

COG-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 (IND #12697)

FAST FACTS

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit. Enrollment on the COG companion osteosarcoma biology and banking study is strongly encouraged for all patients enrolled on AOST0331. Please see the biology and banking study for specific instructions on specimen preparation and shipment.

- ___ 1. 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 calendar days after enrollment.
- ___ 2. Patients must be ≥ 5 years and ≤ 40 years on date of diagnostic biopsy.
- ___ 3. Patients must have high grade osteosarcoma. This includes second malignancies.
- ___ 4. Submission of diagnostic biopsy for rapid central review of diagnostic biopsy materials is required on this study.
- ___ 5. 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
- ___ 6. All tumor (primary, metastatic, or both) is resectable or is expected to become resectable after the initial chemotherapy.
- ___ 7. Some trial groups may have their own protocol for metastatic patients, participating clinicians should check with the relevant Trials Center before registering patients.
- ___ 8. 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.
- ___ 9. Patients must fulfill the following criteria for post-surgical randomization to occur:
 - Local institutional assessment of histologic response in the primary tumor following definitive surgery
 - The combination of cisplatin and doxorubicin must have been administered exactly twice before surgery.
 - Methotrexate must have been administered at least twice but no more than six times before surgery.
 - Recovery from prior therapy allowing administration of chemotherapy as detailed in the protocol.
 - No evidence of disease progression as defined in section 11.2.5
 - No definite progression of metastatic disease and no evidence of new metastatic disease.
 - 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).
 - 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.

- ___ 10. 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.
- ___ 11. No previous treatment for osteosarcoma or previous chemotherapy for any disease. Previous radiotherapy for a prior cancer (other than osteosarcoma) is permitted.
- ___ 12. Patients must have adequate renal function defined as:
 - Glomerular Filtration Rate ≥ 70 mL/min/1.73 m² or
 - A serum creatinine based on age 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).

- ___ 13. Patients must have adequate cardiac function defined as:
 - Shortening fraction of $\geq 28\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by radionuclide angiogram.
- ___ 14. Patients must have 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 $\geq 100 \times 10^9/L$
- ___ 15. Patients must have adequate liver function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- ___ 16. Female patients must have a negative pregnancy test.
- ___ 17. Female patients who are lactating must agree to stop breast-feeding.
- ___ 18. Patients must not be known to be HIV positive. Testing for HIV is not mandatory.
- ___ 19. Sexually active patients of childbearing potential must agree to use effective contraception.
- ___ 20. Patients must be able to cooperate fully with all planned protocol therapy.

REQUIRED OBSERVATIONS:

STUDIES TO BE OBTAINED

- History
- Physical Exam (Ht, Wt, BSA, VS)
- Performance Status
- CBC, differential, platelets
- Urinalysis
- Urine phosphate and creatinine
- Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺, bicarbonate
- Creatinine, BUN, SGOT, SGPT, bilirubin, alk phos
- Total protein/albumin
- Coagulation profile
- Glomerular Filtration Rate ¹
- Left ventricular function (Echo or MUGA)
- Audiogram
- Quality of Life Assessment ²
- Specimen submission (see Section 15.0)
- Central review of films (see Section 17.0) may be requested
- Pregnancy Test
- Sperm banking recommended
- Disease Evaluation by imaging (see Section 17)

¹ There must be some measure of renal function via radioisotope GFR or calculated GFR (see Appendix A.3)

² First time point is at end of cycle 1

TREATMENT PLAN:

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 (\geq 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.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

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, the unique BPC specimen number and the surgical pathology number 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 slides from each block
- A copy of the institutional pathology report(s)
- A copy of the institutional surgical report
- The AOST0331 Pathology Checklist
- Radiograph(s)
- Specimen Transmittal Form

If the patient is also being enrolled on the companion osteosarcoma biology and banking study, you will be asked to send additional specimens at diagnosis. See the biology and banking study for complete instructions.

Materials should be sent by OVERNIGHT carrier for next day delivery. Please call the CHTN Biopathology Center to notify them of the shipment and mark the parcel "**Osteosarcoma AOST0331 Rapid Review.**" Ship the specimens to:

Biopathology Center
Columbus Children's Hospital
700 Children's DR Room WA 1340
Columbus OH 43205
Phone: 1-800-347-2486

BIOLOGY REQUIREMENTS:

Consider enrollment on the companion osteosarcoma biology and banking study.