NCRI
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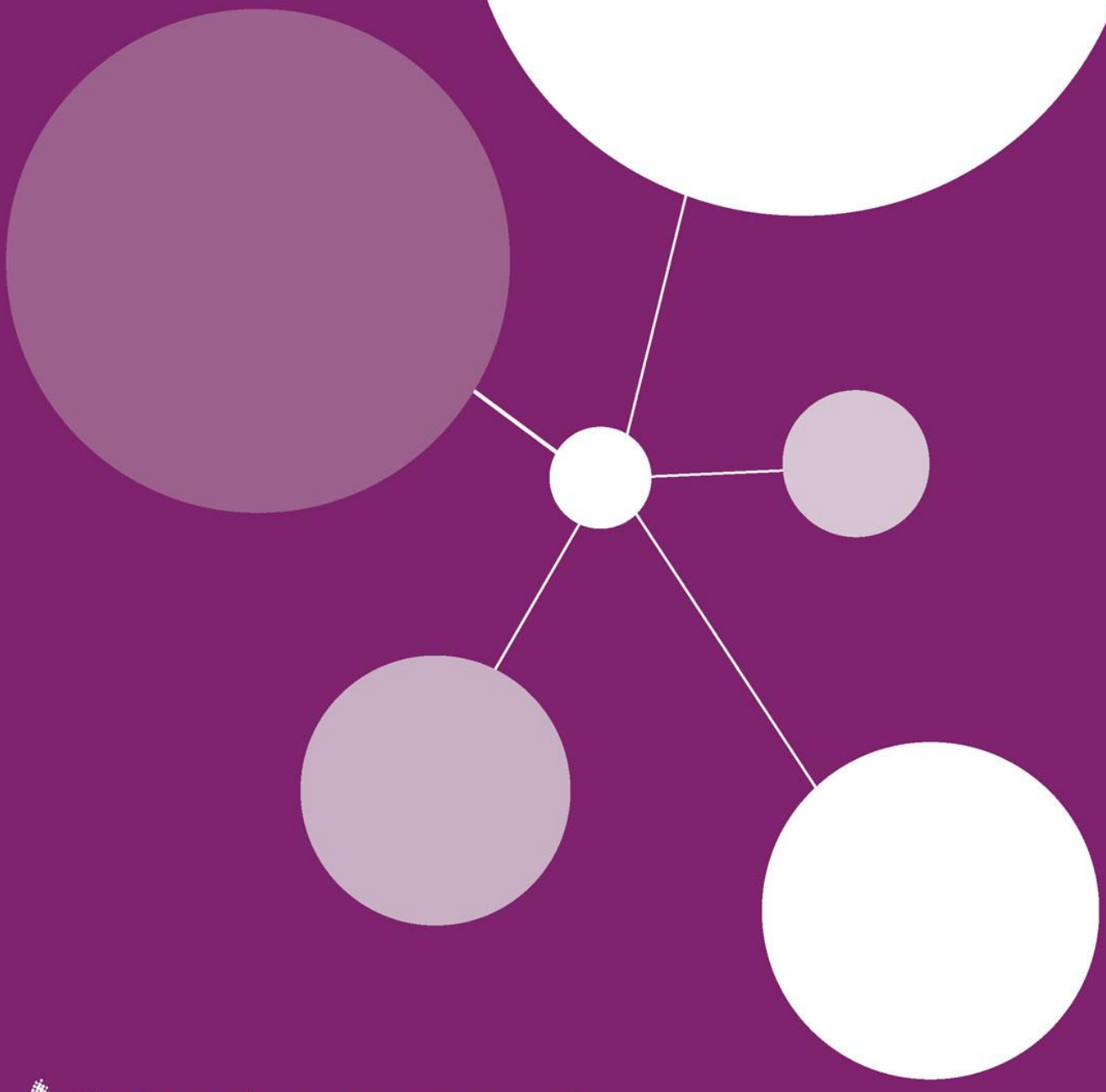
NCRI Children's Cancer & Leukaemia Group

Annual Report 2018-19



Partners in cancer research

NCRI Children's Cancer & Leukaemia Group Annual Report 2018-19

1. Top 3 achievements in the reporting year

Achievement 1

Building on the success of 2017-18 in funding new key trials across the portfolio which have now opened or are opening soon, a major achievement in 2018 was the agreement by CRUK Clinical Trials Committee to fund the ALLTogether trial for Acute Lymphoblastic Leukaemia. As the first line treatment trial in the commonest paediatric cancer, this adds a new key trial for the portfolio alongside other new first line treatment trials in rhabdomyosarcoma, Hodgkin's disease, high risk medulloblastoma and germ cell tumours.

Achievement 2

A number of steps have been made towards the delivery of the new 2018-21 strategy developed in the previous year. These include: appointment of a pathologist to the CSG; strengthening links with late effects researchers, increased consumer voice outside CCL CSG; development of neuroblastoma portfolio; opening of GCT studies; succession planning in novel agents group.

Achievement 3

The CSG hosted a 6th Annual Trials Meeting in November 2018 which was again well received. There was very good participation from a broad range of professionals who are participating in clinical trials across the UK. Feedback was very positive. For 2019/20 we are reviewing the structure and timing of the trials update meeting to broaden attendance and potentially align with other professional meetings.

2. Structure of the Group

Dr Meriel Jenney completed 2 highly successful terms as Chair of the CSG in March 2019 having overseen significant development of the portfolio, strengthened partnerships with site specific CSGs and other partners and strengthening of group membership. She is succeeded by Dr Julia Chisholm.

Mark Gaze stepped down as Neuroblastoma Subgroup chair in March 2018; appointment of a new chair is ongoing. The subgroup thrived under his leadership, developing a portfolio reflecting the entire patient journey in neuroblastoma.

Several members were reappointed to the CSG in March 2019: Dr Henry Mandeville, Professor Bruce Morland and Professor Debbie Tweddle continue to support important areas of work (radiotherapy & sarcoma, liver & bone, neuroblastoma respectively). Dr Guy Makin rotated off the group after a major contribution as ECMC lead. We welcomed Dr Edmund Cheesman as paediatric pathology representative, in line with our main CSG strategy, and Dr John-Paul Kilday (neuro-oncology).

We appointed Loveday Campbell as new consumer member in February 2019 in place of Nick Bird who has made a phenomenal contribution both in the group and in representing its interests externally.

3. Group & Subgroup strategies

Children's Cancer & Leukaemia Group

Portfolio development

A major achievement was funding of the ALLtogether trial for acute lymphoblastic leukaemia due to open early 2020. Through trials funded in 2017-18 and now open or opening soon, the portfolio has developed in line with the strategic aims of the CSG to have trials open for the main tumour types in first line (eg ALL, Hodgkins disease, germ cell tumours, high risk medulloblastoma, rhabdomyosarcoma) and at relapse or progression (eg rhabdomyosarcoma, neuroblastoma). Other trials are currently in development (eg high risk neuroblastoma, osteosarcoma). In addition, the CSG has taken significant steps towards the aim of genomic and personalised medicine trials with the upcoming ESMART and SMPaeds trials.

Increasing early phase activity and participation

Several early phase /personalised medicine portfolio trials have opened/are opening in the past year including PARC (arginase), ESMART and SMPaeds. The CSG has benefitted from regular attendance by Sheona Scales, CRUK ECMC lead, supporting the interface between ECMC and CSG and facilitating access to both academic and pharma sponsored trials.

Successful delivery of clinical trials

A slowing of recruitment in 2018-19 was primarily related to the closure of the UKALL 2011 trial for acute lymphoblastic leukaemia (ALL). This will be addressed in 2019-20 by the opening of new frontline trials in ALL, Hodgkin's disease and rhabdomyosarcoma as well as the genomic medicine initiative. We aim to further develop our links with LCRNs to optimise trial recruitment. In addition, the CSG is working closely with the ECMC network to optimise access to early phase trials for patients with relapsed disease.

UK wide and international links

A number of the new trials are international trials, in collaboration with European partners – e.g. FaR-RMS (rhabdomyosarcoma), high risk medulloblastoma and ESMART. Partnerships continue to work well. As yet there is no direct impact from BREXIT but the CSG is mindful of potential future changes and will proactively collaborate with partners across Europe to ensure ongoing access to European trials for UK children. Our close link with the CRCTU in Birmingham is critical in negotiating the changing European landscape.

In 2019 we will consider the possibility of aligning the Annual Trials meeting with other professional events to widen participation and optimise attendance.

CSG structure and function

The CSG has continued to function well under the leadership of the previous chair. The CSG recognises the importance of working across ages and with other CSGs. This works well in some areas e.g. YOSS subgroup of the Sarcoma CSG, with more work required in other areas. In germ cell tumour the CCL and TYA & GCT CSGs have done an excellent job in promoting studies across the age range. Challenges for the incoming chair include consideration of whether the germ cell tumour subgroup is optimally configured, the place of paediatric

Hodgkin's disease within the CSGs and ensuring closer working with TYA & GCT, Sarcoma and Lymphoma CSGs.

Consumer involvement and impact

The consumer members of the CSG remain extremely active and make an important and significant contribution to the activities of the CSG, including invaluable peer review comments and speaking at the Annual Trials Meetings. Members of the CSG also ensure regular and sustainable patient and public involvement at all stages in the development of clinical trials. There are also links with international PPI groups. One of the consumer members gave a very well received talk at the ACCELERATE conference in early 2019.

Raising Profile

During 2018 CSG members had an important opportunity to work with CRUK to develop their strategy for Kids and Teens. The Chair continues to present the trial portfolio annually at the Children's Cancer and Leukaemia Group (CCLG) winter meeting. The CCLG funds trainees to attend the CSG subgroups, exposing them to clinical trials development and continues to have close links with the site –specific Special Interest Groups of the CCLG to promote the development of portfolio trials in areas not represented by subgroups of the CSG itself.

In the coming year there are plans to participate in a workshop with CTRad and the TYA & GCT CSG.

Central Nervous System Subgroup (Chair, Prof Simon Bailey)

Improve Event Free and Overall Survival

This is being achieved through the introduction of new trials which stratify patients using clinical and molecular biomarkers (e.g. existing PNET 5 study, BIOMEDE). A new study in high risk medulloblastoma, a European SIOPE study led from the UK was successfully funded by CRUK and the Brain Tumour Charity in 2018.

Better identify prognostic and predictive biomarkers and implement their usage

Realtime molecular testing is now routine for some tumour types (e.g. medulloblastoma) and will become more widespread at first diagnosis with the opening of genomic hubs which will routinely profile newly diagnosed patients. Soon to open studies such as SMPaeds and ESMART support molecular characterisation of patients with relapsed disease.

Increase the number of clinical trials for children with CNS tumours

There are currently 4 open clinical trials for CNS tumours in the UK, which are all pan-European trials. There are also a number of clinical studies in late development which, if funded, will expand the portfolio to include most of the commoner paediatric brain tumours including high risk medulloblastoma, infant medulloblastoma, low grade glioma, atypical teratoid rhabdoid tumour and high-grade glioma. A study on convection enhanced delivery of chemotherapy in diffuse intrinsic pontine glioma in collaboration with the private sector is also planned.

Application of molecular diagnostics to routine clinical practice

All children with medulloblastoma now have access to molecular diagnostics to facilitate clinical decision making in patients on and off trial. The development of funded centralised routine molecular diagnostics and pathology review for all children with CNS tumours will be available through Department of Health genomic hubs later in 2019 and studies such as SMPaeds support molecular profiling in the relapse setting.

Germ Cell Tumour Subgroup (Chair, Dr Sara Stoneham)

Apply for funding for international collaborative, risk stratified, randomised extra-cranial GCT trial

The CRUK funding application for AGCT1531 was successful in 2018 with funding of £702, 000 secured.

The CI is the NCRI CCL CSG Germ Cell Tumour Subgroup Chair with co-applicants from the NCRI TYA & GCT Germ Cell Tumour Subgroup and Ovarian Workstream. Co-investigators include the lead for translational biology and the lead for PROMS and are also part of the Germ Cell Tumour Subgroup and the NCRI TYA & GCT CSG. A consumer representative on the NCRI TYA & GCT CSG has also been a key player in trial development

Understand the role of biological marker's in risk assessment and tracking treatment

The group has successfully embedded biological markers (microRNA's) in the AGCT1531 trial for surveillance /disease –response assessment.

Review to investigate the Effectiveness of Chemotherapy Treatments for Paediatric Germ Cell Tumours

NCRI CCL CSG GCT subgroup consulted and developed the paediatric /TYA component of this review jointly with both our US paediatric MaGIC colleagues and in collaboration with our medical oncology colleagues from the NCRI Germ Cell Tumour Subgroup of the TYA & GCT CSG and Ovarian Workstream.

Secure funding stream to support Patient Reported Outcome Measures (PROMS) alongside AGCT1531/GC4

Funding secured for PROMS within the AGCT1531 study through the successful CRUK grant application.

Complete MaGIC trial database analyses for a) TYA patient outcomes and b) dysgerminoma/seminoma and publish

Data from CCLG GC11 and GC2 trials were used in these analyses. NCRI CCL CSG GCT subgroup members were involved in analyses and manuscript writing. This publication has led to a new trial design for both seminoma and dysgerminoma i.e. across male and female patients allowing both our NCRI Gynae Colleagues and NCRI Testis subgroup colleagues to work with us and extends into international collaboration via MaGIC and G3.

Analyse and publish outcomes for GC3

GC3 was analysed by the Children's Oncology Group statistical team and with revisions the trial publication was re-submitted to European Journal of Cancer. The data were presented at SIOP 2018.

This GC3 dataset independently validates the new risk stratification used for AGCT1531 and the validation will be presented at SIOP 2019

Leukaemia Subgroup (Chair, Dr Phil Ancliff)

Open international trials for Ph-pos and infant ALL

Funding is being sought from the Spring 2019 CRUK round for the latest EsPhALL study with the aim to open in Q4 2019/Q1 2020.

The Blinatumomab/Interfant Pilot will open at Great Ormond Street Hospital in Summer 2019. A single centre was chosen in the hope of a more rapid process. Members of the group remain active in the wider Interfant consortium and are active participants in discussions surrounding the next Ph III Infant ALL study. The full study cannot open until the pilot is complete.

Contribute to international collaborations in CML and MDS

The UK group has kindly accepted an offer to join the European EWOG-MDS group. We hope to publish the UK azacytidine/JMML data shortly.

Agree an international first line ALL trial

As detailed above, the major achievement and current workload of our group has been the funding and development of the next ALL trial, ALLTogether (A2G).
A comprehensive protocol has been finalised aiming to open to recruitment in the UK in Q1 2020.

Open registries with linked biological sample collection and studies

A registry/sample collection database has been opened for aplastic anaemia. The major disease trials have linked biological collection and studies. The aplastic anaemia model is being investigated for the other rarer diseases.

Liaise with new agents group to increase portfolio of phase I and II leukaemia trials

One notable achievement of the two groups has been the opening of the selumetinib trial for relapsed ALL. The philosophy of this study was based on translational research performed on samples banked by our group. This is an example of bedside to bench and back to bedside research, all performed in a relatively short time period.

The groups have opened more industry sponsored trials (e.g. daratumumab) and continue to be world leaders in the application of CAR-T cell therapy.

Neuroblastoma Subgroup (Outgoing Chair, Dr Mark Gaze)

Strategy development

Members have produced a new strategy for the Neuroblastoma Subgroup for 2018-2021. The subgroup is a diverse, inclusive one, with knowledgeable, experienced individuals from the medical specialties of paediatric and clinical oncology, surgery and imaging, with biologists, clinical trial professionals, and lay parent/charity representation. It works nationally and internationally. The mission is to improve the survival of children with neuroblastoma, and to reduce the impact of treatment on quality of life. It develops and maintains a wide-ranging and comprehensive portfolio of clinical trials and studies for neuroblastoma including those for:

- First line treatment of high risk disease
- Poor responders
- Patients with relapsed disease
- Patients with better prognosis disease
- Imaging techniques
- Radiotherapy
- Surgery
- Immunotherapy
- Epidemiology
- Pharmacology
- Toxicity and late effects
- Biology, staging and prognosis
- Novel agents in early phase assessment

The Subgroup also:

- Works with the NICE, CCLG, charities and other stakeholders to ensure early adoption of innovative treatments by the NHS once the evidence of benefit is available.
- Educates other healthcare professionals in neuroblastoma clinical trials and best practice through meetings, courses, newsletters and authoritative guidance.
- Develops the next generation of neuroblastoma specialists.

Key Early Phase Clinical Trial Activity

- The MINIVAN trial is run by consortium of centres from the UK, the USA and Germany, led by UK investigators, and sponsored by the University of Southampton. It is an innovative phase I trial combination of molecular radiotherapy with two immunotherapy agents, nivolumab and dinutuximab beta for patients with relapsed or refractory high-risk neuroblastoma. Seven patients have been recruited to cohort 1 so far, all from the UK.

- Recruitment to the phase II LuDO trial of molecular radiotherapy with the new agent 177-Lutetium DOTATATE is now complete. Data are being analysed and prepared for publication.

- The BEACON trial is an Innovative Therapies for Children with Cancer in Europe multi-arm, multistage multicentre Phase II trial for relapsed and refractory disease. It compares backbone chemotherapy with temozolomide alone or with either irinotecan or topotecan, with or without bevicizumab, resulting in six treatment arms. Recruitment to +/- irinotecan, and +/- bevicizumab is now complete. Recruitment to +/- topotecan continues. An amendment is in progress to introduce a new randomisation which would evaluate dinutuximab beta immunotherapy in conjunction with the chemotherapy backbone. Plans for new novel agent Phase II trial – BEACON 2 – are well advanced.

High Risk Neuroblastoma Clinical Trial Activity

- Following completion of recruitment to five separate randomisations, the first high-risk neuroblastoma study has closed. Members have worked with colleagues in the European Neuroblastoma Clinical Studies Group, SIOPEN, to develop a new phase III trial for high-risk neuroblastoma (HR2). Uniquely, after decades in which only systemic therapy questions have been addressed, this trial contains a radiotherapy dose escalation randomisation for residual disease. This will be the world's first phase III radiotherapy randomised trial in neuroblastoma. Other randomisations include a comparison of two induction regimens, and a comparison of single versus double high-dose chemotherapy. A grant application has been prepared for submission to the Cancer Research UK Clinical Research Committee.

- Funding has been awarded by Cancer Research UK for VERITAS, a randomised phase II trial of two double high-dose intensification strategies for poorly responding metastatic high-risk neuroblastoma. Uniquely, this will be the world's first randomised trial comparing a molecular radiotherapy-based approach with chemotherapy alone. The trial is open in France, the sponsor nation, and is going through the UK research governance approvals process, due to open later in 2019.

Other Trial Activity

- The IMAT-neuroblastoma trial, a randomised phase II trial of radiotherapy dose escalation with innovative technology is recruiting well now after a slow start. Eleven centres are now open, and two thirds of the planned total of 50 patients, have been enrolled. The prospective individual patient radiotherapy quality assurance process has worked very well.

- The Cancer Research UK Centre for Drug Development trial of 124-Iodine meta-Iodobenxylguanidine PET imaging has been troubled by unreliability of radiopharmaceutical supply for several unconnected reasons. Despite this, seven evaluable patients have been imaged, with five in the PET/MRI substudy. Plans for a follow-on study are being developed.

- Previous pharmaco-kinetic studies have shown the unreliable bioavailability of 13-cis-retinoic acid when capsules are opened for children unable to swallow them. A new, tutti-frutti flavoured liquid formulation has been developed for such children, and a pharmacokinetic evaluation of this is recruiting well.

- CAR-T cell therapy has transformed the landscape for children with leukaemia. A trial of CAR-T cells for neuroblastoma is underway to establish if it be a valuable addition to the immunotherapy armamentarium.

- An epidemiological study of survival after relapse, with associated biological data, is now open, offering new insights into the management of relapsed neuroblastoma.

Achievements

- Members of the Subgroup contribute to a regular monthly web-based discussion of the management of particularly challenging patients. One of the main aims of this is to promote entry into clinical trials.
- The third annual Neuroblastoma Clinical Trials Day was held in London in September 2018. This was well attended and highly rated. The key aim is to increase awareness

of the wide portfolio of neuroblastoma trials, especially for those who work in centres not represented on the Subgroup. A further iteration is scheduled for September 2019.

- Two new Trainee members of the Subgroup have been appointed, one paediatric and one clinical oncologist, and attended their first meeting. This helps to fulfil our objective of developing the next generation of neuroblastoma specialists.
- There are now advanced plans for a new educational initiative: a two day multidisciplinary course on neuroblastoma which will be held in Leicester on November 2019.
- NICE published evidence-based recommendations on dinutuximab beta (Qarziba) for high-risk neuroblastoma, based on the results of the Subgroup's research in association with SIOPEN, and significant input into the appraisal from Subgroup members and the charity Solving Kids' Cancer represented on our Subgroup.

Novel Agents Subgroup (Chair, Dr Lynley Marshall)

Developing new trials with academic and industry partners

Within this year there have been 29 early phase clinical trials of novel drugs open across the network, including some completing recruitment, some advancing phase, and others newly opened within the reporting period. This includes 21 dose finding (phase I/II) and 8 later phase II trials. Of these, 18 (62%) are commercially sponsored and 11 (38%) academic sponsored trials, some with industry support. Twenty-two include biologically targeted agents, 7 include immunotherapy drugs, 5 of these include immune checkpoint inhibitors. Fifteen are first-in-child trials and 12 include combinations (molecularly targeted agents combined with cytotoxic drugs, other targeted agents (including immunotherapies), radiotherapy or MIBG therapy. Seven trials include patients with haematological malignancies.

Additionally there is a CAR-T cell trial for neuroblastoma and several for acute lymphoblastic leukaemia Several other new clinical trials, academic and commercially sponsored, are in the advanced stages of regulatory submission and set-up to open in 2019. One of these is E-SMART, the first European paediatric adaptively designed multi-arm phase I/II personalised medicine basket trial of molecularly targeted agents alone and in combination (10 arms; 4 pharma partners; academic sponsorship), which will open now that the SMPaeds tumour profiling programme, required for screening, has opened.

Novel agents for poor prognosis tumours at diagnosis and relapse

Our clinical trial portfolio includes novel therapeutic options for paediatric/TYA patients across the age and disease spectrum: relapsed/refractory/poor prognosis CNS and non-CNS solid tumours and leukaemias/lymphomas; disease-specific, target-specific and broader eligibility trials. For the worst prognosis malignancies e.g. diffuse intrinsic pontine glioma (DIPG), upfront studies such as the BIOMEDE phase II trial can test novel targeted agents in combination with

radiotherapy in newly diagnosed patients based on tumour biology. Three arms are open with a new arm planned based on emerging data.

For other poor prognosis tumours, adaptively designed combination phase II studies aim to define the optimal backbone regimen upon which to add novel agents (BEACON for neuroblastoma –new arms including the anti-GD2 antibody Dinutuximab beta are in set up; rEEcur for Ewing's –one of four combination arms recently closed; a new combination arm and future novel agent arm planned). Following the recent completion of the VIT phase II trial, the Frontline and Relapse Rhabdomyosarcoma study (Far-RMS), in set-up, will provide options for rhabdomyosarcoma patients. Clinical trials of agents targeting strong oncogenic drivers (BRAFv600 , the MAPK pathway, ALK, NTRK) are advancing from phase I single agent to phase II combination trials, including (in some diseases) for upfront use.

Develop and deliver biomarker and pharmacokinetic studies

The CRUK-funded Stratified Medicine Paediatrics (SMPaeds) national molecular profiling programme was officially launched in March 2019. Via this programme, patients undergoing tumour biopsy and molecular profiling at disease relapse can be considered for more personalised medicine predictive biomarker-based clinical trials of novel agents. In anticipation, our focus has been on driving forward the development and set up of more molecular enrichment/biomarker-driven studies in both the academic and commercially-sponsored settings e.g. E-SMART (multiple targets and pathways within 10 arms), CRISP and Lorlatinib (ALK/ROS/MET), BRAF/MEK inhibitor combinations, new NTRK inhibitor studies, and others.

Additionally, new early phase trials include novel pharmacodynamic biomarker studies as well as pharmacokinetic studies. Our early phase trial centres are affiliated to laboratories developing and refining techniques for monitoring circulating tumour DNA as a method of tracking response to novel treatments. The Newcastle Pharmacology Group led by Professor Gareth Veal remains internationally forefront in supporting early and later phase therapeutic clinical trials, leading pharmacology studies and developing therapeutic drug monitoring for key drugs or special populations (e.g. neonates/infants, patients with renal compromise and others). Professor Andrew Peet in Birmingham (and others) have developed functional imaging biomarker sub-studies for use in response assessment within clinical trials.

Implementation of the successful renewed and expanded Paediatric ECMC network

The Paediatric ECMC Strategy Group meets regularly to plan and evaluate initiatives across the ECMC themes. Network development has progressed well, with the 11 paediatric ECMC centres working cohesively but also within 4 regional sub-networks, created to facilitate equitable access to clinical trials nationally. Each holds regular regional relapse telephone conferences, whereby data on all paediatric solid tumour relapse patients can be captured, relevant molecular profiling results discussed and patients whose tumours harbour potentially actionable molecular features considered for early phase clinical trials, The appointment of Dr Sheona Scales as Paediatric ECMC Network co-ordinator within the ECMC Programme Office, CRUK, has assisted in driving network activities forward. The establishment of a unified network confidentiality agreement has already facilitated the more effective establishment of

new commercial partnerships, allowing industry partners to share details on new studies via the Programme Office, with close co-ordination between the ECMC Network and Novel Agents Subgroup allowing rapid assessment, input into study design, efficient expression of interest calls for clinical trial participation and strong encouragement to ensure a good geographic distribution of study sites, ideally with at least one study site within each regional network per study. Several companies have made use of this route already.

Implementation of a UK National "multi-omic" molecular profiling platform and National Molecular Tumour Board

The SMPaeds national molecular profiling programme has recently successfully launched and will ultimately include "multi-omic" techniques (customised NGS panel, WES, RNA Seq, low coverage WGS and methylation sequencing) to characterise tumours following biopsies performed at relapse. It will dovetail with Department of Health genomic medicine initiatives aimed at offering molecular profiling to all paediatric cancer patients, including at first diagnosis. The objective of all such initiatives is to help stratify patients for precision based clinical trials where available and to drive forward the development and validation of new prognostic and predictive biomarkers. A National Molecular Tumour Board is currently in set up with defined pathways for the analysis, reporting and communication of results back to referring clinicians, highlighting clinically relevant/potentially actionable molecular aberrations uncovered via the profiling initiatives.

4. Task groups/Working parties

The CCL Group have had no task groups or working parties during the reporting year.

5. 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**	**Level of CSG input**	**Funding amount**
May 2018					
Not applicable					
High Risk Medulloblastoma	Clinical Trial Award (Brain Tumour Charity cofounded)?				
November 2018					
ALLTogether-1: A Treatment study protocol of the ALLTogether Consortium for children and young adults (1-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL)	Clinical Trial Award	Dr John Moppett	Conditionally Supported	Developed by the CSG	
AGCT1531: A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Paediatric and Adult Patients With Germ Cell Tumours	Clinical Trial Award	Sara Stoneham	Supported	Developed by the Germ Cell Tumour Subgroup along with members of the Germ Cell Tumour Subgroup of the TYA & GCT CSG and Ovarian Workstream of the Gynaecological Group.	£702,000
Other committees					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
TIGER: A trial comparing usual dose with high dose chemotherapy for germ cell tumours	CRUK	Robert Huddart		CSG GCT subgroup consulted and developed the	

				paediatric /TYA component jointly with our US paediatric MaGIC colleagues and in collaboration with our medical oncology colleagues from the Ovarian Workstream and TYA & GCT CSG.	

6. Consumer involvement

Consumer members of the CSG have remained very active in their roles through the course of the year. Nick (Bird) has stepped down from his role as of February 2019 and Loveday Langton has now been appointed. Angela (Polanco) will continue in her role as consumer representative. In addition to his role on the main CSG, Nick (Bird) is a member of the Neuroblastoma sub-group.

Through collaborative working and communication with the wider parent communities, Angela and Nick have continued to highlight important issues in childhood cancer research to the members of the CSG. This has prompted active discussions and amendments to trial designs to incorporate the needs of the patients and families at the forefront of the trial. They have contributed to the priority setting of the strategy document and have presented to the group on their role as consumers and the impact that involvement can achieve. Core work has involved attendance and input into the CSG meetings, and review of research applications throughout the year.

Nick (Bird) has been appointed as Research Trustee/Director and Chair of Trustees of Solving Kids' Cancer in London and he has also provided valuable input into the Neuroblastoma sub-group strategy. The unmet needs of children with DIPG and developments in that area of research have continued to be a focus for his consumer involvement and he has attended the biennial Advances in Neuroblastoma Research (ANR) meeting in San Francisco, given a presentation on research advocacy at the NCRI Clinical Trials Meeting and was invited to present at the international multi-stakeholder ACCELERATE conference in Brussels on the development and challenges of anti-GD2 therapies from early inception through to EMA/FDA approval. The session addressed issues relating to national reimbursement and included a panel discussion 'Immunotherapy for children with cancer – challenges and where to go?'. Feedback from this session was particularly positive and welcoming with commendations from pharma, researchers and parents alike. Nick was also a nominated Patient Expert for the NICE appraisal process for dinutuximab beta, leading to its approval in July 2018.

Angela (Polanco) has continued to actively participate in PORT (Paediatric Oncology Reference Team), Wilms Tumour Link Group, CCLG review panels for funding proposals and has also been a named applicant for a trial application to NIHR for Wilms Tumour research. She has recently commenced a PhD programme with the topic of communication of long-term effects in childhood cancer survivors and is an active member of PANCARE, contributing to the international harmonisation guideline for obstetric care of childhood cancer survivors. She has led patient and parent involvement meetings in London with the Wilms tumour community and alongside leading health care professionals and will be leading a workshop on patient and parent involvement in childhood cancer research at the SIOPE European meeting in Prague this year. Angela has also been an active member of CRUK kids and teens advisory panel and has contributed to the development of their childhood cancer research strategy and dissemination to the public. Angela continues to work closely with CCLG and Bethany's Wish and jointly organises the Childhood Cancer Conference UK each year.

One particular issue that both Nick and Angela brought to the attention of the CSG was the publication of research supporting the use of melatonin in children with cancer. This led to the publication of an article in the British Medical Journal with Angela being a named author, highlighting the need for accurate and responsible data for families.

Their involvement in the CSG and wider activities ensure that a parent/patient focus is paramount to childhood cancer research and so that applications meet unmet needs, highlight potential patient benefit and balance scientific/research questions with practicalities for families enrolling poorly children on to a research study.

7. Priorities and challenges for the forthcoming year

Priority 1 Prepare for Quinquennial review which will be held early 2020
Priority 2 Reverse recent fall in trial recruitment: work with partners to facilitate the opening and recruitment into the large number of portfolio trials funded since 2017 and continue to improve networked access to open early phase clinical trials through partnership with ECMC.
Priority 3 Continued development of portfolio to include underrepresented areas (e.g. surgery, non-rhabdomyosarcoma soft tissue sarcoma, relapsed AML)
Challenge 1 Develop opportunities for studies investigating the local control of tumours (e.g. surgical, imaging radiotherapy studies
Challenge 2 Work more closely with TYA and adult partners to facilitate access for younger teenage patients (12+) to adult clinical trials where the indication exists
Challenge 3 Increase understanding of how to integrate the Department of Health molecular profiling strategies (e.g. Genome England) with portfolio precision medicine studies and biomarker driven clinical trials.

8. Collaborative partnership studies with industry

Open and progressing during this reporting period:

The many ongoing collaborations of the Novel Agents Subgroup with industry are listed below:

Commercially sponsored early phase studies:
Abbott (ABT414), Bayer (regorafenib), BMS (Nivolumab), Boehringer-Ingelheim (Afatinib), Celgene (Pomalidomide), Eisai (lenvatinib), Epizyme (Tazometastat), Janssen (Carfilzomib, Daratumumab, Ibrutinib), LOXO Oncology (Larotrectinib), Merck (Pembrolizumab), Novartis (Ceritinib, Dabrafenib, Trametinib), Roche (Cobimetinib)

Academic sponsored early phase:
AstraZeneca (SeluDex), BMS (MiniVan, Animate), Novartis (BIOMEDE), Pfizer (Bosutinib, Inotuzumab), Roche (BEACON, BIOMEDE), Bayer (FaR-RMS).

New/In set-up:

Commercially sponsored early phase studies:
Astellas, AstraZeneca, Dachii-Sanyo, Eisai, Eli-Lilly, Incyte, Roche

Academic sponsored early phase studies:
AstraZeneca, Bayer, BMS, Celgene, Novartis, Pfizer, Roche

9. Appendices

Appendix 1 - Membership of Children's Cancer and Leukaemia Group and Subgroups

Appendix 2 – CCL Group and Subgroup strategies

- A – CCL Group Strategy
- B – Central Nervous System Subgroup Strategy
- C – Germ Cell Tumours Subgroup Strategy
- D – Leukaemia Subgroup Strategy
- D – Neuroblastoma Subgroup Strategy
- E – Novel Agents Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 – Top 5 publications in reporting year

Appendix 5 – Recruitment to the NIHR portfolio in the reporting year

Dr Julia Chisholm (Children's Cancer & Leukaemia Group Chair)

Appendix 1

Membership of the Children's Cancer & Leukaemia Group

Name	Specialism	Location
Dr Mark Gaze	Clinical Oncologist	London
Dr Henry Mandeville	Clinical Oncologist	Sutton
Dr Lynley Marshall	Consultant in Paediatric and Adolescent Oncology Drug Development	Sutton
Mrs Angela Polanco	Consumer	Warwick
Mr Nicholas Bird	Consumer	Epsom
Dr Phil Ancliff	Paediatric Haematological Oncologist	London
Dr John Moppett	Paediatric Haematological Oncologist	Bristol
Dr Amos Burke*	Paediatric Medical Oncologist	Cambridge
Dr Julia Chisholm (Chair)	Paediatric Medical Oncologist	Sutton
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Juliet Gray	Paediatric Medical Oncologist	Southampton
Dr Lisa Howell	Paediatric Medical Oncologist	Liverpool
Dr Meriel Jenney	Paediatric Medical Oncologist	Cardiff
Professor Pam Kearns*	Paediatric Medical Oncologist	Birmingham
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor Bruce Morland	Paediatric Medical Oncologist	Birmingham
Dr James Nicholson*	Paediatric Medical Oncologist	Cambridge
Dr Sara Stoneham	Paediatric Medical Oncologist	London
Professor Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Dr Johann Visser	Paediatric Medical Oncologist	Cambridge
Professor Simon Bailey	Paediatric Neuro-Oncologist	Newcastle
Dr Edmund Cheesman	Pathologist	Manchester
Mrs. Julie Evans	Research Nurse	Leeds
Ms Veronica Moroz	Statistician	Birmingham
Mr Ian Kamaly-Asl	Surgeon	Manchester

* denotes observer member

Membership of the Subgroups

Central Nervous System Subgroup		
Name	**Specialism**	**Location**
Dr David Jenkinson**	Brain Tumour Charity rep	Farnborough
Dr Nicky Thorp	Clinical Oncologist	Liverpool
Professor Barry Pizer	Paediatric Medical Oncologist	Liverpool
Professor Steve Clifford	Paediatric Molecular Oncologist	Newcastle upon Tyne
Dr Jenny Adamski	Paediatric Neuro-Oncologist	Birmingham
Professor Simon Bailey (Chair)	Paediatric Neuro-Oncologist	Newcastle upon Tyne
Professor Richard Grundy	Paediatric Neuro-Oncologist	Nottingham
Professor Darren Hargrave**	Paediatric Neuro-Oncologist	London
Dr Andrew Peet	Paediatric Neuro-Oncologist	Birmingham
Dr Sue Picton	Paediatric Neuro-Oncologist	Leeds
Dr Julia Cockle*	Paediatric Oncology Trainee	Leeds
Dr Rebecca Hill*	Paediatric Oncology Trainee	Newcastle upon Tyne
Dr Tom Jacques**	Pathologist	London
Dr Kim Bull	Psychologist	Southampton
Mr Conor Mallucci	Surgeon	Liverpool

Germ Cell Tumour Subgroup		
Dr Thankamma Ajithkumar	Clinical Oncologist	Cambridge
Dr Alex Freeman	Histopathologist	UCLH
Dr Mark Brougham	Paediatric Medical Oncologist	Edinburgh
Dr Shaun Wilson	Paediatric Medical Oncologist	Oxford
Dr James Hayden	Paediatric Medical Oncologist	Liverpool
Dr James Nicholson	Paediatric Medical Oncologist	Cambridge
Dr Anthony Penn	Paediatric Medical Oncologist	Manchester
Dr Sara Stoneham (Chair)	Paediatric Medical Oncologist	London
Dr Amy Ruffle*	Paediatric Oncology Trainee	Leeds
Dr Mathew Murray	Paediatric Medical Oncologist	Cambridge
Dr Dan Stark	Medical Oncologist	Leeds
Mr Suren Arul	Paediatric Surgeon	Birmingham
Dr Thankamma Ajithkumar	Clinical Oncologist	Cambridge

Leukaemia Subgroup		
Name	**Specialism**	**Location**
Dr Rachael Hough**	Clinical Oncologist	London
Mr Neil Ranasinghe	Consumer	London
Dr Anthony Moorman	Genetic Epidemiologist	Newcastle upon Tyne
Dr Brenda Gibson	Haematologist	Edinburgh
Dr Clare Rowntree	Haematologist	Cardiff
Dr Phil Ancliff (Chair)	Paediatric Haematological Oncologist	London
Dr Denise Bonney	Paediatric Haematological Oncologist	Manchester
Dr Michelle Cummins	Paediatric Haematological Oncologist	Bristol
Dr John Moppett	Paediatric Haematological Oncologist	Bristol
Professor Owen Smith	Paediatric Haematological Oncologist	Dublin
Dr Sujith Samarasinghe**	Paediatric Haematological Oncologist	London
Dr Anupama Rao**	Paediatric Haematological Oncologist	London
Dr Donna Lancaster**	Paediatric Medical Oncologist	Sutton
Professor Josef Vormoor	Paediatric Medical Oncologist	Newcastle upon Tyne

Neuroblastoma Subgroup		
Name	**Specialism**	**Location**
Dr Mark Gaze (Outgoing Chair)	Clinical Oncologist	London
Dr Ben Fulton*	Clinical Oncology Trainee	Glasgow
Mr Nicholas Bird	Consumer	Epsom
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor John Anderson**	Paediatric Medical Oncologist	London
Dr Guiseppe Barone**	Paediatric Medical Oncologist	London
Professor Louis Chesler**	Paediatric Medical Oncologist	Sutton
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Juliet Gray (Incoming Chair)	Paediatric Medical Oncologist	Southampton
Professor Andrew Pearson**	Paediatric Medical Oncologist	London
Dr Ramya Ramanujachar	Paediatric Medical Oncologist	Southampton
Professor Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Dr Kate Wheeler	Paediatric Medical Oncologist	Oxford
Dr Sarah Brown*	Paediatric Oncology Trainee	Southampton
Professor Sue Burchill	Molecular Biologist	Leeds
Dr Simon Wan	Radiologist	London

Professor Keith Wheatley	Statistician	Birmingham
Mr Hany Gabra	Surgeon	Newcastle upon Tyne

Novel Agents Subgroup		
Name	**Specialism**	**Location**
Dr Lynley Marshall (Chair)	Consultant in Paediatric and Adolescent Oncology Drug Development	Sutton
Mrs Angela Polanco	Consumer	Warwick
Professor Steve Clifford	Translational Scientist	Newcastle upon Tyne
Dr Donna Lancaster	Paediatric Medical Oncologist with an interest in haematological malignancies	Sutton
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Professor Pamela Kearns	Paediatric Medical Oncologist with an interest in haematological malignacies	Birmingham
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor Bruce Morland	Paediatric Medical Oncologist	Birmingham
Professor Darren Hargrave	Paediatric Neuro-Oncologist	London
Professor Andrew Peet	Paediatric Neuro-Oncologist	Birmingham
Professor Gareth Veal	Pharmacologist	Newcastle
Dr Charlotte Burns*	Paediatric Oncology Trainee	Cambridge

* denotes trainee member

**denotes non-core member

Appendix 2

Group & Subgroup Strategies

A – CCL Group Strategy

Strategic Objective	Action	CSG Lead	Date	Outcomes
Portfolio development: Neuroblastoma	Developing overarching trial for newly diagnosed high risk patients. Further development of portfolio of trials for patients with refractory and relapsed disease Exploring new approaches to neuroblastoma therapy eg MIBG, Nivolumab, Cellular immunotherapy (CAR-T cells).	Martin Elliott Guy Makin Juliet Gray		HRNBL2 in development VERITAS, MINIVAN, BEACON 2 BEACON 1/2, MINIVAN
Portfolio development: Leukaemia	Strengthen representation across the CSG. Development of new frontline Acute Lymphoblastic Leukaemia Trial (Pan European). Focus on patients with lesscurable diseasekey).	John Moppett		Fully funded. Expected to open Q1 2020

	Reducing toxicity and deescalating treatment for patients with excellent survival. Work towards new study with Philadelphia positive disease. Work with Adult CSG to explore where it is possible to development joint strategy and trials. Develop strategy for relapsed AML. Continue the implementation of CAR-T cell therapy for ALL / lymphoma. Establish a CAR-T programme for AML Integrate GE testing into routine care	Leukaemia Subgroup Chair		
Portfolio development: Germ Cell	Maintain links with key external stakeholders for international trial design: UK – NCRI TYA and GCT CSG; Gynae CSG;	Sara Stoneham		

	International: MaGIC; G3; EORTC – Develop stronger links with European colleagues via SIOPe GCT Build on Malignant Germ cell tumour International Collaborative (MaGIC)= UK and US paediatric oncology initiative to create a large trial database that has enabled development of a new risk stratification for extracranial GCT and a frame work for new trial design internationally. For extra cranial:, Low risk: explore opportunities for reducing therapy (e.g. role of biomarkers) e.g. Stage 1 testis cancer > 11yrs High risk, explore new trial design e.g. MAMS Embed biology in all trial design. Engage with TYA CSG to strengthen interface with medical oncologists and paediatric oncologists on subgroup. Publishing joint analyses from MaGIC. For intracranial – continue SIOPe collaborative Extend links with US/Asia to align language/risk stratification and marker thresholds internationally Embedding biology into all trial design			
Strategic Objective	***Action***	**CSG Lead**	**Date**	**Outcomes**
Portfolio development: Bone Tumour	Continue development of Ewing Studies.			

	Osteosarcoma remains a major gap in the portfolio and a strategic aim will need to collaborate internationally. Improve strategic relationship with sarcoma CSG to ensure access of sarcoma studies to paediatric patients. Focus on survivorship, patients routinely disabled. Local therapy questions (radiotherapy) for next Euro Ewing's Study. Formalise reporting from bone sub group to CCL CSG (similar to YOSS)	YOSS Subgroup Chair / Chairs CCL and Sarcoma CSGs CTRad Link	?	ICONIC study funded and will open ???? Included in trial design
Portfolio Development: CNS tumours	Trials available for all tumour groups Molecular diagnostics informing all trials To be European leader in brain tumour trials To run biological studies to identify those patients whose treatment can be reduces, and those for whom novel treatment strategies are available			Progress in 2018-19; trials in development Coming as new trials open UK leading new high risk medulloblastoma study within Europe Genomics England and SMPaeds

	Note Gaps in portfolio (e.g. embryonal)			
Portfolio Development: Novel Agents Group	Consider structure, size and succession planning within Novel Agents Subgroup.	Chair Novel Agent subgroup	May 2018 Oct/Nov 2018 Apr/May 2019 Ongoing	Dr Lynley Marshall appointed as incoming Novel Agents Subgroup chair Two new paediatric oncology national grid trainees appointed to group New consumer representative appointment to the group, pending acceptance and confirmation. Decision to continue wider Novel Agents Network Subgroup meeting attendance in addition to the NCRI Core Novel Agents Subgroup, to ensure adequate centre, disease type (solid, CNS, haematological malignancies), and professional group representation (paediatric/TYA medical oncologist, research nurse, clinician scientist, translational/ laboratory scientists/trainees) to maximise opportunities to broaden the Novel Agents clinical trial and biomarker portfolio across areas of unmet medical need. Outcome = new trials/trial arms. Close co-ordination between Novel Agents Subgroup Chair/Subgroup and Paediatric

	Following the paediatric ECMC renewal and launch of SMPaeds and (shortly) of ESMART, further development of novel agent trials and longitudinal sampling studies Increase links with tumour site groups – leading early phase studies (in collaboration with site specific groups) Ensure good links with science as well as clinical communities Build capacity in preclinical research			ECMC Programme Office/Co-ordinator, using ECMC network confidentiality agreement to facilitate rapid expert review of proposed new pharma-sponsored early phase trials and quick, co-ordinated responses to expression of interest calls for trial participation. This will help develop and select the best possible studies for UK patients and make the UK attractive to sponsors for setting up and conducting studies efficiently. Outcome will be UK participation +/-leadership on new commercial trials Development of new academic trials/trial arms within basket/adaptively designed trials with sponsors inside and outside of the UK, by ensuring UK clinical and biology experts are embedded within European and other international consortia, both tumour-specific groups and more generic biology and early phase trial consortia (eg ITCC, SIOPEN, SIOPE, EpSSG, IBFM and others). Outcome will be UK participation +/-leadership on new academic investigator-initiated trials. Build network collaboration and optimise use of preclinical resources by facilitating joint

	Build expertise in area of epigenetic targeting			posts and/or projects across translational laboratories and centres affiliated to the Subgroup eg via clinical/research fellowships, joint grant proposals etc. Outcome = more clinical trials/arms/biomarker studies originating from UK centres. Translational outputs within clinical trials via links with Subgroup-affiliated laboratories; clinical trials/trial arms of agents targeting epigenetic mechanisms of action as these become increasingly better understood, preclinical data supports and clinical compounds become available.
Portfolio development: Radiotherapy	Increased number of radiotherapy trials (eg IMAT/HRNBL2/FaR-RMS)) Consider development of trials in Proton Beam Radiotherapy Maintain direct links with CTRad Work with European colleagues on the SIOPE/QUARTET platform to enhance radiotherapy quality assurance in paediatric trials	Henry Mandeville NB Subgroup Chair		More trials with randomised radiotherapy questions open and recruiting. Recruitment of patients treated with protons in radiotherapy trials. Study day with CTRad and TYA CSG planned Far-RMS HRNBL2 PNET V

Portfolio development (Systemic Anti-cancer Therapy)	Explore opportunities to use non-conventional chemotherapy e.g. immunotherapy. Develop pharmacokinectic studies e.g. liquid 13 Cis-retinoic acid.	Juliet Gray Deborah Tweddle		MINIVAN
General Trial Delivery	Working in partnership with European Trials (particularly when not led in UK) Ensuring adequate clinician time for contribution to clinical research and paediatric oncology. Managing complex external research approaches e.g. CED and Mexico (DIPG) Need to work with partners outside of the NHS (where evidence base exists). PROMs to be considered in clinical trial design across paediatric trial portfolio.	CRCTU NIHR lead Chair Novel Agents ALL		Included in ACGT153/GC4 trials (germ cell)

	Work with NIHR to ensure appropriate mapping of funding for the radiotherapy component of multicentre trials	CSG Chair and NCRI lead		
Personalised medicine/genomic strategy	Seek opportunity for genomic sequencing within paediatric cancers e.g. full genomic sequencing for patients with ALL. Focus on rarer diseases where unanswered questions remain e.g. APL, Downs, Leukaemia. Consider clinical leads for each tumour site to coordinate GEL Work. Ensure PPI involvement in genomic and SMP Studies (e.g. Ethics and Biopsy). Maintain direct links with paediatric ECMC network	Chair Novel Agents Subgroup Chairs PPI leads		Genome England due to come on board 2019 Ongoing

Strategic Objective	Action	CSG Lead	Date	Outcomes
Relapse	Maintain focus regarding research questions at time of relapse across all paediatric cancers			
Survivorship and Long Term Follow Up	Strengthen the portfolio of studies in the area of LTFU/Late Effects.	CSG Chair		

	Invite Chair of Late Effects SIG to CSG. Identify lead for late effects and long term follow up studies Focus on patients with bone tumours in whom the majority have a disability following therapy.	NCRI support		
Consumer involvement	Identify points where consumers can support trial development outside the CCL CSG process (e.g. lowering age limits in adult site specific trials and liaising with other CSGs and wider trial development. Develop role in genomics (e.g. ethical approaches to tumour biopsy) Development of long term follow up studies Collaboration with TYA CSG about transition from paediatric to TYA care	Consumer representatives CSG Chair with TYA lead		
Pathology	Appointment paediatric pathologist to CSG. Maintain directs links with CMPath	NCRI support		

	Recognition of pathology and radiology timeline in grant applications. Need to link with Biological Studies Steering Group within CCLG tumour bank. Strongly support TYA biological studies and strengthen interface with TYA Group.			
CSG Structure and Function	Ensure appropriate succession planning across the CSG. Encourage next generation of researchers Identify routes by which UK can participate in NCI Studies and collaborate with International Groups. Work with CRUK to ensure data collection within ECMC Paediatric Network is joined up Explore interface with NIHR (e.g. Just In Time initiative) and other funders. Work with partners (e.g. CCLG and CRCTU) in ensuring dissemination of key results from research.	Sara Stoneham All CRCTU and all members NIHR lead and CSG chair		Trainee scheme ongoing

	Review annual Clinical Trials Study day; closer collaboration with CCLG	CSG Chair CSG chair		

B – Central Nervous System 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.
- Increase the number of trials for children with CNS Tumours
- Better Identify prognostic and predictive biomarkers and implement their usage.

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.

This is being achieved by the introduction of new trials which stratify patients using clinical and molecular biomarkers (eg treatment reduction in PNET 5 for very good risk children with medulloblastoma and intensification of treatment or novel treatments in those with a poor outcome). More detailed molecular testing and the development of new biomarkers further enhances this. Detailed quality of life and neurocognitive outcomes are mandatory in all new trials to document changes in these parameters.

Biomarkers.

Development and discovery of new biomarkers are being discovered and subsequently tested in prospective clinical trials for a number of CNS tumours. Proven molecular biomarkers have been introduced into routine clinical practice after development in research laboratories. Real time molecular testing is routine for some tumour types and will become more widespread with the opening of the genomic hubs. Molecular guided therapy at relapse is becoming more commonplace with the opening of SM-Paeds and its associated E-smart early phase trials programme.

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.

The following trials are open in the UK (all pan European)

- Ependymoma 2 for all children and young people with ependymoma,
- PNET 5 for standard risk medulloblastoma
- BIOMEDE for Diffuse intrinsic pontine glioma
- VINILO for low grade glioma

The following are in late stages of development and have been through the CNS subgroup.

- High Risk Medulloblastoma, funded by CRUK/Brain Tumour Charity (2018), UK led pan European SIOPE study run by CRCTU (Birmingham), will be open in June 2019.
- LOGGIC – SIOPE study for children with low grade gliomas, open in Germany 2019, planned in UK for 2020, funding application to be submitted in 2019.
- ATRT - SIOPE study for children with ATRT, funding application in UK 2019.
- Infant medulloblastoma –SIOPE study for children with children under 3 with medulloblastoma in mid development, potentially funding to be sought 2020.
- CED – convection enhanced delivery of chemotherapy in children with diffuse Intrinsic pontine glioma run by the Sarah Cannon Research Institute in Harley Street. This is awaiting approval by the main CSG and is in late development.
- NIVIGlio for High grade glioma is open in France and funding will be sought in the UK in the near future.

These trials are all underpinned by real time central pathology and radiology review as well as the QUARTET radiotherapy quality assurance initiative for all upcoming and some current trials. Many of the trials have molecular biomarkers in order to stratify treatment. In addition, the majority of trials have a mandatory quality of survival studies built in.

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 development via regional hubs and should be live by mid-2019. This is already in place however for all children with medulloblastoma including for the PNET5 trial and the upcoming high risk and infant trials. 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 – Germ Cell Tumour Subgroup Strategy

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

Strategic aims

Intracranial

- SIOPe CNS GCT collaborative
- Extend links with US and Asia
- Trial Development in IC GCT

- Continue pan-European collaboration with SIOPe; led by UK
- Align language – risk stratifications, marker thresholds etc with COG
- View to aligning next trial design based on ACNS 1123 COG and SIOP CNS GCT II
- Embedding CSF/serum microRNA into trial development
- Under consideration:
  - NGGCT – high risk – intensification, role of HDT
  - Germinoma
- Chemo de-escalation randomisation
- RT de-escalation randomisation

Extra-cranial

- Maintain and develop links with external stakeholders:

- UK
  - NCRI Teenage & Young Adults and Germ Cell Tumour CSG
  - NCRI Testis
  - NCRI Gynae
- International
  - MaGIC
  - G3
  - EORTC via IRCI

Trial development in EC GCT

- Develop common language between stakeholders
  - for staging
  - for risk grouping
  - For surgical approach
- Find shared questions important to answer for stakeholders
  - e.g. role of HDT in relapse

- role of microRNA in disease; role of biomarkers of toxicity across all trial design
- PROMs the same between male and female, TYA and adults.

More specifically:

- Low risk
  - More surveillance. Less chemotherapy. More use of biomarkers.
- Standard risk
  - Less overall dose of chemotherapy. Less toxic chemotherapy.
- High risk
  - Earlier identification of these patients. MAMS trial design- against winner of P3BEP.
- Relapse
  - Son of TIGER - Randomised induction and HDT regimens – international
  - Paediatric – Umbrella trial vs. basket trial options

D – Leukaemia Subgroup Strategy

Strategic aims

- Open international trials for Ph-positive and infant ALL.
- Continue monitoring recruitment to MyeChild01.
- Open ALLTogether
- Develop a cohesive strategy for relapsed ALL.
- 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 – 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.

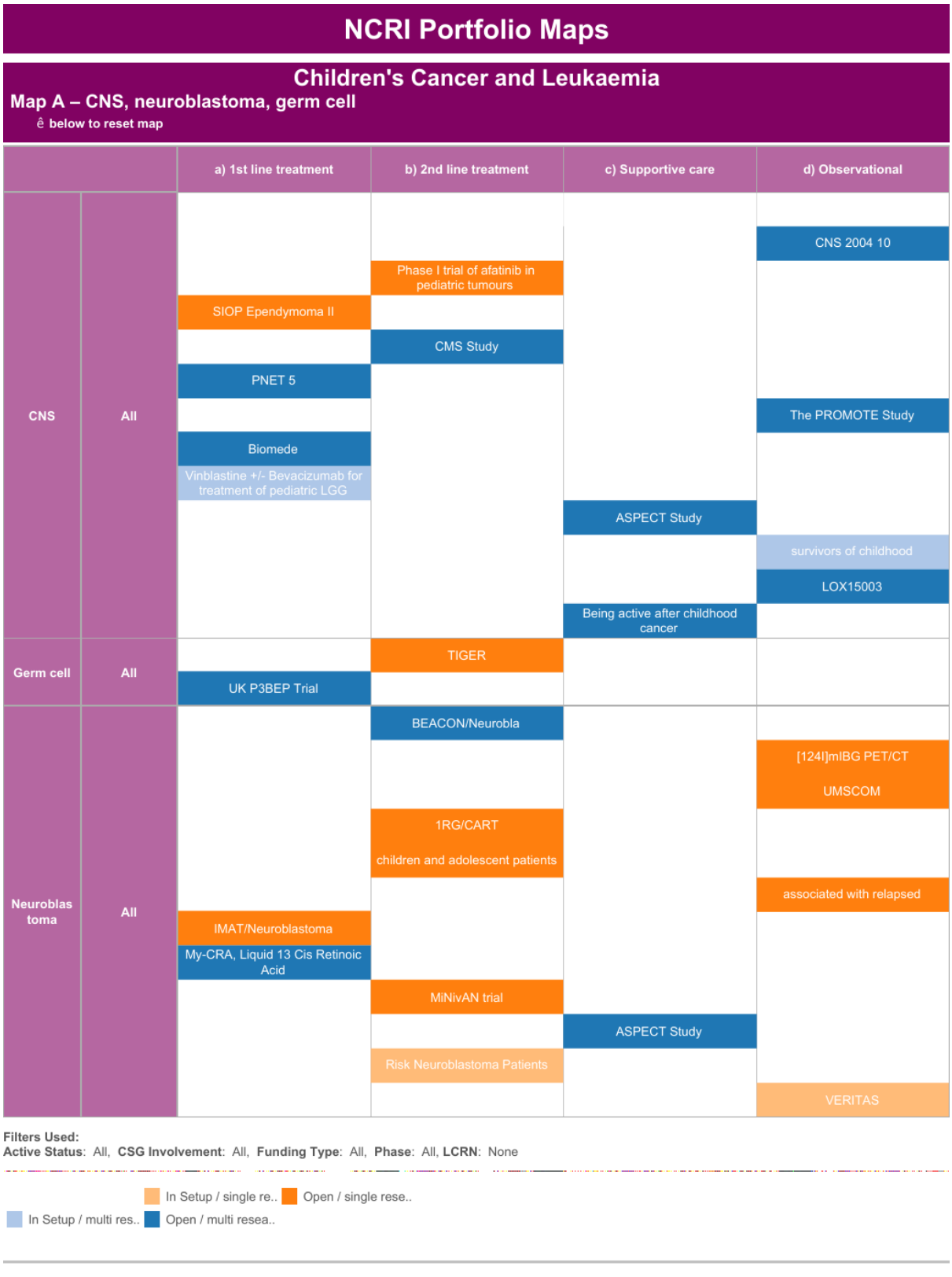
F – Novel Agents Subgroup Strategy

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, with a focus on more combination studies.
- 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.
- Following successful CRUK funding of the Stratified Medicine Paediatrics (SMPaeds), the implementation of a National molecular platform to genomically characterise relapsed solid paediatric cancers and a National Molecular Tumour Board to interpret “actionable mutations” and facilitate precision medicine trials by triaging patients based on biology.
- The Paediatric ECMC Network will develop 4 regional groups covering the whole of the UK to allow coordination and discussion of paediatric relapse cases to consider clinical trials and link with the SMPaeds programme and National Molecular Tumour Board.
- Work with ECMC Network to develop an online clinical trials finder to improve awareness of portfolio clinical trials and promote wider access.
- To link with more academic groups working in basic/ translational science at an early stage with the Novel Agents group to help define and develop promising new targets/ therapies along with colleagues in ECMC combinations alliance and CRUK Centre for Drug Development.

Appendix 3

Portfolio maps



NCRI Portfolio Maps

Children's Cancer and Leukaemia

Map B – Leukaemia, lymphoma, all cancers

ê below to reset map

		a) 1st line treatment	b) 2nd line treatment	c) Supportive care	d) Observational
All cancers	All	ty & pharmacokinetics of regorafen LCH//IV PARC The MaCROS study Study of Ibrutinib in Paediatric Patie Phase I/II, Durvalumab and Tremeli	Lenvatinib Phase I Venetoclax Paediatric Study ate with irinotecan in children with	Molecular Genet	alidation of Chemosensitivity Assay childhood tumours and congenital TRICICL V1 PERMIT SMPaeds od Cancer Patient Populations TD
Leukaemia	All	MyeChild 01 UCART19 CARPALL ovirus after Allogeneic Paediatric Tr 2 Single Arm Study on Patients wi	IntReALL SR 2010 UCART19-PALL study SeluDex CHILD study: Bosutinib in pediatric in paediatric and young adults wit CIN IN RELAPSED OR REFRACT PH1/2 Paed AML		okines on Acute Lymphoblastic Le Bone microarchitecture in ALL
Lymphoma	All	LCH//IV EuroNet-PHL-C2	ITREC in paediatric and young adults wit		ediatric OsseoUs Marrow Assessm

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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In Setup / single re.. Open / single rese..

Designed and maintained by **NCRI Clinical Research Groups (CRGs)** & **NIHR**

Developed by **Mayden®** Analytics

NCRI Portfolio Maps

Children's Cancer and Leukaemia

Map C – Renal, sarcoma, melanoma, hepatobiliary

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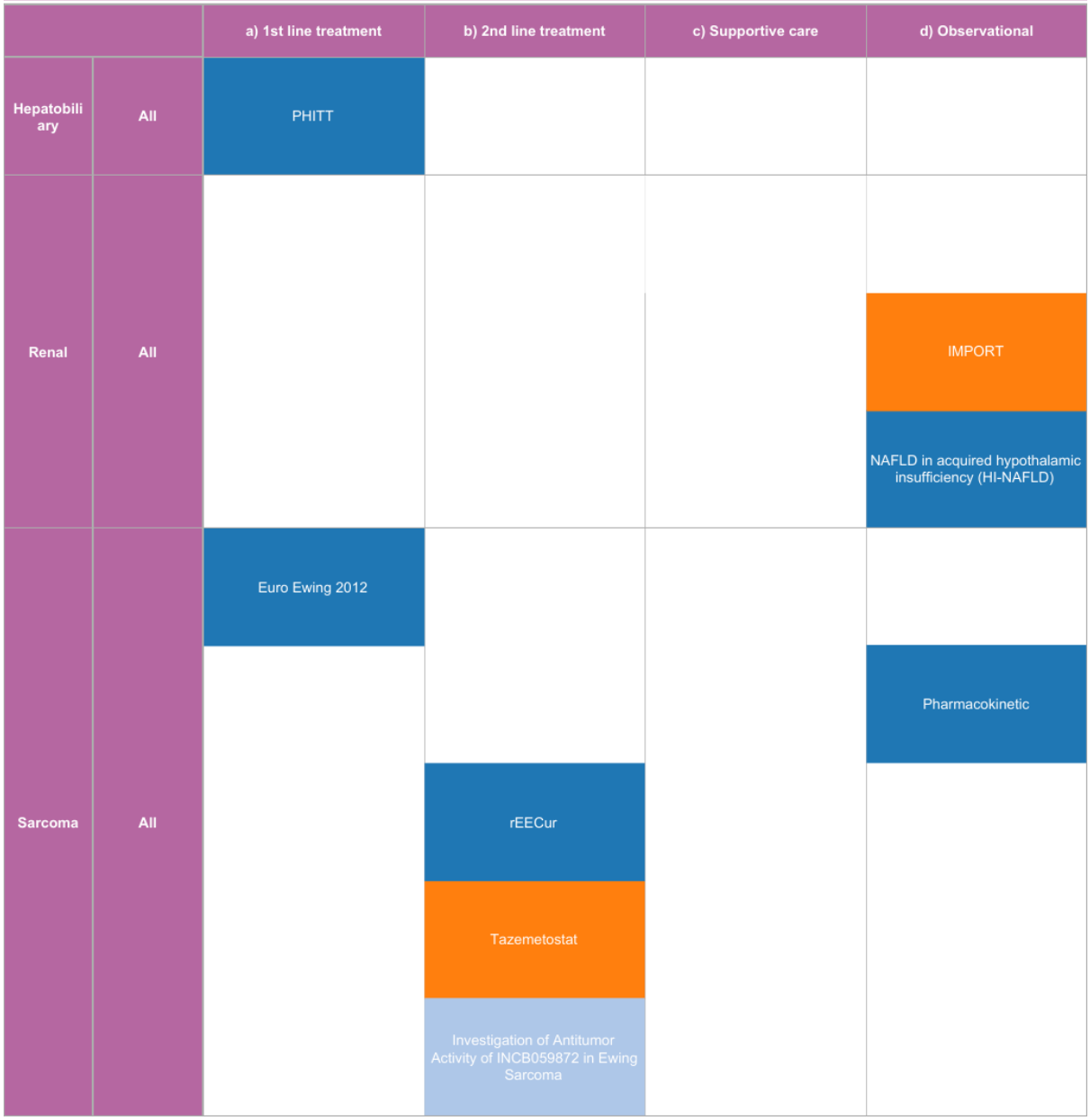

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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NCRI Portfolio Maps

Children's Cancer and Leukaemia

Map D – Novel agents

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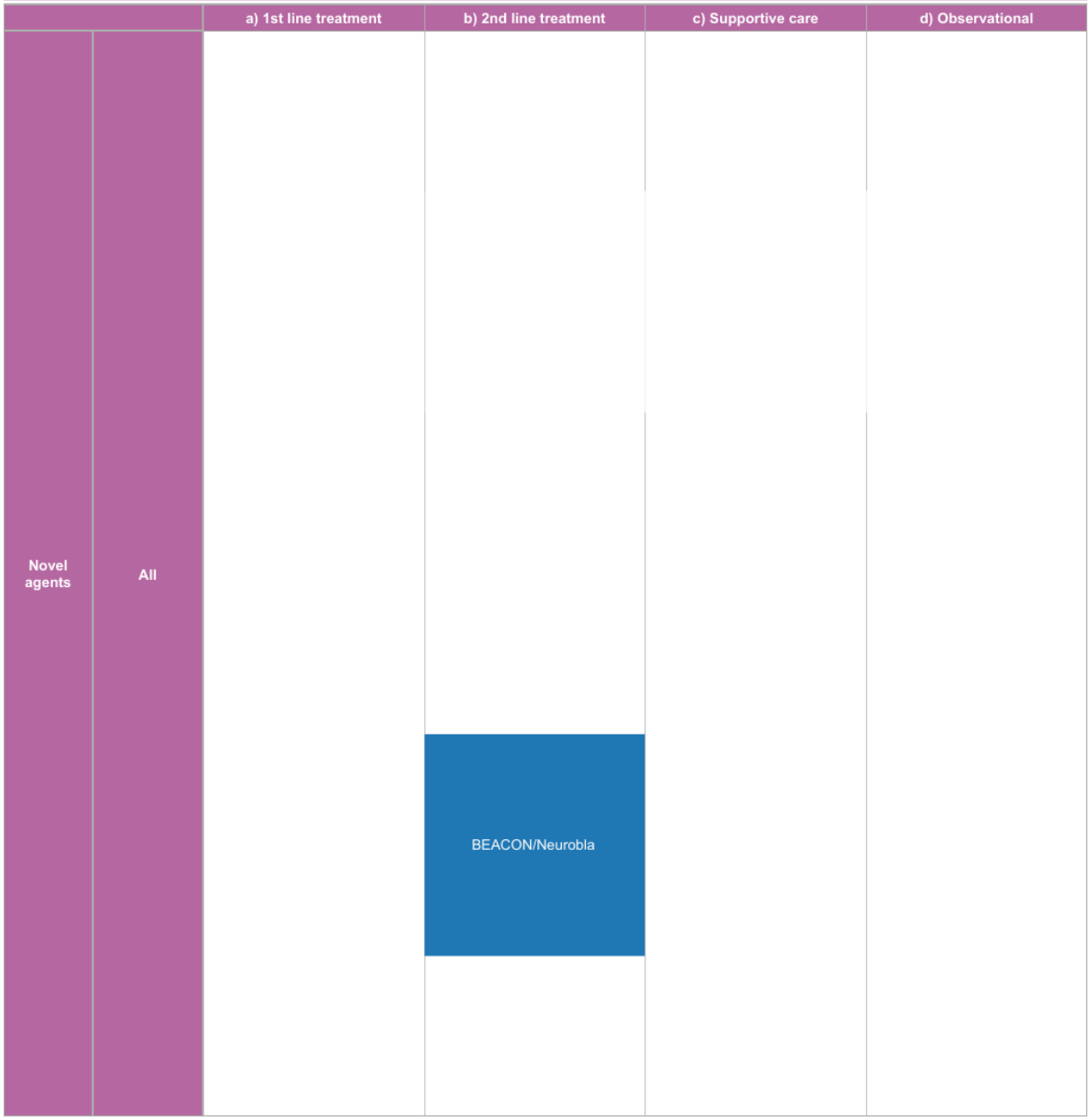

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

Open / multi resea..

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	Group involvement in the trial
1. HR-NBL1/SIOPEN: Lancet Oncol. 2018 Dec;19(12):1617-1629. doi: 10.1016/S1470-2045(18)30578-3.	No evidence that IL2 improved outcomes in patients with high risk neuroblastoma receiving dinatuxumab and cisretinoic acid – defines current standard of care	International study; NCRI portfolio study
2. HIT- SIOP PNET 4: Lancet Oncol. 2018 Dec;19(12):1602-1616. doi: 10.1016/S1470-2045(18)30532-1	Describes molecular signature in medulloblastoma which will be used in future risk stratification	International study; NCRI portfolio study
3. Data from CCLG GC1 and GC2 trials: Gynecol Oncol. 2018 Aug;150(2):253-260. doi: 10.1016/j.ygyno.2018.05.025	Data support exploration of cisplatin-based chemo therapy in all patients with advanced stage dysgerminoma	Based on data for studies that preceded NCRI, leading to new trial design for both seminoma and dysgerminoma i.e. across male and female patients allowing both NCRI Gynaecology Colleagues and NCRI Testis subgroup colleagues to work with CCL CSG and extends into international collaboration via MaGIC and G3 studies.
4. Data from CCLG GC1 and GC2 trials: Eur J Cancer. 2018 Jul;98:30-37. doi: 10.1016/j.ejca.2018.03.004.	Supports new trial design for AGCT1531 – CRUK funded clinical trial for low and standard risk extracranial GCT	Based on data for studies that preceded NCRI. Concept developed by CCG CSG germ cell subgroup in collaboration with NCRI Gynaecology CSG colleagues and NCRI Testis subgroup

		colleagues with international collaboration via MaGIC and G3
5. RMS 2005: Lancet Oncology 2018 Aug;19(8):1061-1071. doi: 10.1016/S1470-2045(18)30337-1.	Showed that addition of doxorubicin to standard chemotherapy did not improve outcomes in high risk rhabdomyosarcoma: informs design of new European FaR-RMS study	Portfolio study (also for sarcoma CSG) of which a CCL CSG member was UK lead and joint international lead. Upcoming FaR-RMS study led by CCL CSG members and members of NCRI YOSS subgroup of sarcoma CSG and is portfolio badged.

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Children's Cancer & Leukaemia Group portfolio, 15 trials closed to recruitment and 16 opened.

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
2014/2015	1605	643	795	643	-	-
2015/2016	1412	715	749	715	-	-
2016/2017	1228	630	594	630	-	-
2017/2018	914	698	468	698	-	-
2018/2019	515	768	368	729	-	-