ANZUP 1604

TIGER Trial News

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Welcome to the first TIGER newsletter

TIGER opened its first site, Princess Alexandra Hospital on 10th August 2018, followed by Box Hill Hospital on 18th September 2018 and Chris O'Brien Lifehouse on 26th September. Peter MacCallum Cancer Centre is completing activation and local approval processes and is expected to open in the coming weeks.

Chris O'Brien Lifehouse was the first site to recruit, with patient 001 randomised on 28th September. Congratulations Peter Grimison, Nina Bhuller and team on a great start to this trial which has been close to ten years in the making.

Study overview:

The aim of this important open-label randomised study is to determine if high dose chemotherapy with TI-CE (induction paclitaxel & ifosfamide with leukapherisis, followed by high-dose carboplatin & etoposide with stem-cell re-infusion) is superior to conventional-dose chemotherapy (CDCT) with TIP (paclitaxel, ifosfamide, cisplatin) as salvage therapy for metastatic germ cell tumours (GCT) that progress after 1st line chemotherapy.

Randomisation

Patients will be randomised to one of the following arms:
Arm A (TIP regimen) 4 cycles of paclitaxel, ifosamide, cisplatin, pegylated G-CSF every 21 days (+/-4 days)
Arm B (TI-CE regimen) 2 cycles of paclitaxel, ifosamide, pegylated G-CSF followed by leukapheresis every 14 days. Then 3 cycles of carboplatin, etoposide, stem cell re-infusion & pegylated G-CSF every 21 days.

420 patients will be recruited internationally to take part in this study.

Arm A (TIP regimen)
Paclitaxel
Ifosfamide
Cisplatin
Pegfilgrastim or Filgrastim

Arm B (TI-CE regimen)
Paclitaxel
Ifosfamide
Filgrastim
Collection of stem cells
Carboplatin
Etoposide
Infusion of stem cells
Pegfilgrastim or Filgrastim

MEET THE TEAM

Study Chairs
Int: Dr Darren Feldman (MSKCC)
Local: A/Prof Peter Grimison

ANZUP Team (Study Sponsor)
Chair & Clinical Lead: Ian Davis
CEO: Margaret McJannett
Project Manager: Simran Chawla

CTC Team (Trial Co-ordination)
Clinical Lead: Martin Stockler
Clinical Research Fellow: Alison Zhang
Project Manager: Kate Ford
Trial Co-ordinator: Anjali Bhardwaj
Clinical Trials Assistant: Portia Westall
Statistician – Andrew Martin
Translational Research Team: Sonia Yip, Michelle Parry & Garry Chang

60 PATIENTS WILL BE RECRUITED FROM AUSTRALIA AND NEW ZEALAND

TIGER (ANZUP 1604)

Current local recruitment:

Site Name	State	Investigator	Date of Activation	Accrual
Chris O'Brien Lifehouse	NSW	Peter Grimison	26 Sept 18	1
Princess Alexandra Hospital	QLD	Euan Walpole	10 Aug 18	
Box Hill Hospital	VIC	Philip Parente	18 Sept 18	
Peter MacCallum Cancer Centre	VIC	Guy Toner	Pending	

Share TIGER updates now!
Follow ANZUP @ANZUPtrials and CTC @TrialsCentre now for regular updates on #TIGER #ClinicalTrials

Current global recruitment: 130

Patient enrolment and data entry

Patient registrations are conducted using OPEN as outlined in the Registration Procedures section of the protocol and in the **OPEN** tab of the CTSU website.

Additional information can be found in the **OPEN Cheat Sheet** located in your site file. For assistance with patient eligibility please refer to the **Randomisation Checklist** included below.

Patient data need to be entered into the Medidata RAVE system which is accessible via the CTSU website.

*****Please remember to complete and submit all applicable forms within 14 days of a visit*****

Note for Investigators

Please promote **TIGER** to clinicians around your state for cross-referral. Let's connect as many patients as possible from regional and rural Australia to this global study.

REMINDER

The following supporting documentation needs to be uploaded into Medidata RAVE:

- Baseline visit (prior to study entry)
  - Evidence of Diagnosis: pathology report demonstrating non-seminoma or seminoma histology
  - Progression of disease – tumour marker level results demonstrating elevation and progressive rise OR pathology report from biopsy of a progressively enlarging or new radiographic site of disease OR surgical and pathology report (see section 6.1.1 of protocol)
- Off Treatment Visit (end of treatment)
  - Evidence of response to study treatment – tumour marker levels, imaging findings. When surgical re-section: operative and pathology reports.
- New Primary (time of progression after study therapy)
  - Tumour marker levels, imaging findings, pathology reports

TIGER is co-funded by **Movember** and is a collaboration between:

- The Alliance for Clinical Trials in Oncology (alliance);
- The Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group; and
- The University of Sydney acting through the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC)

TIGER key contacts:

- **Clinical trial operations: tiger@ctc.usyd.edu.au**
- **Co-ordinating PI (ANZ): A/Prof Peter Grimison peter.grimison@lh.org.au**
- **Sponsor queries (site payments, contracts): Simran Chawla simran.chawla@anzup.org.au**
- **ANZUP ClinTrial Refer app is available for patients to download from iTunes and Google Play**

RANDOMISATION CHECKLIST

This is not a CRF, but recommended to be completed and signed by the Investigator ***before*** randomising a patient. Retain the original for your records.
Please note that this is a guidance document only. For a full list of eligibility criteria, please refer to section 3.2 of the protocol to ensure the patient meets all necessary inclusion and exclusion criteria.

To randomise a patient, follow the randomisation instructions in the Investigator Site File.

Patient Initials:	☐☐☐ *(First, Middle, Last)*	**Date of Birth:**	☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*
Gender:	☐ *(M=Male)*	**Institution Code:**	☐☐☐☐☐
Institution:			

DATA CONVENTIONS: Complete all information whenever possible, use:
UK - Unknown if information unobtainable
ND - Not Done if measure has not been taken or test not performed
N/A - Not Applicable if measure was not required at the particular time the form relates to

INCLUSION CRITERIA

Patients must fulfill **all of the following** criteria to be eligible for this study.

1. Male gender aged ≥ 14 years old	☐ *N=No, Y=Yes*
2. Histologically or cytologically confirmed germ cell tumour (non-seminoma or seminoma); *or* Exceptionally raised tumour markers (AFP ≥ 500ng/mL and/or HCG ≥ 500 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	☐ *N=No, Y=Yes*
3. Evidence of progressive or recurrent GCT following one line of cisplatin-based chemotherapy.	☐ *Tumour biopsy of new or growing or unresectable lesions demonstrating viable non-teratomatous GCT* ☐ *Consecutive elevated serum tumour markers (HCG or AFP) that are increasing* ☐ *Development of new or enlarging lesions in the setting of persistently elevated HCG or AFP*
4. Received 3-6 cycles of cisplatin-based chemotherapy as part of first-line chemotherapy	☐ *N=No, Y=Yes*
5. Must have adequate recovery from prior surgery (e.g. healed scar, resumption of diet etc.)	☐ *N=No, Y=Yes*
6. ECOG performance Status ****see notes section below, status of 0 to 2 is eligible***	☐ *(0-5 see notes)*
7. Laboratory Values — *Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L*	☐☐☐ *mm^3*

RANDOMISATION CHECKLIST

Patient Initials:	☐☐☐ (*First, Middle, Last*)	**Date of Birth:**	☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*

	Platelet Count≥ 100 x 10^9/L	☐☐☐☐ *mm^3*
	Calc. Creatinine Clearance ≥ 50 ml/min by Jeliffe formula or GFR scan	☐☐☐ *mL/min* ***see notes section below***
	Bilirubin ≤ 2 x ULN	☐☐☐ *umol/L* ☐☐ *ULN*
	ALT ≤ 2.5 x ULN	☐☐☐ *U/L* ☐☐ *ULN*
	AST ≤ 2.5 x ULN	☐☐☐ *U/L* ☐☐ *ULN*

8. Negative Serology (antibody test) for the following infectious diseases:	*Human Immunodeficiency Virus (HIV) type 1 and 2*	☐ *N=No, Y=Yes*
	Human T-cell Leukemina Virus (HTLV) type 1 and 2	☐ *N=No, Y=Yes*
	Hepatitis B surface antigen	☐ *N=No, Y=Yes*
	Hepatitis C antibody	☐ *N=No, Y=Yes*
9. Date study treatment planned to start		☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*
10 Date consent form signed		☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*
11. Willing and able to comply with all study requirements, including treatment, timing and nature of required assessments		☐ *N=No, Y=Yes*

EXCLUSION CRITERIA

Patients with any of the following characteristics **will not be eligible** for this study

12. More than one prior line of chemotherapy for GCT *(other than the 1 cycle of salvage chemotherapy)* ***see protocol section 3.2.3.2***	☐ *N=No, Y=Yes*
13. Prior treatment with high-dose chemotherapy (defined as treatment utilizing stem cell rescue)	☐ *N=No, Y=Yes*
14. Prior treatment with TIP. *Only exception is when given as a bridge to treatment on protocol for patient with rapidly progressive disease who cannot wait to complete the eligibility screening process (only one cycle is allowed)*	☐ *N=No, Y=Yes*
15. Concurrent treatment with other cytotoxic drugs or targeted therapies	☐ *N=No, Y=Yes*
16. Radiation therapy (other than to the brain) within 14 days of day 1 of protocol chemotherapy except radiation to brain metastases, must be completed 7 days prior to start of chemotherapy.	☐ *N=No, Y=Yes*

Patient Initials:	☐☐☐ (*First, Middle, Last*)	**Date of Birth:**	☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*

17. Previous chemotherapy within 16 days prior to enrollment except for bleomycin given > 5 days prior to enrollment.	☐ *N=No, Y=Yes*
18. Concurrent malignancy except as allowed in protocol	☐ *N=No, Y=Yes*
19. No late relapse with completely surgically resectable disease	☐ *N=No, Y=Yes*
20. No large (≥2cm) hemorrhagic or symptomatic brain metastases	☐ *N=No, Y=Yes*
21. No secondary somatic malignancy arising from teratoma	☐ *N=No, Y=Yes*

CONFIRMATION OF ELIGIBILITY

Patient eligibility MUST BE confirmed by an investigator with a valid CTEP ID listed on the signature log.

Investigator's Name:	
Investigator's Signature:	
Date:	☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)*

RANDOMISATION RESULT

This section is to be completed AFTER successful randomisation using data provided by the randomisation system.

23. Patient Number	☐☐☐☐☐☐☐
24. Treatment Arm	☐ *A = Arm A: TIP* *B= Arm B: TI-CE (experimental)*
25. Date and time of randomisation	☐☐/☐☐☐/☐☐☐☐ *(dd/mon/yyyy)* ☐☐:☐☐ *(hh:mm, 24 hour time)*

INCLUSION CRITERIA - NOTES

The following notes provide detailed definitions of other criteria.

1. Calculating GFR by Jelliffe Formula

Estimated creatine clearance for patients ≥18 years old will be estimated by the Jelliffe equation modified for BSA. Patients with creatinine clearance estimated > 70ml/min by this formula are eligible. If the creatinine clearance estimated by the Jelliffe method is ≥50mL/min but ≤70mL/min, then a second method to confirm a creatinine clearance of ≥50 mL/min is required. Methods of estimating GFR that can be used for this confirmation consist of a 12 or 24-hour urine creatinine clearance or a nuclear creatinine clearance (radioisotope) test. If the confirmatory creatinine clearance is <50mL/min, then the patient is **not** eligible. If the confirmatory creatinine clearance is ≥50 mL/min, the patient **is** eligible.

Complete the below table to help calculate the Creatinine Clearance:

Characteristic	Value/ Result
Serum Creatinine (umol/L)	
Male = 0	
Age (years)	
Weight (kg)	
Height (cm)	
BSA (Du Bois) **see below*	
GFR by Jelliffee formula adjusted for BSA	

BSA (Du Bois formula) = 0.007184 x (patient height in cm) $^{0.725}$ x (patient weight in kg) $^{0.425}$

= 0.007184 x ( ) $^{0.725}$ x ( ) $^{0.425}$

=

$$\text{CrCl (ml/min)} = \frac{\{[98 - 0.8 \times (\text{age} - 20)] \times [1 - (0.01 \times \text{sex})] \times (\text{BSA}/1.73)\}}{(\text{SCr} \times 0.0113)}$$

$$= \frac{\{[98 - 0.8 \times (\quad - 20)] \times [1 - (0.01 \times 0)] \times (\quad/1.73)\}}{(\quad \times 0.0113)}$$

=

2. ECOG Performance Status of 0, 1 or 2 is eligible. Performance Status of 3, 4 or 5 is ineligible.

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Am.J.Clin.Oncol. (CCT) 5:649-655, 1982.

2. Calculating IPFSG Risk Classification

The prognostic classification was developed by Lorch/Beyer and colleagues and is based on seven individual patient/tumor characteristics at the time of initiation of initial salvage therapy. In this system, each characteristics are associated with a certain point value (ranging from -1 to 3.5 points).

Complete the individual characteristics table below to calculate the IPFSG score:

Characteristic	**Score**
Progression-free interval >3 months = 0 points Progression-free interval ≤3 months = 1 point	
Response to first-line therapy of CR/PR-neg = 0 points Response to first-line therapy PR-pos/SD = 1 point Response to first-line therapy PD = 2 points	
Liver, brain, or bone metastases absent = 0 points Liver, brain, or bone metastases present = 1 point	
Primary tumour site: gonadal = 0 points Primary tumour site: Retroperitoneal = 1 point Primary tumour site: Mediastinal = 3 points	
HCG <1000mIU/mL = 0 points HCG ≥1000mIU/mL = 1 point	
AFP normal = 0 points AFP elevated but <1000 = 1 point AFP ≥1000ng/mL = 2 points	
Histology of pure seminoma = -1 point Histology of non-seminoma = 0 points	
FINAL IPFSG SCORE	

Risk Groups:

**Circle the risk group below*

Very Low Risk	-1 points	**Low**
Low Risk	0 points	
Intermediate-Risk	1-2 points	**Intermediate**
High Risk	3-4 points	**High**
Very High Risk	5 or more points	