Genomic Cancer Clinical Trials Initiative

GENOMIC CANCER CLINICAL TRIALS INITIATIVE

OCTOBER 2019 WORKSHOP REPORT

This report was finalised on 2nd December 2019

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Contents

INTRODUCTION

The Genomic Cancer Clinical Trials Initiative (GCCTI) was established in 2013 and funded by Cancer Australia.

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 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 NHMRC CTC in partnership with ZEST Health Strategies. Scientific and technical input is provided by the NHMRC CTC, with communications, project management and stakeholder engagement by ZEST Health Strategies.

The GCCTI project team in collaboration with Scientific Steering Group (SSG) held a one-day workshop, at the Hotel Pullman, Sydney Airport on **Friday 11th October 2019.**

PURPOSE OF 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, based on molecular characterisation including two or more tumour types and two or more CTGs.

The October 2019 workshop focused on:

- **innovative ideas and new concepts for grant applications,**
- **the sharing of studies and ideas between CTGs relevant to GCCTI,**
- **updates and lessons from existing GCCTI supported trials, and**
- **supporting the prioritisation of concepts for grant applications in 2020.**

As an introduction, Professor Martin Stockler (Chair of the GCCTI Scientific Steering Group and project team) opened the workshop by providing an overview of GCCTI's aims, objectives and its future focus.

The workshop included presentations from experts in the area on innovative ideas and new concepts which may be developed and considered for future grant applications.

An overview and update of various CTG studies, in addition to the existing GCCTI supported ideas and trials (EMBRACE, AUTO-CHECK and SEQUITUR) was also provided. The workshop concluded with a group discussion on future opportunities that GCCTI could engage with to support ideas for new areas, molecular targets, and/or drugs for development.

WORKSHOP WELCOME

OVERVIEW OF GCCTI AND FUTURE FOCUS (MARTIN STOCKLER)

Further information about the Workshop program is presented in Appendix I

The primary aim of the GCCTI is to support the national cancer cooperative trials groups (CTGs) by developing mutation-specific 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 at least four mutation-specific clinical trial concepts and/or 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.

There are also a number of additional outcomes and benefits as a result of the GCCTI:

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

An outline of the future focus of GCCTI over this period included:

- 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.

INNOVATIVE IDEAS AND NEW CONCEPTS

This session involved three presentations and included discussion on ideas and concepts which were at varying stages of development. Robust discussion of each of these ideas and concepts provided presenters with expert multidisciplinary input from the workshop participants to further develop and refine their concepts.

UPDATE TO ANTI-ROR1 THERAPY PROPOSAL (CAROLINE FORD)

The presentation included a refresher on ROR1 and citmtuzumab, a research update, as well as future trial plans.

ROR1 & ROR2

Receptor Tyrosine Kinase-like orphan receptor 1 (ROR1 - proliferation, stem cell niche) and 2 (ROR2 – metastasis) are evolutionarily conserved, type-I membrane proteins that are expressed during embryogenesis. The altered expression of ROR in many human tumours, such as ovarian, endometrial, breast and pancreatic cancer has led to the investigation of ROR as a novel target for anti-cancer therapy.

Cirmtuzumab

Cirmtuzumab is an anti-ROR1 monoclonal antibody, developed by Kipps lab at the University of California San Diego (UCSD). Cirmtuzumab has seen pre-clinical efficacy in chronic lymphocytic leukaemia (CLL), breast, and ovarian cancer.

A study by Choi et.al (2018), which was presented at ASCO and published in *Cell Stem Cell* in May 2018, investigated the use of cirmtuzumab as a single agent (4 biweekly doses only) in 26 patients with relapsed or refractory chronic lymphocytic leukaemia (CLL). The results of the study demonstrated that there were no dose-limiting toxicities or serious adverse effects, with ROR-1 signalling successfully blocked (as measured by Rho-GTPase activation).

A study by Zhang et al., (2019), published with the *Proceedings of the National Academy of Sciences,* looked at cirmtuzumab and paclitaxel combination for locally advanced, unresectable breast cancer. The study began recruiting in 2018 and is still actively recruiting with interim results to be presented at San Antonio Breast Cancer Symposium in December.

Ovarian Cancer

ROR1 is expressed in all subtypes of ovarian cancer and ROR1 expression is associated with shorter OS and PFS in ovarian cancer patients. Knockdown of ROR1 in ovarian cancer cell lines inhibits proliferation, migration and invasion and cirmtuzumab inhibits engraftment of ovarian cancer *in vivo*.

New data presented at AACR Advances in Ovarian Cancer Meeting (Sep 2019) indicates that ROR1 protein expression was detected in 97% (n=275) of High-Grade Serous Ovarian Cancer (HGSOC) patients via IHC. Nanostring analysis of more than 2500 HGSOC patients has confirmed that patients with high ROR1 have a significantly shorter OS (P=0.033) compared to patients with low ROR1. Furthermore, ROR1 expression significantly increased

in platinum resistant HGSOC and two new platinum resistant HGSOC cell lines are about to be tested with cirmtuzumab in.

Endometrial Cancer

New data (with 4A5 antibody) on larger endometrial cancer cohort previously discussed, confirms 2018 findings showing ROR1 overexpression. ROR1 was expressed in 94% of endometrial cancer tissue samples tested and HGSEC patients with high ROR1 had a significantly shorter PFS and OS. There is a new HGSEC cell line (ARK-1) which is testing cirmtuzumab; early incucyte data suggest cirmtuzumab inhibits proliferation.

ROMEO study

Caroline presented on a new trial proposal, 'ROMEO,' a single-arm, prospective, multi-centre phase II exploratory study grouped by two tumour types (endometrial and ovarian cancer) looking at a novel ROR1 targeting monoclonal antibody in combination with paclitaxel in women with high ROR1 expressing advanced/ recurrent endometrial and ovarian cancers. The study, run through centres affiliated with the Australian New Zealand Gynaecological Oncology Group (ANZGOG), will examine the potential benefit of cirmtuzumab in combination with paclitaxel in patients with recurrent unresectable or metastatic endometrial and platinum resistant ovarian cancer who have high ROR1 expression by immunohistochemistry.

The study hypothesises is that cirmtuzumab is an active agent in the treatment of high ROR1 expressing metastatic or recurrent, unresectable endometrial cancer and platinum resistant ovarian cancer and will demonstrate additional activity in combination with paclitaxel compared with responses seen with paclitaxel alone. The primary objective is to determine the six month progression free survival rate for cirmtuzumab and paclitaxel treatment in two separate tumour groups;

1. High ROR1 expressing recurrent, unresectable or metastatic endometrial cancer after failure of 1-2 lines of chemotherapy
2. Metastatic platinum resistant ovarian cancer

Translational objectives are to assess immunohistochemistry and molecular markers of efficacy including to investigate the relationship of ROR1 expression and response and to explore differences in ROR1 expression in archival tissue and fresh biopsy at study entry, to name a few.

Key discussion points:

- The group discussed the potential to expand to other tumour groups
- Exploration of ROR1 expression in Epithelial-mesenchymal transition (EMT) facilitated metastasis, Glioblastoma (GBM) and lung cancers
- Potential next step to progress an anti-metastatic drug, for pre- (and at) surgery

TARGETTING PIK3CA INHIBITORS IN BREAST AND OTHER ADVANCED CANCERS (CHEE LEE)

Dr Chee Lee presented an overview of the potential to target PIK3CA mutations in breast and other advanced cancers.

PI3K activates several molecules involved in cell-cycle progression and survival, and in estrogen receptor (ER) positive breast cancer cells, promotes estrogen-dependent and independent ER transcriptional activity. Hyper-activation of the PI3K pathway, which is the most frequently mutated pathway in breast cancer, promotes antiestrogen resistance. The antiestrogen-resistant breast cancer model often remains sensitive to estrogen and Pi3K inhibition, suggesting that simultaneous targeting of the PI3K and ER pathways may be an effective method for treatment.

Highlighting findings from multiple studies, it was shown that PI3K includes catalytic and regulatory subunits and that there are 4 isoforms of the PI3K catalytic subunit. It was also noted that around 40% of patients with HR+ and HER2- breast cancer presented with an activating tumour mutation of PIK3CA. Furthermore, Pan-PI3K inhibitors target multiple isoforms of PI3K, leading to excess toxicities and marginal efficacy. Alpelisib (BYL719) is a specific inhibitor of the PI3K α-isoform and has demonstrated antitumor activity in preclinical models harbouring PIK3CA alterations. This suggests a strong rationale for targeting the α-isoform of PI3K in patients with PIK3CA mutation.

An update on the SOLAR-1 Phase III randomised controlled trial of 341 subjects investigating the use of Alpelisib (BYL719) for postmenopausal women or men with HR+, HER2-ABC showed that the primary endpoint crossed the pre-specified Haybittle-Puto boundary and the proof of concept criteria were not met in the PIK3CA-non-mutant cohort.

Overall response rate in the PIK3CA-mutant cohort for patients with measurable disease in the Alpelisib + fulvestrant group are at 35.7%, compared to 16.2% for the placebo + fulvestrant group. With regards to all patients, response rate is at 26.6% for Alpelisib and 12.8% for the placebo condition. Eighteen (18) patients discontinued Alpelisib due to hyperglycaemia and 9 patients due to rash; no patients discontinued placebo due to either. The safety profile of the Alpelisib group and the placebo group was similar in the PIK3CA-mutant and PIK3CA-non-mutant cohorts.

Chee illustrated the SANDPIPER study looking at ER-positive/HER2-negative locally advanced or metastatic breast cancer in postmenopausal women with recurrence or progression during or after aromatase inhibitor. The study by Millis et al. (2016) showed that PIK3CA, PTEN and AKT1 mutations occurred more frequently in the presence of hormone receptor overexpression.

Chee outlined the proposed study design for PARAGON-2 which is an extension to the current PARAGON trial by Dr Michael Freelander. This looks at ER+ and/or PR+ endometrial cancer, low grade serous ovarian cancer, high grade serous ovarian cancer with relapse as asymptomatic rise in CA125, platinum-resistant or refractory ovarian cancer and granulosa cells / sex-cord stromal tumours.

In terms of progress the study proposal has been submitted for Norvatis Medical Review Committee in July 2019 and reviewed by the Norvatis Governance Board in August 2019. Verbal support has been provided for drug supply however Novartis are seeking competitive funding and therefore the funding decision is on hold for 12 months.

Key discussion points:

- The group discussed looking at other populations and combination therapy (e.g. with aromatase inhibitors)
- The group discussed the potential to address hyperglycaemia (ADE) and metabolic syndrome, particularly in endometrial cancer

OVERVIEW OF THE AUSTRALIAN EXCEPTIONAL RESPONDERS PROGRAM (MEG BARNET)

Dr Meg Barnet presented an overview of the Exceptional Responders Program which covered the program background and rationale, the Australian and international programs, as well as the role for CTGs and national bodies.

The program examines patients who have responded favourably or poorly to treatment, long-term survivors and the variables associated with this exceptional response. The rationale for the program was the challenge in addressing inter and intra patient heterogeneity. Capturing the population effect was important and effects were likely due to idiosyncrasies in the patient or in cancer, rather than pharmacokinetic variability.

The program is based on the evidence that analysing outliers leads to medical breakthroughs. Multiple international programs have now been established including at Harvard and NCI in the United States, and Princess Margret in Toronto.

Meg noted that the Australian program is now open and recruiting and outlined the quantitative criteria. The analysis will examine blood samples using whole genome sequencing and bio-banking. In addition, the program looks at tumour (predominantly FFPE) using pathology review, DNA/RNA extraction and further analysis such as proteomics, Epigenomics or single cell sequencing. There is inherent heterogeneity in this type of analysis; the program is thus focused on developing subgroups of specific treatment and disease histology to strengthen findings. There is a focus on national promotion and sustained national and international collaborations.

Examples of exceptionally good response subgroups include 3 year survivors of metastatic pancreas adenocarcinoma. One-off exceptional cases may include abscopal response to radiation therapy or exceptionally severe toxicity to single agent immunotherapy. Exceptionally bad response subgroups may include *de novo* platinum resistance in germ cell tumours, or non-response to neoadjuvant Her2-based therapy in breast cancer.

Meg outlined progress to date including centralised ethics approval, infrastructure for referral, blood and archival tissue retrieval and bio-banking, as well as seed funding for 200 cases at $5,000 per case. There are 90 cases recruited at the time of writing this document.

Moving forward national promotion of the program is required to facilitate recruitment and lead to optimal case inclusion. The program is committed to sustained collaboration, such as the co-branding / co-authoring of project outputs.

Key discussion points:

- The group discussed how the program might define and identify target populations for the program e.g. targeting those that have a specific (common) cancer and who have survived above a specific timeframe after treatment
- A key consideration was how the workshop group might be able to assist with recruitment

PRESENTATIONS FROM CTGS

This session involved a presentation from AGITG, MASC Ltd, and ALTG, outlining studies and ideas that other groups might benefit from knowing about.

AGITG (MARK MCGREGOR)

Mark McGregor, on behalf of the Australasian Gastro-Intestinal Trials Group (AGITG), presented on a phase 2 study of oncolytic immunotherapy of metastatic neuroendocrine tumours using intralesional rose bengal disodium in combination with pembrolizumab.

Neuroendocrine tumours have an incidence of 5-7 in every 100,000 (SEER database) and can arise from small bowel, pancreas, lung, large bowel and stomach. The liver is often the frequent site of metastatic disease and neuroendocrine tumours are often indolent but associated with carcinoid syndrome.

Systemic treatments for metastatic disease include somatostatin analogues, peptide receptor radionuclide therapy (PRRT), targeted agents and chemotherapy. Liver-directed treatments include surgery, RFA, TACE, SIR-Spheres and cryoablation.

In relation to immunotherapy, Mark described the need for a therapeutic approach to overcome inadequate immune response to single agent checkpoint inhibition, to create an “inflammatory” state. PV-10/ Rose-Bengal is a small molecule oncolytic immunotherapy able to be injected intralesionally, preferentially retained in tumour cells and rapidly cleared by normal tissue.

The primary objective of Phase 2 single arm trial is to assess the efficacy of IL PV-10 administered in liver metastases arising from neuroendocrine tumours in combination with systemic administration of pembrolizumab. Secondary objectives include assessing safety of IL PV-10 and pembrolizumab, further characterize efficacy based on numerous other endpoints and an exploratory objective is to probe possible changes in immune system signalling and function at the tumour (TME) and systemic (peripheral blood) level.

Mark outlined the key inclusion and exclusion criteria, the study schema and the statistical analyses methods. Assessments will include CT scan, 68 Gallium-DOTATATE PET, Chromogranin A, EORTC QLQ-C30, laboratory bloods, correlative blood samples and optional correlative tumour biopsies.

Mark proposed a number of discussion points including the method for determining radiological response, securing pharma co-sponsor to supply anti-PD1 drug, and recruiting sufficient numbers with rare cancer.

Key discussion points:

- Potential opportunities to open up this treatment to include lung neuroendocrine tumours and other cancer types

MASC LTD (ANTHONY JOSHUA)

Anthony Joshua, from Melanoma and Skin Cancer Trials Limited (MASC Trials Ltd.) presented on Tumour Infiltrating Lymphocytes (TIL). If you would like more information, please contact Anthony at Anthony.Joshua@svha.org.au

OTHER CTGS (GROUP DISCUSSION)

CTG representatives were provided the opportunity to share with the group on studies and ideas that other groups might benefit from knowing about.

Shalini Subramaniam, on behalf of Antony Mersiades, presented the CHALK study – a proposed single-arm, phase 2 trial of alectinib plus chemotherapy as initial treatment for ALK-rearranged metastatic NSCLC led by the Australasian Lung Cancer Trials Group (ALTG) and the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC).

Key discussion points:

- Proof of concept idea discussion around selection and exclusion criteria
- The use of chemotherapy with targeted therapy (e.g. EGFR-mutant NSCLC) has demonstrated significant improvement in survival. Discussion as to whether there are other tumour types and settings where this treatment strategy might be suitable
- Overall survivorship of patients - ensuring targeted treatments are effective

UPDATES FROM GCCTI TRIALS

This part of the workshop included updates on GCCTI supported trial updated and lessons learnt.

AUTO-CHECK (SONIA YIP)

AUTO-CHECK is a translational research study looking at the molecular determinants of autoimmunity and immune adverse events in advanced cancer patients treated with immune checkpoint inhibitors.

Immune checkpoint inhibitors are remarkably active in a variety of cancers. The hypothesis of this study is that a group of patients with a genetic susceptibility to autoimmunity are more likely to develop an immune related adverse event (IRAEs) after treatment with immune checkpoint inhibitors.

The AUTO-CHECK grant, led by Matthew Cook (CIA) and Sonia Yip received Cancer Australia funding in 2017 and commenced in March 2017.

AUTO-CHECK uses data and bio-specimens from 6 multi-site investigator-initiated trials across 4 co-operative trials group (ALTG, ANZGOG, ANZUP and COGNO). These trials span 5 tumour types: mesothelioma (DREAM trial); NSCLC (NIVORAD, ILLUMINATE), SCLC (SCRIBE), renal cell (KEYPAD) and glioblastoma (NUTMEG) – each trial using immune checkpoint inhibitors. It includes a mixed cancer cohort from Canberra Hospital. The study aims include:

1. Baseline molecular predictors of immune-related adverse events (IRAE)
2. Identify common and rare genetic variants that segregate IRAEs, and
3. Changes in peripheral blood lymphocytes (effector, memory and regulatory subsets), and the kinetics and distribution of CTLA4 and PD-1 expression in patients with or without IRAEs.

Blood is shipped in real-time from all participating hospital sites to the ANU where they are processed for peripheral blood mononuclear cells for subsequent analysis. Other whole blood and serum processed and frozen at sites will also be used for AUTO-CHECK.

The first hospital site was activated in June 2017, with 82 (of which 46 unique) sites now activated, an increase from 63 from previously. Recruitment to date as at October 2019 has increased to 83% (248/300) of target participants, from 55% (164/300) in November 2018. Real-time blood shipments from the hospital sites to the ANU central lab have increased from 244 to 425 in the same period, and 45 IRAE blood samples have been collected to date. Phenotyping of peripheral blood mononuclear cells (PBMCs) has commenced and posters have been presented at multiple CTGs' annual scientific meetings. Recruitment will close at the end of 2019.

AUTO-CHECK satisfies the requirements that GCCTI-developed studies involve more than one tumour type and more than one CCTG. Also this translational research study has demonstrated a national collaboration of researchers across multiple disciplines including immunology, medical oncology and translational research. This is reflected in the broad

representation on the study management committee, which includes the study chair of each trial.

Key discussion points:

- The exploration of Hodgkin's lymphoma was flagged as an opportunity moving forward

EMBRACE (KATRIN SJOQUIST)

EMBRACE is a phase II clinical trial of the PARP inhibitor, olaparib, in HR-deficient metastatic breast and relapsed ovarian cancer in patients without germline mutations in BRCA1 and BRCA2.

The trial was awarded funding in Cancer Australia's PdCCRS program in December 2016. The EMBRACE study is led by Dr Katrin Sjoquist and coordinated by the NHMRC Clinical Trials Centre, University of Sydney, in partnership with ANZGOG and BCT (formerly known as the ANZBCTG).

The aim of this trial is to determine activity of olaparib in each tumour cohort (TNBC and HGSOC) as determined by the objective tumour response rate according to RECIST v1.1. The target population are patients with either:

1) Metastatic triple negative (ER-, PR-, HER2-) invasive breast cancer, or
2) Relapsed platinum-sensitive high grade serous ovarian cancer, with an eligible MPSI tumour molecular analysis result.

These cohorts will be administered 300mg of Olaparib orally twice daily until disease progression or unacceptable toxicity, with the primary objective measuring activity of Olaparib in each molecularly enriched cohort. A translational sub study examining resistance and response mechanisms in a subset of ovarian cancer patients has been funded by ANZGOG through its fund for New Research.

The duration of accrual is 3 years with a 6-month minimum follow-up duration. Katrin outlined the eligibility criteria for both the TNBC cohort and the HGSOC cohorts, which is available in full on the ANZCTR website.

Central screening for the pre-study is offered to potentially eligible patients at participating sites, including the Translational Genomics and Epigenomics Laboratory and Olivia Newtown-John Cancer Research Institute (ONJCRI). Following completion of pre-study screening consent, blood and tissue samples are collected.

In January 2019 the EMBRACE pre-screening program was put on hold whilst the protocol was amended to incorporate the relocation of the screening program and new research since trial development. EMRACE pre-screening recommenced 17 May 2019 following local RGO approval for an amended protocol to expand the current inclusion criteria with reference to breast cancer, which will assist with screening and recruitment.

There are currently 9/12 active sites since July 2017, with 3 sites to be opened Q3 2019. Since October 2017, 97 patients have completed pre-screening, of which 9 have now been recruited; recruitment is currently planned to end Q3 2020.

Next steps include ongoing recruitment and translational work with the TBNC cohort. There may be the opportunity to expand in to the breast cancer space if there is interest in exploring PARP inhibitor sensitivity in breast cancer patients. There are plans to expand to

sites more distant from Melbourne given new technical capabilities in samples storage and processing

SEQUITUR (HAO-WEN SIM)

Sequential immunotherapy in patients with underserved rare cancers (or SEQUITUR) is a multi-arm platform trial of open-label, multicentre, sequences of Phase II basket trials using hierarchical modelling and borrowing power across multiple cancer types using a master protocol. A master protocol allows the study of multiple therapies in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm, rather than being wedded to specific treatments.

The aims of the study are:

- To demonstrate that sequential immune checkpoint inhibitor combinations are active and tolerable in rare cancers
- To conduct simulations to evaluate the analysis under various assumptions, borrowing statistical power across the tumour bins
- To explore immunologic and molecular biomarkers

The study design includes combination immunotherapy, sequential therapy, adaptive design and a Bayesian cluster hierarchical model. The primary objective of the study is to evaluate the response rate (RR: (CR+PR)) by tumour type, and RR hierarchically across baskets but also survival, duration and depth of response. Secondary objectives include overall survival, clinical benefit rate and duration, toxicity and quality of life. Immune biomarkers include tumour mutational burden, tumour microenvironment and autoantibodies.

The brain cancer section of the trial (SEQUITUR-Brain) is proceeding, and intends to recruit 300 participants from multiple rare brain cancer baskets (e.g. ependymoma, meningioma, rare gliomas) who will be treated with first sequence of an IO combination. Approximately 120 of these participants will subsequently be treated with a second sequence of another IO combination.

Hao-Wen updated that an immunotherapy grant for $500,000 over 3 years has been provided by the Cure Brain Cancer Foundation, with timelines having been extended by 1 year. The trial is awaiting planning and simulation following a study planning meeting in February 2019 with Scott Berry. Furthermore, the trial is looking at various opportunities for drug supply.

Key discussion points:

- Potential opportunity to expand the study to paediatric gliomas and CNS lymphoma
- An innovative trial design looking at a rare subset of cancers

IDEAS FOR NEW AREAS, MOLECULAR TAREGTS, AND/OR DRUGS FOR DEVELOPMENT

This part of the workshop included updates on other GCCTI ideas for new areas, molecular targets, and/or drugs for development.

OVERVIEW AND PRESENTATION OF 5-FU-BASED PHARMACOGENOMICS CONCEPT (STEPHEN ACKLAND)

Stephen Ackland from the Hunter Medical Research Institute (HMRI) presented a pharmacogenomics idea in relation to fluoropyrimidines (the drugs fluorouracil (5FU), capecitabine and trifluridine). As with many anticancer drugs, these agents have a narrow therapeutic index, and severe or life-threatening toxicity occurs in 10-30% of patients treated with standard doses. Recently 4 SNPs in DPYD have been identified as contributing to reduced 5FU clearance and increased toxicity. These SNPs together occur in about 5-8% of the population. This study would involve DPYD genotyping in patients about to receive one of these drugs for treatment of early or advanced cancer (currently breast, head and neck, upper GI and colorectal cancers), and advising dose modifications in patients harbouring one of these SNPs.

DPYD genotyping is now common practice in France and the Netherlands, and programs of genotype-guided dose modification are proposed, but not yet proven to be cost-effective. If this was progressed in Australia it would be relevant to a sizeable proportion of Australia; it is estimated that there are 10,000 new patients per annum in Australia with these diseases and treated with a fluoropyrimidine.

The proposal is to conduct an implementation science project assessing the feasibility and cost-effectiveness of this strategy in Australia; some preliminary work is already underway (Peter Mac and HMRI).

Whilst support already exists from some key organisations, further support from a broad range of organisations is required, as well as the identification of funding.

Key discussion points:

- Which populations might be targeted – likely all patients to be treated with a fluoropyrimidine (colorectal, upper GI, head and neck and breast)
- Potential for further discussion with AGITG and Cancer Breast Trials
- Pharmacogenomics study would add value, facilitating further research and development towards wider implementation by building a platform and expertise

RISK PREDICTION OF BOWEL CANCER (KRISTI MILLEY)

Kristi Miley, on behalf of the Primary Care Collaborative Cancer Clinical Trials Group (PC4), updated on a project currently under development around genomic-based stratified screening for cancer in primary care. The intervention is a cheek swab, conducted by GPs in primary care settings. The results include a polygenic risk score based on SNP panels for common cancers including prostate, breast, bowel and melanoma. The GP receives a proforma which states which tumour streams the patient has an elevated risk for, which would subsequently inform screening decisions. PC4 is collaborating with the Victorian Comprehensive Cancer Centre (VCCCC) on this initiative.

FINAL GROUP DISCUSSION

The workshop concluded with a group feedback session, facilitated by Martin Stockler, whereby each participant was asked to share with the group an idea generated by the workshop discussion that they found particularly interesting as well as what they might take back from the workshop to their own CTG.

ALLG

- Possible opportunity for collaboration in relation to side effects and immune checkpoints
- Other groups to consider ALLG for primary CNS lymphoma
- Possible discussion between ALLG and COGNO in relation to CNS lymphoma, SEQUITER and a basket lymphoma trial
- Useful to learn of others' experiences of doing platform surveys, particular overcoming the challenges

AGITG

- Potential for ROR-1 to have a place in colorectal cancer treatment as there is an area of therapeutic need within the group, with some caveats around further information required. Potential for more background/ exploration work to be done in this area
- The concept of TIL therapy in a small proportion of colorectal, gastric and upper GI cancers

PoCoG

- Inclusion of quality of life and patient reported outcomes in trials
- Potential opportunities to collaborate in relation to the patient preference aspect of treatment

TROG

- Exceptional responders program might be of interest to radiation oncologists, and perhaps an area TROG could contribute to, as they often see patients over a long period of time with a broad spectrum of tumours
- AUTOCHECK is an interesting area for the group, particularly post-PACIFIC trial, in relation to understanding IR related AEs
- In terms of developing new trials, the work with intralesional PV10 is of interest with possible scope for cross-collaboration and developing trials which combine or compare modalities

ANZGOG

- Workshop provided some potential opportunities for ANZGOG (exceptional responders program and others); open to collaboration with other groups

AGITG

- Taking back the exceptional responders program to individual tumour groups to assist with recruitment including guidance on patients that should be referred

PC4

- Opportunity for PC4 to share information of relevant screening studies and engage with other CTGs which may be interested in the SNP panel idea

MASC Ltd

- Sharing of ideas and the evolving conversation in relation to TIL therapy

ANZCHOG

- Taking back the exceptional responders program and how it might apply in the paediatric space
- Interested in TIL therapy, something to take back to explore opportunities for involvement

Meg Barnet

- A positive of this group is the focus on areas which will not necessarily receive pharmaceutical funding but will improve patient outcomes
- Taking back that there are opportunities and leads to collaborate in relation to the exceptional responders program

COGNO

- In relation to the exceptional responders program, potential to formalise the arrangement with COGNO
- Taking back the ROR 1 and ROR 2 study

Sonia Yip

- In relation to the exceptional responders program, one approach for further recruitment would be to review cases that have been part of previous trials at the Clinical Trials Centre
- Taking back the interest from TROG and any possible future opportunities
- Taking back the Hodgkin's group and exploring possible extensions to the project in this context

ALTG

- Taking back an expression of interest in collaborating with PcCoG with respect to patient preference and study CHALK
- Exploring opportunities in the prostate cancer space

Caroline Ford

- Taking back the feedback about dose dependency
- EMBRACE and the opportunity to look at those pre-screen

Breast Cancer Trials

- Exceptional responders program and any links to a similar program that the Breast International Group is running in Brussels

Stephen Ackland

- Interested in ROR 1 study and exceptional responders program

ANZUP

- Taking back the exceptional responders program and specifically that we should try and identify men who live more than 3 years after their dose of docetaxel for castration resistant prostate cancer

Clinical Trials Centre

- Taking back the ROR 1 study and adaptive TIL therapy

Martin concluded the workshop and informed the group that the next GCCTI workshop would take place early next year. GCCTI will also be working in partnership with ACORD to host a multi-day workshop for early career researchers, likely in the February/ March 2020 period, to support grant proposal development.

Additional feedback on the workshop was also obtained through workshop evaluation forms, with the results presented in the following section.

WORKSHOP EVALUATION

Twenty-eight (28) participants attended the GCCTI October Workshop 2019, representing the following groups/organisations:

- GCCTI project team
- Cancer Trial Groups (CTGs);
    - The Australasian Leukaemia and Lymphoma Group (ALLG)
    - Cooperative Trials Group for Neuro-Oncology (COGNO)
    - Australasian Gastro-Intestinal Trials Group (AGITG)
    - Breast Cancer Trials (BCT)
    - Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG)
    - Psycho-oncology Co-operative Research Group (PoCoG)

Workshop participants were encouraged to complete a post-workshop evaluation form, with twenty (20) responses received (71%), an improvement in completion rate from the last workshop in March 2019 (69%). Similar to the previous workshop, the majority of the responders were clinical researchers and representatives of the CTGs, as well as some academic researchers.

Understanding of the workshop's aim and purpose:

All respondents (100%) indicated that they had a clear understanding of the aim and purpose of the workshop, up from 96% at the March workshop. 70% of respondents 'agreed' and 30% of respondents 'strongly agreed.' One participant commented that they had a better understanding for this workshop compared with the previous workshop they attended.

Usefulness and relevance of the presentations

90% of respondents indicated that they found the content of the workshop presentations useful and relevant - 65% 'agreed' and '25% 'strongly agreed. 10% were undecided.

"Content has improved…more relevant with each meeting"

Participants were given the opportunity to comment on which presentations they found to be most useful and relevant; with responses including:

- ROR study
- EMBRACE
- Exceptional responders program

Organisation of the workshop

All respondents (100%) found the workshop to be well organised, up from 96% at the March workshop. 55% 'agreed' and 45% 'strongly agreed.' One participant described the workshop as:

"*Well paced… adequate time for questions and reflection*"

Another participant commented:

"Very informative and enjoyable day"

Topics/ aspects most interesting/ useful

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

- Innovative ideas and new concepts
- Hearing about work being carried out by other Cooperative Groups
- GCCTI supported trial updates
- Discussion and feedback after each presentation
- The opportunity to network

Participants made the following comments as part of feedback:

"Valuable insight in to how other groups work as well as… ideas for collaboration"

"Opportunity to think more laterally"

Additional suggestions to enhance future workshops included:

Participants were asked for any comments in how workshops could be improved moving forward; the following suggestions were provided:

- Consider inviting a plenary speaker
- More incentives to run trials via GCCTI
- Engagement of Chairs of Boards of CTGs in workshops to get stronger engagement of groups in cross-group initiatives
- A stricter genomic-focus

APPENDIX I – WORKSHOP AGENDA

GENOMIC CANCER CLINICAL TRIALS INITIATIVE[1]
AGENDA

Title: Annual Workshop

Venue: Hotel Pullman, Sydney Airport (191 O' Riordan St, Mascot, NSW, 2020)

Details: Friday, 11th October 9.30am – 3.00pm

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 based on molecular characterisation including two or more tumour types and two or more CTGs. The October workshop will focus primarily on prioritising concepts for grant applications in 2020.

Time	Item	Presenter
9:15am-9:30am	**Arrivals and registration**	
9:30am-9:40am	**Welcome and introductions**	*Martin Stockler*
9:40am-9:50am	**Update on GCCTI achievements**	*Martin Stockler*
9:50am-11:15am	**Innovative ideas and new concepts**	
	• An update on ROR-study	*Caroline Ford*
	• PIK3CA inhibitors in endocrine responsive tumours	*Chee Lee*
	• Overview of the exceptional responders program	*Meg Barnet*
11:15am-11:30am	*Morning Tea*	
11:30am-12:30pm	**CTG studies and ideas: learnings, adaptation, collaboration**	
	• AGITG	*Mark McGregor*
	• MASC Ltd	*Anthony Joshua*
	• **Others**	*Open*

[1] The Genomic Cancer Clinical Trials Initiative (GCCTI) is a grant funded by Cancer Australia and delivered in partnership between NHMRC Clinical Trials Centre and ZEST Health Strategies.

12:30pm – 1.15pm	*Lunch*	
1.15pm – 1:35pm	**GCCTI supported trial updates and lessons** • AUTOCHECK • EMBRACE • SEQUITUR	*Sonia Yip* *Katrin Sjoquist* *Hao-Wen Sim*
1:35 pm – 2:50pm	**Ideas for new areas, molecular targets, and/or drugs for development**	*Group Discussion*
2:50pm – 3:00pm	**Wrap-up and Close**	*Martin Stockler*