Genomic Cancer Clinical Trials Initiative

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http://gccti.org.au

Genomic Cancer Clinical Trials Initiative Newsletter

Welcome to the Genomic Cancer Clinical Trials Initiative (GCCTI) update. The GCCTI was established by Cancer Australia in 2013 and is led by the NHMRC Clinical Trials Centre in partnership with Zest. The initiative aims to facilitate the development of mutation-specific/molecularly-targeted clinical trial concepts that involve cancers from more than one primary site and more than one cancer Cooperative Trials Group (CTGs). The main activities of the GCCTI are to develop capacity, ideas, trial concepts, and grant applications.

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Highlights from the May 2022 GCCTI workshop

The GCCTI Project Team hosted a bi-annual workshop on Friday 6 May 2022, with 37 attendees.

> The workshop focused on strengthening grant applications for submissions in 2022 and beyond.

Presentations and discussion included:

- Updates on grant opportunities
- Review and peer input for grant submissions in 2022 and beyond
- Alternative funding strategies and sources

Further details of the presentations and discussions are available from the GCCTI website here.

Updates on grant opportunities

Representatives from the National Health and Medical Research Council (NHMRC), Medical Research Future Fund (MRFF), and Cancer Australia (CA) presented updates on grants available, along with tips and pointers on how to produce stronger applications. Further details are published in the workshop report here.

Grant review and peer input

The following proposed grants were presented for input from participants.

Idea, concept or proposal	Summary
Randomised trial of denosumab and immunotherapy in advanced solid cancers	• Immune checkpoint inhibition improves survival outcomes in a range of advanced solid malignancies, however, in a subset of patients with solid malignancies and bone cancer, immune checkpoint inhibition leads to poorer response and survival outcomes vs those without bone metastases • Denosumab, a RANK ligand inhibitor, is approved to delay skeletal-related events in solid tumours. Pre-clinical data demonstrates synergistic effects when a RANK ligand and immune checkpoint inhibitor (ICI) are combined • The proposed design is a randomised, controlled, basket trial of combining denosumab with a PBS-subsidised ICI in a range of advanced cancers • The underlying hypothesis is that denosumab will increase the anticancer activity of ICIs by modulation of immune effector cells resulting in a higher proportion of progression-free participants at 12 months (primary endpoint)
Intraperitoneal anti-vascular endothelial growth factor (VEGF) for recurrent, malignant ascites	• Malignant ascites is common and an important problem in ovarian and other cancers, without an approved treatment in Australia • A previous phase 2 trial, REZOLVE, included participants with ovarian cancer, and demonstrated that a single dose of intraperitoneal bevacizumab (IP-bev) after therapeutic drainage of recurrent ascites increased the median paracentesis-free interval by a factor of 4.3 compared with the interval before the dose of IP-bev • REZOLV3R is a proposed phase 3, randomised, controlled, multicentre trial of IP-bev after therapeutic drainage of recurrent malignant ascites in a range of chemotherapy-resistant solid tumours, with a paracentesis-free interval of 28 days or less
Stereotactic radiation as consolidation following immunotherapy	• Checkpoint inhibitors are approved in a wide range of advanced cancers, however complete responses are infrequent, and the majority of treated patients eventually progress • Phase 2 trials have shown that stereotactic ablative body radiation (SABR) can improve progression-free survival, and perhaps overall survival, however, the optimal timing of SABR is unclear • The proposed design is a randomised, phase 2/3 basket trial of adding SABR to oligo-persistent disease after 3 months of treatment with a checkpoint inhibitor in participants with a range of advanced cancers, including non-small cell lung cancer, melanoma, renal cell cancer, and bladder cancer • The hypothesis is that earlier treatment with SABR will delay progression and improve survival by cytoreduction and local control within and beyond the treated field failure
Computational drug repurposing in advanced cancers	• Probeminer is a repurposing platform that mines for ligand-receptor interactions and then quantitatively ranks targets for potential treatments • This proposed pilot study would sequence patients with advanced cancers who have exhausted proven treatments and then use in-silico analyses to determine a potential target for a repurposed drug, and if found, to seek access to the drug, and use time to progression as an indicator of its activity

GeneScreen 5-FU – DPYD guided genotyping for fluoropyrimidine prescribing	• Fluoropyrimidines are widely used in patients with a variety of cancers, however, up to 30% experience significant adverse events • The DPYD gene encodes for DPD, which is the first enzyme in the catabolic pathway of 5-fluorouracil (5-FU). There are over 160 variants of DPYD identified, some of which are associated with increased risk of severe adverse events • GeneScreen proposes to demonstrate cost effectiveness of genotyping DPYD to personalise dosing of 5-FU to those identified with one of the four main functional variants identified in Caucasians to potentially reduce mortality, toxicity and the frequency of toxicity

Attendees provided feedback and suggestions to strengthen the proposals. Details of presentations are available from the GCCTI website here.

Alternative funding strategies and sources

Prof John Simes reflected on traditional funding sources for cancer clinical trials and related research, and possible alternatives. Success rates for applications to NHMRC Clinical Trials and Cohort Studies and Ideas Grants have ranged from 5–12% over the past few years. Alternative schemes and sources were outlined for consideration. Details, including slides, are available at the GCCTI website here.

Update on GCCTI supported studies

EMBRACE

EMBRACE is a phase 2 trial of the poly-adenosine diphosphate-ribose polymerase (PARP) inhibitor, olaparib, in homologous recombination (HR)-deficient metastatic breast and relapsed ovarian cancer in patients without germline mutations in breast cancer gene BRCA1 and BRCA2. This trial aims to determine the activity of olaparib in 2 cohorts (triple negative breast cancer and high-grade serous ovarian carcinoma) based on objective tumour response rate. Funding for the trial from Cancer Australia was secured in December 2016 in an application led by Dr Katrin Sjoquist *et al*., in collaboration with ANZGOG, BCT, and CTC.

Recruitment to the EMBRACE trial closed 31 March 2022 after enrolment of 22 participants from 12 Australian sites and screening of over 200 patients. Analyses in preparation for reporting are underway.

For more information about EMBRACE, see the trial summary at ANZCTR or email embrace@ctc.usyd.edu.au.

AUTO-CHECK

AUTO-CHECK is a translational research study looking at the molecular determinants of autoimmunity and immune adverse events in advanced cancer patients treated with immune checkpoint inhibitors. The hypothesis is that an underlying genetic susceptibility to autoimmunity increases the risk of an immune-related adverse event (IRAEs) after treatment with immune checkpoint inhibitors.

This study was funded in January 2017 by Cancer Australia and is led by Prof Matthew Cook (CIA) and Dr Sonia Yip in a collaboration with 4 CTGs: ALTG (now known as TOGA), ANZGOG, ANZUP and COGNO, the CTC, and the Centre for Personalised Immunology at ANU. Bio-specimens were collected from 6 multi-centre, investigator-initiated trials of immune checkpoint inhibitors spanning 5 tumour types (endometrial, glioblastoma, mesothelioma, NSCLC, renal cell) – each trial using immune checkpoint inhibitors.

AUTOCHECK included 257 participants, and over 450 real-time blood shipments from 48 sites to the central lab in Canberra. Approximately 50 participants had blood samples collected following an immune-related adverse event. Whole genome sequencing and immune-profiling of peripheral blood mononuclear cells has been completed; serological profiling for auto-antibodies is soon to follow.

For more information about AUTO-CHECK, please see this summary or contact autocheck.study@sydney.edu.au.

Upcoming events

Next GCCTI workshop *SAVE THE DATE*

Date/Time: Friday, 28 October 2022; 9.30am – 3.00pm, AEST
Location: Sydney and virtual
Contact: Justine.Lau@zest.com.au

GCCTI welcomes you to attend our next workshop on Friday, 28 October 2022.

This workshop will provide attendees an opportunity to learn and discuss:

- Updates on grant opportunities
- Innovative studies with potential applicability to multiple cancer types and CTGs
- Ongoing and proposed trials in a range of cancer types
- Ideas and proposals for studies that could involve multiple cancer types and CTGs
- Opportunities for collaboration across cancer types and CTGs

Further details will be circulated in due course.

GCCTI support

The primary aim of GCCTI is to facilitate the development of mutation-specific clinical trial concepts that involve cancers from more than one primary site and across more than one CTG.

If you'd like to discuss an idea for a cancer clinical trial that includes multiple primary types and/or multiple CTGs, please complete and submit the idea generation template and forward it to the GCCTI Project Team through Justine Lau at Justine.Lau@zest.com.au. We look forward to hearing from you.

You can also access a range of information and resources from the GCCTI website: http://gccti.org.au

GCCTI

Get in touch
info@zest.com.au

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