

NCRI Melanoma Clinical Studies Group

Introduction

The Melanoma CSG has continued to work to its strategic plan to develop studies in melanoma and non-melanoma skin cancer, interact with other agencies and act in an advisory capacity on national initiatives. The Group has addressed most of the areas highlighted in the 2007 Progress Review and the activities of the Melanoma CSG have contributed to the successful review of the NCRN in 2009.

Membership and structure

The Group has attracted a number of new members, bringing additional expertise to both the main committee and subcommittees. Dr Catherine Acland has strengthened dermatology representation. Prof Bertil Damato has joined the Rare Melanoma Subgroup, bringing internationally recognized expertise in uveal tract melanoma. Dr Peter Bullivent stood down as Consumer Representative for personal reasons and we are grateful to him for his contribution to the Group during the short time he was a member.

The subgroups were reviewed and reconfigured to better reflect opportunities for research over the next 3-5 years. It was recognized that histopathology is a key to accurate diagnosis and treatment, and to research. Many of the research questions addressed by histopathology are part of a bigger project requiring annotated clinical data to correlate with clinical outcomes. It was felt that these would be best addressed by having a histopathology lead on the main committee and this person would also be a member of the translational subgroup rather than a separate subgroup and the Pathology Subgroup was disbanded. The lead histopathologist could be involved with and support the development of guidelines in histopathology particularly where these would allow research questions to be addressed.

The responsibilities of the Education, Prevention and Early Detection Subgroup were also moved back to the main committee, with a nominated lead for this. Professor Rona Mackie will stand down from the CSG in 2009 after many years of dedicated service, and the group will miss her input greatly. Professor Lesley Rhodes will take on the responsibility for this area of work, and is progressing studies in this area. The group is continuing to carry out very high quality epidemiological studies looking at the molecular genetics of melanoma under the leadership of Professor Julia Newton Bishop.

Uveal tract melanoma has been moved from the main committee to the Rare Melanoma Subgroup led by Professor Gus Dagleish. Dr Ernie Marshall will continue to lead on this and the group is strengthened by the addition of Professor Bertil Damato who has an interesting ocular melanoma.

The Non-Melanoma Subgroup continues to make good progress under the leadership of Dr Jerry Marsden with no change in structure.

Professor Mark Middleton took over leadership of the Translational Subgroup, which continues to make good progress and is a major contributor to the Translational CSG.

Tracey Heslop was appointed as portfolio coordinator and took up post in June 2009. Based in Manchester, she will be working 0.3 WTE to develop radiotherapy initiatives, studies in organ transplant patients and raise the profile of the Group.

Portfolio and accrual

The Group has had a further successful year. The AVAST-M aims to randomise 1320 adult patients with stage IIB, IIC or III cutaneous melanoma to either one year of adjuvant bevacizumab (Avastin) or no treatment. The trial is being performed in collaboration with industry (Roche) and the principal investigator is Dr Pippa Corrie, Cambridge University, and opened in July 2007. There are currently 361 patients accrued (27% of target - 16th April 2009) at 32 sites in the UK, and average of 24 patients per month. Attempts to open centres in Europe have so far been unsuccessful because of lack of funding. The second Independent Data and Safety Monitoring Committee took place on 12th March 2009. The IDSMC reviewed the data from the planned interim analysis to assess patient safety and tolerability as well as available outcomes data after recruitment of the first 300 patients. The IDSMC were very happy with recruitment and data collection. There were no safety or ethical concerns with the trial. The TRICC grant for the project Predicting Relapse of Melanoma at High Risk of Recurrence (PROM), has now been activated and is being led by Prof Mark Middleton, University of Oxford.

ITEM, a phase II study of imatinib in patients with metastatic choroidal melanoma was funded by the Feasibility Study Committee in February 2008 and has completed the first phase of the study. The study is being led by Dr Ernie Marshall and is running in 4 centers. The data were reviewed as planned by an IDSMC. There were no ethical or safety issues. Based on the initial outcome data, it was recommended that the study should progress to the second phase.

A pilot study looking at the role of Imiquimod versus surgery in the treatment of lentigo malignant, funded by the Research for Patients Benefit Committee, is being led by Dr Jerry Marsden and is currently in set up.

The Melanoma Lifestyle Study is a feasibility study looking at diet, sun exposure and at the protective role of vitamin D for relapse in malignant melanoma, and was initially funded by the Population and Behavioral Science Committee Grants Committee of CRUK. The principal investigator is Professor Julia Newton-Bishop, Leeds University and the study continues to accrue patients.

A number of studies have closed to recruitment or have been written up during the year.

EORTC 18991, a randomised trial of adjuvant PEG-Intron versus observation in patients with completely resected stage III malignant melanoma, completed accrual in 2006. The data were presented at the ASCO meeting in 2007 and were recently published in the Lancet.

EORTC, a randomized study of ganglioside vaccine versus no treatment as adjuvant therapy for patients with intermediate risk melanoma, was stopped early by the IDSMC. They found an excess of deaths due to disease in the treatment arm. The data was presented at the ASCO meeting in 2008.

EORTC 18032, was a randomised phase III study evaluating the role of dose intensified temozolomide as first line treatment for metastatic melanoma completed accrual in 2007. The chief investigator for this international study was Professor Poulam Patel, University of Nottingham, and the UK was a major recruiter contributing 29% of all the patients recruited in Europe and 21% of the total patients recruited internationally. The results study showed no survival benefit for dose intensified temozolomide over standard chemotherapy. The study results were presented at the European Society of Medical Oncology Meeting in September 2008 and will be submitted for publication.

526 patients were recruited to melanoma studies in 2008/09, representing 6.3% of incidence cases. 292 patients were recruited to RCTs (3.5% of incidence cases) and 234 patients to non RCTs (2.8% of incidence cases).

A list of all studies in the portfolio can be found in Table 1 below:

Table 1: Melanoma CSG portfolio

Acronym	Title	PI(s)	Status
Annual Zoledronate	Effect of an annual infusion of Zoledronate on bone mineral density in patients on long term follow up with cancer remission and anti neoplastic treatment induced bone loss study	Professor Robert E Coleman	Closed
AVAST-M	Adjuvant aVASTin Trial in high risk Melanoma - A randomised trial evaluating the VEGF inhibitor bevacizumab (Avastin), as adjuvant therapy following resection of AJCC stage IIB (T4aN0M0) IIC (T4bN0M0) and III (TxN1-sM0) cutaneous melanoma.	Dr Pippa Corrie	Open
EORTC 18001-88001	Phase III randomized study of adjuvant NA17.A2 antigen and melanoma differentiation peptides in HLA-A2positive patients with primary ocular melanoma at high risk of relapse	Dr Ernie Marshall	Closed
EORTC 18032	Extended schedule, escalated dose Temozolomide versus Dacarbazine in Stage IV Metastatic Melanoma: A randomised phase III study of the EORTC melanoma group	Professor Poulam Patel	Closed
EORTC 18961	Post-operative adjuvant ganglioside GM2-KLH/QS-21 (BMS-248479) vaccination treatment after resection of primary cutaneous melanoma thicker than 1.5 mm (AJCC/UICC	Professor Angus Dalglish	Closed

	stage II, T3-T4N0M0), a 2-arm multicenter randomized phase III trial vs observation		
EORTC 18981	Trial 18981 Temozolomide versus Temozolomide + whole brain radiation in stage IV melanoma patients with asymptomatic brain metastases.	Dr Juergen Becker	Closed
EORTC 18991	Trial 18991 adjuvant Pegintron treatment in stage III melanoma versus observation after regional lymph node dissection a multicenter randomized phase III trial	Professor Alexander Eggermont, Professor Martin Gore	Closed
ITEM	A phase II study of Imatinib in the treatment of patients with metastatic uveal melanoma	Dr Ernie Marshall	Open
Long Term Effects of Chemo on Bone	An investigation of the long term effect of chemotherapy on bone, particularly focusing on the incidence of osteoporosis in such patients	Professor Robert E Coleman	Closed
MAGE 3	Randomised, open phase II study of immunisation with the recombinant MAGE-3 protein combined with adjuvant ASO2B or AS15 in patients with unresectable and progressive metastatic cutaneous melanoma.	Dr Paul Lorigan	Closed
Melanoma Cohort Study	The melanoma follow-up and case-control family study	Professor Julia Newton-Bishop	Open
Melanoma Family Study	A study of familial melanoma (MREC/99/3/45)	Professor Julia Newton-Bishop	Closed
Melanoma Late Relapse Study	A nested case control study of late relapsing melanoma (MREC 99/3/36)		Closed
MOLEMATE	The Molemate UK trial: The management of suspicious pigmented lesions in primary care.	Dr Fiona Walter	Open
NCRN025 - Industry study	NCRN025 - Industry study	Dr Matthew Cooper	Suspended
NCRN058	A randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy of ABT-888 in combination with Temozolomide versus	Dr Mark Middleton	Open

	Temozolomide alone in subjects with metastatic melanoma		
NCRN062 - INDUSTRY STUDY	NCRN062 – Industry study	Professor R Charles Coombes	In set up
NCRN063	NCRN063 – Industry study	Dr Mark Middleton	In set up
NCRN084	NCRN084 – Industry study	Dr Adrian Murray Brunt	In set up
PTK787 / Camel 02	A phase II study to evaluate the efficacy and safety of PTK787 in patients with metastatic cutaneous melanoma	Dr Pippa Corrie	Closed
SINS	A randomised controlled trial of excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma.	Dr Fiona Bath-Hextall	Closed
SLNB feasibility Study in patients with melanoma	Study investigating the diagnosis and treatment of early lymph node involvement in patients with primary cutaneous melanoma by sentinel lymph node biopsy with or without completion of lymphadenectomy & molecular markers	Professor Tim Eisen	Closed
The Melanoma Lifestyle Study	The Melanoma Lifestyle Study	Professor Julia Newton-Bishop	Open

Trials in development

A phase II study of nilotinib in mucosal or acral lentiginous melanoma with a mutation in c-kit mutation is being led by Dr James Larkin from the Royal Marsden Hospital. This study was approved by CTAAC and drug is being provided by Novartis.

The Suave study, a phase II study of sunitinib in uveal tract melanoma is being led by Dr Ernie Marshall. The study was funded by the Feasibility Studies Committee and study drug provided by Pfizer. This study will follow on from the ongoing ITEM study.

A phase II feasibility study looking at the role of adjuvant chemotherapy in Merkel Cell Cancer with a major translational component looking at the role of polyoma virus in this tumour is being led by Dr Neil Steven. An application has been submitted as a full proposal to the MRC, the outline proposal was accepted in January 2009.

Two study outlines were submitted for funding as part of the NCRI/AZ alliance. The first was a study looking at cediranib in patients with brain metastases, and was a joint proposal with the UGI CSG. This study was not approved for a number of reasons and

will be progressed in a different way. The second study was withdrawn as a result of the premature closure of a similar study in the US for futility reasons. Two further proposals have been discussed and outline proposals are being worked up.

Two studies recently submitted to the PBSC were not funded. The first was a pilot study looking at the role of follow up in very low risk patients and the second a study looking at the increased incidence of high risk melanoma in older males, hoping to understand the relative contributions of age and gender related biology and of behaviour. The PIs for these studies are currently in discussion with the funding bodies.

A study looking at the risk of skin cancer in organ transplant recipients is currently in development, with a plan to submit for funding within the next 6 months.

Three first line phase studies have been approved by the by the Industry Trials Adoption Committee and are being set up in the UK. These are a study looking at the role of a *mek* inhibitor in *braf* mutated patients sponsored by Astra Zeneca, a study combining a PARP inhibitor with chemotherapy sponsored by Abbott Pharmaceuticals and a study of a novel vaccine supported by Oncovex.

Meetings

The Group continues to run a joint annual meeting with the Melanoma Study Group. The next meeting will be in Cambridge in June 2009, hosted by Dr Pippa Corrie. The Group also has a fixed slot at the winter MSG meeting to update members of the activities and seek opinions etc.

Research presentations have been or will be made at the Perspectives in Melanoma Meeting 2008, World Melanoma Congress 2009, joint ESMO/ECCO Meeting 2009, and Second World Melanoma Centers Meeting 2009. The results of a randomized phase II study adopted by ITAC and sponsored by Centocor were presented at ASCO 2009.

Collaborations

The Melanoma CSG embraced the AZ alliance and has submitted two study outlines and has discussed a number of others that will be submitted within the next 2-3 months.

Merkel Cell Cancer is a very rare form of skin cancer with only 300-4000 new cases a year in the UK. In addition to the proposal submitted to the MRC, we are in discussion with colleagues in Germany to collaborate on a clinical database for these patients and with colleagues in Germany and the US to carry out a definitive study looking at radiotherapy in early stage disease.

Recognising that others have expertise that complement that of the Group, we have initiated discussions with the Teenage Cancer Trust and the Teenage and Young Adults CSG to look at issues around sun exposure and how to communicate risk in this unique group of patients.

We continue to work closely with the EORTC Melanoma Group and have been major contributors to recent studies.

Other activities

Involvement with appropriate national initiatives in skin cancer is considered an important role for the Group. Over the last year we have contributed to one NICE scoping exercises and we are reviewing the NICE draft information on sun protection resources and physical changes to the environment to prevent skin cancer for the Royal College of Physicians.

The Group is represented on the National Cancer Intelligence Network (NCIN) Skin Site Specific Reference Group. Accurate epidemiological and outcomes data will facilitate research in this area.

3-year strategy

The strategy for the next 3 years is to:

- Continue to provide clinical trials for patients with high risk resectable melanoma and first line therapy for metastatic disease
- Build on the interactions with industry
- Develop trials in non-melanoma skin cancer
- Develop the link with the Melanoma Study Group
- Continued closed interaction with the EORTC Melanoma CSG
- Foster further interaction with other professional groups representing melanoma and non-melanoma skin cancer patients
- Ongoing review of membership and breadth of representation

Priorities for next year

The Group's priorities for next year are to:

- Further increase access to novel agents for early phase studies through interaction with Industry
- Submit for funding specific clinical trial proposals organ transplant recipients
- Support and develop consumer input
- Develop the interaction with the Teenage Cancer Trust and the TYA CSG.
- Increased profile of the Group with other professional and collaborative research groups
- Develop metrics for collection and handling of clinical samples for translational research

Dr Paul Lorigan, Chair

Appendix 1

2008/09 Publications and abstracts

Professor Newton Bishop senior author, with contribution from the NCRI Melanoma CSG Environmental Risk Factors for relapse in melanoma. Beswick et al. *European Journal of Cancer* (in press)

Eggermont et al A randomised phase III study of Pegylated Interferon versus no treatment in patients with stage III melanoma. *Lancet* (in press).

Eggermont et al EORTC 18961: Post-operative adjuvant ganglioside GM2-KLH21 vaccination treatment vs observation in stage II (T3-T4N0M0) melanoma: 2nd interim analysis led to an early disclosure of the results. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 9004) (EORTC study with acknowledged contribution from the NCRI Melanoma CSG)