

COG-AOST06P1: Feasibility and Dose Discovery Analysis of Zoledronic Acid with Concurrent Chemotherapy in the Treatment of Newly Diagnosed Metastatic Osteosarcoma

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.

- ___ 1. Reservation Requirements
Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page: 1. Log in to <https://members.childrensoncologygroup.org>. 2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.* 3. Click **Reservation**. *The Studies Requiring Reservations page appears.*
Prior to obtaining informed consent and enrolling a patient, a reservation must be made with the Statistical and Data Center through the eRDE system.
Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded from: https://members.childrensoncologygroup.org/files/Help/eRDES_ReservationSystem_UserGuide.pdf.
- ___ 2. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 5 calendar days after the date of study enrollment. **Patients who are started on protocol therapy on AOST06P1 prior to study enrollment will not be entered on study.** Please refer to Section 7.0 for information concerning the timing of baseline studies.
- ___ 3. The dose level will be assigned via RDE at the time of study entry.
- ___ 4. Patients must be 40 years of age or younger.
- ___ 5. Patients must be newly diagnosed with biopsy-proven, high-grade metastatic osteosarcoma. Biopsy must be completed within 6 weeks of study enrollment.
- ___ 6. Patients must have osteosarcoma that arises outside of areas of Paget's disease.
- ___ 7. Patients must have a tumor (primary, metastatic, or both) that is resectable or is expected to become respectable after the initial chemotherapy.
- ___ 8. Performance status ECOG ≤ 2 (Karnofsky ≥ 50 for patients > 16 years of age, Lansky ≥ 50 for patients ≤ 16 years of age).
- ___ 9. Patients must not have received previous chemotherapy or radiation therapy.

___ 10. Organ Function Requirements

- Patients must have adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR $\geq 70\text{ml/min/1.73 m}^2$ or
 - A maximum 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.

- Patients must have adequate liver function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
 - SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- Patients must have adequate cardiac function defined as:
 - Shortening fraction $\geq 28\%$ by echocardiogram, or
 - Ejection fraction $\geq 50\%$ by radionuclide angiogram.
- Patients must have adequate bone marrow function defined as:
 - Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$, and
 - Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent)
 - Hemoglobin ≥ 10 g/dL (may receive RBC transfusions).

EXCLUSION CRITERIA

- ___ 1. Females of childbearing potential must have a negative pregnancy test. Pregnant patients are not eligible.
- ___ 2. Female patients who are lactating must agree to stop breast-feeding.
- ___ 3. Patients with known HIV infection are excluded from the study. HIV testing is not required for study entry.
- ___ 4. Patients must not have a prior history of pericarditis, myocarditis, symptomatic arrhythmia or conduction disturbances.

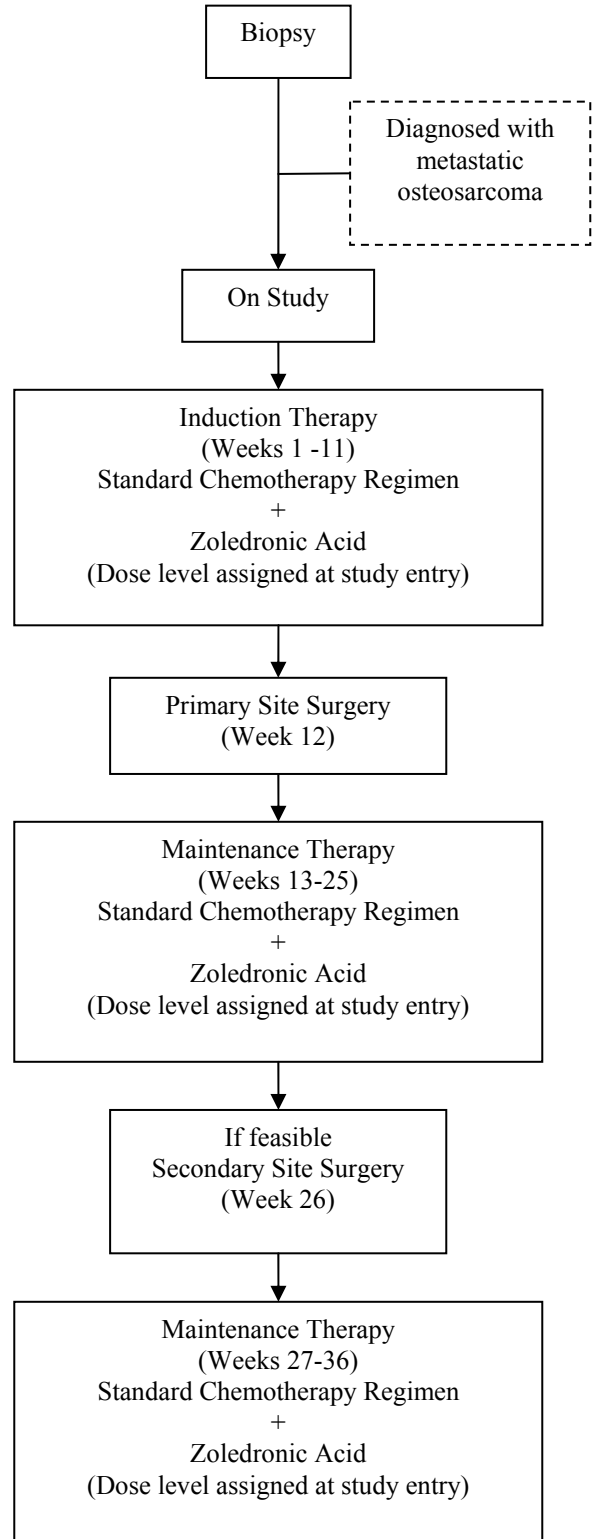
INDUCTION STRATIFICATION FACTORS:

A diagram of treatment can be seen below.

Patients may enroll onto a COG Specimen Collection Study for collection of tumor tissue to help study doctors learn how osteosarcoma develops.

Dose Plan for Patient Groups
Zoledronic Acid (mg/m²/dose [max])
Level 1 1.2 mg/m²/dose [2 mg]
Level 2* 2.3 mg/m²/dose [4 mg]
Level 3 3.5 mg/m²/dose [6mg]
Level 4 4.6 mg/m²/dose [8 mg]

Given at Weeks: 1, 6, 13, 17, 21, 27, 31, 36
* Starting Dose



REQUIRED OBSERVATIONS:

Required Clinical, Laboratory and Disease Evaluations

- Biopsy¹
- Pregnancy test for females of childbearing potential
- History/Physical Exam (Ht, Wt, BSA, VS)
- CBC, Differential, Platelets
- Electrolytes including Ca⁺⁺, PO₄, Mg⁺⁺
- BUN/Creat
- Calculated GFR²
- SGPT, SGOT, Total Bili, Alk, Phos, LDH Albumin
- Urinalysis
- Echocardiogram
- Disease Evaluation By Imaging (see Section 15.0)
- Audiogram
- **Blood** quantification of c-telopeptide, **Urine** quantification of n-telopeptide (see Section 14.2)
- Routine clinical dental exam and panoramic jaw radiograph

1. See Section 14.0 for guidelines on required tissue submission at initial diagnosis.
2. Schwartz Formula: $GFR (mL/min/1.73 m^2) = k (Height) / Serum\ Creatinine$
 Height in cm; Serum Creatinine in mg/dL
 k = Constant k = 0.33 in Premie Infants; 0.45 in Term Infants to 1 year old; 0.55 in Children to 13 years;
 0.55 in Adolescent Females; 0.65 in Adolescent Males

TREATMENT PLAN:

Chemotherapy Regimen

All patients will receive zoledronic acid in combination with the standard chemotherapy backbone used in AOST0121. This includes the following agents: doxorubicin, cisplatin, methotrexate, ifosfamide, and etoposide. This chemotherapy regimen will be delivered over a 36-week treatment period. Induction chemotherapy includes Weeks 1 – 11 and post-Induction Maintenance chemotherapy includes Weeks 13 – 36. Biopsy will be completed prior to Week 1. Primary site surgery will take place at Week 12, and if feasible, secondary site surgery will take place at Week 26. Dosing schedule and administration information are noted below.

Treatment Schema by Week

*1	4	5	6	9	10	12	13	16	17	20	21	24
C	M	M	C	M	M	S	I	M	C	M	I	M
D			D			*	E		D		E	
Z			Z				Z		Z		Z	
							*		*			
26	27	30	31	34	35	36						
S	C	M	i	M	M	I						
	D		D			E			S Surgery			
	Z		Z			Z			* Evaluation			
	*	*				*						

Doses (see Section 4.4 for Therapy Guidelines)

- C = cisplatin 60 mg/m²/dose x 2 days
- D = doxorubicin 37.5 mg/m²/dose x 2 days with dexrazoxane 375 mg/m² before each dose
- M = methotrexate 12 g/m²/dose x 1 day with leucovorin rescue (see Section 4.5 for dose and days)
- I = ifosfamide 2.8 g/m²/dose x 5 days with mesna (see Section 4.5 for dose and days)
- E = etoposide 100 mg/m²/dose x 5 days
- i = ifosfamide 1.8 g/m²/dose x 5 days with mesna (see Section 4.5 for dose and days)
- Z = zoledronic acid: assigned dose x 1 day

*See Section 7.0 for a detailed listing of all study evaluations.

TOXICITIES AN DOSAGE MODIFICATIONS:

See Section 5.0.

PATHOLOGY REQUIREMENTS:

The following material must be submitted to the COG Biopathology Center (BPC) (see address below) within 6 weeks of diagnostic or subsequent surgical procedures. Grace Kim, MD is the COG reviewer for AOST06P1 specimens. Do NOT send specimens directly to Dr. Kim. Send all specimens to the Biopathology Center.

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

- Representative paraffin block with tumor, or if block is unavailable, send 5 unstained slides from a representative block with tumor
- Two H & E stained slides **from all blocks containing tumor**
- A copy of the institutional pathology report(s)
- A copy of the institutional surgical report
- Completed AOST06P1 Pathology Checklist
- Radiological imaging of primary bone tumor only, preferably an electronic image submission [copy of plain radiograph, CT, MRI, and institutional Radiology Report(s)]
- Specimen Transmittal Form

Also see Section 14.1.1 and 14.1.2