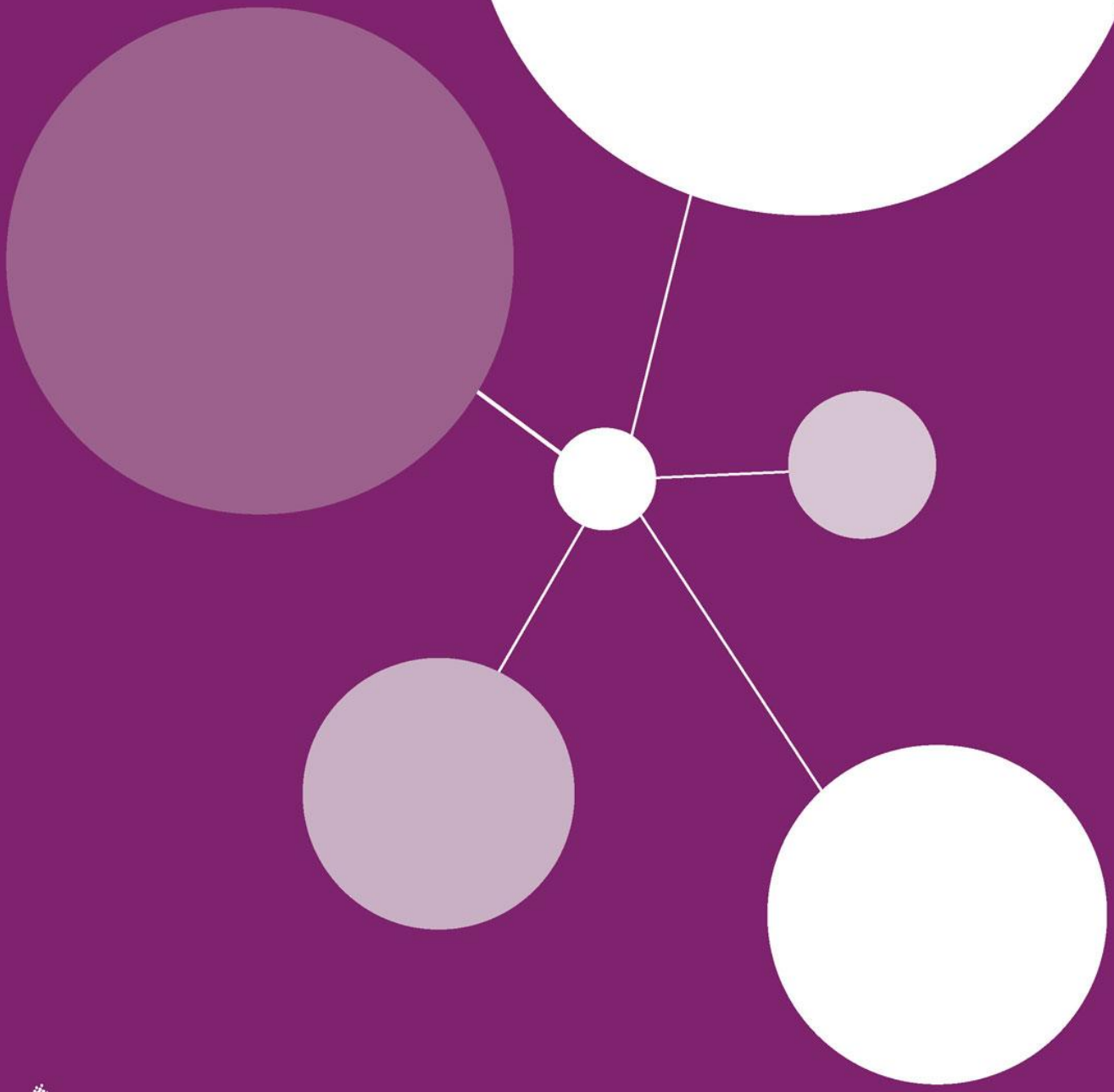
NCRI
National
Cancer
Research
Institute

NCRI Skin Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Skin Cancer CSG
Annual Report 2014/15

1. Executive Summary (including top 3 achievements in the year)

The skin cancer portfolio continues to be dominated by industry-sponsored interventional trials in advanced melanoma. Three registration trials of combination targeted therapies set the standard of care for BRAF mutant advanced melanoma in 2014 and each trial has involved UK recruitment, with CSG members co-authoring each high profile publication. Authorship is largely a reflection of high numbers of recruited patients, generated by effective referral pathways within our regional research networks.

Our academic programme has focused on 'niche' patient groups, with studies funded in 2013/4 to maintain our programme in *c-Kit* mutant melanoma, uveal melanoma and a new study evaluating the abscopal effect of radiotherapy combined with immunotherapy. The cutaneous melanoma trial, PACMEL, continued to struggle with recruitment due to the remarkable changing clinical practice and introduction of now 2 lines of immunotherapy pushing cytotoxic chemotherapy back to 3rd and 4th line therapy. It is hoped that the recruitment target will be achieved in the coming year with the aid of new sites opening in Germany.

A key goal for the CSG is to develop new studies in non-melanoma skin cancer. The Non-melanoma Subgroup met with considerable conflict between surgeons, dermatologists and oncologists regarding trial design of squamous cell carcinoma adjuvant therapies, with strongly held views threatening acceptance of randomising patients, but a proposal will be taken forward in 2015/16. On the other hand, working with the Subgroup, Dr Neil Steven has been awarded an EME grant of around £2M, focusing on primary management of Merkel cell cancer.

The Group has been frustrated by two particular funding rejections this year: MelMart and INTERIM. Both were rated highly by their external independent peer reviewers, but these trials were not considered sufficiently interesting to justify funding. MelMart is moving forward as a feasibility study now coordinated in Australia, with the UK relegated to a participating site. Roche had agreed to supply all IMP free of charge plus a £200K grant for INTERIM, but this international lead will now be lost to the USA and the EORTC.

2. Structure of the Group

The CSG structure has not significantly changed since the last report.

At the end of 2014, were able to appoint 2 CSG trainees (1 medical oncologist, 1 dermatologist) from an impressive and extensive list of applicants as part of the new NCRI CSG trainee initiative. Both have impressive CVs and are highly motivated, as evidenced by their attending the

November CSG meeting which was held within a few days of their appointment. Both are already being integrated in group activities, which will both provide education and experience for the individuals as well as contribute additional expertise and manpower to facilitate progression of new studies.

As raised at the Skin Cancer CSG's last progress review, we have sought to develop 'SPED' as a priority area and Dr Fiona Walter was appointed to the CSG at the start of the year. We have worked this year to build several initiatives in early diagnosis of both primary and secondary melanoma. Working with Dr Walter, I felt we were ready to request formalising a new Early Diagnosis Subgroup for the CSG (a progress review recommendation) and submitted an application in April. Our application was rejected, with a suggestion that the skin cancer work could be absorbed in that of the Primary Care CSG Early Diagnosis Subgroup, to which Dr Walter was recently appointed as Chair.

Post report note: an early diagnosis task group has since been established, which meets prior to each Skin CSG meeting

The LCRN Skin Cancer Subspecialty Leads were appointed this year and although not formally part of the CSG, will hopefully become an important part of our extended structure in the future. To assist in integration, they will receive a 2 page summary 'newsletter' after each CSG meeting and will be invited to the 3 yearly strategy day (next due November 2015).

3. CSG & Subgroup strategies

Main CSG

The NCRI Skin Cancer CSG strategy established after the 3 year progress review in February 2014 is to enhance our research activity, by:

- Developing trials in early stage disease and/or diagnosis and prevention
- Establishing a screening and prevention subgroup to promote development of research in this area
- Developing a translational research programme
- Working with Pharma/CROs to assure rational and optimal placement of commercial studies
- Working with other CSGs in relevant areas, e.g. CNS, TYA, palliative and supportive care, primary care, SPED

In addition, the CSG aims to:

- Complete recruitment to the current academic cutaneous melanoma trial, PACMEL
- Maintain a programme of trials in rare melanoma subtypes: uveal and C-Kit mutant melanoma
- Secure a stable, high recruiting national study to replace AVAST-M
- Establish trials in common (SCC) and uncommon (Merkel cell) non-melanoma skin cancer
- Establish novel combination therapy studies, exploiting modalities such as radiotherapy and immunotherapy

Progress towards achieving these goals is discussed in Section 12.

Non-Melanoma Subgroup (Chair, Dr Catherine Harwood)

The aim of the Non-melanoma Subgroup is to promote and support high quality, multi-centre, clinical trials, translational research and other activities in the field of non-melanoma skin cancer. In particular, the group aims to (1) support initiatives in providing an evidence base for treatment of the common keratinocyte skin cancers (SCC and BCC), and (2) foster and support research for rarer non-melanoma skin cancers such as Merkel cell carcinoma, DFSP, Kaposi sarcoma.

Our 2 key aims defined at the CSG strategy day in November 2012 were the development of trials in management of MCC (with additional development of UK MCC guidelines) and of primary SCC.

In March 2015, the MCC study, *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),* was finally approved for funding by EME, with an award of almost £2Million.

UKMCC-1, a single arm clinical trial of pazopanib in advanced Merkel cell carcinomais recruiting steadily and we hope accrual to be completed by the end of the year. Progress in SCC is proving more challenging. The SPOT study (RfPB funded SCC prevention with topical treatment in organ transplant recipients) finally opened to recruitment.

There has been extensive consultation regarding an SCC clinical trial, COMMISSAR: Conventional versus Mohs micrographic Surgery for high risk SCC and the role of Adjuvant Radiotherapy. This multicentre, randomised study of management of primary high risk SCC in terms of excision margins and use of adjuvant RT has been designed as a 2-stage RCT for high risk SCC in which 6mm excision margins will be compared with Mohs' micrographic surgery in the first stage and adjuvant radiotherapy versus observation in the second stage. Primary outcome will be locoregional recurrence at 3y. The trial design has been a protracted process and has been presented to surgical and dermatology stakeholders. The TMG is now conducting a clinician survey on trial design and willingness to participate, which is being sent out to SSMDTs, and a patient perspective survey. Working groups are being established to finalise RT, surgery and pathology protocols and power calculations are in progress. The aim is to apply for funding in the last quarter of 2015.

Other initiatives in DFSP (Mohs' versus wide local excision) and BCC (CIRCLE – Comparison of Imiquimod Randomised against Curettage or Conventional Local Excision) are under consideration.

4. Task groups/Working parties

Early Diagnosis

In our efforts to address early diagnosis of melanoma, Dr Corrie and Dr Walter brought together a group of colleagues both within and without the CSG to focus on this area, so in effect generating a working party (see Appendix 1). We formally met for the first time on 14th May, prior to the main CSG meeting and the meeting was very productive. We discussed 3 initiatives:

1) MelaTools (Lead: Dr Walter) and MelaScreen proposal (Leads Dr Walter & Dr Corrie)

Melatools has completed accrual and the health economic analysis of this study will inform what population might be relevant to take forward a melanoma screening feasibility study, MelaScreen

2) ASICA Phase II trial proposal – Achieving Self Directed Integrated Cancer Aftercare (Lead Professor Murchie)

Professor Peter Murchie, academic GP in Aberdeen, has developed and evaluated a novel App to aid patients after primary melanoma resection to self assess for the risk of melanoma recurrence. Professor Murchie would like to test this in a randomised feasibility study. The group set about designing the study proposal.

3) Staging and surveillance of high risk resected stage III melanoma (Leads Dr Gupta & Dr Brown).

Dr Gupta summarised the results of an sMDT survey of staging and surveillance practice across the UK and presented this at the main CSG meeting. He and Dr Brown will consider the recommendations of the group for potential future research in this area.

Uveal Melanoma National Guidelines

A task group chaired by Dr Paul Nathan and funded by Melanoma Focus was set up to establish national guidelines for uveal melanoma management. This extensive and challenging task was completed this year and the guidelines have been endorsed by NICE and published, setting new standards of care from which to continue to build our clinical trials framework in this rare melanoma subgroup.

Translational research

Prior to our November CSG meeting, CSG members Professor Middleton, Professor Plummer and Dr Corrie met with Professor Christian Ottensmeier to discuss opportunities for translational research. The strongest funding opportunity was for the CSG to work with Professor Ottensmeier as collaborators on his immune monitoring CRUK Accelerator award application. The CSG provided support at a number of levels – scientific expertise at specific sites including Oxford and Newcastle, and access to patient tumour samples via the regional research networks which would be coordinated through the NCRI and LCRNs. Unfortunately, the grant application was not successful, so this area of research remains on hold.

5. Patient recruitment summary for last 5 years

In the Skin CSG portfolio, 8 trials closed to recruitment and 5 opened.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2010/2011	786	632	786	500	9.5	6.0
2011/2012	705	505	691	505	8.3	6.1

Table 2 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	534	140	534	140	4.3	1.1
2013/2014	534	403	530	403	4.3	3.3
2014/2015	622	217	609	175	4.9	1.4

6. Links to other CSGs, international groups and network subspecialty leads

CSGs

The rejection of our application to establish a new Early Diagnosis Subgroup will bridge a link with the Primary Care CSG.

Our CSG has an interest to pursue opportunities for stereotactic radiotherapy for solitary/limited brain metastases. Our radiation oncologist has been tasked with discussing opportunities to work with the Brain CSG in this regard.

Europe

We are utilising links with DeCOG to assist with recruitment to PACMEL.

The EORTC has 2 adjuvant studies involving the UK: EORTC 18081 is open to recruitment in a number of UK sites, but numbers are very low due to tight eligibility criteria (ulcerated primary with negative SLN). EORTC 1325 (see above) is due to open in Q2 2015 and should be a high recruiting study.

Australasia

The UK has assisted in recruiting to 2 ANZMTG trials this year. Both studies involved challenging patient groups and hence the numbers of recruited patients are very low.

As already discussed, the ANZMTG is now leading conduct of the MelMart study – an opportunity for the UK to lead internationally lost, sadly.

7. Funding applications in last year

Funding submissions made by the Skin CSG in the last year can be seen below in table 3:

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
None			
November 2014			
Melanoma Margins Trial (MelMarT): A Phase III, multi-centre, multi-national randomised control trial investigating 1cm v 2cm wide excision margins for primary cutaneous melanoma	Full Application	Mr Marc Moncrieff	Not funded
PERM: A Randomised Phase II Study Assessing Enhancement of Response to MK3475 by High Dose Palliative Radiotherapy in Patients with Advanced Melanoma	Feasibility Application	Dr James Larkin & Dr Paul Nathan	Funded
March 2015			
INTERIM: A randomised phase II study of intermittent schedules of vemurafenib and cobimetinib in patients with BRAFV600 mutated unresectable or metastatic melanoma	Feasibility Application	Dr Pippa Corrie	Not funded
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
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)	EME – Full application	Dr Neil Steven	Funded

8. Collaborative partnership studies with industry

Industry-sponsored international multicentre registration melanoma interventional trials are a major part of our research activity. Currently there are 5 advanced and 2 adjuvant commercial studies open to recruitment and 2 more in set up.

In virtually all cases, CSG members are involved in recruiting to these commercial studies, are often the UK Chief Investigators and have contributed to the trial development and design at preliminary advisory boards and steering committees. Access to these trials is highly competitive and the UK may hope to gain between 5 and 8 sites generally. Efficient recruitment to time and target is important as this may help to influence future placement of trials here and expansion of site numbers. Successful recruitment to commercial sponsored studies may also influence provision of novel agents for investigator-initiated studies.

According to the January 2015 NIHR recruitment report, of the last 19 commercial studies in the melanoma portfolio, 84% recruited to time and target, so hopefully this is a very positive signal to industry regarding UK capability and efficiency.

9. Impact of CSG activities

Clinical Practice

The CSG has been intimately involved in bringing key commercial sponsored registration trials to the UK, which have literally transformed management of advanced melanoma in the last 5 years. This has enabled patients to access state of the art treatment in a timely fashion, closing the gap on the US and other international leaders where sometimes breakthroughs happen in advance of UK access. Early access within trials also enables clinicians to gain experience with using new agents and managing new toxicities and therefore be in a strong position to influence commissioning decisions both nationally and locally.

CSG members provide expert advice on behalf of the RCP for NICE appraisals, of which there have been 10 technology appraisals either completed or underway in the last 5 years associated with new treatments for advanced melanoma, which have and continue to radically change clinical practice. Of the 4 completed appraisals ALL have provided positive guidance, enabling patients in England to access the same treatments available in the USA and other leading nations and so improve outcomes from this devastating disease.

There have been several other different types of NICE appraisals associated with melanoma and non-melanoma skin cancer in the last year, including electrochemotherapy, skin cancer prevention guidance and melanoma management guidelines, all of which the CSG has contributed significant feedback to.

Although NICE appraisals are not directly research activities, CSG members are well placed to advise on interpretation of clinical trial results and how they should impact on clinical practice. It should be noted that this is quite time consuming activity.

The CSG is keen to embrace the new LCRN skin cancer subspecialty leads and will be inviting them to our forthcoming strategy day in November 2015.

Funding for academically led/developed trials

The Group has been disappointed by two particular funding rejections this year: MelMart and INTERIM. Both studies were rated highly by their external independent peer reviewers, but these trials were not considered sufficiently interesting to justify funding. MelMart is moving forward as a feasibility study now coordinated in Australia, with the UK relegated to a participating site. Roche had agreed to supply all IMP free of charge plus a £200K grant for INTERIM, but this international lead will now be lost to the USA and the EORTC.

The CSG would also like to raise a concern about NCRN 2951 (SUMIT) being rated red on the RAG report. The first site to open SUMIT globally was in the UK, the study recruited over 100% target in the UK and overall, the trial closed ahead of time even though it was recruiting a rare group of advanced uveal melanoma patients.

10. Consumer involvement

The CSG has 2 consumer representatives: John Rouse and Simon Rodwell. Mr Rodwell co-founded the national melanoma charity, Melanoma Focus and is its CEO. Mr Rouse retired from the CSG in May 2015 and has been instrumental in identifying a potential replacement for him,

who attended as an observer at our May 2015 meeting and we hope will apply to be our consumer representative in due course.

During the past year Mr Rouse was a member of the NICE Melanoma Guideline Development Group, and an Involvement Coach for Cancer Research UK, talking to PhD students about the benefits of patient and public involvement in clinical trial management and implementation. He has attended an EORTC training course, and a Melanoma Patients Network Group meeting in Brussels. Mr Rouse has worked with Jo Bird at Sheffield on the UNITI study, and was a judge for the Quality in Cancer awards, presented at the Britain Against Cancer conference. He attended the NCRN/ECMC/AZ Novel Compounds workshop, and the National Cancer Patients conference. He is an active member of the Facebook Group "Melanomamates", now with over 1,000 patient and carer members. We are very grateful to his contributions over several years now and wish him well in his retirement.

Mr Rodwell has been involved in developing a short film, 'Taking Part in Clinical Trials: how patients can make a difference', which he scripted and presented, funded by the Eastern Academic Health Sciences Network. The film aims to encourage patient involvement in clinical trials. He was also a member of trials management groups for the Platelet Responsiveness and Outcome from Platelet Transfusion (PROmPT) study (now closed) and the MelaTools Programme (GP and patient interventions to improve early diagnosis of melanoma in primary care), and advised on various trial patient leaflets and information sheets for investigator-initiated studies based in the Eastern Region. In his role as CEO of Melanoma Focus, Mr Rodwell is responsible for the charity's interaction with the CSG. Now well established as the main national melanoma charity, Melanoma Focus has a 220-strong professional membership that includes the UK's leading melanoma clinicians, scientists and specialist nurses. Examples of collaborative initiatives with the CSG include joint responses to NICE STAs and posting, on a members-only web page, background information about the NCRI's efforts to persuade NHS England to continue to allow the use of a combination BRAF/MEK inhibitor therapy. During the year Melanoma Focus's activities included: continued support and funding for the uveal melanoma guidelines, which gained NICE accreditation in January 2015; the start of a new project to draw up clinical guidelines for mucosal melanoma; recruitment of further Trusts to the melanoma database project; and a call for submissions for a third research study funded under the charity's patient impact programme. Meanwhile the two Melanoma Focus annual study day meetings remain popular with the melanoma community and provide fora for discussion of NCRI research activities.

11. Open meetings/annual trials days/strategy days

The CSG contributes to the national melanoma conference run by the national charity, Melanoma Focus, on an annual basis. The last meeting, held at the Royal College of Obstetricians and Gynaecologists, October 2014, was highly successful and provided a forum to present an update of the NIHR portfolio. The NCRI CSG Secretariat provided a trials summary booklet, which was included in the delegate pack, name badges for delegates and speakers and assisted with registration on the day.

12. Progress towards achieving the CSG's 3 year strategy

Key aims of the CSG's and progressing towards achieving them are outlined below:

- Developing trials in early stage disease and/or diagnosis and prevention

- Establishing a screening and prevention subgroup to promote development of research in this area - a set of lead clinicians has been identified, met in May 2015 and is well placed to become a formal subgroup, which in our view would facilitate progress. We will appeal the decision not to approve formation of the Early Diagnosis Subgroup.
- Developing a translational research programme - our plan to collaborate on a major CRUK Accelerator award application led by Professor Ottensmeier was unsuccessful when CRUK rejected it earlier this year
- Working with Pharma/CROs to assure rational and optimal placement of commercial studies - limited success, but ongoing communications. Establishment of the new LCRN subspecialty leads may be helpful in this regard. We are already utilising these appointments to ensure regional placement of non-commercial studies.
- Working with other CSGs in relevant areas, e.g. CNS, TYA, Supportive & Palliative Care, Primary Care, SPED - Interaction with primary care and SPED have been discussed; need to pursue Brain CSG.

In addition, the CSG aims to:

- Complete recruitment to the current academic cutaneous melanoma trial, PACMEL - strategy is in place, by extending to new sites in Germany
- Maintain a programme of trials in rare melanoma subtypes: uveal and C-Kit mutant melanoma - new non-commercial studies (SELPAC and PIANO) due to open in 2015/16
- Secure a stable, high recruiting national study to replace AVAST-M - MelMart funding application was rejected; now opening across surgical sites for participation in a Australia-led study
- Establish trials in common (SCC) and uncommon (Merkel cell) non-melanoma skin cancer, establish novel combination therapy studies, exploiting modalities such as radiotherapy and immunotherapy - EME Merkel cell study funded; PERM funded

13. Priorities and challenges for the forthcoming year

The main priorities for the Skin CSG are to:

- Establish the Early Diagnosis Subgroup
- Submit an SCC study to a national funding body
- Integrate the new LCRN Subspecialty leads in the new NRCI-LCRN research structure

The main challenges for the Skin CSG are to:

- Complete accrual to PacMel against competition from Pharma studies
- Secure funding for a large scale, high recruiting study (SCC or other)
- Identify and fund a translational research strategy

14. Concluding remarks

Melanoma systemic therapy continues to evolve based on remarkable outcome improvements identified in clinical trials of novel agents. The UK plays a significant role in the conduct of these ground-breaking trials and therefore in changing global clinical practice. Most of these trials are currently controlled by industry and the CSG works to influence their conduct at every step of the process, from trial design through to NHS commissioning.

The CSG has a key role in developing the non-commercial trial portfolio and seeks to prioritise research in rarer melanoma subtypes of less interest to industry. There is also huge untapped opportunity in non-melanoma skin cancer. However, as demonstrated by MelMart, funding of large scale trials is challenging.

A positive new initiative this year is the introduction of a new group of specialist doctors charged with working between LCRNs and the NCRI CSGs, providing a key link between trial participation and development. We look forward to working with our new skin cancer subspecialty leads over the coming year and hope they will aid us in developing a useful portfolio, which can be delivered successfully over the coming years.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Non-melanoma Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Dr Pippa Corrie (Skin CSG Chair)

Appendix 1

Membership of the Skin CSG

Name	Specialism	Location
Dr Rebecca Lee*	Clinical Research Fellow	Manchester
Dr Jim Lester	Clinical Oncologist	Sheffield
Mr Simon Rodwell	Consumer	Bury St Edmunds
Mr John Rouse	Consumer	Clay Cross
Dr Girish Gupta	Dermatologist	Lanarkshire
Dr Catherine Harwood	Dermatologist	London
Dr Charlotte Proby	Dermatologist	Dundee
Dr Rubeta Matin*	Dermatologist	Oxford
Dr Fiona Walter	General Practioner	Cambridge
Dr Ewan Brown	Medical Oncologist	Edinburgh
Dr Pippa Corrie (Chair)	Medical Oncologist	Cambridge
Dr Sarah Danson	Medical Oncologist	Sheffield
Dr James Larkin	Medical Oncologist	London
Professor Mark Middleton	Medical Oncologist	Oxford
Dr Clive Mulatero	Medical Oncologist	Leeds
Dr Paul Nathan	Medical Oncologist	Mount Vernon
Professor Fiona Bath-Hextall	Professor of Evidence Based Healthcare	Nottingham
Mr Oliver Cassell	Surgeon	Oxford
Mr Marc Moncrieff	Surgeon	Norwich
Professor Keith Wheatley	Statistician	Birmingham

* denotes trainee

Membership of the Subgroups

Non-melanoma Subgroup		
Name	**Specialism**	**Location**
Dr Christina Yap	Biostatistician	Birmingham
Dr Pat Lawton	Clinical Oncologist	Nottingham
Mr Simon Rodwell	Consumer	Bury St Edmunds
Dr Catherine Harwood (Chair)	Dermatologist	London
Dr John Lear	Dermatologist	Manchester
Dr Charlotte Proby	Dermatologist	Dundee
Dr Jerry Marsden	Dermatologist	Birmingham
Dr Neil Steven	Medical Oncologist	Birmingham
Dr Jenny Nobes	Medical Oncologist	Norwich
Dr Steve Nicholson	Medical Oncologist	London
Mr Marc Moncrieff	Surgeon	Norwich

Early Diagnosis 'Task Group'		
Name	**Specialism**	**Location**
Dr Girish Gupta	Dermatologist	Glasgow
Dr Catherine Harwood	Dermatologist	London
Dr Rubeta Matin*	Dermatologist	Oxford
Dr Charlotte Proby	Dermatologist	Dundee
Professor Peter Murchie	General practice	Aberdeen
Dr Fiona Walter (Chair)	General practice	Cambridge
Dr Ewan Brown	Medical Oncologist	Edinburgh
Dr Pippa Corrie	Medical Oncologist	Cambridge

*denotes trainee

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

Our strategy established after the 3 year progress review in February 2014 is to enhance our research activity, by:

- Developing trials in early stage disease and/or diagnosis and prevention
- Establishing a screening and prevention subgroup to promote development of research in this area
- Developing a translational research programme
- Working with Pharma/CROs to assure rational and optimal placement of commercial studies
- Working with other CSGs in relevant areas, eg. CNS, TYA, palliative and supportive care, primary care, SPED

In addition, the CSG aims to:

- Complete recruitment to the current academic cutaneous melanoma trial, PACMEL
- Maintain a programme of trials in rare melanoma subtypes: uveal and C-Kit mutant melanoma
- Secure a stable, high recruiting national study to replace AVAST-M
- Establish trials in common (SCC) and uncommon (Merkel cell) non-melanoma skin cancer
- Establish novel combination therapy studies, exploiting modalities such as radiotherapy and immunotherapy

B – Non-melanoma Subgroup Strategy

The aim of the Subgroup is to promote and support high quality, multi-centre, clinical trials, translational research and other activities in the field of non-melanoma skin cancer. In particular, the group aims to (1) support initiatives in providing an evidence base for treatment of the common keratinocyte skin cancers (SCC and BCC), and (2) foster and support research for rarer non-melanoma skin cancers such as Merkel cell carcinoma, DFSP, Kaposi sarcoma.

Our 2 key aims defined at the CSG strategy day in November 2012 were:

1. Development of a clinical trial for management of MCC (with additional development of UK MCC guidelines)

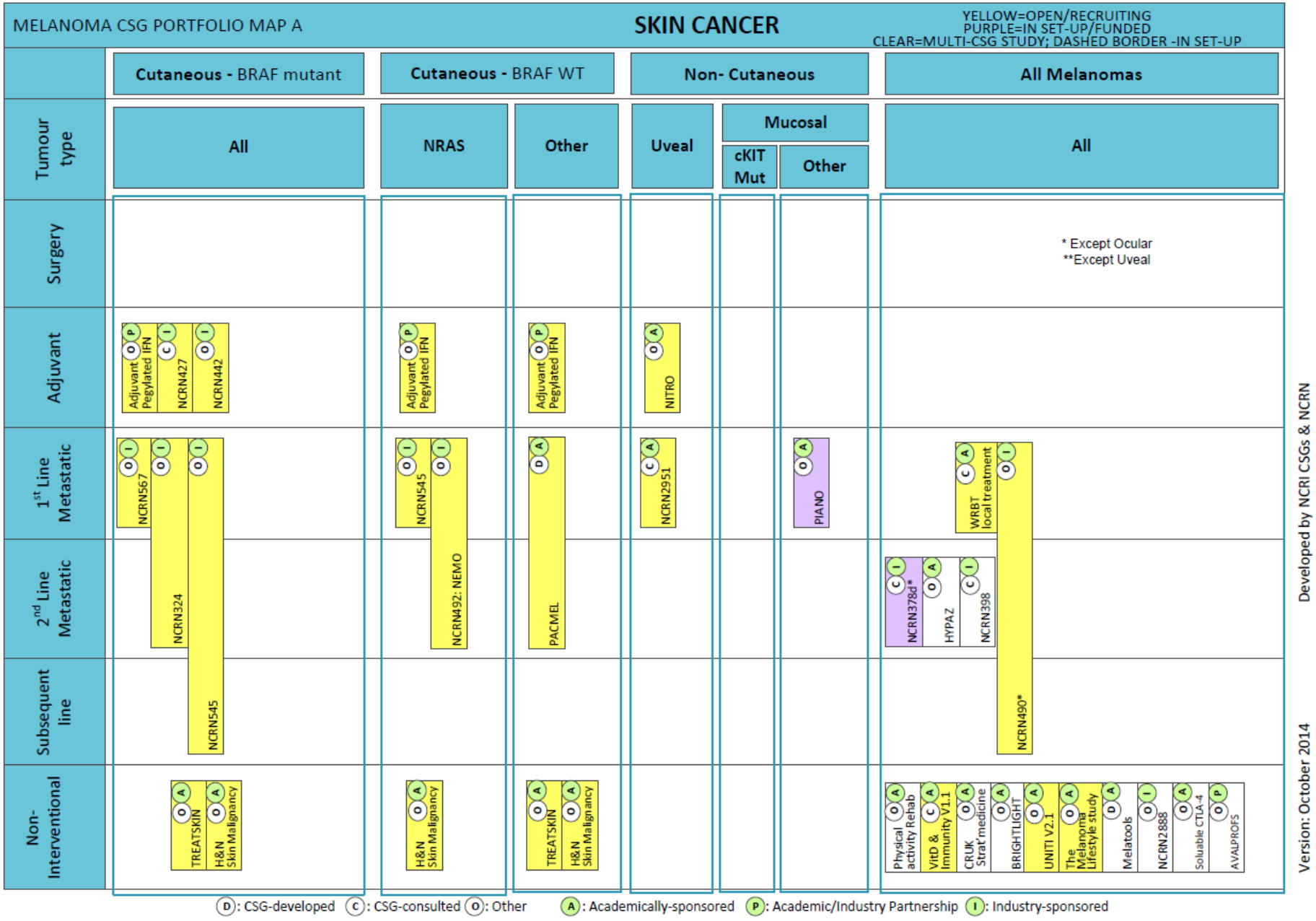
2. Development of a clinical trial in management of primary SCC.

Appendix 3

Portfolio maps

Key for Skin Cancer Industry Studies –August 2014

NCRN324	**BRIM-P** - An open-label, multicenter, single-arm, Phase I dose-escalation with efficacy tail extension study of RO5185426 in pediatric patients with surgically incurable and unresectable Stage IIIC or Stage IV melanoma harboring BRAFV600 mutations
NCRN378d	An Open-Label, Multicenter, Phase 2 Study of Poly(ADP-Ribose) Polymerase (PARP) Inhibitor E7449 in Combination with Temozolomide (TMZ) in Subjects with Advanced Melanoma - PHASE II ARM 2 (cohort 3)
NCRN398	**Image** - A Multi-National, Prospective, Observational Study in Patients with Unresectable or Metastatic Melanoma
NCRN423	**COMBI-V** - BRAF inhibitor, dabrafenib + MEK inhibitor, trametinib vs. BRAF inhibitor vemurafenib
NCRN426	A phase III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 1 to 2 months schedule to adults of 18 years of age with solid tumours.
NCRN427	Dabrafenib (GSK2118436) + trametinib (GSK1120212) vs. placebo
NCRN442	Vemurafenib (ro5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence
NCRN490	A Phase 2 Study of Ipilimumab in Children and Adolescents (12 to < 18 years) with Previously Treated or Untreated, Unresectable Stage III or Stage IV Malignant Melanoma
NCRN492	**NEMO** - A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus Dacarbazine in patients with previously untreated advanced unresectable or metastatic NRAS mutation positive melanoma
NCRN494	Exploratory open label study of GM-CSF coding oncolytic adenovirus CGTG-102, with low dose cyclophosphamide. Part I in patients with refractory injectable solid tumours; Part II in soft tissue sarcoma, breast cancer and melanoma
NCRN524	Safety and efficacy of MK-3475 vs.Ipilimumab in patients with advanced melanoma
NCRN545	An Open-Label, Phase 1, Dose-Escalation Study of MLN2480 in Patients with Relapsed or Refractory Solid Tumours Followed by a Dose-Expansion Phase in Patients with Metastatic Melanoma
NCRN567	A Phase III randomized, 3-arm, partially double-blind, multicenter, study of the combination of LGX818 plus MEK162 compared with vemurafenib, and of LGX818 compared with vemurafenib for the treatment of patients with unresectable stage IIIC or Stage IV melanoma with BRAF V600 mutation
NCRN2712	An Open-Label, Multicenter, Phase 1/2 Study of Poly(ADP-Ribose) Polymerase (PARP) Inhibitor E7449 as Single Agent in Subjects with Advanced Solid Tumors or with B-cell Malignancies and in Combination with Temozolomide (TMZ) or with Carboplatin and Paclitaxel in Subjects with Advanced Solid Tumors - PHASE I
NCRN2888	A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors
NCRN - 2951	SUMIT - Selumetinib + Dacarbazine VS Placebo + Dacarbazine in Metastatic Uveal Melanoma A Randomised, Double-Blind Study to Assess the Efficacy of Selumetinib (AZD6244, Hyd-Sulfate) in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine as First Systemic Therapy in Patients with Metastatic Uveal Melanoma (SUMIT)
NCRN-2960	A Phase 2 Open-label, Multicenter, Single arm Trial to Evaluate the Immunoprofile of Subjects With Unresected Stage IIIB - IVM1a Melanoma Treated with Talimogene Laherparepvec (protocol ID: 20120325)
NCRN-3309	A Phase 1b/2, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With MK-3475 for Treatment of Previously Untreated, Unresected, Stage IIIB to IVM1c Melanoma (protocol ID: 20110265)


MELANOMA CSG PORTFOLIO MAP A
SKIN CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Cutaneous - BRAF mutant
Cutaneous - BRAF WT
Non- Cutaneous
All Melanomas
Tumour type
All
NRAS
Other
Uveal
Mucosal
cKIT Mut
Other
All
Surgery
Adjuvant
1st Line Metastatic
2nd Line Metastatic
Subsequent line
Non-Interventional
* Except Ocular
**Except Uveal
Adjuvant Pegylated IFN
NCRN427
NCRN442
NITRO
NCRN567
NCRN324
NCRN545
NCRN492: NEMO
PACMEL
NCRN2951
PIANO
WRBT local treatment
NCRN3778d*
HYPAZ
NCRN398
NCRN490*
TREATSKIN
H&N Skin Malignancy
Physical activity Rehab
VitD & Immunity V1.1
CRUK Strat medicine
BRIGHTLIGHT
UNITI V2.1
The Melanoma Lifestyle study
Melatools
NCRN2888
Soluable CTLA-4
AVALPROFS
(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored
Developed by NCRI CSGs & NCRN
Version: October 2014

MELANOMA CSG PORTFOLIO MAP B
SKIN CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Non-Melanoma
SCC
BCC
Merkel cell
Other
Pre-Diagnosis
Neoadjuvant
Surgery
Adjuvant
Metastatic
Non-interventional
SPOT
Axi-STS
UKMCC1
SCART
Physical activity Rehab
CRUK Strat' medicine
BRIGHTLIGHT
Skin Cancer stem cells
H&N Skin Malignancy
Mol Path of non-melanoma
NCRN2888
AVALPROFS
(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored
Version: October 2014
Developed by NCRI CSGs & NCRN

Appendix 4

Publications in the reporting year

PACMEL

Coupe N, Corrie P, Hategan M, Larkin J, Gore M, Gupta A, Wise A, Suter S, Ciria C, Love S, Collins L, Middleton MR. A phase 1 dose escalation trial of trametinib (GSK1120212) in combination with paclitaxel (2015). *Eur J Cancer* 51(3):359-66.

NCRN 423 COMBI-V

Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, Lichinitser M, Dummer R, Grance F, Mortier L, Chiarion-Silnei V, Drucis K, Krajsova I, Hauschild A, Lorigan P, Wolder P, Long GV, Flaherty K, Nathan P, Ribas A, Marin A-M, Sun P, Crist W, Legos J, Rubin SD, Littl SM, Schadendorf D. Improved overall survival in melanoma with combined dabrafenib and trametinib (2015) N Engl J Med Jan 1; 372(1) : 30-9

COMBI-D

Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma (2014) *N Engl J Med*. Nov 13;371(20):1877-88

Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion-Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Swann S, Legos JJ, Jin F, Mookerjee B, Flaherty K. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015 May 29. pii: S0140-6736(15)60898-4. doi: 10.1016/S0140-6736(15)60898-4. [Epub ahead of print] PMID: 26037941

Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, Grob JJ, Bondarenko I, Garbe C, Lebbe C, Larkin J, Chiarion-Sileni V, Millward M, Arance A, Mandalà M, Flaherty KT, Nathan P, Ribas A, Robert C, Casey M, DeMarini DJ, Irani JG, Aktan G, Long GV. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. *Eur J Cancer*. 2015 May;51(7):833-40. doi: 10.1016/j.ejca.2015.03.004. Epub 2015 Mar 17.

CANC - 3828 vemurafenib in patients with BRAFV600 mutation-positive malignancies

Larkin J, Del Vecchio M, Ascierto PA, Krajsova I, Schachter J, Neyns B, Espinosa E, Garbe C, Sileni VC, Gogas H, Miller WH Jr, Mandalà M, Hospers GA, Arance A, Queirolo P, Hauschild A, Brown MP, Mitchell L, Veronese L, Blank CU. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study (2014) *Lancet Oncol*. Apr;15(4):436-44.

DOC-MEK

Gupta A, Love S, Schuh A, Shanyinde M, Larkin JM, Plummer R, Nathan PD, Danson S, Ottensmeier CH, Lorigan P, Collins L, Wise A, Asher R, Lisle R, Middleton MR. A double-blind randomized phase II trial of docetaxel with or without selumetinib in wild-type BRAF advanced melanoma (2014) *Ann Oncol*. May;25(5):968-74

CO-BRIM

Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, Mandal M, Demidov L, Stroyakovsky D, Thomas L, de la Cruz Merino L, Dutriaux C, Garge C, Sovak MA, Chang I, Choong N, Hack SP, McArthur GA, Ribas A. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; 371:1867-76.

CHECKMATE 037

Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, Hoeller C, Khushalani NI, Miller WH Jr, Lao CD, Linette GP, Thomas L,Lorigan P, Grossmann KF, Hassel JC, Maio M, Sznol M, Ascierto PA, Mohr P, Chmielowski B, Bryce A, Svane IM, Grob JJ, Krackhardt AM, Horak C, Lambert A, Yang AS, Larkin J. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015 Apr;16(4):375-84. doi: 10.1016/S1470-2045(15)70076-8. Epub 2015 Mar 18.

Appendix 5

Major international presentations in the reporting year

Immunocore

M Middleton, J Evans, N Steven, P Corrie, C Mulatero, M Sznol, D Baker, G Bossi, K Adams, J Harper, A Johnson, W Shingler, D Smethurst, N Hassan, Y McGrath, B Jakobsen. A phase 1 study of IMCgp100: durable responses with a novel first-in-class immunotherapy for advanced melanoma. *AACR* 2014 abstract

Millennium study

M Middleton, DW Rasco, AJ Olszanski, P Corrie, P Lorigan, R Plummer, J Larkin, A Pavlick, X Zhou, Z Yuan, E Gangoli, M Kneisssl, V Bozon & R Gonzalez. First-in-human phase 1 study of MLN2480, an investigational pan-RAF kinase inhibitor, in patients with relapsed or refractory solid tumors, including BRF/NRAS-mutant melanoma. *Eur J Cancer* 2014;50 Suppl 6; 117 (364).