COG-AEWS1221: Randomized Phase 3 Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479, NSC# 750008, IND# 120449) to Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma

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

___2. Reservation Requirements

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

___3. Randomization will take place at the time a patient is enrolled via OPEN.

___4. Patients ≤ 50 years of age at enrollment will be eligible for this study.

Note: Infants and small children are eligible for this study, however, the treating physicians and family must be prepared to deliver adequate local control as required in this study (see Section 13.0 and 17.0).

___5. Diagnosis

Patients with histologic diagnosis (by institutional pathologist) of newly diagnosed Ewing sarcoma or peripheral primitive neuroectodermal tumor (PNET) arising from bone or soft tissue and with metastatic disease involving lung, bone, bone marrow, or other metastatic site.

For the purpose of 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. If there is any doubt whether lesions are metastatic, a biopsy of those lesions should be performed.

- Contralateral pleural effusion and/or contralateral pleural nodules.
- Distant lymph node involvement.
- Patients with pulmonary nodules are considered to have metastatic disease if the patient has:
  - Solitary nodule ≥ 0.5 cm or multiple nodules of ≥ 0.3 cm unless lesion is biopsied and negative for tumor;
  - Patients with solitary nodule < 0.5 cm or multiple nodules < 0.3 cm are not considered to have lung metastasis unless biopsy documents tumor.
- Bone marrow metastatic disease is based on morphologic evidence of Ewing sarcoma based on H&E stains. In the absence of morphologic evidence of marrow involvement on H&E, patients with bone marrow involvement detected ONLY by flow cytometry, RT-PCR, FISH, or immunohistochemistry will NOT be considered to have clinical bone marrow involvement for the purposes of this study.

This study requires bilateral bone marrow biopsies at study entry. The suggested approach for patients with large pelvic tumors in which a posterior iliac crest bone marrow biopsy would track through the tumor is to instead undergo 2 marrow biopsies on the contralateral side (either 2 posterior biopsies or one posterior and one anterior biopsy).

- Bone metastasis: This study utilizes whole body FDG-PET scans to screen patients for bone metastases. Areas suspicious for bone metastasis based on FDG-PET scans require confirmatory anatomic imaging with either MRI or CT (whole body FDG-PET/CT or FDG-PET/MR scan acceptable). Whole body technetium bone scans may be performed at the discretion of the investigator and are not required. For patients without other sites of metastatic disease whose sole metastatic site to qualify for study entry is a single area suspicious for bone metastasis identified by FDG-PET, confirmatory biopsy or anatomic imaging evidence of an associated soft tissue mass at that site is required for study entry.

___6. Adequate Tumor Tissue for Submission

Patients must have adequate tumor tissue to meet the minimum requirement for submission (see Section 15.2). Enrolling institutions are reminded that submission of pre-treatment serum, tumor tissue and whole blood according to Sections 15.1, 15.2, and 15.3 is required.

___7. Prior Therapy: Surgery

Patients should only have had a biopsy of the primary tumor without an attempt at complete or partial resection. Patients will still be eligible if excision was attempted or accomplished as long as adequate anatomic imaging (MRI for most primary tumor sites) was obtained prior to surgery.

___8. Organ Function Requirements

- Adequate Renal Function Defined As:
  - Creatinine clearance or radioisotope GFR $\geq$ 70 mL/min/1.73 m^2 or
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
< 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
$\geq$ 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.

- Adequate Liver Function Defined As:
  - Total bilirubin $\leq$ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) < 3 x upper limit of normal (ULN) for age (except for patients with liver metastasis who may enroll if ALT < 5 times ULN for age).
- Adequate Cardiac Function Defined As:
  - Shortening fraction of $\geq$ 27% or
  - Ejection fraction of $\geq$ 50%
- Normal blood glucose for age

  Patients must have a normal blood sugar level for age to participate. If an initial random draw (ie. non-fasting) blood glucose value is out of range, it is acceptable to repeat this test as a fasting draw.

EXCLUSION CRITERIA:

___1. Patients with regional node involvement as their only site of disease beyond the primary tumor will not be eligible.
___2. Patients whose primary tumors arise in the intra-dural soft tissue (eg. brain and spinal cord) are not eligible.
___3. Patients who have received prior chemotherapy or radiation therapy are not eligible.
___4. Pregnancy and Breast Feeding
Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained. Lactating females are not eligible unless they have agreed not to breastfeed their infants for the duration of protocol therapy. Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of protocol therapy.
___5. Patients with known pre-existing diabetes mellitus will be excluded from study.
___6. Concomitant Medications Restrictions
(Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.)
Patients receiving chronic pharmacologic doses of corticosteroids are not eligible. For the purposes of eligibility, chronic exposure is defined as anticipated exposure of > 3 weeks, including the sum of both pre-enrollment and anticipated post-enrollment dosing. Patients on acute corticosteroid therapy (≤ 3 weeks of total planned exposure) must still meet the normal blood glucose requirement in Section 3.2.5.4. Patients receiving chronic inhaled corticosteroids or chronic physiologic replacement doses of corticosteroids are eligible.

REQUIRED OBSERVATIONS:

<u>Required and Optional Clinical, Laboratory and Disease Evaluations at Study Entry, during Induction and at the end of Induction</u>

STUDIES TO BE OBTAINED

- History and Physical Exam
- Height, Weight, BSA
- CBC, differential, platelets
- Urinalysis
- Urine or serum pregnancy test [4]
- Electrolytes including Ca++, PO4, Mg++
- Creatinine, SGPT (ALT), Total bilirubin
- Albumin
- Fasting metabolic labs: Glucose, Hemoglobin A1c, Lipid panel [1]
- EKG
- Echocardiogram or MUGA
- Plain film of primary tumor (Recommended at baseline for bone tumors only)
- MRI or CT of primary tumor [2]
- Chest CT [3]
- FDG-PET scan, including primary tumor SUV [6]
- Anatomic imaging of bone and soft tissue metastases [6]
- MRI or CT and FDG-PET scans submitted for imaging aims [8]
- Bilateral bone marrow aspirates and biopsies
- Serum for ganitumab pharmacokinetics (only for first 10 patients < 21 years of age in Regimen B) [7]
- Submission of bone marrow aspirate (optional) [5]
- Peripheral blood in serum separator tube (required) [5]
- Unstained slides (required at study entry) [5]
- Peripheral blood in EDTA tube (required at study entry) [5]

1. Lipid panel includes total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
2. MRI preferred for most primary tumor sites.
3. CT scan of the chest should use spiral technique (if available) with a single breathhold, for patients able to cooperate. If whole body PET/CT obtained with thin cuts through chest, this scan may substitute for required chest CT scan otherwise a dedicated chest CT is required.
4. Pregnancy test required prior to study enrollment for females of childbearing potential only.
5. See Section 15.0 and Appendix II for specimen submission for required and optional studies.
6. Sites suspicious for bone or soft tissue metastasis by FDG-PET scan at study entry should be imaged further with MRI or CT (whole body CT as part of PET/CT is acceptable) at study entry and at end-Induction.

7. Serum samples for ganitumab concentrations are required for the first 10 patients < 21 years of age in Regimen B. See Section 15.5 for specimen requirements.
8. See Section 16.3 for instructions on submitting CT or MRI and FDG-PET images for imaging correlative aims.

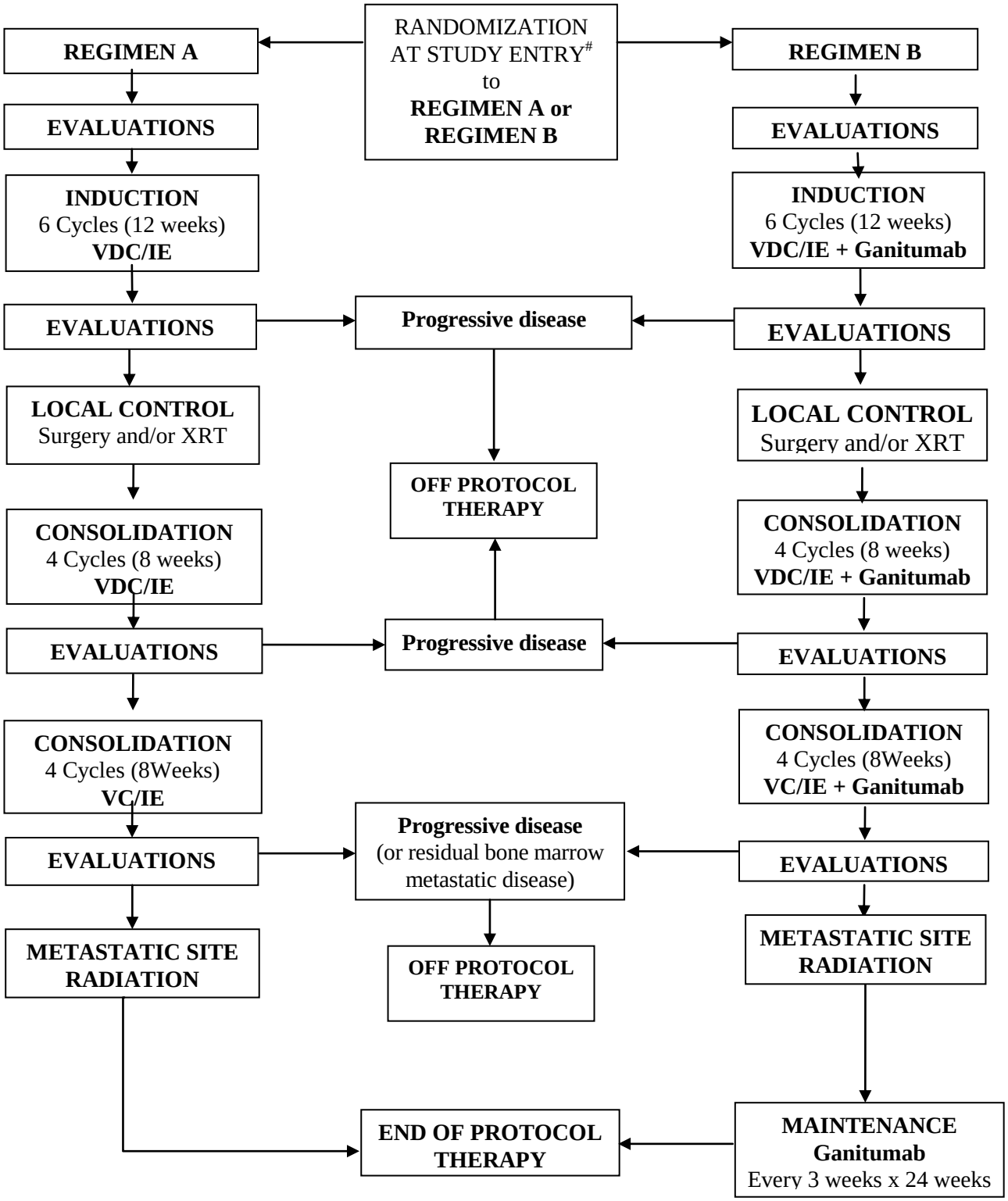
TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
See Appendix II

BIOLOGY REQUIREMENTS:
See Appendix II

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



All Patients will be randomized at study entry to receive either Regimen A or Regimen B. The first 10 patients < 21 years old randomized to Regimen B will submit mandatory trough serum samples for ganitumab concentrations (completed as of July 2015).

VDC:	vincristine-doxorubicin-cyclophosphamide
IE:	ifosfamide-etoposide
Ganitumab:	IGF-1R monoclonal antibody
XRT:	radiation therapy