ANZMTG Australia and New Zealand Melanoma Trials Group

ANZMTG Scientific Research Meeting

Thursday 9th October 2014 from 12:00pm to 5:00pm
Harry Perkins Institute of Medical Research,
Perth, Western Australia

ANZMTG Annual Scientific Meeting 2013 Minutes

Meeting commenced at 12:00pm

1. **Introduction and welcome**

ANZMTG Executive Committee Member, Professor Mark Shackleton (MS) welcomed all participants to the meeting (Appendix 1), and provided a brief overview of the schedule for the meeting.

2. **Review and discussion of ANZMTG's New Research Proposals**

Professor Mark Shackleton (MS) chaired this session.

i. NRP 02.14
Does knowledge of personal genetic risk of melanoma motivate behaviour change? A randomised controlled trial – Anne Cust

Anne Cust (AC) presented the new research proposal via teleconference. AC outlined primary melanoma prevention strategies such as sun exposure and sun exposure, and early detection as secondary prevention strategy. AC also stated that traditional skin cancer prevention has focused on identifying those at high-risk based on their phenotype, or targeted at everyone regardless of phenotype, and that social and behavioural theory suggests that the highly personalised nature of providing genetic risk information may be a more powerful motivator of behaviour change than standard approaches. We know of many genetic variants that influence the risk of developing melanoma. However, we don't know whether knowledge of personal genetic risk influences risk-reducing sun protection and skin examination behaviours.
AC outlined the hypotheses of the trial that i. participants with a high genetic risk for melanoma will decrease their sun exposure, increase sun protection behaviours and increase skin examinations; ii. participants with average or low genetic risk for melanoma will not change these behaviours. Consenting participants will have saliva sample collected, genotyping and risk calculation performed, and then randomised to either the intervention arm (genetic risk information+ genetic counsellor + general educational materials) vs control arm (General educational materials only). Participants are then followed up at 1 month and 12 months post-feedback. AC described the eligibility criteria but specifically highlighted the recent updates in the eligibility criteria including inclusion younger people in the target population now 18-59 years (instead of 50-74 yrs); and inclusion of low-risk phenotype (i.e. those with olive or darker complexion) and those of European ancestry. Recruitment will be via the electoral roll, with a recruitment target of 2,800 participants allowing for 15% drop-out. AC described the outcome measures including the use of a wrist band that objectively measures sun exposure. AC also noted the potential benefits and significance, and pointed out the potential harms to participants and steps to minimise these potential harms.
AC advised that the study has received a seed grant from Sydney Catalyst Translational Research Centre (Cancer Institute NSW), with recruitment planned to commence in Jan/Feb 2015.

Comment: Paul White provided feedback from the consumer reviewer that then it is possible insurance companies will specifically ask for a person's melanoma genetic risk which will disadvantage the participants.

ii. NRP 03.14

PET and Role of Imaging / Sentinel LN biopsy in Merkel Cell Carcinoma (PRISM) – A Prospective multisite evaluation of the roles of 18F-FDG PET and SLN mapping ± biopsy in the diagnostic work-up of MCC – Louise Emmett

Louise Emmett (LE) introduced Merkel Cell Carcinoma (MCC) and provided some figures on incidence, regional nodal disease behaviour, and prognosis. MCC is highly radiosensitive to both the local and regional sites while accuracy of sentinel lymph node biopsy (SLNB) is controversial and varies.
LE reported that there is strong interest across sites in Australia in collaborating to collect prospective data to develop recommendations for appropriate staging and management. Furthermore, LE gathered from recent multi-site teleconferences that many are in support of a prospective multisite imaging trial looking at management impact and diagnosis, a substudy trial in cT1N0 patients with radiotherapy based on SLNB results, and concurrently assessing Circulating Tumour DNA (and tissue banking) within the same prospective patient population. A number of Australian sites and Copenhagen University Hosopital in Denmark are interested.
LE described the aims of the study including the investigation of the management impact, diagnostic & prognostic value of 18F-FDG PET/CT in all stages of MCC. Other aims include assessment of utility and management impact of SLN mapping, determining diagnostic accuracy of SLNB, and collect circulating tumour DNA. LE presented the trial schema and study design. This is a non-randomized, prospective multisite design which aims to recruit 100 patients with histologically documented MCC. LE also outlined the collection of data, the treatment plan which will be left to the treating clinician's discretion except for the cT1N0 optional substudy, and other specific trial logistics. All the eligibility criteria have been defined.
LE outlined the requirements for the 2 stages of the study (F18 FDG PET CT and SLNB) including the forms which have been designed to ensure that the data needed is collected. A minimum of 2 year follow up will be required which will be composed of the collection of questionnaires completed by treating physicians, recurrences, therapies administered, biopsies, cTDNA (bloods), tissue banking, consideration of ultrasound on SLN site in patients not on T1N0 substudy without previous treatment or SLNB.LE also outlined the components and the questions that will be asked for the early-stage cTN0 substudy. A concurrent circulating tumour DNA concurrent translational research component was also described outlining the aims, endpoints, and practicalities of the biospecimen collection.
LE noted the requirements to run the study including support to develop the full protocol, database, follow up coordination, multi-site ethics submission, funding for imaging, RT substudy, and the translational component.

Question: What if pet scan indicated regional involvement?

Response: This is controversial and currently up for discussion

Comment: This is usually for elderly patients, and in a study the average was 74 years old.

Question: How many participatint would you need?

Response: The aim is to get a 100 participants and 40 participants from each state is feasible.

Comment: Victoria Mar commented that site would not normally do snb, accuracy with ultrasound.

iii. NRP 06.14

Predictive significance of circulating tumour cells (CTCs) and serum vascular endothelial growth factor (VEGF) in advanced melanoma patients treated with immunotherapy (Ipilimumab/anti-PD1/PDL1) – Adnan Khattak

Adnan Khattak (AK) provided an introduction regarding melanoma and the recent advances including the improved survival with BRAF/MEKi & immunotherapy (ipilimumab/anti-PD1/anti-PDL1). He pointed out that there is a lack of predictive biomarkers of who will respond to treatment. AK presented some background information on liquid biopsies based on recent data and papers published. He explained the process and advantages in investigating liquid biopsies, and pointed out how circulating tumours cells (CTC) are able to detect recurrences and resistance. AK stated that CTC number has been shown to correlate with clinical outcome in several cancers including breast, prostate, colon, lung cancer and melanoma presenting data from a few studies.

AK presented his proposal describing the aims of the trial which is to investigate biomarkers predictive of treatment response in patients with advanced melanoma being treated with immunotherapy, and to assess the feasibility of serial CTC (plus ctDNA) collection & quantification in Australian cancer centres. AK hypothesised that advanced melanoma patients with a high pre-treatment CTC count, serum VEGF levels and an increase in CTC count/VEGF levels while on treatment are less likely to respond to immunotherapy with a poor long term survival. Progression free survival, overall survival and objective response rate will be the outcomes of this study with exploratory endpoints including neutrophil/lymphocyte ratio, absolute lymphocyte count, and serum LDH. Patients diagnosed with advanced (unresectable stage III /stage IV) melanoma starting treatment with immunotherapy are the main target patients, and exclusion of Patients being treated with immunotherapy in the adjuvant setting or reinduction.

AK described the logistics of the trial including the sample collection timepoints depending on the treatment being administered to patients, and the CTC and VEGF analysis at Edith Cowan University Labs. AK explained the statistical components and also mentioned that the pilot study aims to recruit 75 patients. Current collaboration is between 3 WA sites and ethics approved in 2013. AK also advised the financial components of the study and the limited funds currently existing.

AK advised that funding, interstate participation CTC quantification techniques, using cf-DNA vs CTCs are the current challenges to this proposal. AK outlined the importance of this study which could potentially better identify patients most likely to benefit from novel agents, and potentially demonstrate cost effectiveness.

Comment: David Gyorki pointed out that it may be problematic to deny patients treatment based on high circulating cells.

Response: AK noted that these are the current findings they have collected and that they are not absolute like any biomarkers and taking into account the heterogeneity of melanoma tumours. It may be that we will need to work on CTCs and biomarkers to come up with the best treatment for patients. There are a lot of challenges to face and we need to work on what we currently have.

Comment: John Thompson noted that there have been so much work and studies which have been done on circulating cells over the years and experts seem to come short of conclusions as to the role of circulating cells on prognosis. What has changed?

Response: AK advised that the data he presented were PCR based and that there is a need to standardise the quantification of CTCs which can be laborious. He further pointed out that there is a need to comprehensively examine CTCs with tumour DNAs.

Comment: Mark Shackleton mentioned that there are already a lot of ways to disease progression including imaging.

Comment: Michael Millward advised that there is a potential in this method but may not be in the shorter term of the patient's journey. It may well be that imaging is the best way to detect progression but there is a potential added information from this type of testing.

Comment: Gerald Fogarty asked whether there are any studies / finding on the effect of surgery or radiotherapy on VEGF and CTC levels.

Response: MS noted that there have been some data published from the lung department at PMCC showing that CTC levels have increased after radiotherapy but the clinical implications are unknown. MS experience on mice studies also shows an increased on resected tumours.
MS also pointed out that it is worth looking at CTC-DNA vs CTC and whether one is better than the other including the diagnostic importance – at this stage this is not known.

Comment: Mel Zimman noted the latest technology being used to perform testings.

iv. NRP 05.14
A randomized controlled trial in T1N0 Merkel Cell Carcinoma of either radiotherapy to the primary site or wide local excision following diagnostic biopsy – Gerald Fogarty

Gerald Fogarty (GF) highlighted that merkel cell carcinoma (MCC) is a rare form of melanoma and Perth has the highest incidence in the world. GF also noted that there has never been a completed randomised phase III trial for this disease. A trial in France closed recruitment early due to SNB not able to be accounted for in the eligibility criteria. GF outlines the aims of the trial which is looking at the primary tumour outcome using surgery vs radiotherapy, and an optional study looking at the addressing the important component in MCC which is the nodes. GF described the referral pathway in the UK, where MCC studies are likely to flourish, from the GP, the dermatologists in the local hospital, and onto the on the Skin Specialist Multi-Disciplinary Teams (SSMDT). GF also reported the responses from 23 SSMDTs in the UK regarding the treatment patterns for the primary tumour and the nodes including surgery, radiotherapy and adjuvant treatment which provides the basis of doing a clinical trial.
GF provided an overview of the proposed study design which will compare radiotherapy and surgery for T1/T2 lesions after excisional biopsy. The sentinel node biopsy component can be performed as per local practice ie. observation, radiotherapy or surgery. The primary outcome measure of the study is loco-regional failure and GF has been heavily involved in the RT method of measure of this study. Data on recurrence at the primary site or regional nodal basin(s) and 5-year randomised clinical trial
GF provided some key trial logistics including the initial feasibility phase which will be conducted over 3 years and timelines of the study treatment administration. The study will involve a substudy including tissue banking, economic substudy in transit will be collected. The proposed sample size is 250 patients and assumes an event rate of 20%. The University of Birmingham will act as the trial sponsor.
GF stated that most institutions have gone past the point of equipoise for this concept but feels the trial will have a low chance of getting up and running in Australia. Based on the data that GF presented, he would support the conduct the trial and Perth is in the best position to conduct this alongside the institutions in the UK.

Comment: Michael Henderson commented that there are no differences particularly in morbidity between surgery and radiotherapy in treating primary tumour and therefore this is not an important question to address. He suggested that the fundamental question is to find out what tumour characteristics will be suitable for surgery with radiotherapy vs radiotherapy alone.

Response: GF drew attention to the differences in practices from the survey presented, particularly the nodal management for those who are willing to examine the question as the nodal status determines the outcome for these patients

Comment: Bryan Burmeister agrees with Michael Henderson that primary tumours should be treated surgically. For example, patients from the country will prefer surgery rather than travel to the main institutions to receive radiotherapy for several weeks.

Comment: Mark Shackleton wanted to know the differences in the figures between the virus associated MCC, and the UV-induced MCC, and whether patients with virus associated MCC are eligible to this study

Response: GF advised that this is a stratification factor in the study. In the UK, the proportion of virus associated MCC to none virus associated MCC is 80:20. Unsure of Australian figures.

Comment: MH noted that there was an excellent presentation from someone from Berlin during a recent meeting in Hamburg about MCC, and noted that the reason that more virus associated MCC are detected in Europe as compared in Australia is that the method of testing is much older in Australia. Although, we cannot be sure as to the reason. There are certainly more UV-induced MCC in Australia.

Comment: MS noted that clinicians may find that it is not worth asking this question but the point of view of consumers/patients will also need to be taken into account.

Consumer Feedback: Paul White (PW) mentioned that the lingo/abbreviations of the study was difficult to understand and partly because consumers do not understand MCC. The following questions were raised: What led to the researcher wanting to test one or the other of the treatments? What prompted the hypothesis? Why radiation or wide local excision? Why not both? (MS asked what do patients prefer?). One consumer can see the importance of evaluating and comparing treatments but thought it was standard treatment to do wide excisions – the radiation is the variable. PW noted that consumers preferred surgery at first and then use other means to treat later on.

v. NRP 01.14 / ANZMTG 02.14
An open label, single arm, phase I/II multicentre study to evaluate the safety and efficacy of the combination of Dabrafenib, Trametinib and palliative radiotherapy in patients with unresectable Stage IIIc and Stage IV BRAF V600E/K mutation-positive cutaneous melanoma (CombiRT) – Tim Wang

Tim Wang (TW) provided background on the role and effectiveness of BRAF/MEK inhibitors in BRAF mutant metastatic melanoma. Despite good initial response, the tumour eventually develops resistance to BRAF inhibitor leading to disease progression. Disease progression in clinically significant sites such as brain, bone, lymph nodes and soft tissue will benefit from local palliative radiotherapy (RT). TW presented data on the synergistic effect of the combination of RT and BRAF inhibitors. TW also presented case series to demonstrate the safety and toxicity profiles of the combination of these 2 modalities of treatment – increased acute skin toxicity, with no other increased acute toxicity, and 1 case of liver toxicity. TW also provided some background on the effectiveness of the combination of dabrafenib and trametinib.
TW outlined the study objectives of the trial with the primary objective to establish a toxicity profile for patients receiving dabrafenib and trametinib in combination with RT. Several objectives were also outlined including pain, overall disease response, local treatment response, and an optional translational objective involving tissue and serum collection. TW explained the dose and frequency of dabrafenib and trametinib, and the commencement of RT. The study aims to recruit 30 patients. Common Terminology Criteria for Adverse Events (CTCAE Version 3.0) will be used to assess toxicity will be used in this study. TW also described the rules for RT escalation, and the timing of RT administration. A table of assessment outlining the examinations, assessments, imaging, blood and biochemistry throughout the duration of the study was also presented.
TW reported that the study is now approved and sponsored by ANZMTG, study document and database development are in development, funding from GSK approved. Westmead, Melanoma Institute Australia Mater, Royal Prince Alfred Hospital, Peter MacCallum Cancer Centre, Princess Alexandra Hospital and other interested sites will participate. It is anticipated that the study will commence in 2015. TW further elaborated on the tumour biopsy, serum collection and biomarker timing.

Comment: Gerald Fogarty referred back to the cases presented and drew attention to the skin effects. He recommended that palliation radiotherapy be considered and that the dosing is revised eg. increasing the dosage instead of the higher dose straight away.

Response: TW noted that the higher dosage in the protocol are reserved for bulky unresecteable stage III disease. It was considered to start with a different dose level but there was no real evidence at this stage.

The cases that were presented were pre-clinical, and most of the clinical cases that TW has dealt with have only had cutaneous toxicities (<Grade 4). TW agrees that the aim is palliative radiation and this study is looking at a balance of local control and side effects. For most cases, the skin heals.

Comment: David Gyorki asked whether TW has looked restrospectively at the number of cases where a patient received concurrent vemurafenib with radiotherapy which shouldn't be hard to find and if it is not much more than 5 cases (reference to the 5 cases presented by TW), then the rationale of the current proposal should be considered.

Response: TW pointed out that it would be interesting whether the stopping period from the drugs will affect the occurrence of skin reaction and referred to a leptomeningeal disease case he encountered where cutaneous effects occurred after administration of drug.

Comment: Bryan Burmeister commented that there are a number of questions that need to be addressed including whether there is really a synergistic effect at tumour interface and the timing gap from cessation of BRAF inhibitor to commencement of RT. BB advised that the dosing should be adhered to whilst addressing the timing question.

Response: TW commented that the trial will collect the timing as to when each patients commence RT.

Comment: MS acknowledged that this trial will not answer the question regarding the synergy between the BRAFi and RT but is more of a safety study. It is worthwhile to know what the dosage is required for these patients.

Consumer Feedback: Paul White commended TW slides as he thought the presentation was clear. With regards to the review, one consumer stated that, "hI spent an easy 20 minutess just on the intro, googling words to understand what they are. It honestly made me feel ill equipt, and disappointed in myself for something I was trying to help you with". PW advised that this was a common theme for all the new concepts that were submitted.

vi. NRP 07.14
Stereotactic Radiosurgery versus Observation for patients with Melanoma brain metastases being started on a BRAF Inhibitor (ROMA study) – Gerald Fogarty

Gerald Fogarty introduced the study as the sequel to the ANZMTG 01.07 WBRTMel Trial. He explained the rationale of this concept and noted that melanoma brain metastases (MBM) control even more important now with increased overall survival with new systemic treatment. Stereotactic radiosurgery/radiotherapy (SR) is often given prior to any systemic drug therapy to MBMs. However, SR treated MBMs can still progress & give rise to side effects especially in long term survivors. Targeted therapies are active in BRAF-mutant MBMs with in-brain control having a median of 6 months without previous SR. Metastases that progress are usually those present at the beginning of treatment. GF stated that the aim of this trial is to determine the sequencing of RT and BRAF drugs. The trial involves what is essentially a standard treatment (SR up front) now.
GF outlined the study objectives looking at in-brain control of MBMs, quality of life, neurological death, neurocognitive function and health economics. The study will also look at abscopal effect with RT and systemic therapies. The hypothesis put forward is that RT can be safely delayed until in brain progression in oligo MBMs (5 or less). GF also presented the main inclusion and exclusion criteria, stating that newly diagnosed oligo-metastatic melanoma to brain (1 to 5 MBMs) about to be started or just started on new drugs is the target population for this study. This is a 1:1 randomisation, controlled, multi-centre, international clinical trial. GF mentioned some of the main assessments and requirements including MRI scans, SR timeframe, collection of bloods for immunological study, physical examnications, QoL, NCF, economic evaluation, and steroid use monitoring. GF presented a number of figures which will be considered

for the design of the study and his methods to calculate the current proposed sample size. He estimated that approximately 100 patients could be recruited to this trial.
GF reported that some of the failed screenings from the ANZMTG 01.07 WBRTMel Trial can be recruited to the ROMA study. All participating ANZMTG 01.07 WBRTMel Trial sites will be asked to participate including the high recruiting international sites. Peter Hersey will be asked to examine the immunological component of the study and ANZMTG will coordinate all trial activities. The trial can start as soon as possible and an application could be lodged for seed funding in February 2015.

Comment: Mark Shackleton mentioned that the brain metastases, particularly for the BRAF mutant group is a major clinical problem discussed at major neurological multidisciplinary meetings. Because of the high response rates, only those lesions in the anatomically sensitive areas are resected or treated with SRS and treated with BRAF inhibitors as quickly as possible and almost all responds.

Comment: Michael Millward agrees and this is what they do in his department. Michael mentioned that some patients may not benefit with upfront SRS, and he is not sure whether it is a good idea to combined BRAFi and immunotherapy concurrently - (GF clarified that it wouldn't be for the same patients but can be conducted for different patients in this trial).

Comment: MS further explained the current clinical scenario with the use of immunotherapies, BRAFi and PD-1 in melanoma brain metastases. It seems most patients will continue to have Surgery +/- radiotherapy upfront with further immunotherapy later on.
The real clinical question is when the response plateaus on imaging after the patient has an initial response on BRAFi. Should RT be administered or keep treating with drugs until a progression is seen? Treat with BRAFi with nadir response and then treat residual disease on imaging with radiotherapy, but these has its own challenges.

Comment: Bryan Burmeister advised that the SRS dosing should be standardised, and made suggestions on potential dosing to take into account neurological structures. The dosing of these two modalities should be ensured as therapeutic.

Consumer Feedback: Paul White read out the consumer reviewers' comments, "The aim is clear and logical, the background and briefing is a little confusing. This is a cut and paste affair - sorry: to be fair, i can't judge because I can't understand. I want to say yes, because that's the easy thing to do,and I can rationalise this because it's cancer research BUT, if we have limited funds and resources to allocate, I'd rather know how this compares to other trials." In addition with regards to trial risks, "It might be difficult to recruit patients when they are informed of the hypothesis. One possible question might be 'are you conducting this trial to confirm what your clinical experience is already demonstrating'. If the response is yes, then this may lead to patients being reluctant to join the trial. If I was a patient being asked to join this trial, I would like to read all available data/literature beforehand and to ask what has been the clinicians' experiences to date at the various treatment centres." On the main most reviewers liked the concept.

Overall Comments from the AMCA (Consumer Review) by Paul White

Comment: PW indicated that consumers found the lingo and the abbreviations very difficult during the process of review for all trials. PW advised that Investigators need to ensure that the studies are clearly articulated in a language that will be understood by non-clinicians, and that a lay summary needs to be submitted when these are reviewed by the consumers.
PW acknowledged that this is the first time this review is being conducted and reported on during the ASM and therefore a more structured approach to ensure consumers are able to properly review the materials will be considered in future.

Comment: Mark Shackleton acknowledged that the main message from the consumer reviews this year was the difficulty for the reviewers to understand the new concepts. He noted that it is important that the consumers and funders are able to readily read and understand the studies being proposed. He proposed a lay summary to be included in the reviews.

Comment: Louise Emmett advised that lay summaries and Participant Information Consent Forms are normally provided to ethics committees for ethics reviews and suggested that this could also be provided to consumers when conducting the review.

MS provided an overview of the review and approval process of the new concepts and thanked all the applicants of the new proposals for their presentations.

3. ANZMTG Approved Trials in Development Update

Doctor Donna Milne (DM), ANZMTG Executive Committee Member, chaired this session.

i. ANZMTG 01.12
Inguinal or Ilio-inguinal Lymph Node Dissection for patients with metastatic melanoma to groin lymph nodes and no evidence of pelvic disease on PET / CT Scan–A randomised phase III trial (EAGLE FM) – Chris Allan on behalf of Study Chair, Andrew Spillane

Chris Allan (CA) presented an update on the trial via teleconference, on behalf of A/Prof Andrew Spillane, EAGLE FM Study Chair. CA opened the presentation by outlining that currently there is variability in practice when handling metastatic disease to the groin with some institutions/surgeons performing inguinal lymphadenectomy (IL) and others an ilio-inguinal lymphadenectomy (I-IL). Rational based evidence is needed to inform practice in managing this disease. The null hypothesis of this trial is that patients with inguinal (superficial groin) LN metastatic melanoma with negative pelvic LN on PET / CT Scan having IL experience non-inferior disease-free survival compared with patients having I-IL, within a margin of non-inferiority of 7%.

Therefore in this study patients will be randomised to one of the two surgical arms with the primary endpoint being disease free survival (DFS), assessed at 60 months and a number of secondary endpoints which will include overall survival, distant diease free survival, regional recurrence free survival, imaging, morbidity and QoL, health economics components. CA also highlighted that there are 2 phases to the study – the first phase which aims to recruit 65 patients over 2 years, and a the total target of 634 patients in the following 3 years. The aims of the first phase are to evaluate the study documents, develop recruitment strategies and demonstrate active recruitment. Recruitment from the first phase will form part of the total target recruitment of the second phase, and data from the patients recruited during the first phase will be combined with the full phase and utilised in the final data analysis.

CA provided an overview of the study design and the study population, and outlined the inclusion and exclusion criteria, and study assessments of the study.

CA reported on the current progress of the trial. Multiple grant applications were submitted in 2014 with sufficient funding granted to conduct the first phase of the trial. 2 more grant results are awaited. CA highlighted that there is numerous support from many Investigators from institutions around the world from a feasibility survey that was circulated. The trial has completed all infrastructure arrangements and study documents including the protocol, CRFs, database, and recently received ethics approval. 3 Australian sites are in the start-up process and it is anticipated that the first patient will be recruited by the end of the year. All international sites will also be contacted to commence activities locally.

QN: The primary endpoint of this study is DFS in the pelvic region. Wouldn't a primary endpoint of overall survival be more appropriate?

QN: Have there been considerations to stratify on the use of adjuvant treatment as this may have an effect on the primary endpoint.

Response: It was noted that the trial will collect information on adjuvant therapy including targeted therapies, immunotherapies, adjuvant radiotherapy etc. so that these can be accounted for during the analyses.

ii. ANZMTG 02.12
A randomised controlled multicentre trial of imiquimod versus radiotherapy for lentigo maligna when staged surgical excision with 5mm margins is not possible, is refused or fails (RADICAL) – Gerald Fogarty

Gerald Fogarty (GF) presented the trial on behalf of Dr Pascale Guitera, RADICAL Principal Investigator. GF provided some background information on melanoma stating that Lentigo maligna (LM) is a form of melanoma in situ that occurs on exposed sun-damaged skin of elderly people, and that Australia has the highest incidence of LM in the world and with an aging population. GF advised that surgical treatment is the preferred modality of treatment, however, LM are often occurring close to the anatomical and facial features making it difficult to achieve clear margins. GF reported on the lack of class 1 evidence for radiotherapy or imiquimod and therefore there is a need for this trial to ensure there is an evidence based approach to treatment guidelines for LM in Australia and worldwide. An LM case was presented which used reflectance confocal microscopy to map the LM and radiotherapy as the treatment modality.
GF outlined the study hypothesis that the treatment of LM with topical imiquimod is superior to treatment with radiotherapy and will result in significantly improved cure rates and cosmesis. He pointed out the study primary endpoint being LM treatment failure (as determined by systematic biopsy) at 6 months following treatment. 266 patients over 3 years to receive either imiquimod or radiotherapy are need for the study. There are several substudies including the difference in the cumulative incidence of invasive melanoma; and utility of Reflectance Confocal Microscopy (RCM) compared with standard biopsy in diagnosing recurrence; an assessment of long-term LM treatment failure, quality of life, cosmetic outcomes and cumulative incidence of invasive melanoma within treatment fields.
GF reported that 4 Australian sites are interested to participate including Melanoma Institute Australia, NSW (lead site), Princess Alexandra Hospital, QLD, The Alfred Hospital, VIC, and Royal Adelaide Hospital, SA. There are interests received from Sir Charles Gairdner, WA and sites in the US and the UK. GF also noted that the trial has received sufficient funding to run the pilot study, and currently awaiting the results of the grant submissions from 2014. All infrastructure arrangements are in development and the pilot study is anticipated to start Q4 of 2014.

Comment: Victoria Mar commented that there may be some difficulties encountered for some centres to acquire an RCM for this study. It was noted that the study will be using RCM at some centres and dermoscopy on others. How will this difference be accounted for?

Response: Dr Guitera is leading the RCM use and will be conducting training at the Melanoma Institute Australia. Those participating in the study will be invited to ensure that the process is standardised.

Comment: Clinicians are reluctant to excise no more than a month.

Comment: Tim Wang noted that this is an important study which could change the practice management of LM.

iii. ANZMTG 03.12
Melanoma Excision Margins Trial - A phase III, multi-centre, multi-national randomised control trial investigating 1cm vs 2cm wide excision margins for primary cutaneous melanoma (MelMarT) – Michael Henderson

Michael Henderson (MH) presented the trial on behalf of Marc Moncrieff and Andrew Spillane. MH provided the background literature for this study with the conclusion that in 2009, Cochrane review advised that further randomised trials would be needed to clarify optimal excision margins for primary cutaneous melanoma and that current data suggest that 'narrow' margins produce similar outcomes to 'wider' margins so perhaps trials should compare 1cm versus 2cm margins. MH also provided some previous studies and analysis on QoL, morbidities, and cost-effectiveness which support the need for further evaluation of the margins in a clinical trial.
An overview of the trial inclusion and exclusion criteria was provided and it was emphasised that this would be a large study requiring more than 10,000 participants.
MH outlined the study details including the study objectives, hypotheses, design, stratification and randomisation, schema, inclusion and exclusion criteria, statistical considerations, and the assessments involved.
MH reported that there is dedicated funding available to support the pilot project for 1 year. The study is awaiting the result of the Cancer Australia submission for 2014. MH also noted that the UK application to run the study in the UK was rejected by NHS in 2013, but awaiting the result for the 2014 submission expected by the end of the year. The application will be crucial to support the full phase of the study. Submission to local HREC in May 2014 with the outcome expected in October 2014. All study documents have been completed with other infrastructure arrangements such as the online randomisation system and database system nearing completion. Endorsement for the trial has been received from SWOG, NCIC, and EORTC, and it is hoped that these groups will also be participating in the pilot phase of the study.

Comment: MH emphasised that the ANZMTG will be centrally coordinating the activities with Marc Moncrieff as the International Principal Investigator. ANZMTG have worked on all the study documents and infrastructure arrangements. Marc Moncrieff's submissions have received positive feedback and it is likely that his site in the UK will be activated soon.

Comment: Gerald Fogarty that it would certainly be great to have all the interested international sites and collaborators on board this study.

Comment: 1cm vs 2cm beyond equipoise?

4. Closed and Current ANZMTG Clinical Trials Update

x. ANZMTG 01.07
Whole Brain Radiotherapy following local treatment of intracranial metastases of melanoma - A randomised phase III trial (WBRTMel) – Gerald Fogarty

Gerald Fogarty (GF) opened with an overview as to why this trial is necessary, stating that WBRT is a controversial treatment, 30-80% of melanoma patients will develop brain disease and that this is the first single histology WBRT trial to be conducted. GF then went on to give an overview of the trial design, outlining the primary endpoint and inclusion and exclusion criteria. GF noted that there is continuous funding from Cancer Australia. There have been 151 patients randomised to date with the target recruitment of 200 patients. The trial is open at 27 sites throughout Australia, UK, US, and Norway, with new interest from other countries such as China, Brazil and Germany. GF highlighted the outcomes of the interim analysis which was performed at 12 months from randomisation of the 100th patient in December 2013. Parameters such as histopatholgy, intracranial failures from MRI scans, QoL and neurocognitive function, data quality, and safety data were reviewed. GF and the WBRT team were blinded to the study arms. GF reported on the demographics of the patients in the study.GF outlined that the Data Safety Monitoring Committee (DSMC) concluded that the trial is safe and that the data quality is excellent. The DSMC further recommended that the trial should continue to complete recruitment. GF provided an update on the recruitment and screening activities at each site, with Melanoma Institute Australia (NSW) and the Radium Hospital (Norway) leading the activities. GF reported that patients are greatly influenced by the advise they receive from their neurosurgeon which will affect their participation into the trial.

GF highlighted the recent recommendations by the American Society for Radiation Oncology (ASTRO) to avoid routine adjuvant whole brain radiotherapy to stereotactic radiosurgery (SRS) for limited brain metastases as they argue that randomised studies have demonstrated no overall survival benefit from the addition of adjuvant WBRT to SRS. GF noted that the basis used by ASTRO's claims are not based on high quality evidence such as a prospective phase III randomised trial. GF also noted that if these recommendations affect the WBRT trial, the opportunity to evaluate hippocampal sparing technique in reducing the effect on neurocognitive function will also be affected.

The presentation ran overtime and therefore nil comments or questions were raised.

xi. ANZMTG 01.09
A randomised trial of post-operative radiation therapy following wide excision of neurotropic melanoma of the head and neck (RTN2) – Bryan Burmeister on behalf of Study Chair, Matthew Foote

Bryan Burmeister (BB) presented the trial on behalf of Matthew Foote, Study Chair. BB initial came up with the study concept which was later handed onto Matthew Foote. He provided an overview of the trial and an update on the current progress of the trial. BB reported that the aim of this study was to determine whether radiotherapy after surgery improved local control of melanoma of the head and neck. The study has a simple two-arm design and the primary endpoint is time to in-field relapse. BB reported that currently there are 27 patients on trial and 15 Australian and 1 US sites involved in the study with interests in participation from Norfolk and Norwich University Hospital (UK) and MD Anderson (Texas, US). BB also reported that the full management of the trial is currently being transferred from TROG to ANZMTG. ANZMTG has completed the trial database and the online Randomisation System is nearing completion. The ANZMTG Operational team are working closely with Matt Foote in the next few months for a smooth management transition and to establish regular monthly meetings. The trial has received Cancer Australia funding support and BB reminded everyone of the eligibility criteria for patient recruitement.

Comment: BB suggested that the protocol should be amended to reduce the sample size based on the recent results from a phase II study published by MD Anderson and the units at Tampa, Florida. The current recruitment target is 100 patients over 5 years and it is hard to assure this can be met within the planned timeframe. BB would suggest that the sample size be reduced to 50 patients as suggested by the recently published phase II study.

xii. ANZMTG 02.09
Vitamin D Following Primary Treatment of Melanoma at High Risk of Recurrence (Mel-D) – John Thompson on behalf of Study Chair, Robyn Saw

John Thompson (JT) presented the trial on behalf of Robyn Saw, Study Chair. JT outlined the rationale for the trial and provided an overview of the design. JT reported that the trial achieved recruitment target in early September 2014 after it was activated in December 2010. JT also reported that safety reviews have been conducted and confirmed that the study is able to continue with no changes as no issues were raised regarding safety. The trial is now on follow up until September 2016 with good quality follow up data and excellent study drug compliance. JT also highlighted that the protocol manuscript has been accepted to be published by BMC Cancer online. An interim analysis is planned at the end of 2014 / early 2015 when approximately 50% of the patients have completed follow up. A proposal will be put forward for this trial to move into a Phase III study, if favourable outcomes are achieved in the phase II interim results. The phase III proposal will hypothesise that the addition of oral high dose vitamin D therapy in patients who have completed primary treatment for melanoma and are at high risk of recurrence will prolong time to recurrence, improve overall survival at 5 years, and be both safe and tolerable.

Nil comments or questions were raised.

xiii. ANZMTG 01.13 A randomised controlled trial of a psycho-educational intervention for melanoma survivors at high risk of developing new primary disease. – Anne Cust

Anne Cust (AC) presented the new research proposal via teleconference in the morning. AC provided a quick overview of the study. AC explained the psycho-educational component (booklet) and the telephone-based support sessions facilitated by a clinical psychologist, aimed at addressing fear of cancer recurrence and fear of developing new primary disease in melanoma survivors. The newly developed psycho-educational booklet integrates the best available evidence for supporting melanoma patients, using a format that is easily understood and accessible. She reported on the changes to the telephone-based support sessions due to the time and resources for both the psyschologists and the patients – which seemed to be more practical. Patients with stage 0/I/II melanoma attending the high risk clinics are available to join the study. The recruitment target is 216 patients. AC reported that the study is recruiting at 3 High Risk Clinics including Melanoma Institute Australia, Royal Prince Alfred Hospital, and Newcastle skin check with Westmead starting soon. 200 patients have been consented with 163 randomised to date. AC advised that there have been very minimal withdrawals from participation, and that the follow-up for the primary outcome (6 months) will continue until the end of 2015. The longer term follow up will continue until 2016.

Comment: Mark Shackleton asked AC to provide an quick overview of the magnitude of the problem that is being addressed by this study.

Response: AC advised that AC and Nadine Kasparian, Co-Investigator of this research, found that 70% of patients diagnosed with melanoma had some fear of melanoma recurrence and that these patients felt that they had unmet needs. AC also reported that these patients felt different to patients who had other forms of cancers and felt that they were not able to use the resources made available by Cancer Council. Initially, it was thought that only patients with fear of recurrence would be the target sample for the study but it was decided that the study should be rolled out to all patients who have had melanoma and to particularly examine some of the secondary endpoints such as anxiety, depression etc.

v. Improving Consumer Engagement in ANZMTG Research – Paul White

Paul White (PW) presented on the collaboration between ANZMTG and Consumers working together to improve awareness, research and funding into melanoma. He presented as the Australian Melanoma Consumer Alliance (AMCA) Committee Chairman and ANZMTG Executive Committee Member. PW introduced the members of AMCA which consists of the core Melbourne Melanoma Project (MMP) Members and a number of invited participants from states across Australia. PW reported on an ANZMTG led meeting/workshop which brought together all AMCA members to discuss and develop a broad range of goals to be achieved.
PW then elaborated on the progress to date:

- Development of centralised information portal for patients, family members and carers through the ANZMTG website and the Melanoma Institute Australia ClinTrial Refer Melanoma application
- Encourage researchers to seek consumer input into trials and increase the number of consumers reviewing trial documents through submission of study documents for consumer review. ANZMTG Standard Operating Procedures will mandate the review process for new protocols drafted.
- Increasing the knowledge of consumers so that they are more confident to be involved in research. Funds have been made available to allow consumers to attend relevant meetings. Future workshops will be conducted to train consumers to review synopses and protocols.
- Melanoma Patients Australia has impacted upon a broad range of AMCA aims by establishment of ties through international and national counterparts.
- Achievements by the Australian Melanoma Research Foundation (AMRF)

PW also provided an insight to future plans such as the facilitation of consumer and research engagement through organised workshops so that both can learn from one another. In addition, there is a need to raise melanoma awareness and lobby state and federal government regarding key issues.

PW is continuing to push for funding on these melanoma consumer activities. At the moment, the voice of melanoma is highly being recognised.

Comment: Mark Shackleton congratulated and encouraged the work of the consumers as he recognised that the research work and finding out new treatments for diseases are results of the drive from the consumer activities.

Appendix 1:
ANZMTG 2014 Research Meeting Attendance Record

No.	Title	First Name	Surname	Institution
1	Ms	Fiona	Baldacchino	Sir Charles Gairdner Hospital
2	Dr	Adam	Broad	Barwon Health
3	Prof	Bryan	Burmeister	Princess Alexandra Hospital
4	Dr	Anne	Cust	University of Sydney
5	A/Prof	Louise	Emmett	Melanoma Institute Australia
6	Prof	Gerald	Fogarty	Melanoma Institute Australia
7	Ms	Claire	Haworth	Sir Charles Gairdner Hospital
8	Prof	Michael	Henderson	Peter MacCallum Cancer Centre
9	Prof	Meenhard	Herlyn	The Wistar Institute
10	Ms	Val	Jakrot	Melanoma Institute Australia
11	Ms	Mary-Anne	Kedda	Sir Charles Gairdner Hospital
12	Dr	Adnan	Khattak	Royal Perth Hospital
13	Mr	Alan	Lucas	ANZMTG
14	Ms	Sonia	Mailer	Melbourne Melanoma Project
15	Dr	Victoria	Mar	The Alfred Hospital
16	Prof	Michael	Millward	Sir Charles Gairdner Hospital
17	Dr	Donna	Milne	Peter MacCallum Cancer Centre
18	Ms	Libby	Paton	ANZMTG
19	Dr	Mark	Shackleton	Peter MacCallum Cancer Centre

20	Ms	Elizabeth	Smith	Melanoma Institute Australia
21	Dr	Peter	Smith	Western General Surgery
22	Prof	John	Thompson	Melanoma Institute Australia
23	Mr	Chris	Vearing	Merck Sharpe & Dohme Australia
24	Dr	Tim	Wang	Westmead Hospital and Nepean Cancer Care Centre
25	Ms	Nicola	Ware	Melanoma Institute Australia
26	Mr	Paul	White	Australian Melanoma Consumer Alliance
27	Ms	Anne	Woollett	Barwon Health
28	Ms	Aylin	Yahya	Sir Charles Gairdner Hospital
29	Prof	Mel	Ziman	Edith Cowan University
30	Ms	Lilie	Herawati	MSD Australia
31	Ms	Elizabeth	Kernutt	Sir Charles Gairdner Hospital
32	Dr	Elin	Gray	Edith Cowan University
33	Dr	David	Gyorki	Peter MacCallum Cancer Centre
34	Dr	Mike	He	Calvary Private Clinic, Canberra
35	A/Prof	Nikolas	Haass	University of Queensland
36	Prof	Graham	Mann	Melanoma Institute Australia / Westmead Millenium Institute

ANZMTG 2014 Research Meeting Apologies Record

No.	Member name	Institution
1	Rosemary Harrup	Royal Hobart Hospital
2	Rachael Morton	University of Sydney
3	Bill McCarthy	University of Sydney
4	Alison Button-Sloan	Consumer (QLD)
5	Andrew Spillane	Melanoma Institute Australia

6	Marc Moncrieff	Norfolk & Norwich University Hospital
7	Matthew Foote	Princess Alexandra Hospital
8	Richard Martin	Waitemata District Health Board (Northshore and Waitakere),
9	Robyn Saw	Melanoma Institute Australia
10	Victoria Steel	ANZMTG
11	Vidoslav Balnozan	ANZMTG
12	Charles Balch	John Hopkins Research Network
13	Grant MacArthur	Peter MacCallum Cancer Centre
14	Claire Haworth	Sir Charles Gairdner Hospital