Genomic Cancer
Clinical Trials Initiative

NEWSLETTER

EDITION 7
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http://gccti.org.au

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 national cancer cooperative trials group (CCTG). The main activities of the GCCTI are to develop capacity, ideas, trial concepts, and grant applications.

IN THIS EDITION

Highlights from the October 2022 GCCTI workshop

The GCCTI Project Team hosted a bi-annual workshop on Friday 28 October 2022, with 37 attendees.

The workshop aimed to provide a forum for Australia's leading cancer researchers, CCTGs, and the GCCTI Scientific Steering Group to discuss and generate ideas and opportunities for studies and grants involving cancers from multiple primary sites and multiple CCTGs.

Presentations and discussion included:

- Updates on grant opportunities
- Statistical sharing and borrowing in clinical trials
- Microbiome and molecularly targeted cancer treatment
- Circulating tumour DNA (ctDNA) guiding treatment of multiple cancer types

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

Updates on grant opportunities

Representatives from the 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**.

Plenary presentations

The following proposed grants were presented for input from participants.

Idea, concept or proposal	Summary
Statistical sharing and borrowing in clinical trials	
Statistical information borrowing in clinical trials	• Information borrowing involves using information available in relevant population(s) to supplement and improve the ability to answer the aim of a trial » Information borrowed may be from different subgroups, tumour types, or a different trial design (e.g. randomised vs non-randomised) • Information borrowing provides increased information, but also the potential to introduce bias, therefore, information borrowing is reliant on statistical modelling and analyses • Information borrowing is becoming increasingly common and allows for flexible trial designs, such as in: » Basket studies – a targeted therapy evaluated on multiple tumour types with a common marker » Umbrella studies – multiple targeted therapies for a single tumour type » Platform studies – infrastructure for comparative evaluation of multiple treatments by interim analyses, without pre-specifying all treatments to be studied and the ability to add or drop treatments » Adaptive studies – when any of the above studies have designs that adapt over time in response to the accumulating data
Microbiome and molecularly targeted cancer treatment	
Harnessing the power of the microbiome in the cancer field	Microbiota in the gut • The pH of the gut is one of the factors that determines an individual's response to chronic *H. pylori* infection later in life; those with a low pH (high acidity) are more susceptible to the duodenal ulcer phenotype and those with high pH (low/no acid) are more susceptible to the gastric cancer phenotype • Transplanting human gastric microbiota into germ-free mice provides a novel animal model for studying human gastric diseases • Medications (including non-antibiotic drugs, such as anti-psychotics, morphine and proton pump inhibitors (PPIs)) may directly kill human gut bacteria » Prolonged treatment with PPIs is associated with an increased risk of colorectal cancers. Given that PPIs are commonly prescribed in oncology to help prevent side effects of cancer therapy, the risk/benefit of PPIs should be considered before prescribing

(continued)	**Microbiota in the mouth** • The microbiome within the mouth affects oral diseases such as oral cancers, caries and periodontitis, and systemic diseases such as obesity, diabetes, liver diseases, pancreatic cancer and colon cancer **Faecal microbiota transplantation** • There is some evidence of faecal microbiota transplantation (FMT) being beneficial for inflammatory bowel disease • FMT also promotes response in immune cell infiltrates and gene expression profiles and overcomes resistance to anti-PD-1 therapy in melanoma patients
Neoadjuvant immuno-therapy the gut microbiome and circulating immune susbsets	• The gut microbiota modulates immune process both locally and systemically and is likely to influence both response and toxicity development during immunotherapy • *Ruminococcaceae*-dominated microbiomes was associated with a higher fibre diet and compared with *Bacteroidaceae*-dominated microbiomes had: » Higher rates of response » Significantly higher microbial diversity » Higher relative abundance of methanogens • When comparing different cohorts across countries and cancer types, the assemblage of microbial communities is an important factor to consider
Harnessing the microbiome – potential targets and multicancer trials	• Unlike other diseases, the relationship between the human microbiome and cancer evolution and treatment is complex due to the differing tumour types, location, and settings • Studies involving interventions targeting the microbiome in cancer therapy are generally early phase and focused on immunotherapy
ctDNA guiding treatment of multiple cancer types	
ctDNA guiding adjuvant chemotherapy in early stage colon cancer	• Treating minimal residual disease (MRD) using adjuvant chemotherapy helps improve survival in patients with colorectal cancer; however, to date, there is no assay that accurately measures MRD • ctDNA has been used to detect MRD after curative treatment (e.g. primary removal), where detection has been associated with recurrence • DYNAMIC was a multicentre, randomised, phase 2, non-inferiority trial of patients with stage 2 colon cancer (n=455) • ctDNA-guided management was non-inferior to standard management » Three-year recurrence-free survival was 86.4% among ctDNA-positive patients who received adjuvant chemotherapy and 92.5% among ctDNA-negative patients who did not • ctDNA dynamics (post-surgery or post-chemotherapy) reflects treatment benefit and ctDNA clearance can be used as a surrogate marker for adjuvant treatment benefit

ctDNA captures distinct clonal dynamics following alternating osimertinib and gefitinib therapy in advanced EGFR T790M positive non-small cell lung cancer	• OSCILLATE was a single arm, phase 2 trial to investigate whether alternating osimertinib and gefitinib would alter selection pressures that drive clonal evolution to delay the development of osimertinib resistance in advanced, non-small cell lung cancer (NSCLC) with the epidermal growth factor receptor (EGFR) T790M mutation • Serial ctDNA analysis revealed distinct clonal dynamics with decrease and clearance of both the activating EGFR and T790M mutations predictive of treatment response and clinical outcomes • Importantly, the alternating regime was associated with frequent loss of T790M ctDNA in 73% of participants and no evidence of the EGFR C797S resistance mutation at disease progression; despite achieving this goal, the study did not reach the pre-specified target 12-month progression-free survival (PFS) of 65% required to warrant further evaluation
Incorporating ctDNA studies in cancer trials	• ctDNA is shed from the tumour into the blood of an individual • Studies of ctDNA can be incorporated into a trial as an exploratory objective, where samples are collected prospectively and the laboratory analyses are then conducted retrospectively » Study design considerations include the selection of blood timepoints, alignment with other study assessments and whether results are returned to the treating clinician/participant • Alternatively, ctDNA results obtained in real-time can be used to i) determine participant eligibility, stratification; or ii) guide treatment of participants » Study design considerations include turn-around time from blood draw to return of results. **Pre-analytical considerations** • The choice of blood collection tube type needs to be considered

Further details on topics and discussions are available to download from 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. Reporting is now underway.

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

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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 and also a cohort at Canberra Hospital.

AUTO-CHECK 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 underway.

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, 31 March 2023; 9.30am – 3.00pm, AEDT

Location: Education Room, Chris O'Brien Lifehouse and virtual

Contact: **info@gccti.org.au**

GCCTI welcomes you to attend our next workshop on Friday, 31 March 2023. This workshop will focus on strengthening grant applications for submission in 2023 and beyond.

Planning a grant application for submission in 2023 or beyond?

If so, we invite you to present your idea and progress to date for peer review and feedback at the workshop. To submit an expression of interest, simply email GCCTI at **info@gccti.org.au**

Note: proposed grants for presentation need not be eligible for GCCTI support.

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AGITG Idea Generation Workshop, 19 May 2023

Date/Time: Friday 19 May 2023 9:00am – 12:00pm

Location: Virtual workshop

More information: **https://gicancer.org.au/idea-generation-workshop-late-stage-colorectal-workshop/**

Contact: Louise Christophersen **louise@gicancer.org.au**

The Australasian Gastro-Intestinal Trials Group (AGITG) are delighted to host an Idea Generation Workshop focusing on late stage colorectal cancer with Convenors A/Prof Cherry Koh and Dr Matthew Burge.

Submit up to one paragraph outlining your idea(s) to: **gicancer.org.au/CRCworkshop** by 9 am AEST, Monday 6 April 2023.

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 CCTG.

If you'd like to discuss an idea for a cancer clinical trial that includes multiple primary types and/or multiple CCTGs, please complete and submit the **idea generation template** and forward it to the GCCTI Project Team at **info@gccti.org.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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GET IN TOUCH
info@gccti.org.au

GCCTI is funded by Cancer Australia and delivered in partnership between NHMRC Clinical Trials Centre and Zest.