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 aim of the initiative aims to facilitate the development of clinical trials that involve cancers from multiple primary sites and multiple Cancer Cooperative Trials Groups (CTGs). The main activities of the GCCTI are to develop capacity, ideas, and grant applications.

In this edition:

Highlights from the October 2021 GCCTI workshop

The GCCTI Project Team hosted a bi-annual workshop on Friday 1 October 2020, with 49 participants in attendance.

> The workshop focused on innovative ideas and new concepts, including the sharing of existing studies and ideas between Cancer Cooperative Trial Groups (CTGs), to harbour opportunities for collaboration across cancer types and CTGs.

Presentations and discussion included:

- Updates on current grant opportunities and recent changes
- Proposed trials involving multiple cancer types and groups
- Theranostic trials and targets
- Reflection and feedback

Further details of the presentations and discussions that took place at the workshop is available to download from the GCCTI website here.

Proposed trials involving multiple cancer types and groups

Trials involving more than one cancer type or CTG were presented

Idea/concept/proposal	Summary

REZOLV3R: intraperitoneal anti-vascular endothelial growth factor (VEGF) for malignant ascites	• The treatment for malignant ascites in Australia is inconsistent
	• A previous study, REZOLVE involving patients with epithelial ovarian cancer, demonstrated that administering bevacizumab into the peritoneum following therapeutic ascetic drainage:
	  ○ increased the median paracentesis-free interval by 4.29 times (compared with prior to study entry)
	  ○ is safe
	• REZOLV3R is a Phase III randomised trial of intraperitoneal bevacizumab following therapeutic ascetic drainage in recurrent malignant ascites from refractory (intra-abdominal) solid tumours of the gastrointestinal and gynaecological tracts
	• The study design of REZOLV3R is evolving with presentations to and input from interested CTGs

Denosumab and immunotherapy in advanced cancers with bone metastases	• RANK ligand (RANKL) is expressed on osteoclasts and contributes to hypercalcemia of malignancy and to skeletal-related events due to bone metastases. Further, high levels of RANKL expression are associated with tumour growth, poor prognosis, and suppression of effector T-cell function • Denosumab is approved to delay skeletal related events in a range of solid tumours and for hypercalcaemia of malignancy refractory to treatment with bisphosphonates • It is proposed that inhibition of RANKL with denosumab will increase the anticancer activity of immune checkpoint inhibitors via modulation of immune effector cells resulting in a higher proportion of participants progression free at 12 months • A grant application is proposed for 2022

Recommending therapy outside standard indications – application of an extrapolation framework	• Precision oncology is increasingly used in patients with advanced cancers who have exhausted their standard treatment options; it helps match therapies to the molecular profile of the patient's tumour, however, recommendation outside the standard indication is a problem faced by clinicians
	• A framework has been designed to assess the appropriateness of recommending therapy in non-standard indications. The framework systematically extrapolates data from standard indications and may be applied to help:
	  ○ incorporate clinical trials in the future across different biomarkers
	  ○ assess evidence for regulators and stakeholders
	  ○ assist clinical decisions in non-standard indications

Topical androgen gel for fatigue in palliative care	• Fatigue is one of the most common symptoms and underreported in advanced cancer, which may be caused by multidimensional factors (e.g. pain and anaemia) • In a non-cancer population, topical androgen diminishes fatigue and improves quality of life. However, there is only one randomised control trial in a patient population with cancer; the trial demonstrated a trend towards an improvement in fatigue • The current study, a prospective randomised, placebo-controlled trial, aims to assess the activity and safety for testosterone replacement for fatigue in advanced cancer (vs placebo) • It is anticipated the study will run for 3 years, recruiting 70–80 patients in each arm and will include an interim analysis at 6 months

The GCCTI project team will work with interested CTGs and members to explore and strengthen existing and new concepts for grant submission. For more information, please get in touch with the GCCTI Chair, Martin Stockler.

Theranostic trials and targets

Trials in theranostics, the combination of diagnosis and therapeutic approaches to improve cancer care, were presented, including discussions about their applications in other cancer types.

Target	Summary
Prostate specific membrane antigen (PSMA)	• PSMA is expressed in ~95% of all prostate cancers and in metastatic and castration-resistant carcinomas and is easily detectable using imaging • Tumour expression in cancers other than prostate cancer is dependent on the transcription of PSMA and its potential as a theranostic target is yet to be explored; in particular, cancers where neo-angiogenesis on PSMA is evident
Automation of radiolabelling	• Radiosynthesis of positron emission tomography (PET) tracers has been challenging due to the expertise required and the risk of exposure • A platform has been developed to allow for production to be automated. This allows shipping PET tracers to multiple sites across the country • There is particular interest in clinical trial concepts that establish whether programmed death-ligand 1 (PD-L1) imaging can be used as a robust biomarker in patients receiving first- and second-line immunotherapy and biologically targeted local therapies. Both cost and expertise need to be considered when designing larger, multicentre trials, however, it is anticipated that using the developed platform may automate production and allow for multiple trial sites

Cell death indicator (CDI)	• Imaging and targeting cell death has potential importance in both diagnosis and treatment in cancer • Cell death indicator (CDI) has been developed as a marker to identify cell death • Preclinical studies in mice have successfully demonstrated higher CDI accumulation within tumours in mice that received chemotherapy compared to those that received no treatment • Studies have progressed to first-in-human studies demonstrating CDI radiolabelled with ^{68}Ga is safe, has excellent biodistribution, favourable dosimetry and detects de novo tumour cell death

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

Update on GCCTI supported studies

EMBRACE

The EMBRACE study is a Phase II clinical 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 (BRCA)1 and BRCA2. This trial aims to determine the activity of olaparib in each tumour cohort (triple negative breast cancer and high-grade serous ovarian carcinoma) as determined by the objective tumour response rate, according to RECIST v1.1.

The application was successful in securing Cancer Australia funding in December 2016 and is led by Dr Katrin Sjoquist, Paul Waring *et al.*, in collaboration with ANZGOG and BCT.

COVID-19 and other challenges have delayed recruitment. After two pauses in recruitment, the study has resumed recruitment. There are currently 12 active sites across Australia. A total of 19 participants have been recruited from more than the180 patients screened.

For more information about EMBRACE, please visit the ANZCTR website or contact 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 of this study is that a group of patients with a genetic susceptibility to autoimmunity are more likely to develop 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.

AUTO-CHECK collected bio-specimens from 6 multi-site investigator-initiated trials across 4 CTGs (ALTG (now known as TOGA), ANZGOG, ANZUP and COGNO), with trials spanning 5 tumour types (endometrial, glioblastoma, mesothelioma, NSCLC, renal cell) – each trial using immune checkpoint inhibitors.

AUTOCHECK includes 257 participants with over 450 real-time blood shipments from 48 sites to the central lab situated in the Australian National University. Approximately 50 participants had blood samples following an immune-related adverse event. Whole genome sequencing has been completed. Immune profiling of peripheral blood mononuclear cells (PBMCs) is over 80% complete, and serological profiling is soon to follow.

For more information about AUTO-CHECK, please visit the ANZCTR website or contact autocheck.study@sydney.edu.au.

Upcoming events

GCCTI Workshop

A GCCTI Grant Development Workshop will be held in April 2022**.** This workshop will focus on strengthening grant applications for submission in 2022 and beyond.

Further details will be circulated in due course.

PaCCSC & CST Annual Research Forum, 17–18 March 2022

Clinical trials: new priorities

Date/Time: Thursday 17 March 2022 8:00am – 2:00pm and Friday 18 March 2022 10:00am – 7:00pm (AEDT)
Location: Forum via Zoom
Registrations: www.uts.edu.au/paccsc-cst-forum-2022
Contact: cst@uts.edu.au

The Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Symptom Trials (CST) Annual Research Forum is our principal annual event. Past forums have showcased new research, provided networking opportunities and forged new collaborations.
This year's theme is Clinical Trials: new priorities.
At PaCCSC and CST, we are setting new research priorities to ensure our research program is focused in the areas of greatest need as well as on communities who are underrepresented in research and clinical trials.

Our guest speakers will share their expertise in these areas and lead discussion on how we can best meet the challenges facing our diverse communities. The forum will be online again and will include four themed sessions.
We look forward to seeing you at the forum!

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. The GCCTI Project Team would like to thank you for your continued support and collaboration in 2021.

If you'd like to discuss an idea for a cancer clinical trial that includes multiple primary types and 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

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GCCTI

Get in touch
info@zest.com.au

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