Genomic Cancer
Clinical Trials Initiative

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October 2021 Workshop – Report

This report was finalised on Monday, 14 February 2022

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Contents

Introduction

The Genomic Cancer Clinical Trials Initiative (GCCTI) was established and funded by Cancer Australia in 2013. The GCCTI is a technical service that aims to support the national cancer cooperative trials groups (CTGs) funded under Cancer Australia's *Support for Cancer Clinical Trials* program. The GCCTI aims to develop **mutation-specific/molecularly-targeted clinical trial concepts** and **grant applications involving cancers from more than one primary site and more than one CTG**.

GCCTI is led by the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC) in partnership with Zest. Scientific technical expertise is provided by the NHMRC CTC, and project management, stakeholder engagement and communications expertise is provided by Zest.

The GCCTI project team held a one-day workshop, virtually via Zoom, on **Friday 1 October 2021**.

Purpose of the workshop

The GCCTI annual workshops aim to provide a forum for Australia's leading cancer researchers, CTGs, and the GCCTI Scientific Steering Group (SSG) to discuss ideas and opportunities for studies and grants involving cancers from multiple primary sites and multiple CTGs.

The October 2021 workshop focused on learning and discussing:

- the latest changes in grant opportunities for clinical cancer studies
- innovative studies with potential applicability to other cancer types and CTGs
- ongoing and proposed trials of imaging and theranostics 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.

As an introduction, Professor Martin Stockler (Chair of the GCCTI SSG and project team) opened the workshop by providing an overview of GCCTI's aims, objectives, progress to date, and future focus. This introduction was followed by a series of presentations from experts from different fields on innovative ideas that may be developed into cross-disciplinary collaborations.

The workshop included four key sessions. The first session provided participants with an update on grant opportunities (including recent changes) in Australia, with a presentation from a representative of Cancer Australia. The second session focused on trials involving multiple cancer types and groups with presentations on i) intraperitoneal chemotherapy for malignant ascites; ii) combining targeted therapy and immunotherapy for bone metastases; iii) a framework to identify those who might benefit from a targeted therapy beyond its approved indication(s); and iv) using a topical androgen for fatigue in advanced cancer. The third session focused on theranostics and targets, with presentations from various groups on prostate specific membrane antigen (PSMA), programmed death-ligand 1 (PD-L1) quantification and cell death indicator (CDI). The fourth and final session provided

The workshop program is included in Appendix I

participants with an opportunity to reflect, plan, and provide advice on current and potential projects.

Workshop welcome

Overview of the GCCTI and the focus for the future (Martin Stockler)

The main aim of GCCTI is to help support the national cancer CTGs by developing mutation-specific/molecularly-targeted clinical trials concepts and grant applications involving cancers from multiple primary sites and/or multiple CTGs.

The GCCTI is funded by Cancer Australia. The scope and key deliverables of the GCCTI from 2018–21 are to:

- Develop mutation-specific/molecularly-targeted clinical trial concepts and protocols that involve collaboration with more than one CTG and other key clinicians/groups
- Submit grant applications for funding of these trials, including budget preparation
- Include quality of life and pharmaco-economic measures, where applicable (to be developed collaboratively with the Cancer Australia Chair in Quality of Life and Health Economics Service)
- To host annual workshops with all CTGs and key stakeholders to identify potential targets for the development of mutation-specific cancer clinical trial protocols.

Outcomes and benefits as a result of the GCCTI:

- **Molecularly-focused networks** of researchers, clinicians, and scientists
- **Increased capacity** to conduct genomic cancer clinical research
- **Strategies for managing challenges** associated with trials of targeted treatments
- **Structures to support the conduct** of trials that include multiple primary sites and multiple CTGs.

Continued engagement with Technical Services, including:

- Cancer Australia Quality of Life technical service (CQEST)
- Cancer Research Economics Support Team (CREST)
- Asia-Pacific Clinical Oncology Research Development Initiative (ACORD).

There are several ways that individuals can engage with the GCCTI, as follows:

- Developing and submitting concepts/ideas to GCCTI
- Working with GCCTI and other CTGs to design trials based on identified concepts

- Contributing to idea generation and prioritisation by attending GCCTI workshops and communicating with other CTGs, researchers, and the GCCTI project team.
- Inputting into grant applications by joining GCCTI supported grant development teams.

Update on GCCTI-supported projects

EMBRACE

This presentation was delivered by Dr Katrin Sjoquist, Senior Research Fellow, NHMRC CTC, University of Sydney.

Poly adenosine diphosphate-ribosome polymerase (PARP) inhibitors are safe and effective in ovarian and breast cancers arising in patients with germline breast cancer gene 1 (BRCA1) and BRCA2 mutations, however, their role in other loss or dysfunction of homologous recombination deficiency (HRD) pathways have yet to be elucidated. EMBRACE hypothesised that tumours with somatic BRCA1 or BRCA2 inactivating mutations, germline or somatic inactivating mutations in other homologous repair (HR) genes, or somatic BRCA1 gene silencing by promoter methylation are equally sensitive to PARP inhibitors compared to tumours due to germline BRCA1 or BRCA2 inactivating mutations.

EMBRACE began recruiting in October 2017 with the aim to recruit 60 patients (30 patients each with breast cancer or ovarian cancer). Recruitment has paused twice due to support withdrawn from the pre-screening pathology and COVID-19 lockdown in Melbourne; recruitment resumed in August 2020. A total of 182 patients have been screened, and 18 qualified and enrolled into EMBRACE. This is a challenging study because there is no established way to identify potential participants.

EMBRACE is an important study demonstrating challenges in recruitment and the importance of screening patients for multiple trials. Processes that allow for screening into multiple trials need to be improved and streamlined. Particular challenges identified include:

- Patients identified as potential participants early in their disease course must be given appropriate information that accounts for an interval between screening and experimental treatment that is uncertain and possibly long
- Tests that are not within standard of care need sustainable funding models.

AUTO-CHECK

This presentation was delivered by Dr Sonia Yip, Translational Research Lead, NHMRC CTC, University of Sydney.

AUTO-CHECK is a translational research study across six CTG trials coordinated by the CTC, in collaboration with ALTG/TOGA, ANZGOG, ANZUP, and COGNO. AUTO-CHECK hypothesised that genetic susceptibility may contribute to immune-related adverse events after treatment with immune checkpoint inhibitors. The study includes patients with mesothelioma, non-small cell lung cancer, endometrial cancer, clear cell renal cell carcinoma, and glioblastoma being treated with antibodies to PD-L1, PD-1, and CTLA4. An additional cohort from the Royal Canberra Hospital includes various tumour types treated with immune checkpoint inhibitors. Blood samples were obtained at baseline, Week 6–12, and at the time of the immune-related adverse event.

To date, 261 participants from 86 cancer departments have contributed to the study and 50 have provided blood samples taken at the time of immune-related adverse event. Progress has been presented at CTG scientific meetings. Analyses including phenotyping of peripheral blood mononuclear cells is ongoing and genotyping will commence in 2021 Q4.

Potential collaborations and further analyses were discussed to offer additional samples and to use the existing blood samples collected.

Session 1: Updates on current grant opportunities and recent changes

Update on Cancer Australia Grants (Gayle Jones)

This presentation by Dr Gayle Jones, Assistant Director for National Research and Data at Cancer Australia, provided an update on the status of Cancer Australia's grants programs.

Priority-driven Collaborative Cancer Research Scheme (PdCCRS)
The PdCCRS:

- is Cancer Australia's annual national research grants funding scheme, joining agency with other government and non-government organisations to collaboratively fund national cancer research projects in areas of identified research priority (https://www.canceraustralia.gov.au/research-data/research/priority-driven-research)
- funds research in tumour areas of high burden of disease, cancers of low survival, and rare or less common cancers
- focuses on patient-centred research, clinical practice, policy, and/or care to directly improve cancer outcomes
- has been recognised as the gold-standard internationally, which has resulted in several international funders seeking co-funding opportunities.

Priority-driven Collaborative Cancer Research Scheme International (PdCCRSi)

PdCCRSi, established in 2018, is a collaborative grants program partnering international funders of cancer research to support Australia-based cancer research investigators. It uses a merit and peer review process to identify applications that address the priorities common to both Cancer Australia and the international funder. PdCCRSi is complementary to PdCCRS.

Grants in collaboration with World Cancer Research Fund International (WCRFi)

- 2020/21 funding outcomes to be announced in the coming weeks
- 2021/22 funding round open for applications (closes 15 November 2021)
    - Seeking applications relating to diet, nutrition (body composition) and physical activity in primary cancer care and prevention
    - Grants available include seed grants (60,000 GBP for 2 years) or investigator-initiated grants (300,000 GBP for up to 3 years)

- Details at: www.canceraustralia.gov.au/research/research/priority-driven-research/call-grant-application-collaboration-world-cancer-research-fund-international-2021-22.

PdCCRS research priorities

Research priorities are updated on a 3-year cycle. The 2022–24 priorities will be established based on the results of the National Audit of funding to cancer research projects and programs 2012–20.

It was noted that many applications were not selecting all potential priorities that directly align with the research proposal. If a research priority is not selected, Cancer Australia are unable to recommend the application to the research partner/s and limits co-funding opportunities.

Research priorities no longer included clinical trials that help improve patient outcomes, but it was suggested that General research or Translational research (treatment) were applicable to clinical trials; this was not apparent to applicants and it was suggested to Cancer Australia that clinical trials needed their own category.

PdCCRS timelines

PdCCRS grants for 2022 will open in March 2022 with Ideas Grant closing in May 2022 and CTCS Grants Scheme closing in September 2022. Outcomes for applications to the Ideas Grant scheme are expected in December 2022 and for the CTCS Grants scheme in May 2023.

Support for cancer clinical trials will open up very shortly and grant guidelines will be posted on GrantConnect (www.grants.gov.au).

Session 2: Proposed trials involving multiple cancer types and groups

This session included four presentations including intraperitoneal anti-vascular endothelial growth factor (VEGF) for malignant ascites, denosumab and immunotherapy RP2 basket trial, human epidermal growth factor receptor 2 (HER2) targeted therapy for HER amplification outside standard indications, and topical androgen gel for fatigue in advanced cancer.

Intraperitoneal anti-VEGF for malignant ascites: REZOLV3R (Katrin Sjoquist)

This presentation was delivered by Katrin Sjoquist, Senior Research Fellow, NHMRC CTC, University of Sydney.

In Australia, there is no approved treatment for malignant ascites and the standard of care varies across centres. However, periodic drainage or insertion of a catheter leading to the site of accumulation are common practices for recurrent ascites.

The proposal for REZOLV3R trial is based on REZOLVE, a phase 2 trial of intraperitoneal bevacizumab (IP-bev) to treat symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer.[1] REZOLVE demonstrated that IP-bev was safe with activity supported by a 4.29 times improvement in the median paracentesis-free interval following treatment compared to trial recruitment.

REZOLV3R is a proposed phase 3 randomised trial of IP-bev following therapeutic drainage of recurrent malignant ascites from refractory (intra-abdominal) solid tumours of the gastrointestinal and gynaecological tracts. During the development of REZOLV3R, bevacizumab (Roche) has been withdrawn from the Pharmaceutical Benefits Scheme (PBS) and replaced by a biosimilar, MVASI (Amgen), that has an unrestricted approval for intravenous use, but not for intraperitoneal administration.

Feedback from participants was sought prior to further discussion with CTGs, in particular, regarding the proposal's feasibility, optimal comparator and endpoints.

- **Given the unrestricted availability of intravenous MVASI, should the trial proceed?**
  Yes, recurrent ascites still develops in patients previously treated with intravenous bevacizumab, and such patients might still benefit from intraperitoneal treatment.

Evidence is lacking that intravenous bevacizumab is beneficial for recurrent ascites.

- **Appropriate background management and comparator for control group?**
  Management of recurrent ascites varies widely and typically includes intermittent drainage via repeated puncture or via a long-term, indwelling catheter. The trial could include participants using either of these drainage strategies. Intraperitoneal instillation of drugs is not part of standard of care.
  Options for the comparator treatment in the control group could include drainage without any subsequent instillation, or drainage followed by intraperitoneal instillation of a similar volume and of type of fluid used in the experimental group, but without bevacizumab/MVASI.
  An alternative option would be to compare intraperitoneal MVASI with intravenous MVASI, acknowledging the lack of evidence supporting the efficacy of intravenous MVASI/bevacizumab for recurrent ascites.
  The ratio of time from randomisation to next tap divided by time to previous tap to randomisation, as used in REZOLVE, was supported as the **ideal primary endpoint**. The possibility of allowing use of the study treatment after subsequent taps was raised and supported, to provide all participants with access to treatment at some point.
  The proposed **target population** is patients with recurrent ascites due to gastrointestinal or gynaecological malignancies. Patients with peritoneal mesothelioma, or perhaps even other malignancies, might also be suitable.
  The **sample size** requires further specification of the design and endpoints, but is probably in the order of one to two hundred participants.

Workshop participants keen to work on the idea further included Richard De Abreu Lourenco and Haryana Dhillon.

Reference:

1. Sjoquist *et al*. *Gynecologic Oncology* 2021; 161(2):374–81.

Denosumab and immunotherapy in advanced cancers with bone metastases: a randomised trial (Martin Stockler)

This presentation was delivered by Martin Stockler, Professor of Oncology and Clinical Epidemiology, NHMRC CTC, Central Clinical School.

RANK ligand (RANKL) is expressed on osteoclasts and contributes to hypercalcemia of malignancy and to skeletal-related events due to bone metastases. Furthermore, high levels of RANKL expression are associated with tumour growth, poor prognosis, and suppression of effector T-cell function. There are several trials evaluating the potential benefit of RANKL inhibition in lung cancer and melanoma.

Denosumab is TGA-approved, but is not PBS-listed to delay skeletal-related events in a range of solid tumours with bone metastases, or for hypercalcaemia of malignancy refractory to treatment with bisphosphonates.

We hypothesise 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 being progression free at 12 months. We propose to recruit patients with advance cancers and bone metastases who are eligible for treatment with PBS-reimbursed immunotherapy, and for denosumab that is TGA-approved, but not PBS-listed. Participants will be randomised to receiving immunotherapy as per standard of care (SOC), with or without denosumab administered at the same time as immunotherapy. Denosumab will be provided free of charge by Amgen through an existing access program.

Feedback and comments from participants were as follows:

- **Suitability for GCCTI**
  This proposal fits the Cancer Australia GCCTI criteria of including multiple cancer types and multiple CTGs, and is testing the addition of a molecularly-targeted treatment. It was recommended that molecularly-based, translational-correlative studies would strengthen the proposal.
- **Patient group qualifying for multiple studies**
  Concerns were raised that the target population for this trial was a much studied group and may be eligible for other immunotherapy trials. The trial would need to compete with these trials and with access to study treatments as SOC.
- **Stratify by cancer type and volume (number) of bone metastases**

Workshop participants keen to work on the idea further included Fiona Hegi-Johnson and Lillian Leigh.

Should I recommend HER2 targeted therapy for HER2 amplification identified by Next-generation sequencing outside standard indications? – Application of an extrapolation framework (Doah Cho)

This presentation was delivered by Doah Cho, PhD candidate at NHMRC CTC and Medical Oncologist at St George Private Hospital.

Massive parallel sequencing technologies, such as next-generation sequencing (NGS), allow multiple biomarkers to be detected simultaneously and are increasingly used in clinical practice to increase targeted treatment opportunities particularly for patients with advanced cancers who have exhausted standard treatment options. However, clinicians are faced with the dilemma of whether to use therapy off-label for non-standard indications. An example of this is the use of trastuzumab in combination with chemotherapy, which have demonstrated clinical benefit in HER2-positive breast, gastric or gastro-oesophageal junction, and uterine serous carcinomas. However, HER2 amplification can be detected using NGS in other cancer types for which no randomised controlled trial evidence exists to guide clinical practice (off-label trastuzumab).

To estimate the likelihood of benefit for off-label trastuzumab, it may be possible to extrapolate data from studies from standard indications. A framework was developed to help assess when extrapolation is appropriate for targeted therapies from one cancer type to another should the biomarker be the same. The presentation demonstrated how the framework would be applied by using the example of off-label trastuzumab. The following is a list of considerations when applying this framework:

- Analytical validity – reliability of the NGS assay for detecting HER2 amplification across a range of tumour types
- Biomarker actionability – evidence supporting actionability of HER2 amplification and trastuzumab in non-standard indications
- Natural history – whether the better outcome of patients with HER2 amplification treated with trastuzumab in the non-standard indication is due to better prognosis rather than the effect of trastuzumab
- Treatment outcome efficacy – whether there are signals of trastuzumab activity in the non-standard indications and its likelihood to translate into clinical benefit
- Treatment outcome safety – whether there is evidence to suggest the safety profile in the non-standard indication is different to the standard indication

- Informed consent and shared decision making – how clinicians should engage patients in shared decision-making and facilitate an informed consent for off-label trastuzumab, including implications.

The framework is a systematic approach to assist in assessing the appropriateness of extrapolating evidence from standard indications for off-label application. It is anticipated that the framework may be:

- incorporated into clinical trials in the future across different biomarker-targeted therapy matches
- useful for regulators and stakeholders assessing extrapolated evidence
- useful for clinical decisions when considering off-label targeted treatment recommendations when an appropriate clinical trial is not available.

Workshop participants who wanted to discuss or consider the idea further included Fiona Hegi-Johnson, Lillian Leigh, Haryana Dhillion, Lorraine Chantrill.

Topical androgen gel for fatigue in advanced cancer (Megan Ritchie)

This was presented by Dr Megan Ritchie, Palliative Care Physician and researcher at Concord Hospital. The proposal involves multiple cancer types and the androgen receptor.

Fatigue is among the most common and under-reported symptoms in advanced cancer, and often multifactorial (e.g. pain, cytokines, anaemia, cachexia etc.). Treatment options for cancer-related fatigue are limited.

Hypogonadism is demonstrable in up to two thirds of men with advanced cancer. In non-cancer populations, topical androgens can help reduce fatigue and improve quality of life in men with hypogonadism. However, only one randomised control trial (RCT) of androgen therapy has been conducted in patients with cancer, demonstrating a trend towards improved fatigue. In women, androgen levels are approximately one twentieth of those in men and androgen deficiency may be associated with reduced energy, bone mass, muscle mass, and quality of life.

Androgen gel application for replacement is well-tolerated with few serious toxicities. Sex specific effects in women include voice change, excess hair growth, and acne; and in men, polycythaemia. These adverse effects can be mitigated by early detection and intervention.

The proposed study is a placebo-controlled RCT, that aims to assess the activity and safety of testosterone gel (vs placebo gel) for fatigue in advanced cancer. The study is being

conducted in collaboration with the Andrology Department at Concord Hospital, which is supporting the study to be conducted and performing hormone assays. The study is planned to recruit and follow 150 participants over 3 years with a single interim analysis.

Feedback and comments from participants were as follows:

- **Application site**
  It was recommended that topical androgens be applied on the skin anywhere suitable on the body, not to the scrotum, as sometimes suggested.
- **Accessibility of the study**
  Many patients, including those undergoing radiation therapy, would be suitable for this study. For the current proposal, participants would need to attend Concord Hospital for pathology testing, which may limit access.
- **Prophylactic use**
  If the use of androgen could help improve fatigue, perhaps prophylactic use of androgens might prevent or reduce the establishment of fatigue. There was discussion about including patients earlier in their cancer trajectory. For the current study, patients must already have troublesome fatigue.

Session 3: Theranostic trial and targets

3.1 PSMA beyond the prostate (Louise Emmett)

This was presented by Prof Louise Emmett, Director of Theranostics and Nuclear Medicine at St Vincent's Hospital, Sydney.

PSMA is expressed in prostate epithelium and in other human tissues; it is over-expressed in approximately 95% of prostate cancers, including those that are metastatic and castration-resistant. This makes PSMA an excellent theranostic target in prostate cancer.

The development of small molecule peptides in early 2010 that bind to PSMA has revolutionised imaging and management of prostate cancer. These peptides bind tightly to the enzymatic domain of the extracellular component of the receptor and are rapidly internalised by the cell producing high quality images with low background activity. PSMA-positron emission tomography (PET) computed tomography (CT) scanning allows users to:

- Measure total tumour volume
- Identify site of tumour(s)
- Quantify volume and intensity
- Predict prognosis.

Radioisotopes can be linked to the small molecule peptides for theranostic purposes. For example, the use of Ga^{68} PSMA-11 can be used for imaging and can be replaced by Lu^{177} DKFZ-617 PSMA for treatment. In addition to Lu^{177}, other radionuclides that are persistent, powerful, and act over short distances include I^{131}, Y^{90}, Cu^{67}, Re^{186} and Ac^{225}.

Considerations when designing biologically targeting radiotherapy include:

- Therapeutic radio-isotope to be linked
- Cancer type, location, number of receptors expressed on the cancer cell surface
- Strength of peptide-receptor binding
- Power and range of internalised radioactive decay
- Radiation sensitivity of the cancer cell.

It is known that PSMA is expressed in malignancies other than prostate cancer, although apparently the transcription of PSMA is activated by endothelial cells in tumour neovasculature. PSMA-avidity on imaging has been demonstrated in several other malignancies, but its potential as a theranostic has not been explored in other malignancies, particularly in those cancers where neo-angiogenesis on PSMA is evident.

Feedback and comments from participants were as follows:

- **PSMA as a biomarker response to angiogenic therapy**
  PSMA may be a good response marker to angiogenic therapy. There is evidence of PSMA as a marker in renal cell carcinoma responding to VEGF therapy, but little evidence in other cancers.
- **Agents remaining in the cell**
  There was discussion about how to determine whether the agent remained in the cell and was not washed out. By imaging serially over a few hours, it can be determined if the agent enters the cell and stays in the cell. Agents with longer half-lives were recommended.
- **Radionuclides remaining in the cell**
  For therapy to be successful, the radionuclide must remain in the cell without being washed out. Serial imaging over a few hours may help determine whether the radionuclide remains in the cell. The theranostic potential of gallium is limited by its half-life of approximately one hour. It was advised to use PSMA agents with a longer half-life to help increase the time it remains in the cell.
- **Fibroblast activating protein**
  Fibroblast activating protein is a candidate for theranostics and is known to be concentrated in the matrix of 23 different types of cancer and has been developed to stay in the cells for up to nine days. Unfortunately, current inhibitors leave the cell too quickly for it to have theranostic potential.

3.2 Imaging of cancer immunotherapy targets with positron emission tomography: characterising PD-L1 with ^{89}Zr-Durvalumab (Fiona Hegi-Johnson)

This was presented by Dr Fiona Hegi-Johnson, Director of TROG and Chair of TROG Lung Working Party from the Peter MacCallum Cancer Centre, Victoria.

This presentation focused on zirconium radiolabelling of immune checkpoint inhibitors being evaluated in a clinical trial of PD-L1 inhibitor using a PET tracer as a framework.

Despite there being many immunePET pre-clinical studies, studies in humans are often limited, small (<20 patients) and from a single site. Further, there is little variation in what is being studied, usually a full monoclonal antibody linked with zirconium. Zirconium is widely used due to its long half-life (78 hours) that matches with the monoclonal antibodies. In Australia, due to its land mass, radiochemistry is required on site, however, there is high demand for expertise as radiolabelling is time consuming and poses risk of exposure.

To develop a human PET tracer with a given antibody, pre-clinical testing for biodistribution is performed by administering the tracer in mice with high PD-L1 expressing tumours. To determine the feasibility of using the tracer in multicentre trials, standardised imaging credentialing and the possibility to upscale the manufacturing of the tracer are studied.

Automated radiosynthesis using the iPHASE MultiSyn disposable cassette system has been validated across all trial sites and will be used for a biodistribution study in non-small cell lung cancer. It involves shipping a frozen cassette containing the PET tracer to each trial site. To prepare, each trial site adds zirconium that is labelled automatically. This results in:

- Decreased production time (from 2.5 hours to 40 minutes)
- Minimised radioisotope exposure to the operator
- Multiple consecutive productions on the same day.

Further studies on PD-L1 have been planned for 2022:

- PD-L1 positive mesothelioma, using sequential PD-L1 imaging during systemic therapy (30 patients)
- Follicular lymphoma, using baseline PD-L1 imaging and sequential cluster of differentiation-8 (CD-8) imaging, which is one of the first studies using dual novel tracer PET (10 patients).

There is particular interest in clinical trial concepts that establish whether 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.

Another non-invasive biomarker, circulating tumour DNA (ctDNA), was compared with PET. Studies have shown that both early on-treatment ctDNA and a multiparametric model can predict immune checkpoint inhibitor (ICI) response. By adding PET with ctDNA, clinicians are able to:

- Capture spatial and clonal heterogeneity
- Identify mechanisms of resistance of oligoprogressive/resistant lesions non-invasively
- Offer an individualised approach based on the biology of an individual lesion
- Integrate local therapies with immunotherapy based on biology not just anatomy.

Feedback and comments from participants were as follows:

- **PD-L1 imaging is a great idea but not brand new**
  Encouragement to target CD3 with a pipeline of molecules in early phases. There is also interest in hypoxia and CD8 imaging.
- **Novel PET tracers to characterise tumours**
  Several novel PET tracer studies were presented at ASCO 2021. US National Institutes of Health (NIH) has prioritised CD8 imaging and other imaging to find potential biomarkers for immunotherapy. Advances in PET technology will soon increase access to zirconium imaging.
- **Development of minibodies**
  Antibodies take a long time to concentrate, it was questioned whether there was consideration for the development of minibodies or something that would have a shorter development time. Currently, the science is being established. Each antibody provided for a PET tracer production is usually split and made smaller and linked to other isotopes. Cu^{64} and Cu^{67} are also being currently studied.
- **Specificity of the therapeutic antibody with the labelling**
  There was a question about how generalisable it would be to use durvalumab as a targeting agent. First, in the metastatic space in Australia, pembrolizumab is mostly used, however, studies suggest that the response can still be predicted by using duravlumab on patients treated with pembrolizumab.

3.1 CDI as a theranostic (Ivan Ho Shon)

This was presented by Dr Ivan Ho Shon, a Senior Staff Specialist in the Department of Nuclear Medicine and PET, Prince of Wales Hospital and Conjoint Senior Lecturer of the University of New South Wales.

The imaging and targeting of cell death has potential importance both as a diagnostic and therapeutic tool in cancer. However, until now there have been no means to effectively image or target cancer cell death. A compound now known as CDI has been developed that identifies cell death via apoptotic and non-apoptotic pathways. CDI identifies dead and dying cells as it is unable to enter viable cells and can only penetrate intracellularly once the cell has committed to dying.

Preclinical studies successfully demonstrated that imaging of treatment-related tumour cell death in mice was possible with CDI. There was significantly higher amounts of CDI accumulation within tumours in mice that received chemotherapy compared to tumours in mice that received no treatment, and this correlated to histochemical stains of cell death in excised tumours. CDI radiolabelled with ^{68}Ga for PET scanning has now progressed to first-

in-human studies. This trial has shown that ^{68}Ga-CDI is safe, has excellent biodistribution and favourable dosimetry, and can detect *de novo* tumour cell death in patients. A proof-of-concept study will be open soon.

Feedback and comments from participants were as follows:

- In the proof-of-concept study ^{68}Ga-CDI PET scanning will be performed and correlated with tumour regression grade from histologic examination in two arms. The study is currently restricted to a single site.

Workshop participants who would like to discuss or consider the theranostics idea further included Ivan Ho Shon, Richard De Abreu Lourenco, Martin Stockler, Hao-Wen Sim, Louise Emmett, Fiona Hegi-Johnson, Ben Kong, and Katrin Sjoquist.

Session 4: Reflection, plans, feedback, advice

The last session of the day was to review the objectives and planning of GCCTI and to receive feedback and advice from its stakeholders. Participants provided the following input:

- It was positive to see presentations of all new concepts and trials that have come to their fruition that are recruiting patients; there was also a lot of potential in the new areas presented, such as theranostics. Topics from the presentations were applicable across multiple disciplines
- The discussion around concepts on how to think about tumours from a molecular target viewpoint and considerations into study design across multiple tumour types were also of interest
- The expansion beyond the original scope of genomic targets to more generic, multicancer targets was welcomed
- Investigators were encouraged to seek input and involve relevant cancer cooperative trial groups
- The workshop facilitated collaboration across all tumour groups. This is important for a nuclear medicine trials network. Oncology is becoming more molecularly targeted, and it is great to be able to reach out to other groups who can advise and support
    - Several cancer cooperative groups have sought and welcomed input from imaging and nuclear medicine
- Paediatric tumours typically harbour distinct, often unique, molecular aberrations compared with adult tumours, and it remains challenging to include paediatric participants in GCCTI-supported proposals.

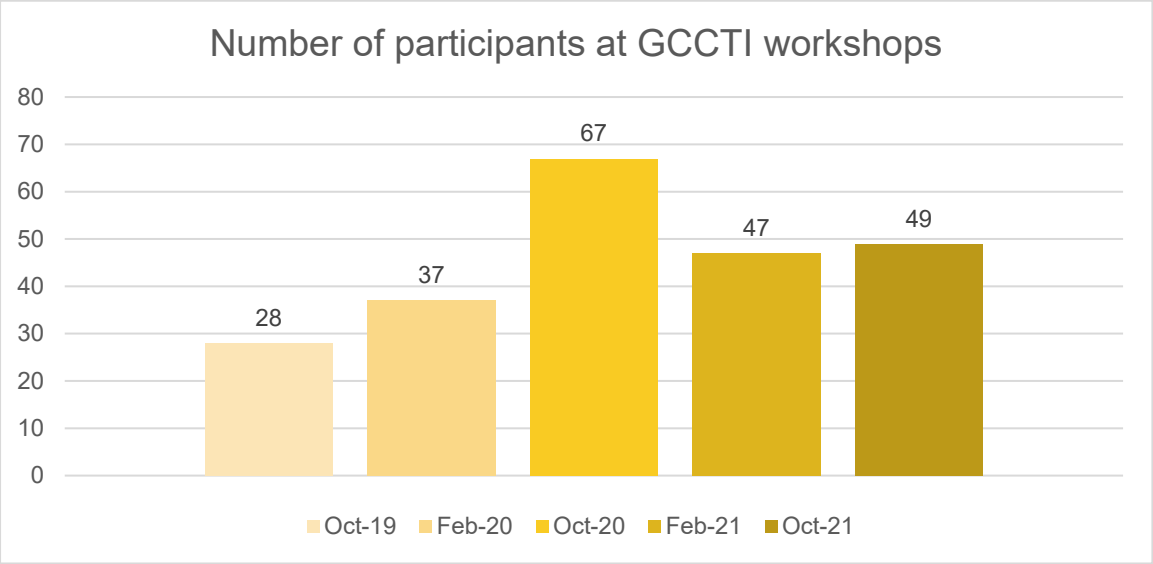
Workshop Evaluation

Workshop participants were encouraged to complete an online post-workshop evaluation survey, with 16 responses received (33% response rate).

The majority of respondents were clinical researchers (56%) and academic researchers (31%). Other respondents included basic scientist, representatives of consumer organisations or funding bodies, health economics advisor and representatives of CTGs.

Participant numbers

Forty nine (49) participants attended the GCCTI October 2021 workshop, an increase from the 47 participants who attended the previous GCCTI workshop held in February 2021.



Organisations/groups from which participants attended

Participants attended from the following organisations/groups from across the country:

- Auckland District Health Board
- Cancer Australia
- Christchurch Hospital, NZ
- Concord Hospital
- Eastern Health
- Garvan Institute of Medical Research
- Flinders University
- Hudson Institute of Medical Research, Vic
- Liverpool Hospital
- Monash University, Vic
- NHMRC Clinical Trials Centre
- Peter MacCallum Cancer Centre
- Prince of Wales Hospital, NSW
- Queensland Children's Hospital
- Queensland Health
- Royal Adelaide Hospital
- Royal Prince Alfred Hospital, NSW
- Royal Women's Hospital, Vic

- The University of Melbourne
- The University of New South Wales
- The University of Newcastle, NSW
- The University of Sydney
- University of Technology Sydney
- University of Western Australia
- Wollongong Hospital

- Cooperative Clinical Trials Groups (CTGs)
  1. AGITG
  2. ALLG
  3. ANZCHOG
  4. ANZGOG
  5. ANZSA
  6. ANZUP
  7. Australasian Leukaemia and Lymphoma Group
  8. BCT
  9. COGNO
  10. MASC
  11. CST
  12. PC4
  13. PoCoG
  14. TROG

Understanding the workshop's aim and purpose

88% of respondents indicated that they had a clear understanding of the aims and purpose of the workshop.

44% of respondents each 'agreed' and 'strongly agreed'. Two respondents were undecided.

Usefulness and relevance of the presentations

88% of respondents indicated that they found the content of the workshop presentations useful and relevant.

63% of respondents 'agreed' and 25% of respondents 'strongly agreed'. One respondent each were undecided or disagreed.

The respondent who disagreed made the following comment:

"…not involved with any of the proposals as does not relate to our area."

Organisation of workshop

All respondents (100%) thought that the workshop was well organised.

38% of respondents 'agreed' and 63% of respondents 'strongly agreed'.

Topics/aspects most interesting/useful

Participants were asked to comment on which workshop topics and aspects they found most interesting. Participants found all elements of the workshop interesting and useful, including:

- Theranostic presentations and discussions
- Ideas for trials, novel trial designs
- Grant update from Cancer Australia
- Extrapolation framework
- Discussions about GCCTI-supported studies

Participants noted the following comments as part of the feedback survey:

"The presentation topics were all very appropriate ideas currently being generated so I felt there was a very good atmosphere conductive to contribution of ideas."

"Trial designs that span multiple tumour types very helpful to [get me] thinking about our future work."

"Presentations by clinicians and researchers that will help inform future cross-CTG collaborations."

"The interdisciplinary discussion was extremely value to progress ideas in their infancy to more mature trial concepts."

Additional comments/suggestions to enhance future workshops

Participants were asked for any additional comments on how workshops could be improved moving forward; the following suggestions were provided.

- For the online format, introductions could be condensed to a pre-survey of all participants that could be presented as a slide
- Some participants preferred the online format while others were looking forward to a face-to-face meeting beyond COVID-19 restrictions
- Extra background information and how each concept fits into the overall aims of GCCTI would be helpful for newcomers in the future

Participants noted the following comments as part of the feedback survey:

"…really well run and organised."

"Plenty of time for discussions – fabulous organisation!"

Genomic Cancer
Clinical Trials Initiative

Appendix 1 – Workshop Agenda

Venue Virtual Workshop via Zoom

Date Friday 1 October 2021

Time 9.00am – 3.30pm

Purpose To provide a forum for Australia's leading cancer researchers, cooperative trials groups, and the GCCTI Scientific Steering Group to discuss ideas and opportunities for studies and grants involving cancers from multiple primary sites and multiple CTGs.

Time	Item	Presenter
9:00 am	**Logging in and registration**	
9:15 am	**Welcome and introductions**	*Martin Stockler*
	Overview of GCCTI and achievements to date	
9:45 am	**Update on grant opportunities and recent changes**	*Gayle Jones*
11:00 am	**Proposed trials involving multiple cancer types and groups**	
	• Intraperitoneal anti-VEGF for malignant ascites: REZOLV3R	*Katrin Sjoquist*
	• Denosumab and immunotherapy RP2 basket trial: DAIS	*Martin Stockler*
	• Should I recommend HER2 targeted therapy for HER2 amplification identified by Next-Generation Sequencing outside standard indications? - Application of an extrapolation framework	*Doah Cho*
	• Topical androgen gel for fatigue in advanced cancer	*Megan Ritchie*
12:30 pm	*Break*	
1:00 pm	**Theranostic trials and targets**	
	• PSMA and other theranostics beyond the prostate	*Louise Emmett*
	• Zirconium radiolabelling and PD-L1 quantification	*Fiona Hegi-Johnson*
	• CDI as a theranostic	*Ivan Ho Shon*
2:30 pm	**Reflection, plans, feedback, and advice**	*Group Discussion*
	Review of GCCTI objectives and planning *Stakeholder feedback and advice*	
3.15 pm	**Wrap-up and close**	*Martin Stockler*