Genomic Cancer
Clinical Trials Initiative

Genomic Cancer Clinical Trials Initiative

October 2020 Workshop - Report

This report was finalised on Tuesday 15 December 2020

Genomic Cancer Clinical Trials Initiative

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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 clinical trials 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 and technical input is provided by the NHMRC CTC, with project management, stakeholder engagement and communications undertaken by Zest.

The GCCTI project team in collaboration with the Scientific Steering Group (SSG) held a one-day ideas generation workshop, virtually via Zoom videoconference, on **Friday 30 October 2020.**

Genomic Cancer Clinical Trials Initiative

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 to discuss ideas and opportunities for studies and grants involving cancers from multiple primary sites and multiple CTGs.

The October 2020 workshop focused on:

- innovative ideas and new concepts for grant applications
- the sharing of existing studies and ideas between CTGs relevant to GCCTI
- supporting the prioritisation of concepts for grant applications in 2021.

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 and new concepts which may be developed and considered for future grant applications.

The workshop included four key sessions. The first session provided participants with information on current grant opportunities (including recent changes) in Australia, with presentations from representatives of key funding bodies. The second session focused on systemic therapy and radiotherapy across multiple tumour types with presentations on combing radiotherapy and dugs for brain metastases, as well as combining SABR and drugs for metastases outside of the brain. The third session focused on the topic of understanding, interpreting, applying and explaining difficult results of genetic profiling, with presentations from a range of perspectives. The fourth and final session provided participants with an opportunity to hear updates on and discuss current studies and proposals.

The workshop program is included in Appendix I

Workshop welcome

Overview of the GCCTI and future focus (Martin Stockler)

The primary aim of the GCCTI is to support the national cancer cooperative trials groups (CTGs) by developing clinical trials concepts and grant applications involving cancers from more than one primary site and more than one CTG.

The scope and key deliverables of the GCCTI from 2018-21 are to:

- Develop 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 preparation of budgets
- To 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 an annual workshop 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:

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

Focus of GCCTI over this period includes:

- Continued engagement with the Cancer Australia supported Technical Services
- Understanding and adapting to the changing grant processes and cycles
- Increased focus on consumer engagement
- Leveraging opportunities for international collaboration

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

Session 1: Updates on current grant opportunities and recent changes

This session involved two presentations covering current grant opportunities, guidelines, assessment criteria, recent changes, and success strategies for grant submissions.

1.1 Update on NHMRC Grants Programs (Davina Ghersi)

This presentation by Adjunct Professor Davina Ghersi from NHMRC focused on the NHMRC Clinical Trials and Cohort Studies Grants.

Future applicants are encouraged to visit the Grant Connect website to download and review various critical documents before commencing proposal development, such as the latest *Clinical Trials and Cohort Studies Grants Guidelines*, and the *Guide to applicants on preparing an application* (which includes Category Descriptors).

Applicants were also encouraged to review the relevant standards (SPIRIT, STROBE and PRISMA) and visit the NHRMC website to further understand the funding process. Applicants are encouraged to familiarise themselves with the category descriptors early on in the process of preparing an application. Category descriptors form the criteria applied by the Grant Review Panel (GRP) and are a crucial part of the assessment.

The following key strategies for successful grant applications were outlined:

- Use systematic review (such as a PRISMA flow chart and checklist) to demonstrate the significance of the proposed research, including how the systematic review was completed and how this information informed the proposed methods and trial design.
- Reference the review of relevant clinical trials registries to demonstrate that the proposal is novel, and does not duplicate current research studies.
- Demonstrate the need for a study addressing the proposed question.
- Articulate the anticipated end-users of the study results, including the relevance of the research question to them, and involve them meaningfully in the trial design.
- Provide a table of milestones and performance indicators with corresponding dates. The approach should be specific to the proposed research and provide for effective monitoring of progress at twelve-month intervals.
- Be realistic with recruitment targets, including sample size.
- Be aware of other, relevant NHMRC policies such as the Gender equality strategy.

Volunteering to sit on grant review panels is also encouraged to increase applicant insight in to the review process. Finally, Davina noted changes to NHMRC's Grant Schedule and Policies in Response to COVID-19, and outlined NHMRC's support for MRFF funded clinical trials programs, encouraging applicants to register with GrantConnect to receive updates on MRFF programs.

1.2 Update on Cancer Australia Grants (Paul Jackson)

This presentation by Dr Paul Jackson, General Manager of Knowledge Management at Cancer Australia, provided an update on the status of Cancer Australia's granting programs.

Priority-driven Collaborative Cancer Research Scheme (PdCCRS)
The PdCCRS is Cancer Australia's annual national research grants funding scheme, in which the agency joins with other government and non-government organisations to collaboratively fund national cancer research projects in areas of identified priority (https://www.canceraustralia.gov.au/research-data/research/priority-driven-research).

Applications to the PdCCRS can be submitted via the NHMRC Ideas Grants scheme or the NHMRC Clinical Trials and Cohort Studies (CTCS) Grants scheme. Due to the impact of COVID-19, timelines for the assessment of applications to the 2020 PdCCRS round have been amended. Assessment of applications received though the Ideas Grants and CTCS Grants schemes will take place between December 2020 and February 2021. Outcomes for applications to the Ideas Grant scheme are expected in March 2021, and for the CTCS Grants scheme in May 2021.

Applications for the 2021 PdCCRS should open in March 2021 (Ideas Grants scheme) and June 2021 (CTCS Grants scheme).

***Support for Cancer Clinical Trials* program**
Through the *Support for Cancer Clinical Trials* program Cancer Australia funds the 14 national Collaborative Cancer Clinical Trials Groups to build their capacity to develop cancer clinical trials protocols to a stage where an application can be made to competitive funding schemes to fund the trial. To assist the Groups in this work, Cancer Australia also supports National Technical Services in quality-of-life, health- and pharmaco-economics, the Genomic Cancer Clinical Trial Initiative, and ACORD Workshops. Further information about the program can be found at: https://www.canceraustralia.gov.au/research-data/support-clinical-trials

Session 2: Systemic therapy and radiotherapy across multiple tumour types

This session included two presentations; one on combining radiotherapy and drugs for brain metastases, and another on combining SABR and drugs for metastases outside the brain.

2.1 Combining radiotherapy and drugs for brain metastases (Mark Pinkham)

This presentation was delivered by Mark Pinkham who is a Radiation Oncologist at the Gamma Knife Centre of Queensland, Princess Alexandra Hospital.

10- 50% of patients with advanced malignancy can develop brain metastases (BM) which can lead to significant morbidity and/or mortality if not controlled. Survival varies according to the extent of intracranial and extracranial disease. Conventional paradigm has been to offer more aggressive local therapies to those with a more favourable prognosis expected, reserving whole-brain radiotherapy (WBRT) or best supportive care (BSC) for those with a less favourable prognosis.

In relation to the role of local therapy, for single BM, surgery and SRS both improve LC and OS compared to WBRT in older mixed-histology trials. For 2-3 BM, SRS improves LC, functional independence and steroid requirement at 6 months compared to WBRT (also OS in RPA class 1). For 4-15 BM, SRS preserves NCF better than WBRT, same OS. The view that SRS is the future of radiotherapy for BM by using high precise dose, maximal tumour injury, and minimising normal tissue injury by steep dose gradients, was put forward. The appetite for combinations with WBRT are waning; main area of interest is combinations with SRS.

Multimodality BM management

- Optimal sequencing and integration of drug therapies
- Interactions between high dose RT-IO (augment RR and potentially RN risk)
- SRS for >3 BM, technical implications/RT-QA
- Pre-operative SRS
- Local control in (inoperable) BM >3cm or symptomatic BM
- Preventing new BM, management of high-velocity disease
- Leptomeningeal disease

SRS-drug combinations

The rationale for SRS-drug combinations includes: improve local control (treatment intensification, biological co-operation, the enhancement of drug delivery or effects), distant intracranial control (spatial co-operation, abscopal effects), and the improvement of normal tissue tolerance (reduce risk of neurotoxicity e.g. RN).

Some of the practical considerations of SRS-drug combinations include impact of branched evolution of the intracranial disease, drug delivery, BBB, perfusion dynamics and tumour interstitial pressure, incorporating new agents that are compatible with treatment for EC, and variation in risk-benefit for individual BM.

Possible future directions of SRS-drug combinations include IO-SRS (timing, SRS dose and fractionation, and reduced-dose SRS), Drug-SRS (PI3K, CDK, HER3, EGFR and 'Adjuvant' therapies), and opportunistic pre-operative studies (Pre-op SRS and pre-op drug or IO, and BBB manipulations with low dose SRS).

2.2. Combining SABR and drugs for metastases outside the brain (Shankar Siva)

This presentation was delivered by Associate Professor Shankar Siva who is a Radiation Oncologist at the Peter MacCallum Cancer Centre. The presentation began by providing the rationale for Local Therapy **(**with a focus on lung cancer): Oligometastatic Disease, Local Consolidation or Oligoprogression, and Synergy with IO.

It was highlighted that metastasis is not a singular event, but an evolutionary process, and that local control may be important (the theory of Local Therapy was presented). In terms of metastatic cascades, one metastasis evolves to seed other metastases, in rapid succession with little intervening evolutionary time; there is not necessarily an immediate metastatic shower throughout the body.

Upfront SABR for Oligometastatic disease

In the SABR-COMET study, a randomised phase II trial with two arms, patients were either provided palliative RT to any symptomatic sites or treated with SABR to all the sites of a known disease. Patients received further chemotherapy at the discretion of the medical oncologist, and follow-up over five years. Results demonstrated that in the SABR arm, overall survival rates and progression-free survival rates were higher (double) than in the control arm.

Local consolidation or Oligoprogression

Studies have looked at SBRT for Oligoprogression. The first is the STOP study looking at SBRT for Oligoprogression in NSCLC, a randomised control trial targeted at 54 patients. The study has two arms; a standard of care arm with systemic therapy and a SABR arm with systemic therapy. The second is the HALT study in the UK, looking at oligoprogression in EGFR, ALK and NSCLC, a randomised control trial targeted at 11 patients, where patients are randomised (2:1) to either SABR with continued systemic therapy or to systemic therapy alone.

Another study in London, Canada (Gomez et al., Lancet Oncology 2016), of a multicentre phase 11 RCT, showed results of local consolidation after systemic treatment improves progression-free survival rates. At an extended follow up of 38.8 months, the median PFS time in the LCT arm was 14.4 months, and in the MT/O arm was 4.4 months. This outcome retained statistical significance, with a p-value of 0.022. In terms of survival probability, the median OS time in the MT/O arm was 17.0 months and was 41.2 months in the LCT arm.

SABR and synergy with immunotherapy

SABR is immunogenic through its direct antigenic effect, and by upregulation of MHC-1 for cross-presentation of TAAs, allowing proliferation, priming and trafficking of activated CD8+T-cells at the tumour site, resulting in immunogenic cell death. Furthermore, a pooled analysis study of two randomised trials for metastatic non-small-cell lung cancer demonstrated that overall survival was 19.2 months for the pembrolizumab + radiotherapy cohort, compared with 8.7 months with the pembrolizumab alone cohort.

Toxicity of combining agents

The TOaSTT study demonstrates that of 483 patients treated with SABR, Acute G3+AEs of SBRT+TT/ICI is 12%. There is no synergy with the toxicity rate; instead, it appears to be an additive due to local toxicity from radiation and systemic toxicity from the drug therapy, not likely an amplified effect.

Summary

The combination of SABR and systemic therapy can be appropriate for upfront ablation of oligometastases, for oligoprogression to enable maintenance of current systemic therapy, local consolidation of persistent disease and synergy with immunotherapy. Unanswered questions include the timing of SABR around systemic therapy, the ideal dose/fractionation, single site irradiation or maximal cytoreduction, and cytoreduction of primary disease.

Session 3: Understanding, interpreting, applying and explaining difficult results of genetic profiling

3.1 Clinical understanding and conveying imprecision of precision medicine (Doah Cho)

This presentation was delivered by Dr Doah Cho, a PhD candidate at NHMRC CTC and a medical oncologist at St George Private Hospital.

The National Research Council Committee 2011 defines 'precision medicine' as the "tailoring of medical treatment to the individual characteristics of each patient…the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment."

Successful examples of precision medicine in oncology include Vemurafenib, a BRAF inhibitor, shown to be active across a number of different cancer types harbouring BRAF V600 mutations (*NEJM* 2015), and Larotrectinib, a TRK inhibitor which showed durable histology-agnostic activity and an objective response rate of 75% in TRK fusion positive cancers (*NEJM* 2018). However, results from studies such as SHIVA (*Lancet Oncol* 2015) and MOSCATO-01 (*Cancer Discov* 2017) have tempered those successes.

A number of variables exist that threaten the 'precision' of precision medicine, including:

- Analytical validity of the diagnostic biomarker assay
- Diverse molecular mechanisms of carcinogenesis, disease progression and therapy resistance
- Low prevalence of actionable biomarker targets
- Spatial and temporal tumour heterogeneity within and between patients
- Clinical validity of the biomarker target
- Additive and often unpredictable toxicities of combination targeted therapies

There is also an inherent tension between precision medicine (N-of-1 prediction, greater statistical uncertainty, and testing a 'biomarker ensemble') and traditional evidence generation methods (larger heterogenous populations, greater statistical certainty, and testing a single therapeutic strategy) (Hey and Kesselheim *Science* 2016, Aron *J Eval Clin Prac* 2019, Hunter and Longo *NEJM* 2019).

Studies comparing decision support platforms stress the importance of assay validation. Comparisons between decision support tools used on the same tumour samples have found major differences between variant classification and treatment recommendations (Perakis et.al. *ESMO Open* 2020). The foundation of precision medicine is the precise characterisation of actionable molecular alterations to guide choice of matched therapy. Without this, patients may be matched to the wrong, ineffective therapy or miss out on more effective therapy - which is exactly what precision medicine is trying to avoid.

Variant classification and reporting recommendations have been published for both germline and somatic alterations. While theses classification systems have helped us to categorise variants, studies have found classification is still often discordant between labs and reporting format heterogeneous. Unfortunately, the most common variant falls under tier 3 - variants of uncertain or unknown clinical significance (VUS). Rates of VUS detection increases as more genes, particularly less-studied genes, are tested in the panels and VUS rates are disproportionately higher in ethnic minorities due to less phenotypic data. Clinicians should avoid using VUS in clinical decision making and should undertake efforts to resolve the classification of the variant as pathogenic or benign. (Plon et.al. *Hum Mutat* 2008, Li et.al. *J Mol Diagn* 2017, Richards et.al. *Genet Med* 2015).

Some of the challenges for clinicians include lack of understanding of and formal training in genomics and new technology, difficult and unfamiliar nomenclature used in genomic reports, misconceptions regarding the capability of technology and significant variation in language used to describe multiplex testing. There is considerable variation in physicians' attitudes about test result disclosure and actionability (Gray et al. *JCO* 2014, Weipert et.al. J *Genet Couns* 2018).

Some of the barriers for patients include the level of awareness and misconceptions of the terms 'personalised medicine' and 'precision medicine', confusion between somatic and germline testing resulting in concerns/anxiety associated with germline testing when asked about somatic testing, anxiety and confusion associated with receiving a VUS result, misleading online marketing of direct-to-consumer tests (potential benefits not adequately balanced with limitations) in the context of emotional vulnerability of often dealing with a life threatening diagnosis (Gray et.al. J Oncol Pract 2012, Gray et.al. JNCI 2015).

Undoubtedly precision medicine is the way forward and has already remarkably changed the disease trajectory for some cancers however there are obstacles that we need to understand better and address to fully realise the promise and potential of precision medicine.

3.2 What do patients understand, and what information do they desire, when consenting to comprehensive genome profiling? (Phyllis Butow)

This presentation was delivered by Professor Phyllis Butow from the Psycho-Oncology Co-operative Research Group (PoCoG).

Genomic testing has entered clinical practice, offering the promise of tailored treatment. But do patients understand the benefits and potential costs of testing, the probability of an actionable result, and other possible outcomes they may face?

There is a psychological impact of CGP results. Even if patients understand the low chance of an actionable result, CGP may cause an emotional roller coaster of hope and dashed hope. If clinically actionable results are found, and no trial/treatment is available, patients may feel angry and/or abandoned.

CGP results are also not simple to interpret. Apart from actionable/non-actionable results, CGP results can identity variants with uncertain therapeutic potential (which can be confusing) and occasionally, variants with a germline origin (relevant to family) can be a burden that cancer patients are ill-prepared for. Thus CGP can engender significant uncertainty and distress.

How should we best communicate with patients about these issues?
A recent review of recent published research (2010–2017) on the communication of cancer-related genetic and genomic testing (CGT) information identified 513 papers, with more attention paid to outcomes of CGT results disclosure than to the process of results disclosure, as well as the identification of research gaps including the process of CTG communication (Kaphingst KA et al, Genetics in Medicine 2019; 21 (8):1691–1698)**.**

One study found that in genome sequencing consent appointments, consenters usually emphasised participant choice about secondary findings, but less often emphasized uncertainty about associated disease risks, and did not actively encourage questions (Sanderson SC. Genetics in Medicine 2019; 21, 1083–1091). A survey of US

genetic/genomic researchers suggested that most researchers and participants endorsed disclosure of risks, benefits, impact on family members, data security and procedures, for return of results in the event of death of incapacity and for re-contact. It also found that most researchers are only willing to devote <30 minutes to this process, and they were concerned that information would overwhelm participants (many participants are also concerned about being overwhelmed (Applebaum PS et al, Genet Med 2014;16(5):367-73).

The Australian Pancreatic Genome Initiative have developed a practical framework for communicating genomic research results. The framework positions the return of results as a shared responsibility (involving coordination) between researchers and clinical teams, and states that participants should opt-in to what results they receive. It acknowledges that the practicality of communicating results needs to be considered, and clinicians should give careful thought regarding how best to share the results. But the guidelines are more procedural; how to word explanations is not covered.

The PiGeOn (Psychosocial issues in Genomic Oncology) Project, a sub study of MoST, measured several quantitative measures at baseline and post results. Results show that many patients don't want full understanding about CGP, and are satisfied with 'gist' level understanding. After the return of the results, psychological outcomes revealed significant distress, and patient knowledge was not among a number of predictors of psychological distress.

In summary, patients primarily want, and have, basic 'gist' information about CGP. Knowledge does not seem to impact outcomes and improving explanations and consent may not reduce distress. The challenge is how to balance ethical informed consent against the potential to overwhelm patients. Furthermore, receiving non-actionable results increases distress, particularly in a desperate population with advanced cancer; these patients should be evaluated for the need for psychological support.

3.3 Consumer perspective (Lillian Leigh)

The presentation delivered by Lillian Leigh, a Patient Advocate, offered some consumer perspectives of understanding, interpreting, applying and explaining difficult results of genomic profiling. Lillian has had personal experiences of ROS1 cancer, including the financial challenge of self-funding treatment, adverse event and progression, clinical trial participation, fear of resistance, a feeling of urgency, the power of connecting with others

with similar experience, and understanding the 'foreign language' of genomics. In preparing this presentation, Lillian consulted with 17 other people that have experienced EGFR, ALK and ROS1 cancer across Australia and New Zealand, drawing out the key themes from those discussions.

Where are we now

Many patients are cautiously hopeful, and there is sometimes a need for self-advocacy to access the most basic biomarker tests. There can be a lack of information available pre and post-testing. Sometimes, clinicians make assumptions about patient preferences or circumstances which unintentionally limit treatment options. Patients also described a lack of support when receiving results. Fear of resistance, uncertainty after progression, and fear of being forgotten (particularly with rare cancers) are common experiences of cancer patients.

Where are we (hopefully) heading

In the future, utopian world, cancer is more of a curable or chronic disease that can be easily managed by patients and clinicians; genomic and biomarker tests are simple, accurate and timely for both diagnosis and monitoring, as well as subsidised and standard of care. Patients are well supported when they receive results: results are thorough but simple to understand, provided to the patient in a simple written form, all options are presented with the associated pros and cons, and genetic counsellors are available to answer questions, as well as links to further evidence-based resources. People are connected to patient groups for the same subtype.

Road map and take-home messages

- Keep collaborating to accelerate research
- Deliver results with empathy, sensitivity & without assumptions
- Offer additional support
- Keep finding ways to overcome resistance
- Don't forget about the "smaller slices of the pies" (rare subtypes)

3.4 Translational researcher perspective: Precision medicine – are we there yet? (Anna DeFazio)

This presentation was delivered by Professor Anna DeFazio. Anna began by outlining her perspective on the role of precision medicine (and its challenges) in cancer care: an approach to patient care that allows doctors to select treatments that are most likely to help

patients based on a genetic understanding of their disease. Some of its challenges include identifying the appropriate test, the availability of treatments, whether treatments targeted to the same alteration work in different tumour types, the need to screen large numbers of patients to identify small numbers that are eligible, and the disappointment and time wasted for the patient if not eligible.

INOVATe

INOVATe is a real-time tumour profiling study that recruited 520 eligible patients from 2016 to July 2020 across 14 sites, conducted testing with patients at diagnosis, and at relapse, to triage patients into the appropriate marker-driven clinical trials and assess efficacy, impact, enablers, and barriers. This study included molecular testing tailored for ovarian cancer and for clinical trials that were open or due to open. *BRAF*, *KRAS* and *NRAS* mutations were found in tumours from women with low-grade serous ovarian cancer (LGSC) and were relatively easy to call as they are activating mutations occurring in 'hot-spot' regions. However, interpretation of the mutations in these genes varies between cancer types. In colorectal cancer, 'patients with tumours harboring mutations in *KRAS* are unlikely to benefit from anti-EGFR antibody', whereas in LGSC, mutations may indicate benefit from Ras/Raf pathway targeted agents (ALEGRO trial).

Whole-genome single nucleotide polymorphism (SNP) array profiling, was used to determine which women had HR-deficient tumours, which may predict response to PARP inhibitors. Interpretation challenges include determining the true 'biological' cut-point, response to PARPi in the 'equivocal' zone and in non-HGSC cases, and the confounding effect of reversion mutations.

A case study which demonstrates the complexity of interpretation was presented, using an example of a 55-year old patient with concurrent endometrial and ovarian carcinomas. Two independent tumours were identified; a uterine mass (stage 1A) and left ovarian mass (stage 2C). Upon investigation mutations were found in a large proportion of the genes tested, some of which were potentially 'targetable', including *BRCA2* and *PIK3CA*. It was found that all MMR staining was preserved, no microsatellite instability was detected, and MSH6, *BRCA1* and *BRCA2* germline were mutation-negative. Mutation signature analysis demonstrated that the proposed aetiology was a polymerase epsilon exonuclease domain (POLE) mutation, which was subsequently confirmed by sequencing.

In conclusion, whilst the concept of ‘precision’ cancer treatment is simple; implementation is complex and there are still significant challenges. The relationship between gene alteration and targeted treatment is not always straight-forward. Molecular analysis has proven useful in clarifying difficult diagnoses, indicating inherited predisposition, as well as suggesting new trials and treatments.

Session 4: Ideas for new areas, molecular targets, and drugs for development including progress on current progress

4.1 Rank-ligand inhibition and immune checkpoint inhibition (Craig Gedye and Angelina Tjokrowidjaja)

This session was jointly delivered by Craig Gedye and Angelina Tjokrowidjaja, with Craig providing an update on the KEYPAD trial in renal cell carcinoma, followed by Angelina presenting a proposal which explores application of this concept across multiple tumour types.

The KEYPAD trial, led by Craig Gedye for ANZUP is a single-arm multi-centre phase II trial which looks to evaluate the activity of Denosumab and Pembrolizumab in clear cell renal carcinoma; the trial is currently active and recruiting. The trial has faced logistical challenges, for example recruitment has slowed down as a result of changing treatment patterns for this disease. There are a number of relevant and promising clinical trials already ongoing and it is hoped there will be an effective signal in KEYPAD. Clinicians with a KEYPAD trial site nearby are encouraged to consider cross-referring, to support completion of this trial.

Angelina Tjokrowidjaja then presented on a research concept to apply the KEYPAD concept across multiple tumour types, with a proposal for an open-label Phase 2 basket trial to evaluate the activity of denosumab and immunotherapy in advanced cancers. There is a wide spectrum of advanced malignancies that express RANK/RANKL, and RANK/RANKL expression is associated with a worse prognosis in several malignancies. RANKL blockade and immune checkpoint inhibition shows improved tumour suppression and enhancement of effector T cell function. Taking these factors into consideration this research concept will explore activity of combination denosumab and immunotherapy in an open-label Phase 2 basket trial across multiple tumour types.

4.2 REZOLVE3R (Katrin Sjoquist)

This presentation from Katrin Sjoquist was about a new proposal REZOLVE3R, which has developed out of the REZOLVE study.

The idea has developed in the context of the following problems: malignant ascites is a common and important cause of morbidity in patients with a variety of cancer types including ovarian cancers, there is no treatment approved in Australia for malignant ascites, and VEGF plays a pivotal role in malignant ascites but Bevacizumab recognises and binds to all major isoforms of human VEGF-A and prevents VEGF from interacting with its receptors and inhibits activation of downstream signaling pathways.

Turning to promising solutions, Bevacizumab is active in advanced ovarian cancer administered intravenously. Following a pilot study by by El-Shami in 2007 it was proposed have proposed that an (intermittent) IP dose of 5mg/kg bevacizumab administered IP following drainage of malignant ascites would be safe and active.

The primary objective of REZOLVE (ANZGOG 1101), led by study Chairs Michael Friedlander and Katrin Sjoquist, was to evaluate the activity of IP bevacizumab to reduce the formation or delay the re-accumulation of malignant ascites (median time from first to second therapeutic ascitic drainage). Of note, the time to repeat paracentesis (P0 to P1 or death) was 4.29 (95% CI 2.4 to 5.8) times higher following first dose of IP bevacizumab compared with the time between paracenteses prior to study entry (P-1 to P0).

Other results include:

- Median time from P0 to P1 or death (puncture-free survival) was 48 days (range 8 to 248 days)
- Proportion free of paracentesis at 42 days using competing risk analysis was 77% (95% CI 58 to 92)
- Median Overall survival 84 days (95% CI: 49 to 159)
- Proportion alive and paracentesis free at 42 days = 64 % (95% CI 40-80)

REZOLV3R is a proposed randomised controlled phase III study of (a single dose of) IP bevacizumab following therapeutic ascitic drainage of recurrent malignant ascites from refractory (intrabdominal) solid tumours of the Gastrointestinal and gynaecological tracts, compared to usual standard care alone. The target population is those with recurrent,

cytologically confirmed malignant ascites from primary gynaecological or gastrointestinal tract cancers suitable for paracentesis (ECOG 0-3).

Proposed design of REZOLV3R is a randomised multicenter national (or international) phase III open label controlled trial with stratification by primary tumour site, performance status, median time since prior paracentesis, and perhaps country. Current thinking on the primary objective is to compare paracentesis free survival between arms (or paracentesis free interval), with secondary objectives of paracentesis free interval/survival by primary tumour type/site, cost effectiveness, complication rate/toxicities, patient and carer satisfaction, ratio of paracentesis free intervals pre and post IP bevacizumab, QTwist, and OS.

Aspects currently for discussion include the control arm, a 2x2 factorial design, patient population, clinical inclusion criteria, coverage of other primary sites, and pleural effusions.

4.3 BCL-XL in mesothelioma (Tom John)

BCL-XL inhibition in combination with cisplatin is effective in malignant pleural mesothelioma due to its dependency on the BCL-XL pro-survival protein.

Background Mesothelioma has an incidence rate of 2.5 per 100,000 people and has the lowest 5 year survival of all cancers in Australia with a median survival of 12 months. Furthermore, systemic treatments have been limited to chemotherapy. Malignant pleural mesothelioma (MPM) is a lethal malignancy with limited therapeutic options. Evasion of cell death is one consequence of over-expression of pro-survival BCL-2 proteins.

Design Using the H-Score method, the association between the BCL-2 family protein expression and survival in 326 MPM patients were evaluated. *In vitro* assays were performed to evaluate the efficacy of BCL-XL inhibitors with cisplatin in MPM cell lines. BCL-XL inhibitors in combination with cisplatin were tested *in vitro* and *in vivo*.

Results Patients with high BCL-2 expressing tumours had a worse OS, and high BCL-XL expression had a non-significant trend towards inferior OS. Potent cell killing was observed *in vitro* with BCL-Xl inhibition using A-1331852 and ABT-263. Enhanced apoptic-mediated cell killing occurred when ABT-263 or A-1331852 were titrated with cisplatin. In the xenograft model, significant anti-tumour response and improved survival was observed with the combination of cisplatin and A-1331852 or ABT-263.

Conclusion High BCL-XL and BCL-2 are associated with poor survival in MPM. BCL-XL inhibition in combination with cisplatin demonstrated significant responses *in vitro* and *in vivo*, supporting expansion to human trials.

Update: Human trials have commenced, with results awaited.

4.4 Quizartinib/FLT3 TKI to reduce myelotoxicity of chemotherapy (Carolyn Grove and Wally Langdon)

This presentation delivered by Carolyn Grove and Wally Langdon provided an update on the Quizescence Phase 1 Trial Concept: Preventing chemotherapy-induced myelosuppression by repurposing the FLT3 inhibitor quizartinib. This trial is led by ALLG in collaboration with University of Western Australia, NHMRC Clinical Trials Centre and Cancer Centre: QE II Medical Centre.

Overview

Chemotherapy-induced myelosuppression is a major complication for cancer patients causing high rates of morbidity and mortality. Furthermore myelosuppression is frequently managed by delaying and/or reducing the scheduled dose, and, as a consequence, the efficacy of the treatment can be compromised. Added to this, elderly patients are more susceptible to chemotherapy-induced myelosuppression and they often receive a reduced dose, which contributes to the poorer outcome in this group. Since chemotherapy is the cornerstone for treating many types of cancer, the development of compounds that inhibit myelosuppression would provide relief from its harmful side effects and allow for more effective cancer treatments.

It is known that a single dose of quizartinib induces the transient quiescence of FLT3+ haematopoietic progenitors. It is also know that quizartinib-priming significantly enhances bone marrow recovery after 5-FU treatment and quizartinib protects mice from lethal myelosuppression caused by serial 5-FU treatment. Quizartinib also protects haematopoietic progenitors from gemcitabine cytotoxicity. However, in contrast to vehicle + 5-FU mice, vehicle + GEM treated mice show a faster recovery of LK and LSK cells, which is evident by day 3. Thus, in mice, 5-FU is more effective than gemcitabine in eliminating progenitors.

As part of this research it has been found that (also presented at the February 2020 GCCTI workshop):

- a priming dose of quizartinib protects mice from myelosuppression caused by 5-FU, gemcitabine and cytarabine.
- Quizartinib's protection of haematopoietic progenitors alleviates multi-lineage myelosuppression. Therefore it is more broadly effective than current measures and it is safe and simple.
- Mouse models of AML are successfully treated with 10 day cycles quizartinib priming in combination with high-dose 5-FU.

Although quizartinib priming does not protect haematopoietic progenitors from paclitaxel cytotoxicity we found that it does protect haematopoietic progenitors from a combination of paclitaxel and gemcitabine.

Further preclinical experiments support the concept design (in the mouse), as follows:

- Quizartinib priming protects haematopoietic progenitors from paclitaxel and gemcitabine treatment. This is most evident 2 days after treatment.
- This results in a more rapid recovery of myeloid lineage cells in the bone marrow. However, a recovery of haematopoietic progenitors in vehicle primed mice is observed by day 3, so the window where we see profound protection is shorter than with 5-FU.
- The rapid recovery of the bone marrow that occurs with quizartinib priming may be beneficial when the treatment is repeated every 7 days.

4.5 Targeted therapy in urothelial, biliary, lung, endometrial, and others (Alison Zhang)

This presentation was delivered by Alison Zhang, Medical Oncologist at the Chris O'Brien Lifehouse and Macquarie University Hospital.

The concept presented is at the early stages of development, and is titled FIST (FGFR inhibitor in solid tumours). This study has been initiated in the context of FGFR inhibitors starting to become more relevant in urothelial cancers, a cancer which Alison commonly works with.

Fibroglast growth factor/fibroblast growth factor receptor (FGR/FGRF) is a receptor tyrosine kinase signaling a pathway that has a crucial role in tumour proliferation, angiogenesis, migration and survival. There are 4 transmembrane tyrosine kinase receptors (FGR1-4) identified in the FGFR family and these can become activated by mutation, translocation or gene amplication.

Downstream signaling of this pathway can trigger the MAPK pathway, PI3K/Akt pathway, phosphorylation and activation of STAT3 (signal transducer and activator of transcription) and PLCy activation resulting in DNA transcription. Molecular alterations in FGFR pathway occurs in various tumour types.

The aim of this study (a single-arm, multicenter Phase II trial) is to determine the activity and safety of xx (FGFR inhibitor in multiple solid tumours), with primary objective being objective tumour response and looking at patients in advanced stages of cancer with pathologically-confirmed metastatic solid cancers of any histological type, after their first line of effective therapy.

4.6 Investigator initiaed phase I clinical trial of hydroxychloroquine with carfilzomib in multiple myeloma (Silvia Ling)

This presentation was delivered by Silvia Ling and provided an update on a Phase I Study of Hydroxychloroquine in Combination with Carfilzomib and Dexamethasone for Relapsed/Refractory Multiple Myeloma.

This study evaluates the safety and tolerability of adding hydroxychloroquine to carfilzomib in the treatment of relapsed/refractory multiple myeloma.

Multiple myeloma is a malignancy of plasma cells and it is the second most common blood cancer. It remains incurable with a median survival of 4-6 years; incidence in Australia is about 7 per 100,000. In current treatment, the 2nd generation proteasome inhibitor carfilzomib is a standard of care and is PBS-reimbursed.

The study is based on a pivotal Phase III ENDEAVOR trial comparing carfilzomib/Dexamethasone with bortezomib/dexamethasone. Bortezomib is the first generation proteasome inhibitor and carfilzomib is the second generation proteasome inhibitor. Carfilzomib yields a response rate of 76%.

The primary objectives of the study are to identify the maximum tolerated dose and recommended phase II dose of hydroxychloroquine combined with standard dosing of carfilzomib (carfilzomib will be PBS-funded due to being used in standard therapy) and to investigate the incidence of adverse events and toxicities associated with combination treatment. The secondary objective is to look at clinical activity.

4.7 ANTI-ROR therapy (Caroline Ford)

ROR1 is a Wnt receptor upregulated in ovarian and endometrial cancer (and many other cancer types) – a novel target that has been through Phase 1 and II trials in the US. Cirmtuzumab is a monocolonal antibody that binds to ROR1 and inhibits ROR1 signaling.

Work has been underway with ANZGOG in the past couple of years to develop a proposed clinical trial 'ROMEO': a single-arm, prospective, multicenter phase II exploratory study grouped by two tumour types (endometrial and ovarian cancer). The study will examine the potential benefit of cirmtuzumab (the ROR1 monoclonal) in combination with paclitaxel in patients with recurrent unresectable or metastatic endometrial and platiunum resistant ovarian cancer who have high ROR-1 expression by immunohistochemistry (baseline biopsy). There is now some *in vitro* data from Caroline's laboratory showing some potential synergy of cirmtuzumab with platimuns and also with paclitaxel. The study will be run through centres affiliated with ANZGOG.

There had been some thinking that pancreatic cancer may be a potential tumour, however following some research this year (2020), it is now believed that pancreatic cancer would not be a good target, as there was no evidence that ROR1 is playing a strong role in this cancer (other researchers are continuing to pursue this line of inquiry and are looking at larger cohorts).

Following other analysis in TCGA and CGGA cohorts, a strong signal was found in adult low grade glioma, which appears to be consistent across the sub-types. Analysis also shows correlation of ROR1 with higher grade and with more aggressive sub-types of this disease.

With some promising results in the breast cancer trial (triple negative cancer) there is potential for expansion of a ROR1 trial, noting the complexity of different cancers and combinations that one might treat with.

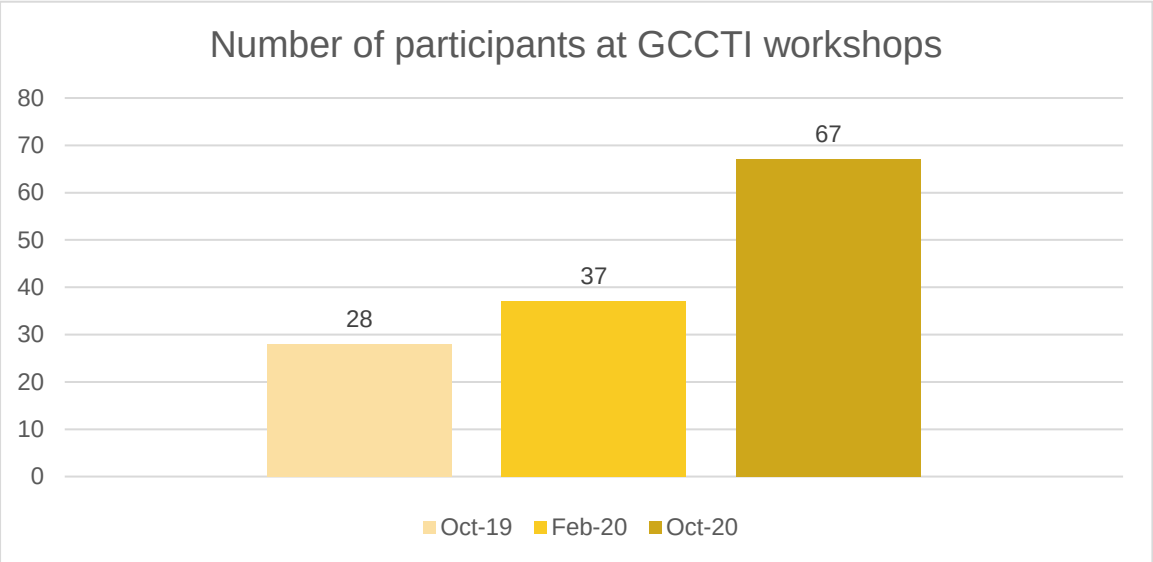
Workshop Evaluation

Workshop participants were encouraged to complete an online post-workshop evaluation survey, with 44 responses received (66% response rate).

The majority of respondents were clinical researchers (55%) and representatives of CTGs (45%). Other respondents included academic researchers and representatives of consumer organisations or funding bodies.

Participant numbers

Sixty-seven (67) participants attended the GCCTI October 2020 workshop, a significant increase from the 37 participants who attended the previous GCCTI workshop held in February 2020.



Organisations/groups from which participants attended

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

- AFCA
- Austin Health
- Australian Government Department of Health
- Calvary Mater Newcastle
- Cancer Australia
- Chris O'Brien Lifehouse, Royal Prince Alfred, Sydney
- Concord Hospital
- Gamma Knife Centre of Queensland
- Hunter Cancer Research Alliance
- Icon Cancer Centre

- ISLHD Cancer Care Services
- Kinghorn Cancer Centre, Garvan Institute
- Liverpool Hospital
- Macquarie University
- Murdoch University
- NHMRC Clinical Trials Centre
- Peter MacCallum Cancer Centre
- RMIT
- Sir Charles Gairdner Hospital
- St Vincent's Hospital
- The Children's Hospital at Westmead
- The Royal Children's Hospital
- The University of Melbourne
- The University of New South Wales
- The University of Newcastle, NSW
- The University of Queensland
- The University of Sydney
- University of Technology Sydney
- University of Western Australia
- Western Sydney Area Health Service
- Westmead Institute for Medical Research
- Cooperative Clinical Trials Groups (CTGs)
    1. AGITG
    2. ALLG
    3. ANZCHOG
    4. ANZGOG
    5. ANZSA
    6. ANZUP
    7. BCT
    8. COGNO
    9. MASC
    10. PaCCSC / CST
    11. PC4
    12. PoCoG
    13. TOGA
    14. TROG

Understanding the workshop's aim and purpose

97% of respondents indicated that they had a clear understanding of the aims and purpose of the workshop.

57% of respondents 'agreed', and 40% of respondents 'strongly agreed'. One respondent was undecided.

Usefulness and relevance of the presentations

89% of respondents indicated that they found the content of the workshop presentations useful and relevant.

49% of respondents 'agreed', and 40% of respondents 'strongly agreed'. Four respondents were undecided. Two respondents commented that some presentations were less relevant to specialists who work in radiation oncology and surgery due to their emphasis on systemic therapies. Other respondents noted:

"Clear presentations of material that can otherwise often be… overly technical."

"Excellent combination of information, developments and opportunities, well done."

Organisation of workshop

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

40% of respondents 'agreed' and 60% 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:

- Updates on current grant opportunities and recent changes
- Discussion of concepts in development
- Multiple perspectives on genetic profiling, including the consumer perspective
- Opportunities to interact across disciplines
- New trial ideas, particularly those involving and exploring new treatments to target areas identified in basic biology

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

"All of it enjoyed…overall very interesting and great to see some potential new trial ideas emerging."

"the… genetic profiling session provided a good overview and generated discussion for research possibilities beyond just clinical treatment questions."

"…consumer perspective (was) excellent."

"…imprecision of precision medicine with different stakeholder viewpoints (clinician research, consumer representative/advocate, translational researcher) was very informative and

highlighted the need for ongoing research and for more resources to support clinicians communicating to patients."

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.

- Further clarity on next steps after expressing interest in a project, including the role of the GCCTI
- Additional time for discussion
- Consider more emphasis on clinical and scientific topics

Genomic Cancer Clinical Trials Initiative

Appendix 1 – Workshop Agenda

Venue Virtual Workshop via Zoom

Date Friday 30 October 2020

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 including two or more tumour types and two or more CTGs.

Time	Session:	Presenter
9:00–9:15am	*Logging in and registrations*	
9:15–9:30am	**Welcome and introductions**	*Martin Stockler*
	Overview of GCCTI and achievements to date	*Martin Stockler*
Session 1 9:30–10:00am	**Updates on current grant opportunities and recent changes**	
	Update on NHMRC Grant Programs	*Davina Ghersi*
	Update on Cancer Australia Grants	*Paul Jackson*
Session 2 10:00–11:00am	**Systemic therapy and radiotherapy across multiple tumour types**	
	Combining radiotherapy and drugs for brain metastases	*Mark Pinkham*
	Combining SABR and drugs for metastases outside the brain	*Shankar Siva*
11:00–11:15am	*Break*	
Session 3 11:15–12:45pm	**Understanding, interpreting, applying & explaining difficult results of genetic profiling**	
	Clinical understanding and conveying imprecision of precision medicine	*Doah Cho*
	What do patients understand, and what information do they desire, when consenting to comprehensive genome profiling?	*Phyllis Butow*
	Consumer perspective	*Lillian Leigh*
	Translational researcher perspective: Precision medicine – Are we there yet?	*Anna DeFazio*
12:45–1:30pm	*Lunch*	
Session 4 1:30–3:15pm	**Ideas for new areas, molecular targets, and/or drugs for development including progress on current projects**	*Group discussion*
	Rank-ligand inhibition and immune checkpoint inhibition	*Craig Gedye/ Angelina Tjokrowidjaja*
	REZOLVE2	*Katrin Sjoquist*
	BCL-XL in mesothelioma	*Tom John*
	Quizartinib/FLT3 TKI to reduce myelotoxicity of chemotherapy	*Carolyn Grove/ Wally Langdon*

	Targeted therapy in urothelial, biliary, lung, endometrial, and others	*Alison Zhang*
	Investigator initiated phase I clinical trial of hydroxychloroquine with carfilzomib in multiple myeloma	*Silvia Ling*
	ANTI-ROR1 Therapy	*Caroline Ford*
3.15–3.30pm	**Wrap-up and close**	*Martin Stockler*