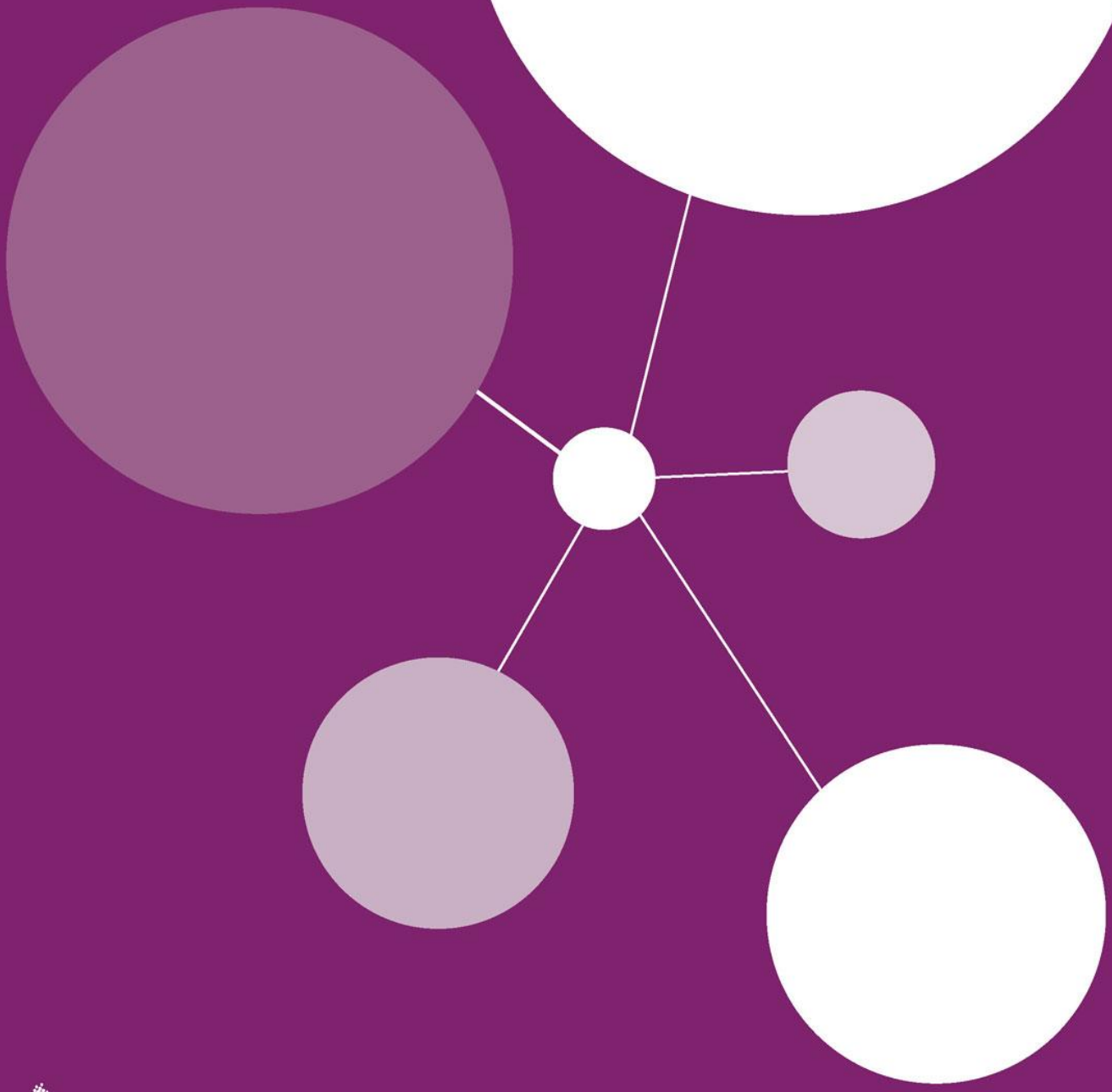
NCRI
National
Cancer
Research
Institute

NCRI Sarcoma Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Sarcoma CSG Annual Report 2014/15

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

Achievements

- First oral presentations of several of our major NCRI trials including:
  - RMS 2005 at SIOP 2014
  - Axi-STS at CTOS 2014
  - GeDDiS at ASCO 2015
- First publications from EURAMOS in major oncology journals:
  - Whelan JS, Bielack SS, Marina N, et al. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. Ann Oncol 2015; 26: 407-14.
  - Bielack SS, Smeland S, Whelan JS, et al. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. J Clin Oncol. 2015 Jun 1. DOI:10.1200/JCO.2014.60.0734.
- Appointment of Mr Lee Jeys as chair from July 2015. He will provide a focus on the local treatment of sarcomas and foster interest in research studies in surgery and radiotherapy.

Challenges

Following from the transition from the NCRN network to the Clinical Research Networks (CRN), researchers will have to work harder to justify continued infrastructure funding for cancer. It is increasingly important to meet recruitment targets, time-to-recruit and time-to-first-patient metrics. In sarcoma, it is important to develop a portfolio with a balance of observational, interventional, biomarker and commercial studies.

It remains challenging to develop successor trials in a timely fashion, but we hope that establishing working parties to focus on specific clinical questions (e.g. gynae sarcoma, lung metastases, surgical studies) will address this. We hope that the identification of Sarcoma Subspecialty Leads in each Clinical Research Network will widen participation in sarcoma studies and ensure that trials are opened promptly across the country.

2. Structure of the Group

After many years as a member (and previous chair) of the group, Professor Robert Grimer rotated off the CSG. He will continue to influence sarcoma strategy through his work as chair of the NCIN Sarcoma Site Specific Clinical Reference Group. Mr David Gourevitch and Professor Nick Athanasou also completed their terms on the CSG.

Dr Charlotte Benson, Mr Jonathan Gregory and Dr Malee Fernando joined the group bringing expertise in medical oncology, sarcoma surgery and histopathology respectively.

At the start of the reporting year we also said goodbye to one of our experienced consumer representatives, Mrs Karen Delin, who was replaced by Mr Michael Maguire in April 2014.

Following the call for trainee members, applications were received from 13 doctors in specialty training. Dr Jane Margetts and Mr Jonathan Stevenson were appointed to the Sarcoma CSG and welcomed to their first meeting in May 2015.

The structure of the subgroups remains unchanged from previous years.

3. CSG & Subgroup strategies

Main CSG

The Group maintains a portfolio of studies in soft tissue sarcomas (STS), including gastro-intestinal stromal tumours (GIST) and an increasing number of histological subtype-specific sarcomas. In first line for advanced disease, recruitment to GeDDiS was completed in January 2014 and preliminary results will be presented at ASCO in June 2015. The CSG is working on a study proposal for patients with STS metastatic to lung, but a commercial trial of treatment in first line advanced STS has opened in the interim, comparing doxorubicin + olaratumab to doxorubicin + placebo. Other systemic treatment studies are open for alveolar soft part sarcoma (CASPS), angiosarcoma and synovial sarcoma (Axi-STS), Kaposi sarcoma (SCART), and dedifferentiated liposarcoma (EORTC-1202-STBSG). A grant application has been submitted to allow UK centres to join the Scandinavian Sarcoma Group XII trial of 12 versus 36 months adjuvant imatinib in resected GIST. The group continues to work with IRCI and others to develop new protocols, for example in synovial sarcoma and desmoplastic small round cell tumours.

Studies of local sarcoma treatments are more difficult to develop and recruit to. Following the successful completion of VORTEX, IMRiS (phase 2 study of Intensity Modulated Radiotherapy in Sarcoma) is in set up. The randomised study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma (STRASS, EORTC 62092) is recruiting slowly but steadily.

The Group is keen to support translational studies and ensure that our clinical trials maximise their information yield by having translational endpoints and substudies. The International Sarcoma Kindred Study (ISKS) is a global multi-site prospective cancer genetics study that is open at several UK sites.

Bone Tumour Subgroup (Chair, Mr Craig Gerrand)

Euro Ewing 2012, a major international collaborative study of first line chemotherapy for Ewing sarcoma opened in early 2014 and recruitment is gradually increasing as more centres open. Euro Ewing 2012 is not only an important clinical study, but incorporates biological and pharmacokinetic/toxicity substudies in laboratories in Leeds and Newcastle. Two clinical trials are open for patients with advanced Ewing sarcoma – LINES and rEECur. LINES has a strong translational element, while rEEcur utilises an innovative multi-arm trial design.

There is presently no first line study for osteosarcoma on the portfolio, reflecting the lack of new agents available. Recent discussions to address this have focussed on joining studies already open elsewhere in the EU, and the feasibility of this is being investigated. However, a study of mifamutide in advanced osteosarcoma (MEMOS) and an observational study to optimise circulating tumour cell detection have opened.

To address gaps in the portfolio, a surgical studies workshop was held in November 2014. This attracted enthusiastic investigators and generated several trial ideas. One is being developed with a grant application in preparation. Another group is looking at potential studies in chondrosarcoma, with an international consensus meeting in development.

Further initiatives include a partnership with the Bone Cancer Research Trust. This presents opportunities to bring patient and charity voices to the group, increases the resources available to the group and encourages alignment of research strategies.

An exploratory meeting with members of the CLRN/NCRI Psychosocial Oncology & Survivorship CSG is planned to investigate areas of common interest.

Young Onset Soft tissue Sarcoma (YOSS) Subgroup (Chair, Dr Bernadette Brennan)

For rhabdomyosarcoma (RMS), the RMS 20015 study remains open, but discussions are advanced for a successor study. A proposal is ready to be submitted for funding to CTAAC. It includes a phase I-III design to bring in both new chemotherapy combinations and mTOR inhibitors. It will also address questions on radiotherapy, PET assessment of response using a new stratification based on the genetic fusion status of the tumours. In relapsed RMS, the VIT study recently closed. A similar successor study proposal is being developed for this patient group, incorporating the addition of an mTOR inhibitor and pazopanib in a MAMS design. The support of the YOSS Subgroup and full CSG have been obtained.

In non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), EpSSG NRSTS 2005 remains open but the malignant rhabdoid stratum has closed and is being analysed for publication. This has led to a planned meeting of a new European consortium for a European Rhabdoid study at all anatomical sites - EURO RHABDOID 2017. In addition, the first meeting of EUROJOSS took place, with the aim of setting up the first all age trial in Europe for synovial sarcoma. It included representation from all European sarcoma groups and the EpSSG which runs the largest paediatric sarcoma studies in Europe.

An ambitious application entitled “Improving effectiveness of treatments for children with soft tissue sarcomas” is being assessed by the EU scheme Horizon 2020. The overall aim is to increase the rate of survival and improve the quality of life for children with STS by optimising the effectiveness of established treatment protocols and promoting of basic research. Specifically, it

is proposed to prospectively test novel molecular markers for risk stratification of patients, assess the efficacy of circulating biomarkers for Minimal Residual Disease (MRD) and identify a rationale and provide pre-clinical evidence for new molecular therapeutic targets and anti-cancer drugs, which will then be tested in treatment protocols.

The group recognises the continuing challenges:

- to increase participation of the TYA population in trials.
- the necessity for stable international consortia to develop trials where patient numbers in the UK are small.
- obtaining access to new agents from pharma companies for younger patients.

4. Task groups/Working parties

Gynaecological Sarcoma Working Group

This working group was set up in 2011 to develop trials and improve outcomes for this long-neglected patient group. The uterine leiomyosarcoma study (CI, Dr Hatcher) has been developed through the International Rare Cancers Initiative (IRCI) and opened last year. It evaluates adjuvant chemotherapy in completely resected high grade uterine leiomyosarcoma. The HGUS study (CI, Dr Earl) has been developed by the same group and is now in set-up after obtaining CTAAC funding. It will be a randomized phase II study evaluating the role of maintenance cabozantinib in High Grade Uterine Sarcoma (HGUS) after stabilization or response to chemotherapy.

Lung Metastases Working Group

This working group is in development, led by Dr Aisha Miah. The group is working up a proposal for an observational study of all patients with lung metastases that will provide prospectively collected data on the outcomes of lung metastectomy, RFA, SABR, etc.

5. Patient recruitment summary for last 5 years

In the Sarcoma CSG portfolio, 1 trial closed to recruitment and 4 opened. Following the closure of EURAMOS and the two trials open to the generality of STS patients (VORTEX and GeDDiS), recruitment to interventional studies has fallen. Newer trials are restricted to histologically or biologically defined patient subgroups, so accrual is less.

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	174	183	128	183	-	-
2011/2012	187	207	133	207	-	-

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	194	272	151	272	4.7	7.8
2013/2014	43	195	25	195	-	-
2014/2015	145	115	145	115	-	-

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

Links with other NCRI CSGs

The Sarcoma CSG has close links with the TYA and Childrens' Cancer & Leukaemia CSGs. The Gynaecological Sarcoma Working Party is shared with the Gynaecological Cancer CSG. Several protocols developed by the Sarcoma CSG are included in the portfolios of other CSGs, e.g. Axi-STS and SCART, which are shared with the Skin Cancer CSG. During the year, new links have been forged with the Psychosocial Oncology & Survivorship CSG, which it is planned to involve in developing PROMS and QoL endpoints for studies in development.

International links

There are strong links with the EORTC Soft Tissue & Bone Sarcoma Group through many shared members and trials. We are active participants in the IRCI initiative, with two IRCI trials in the portfolio. The CASPS trial now includes centres in Australia as well as Europe. Professor Bass Hassan provides a link with EuroSARC and Dr Sandra Strauss provides a link with the USA Sarcoma Alliance for Research through Collaboration (SARC). Close collaborations are also maintained with EOI, SIOP and COSS through Professor Jeremy Whelan and Dr Bernadette Brennan. We are developing a collaboration with the Scandinavian Sarcoma Group to open their GIST trial in the UK.

7. Funding applications in last year

As noted above, a CTAAC application has been submitted for consideration at the July 2015 meeting and number of funding applications are in development. Support has been obtained from Sarcoma UK for the ISKS study to open in the UK.

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			
None			
March 2015			
None			

8. Collaborative partnership studies with industry

Six academic studies are partnerships with industry: MEMOS (Takeda), LINES (Astellas), Axi-STS (Pfizer), CASPS (AZ), PARAGON (AZ) and SCART (AZ). All six are open and recruiting. These trials address rare tumour types that would not otherwise have attracted the attention of pharma.

9. Impact of CSG activities

Our publications are testament to the high impact of our clinical research (Appendix 4). The routine management of bone and soft tissue sarcomas has been guided by NCRI-supported trials. In particular, the EORTC trials 62931 and 62012 are the foundation of STS management in the UK and Europe. 62931 confirmed that adjuvant chemotherapy offers no survival advantage over observation alone in resected high-risk soft tissue sarcoma. 62012 demonstrated no survival advantage for doxorubicin and ifosfamide over doxorubicin alone in first line chemotherapy for advanced soft tissue sarcoma. Following analysis of the MMT95 and RMS 2005 trials, IVA remains the standard chemotherapy for rhabdomyosarcoma.

Over many years, the majority of bone sarcoma patients have been treated within clinical trials including EuroEWING-99, BO-06 and EURAMOS-1, which have shaped routine clinical practice.

The trials themselves can be used as vehicles to drive service development and streamline referral pathways. The EORTC 62024 trial of adjuvant imatinib in GIST identified centres with interest and expertise in GIST, and established referral pathways for patients from GI surgeons to sarcoma oncologists. We hope that the gynaecological sarcoma trials will also foster new collaborations and pathways for these patients.

Ultimately our trials are practice-changing when they lead to new drugs being licensed (e.g. pazopanib for STS) or inform NICE, ESMO and ASCO practice guidelines. We anticipate that our NCRI-led trials, VORTEX and GeDDiS will have such impact.

10. Consumer involvement

Mr Robert Wensley

I have attended both meetings of the Sarcoma CSG during this year. During the meetings I have reported back in detail my activities as a consumer representative and also my views on the open trials, their recruitment rates, outcomes as reported and other issues raised round the table. I have, in addition, commented on trials proposed for inclusion in the CSG portfolio, including IMRiS and those submitted by Professor Chisholm and Dr McNally. A high priority for me is to support the recruitment of suitable patients to trials through close review of patient information sheets for trials such as ESPRIT and IMRiS, to ensure they are clear, unambiguous and easy to read by patients and they contain no statements that might suggest to the patient or their carers that the proposed treatment poses significantly more risks than the current NICE approved 'best practice' treatment. The best planned trials need to recruit sufficient patients so that the results obtained are valid.

I have no links to other CSGs except through the meetings of the Consumer Forum, and the JISCMail system, through which I have commented on many topics. These topics cut across the work of many if not all the CSGs. I have taken part in research surveys concerning 'Reporting of

Patient Involvement in Research (GRIPP), impact of Scientific Mentors on the effectiveness of PPI representatives on CSGs, Patients and Nutrition Survey, and Anaesthesia and Peri operative Care.

Mr Michael Maguire

In my first year involved with the group I have spent much of my time developing my knowledge and understanding of clinical trials and research as well as understanding the scope of my involvement. I have attended two CSG meetings and the following conferences: NCIN, NCRI, BSG and NAEDI, where I participated in poster the judging panel. I have attended several study days on cancer biology, clinical trial design and statistics. I have also commented on two trial proposals referred to the Sarcoma CSG as well as the Sarcoma CSG response to the NHS England consultation on investing in specialised services.

This year has enabled me to see where my skills can be best used to participate and add value to the group. I have raised the issue of access to sarcoma and trials information and the coordination of information providers at the meeting and I hope to pursue that further this year.

My links to other CSGs are through the Consumer Forum (formerly the Consumer Liaison Group). I have developed informal connections with international groups through networking at conferences and through other consumer members. I hope to develop my network this year with specific relation to the Sarcoma CSG portfolio.

I have attended CRUK open meetings on the Health Information and a Your Say Your Day event. The result was that CRUK did not feel it necessary to produce information booklets for the various types of cancer because of the quality of the information already available. I have joined the AstraZeneca patient panel and participated in 'extremely helpful' discussions on their PROACT trial, which is a great application that will provide extremely useful feedback for clinicians and scientists whilst providing excellent support for patients.

11. Open meetings/annual trials days/strategy days

The British Sarcoma Group meeting (25 - 27 Feb 2015) was held in Nottingham and chaired by Professor Robert Grimer. It included a session on clinical trials, showcasing the NCRI portfolio; first results from VORTEX, EURAMOS and Axi-STS; introducing the EuroEWING-2012, IMRiS and rEEcur trials; and reviewing CASPS. It was well attended by a multidisciplinary audience including clinicians, research nurses, patients and carers. This meeting offers an excellent platform for increasing awareness of the trials portfolio.

As noted above, a surgical studies workshop was held in November 2014, which was well attended and generated interesting study proposals. A Bone Subgroup strategy day will be held in May 2015 and a main CSG strategy day will be arranged for late 2015/early 2016 when Mr Jeys takes over as CSG Chair.

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

The current strategy was developed in 2011 and many of the objectives have been achieved. It was reviewed by the Progress Review Panel in 2013. An urgent priority for the incoming CSG

chair will be to review and refresh this strategy in the context of developments in precision medicine and the reorganisation of the Clinical Research Network. As mentioned above, this will take place in late 2015/early 2016.

13. Priorities and challenges for the forthcoming year

Priorities for the Sarcoma CSG in 2015/16 will be to:

- Review and refresh the strategy for the group in the context of developments in precision medicine and the reorganisation of the Clinical Research Network
- Continue development of successor trials, for both localised disease and advanced soft tissue sarcoma. Grant applications are in preparation for studies in patients with rhabdomyosarcoma and STS lung metastases
- Liaise with subspecialty leads for sarcoma in each CRN to ensure improved access to sarcoma clinical trials across the country, and encourage collaborative working within each network to prevent duplication of effort (e.g. by opening a very rare tumour type trial in more than one centre).

Challenges for the CSG will be:

- Increasing recruitment to portfolio studies. To maintain NIHR funding for trial infrastructure, it will be important to maintain and increase recruitment. This is particularly difficult as trials become more niche in the era of precision medicine. It may be necessary to develop some large observational studies with biomarker endpoints in order to balance the portfolio.
- Increasing the translational science yield from every trial. Each new trial should incorporate biomarker and imaging endpoints, to help earlier identification of patients with most chance of benefit.
- Increasing collaborations with other NCRI groups, including Biomarkers & Imaging, Gastrointestinal, Gynaecological, Psychosocial Oncology and TYA.

14. Concluding remarks

It has been my pleasure and privilege to work with a talented and hardworking group of researchers in the CSG and NCRI Secretariat for the past 6 years. During this time, three trials developed by the CSG have completed recruitment and presented preliminary results. I hope these will be the first of many NCRI trials. As a result of the increasing momentum of the group, we have been invited to join other national sarcoma groups in collaboration with the EORTC. Mr Lee Jeys will succeed me as chair, and I'm sure he will take the group to greater achievements.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

A – Main CSG Strategy

B – Bone Tumour Subgroup Strategy

C – Young Onset Soft tissue Sarcoma (YOSS) Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Professor Penella Woll (Sarcoma CSG Chair)

Appendix 1

Membership of the Sarcoma CSG

Name	Specialism	Location
Dr Ramesh Bulusu	Clincial Oncologist	Cambridge
Dr Aisha Miah	Clincial Oncologist	London
Dr Beatrice Seddon	Clincial Oncologist	London
Dr Paula Wilson	Clincial Oncologist	Bristol
Mr Michael Maguire	Consumer	Essex
Mr Robert Wensley	Consumer	Blackburn
Dr Malee Fernando	Histopathologist	Sheffield
Dr Charlotte Benson	Medical Oncologist	London
Professor Bass Hassan	Medical Oncologist	Oxford
Dr Helen Hatcher	Medical Oncologist	Cambridge
Dr Sandra Strauss	Medical Oncologist	London
Professor Jeremy Whelan	Medical Oncologist	London
Professor Penella Woll (Chair)	Medical Oncologist	Sheffield
Dr Jane Margetts*	Medical Oncologist	Newcastle
Dr Bernadette Brennan	Paediatric Oncologist	Manchester
Dr Angela Edgar	Paediatric Oncologist	Edinburgh
Dr Kevin Bradley	Radiologist	Oxford
Mr Roger Wilson	Sarcoma UK	Shropshire
Mrs Sharon Forsyth	Senior Trials Coordinator	London
Dr Piers Gaunt	Statistician	Birmingham
Mr Craig Gerrand	Surgeon	Newcastle
Mr Jonathan Gregory	Surgeon	Manchester
Mr Jonathan Stevenson*	Surgeon	Shropshire

* denotes trainee

Membership of the Subgroups

Bone Tumour Subgroup		
Name	**Specialism**	**Location**
Professor Susan Burchill	Cancer Biologist	Leeds
Dr Fiona Cowie	Clinical Oncologist	Glasgow
Dr Sandra Strauss	Medical Oncologist	London
Professor Jeremy Whelan	Medical Oncologist	London
Professor Donald Salter	Pathologist	Edinburgh
Dr Bernadette Brennan	Paediatric Oncologist	Manchester
Dr Bruce Morland	Paediatric Oncologist	Birmingham
Mr Matthew Sydes	Statistician	London
Professor Keith Wheatley	Statistician	Birmingham
Mr Craig Gerrand (Chair)	Surgeon	Newcastle
Mr Jonathan Stevenson*	Surgeon	Shropshire

Young Onset Soft tissue Sarcoma (YOSS) Subgroup		
Name	**Specialism**	**Location**
Dr Anna Kelsey	Histopathologist	Manchester
Dr Helen Hatcher	Medical Oncologist	Cambridge
Madeleine Adams*	Paediatric Oncologist	Cardiff
Dr Bernadette Brennan (Chair)	Paediatric Oncologist	Manchester
Dr Julia Chisholm	Paediatric Oncologist	London
Dr Mark Gaze	Paediatric Oncologist	London
Dr Meriel Jenney	Paediatric Oncologist	Cardiff
Dr Kieran McHugh	Radiologist	London
Mr Tim Rogers	Surgeon	Bristol
Dr Janet Shipley	Translational Scientist	London

* denotes trainee

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy (2011)

In response to the Progress Review in 2010 and CSG Strategy Meeting in May 2011, a clear strategy for the next three years has been identified. The strengths of the NCRN and the Sarcoma CSG were recognised, along with opportunities for closer collaboration with other CSGs and international groups. However, a number of gaps were identified in the trials portfolio, particularly in early diagnosis and surgical management. Plans were made to develop trials in these areas, incorporating bio-banking and correlative translational research. It was acknowledged that we will need to develop successor trials for the existing successful trials in the portfolio. Indeed, the Bone Subgroup have been active in developing their ideas with international collaborators and are planning grant submissions later this year. CSG members have successfully developed two trials through the NCRN/AstraZeneca initiative and are intending to liaise with other industry partners to develop successor trials. A trial proposal proforma has been developed and is now available to download from the CSG website.

The Group is aware that despite the low numbers of sarcomas, patients with these conditions are treated at a limited number of centres, all of whom should be entering patients into trials. There are a number of exciting new agents potentially available for treatment and investigation. In order to improve access to trials, the CSG is circulating a newsletter to sarcoma and research leads in every cancer network. This details the open trials and shows which centres are participating. This list is also available on the British sarcoma Group website. The Group will liaise with other national and international groups (including the EORTC) to maximise the potential for collaborations.

3-year strategy

- Raise awareness of sarcoma trials through enhanced patient information and identifying research champions in every NCRN network. We will work with Sarcoma-UK to ensure that all patients have access to up-to-date information about current trials.
- Increase recruitment to portfolio studies. We will identify sarcoma centres that are not engaged with the trials portfolio and seek to support them in referring patients to research-active centres and setting up trials.
- Develop and exploit formal collaborations with other NCRN groups including:
    - Upper GI Cancer CSG – for GIST trials
    - Gynaecological Cancer CSG – joint working group for gynaecological sarcoma trials
    - CT-Rad – for radiotherapy trials
    - Biomarker & Imaging CSG
- Identify suitable international sarcoma trials at an early stage of development, for adoption onto the NCRN portfolio. To do this, we will need to formalise links with groups including the EORTC STBSG, SARC, EuroBoNeT, Conticanet, etc.
- Develop successor trials for the existing portfolio, particularly ensuring that there are first line trials for local and metastatic disease. Exploit the AstraZeneca/NCRN, AstraZeneca/NAC and other industry collaborations to access pipeline drugs. Identify scientifically interesting industry studies for adoption onto the portfolio.

- Increase the translational science yield from every trial. Explore opportunities for systematic tissue collections through a national or trial-related biobank. Consider evaluating novel trial endpoints, such as MR or PET imaging. All new trial proposals should include a comprehensive translational research plan.

Priorities for the next year

- Increase recruitment into portfolio studies. It is essential that adequate numbers of patients are recruited in the two major randomised trials (VORTEX and GeDDiS).
- Ensure rapid and smooth adoption of suitable EORTC trials onto the portfolio, through the NCRI-EORTC liaison office.
- Improve the availability of information on trials available nationally through a sarcoma trials database and newsletter.
- Develop new trial proposals on themes identified at the Strategy Day:
    - A randomised trial of different excision margins for superficial sarcomas - WIGWAMS – Mr Grimer to lead.
    - A randomised trial of non-anthracycline chemotherapy vs best supportive care for elderly patients with advanced soft tissue sarcomas – Dr Seddon to summarise.
    - Golf ball study – a study of an educational intervention to promote earlier diagnosis of sarcomas – Mr Jeys/ Mr Grimer to lead.
    - Develop a collaborative gynaecological sarcoma group through the NCRI/EORTC/NCI links – Dr Hatcher to lead.

B – Bone Tumour Subgroup Strategy

At the time of writing the Bone Subgroup does not have a formally agreed strategy document. However, we have interpreted the vision of the NCRI to promote co-operation in cancer research for the benefit of patients, the public and the scientific community in the following ways:

- Partnership with Bone Cancer Research Trust (BCRT), the lead funder of primary bone cancer research in the UK
- Expansion of the group to include representatives of every bone tumour surgical centre in England and representation from the devolved nations
- Bringing the patient voice to meetings through BCRT representation
- Promoting an open door policy to bring in researchers with new ideas for discussion
- Encouraging a new generation of researchers with trainee representation
- Developing key partnerships with researchers and other groups
- Exploring ways in which all patients with bone tumours can be offered studies

C – Young Onset Soft tissue Sarcoma (YOSS) Subgroup Strategy

Agreed strategic priorities for YOSS

1. To open a first line study in Rhabdomyosarcoma across all ages
2. To build on current relapse studies in RMS using VIT as backbone
3. To develop an all age European study in Synovial Sarcoma
4. To build on the outcomes of other rare sarcomas from the NRSTS study to develop further clinical trials
5. To embed biological studies, biomarkers and novel targets into clinical trial portfolio

Planned implementation

1. To open a first line study in Rhabdomyosarcoma (RMS) across all ages

The next upfront study in RMS to succeed RMS 2005 is a fairly mature proposal which is ready to submit for funding to CTACC. It includes a phase I-II design to bring in both new chemotherapy combinations and MTOR inhibitors. A question on radiotherapy, response with PET and a new stratification bases on genetic fusion status is included. Importantly it will allow entry up to the age of 50 years. In summary the specific proposal includes:

Chemotherapy Question

- Phase I (dose intensifying) →Phase II MAMS design → Phase III.
- Phase I/II limited to VHR local patients and metastatic patients
- Phase III (including high risk localised patients once toxicity/safety has been proven). Arms likely to be IrIVA- addition of irinotecan to the backbone chemotherapy of IVA
- ciHD IVADo- addition of high dose continuous ifosfamide

Maintenance Question

- 6 v 12 months–vinorelbine/cyclophosphamide
- +/- MTOR inhibitor

Radiotherapy Question

- Development of European platform for all paediatric tumours including RMS for QA review of XRT fields and data, including radiology, sites of relapse and relapse related to radiation field.
- A randomised radiotherapy question using PET to define response in either operable/inoperable tumours. Questions – pre versus post-operative therapy, dose of radiotherapy depending on response

2. To build on current relapse studies in RMS using VIT as backbone

A similar strategy in relapsed RMS has been developed and approved by the main sarcoma group as well as YOSS for a study building on the closed VIT study with the addition of an mTOR inhibitor and pazopanib in a MAMS design. This includes co-operation and involvement of the ITCC, to bring to clinical trial new agents in pharma pipeline developed with ITCC. In summary the specific proposal includes:

- Phase I → phase II → phase III seamless progression depending on results in the early part of the study in a MAMS design.

Potential arms include:

- VI(T) +/- Pazopanib
- VI(T) +/- mTOR inhibitor
- VI +/- Doxorubicin

3. To develop an all age European study in Synovial Sarcoma

The first meeting of EUROJOSS in order to set up the first all age trial in Europe for synovial sarcoma occurred in Paris in December 2014. It included representation from all European sarcoma groups and the EpSSG which runs the largest paediatric sarcoma studies in Europe-Italians, French sarcoma group, Scandinavian Sarcoma Group, UK, Germany, Poland, Netherlands. Agreements - need for a co-operative perspective study at a European level, multi-national, multi-institutional joint study for adult and paediatric patients. Over-arching protocol including low risk localised tumours, high risk localised tumours and metastatic. Randomised question at least and ancillary biology. A randomised study may conclude a MAMS design re considering backbone therapy for high risk synovial sarcoma +/- targeted agents. Arms include high dose single agent ifosfamide, trabectadin, ifosfamide/dox, +/- pazopanib.

Currently work is looking at collecting more samples to examine the role of genomic index (GI). Trying to define better high risk localised tumour group +/- metastatic patients in terms of planning a MAMS design hence discussion with biostatistician in the Bordeaux Unit.

4. To build on the outcomes of other rare sarcomas from the NRSTS study to develop further clinical trials

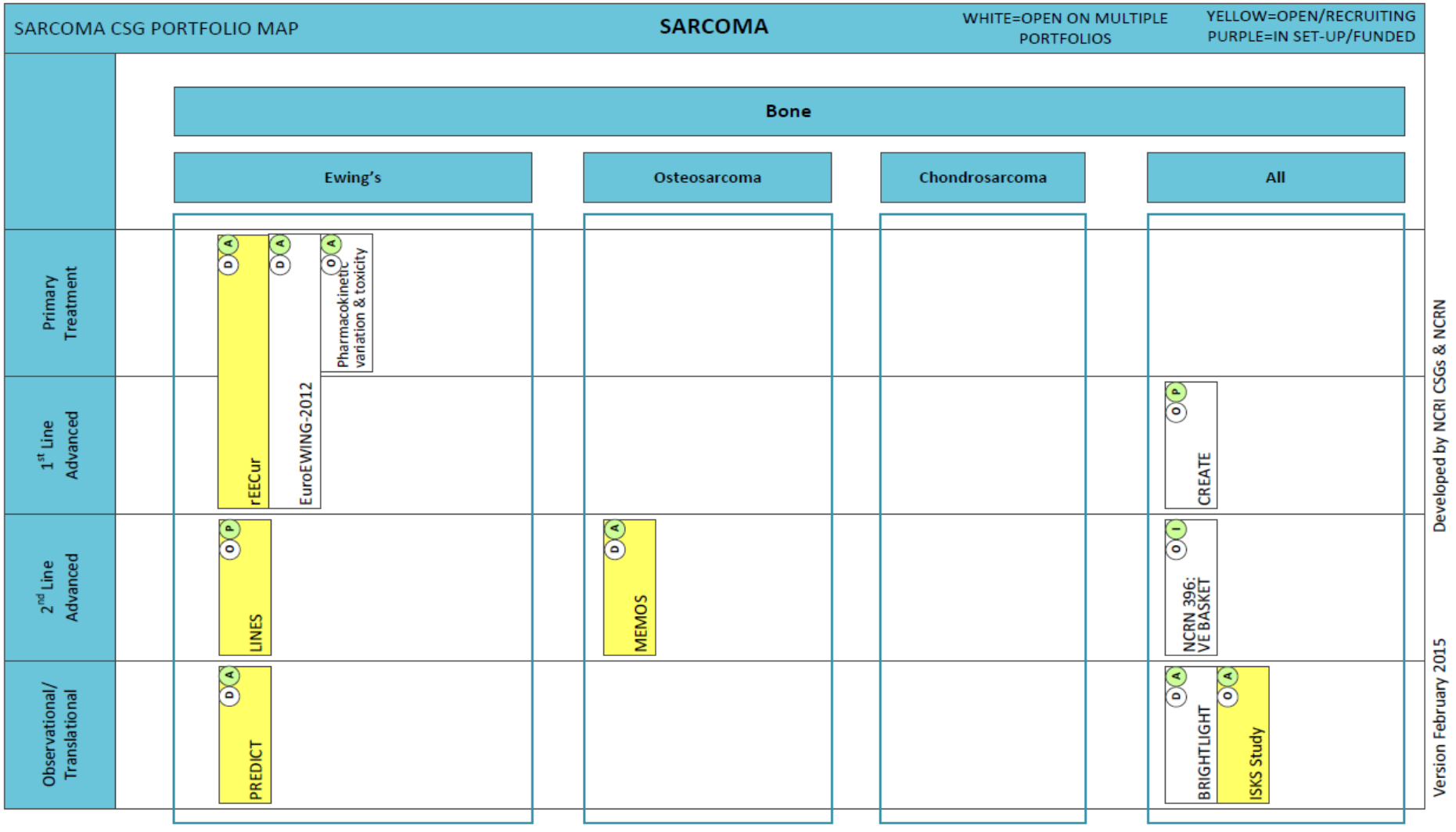
In NRSTS the Malignant Rhabdoid component of the NRSTS 2005 study has been closed and is being analysed for publication. This had led to a planned meeting of a new European consortium for a European Rhabdoid study at all anatomical sites - EURO RHABDOID 2017.

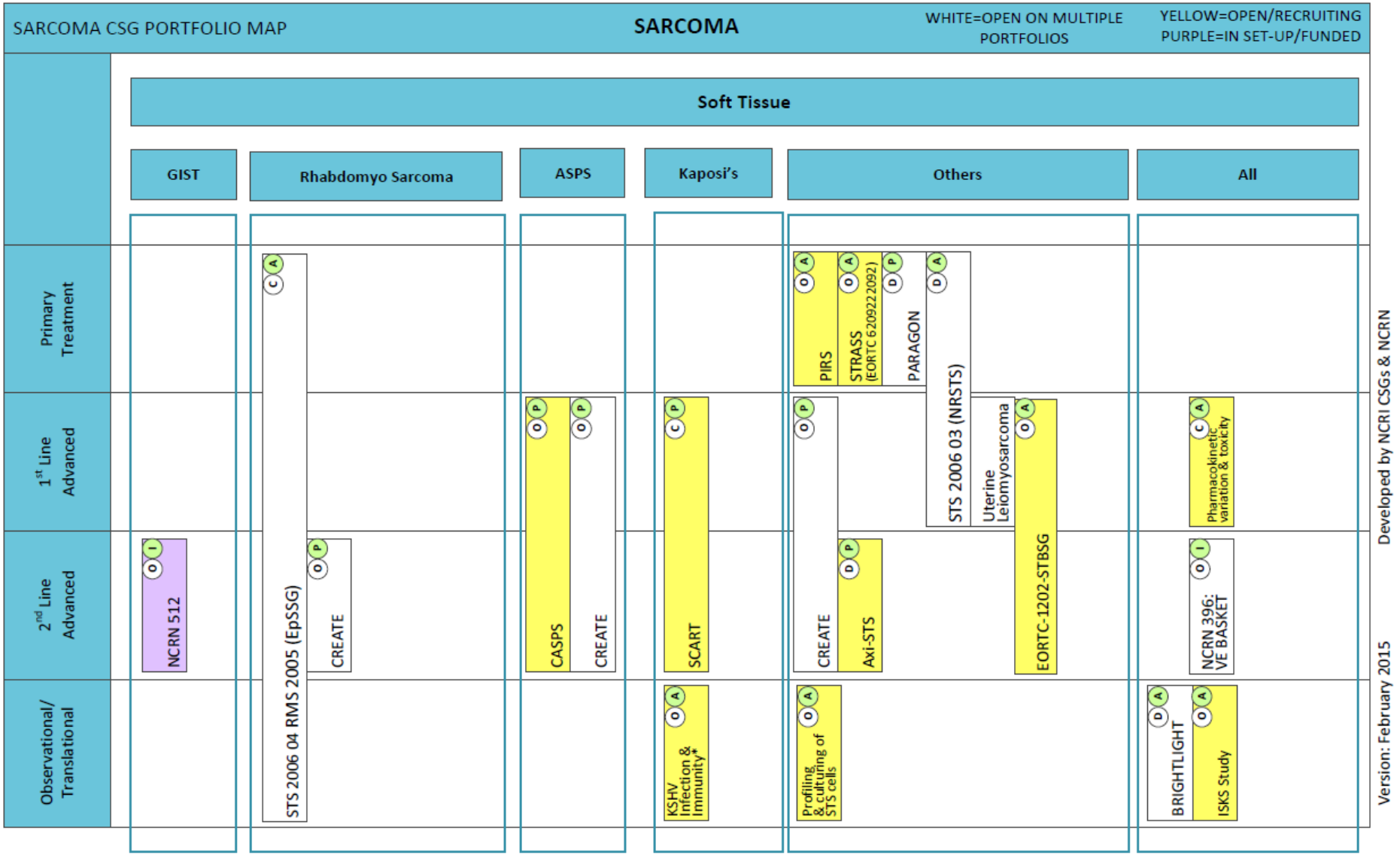
5. To embed biological studies, biomarkers and novel targets into clinical trial portfolio

An application to Horizon 2020 is in the last stage of assessment titled-Improving effectiveness of treatments for children with soft tissue sarcomas. The overall aim of this biological proposal is to increase the rate of survival and improve the quality of life for children with STS by optimising the effectiveness of established treatment protocols and promotion of basic research by specifically prospectively test novel molecular markers for risk stratification of patients, assess the efficacy of circulating biomarkers for Minimal Residual Disease (MRD) and identify rationale and provide pre-clinical evidence for new molecular therapeutic targets/specific anti-cancer drugs alongside conventional treatments. Lastly to incorporate and assess the best pre-clinically tested compounds into treatment protocols.

Appendix 3

Portfolio maps





*study suspended

NCRN 396: An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers (VE BASKET)
NCRN 512: Efficacy & safety of masitinib to sunitinib in patients with gastrointestinal stromal tumor after progression with imatinib at 400mg as first line treatment

(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

Appendix 4

Publications in the reporting year

BRIGHTLIGHT

Fern LA, Lewandowski JA, Coxon KM, Whelan J; National Cancer Research Institute Teenage and Young Adult Clinical Studies Group, UK. Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials. *Lancet Oncol* 2014; 15(8): e341-50.

Taylor RM, Mohain J, Gibson F, Solanki A, Whelan J, Fern LA. (2015) Novel participatory methods of involving patients in research: naming and branding a longitudinal cohort study, BRIGHTLIGHT. *BMC Medical Research Methodology*, 15: 20

EORTC 62005

Lee CK, Goldstein D, Gibbs E, Joensuu H, Zalcberg J, Verweij J, Casali PG, Maki RG, Cioffi A, Mcarthur G, Lord SJ, Yip D, Kanjanapan Y, Rutkowski P. Development and validation of prognostic nomograms for metastatic gastrointestinal stromal tumour treated with imatinib. *Eur J Cancer* 2015; 51: 852-60.

EORTC 62931

Le Cesne A, Ouali M, Leahy MG, Santoro A, Hoekstra HJ, Hohenberger P, Van Coevorden F, Rutkowski P, Van Hoesel R, Verweij J, Bonvalot S, Steward WP, Gronchi A, Hogendoorn PC, Litiere S, Marreaud S, Blay JY, Van Der Graaf WT. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. *Ann Oncol* 2014; 25: 2425-32.

EORTC studies including 62971 & 62012

Young RJ, Natukunda A, Litière S, Woll PJ, Wardelmann E, van der Graaf WT. First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. *Eur J Cancer* 2014; 50: 3178-86.

EpSSG NRSTS 2005

Ferrari A, De Salvo GL, Brennan B, van Noesel MM, De Paoli A, Casanova M, Francotte N, Kelsey A, Alaggio R, Oberlin O, Carli M, Ben-Arush M, Bergeron C, Merks JHM, Jenney M, Stevens MC, Bisogno G. Orbach D. Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005). *Ann Oncol* 2015; 26: 567-72.

EURAMOS

Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, Krailo MD, Gebhardt M, Pápai Z, Meyer J, Nadel H, Randall RL, Deffenbaugh C, Nagarajan R, Brennan B, Letson GD, Teot LA, Goorin A, Baumhoer D, Kager L, Werner M, Lau CC, Sundby Hall K, Gelderblom H, Meyers P,

Gorlick R, Windhager R, Helmke K, Eriksson M, Hoogerbrugge PM, Schomberg P, Tunn PU, Kühne T, Jürgens H, van den Berg H, Böhling T, Picton S, Renard M, Reichardt P, Gerss J, Butterfass-Bahloul T, Morris C, Hogendoorn PC, Seddon B, Calaminus G, Michelagnoli M, Dhooge C, Sydes MR, Bernstein M; EURAMOS-1 investigators. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. *J Clin Oncol*. 2015 Jun 1. pii: JCO.2014.60.0734. [Epub ahead of print]

Whelan JS, Bielack SS, Marina N, Smeland S, Jovic G, Hook JM, Krailo M, Anninga J, Butterfass-Bahloul T, Böhling T, Calaminus G, Capra M, Deffenbaugh C, Dhooge C, Eriksson M, Flanagan AM, Gelderblom H, Goorin A, Gorlick R, Gosheger G, Grimer RJ, Hall KS, Helmke K, Hogendoorn PC, Jundt G, Kager L, Kuehne T, Lau CC, Letson GD, Meyer J, Meyers PA, Morris C, Mottl H, Nadel H, Nagarajan R, Randall RL, Schomberg P, Schwarz R, Teot LA, Sydes MR, Bernstein M; EURAMOS collaborators. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. *Ann Oncol* 2015; 26: 407-14.

ET 2000 03 (EURO-E.W.I.N.G. 99)

Bölling T, Braun-Munzinger G, Burdach S, Calaminus G, Craft A, Delattre O, Deley MC, Dirksen U, Dockhorn-Dworniczak B, Dunst J, Engel S, Faldum A, Fröhlich B, Gadner H, Göbel U, Gosheger G, Hardes J, Hawkins DS, Hjorth L, Hoffmann C, Kovar H, Kruseova J, Ladenstein R, Leuschner I, Lewis IJ, Oberlin O, Paulussen M, Potratz J, Ranft A, Rössig C, Rübe C, Sauer R, Schober O, Schuck A, Timmermann B, Tirode F, van den Berg H, van Valen F, Vieth V, Willich N, Winkelmann W, Whelan J, Womer RB. Development of Curative Therapies for Ewing Sarcomas by Interdisciplinary Cooperative Groups in Europe. *Klin Padiatr* 2015; 227: 108-115.

Le Deley MC, Paulussen M, Lewis I, Brennan B, Ranft A, Whelan J, Le Teuff G, Michon J, Ladenstein R, Marec-Bérard P, van den Berg H, Hjorth L, Wheatley K, Judson I, Juergens H, Craft A, Oberlin O, Dirksen U. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. *J Clin Oncol* 2014; 32: 2440-8.

Morland B, Platt K, Whelan JS. A phase II window study of irinotecan (CPT-11) in high risk Ewing sarcoma: a Euro-E.W.I.N.G. study. *Pediatr Blood Cancer* 2014; 61: 442-5.

Volchenboum SL, Andrade J, Huang L, Barkauskas DA, Krailo M, Womer RB, Ranft A, Potratz J, Dirksen U, Triche TJ, Lawlor ER. Gene expression profiling of Ewing sarcoma tumors reveals the prognostic importance of tumor-stromal interactions: A report from the Children's Oncology Group. *J Pathol Clin Res* 2015; 1: 83-94.

OTIS

Michelagnoli M, Whelan J, Forsyth S; OTIS Trial Management Group, Site Investigators. A phase II study to determine the efficacy and safety of oral treosulfan in patients with advanced pre-treated Ewing sarcoma ISRCTN11631773. *Pediatr Blood Cancer* 2015; 62: 158-9.

PALETTE (EORTC 62072)

Coens C, van der Graaf WT, Blay JY, Chawla SP, Judson I, Sanfilippo R, Manson SC, Hodge RA, Marreaud S, Prins JB, Lugowska I, Litière S, Bottomley A. Health-related quality-of-life results from PALETTE: A randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Global Network Study (EORTC 62072). *Cancer* 2015 May 29. doi: 10.1002/cncr.29426.

TRUSTS (EORTC 62091)

Bui-Nguyen B, Butrynski JE, Penel N, Blay JY, Isambert N, Milhem M, Kerst JM, Reyners AK, Litière S, Marréaud S, Collin F, van der Graaf WT; European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC/STBSG) and the Sarcoma Alliance for Research through Collaboration (SARC). A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: The TRUSTS trial. *Eur J Cancer* 2015 Jul;51(10):1312-20. doi: 10.1016/j.ejca.2015.03.023. Epub 2015 Apr 23.

Uterine leiomyosarcoma and HGUS trials

Bogaerts J, Sydes MR, Keat N, McConnell A, Benson A, Ho A, Roth A, Fortpied C, Eng C, Peckitt C, Coens C, Pettaway C, Arnold D, Hall E, Marshall E, Sclafani F, Hatcher H, Earl H, Ray-Coquard I, Paul J, Blay JY, Whelan J, Panageas K, Wheatley K, Harrington K, Licitra L, Billingham L, Hensley M, McCabe M, Patel PM, Carvajal R, Wilson R, Glynne-Jones R, McWilliams R, Leyvraz S, Rao S, Nicholson S, Filiaci V, Negrouk A, Lacombe D, Dupont E, Pauporté I, Welch JJ, Law K, Trimble T, Seymour M. Clinical trial designs for rare diseases: studies developed and discussed by the International Rare Cancers Initiative. *Eur J Cancer* 2015; 51: 271-81.

Appendix 5

Major international presentations in the reporting year

Axi-STS

Woll PJ, Gaunt P, Judson I, Scurr M, Strauss S, Seddon B, Leahy M, Marples M, Hughes A, Kaur B, Billingham L. Axi-STS: an NCRI Sarcoma Clinical Studies Group phase II trial of the VEGFR inhibitor axitinib in advanced soft tissue sarcoma (STS). Connective Tissue Oncology Society, Berlin, Oct 2014.

Woll PJ, Gaunt P, Judson I, Scurr M, Strauss S, Seddon B, Leahy M, Marples M, Hughes A, Kaur B, Billingham L. Axi-STS: an NCRI Sarcoma Clinical Studies Group phase II trial of the VEGFR inhibitor axitinib in advanced Soft Tissue Sarcoma (STS). NCRI Annual Meeting, Liverpool, Nov 2014.