SYNOPSIS AND SCHEMA

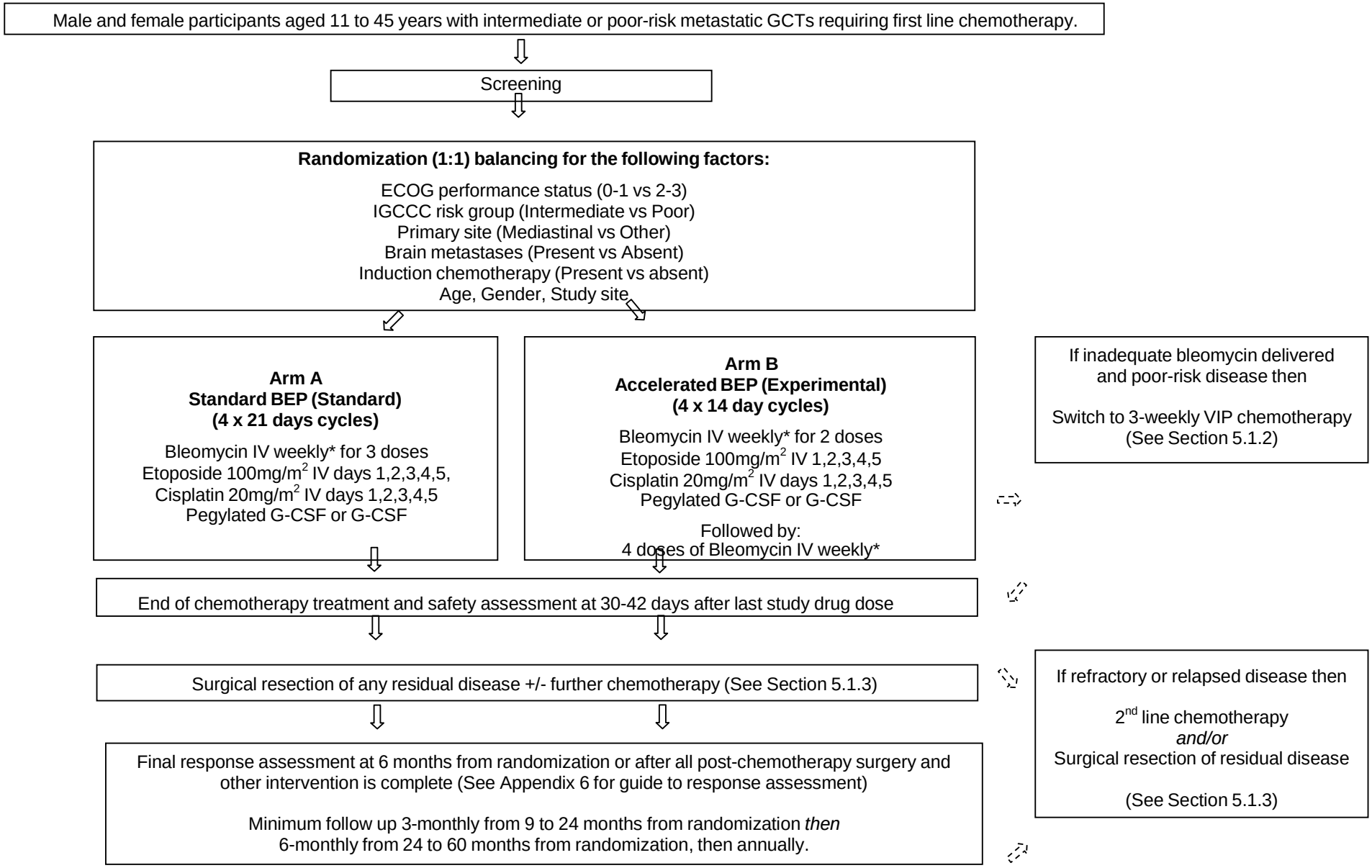
PROTOCOL SYNOPSIS

Background	Current first-line chemotherapy for intermediate- and poor-risk metastatic germ cell tumours (GCTs) is inadequate.
General aim	To determine if accelerated BEP (Bleomycin, Etoposide, cisPlatin) is superior to standard BEP as first-line chemotherapy for intermediate and poor-risk metastatic GCTs.
Primary objectives (endpoints)	To compare the two treatment arms with respect to: 1) Progression-free survival (disease progression or death)
Secondary objectives (endpoints)	To compare the two treatment arms with respect to: 2) Response following treatment completion (protocol-specific response criteria) 3) Adverse events (worst grade according to NCI CTCAE v4.03) 4) Health-related quality of life (Summary scales from QLQ-C30 & -TC-26) 5) Treatment preference (Proportion preferring each treatment arm) 6) Delivered dose-intensity of chemotherapy (Relative to standard BEP) 7) Overall survival (death from any cause)
Correlative objectives	In the future, funding permitting, we will determine associations between biomarkers to be specified and their correlations with clinical outcomes.
Design	Open-label, randomised, stratified 2-arm multicentre phase 3 clinical trial undertaken in two stages.
Population	Male and female participants aged 11 to 45 years with intermediate or poor-risk metastatic GCTs arising in testis, ovary, retro-peritoneum, or mediastinum considering first-line chemotherapy.
Study treatments	"Standard BEP" or "Accelerated BEP"; comprising 4 cycles of: - cisplatin 20mg/m^2 IV days 1,2,3,4,5; - etoposide 100mg/m^2 IV days 1,2,3,4,5; - bleomycin IV weekly* for 3 or 2 doses respectively; and - pegylated GCSF or GCSF; given every 3 weeks or every 2 weeks respectively. This is followed by 4 additional doses of bleomycin IV weekly* in the accelerated BEP arm. Total planned duration of chemotherapy is 12 weeks in both arms. * Modified if age < 16 years. If inadequate bleomycin delivered and disease is poor risk, then switch to VIP chemotherapy. Surgical resection +/- further chemotherapy for residual disease.
Assessments	Assessments weekly during protocol chemotherapy. End of chemotherapy treatment and 30 day safety assessment at 30-42 days after last study drug dose. Final response assessment at 6 months from randomisation or after all post-chemotherapy surgery is complete (whichever is later). Follow-up assessments 3-monthly from 9 months to 2 years (24 months) from randomisation, then 6-monthly to 5 years (60 months) from randomisation, then annually.

Statistical considerations	The study will recruit a total sample size of 500 participants (250 per arm). A study of 500 patients followed until 140 PFS events are observed will provide >80% power at the 5% level of significance to detect a hazard ratio of 0.6. An effect of this size corresponds to a 7% improvement in PFS at 2 years from 81% with standard BEP to 88% with accelerated BEP.

COG AGCT1532 (P3BEP Trial)

StudySchema



4 SUBJECT POPULATION

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be *no exceptions* made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the coordinating centre prior to registration.

4.1 *Target Population*

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

4.2 *Inclusion criteria*

1. Age ≥ 11 years and ≤ 45 years on the date of randomisation
2. Histologically or cytologically confirmed germ cell tumour (non-seminoma or seminoma); *or*

   Exceptionally raised tumour markers (AFP ≥ 1000ng/mL and/or HCG ≥ 5000 IU/L) without histologic or cytologic confirmation in the rare case where pattern of metastases consistent with GCT, high tumour 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 IGCCC classification[30] (modified with different LDH criteria for intermediate risk non-seminoma, and inclusion of ovarian primaries).See table below:

Primary site	Histology	Prognostic category	Clinical factors
Testis *or* Retro-peritoneum *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 × ULN and ≤ 10 × ULN**
		Poor	Mediastinal primary *or* Liver, bone, brain or other non-pulmonary visceral metastases *or* Poor markers – *any* of AFP > 10 000 ng/mL* or HCG > 50 000 IU/L or LDH > 10 × 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 tumour histology (any of yolk sac, choriocarcinoma, embryonal carcinoma, mixed malignant GCT)	FIGO[42]/COG[6] 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

* Many laboratories report AFP in kU/L, but the International Germ Cell Consensus Classification expresses AFP in ng/ml (ie. 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

*** *Note:* Abnormal AFP implies presence of non-seminoma

6. Adequate bone marrow function with ANC ≥1.0 x 10^9/L, Platelet count ≥100 x 10^9/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 (see Appendix 5), unless calculated to be < 60 ml/min or borderline in which case GFR should be formally measured, eg. with EDTA scan
9. ECOG Performance Status of 0, 1, 2, or 3 (see Appendix 4)
10. Study treatment both planned and able to start within 14 days of randomisation.
11. Willing and able to comply with all study requirements, including treatment, timing and nature of required assessments
12. Able to provide signed, written informed consent

4.3 *Exclusion criteria*

1. Other primary malignancy (EXCEPT adequately treated non-melanomatous carcinoma of the skin, germ cell tumour, or other malignancy treated at least 5 years previously with no evidence of recurrence)
2. Previous chemotherapy or radiotherapy, except:
   a. pure seminoma relapsing after adjuvant radiotherapy or adjuvant chemotherapy with 1-2 doses of single agent carboplatin
   b. non-seminoma and poor prognosis by IGCCC criteria or stage IV malignant ovarian germ cell tumour in the rare case where low-dose induction chemotherapy is given prior to registration because patient is not fit enough to receive protocol chemotherapy (eg. organ failure, vena cava obstruction, overwhelming burden of disease). Acceptable regimens include cisplatin 20 mg/m^2 days 1-2 and etoposide 100 mg/m^2 days 1-2; carboplatin AUC 3 days 1-2 and etoposide 100 mg/m^2 days 1-2; or baby-BOP.[43] Patients must meet all other inclusion and exclusion criteria at the time of registration.
   c. Participants who need to start therapy urgently prior to completing study-specific baseline investigations may commence study chemotherapy prior to registration and randomisation. Such patients must be discussed with the coordinating centre prior to registration, and must be registered within 10 days of commencing study chemotherapy.
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 participant to undergo the 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