



# Treatment options for children with relapsed or refractory high-risk neuroblastoma

An information guide for parents and families

The purpose of this factsheet is to tell you about treatment opportunities that are available in the UK for treating children with relapsed or refractory high-risk neuroblastoma.

Choosing which treatment is right for your child will depend on a number of things, including where their disease is and what treatment they have previously been given. Your child's own doctor will be able to help you decide which is the most appropriate treatment for your child at this time.

## Your child will have one of the following disease types:

### REFRACTORY

This means that your child's neuroblastoma has not responded adequately and may be resistant to treatment. Children with refractory disease can have a slower course of progression.

### RELAPSED

This means that your child has had a good initial response but the neuroblastoma came back during or after treatment. Relapsed disease usually behaves differently to refractory disease and factors such as the length of time taken to relapse, MYCN gene status and the child's age are important. Currently, there is no standard treatment that has been shown to be most effective for initial treatment of relapsed neuroblastoma so each child will receive a treatment plan tailored to their specific needs [1].

### PROGRESSIVE

This means that your child's neuroblastoma has spread to new places in their body without showing a response to initial treatment.



## How do we decide which treatment is best?

The UK currently offers national and international trials/studies for relapsed and refractory neuroblastoma. There are also numerous other early phase trials designed for children with various types of relapsed or refractory cancers, not just those with neuroblastoma. Some of these target specific genes or mutations in the tumour so eligibility may depend on the genetics of your child's tumour.

Your child's doctor has access to networks of experts to help form a treatment plan for your child. Your doctor will be able to advise you which trial is suitable for your child based on their disease, their previous treatment, if they have specific gene changes, the expected side effects of any new treatment, and the distance required to travel to the nearest trial centre.

### CCLG Neuroblastoma National Advisory Panel

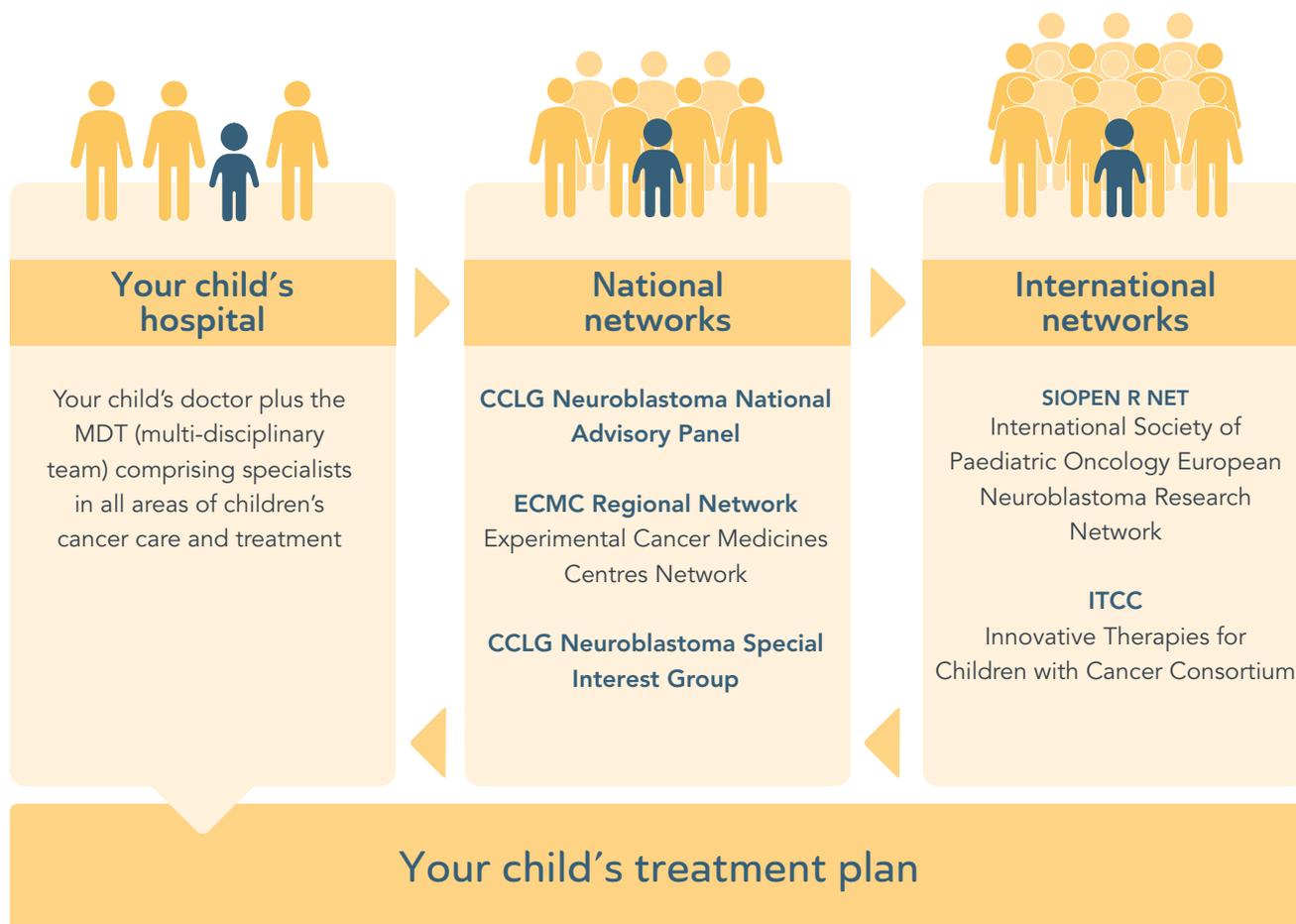
The Neuroblastoma National Advisory Panel comprises the most experienced clinicians from around the UK in treating neuroblastoma. Panel members are often members of international networks and will sometimes ask for advice from experts around the world.

The panel meets regularly and individual cases are presented anonymously together with any relevant scans and tumour genetics. Each case is discussed in detail to share expertise and advise on the best treatment plan for your child.

Your doctor can submit your child's case to the panel and will discuss this with you. You can also ask your doctor to arrange this and include your own specific questions. You will be given detailed feedback on what is discussed and advised by the panel.

### ECMC Regional Network Discussion Panels

Your doctor has access to the ECMC (Experimental Cancer Medicine Centres) regional network where individual cases of any relapsed/refractory cancers are discussed. The type and biology of your child's tumour is reviewed with the aim of identifying any targeted early phase trials that are available.



## What are the different treatment types?

### Chemotherapy

Chemotherapy is the most common treatment option used and can be given as a single drug, multiple drugs, or in combination with radiotherapy, surgery, or immunotherapy. It can be given by mouth (orally) or intravenously (through a vein).

Currently, no specific chemotherapy combination has been shown to be the best for initial treatment of relapsed neuroblastoma [1]. For disease that has recurred in more than one place or has returned distant to where it first started (metastatic relapse), a patient will be treated with chemotherapy that might be different to what they received when first diagnosed.

### Molecular radiotherapy

Molecular radiotherapy uses 'radioactively-labelled' medicines that travel to sites of neuroblastoma around the body and delivers radiation to these areas of disease. This includes mIBG therapy and lutetium dotatate (LuDO) therapy.

### Immunotherapy

Immunotherapy uses the patient's own immune system to recognise and attach to specific molecules produced by cancer cells to alter their behaviour. A patient's neuroblastoma cells may have to be tested to see if they have specific changes that can be targeted by immunotherapy drugs because not everyone's cancer cells will have the same genetic changes.

## What are the different types of research trials/studies?

### Early phase trials

An early phase clinical trial (called phase 1 or 2 trial) is usually a small trial recruiting only a few patients and is often open to children with any type of cancer. These trials look at how a new treatment works in the body, what doses are required, and potential side effects.

It is important to remember that these are often experimental trials so any new drugs may not have been proven to work for children with neuroblastoma and may therefore not always help your child. These trials are usually open in a limited number of centres and you may be required to travel to these centres in order to participate.

### Epidemiological and biological studies

These studies collect clinical and biological information to help us understand how neuroblastoma can start and spread, and therefore what treatment strategies could work best. Usually, these studies involve giving permission to use anonymised information about your child and their neuroblastoma.

Blood and bone marrow samples can increase our understanding of progression and relapse to identify children at greatest risk and matching them to the most effective treatment. Sometimes, extra blood tests may be requested at a time when your child is scheduled to have a routine blood test. Samples will not be taken for research without consent [3].

### Neuroblastoma Epidemiological Study

This study is open in many hospitals and is looking at clinical and biological factors associated with relapsed neuroblastoma. All patients in the UK who are less than 40 years of age and have relapsed or refractory disease will be recruited to this study. Please speak to your doctor if you do not want your child to be entered [2].

### Stratified Medicine Paediatrics (SMPaeds)

This is a national molecular tumour profiling study that looks at genetic changes in children with relapsed or refractory cancer. Tumours at relapse are analysed to determine if there is a treatment that can be given to target a particular genetic error, either as part of a new trial called eSMART, or within other trials of targeted drugs that may be available [4].

## Clinical trials/studies currently open to patients

Details of trials and studies included in this factsheet are correct at the time of print. Your child's doctor will be able to give you the most up to date information.

### VERITAS

**Location:** *The Royal Marsden Hospital London, Royal Aberdeen Children's Hospital, Bristol Royal Hospital for Children, Royal Hospital for Children Glasgow and, Royal Manchester Children's Hospital*

This phase 2 study compares two treatment strategies for metastatic neuroblastoma patients who have responded poorly to initial chemotherapy.

It looks at whether giving high-dose treatment with molecular radiotherapy and topotecan, followed by autologous stem cell transplant (Arm A), or giving high-dose thiotepa followed by autologous stem cell transplant (Arm B) improves the response to treatment in refractory neuroblastoma.

Patients will need to have a mIBG scan which shows active neuroblastoma disease at diagnosis and at the end of induction treatment. The molecular radiotherapy uses <sup>131</sup>I-mIBG. This molecule attaches to neuroblastoma cells which are active on the mIBG scan and delivers high-dose radiotherapy to them, thereby killing them.

### Y-mAbs GM-CSF + naxitamab

**Location:** *Royal Hospital for Children Glasgow, Leeds Children's Hospital, The Royal Marsden Hospital London and, Southampton Children's Hospital*

This phase 2 study is appropriate for patients with refractory and relapsed neuroblastoma with bone or bone marrow disease. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a white blood cell factor which stimulates the body to make more immune cells like granulocytes and macrophages. Naxitamab is a type of monoclonal anti-GD2 antibody; a form of immunotherapy that targets a molecule on neuroblastoma cells called GD2.

This trial will look at whether GM-CSF and naxitamab given every four weeks can work together to make the body produce an immune reaction to destroy neuroblastoma cells in the bone or bone marrow, how the drug doses change in the body, and assess the side effects of treatment. Treatment can be given for up to a total of 101 weeks. How well your child is responding to treatment will be assessed using mIBG or PET scans.

### eSMART

**Location:** *Birmingham Children's Hospital, The Royal Marsden Hospital London, Manchester Children's Hospital, The Great North Children's Hospital Newcastle-upon-Tyne and, Great Ormond Street Hospital (GOSH) London*

Cancer cells can have multiple gene changes, some of which may be targetable with future drugs. Tumour profiling helps identify targetable cancer gene changes and pathways.

ESMART is a 'basket trial' which will use the tumour profiling information from your child's tumour to better inform doctors about which cancer pathways to target and therefore which treatment to apply. Multiple arms of treatment will be open to decide which option shows the most promising results.

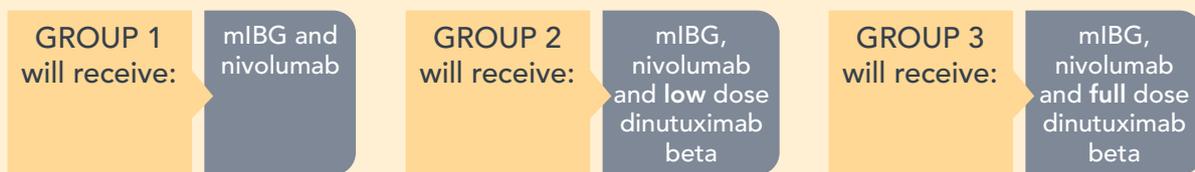
## MiNivAN

**Location:** *University College London Hospital (UCLH) and Southampton Children's Hospital*

This phase 1 study is looking at three treatments: mIBG molecular radiotherapy, nivolumab, and dinutuximab beta. Nivolumab is an anti-PD1 (anti-programmed cell death protein 1) antibody (a type of immunotherapy) that stimulates the body to fight cancer cells.

- mIBG treatment is molecular radiotherapy which is delivered in London twice and two weeks apart.
- nivolumab and dinutuximab beta is delivered in Southampton two weeks after the second mIBG treatment (two weekly for nivolumab, and six weekly for dinutuximab beta).

All three treatments are delivered intravenously. There are three groups in this study and patients will be grouped based on when they take part in the study:



The MiNivAN study is looking to see how well the combination of treatments work, how acceptable the treatment is, and what the side effects are.

## New approaches to neuroblastoma therapy consortium (NANT)-sponsored lorlatinib

**Location:** *The Royal Marsden Hospital London*

This phase 1 study is appropriate for patients with refractory and relapsed neuroblastoma who have a mutation in a gene called anaplastic lymphoma kinase (ALK-mutation) in their tumour. Around 10% of children with neuroblastoma have ALK-mutation in their tumour at diagnosis, but the incidence is higher at relapse. ALK-mutations (or other genetic abnormalities of ALK including ALK amplification) can be targeted by ALK-inhibitor drugs such as lorlatinib.

Lorlatinib is a tablet that is given daily during a 28-day cycle, but a liquid formulation is being developed. Once a recommended dose is found, intravenous chemotherapy (cyclophosphamide and topotecan) will be given on days 1-5 of the cycle. This trial will look at finding the right dose of lorlatinib, understanding how it works in the body, its side effects, and how well the tumours respond to treatment.

## Crizotinib (CRISP)

**Location:** *The Royal Marsden Hospital London and Leeds Children's Hospital*

This phase 1 trial is for patients with relapsed/refractory cancers that have an ALK-mutation or other genetic abnormality of ALK. Crizotinib is an ALK-inhibitor which could target neuroblastoma cells with ALK-genetic abnormalities. Crizotinib is given orally in combination with temsirolimus (a drug that blocks an overactive protein in cancer cells). This study is looking to find the right dose of crizotinib, understand how it works in the body and its side effects.

## Ongoing research

New studies to treat neuroblastoma and other relapsed/refractory cancers are continuously in development. The process of opening new studies is long and complex, and it is not possible to say for certain when new studies will open or whether your child might be eligible until these studies are finalised and open for recruitment.

To find out more about taking part in any trials please refer to the websites below:

- [www.cancerresearchuk.org/about-cancer/find-a-clinical-trial](http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial)
- [www.clinicaltrials.gov/ct2/home](http://www.clinicaltrials.gov/ct2/home)
- [www.itcc-consortium.org/trials/solid-tumor](http://www.itcc-consortium.org/trials/solid-tumor)
- [www.ecmcnetwork.org.uk](http://www.ecmcnetwork.org.uk)

## Seeking a second opinion

Your child's case will be discussed at the MDT (multi-disciplinary team) meetings in your main hospital so, in most cases, other consultants will be helping to form the best plan for treatment. However, you may decide that you would like a second opinion and may find this reassuring.

You can ask for a second opinion from another doctor in your main hospital or, if you would like your child's case to be reviewed in another hospital, you can ask your consultant to refer you for a second opinion to another principal treatment centre. This is likely to involve sending scans and biopsy results prior to any meeting. Your doctor will support you to do this.

If you would like your child's case to be reviewed by a team at a private hospital or by a doctor outside of the UK you can request a summary of your child's case and copies of scans for you to send to them. Some hospitals may charge you for this.

## Going abroad for treatment

Finding out that your child's cancer has not responded to treatment is very distressing. We are committed to improving outcomes for children with refractory or relapsed neuroblastoma in the UK, through multiple open clinical trials and the development of additional trials. If you are considering having treatment abroad for your child, it may be helpful to ask your doctor whether:

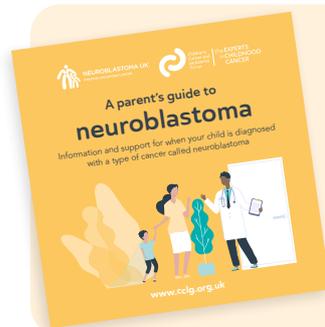
- any pre-clinical evidence exists for the treatment that is relevant to neuroblastoma, for example, in laboratory studies using cells in culture or animal models
- there have been other studies of similar drugs trialled in neuroblastoma
- the drug has been trialled in adults and if so, what side effects were seen
- it will involve being away from home for a long time

A number of US groups are investigating giving children further treatment, such as a bivalent vaccine and difluoromethylornithine (DFMO) at the end of standard treatment, to further reduce the chances of relapse. The outcomes reported to date, after receiving either a bivalent vaccine or DFMO, are broadly similar to those reported by SIOPEX (the European Neuroblastoma Specialist Group) in patients who have responded well to standard high-risk treatment [5].

Both of these treatments are being tested in a non-randomised way, in that all children receive either the vaccine or DFMO. This makes it impossible to know what additional impact the DFMO and/or vaccine treatment is having on the outcome. At present, the vaccine and DFMO studies are not designed to answer the important question of whether DFMO or the vaccine prevents a relapse occurring in some children.

Your child's doctor is the only one who knows your child's individual condition and will be in the best position to tell you about developments and discoveries in cancer medicine that could help your child - they will be more than happy to explain anything to you.

Don't worry that your child's doctor will be offended if you turn up with a list of questions about things you have found out online. They will take you seriously and give you honest, balanced advice based on your child's individual situation.



The CCLG booklet  
'A parent's guide to  
neuroblastoma'  
is available **FREE** of charge  
from your child's hospital

All CCLG booklets and  
leaflets can be downloaded  
or ordered from our website:

**[www.cclg.org.uk/  
publications](http://www.cclg.org.uk/publications)**

## References

1. Herd F, et al. A systematic review of re-induction chemotherapy for children with relapsed high-risk neuroblastoma. *Eur J Cancer* 2019; 111:50-58. Doi: 10.1016
2. Basta et al. Clinical and Biological factors associated with relapse and length of survival following relapse in UK neuroblastomas. IRAS ID 202736. Further information about the study and a study guide for families can be found on the Solving Kids' Cancer and Neuroblastoma UK websites [www.solvingkidscancer.org.uk/News/investigating-clinical-and-biological-factors-associated-with-relapse](http://www.solvingkidscancer.org.uk/News/investigating-clinical-and-biological-factors-associated-with-relapse) and [www.neuroblastoma.org.uk/newcastle-epidemiology-study](http://www.neuroblastoma.org.uk/newcastle-epidemiology-study)
3. Viprey et al, Detection of mRNA in bone marrow and blood by RT-qPCR predicts event-free and overall survival in children with stage 4 neuroblastoma at diagnosis: a SIOPEX Molecular Monitoring Group study. *Journal of Clinical Oncology*, 32;1074-83, 2014. CCLG biological study number 2019 BS 05. Contact Sue Burchill [medccrg@leeds.ac.uk](mailto:medccrg@leeds.ac.uk).
4. Cancer Research UK. Stratified Medicine Paediatrics (SMPaeds) - a study looking at genetic changes in children's cancer. ISRCTN21731605 <https://doi.org/10.1186/ISRCTN21731605>. [Smpaeds@trials.bham.ac.uk](mailto:Smpaeds@trials.bham.ac.uk)
5. Children's Cancer and Leukaemia Group. Outcome after high-risk neuroblastoma treatment in Europe. [www.cclg.org.uk/keeping-you-informed/outcome-after-high-risk-neuroblastoma-treatment-in-europe](http://www.cclg.org.uk/keeping-you-informed/outcome-after-high-risk-neuroblastoma-treatment-in-europe). [Last accessed March 2020]



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Group

the EXPERTS  
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CANCER

## Children's Cancer and Leukaemia Group (CCLG) is a leading national charity and expert voice for all childhood cancers.

Each week in the UK and Ireland, more than 30 children are diagnosed with cancer. Our network of dedicated professional members work together in treatment, care and research to help shape a future where all children with cancer survive and live happy, healthy and independent lives.

We fund and support innovative world-class research and collaborate, both nationally and internationally, to drive forward improvements in childhood cancer. Our award-winning information resources help lessen the anxiety, stress and loneliness commonly felt by families, giving support throughout the cancer journey.

Our work is funded by donations. If you would like to help, text 'CCLG' to 70300 to donate £3. This will cost £3 plus a standard rate message.

We are grateful to all those who have contributed to this publication. We make every effort to ensure that information is accurate and up to date at the time of printing. CCLG does not accept responsibility for information provided by third parties, including those referred to or signposted to in the publication. Information in this publication should be used to supplement appropriate professional or other advice specific to your circumstances.

CCLG publications on a variety of topics related to children's cancer are available to order or download free of charge from our website. If you have any comments on this booklet, please contact us at [publications@cclg.org.uk](mailto:publications@cclg.org.uk).

This version has been reviewed and updated by Professor Deb Tweddle (Professor of Paediatric Oncology, Great North Children's Hospital Newcastle and Neuroblastoma UK Medical Trustee), Dr Tasnim Arif (Paediatric Oncologist, Great North Children's Hospital, Newcastle) and Dr Lynley Marshall (Consultant & Paediatric Clinical Research Lead, The Royal Marsden & The Institute of Cancer Research, London) on behalf of the CCLG Neuroblastoma Special Interest Group, the NCRI Children's Clinical Studies Group Neuroblastoma subgroup and the NCRI Children's Novel Agents subgroup on behalf of Neuroblastoma UK and in conjunction with the CCLG Information Advisory Group, comprising multiprofessional experts in the field of children's cancer.

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