higher thresholds for platelet transfusion, e.g. 20,000/µL. Higher thresholds should also be used during septic episodes.

8.4.3
Appropriate national and institutional guidelines should be followed regarding filtering and irradiation of blood products.

8.5 Pneumocystis carinii

Pneumocystis carinii prophylaxis is recommended even though the risk of pneumocystis infection in this population is relatively low.

Trimethoprim/Sulfamethoxazole (TMP/SMX) **should not be administered with or close to the administration of high dose methotrexate**. Sulfonamides can displace methotrexate from plasma binding sites and increase free methotrexate. Trimethoprim can interfere with the microbiological DHFR assay for methotrexate; no interference occurs with the RIA. In addition, both agents have similar toxicities, and the administration of TMP/SMX increases the risk of high dose methotrexate toxicity.

8.6 Magnesium supplementation

It may be helpful to supplement magnesium beginning with the first cisplatin-containing course and up to approximately three months after completion of chemotherapy. Intravenous magnesium supplementation in the hydration fluids should be considered during administration of cisplatin or ifosfamide. This would involve:

Post-cisplatin - hydration with D5W ½ NS + 10 mEq KCl/L + 20mEq $MgSO_4$/L at 125 mL/m^2/hr

After therapy - supplement Mg with preparations such as:
Magnesium oxide (2 caps/m^2 - 7 mEq /140 mg capsule) or
Magnesium gluconate (6 tablets/m^2 - 2.2 mEq/500mg tab) or
Maalox #1 (2 tabs/m^2 - 7 mEq/tab)

8.7 Neurotoxicity associated with ifosfamide

Guidance for dose adjustment is found in section 5.3 & 5.4. If Grade 4 neurotoxicity occurs during ifosfamide administration, investigators may consider administration of methylene blue at 2 mg/kg (maximum dose 50 mg) on the day this occurs. The dose may be repeated at 4 hours and 8 hours after, following which ifosfamide should be discontinued and no further ifosfamide will be administered. Investigators should consider substituting cyclophosphamide and mesna, both 500 mg/m² x 5 days. Hypersensitivity, renal impairment and G-6PD deficiency are contraindications to administering methylene blue.

8.8 Hydration Routines

Hydration routines for chemotherapy administration are detailed above.

8.9 Bisphosphonates

Some investigators may choose to use bisphosphonates after surgery. The benefits of this have as yet not been prospectively evaluated in this group of patients. Administration of bisphosphonates should be recorded on Form (end of treatment)

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

The duration of the MAP regimen is 29 weeks and the duration of the MAPIE regimen is 40 weeks. In the MAPifn arm, duration of therapy will be two years in total. Surgery is intended to be performed at Week 11 in all arms.

Patients may be withdrawn from protocol treatment for the reasons listed below.

- Relapse, or tumor progression
- Serious adverse events (including second malignancies) or other major toxicity prohibiting continuation of protocol therapy
- Pregnancy
- Personal wish of the patient
- Any other situation where continued protocol treatment may not be in the best interest of the patient

The reason for terminating treatment should be recorded on the appropriate data entry screen along with all other post-treatment investigations (see Section 7.1).

Patients who do not meet the criteria for randomization are off protocol therapy, however, these patients will be followed up for 10 years after the last patient starts the study, for the purpose of follow-up. Treatment recommendations for patients who are not randomized are:

- If the required amount of pre-operative chemotherapy to qualify a patient for randomization has not been given, then give post-operative chemotherapy according to the MAP schedule.

- If patients experience tumor progression during pre-operative treatment, give post-operative chemotherapy according to the MAPIE schedule.

- If the surgery is not macroscopically complete, the patient should receive radiotherapy and/or other experimental treatment as appropriate.

9.2 Off Study Criteria

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

10.0 STATISTICAL CONSIDERATIONS

10.1 Endpoints

The primary endpoint for EURAMOS-1 is event-free survival (EFS), secondary endpoints are overall survival (OS), toxicity and quality of life. For the statistical comparison of the randomized arms, EFS and OS will be measured from date of randomization to date of the event or death as appropriate; surviving patients will be censored at the date last known to be alive. For reporting EFS and OS estimates at specific timepoints, these measures will be calculated from date of diagnostic biopsy. Treatment comparisons of EFS and OS will also be conducted in the subgroup of localized patients. Trial conclusions will be based on all endpoints. Events are defined as death, detection of local recurrence or metastasis, progression of metastatic disease, or detection of a secondary malignancy. Toxicity will be assessed using the CTCAE v3.0. Good histological response is defined as < 10% viable tumor.

10.2 Sample Size

Sample size calculations for this trial have been calculated using the method of George and Desu (George and Desu, 1974). The good histological response rate for the MAP induction regimen, estimated from INT 0133, is 45%. Analysis of EFS is planned to take place around two years after the closure to recruitment to the trial, analysis of OS is planned for around four years after closure.

Based on the previous experience of the participating groups, 3-year EFS for the MAP regimen is expected to be 70% for good responders and 45% for poor responders; 5-year OS is also expected to be 70% for good responders and 45% for poor responders.

Setting a two-sided significance level of 5% and 80% power, around 525 events are required. Assuming 400 patients registered per year, it is proposed that 1260 patients be randomized into EURAMOS-1. The original planning parameters indicated that, of these, 567 were anticipated to be good responders and 693 poor responders. Data that became available in September 2010 confirming the proportion of good:poor responders was, instead, around 53:47, rather than the expected 45:55. Previous data from COSS suggested that 10% of patients registered at the start of treatment are not randomized following surgery because of disease progression. In EURAMOS-1, the non randomization rate has been higher at around 30-35% for many reasons, including disease progression, insufficient pre-operative chemotherapy and withdrawal of consent. Thus enrollment will be extended to 30 June 2011 to obtain the maximum enrollment of 2300.

To detect an absolute improvement of 10% in good responders from 70% to 80% (hazard ratio 0.63), in 3-year EFS and 5-year OS requires around 147 events to be reported. To detect an absolute improvement of 10% in poor responders, from 45% to 55% (hazard ratio 0.75), in 3-year EFS and 5-year OS requires around 378 events. The analysis for the randomized question amongst good responders and for the poor responders should be undertaken in the third quarter of 2013.

10.3 Sample size for patients with localized disease

At least 85% of patients randomized into EURAMOS 1 are expected to have localized disease at registration. A minimum of 650 good responders with localized disease and 565 poor responders with localized disease may thus be available for analysis. Due to the better prognosis for localized disease, EFS and OS are expected to be slightly higher for this cohort compared to the whole trial population.

In good responders with localized disease, assuming a two-sided significance level of 5% and 80% power, 98 events are required to detect an improvement of 10%, from 75% to 85% (hazard ratio 0.56) in 3-year EFS and 5-year OS. In poor responders with localized disease, 270 events are required to detect an improvement of 11%, from 50% to 61% (hazard ratio 0.71), in 3-year EFS and 5-year OS (2-sided

significance level of 5%, 80% power). With the assumed proportion of patients having localized disease, it is expected to have reasonable power in the localized disease setting when the main analyses are performed.

10.4 Intended Analysis

The two arms will be compared on an intention-to-treat basis. Differences in event-free survival and overall survival will be assessed using the logrank test and expressed using hazard ratios with appropriate confidence intervals. Proportions of patients experiencing grade 3 and 4 toxicities will be compared using chi-square tests or Fisher"s exact tests where appropriate. Differences in EFS and OS will be assessed for the subgroup of patients with localized disease. No other subgroup analyses are planned but the consistency of treatment effect within specified groups, e.g. site of disease, will be examined. A full statistical analysis plan will be developed separately.

10.5 Interim Analyses

The data will be reviewed and formal interim analyses performed at regular intervals (approximately 6 monthly) by an IDMC who will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients.

A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates.

The Haybittle-Peto stopping rule will be adopted for this trial (Haybittle, 1971; Peto et al, 1976). The trial will be stopped for good or poor responders if the p-value for the analysis of EFS is below 0.001. This approach has the advantage of not requiring the number of interim analyses to be specified, and not increasing the Type I error of the final analysis by more than a nominal amount. The IDMC will make recommendations to the TSC as to the continuation of the trial.

It is important that interim analyses of EURAMOS-1 examine the safety of the patients who have been entered into it. If, at interim analysis, the lower bound of the 95% confidence interval for the proportion of patients in each arm who died due to toxicity exceeds 3%, the future of the trial will be discussed with the TSC. The minimum number of toxic deaths for which the lower bound of the 95% CI exceeds 3% is shown in the table below.

Number of patients	Number of toxic deaths
50	5
100	8
150	10
200	12
250	14
300	16

At each interim analysis, all reported grade 4 CTCAE toxicities will be presented by arm. Any perceived excess in grade 4 toxicity, in any arm, will lead to further investigation to determine the safety of that arm. As the toxicity profiles of MAP and MAPIE are known from the results of INT 0133 and P9754, further stopping rules for chemotherapy toxicity are not warranted.

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. See Appendix A.1 for details on trial committees.

10.5.1 Stopping rules for pegylated interferon alfa-2b

Experience from the Karolinska Hospital in Sweden suggests that interferon-α is not associated with major acute or long-term toxicity in osteosarcoma (Strander et al, 1995). Interferon-α has an excellent safety record in other diseases, and we would not expect to see major toxicities arising from it in this trial. However, it would be prudent to monitor the safety of patients who receive pegylated interferon α-2b carefully.

If any toxic death occurs that is attributable to pegylated interferon α-2b, the IDMC and TSC will be consulted within 7 days with a view to discontinuing this arm. If, at interim analysis, > 25% of patients who started pegylated interferon α-2b have subsequently ceased treatment for any reason other than disease progression, relapse or death, the TMG will discuss whether to discontinue this arm with the IDMC and TSC. Permanent, early discontinuation of pegylated interferon α-2b should be discussed with the regional PI whenever possible. At interim analysis, all grade 4 toxicities observed during treatment with pegylated interferon α-2b will be reported. If any individual non-hematological toxicity criterion is associated with grade 4 toxicity in more than 5% of patients, the continuation of this arm will be reviewed with the IDMC and TSC.

10.6 **Gender and Minority Accrual Estimates**

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

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	28	143	171
Not Hispanic or Latino	943	1186	2129
Ethnic Category: Total of all subjects	971	1329	2300
Racial Category			
American Indian or Alaskan Native	0	20	20
Asian	47	47	94
Black or African American	201	171	372
Native Hawaiian or other Pacific Islander	10	0	10
White	713	1091	1804
Racial Category: Total of all subjects	971	1329	2300

This information was derived from the last POG/CCG intergroup localized osteosarcoma study P9754

11.0 EVALUATION CRITERIA

11.1 **Common Terminology Criteria for AdEERS v4.0 (CTCAE)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting via AdEERS beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and a copy can be downloaded from the CTEP web site (http://ctep.cancer.gov).

11.2 Response Criteria for Patients with Solid Tumors

11.2.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable lesions to be followed for response.

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

11.2.2 Quantification of Disease Burden

Product of the maximal transverse dimensions (X, Y, and Z) as described:

a. In the axial plane, find the imagine showing the largest area of tumor and measure the tumor in the longest dimension (X).
b. On the same axial image, measure the tumor in longest dimension (Y) perpendicular to (X).
c. Then, determine the length of the tumor (Z) in the longitudinal axis.

The disease burden measurement is the product of X Y x Z.

11.2.3 Complete Response (CR)

Disappearance of all target lesions.

11.2.4 Partial Response (PR)

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry.

11.2.5 Progressive Disease (PD)

- At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment ***IN ASSOCIATION WITH*** clinical features of progression such as increased pain, inflammatory signs, rising alkaline phosphatase. Clinical assessment must be repeated in no less than 3 weeks to be regarded as progressive disease. (OR)

- The appearance of one or more new lesions.

Also refer to Appendix A.6 of the Intergroup document (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

11.2.6 Stable Disease (SD)

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

11.2.7 Response Assessment

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

11.3 Best Response

Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second

evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

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

12.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

12.3 Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria v. 4.0 (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE.

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.*
For investigational agents that are not commercially available and are being studied under a company's IND or an investigator held IND, expected AEs are usually based on the Investigator's Brochure.
Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

12.4 Reporting methods

- The reporting methods described below are specific for clinical trials evaluating agents for which the IND is held by COG, an investigator, or a pharmaceutical company. It is important to note that these procedures differ slightly from those used for reporting AEs for clinical trials for which CTEP holds the IND.

- Use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov.

An AdEERS report must be submitted by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm, or
- **If the AdEERS web-based application is unavailable**, Fax to COG (626-241-1795; attention COG AE Coordinator) the completed NCI Adverse Event Expedited Report on the paper template.

- Fax supporting documentation for **AEs related to investigational agents** to: COG (fax # 626-241-1795; attention: COG AE Coordinator).
- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI**. Fax this material to COG (fax # 626-241-1795; attention: COG AE 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.**

12.5 When to report an event in an expedited manner

- Some adverse events require notification within 24 hours (refer to Table A) via e-mail to the COG AE Coordinator.
- Submit the report **within 5 calendar days** of learning of the event.

12.6 Other recipients of adverse event reports

COG will forward reports and supporting documentation to the Study Chair, to the drug company (for industry sponsored trials) and to the FDA (when COG holds the IND).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

12.7 Reporting of Adverse Events for investigational agents

Reporting requirements are provided in Table A. The investigational agent used in this study is PEG-Intron (pegylated interferon alfa-2b) [redacted]. COG is the IND holder.

Table A

Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4[3] & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	**24-Hour;** 5 Calendar Days	5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in Non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Please see exceptions below under section entitled "Additional Instructions or Exceptions."

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Note: All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.

Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via e-mail to COG AE Coordinator within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
- "5 calendar days" - A complete AdEERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- Protocol specific reporting of AEs, in addition to the AdEERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via AdEERS per the timelines outlined in the table above.
- **Grades 1- 4 myelosuppression do not require expedited reporting unless unexpected.**

12.8 Reporting of Adverse Events for commercial agents – AdEERS 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 AdEERS report to be submitted **within 5 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.

AdEERS 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			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via AdEERS.

12.9 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for AdEERS reporting.

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

As of August 25, 2010, all secondary malignancies should be reported via AdEERS.

13.0 RECORDS AND REPORTING

13.1 Categories of Research Records

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

1. Non-computerized Information: Pathology Narrative Reports, Surgical Reports. These forms are submitted through the Document Imaging System in the eRDES.

2. Reference Labs‟ required reports, and QARC data: These data accompany submissions to these centers, which forward their review data electronically to the COG Statistics and Data Center.

3. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes submission schedule.

13.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

14.0 SURGICAL GUIDELINES

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

14.1 **Biopsy**

The diagnosis of high-grade osteosarcoma must be verified histologically within 14 days of study enrollment. In order to ensure appropriate biopsy techniques and an appropriate evaluation of the obtained material, it is strongly recommended that biopsies should only be performed in specialized centers. Open biopsy may be performed in order to obtain sufficient material for rapid central review and ancillary studies. The biopsy specimen should be forwarded to the institutional pathologist without prior fixation. Enrollment on a COG osteosarcoma specimen collection study is strongly encouraged.

14.2 **Definitive Surgery**

For osteosarcoma, surgery is the local treatment of choice. Complete surgical removal of all affected sites is mandatory whenever feasible. Rapid central review will be done on the surgical specimen.

14.2.1 Definitive Surgery of the Primary Tumor

Surgery of the primary tumor is scheduled for 11 weeks after the commencement of chemotherapy. Surgery should be performed in a manner which guarantees wide or radical margins according to Enneking"s classification. While it is most often possible to reach such margins without sacrificing the affected limb, mutilating surgery may become necessary if this is not the case. The indication for limb-salvage must be made with particular caution if a poor tumor response to preoperative chemotherapy is anticipated by clinical investigations or appropriate imaging studies. Marginal or intralesional surgery should be avoided whenever possible and must be restricted to situations where wide or radical margins are not achievable by any means. As inappropriate surgery may easily lead to local recurrence and death in otherwise curable patients, it is strongly recommended that osteosarcoma surgery should only be performed in specialized centers.

14.2.2 Definitive Surgery Guidelines

14.2.2.1. Prior to definitive surgery the following parameters are recommended:

Neutrophils	$>1.0 \times 10^9$/L
Platelets	$> 80 \times 10^9$/L

14.2.2.2 Indications for limb salvage surgery:

- Tumor resectable with wide margins
- Reconstruction possible and likely to be successful
- Patient aware of risks/benefits of limb salvage

14.2.2.3 Indications for amputation:

- Inability to completely resect the tumor without leaving residual disease
- Extensive involvement of neurovascular bundle
- Patient preference

There will be many situations where the decision is not easy, in particular when there has been a poor response to chemotherapy, there is extensive soft tissue involvement and the tumor is adjacent to the main neurovascular bundle. In these situations seek a second opinion from one of the main surgical centers.

14.2.3 Reconstruction after limb salvage surgery

There are many types of limb salvage reconstruction available. Remember that the principle aim of the surgeon is to completely resect the tumor with wide margins. This principle should never be sacrificed in order to make limb salvage reconstruction easier. The patient will want a reconstruction that will function well and have few complications. In some situations an amputation may give a better and more predictable result than attempts at reconstruction (e.g. distal tibia).

The following reconstruction options represent standard treatment but are NOT meant to exclude other options:

14.2.3.1
Distal Femur – in most cases use of an endoprosthesis will give a good result. If the tumor involves the knee joint an extra-articular resection should be carried out.

14.2.3.2
Proximal Tibia - use of an endoprosthesis will work well if the extensor mechanism is reconstructed. A gastrocnemius muscle flap should be part of the soft tissue reconstruction.

14.2.3.3
Proximal Femur – modular endoprostheses work well. Because of the significant risk of dislocation a large unipolar or bipolar head is recommended.

14.2.3.4
Proximal Humerus – reconstructive options include the use of a prosthesis, a fibula graft (vascularized) or a turn down of the clavicle (claviculo pro humero).

14.2.3.5
Pelvis – all surgical reconstructions are high risk and should be carried out at a center with appropriate expertise.

14.2.3.6
Diaphyseal tumor – When the joints can be spared above and below a tumor in a long bone then a biological reconstruction is preferred – either using an allograft or an autograft (or a combination)

14.2.3.7
Young children with long bone tumors – extendable endoprostheses have proved useful but have a significant risk of complications. Families must be fully informed about risks/benefits and the inevitability of the need for further surgery. Rotation plasty should be considered in these cases.
IF THERE IS INSUFFICIENT LOCAL EXPERTISE, REFER TO A SURGICAL REPRESENTATIVE ON THE COG AOST0331 COMMITTEE

14.2.4 Surgery of pelvic and other axial tumors

Osteosarcomas arising in the axial skeleton (excluding craniofacial bones) which are deemed resectable with curative intent are eligible for inclusion in this protocol. Subsequent surgical management of such tumors may include amputation (fore or hind quarter for shoulder girdle and pelvic tumors) or complex reconstruction. The chosen approach should be anticipated to achieve the safest oncological margin and at least macroscopic resection.

14.2.5 Surgery of primary metastases

If primary metastases are present, all of these must also be resected completely, regardless of their number and site, if the affected patient is treated with curative intent. Resection is strongly recommended for patients felt to have definite or possible pulmonary metastases at initial diagnosis. The preferred time-point for surgery of primary metastases may be between protocol weeks 11 and 20, but other dates may be chosen at the discretion of the treating physicians. For pulmonary metastases, thoracotomy with manual exploration of both lungs is strongly recommended, even when imaging studies suggest unilateral disease. The use of thoracoscopic techniques is strongly discouraged, as they lack sensitivity and may be associated with an increased risk of intraoperative tumor dissemination. In order to avoid complications associated with delayed methotrexate excretion due to third-spacing into pleural effusions, thoracotomy should not be followed by high-dose methotrexate, but rather by other chemotherapeutic agents.

14.3 Treatment of Relapsed Disease

EFS is the primary endpoint of EURAMOS 1 and therapy of relapsed disease is not prescribed in this trial. In order to achieve a homogeneous standard of patient care, the EURAMOS investigators have summarized their joint opinion about how patients who experience a relapse following therapy on the EURAMOS 1 trial might be treated in Appendix A.7. COG institutions are reminded to check the COG website for open COG studies for osteosarcoma.

15.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Before entering patients in this trial clinicians should discuss this protocol with their pathologist and provide them with appropriate documents.

15.1 Biopsy

All COG patients enrolled on AOST0331 require rapid central review of their diagnostic biopsy material. Biopsy materials must be submitted in a timely manner so that the review results can be reported back to the treating institution within 14 days of study enrollment, and within 21 days of the diagnostic procedure. Lisa Teot, M.D. is the COG reviewer for AOST0331 specimens. Do NOT send specimens directly to Dr. Teot. Send all specimens to the Biopathology Center as specified below.

Please label all materials with the patient‟s COG Patient Identification Number and the surgical pathology identification (SPID) from the corresponding institutional pathology report(s).

Required materials at the time of the initial biopsy for rapid central review are:

- Representative paraffin blocks with tumor, or if blocks are unavailable, send 1 unstained slide from a representative block with tumor
- One H & E stained slide from each block
- A copy of the institutional pathology report(s)
- A copy of the institutional surgical report
- The AOST0331 Pathology Checklist
- Radiological Imaging (copy of plain radiograph, CT, MRI) or electronic image submission and institutional Radiology Report(s)
- Specimen Transmittal Form

Materials should be sent by Federal Express Overnight carrier for next day delivery using account number 2504-6481-9. Mark the parcel "**Osteosarcoma AOST0331 Rapid Review**." Ship the specimens to:

Biopathology Center
Nationwide Children‟s Hospital
700 Children‟s DR Room WA1340
Columbus OH 43205
Phone: 614-722-2894

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed of each patient enrolled on AOST0331 and request that the materials be forwarded to the Biopathology Center. The Biopathology Center and the review pathologist will not request materials.

Enrollment on a COG osteosarcoma specimen collection study is strongly encouraged for all patients enrolled on AOST0331. Please see the specimen collection study for specific instructions on specimen preparation and shipment. Fresh tissue is requested whenever possible.

15.2 **Resection/amputation**

Given the goals of the present trial, timely resection specimen analysis is of paramount importance. This means that at all times the handling of the resected specimens are of peak priority including the initial handling, decalcification, administration, and dispatching the material for central review.

The examination has three objectives:

1) Assessment of resection margins
2) Assessment of the response to chemotherapy (See Section 15.3)
3) Estimation of the amount of cartilaginous differentiation being more or less than 30% of the tumor volume.

To provide documentation of the soft tissue margins, the initial gross examination should be performed on the fresh specimen. Measurement of the narrowest resection margin (mm) is of most value. Histological sections should be taken in any area where excision margins appear dubious. Ideally, the specimen should be prepared by dividing it longitudinally in the plane of maximum tumor diameter, and the whole of this slab should be divided into blocks for preparation of histological sections. Radiological imaging of the specimen is of value in determining the maximum tumor diameter. A photograph and a diagrammatic map of the specimen should be prepared indicating the site of individual blocks. For quantitating the effects of chemotherapy *only* the sections where tumor was present or was thought to have been present should be assessed. Normal adjacent bone and soft tissue areas should *not* be included in the area quantitated. If there is difficulty in handling specimens at any stage the review pathologists are anxious to help.

Sections from each block encompassing the largest diameter of the resected tumor (not the complete specimen) will be required by a review pathologist.

With Amendment #3, institutional assessment of histologic response will be used to determine whether the patient meets the criteria for randomization within 35 days of the surgical procedure. However, every effort should be made to obtain Rapid central review of the surgical material to assess histologic response and provide the required materials to the BPC within 21 days of the resection/amputation in order to complete the review within 35 days of the surgical procedure.

Please label all materials with the patient‟s COG Patient Identification Number and the surgical pathology identification (SPID) from the corresponding institutional pathology report(s).

Materials required at the time of resection/amputation:

- Representative paraffin blocks with tumor or if blocks are unavailable send 1 unstained slide from each block encompassing the largest diameter of the resected tumor.
- One H&E stained slide from each tumor block of the resected specimens
- Map indicating from which point sections are taken
- A copy of the institutional pathology report(s) which includes measurement of the tumor in two dimensions and margins of excision (mm)
- A copy of the institutional surgical report

- Radiological Imaging (copy of plain radiograph, CT, MRI) or electronic image submission and institutional Radiology Report(s)
- The AOST0331 Pathology Checklist
- Specimen Transmittal Form

It is the responsibility of the Principal Investigator enrolling a patient on this trial to request the submitting pathologist to send the appropriate set of forms, local pathology report including the schematic block map, and specimens to the Biopathology Center.
Materials should be sent by Federal Express Overnight carrier for next day delivery using account number 2504-6481-9. Mark the parcel "**Osteosarcoma AOST0331 Rapid Review**." Ship the specimens to:

Biopathology Center
Nationwide Children"s Hospital
700 Children"s Drive, WA 1340
Columbus, OH 43205
Phone: (614) 722-2894

15.3 Procedure for Quantitation

The amount of viable tumor is reported as less than 10% of the tumor area in cases showing a good response and greater than or equal to 10% in cases showing a poor response.

In most cases, the amount of viable remnant tumor is obvious (<10% vital or nearly all vital). In these instances, one can assign response to one of the above-mentioned categories. For problematic (non-obvious) cases, graph paper with 2mm squares can be photocopied (actual size) on to acetate sheets for overhead projection. This may be cut into rectangles and fixed over the cover slip using double-sided Sellotape. The entire tumor-bearing areas can thus be measured and totaled.

The same method may be used for quantifying the amount of cartilaginous differentiation. When more than 30% of an osteosarcoma is composed of chondroblastic areas, intimately associated and mixed with non-chondroid-elements it is considered as chondroblastic osteosarcoma. Viable chondroblastic areas are characteristically composed of nodular, bluish hyaline cartilage, with moderately to severely pleomorphic malignant cells. The microscopic appearance is of chondrosarcoma grade 2-3. Necrotic cartilaginous areas are recognized as a confluent, very pale to light eosinophilic homogeneous matrix with vesicular-appearing lacunae in which shadows of necrotic cells can be seen. Grossly, an overt chondroid appearance is rare so the diagnosis is made on histology.

16.0 SPECIAL STUDIES

16.1 Quality of Life

Treatment for osteosarcoma is associated with both short and long-term toxicities from chemotherapy as well as functional disability as a result of the need for skeletal reconstruction after resection of the primary tumor. The toxicity profile of the standard chemotherapy in this protocol is well recognized but additional toxicities may be anticipated with the addition of ifosfamide and etoposide for poor responders (MAPIE) and with pegylated interferon alfa-2b for good responders.

The main objective of QL assessment within AOST0331 is to determine the impact on QL (both short- and long-term) for two interventions in two groups of patients: (1) poor responders: the impact of the addition of ifosfamide and etoposide to the standard chemotherapy; and (2) good responders: the impact of maintenance therapy with interferon. Describing and comparing the impact of these regimens on QL will lead to a better understanding, from the patients" perspective, of the nature of treatment related side-

effects, both short- and long-term. These data will help define future treatment options for these patients. Additionally, the assessment of QL within EURAMOS 1 will allow more global concerns to be addressed, for example whether QL is affected by surgical factors, patient maturity (emotional and physical) and other characteristics such as gender, and site of primary tumor.

16.2 QL Instruments

For patients aged 16 and over, QOL will be assessed using the EORTC QLQ-C30 questionnaire. Those completing the EORTC questionnaire will not have a parent questionnaire. For patients aged 15 and under the Peds QL questionnaire will be used, which has been validated in North America, but not in all European languages.[2] Peds QL has questionnaires for three age groups: 5-7 years, 8-12 years and 13-15 years. For those 5 to 7 years old there is an interviewer administered questionnaire. For patients 8 to 15 there are self-report questionnaires. A parent questionnaire must be completed for all patients aged 5 to 15. Patients who become 16 years old during the course of the trial should continue to use the pediatric instrument for further assessments. Peds QL has been validated up to the age of 18. Please see the administration guidelines for details.

16.3 Timing of QL Assessments

- 1st QOL Time Point: 1st QOL assessment for child (and parent if applicable) is to be completed at the end of Cycle 1(after 2nd methotrexate) and prior to start of Cycle 2.
- 2nd QOL Time Point:
  - MAP arm and MAPifn Arms: 2nd QOL assessment for the child (and parent if applicable) is to be completed after recovery from the doxorubicin of Week 22/Cycle 5 and prior to the methotrexate of Week 24/Cycle 5.
  - MAPIE Arm: 2nd QOL assessment for the child (and parent if applicable) is to be completed after recovery from the doxorubicin and ifosfamide of Week 20/Cycle 5 and prior to the start of methotrexate of Week 23/Cycle 5
- 3rd QOL Time Point: 3rd QOL assessment at week 72+/- 4. (18 months after the start of treatment)
- 4th QOL Time Point: 4th QOL assessment at week 144+/- 4 weeks (3 years after the start of treatment)

Once completed, QL forms should be returned to the COG Statistics and Data Center. The COG Patient Identification number and date of completion should be recorded on each form.

17.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

17.1 Osteosarcoma Imaging Recommendations

17.1.1 Imaging at Presentation and Immediately Prior to Surgery

Site	Anatomic Imaging	Functional Imaging
Primary and bone metastases	AP and lateral radiographs	
Primary and bone metastases	MRI with gadolinium	
Whole body*		MDP bone scintigraphy (add SPECT of lungs if pulmonary metastases suspected)
Whole body*		Thallium scintigraphy
Whole body*		FDG-PET (if available)
Chest	CT	
Chest	AP and lateral radiographs	

*Not all three studies are required for study entry. Please use same method at subsequent evaluations.

Definition of lung metastases: minimum criteria determined by spiral CT scanning are 3 or more lesions, which are ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. These patients will be classified as having "certain" pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as "possible" metastatic disease.

Definition of bone metastases: must include confirmation of bone scintigraphy or plain radiograph abnormalities either by MRI scan or biopsy or both.

17.1.2 Baseline imaging after surgery

Site	Anatomic Imaging	Functional Imaging	Timing
Primary and bone metastases	AP and lateral radiographs		Within 2 weeks of surgery
Primary and bone metastases	MRI with gadolinium; MRI may not be useful if a massive internal prosthesis is in place		6 weeks post-surgery

17.1.3 Surveillance imaging while on Chemotherapy

Site	Anatomic Imaging	Functional Imaging	Timing
Primary and bone metastases	AP and lateral radiographs		q 16 weeks
Primary and bone metastases	MRI with gadolinium		If required for symptoms or abnormal imaging
Whole body		MDP bone scintigraphy (add SPECT of lungs – if available - if pulmonary metastases suspected)	q 16 weeks
Whole body		Thallium scintigraphy (optional)	If required for abnormal imaging
Whole body		FDG-PET (if available)	If required for abnormal imaging
Chest	CT		q 16 weeks if previously abnormal, sooner if indicated
Chest	AP and lateral radiographs		q 2 months

17.1.4 Surveillance imaging Post-Chemotherapy

This table is provided as a guideline and surveillance imaging post-chemotherapy should occur as per local institutional standards and as appropriate for individual patient care.

Site	Anatomic Imaging	Functional Imaging	Timing
Primary and bone metastases	AP and lateral radiographs		q 3 months x 4 q 6 months x 4 q 12 months x 2
Primary and bone metastases	MRI with gadolinium		If required for symptoms or abnormal imaging
Whole body		MDP bone scintigraphy (add SPECT of lungs if pulmonary metastases suspected)	q 3 months x 4 q 6 months x 4 q 12 months x 2
Whole body		Thallium scintigraphy	If required for abnormal imaging
Whole body		FDG-PET (if available)	If required for abnormal imaging
Chest	CT		q 3 months x 4 q 6 months x 2 then if abnormal radiographs
Chest	AP and lateral radiographs		q 6 months x 6 (starting after last scheduled chest CT

18.0 RADIATION THERAPY GUIDELINES

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

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

18.1 Radiation Therapy Guidelines

As stated above, complete surgery is the local treatment of choice in osteosarcoma. Radiotherapy is reserved for situations where complete surgery cannot be achieved. Radiotherapy is, however, recommended for inoperable sites or those that could only be operated with inadequate margins. It is strongly suggested that participating institutions use the information and consulting systems set up by their respective groups before assuming inoperability, because some lesions which at first seem inoperable may turn out to be operable for specialized tumor surgeons. Further recommendations about how to proceed in specific situations may vary between groups. When radiotherapy is indicated, chemotherapy should not be interrupted for radiotherapy which is generally best deferred until the end of chemotherapy. Radiotherapy may be administered during treatment with interferon but it is not anticipated that the need will arise except in most uncommon circumstances.

Chemotherapy can be continued during radiotherapy, but enhancement of radiation toxicity is likely to occur with several agents and at the radiation doses recommended may result in severe acute and late side effects. This is of particular concern where spinal cord is in the field. High-dose methotrexate should be

avoided during radiotherapy. Doxorubicin should be avoided in radiation treatment of axial tumors as intestinal toxicity will be enhanced and this agent will also increase skin toxicity. Concurrent ifosfamide should be avoided where significant volume of bladder is in the radiation field

The patients treated with *post-operative irradiation* should receive a total dose of 60 Gy in 2 Gy fractions where margins are microscopically involved and 66 Gy where macroscopic tumor tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70 Gy should always be attempted.

The use of intraoperative electron boost irradiation or brachytherapy by high-dose rate afterloading techniques is permitted in cases where macroscopic tumor tissues are left behind or where the surgical margins obviously are inadequate.

Three-dimensional planning is required for this study. The use of IMRT is allowed. If 3D conformal planning is used, institutions must have an approved 3D benchmark on file at QARC. If IMRT is used, the IMRT Questionnaire and Benchmark must be completed and submitted to QARC. The benchmark material is available from the QARC website (www.qarc.org).

18.1.1 Equipment

18.1.1.1 Modality
X-rays with nominal energy of 4 MV or greater. Co-60 is not allowed on this study. Proton Radiation is not allowed on this study.

18.1.1.2 Calibration
The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

18.1.2 Target Volume Definitions
ICRU-50 and 62 prescription methods and nomenclature shall be utilized for this study.

Gross Tumor Volume (GTV): The GTV is the gross tumor, either palpable or visible/demonstrable by imaging techniques. Its delineation should preferentially be done in collaboration with a radiologist.

Clinical Target Volume (CTV): The CTV contains the demonstrable GTV and/or sub-clinical microscopic malignant disease. Original tumor extension should guide the delineation of CTV. Ideally this should be done in collaboration with the treating surgeon. In axial tumors a safety margin of 2 cm added to GTV should be attempted. For an extremity osteosarcoma a margin of 4-5 cm may be advisable.

Planning Target Volume (PTV): For the purpose of this study, a margin for set up error or patient movement is to be added to the Clinical Target Volume. The PTV for this study will be 0.5 to 1.0 cm.

18.1.3 Target Dose

18.1.3.1 Prescription Point
The prescription point is at or near the isocenter. If IMRT is used, dose may be prescribed to an isodose surface that encompasses the PTV provided that the dose uniformity requirements in Section 18.1.3.5 are satisfied.

18.1.3.2 Dose Definition
Dose is specified in Gy to muscle.

18.1.3.3 Tissue Heterogeneity
Density corrections are not required, however, inhomogeneity correction for air or bone attenuation may be applied. This typically applies in the setting of CT-based treatment planning where radiation dose distributions and treatment calculations are automatically generated based upon the CT densities of the treatment-planning scan.

18.1.3.4 Prescription Dose and Fractionation
The patients treated with *post-operative irradiation* should receive a total dose of 60 Gy in 2 Gy fractions where margins are microscopically involved and 66 Gy where macroscopic tumor tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70 Gy should always be attempted.

18.1.3.5 Dose Uniformity
A maximum dose variation within the PTV between 95-105% according to the dose plan should be attempted. Hot spots outside the PTV with a maximum of 110% are acceptable only if total volume is less than 10 cm^3. Moreover, single *hot spots* should not exceed 5 cm^3. Wedges, compensators, beam segmentation, and other methods of generating a uniform dose distribution are encouraged.

18.1.3.6 Rests/interruptions
There are no planned rests on this study. In case of holidays or machine breakdowns, the overall treatment time might be extended where the indication is adjuvant, whereas in case of macroscopic tumor tissue compensation by adding an extra fraction (separated by a minimum of 6 hours on a treatment day) should be considered. This may not be appropriate where spinal cord, brachial or lumbar plexus is in the high dose volume. Please justify in the comments any interruptions for greater than three treatment days.

18.1.4 Treatment Technique

18.1.4.1
Volume-based (CT scan) treatment planning is required in this protocol. Techniques which shield/protect normal tissue are essential providing that they do not compromise treatment of the PTV. The use of IMRT is allowed. Fields should be chosen to minimize dose to organs at risk as defined in section 18.1.5. Multiple beam techniques, both coplanar and non-coplanar may be used to achieve the objective. If the target volume extends to the surface of the patient, adequate dose coverage should be obtained using bolus material rather than a mixed beam technique. Intraoperative radiation therapy (IORT) and brachytherapy are also allowed on this study.

18.1.4.2 IORT
If IORT is delivered, the electron energy chosen must insure appropriate target dose at both the surface and at depth. The electron energy will be calculated to the 90% line. Bolus may be permitted to insure appropriate surface dose. The IORT Physics Reporting Form and RT-2 form must be filled out with IORT as a separate target if this mode of therapy is used. CT scan is required for submission with the target area and dosimetry identified on the CT study. IORT may be delivered at the time of primary surgical excision.

18.1.4.3 Brachytherapy
Both high dose rate (multiple fractions acceptable) and low dose rate techniques are permitted for this study. If multiple fractions are chosen for high dose rate, the total dose should remain as stated in Section 18.1.3.4. The dose should be calculated to a 1 cm depth or appropriate depth as defined on computer tomography. CT study with the catheters in place is strongly encouraged with dosimetry placed on the CT

study for review. If CT is not available, then orthogonal images and dosimetry in at least two planes is required for submission and review.

18.1.4.2 Patient Position
Reproducible setups are critical and the use of immobilization devices is strongly encouraged.

18.1.4.3 Field Shaping
Field shaping can be done with blocks or multi-leaf collimation.

18.1.5 Organs at Risk:
All structures that may be associated with serious late toxicity should be delineated and dose-volume-histograms generated. The following maximum radiation doses should be respected:

Cervical cord (more that 5 cm length): 45 Gy
Cervical cord (less 5 cm): 50 Gy
Brain tissue: 60 Gy
Optic nerve/chiasm: 50 Gy
Intestine: 50 Gy, depending on volume
Liver:
Whole liver 20Gy: If less than ¼ volume is irradiated, 50 Gy
Kidney: 20 Gy (> 1/3)
Heart: 30 Gy
Lung: 20 – 60 Gy depending on volume
Urinary bladder: 60 Gy

18.1.6 Dose Calculation and Reporting
If conformal techniques are used to treat patients on this study, a 3D treatment planning benchmark needs to be completed and submitted to QARC. If IMRT is used, the IMRT Questionnaire and Benchmark must be submitted. The benchmark material can be obtained from QARC (www.QARC.org).

18.1.6.1 Prescribed Dose
For 3D conformal techniques: The monitor units required to deliver the prescribed dose must be submitted using the RT-1 Dosimetry Summary Form for each field.

For IMRT techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the IMRT Dosimetry Summary Form. The monitor units generated by the IMRT planning system must be independently checked prior to the patient‟s first treatment. Measurements in a QA phantom can suffice for a check as long as the plan‟s fluence distributions can be recomputed for a phantom geometry.

For IORT: The IORT Physics Reporting Form shall be submitted.

For brachytherapy: The Brachytherapy Physics Reporting Form shall be submitted.

18.1.6.2 Dose Uniformity
The maximum and minimum doses in the PTV shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from DVH‟s.

18.1.6.4 Critical Organs
Dose volume histograms for the critical organs indicated in section 18.1.5 shall be calculated whenever the critical organs are included in the radiation therapy treatment fields. The appropriate dose volume histograms shall be submitted with the QA documentation.

18.1.6.5 Isodose Distribution

A hard copy isodose distribution for the total dose plan in the axial, sagittal and coronal planes at the center of the planning target volume must be submitted. These dose distributions must include the following:

A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT images. However, if such hard copy presents difficulty, similar plots without gray scale image are acceptable if enough critical contours are identifiable to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

18.1.7 Quality Assurance Documentation

18.1.7.1

Within three days of the start of radiotherapy, the following data for 3D or IMRT plans shall be submitted for on treatment review:

a. Copies of all diagnostic materials used in defining the target volume. The initial (pre-study) imaging is required.
b. Photographs of the patient in the treatment position with the fields marked.
c. Prescription sheet for the entire treatment course.
d. Copies of the worksheets and printouts used for calculations of monitor settings to give the prescribed dose.
e. Color copies of isodose distributions to demonstrate that the dose variation is within protocol guidelines. The target volume must be clearly shown.
f. Documentation of an independent check of the calculated dose if IMRT is used.
g. Simulator films (if used as part of the treatment planning process) and digitally reconstructed radiographs of each treatment portal (if possible). If these are used as the basis for defining coverage it is imperative that the GTV and PTV be outlined on the simulator films or DRR"s of all fields.
h. First day portal films (or hard copy of real time portal images) if achievable.
i. A completed appropriate (RT-1 or IMRT) Dosimetry Summary Form.
j. One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
k. Beam"s eye views if 3D conformal planning is used.
l. A "room view" display of all fields and their angles, if available, should be submitted.
m. Dose volume histograms for the total treatment for the GTV and PTV and the normal tissues specified in section 18.1.6. If IMRT is used, a DVH shall also 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.

18.1.7.2

For brachytherapy the following data shall be submitted:

a. The Brachytherapy Physics Reporting Form.
b. The strength of the isotope.
c. Appropriate films used for localization of sources.
d. Computer printouts of the isodose distribution and the algorithm used for the calculations.
e. Copies of all diagnostic materials used in defining the target volume.

18.1.7.3
For IORT the following data shall be submitted:

a. The IORT Physics Reporting Form.

18.1.7.3
Within one week of the completion of radiotherapy, the following data shall be submitted.

a. Copies of additional simulation films and verification (portal) films for any major field modifications made subsequent to the initial reporting data.
b. The RT-1 or IMRT Dosimetry Summary Form if any changes have been made subsequent to submission of previous.
c. The RT-2 Radiotherapy Total Dose Record form.
d. A copy of the patient‟s radiotherapy record including the prescription, and daily and cumulative doses to all required areas, including target volumes and normal tissues.
e. Copies of calculations performed subsequent to the submission of the previous data.

These data should be forwarded to:

Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rhode Island 02903-1025
Telephone 401-454-4301
FAX 401-454-4683

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

QARC Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rhode Island 02903-1025
Telephone 401-454-4301

Questions regarding the radiotherapy section of this protocol should be directed to:

18.1.8 Definitions of Deviations in Protocol Performance

18.1.8.1 Prescription Dose:
Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.
Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%

18.1.8.2 Dose Uniformity:
Minor Deviation: Dose variations greater than that specified in Section 18.1.3.5.

18.1.8.3 Volume:
Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.

Major Deviation: Transection of tumor (GTV) or potentially tumor bearing area (CTV) (i.e. geographic miss of any part of the GTV).

19.0 RECOMMENDED GUIDELINES FOR TREATMENT ADMINISTRATION

Please see Appendix B6 of the Intergroup Study document on the protocol page for detailed information (https://members.childrensoncologygroup.org/Prot/AOST0331/AOST0331_Euramos.pdf).

19.1 **Doxorubicin/Cisplatin** (including recommendations for hydration). Cisplatin and doxorubicin may be given simultaneously through 2 separate lines connected via a side port (Y-site).

19.1.1
Prehydration: Achieve SG ≤ 1.010. Administer oral or IV hydration of 1.5-2 L/m^2 over 12 hours (or employ similar regimen).

19.1.2
Day 1-2
Hour 0: Start doxorubicin 75 mg/m^2 by intravenous infusion over 48 hours. Dilute doxorubicin in 480 mL D5W and administer at 10 mL/hr x 48 hours
Hour 0-2: Mannitol 10 g/m^2 in 500 mL/m^2 D5W ½ NS
Hour 2-6: Cisplatin 60 mg/m^2 in 1000 mL/m^2 D5W NS + 10g/m^2 mannitol. Repeat x 2 days
Hour 6-24: Post-cisplatin hydration with D5W ½ NS + 10 mEq KCl/L + 20mEq $MgSO_4$/L at 125 mL/m^2/hr. Repeat on day 2

19.2 **Doxorubicin/Ifosfamide**

19.2.1
Day 1,2 Doxorubicin 75 mg/m^2 IV over 48 hours. Dilute in 480 mL D5W and administer at 10 mL/hr x 48 hours

19.2.2
Day 1,2,3 Ifosfamide/Mesna:
Hours -4 to 0: 1 liter/m^2 of oral or IV fluids to achieve urine specific gravity ≤1.010
Hours 0-4: Ifosfamide 3 g/m^2 IV over 4 hr in 800 mL/m^2 D5W ½ NS with Mesna 600 mg/m^2
Hours 4-7: Mesna 600 mg/m^2 IV in 600 cc D5W ¼ NS
Hours 7,10,13: Mesna 600 mg/m^2 IV over 15 minutes
Hours 7-24: IV or PO hydration with D5W ¼ NS+ 10 mEq KCL/L @ 100 mL/m^2/hr.
Alternatively the identical dose of Mesna can begin by continuous infusion.

19.3 High Dose Methotrexate
(including recommendations for hydration and monitoring of fluid status) High-dose methotrexate should be given at pre-surgery dose with no adjustment for limb loss.

19.3.1
Hours -6 to 0: D5W +40-60mEq $NaHCO_3$/L +10 mEq KCl/L at 200 mL/m^2/hr to achieve urine pH ≥ 7.0.

19.3.2
Hours 0-4: Methotrexate 12g/m^2 in 500 mL/m^2 D5W +40 mEq $NaHCO_3$/L at 125 mL/m^2/hr (maximum dose: 20 grams) IV over 4 hours. All doses should be rounded up to next highest full gram value.

19.3.3
Hours 4-54: Post-hydration with D5W +40mEq $NaHCO_3$/L +10 mEq KCl/L at 125 mL/m^2/hr.

19.3.4
Hour 24: Begin Leucovorin 15 mg/m^2 PO/IV, q6 hrs. Beginning at T= 24h (from beginning of

methotrexate infusion) and continuing until serum methotrexate is < 0.1μM or until delayed excretion criteria is reached (see section below).

19.3.5
MTX levels - Ideally these should be obtained at T=4, 24, 48, 72, (96) hrs with immediately available results. IF only AM values can be immediately available, draw MTX levels at T=4, 24, and q AM.

19.3.5.1
Methotrexate toxicity—recommendations for management*

Excretion/Toxicity	24 Hour MTX Level	48 Hour MTX Level	72 Hour MTX Level	Leucovorin Dosing/Intervention
Expected Excretion	≤ 10 μM (1×10^{-5} M)	< 1 μM (1×10^{-6} M)	< 0.1 μM (1×10^{-7} M)	Maintain hydration 125 ml/m^2/hr **15 mg/m^2 q6h PO/IV** Until MTX level < 0.1μM (1×10^{-7} M)
Grade I (**Mild toxicity-delayed excretion)**			≥ 0.1 μM and <0.5 μM ($1\text{-}5 \times 10^{-7}$ M)	Maintain hydration 125 ml/m^2/hr **15 mg/m^2 q6h PO/IV** Recheck level @ 96hrs if < 0.08μM (8×10^{-8} M) discontinue leucovorin If parameters not met @ 96 hours discontinue leucovorin when level < 0.05μM (5×10^{-8} M)
Grade I **(Mild toxicity)**	>10 and < 50 μM ($1\text{-}5 \times 10^{-5}$ M) **AND/OR** 25- 50 % increase in serum creatinine, Grade I-II stomatitis	≥ 1 μM and < 5 μM ($1\text{-}5 \times 10^{-6}$ M) **AND/OR** 25- 50 % increase In serum creatinine, Grade I-II stomatitis	0.5-5 μM ($0.5\text{-}5 \times 10^{-6}$ M) **AND/OR** 25- 50 % increase in serum creatinine, Grade I-II stomatitis	Increase hydration 200 ml/m^2/hr **15 mg/m^2 q6h PO/IV** Until MTX level < 0.1μM (1×10^{-7} M) or Until criteria for delayed excretion met
Excretion/Toxicity	**24 Hour MTX Level**	**48 Hour MTX Level**	**72 Hour MTX Level**	**Leucovorin Dosing/Intervention**
Grade II **(Moderate toxicity)**	>10 and < 50 μM ($1\text{-}5 \times 10^{-5}$ M) **AND/OR** •50- 100 % increase in serum creatinine, •On previous or current course of HDMTX: Grade III-IV stomatitis, myelosuppression	≥ 1 μM and < 5 μM ($1\text{-}5 \times 10^{-6}$ M) **AND/OR** 50- 100 % increase in serum creatinine, On previous or current course of HDMTX: Grade III-IV stomatitis, myelosuppression	0.5-5 μM ($0.5\text{-}5 \times 10^{-6}$ M) **AND/OR** •50- 100 % increase in serum creatinine, •On previous or current course of HDMTX: Grade III-IV stomatitis, myelosuppression	Increase hydration 200 ml/m^2/hr **15 mg/m^2 q3h IV**** Until MTX level < 0.1μM (1×10^{-7} M) or Until criteria for Delayed excretion met
Grade III **(Severe toxicity)** **Consider Glucarpidase*** *(Carboxypeptidase G2)***	≥ 50 μM and < 500 μM ($5\text{-}50 \times 10^{-5}$ M) **OR** > 100 % increase In serum creatinine	≥ 5 μM and <100 μM (5×10^{-6} M) – (1×10^{-4} M) **OR** > 100 % increase In serum creatinine	≥ 5-50 μM ($0.5\text{-}5 \times 10^{-5}$ M) **OR** > 100 % increase In serum creatinine	Increase hydration 200 ml/m^2/hr **150 mg/m^2 q3h IV**** Until MTX level < 0.1μM (1×10^{-7} M) or Until criteria for Delayed excretion met

Grade IV **(Life threatening)** **Consider Glucarpidase*** *(Carboxypeptidase G2)***	≥ 500 µM (5 x 10^{-4} M)	≥ 100 µM (1 x 10^{-4} M)	≥ 50 µM (5 x 10^{-5} M)	Increase hydration 200 ml/m^2/hr **1500 mg/m^2 q6h IV**** **(maximum dose 1500mg)** Until MTX level< 0.1µM (1 x 10^{-7} M) or Until criteria for Delayed excretion met

** For elevated methotrexate levels or delayed excretion monitor serum creatinine q12-24 hours and methotrexate levels q 24 hours. Doses of leucovorin > 25 mg PO should be given IV due to the saturation of absorption. During methotrexate administration maintain urine pH > 7.0 at all times.*

*** It is possible to reduce the dose of leucovorin on the following days in relation to the reduction in the methotrexate level. When the methotrexate level is in the range of 0.2 – 0.9 µM, give doses of 15mg/m^2 every 6 hours until one dose after the serum level is <0.1 µM or until criteria for delayed excretion met. Please note that leucovorin contains calcium and should not be given at rate faster than 160mg per minute.*

****Glucarpidase (Carboxypeptidase G2, Voraxaze™) is as an investigational agent and is available in the US under a Treatment Protocol for patients receiving high dose methotrexate. To obtain supplies of glucarpidase in the US contact AAIPharma 24-hour Access Call Center at 866-918-1731. Additional information can be found at http://www.btgplc.com/BTGPipeline/273/Voraxaze.html.*

SEVERE TOXICITY REQUIRES PROMPT INTERVENTION - In cases of severe MTX toxicity, contact AAIPharma 24-hour Access Call Center at 866-918-1731 to obtain supplies of carboxypeptidase (glucarpidase, Voraxase). Additional information can be found at http://www.btgplc.com/BTGPipeline/273/Voraxaze.html

Patients with severe Methotrexate (MTX) toxicity may experience renal failure, hepatic dysfunction and myelosuppression. Monitor I & O, weight, CBC, differential, platelets, BP, SGPT, bilirubin, serum creatinine, and MTX levels daily. Patients may have severely delayed MTX excretion with MTX levels > 10^{-7} M (0.1 µM) and serum creatinine > 50% of baseline levels for more than 2l days.

It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia and/or Grade 3 or 4 hypertransaminasemia for longer than 3 weeks will result in discontinuation of MTX if no other etiology is apparent. Notify study coordinator.

In the event of severe toxicity or recurrent moderate toxicity that does not have an obvious correctable cause, consider decreasing MTX cycles to individual rather than two paired weekly MTX cycles. If moderate or severe toxicity recurs, consider eliminating MTX cycles.

19.4 **Ifosfamide/Etoposide** (including recommendations for hydration, supportive care)

19.4.1
Day 1-5: Ifosfamide/Mesna/Etoposide
Hours -4 to 0: D5W ½ NS at 250 mL/m^2/hr to achieve SG ≤ 1.010
Hours 0-1: Etoposide 100 mg/m^2 in 250 mL/m^2 D5W ½ NS
Hours 1-5: Ifosfamide 2.8 gm/m^2 over 4 hr in 800 mL/m^2 D5W ½ NS with Mesna 560 mg/m^2
Hours 5-8: Mesna 560 mg/m^2 IV in 600 cc D5W ¼ NS
Hours 8,11,14: Mesna 560 mg/m^2 IV over 15 minutes
Hours 8-24: IV or PO hydration with D5W ½ NS + 10 mEq KCl/L @ 100mL/m^2/hr.
Alternatively the identical dose of Mesna can begin by continuous infusion.

APPENDIX I: TABLE OF CLINICALLY RELEVANT DRUG SUBSTRATES FOR CYP 2C9 AND CYP2D6

CYP 2C9 SUBSTRATES	CYP 2D6
NSAIDs: diclofenac ibuprofen piroxicam Oral Hypoglycemic Agents: tolbutamide glipizide Angiotensin II Blockers: NOT candesartan irbesartan losartan NOT valsartan Other: celecoxib fluvastatin naproxen phenytoin sulfamethoxazole tamoxifen tolbutamide torsemide warfarin	Beta Blockers: S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine imipramine paroxetine Antipsychotics: haloperidol risperidone thioridazine Other: aripiprazole codeine dextromethorphan duloxetine flecainide mexiletine ondansetron tamoxifen tramadol venlafaxine

Adapted from table prepared by Division of Pharmacology School of medicine Indiana University located at http://medicine.iupui.edu/flockhart/

APPENDIX II YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AOST0331 (EURAMOS 1) (for children 7 through 12 years of age)

A Treatment Study for Children with Osteosarcoma Based on Tumor Response to Chemotherapy Given Before Surgery

1. We have been talking with you about your bone tumor(s), called osteosarcoma. After doing tests we have found you have this kind of tumor.

2. We are asking you to take part in a research study to try a new way of treating your osteosarcoma. 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 a new way to treat osteosarcoma.

3. Children who are part of this study will have two parts to their treatment. One part will be to get chemotherapy (a medicine that kills cancer cells), and then have an operation (surgery) to remove the tumor(s). The second part will be to start a new chemotherapy plan. Which new plan you get will depend on how well the earlier chemotherapy worked for you.

4. In the second part of the study you will be randomly assigned to get either the same chemotherapy you received in the first part or you will receive the same therapy plus new drug. This is called Randomization. This is a lot like flipping a coin. A computer decides which chemotherapy plan you will be on, not you or your doctor. The reason for this is to make sure there are the same number of people on both treatments. Studies like this are done to learn which type of treatment works best. We do not know if one treatment is better than another.

5. Something called a central line is often used for children getting chemotherapy into a vein, so they can receive chemotherapy through it instead of getting poked by a needle. A central line is a special type of tubing that is put into a large vein in your chest. If you have a central line you should not have to get poked too many times to get chemotherapy or have blood samples taken.

6. 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 one of the experimental treatments, we hope the experimental treatment will be better at getting rid of the cancer than the normal treatment. But, we don’t know for sure if there is any benefit of being part of this study.

7. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” If you get one of the experimental treatments, a risk to you from this study is that you may have more side effects from the experimental treatment. Other risks are that your treatment will take longer to complete and may not be any better than the normal treatment in getting rid of the cancer. Other things may happen to you that we don’t yet know about.

8. 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.

9. We are asking your permission to save some of the tumor tissue that was taken during your operation to use for future research. You do not have to agree to let us save this tissue to be a part of this study.

10. We are also asking you to answer some questions about what your life is like and how you feel about your diagnosis and treatment. We would ask these questions 4 different times during or after your treatment. You do not have to agree to answer these questions to be a part of this study. After you get your chemotherapy, you will be checked regularly in the clinic to see how well the drugs are working and to answer the questions about how you feel.

INFORMATION SHEET REGARDING RESEARCH STUDY AOST0331 (EURAMOS 1)
(for teens 13 through 17 years of age)

A Treatment Study for Children and Teens with Osteosarcoma Based on Tumor Response to Chemotherapy Given Before Surgery

1. We have been talking with you about your bone tumor(s), called osteosarcoma. After doing tests we have found you have this kind of tumor.

2. We are asking you to take part in a research study because you have osteosarcoma. 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 a new way to treat osteosarcoma.

3. Children and teens who are part of this study will receive treatment in two parts. One part will be to get chemotherapy (a medicine that kills cancer cells), and then have an operation (surgery) to remove the tumor(s).

   The second part will be to start a new chemotherapy plan, which will be determined by how well the earlier chemotherapy worked for you:
   - If the chemotherapy worked really well (90% or more of the cancer cells were destroyed), you will either continue with the same chemotherapy OR get the same chemotherapy PLUS one new drug.
   - If the chemotherapy worked not so well (fewer than 90% of the cancer cells were destroyed), you will either continue with the same chemotherapy OR get the same chemotherapy PLUS two new chemotherapy drugs.
   - If the chemotherapy did not affect the cancer cells at all, your doctor will take you off this study and develop a new treatment plan for you.

4. The second part of the study is called a randomized study, because you will be randomly assigned to get one treatment plan or the other. This is like flipping a coin and saying, "Heads means I get the same chemotherapy, but tails means I get the same chemotherapy AND something new," except that a computer will determine which chemotherapy plan you would be on. The decision about which treatment you receive is not made by you or your doctor directly. The reason for this is to make sure there are the same number of people on both treatments. Studies like this are done to learn which type of treatment works best. We do not know if one treatment is better than another.

5. Something called a central line is often used for people getting chemotherapy into a vein, so they can receive chemotherapy through it instead of getting poked by a needle. A central line is a special type of tubing that is put into a large vein in your chest. If you have a central line you should not have to get poked to get chemotherapy or have blood samples taken.

6. 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 one of the experimental treatments, we hope the experimental treatment will be better at getting rid of the cancer than the standard treatment. But, we don't know for sure if there is any benefit of being part of this study.

7. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." If you get one of the experimental treatments, a risk to you from this study is that you may have more side effects from the experimental treatment. Other risks are that the experimental treatment will take longer to complete and may not be any better than the standard treatment in getting rid of the cancer. Other things may happen to you that we don't yet know about.

8. 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.

9. We are also asking your permission to save some of the tumor tissue that was taken during your operation to use for future research about cancer and other diseases. You do not have to agree to let us save this tissue to be a part of this study.

10. We are also asking you to answer some questions about what your life is like and how you feel about your diagnosis and treatment. We would ask these questions 4 different times during or after your treatment. You do not have to agree to answer these questions to be a part of this study. After you get your chemotherapy, you will be checked regularly in the clinic to see how well the drugs are working and to answer the questions about how you feel.

REFERENCES

1. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-76, 1993
2. Varni JW, Burwinkle TM, Katz ER, et al: The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer 94:2090-106, 2002

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

AOST0331, A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histologic Response to Pre-Operative Chemotherapy (EURAMOS 1)

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required and the assent (agreement) of your child may be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

PART 1- INDUCTION THERAPY

This study is a clinical trial (a research study involving human subjects). Clinical trials only include individuals who choose to take part in them. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to take part in this study because you have osteosarcoma, a form of cancer that develops in bone. Osteosarcoma is the most common cancerous bone tumor in children and young adults. Study doctors would like to find out how best to treat subjects with osteosarcoma by comparing how subjects do when treated with different anti-cancer drugs. The EURAMOS 1 trial is open to all osteosarcoma subjects who have high grade tumor that can be removed by surgery; high grade tumor means that the osteosarcoma tumor cells grow very fast. The tumors must be in the legs, arms, or backbone, and can still be in the place(s) where they first started (this is called localized disease) or can have spread to other places in the body (this is called metastatic disease) as long as all the tumors can be taken out with surgery.

Why is this study being done?

This study is being done to try to find out the best way to treat osteosarcoma subjects who have tumors that can be removed by surgery. The standard anti-cancer drugs used to treat subjects with osteosarcoma are doxorubicin, cisplatin, and methotrexate (together called MAP). In previous research studies using MAP study doctors found that by looking at pieces of the tumor under a microscope after some MAP has been given, they can estimate how many tumor cells have been killed; if the tumor cells are almost all destroyed (about 90% or more, called a good response), there is a good chance that the tumor will go away if we continue to use these standard drugs. If the tumor cells are not as easily killed by MAP (less than 90% of the cells killed, called a poor response), the chance that the disease will go away is not as good, meaning the tumor is more likely to return later.

For subjects who have a poor tumor response to MAP, study doctors would like to find out if adding two other common anti-cancer drugs (ifosfamide and etoposide) to MAP will help get rid of the tumor in more subjects. We do not know if adding ifosfamide and etoposide to the MAP regimen will increase the chance of getting rid of the tumor. Ifosfamide and etoposide have been chosen for use in this study because in some previous studies of children with metastatic

osteosarcoma, the addition of ifosfamide and etoposide to MAP brought about a better outcome. Adding ifosfamide and etoposide to the MAP chemotherapy treatment is experimental. For subjects who have a good tumor response to MAP therapy, study doctors would like to know if adding a "biologic" drug, interferon, after MAP, will help make sure the tumor cells do not return later. Interferon is produced naturally in the body. The exact way interferon works is not known; it may directly kill cancer cells, or it may interfere with the blood supply to the tumor, or it may make the body's immune system work better (the immune system recognizes and destroys "foreign" cells). This study will use pegylated interferon alfa-2b, interferon that has been modified to last longer in the body so it can be given less often. The use of interferon was shown in some previous studies of subjects with other diseases to increase the time before the disease came back: we do not know if giving interferon will increase the chance of getting rid of the tumor for subjects with osteosarcoma. Adding pegylated interferon alfa-2b after the MAP chemotherapy treatment is experimental.

Because this study will have a large number of subjects treated in the same ways, study doctors will be able to tell if these drugs do improve the outcome for subjects with osteosarcoma. It is important to study the addition of these chemotherapy drugs and the biologic drugs because the addition of these drugs will also add side effects and lengthen the total amount of treatment time.

The aims of this study are, then:

- **To see if the addition of ifosfamide and etoposide to MAP chemotherapy will help get rid of the disease in subjects who have a poor tumor response to MAP alone.**
- **To see if the addition of interferon after MAP chemotherapy can help get rid of the disease in subjects who have a good tumor response to standard chemotherapy.**

Study doctors would also like to look at the tumor tissue to see if there are things about the genetic make-up of these tumors that can be used to predict how subjects will respond to therapy. Study doctors would also like to know how the disease and the therapy affect the lives of subjects and their families.

How many people will take part in the study?

There will be about 2300 subjects taking part in this study.

What will happen if I take part in this research study?

Before you begin the study …

If you take part in this study, you will have the following tests and procedures. These are part of regular cancer care and may be done even if you do not join in this study:

- History and physical examination
- Blood tests
- Urine tests
- Pregnancy Test*
- Echocardiogram (picture of the heart in motion)
- MRI (magnetic resonance imaging) of disease sites
- X-ray of disease sites and the chest
- CT scan (an X-ray procedure) of disease sites and the chest
- Bone Scan (picture of the bones)
- Audiogram (hearing test)
- Nuclear Medicine Scans

** Given to females of childbearing age prior to treatment*

Because you are in this study we will want to know your view of how your life has been affected by cancer and its treatment. You will be asked to fill out some questionnaires; these are called Quality of Life Assessments; they will be done after you have had about 6 weeks of chemotherapy, about three months after surgery, at 18 months after the start of all the study therapy, and at 3 years after the start of all the study therapy. It will take about 10 minutes to complete the questionnaires; if your child is on this study, you and your child will be given different questionnaires. You do not have to take part in these Quality of Life assessments to be part of this research study.

All subjects who are enrolled on this study will begin treatment with the standard drugs for osteosarcoma therapy: doxorubicin, cisplatin and methotrexate (MAP). Following 10 weeks of chemotherapy subjects will have surgery to take out the tumor(s). The tumor tissue will be looked at under a microscope to find out how many of the tumor cells have been killed; briefly, if 90% or more of the tumor cells have been killed, this will be called a good tumor response. If less than 90% of the tumor cells have been killed, this will be called a poor tumor response. If there is no change in the tumor, you will be taken off therapy and other treatment options will be discussed.

The therapy you will get on the second part of the study will depend on whether you have a good or a poor tumor response, and then will depend on randomization to one of two different treatment regimens. Randomization means that you are being put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose which group you will be put in. You will have an equal chance of being placed in any group. Your study doctor will discuss the treatments with you and you will be asked to sign another consent for the second part of the study. Your study doctor may think that you need to start chemotherapy after your surgery and before all the information is known for the randomization. In this case, you will start on a cycle of MAP chemotherapy before signing the consent for the randomized part of the study.

Here is the treatment plan for the entire study:

Phase	Treatment	Treatment Details
Part 1	Induction Therapy	Same for all subjects
	MAP Chemotherapy: (Methotrexate, Doxorubicin, and Cisplatin)	Approximately 10 weeks of therapy
Surgery	Local Control	Occurs at week 11
	% of tumor cells killed will be determined	Discussion about Part II treatment Signing another consent for Part 2 treatment
Part 2	Maintenance therapy	Begins after recovery from surgery
	Good response to MAP - Randomization to either: i. MAP (Methotrexate, Adriamycin, Cisplatin) **or** ii. MAPifn (Methotrexate, Adriamycin, Cisplatin + Pegylated interferon alfa-2b)	 Treatment duration approximately 7 months Treatment duration approximately 7 months for chemotherapy, and up to 2 years of Pegylated interferon alfa-2b (as long as the treatment does not cause significant side effects and there is no evidence of disease progression)
	Poor response to MAP – Randomization to either: i. MAP(Methotrexate, Adriamycin, Cisplatin) **or** ii. MAPIE (Methotrexate, Adriamycin, Cisplatin + Ifosfamide, Etoposide)	 Treatment duration approximately 7 months Treatment duration approximately 10 months

Methods for Giving Drugs

Various methods will be used to give the drugs to you. Some drugs may be given by tablet or liquid through the mouth (oral). Some drugs may be given using a needle inserted just under the skin (subcutaneous). Other drugs may be given using a needle inserted into a vein (IV, or intravenous).

The drugs for the induction therapy on this study are given in this way:

MAP (Induction)

Week	Day	Drug	Method
1,6	1,2 1,2	Doxorubicin* Cisplatin	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours
4,5,9,10	1 2	Methotrexate Leucovorin[#]	Given by vein over 4 hours Given by vein 24 hours after the start of Methotrexate, every 6 hours, until Methotrexate level has sufficiently cleared from the blood (determined by a blood test) *If surgery is delayed, you (your child) may get more methotrexate prior to surgery. If you have (your child has) difficulty recovering from the effects of the methotrexate therapy you (your child) may only have methotrexate twice before surgery instead of four times.*
11			Surgical removal of tumor

*Dexrazoxane may be given with doxorubicin.

[#] Small doses may be given by mouth.

Central Line
For drugs to be given by vein, your study doctor will likely recommend that you have a central venous line placed. A central line is a type of tubing inserted into a large vein in the chest by a surgeon during a short operation. The central line is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. How the tubing is inserted and all the risks associated with central lines will be explained to you, and all of your questions about the central line will be answered, when you sign a separate consent for the central line.

Surgery
Subjects on this study will undergo surgery after Induction chemotherapy. You will be asked to sign a separate consent form for the surgical procedure. The planned surgery will be explained to you and your questions about it answered by your surgeon when you sign the consent for the surgical procedure.

Some of the tissue already taken to make your diagnosis will be sent to a central review center as part of COG quality control; there will also be central review of the slides used to find out how many cancer cells have been killed after the induction therapy with MAP.

Radiation therapy
A small number of subjects on this study may need to have radiation therapy to help control the tumor; this would only be done if the tumor cannot be completely taken out with surgery. You will be asked to sign a separate consent for the radiation therapy. All your questions about the radiation therapy will be answered and the procedure explained when you sign the consent for radiation therapy.

How long will I be in the study?

We think if you complete therapy with MAP alone on this study, the treatment will last for about 7 months. Treatment on the MAPIE therapy will last about 10 months. Treatment with MAP plus pegylated interferon alfa-2b will take about 7 months for the completion of MAP, but you will get pegylated interferon alfa-2b for up to two years, as long as the treatment does not cause bad side effects and there is no evidence the disease has come back. After treatment, subjects will have follow-up examinations and medical tests. We will continue to collect some medical information about how you are doing for 10 years after you start the study.

The study doctors may decide to take you off the study if your cancer gets worse or you have side effects from the treatment that are too bad.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the therapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

While on Part 1 of this study you are at risk for the side effects known about MAP therapy listed in the attached Appendix. You should discuss these with the study doctor and/or your regular doctor. There are other drugs that may be given to make the side effects of the drugs less serious and uncomfortable. There are no additional risks to you from the MAP therapy on Part 1 of the study as compared to getting this standard therapy without being on the study.

In Part 2 of the study, the addition of ifosfamide and etoposide for subjects with a poor tumor response to pre-surgery MAP will cause additional side effects and prolong the length of treatment and may not improve the chance that the disease will go away. The addition of Pegylated interferon alfa-2b for subjects with a good tumor response will cause additional side effects and prolong the length of treatment and may not improve the chance that the disease will go away. There may also be other side effects that we cannot predict when these drug combinations are used.

Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, permanent, or even fatal. You will be watched closely and the drugs will be stopped if bad side effects develop. Finally, a few subjects who survive cancer develop a second form of cancer.

Surgical risks:
The surgeon will talk to you about the risks of the surgery when you sign the consent for surgery after induction chemotherapy. In general, surgery may result in one or more of the following side effects: bleeding, infection, problems with wound healing, pain, scar, adhesions, loss of nerve or organ function, or blood vessel damage. Depending on the type of anesthesia required, there may be one or more of the following side effects: nausea, vomiting, air passage obstruction, breathing problems, or heart irregularity. In rare instances death may occur during or after surgery.

Reproductive Risks

For Women:
The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your regular doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid nursing.

For Men:
The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your regular doctor immediately.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the drug therapy in this study will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about treating osteosarcoma. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Instead of being on this study, you have these options:

- The standard treatment for osteosarcoma, which is chemotherapy with doxorubicin, cisplatin and methotrexate (MAP) without being on this study
- Another experimental treatment (if available)

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

Will my medical information be kept private?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is attached at end of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group,**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in keeping research safe for people,**
- **The Institutional Review Board (IRB) of this hospital,**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute,**

- **Representatives of Schering-Plough, the company that will be supplying pegylated interferon alfa-2b for this study**
- **Representatives of the cooperating pediatric research groups.**

It is very unlikely that the research testing might uncover important information about you or your current or future health. If this unlikely event occurs, the researchers may contact your doctor through Children's Oncology Group about what the test results might mean. Only your doctor will be notified and the information will remain confidential. Your doctor may discuss this unexpected finding with you, and may recommend consultation with a genetic counselor and/or repeat testing in a clinical (not research) laboratory if necessary. It is possible that your doctor may recommend that no additional action is necessary.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

This study includes providing specimens to the researcher, there are no plans for you to profit from any new products developed from research done on your specimens.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study has no plans to pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here)*

Please note: This section of the informed consent form is about additional research studies that are being done with subjects who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

Consent to take part in Quality of Life Assessment research:

We want to know your view of how your life has been affected by cancer and its treatment. This "Quality of Life" study looks at how you feel, physically and emotionally, during the cancer treatment. It also looks at how your family adapts to the cancer treatment. This information will help doctors and nurses better understand how subjects and families feel during treatments and what effects the medicines are having.

You will be asked to complete surveys at 4 time points: after you have had about 6 weeks of chemotherapy, about three months after surgery, 18 months after the start of study therapy, and 3 years after the start of study therapy. If your child is on this study, you and your child will be given different questionnaires. It takes about 10 minutes to fill out the questionnaires and this usually can be done during a clinic visit.

If any questions make you (or your child) feel uncomfortable, you (or your child) may skip those questions and not give an answer.

If you agree to take part in the Health Related Quality of Life Assessment, we will do our best to make sure that your answers to the questionnaires are kept private.

You may change your mind about completing the questionnaires at any time. If you change your mind, please let the study doctor know and you will not be given any more questionnaires.

Please circle your answer. After circling "yes "or "no" please write your initials in the space provided.

I choose to take part in the Quality of Life Assessment. I agree to fill out (and allow my child to fill out) the four Quality of Life Questionnaires.

YES NO INITIALS_____ DATE_____

Consent to Use Tissue for Research [*do not use this section if the patient has already enrolled on a specimen collection study*]

You had a biopsy to see if you had cancer. You had or will have surgery to remove your tumor(s). Information about the tumor will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is leftover from your biopsy and any surgery for future research. If you agree, this tissue will be kept, labeled only with a code number, and may be used in research to learn more about cancer and other diseases. Please read the information sheet called " Providing Your Tissue For Research: What You Need To Know?" to learn more about tissue research.

[Note to Local Investigator: This information sheet is available on the COG web site at: https://members.childrensoncologygroup.org/prot/reference_materials.asp *under* **CONSENTS AND IRB FORMS***]*

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While this institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No" and write your initials in the space provided.

If you have any questions, please talk to the study doctor or nurse, or call our research review board at IRB's phone number.

No matter how you answer the following two questions, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   YES NO Initials _____

2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   YES NO Initials _____

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form.
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in the first part (Induction) of this study.

Participant _____ Date_____

Parent (or Guardian) _____ Date_____

APPENDIX I: Risks and side effects related to MAP chemotherapy

Risks and side effects related to doxorubicin include those which are:

Likely	Less Likely	Rare but serious

• Nausea
• Vomiting
• Temporary hair loss
• Pink or red color to urine, sweat, tears, saliva
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of platelets causes you to bruise and bleed more easily
• Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function
	• Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)
	• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid
	• Facial Flushing
	• Fever/chills
	• Hives
	• High levels of uric acid in the blood which could damage the kidneys
	• Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed.
	• Damage to the skin if the medication leaks from a vein
	• Thickening and hardening of the veins through which the medication is given
	• Reddening reaction of the vein through which the drug is given
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Tearing and inflammation of the eyes
	• Loss of appetite
	• Redness and burning at sites which have received radiation in the past
	• Diarrhea
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Ulceration of the lower intestinal tract
		• An irregular heart beat which can be life-threatening
		• Severe damage to the heart muscle which may lead to severe heart failure
		• A new cancer or leukemia resulting from this treatment.

The risk of heart damage may be greater in very young children than in older ones.

Risks and side effects related to cisplatin include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• fewer red blood cells and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or in the vein
• Loss of appetite
• Damage to the ear causing difficulty in hearing high pitched sounds
• Temporary and mild increases in levels of certain chemicals in the blood because the kidney is not working as well as normal
	• Abnormal levels of certain salts in the body like sodium, calcium, potassium and phosphate
	• Metallic taste
	• Rash
	• Numbness and tingling in the fingers and toes
	• Temporary changes in vision
	• Damage to the ear causing hearing loss, balance problems and ringing in the ears
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Inflammation and discomfort in the vein through which the medicine was given
	• Damage to the skin may occur if the medication leaks from the vein
		• Allergic reactions which may be severe and life-threatening, causing difficulty in breathing, rapid heart rate, facial swelling and or a drop in blood pressure
		• Damage to the kidney which may be permanent
		• Deafness
		• Seizures
		• Damage to the vision which could lead to blurred vision, blue-green color blindness and to loss of vision which usually goes away after stopping the drug.
		• Decrease in muscle and nerve reflexes that may affect normal functions such as walking
		• Leukemia later in life

Risks and side effects related to methotrexate include those which are:

Likely	Less Likely	Rare but Serious
• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea • Vomiting • Loss of appetite • Diarrhea • Chills and/or fever • Inflammation and/or sores in the mouth, gums, throat and/or esophagus • Inflammation of the intestines which may cause bleeding • Sensitivity to sunlight and increased risk of sunburn • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak. ○ A low number of white blood cells can make it easier to get infections. ○ A low number of platelets causes you to bruise and bleed • Learning disability • Dizziness • Sense of not feeling well or tiredness • Drowsiness • Blurred vision • Rashes with itching and hives • Hair loss, inflammation of the hair follicles • Acne • Tearing and inflammation of the eyes • Darkening of the fingernails	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys. • Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet • Damage, inflammation and/or scarring of lung tissue which may make you short of breath and cough • Seizures • Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes • Temporary loss of function or feeling in the lower part of the body (partial paralysis) • Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or could lead to a coma. • Inflammation and scarring of the liver • Damage to the bone which could lead to arthritis pain and weakness of the bone • Inflammation of the heart • Fluid buildup around the heart • Damage to the kidney

Leucovorin is given with methotrexate:

Risks and side effects related to leucovorin include those which are:

Likely	Less Likely	Rare But Serious
	• Rash with itching and/or hives	• Severe allergic reaction which can be life-threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Convulsions

Sometimes dexrazoxane is given along with doxorubicin to help prevent heart damage.

Side effects of dexrazoxane include those which are:

Likely	Less Likely	Rare but serious
• Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily	• Mild nausea and/or vomiting • Loss of appetite • A feeling of extreme tiredness or not feeling well • Diarrhea • Increases in the blood of fats (triglycerides) and an enzyme made by the pancreas (amylase) • Temporary increases in the blood of iron and decreases in the blood of calcium and zinc • Damage to the skin if the medication leaks from a vein • Thickening and hardening of the veins or pain in the vein through which the medication is given • Temporary elevation in the blood of certain enzymes and bilirubin found in the liver • It may take longer for the blood to clot	• A new cancer or leukemia resulting from this treatment

Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

AOST0331, A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histologic Response to Pre-Operative Chemotherapy (EURAMOS 1)

PART 2- For subjects with a good tumor response to Induction Therapy

Why is this part of the study being done?

Now that you have finished Part 1 of therapy you are being asked to continue on Part 2 of the study. Because your tumor has shown a good response to the MAP therapy in Part 1 (more than 90% of the tumor cells have been killed) you are eligible to be randomized to get either more MAP chemotherapy or MAP chemotherapy plus pegylated interferon alfa-2b.

Continuing with MAP therapy alone should result in a very good outcome, but study doctors would like to know if adding the "biologic" drug interferon, after all MAP therapy is complete, will help make sure the tumor cells do not return later. Adding pegylated interferon alfa-2b after MAP chemotherapy treatment is experimental.

This study will use pegylated interferon alfa-2b, interferon that has been modified to last longer in the body so it can be given less often.

How many people will take part in the study?

There will be about 706 subjects with a good tumor response continuing on to Part 2 of the study.

What will happen if I take part in this part of the research study?

You will be assigned to one of the two treatments by randomization. Randomization means that you are being put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the study doctor will choose which group you will be put in. You will have an equal chance of being placed in any group. You will be randomized to get continued standard treatment with MAP or treatment with MAP and then pegylated interferon alfa-2b (MAPifn); this is called maintenance therapy**.**

If you join in Part 2, you will also continue to have common medical tests to help your doctor find out about your health and how the treatment is going. These tests are part of regular cancer care and may be done even if you do not join in this study:

- History and physical examination
- Blood tests
- Urine tests
- Echocardiogram (picture of the heart in motion)
- MRI (magnetic resonance imaging) of disease sites

- X-ray of disease sites and the chest
- CT scan (an X-ray procedure) of disease sites and the chest
- Bone Scan (picture of the bones)
- Audiogram (hearing test)
- Nuclear Medicine Scans

Methods for Giving Drugs

Various methods will be used to give the drugs to you (your child). Some drugs may be given by tablet or liquid through the mouth (oral). Some drugs may be given using a needle inserted just under the skin (subcutaneous). Other drugs may be given using a needle inserted into a vein (IV or intravenous).

The drugs for the study are given in this way:

MAP

Week	Day	Drug	Method
12, 17	1,2 1,2	Doxorubicin* Cisplatin	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours
22, 26	1,2	Doxorubicin	Given as a continuous infusion through a vein over 48 hours
15,16,20,21,24,25,28,29	1 2	Methotrexate Leucovorin#	Given by vein over 4 hours Given by vein 24 hours after the start of Methotrexate, every 6 hours, until Methotrexate level has sufficiently cleared from the blood (determined by a blood test)

* Dexrazoxane may be given with doxorubicin.
# Small doses may be given by mouth.

MAPifn

Week	Day	Drug	Method
12, 17	1,2 1,2	Doxorubicin* Cisplatin	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours
22, 26	1,2	Doxorubicin	Given as a continuous infusion through a vein over 48 hours
15,16,20,21,24,25,28,29	1 2	Methotrexate Leucovorin#	Given by vein over 4 hours Given by vein 24 hours after the start of Methotrexate, every 6 hours, until Methotrexate level has sufficiently cleared from the blood (determined by a blood test)
Weekly from week 30-104 *	1	Pegylated Interferon Alfa-2b	Given as an injection into the tissue under the skin *Therapy could last until week 104 as long as the treatment does not cause significant side effects and there is no evidence that the disease has come back.

*Dexrazoxane may be given with doxorubicin.
Small doses may be given by mouth.

Central Line
For drugs to be given by vein, your study doctor will likely recommend that you (your child) have a central venous line placed. A central line is a type of tubing inserted into a large vein in the chest by a surgeon during a short operation. The central line is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. How the tubing is inserted and all the risks associated with central lines will be explained to you, and all of your questions about the central line will be answered, when you sign a separate consent for the central line.

How long will I be in the study?

If you join in the second part of the study, we think you will be treated for about 7 months if randomized to MAP therapy alone, and about 7 months for the basic chemotherapy plus up to two years of therapy with weekly pegylated interferon alfa-2b (as long as there is benefit) if randomized to the pegylated interferon alfa-2b therapy.. After treatment, subjects will have follow-up examinations and medical tests. We will continue to collect some medical information about how you are doing for 10 years after you start the study.

The study doctors may decide to take you off the study if your cancer gets worse or you have side effects from the treatment that are too bad

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the therapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

While on this part of the study you are at risk for the side effects listed in Appendix I for MAP therapy as you were in Part 1. You should discuss these with the study doctor and/or your regular doctor.

If you are randomized to get pegylated interferon alfa-2b, you will be at risk for additional side effects. The length of treatment will be longer and the drug may not improve the chance that the disease will go away. You will be watched closely and the pegylated interferon alfa-2b will be stopped if bad side effects develop.

Risks and side effects related to Peginterferon alpha-2b include those which are:

Likely	Less Likely	Rare but serious

• Nausea
• Fever and chills including shaking chills
• Flu like symptoms with headache, tiredness, aches and pains
• Aches and pains in the joints and/or muscles
• Pain, irritation and bruising or redness at the site of the injection
• Mood changes including depression, inability to sleep, irritability and agitation, anxiety, and mood swings
• Loss or thinning of hair
	• Vomiting
	• Constipation or Diarrhea
	• Loss of Appetite
	• Weight Loss
	• Pain in the abdomen
	• An upset stomach
	• A dry mouth
	• High blood sugar which may require treatment
	• High levels of fats (triglycerides) in your blood
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Dizziness
	• Throat or sinus irritation, runny nose and cough
	• A decrease in blood pressure
	• Rash, hives or itchiness
	• Heart problems including an irregular or rapid heart beat, chest pain
	• Low blood pressure
	• Facial flushing with redness and a feeling of warmth
	• Fewer white cells, red cells and platelets in the blood
	  ○ a low number of white blood cells may make it easier to get infections
	  ○ a low number of red blood cells can make you feel tired and weak
	  ○ a low number of platelets causes you to bruise and bleed more easily
	• Increased sweating
	• Confusion and difficulty with concentration when doing various tasks
	• Decrease or increase in your thyroid hormones
	• Shortness of breath
	• Feeling of weakness
	• Sleepiness
	• An irregular menstrual cycle (period)
		• A severe allergic reaction that can be life-threatening and may lead to difficulty in breathing, a drop in blood pressure, and an irregular heart beat.
		• Heart attack or fluid collecting around the heart that can be life-threatening or fatal.
		• Life threatening or fatal changes in moods have occurred including severe depression or feelings of suicide; feelings of aggressiveness that may even lead to the desire to commit murder.
		• Inflammation of your colon (large bowel) which could lead to bloody diarrhea and may be life threatening
		• Inflammation of your pancreas which could cause pain in your abdomen and may be life-threatening
		• If you have ever been told that you have a disease such as lupus, rheumatoid arthritis or other disease that is caused by a disturbance in your immune system "autoimmune disease". Peginterferon may cause these to be worse.
		• Bleeding into the eye leading to loss of sight or blurred vision
		• Damage to your lungs which could lead to shortness of breath and may be life threatening
		• Severe blood infections which will need to be treated and may be life threatening
		• Severe sudden onset of kidney damage

Reproductive Risks

For Women:

The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your regular doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid nursing.

For Men:

The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your regular doctor immediately.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that interferon will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about osteosarcoma. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Instead of being on this study, you have these options:

- **The standard treatment for osteosarcoma which is chemotherapy with doxorubicin, cisplatin and methotrexate (MAP) without being on this study.**
- **Another experimental treatment (if available)**

Please talk about these options with your regular doctor as well as other trusted personal and family advisors.

Will my medical information be kept private?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is attached at end of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group,**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in keeping research safe for people,**
- **The Institutional Review Board (IRB) of this hospital,**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute,**
- **Representatives of Schering-Plough, the company that will be supplying pegylated interferon alfa-2b for this study,**
- **Representatives of the cooperating pediatric research groups.**

It is very unlikely that the research testing might uncover important information about you or your current or future health. If this unlikely event occurs, the researchers may contact your doctor through Children's Oncology Group about what the test results might mean. Only your doctor will be notified and the information will remain confidential. Your doctor may discuss this unexpected finding with you, and may recommend consultation with a genetic counselor and/or repeat testing in a clinical (not research) laboratory if necessary. It is possible that your doctor may recommend that no additional action is necessary.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The drug company that produces Peg-Intron (pegylated interferon alfa-2b) will provide the drug free of charge for subjects randomized to get pegylated interferon alfa-2b therapy.
You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at *http://cancer.gov/clinicaltrials/understanding/insurance-coverage*. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study has no plans to pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form.
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant _____ Date_____

Parent (or Guardian) _____ Date_____

APPENDIX I: Risks and side effects related to MAP chemotherapy

Risks and side effects related to doxorubicin include those which are:

Likely	Less Likely	Rare but serious

• Nausea
• Vomiting
• Temporary hair loss
• Pink or red color to urine, sweat, tears, saliva
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of platelets causes you to bruise and bleed more easily
• Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function
	• Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)
	• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid
	• Facial Flushing
	• Fever/chills
	• Hives
	• High levels of uric acid in the blood which could damage the kidneys
	• Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed.
	• Damage to the skin if the medication leaks from a vein
	• Thickening and hardening of the veins through which the medication is given
	• Reddening reaction of the vein through which the drug is given
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Tearing and inflammation of the eyes
	• Loss of appetite
	• Redness and burning at sites which have received radiation in the past
	• Diarrhea
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Ulceration of the lower intestinal tract
		• An irregular heart beat which can be life-threatening
		• Severe damage to the heart muscle which may lead to severe heart failure
		• A new cancer or leukemia resulting from this treatment.

The risk of heart damage may be greater in very young children than in older ones.

Risks and side effects related to cisplatin include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• fewer red blood cells and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or in the vein
• Loss of appetite
• Damage to the ear causing difficulty in hearing high pitched sounds
• Temporary and mild increases in levels of certain chemicals in the blood because the kidney is not working as well as normal
	• Abnormal levels of certain salts in the body like sodium, calcium, potassium and phosphate
	• Metallic taste
	• Rash
	• Numbness and tingling in the fingers and toes
	• Temporary changes in vision
	• Damage to the ear causing hearing loss, balance problems and ringing in the ears
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Inflammation and discomfort in the vein through which the medicine was given
	• Damage to the skin may occur if the medication leaks from the vein
		• Allergic reactions which may be severe and life-threatening, causing difficulty in breathing, rapid heart rate, facial swelling and or a drop in blood pressure
		• Damage to the kidney which may be permanent
		• Deafness
		• Seizures
		• Damage to the vision which could lead to blurred vision, blue-green color blindness and to loss of vision which usually goes away after stopping the drug.
		• Decrease in muscle and nerve reflexes that may affect normal functions such as walking
		• Leukemia later in life

Risks and side effects related to methotrexate include those which are:

Likely	Less Likely	Rare but Serious
• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea • Vomiting • Loss of appetite • Diarrhea • Chills and/or fever • Inflammation and/or sores in the mouth, gums, throat and/or esophagus • Inflammation of the intestines which may cause bleeding • Sensitivity to sunlight and increased risk of sunburn • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak. ○ A low number of white blood cells can make it easier to get infections. ○ A low number of platelets causes you to bruise and bleed • Learning disability • Dizziness • Sense of not feeling well or tiredness • Drowsiness • Blurred vision • Rashes with itching and hives • Hair loss, inflammation of the hair follicles • Acne • Tearing and inflammation of the eyes • Darkening of the fingernails	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys. • Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet • Damage, inflammation and/or scarring of lung tissue which may make you short of breath and cough • Seizures • Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes • Temporary loss of function or feeling in the lower part of the body (partial paralysis) • Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or could lead to a coma. • Inflammation and scarring of the liver • Damage to the bone which could lead to arthritis pain and weakness of the bone • Inflammation of the heart • Fluid buildup around the heart • Damage to the kidney

Leucovorin is given with methotrexate:

Risks and side effects related to leucovorin include those which are:

Likely	Less Likely	Rare But Serious
	• Rash with itching and/or hives	• Severe allergic reaction which can be life-threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Convulsions

Sometimes dexrazoxane is given along with doxorubicin to help prevent heart damage.

Side effects of dexrazoxane include those which are:

Likely	Less Likely	Rare but serious
• Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily	• Mild nausea and/or vomiting • Loss of appetite • A feeling of extreme tiredness or not feeling well • Diarrhea • Increases in the blood of fats (triglycerides) and an enzyme made by the pancreas (amylase) • Temporary increases in the blood of iron and decreases in the blood of calcium and zinc • Damage to the skin if the medication leaks from a vein • Thickening and hardening of the veins or pain in the vein through which the medication is given • Temporary elevation in the blood of certain enzymes and bilirubin found in the liver • It may take longer for the blood to clot	• A new cancer or leukemia resulting from this treatment

Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

AOST0331, A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histologic Response to Pre-Operative Chemotherapy(EURAMOS 1)

PART 2 – For subjects with a poor tumor response to Induction Therapy

Why is this part of the study being done?

Now that you have finished Part 1 of therapy you are being asked to continue on Part 2 of the study. Because your tumor had a poor response to induction chemotherapy (less than 90% of the tumor cells have been killed) you are eligible for more treatment with MAP chemotherapy or MAP chemotherapy plus ifosfamide and etoposide.

Continuing with MAP therapy may still result in a good outcome, but study doctors would like to know if adding two other commonly used anti-cancer drugs (ifosfamide and etoposide) to MAP will improve the outcome and prevent the disease from returning later. Adding ifosfamide and etoposide to the MAP chemotherapy treatment is experimental.

How many people will take part in the study?

There will be about 615 subjects with a poor tumor response continuing on to Part 2 of the study.

What will happen if I take part in this part of the research study?

You will be assigned to one of the two treatments by randomization. Randomization means that you are being put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the study doctor will choose which group you will be put in. You will have an equal chance of being placed in any group. You will be randomized to get continued standard treatment with MAP alone or treatment with MAP and the addition of ifosfamide and etoposide (MAPIE). This is called maintenance therapy.

If you join in Part 2, you will also continue to have common medical tests to help your doctor find out about your health and how the treatment is going. These tests are part of regular cancer care and may be done even if you do not join in this study:

- History and physical examination
- Blood tests
- Urine tests
- Echocardiogram (picture of the heart in motion)
- MRI (magnetic resonance imaging) of disease sites
- X-ray of disease sites and the chest
- CT scan (an X-ray procedure) of disease sites and the chest

- Bone Scan (picture of the bones)
- Audiogram (hearing test)
- Nuclear Medicine Scans

Methods for Giving Drugs

Various methods will be used to give the drugs to you (your child). Some drugs may be given by tablet or liquid through the mouth (oral). Some drugs may be given using a needle inserted just under the skin (subcutaneous). Other drugs may be given using a needle inserted into a vein (IV or intravenous).

The drugs for the study are given in this way:

MAP

Week	Day	Drug	Method
12, 17	1,2 1,2	Doxorubicin* Cisplatin	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours
22, 26	1,2	Doxorubicin	Given as a continuous infusion through a vein over 48 hours
15,16,20,21,24,25,28,29	1 2	Methotrexate Leucovorin#	Given by vein over 4 hours Given by vein 24 hours after the start of Methotrexate, every 6 hours, until Methotrexate level has sufficiently cleared from the blood (determined by a blood test)

* Dexrazoxane may be given with the doxorubicin.
# Small doses may be given by mouth.

MAPIE

Week	Day	Drug	Method
12, 28	1,2 1,2	Doxorubicin* Cisplatin	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours
20,36	1,2 1-3 1-3	Doxorubicin Ifosfamide Mesna	Given as a continuous infusion through a vein over 48 hours Given by vein over 4 hours Given by vein as a continuous infusion over 24 hours, until at least 12 hours following the completion of the last Ifosfamide dose
16,24,32	1-5 1-5 1-5	Ifosfamide Etoposide Mesna	Given by vein over 4 hours Given by vein over 1 hour Given by vein as a continuous infusion over 24 hours, until at least 12 hours following the completion of the last Ifosfamide dose
15,19,23,27,31,35,39,40	1 2	Methotrexate Leucovorin#	Given by vein over 4 hours Given by vein 24 hours after the start of Methotrexate, every 6 hours, until Methotrexate level has sufficiently cleared from the blood (determined by a blood test)

* Dexrazoxane may be given with the doxorubicin
# Small doses may be given by mouth.

Central Line
For drugs to be given by vein, your study doctor will likely recommend that you (your child) have a central venous line placed. A central line is a type of tubing inserted into a large vein in the chest by a surgeon during a short operation. The central line is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. How the tubing is inserted and all the risks associated with central lines will be explained to you, and all of your questions about the central line will be answered, when you sign a separate consent for the central line.

How long will I be in the study?

We think you will be treated for about 7 months if randomized to MAP therapy alone, and about 10 months if randomized to get MAP plus ifosfamide and etoposide. The study doctors may decide to take you off the study if your cancer gets worse or you have side effects from the treatment that are too bad. After treatment, subjects will have follow-up examinations and medical tests. We will continue to collect some medical information about how you are doing for 10 years after you start the study

The study doctors may decide to take you off the study if your cancer gets worse or you have side effects from the treatment that are too bad.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the therapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What risks or side effects can I expect from being in the study?

While on this study you are at risk for the side effects listed in Appendix I for MAP therapy as you were in Part 1 of the study. You should discuss these with the researcher and/or your regular doctor.

If you are randomized to get ifosfamide and etoposide, there may also be other side effects that we cannot predict when MAP therapy is used together with ifosfamide and etoposide. Adding ifosfamide and etoposide to MAP therapy will cause additional side effects and prolong the length of treatment and may not improve the chance that the disease will go away. You will be watched closely and the ifosfamide and etoposide will be stopped if bad side effects develop.

Risks and side effects related to etoposide include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Hair Loss
• A feeling of weakness or tiredness
• fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
	• Loss of appetite
	• Decreased blood pressure during the infusion which may require treatment
	• Rashes
	• Diarrhea
	• Pain in the abdomen
	• Mouth sores
	• Tingling sensation or loss of sensation in fingers or toes
	• A feeling of extreme tiredness or weakness
	• The finger or toe nails may loosen from their nail beds
	• Inflammation of the vein through which the medication was given
	• Chest pain
		• Damage to the liver
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever
		• A new cancer or leukemia resulting from this treatment
		• Severe rashes which can result in loss of skin and damage to mucous membranes
		• Absence or decrease of monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid

Risks and side effects related to ifosfamide include those which are:

Likely	Less Likely	Rare but serious

• Nausea
• Vomiting
• Hair loss
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
• Slight decrease in kidney function
	• Drowsiness
	• Confusion
	• Depression
	• Loss of appetite
	• Diarrhea or constipation
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Seizures
	• Abnormal hormone function affecting levels of salt in the blood and urine
	• Abnormal heart beat or rhythm.
	• Blood in the urine that is only seen under the microscope
	• Body loss of certain important salts and
		• Damage to brain tissue with very high doses that may lead to coma
		• Kidney failure or damage
		• Damage to the bladder which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also scarring of the bladder
		• A new cancer or leukemia resulting from this treatment
		• Damage to heart muscle which may make you tired, weak, feel short of breath, and retain fluid
		• Abnormal bone growth and development

	minerals (such as sodium, potassium, phosphate and bicarbonate) and retention of acids in the blood • Failure of the ovaries to function normally which may be permanent and which may decrease the ability to have children • Inflammation and burning along the vein where the medicine is given • Elevation in the blood of certain enzymes found in the liver which may mean liver irritation or damage • Structures in the kidney that remove acid from the blood are impaired which may lead to a build up of acid levels in the blood and affect the balance of electrolytes in the blood	

Subjects who get ifosfamide will also get a drug called mesna to protect the bladder from bleeding:

Risks and side effects related to mesna include those which are:

Likely	Less Likely	Rare but serious
	• Nausea • Vomiting • Stomach pain • Headache • Pain in arms, legs and joints • Tired feeling • Rash • Temporary low blood pressure • Diarrhea • Fever • Facial flushing with red cheeks • Nervousness • Dizziness • Confusion • Swelling around the eyes • Coughing • Rapid heart rate	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever

Reproductive Risks

For Women:

The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your regular doctor immediately.

If you are nursing a baby, the drugs used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid nursing.

For Men:

The treatment on this study can damage sperm. You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated on this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated on this study. You may need to continue this for a while, even after you finish the cancer treatment, so talk to your doctors about the length of time you need to avoid pregnancy or abstain. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your regular doctor immediately.

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. While doctors hope that adding ifosfamide and etoposide to MAP will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about osteosarcoma. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Instead of being on this study, you have these options:

- **The standard treatment for osteosarcoma which is chemotherapy with doxorubicin, cisplatin and methotrexate (MAP) without being on this study.**
- **Another experimental treatment (if available)**

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

Will my medical information be kept private?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is attached at end of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- **The Children's Oncology Group,**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in keeping research safe for people,**
- **The Institutional Review Board (IRB) of this hospital,**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute,**
- **Representatives of Schering-Plough, the company that will be supplying pegylated interferon alfa-2b for this study,**
- **Representatives of the cooperating pediatric research groups.**

It is very unlikely that the research testing might uncover important information about you or your current or future health. If this unlikely event occurs, the researchers may contact your doctor through Children's Oncology Group about what the test results might mean. Only your doctor will be notified and the information will remain confidential. Your doctor may discuss this unexpected finding with you, and may recommend consultation with a genetic counselor and/or repeat testing in a clinical (not research) laboratory if necessary. It is possible that your doctor may recommend that no additional action is necessary.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study has no plans to pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/.

If you are in the United States, you may call the NCI's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant _____ Date_____

Parent (or Guardian) _____ Date_____

APPENDIX I: Risks and side effects related to MAP chemotherapy

Risks and side effects related to doxorubicin include those which are:

Likely	Less Likely	Rare but serious

• Nausea
• Vomiting
• Temporary hair loss
• Pink or red color to urine, sweat, tears, saliva
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of platelets causes you to bruise and bleed more easily
• Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function
	• Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)
	• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid
	• Facial Flushing
	• Fever/chills
	• Hives
	• High levels of uric acid in the blood which could damage the kidneys
	• Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed.
	• Damage to the skin if the medication leaks from a vein
	• Thickening and hardening of the veins through which the medication is given
	• Reddening reaction of the vein through which the drug is given
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Tearing and inflammation of the eyes
	• Loss of appetite
	• Redness and burning at sites which have received radiation in the past
	• Diarrhea
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Ulceration of the lower intestinal tract
		• An irregular heart beat which can be life-threatening
		• Severe damage to the heart muscle which may lead to severe heart failure
		• A new cancer or leukemia resulting from this treatment.

The risk of heart damage may be greater in very young children than in older ones.

Risks and side effects related to cisplatin include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• fewer red blood cells and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make you feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes you to bruise and bleed more easily
• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or in the vein
• Loss of appetite
• Damage to the ear causing difficulty in hearing high pitched sounds
• Temporary and mild increases in levels of certain chemicals in the blood because the kidney is not working as well as normal
	• Abnormal levels of certain salts in the body like sodium, calcium, potassium and phosphate
	• Metallic taste
	• Rash
	• Numbness and tingling in the fingers and toes
	• Temporary changes in vision
	• Damage to the ear causing hearing loss, balance problems and ringing in the ears
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• Inflammation and discomfort in the vein through which the medicine was given
	• Damage to the skin may occur if the medication leaks from the vein
		• Allergic reactions which may be severe and life-threatening, causing difficulty in breathing, rapid heart rate, facial swelling and or a drop in blood pressure
		• Damage to the kidney which may be permanent
		• Deafness
		• Seizures
		• Damage to the vision which could lead to blurred vision, blue-green color blindness and to loss of vision which usually goes away after stopping the drug.
		• Decrease in muscle and nerve reflexes that may affect normal functions such as walking
		• Leukemia later in life

Risks and side effects related to methotrexate include those which are:

Likely	Less Likely	Rare but Serious
• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea • Vomiting • Loss of appetite • Diarrhea • Chills and/or fever • Inflammation and/or sores in the mouth, gums, throat and/or esophagus • Inflammation of the intestines which may cause bleeding • Sensitivity to sunlight and increased risk of sunburn • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak. ○ A low number of white blood cells can make it easier to get infections. ○ A low number of platelets causes you to bruise and bleed • Learning disability • Dizziness • Sense of not feeling well or tiredness • Drowsiness • Blurred vision • Rashes with itching and hives • Hair loss, inflammation of the hair follicles • Acne • Tearing and inflammation of the eyes • Darkening of the fingernails	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys. • Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet • Damage, inflammation and/or scarring of lung tissue which may make you short of breath and cough • Seizures • Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes • Temporary loss of function or feeling in the lower part of the body (partial paralysis) • Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or could lead to a coma. • Inflammation and scarring of the liver • Damage to the bone which could lead to arthritis pain and weakness of the bone • Inflammation of the heart • Fluid buildup around the heart • Damage to the kidney

Leucovorin is given with methotrexate:

Risks and side effects related to leucovorin include those which are:

Likely	Less Likely	Rare But Serious
	• Rash with itching and/or hives	• Severe allergic reaction which can be life-threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Convulsions

Sometimes dexrazoxane is given along with doxorubicin to help prevent heart damage.

Side effects of dexrazoxane include those which are:

Likely	Less Likely	Rare but serious
• Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily	• Mild nausea and/or vomiting • Loss of appetite • A feeling of extreme tiredness or not feeling well • Diarrhea • Increases in the blood of fats (triglycerides) and an enzyme made by the pancreas (amylase) • Temporary increases in the blood of iron and decreases in the blood of calcium and zinc • Damage to the skin if the medication leaks from a vein • Thickening and hardening of the veins or pain in the vein through which the medication is given • Temporary elevation in the blood of certain enzymes and bilirubin found in the liver • It may take longer for the blood to clot	• A new cancer or leukemia resulting from this treatment

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