The Children & Young People's Cancer Association

Treatment for relapsed or refractory neuroblastoma

Information for parents, carers and families of children whose neuroblastoma has come back or not responded to treatment

The purpose of this factsheet is to help you find out about what treatment options may be available and the kinds of support which may help you to decide what is right for your child.

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.

How you might feel

Being told your child's neuroblastoma has come back or not gone away with treatment can come as a huge shock. Lots of emotions from the first diagnosis may have come flooding back. It can also bring new or different feelings of fear and devastation, along with worries about the unknown and decisions you may need to make. It is common to feel scared and angry or even feel numb. However, you have something now that you didn't have before - experience and knowledge. You know a lot about what to expect and how to cope. Whilst this doesn't make the news any easier to deal with, remembering this may help you feel stronger and more resilient, putting you in a better position to navigate the treatment ahead. The CCLG booklet 'When your child's cancer comes back or doesn't respond to initial treatment' has information and support including coping strategies for you and your family.

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 certain treatment.

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.

Progressive

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

Currently, there is no standard treatment protocol for initial treatment of relapsed or refractory neuroblastoma[1]. However, results from recent trials (BEACON[2]) suggest that combining bevacizumab with irinotecan and temozolomide (BIT) should be the first option, unless the tumour has an ALK mutation or amplification in which case an ALK inhibitor combined with chemotherapy[3] should be used.

Studies in the US[4,5] have shown that combining immunotherapy (dinutuximab) with chemotherapy are also effective. Further research is continuing into these combinations and the BEACON2 trial will compare BIT with chemoimmunotherapy for relapsed patients. The BEACON2 trial will also test new treatments for patients who have relapsed more than once.

In all cases, treatment will be tailored to each child's specific needs, taking into account the genetics and spread of the disease as well as previous treatment and the child's overall health.

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).

For disease that has recurred in more than one place or has returned distant to where it first started (metastatic relapse), a patient may 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.

Targeted therapies

Targeted therapies are drugs which have been developed to target and block specific genetic or biological pathways or markers which are needed for a tumour to grow. In neuroblastoma treatment, targeted therapies include ALK inhibitors and bevacizumab.

ALK inhibitors work by blocking signals that tell cancer cells to divide so stops them from growing. These drugs, usually taken orally, can be used for tumours which have an ALK mutation in their biological make-up.

Bevacizumab targets a protein which helps cancers to grow blood vessels. All cancers need a blood supply to be able to survive and grow. Bevacizumab blocks this protein with the aim of starving the cancer cells of their blood supply to reduce the tumour growth.

Research into targeted therapies is ongoing and scientists continue to look for genetic markers which could provide targets for new treatments.

Eflornithine (Difluoromethylornithine or DFMO)

Eflornithine (Difluoromethylornithine or DFMO) is an oral drug, which has been investigated for its effects in neuroblastoma. Since this drug was approved in the US for use for patients with high-risk neuroblastoma who have had a response to prior treatment including anti-GD2 immunotherapy, it has been made available to UK patients under a temporary scheme from the pharmaceutical company, Norgine, while NHS funding bodies review whether it can be provided by the NHS in the long term. Therefore, the UK Neuroblastoma Clinical Trials Group and CCLG Neuroblastoma Special Interest Group suggest that treatment with DFMO for high-risk neuroblastoma patients is considered and discussed with patients and families who are completing frontline therapy or relapse therapy[6]. More information can be found on our website here **www.cclg.org.uk/neuroblastoma**

What are the different types of research trials/studies?

Early phase trials (phase 1 and phase 2)

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 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 in order to participate.

Phase 3 trials

If the results from phase 1 and phase 2 trials suggest a drug or treatment is both safe and effective, it will then be compared with the current or 'standard' treatment in a phase 3 trial. These trials involve large numbers of patients and usually run for much longer than phase 1 and 2 trials. As the number of children with cancer is relatively small, there is often strong international collaboration with overseas research organisations so children across many countries can take part in a clinical trial. Your child may have had initial treatment as part of a phase 3 trial.

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.

When you agree for your child's tumour samples to be used for reserach, they are sent to the VIVO Biobank in Newcastle. The biobank stores the samples so that reserachers can use them. Having a single resource for samples means that a wide scope of research can be done, that could hopefully result in better outcomes in the future. To find out more about how samples are used here see **www.cclg.org.uk/magazine-articles/donating-cancer-samples-research**

How do we decide which treatment is best?

When your child was first diagnosed, a sample of their tumour was tested to look at its genetics and biological make-up. Another biopsy is usually taken at relapse to do these tests again because sometimes tumour biology changes. This can be useful to find any new markers which may be able to be targeted with treatment. There are also experimental studies looking at tissue and trying to identify targets for treatment.

Some neuroblastoma cells have a gene mutation called *ALK* (anaplastic lymphoma kinase). Around 15%[7,9] of neuroblastoma tumours show this mutated gene at diagnosis. This increases to about 20-25%[7,8] at relapse.

Currently, all children and young people with cancer in England are offered a Whole Genome Sequencing (WGS) test. This test is not yet routinely available in Wales, Scotland and Northern Ireland. The test compares the DNA from tumour cells to normal cells to look for tumour related mutations. By studying normal cell DNA, it is possible to look for genes linked to inherited cancers. This can potentially help doctors to understand more about your child's diagnosis and treatment. If your child has not already had this test, your doctor will discuss it with you.

The UK currently offers national and international trials and studies for relapsed and refractory neuroblastoma. There are also 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 if any trials may be 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

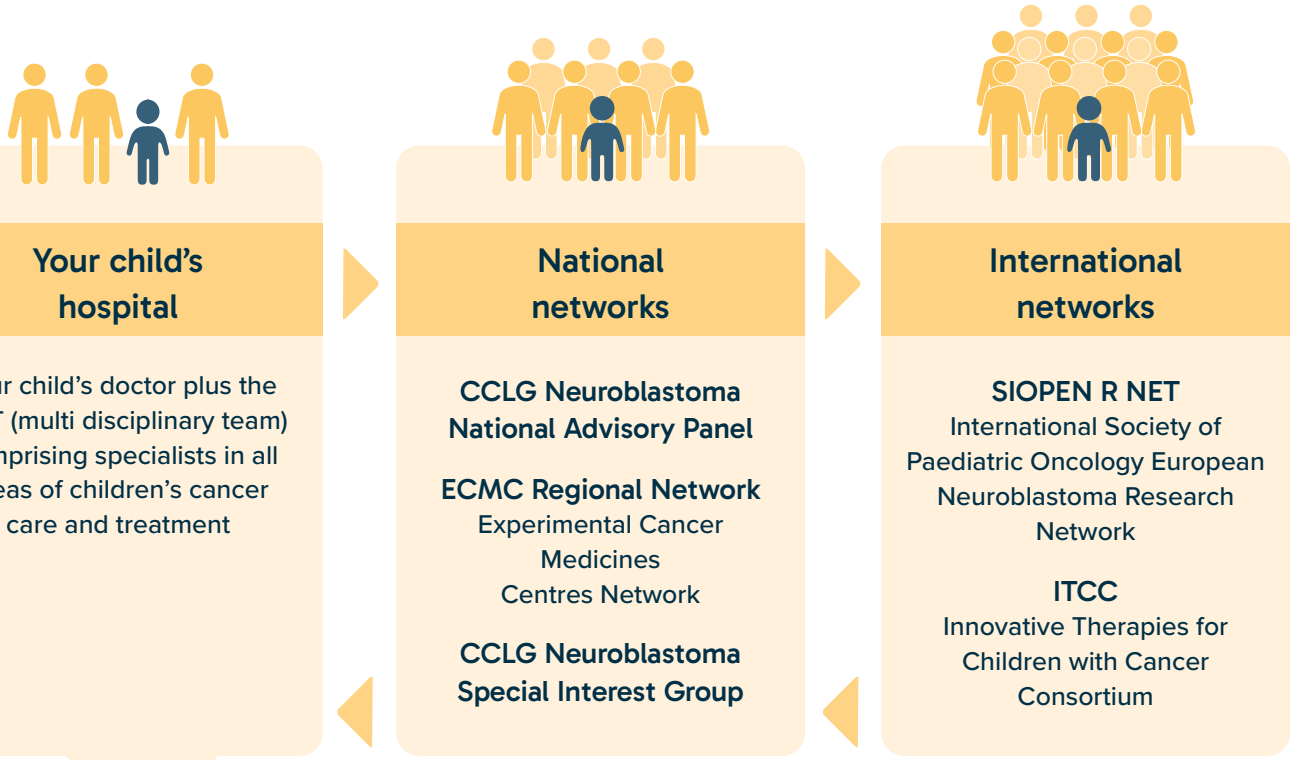
The Neuroblastoma National Advisory Panel is made up of experts in treating neuroblastoma from across the UK. Panel members are often members of international networks and will sometimes ask for advice from experts around the world. The panel meets regularly and individual cases are presented anonymously 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 or 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.

Professionals involved in your child's treatment planning



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.

Ongoing research

New studies to treat neuroblastoma and other relapsed or 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**
- **www.clinicaltrials.gov/ct2/home**

Going outside the UK for treatment

Finding out that your child's cancer has not responded to treatment is very distressing. Researchers and healthcare professionals 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

Be aware that not all treatments available abroad have been tested in a non-randomised way. This makes it very difficult to know what impact a treatment may have on outcomes. Statistics may also not take into account the different treatment paths that children have followed before entering a trial.

Making a decision

There is not one single treatment path for every child with relapsed or refractory neuroblastoma, so making decisions about treatment can be overwhelming. You may want to be involved in making these decisions or you may want your medical team to make them for you. It is up to you how much you want to be involved. It is important to be honest with your child's team about how much you would like to be involved and to feel comfortable asking all the questions you need. You may change how you feel about your involvement. There is no right or wrong answer about what is expected.

The Redmapp website has been created in partnership with parents. It includes lots of support for parents and families making decisions about treatment for relapsed or refractory neuroblastoma. It has helpful suggestions on how to work in partnership when making decisions, including a downloadable list of questions to support conversations. There are videos from professionals covering terminology, emotional impact and working with your medical team to help support your understanding and decision making. It also includes videos from parents who have been in a similar situation.

Visit **www.redmapp.org.uk** for more information.

Your child's doctor knows your child's individual condition well 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.

If you are unhappy or have concerns about the care being given to your child it is important that you find support. You can talk to your outreach nurse (sometimes called keyworker, clinical nurse specialist or POONS) or the Patient Advice and Liaison Service (PALS) at your hospital. See more information here: **www.nhs.uk/nhs-services/hospitals/what-is-pals-patient-advice-and-liaison-service**

Further help and support

CCLG: The Children & Young People's Cancer Association Information on childhood cancer, funding of research, and a full range of award-winning patient information resources, including Contact magazine for families of children with cancer. **www.cclg.org.uk**

Download or order free of charge 'A guide to neuroblastoma' and 'When your child's cancer comes back' **www.cclg.org.uk/publications**

Redmapp Website developed to support parents when making treatment decisions for their child with relapsed or refractory neuroblastoma in the UK. **www.redmapp.org.uk**

National Neuroblastoma Advisory Panel video Watch Dr Ramya Ramanujachar talk about how the panel works. From the Redmapp website **https://youtu.be/QBuvDODIStw**

Neuroblastoma terminology video Watch Professor Juliet Gray explain some commonly used terminology. From the Redmapp website. **www.youtube.com/watch?v=cmm_5SsCy08**

Experimental Cancer Medicine Centres (ECMC) Regional network of researchers, scientists and clinicians working in early phase trials. **www.ecmcnetwork.org.uk**

Innovative Therapies for Children and Adolescents with Cancer (ITCC) European group working to improve access to new drugs for children and adolescents. **www.itcc-consortium.org**

SIOPEN Brings together clinicians from across Europe and beyond to improve the outcomes for patients with neuroblastoma. International collaboration is vital because it ensures there are enough patients to take part in clinical studies. This allows us to learn more about the condition and improve treatments. **www.siopen.org**

Teenage and Young Adult Research (TYAR) Information for teenagers and young adults about clinical trials, biobanking and genomics. **www.tyar.org**

Solving Kids' Cancer UK

Solving Kids' Cancer UK is a dedicated children's cancer charity, with a particular focus on neuroblastoma.

They strive for better outcomes for children affected by cancer both now and in the future under three key pillars of research, support and awareness. SKC are passionate about speeding up pioneering clinical research to save lives and improve outcomes. Their Family Support Services provide emotional, practical and financial support to families across the UK. Together with partners, they advocate for greater and better access to treatments that will improve survival and quality of life for children with cancer.

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Registered charity England and Wales (1135601) and Scotland (SC045094)

NEUROBLASTOMA UK
FIGHTING CHILDHOOD CANCER

Neuroblastoma UK is a charity dedicated to funding research into causes and treatment of neuroblastoma.

It has been dedicated to funding research to improve the understanding of neuroblastoma and move treatment forwards, for over 40 years. In addition to awarding grants to researchers, it has facilitated communications and collaboration between UK and international researchers, through its well-attended biennial research symposia. NBUK works closely with other organisations, such as Solving Kids' Cancer and CCLG, to raise awareness and campaign for better funding and treatment of childhood cancer.

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Trusted Information Creator
Patient Information Forum

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We are CCLG: The Children & Young People's Cancer Association, a charity dedicated to creating a brighter future for children and young people with cancer. Powered by expertise, we unite the children and young people's cancer community, driving collective action and progress.

We fund and lead pioneering research, provide trusted information and guidance for children and young people with cancer and their families, and bring together professionals to improve treatment, care, and outcomes.

Our expert information helps children and young people and everyone supporting them, to navigate the challenges of cancer and its impact, offering reassurance and clarity when it's needed most.

We make every effort to ensure that this information is accurate and up to date at the time of printing. Information in this publication should be used to supplement appropriate professional or other advice specific to your circumstances.

Our work is funded by donations. If you would like to help, visit **www.cclg.org.uk/donate** or text '**CCLG**' to **70085** to donate **£3.** You may be charged for one text message at your network's standard or charity rate. CCLG will receive 100% of your donation.

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