COG-AGCT1532: A Randomized Phase 3 Trial of Accelerated versus Standard BEP Chemotherapy for Patients with Intermediate and Poor-risk Metastatic Germ Cell Tumors

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

PATIENT ELIGIBILITY:
<u>Important note</u>: 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. Study Enrollment
For this study, patients will be enrolled on two platforms: ANZUP's InForm and the Oncology Patient Enrollment Network (OPEN). All COG and NCTN participants, without exception, must meet all eligibility criteria, have signed study consent and be enrolled in OPEN **before** treatment begins. Subjects should be registered and randomized in InForm as soon as possible but **must** do so within 10 days of commencing chemotherapy. Note that these requirements differ from those of the primary ANZUP protocol.

___2. **Enrollment in ANZUP's InForm**
Because this study is a collaboration with a foreign lead site, all site staff will use ANZUP's InForm to enroll and randomize patients. Data entry will also be done via InForm. See Section 1.1.3.1

___3. **Central Screening for Eligibility of First Patient Enrolled at Each Site**
For the first patient at any site, a central review of eligibility is required by the COG Study Chair or delegate before the patient can be enrolled. After baseline investigations are completed, study consent will be obtained and the patient will be registered in COG. Sites will then complete and submit the Randomization Checklist along with the following source documentation to the COG Study Chair Dr. Farzana Pashankar at farzana.pashankar@yale.edu ***and*** the COG study research coordinator at rave_AGCT1532@childrensoncologygroup.org:
- Histopathology report
- Baseline CT scan report (to be done within 21 days prior to randomization date)
- Baseline bloods, including tumor markers (LDH, HCG, AFP) (to be done within 7 days prior to randomization date)

The COG Study Chair will review and confirm eligibility within 24 hours via email to the site, COG, and ANZUP. After confirmation of eligibility is obtained, the site will enroll the patient. See Section 1.1.5.

___4. **Subsequent Patient Enrollment at Each Site**
After the first patient has been enrolled at a site, for subsequent patients central screening of eligibility is not required. After obtaining consent, sites will enroll patients in OPEN and login to InForm to enroll and randomize patients.

___5. **First Patient Randomized at Each Site**
For the first patient at each site, after the site receives central confirmation of eligibility from the COG Study Chair, the site will login to InForm with the previously provided login ID to randomize the patient.

___6. **Target Population**
Male and female participants aged between 11 years and 45 years with metastatic germ cell tumors (non-seminoma or seminoma) of intermediate or poor prognostic category with adequate bone marrow, hepatic, and renal function.

___7. **Timing**
All COG/NCTN participants are required to sign the study consent before starting treatment. All COG and NCTN participants, without exception, must meet all eligibility criteria, have signed study consent and be enrolled in OPEN **before** treatment begins. Subjects should be registered and randomized in InForm as soon as possible but **must** do so within 10 days of commencing chemotherapy. Note that these requirements differ from those of the primary ANZUP protocol.
The date protocol therapy is projected to start must be no later than fourteen (14) calendar days after the date of study enrollment in OPEN.
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___8. Assent of children age 11 and older is a necessary condition for proceeding with the research.

INCLUSION CRITERIA:

___1. Age ≥ 11 years and ≤ 45 years on the date of randomization.
___2. Histologically or cytologically confirmed germ cell tumor (non-seminoma or seminoma) OR exceptionally raised tumor markers (AFP ≥ 1000 ng/mL and/or HCG ≥ 5000 IU/L) without histologic or cytologic confirmation in the rare case where pattern of metastases consistent with GCT, high tumor burden, and a need to start therapy urgently.
___3. Primary arising in testis, ovary, retro-peritoneum, or mediastinum.
___4. Metastatic disease or non-testicular primary.
___5. Intermediate or poor prognosis as defined by the IGCCC classification (modified with different LDH criteria or intermediate risk non-seminoma, and inclusion of ovarian primaries). See table below:

Primary Site	**Histology**	**Prognostic Category**	**Clinical Factors**
Testis *or* Retroperitoneum *or* Mediastinum	Non-seminoma	Intermediate	Testes/retroperitoneal primary *and* No liver, bone, brain, or other non-pulmonary visceral metastases *and* Intermediate markers# – *any* of AFP ≥ 1000 ng/mL and ≤ 10,000 ng/mL* HCG ≥ 5000 IU/L and ≤ 50,000 IU/L LDH ≥ 3.0 x ULN and ≤ 10 x ULN**
		Poor	Mediastinal primary *or* Liver, bone, brain, or other non-pulmonary visceral metastases *or* Poor markers# – *any* of AFP > 10,000 ng/mL* HCG > 50,000 IU/L or LDH > 10 x ULN
	Seminoma	Intermediate	Any primary site *and* Liver, bone, brain, or other non-pulmonary visceral metastases *and* Normal AFP***, any HCG, any LDH
Ovary	Malignant germ cell tumor histology (any of yolk sac, choriocarcinoma, embryonal carcinoma, mixed malignant GCT)	FIGO/COG stage IV	Distant metastases involving liver/spleen parenchyma and/or extra abdominal organs (including but not limited to inguinal lymph nodes and lymph nodes outside abdominal cavity, lungs, bone, brain) and/or pleural effusion with positive cytology.

If orchidectomy has been performed, baseline serum tumor markers must be repeated following surgery and must only be used to determine prognosis when at their lowest post-operative level immediately before chemotherapy.
* Many laboratories report AFP in kU/L, but the International Germ Cell Consensus Classification expresses AFP in ng/mL (i.e., microg/L). According to WHO standard code 72/225, 1 international unit of AFP corresponds to 1.21 nanogram, so 1 kU of AFP corresponds to 1.21 microgram.
** Note: Different LDH criteria from IGCCC criteria presented in Appendix 3 of the main ANZUP protocol.
*** Note: Abnormal AFP implies presence of non-seminoma.

___6. Adequate bone marrow function with ANC ≥ 1.0 x 109/L, Platelet count ≥ 100 x 109/L.
___7. Adequate liver function where bilirubin must be ≤ 1.5 x ULN, except participants with Gilbert's Syndrome where bilirubin must be ≤ 2.0 x ULN; ALT and AST must be ≤ 2.5 x ULN, except if the elevations are due to hepatic metastases, in which case ALT and AST must be ≤ 5 x ULN.
___8. Adequate renal function with estimated creatinine clearance of ≥ 60 mL/min according to the Cockcroft-Gault formula for patients ≥ 18 years (see Appendix 5 of the main ANZUP protocol), unless calculated to be < 60 mL/min or borderline in which case GFR should be formally measured, e.g., with EDTA scan.
- For patients < 18 years of age, adequate renal function is defined as:
  - Creatinine clearance or radioisotope GFR > 60 mL/min/1.73 m^2
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
11 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[55] utilizing child length and stature data published by the CDC.

___9. Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
___10. Study treatment both planned and able to start within 14 days of study enrollment in OPEN.
___11. Willing and able to comply with all study requirements, including treatment, timing, and nature of required assessments.

EXCLUSION CRITERIA:

___1. Other primary malignancy (EXCEPT adequately treated non-melanomatous carcinoma of the skin, germ cell tumor, or other malignancy treated at least 5 years prior with no evidence of recurrence).
___2. Previous chemotherapy or radiotherapy, except:
- Pure seminoma relapsing after adjuvant radiotherapy or adjuvant chemotherapy with 1-2 doses of single agent carboplatin.

___3. Significant cardiac disease resulting in inability to tolerate IV fluid hydration for cisplatin.
___4. Significant co-morbid respiratory disease that contraindicates the use of bleomycin.
___5. Peripheral neuropathy ≥ Grade 2 or clinically significant sensorineural hearing loss or tinnitus.
___6. Concurrent illness, including severe infection that may jeopardize the ability of the participants to undergo procedures outlined in this protocol with reasonable safety.
___7. Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration.
___8. Known allergy or hypersensitivity to any of the study drugs.
___9. Presence of any psychological, familial, sociological, or geographical condition that in the opinion of the investigator would hamper compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse.

REQUIRED OBSERVATIONS:

Required Observations in Arm A: Standard BEP (Standard) – Cycles 1 – 4

All studies indicated on Day 1 must be performed prior to the start of protocol therapy as indicated below.

- History and physical examination (or within 3 days prior)
- Respiratory symptoms/sign (or within 3 days prior)
- ECOG PS (or within 3 days prior)
- Adverse Event assessment (or within 3 days prior)
- Hematology: CBC (or within 24 hours prior)
- Biochemistry: CMP, GFR, calcium, magnesium, phosphate (or within 24 hours prior) weekly. Note - It is recommended that GFR is estimated with the Cockcroft-Gault formula for patients ≥ 18 years of age(which requires serum creatinine, weight and age; see Appendix 5 of ANZUP 1302) or alternatively (eg. if < 60 mL/min or borderline) by quantitative measurement, eg. EDTA scan. For patients < 18 years of age, use the Schwartz formula (see Section 1.2.2.8).
- Tumor markers: AFP, B-HCG, LDH (or within 3 days prior)
- Lung function (PFT optional but recommended if available and feasible, within 3 days prior)
- Chest X-Ray (or within 3 days prior) - When performed and results are normal at screening, it does not need to be repeated on Cycle 1, Day 1, however chest x-rays are mandatory on Day 1 of each subsequent cycle
- Audiometry (or within 3 days prior)

TREATMENT PLAN:
The goal of this study is to improve treatment for patients with intermediate to poor-risk metastatic germ cell tumors (GCTs) Among these patients, this trial will evaluate in a randomized, unblinded fashion whether accelerated BEP (Bleomycin, Etoposide, and cisPlatin) is superior to standard BEP as first-line chemotherapy for intermediate and poor-risk metastatic GCTs.

See the Parenteral Chemotherapy Administration Guidelines (CAG) for children on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Appendix 7-F Section 3.1

SPECIMEN REQUIREMENTS:
None