COG-AOST2032: A Feasibility and Randomized Phase 2/3 Study of the VEFGR2/MET Inhibitor Cabozantinib in Combination with Cytotoxic Chemotherapy for Newly Diagnosed Osteosarcoma

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

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
Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

___2. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.

___3. All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___4. **Clinical Studies**
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 28 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___5. **Disease/Staging Imaging**
Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___6. Co-enrollment on AOST2031
Patients with osteosarcoma and pulmonary metastases may be eligible for co-enrollment on AOST2031. However, newly diagnosed patients should NOT be enrolled on AOST2031 at the time of diagnosis and enrollment on AOST2032. Patients may be enrolled on AOST2031 at the time thoracic surgery is being planned.

___7. Age
Patients must be < 40 years of age at the time of enrollment.

___8. Body Surface Area (BSA)
Patients must have a body surface area of ≥ 0.8 m^2 at the time of enrollment.

___9. Diagnosis
Patients must have histologic diagnosis (by institutional pathologist) of newly diagnosed high grade osteosarcoma. Primary tumors of all extremity and axial sites are eligible as long as diagnosis of high-grade osteosarcoma is established. Osteosarcoma as a second malignancy is eligible if no prior exposure to systemic chemotherapies.

- **Feasibility Phase**
  Patients must have metastatic disease and a resectable primary tumor. Designation of a primary tumor as resectable will be determined at the time of diagnosis by the institutional multidisciplinary team.

  For this study, metastatic disease is defined as one or more of the following:
  - Lesions which are discontinuous from the primary tumor, are not regional lymph nodes, and do not share a bone or body cavity with the primary tumor. Skip lesions in the same bone as the primary tumor do not constitute metastatic disease. Skip lesions in an adjacent bone are considered bone metastases.
  - Lung metastases: defined as biopsy-proven metastasis or the presence of one or more pulmonary lesions ≥ 5 mm, OR multiple pulmonary lesions ≥ 3 mm or greater in size.
  - Bone metastases: Areas suspicious for bone metastasis based on ^{18}F-FDG-PET scan (or whole body technetium-99 bone scan if ^{18}F-FDG-PET is unavailable at the treating institution) require confirmatory biopsy or supportive anatomic imaging of at least one suspicious site with either MRI or CT (whole body ^{18}F-FDG-PET/CT or ^{18}F-FDG-PET/MR scans are acceptable).

- **Efficacy Phases** (Phase 2/3)
  Patients with both localized and metastatic disease are eligible for the efficacy phase, regardless of resectability. Patients will be enrolled to two separate cohorts:
  - Cohort 1 (**Standard Risk**): Patients with non-pelvic primary osteosarcoma deemed to be resectable at the time of diagnosis by the institutional multidisciplinary team, without evidence of metastatic lesions.
  - Cohort 2 (**High-Risk**): Patients with a primary pelvic tumor, a primary tumor designated as unresectable by the institutional multidisciplinary team, AND/OR radiographic evidence of metastatic lesions (see Section 3.2.3.1).

___10. Organ Function Requirements

- Adequate renal function defined as:
  - 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 GFR74 utilizing child length and stature data published by the CDC.

OR a 24 hour urine Creatinine clearance ≥ 70 mL/min/1.73 m^2

OR a GFR ≥ 70 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

Note: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

- Adequate liver function defined as:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 135 U/L*
    (a) *Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

- Adequate cardiac function defined as:
  - No history of congenital prolonged QTc syndrome, NYHA Class III or IV congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias or
  - Shortening fraction of ≥ 27%, or
  - Ejection fraction of ≥ 50%, or
  - QTcF < 480 msec on electrocardiogram. Patients with Grade 1 prolonged QTc (450-480 msec) at time of study enrollment should have correctable causes of prolonged QTc addressed if possible (i.e., electrolytes, medications).

- Adequate bone marrow function defined as:
  - Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
  - Platelet count ≥ 100,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment
  - Hemoglobin ≥ 8.0 g/dL

- Adequate coagulation defined as:
  - International normalized ratio (INR) ≤ 1.5

___11. HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible as long as they are NOT receiving anti-retroviral agents that are strong inhibitors or inducers of CYP3A4, CYP2D6, and/or MRP2 transporter protein.

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix XII.

EXCLUSION CRITERIA:

___1. Patients who have received previous systemic therapy for osteosarcoma or a prior oncologic diagnosis.
___2. Patients who have central nervous system metastases.
___3. Patients with central cavitating pulmonary lesions invading or encasing any major blood vessels in the lung.
___4. Patients who are unable to swallow tablets. Tablets cannot be crushed or chewed.
___5. Patients with gastrointestinal disorders including active disorders associated with a high risk of perforation or fistula formation. Specifically, no clinically significant GI bleeding, GI perforation, bowel obstruction, intra-abdominal abscess or fistula for 6 months prior to enrollment, no hemoptysis or other signs of pulmonary hemorrhage for 3 months prior to enrollment.
___6. Patients with active bleeding or bleeding diathesis. No clinically significant hematuria, hematemesis, or hemoptysis or other history of significant bleeding within 3 months prior to enrollment.
___7. Patients with uncompensated or symptomatic hypothyroidism. Patients who have hypothyroidism controlled with thyroid replacement hormone are eligible.
___8. Patients with moderate to severe hepatic impairment (Child-Pugh B or C).
___9. Patients who have had primary tumor resection or attempted curative resection of metastases prior to enrollment.
___10. Patients who have undergone other major surgical procedure (eg, laparotomy) within 14 days prior to enrollment. Thoracoscopic procedures for diagnostic purposes (biopsy of lung nodule) and central access such as port-a-cath placement are allowed.
___11. Patients with a history of serious or non-healing wound or bone fracture (pathologic fracture of primary tumor is not considered exclusion).
___12. Patients with any medical or surgical conditions that would interfere with gastrointestinal absorption of cabozantinib.
___13. Patients with previously identify allergy or hypersensitivity to components of the study treatment formulations.
___14. Patients who are receiving any other investigational agent not defined within this protocol are not eligible.
___15. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
___16. Prior Therapy
- Patients who received enzyme-inducing anticonvulsants within 14 days prior to enrollment (see Appendix III).
- Patients with a prior history of hypertension (> 95th percentile for age, height, and gender for patients < 18 years and > 140/90 mmHg for patients ≥ 18 years requiring medication for blood pressure control (see Appendix IV).
- Patients who are receiving drugs that prolong QTc (see Appendix V).
- Patients receiving anticoagulation with oral coumarin agents (eg, warfarin), direct thrombin inhibitors (eg, dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines) and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH and direct factor Xa inhibitors rivaroxaban or apixaban are allowed in subjects who are on a stable dose for at least 6 weeks before the first dose of study treatment, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
- Patients receiving strong CYP3A4 inducers or strong CYP3A4 inhibitors. See Appendix VI for a list of strong CYP3A4 enzyme inducers and strong inhibitors.

Note: Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

___17. Pregnancy and Breastfeeding,
- Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of protocol therapy.

REQUIRED OBSERVATIONS:

Required Observations - Induction, Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. Comments box for site use is available on page 3 of the Therapy Delivery Map.

a. Physical exam with vital signs, height and weight.
b. Blood pressure (BP). BP will be measured with an appropriately sized cuff at rest. BP measurement will be repeated within the same day if BP is elevated (see Appendix IV and Section 5.7). If both BP measurements are elevated, followed the guidelines in Section 5.7. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within an acceptable range.
c. CBC, differential and platelets. Baseline, prior to each week with chemotherapy administered. Recommended at least weekly for good patient care.
d. Electrolytes (Na+, K+, CO2, Cl-), BUN, creatinine, Ca^{2+}, PO4, Mg^{2+}. Baseline, prior to each week with chemotherapy administered. Recommended weekly for good patient care.
e. Bilirubin, ALT, AST & alkaline phosphatase. Baseline, prior to each week with chemotherapy administered.
f. Total protein & albumin.
g. Amylase, lipase.
h. TSH.
i. PT, INR, aPTT. Baseline only.
j. Urinalysis.
k. Pregnancy test.
l. Fertility consult (recommended). See Section 4.1.6.
m. Cardiac evaluation (echocardiogram).
n. ECG with QTc interval.*
o. Audiogram.
p. MRI (strongly preferred) or CT of primary tumor. See Section 16.0.
q. X-ray of full involved bone. See Section 16.0.
r. CT Chest.
s. Chest X-ray. Baseline only.
t. ^{18}F-FDG-PET scan or Tc^{99} bone scintigraphy. Note: FDG-PET is strongly preferred but Tc^{99} bone scintigraphy may be obtained if PET is not available at the treating institution.
u. Anatomic imaging of bone/soft tissue metastases by MRI or CT (CT of metastasis as part of PET/CT is acceptable). See Section 16.0.
v. Growth plate evaluation. Only required for patients aged < 18 years. If patient is found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained at the end of therapy.
w. Submission of operative notes and pathology reports.
x. Blood for banking (optional). Baseline only. See Section 15.2.1.2.
y. Pharmacokinetics. Perform pre-cabozantinib administration. See Section 15.1.1.

*Contact Drs Carberry, Ratnasamy and Sedore and request that the EKG include a QTc calculated using the Fridericia's correction formula.

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TREATMENT PLAN:
The goal of this study is to evaluate the addition of cabozantinib to standard MAP chemotherapy in newly diagnosed osteosarcoma patients. Treatment will consist of two phases. The feasibility phase will assess for dose limiting toxicities (DLTs) and define the maximum tolerated dose (MTD) of cabozantinib when used in combination with MAP chemotherapy in a limited number of patients with metastatic disease and a resectable primary tumor. After feasibility of combination therapy is established, the efficacy phase will determine the efficacy of cabozantinib in combination with MAP chemotherapy compared to MAP alone in two separate cohorts: patients with standard risk disease (localized and resectable primary tumors), and patients with high-risk disease (metastatic disease, and/or an unresectable or pelvic primary tumor). The efficacy phase will consist of a randomized phase 2 study, with expansion to a randomized phase 3 study following review of outcomes from the phase 2 portion. The protocol will be amended after the feasibility phase and prior to starting the efficacy phase based upon the cabozantinib dose as determined by the feasibility phase.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
Optional Banking
Blood, Pre-Treatment Streck tubes as per 15.2.1.2
Tissue, Priority #1 FFPE tumor
Priority #2 Snap Frozen
Also see Section 14.1.2.3

BIOLOGY REQUIREMENTS:
PK studies of cabozantinib will be required for patients participating in the feasibility/dose finding phase only.