ANZMTG Australia and New Zealand Melanoma Trials Group

ANZMTG 2011 Annual General Meeting
Friday 25 November 2011, 1:20pm to 1:30pm
Lecture Theatre, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne

Annual General Meeting Minutes

Meeting commenced at 1:20pm

1. **Greetings and apologies**

The Chair of the ANZMTG, Professor John Thompson (JT) welcomed the 50 members present at the Annual General Meeting (see Appendix 1).

All members were provided with the Agenda and the following documents:

a. ANZMTG 2010 Annual General Meeting Minutes
b. ANZMTG 2011 Chairman's Report
c. ANZMTG 2010-2011 Financial Report
d. ANZMTG 2011 Clinical Trials Summary
e. ANZMTG 2011 Membership Summary

The Chair noted that apologies had been received from 20 members (see Appendix 1).

2. **Minutes of 2010 Annual General Meeting, 6 November 2010**

The Minutes of the previous Meeting held on 6 November 2010 were adopted as a true record.

3. **Chairman's report**

3.1 Funding

Professor Thompson noted that ANZMTG had received renewed infrastructure funding through Cancer Australia over the period 1 July 2010 to 30 June 2013. Other sources of funding include the NHMRC Whole Brain Radiotherapy (WBRT) Mel Project Grant (2007 – 2011; 2011 – 2014) and the Melanoma and Skin Cancer Research Institute (MASCRI) Mel D Grant.

3.2 Executive Committee

The committee met quarterly in 2011 in accordance with the required frequency of meetings.

3.3 Staffing

ANZMTG Central Office has 3.5 full time equivalent (FTE) positions (including 1 x 1.0FTE executive officer, 2 x 1.0FTE project officers and 0.5FTE Clinical Data Coordinator). These positions are fully funded as part of the Cancer Australia infrastructure grant.

3.4 Membership

The Chair reported that the current ANZMTG membership consists of approximately 508 members (including 460 full members and 48 associate members). ANZMTG seeks to double its membership by 2013 and continues to actively promote membership to individuals and groups involved in melanoma research in Australia and New Zealand.

3.5 Clinical Trials

Professor Thompson directed attendees to the summary of current and proposed ANZMTG clinical trials provided and mentioned that new research proposals would be presented and discussed during the after-lunch session of the Annual Scientific Meeting (ASM) immediately following the AGM. The Chair noted that the current trials supported by ANZMTG would be presented and discussed in the afternoon session of the ASM. The Chair emphasised that ANZMTG is always willing to support new trial sites, and invited interested parties to contact the ANZMTG office for more information. The Chair directed attendees to the attachment to the Chairman's report outlining the publications and presentations given for ANZMTG trials throughout 2011. The Chairman's report was closed by reference to the acknowledgements for

support including Libby Paton, Executive Officer and her team in the ANZMTG office and the input of Cancer Australia to the group's achievements.

4. **Finance report**

   Libby Paton, ANZMTG Executive Officer, (LP) referred to the 2010/2011 Statement of Income and Expenditure provided to attendees in reporting that the primary source of income for the group is Cancer Australia grant funding. LP reported that approximately $241,000 had been expended on salaries of ANZMTG staff members in the 12 months to 30 June 2011 and just under $122,000 related to the administration and conduct of clinical trials. The group was informed that the conditions of the new 3-year Cancer Australia were relatively restrictive in regard to permitted expenditure and that alternative sources of funding had been sought. To this end, LP reported that ANZMTG had been successful in securing a grant from the NHMRC to fund the WBRT in Metastatic Melanoma trial [ANZMTG 01.07] until 2014, and a MASCRI grant to fund the Mel D trial. The finance report was closed by noting that ANZMTG had an operating balance of approximately $287,000 to 30 June 2011. The operating funds are committed funds and will be expended on salaries and projects.

5. **Operations report**

   LP delivered the 2011 Operations Report. For the sake of brevity LP referred the members to the ANZMTG Clinical Trial Summary for a full overview of the clinical trial progress achieved in the last year, since the previous meeting. LP confirmed that the group had employed a second project officer (1.0FTE) and a part-time Clinical Data Coordinator (0.5FTE) in the past 12 months which has brought the group operations to a 3.5 FTE capacity. LP reported that quarterly newsletters were distributed to all members electronically and posted to clinics during 2011, and called for members to notify ANZMTG of upcoming events and activities which could be featured in future newsletters. The 2011 ANZMTG Membership Report was reviewed and LP confirmed that new members can sign up online through the ANZMTG website. In regard to the current membership, Libby confirmed that the goal of ANZMTG to double its membership from a total of 300 in 2010 to 600 within the next 3 years was progressing well with a current membership level of 508 (including 425 Australian, 36 New Zealand and 47 international members). In addition, LP confirmed that ANZMTG had undertaken a number of other activities during 2011 including a survey of all members , a melanoma community survey (reports for both were in preparation) and lastly, LP informed the group that 3 Melanoma Community Forums had been held in 2011 (Sydney; May and October 2011 and Perth; November 2011).

   LP thanked the executive committee, staff, members and other key stakeholders for the interest and participation over the past year.

6. **Terms of Reference and Nomination Process for the Executive Committee**

   In June 2011, an election was held for the position of the ANZMTG Chairman and Professor John Thompson was nominated for another term. Terms of Reference have been agreed and the representative term is 3+3 years.

7. **Other business**

   There was no other business.

8. **Meeting close**

   The Chair closed the ANZMTG Annual General Meeting at 1:30pm and commenced the after-lunch session of the ASM.

Meeting concluded at 1:30pm

Appendix 1:
ANZMTG 2011 Annual General Meeting Attendance Record

	Name	
	Executive Committee Members	**Institution**
1	John Thompson	MIA, NSW
2	Rachael Morton	University of Sydney, NSW
3	Bryan Burmeister	Princess Alexandra Hospital, QLD
4	Michael Henderson	Peter MacCallum Cancer Centre, VIC
5	John Kelly	The Alfred Hospital, VIC
6	Ben Brady	Cabrini Health, VIC
	ANZMTG staff	
7	Elizabeth Paton	ANZMTG
8	Kate Morrow	ANZMTG
9	Hector Fuentes	ANZMTG
10	Paul Wagland	ANZMTG
	Full ANZMTG members	
11	Gerald Fogarty	MIA / Mater Sydney, NSW
12	Matthew Foote	Princess Alexandra Hospital, QLD
13	Julie Winstanley	University of Sydney, NSW
14	Richard Fischer	Peter MacCallum Cancer Centre, VIC
15	Donna Gillen	The Alfred Hospital, VIC
16	Marisa Cikos	The Alfred Hospital, VIC
17	Kathy Pope	Peter MacCallum Cancer Centre, VIC
18	Anne Woollett	Melbourne Melanoma Project, VIC
19	Phillip Parente	Austen Health, VIC
20	Victoria Atkinson	PAH
21	Grant McArthur	Peter MacCallum Cancer Centre, VIC
22	Carolyn Williams	SKMRC, WA
23	Andrew Spillane	MIA, NSW
24	Georgina Long	MIA, NSW
25	Alex Menzies	MIA, NSW
26	Julie Howle	MIA, NSW
27	Angela Neville	Launceston General Hospital, TAS
28	Brett Frenkiel	Royal Children's Hospital, VIC
29	Robert Tasevski	Royal Melbourne Hospital, VIC
30	Martin Ashdown	University of Melbourne, VIC
31	Sian Fairbank	Peter MacCallum Cancer Centre, VIC
32	Simon Donahoe	Peter MacCallum Cancer Centre, VIC
33	Marisa Cikos	The Alfred Hospital, VIC
34	Jonathan Cebon	Austin Health, VIC
35	Vanessa Estall	Peter MacCallum Cancer Centre, VIC
36	Jonathan Tomaszewski	Peter MacCallum Cancer Centre, VIC
37	Carmen Hansen	Peter MacCallum Cancer Centre, VIC
38	Elizabeth Lehunt	Peter MacCallum Cancer Centre, VIC

39	Damien Kee	Peter MacCallum Cancer Centre, VIC
40	John Spillane	Peter MacCallum Cancer Centre, VIC
41	Mark Shackleton	Peter MacCallum Cancer Centre, VIC
42	Christopher McCormack	Peter MacCallum Cancer Centre, VIC
43	Margaret Chua	Peter MacCallum Cancer Centre, VIC
44	Nicole Haynes	Peter MacCallum Cancer Centre, VIC
45	Michael Lim-Joon	Peter MacCallum Cancer Centre, VIC
46	Rod Sinclair	St Vincents Hospital Melbourne, VIC
47	Jessica Dortmans	Royal Perth Hospital, WA
48	Catherine Mandel	Peter MacCallum Cancer Centre, VIC
49	Jim Hagekyriakou	Peter MacCallum Cancer Centre, VIC
50	Tina Thorpe	Peter MacCallum Cancer Centre, VIC

Apologies received from the following members:

1	Margaret McJannett
2	Jacquie Ruhl
3	Julie Teraci
4	Carol Johnson
5	Jim Tomlinson
6	Robyn Saw
7	Lauren Haydu
8	Jon Stretch
9	Rick Kefford
10	Kerwin Shannon
11	Angela Hong
12	Bruce Armstrong
13	Michael Brown
14	Ian Davis
15	Tim Wang
16	Siddhartha Baxi
17	Matt Carlino
18	Leuh Peut
19	Pascale Guitera
20	Nicola Ware

ANZMTG 2011 Annual General and Scientific Meeting
Friday 6 November 2011, 10:30am to 5:30pm
Lecture Theatre, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne

ANZMTG Annual Scientific Meeting 2011 Minutes

Meeting commenced at 10:30am

ANZMTG Chairman, Professor John Thompson (JT) welcomed all participants to the meeting. JT confirmed a number of apologies had been received (see Attendance record; Appendix 1).

CURRENT MELANOMA RESEARCH PRESENTATIONS

1. **Recent advances in dermatology**

John Kelly [JK] presented an overview of advances in dermatology and melanoma in the past 12 months, including the key findings of the following studies:

- Blum A et al. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction. Arch Dermatol 2011; 147(10):1181-7.
- Sepehr A et al. Long-term outcome of Spitz-type melanocytic tumors. Arch Dermatol 2011; 147(10):1173-9.
- Brewer JD et al. Malignant melanoma in solid transplant recipients. Arch Dermatol 2011; 147:790-6.
- Ly L et al. Efficacy of imiquimod cream, 5%, for lentigo maligna after complete excision. Arch Dermatol 2011; 147(10):1191-5.
- Wagas et al. The Contribution of Nodular Subtype to Melanoma Mortality in the United States, 1978 to 2007. Arch Dermatol 2011; Sep 19.
- Tejera-Vaquerizo A et al. Growth rate as a prognostic factor in localized invasive cutaneous melanoma. J Eur Acad Dermatol Venereol. 2010 Feb;24(2):147-54.
- Kvaskoff M et al. Risk Factors for Lentigo Maligna Melanoma Compared With Superficial Spreading Melanoma. Arch Dermatol 2011; Oct 17.
- Hedblad MA. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol 2011; Oct 24.
- Hendi A et al. Melanocytes in nonlesional sun-exposed skin: A multicenter comparative study. J Am Acad Dermatol 2011; 65(6):1186-93.
- Wachsman W et al. Noninvasive genomic detection of melanoma. Br J Dermatol 2011; 164(4):797-806.
- Christopher K et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2011; 65(5): 1032-1047.
- Argenziano G. Accuracy in melanoma detection: A 10 year multicenter survey. J Am Acad Derm 2011; Oct 6

JK concluded that there were a number of newer topical agents which can be used in a dermatology setting for suspicious lesions however these therapies are better used in an adjuvant setting and that surgery remains necessary.

2. **Surgical oncology update – advances in melanoma surgery**

John Thompson [JT] presented an overview of the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) and MSLT-II trials, and surgical trials investigating excision margins and resection of metastatic disease.

- Final results from MSLT-I are due soon. Don Morton presented some of the final results at the Society of Surgical Oncology meeting in March 2011 but these results are currently embargoed.
- MSLT-II is the follow on study that will determine if complete lymph node dissection (CLND) is necessary in patients who are sentinel lymph node biopsy (SNLB)-positive. The study has recruited 1349 patients up to October 2011.

- JT reported that the findings from the Scandinavian excision margin trial have recently been published. No significant difference was seen in local control or survival between the 2 cm compared with a 4-cm excision margin [Gillgren P et al. Lancet 2011; 378(9803):1635-42].
- Data were presented on patients with stage 4 disease from the CancerVax trial. Don Morton has not published these data yet.
- A review of management options for in-transit metastases has been published recently (Testori A et al. J Surg Oncol 2011; 104(4):391-6). JT reported data from his own unit on the management of in-transit metastases that found survival was not as good as that predicted by American Joint Committee on Cancer (AJCC) staging.
- JT noted that encouraging results with high response rates are being reported with topical diphencyprone and rose bengal (PV10) as a treatment for in-transit metastases. JT added that regional therapies are often associated with a bystander effect.

3. Current radiotherapy research in respect to melanoma treatment

Bryan Burmeister [BB] presented an overview of future directions in radiation oncology for melanoma.

- BB noted that adjuvant radiotherapy studies had achieved mixed results in the past.
- The TROG96.06 phase II study showed a positive and convincing in-field control and this study has proceeded to a randomised controlled trial (RCT)[ANZMTG 01.02].
- BB noted that key questions that need to be answered in future clinical trials include:
  - Can CLND be delayed in some patients with palpable disease? (e.g. perform SLNB and compare standard care versus pre-operative radiotherapy followed by dissection)
  - Can CLND be omitted following SLNB and is there a role for radiotherapy in lieu of dissection? (e.g. excise palpable or positive LN and proceed either to dissection or adjuvant radiotherapy)
  - Can SLNB be replaced with elective radiotherapy in high-risk patients? (e.g. perform wide local excision and if there is a high risk of having a positive LN, compare SLNB with elective radiotherapy).
- BB discussed a number of areas of potential research including:
  - Regional node radiotherapy. BB reported that data from a breast cancer trial (NCIC MA 20, Whelan et al) presented at the American Society of Clinical Oncology meeting in June 2011 showed regional node radiotherapy contributed little to improvement in overall survival
  - Need for further research to identify predictors or biomarker of radiosensitivity of melanoma cells in order to develop more effective treatments
  - Potential interaction of radiotherapy with the newer biological agents as in-vitro studies suggest there is synergy between these two treatment modalities.

4. Personalised medicine – Targeted therapies

Grant McArthur [GM] reported that a number of oncogenes have been identified for melanoma including BRAF (present in 50% of melanomas), NRAS, ERBB4, EPH and KIT, and personalised therapies targeting these oncogenes are likely to become a key focus of research into the future.

- A number of new small molecule inhibitors of the KIT/RAS/RAF/MEK/ERK pathway have been developed in the past few years, and most of these agents target mutant BRAF (mutation V600E).
- The major study reported in the past 12 months is the phase III study comparing the BRAF kinase inhibitor vemurafenib versus dacarbazine (standard care) with in patients with metastatic melanoma. Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation [Chapman PB et al. New Engl J Med 2011; 364(26):2507-16]. Data from the phase I and phase II studies with vemurafenib were also presented.
- BRAF inhibitors are associated with unusual toxicities including cutaneous squamous cell carcinoma, keratoacanthoma and skin papilloma which are driven by RAF mutations in the skin. These toxicities can be managed with local treatments.
- MEK inhibitors were also discussed, particularly the promising findings of a phase II study with trametinib (25% response rate) [Lewis et al, Perspectives 2011; unpublished].

- Mechanisms of resistance to BRAF inhibition were also discussed including the role of combining BRAF and MEK inhibitors. Combining dabrafenib and trametinib has resulted in less toxicity than using either of these agents alone.
- Studies with KIT inhibitors (imatinib) are also showing promising activity in metastatic melanoma [Carvajal RD et al. JAMA 2011; 305(22):2327-34].

GM discussed the important advances being made in better understanding melanoma cancer genomics and stressed that personalised therapy will be the future for melanoma treatment and in his closing remarks referred to the Sanger Institute's COSMIC database (Catalogue of Somatic Mutations in Cancer).

QN. In patients who have progressed on a BRAF inhibitor, why do you continue with the BRAF inhibitor when these patients are then treated with a MEK inhibitor? If you simply switch to the MEK inhibitor the results are disappointing compared to continuing the two drugs together in terms of getting tumour shrinkage again after progression. In part that is due to dose-limiting toxicity with MEK inhibitors such as diarrhoea. You cannot push the dose up too high to completely turn off the pathway without getting side effects, but this risk is reduced by using the two drugs together and this is more effective in shutting off the pathway. It's also been suggested from prostate cancer studies that you may get less development of resistance by cycling the use of the BRAF inhibitor rather than using it continuously.

5. Immunology and melanoma

Jonathon Cebon [JC] explained that immunosurveillance is important in melanoma and that melanoma is more common in the presence of immunodeficiency, tumour infiltrating lymphocytes and paraneoplastic syndromes (e.g. vitiligo, chorioretinis).

- JC reported that the monocloncal antibody ipilimumab (an antibody against the CTLA-4 molecule that regulates the immune system) has been approved by the Therapeutic Goods Administration in 2011 for the treatment of advanced metastatic melanoma.
- Ipilimumab has been shown to have a modest impact on long term survival. Key studies include:
    - Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma. New Engl J Med 2010; 363(8):711-23
    - Robert C et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New Engl J Med 2011; 364(26):2517-26.
- The response to ipilimumab is delayed which allows tumour progression before any regression can occur. This delayed response needs to be considered in selecting patients for treatment, as some patients may not have sufficient time available to wait for the immune response to take place.
- Ipilimumab therapy is associated with a range of autoimmune toxicities (e.g. coloenteritis, hepatitis, etc) that can be life threatening in some patients.
- The antigens that mediate anti-cancer immunity are being identified and include:
    - differentiation antigens (e.g. Melan A, tyrosinase, gp100)
    - cancer testis (CT) antigens (MAGE family members, NY-ESO1)
    - products of cancer-related mutations
    - gangliosides (GM2, GD3).
- Vaccines against some of these antigens have been tested in clinical trials but results have been disappointing, as although an immune response has been generated this has not resulted in clinical regression.
- Other areas of research include:
    - identification of a predictive signature in tumours that may predict clinical outcomes
    - the evolution of immunity with disease progression (elimination-equilibrium-escape stages) and how this may impact on the selection of immunotherapy strategies
    - the involvement of the RAS/RAF/MEK pathway with T-cell signalling and selection of therapeutic strategies.
- JC concluded that the role of immune modifying agents should be considered when designing future clinical trials.

QN. Is there a danger in using small molecule inhibitors if they are having an effect on T lymphocytes?

You need to distinguish between BRAF and MEK inhibitors as they have very different effects on lymphocytes. Evidence with BRAF inhibitors suggests that there is little deleterious effect on lymphocytes. For example, there is up-regulation of the melanoma tumour antigens such as Melan A with no adverse effect on T-cell function. MEK inhibitors are different as they will stop lymphocytes from proliferating.

QN. How would you decide what local treatment to combine with immunotherapy?
Ipilimumab will only be provided by the manufacturer to conduct trials with currently approved treatments for melanoma. To this end, only agents like Bacillus Calmette-Guérin (BCG) can be used in any such trial as it is approved in Australia for melanoma treatment. Purchase of ipilimumab on its own for studies with other non-approved agents like Rose Bengal would not be possible.

QN. Could you use ipilimumab for local rather than metastatic disease?
Yes as you may be able to prevent metastatic disease if you intervene early however access to the drug remains resturcted in Australia and is not yet available for that purpose.

QN. Could you look at biomarkers to decide what local agents to combine with ipilimumab?
Biomarker studies have only been done with small samples and have not been validated as yet. PDL-1 is a molecule found on melanoma cells that turns off the immune system. If you find a subset of melanomas or a certain subset of melanoma treatments that up-regulate this PDL-1 molecule on the melanoma cells, they you may be able to use an antibody to turn that molecule off specifically. It's like personalising immunotherapy in the way that you personalise the BRAF inhibitor. The comment was made that you would need to intervene early with immunotherapy prior to the tumour developing escape mechanisms.

QN. Can immunotherapy be combined with radiotherapy?
Whole body radiotherapy is immunosuppressive, but regional radiotherapy may actually enhance immunity as it causes inflammation in the tumour which is associated with necrosis of disease and release of antigens. If you follow this with stimulation of the immune system you may be able to enhance the tumour response.

6. **Consumer Input**

   Consumer representative, Campbell Rose [CR] reported that the melanoma consumer reference group (CRG) began its work with the Melbourne Melanoma Project (MMP). In over 2 years it has evolved into a national group with 9 members drawn from the Eastern States and Western Australia. The CRG has established a 3-page Research Review Protocol (RRP) to aid the members in reviewing and proving consumer input for research proposals put forward by ANZMTG researchers. The RRP is being used by other consumer groups including the prostate cancer group. So far the CRG has reviewed 10 submissions: 7 intended for Cancer Australia (CA) grant funding and 3 for Victorian Cancer Agency (VCA) funding. CR confirmed that ANZMTG had utilised this process with the review and development of both membership and consumer survey initiatives. The CRG has also been involved in 2 surveys. CR reported that a consumer website has been established through MMP funding and this resource needs to be advertised and used more widely. The CRG are currently working with US consumer groups to improve fund raising and patient advocacy activities.

   CR emphasised that melanoma research needs to be relevant to the consumer. Issues that are important to consumers include how research will impact on the consumer and change the course of the disease, developing a database to inform evidence-based care and the socio-economic impact of melanoma which is currently under-recognised. CR supported the role of databases in informing research and encouraged ANZMTG to prioritise this work, and added that he could assist ANZMTG in raising funds for such a project. CR concluded that a national strategy was required that included a blueprint for research into melanoma that details the relevance to consumers so that they can advocate to government for funding to appropriately resource researchers.

7. **The Melbourne Melanoma Project Melanoma Database Experience**

   Anne Woollett [AW], MMP Database Project Manager, reported that the MMP was funded by the VCA. The objective of the database project was to collect clinical information and coordinate the collection of biospecimens to support VCA-funded melanoma research projects and facilitate recruitment into clinical

trials. This year the MMP database has collated data from melanoma patients treated at several large public institutions in Victoria.

In setting up the database a range of issues had to be considered including deciding on the content that would be relevant to the end user. Other relevant issues included budget, security, confidentiality of the donor and contributing site, the need multiple data entry points, and the need for infrastructure support and upgrades. AW explained that the MMP developed a tool to aid in selection of an appropriate vendor. She noted that MMP were happy to share this tool with organisations that may be considering setting up or updating a database.

To date the MMP database has recruited 800 cases, and MMP are currently exploring collaboration opportunities with the Melanoma Research Database at Melanoma Institute Australia (MIA). AW noted that researchers were welcome to access data from the MMP database for their research. She explained that the application process was simple and free and involved completion of an application form. Use of the MMP database had to be acknowledged in any research publications. AW added that the more researchers that used the MMP database, the stronger the case for MMP to seek ongoing funding from VCA. Discussion ensued about the difficulty in obtaining funding to sustain existing melanoma databases, and the suggestion was made that a combined approach to Federal government may be the most appropriate step going forward. Discussion ensued about the need for shared responsibility for data entry between clinicians and data management staff to ensure that data are captured, and that data quality is maintained. The suggestion was made that ANZMTG should consider a national database or linking smaller databases to inform its national research agenda.

Comments. There was general consensus reached on the importance of an efficient and effective database which will generate significant output in terms of clinical practice, staging, guidelines and new publications. Standardisation of the data capture will also ensure that patient information is benchmarked ensuring more consistency for patients, good quality assurance process and will better support research activities. Ensuring the quality of the database also relies heavily on competent and qualified data management staff at each site.

PRESENTATION OF NEW RESEARCH PROPOSALS

1. **A multicentre randomised clinical trial evaluating ilio-inguinal and inguinal dissection for patients with metastatic melanoma – Andrew Spillane (proposal distributed with the meeting papers)**

Andrew Spillane [AS] explained that surgeons are split in their opinion as to what is the most effective therapy for metastatic melanoma in groin lymph nodes – ilioinguinal or inguinal dissection – and that there is little difference in morbidity between these two types of dissection. A recently published quality assurance study found that thorough groin regional lymph node dissections have a predictable LN yield and that lymph node ratio is the strongest predictor of survival outcome. The study authors concluded that because pelvic lymph nodes are frequently positive ilioinguinal dissection should be considered for all patients, especially those with macroscopic metastases to groin lymph nodes [Spillane et al. Ann Surg Oncol 2011; 18(9):2521-8].

The proposal is for a RCT that would randomise patients with inguinal lymph node involvement to ilioinguinal or inguinal dissection. PET scans would be performed as part of study to assess the value of PET in staging the pelvis. The primary endpoint would be disease-free survival (DFS), and the secondary endpoints would include overall survival (OS), morbidity, Quality of Life (QoL), intensity of the PET CT and biomarkers of recurrence. The proposed recruitment target is 600-650 patients (up to 380 patients per arm).

Review of the current database indicated that single centre recruitment only through MIA will be slow which means that this proposal would be better conducted as a multicentre trial.

QN. If patients meet the criteria for radiotherapy could this be a possible third arm to the study?

Data are lacking on morbidity associated with radiotherapy for deep pelvic nodes. It was suggested that data from ANZMTG 01.02 be reviewed to assess what happened to patients who received a combined inguinal-pelvic dissection versus inguinal dissection +/-radiotherapy to provide some data, while acknowledging that ANZMTG 01.02 was not randomised to specifically answer this question.

QN. Unless your study gets completed in the next 18 months, results from ipilimumab and BRAF inhibitor studies are likely to show a benefit for relapse free survival and become a standard of care and thus blunt the impact on what you may see in your study.
We can only await the results from those studies. Our study will not exclude adjuvant or neoadjuvant trials as this is all part of the landscape for the next 6-12 months and has to be taken into account. Our study will at least standardise morbidity data. Importantly this proposal will address a common practical issue faced by surgical oncologists and will determine what standard of care should be for these patients.

2. Radiotherapy followed by selective nodal dissection for bulky and/or inoperable nodal melanoma – Matthew Foote (proposal distributed with the meeting papers)

Matthew Foote [MF] reported that currently there is no standard treatment approach for patients with bulky and/or inoperable stage IIIb/IIIc disease. Patients with stage 3 disease have a high risk of relapse, hence the priority is to obtain best regional control with the least morbidity. Patients generally receive both radiotherapy and surgery but the order of these two modalities is at the treating clinician's discretion.

This study aims to formalise the treatment approach with the hypothesis being that pre-operative radiotherapy will be effective in the regional (nodal) management of patients with bulky (greater than 6 cm) and/or inoperable stage IIIb and IIIc disease. MF noted that "high-volume nodal disease" may be a more appropriate title for the study. He presented the findings of a pilot feasibility study with 12 patients (3b, 3c or 4 disease) who were given pre-operative radiotherapy, a pre- and post radiotherapy PET scan and planned nodal dissection at 12 weeks. This pilot is currently opening and accruing at Princess Alexandra Hospital.

The proposal is for a phase II non-randomised study of pre-operative radiotherapy followed by nodal dissection. The eligibility criteria are still being considered. The primary endpoint is regional (in-field) control rate at 1 year. Secondary endpoints include clinical, radiological and pathological response rate, the predictive value of PET, treatment related toxicity, and the effect on planned nodal dissections. A total sample of 30 patients will need to be recruited and this requires a multi-site approach. A RCT will be considered in future.

QN. What's the main goal of the study?
It's a sequencing trial for patients with bulky disease at highest risk of metastatic melanomas. The primary endpoint is in-field control rate but from our pilot there will be a significant number of patients, say a quarter, who will avoid the morbidity of regional surgery.

QN. In sarcoma surgery occurs at 4-8 weeks post-radiotherapy, why is nodal dissection at 12 weeks?
Clinically we see these patients responding up to 12 weeks and longer so we want to see more response before surgery. In head and neck disease the response to radiotherapy is slower.

QN. Should you be selecting patients based on extracapsular extension and tumour number as these are more predictive of relapse than tumour size?
I agree extracapsular extension is important and based on the tumour size criteria (6cm node) all of these patients would have extracapsular extension.

3. Paediatric melanoma database – Sian Fairbank, Brett Frenkiel

Brett Frenkiel [BF] presented a case study of an 8 ½ year old boy with spitzoid melanoma who was treated according to standard of care for adults. Sian Fairbank [SF] noted that this case highlights that there is a lack of data in the literature for paediatric patients and how they should be managed. In children, melanoma has greater heterogeneity and may be a different entity to the disease that is seen in adults. Children are more likely to have spitzoid or amelonotic tumours and greater vascular invasion, and thicker lesions. In children

SLNs are more likely to be positive, but this does not appear to be a predictor of outcome due to the spitzoid population finding its way into these data.

SF stated that there are still major gaps in knowledge in regard to paediatric melanoma, raising the possibility that children and adolescents are being offered treatment that was not evidence based. She noted that Australian paediatric cancer registries only report 14 melanoma cases a year, and that the National Cancer Registry reports 96 cases a year but this total is likely to include atypical spitz and in-situ melanomas. The differences in the manner in which these data are collected make accurate estimates difficult, but it is likely that there are 30 cases a year of invasive melanoma in children in Australia. Retrospective databases have been set up overseas, but prospective databases would be preferable even though they are more costly and resource intensive. SF suggested that data collection for a prospective paediatric melanoma database in should include predisposing factors and pathology, and that a tissue bank should also be considered.

QN. What is your definition of paediatric?
Up to 18 years, but you would probably have to look at 3 groups: pre-pubescent, then those up to 18 years of age and then the younger adults (up to 21 years of age).

QN. Would an international rather than national approach to setting up a paediatric database be better?
Ideally an international approach would be better as it would give you greater numbers to look at subgroups. Ben Brady suggested that SF contact Len Sender in Los Angeles who is interested in this area of work.

Comment. In the paediatric age group you need to be careful of the pathology review because most of what is called melanoma is actually benign spitz nevus that has been misread. Also spitzoid and paediatric melanoma outside the spitz context has a high rate of SLN positivity but a low rate of progression to life-threatening melanoma. We should not be subjecting children to intervention in the face of this evidence. Melanoma in children is a different disease to that in adults. If you are going to proceed with a paediatric database it should be prospective, online and auspiced, funded and managed by one group. A common data set will be needed, as well as a quality assurance pathology review. To begin you will need to conduct a literature review of paediatric melanoma to determine what data to collect and in what age groups.

4. How can we conduct combined therapy trials effectively? – Georgina Long
Georgina Long [GL] discussed ideas for conducting systemic trials with combination therapy in metastatic disease that may provide results quickly and effectively. She discussed the pros and cons of phase I combination studies, 'pick the winner' studies and tissue studies as a surrogate for efficacy.

GL noted that traditional phase I studies to assess combination therapies are slow and expensive and dependent on the involvement of pharmaceutical companies. GL proposed an 'N=1' phase 1 trial where tissue is taken from a patient and combinations are tested for safety in a Petri dish in order to select which combination to investigate further. She conceded that an 'N=1' phase trial would not yield data on efficacy.

GL explained that 'pick a winner' trials are dependent on phase I studies already having identified suitable combinations to test, and are reliant on understanding the mutations involved with the disease based on tissue and cell line studies. The premise of 'pick a winner' studies is that you look for a signal of efficacy, and if it is absent that arm of study is closed, and this process continues until an effective combination is chosen and taken into phase III development.

GL stated that tissue studies are critical in the era of targeted therapies. She outlined a protocol being used at MIA and Westmead called the Treat, Excise, Analyse, Melanoma (TEAM) protocol. A biopsy is performed prior to giving a new therapy and then 7 days after starting treatment and at progression to look for predictors of response and resistance. GL presented some data from these tissue studies at MIA. She also discussed potential areas for research with systemic therapies including stage 4 resected to no evidence of disease, treatment beyond regression and neoadjuvant trials.

QN. Should ANZMTG consider setting up a neodjuvant group to investigate systemic therapies and RT?

That is certainly how things are progressing internationally.

QN. When secondary resistance develops it's often a heterogenous phenomenon but you're limited to the tissue sample that you have at the end of the biopsy needle. Does this not affect your results in terms of assessing predictors?
I agree so that is why we focus firstly on predictors of response rather than resistance. Sampling of the progress lesions may inform us of resistance mechanisms that may be present in some lesions in some patients only.

QN. How do you control for the variability in the site and type of biopsy when interpreting results?
We have a central coordinating pathologist who deals with the specimens when they come in which is important for quality assurance.

5. **Phase I study combining BRAF inhibitor with radiation therapy for the treatment of subcutaneous metastases from BRAF mutant metastatic melanoma – Gerald Fogarty on behalf of Tim Wang (proposal distributed with the meeting papers)**

Gerald Fogarty [GF] stated that BRAF inhibitors can produce a significant clinical response and improve survival for patients with BRAF-mutant metastatic melanoma. However, despite a good initial response the tumour eventually develops resistance to the BRAF inhibitor leading to disease progression. Radiotherapy is used for palliation in these patients, but the BRAF inhibitor has to be ceased for 24 hours prior to palliative radiotherapy and cannot resume until at least 24 hours after treatment (a requirement by the manufacturer). GF added that in pre-clinical studies BRAF inhibitor has been shown to radiosensitise BRAF-mutant melanoma cells.

This study will assess continuous BRAF inhibitor during radiotherapy at three dose levels for radiation dose escalation: 10Gy in 5 fractions, 20 Gy in 5 fractions and 25 Gy in 5 fractions. The primary endpoint is toxicity and secondary endpoints are treatment response, time to local progression, and FDG avidity on PET/CT before and after radiotherapy. The proposed sample size is 9-12 patients. The proposal involves 2 phases; the first being a proof of concept to determine safety efficacy and tolerability of the regime and the second will investigate activity of lesions in the brain.

QN. Have you considered keeping the radiotherapy dose steady and moderating the dose of BRAF inhibitor instead?
The dose of radiotherapy is the focus because we are looking a palliative radiotherapy following progression on the BRAF inhibitor. To this end a preference was stated that a palliative endpoint be evaluated.

QN. Yes but for those patients you want to give a radiotherapy dose that's going to work. The issue is that currently we have to stop the BRAF inhibitor. Could you test stopping the BRAF inhibitor versus continuing it at say 25% or 50% of the dose?
This study will address this question as we don't know if the dose of BRAF inhibitor will make up for the loss in radiotherapy dose but the study will find that out. The ultimate aim of the study is to find out if this combination is effective at controlling cerebral metastatic disease.

QN. If what you are ultimately trying to find out is what is the safety of fractionated radiotherapy and BRAF inhibitor for brain metastases, how much valuable safety information will you get from irradiating subcutaneous metastases?
I think you'd still get enough safety information to tell you that the radiation toxicity is not enhanced by the BRAF inhibitor being present. But in the next stage with the whole brain radiotherapy (WBRT) we would start with a lower fraction size and then ramp up, but here we are dealing with palliative doses.

Comment. Invitation extended to GF that a solar simulator is available at St Vincents Hospital Melbourne and this could be used to quantify the band that is causing the photo-toxic reactions to BRAF inhibitor. This resource would be available should the CI wish.

Comment. There was discussion surrounding cessation of BRAF and whether disease flares or returns to the natural course of disease. There was general consensus that no flare per se is seen in these patients.

6. **Prospective study evaluating combination therapy of BCG vaccine and ipilimumab for patients with stage III/IV disease – Jonathon Cebon (proposal distributed with the meeting papers)**

Jonathon Cebon [JC] explained that intralesional (IL) BCG can be effective in inducing the regression of cutaneous metastatic melanoma. The monoclonal anti-CTLA-4 antibody ipilimumab was recently approved by the Federal Drug Administration in the US as an anticancer therapy for melanoma. In view of the favorable clinical effect of these two approaches and the potential for synergy, the proposed study will evaluate repeated dosing of ipilimumab administered following IL BCG in patients with unresectable and progressive metastatic cutaneous melanoma. It is anticipated that antigen specific T cell responses will be primed by BCG and can subsequently be amplified by ipilimumab.

JC outlined some potential problems with this regimen including the likelihood that BCG would induce intense local inflammatory responses that may be enhanced by ipilimumab. BCG can also disseminate and cause symptoms hence isoniazid will be used prophylactically to kill off life BCG prior to ipilimumab being given. The primary objective is assessment of safety and secondary objectives are assessment of efficacy and immunogenicity (using Seromics). A single centre pilot study is currently under consideration by the Austin Hospital Ethics Committee. The pilot has a sample size of 9 evaluable patients with possible expansion to 18 evaluable patients. If a strong signal of activity is seen with this combination and it is shown to be safe, more patients will be recruited, specifically patients with readily accessible subcutaneous or in-transit disease where lesions can be readily measured, biopsied and injected with BCG. The primary endpoint of the pilot is evaluating safety and tolerability of the regime. If the pilot is successful the proposal is to proceed to a multicentre randomised clinical trial.

QN: Why are you choosing BCG?

BCG has been chosen because the manufacturers of ipilimumab will only support combination studies with currently accepted treatments for melanoma. Discussions are currently underway with the manufacturer.

QN. Are you concerned about hepatic toxicity with isoniazid?

We are only using it for a short term for a month.

QN. Why not use a heat-killed BCG vaccine to lessen the chance of dissemination?

The live infection is what probably enhances the immune response, but we don't know that. The strain of BCG is important as some are more toxic than others.

7. **Prospective non-comparative trial examining safety & efficacy of combining Ipilimumab and palliative radiotherapy in patients with metastatic melanoma – Kathy Pope and Nicole Haynes (proposal distributed with the meeting papers)**

Kathy Pope [KP] reported that there are few clinical data regarding the use of Ipilumimab combined with palliative radiotherapy. Given recent results showing ipilimumab improves overall survival in some patients, the use of this agent is increasing in melanoma. It has been suggested that radiotherapy may increase the effectiveness of Ipilimumab, as shown in preclinical mice models in breast and lung cancers however there is yet no evidence for melanoma. Nicole Haynes [NH] presented an overview of mechanisms of action and pre-clinical data in this context.

KP reported that the aim of the proposed study will be to assess the safety and effectiveness of concurrent Ipilumimab and palliative radiotherapy for treatment of soft tissue metastases (subcutaneous nodules and nodal disease). The intervention will be ipilimumab treatment (randomisation to 3mg/kg or 10 mg/kg) and palliative radiotherapy (physician's discretion - 8Gy/1#, 20Gy/5# usually). The primary endpoint is safety [percentage of patients experiencing serious adverse events in the first 3 months of treatment]. Secondary objectives are response rate at irradiated and un-irradiated sites, duration of response, overall survival and biomarkers. Eligible patients will be those with stage IIIc or IV metastatic disease that is amenable to biopsy

and measurement, and a sample size of 30 patients is proposed. KP is interested to collaborate with both ANZMTG and TROG.

QN. What is the rationale for the sequencing of radiotherapy and ipilimumab?
We don't know what is the best sequence, and are only guided by overseas protocols and pre-clinical studies. KP confirmed her preference would be to dose the same day as RT treatment. She reported another current study run by Stanford University with up to a 48 hour window between radiotherapy and dosing.

QN. Where is your control group as you cannot demonstrate the contribution of ipilimumab without one?
There is none in this trial but we will consider this for future trials. We may do internal controls in the same patient in this phase I study to assess the contribution of ipilimumab, but this is study is only for safety.

Comment. Priming the immune system with radiotherapy can induce a primarily regulatory or primarily effector response. Adding ipilimumab will then accelerate this immune response causing either a complete response (effector response has been accelerated) or disease progression (regulatory response has been accelerated). I suggest you monitor the peripheral blood to see what the population of effector and regulatory cells in the immune system are doing as otherwise you may lose the effect of the ipilimumab in all this noise, and this may also give you an answer on safety earlier.

Comment. A recommendation was to remove RECIST criteria and only use immune response as an endpoint.

Comment. BMS is running a current trial evaluating the efficacy of 3mg v 10mg / kg and these results may influence the proposed trial design.

8. (i) Melanoma vaccine timed immunotherapy trial and (ii) ILI common data set collection – Brendon Coventry

Brendan Coventry [BC] presented an overview of the Vaccinia Melanoma Cell Lysate (VMCL) vaccine trial (Hersey P et al, JCO 2002) that suggested a small subset of patients with stage 3 disease were responding to the vaccine. More recent work in patients with stage 4 disease suggested that vaccine frequency could affect response to the vaccine, and that repetitive ongoing vaccination achieved a strong, durable complete response rate (CRR 18.9%) and overall response rate (ORR 81%) that are comparable to response rates achieved with the newer agents that are available. The efficacy of the vaccine is also dependent on the timing of vaccination and whether this occurs during expansion of effector cells versus expansion of regulator cells in the immune system.

The first proposal is for a RCT comparing timed/targeted VMCL therapy with or without chemotherapy versus standard untimed/random VMCL with or without chemotherapy. Serial blood tests will be carried out to assess the pre-existing endogenous immune response (as per oscillation in cycle of effector vs regulator cells). The target recruitment would be 60 patients per arm and this would require 3-4 sites to recruit the required numbers in a timely manner.

QN. How often do you conduct your serial CRP measurements?
Daily as this is needed to get more accurate results. You need to obtain enough points to resolve the curve. Our patients go to the nearest pathology centre to have their CRP measurements done.

(ii) ILI common data set collection

The second proposal is to collect an Isolated Limb Infusion (ILI) common data set. BC reported that ILI data from 5 centres were currently being collected but that it would be easier if a common data set were collected prospectively. Consultation would be required to develop a uniform protocol. Data that would be collected could include standard demographics, clinical outcomes and immunological profile given the large bystander response with some cancers. BC noted that the establishment of such a common data set would be a world-first and provide the largest standardised database for ILI and its outcomes to inform improved application of this technique.

Comment. Centralising blood collection through DHM with courier shipments to Royal Adelaide Hospital could work well.

9. A multicentre randomised clinical trial evaluating adjuvant radiotherapy vs imiquimod vs observation for high risk lentigo maligna post resection – John Kelly

John Kelly [JK] explained that the aim of this proposed study was to compare the efficacy of Imiquimod versus radiotherapy for unresected lentigo maligna. The recruitment target is 150 patients aged over 18 years, those aged <60 years will receive imiquimod and those >60 years will be randomised to either imiquimod or radiotherapy. Follow up is proposed at 12 and 24 months using Woods lamp examination, dermoscopy or confocal microscopy. Endpoints would include recurrence of lentigo maligna, disease-specific mortality and QoL. Details of the imiquimod dosing schedule and radiotherapy protocol are to be determined. JK reported that sites in Sydney, Melbourne and Brisbane had expressed interest in this trial.

Comment. MIA has initiated a new high risk lentigo maligna clinic in Sydney. All clinics are represented at the clinic which is coordinated by Dr Pascale Guitera.

QN. What is the recurrence rate for lentigo maligna for each of these treatments when they're used as monotherapy?

For radiotherapy approximately 70-80% of patients have a durable response, but no long-term follow up data are available for imiquimod. Excisional studies at the end of treatment show complete response rates of 50-80%.

QN. Why have a cut-off of 60 years for radiotherapy, isn't it discriminatory to have age limits to enter a trial?

This is driven by concern about the long-term cosmetic impact of radiation, but the protocol is at an early stage and input on whether there should be age limits is welcomed.

QN. How will you assess the extent of the lentigo maligna?

It will be based on the best surgical attempt at excision ,which for whatever reason, cannot be made complete and the tumour goes to the edges. There would be room in the protocol to put in confocal or shave biopsy assessment of that, so we could consider in the protocol some assessment of the extent of the residual lentigo maligna at baseline.

QN. Why does the proposal list observation as a third arm?

The study compares imiquimod versus radiotherapy for residual lentigo malinga following resection. There may be an option to use it in say in very elderly patients who may refuse surgery or who are unsuitable for surgery, but the majority of patients would have had a resection but incomplete excision.

QN. Guidelines for lentigo maligna also recommend cryotherapy, will you include this as an option?

Most studies with cryotherapy are small with little follow up. My personal experience with cryotherapy is that it results in a lot of recurrence down the track so I think it is a poor option.

QN. Will you compare effectiveness of assessment with Woods lamp, dermoscopy and confocal microscopy?

Yes as some centres will not have confocal so it will be good to capture this data.

10. A population study investigating the incidence of advanced melanoma in WA - a prospective study – Carolyn Williams (proposal distributed with the meeting papers)

Carolyn Williams [CW] reported that the population database for melanoma in WA was set up over 6 years ago and recruitment stopped in March 2010.

SKMRC approached all melanoma patients via the GP diagnosis records via the Cancer Council Western Australia Cancer Registry. A total of 1643 samples have been collected (52% patients consented). CW presented data on the information collected including demographic information (e.g. age, gender, family history, sun exposure, etc) and pathology records and also reported that serum, DNA and RNA had been collected from a subset of patients.

The proposal is to re-engage the population of volunteers in WA to monitor them prospectively, and to also collect additional data with the assistance of national collaborators towards a national population database.

QN. Did you collect any tissue?
No, but we would like to discuss tissue collection as part of the proposal.

QN. Is the database accessible to others?
Yes, data has been used by local researchers but is available to other researchers and the application involves a simple online process and it's free to access.

11. Quality of life in melanoma – Donna Milne
Donna Milne [DM], Senior Nurse Coordinator, Skin and Melanoma Service, Peter MacCallum Cancer Centre presented a proposal for a QoL study in melanoma. The key points of the proposal are:

- Background – need to identify patients at greatest need of supportive care
- Aim – to understand the clinical, behavioural and attitudinal characteristics of patients with melanoma attending follow up
- Potential design options – cross sectional survey; or concurrent study with survey and qualitative study on healthy life-style behaviours; or prospective, longitudinal mixed-methods study
- Patients – stages 1-3 (non-stage IV melanoma) who have had any treatment past or current
- Clinical characteristics – standard demographics; histological features of diagnosis, etc
- Behavioural and attitudinal characteristics – distress, anxiety, depression, supportive care needs, QoL and healthy life-style behaviours
- Potential outcome measures – Distress Thermometer, Impact of Events Scale, Brief Symptom Inventory 53; Hospital Anxiety and Depression Scale or State-Trait Anxiety Inventory; Supportive Care Needs Survey or Peter Mac Supportive Needs Survey Tool; FACT-M or EORTC QLQ-30 for QoL; skin screening behaviours.

Comment. John Kelly reported that his group had received funding to do a survivorship study in southern Victoria and suggested there was potential for collaboration.

Comment. Julie Winstanley reported that the new EORTC Melanoma Manual will be available for piloting in 3-6 months and could be incorporated into this study if the timing was suitable. She offered to discuss selection of instruments with DM.

Comment. Discussion ensued about the type of interventions that may follow on from this study and DM confirmed she is not yet sure what they would be. Some suggestions included nurse-led clinics and melanoma-specific cancer support help lines (eg. Cancer Council helpline). DM confirmed that this proposal had been presented to the PC4 Group New Proposals Workshop during the year.

QN. Will you assess the quality of clinical follow up?
This may be considered for the next phase once our interventions have been developed. DM noted that during the discussions at both the PC4 and ANZMTG meetings how important others considered the longer term follow up data for the proposal and she is considering including it in the current proposal.

CURRENT ANZMTG CLINICAL TRIAL PRESENTATIONS

1. **ANZMTG 01.09RP QoL & QoL activities – Julie Winstanley**
   Improving Quality of Life measurement for melanoma patients: Validity and reliability study of QOL instruments in a NSW population (MELQOL) & EORTC Melanoma Module (MELMOD)

   Julie Winstanley [JW] reported that QoL is becoming increasingly important in melanoma trials hence it is important to ensure that QoL instruments are reliable and appropriate for melanoma. At present there is confusion as to which instruments to use and generic cancer instruments (SF36, QLQ-C30) being used have not necessarily been validated for melanoma. There is need for melanoma-specific instruments and a need to develop instruments in languages other than English to reflect the international nature of research.

   The MELQOL study aims to assess how existing instruments behave in an Australian melanoma population and within Australian research activities, with the view to developing new items to measure QoL. JW advised that only two specific instruments exist for melanoma, the rarely used MM-Module (which has not been internationally validated) and the more commonly used FACT-M questionnaire. JW added that results obtained from such instruments underwent factor analysis, however Rasch analysis is now the standard way to develop new scales and allows ordinal scales to be converted to interval scales which reduces measurement error. A Rasch analysis has been performed on a subscale of FACT-M and revealed that some items do not fit and could be left out. A modified FACT-M was tested at MIA and found to be working better than the original. These findings are being prepared for publication and may lead to a modified FACT-M being used in future. In addition, a new melanoma module is being developed. JW reported that the qualitative work done to date has identified a number of issues in melanoma patients that are mostly related to psychosocial issues rather than physical symptoms and treatment issues. These findings are also being written into a paper.

   JW stated that funding has recently been received from the EORTC to perform an international validation of a new melanoma module. The EORTC Melanoma Module study is currently in phase I and the module will be trialled in April or May 2012. Work is continuing on a questionnaire and when this is finalised potential sites for testing will be sought.

   QN. If most issues are not melanoma-specific but psychosocial why can't you use a generic cancer instrument like QLQ-C30?
   We are also collecting data simultaneously with the QLQ-C30 and what we're finding is that the majority of melanoma patients who are stage 1-3 are very well physically and we cannot detect any improvement in QoL using the QLQ-C30. We need to develop an instrument that actually taps into the issues that concern melanoma patients which is often not related to treatment but to living with melanoma and the desire to carry on living a normal life.

   Comment. Brendon Coventry registered his interest to be involved in any further pilot testing.

2. **ANZMTG 01.02 Adjuvant Rx – Michael Henderson**
   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 [MH] reported that this trial has closed and the final manuscript is in draft. The primary endpoint of this study is time to lymph node field relapse. The interim analysis has revealed a significant reduction in the risk of lymph node field relapse in patients who underwent radiotherapy (publication being prepared). There was no difference in relapse free survival or overall survival between the study arms at this time. The study closed at the end of 2011, and data analysis is proceeding with the final report due in mid-2012

   QN. Are there any data on lymphoedema or salvage surgery?

Yes but data for long term toxicity has not been evaluated yet. Numbers for salvage surgery are very small in the interim analysis hence it's difficult to interpret the findings.

QN. What proportion of patients received treatment other than radiotherapy?
One-third of patients received interferon.

QN. Will the findings change practice?
In patients at low risk (20-30% lymph node field relapse) I would be confident of putting them in a study of systemic therapy if they could not have radiotherapy.

QN. Did you collect tissue to compare those who did and did not relapse?
A proposal has been put forward to do molecular studies on tissue from patients who had their first relapse. Angela Hong at MIA is leading these activities.

3. **ANZMTG 01.07 WBRT Mel – Gerald Fogarty**
Whole brain radiotherapy following local treatment of intracranial metastases of melanoma – A randomised phase III trial

GF provided an overview of trial design and eligibility criteria. He reported that trial accrual had reached 67/200 patients, one of the fasting accruing WBRT trials ever. UK and Norway sites have joined the trial. A consumer DVD has been developed to assist with trial recruitment given the high rate of screen fails at some sites and will be distributed through the melanoma survivor groups (DVD has been approved by ethics). The video was shown during the presentation.

GF confirmed that some of the trial data will be shared with US Radiation Trials Oncology Group (RTOG) to conduct a substudy comparing WBRT neuro-cognitive function for patients with and without hippocampal sparing. Negotiations with RTOG are underway. GF stated that hippocampal sparing is the future of WBRT and that this was an important proposal to evaluate the impact on hippocampal sparing. GF confirmed that the current WBRT Mel protocol allows for hippocampal sparing, approved by ethics but is not being utilised at present.

GF reiterated that recruitment has been comprehensively followed and the significant patient contribution from MIA and Radium Hospital Norway was noted. GF confirmed that a number of substudies have commenced this year.

4. **ANZMTG 01.07 WBRT Mel Substudy – Rachael Morton**
Health economic evaluation of WBRT trial

Rachael Morton [RM] reported that WBRT is resource intensive in terms of capital equipment and staff costs. Treatment costs in Australia in terms of Diagnosis-Related Group (DRG) are estimated at >$20,000 per patient for a course of 10 fractions which is comparable to the cost for other cancer treatments. The effects of WBRT in melanoma are unknown including whether there is improved intracranial control, improved survival and the effects on neurotoxicity and QoL. RM noted that WBRT may increase or decrease Health-Related QoL (HRQoL) and this will be formally assessed as part of this substudy.

RM stated that no health economic studies have been done for WBRT in melanoma. This substudy will assess, from an Australian health care system perspective, what are the incremental costs and benefits of WBRT compared to observation in the WBRT Mel trial. The primary endpoint of the WBRT trial is distant intracranial failure at 12 months so the primary endpoint of the substudy will be incremental cost per distant intracranial failure avoided. Secondary outcomes will be cost per life year gained and cost per quality-adjusted life year. The QLQ-C30 and Brain Metastases Module will be used to assess QoL. RM explained the concept of plotting the results on a cost-effectiveness plane. RM concluded that the substudy will produce some reliable estimates of cost effectiveness, and the analysis of individual patient

data will permit a range of statistical exploration particularly looking at subgroup differences. It is hoped that this type of evaluation will help to guide health policy decisions regarding allocation of resources.

QN. Should health economic analysis be included in all such studies?
CA is looking to support health economic evaluation as part of investigator-initiated studies. For some trials however modelling of health economic outcomes is a better way to go.

5. **ANZMTG 01.09 Mel D – Rachael Morton**
Vitamin D following primary treatment of melanoma at high risk of recurrence: A pilot placebo controlled randomised phase II trial

RM reported that a loading dose of 500,000 IU plus monthly doses of 50,000 IU will be used to achieve a 1,25(OH)2 vitamin D ≥ 80 nmol/L. The primary endpoint is dose sufficiency of this high-dose vitamin D regimen. Secondary endpoints include patient compliance and safety (calcium levels, kidney function and kidney stones). To date 19 have been randomised (target of 75 patients) and there have been 63 screen failures, and 1 patient withdrawal. RM said that accrual was slow but progressing, and that no safety issues had been reported to date.

If the phase II trial is positive a phase III trial will be proposed which will be a multicentre RCT.

QN. Is sun exposure being documented?
This was originally planned however the trial management committee considered that capturing this information was difficult and it may be considered for the phase III design.

6. **ANZMTG 02.09 RTN2 – Matthew Foote**
A randomised phase III trial of post-operative radiation therapy following wide excision of neurotropic melanoma of the head and neck

MF reported that the aim of this study is to determine if radiotherapy after surgery improves local control. The primary endpoint is time to in-field relapse and secondary endpoints include patterns of relapse, toxicity and QoL. The study has a target recruitment of 100 patients. Seed funding of $20,000 has been provided by TROG, and central data management is being done at Princess Alexandra Hospital (PAH). Capitation for non-PAH centres is $2000 per patient, and a grant submission will be made to try and improve capitation. The study is open at PAH, Mater Hospital, and Peter Mac, and will be opening soon at Royal Brisbane Hospital, MIA/Royal Prince Alfred Hospital/Poche Centre, and Westmead. To date 6 patients have been randomised and the pace of accrual is expected to improve once other additional sites are opened. MF reported that there is overseas interest from sites in NZ, UK (awaiting protocol amendment), Italy and Canada.

7. **JWCI Stage IV – John Thompson**
A phase III randomised trial of surgical resection with BCG versus best medical therapy as initial treatment in stage IV melanoma

JT reported that this trial run by Don Morton of the John Wayne Cancer Institute, California had opened but only 8 patients had been randomised internationally. 14 hospitals are open (9 in USA and 5 internationally). ANZMTG will centrally coordinate the ANZ sites. The trial involves the randomisation of patients with AJCC stage IV melanoma from a cutaneous melanoma or metastases of unknown primary who are then randomised to either surgery plus BCG or best medical therapy in a 1:1 ratio. Patients who fail may then cross-over.

JT explained that the CancerVax trial showed 40% survival at 5 years in patients with resected stage 4 disease but it was unclear if this was due to BCG. The JWCI trial had been set up to answer this question. JT queried whether the trial could recruit adequate numbers given the number of competing studies (including a new immunotherapy proposal for patients with stage IV disease).

Comment. Suggestion was made that stereotactic radio surgery (SRS) could also be used on the surgical arm which may boost recruitment. JFT agreed and said this was worthwhile discussing with Don Morton.

8. MelMarT – John Thompson

UK melanoma study group: Melanoma Margins Trial

JT reported that optimal excision margins are still not known. International trials have compared 2cm vs 4cm and 1cm vs 3 cm margins but these studies have not shown any significant difference in local control or survival. MelMart will compare 1 cm vs 2cm margins with a target recruitment of 10,000 patients internationally and a 10-year follow up. Libby Paton reported that a feasibility study has been done with ANZMTG sites and any centres not contacted should email her. A final protocol from the UK (which includes a health economic evaluation) is pending and once this is available ANZMTG will begin opening local sites.

9. ANZMTG 01.10 CARPETS

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

No presentation was made for this trial.

Meeting close

Michael Henderson and John Thompson thanked the presenters and participants for their contributions and closed the meeting at 5.30pm.

Meeting concluded at 5:30pm

Appendix 1:
ANZMTG 2011 Research Meeting Attendance Record

	Name	
	Executive Committee Members	**Institution**
1	John Thompson	MIA, NSW
2	Rachael Morton	University of Sydney, NSW
3	Bryan Burmeister	Princess Alexandra Hospital, QLD
4	Michael Henderson	Peter MacCallum Cancer Centre, VIC
5	John Kelly	The Alfred Hospital, VIC
6	Ben Brady	Cabrini Health, VIC
7	Campbell Rose	ANZMTG Consumer Representative, VIC
	ANZMTG staff	
8	Elizabeth Paton	ANZMTG
9	Kate Morrow	ANZMTG
10	Hector Fuentes	ANZMTG
11	Paul Wagland	ANZMTG
	Full ANZMTG members	
12	Gerald Fogarty	MIA / Mater Sydney, NSW
13	Matthew Foote	Princess Alexandra Hospital, QLD
14	Julie Winstanley	University of Sydney, NSW
15	Richard Fischer	Peter MacCallum Cancer Centre, VIC
16	Donna Gillen	The Alfred Hospital, VIC
17	Marisa Cikos	The Alfred Hospital, VIC
18	Kathy Pope	Peter MacCallum Cancer Centre, VIC
19	Anne Woollett	Melbourne Melanoma Project
20	Phillip Parente	Austen Health, VIC
21	Victoria Atkinson	Princess Alexandra Hospital, QLD
22	Grant McArthur	Peter MacCallum Cancer Centre, VIC
23	Carolyn Williams	SKMRC, WA
24	Andrew Spillane	MIA, NSW
25	Georgina Long	MIA, NSW
26	Alex Menzies	MIA, NSW
27	Julie Howle	MIA, NSW
28	Angela Neville	Launceston General Hospital, TAS
29	Brett Frenkiel	Royal Children's Hospital, VIC
30	Robert Tasevski	Royal Melbourne Hospital, VIC
31	Brendon Coventry	Royal Adelaide Hospital, SA
32	Martin Ashdown	University of Melbourne, VIC
33	Sian Fairbank	Peter MacCallum Cancer Centre, VIC
34	Simon Donahoe	Peter MacCallum Cancer Centre, VIC
35	Marisa Cikos	The Alfred Hospital, VIC
36	Jonathan Cebon	Austin Health, VIC
37	Vanessa Estall	Peter MacCallum Cancer Centre, VIC
38	Jonathan Tomaszewski	Peter MacCallum Cancer Centre, VIC

39	Carmen Hansen	Peter MacCallum Cancer Centre, VIC
40	Elizabeth Lehunt	Peter MacCallum Cancer Centre, VIC
41	Damien Kee	Peter MacCallum Cancer Centre, VIC
42	John Spillane	Peter MacCallum Cancer Centre, VIC
43	Mark Shackleton	Peter MacCallum Cancer Centre, VIC
44	Christopher McCormack	Peter MacCallum Cancer Centre, VIC
45	Margaret Chua	Peter MacCallum Cancer Centre, VIC
46	Nicole Haynes	Peter MacCallum Cancer Centre, VIC
47	Michael Lim-Joon	Peter MacCallum Cancer Centre, VIC
48	Rod Sinclair	St Vincents Hospital Melbourne, VIC
49	Jessica Dortmans	Royal Perth Hospital, WA
50	Catherine Mandel	Peter MacCallum Cancer Centre, VIC
51	Jim Hagekyriakou	Peter MacCallum Cancer Centre, VIC
52	Tina Thorpe	Peter MacCallum Cancer Centre, VIC
	Associate ANZMTG members	
53	Stephen McKechnie	Medical Manager - Roche
54	Ciara O'Callaghan	Medical Manager - Roche
55	Paul White	MMP CRG Representative
56	Nicola White	Consumer
57	Linda White	Consumer

Apologies received from the following members:

1	Margaret McJannett
2	Jacquie Ruhl
3	Julie Teraci
4	Carol Johnson
5	Jim Tomlinson
6	Robyn Saw
7	Lauren Haydu
8	Jon Stretch
9	Rick Kefford
10	Kerwin Shannon
11	Angela Hong
12	Bruce Armstrong
13	Michael Brown
14	Ian Davis
15	Tim Wang
16	Siddhartha Baxi
17	Matt Carlino
18	Leuh Peut
19	Pascale Guitera
20	Nicola Ware