Protocol for the P3BEP trial (ANZUP 1302): an international randomised phase 3 trial of accelerated versus standard BEP chemotherapy for adult and paediatric male and female patients with intermediate and poor-risk metastatic germ cell tumours

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Abstract

Background: Bleomycin, etoposide, and cisplatin (BEP) chemotherapy administered every 3 weeks for 4 cycles remains the standard first line treatment for patients with intermediate- and poor-risk metastatic germ cell tumours (GCTs). Administering standard chemotherapy 2-weekly rather than 3-weekly, so-called ‘accelerating chemotherapy’, has improved cure rates in other cancers. An Australian multicentre phase 2 trial demonstrated this regimen is feasible and tolerable with efficacy data that appears promising. The aim of this trial is to determine if accelerated BEP is superior to standard BEP as first line chemotherapy for adult and paediatric male and female participants with intermediate and poor risk metastatic GCTs.

Methods: This is an open label, randomised, stratified, 2-arm, international multicentre, 2 stage, phase 3 clinical trial. Participants are randomised 1:1 to receive accelerated BEP or standard BEP chemotherapy. Eligible male or female participants, aged between 11 and 45 years with intermediate or poor-risk metastatic GCTs for first line chemotherapy will be enrolled from Australia, the United Kingdom and the United States. Participants will have regular follow up for at least 5 years. The primary endpoint for stage 1 of the trial (n = 150) is complete response rate and for the entire trial (n = 500) is progression free survival. Secondary endpoints include response following treatment completion (by a protocol-specific response criteria), adverse events, health-related quality of life, treatment preference, delivered dose-intensity of chemotherapy (relative to standard BEP), overall survival and associations between biomarkers (to be specified) and their correlations with clinical outcomes.

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shrinking tumours induced by chemotherapy [9, 10]. Ac-
shorter cycles can overcome the rapid regrowth of
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doses more frequently has increased cure rates in other
cancers, including breast cancer, lymphoma (prior to ri-
tuximab) and Ewing’s sarcoma [6–8]. The hypothesised
mechanism is that accelerated chemotherapy with shorter cycles can overcome the rapid regrowth of shrinking tumours induced by chemotherapy [9, 10]. Accelerated chemotherapy is feasible with the development and availability of therapeutic granulocyte colony-stimulating factor (G-CSF) e.g. filgrastim, which reduces the duration of leukopenia [11]. Accelerated regimens may be preferable to patients as treatment is completed faster, it may improve compliance and has minimal additional financial cost.

A single arm phase 2 trial of 43 patients demonstrated that the regimen is feasible and tolerable [12]. The long term efficacy data appears promising with 5 year overall survival of 92% (95% CI 54% to 99%) for patients with poor prognostic features and 94% (95% CI 63% to 99%) for patients with intermediate prognostic features [13].

The aim of this phase 3 trial is to determine if accelerated BEP is superior to standard BEP as first-line chemotherapy for intermediate and poor-risk metastatic GCTs.
Initial response assessment is measured at the 30–42 day safety assessment. Final response assessment at 6 months from randomisation or after all post-chemotherapy surgery and other interventions are completed. Participants will continue regular follow-up for at least 5 years.

Eligibility criteria
Key inclusion and exclusion criteria include age between 11 and 45 years, intermediate or poor prognosis germ cell tumour as defined by IGCCC (modified with different lactate dehydrogenase criteria for intermediate risk non-seminoma, and inclusion of ovarian primaries) and adequate organ function. Participants who need to start therapy urgently may commence study chemotherapy prior to registration and randomisation given the treatment is identical for the first 2 weeks and forms part of standard of care management. Such participants must be discussed with the coordinating centre prior to subsequent registration, and they must then be registered within 10 days of commencing chemotherapy. The full eligibility criteria are listed in Table 1.

Treatment
The experimental arm is accelerated BEP given as bleomycin 30,000 international units (IU) (15,000 IU/m² in participants aged less than 16) intravenously (IV) weekly on day 1 and 8, etoposide 100 mg/m² on days 1–5 and cisplatin 20 mg/m² on days 1–5 every 2 weeks for 4 cycles, followed by single agent bleomycin 30,000 IU (15,000 IU/m² in participants aged less than 16 years) IV once a week for a further 4 weeks to a total of 12 doses of bleomycin. The control arm is standard BEP given as bleomycin 30,000 IU (15,000 IU/m² in participants aged less than 16) IV weekly on day 1, 8 and 15, etoposide 100 mg/m² on days 1–5 and cisplatin 20 mg/m² on days 1–5 every 3 weeks for 4 cycles. G-CSF support is given in both treatment arms.

Every attempt should be made to deliver chemotherapy at full dose and without delay from the planned schedule, as dose and dose-intensity are important predictors of outcome. Dose reductions for etoposide are specified in the protocol. There are no dose reductions for cisplatin or bleomycin allowed. Study treatment will be permanently discontinued for unacceptable toxicity, delay of day 1 of treatment for more than 21 days due to treatment-related adverse events, unequivocal progression, occurrence of an exclusion criteria or illness affecting participant safety, failure to comply with the protocol or if the investigator does not think it is in the participant’s best interest to continue. If a participant...
develops pulmonary toxicity then bleomycin should be stopped. If the participant has poor risk disease and less than 8 doses of bleomycin have been administered then the participant should stop BEP, and ifosfamide and mesna should be used with cisplatin and etoposide, as per the etoposide, ifosfamide, cisplatin (VIP) regimen. Surgical resection of residual masses and subsequent treatment following the completion of chemotherapy are specified in the protocol.

**Assessment schedule**
Participants are assessed at baseline, prior to each cycle of chemotherapy, at completion of study treatment, then at 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months from randomisation (Table 2). Assessments at each time point include performance status, adverse events, blood tests (blood count, biochemistry, tumour markers), quality of life (up to 12 months), lung function tests (for Australian sites up to 12 months), CT imaging (at baseline; after randomisation at 4, 12, 24 and 60 months; and as clinically indicated), disease status, subsequent treatment and survival. Biospecimens including tumour tissue (formalin-fixed paraffin-embedded) and blood (whole blood and plasma) at baseline will be collected from consenting participants for use in future translational research.

**Statistical analysis**
Stage 1 of the study will recruit 150 participants (75 per arm) which will provide 80% power at the 5% level of significance to detect an improvement in the favourable response rate from 59% with standard BEP to 80% with accelerated BEP. If results from Stage I are promising,
Stage 2 of the study will recruit an additional 350 participants for a total sample size of 500 participants. 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.

Discussion
The results of this study will determine if accelerated BEP chemotherapy is superior to standard BEP chemotherapy in the first-line treatment of intermediate and poor-risk metastatic GCTs. The collection of biospecimens will allow for future translational research studies to determine associations between biomarkers (to be specified) and their correlations with clinical outcomes. This is the first international randomised clinical trial for intermediate and poor-risk metastatic extra-cranial GCTs involving both adult and pediatric age groups open to both males and females.

Abbreviations
ANZUP: Australian and New Zealand Urogenital and Prostate Cancer Trials Group; BEP: Bleomycin, etoposide, and cisplatin; G-CSF: Granulocyte colony-stimulating factor; GCT: Germ cell tumour; IGCCC: International Germ Cell Consensus Classification; IU: International units; IV: Intravenous; NHMRC: National Health and Medical Research Council Clinical Trials Centre; PFS: Progression-free survival

Table 2 Schedule of Assessments

| Visit                                                                 | Baseline | On treatment: BEP chemotherapy Cycles 1 to 4 | End of BEP chemotherapy safety assessment (Initial response assessment) | Final response assessment | Follow-up until progression | Follow-up after progression |
|-----------------------------------------------------------------------|----------|---------------------------------------------|------------------------------------------------------------------------|---------------------------|-----------------------------|-----------------------------|
| Within 21 days prior to randomisation                                  | X        | X                                           | X                                                                      | X                         | X                           | X (until 60 months)          |
| Day 1 of Cycle (or within 3 days)                                     | X        | X                                           | X                                                                      | X                         | X (12, 24, 36, 60 months)   |                             |
| Day 8 and 15 of Cycle (or within 3 days)                              | X        | X                                           | X                                                                      | X                         | X (9, 12, 18 months)        |                             |
| 30–42 days after the last dose of study treatment                     | X        | X                                           | X                                                                      | X                         | X                           |                             |
| 6 months from randomisation, or after completion of all post-chemo surgery and other interventions (± 1 month) | X        | X                                           | X                                                                      | X                         | X                           |                             |
| 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months from randomisation, then annually (± 1 month) | X        | X                                           | X                                                                      | X                         | X                           |                             |
| Every 6 months (± 1 month)                                            | X        | X                                           | X                                                                      | X                         | X                           |                             |

Clinical assessment X X X X X (until 60 months)
Respiratory symptoms/signs X X X X X
Adverse Event X X
Blood tests including tumour markers X X X X X X (until 60 months)
CT imaging X X X X
Chest X-Ray X X X
Patient-Rated Measures X X X X X (9, 12, 18 months)
Translational blood and tissue Optional
Patient Status X X X X X

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Authors’ contributions
Authors’ contributions: PG is the study chair, and GT is the deputy study chair. PG, GT, MS, AM, SY and IDD were involved with the study conception and design. NL, HC, NW, AY, DM, FP, LF, RM, RW, HT were involved with acquisition of data. AM has planned the statistical analyses for this study. This manuscript was drafted by NL, HC and PG and critically reviewed by GT, MS, AM, SY, NW, AY, DM, FP, LF, RM, RW, HT and IDD. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was approved by the ethics committee of the Sydney Local Health District (RPAH zone, HREC/13/RPAH/226) on 5th July 2013. This provided central ethics approval. Local ethical approval has been obtained for all participating centres. The study will be performed in accordance with the Declaration of Helsinki and satisfy the regulatory requirements in Australia, United Kingdom and United States of America. Written informed consent was obtained from all patients included in the study.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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