NCRI
National
Cancer
Research
Institute

NCRI Children's Cancer & Leukaemia Clinical Studies Group

Annual Report 2016-17

Partners in cancer research

NCRI Children's Cancer & Leukaemia CSG Annual Report 2016-17

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

An important focus of the CSG this year has been to strengthen the translational science portfolio. This has been demonstrated through recent successful funding applications of two key translational studies and the appointment of two new members with a focus on the pathology and biology of childhood cancer.

A challenge for the Group was that several studied have closed within the past 12-18 months; however, the number of studies in development and submitted for funding has been high and we anticipate several studies opening in 2017-2018.

The CCL CSG held an annual trials meeting in November which was highly successful with a larger registration than in previous years. The meeting now brings together all trials in children's cancer with the leukaemia trials moving this year from a joint meeting with the adult Haem Onc CSG into a meeting focused on children's cancer and leukaemia trials across the portfolio.

The CSG Subgroups are particularly active with new studies in development and submitted for funding across all Subgroups.

2. Structure of the Group

The Group now has a good balance of representation across the wide range of tumour sites seen within children's cancer and leukaemia, and the geographical balance is also improving. There is also an increased focus on pathology and opportunities for translational research with the appointment of Dr Deborah Tweddle and Professor Andy Hall.

The Subgroups continue to be extremely active, developing clinical trials across the portfolio. There is also a strengthening partnership with the CCLG Special Interest Groups.

We would like to thank Professor Ajay Vora and Dr Antony Michalski for their huge contribution as CSG Subgroup Chairs in leukaemia and brain tumours respectively. We look forward to working with Dr Philip Ancliff and Professor Simon Bailey as they take over responsibility for these very active Subgroups.

The CCL CSG/CCLG trainee scheme continues to be very popular and there was recruitment of the second cohort of trainees to all subgroups last summer. Feedback to date has been positive, with mentors and projects assigned to all new recruits.

3. CSG & Subgroup strategies

Main CSG

A key CSG strategy continues to be addressing the unmet need for patients with rare tumours (with poor outcomes) and those who relapse, and the need to increase availability of and participation in early phase clinical trials. There has been significant progress towards this during the reporting period with the recently funded translational studies, the increase in funding for paediatric ECMC centres and improving access to new agents through close working with the pharmaceutical industry.

Another important theme of work for the Group is our partnership with the TYA CSG in developing studies that cross the age barriers and potentially improve outcomes for patients through childhood, adolescence and into adulthood. An example of a major achievement in this area is the funding of the collaborative International Phase III Study for Low and Standard Risk Extracranial Germ Cell Tumours which also includes translational biological elements. The Germ Cell Tumour Subgroup is working across CSGs (with the Testis and Gynaecological CSGs) creating a national consensus approach to the treatment of patients with GCT stratified for age and risk and a further grant is being submitted in June 2017.

The CSG is working with partners to expand clinical trial capacity for children's cancer research in the UK. There is a focus on the timely opening of studies and addressing the challenges of opening studies with sponsors outside the UK. Further to feedback from the 2015-16 annual report, the Group held an in-depth discussion in their October CSG meeting to discuss optimal structures for increased capacity, which was followed up by the Chair in a call to the NCRI Clinical Director.

CNS Subgroup (Chair, Professor Simon Bailey)

Dr Michalski, who has done an outstanding job of leading the CNS Subgroup for a number of years, stepped down and was replaced by Professor Bailey.

A number of European studies are open in the UK including the SIOP ependymoma study, a Europe wide umbrella study (opened December 2015) which is open in 12 centres with more due to open. This is underpinned by a national MDT for ependymoma. The SIOP CNS germ cell study continues to recruit in many UK centres. PNET5, the European standard risk medulloblastoma study is open in five UK centres, with a funding request to open further centres. This is underpinned by a national molecular diagnostic service which essential for the trial but is being extended for all children with medulloblastoma. The BIOMEDE study for children with diffuse intrinsic pontine glioma is open in a number of centres. This study requires an upfront biopsy before allocation to a treatment group with early phase agents. A number of other European trials, some being led by the UK, are in development for a number of tumour types. This is in addition to the increasing number of early phase trials for children with CNS tumours.

Neuroblastoma Subgroup (Chair, Dr Mark Gaze)

The Subgroup has been very active, with face-to-face meetings on 20 September 2016 and 17 March 2017 and supplemented by four telephone conferences. The Subgroup also held a national Neuroblastoma Clinical Trials Meeting on 21 September 2016 in association with the CCLG to showcase our clinical trial portfolio, with consumer involvement from both Neuroblastoma UK and Solving Kids' Cancer. There were around 70 delegates and the feedback was excellent, prompting us to make this an annual event.

Membership has been refreshed following the departure of Mr Squire and Dr Morgenstern, by the recruitment of a radionuclide radiologist, Dr Simon Wan, and paediatric surgeon Mr Hany Gabra. In addition, we have an active and influential consumer member in Mr Nicholas Bird, and a trainee representative who is undertaking projects under the mentorship of the former Chair, Dr Wheeler.

The Subgroup's key international randomised phase III trial, the SIOPEN High-Risk Study, is nearing its conclusion, as recruitment to its fourth and fifth randomisations are completed. A landmark paper has been published in Lancet Oncology with the results of the high-dose chemotherapy randomisation, showing improved survival and lower toxicity with the European schedule compared with the American.

Leukaemia Subgroup (Chair, Professor Ajay Vora [outgoing], Dr Phil Ancliff [incoming])

Professor Ajay Vora has completed a four year term as Chair and handed over to Dr Phil Ancliff from March 2017. Dr Alice Norton has been appointed as co-lead for new agents and Amy Mitchell, statistician for UKALL 2011, has been appointed for input on statistical matters.

Recruitment to the first (R1-dexamethasone) randomisation of UKALL 2011 was closed on 31 March 2017 following a review of the R1 data by the DMC which showed that the short dexamethasone was unlikely to be associated with fewer side effects. We are partnering with Dutch (DCOG), German (COALL), Scandinavian (NOPHO), Belgian (BSPHO) and Portuguese (SHOP) groups to develop a successor international trial for first line treatment of children and young persons with ALL.

The standard risk arm of the international relapse ALL trial, IntReALL, is open in Manchester with other centres to open over the next few months. The pharma-led Blinotumumab randomisation for high risk relapse has opened to recruitment. The first line AML trial, MyeChild01 started recruiting in June 2017.

A pilot international study of Blinatumomab for infant ALL and an international study for Ph+ ALL (EsPhALL-COG collaboration) will open in 2017. The Subgroup has supported new agent studies for relapse and refractory ALL and CML.

Novel Agents Subgroup (Chair, Dr Darren Hargrave)

The Novel Agents Subgroup remains very active with the portfolio including 20 open trials: 11 dose finding (phase I/II) and nine phase II trials. Of these, 60% are pharma industry sponsored. The portfolio focuses on targeted therapies including ALK, BRAF, DNA methytransferase, ERBB, EZH2, MEK and VEGFR inhibitors. There has also been an increase in immunotherapy studies, e.g. the CRUK-sponsored, first in human study of 1RG-CART therapy in patients with relapsed or refractory neuroblastoma has recruited 10 patients, with nine cell therapy products made and six infusions administered. Also, completion of the first phase of the immune checkpoint inhibitors pembrolizumab and atezolizumab in relapsed refractory childhood tumours.

There have been multiple presentations from the portfolio including six at the ASCO and ESMO annual meetings. There are at least eight early phase trials planned to commence in 2017-2018. The Newcastle Cancer Centre Pharmacology Group provides national support for paediatric pharmacology studies, with nine open studies and 94 patients recruited in this reporting year.

In addition to the Subgroup's core activity of early phase trials, there have been two major initiatives this year. Firstly, the Paediatric Experimental Cancer Network renewal (led by Dr Guy Makin) was developed and submitted for an expanded and enhanced paediatric ECMC to facilitate the delivery of early phase trials, biomarker studies and translation of preclinical work to

trial development. The renewal was successful and for the first time, the NIHR, CRUK and Chief Scientist Office for Scotland will all be supporting the additional funding for the expanded network. The second major initiative has been the development of a National Molecular Profiling programme to facilitate precision medicine/biomarker stratified early phase clinical trials and this has been led by Professor Louis Chesler and Dr Darren Hargrave. £1.5M was awarded from Children with Cancer UK to setup and support the infrastructure to run a customised paediatric NGS panel for children with cancer in the UK. In addition, the Subgroup developed and submitted to CRUK a related proposal for Stratified Medicine Paediatrics to expand the targeted NGS panel to a "multi-omic" platform focusing on paediatric and TYA relapsed solid/brain tumours. The final decision from CRUK will be expected in the next reporting year.

Germ Cell Tumour Subgroup (Chair, Dr Sara Stoneham)

Major achievements

- Collaborative international phase III trial design for low risk and standard risk extracranial GCT patients agreed, funded and recently opened in first country (USA).
- Opening of international phase III trial for all high risk extracranial GCT patients in the UK; this includes male and female and inclusive eligibility for children and TYA.
- Both new clinical trials include translational biology elements with confirmatory testing of new diagnostic/surveillance biomarkers.
- Cross-cutting NCRI CSG trial endorsement in UK from the NCRI Testis, Gynaecological and CCL CSGs, thus for the first time creating a national consensus approach to treatment of patients with GCT better stratified for age and risk.
- On-target recruitment to international SIOP intracranial GCT clinical trial.
- Active participation in the NHSe GeCIP testis domain.

Areas of strength

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

4. Task groups/Working parties

The CSG currently has no active working parties.

5. Patient recruitment summary for last 5 years

In the Children's Cancer & Leukaemia CSG portfolio, 11 trials closed to recruitment and 8 opened.

Table 1 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	-	-
2016/2017	1228	630	594	630	-	-

The slight fall in the number of cancer patients recruited to interventional and non-interventional studies this year reflects the reduction in the numbers of trials in the CSG portfolio last year. However, a number of new studies have now been funded and it is anticipated that the recruitment will increase significantly in the coming 12-18 months.

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

Professor Andy Hall has been appointed this year and will represent the CCL CSG at CM-Path. The Chair has contributed to the NCRI strategic work on the Living With and Beyond Cancer (LWBC) initiative.

The Group is developing formal links with the National Sub-Specialty Leads (SSLs) and a report will be sent to all SSLs following each CSG meeting, highlighting the development of new studies and important developments relevant to study implementation across the network.

The CSG also has close links to other Partners. The Chair coordinated a research update session at the CCLG's Annual Meeting in January. This comprised of an overview of the CSG strategy and portfolio, a presentation about the role of the CRCTU and NIHR and the development of the new paediatric ECMC Centres, for which further funding has been secured, making an expansion of early phase studies across the UK now possible.

The CSG has actively engaged with CRUK regarding the Kids and Teens campaign. In addition to increasing the profile of the campaign, the CSG has provided an opportunity for the consumer members to debate the role of the campaign directly with CRUK.

7. Funding applications in last year

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
May 2016			
A Phase Ib study of ch14.18/CHO in combination with IL-2 and zoledronate in patients with relapsed/refractory neuroblastoma	Outline application	Dr Juliet Gray & Professor Pamela Kearns	Not funded
Stratified Medicine Paediatrics - a feasibility study to deploy prospective genome sequencing for children with newly diagnosed or recurrent solid tumours using a targeted rapid capture panel approach	Outline application	Professor Louis Chesler & Dr Darren Hargrave	Full Application Invited (Preliminary)
November 2016			
PARC: A Phase II study evaluating the activity of Pegylated recombinant human Arginase (BCT-100) in Relapsed/refractory Cancers of childhood	Full (Feasibility Study)	Dr Francis Mussai	Preliminary
SIOP-PNET5-MB: An international prospective study on clinically standard-risk medulloblastoma in children older than 3 to 5 years with low-risk biological profile or average-risk biological profile	Full application	Dr Antony Michalski	Not Supported
CCLG tissue bank	Sample Collection	Dr Deborah Tweddle	Supported

The CSG has again been successful with the funding applications as noted above [to note the full application for SMPaeds and the resubmission of the PARC Study have been successfully funded along with 2 other national portfolio studies at the most recent CRUK CRC committee]. The SIOP-PNET5-MB Study has been supported by the Birmingham CRCTU and will now be opening across the UK.

8. Collaborative partnership studies with industry

There are 11 open industry-sponsored studies and many more in set-up/discussion with pharma partners including: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Celgene, Epizyme, GSK, Hoffmann-La Roche-Genentech, Johnson & Johnson, Merck, Novartis and Pfizer. Working with the European ITCC group, the first multi-Pharma paediatric basket study eSMART has been developed and submitted to CRUK for funding support. The Group has been working with the ECMC combinations alliance to further expand new industry connections and it is expected that several agents will move forward into later phase studies in the next reporting year.

9. Impact of CSG activities

The SIOPEN High Risk Neuroblastoma Trial will be closing this year. Members of the Neuroblastoma Subgroup have participated in the design and leadership of this international study in a rare disease. This study has an adapted multiple stage approach with the instruction of new randomisations as older ones closed (five randomisation questions in total, covering induction, consolidation and minimal residual disease treatment with immunotherapy, as well as supportive care). This has led to improvements in outcome for children with very poor prognosis cancer and has also managed to demonstrate a reduction in treatment related toxicity. A significant benefit identified through the first two randomisations of this trial have now been adopted as a standard of care internationally.

The CSG continues to provide regular advice to NCRI funders, particularly the CRUK Clinical Research Committee. The CSG is also contributing to the national strategy for cancer genetics/molecular pathology, collaborating with scientific and clinical partners across the UK to provide specific advice regarding future genomic testing in children's cancer.

10. Consumer involvement

Two new consumers were appointed in February 2016 and they have been very active in their contribution to the work of the CSG. We particularly appreciate their thoughtful and informed contributions to the (many) studies that we are asked to review that have been submitted to the clinical trials committees for funding.

Angela Polanco
As a consumer member, I have contributed to trial proposals, funding applications and provided insight to researchers at CSG meetings, emphasising the importance of the patient role in research development and advocating patient-focused research.

I am a member of the Novel Agents Subgroup and have attended international meetings to represent collaborative efforts to accelerate drug development for children with cancer. I have also actively participated in the NCRI Consumer Forum meetings and presented scientific posters at conferences.

I have commenced an MSc by research with a project relating to childhood cancer survivorship and continued to participate within European initiatives to raise awareness of childhood cancer research funding, survivorship issues and novel drug therapy campaigns.

As a CSG member, I have been given the opportunity and support to be an active part of a collaborative effort to help further childhood cancer research and be a voice for children and families.

Nick Bird
Since joining the CSG last February, I have actively participated in all main CSG meetings. Outside of meetings, I have reviewed and commented on a number of research study proposals and funding applications from a consumer perspective.

As a member of the Neuroblastoma Subgroup, I have participated in meetings and teleconferences, principally around access to anti-GD2 antibody therapy in the UK and input into discussions about ongoing and future research.

11. Open meetings/annual trials days/strategy days

Another successful and well attended annual trials day was held in November with a larger venue as the meeting was oversubscribed the previous year. Although the majority of attendees were consultants or doctors in training, the meeting was also well attended by research nurses and trial coordinators. The feedback was very positive with ratings of excellent or very good from almost all participants.

We aim to ensure that all paediatric cancer principle treatment centres are represented. We also encourage attendance from the paediatric oncology shared care centres where clinical trials are open. Planning for the 2017 meeting is already well underway.

12. Priorities and challenges for the forthcoming year

Priorities

- To focus on the inclusion of radiotherapy and surgery questions within clinical trials. The new study in Frontline and Relapsed RMS (FaR-RMS) study has three key randomisation questions relating to the role of radiotherapy in RMS. The role of surgery (and definition of tumour resectability) is also integral to this randomisation.
- To improve access for all children with cancer to clinical trials. In particular, to address the barriers to recruitment into early phase studies of new therapeutic agents.
- To work more closely with other CSGs in the development of clinical trials open to patients of all ages and address the gaps in the portfolio.

Challenges

- To work with partners to ensure timely opening of the recently funded studies and improve recruitment overall.
- To implement pathways for patients with high risk and relapsed cancers to the stratified medicines programme.
- To develop clinical trials addressing the unmet need of children with very rare tumours which may have a poor prognosis and the challenges of international collaboration and funding for such studies.

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
Dr Phil Ancliff	Consultant Haematologist	London
Mr Nicholas Bird	Consumer	Epsom
Mrs Angela Polanco	Consumer	Warwick
Mr Neil Meemaduma*	Children with Cancer UK	London
Dr John Moppett	Paediatric Haematologist	Bristol
Professor Simon Bailey	Paediatric Oncologist	Newcastle
Dr Amos Burke	Paediatric Oncologist	Cambridge
Dr Julia Chisholm	Paediatric Oncologist	London
Dr Angela Edgar*	Paediatric Oncologist	Edinburgh
Dr Martin Elliot	Paediatric Oncologist	Leeds
Dr Mark Gaze	Paediatric Oncologist	London
Dr Juliet Gray	Paediatric Oncologist	Southampton
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 James Nicholson*	Paediatric Oncologist	Cambridge
Dr Sara Stoneham	Paediatric Oncologist	London
Professor Bruce Morland	Paediatric Oncologist and Clinical Director	Birmingham
Mrs Julie Evans	Paediatric Oncology Senior Research Nurse	Leeds
Professor Andy Hall	Pathologist	Newcastle
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

*denotes ex-officio/observer member

Membership of the Subgroups

Central Nervous System (CNS) Subgroup		
Name	**Specialism**	**Location**
Ms Erica Moyes	Brain Tumour Charity	Farnborough
Dr Nicki Thorpe	Clinical Oncologist	Liverpool
Dr Tom Jacques	Neuropathologist	London
Dr Chris Lethaby*	Paediatrician	Leeds
Dr Jenny Adamski	Paediatric Neuro-Oncology	Birmingham
Professor Simon Bailey (Chair)	Paediatric Neuro-Oncology	Newcastle
Professor Richard Grundy	Paediatric Neuro-Oncology	Nottingham
Professor Colin Kennedy	Paediatric Neurologist	Southampton
Professor Steve Clifford	Paediatric Oncologist	Newcastle
Dr Darren Hargrave	Paediatric Oncologist	London
Dr Andrew Peet	Paediatric Oncologist	Birmingham
Dr Sue Picton	Paediatric Oncologist	Leeds
Professor Barry Pizer	Paediatric Oncologist	Liverpool
Mr Connor Mallucci	Surgeon	Liverpool

Novel Agents Subgroup		
Name	**Specialism**	**Location**
Dr Sam Behjati*	Clinical Fellow	Cambridge
Mrs Angela Polanco	Consumer	Warwick
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 Gareth Veal	Paediatric Pharmacologist	Newcastle

Germ Cell Tumour (GCT) Subgroup		
Name	**Specialism**	**Location**
Dr Gail Horan	Clinical Oncologist	Cambridge
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
Dr Sarita Depani*	Paediatric Oncology GRID Trainee	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 (incoming Chair)	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 (outgoing Chair)	Paediatric Haematologist	Sheffield
Dr Donna Lancaster**	Paediatric Oncologist	London

Neuroblastoma Subgroup		
Name	**Specialism**	**Location**
Mr Nicholas Bird	Consumer	Epsom
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 (Chair)	Paediatric Oncologist	London
Dr Juliet Gray	Paediatric Oncologist	Southampton
Dr Guy Makin	Paediatric Oncologist	Manchester
Dr Lynley Marshall**	Paediatric Oncologist	London
Professor Andy Pearson**	Paediatric Oncologist	London
Dr Ramya Ramanujachar	Paediatric Oncologist	Southampton
Professor Deborah Tweddle	Paediatric Oncologist	Newcastle
Dr Kate Wheeler	Paediatric Oncologist	London
Dr Elwira Szychot*	Paediatric Oncology GRID Trainee	London
Professor Sue Burchill	Professor of paediatric & adolescent cancer research	Leeds
Dr Simon Wan	Radionuclide Radiologist	London
Professor Keith Wheatley	Statistician	Birmingham
Mr Hany Gabra	Surgeon	Newcastle

* denotes trainee member

**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – 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	

B – CNS Subgroup Strategy

Strategic aims

- Improve Event Free and Overall Survival for all patients CNS tumours with a poor prognosis and reduce morbidity and long term toxicity in those with good risk CNS tumours.
- To better identify prognostic and predictive biomarkers and to implement their use in clinical trials using routine real time molecular diagnostics for all CNS tumour types.

Trials

The number of clinical trials for children with CNS tumours needs to be increased. This will be done at a European level due to the rarity of the diseases. There are a number of trials in development as well as some diseases for which there are no planned trials and alternative strategies need to be developed.

Application of molecular diagnostics to routine clinical practice

The development of funded centralised routine molecular diagnostics and pathology review for all children with CNS tumours is in the process development. This is in place for the PNET5 trial and is in late development for high risk and infant medulloblastoma as well as other embryonal tumours. This process for other CNS tumour types are in earlier stages of development although a central review process is in place for ependymoma with a weekly national MDT.

C – Neuroblastoma Subgroup Strategy

Strategic aims

1. Improve Event Free and Overall Survival for all Neuroblastoma patients.
2. Diagnosis, staging and risk stratification: Refine the prognostic significance of tissue and imaging biological markers and integrate them into stratification of treatment groups in clinical trials.
    - Finalise analysis in current HR study of data linking biological markers and radiology, specifically mIBG scans 2016.
    - Evaluate FDG PET and mIBG PET.
    - Undertake an international retrospective study of ALK mutation testing and next generation sequencing for selected genes from banked DNA samples from patients treated on the high risk Neuroblastoma trial.
3. Define molecular targets in NBL: Introduce molecular targeted treatments upfront into ultra-high risk and relapsed patient studies.
    - Continue to increase the portfolio of molecularly driven early phase trials for patients with relapsed neuroblastoma in conjunction with the NCRI New Agents Subgroup.
4. High Risk NBL
    - Continue to enrol all eligible UK patients in the SIOPEN HR trial.
    - Work with the European group to develop the next high risk trial for 2017.
        - Induction chemotherapy: Continue enrolling into R3 to evaluate the best induction regimen.
        - Local therapy: Establish evidence for current local therapy in HR NBL, radiotherapy dose and extent of field and timing and extent of surgical excision of primary tumour.
        - Immunotherapy: Define and refine immunotherapy administration to maximise effectiveness and minimise toxicity.
            - Get the R4 in HR NBL 1 open in the UK and in all centres by 2015 Q3.
            - Open the Phase 1b trial of zoledronate and IL-2 combined with ch14.18 anti-GD2 antibody 2015.

        - Facilitate data collection and analysis regarding immunotherapy in HR study and LTI study 2017.
    - Surveillance: Monitor off treatment HR patients with imaging and molecular monitoring and link with clinical data to better understand patterns of relapse.
        - Set up a randomised maintenance treatment study with biomarker monitoring alongside maybe including DFMO 2016.
    - Refractory disease
        - Get SIOPEN Veritas clinical trial open in the UK by 2016.
    - Relapsed disease: To better understand the biology and clinical characteristics of relapsed Neuroblastoma.
        - Continue recruitment into BEACON study and get amendment through UK regulatory process for additional third randomisation with TOTEM 2015.
        - Await outcome of a grant application for a national retrospective genetic and Epidemiological study of relapsed Neuroblastoma 2015.
5. Low and Intermediate Risk NBL: Facilitate registration and collection of toxicity and outcome data for these Neuroblastoma patients who are not currently treated within a clinical trial as unable to get the SIOPEN LINES trial open in the UK in 2012.
    - Participate in the PICORET study, a Horizon 2020 project that is comparing outcome in comparable patients treated within and without a clinical trial. Await grant application 2015 Q4 and, if favourable, participate.
    - Achieve UK participation in the SIOPEN spinal cord compression study 2015/16.
    - Plan for involvement in next low and intermediate risk NBL trial if it involves further randomisations.

D – Leukaemia Subgroup Strategy

Strategic aims

- Open international trials for Ph-pos and infant ALL.
- Continue monitoring recruitment to UKALL 2011, MyeChild01 and InteReALL.
- Contribute to international collaborations in CML and MDS.
- Agree an international first line ALL trial.
- Open registries with linked biological sample collection and studies for APL, DS-AML, CML and MDS.
- Liaise with new agents group to increase portfolio of phase I and II leukaemia trials testing antibody and cellular therapy and targeted agents, especially for T-cell and AML where there is an unmet need.

E – Novel Agents Subgroup Strategy

Strategic aims

- To continue to develop and deliver novel agent studies for children and TYA across the cancer spectrum in partnership with academic and industry partners.
- To focus on novel agents for poor prognosis tumours at diagnosis and relapse in collaboration with tumour specific subgroups.
- To develop and deliver biomarker and pharmacokinetic studies.
- Implementation of the successful renewed and expanded Paediatric ECMC network with the aim of better linking translational science with early clinical trials and improving recruitment to early phase clinical trials, biomarker and pharmacokinetic studies.

- To develop, secure funding for and implement a UK National "multi-omic" molecular profiling platform for children and TYA with relapsed cancers to facilitate and enable precision/stratified medicine trials and advance the understanding of tumour evolution.
- Development of a UK National Molecular Tumour Board linked with the ECMC Paediatric Network to feedback results from the molecular profiling programmes to better inform clinical trial options for patients and recruitment to the NIHR portfolio.

F – Germ Cell Tumour Subgroup Strategy

Key aim

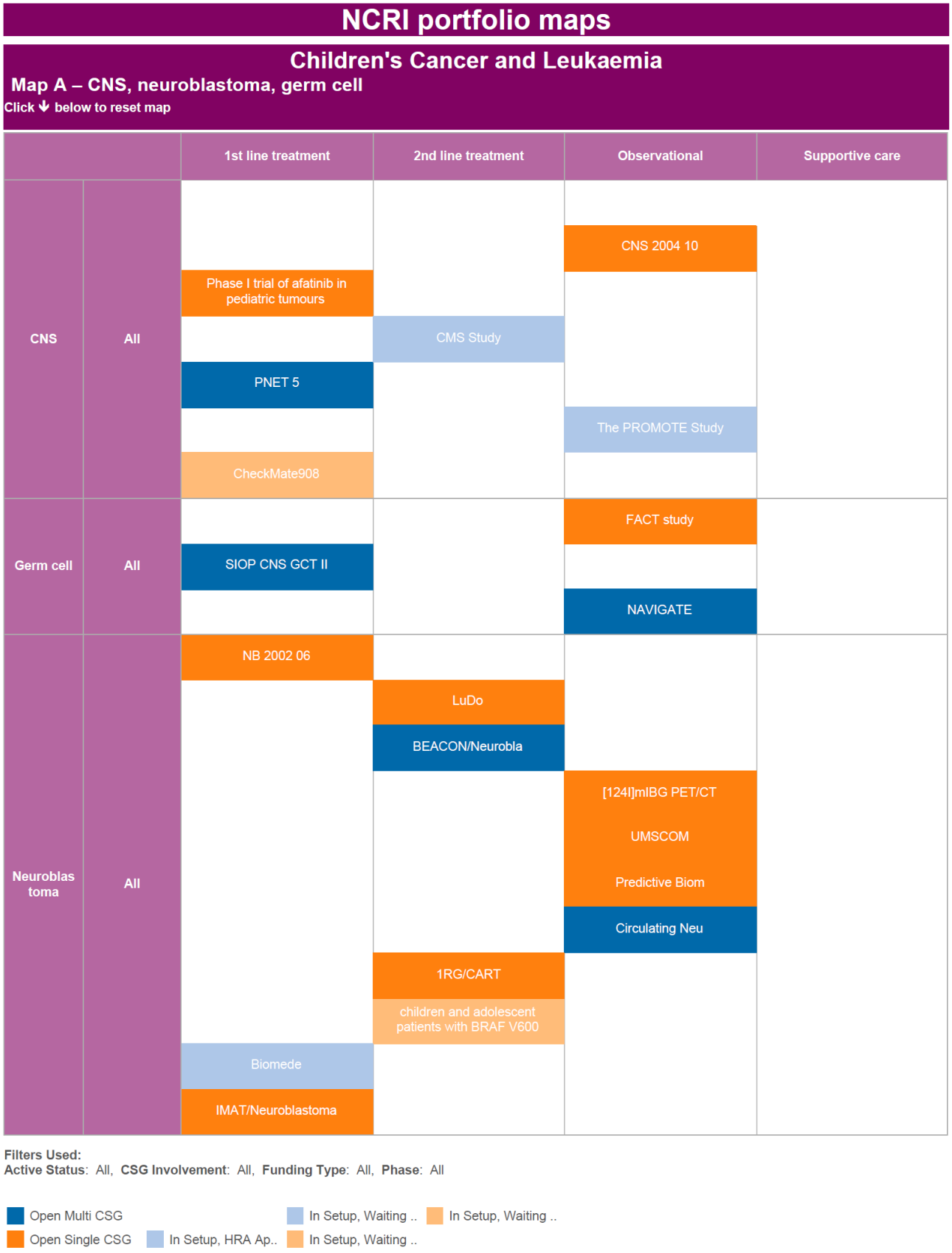
To improve overall survival and quality of survival for all patients diagnosed with a GCT.

Strategic aims

- Continue excellent recruitment to SIOP CNS GCT II for intracranial GCT.
- Submit application to CTAAC December 2016 for funding for international collaborative, risk stratified, randomised extra-cranial GCT trial. Hosted and supported at Birmingham CTU.
- Understand role of biological marker's in risk assessment and tracking treatment response and surveillance in marker negative GCT.
- Ensure trial eligibility for TYA patients in randomised clinical trial for relapsed patients GCT.
- 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.
- Secure funding stream to support PROMS alongside AGCT1531/GC4.
- Complete MaGIC (Malignant Germ Cell Tumour International Collaborative) trial database analyses for a) TYA patient outcomes and b) dysgerminoma/seminoma and publish.
- 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	Anti/Pd/L1 Ab	Lenvatinib	Adverse drug reactions in a children's regional oncology unit BCCSS IntReALL SR 2010 Validation of Chemosensitivity Assay. Investigating how childhood tumours and congenital disease develop Delays to Diagnosis of Childhood Cancer: A Qualitative Study Establishing prospective Asparaginase activity monitoring	Molecular Genet Dabrafenib in paediatric BRAF
Leukaemia	All	UKALL 2011 UCART19 CARPALL	DACOGEN UCART19-PALL study	CaspaCIDe TCR ab haplo HSCT The impact of adipokines on Acute Lymphoblastic Leukaemia outcomes	
Lymphoma	All	UKALL 2011 EuroNet PHL/LP1 Inter/B/NHL Rit	EuroNet PHL/LP1		

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

Open Multi CSG | In Setup, HRA Ap.. | In Setup, Waiting .. | Suspended Single..
Open Single CSG | In Setup, Waiting .. | In Setup, Waiting ..

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
Hepatobiliary	All	PHITT			
Melanoma	All	Ipi in paediatric melanoma	Ipi in paediatric melanoma		
Renal	All			IMPORT	
		Ipi in paediatric melanoma	Ipi in paediatric melanoma		
Sarcoma	All	Euro Ewing 2012			
				Pharmacokinetic	
		rEECur	rEECur		
				PREDICT	
			Tazemetostat		

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

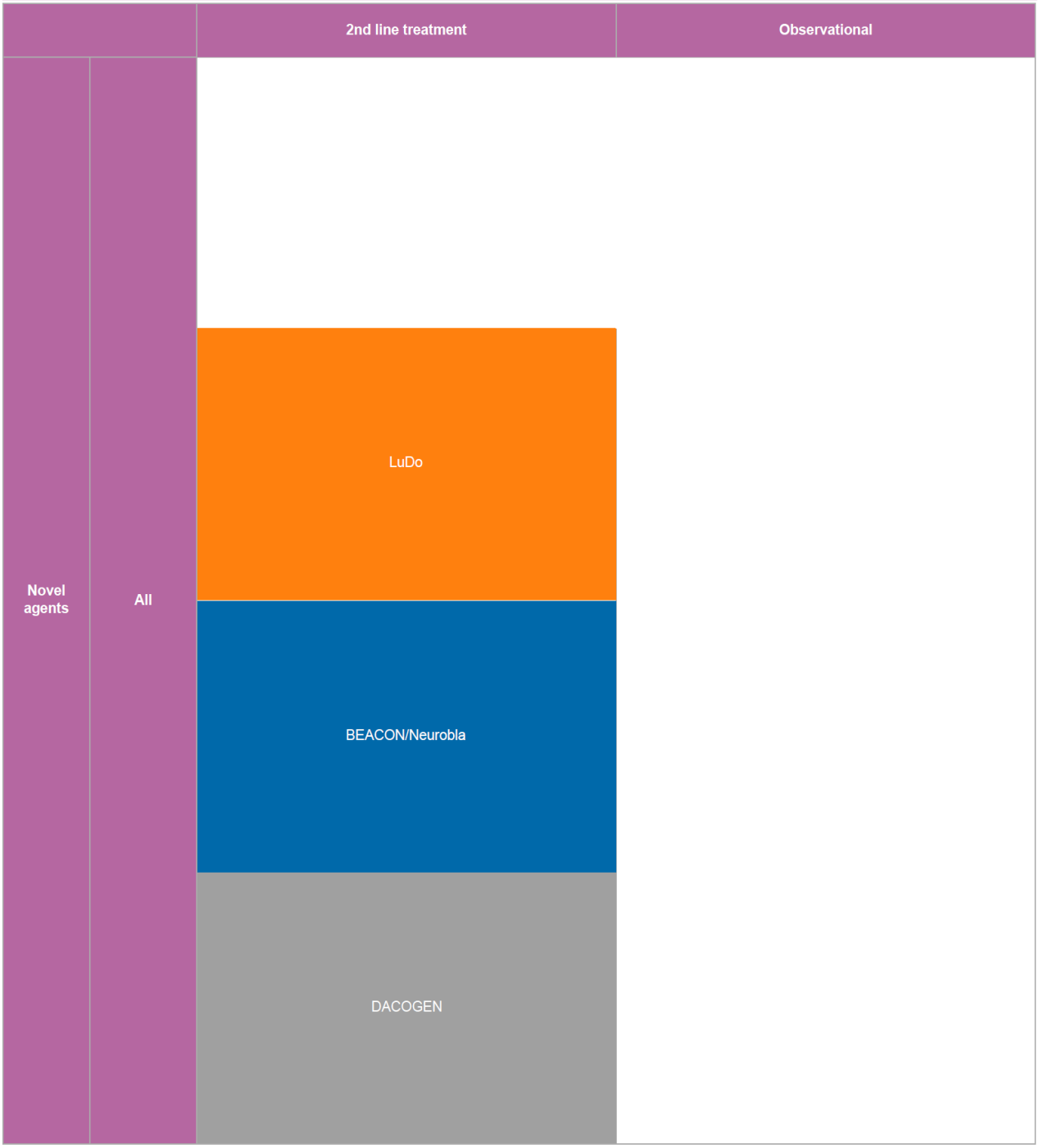
Open Multi CSG
Suspended Multi ..
Open Single CSG
In Setup, Waiting ..

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

Open Multi CSG
Open Single CSG
Suspended Single..

Appendix 4

Publications in the reporting year

Study	Reference
EpSSG RMS 2005	A Ferrari, Access to clinical trials for adolescents with soft tissue sarcomas: enrolment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols, Pediatr Blood Cancer. 2016 Nov 24. doi: 10.1002/pbc.26348
STS 2006 03 NRSTS	Chisholm JC, Merks JH, Casanova M, Bisogno G, Orbach D, Gentet J, Thomassin Defachelles, A, Chastagner PB, Lowis S, Ronghe M, McHugh K, van Rijn RR, Hilton M, Bachir J, Furst-Recktenwald S, Geoerger B, Oberlin O. BERNIE: Open-label randomised phase II study of bevacizumab plus chemotherapy in pediatric metastatic rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcoma (NRSTS). J Clin Oncol 34, 2016 (suppl; abstr 11054).
Factors associated with recurrence and survival in neuroblastoma	Nermine O Basta, Gail C Halliday, Guy Makin, Jillian Birch, Richard Feltbower, Nick Bown, Martin Elliott, Lucas Moreno, Giuseppe Barone, Andrew DJ Pearson, Peter W James, Deborah A Tweddle, Richard JQ McNally, Factors associated with recurrence and survival length following relapse in patients with neuroblastoma. British Journal of Cancer (2016) 115, 1048–1057 doi: 10.1038/bjc.2016.302
MMT95	T Rogers, Paratesticular rhabdomyosarcoma in children and adolescents- Outcome and patterns of relapse when utilizing a non-surgical strategy for lymph node staging. Report from the International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour (MMT) 89 &95 studies, Pediatric Blood & Cancer, 10.1002/mpo.26486
	Zimmermannova O, Zaliova M, Moorman AV, et al. Acute lymphoblastic leukemia with aleukemic prodrome: preleukemic dynamics and possible mechanisms of immunosurveillance. Haematologica 2017. Russell LJ, Jones L, Enshaei A, et al. Characterisation of the genomic landscape of CRLF2-rearranged acute lymphoblastic leukemia. 2017;56:363-72.
	O'Connor D, Moorman AV, Wade R, et al. Use of Minimal Residual Disease Assessment to Redefine Induction Failure in Pediatric Acute Lymphoblastic Leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35:660-7.
	Vora A, Andreano A, Pui CH, et al. Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy. JClinOncol 2016;34:919-26.

UKALL2003	Schwab C, Ryan SL, Chilton L, et al. EBF1-PDGFRB fusion in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL): genetic profile and clinical implications. Blood 2016;127:2214-8.
	Musgrave KM, van Delft FW, Avery PJ, et al. Cerebral sinovenous thrombosis in children and young adults with acute lymphoblastic leukaemia - a cohort study from the United Kingdom. BrJ Haematol 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. Leukemia2016;30:32-8.
	Zaliova M, Moorman AV, Cazzaniga G, Stanulla M, Harvey RC, Roberts KG, Heatley SL, Loh ML, Konopleva M, Chen IM, Zimmermannova O, Schwab C, Smith O, Mozziconacci MJ, Chabannon C, Kim M, Frederik Falkenburg JH, Norton A, Marshall K, Haas OA, Starkova J, Stuchly J, Hunger SP, White D, Mullighan CG, Willman CL, Stary J, Trka J, Zuna J. Characterization of leukemias with ETV6-ABL1 fusion. Haematologica. 2016 Sep;101(9):1082-93.
	Moorman, Anthony V.; Enshaei, Amir; O'Connor, David; Bartram, J; Hancock, J; Harrison, C; Samarasinghe, S; Moppett, J; Vora, AJ ; Goulden, N. Integrating Genetic Risk Factors with Age, Presenting White Cell Count and MRD Response As Continuous Variables to Predict Relapse in Paediatric Acute Lymphoblastic Leukemia (ALL). BLOOD Volume: 128 Issue: 22 Meeting Abstract: 603 Published: DEC 2 2016
	Schwab, C; Enshaei, A; Roberts, KG; Russell, LJ; Harvey, RC ; Chen, IML; Willman, CL; Mullighan, C ; Vora, AJ; Moorman, AV; Harrisonm CJ The Frequency and Outcome of Ph-like ALL Associated Abnormalities in Childhood Acute lymphoblastic Leukaemia Treated on MRC UKALL2003. BLOOD Volume: 128 Issue: 22 Meeting Abstract: 2914 Published: DEC 2 2016
R3	Erhorn A, Minto L, Venn NC, Law T, Yu J, Schwab C, Davies R, Matheson E, Davies A, Sonneveld E, den Boer ML, Love SB, Harrison CJ, Hoogerbrugge PM, Revesz T, Saha V, Moorman AV. Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia. Irving JA, Enshaei A, Parker CA, Sutton R, Kuiper RP, Blood. 2016 Aug 18;128(7):911-22.
	Ryan SL, Matheson E, Grossmann V, Sinclair P, Bashton M, Schwab C, Towers W, Partington M, Elliott A, Minto L, Richardson S, Rahman T, Keavney B, Skinner R, Bown N, Haferlach T, Vandenberghe P, Haferlach C, Santibanez-Koref

	M, Moorman AV, Kohlmann A, Irving JA, Harrison CJ. The role of the RAS pathway in iAMP21-ALL. Leukemia. 2016 Sep;30(9):1824-31.
	Frismantas V, Dobay MP, Rinaldi A, Tchinda J, Dunn SH, Kunz J, Richter-Pechanska P, Marovca B, Pail O, Jenni S, Diaz-Flores E, Chang BH, Brown TJ, Collins RH, Uhrig S, Balasubramanian GP, Bandapalli OR, Higi S, Eugster S, Voegeli P, Delorenzi M, Cario G, Loh ML, Schrappe M, Stanulla M, Kulozik AE, Muckenthaler MU, Saha V, Irving JA, Meisel R, Radimerski T, Von Stackelberg A, Eckert C, Tyner JW, Horvath P, Bornhauser BC, Bourquin JP. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. Blood. 2017;129(11):e26-e37.
SIOPEN High-Risk Neuroblastoma Study	Ladenstein R, Pötschger U, Pearson AD, Brock P, Luksch R, Castel V, Yaniv I, Papadakis V, Laureys G, Malis J, Balwierz W, Ruud E, Kogner P, Schroeder H, de Lacerda AF, Beck-Popovic M, Bician P, Garami M, Trahair T, Canete A, Ambros PF, Holmes K, Gaze M, Schreier G, Garaventa A, Vassal G, Michon J, Valteau-Couanet D; SIOP Europe Neuroblastoma Group (SIOPEN). Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017 Apr;18(4):500-514. doi: 10.1016/S1470-2045(17)30070-0. Epub 2017 Mar 2
	Lewington V, Lambert B, Poetschger U, Sever ZB, Giammarile F, McEwan AJ, Castellani R, Lynch T, Shulkin B, Drobics M, Staudenherz A, Ladenstein R. 123I-mIBG scintigraphy in neuroblastoma: development of a SIOPEN semi-quantitative reporting, method by an international panel. Eur J Nucl Med Mol Imaging. 2017 Feb;44(2):234-241. doi: 10.1007/s00259-016-3516-0. Epub 2016 Sep 24.
	Gaze MN. Semi-quantitative scoring of skeletal metastases by 123I-mIBG scintigraphy in high-risk neuroblastoma. Eur J Nucl Med Mol Imaging. 2017 Mar 3. doi: 10.1007/s00259-017-3660-1. [Epub ahead of print] No abstract available.
SIOPEN phase II study of Topotecan, Vincristine and Doxorubicin in poorly responding high-risk neuroblastoma patients	Amoroso L, Erminio G, Makin G, Pearson AD, Brock P, Valteau-Couanet D, Castel V, Pasquet M, Laureys G, Thomas C, Luksch R, Ladenstein R, Haupt R, Garaventa A; SIOPEN Group. Topotecan-Vincristine-Doxorubicin in Stage 4 High Risk Neuroblastoma Patients Failing to Achieve a Complete Metastatic Response to Rapid COJEC - a SIOPEN Study. Cancer Res Treat. 2017 Mar 21. doi: 10.4143/crt.2016.511.
Anti-GD2 long-term infusion study	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. Pharmacokinetics and

	pharmacodynamics of ch14.18/CHO in relapsed/refractory high-risk neuroblastoma patients treated by long-term infusion in combination with IL-2. MAbs. 2016;8(3):604-16. doi: 10.1080/19420862.2015.1130196. Epub 2016
Pilot study to investigate the experiences of families participating in paediatric pharmacology cancer trials	Errington J, Malik G, Evans J, Baston J, Parry A, Price L, Johnstone H, Peters S, Oram V, Howe K, Whiteley E, Tunnacliffe J, Veal GJ. Investigating the experiences of childhood cancer patients and parents participating in optional non-therapeutic clinical research studies in the UK – a qualitative study. Ped Blood Cancer 2016 63: 1193-1197
Cyclo NHL Study (PK 2005 02)	Veal GJ, Cole M, Chinnaswamy G, Sludden J, Jamieson D, Errington J, Malik G, Hill CR, Chamberlain T, Boddy AV. Cyclophosphamide pharmacokinetics and pharmacogenetics in children with B-cell non-Hodgkin's lymphoma. Eur J Cancer 2016 55: 56-64
A Phase I/II trial of AT9283, a selective inhibitor of aurora kinase in children with relapsed or refractory acute leukaemia: challenges to run early phase clinical trials for children with leukaemia	Vormoor B, Veal GJ, Griffin MJ, Boddy AV, Irving J et al. Ped Blood Cancer 2017 64: e26351
Development of a physiologically based pharmacokinetic model of actinomycin D in children with cancer	Walsh C, Bonner JJ, Johnson TN, Neuhoff S, Ghazaly EA, Gribben JG, Boddy AV, Veal GJ. Br J Clin Pharmacol 2016 81: 989-998
Pharmacokinetics and pharmacogenetics of 13-cis retinoic acid in Indian high-risk neuroblastoma patients	Gota V, Chinnaswamy G, Vora T, Rath S, Yadav A, Gurjar M, Veal G, Kurkure P. Cancer Chemother Pharmacol 2016 78: 763-768
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 77: 685-692
Personalisation of dexamethasone therapy in childhood acute lymphoblastic leukaemia	Jackson RK, Irving JAE, Veal GJ. Br J Haem 2016 173: 13-24

Appendix 5

Major international presentations in the reporting year

Study	Conference details
Inter B-NHL Ritux 2010	Veronique Minard-Colin, Anne Auperin, Marta Pillon, Amos Burke, James Robert Anderson, Donald A. Barkauskas, Keith Wheatley, Rafael Delgado, Sarah Alexander, Anne Uyttebroeck, Catherine Bollard, Jozsef Zsiros, Monika Csoka, Gisele Goma, Anne Tulard, Catherine Patte, Thomas G. Gross; Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy (CT) regimen. J Clin Oncol 34, 2016 (suppl; abstr 10507)
Utilisation of therapeutic drug monitoring (TDM) approaches for the treatment of neonates and children with cancer	Speaker presentation, British Pharmacology Society Meeting, London (December, 2016)
SIOPEL 6 PD Study (SIOPEL 6 sub-study)	107th Annual Meeting of the AACR, New Orleans, USA - Cisplatin-DNA adduct formation in patients receiving cisplatin +/- sodium thiosulphate (STS) in the SIOPEL 6 randomised phase III trial (April 2016)
Dose individualisation based on therapeutic drug monitoring as a valuable tool in the application of precision medicine	Speaker presentation, Children with Cancer UK Childhood Cancer 2016 Meeting, London (September, 2016)
HR-NBL-1/ESIOP PK study (NB 2002 06 sub study)	17th Advances in Neuroblastoma Research Meeting, Cairns, Australia (June, 2016) – Presentation (1): Busulfan and melphalan pharmacokinetics in high-risk neuroblastoma patients treated on the HR-NBL1/SIOPEN trial. Presentation (2): Clinical follow-up of high-risk neuroblastoma patients receiving individualised 13-cis-retinoic acid based on pharmacological exposure as part of a national UK study.
Dexamethasone PK Study (UKALL 2011 sub-study)	107th Annual Meeting of the AACR, New Orleans, USA - Pharmacokinetics of Standard versus Short High Dose Dexamethasone Therapy in Childhood Acute Lymphoblastic Leukaemia – Results from the UKALL 2011 Trial (April 2016)