NCRI
National
Cancer
Research
Institute

NCRI Children's Cancer & Leukaemia Clinical Studies Group

Annual Report 2015-16

Partners in cancer research

NCRI Children's Cancer & Leukaemia CSG Annual Report 2015-16

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

The CCL CSG continues to be very active. The number of patients participating in clinical studies across the UK continue to rise. A highlight was funding for a key phase III study in liver tumours. This is an international collaboration with researchers from Europe and the UK (PHITT).

The CSG has a major focus on the integration of precision medicine recognising the important of a better understanding of the molecular profiles of children's cancers and the need for new targeted therapies. The integration of genomic profiling of cancer and leukaemia in children is a key strategic aim of the CSG and there are several studies in development in this area.

The third CCL Annual Trials meeting was very well attended again and we will need to move to a larger venue next year to accommodate all those who wish to attend. The trainee programme continues to thrive. This very popular scheme is now embedded within the CCL Subgroups and is key to developing skills for future generations of researchers.

2. Structure of the Group

The Subgroups continue thrive and many work in partnership with the CCLG Special Interest Groups in developing new studies across the portfolio.

Three members of the CSG are paediatric neurooncologist and we are delighted that a paediatric neurosurgeon has also joined the CSG. The development of more studies in childhood brain tumours is a priority for the CSG.

Dr Kate Wheeler is retiring as Chair of the Neuroblastoma CSG after several successful years with a very high level of activity this Subgroup. She will be replaced by Dr Mark Gaze. We were delighted to welcome two new consumer representatives to the CSG; Mrs Angela Polanco and Mr Nicolas Bird who joined the group in February. We particularly want to acknowledge the huge contribution that Danielle Horton-Taylor and Christopher Copland have made in recent years as consumer membership and members of the group. They have been members for six years - their commitment and vision have had a significant impact on the working of the CSG over that time and we will miss them.

3. CSG & Subgroup strategies

Main CSG

The CSG strategy highlights the unmet need for patient who relapse and the need to increase availability of and participation in early phase clinical trials. The development of pathways for genomic profiling of children's tumours is a key action together with improving access to new agents through close working with the pharmaceutical industry.

This is being addressed in a number of ways as detailed in the strategy document. Studies that have been approved within the New Agent Subgroup are now presented and reviewed formally at the main CSG. This is raising awareness of these studies across the wider group and the process provides helpful review from the clinical perspective and will hopefully improve access to a wider group of patients.

Another important strategic aim is the need to raise the profile of the CSG and ensure that the outcomes from clinical trials are disseminated. The links with the CCLG Special Interest Groups are strengthening and there is a plan for a formal presentation by the CSG at the next CCLG meeting to further explore how to raise the profile of the CSG, share important results and work more closely together across the children's cancer research community.

Whilst the majority of studies are developed and run through the CRCTU in Birmingham, which has a vast experience in the development of studies in children, it is recognised that there may be limitation on the capacity of the CRCTU. This is being addressed in that the CRCTU is hoping to expand its capacity, particularly for the development of tumours for children with brain tumours. Discussions are also underway with other CTUs, for example there are ongoing discussions with the UCL CTU regarding development of the next clinical trial in acute lymphoblastic leukaemia.

CNS Subgroup (Chair, Dr Antony Michalski)

The SIOP Ependymoma trial opened to recruitment in the UK in December 2015. This umbrella study for infants and children with ependymoma is being run Europe wide and will be the most comprehensive study for this patient group. The SIOP CNS Germ Cell Tumour study is open and is recruiting in most centres in the UK. The PNET5 study has had a long gestation due to problems with the international sponsor. The study is due to open using remaining existing funding and an application for funding to complete the study is due to be submitted in June 2016. SIOP studies for young children with medulloblastoma and for children with high risk medulloblastoma are in late development with international sponsors. The BIOMEDE study for children with diffuse intrinsic pontine glioma will open later in 2016. All of these studies have molecular diagnostics or bolt on studies.

Translational studies characterising the molecular pathology of tumours have attracted funding and are due to open in 2016-7.

Neuroblastoma Subgroup (Chair, Dr Kate Wheeler - Dr Mark Gaze as of April)

The Neuroblastoma Subgroup has continued to be very active in the year 2015/2016 under the Chairmanship of Dr Kate Wheeler, who came to the end of her five year term of office in March 2016. Dr Mark Gaze has been appointed to take over this role. The Subgroup has had two formal meetings on 22.9.15 and 16.3.16, supplemented by regular telephone conferences. Many

members of the Subgroup also have active roles on the main CCL CSG and participate energetically in the European Neuroblastoma Clinical research Group, SIOPEN.

The main strategic aim is to support, maintain and enhance a balanced portfolio of early and late phase clinical trials in neuroblastoma, especially high-risk disease which carries the worst prognosis. This has been achieved with the open European SIOPEN High-Risk Neuroblastoma Trial for newly diagnosed patients which currently has two recruiting randomisations, and a series of early phase trials, both open and funded and in development, for patients with relapsed and refractory disease. Two major manuscripts arising out of the High-Risk trial one on the MAT randomisation and the other on the impact of surgical resection have been submitted for publication.

Leukaemia Subgroup (Chair, Professor Ajay Vora)

Strategy 2015-2017:

1. Improve recruitment to second randomisation of UKALL 2011 by allowing registration only entry - Amendment in submission.
2. Agree international trials for Ph-pos, infant AL and successor to UKALL 2011. Schema for all trials agreed - Protocol writing committees and working groups are being established.
3. Open MyeChild - Opened at two centres May 2016, roll out over subsequent three months.
4. Open registries with linked biological sample collection and studies for APL, DS-AML, CML and MDS - Dataset agreed and application for funding submitted.
5. Liaise with new agents group to increase portfolio of phase I and II leukaemia trials testing immune based and targeted agents - Two cellular therapy studies will open at GOSH/UCLH in May 2016.

Novel Agents Subgroup (Chair, Dr Darren Hargrave)

The portfolio includes 17 open trials: 12 dose finding (phase I/II) and five phase II trials. Of these, 65% are Pharma industry sponsored. The portfolio focuses on targeted therapies including; ALK, BRAF, DNA methytransferase, ERBB, EZH2, MEK, VEGFR inhibitors. This year has shown a strong focus on immunotherapy studies including: the anti-GD2 monoclonal antibody therapy study, opening of phase I studies of immune checkpoint (PD-1 & PDL-1) and a major achievement being the opening of a CRUK sponsored first in human study of 1RG-CART therapy in patients with relapsed or refractory neuroblastoma. 1RG-CART therapy is a novel immunotherapy in which patients have their T-cells modified to express a chimeric antigen receptor (CAR) which targets GD2 expressed on the surface of neuroblastoma cells.

Over the last year, six early phase studies have been successfully completed and four have been presented at ASCO. The Newcastle Cancer Centre Pharmacology Group provides national support for paediatric pharmacology studies with nine open studies and over 100 patients recruited this year. The Subgroup has worked with CRUK in developing a proposal for a Paediatric Stratified Medicine Programme to pilot a customized paediatric NGS targeted panel which we hope will be funded and opened over the next year.

Germ Cell Tumour Subgroup (Chair, Dr Sara Stoneham)

Achievements:

1. A successful application to secure $2.3m St. Baldrick's Foundation grant (2015-20) to underpin biological studies in upcoming international GCT clinical trials, focussing on whole-exome sequencing and circulating nucleic acids.

2. Combined trial endorsement from NCRI Testis CSG, Gynaecological CSG and CCL CSG, thus for the first time creating a national consensus approach to treatment of patients with GCT both stratified for age and risk and irrespective of medical professional in charge of care.
3. Two publications 2015/2016 from MaGIC database analyses.

Areas of strength:

1. International collaboration and cross NCRI CSG working.
2. Deliberate consideration of design to ensure eligibility of TYA patients in trial design.
3. Trial design agreed across different medical disciplines currently delivering regimens for male and female patients differently.

4. Task groups/Working parties

There are no working parties within the CCL CSG currently.

5. Patient recruitment summary for last 5 years

Within the Children's Cancer & Leukaemia CSG portfolio, 11 trials closed to recruitment and 2 opened. The gaps in the portfolio continue to be addressed with Phase II/III studies opening for many of the more common tumour types. The focus is now on the development of studies where there are gaps (most notably for some children with brain tumours and bone sarcomas). In addition, there is the need to incorporate the systematic molecular testing of tumours both at the time of diagnosis and relapse.

The number of patients recruited to interventional clinical trials continues to steadily rise.

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
2011/2012	1033	311	615	311	-	-

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	1077	491	632	483	-	-
2013/2014	1419	625	751	625	-	-
2014/2015	1605	643	795	643	-	-
2015/2016	1412	715	749	715	-	-

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

Several studies within the CCL CSG portfolio are in development have been developed with other CSGs, e.g. the next international collaborative, risk stratified, randomised extra-cranial GCT trial and the new international trial for patients with newly diagnosed and relapsed rhabdomyosarcoma. Both studies will be sponsored in the UK by the Birmingham CRCTU. There are ongoing direct links with the TYA CSG and members of the CCL CSG contributed to the TYA strategy day.

7. Funding applications in last year

Table 3 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
July 2015 (CTAAC)			
None			
December 2015			
LCH IV biomarker studies	Full application	Professor Matthew Collin	Funded
May 2016			
A Phase Ib study of ch14.18/CHO in combination with IL-2 and zoledronate in patients with relapsed/refractory neuroblastoma	Full application	Dr Juliet Gray & Professor Pamela Kearns	Not funded
Stratified Medicine in Paediatrics	Outline application	Professor Louis Chesler & Dr Darren Hargrave	Full Application Invited (Preliminary)
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Seludex: Phase I/II expansion study of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult ALL	ECMCs Combinations Alliance	Professor Josef Vormoor	Funded

8. Collaborative partnership studies with industry

There are 12 open industry sponsored studies and many more in set-up / discussion with Pharma partners including the following companies: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Celgene, Epizyme, GSK, Hoffmann-La Roche-Genentech, Johnson & Johnson, Merck, Novartis and Pfizer. Collaborations with industry are very strong in the Novel Agents Subgroup for early phase trials and two randomized later phase II trials (sponsored by Roche-Genentech) in newly diagnosed high risk tumours (high grade glioma and metastatic sarcoma) completed and had had significant UK contributions in terms of leadership and accrual and will be due to report outcomes this year. The first study was approved this year via the ECMC combinations alliance.

9. Impact of CSG activities

The clinical trial portfolio continues to have a direct impact on clinical practice. Of particular note, the Inter -B-NHL Ritux 2010 study had been halted at the first interim analysis. The addition of

rituximab to standard chemotherapy in high-risk paediatric B-NHL has been shown to result in a significant increase in event free survival. This is practice changing and the study has now resumed with all high-risk B-NHL patients receiving rituximab with chemotherapy as standard of care.

For patients with neuroblastoma as a result of recent trials immunotherapy using a monoclonal antibody anti GD2 is considered internationally as part of standard treatment for patients with HR disease. When the current high risk study closes there will need to be provision for this aspect of treatment for these patients.

10. Consumer involvement

Danielle Horton-Taylor:
I have continued my work with the Paediatric Oncology Reference Team (PORT), which supports the involvement of parents and children in research.

I presented at events including CRUK's Children's Cancer Events; the Children's Cancer Conference 2015 (in conjunction with Bethany's Wish) on Clinical Trials and Consent/Assent; and the Childhood Cancer International Europe conferences in 2015 (Trials and Consent) and in 2016 (Survivorship).

I attended the NCRAS Cancer Outcomes Conference, the NCRI Conference (where I was a consumer rep on the Scientific Committee), and Cancer Drug Development Forum meetings (CDDF).

I sit on the CRUK Grand Challenge Patient Panel, on the Genomics England GECIP for Childhood Solid Tumours, and on the TRECA Patient and Parent Advisory Group. I participated in the proposal for reforming the Paediatric Medicines Regulation (PMR.)

I continue to review patient information sheets and consent forms and remain involved in trial design and recruitment challenges.

Christopher Copland:
The focus of activities this year has been at a European level. I presented at the Childhood Cancer International (CCI) European meeting in Malmo in May on the Euro Ewing's Consortium. While there, I planned with fellow parents the setting up Unite2Cure, a network with the immediate aim of reforming the Paediatric Medicines Regulation. U2C has rapidly established itself as a focus for lobbying and discussion on improved treatments for children with cancer and is now an official partner in the Cancer Drugs Development Forum. I participated in CDDF working group meetings in October and December and, in association with this, visited the European Medicines Agency to learn more about their work. During this period, I also presented at the Bone Sarcoma Meeting in Vienna and at the Euro-Ewing's Meeting in London.

In January, I arranged a meeting with MEP, Glenis Willmott, regarding the Paediatric Medicines Regulation, which was also attended by colleagues from CDDF and CRUK. Soon after, I participated in the CDDF annual meeting in Brussels and helped present the resulting action plan on Childhood Cancer Day in the European Parliament. With Danielle, I gave a one hour workshop on children's cancer at the NCRI Consumer Forum and with colleagues from Unite2Cure presented on our campaign at CCI in Belgrade. I acted as one of the representatives of U2C in a meeting with the European Health Commissioner in May. We are looking forward to a resolution, sponsored by Ms

Willmott, being debated in the European Parliament later this year to coincide with the ten year Review of the PMR.

11. Open meetings/annual trials days/strategy days

The feedback from the CCL Annual Trials day was again very positive with the programme rated as excellent and highly relevant by the majority of attendees. The challenge is that the activity of the CSG is very high and it is difficult to fit everything into a one day program. We are hoping to secure a larger venue for the next meeting as registration requests exceeded available places. The programme included leukaemia trials as well as other cancer trials for the first time and this was well received by the participants.

12. Priorities and challenges for the forthcoming year

A priority for the CSG continues to be the implementation of the strategic plan with an emphasis on the development of precision medicine within paediatric cancer.

The challenges for the CSG are:

1. The development of clinical trials with a focus on radiotherapy and surgery continues to be a challenge. There is some progress on this with the development of radiotherapy questions within the next study in rhabdomyosarcoma.
2. The development of supportive care studies - there is a focus on this at our upcoming meeting and we will be working with other CSGs to address the gaps in this area within the portfolio.
3. The urgent need to develop strategies for the genomic profiling of tumours for children with leukaemia and cancer at the time of diagnosis and at the time of relapse of their disease.

13. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

- A – Main CSG Strategy
- B – CNS Subgroup Strategy
- C – Neuroblastoma Subgroup Strategy
- D – Leukaemia Subgroup Strategy
- E – Novel Agents Subgroup Strategy
- F – Germ Cell Tumour Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Dr Meriel Jenney (Children's Cancer & Leukaemia CSG Chair)

Appendix 1

Membership of the Children's Cancer & Leukaemia CSG

Name	Specialism	Location
Dr Henry Mandeville	Clinical Oncologist	Sutton
Mr Nicholas Bird	Consumer	Epsom
Mrs Angela Polanco	Consumer	Warwick
Ms Karen Howe	Nurse	London
Dr John Moppett	Paediatric Haematologist	Bristol
Professor Ajay Vora	Paediatric Haematologist	Sheffield
Dr Amos Burke	Paediatric Oncologist	Cambridge
Dr Julia Chisholm	Paediatric Oncologist	London
Dr Martin Elliot	Paediatric Oncologist	Leeds
Dr Mark Gaze	Paediatric Oncologist	London
Dr Darren Hargrave	Paediatric Oncologist	London
Dr Lisa Howell	Paediatric Oncologist	Liverpool
Dr Meriel Jenney (Chair)	Paediatric Oncologist	Cardiff
Dr Pamela Kearns	Paediatric Oncologist	Birmingham
Dr Guy Makin	Paediatric Oncologist	Manchester
Dr Anthony Michalski	Paediatric Oncologist	London
Dr James Nicholson	Paediatric Oncologist	Cambridge
Dr Sara Stoneham	Paediatric Oncologist	London
Professor Bruce Morland	Paediatric Oncologist and Clinical Director	Birmingham
Dr Deborah Tweddle	Professor of Pediatric Oncology	Newcastle
Dr Alasdair Rankin	Research Director, Bloodwise	London
Professor Keith Wheatley	Statistician	Birmingham
Mr Ian Kamaly-Asl	Surgeon	Manchester

Membership of the Subgroups

Central Nervous System (CNS) Subgroup		
Name	**Specialism**	**Location**
Ms Erica Little	Brain Tumour Charity	Farnborough
Dr Nicki Thorpe	Clinical Oncologist	Liverpool
Professor Simon Bailey	Paediatric Neuro-Oncology	Newcastle
Professor Colin Kennedy	Paediatric Neurologist	Southampton
Professor Steve Clifford	Paediatric Oncologist	Newcastle
Dr Darren Hargrave	Paediatric Oncologist	London
Dr Mette Jorgensen*	Paediatric Oncologist	London
Dr Antony Michalski (Chair)	Paediatric Oncologist	London
Dr Andrew Peet	Paediatric Oncologist	Birmingham
Dr Sue Picton	Paediatric Oncologist	Leeds
Professor Barry Pizer	Paediatric Oncologist	Liverpool
Dr Heidi Traunecker	Paediatric Oncologist	Cardiff
Mr Connor Mallucci	Surgeon	Liverpool
Patricia O'Hare*		

Novel Agents Subgroup		
Name	**Specialism**	**Location**
Professor Ajay Vora	Paediatric Haematologist	Sheffield
Dr Josef Vormoor	Paediatric Haematologist	Newcastle
Professor Steve Clifford	Paediatric Oncologist	Newcastle
Dr Martin Elliot	Paediatric Oncologist	Leeds
Dr Darren Hargrave (Chair)	Paediatric Oncologist	London
Professor Pam Kearns	Paediatric Oncologist	Birmingham
Dr Guy Makin	Paediatric Oncologist	Manchester
Dr Bruce Morland	Paediatric Oncologist	Birmingham
Dr Andrew Peet	Paediatric Oncologist	Birmingham
Dr Britta Vormoor*	Paediatric Oncologist	Newcastle
Dr Gareth Veal	Paediatric Pharmacologist	Newcastle

Germ Cell Tumour (GCT) Subgroup		
Name	**Specialism**	**Location**
Dr Gail Horan	Clinical Oncologist	Cambridge
Dr Chris Barton*	Clinical Research Fellow	Liverpool
Dr Dan Stark	Medical Oncologist	Leeds
Dr Claire Thornton	Pathologist	Belfast
Dr Mark Brougham	Paediatric Oncologist	Edinburgh
Dr Juliet Hale	Paediatric Oncologist	Newcastle
Dr James Hayden	Paediatric Oncologist	Liverpool
Dr Mathew Murray	Paediatric Oncologist	Cambridge
Dr James Nicholson	Paediatric Oncologist	Cambridge
Dr Anthony Penn	Paediatric Oncologist	Manchester
Dr Sara Stoneham (Chair)	Paediatric Oncologist	London
Mr Suren Arul	Surgeon	Birmingham

Leukaemia Subgroup		
Name	**Specialism**	**Location**
Dr Rachael Hough**	Clinical Oncologist	London
Mr Neil Ranasinghe	Consumer	London
Dr Anthony Moorman	Epidemiologist	Newcastle
Dr Brenda Gibson	Haematologist	Manchester
Dr Clare Rowntree	Haematologist	Cardiff
Dr Phil Ancliff**	Paediatric Haematologist	London
Dr Denise Bonney	Paediatric Haematologist	Manchester
Dr Michelle Cummins	Paediatric Haematologist	Bristol
Dr John Moppett	Paediatric Haematologist	Bristol
Dr Anupama Rao**	Paediatric Haematologist	London
Dr Sujith Samarasinghe**	Paediatric Haematologist	Newcastle
Professor Owen Smith	Paediatric Haematologist	Dublin
Professor Josef Vormoor	Paediatric Haematologist	Newcastle
Professor Ajay Vora (Chair)	Paediatric Haematologist	Sheffield
Dr Donna Lancaster**	Paediatric Oncologist	London
Dr David O'Connor*	Specialist trainee in Haematology	West Midlands
Caroline Furness*		

Neuroblastoma Subgroup		
Name	**Specialism**	**Location**
Dr Gail Halliday*	Consultant Haematologist	Newcastle
Dr John Anderson**	Paediatric Oncologist	London
Professor Louis Chesler**	Paediatric Oncologist	Sutton
Dr Penelope Brock**	Paediatric Oncologist	London
Dr Martin Elliott	Paediatric Oncologist	Leeds
Dr Mark Gaze	Paediatric Oncologist	London
Dr Juliet Gray	Paediatric Oncologist	Southampton
Dr Guy Makin	Paediatric Oncologist	Manchester
Dr Lynley Marshall**	Paediatric Oncologist	London
Dr Daniel Morgenstern	Paediatric Oncologist	London
Professor Andy Pearson**	Paediatric Oncologist	London
Dr Ramya Ramanujachar	Paediatric Oncologist	Southampton
Professor Deborah Tweddle	Paediatric Oncologist	Newcastle
Dr Kate Wheeler (Chair)	Paediatric Oncologist	London
Mr Roly Squire	Paediatric Surgeon	Leeds
Professor Sue Burchill	Professor of paediatric & adolescent cancer research	Leeds
Professor Keith Wheatley	Statistician	Birmingham
Sally George*		

* denotes trainee member

**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

Main CSG Strategy

Children's Cancer & Leukaemia CSG Strategy: September 2014 – June 2016

This strategy timeline has been produced to support the CCL Research Strategy Plan of Implementation (Draft v0.3 September 2014). It runs from September 2014 until June 2016, and will be reviewed and updated (by MJ, JB and SA) on a regular basis.
The document is composed of the following:

Page 2 – 5: NCRI CCL CSG Strategy: plan of implementation, containing agreed strategic objectives (1-6), specific actions, CSG leads and proposed deadlines.

Page 6 – 7: Overview of the entire strategy timeline, spread over two pages; September 2014 – July 2015 (Page 6) and August 2015 – June 2016 (Page 7).

Page 8 – 9: Strategic objectives 1a – 1e, spread over two pages; September 2014 – July 2015 (Page 8) and August 2015 – June 2016 (Page 9). Same information as shown in the pink boxes of the plan of implementation (pages 2 – 3) and pink arrows of the overview (pages 6 – 7).

Page 10 – 11: Strategic objectives 2, 3a – 3c, spread over two pages; September 2014 – July 2015 (Page 10) and August 2015 – June 2016 (Page 11). Same information as shown in the grey and teal boxes of the plan of implementation (pages 3 – 4) and the grey and teal arrows of the overview (pages 6 – 7).

Page 12 – 13: Strategic objectives 4, 5 & 6, spread over two pages; September 2014 – July 2015 (Page 12) and August 2015 – June 2016 (Page 13). Same information as shown in the orange, yellow and blue boxes of the plan of implementation (pages 4 – 5) and the orange, yellow and blue arrows of the overview (pages 6 – 7).

CCL strategy leads

AB	Amos Burke	JB	Jane Beety
AE	Angela Edgar	JC	Julia Chisholm
AM	Anthony Michalski	JN	James Nicholson
AP	Andy Pearson	KW	Kate Wheeler
AV	Ajay Vora	MG	Mark Gaze
CC	Chris Copland	MJ	Meriel Jenney
DH	Darren Hargrave	MMcC	Martin McCabe
DHT	Danielle Horton-Taylor	MP	Mark Powis
DR	Derek Roebuck	PK	Pamela Kearns
EL	Eileen Loucaides	SA	Seema Alexander
GM	Guy Makin	SS	Sara Stoneham

Strategic objective	Action	CSG Lead	Date	Outcomes
1a. Portfolio development (general)	Development of prioritisation process for the development and set up of studies that takes account of CRCTU and PTC capacity, available funding opportunities and clinical need Determine level of use of tissue bank samples for clinical research	AM/ KW/ AV/ AP/ SS DH with tissue banks	Dec 2014 Report 6-monthly	Ongoing prioritisation (four monthly). Active discussion regarding use of tissue samples.
1b. Portfolio development (local control)	CSG subgroups to identify potential surgical studies, to be coordinated across the CSG Engage with Royal College of Surgeons initiative to increase the number of surgeons receiving training in clinical trials, by encouraging paediatric surgeons to attend national training events Link with CTRad to expand RT studies in CCL portfolio, including establishing a research programme for proton beam therapy as this facility is established in the UK	Subgroup Chairs/ MJ MP (await report from surgical workshop) MG	Ongoing Oct 2015 Jun 2015	Formal links with CT RAD established (Mark Gaze).
1c. Portfolio development (cross cutting themes)	Identify leads within the CSG to link with the following cross cutting CSGs and advisory groups: •Psychosocial Oncology and Late Effects Special Interest Group (survivorship and late effects) •Palliative and Supportive Care •Primary Care •Screening, Prevention and Early Diagnosis (SPED) Advisory Group	LC to put on agenda CSG Chair attended CCL meeting Led by GM TBD at next CSG mtg	 Jun 2015 Jun 2015	. Studies shared with cross cutting groups through concept registration form ongoing.
1d. NCRI Teenage and Young Adult CSG (TYA CSG)	Establish regular contact with NCRI TYA CSG to work together to widen participation in research studies by young people, and share papers Agree most effective way of adult and paediatric groups working together, e.g. Hodgkins and Sarcoma. Ongoing discussed as new trials develop eg FaR RMS. Invite AE to CCL CSG	MJ/ SS/ JC MJ/ SS/ JC AB/ AE MJ/ LC	Apr 2015 (TYA Strategy Day) Apr 2015 Feb 2015 Nov 2014	Attended . Ongoing discussion regarding sharing of studies. Complete

Strategic objective	Action	CSG Lead	Date	Outcomes
1e. National Cancer Intelligence Network (NCIN)	Establish clear link with NCIN Children Teenage and Young Adults Site Specific Clinical Reference Group (CTYA SSCRG) Explore with NCIN the development of relapse studies that use relapse data from national data sets	MJ/ MMcC DH/GM	Winter 2014	Complete Ongoing - see objective 2
2. Increasing early phase activity and participation	Increase the availability of early phase studies for patients at all PTCs by: •Agreeing a development plan so more PTCs are able to undertake and deliver early phase studies to time and target •Promoting and monitoring the referral of patients between centres so that more patients are considered for early phase studies •Developing an information portal for parents and patients to gain knowledge of early phase trials (website?) Address the Paediatric Investigation Plan issue through the MHRA MJ on MHRA Paediatric Medicines Group Develop plan for how to take forward research opportunities with: •New drugs which show activity in childhood cancers but have been withdrawn from development by pharmaceutical companies •Increasing predictive biomarker studies that are undertaken by more pre-screening to effectively target novel agents and increase response rates •Increasing number of pharmacodynamics biomarkers to increase understanding of drug interactions with targets	DH/ PK/ GM DHT/ CC AP/ PK/ MJ AP/PK	May 2015 2016 Ongoing June 2015	Active discussions within CSG - ongoing New Agent Studies approved by Sub Group now presented at main CSG. CSG important forum for discussion / approval of trials of new agents and integration into clinical pathway
3a. Raising profile	Routine dissemination of results from studies through Annual Trials meetings and Annual Report Clarify links with CCLG Special Interest Groups, holding back to back meetings where appropriate Submission of abstracts to : •NCRI Cancer Conference •European Cancer Organisation (ECCO) •NCIN Conference •SIOP •BSH	MJ/ EL/ All AM/ KW/ AV/ AP/ SS All	Nov 2014 May 2015 June 2015 Ongoing	Complete Successful review meetings ongoing Links are strengthening across CSGs and CCLG Special Interest Groups. Ongoing discussion re dissemination of important results required

Strategic objective	Action	CSG Lead	Date	Outcomes
3b. Ensuring successful delivery of studies through integration with NIHR CRN: Cancer to engage with PTCs	Clarify position of UK and Ireland CCL Clinical Research Forum within the new NIHR CRN structures and implement appropriate reporting structures	AB (NSL)	Feb 2014	Cancer National Theme Group
	Work with PTCs in England to ensure they are able to provide equity of access to the clinical research portfolio for their patients	AB (NSL)	Ongoing	
	Monitor studies that are open at PTCs within England and facilitate the development of balanced local portfolio	AB (NSL)	Ongoing	
	Input into emerging processes within England fir Local Clinical Research Networks to improve delivery of studies to time and target	AB (NSL)	Ongoing	NIHR CRN Speciality Objective
	Continue to develop and monitor the shared care model for POSCUs so they can participate in suitable studies, including consideration of shared care model between PTCs	AB (NSL)/PK	Ongoing	
	Promote the need for PTC research staff to access work force development opportunities within their LCRN and region in England	RDMs via AB (NSL)	Ongoing	
	Facilitate agreement of a set of data items that PTCs agree to collect to benchmark their performance with each other, including supplying information about whether patients are eligible for studies	AB (NSL) /MMcC	Mar 2016	
	Monitor resources provided for PTC and POSCU research teams in England, and flag where difficulties are encountered to NIHR CRN CC	AB (NSL)	Ongoing	
	Contribute as far as possible to NIHR CRN: Cancer Speciality Objectives so they reflect what LCRNs need to deliver to ensure CCL patients can access the full portfolio of studies within England	AB (NSL)	2015, then annual	
3c. Maximise output from clinical trials	Establish working groups for studies within 6 weeks of funding award to facilitate swift set up, including representation from CI, CRCTU, NIHR CRN: Cancer	CI/CRCTU/AB	Winter 2014	Ongoing.
4. Strengthen UK wide and international working	Refine clear prioritisation process for international clinical trials to be submitted for funding to optimise the timing of applications	PK/ All	Ongoing	Several new International studies reviewed – part of regular CSG responsibility Successful funding of PHITT Study.
	Define funding opportunities for travel to attend meetings with international partners	TBD		
	Target seventh EU funding (Horizon 2020) for international studies where appropriate.	DH		

Strategic objective	Action	CSG Lead	Date	Outcomes
5. CSG structure and function	Establish Renal Working Party	MP	Jun 2015	Complete
	Establish Hepatobiliary Working Party	DR	Jun 2015	Complete
	Consider case for Germ Cell Tumour Subgroup	JN/ EL/ MJ	Done	Complete
	Consider establishing Working Party to develop appropriate research studies for patients with retinoblastoma. Discuss with Sue Picton in order to liaise with Retinoblastoma Special Interest Group	AB/ MJ/ SP	Jun 2015	Complete
	Central Nervous System and Brain Subgroup to consider setting up Working Party if appropriate	AM	Jun 2015	Complete
	Agree mechanism and governance for co-opting trainee registrars onto the main CSG and subgroups, including: •Transparency •Role •Selection Process •Tenure Period •Funding through CCLG and Cancer Research UK	MJ/ MG	Done	Complete
6. Patient and Public Involvement and Impact	Increase the number of consumers involved in the Paediatric Oncology Reference Team (PORT) through advertising for membership via the CCLG and members clinics	All	Ongoing	
	Increase the number of children in less developed countries that participate in clinical trials	DHT/ CC/ PK with relevant CCLG SIG	Ongoing	

CNS Subgroup Strategy

The CNS Subgroup has continued to work with European partners to develop, open and run studies into high risk brain tumours in childhood. The majority of the studies are run via SIOP. They all have translational elements with tissue collection and biological studies mandated. Most have up front molecular diagnostics and risk stratification. The challenge is to develop studies which are relevant to specific subgroups of these rare diseases while keeping the duration of the studies short enough for them to remain current in a landscape of rapid change in knowledge of molecular pathology, target identification and new drug development.

The Subgroup and its affiliated research groups have been successful in attracting funding for translational research with comprehensive molecular and clinical characterisation of tumours. There are close interactions with other national initiatives such as the 100k genome project.

The Subgroup has user involvement via the Brain Tumour Charity and values parent and patient input into study development.

The membership of the Subgroup will change substantially over the coming year with a number of members reaching the end of their tenure. This will provide an opportunity to review the priorities of the subgroup and ensure that areas of research that are currently not being addressed are being represented.

Neuroblastoma Subgroup Strategy

See main CSG strategy document.

Leukaemia Subgroup Strategy

See main CSG strategy document.

Novel Agents Subgroup Strategy

See main CSG strategy document.

Germ Cell Tumour Subgroup Strategy

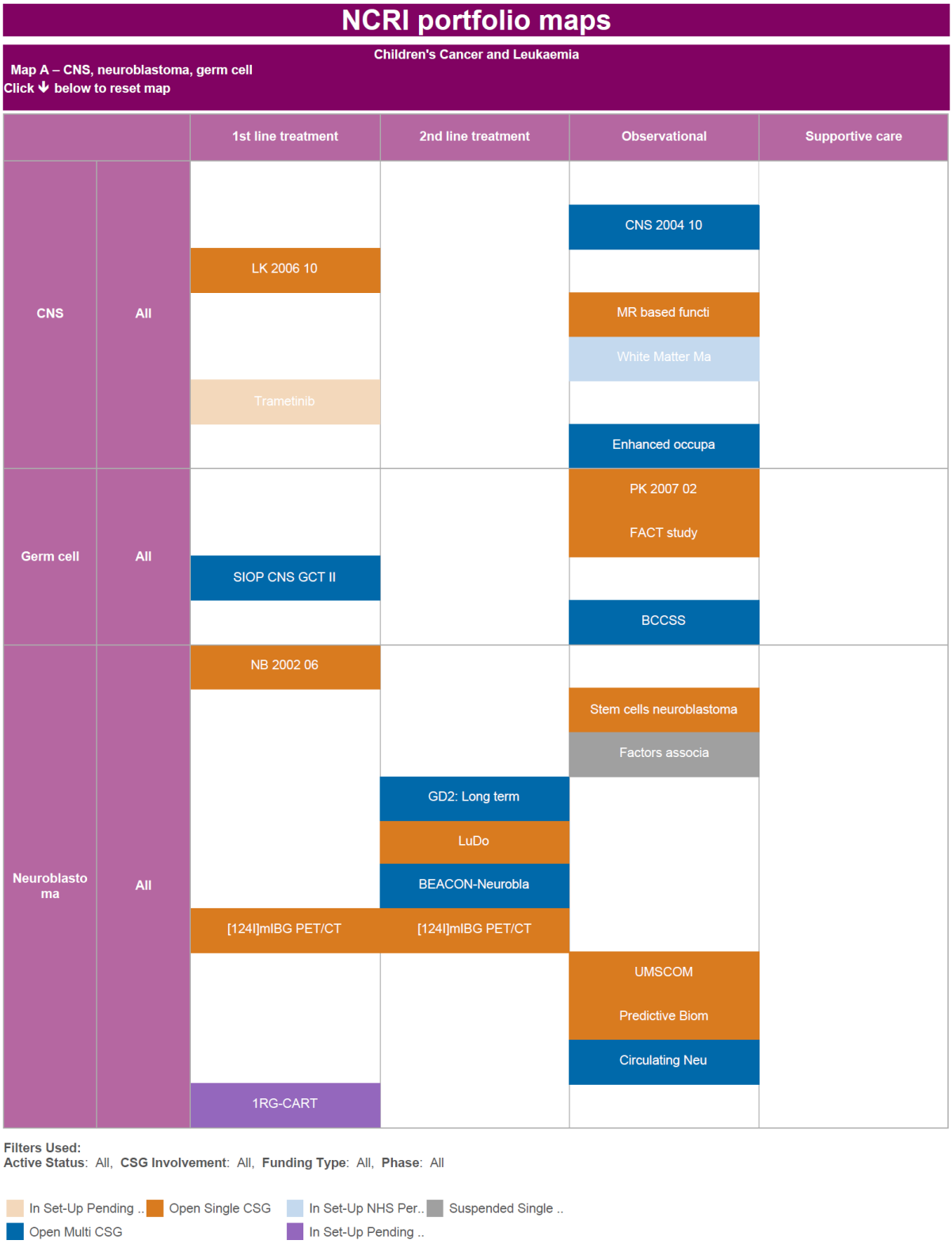
Key aim: Improve OS and quality of survival for all patients diagnosed with a GCT.

Strategic Aims for 2016:

1. Continue excellent recruitment to SIOP CNS GCT II for intracranial GCT.
2. Submit application to CTAAC December 2016 for funding for international collaborative, risk stratified, randomised extra-cranial GCT trial. Hosted and supported at Birmingham CTU.
3. Understand role of biological marker's in risk assessment and tracking treatment response and surveillance in marker negative GCT.
4. Ensure trial eligibility for TYA patients in randomised clinical trial for relapsed patients GCT.
5. Systematic Review to investigate the Effectiveness of Chemotherapy Treatments for Paediatric Germ Cell Tumours – joint project between CSG subgroup and with Birmingham CTU to support evidence base for proposed clinical trial.
6. Secure funding stream to support PROMS alongside AGCT1531/GC4.
7. Complete MaGIC (Malignant Germ Cell Tumour International Collaborative) trial database analyses for 1) TYA patient outcomes and b) dysgerminoma/seminoma and publish.
8. Analyse and publish outcomes for GC3.

Appendix 3

Portfolio maps



NCRI portfolio maps

Children's Cancer and Leukaemia

Map B – Leukaemia, lymphoma, all cancers
Click ↓ below to reset map

		1st line treatment	2nd line treatment	Observational	Supportive care
All cancers	All	Cobimetinib Anti-Pd-L1 Ab	Lenvatinib Pembrolizumab	NUMeRICC IntReALL SR 2010	Molecular Genet BoHEMIaN Study Dabrafenib in paediatric BRAF CANC - 4814
Leukaemia	All	UKALL 2011 BOSUTINIB in CML Treosulfan Azacitidine Carfilzomib + Dex + …	DACOGEN ACP-196	The genetic aet CaspaCIDe	
Lymphoma	All	UKALL 2011 EuroNet PHL-LP1 Inter-B-NHL Rit	EuroNet PHL-LP1 Pembrolizumab	CaspaCIDe	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG
Open Multi CSG In Set-Up Pending ..

NCRI portfolio maps

Children's Cancer and Leukaemia

Map C – Renal, sarcoma, melanoma, hepatobiliary
Click ↓ below to reset map

		1st line treatment	2nd line treatment	Observational	Supportive care
Melanoma	All	Ipi in paediatric melanoma	Ipi in paediatric melanoma		
			Pembrolizumab		
Renal	All				
				IMPORT	
		Ipi in paediatric melanoma	Ipi in paediatric melanoma		
Sarcoma	All	STS 2006 03 NR			
		STS 2006 04 RMS			
		Sunitinib	Sunitinib		
		Euro Ewing 2012			
				Pharmacokinetic	
			Afatinib		
		rEECur	rEECur		
				PREDICT	

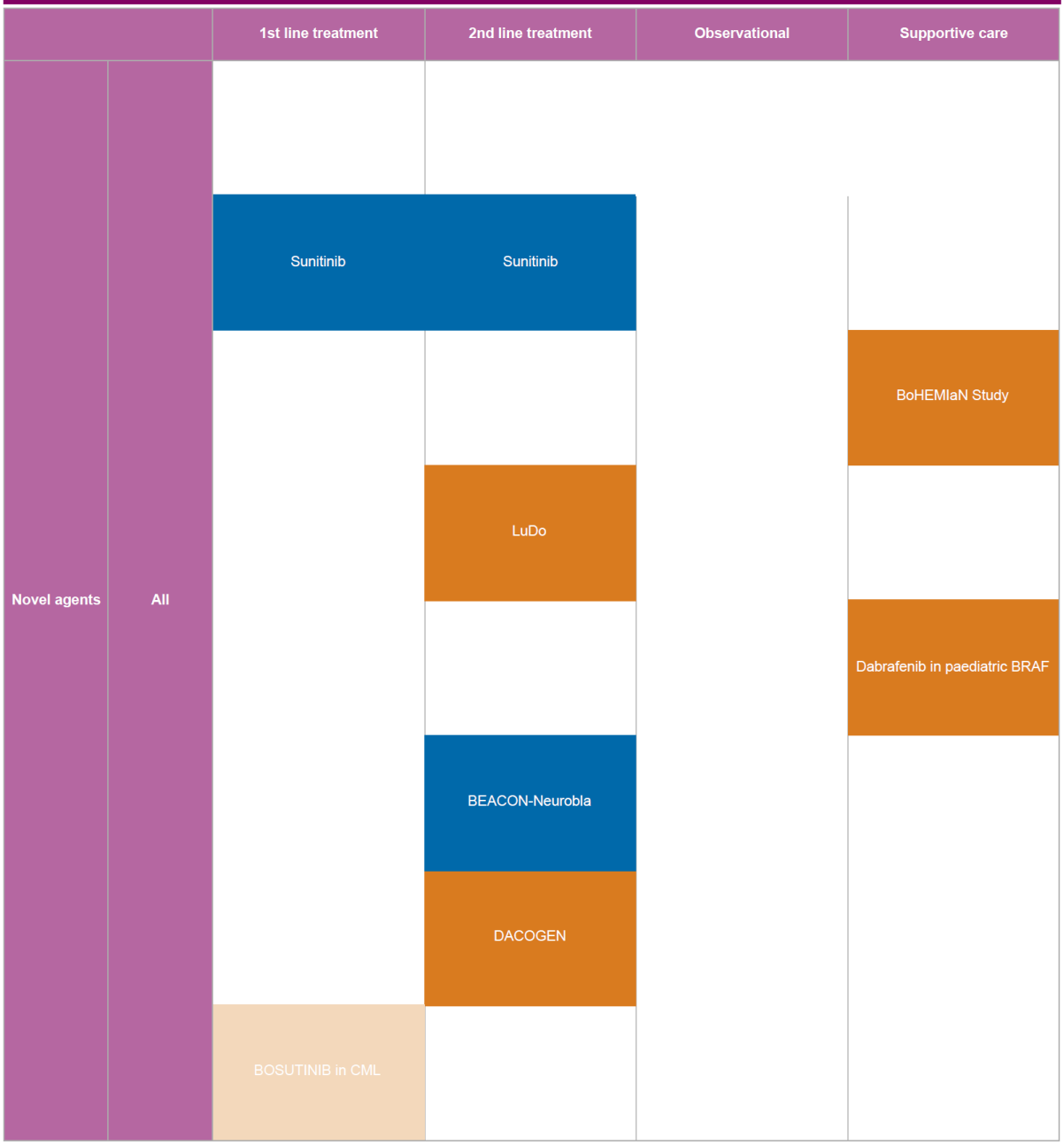
Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG
Open Multi CSG

NCRI portfolio maps

Children's Cancer and Leukaemia

Map D – Novel agents
Click ↓ below to reset map



Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG
Open Multi CSG

Appendix 4

Publications in the reporting year

UKALL 2003

Vora A, Andreano A, Pui CH et al. Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy. J Clin Oncol 2016.

Boer JM, van d, V, Rizopoulos D et al. Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. Leukemia 2016;30(1):32-38.

Patrick K, Vora A. Update on biology and treatment of T-cell acute lymphoblastic leukaemia. Curr Opin Pediatr 2015;27(1):44-49.

Lennard L, Cartwright CS, Wade R, Vora A. Thiopurine dose intensity and treatment outcome in childhood lymphoblastic leukaemia: the influence of thiopurine methyltransferase pharmacogenetics. Br J Haematol 2015;169(2):228-240.

Pui CH, Yang JJ, Hunger SP et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. J Clin Oncol 2015;33(27):2938-2948.

Gabriel AS, Lafta FM, Schwalbe EC et al. Epigenetic landscape correlates with genetic subtype but does not predict outcome in childhood acute lymphoblastic leukemia. Epigenetics 2015;10(8):717-726.

Jenkinson S, Kirkwood AA, Goulden N, Vora A, Linch DC, Gale RE. Impact of PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. Leukemia 2015.

Fischer U, Forster M, Rinaldi A et al. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet 2015;47(9):1020-1029.

Vicente C, Schwab C, Broux M et al. Targeted sequencing identifies associations between IL7R-JAK mutations and epigenetic modulators in T-cell acute lymphoblastic leukemia. Haematologica 2015;100(10):1301-1310.

Boer JM, van d, V, Rizopoulos D et al. Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. Leukemia 2015.

Hough R, Rowntree C, Goulden N et al. Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003. Br J Haematol 2015.

Lennard L, Cartwright CS, Wade R, Vora A. Thiopurine methyltransferase and treatment outcome in the UK acute lymphoblastic leukaemia trial ALL2003. Br J Haematol 2015;170(4):550-558.

Alexander S, Pole JD, Gibson P et al. Classification of treatment-related mortality in children with cancer: a systematic assessment. Lancet Oncol 2015;16(16):e604-e610.

Mehta PA, Zhang MJ, Eapen M et al. Transplantation Outcomes for Children with Hypodiploid Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant 2015;21(7):1273-1277.

Vijayakrishnan J, Henrion M, Moorman AV et al. The 9p21.3 risk of childhood acute lymphoblastic leukaemia is explained by a rare high-impact variant in CDKN2A. Sci Rep 2015;5:15065.

Interfant 99

Driessen EM, de LP, Campbell M et al. Outcome of relapsed infant acute lymphoblastic leukemia treated on the interfant-99 protocol. Leukemia 2015.

AML 12, 15 and 17

de Rooij JD, Beuling E, van den Heuvel-Eibrink MM et al. Recurrent deletions of IKZF1 in pediatric acute myeloid leukemia. Haematologica 2015;100(9):1151-1159.

Gabriel AS, Lafta FM, Schwalbe EC et al. Epigenetic landscape correlates with genetic subtype but does not predict outcome in childhood acute lymphoblastic leukemia. Epigenetics 2015;10(8):717-726.

Klein K, Kaspers G, Harrison CJ et al. Clinical Impact of Additional Cytogenetic Aberrations, cKIT and RAS Mutations, and Treatment Elements in Pediatric t(8;21)-AML: Results From an International Retrospective Study by the International Berlin-Frankfurt-Munster Study Group. J Clin Oncol 2015;33(36):4247-4258.

Zwaan CM, Kolb EA, Reinhardt D et al. Collaborative Efforts Driving Progress in Pediatric Acute Myeloid Leukemia. J Clin Oncol 2015;33(27):2949-2962.

GCT II study

Pashankar F, Hale JP , Dang H, Krailo M, Brady W, Rodriguez-Galindo C, Nicholson JC, Murray MJ, Bilmire DF, Stoneham S, G Arul S, Olson TA, Stark S, Shaikh F, Amatruda JF, Covens A, Gershenson DM , Frazier AL. Is Adjuvant Chemotherapy indicated in Ovarian Immature Teratoma? A Combined Data Analysis from The Malignant Germ Cell Tumors International Collaborative. Cancer. 2016 Jan 15;122(2):230-7. doi: 10.1002/cncr.29732

Adaptive dosing of anticancer drugs in neonates: facilitating evidence-based dosing regimens

Veal GJ, Errington J, Sastry J, Chisholm J, Brock P, Morgenstern D, Pritchard-Jones K, Chowdhury T. Cancer Chemother Pharmacol. 2016 Apr;77(4):685-92. doi: 10.1007/s00280-016-2975-0. Epub 2016 Feb 13.

Assessment of Primary Site Response in Children With High-Risk Neuroblastoma: An International Multicenter Study

Bagatell R, McHugh K, Naranjo A, Van Ryn C, Kirby C, Brock P, Lyons KA, States LJ, Rojas Y, Miller A, Volchenboum SL, Simon T, Krug B, Sarnacki S, Valteau-Couanet D, von Schweinitz D, Kammer B, Granata C, Pio L, Park JR, Nuchtern J. J Clin Oncol. 2016 Mar 1;34(7):740-6. doi: 10.1200/JCO.2015.63.2042. Epub 2016 Jan 11.

Additional Therapies to Improve Metastatic Response to Induction Therapy in Children With High-risk Neuroblastoma

Schrey D, Vaidya SJ, Levine D, Pearson AD, Moreno L.J Pediatr Hematol Oncol. 2015 Apr;37(3):e150-3. doi: 10.1097/MPH.0000000000000308.

Pharmacokinetics and pharmacodynamics of ch14.18/CHO in relapsed/refractory high-risk neuroblastoma patients treated by long-term infusion in combination with IL-2

Siebert N, Eger C, Seidel D, Jüttner M, Zumpe M, Wegner D, Kietz S, Ehlert K, Veal GJ, Siegmund W, Weiss M, Loibner H, Ladenstein R, Lode HN. MAbs. 2016 Apr;8(3):604-16. doi: 10.1080/19420862.2015.1130196. Epub 2016 Jan 19.

Neuroblastoma Arginase Activity Creates an Immunosuppressive Microenvironment That Impairs Autologous and Engineered Immunity

Mussai F, Egan S, Hunter S, Webber H, Fisher J, Wheat R, McConville C, Sbirkov Y, Wheeler K, Bendle G, Petrie K, Anderson J, Chesler L, De Santo C. Cancer Res. 2015 Aug 1;75(15):3043-53. doi: 10.1158/0008-5472.CAN-14-3443. Epub 2015 Jun 8

Is adjuvant chemotherapy indicated in ovarian immature teratomas? A combined data analysis from the Malignant Germ Cell Tumor International Collaborative

Pashankar F, Hale JP, Dang H, Krailo M, Brady WE, Rodriguez-Galindo C, Nicholson JC, Murray MJ, Bilmire DF, Stoneham S, Arul GS, Olson TA, Stark D, Shaikh F, Amatruda JF, Covens A, Gershenson DM, Frazier AL. Cancer. 2016 Jan 15;122(2):230-7. doi: 10.1002/cncr.29732. Epub 2015 Oct 20

Pediatric and Adolescent Extracranial Germ Cell Tumors: The Road to Collaboration

Olson TA, Murray MJ, Rodriguez-Galindo C, Nicholson JC, Billmire DF, Krailo MD, Dang HM, Amatruda JF, Thornton CM, Arul GS, Stoneham SJ, Pashankar F, Stark D, Shaikh F, Gershenson DM, Covens A, Hurteau J, Stenning SP, Feldman DR, Grimison PS, Huddart RA, Sweeney C, Powles T, Lopes LF, dos Santos Agular S, Chinnaswamy G, Khaleel S, Abouelnaga S, Hale JP, Frazier AL. J Clin Oncol. 2015 Sep 20;33(27):3018-28. doi: 10.1200/JCO.2014.60.5337. Epub 2015 Aug 24

Appendix 5

Major international presentations in the reporting year

There were no presentations during this reporting year.