ANZMTG Australia and New Zealand Melanoma Trials Group

ANZMTG Scientific Research Meeting

Wednesday 20th November 2013 from 10:00am to 4:30pm
Russell Strong Auditorium, Princess Alexandra Hospital
Brisbane, QLD, Australia

ANZMTG Annual Scientific Meeting 2013 Minutes

Meeting commenced at 10:30am

1. **Introduction and welcome**

ANZMTG Chairman, Professor John Thompson (JT) welcomed all participants to the meeting (Appendix 1).

2. **Closed and Current ANZMTG Clinical Trials**

Professor Bryan Burmeister (BB) chaired this session.

i. ANZMTG 01.02 Adjuvant Rx

A randomised clinical trial of surgery versus surgery plus adjuvant radiotherapy for regional control in patients with completely resected macroscopic nodal metastatic melanoma – Michael Henderson

Michael Henderson (MH) gave an update on this trial, which had closed. The primary endpoint of this study was time to lymph node field (LNF) relapse. The results were similar to the interim analysis, which showed a significant reduction in the risk of LNF relapse in patients who underwent radiotherapy (15% difference in cumulative incidence of relapse when compared to the observation arm).

Reporting of radiotherapy related adverse events (AEs) indicated toxicity was minimal and typical of radiotherapy treatment. A difference in lymphoedema severity was shown between those patients on the observation arm and those who had radiotherapy added to their surgery, with a 7% increase in limb circumference on the observation arm and a 14% increase in patients on the radiotherapy arm.

At the 2012 ASM quality of life (QoL) data had not been reviewed. However results were available for discussion at this meeting. Completion of the Fact G and Regional Symptomology Questionnaire revealed that although graphically the observation arm seems to do a lot better, there is not a significant difference in the results, although recovery was slowed by having radiotherapy with the surgery.

MH suggested a number of further studies that should be considered following on from this study; molecular predictors, inguinal vs Ilio-inguinal dissections, cervical lymphadenectomy and extent of surgery, whether less aggressive surgery is actually more beneficial to the patient overall.

It was noted that a lot of QoL data had been obtained through the trial and that a separate paper should be written on this alongside the radiotherapy quality assurance performed for the study.

QN. Patients undergoing salvage radiotherapy on the observation arm look to do as well as those initially randomised to receive radiotherapy upfront. Does this argue against radiotherapy? The confidence interval of the results is quite wide and so caution should be taken when interpreting them in this way. This trial was commenced in an era when targeted therapies were not available and now, even though there are systemic therapies that exist to resolve distant disease, we still need something for local control of the disease.

It was suggested that the results of the same trial in this era may look slightly different. The median time to developing LNF relapse was 7 months and those that died prior to this median marker had metastatic disease. Current systemic therapies may have meant patients in this trial would have lived longer, therefore more events may have been captured and perhaps these would have inflated the median time to LNF relapse

ii. ANZMTG 01.07
Whole brain radiotherapy following local treatment of intracranial metastases of melanoma – A randomised phase III trial and overview of current substudies – 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 reported that a feasibility study was conducted before moving into the Phase III study currently accruing patients and that from the feasibility it was determined that survival of patients was approximately 50% at 12 months and that recruitment (which it had been thought could be difficult) was achievable.

Currently the trial has 21 sites open across the globe, with further sites potentially opening in the UK, Brazil, China, Germany and Tasmania. Melanoma Institute Australia, The Radium Hospital and Princess Alexandra have all been crucial in recruiting a large proportion of the 130 patients on study so far. GF stated that there are a number of challenges to running the study including reaching the patients, problems and delays in patient referrals which mean that stipulations of the inclusion/exclusion criteria are not met, new radiotherapy technologies (hippocampal sparing is now available and is taking place for patients treated through The Mater Hospital), changes in staffing at sites and keeping the sites engaged. Some of which may be attributed to the current slow recruitment rate.

GF commented that there are a large number of QA measures being followed to ensure high quality data is obtained from this study and that data is being further utilised for a number of sub studies.

QN: To what extent does salvage therapy in the control group make analysis difficult? Salvage treatment will not have any impact on the endpoints, as salvage therapy would not occur until new disease is seen.

iii. ANZMTG 01.09
A phase III trial of postoperative radiation therapy following wide excision of neurotropic melanoma of the head and neck – Matthew Foote

Matthew Foote (MF) 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. MF reported that currently there are 20 patients on trial and 14 sites involved in the study with recent interest in participation from Norfolk and Norwich University Hospital (UK) and Memorial Sloan-Kettering (US). In the past year there has been a protocol amendment approved in Victoria and Queensland (yet to be approved in New South Wales) and an open letter sent to investigators and the trial featured in the TROG newsletter in an effort to raise awareness of the study. MF provided a reminder as to the inclusion and exclusion criteria and stated that despite not being successful in obtaining NHMRC funding, he is confident the trial may receive Cancer Australia funding.

Comment: GF suggested to MF that if another protocol amendment was to occur it would be worthwhile building in an interim analysis to take place at 50 patients. This may answer the question and accrual to 100 patients as currently required may not be necessary.

QN: Found in my experience that neurotropism is found at recurrence and then when the primary report is reviewed again it is discovered that neurotropism was present. Is there a standard for the

histopathological reports? Prof. Richard Scolyer is performing central review of histopathology reports to ensure all trials participants are eligible. We do need neurotropism to be identified within the report for the primary for the patient to enter the study.

QN: Why was a 5mm margin chosen? Sites felt they would not be able to randomise to the protocol if the microscopic margin was not defined and therefore this margin was put in place to ensure more sites came onboard.

iv. ANZMTG 02.09
Vitamin D following primary treatment of melanoma at high risk of recurrence: a pilot placebo controlled randomised phase II trial – Robyn Saw

Robyn Saw (RS) outlined the rationale for the trial and provided an overview of the design. RS stated the aims of the study are to see if recruitment is achievable, assess compliance of patients, observe the side effects and confirm if oral vitamin D achieves a serum vitamin D level of 80nmol/L or more. Currently 58 patients have been randomised, with 16 off trial and 42 in follow up. There has been increased activity this year as pathology reports are now reviewed to ensure no potential patients are missed. RS reported that there have been no SAEs, only mild AEs, high compliance and that patient feedback regarding the study has been positive. A manuscript in relation to the study is about to be submitted to Biomed Central Cancer and an interim analysis is due to take place next year once half of the patients accrued have completed the study. A proposal will be put forward for this trial to move into a Phase III study.

QN: Do you look at the vitamin D levels on a regular basis and is there accountability for geographical location of the participant? The vitamin D trial is blinded and although reviewed by a designated team member for safety, they have not been reviewed by all and so nobody has looked at the data with regards to vitamin D and the relation to geographical location.

v. ANZMTG 01.11
Phase I study of safety and immune effects of an escalating dose of autologous GD2 chimeric antigen receptor-expressing peripheral blood T cells in patients with metastatic melanoma – Michael Brown

The CARPETS trial was not formally presented. BB read out the overview of the study within the ASM booklet, stating that since last year the case report forms (CRFs) and database have been developed and it's confirmed the trial will commence once the TGA Clinical Trial Exemption Form is approved.

vi. EORTC QoL Melanoma module

No presentation was given for this study. BB read out an excerpt from the ASM booklet stating that MELQOL was completed in 2010 and that a study following this, named MELMOD, is currently underway and has accrued half of the required participants.

QN: Are the team still looking for people to participate in MELMOD? Yes, however this is not funded. Clinicians are to provide the forms to the participants and ensure they are returned. The ethics submission for this is not laborious and so that should not be an obstacle for participation.

ACTION: Julie Winstanley is to be advised that an email should be circulated to garner some interest in the study and get further sites onboard.

3. ANZMTG Approved Trials in Development

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

Chris Allan (CA) opened the presentation by outlining why this trial is necessary; 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. 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 QoL and health economics components.

The null hypothesis of this trial is that IL has a non-inferior disease free survival compared with I-IL, except where there is a difference between the two arms in median DFS of 4.3 months. If I-IL patients have a DFS of >4.3 months then this indicates that I-IL is the superior method of groin disease management.

An overview of the inclusion/exclusion criteria were presented, followed by a description of the lymphoedema prevention substudy, in which after surgery patients will be randomised to receive standard care or standard care plus early intervention involving the use of compression garments, lymphatic drainage and exercise.

CA highlighted that 634 participants will be required for the main study and 250 for the substudy. It was stated that feasibility surveys indicate interest of 45 institutions from 18 countries, with an expectation that half of the required patients would come from Australia, a third from the UK, a fifth from Europe and the remainder from other regions.

Unfortunately NHMRC funding was not successful this year. An application for funding will be resubmitted in 2014 which will focus on the primary endpoint, as the secondary endpoints may have over complicated the trial for reviewers. The lymphoedema substudy may also be separated out from the main study. News is being awaited regarding Cancer Australia and Cancer Council funding and it was noted that ANZMTG are able to request international sites seek opportunities for local funding of the trial.

QN: It's hard to understand how within the trial it is expected to see an improvement in DFS when this is impacted by the genetic make-up of the melanoma as opposed to the intervention. Also, people have expressed concern with the number of patients required for the primary endpoint, has there been any support in using a secondary endpoint as a composite endpoint so that less numbers are required? The DFS relates to pelvic relapse, we will look at the rate of pelvic nodal failure and expect this to be higher in those patients who have only had an inguinal dissection. Secondary to this we want to ascertain if patients are worse off by having two operations; is the morbidity better or worse in this situation?
Comment: I agree that these are good questions, but the vast majority of relapses will be distant and therefore this will dilute the DFS.
Comment: I disagree (that this will dilute the DFS endpoint). This should be designed as in the adjuvant trial where you capture the first site of relapse, so in this study relapse of the pelvic region is likely to be first and this is what should be looked at. However, DFS is also important because it may be interesting to see whether periaortic relapse rate will be delayed by having a pelvic node dissection.
QN: Would it then be important to look at isolated/regional relapse?
Comment: It would have to be contiguous nodal relapse.
QN: I did a study previously using CT scan which picked up a significant (20 – 35%) false postitive pelvic involvement when a patient had inguinal involvement. Is this being looked at in the study?
Comment: Yes it is built into the study well.

Comment: I have seen some perform pelvic dissection when there is no obvious pelvic involvement, which is quite a big procedure. I think QA in this study will be a big issue,particularly when you're doing operations and know that itis not actually going to retrieve numbers of nodes involved melanoma. I like the idea of the study but have conflicting feelings.
Comment: I like the idea of a randomised trial looking at overall survival. Our internal figures and cases show a pelvic recurrence of 5%, and another 5% who will have distant recurrence elsewhere, and another group who will have systemic recurrence and no pelvic recurrence, therefore, there will be more patients with systemic recurrence than pelvic recurrence. The endpoint will then be tricky because there will be a higher T3 survival in the pelvic node dissection by about 5%. The issue then is the number required for the endpoint that we want which is OS, particularly now with the emergence of new therapies.

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

GF explained the aim of the study is to compare the efficacy of imiquimod versus radiotherapy (given at a maximum dose of 60Gy in 30 fractions) for lentigo maligna that has been mapped with reflectance confocal microscopy (RCM). Pictorial examples of treating lentigo maligna with radiotherapy and imiquimod were shown and GF highlighted the benefits of involving RCM in this study, stating that it allows accurate mapping of the whole lesion, allows for early detection of disease and decreases the need for biopsies.

The primary endpoint of the trial will be the proportion of patients with lentigo maligna treatment failure, as determined by RCM, at one year following treatment. A total of 266 patients will be required to power the study, with four sites currently selected to take part based on RCM availability and interest from international centres.

NHMRC funding was unsuccessful this year and will be resubmitted next year, possibly with a revised hypothesis that may make the trial more attractive to reviewers.

QN: What if there are atypical melanocytes in the biopsy, as this does not suggest lentigo maligna?
Pascale has worked with Prof. Richard Scolyer to outline the features of lentigo maligna when observed in a biopsy or via RCM. This will be used to determine what is lentigo maligna and what are atypical melanocytes; it is appreciated that is a difficult thing to get right.

QN: Can I confirm how narrow the margin is for excision, as in the booklet it states surgical margins of excised lesions is to be <1mm? Yes that is correct, we need to ensure some disease is still present in order for it to be detectable by RCM

iii. ANZMTG 03.12
Melanoma Excision Margins Trial (MelMarT) – Michael Henderson

MH stated that historically wide excision is used to remove melanoma. Currently there is no consensus as to the optimal excision margins for primary tumours, with a Cochrane review suggesting the need for a trial in this area. MelMarT will compare 1cm vs 2cm margins in primary cutaneous melanoma, with a dual primary endpoint point assessing whether reducing the excision margin impacts upon local recurrence rates and melanoma specific survival. MH highlighted that margins are an important consideration in tumour excision, as with a wider margin there can be increased morbidity and reconstruction. It was stated there is increasing evidence that the majority of local recurrences represent in-transit recurrence or progression of microsatellites, suggesting smaller margins would not necessarily impact local recurrence rates in a negative manner.

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.

Endorsement for the trial has been received from SWOG, NCIC, EORTC and ANZMTG. However it was unfortunately not successful in obtaining NHMRC funding this year and will be resubmitted next year. MH stated that to improve the submission consideration is being given to including translational programs, a stronger health economics component and reducing the cost of the study. The follow up is intensive and requires a large amount of funding.

QN: The most intensive part of the follow up is the QoL which requires many resource hours from nurses, however if this aspect is ignored it draws criticism. Can the cost be reduced? Potentially a web based QoL could be considered and the statistics could be reviewed to see if reliable results could be obtained for the QoL and health economics component using a smaller population for these components.

QN: Could a five year follow up be considered? It is true that not everyone would require a ten year follow up. However without this there is no way to pick up recurrence as it is not captured in the cancer registry databases.

QN: How much selection bias will there be? For example if someone has melanoma on their face they may not be willing to enter a study where they could be randomised to wider margin. This bias is acknowledged. It has been suggested that there could be bias towards entering patients with melanoma on the trunk, clinicians may not want to randomise those with a primary of the head, neck or limb.

Comment: Consider submitting the trial to the NHMRC as a pilot study of 1000 patients. Accrue participants quickly within two years and use this to develop the best techniques for recruiting patients and then progress the trial.

iv. ANZMTG 04.12
Radiotherapy followed by selective nodal dissection for high volume regional melanoma (REFORM) – Matthew Foote

MF provided an overview of the single arm, Phase II trial looking at the impact of radiotherapy being given prior to surgery in patients with bulky and/or inoperable stage IIIb/IIIc disease. Patients with stage III, high volume disease have a high risk of relapse, with many relapsing in the first year. It is hypothesised that pre-operative radiotherapy will be effective in the nodal management of these patients. The primary endpoint for the study will be to show that radiotherapy followed by dissection is both safe and efficacious using the measurement outcome of a one year major complication free nodal control rate.

Recent amendments to the study include addition of QoL C30 and LymQoL for the arm and leg, and the use of novel PET predictors which includes MTV (metabolically active tumour volume) and TLG (Total lesion glycolysis).

Despite this now being an era of systemic therapies it is still believed that this trial has scientific relevance and both Princess Alexandra Hospital and Sir Charles Gairdner Hospital are interested in participating and accruing some of the 35 patients required.

The study currently has no funding. The Princess Alexandra Foundation has been approached for $75,000 and whether or not funding will be given will be known in December 2013.

QN: What's your experience in this group of patients? There are two subsets, one group that has one large deposit and one subset with multiple deposits. It is anticipated that the latter will do worse, although both groups are a challenge.

QN: Should you consider shrinking the nodes down with something that has an impact on other disease too, such as PD-1? It could be possible to do an adjuvant study with industry or once some newer therapies are approved you could set up your own investigator lead study incorporating these. Both radiotherapy and systemic therapies are effective against this disease. Why not perform radiotherapy upfront and then keep the systemic therapies for relapse? Overall response to radiotherapy in soft tissue melanoma is 80% which is better than many systemic therapies.

Comment: We need to discuss radiation sensitivity and consider biopsying melanoma, irradiating it and seeing the radiotherapy response. This nodal disease can form part of that but we can also look at other areas such as the lung and liver.

4. New Research Proposals

i. NRP 01.13

112195: A randomised controlled trial with embedded biological discovery and validation leading to the rational treatment of people with the rare virus-associated aggressive skin malignancy, Merkel Cell Carcinoma (MCC) – Gerald Fogarty

GF outlined the characteristics of Merkel Cell Carcinoma and gave an overview of a three arm trial with a double randomisation approach that was initially being considered by the UK. The three arms being considered in the UK were a biopsy followed by radiotherapy of the primary and surrounding tissue versus Combined Modality Treatment with up to 10mm marginal excision and radiotherapy to the surrounding tissue versus a wide local excision with 20mm circumferential margins. GF was asked for advice regarding the trial design and suggested that two separate trials be developed, the first looking at the primary site and the second looking at regional disease. GF commented that the most controversy lies in the wide local excision versus radiotherapy and therefore this should be looked at in the first study, then a second trial be developed regarding treatment of nodal disease.

GF worked with Lauren Haydu (LH) to determine a reasonable trial design and a sensible number of patients, determining that for a superiority trial of radiotherapy versus wide local excision only 76 patients will be required to power the study.

GF outlined the pros and cons of such a trial, highlighting that it would be advantageous to solve an existing problem and to engage dermatologists and cancer clinics. GF noted some possible obstacles would be funding, a clash with the TROG MP3 trial and the feelings of some radiation oncologists who might not be happy to randomise to this.

QN: Would this study be for T1 patients only? GF confirmed this was correct which lead to it being stated that there would in that case be no overlap with the TROG MP3 study, as that is for T2 only. It was then commented that nine out of ten cases of Merkel Cell Carcinoma would be suitable for this study over MP3.

QN: Is there not already enough data that we know the answer as to whether radiotherapy is more beneficial than wide local excision? Yes, there is. However we are lacking the randomised trial evidence to prove this

Comment: It will be difficult to get consistent information regarding margins in the wide local excision group, as everyone has a different practice. It will be necessary to mandate a certain margin around the Merkel Cell Carcinoma.

Leading on from the above comment, GF enquired as to what a defined margin would be for a 10mm lesion, to which a member of the audience stated it was 20mm. GF then stated that based on this perhaps lesions eligible for the trial should be 10mm or less as opposed to the currently proposed 20mm.

ii. NRP 02.13
A randomised phase II study of immunotherapy with DPCP treated autologous melanoma vaccines – Peter Hersey

Peter Hersey (PH) commenced the presentation by describing an open label, single arm study in which 54 patients were given DNCB treated autologous melanoma vaccines. The results of which showed a median overall survival of 36 months when data was compared to a control group via matched pair analysis. Garnering this information it was decided to move forward with this study using DPCP instead of DNCB. The decision for this was due to DPCP being routinely used, there being no patent and it being shown to be effective in treating disease.

The trial is designed as a randomised, phase II study in which all patients are sensitised to DPCP. Eligible patients are then randomised to immunotherapy with autologous DPCP melanoma vaccine or normal follow up. A total of 88 patients will be required to power the study. However if after 14 patients complete two years of follow up and fewer than 6 are alive, the study will be terminated.

PH quelled potential questions as to whether this study would be worthwhile in an era of treatments such as anti-PD1 and anti CTLA-4, by stating that 30% of patients do not respond to checkpoint inhibitors and that where a response is seen, only 11% of patients show a complete response to these treatments. PH acknowledged that DPCP autologous vaccines are seen as a low cost approach to increase immune responses against tumour cells and that once potency is established, conduction of a Phase I study with an anti PD1/anti PD-L1 drug should take place. Combination treatments are the future in combating melanoma.

QN: Will people that have failed BRAF live long enough for you to see a response and in these instances where a patient has failed BRAF, would you not offer PD1 instead of a vaccine given this late stage disease? Yes, they would live long enough and with regard to treatment options we are in a field that constantly changes and we need to offer what is best for the patient at the time. There is room for this vaccine to be an option.

iii. NRP 03.13
Prospective Randomized Trial Comparing Complex Decongestive Therapy (CDT) Alone vs CDT and Vascularized Lymph Node Transfer vs CDT and Adipofascial Free Flap in Treatment of Secondary Lymphoedema – Sydney Ch'ng

Sydney Ch'ng (SC) outlined a proposed three arm trial in which a range of treatments would be compared for secondary lymphoedema. Patients would be randomised to complex decongestive therapy (CDT) or CDT with vascularised lympho node transfer (VLNT) or CDT and adipofascial free flap treatment.

Transferring lymph nodes to areas required restores lymphatic pathways and lymph nodes produce VEGF-C to encourage lymphangiogenesis, giving a cumulative effect over time. However there is some controversy as to whether surgical intervention such as VLNT or adipofascial free flap treatment provides any greater improvement than the non-surgical CDT, which is why this trial is needed.

SC gave an overview as to the primary and secondary outcomes of the trial, stating that calculations regarding the sample size population are still being performed, however an estimate of 50 patients per arm is likely to be accurate.

SC commented that Macquarie Hospital (NSW), St. Vincents (VIC) and The Alfred (VIC) have shown an interest in the study and that MIA would be a suitable candidate site.

QN: Entry into the study is at a minimum of one year after surgery. What about those patients who have endured lymphoedema for a long length of time and tried CDT previously, they may not be happy being

randomised to the first arm of the study and clinicians may not have equipoise, they may want patienst to receive the new treatments? People in the first arm may see a similar outcome as those patients in arms 2 and 3 with good compliance; their results might be equally as good.

iv. NRP 04.13
Large multicentre observational study to monitor and improve routine imaging of volatile naevus for patients with advanced melanoma – Peter Soyer

Peter Soyer (PS) opened his talk by describing the physiology volatile naevi and showed evidence of naevi altering in a patient who was taking part in a study trialling dabrafenib with or without trametinib. Testing of the naevi showed that those involuting were BRAF mutant and those that did not change were BRAF wildtype.

PS hypothesises that changes in naevi of different patients are due to differences in the germline phenotype and he would like to investigate this by using body photography/biopsies, suggesting that imaging be performed at Baseline, appropriate therapies then given and photography/biopsies repeated 3 monthly up to a period of two years.

QN: This is an interesting study, would you want to collaborate on this? Do you need large numbers? Not sure with regards to the numbers required, but it would be beneficial to collaborate with other centres.

QN: Would it be worthwhile monitoring naevi in people without disease too? It is documented that naevi disappear with age. There is already good documentation as to the behaviour of naevi in those people without disease.

v. NRP 05.13
ANZMTG / POCOG collaboration: 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) reminded the audience that guidelines exist to say that psychological support should be available to melanoma patients, however there is no evidence outlining which form of psychological care is best.

Nadine Kasparian (NK) and her colleagues conducted a survey which demonstrated a need for care, with 71% of those patients surveyed feeling fearful regarding their melanoma.

In this study it is proposed that 172 patients will be randomised to receive either standard care (a Cancer Council booklet) or the intervention, which will be the Cancer Council booklet, a melanoma booklet and five telephone calls with a psychiatrist. The primary outcome of this will be reducing the fear of recurrence in high risk patients alongside analysis of the QoL, Doctor and patient communication and cost effectiveness.

AC provided an overview as to eligibility criteria and outlined the visit structure that a patient would follow. She also commented that the melanoma booklet had been piloted among 19 patients and 10 health professionals and was well received, although some adjustments are being made to the final booklet based on feedback.

QN: There is concern that you will nurture fear in some patients, is this a worry? Yes, talking about fear may increase fear in some people but this is why this study is important, so that we can measure those outcomes. Phone calls will be adapted specifically to each patient and so if people have high anxiety, this is something we can address.

QN: Have you considered collecting survival data for the study? No, there is not enough power within our numbers to reliably inform this.

Comment: An important part of this study should be identifying patients at screening who need the most support. It should be considered that in practice the support you are proposing could not be given to all high risk patients within Australia.

5. Melanoma Research Presentations

i. Consumer engagement – Australian Melanoma Consumer Alliance Annual Update on recent milestones and achievements – Paul White

Paul White (PW) provided an overview of what MMP represent and the work that they have been doing. PW explained that MMP is a group of volunteers who all share a common vision to increase awareness of and wipe out melanoma in Australia. PW outlined some of the activities that MMP is involved with including tissue collection, method of communicating the message online ie. social network/websites, newsletters and brochures, and involvement in melanoma research/studies.
PW explained that the Australian Melanoma Consumer Alliance (AMCA) is not an organisation but a group of people composed of the MMP core group, and other national melanoma advocates from different Australian states.
PW reported on the ANZMTG Consumer Workshop which was held in June 2013 and was attended by AMCA. The purpose of the workshop was to improve research and services to align with consumer priorities. A number of key outcomes resulted from the forum including the refinement of consumer involvement in clinical trial processes, development of a national resource of information, and advocacy of tissue collection.
PW noted that Cancer Australia has provided funding to support consumer activities such as annual research meetings, education and training on clinical trials, and facilitating information provision. PW advised that the vision for the next 12 months was to have a "one stop shop" of resources and information for melanoma sufferers. There is still a lot of work to be done nationally and AMCA would like to ask for support for their partners and the work that they do.

QN: How does AMCA, composed of a group of people from different states, assist a patient with their melanoma journey?

Comment: AMCA is in the process of establishing a well-defined process and mechanics that can be used nationally by all patients once diagnosed with melanoma. A part of this would be cases where a patient is seen by a particular specialist and is able to be provided with a resource that would assist them with information / contacts on the first steps after being diagnosed. There is much information available from many different sources but patients are often at a loss as to where to find the information they need. Therefore, one of the aims is to provide a standard resource nationally which points out to patients how they find the information they need.

QN: Is there any cross-over with other skin cancers, merckel cell carcinoma, non-melanoma skin cancer with the work that you do?

Comment: Nothing as yet apart from melanoma as their work has been driven by the MMP agenda.

ii. Recent advances in the management of Melanoma treatment

a. Surgery Update – John Thompson

Prof John Thompson provided an updated on the MSLT I clinical trial, which is the largest melanoma surgical clinical trial to have been completed. He provided an overview of the final results, which are currently embargoed.

b. Update on clinical trials for Advanced Melanoma – Victoria Atkinson

Victoria Atkinson (VA) provided a brief update on the recently reported trials on immune based therapies, including the recently reported data on MK-3475 which was reported at ASCO and published by the New England Journal in 2013. The MSD PD1 monotherapy is well tolerated with a low incidence of adverse events which can be easily managed. VA presented a waterfall plot showing the response rates for MK-3475 (formerly labelled as Lambrolizumab). The phase I study confirmed a good RECIST Response Rate of 38% (44/117) with median progression free survival at 7 months.
The MSD randomised phase III Ipilimumab vs MK-3475 at 2 different dosing schedules is currently running with Australia meeting its recruitment target, and therefore needing to request for therapies on a case by case basis.
The phase I trial looking at the addition of Nivolumab to Ipilimumab was reported at ASCO and in the New England Journal 2013. VA showed the response rates of treated patients and also indicated that the majority of the Grade 3 or 4 adverse events are likely to be connected to Ipilimumab immune effects rather than the Nivolumab, which is normally well tolerated. The BMS phase III trial has now been recruiting for a while.
The results of these 2 phase III trials are expected late next year and if confirmed, trials looking at PD1 anti-bodies after resected stage III diseases are likely to be conducted.

VA reported on the BRIM 7 phase I trial which looked at Vemurafanib with Combimetinib which was published early in 2013 and was presented at ESMO 2013. The therapy showed very good objective response rates (85%) in patients. The phase III trial is underway and is likely to close in December 2013 and is expected to reflect the results from the phase I trial.

VA provided a quick overview of the timelines for the reporting of the trials closed and awaiting publication such as the Adjuvant Ipilimumab in resected Stage III, Drabrafenib +/- Trametinib in Stage IIIc unresected and IV (Combi-D), and the Drabrafenib + Trametinib vs Vemurafanib (Combi-V). It is anticipated that the results of these trials will be reported next year.

VA provided a brief update on the open phase III randomised multi-centred trials. VA highlighted that there has been some difficulty in recruitment with the studies on BRAF mutant unresectable Stage IIIC/IV melanoma due to the availability of Dabrafenib, which is expected to be listed on the PBS in Dec 2013, and Trametinib. The Adjuvant BRAF mutant trials are recruiting well in Australia and reports are expected in 2016. Recruitment on the NRAS mutant trial, NEMO, will be challenging due to the other immune-based therapy trials but this trial will allow another option of treatment for patients. For BRAF wild type, VA highlighted 3 trials which are recruiting well and are expected to close very soon including the BMS CA209-066, BMS CA209-066, and MSD MK3475-006 trials.

QN: Are there trials for BRAF negative adjuvant treatment for resected stage III?

Comment: There are no BRAF wild type adjuvant trials but there is the difficult option of choosing interferon. VA assumes that BMS will move onto an adjuvant nivolumab study but they have to wait for the result of the phase III trial to show that it is better than dacarbazine, which is expected soon.

iii. What is health economics and how will it influence trial design for melanoma protocols and how will it guide health policy, pricing and access to new treatments? – Marion Haas

Marion Haas (MHa) provided overview of health economics. MHa described the application of theories and tools of economics to the topics of health and health care. MHa explained that health economic evaluations within a trial are designed to determine the cost-effectiveness of the new intervention/therapy. And lastly, MHa explained how health economics influence policy making by using the Pharmaceutical Benefits Advisory Committee process as an example.

QN: Are toxicity and side effects of treatments taken into account in the decision making, in particular the use of Vemurafenib?

Comment: It depends on what's in the trial and how it is being used in the trial. The difference in the effects of the two comparator arms in the trial will always need to be taken into account, and is presented to the PBAC.

QN: Do they take into account the patient's ability to work and contribute to the economic environment, and the lack of hospital admissions against the savings in hospitals?

Comment: The issue of productivity is an interesting issue and can be a fraught question. In traditional economic terms, it depends on whether the patient is replaced by another person or not, or whether an unemployed person takes the patient's place. Regarding the hospital admission, a hospital bed is a filled bed, and the reality is that resources savings in melanoma will not go back to melanoma but the great big hole that is money needed for hospitals.

QN: How do you estimate the overall cost to the community of a person who goes on to disseminated care? How much will it cost the insurance company?

Comment: Theoretically this is possible to estimate and will depend on the number of people involved, and from which perspective it is being taken from eg. from the whole community's or the health system's perspective.

Appendix 1:
ANZMTG 2013 Research Meeting Attendance Record

Title	First Name	Surname	Institution
Mr	Alan	Lucas	ANZMTG
Dr	Anne	Cust	University of Sydney
Ms	Annette	Pflugfelder	Eberhard Karls University
Mrs	Aylin	Yahya	Sir Charles Gairdner Hospital
Prof	Bill	McCarthy	University of Sydney
Prof	Bryan	Burmeister	Princess Alexandra Hospital
Ms	Caroline	Ryan	Roche
Dr	Chris	Allan	Princess Alexandra Hospital
Prof	Claus	Garbe	Eberhard Karls University
Ms	Elizabeth	Paton	ANZMTG
Dr	Gerald	Fogarty	Melanoma Institute Australia
Ms	Jacqui	Keller	Royal Brisbane and Women's Hospital
Ms	Jennifer	Edmunds	Royal Brisbane and Women's Hospital
Prof	John	Thompson	Melanoma Institute Australia
Prof	John	Kelly	The Alfred Hospital
Dr	Julie	Howle	Westmead Hospital
Ms	Julie	Fraser	Melanoma Patients Australia
Ms	Katrina	Vanin	Glaxo-Smith Kline
Ms	Lauren	Haydu	Melanoma Institute Australia
Prof	Marion	Hass	CREST

Title	First Name	Surname	Institution
Prof	Mark	Smithers	Princess Alexandra Hospital
Dr	Mark	Zonta	The Mater Hospital
Dr	Matthew	Foote	Princess Alexandra Hospital
Prof	Michael	Henderson	Peter MacCallum Cancer Centre
Dr	Michael	Collins	Townsville Hospital
Mr	Paul	White	Australian Melanoma Consumer Alliance
Prof	Peter	Soyer	University of Queensland
Prof	Peter	Hersey	University of Sydney
Mr	Phillip	Mansfield	Bristol-Myers Squibb
Ms	Rebecca	Pincus	Royal Brisbane and Women's Hospital
Dr	Rebecca	Read	Royal Prince Alfred Hospital
Dr	Robyn	Robyn Saw	Melanoma Institute Australia
Dr	Sarah	Smithson	Victorian Melanoma Service
Dr	Sydney	Ch'ng	Melanoma Institute Australia
Ms	Tamara	Etto	Bristol-Myers Squibb
Dr	Teresa	Lee	Melanoma Institute Australia
Ms	Tilly	Ryan	Melanoma Patients Australia
Dr	Victoria	Atkinson	Princess Alexandra Hospital
Miss	Vikki	Steel	ANZMTG

ANZMTG 2013 Research Meeting Apologies Record

1	Campbell Rose
2	Andrew Spillane
3	Pascale Guitera
4	Rachael Morton
5	Vanessa Neve
6	Angela Hong
7	Mary-Anne Kedda
8	Janelle Meakin
9	Elke Hacker
10	Bill McHugh