The Children & Young People's Cancer Association

Children's Cancer Clinical Research Group: New Agents Group

Newsletter March 2025

Contents

Welcome to the New Agent Group Newsletter. The purpose of this document is to promote access to innovation for children and young people in the UK.

This public facing document is designed to show possible opportunities.

Innovative therapies are a rapidly moving field and access to studies change frequently so we cannot guarantee that all studies listed have availability and the complexity of studies mean not all patients will be eligible.

Whether a particular clinical trial is an appropriate and sensible choice for an individual patient is often complex. Particular understanding of cancer biology may be required.

We hope to identify opportunities and facilitate access. Resources available to identify innovation include

1) the EC TrialFinder that can be accessed by anyone with an NHS.net email,
2) via the ECMC Relapse MDTs,
3) the trial guide in this newsletter,
4) the chair of the New Agents group.
5) individual investigators listed by trials

Through the use of clinical trials we have greatly improved the chances of survival and quality survival for children and young people. The challenges that remain are

1) to find curative therapies for 15-20% of patients who are not cured and
2) to be gentler with the therapies that cure so that our curative therapy leads to less toxicity.

Innovative therapies must be our best chance of achieving these aims. In order to best adopt new treatments we need to learn from each child or young person accessing innovation. This guide is as complete and accurate as it has been feasible to achieve. Not all opportunities listed will be available at the point where a patient might wish to access. These are however possibilities If there are inaccuracies or omissions we are grateful for such feedback directly to info@cclg.org.uk and if you have questions raised which you cannot address with your treating team we will also try to help via this route

If you find the newsletter useful and particularly if it plays a part in accessing innovation for your patients we should also be grateful for this feedback

EC Trial Finder

The EC trial finder is a major initiative designed to facilitate trial access. It is an ECMC and CRUK collaborative project designed to enhance access to clinical trials within the ECMC network.

The website based application enables the search for disease and target based therapies. It is continually updated and provides a summary of relevant studies as well as contact details for access.

The information required to interrogate the trial finder is specialist and the output also is best interpreted by clinicians so at present this site is available only to NHS clinicians. Your treating doctor can access this database. The database is routinely used when patients are considered by the ECMC regional Relapse Panels.

The site may be accessed at

https://www.ecmcnetwork.org.uk/ec-trial-finder

ECMC Regional Relapse Advisory Panels

All Principal Centres and specialists caring for children and young people with cancer can seek advice and information about innovation through the ECMC regional discussion panels which are available to clinicians from all centres. The panels are stablished on a regional and geographic basis. There are 4 panels, a Northern one comprising Aberdeen, Glasgow, Edinburgh, Belfast, Newcastle and Dublin. M62 corridor, Liverpool, Manchester, Leeds and Sheffield, SouthWest - Birmingham,Cardiff, Bristol, Nottingham and Leicester and South East London GOS and RMH, Oxford, Cambridge and Southampton

The meetings include the investigators for early phase trials and can offer guidance and highlight trial and innovation opportunities.

All PTCs should be aware how to engage with their local MDT. A proforma containing a minimum dataset is usual. This offers the opportunity to prospectively gather data in a manner which we had hitherto been unable to do.

Meetings are usually virtual and are held weekly or as required. If additional guidance is required please contact info@cclg.org.uk

Current Trial Portfolio

Name of Trial: DETERMINE (Determining Extended Therapeutic indications for Existing drugs in Rare Molecularly defined Indications using a National Evaluation platform trial):

Drug or therapy involved:

Treatment Arm 1, Alectinib – ALK positive cancers except Non-small cell lung cancer -Open **Weight more than 40kg**

Treatment Arm 2, Atezolizumab – High tumour mutational burden (TMB) or microsatellite instability-high (MSI-high) or proven constitutional mismatch repair deficiency (CMMRD) disposition - Open

Treatment Arm 3, Entrectinib - ROS1 gene fusion positive cancers- Open

Treatment Arm 4, Trastuzumab/Pertuzumab - HER2 amplification or mutations - Open

Treatment Arm 5, Vemurafenib/Cobimetinib – BRAF positive cancers –**Over 18 years only** Closed

Treatment Arm 6, Capmatinib - cancers harbouring MET dysregulations –Not yet open **Patients must be over the age of 18**.

Sites

Contact details

Birmingham Children's Hospital

Bristol Royal Hospital for Children

Addenbrookes Hospital Cambridge

Noah's Ark Children's Hospital for Wales Cardiff

The Royal Hospital for Children Glasgow

Leeds Children's Hospital

Alder Hey Children's Hospital Liverpool

The Royal Marsden Hospital

Chief Investigator

Great Ormond Street Professor

Manchester Children's Hospital

Great North Children's Hospital Newcastle

Southampton Children's Hospital

Link to more detail

https://www.cancerresearchuk.org/funding-for-researchers/our-research-infrastructure/our-centre-for-drug-development/determine-overview

Name of trial: ESMART

Drug or therapy involved: Multiple arms previously and further arms expected currently only open to Arm I only in UK. Drug: Enasidenib

Target or mechanism: Enasidenib inhibits the mutant IDH2 enzyme, reducing the production of 2-hyrdroxyglutarate, which bocks cell differentiation.

Eligible conditions: IDH2 mutated relapsed/ refractory myeloid malignancies.
Patient must have documented IDH2 gene-mutated disease and had at least 2 prior induction therapy.
Patient with IDH2 germline mutations and significant clinical deficit of the disease will be allowed.
For patients with documented IDH2 mutation, the inclusion criteria of extensive molecular profiling of the recurrent tumour may be waved.

Sites

Contact details

Birmingham Children's Hospital

The Royal Marsden Hospital

Great Ormond Street

Manchester Children's Hospital

Great North Children's Hospital Newcastle

Link to more detail

https://clinicaltrials.gov/study/NCT02813135

Name of Trial: BEACON 2

A Multi-Arm, Multi-Stage Platform Trial For Relapsed Neuroblastoma

Drug or therapy involved: Dinutuximab beta, bevacizumab Irinotecan Temozolomide

Eligible conditions: Neuroblastoma

Target or mechanism: Immunotherapy

Key exclusion: non measurable disease previous progression

Sites

Contact details

Alder Hey Children's Hospital Liverpool

Manchester Children's Hospital

Addenbrookes Hospital Cambridge

Opening at many sites across UK

Name of Trial: Pembrolizumab A Phase I/II Study of Pembrolizumab (MK-3475) in Children with Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma (KEYNOTE-051)

Drug or therapy involved: Pembrolizumab

Eligible conditions: Melanoma, relapsed/refractory classical Hodgkin lymphoma microsatellite-instability-high (MSI-H), tumor-mutational burden-high ≥10 mutation/Mb (TMB-H) solid tumors

Target or mechanism: PD-1 Checkpoint Inhibitor

Sites

Contact details

The Royal Marsden Hospital

Link to more detail

https://clinicaltrials.gov/study/NCT02332668

Name of Trial: The MiNivAN study A phase I study of 131-I mIBG followed by Dinutuximab beta in children with relapsed / refractory neuroblastoma

Drug or therapy involved: 131-I mIBG Dinutuximab beta, Nivolumab

Eligible conditions: Recurrent or refractory Neuroblastoma

Target or mechanism: MIBG targeted radiotherapy, Immunotherapy

Key exclusion: Non MIBG avid Neuroblastoma, no previous PD1 PD-L1 checkpoint therapy

Sites

Contact details

Southampton Children's Hospital

Name of Trial: Palbociclib

Drug or therapy involved: Palbociclib, Irinotecan, Temozolomide, Topotecan, Cyclophosphamide

Eligible conditions: paediatric patients with recurrent or refractory solid tumours. **Only Neuroblastoma at present**

Target or mechanism: Kinase inhibitor – blocking proteins cyclin-dependent kinases CDK4 and CDK6.

Key exclusion: Prior progression through previous Irinotecan, Temozolomide, Topotecan and Cyclophosphamide treatment regimens.

Sites

Contact details

The Royal Marsden Hospital

Great North Children's Hospital Newcastle

The Royal Hospital for Children Glasgow Dr Milind Ronghe milind.ronghe@ggc.scot.nhs.uk

Name of Trial: Ponatinib An open-label, single arm, Phase 1/2 study evaluating the safety and efficacy of ponatanib for the treatment of recurrent or refractory leukaemias or solid tumours in paediatric participants

Drug or therapy involved: Ponatinib

Eligible conditions: Leukaemia, RET, FLT3, KIT, FGFR, PDGFR, TIE2, VEGFR, or any other mutations where ponatinib may have biological activity (eg, EPH receptors and SRC families of kinases)

Target or mechanism: multi targeted Tyrosine Kinase inhibitor

Sites

Contact details

The Royal Marsden Hospital

Alder Hey Children's Hospital Liverpool

The Royal Hospital for Children Glasgow

https://clinicaltrials.gov/study/NCT03934372

Name of Trial: CRISP A phase1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies

Drug or therapy involved: Crizotinib, Temsirolimus

Eligible conditions: Neuroblastoma with ALK or MET mutation, IMT

Target or mechanism: ALK, MET, ROS 1

Sites

Contact details

The Royal Marsden Hospital

Addenbrookes Hospital Cambridge

Leeds Children's Hospital

Birmingham Children's Hospital

https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-005437-53/NL

Name of Trial: GLO-BNHL Glo-BNHL is an adaptive prospective early phase international multicentre platform clinical trial designed to evaluate the safety and efficacy of novel agents for the treatment of children, adolescents and young adults with relapsed and/or refractory B-cell non-Hodgkin Lymphoma (r/r B-NHL).

Drug or therapy involved:

Treatment Arm I: bispecific antibody (BsAb)

• Treatment Arm II: antibody-drug conjugate (ADC) with standard chemotherapy

• Treatment Arm III: chimeric antigen receptor (CAR) T-cells

Eligible conditions: Relapsed/ refractory B-cell non-Hodgkin Lymphoma (r/r B-NHL).

Sites

Contact details

Bristol

Manchester

https://www.birmingham.ac.uk/research/crctu/trials/glo-bnhl/professionals

Name of Trial: rEECUR

Drug or therapy involved: Ifosfamide, Ifosfamide + Lenvatinib

Eligible conditions: relapsed/ refractory Ewings Sarcoma

Target or mechanism: cytotoxic chemotherapy and multi-targeted Tyrosine Kinase Inhibitor

Key exclusion: Enrollment in previous arms,

Multiple UK sites

https://www.birmingham.ac.uk/research/crctu/trials/reecur

Name of Trial: CabOSTar

Drug or therapy involved: Cabozantanib

Eligible conditions: Osteosarcoma relapsed with measurable or evaluable disease after chemotherapy

Target or mechanism: multi-targeted Tyrosine Kinase Inhibitor

Key exclusion: complete resection of disease, previous Cabozantanib

UCL

Birmingham

Manchester

Newcastle

Record History | NCT06341712 | ClinicalTrials.gov

Name of Trial: INBRx

Drug or therapy involved: INBRX109 with Temozolomide and Irinotecan

Eligible conditions: relapsed/ refractory Ewings Sarcoma

Target or mechanism: DR5 agonist antibody with Cytotoxic chemotherapy

Key exclusion: more than 2 previous lines of therapy,

UCL

Manchester

RMH

Newcastle

Study Details | Phase 1 Study of INBRX-109 in Subjects with Locally Advanced or Metastatic Solid Tumors Including Sarcomas | ClinicalTrials.gov

Name of Trial: Ymabs A Pivotal Phase 2 Trial of Antibody Naxitamab (hu3F8) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in High-Risk Neuroblastoma Patients with Primary Refractory Disease or Incomplete Response to Salvage Treatment in Bone and/or Bone Marrow

Drug or therapy involved: naxitamab + GMCSF

Eligible conditions High-risk neuroblastoma patients with either primary refractory disease or incomplete response to salvage treatment (in both cases including stable disease, minor response and partial response) evaluable in bone and/or bone marrow

Target or mechanism: Immunotherapy

Key exclusion: Evaluable neuroblastoma outside bone and bone marrowPI: Dr Quentin

Sites

Contact details

Leeds Children's Hospital

Southampton Children's Hospital

The Royal Hospital for Children Glasgow

https://clinicaltrials.gov/study/NCT03363373

Name of Trial: 5FU Pilot Institutional Study Evaluating 5-fluorouracil Following Radiation Therapy in Children and Young Adults with Relapsed/refractory Ependymoma

Drug or therapy involved: 5FU 5-fluorouracil

Eligible conditions: Recurrent refractory Ependymoma aged 1-24

Target or mechanism: Cytotoxic chemotherapy

Sites

Contact details

The Royal Marsden Hospital

https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001470-34/GB

Name of Trial: SCOOP A PHASE 1, MULTICENTRE, OPEN-LABEL, DOSE-ESCALATION AND COHORT EXPANSION STUDY OF NIRAPARIB AND DOSTARLIMAB IN PAEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMOURS

Drug or therapy involved: Nirasparib (PARP inhibitor) Dostarlimab (PD1 inhibitor)

Eligible conditions: paediatric patients with recurrent or refractory solid tumours. **Only reopening for neuroblastoma at present**

Target or mechanism: Combination PARP and Checkpoint inhibition

Sites

Contact details

Birmingham Children's Hospital

Manchester Children's Hospital

The Royal Marsden Hospital

Link to more detail

https://clinicaltrials.gov/study/NCT04544995

Name of Trial: CARE A Study of Repotrectinib in Pediatric and Young Adult Subjects Harboring ALK, ROS1, OR NTRK1-3 Repotrectinib

Eligible conditions: paediatric patients with NTRK, ROS1 activating mutations

Target or mechanism: NTRK and ROS1 inhibitor

Sites

Contact details

Alder Hey Children's Hospital Liverpool

Manchester Children's Hospital

The Royal Marsden Hospital

Cardiff

Opening soon GOS

Link to more. Detail

https://www.clinicaltrials.gov/study/NCT04094610?aggFilters=ages:child,funderType:industry,phase:1%202,studyType:int&spons=Turning%20Point%20Therapeutics&rank=1

Name of Trial: Alectinib IMATRIX

Drug or therapy involved: Alectinib

Eligible conditions: paediatric patients with ALK **fusion** positive **(not merely mutation)** solid or CNS tumours for whom prior treatment has proven to be ineffective or there is no satisfactory treatment available.

Target or mechanism: ALK Fusion Positive solid or CNS tumours.

Key exclusion: Diagnosis of Anaplastic Large Cell Lymphoma (ALCL), any GI disorders, history of organ transplant, recent allogeneic or autologous stem cell infusions.

Sites

Contact details

Great Ormond Street

Manchester Children's Hospital

Great North Children's Hospital Newcastle

The Royal Marsden Hospital

Link to more detail

https://clinicaltrials.gov/study/NCT04774718

Name of Trial: Relativity A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Drug or therapy involved: Relatimab and Nivolumab.LAG3 and PD1 dual checkpoint inhibition

Eligible conditions: Paediatric and young adult participants with recurrent or refractory classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma.

Target or mechanism: Relatimab is a human antibody LAG-3. Relatlimab binds to a defined epitope on LAG-3 with high affinity and specificity and potently blocks the interaction of LAG-3 with its known ligands, MHC Class II and fibrinogen-like protein 1 (FGL-1).

Nivolumab is a human monoclonal antibody (IgG4-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor.

Key exclusion: Secondary CNS lymphoma involving the brain, spinal cord, or with leptomeningeal seeding. Pre-existing neuropathy of more than Grade 2. Concurrent or active GvHD.

Sites

Contact details

Alder Hey Children's Hospital Liverpool

The Royal Marsden Hospital

Great North Children's Hospital Newcastle

https://clinicaltrials.gov/study/NCT05255601

Name of Trial: Lightbeam MK-9999 (O1A) A Phase 1/2 Substudy to Evaluate the Safety and Efficacy of Zilovertamab Vedotin in Pediatric and Young Adult Participants With Hematologic Malignancies or Solid Tumors

Drug or therapy involved: Zilovertamab Vedotin

Eligible conditions: B-ALL, neuroblastoma, Ewing sarcoma and DLBCL/Burkitt lymphoma.

Target or mechanism: ROR1 (receptor tyrosine kinase-like orphan receptor 1) is the therapeutic target being investigated for B-ALL, neuroblastoma, and Ewing sarcoma in the paediatric population.

Key exclusion: History of solid organ transplant, Down syndrome, GvHD, received prior therapy with a ROR1-directed therapy.

Sites

Contact details

Great North Children's Hospital Newcastle

The Royal Marsden Hospital

Cardiff

https://clinicaltrials.gov/study/NCT06395103#contacts-and-locations

Solid and Brain Tumour CAR-T therapies

Name of Trial: MAGNETO Multi-modular Chimeric Antigen Receptor targeting GD2 in NEuroblasTOma

Drug or therapy involved: GD2 CAR-T

Eligible conditions: Relapsed/ refractory Neuroblastoma

Target or mechanism: GD2 CAR-T

Great Ormond Street

Name of Trial: CARMIGO Chimeric Antigen Receptor (CAR)-T cells to target GD2 for Diffuse Midline Glioma (DMG)

Drug or therapy involved: Palbociclib, Irinotecan, Temozolomide, Topotecan, Cyclophosphamide

Eligible conditions: Diffuse Midline Glioma

Target or mechanism: Kinase inhibitor – blocking proteins cyclin-dependent kinases CDK4 and CDK6.

Key exclusion: Prior progression through previous Irinotecan, Temozolomide, Topotecan and Cyclophosphamide treatment regimens.

Sites

Contact details

Great Ormond Street

Haematological malignancy CAR-T trials

Suitability and access to CAR-T is decided on a supraregional expert basis. Tisagenlecleucel Chimeric Antigen Receptor T Cell is commissioned by the NHS for relapsed and refractory B-cell acute lymphoblastic leukaemia at the following sites

Great Ormond Street Hospital

Newcastle University Hospitals NHS Trust

Manchester University Hospitals NHS Foundation Trust

Patients identified by treating clinicians who might benefit need to be discussed at the national MDT. Patients may be appropriate for NHS commissioned CAR-T or for one the following trials

Available studies

TVTCAR7 study

CARAML study

AUTO-PY1

Frontline studies including Innovative therapies

Name of trial: LOGGIC / DAY 101 002 DAY101 Vs. Standard of Care Chemotherapy in Pediatric Patients with Low-Grade Glioma Requiring First-Line Systemic Therapy (LOGGIC/FIREFLY-2)

Drug or therapy involved: DAY101 Monotherapy (Tovorafenib) Versus Standard Of Care Chemotherapy.

Target or mechanism: Type-II RAF kinase inhibitor. Tovorafenib inhibits BRAF V600E mutation and both wild-type BRAF and CRAF enzymes and, importantly, does not paradoxically activate MAPK signaling in tumors harboring BRAF fusions, including the KIAA1549:BRAF fusion.

Eligible conditions: Paediatric Low-Grade Glioma harboring an activating RAF alteration requiring first-line systemic therapy.

Key exclusions: Schwannoma, Subependymal giant cell astrocytoma (Tuberous Sclerosis) Diffuse intrinsic pontine glioma, even if histologically diagnosed as WHO Grade I-II.

Additional activating molecular alterations (even if histologically low-grade) including, but not limited to any of the following:

a) IDH 1/2 mutation

b) Histone H3 mutation

c) Fibroblast growth factor receptor (FGFR) mutations or fusions

d) MYBL alterations

e) NF-1 LOF mutation

Known or suspected diagnosis of neurofibromatosis Type 1 or 2 (NF-1/NF-2) via genetic testing or current diagnostic clinical criteria.

Sites

Contact details

Bristol Royal Hospital for Children
Addenbrookes Hospital Cambridge

Birmingham Children's Hospital

Leeds Children's Hospital

Alder Hey Children's Hospital Liverpool
Manchester Children's Hospital

Great North Children's Hospital Newcastle

The Royal Marsden Hospital

The Royal Hospital for Children Glasgow

https://clinicaltrials.gov/study/NCT05566795

Name of trial: INTER-EWING - 1

Drug or therapy involved: Randomisation for high risk patients VDC/IE +/- Cabozantanib

Target or mechanism: Evaluate patient outcomes with increased treatment (6 extra cycles post consolidation).

Eligible conditions: Newly diagnosed Ewing Sarcoma.

Multiple UK sites

https://www.isrctn.com/ISRCTN17938906

Trial name: FaR-RMS

Drug or therapy involved:

- CT3 arm for relapsed patients only, which comparison of VI v VI + Rego.

Target or mechanism: mTKI

Eligible conditions: Children and adults with relapsed Rhabdo MyoSarcoma.

Multiple UK sites

https://www.isrctn.com/ISRCTN45535982?q=FaR-RMS&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10

Name of trial: ACTION

Drug or therapy involved: ONC201
Given in frontline following radiotherapy
Eligible conditions: H3K27M mutant glioma- but **not DIPG**
Body weight greater than 10kg no age limit
Leeds

Glasgow

The Royal Marsden

Newcastle

https://clinicaltrials.gov/study/NCT05580562

Patient Access Schemes and Cancer Drug Fund

Therapies may be accessed as innovation from sponsors or via the Cancer drug fund. It is imperative that we capture data to understand both the toxicities of these therapies and their efficacy. This data can be captured by enrolment in the **SACHA trial.** Enrolment of patients in SACHA is strongly recommended where innovation is accessed outside clinical trials. If you do not have the study open we strongly encourage you to become a site if you do access one of the products listed

Name of Trial: SACHA Secured Access to innovative medicines for CHildren adolescents and young adults with cAncer

Drug or therapy involved: Non trial administration of innovative agent

Eligible conditions: Any cancer in children or young adults

Open at Oxford, UCH London, Birmingham, Sheffield, Newcastle, The Royal Marsden, Southampton, Leeds, Liverpool, Glasgow, Aberdeen

The SACHA trial started in France and has already provided crucial data which is guiding treatement.

More information

Be Part of Research - Trial Details - SACHA International

Access on these schemes is not guaranteed and often criteria need to be met and a case needs to be made.

Cabozantanib. Multi targeted tyrosine kinase inhibitor. Has been investigated in sarcomas with some evidence of activity.

Sponsor Ipsen

Application requires clinical details and justification for the request drug information at links below

Cabometyx (cabozantinib - tablets), SPC available
here: https://www.medicines.org.uk/emc/product/4331/smpc

Cometriq (cabozantinib – capsules), SPC available
here: https://www.medicines.org.uk/emc/product/4407

Lorlatinib ALK inhibitor. Rationale for use in cancers with suspected ALK driver mutation either fusion or amplification.

Sponsor Pfizer

Eflornithine- DFMO

Inhibitor of Ornithine Decarboxylase. Suggested as an adjuvant treatment after current conventional therapy for high risk neuroblastoma. Data from phase 2 trial compared to matched historical controls suggest benefit. Approved by FDA. This is now available from Norgine on an expanded access programme.

ONC 201

ONC 201 or dordaviprone is a small molecule inhibitor of DRD2. It has been investigated for H3 K27M diffuse midline gliomas. The drug is oral capsule.

The drug is supplied by Chimerix.

Regorafenib. Multi targeted tyrosine kinase inhibitor. Has been investigated in sarcomas with some evidence of activity.

Bayer do not have a managed access programme.

However they may make the drug available on a single Named Patient Supply basis.

Larotrectinib

NTRK inhibitor. High response rate in NTRK driven tumours. Available via a managed access agreement in England and Wales through the cancer drug fund

Dabrafenib with Trametinib for BRAFV600 mutant gliomas

Available through Cancer drug fund in England and Wales

Possible options for innovation by diagnosis

Innovative therapy may be available on the basis of the primary diagnosis. Below are listed the most likely innovative therapies which may be available by means of the trial or access programme which is referenced. More details on the trial or access programme is available in the preceding text. There may be a rationale for exploring a therapy based on the diagnosis and evidence that a particular tumour subset may be susceptible to an agent or combination. The presence of particular mutations or abnormalities which are not specific to a single cancer can also make a treatment plausible. We call these Agnostic indications- they are specific for the mistake but not for a cancer type. Agnostic abnormalities are however often associated with certain cancers and very rare or absent in others. We consider both cancer specific and agnostic possibilities for innovative therapies

Acute Lymphoblastic Leukaemia

Advice will be available via the national leukaemia MDT and this is the recommended pathway. This will include consideration of CAR-T and SCT.

Trials which could include ALL -**Ponatinib, Inotuzumab, Lightbeam 1a TVTCAR7 study, CARAML** study, **AUTO-PY1**

Acute Myeloid Leukaemia

Ponatinib, Agnostic targets

Non Hodgkins Lymphoma

Glo-BNHL, **Relativity**, **Lightbeam 1a,** Agnostic targets

Hodgkins Lymphoma

Relativity, Agnostic targets

Neuroblastoma

BEACON 2, MINIvAN, **CRISP** (ALK mutation), **Ymabs,** SCOOP, **LightBeam 1a, MAGNETO**, Agnostic targets, Access programmes- **Lorlatinib**, **DFMO**

High Grade Glioma

The search for specific targets is particularly applicable for high grade glioma since targets which may yield benefit with currently available agents are relatively more frequent.

ACTION-ONC201 is available in first line for DMG. **DETERMINE** if target present, **Pembrolizumab** if MSI or high TMB, **Ponatinib** if RET, FLT3, KIT, FGFR, PDGFR, TIE2, VEGFR. Access programmes **Lorlatinib**, **ONC201, Larotrectinib, Dabrafenib/Trametinib**

Wilms tumour

Agnostic targets (infrequently present)

Rhabdomyosarcoma

FaR-RMS, Agnostic targets,

Ewings Sarcoma

INTER-EWING-1 Upfront innovation, **rEECUR**, **Lightbeam, INBRX-109**, Agnostic targets, Access programmes **Cabozantanib**, **Regorafenib**

Osteosarcoma

SCOOP, **CaboSTar,** Agnostic targets, Access programmes **Cabozantanib**, **Regorafenib**

Other soft tissue Sarcoma

Agnostic targets, Access programmes **Cabozantanib**, **Regorafenib**

Low grade gliomas

LOGGIC upfront innovation, Agnostic targets, Access programmes, **Lorlatinib, Dabrafenib/Trametinib, Larotrectinib**

Ependymoma

5FU, Agnostic targets

Melanoma

Pembrolizumab, Agnostic Programmes, **Dabrafenib/Trametinib**

Possible options by agnostic target marker

Another means to access innovation is by demonstration of a driver mutation or phenotype which can be targeted by an innovative therapy. These mutations may be effectively targeted irrespective of the tumour of origin and hence they are termed tumour agnostic. Tumours with the following mutations have targeted therapy available by means ot the referred trial or access programme. More details on the trial or access programme is available in the preceding text.

ALK presence of activating mutation or fusion.

Trials available

DETERMINE weight above 40kg only

CRISP Neuroblastoma and IMT only

ALECTINIB iMATRIX ALK fusion only

Access programme

Lorlatinib

High Tumour Mutational Burden/ Microsatellite Instability

Trials available

DETERMINE-atezolizumab

Pembrolizumab

ROS-1 mutation

Trials available

DETERMINE-entrectinib

CARE Repotrectinib

IDH2 mutation

Trials available

ESMART

RET, FLT3, KIT, FGFR, PDGFR, TIE2, VEGFR

Trials available

Ponatinib

BRAF V600

Access programme via CDF

Dabrafenib/Trametinib

NTRK fusion

Access programme via CDF

Larotrectinib