Gilteritinib for Acute Myeloid Leukaemia (AML)

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

Gilteritinib (Xospata, Astellas Pharma Europe B.V) is a highly specific, second-generation tyrosine kinase inhibitor which has been developed for the treatment of patients with acute myeloid leukaemia (AML) who have an FMS-like tyrosine kinase 3 (FLT3) mutation.

For more information, talk to your haematologist, clinical nurse specialist or hospital pharmacist.

This booklet was put together by our Patient Information Writer, Isabelle Leach. It was then peer reviewed by Dr Steve Knapper. We are also grateful to Katherine Murray for their contribution as a patient reviewer.

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

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In this booklet

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

What is gilteritinib?

Gilteritinib (Xospata, Astellas Pharma Europe B.V) is a highly specific, second-generation tyrosine kinase inhibitor which has been developed for the treatment of patients with AML who have an FMS-like tyrosine kinase 3 (FLT3) mutation.

Tyrosine kinase enzymes are catalysts in cells which control various functions. Tyrosine kinase inhibitors are cancer drugs which can switch 'off' tyrosine kinase enzymes that are permanently active due to a mutation.

Gilteritinib is particularly active against FLT3, a tyrosine kinase that is frequently mutated in AML which means it is highly specific. It is referred to as second-generation because it has been developed by building upon a group of drugs already in use.

What are FLT3 mutations?

FLT3 mutations are among the most common mutations in patients with AML.

FLT3 mutations can be divided into two defined subtypes: the FLT3 internal tandem duplication mutation or FLT3-ITD and the FLT3 mutation in the tyrosine kinase domain or FLT3-TKD. About 75% of FLT3 mutations are the ITD subtype, which is associated with poorer outcomes.

Approximately 30% of patients with AML have a FLT3 mutation in their cells, which makes these cells multiply and prevents their natural death. Having either the FLT3-ITD or FLT3-TKD gene mutation increases the risk of AML relapsing or becoming refractory. A relapse occurs when the leukaemia initially responds to treatment but after six months or more, the leukaemia recurs. Whereas with refractory leukaemia, the treatment does not result in a remission, but the condition may be stable.

Who receives gilteritinib?

Gilteritinib is given as a single drug for the treatment of the following groups of patients who have relapsed or have refractory AML with a FLT3 gene mutation, which is confirmed by a validated test.

Adults

NICE has approved gilteritinib use for adult patients who have relapsed or refractory AML with confirmed FLT3-ITD or FLT3-TKD gene mutations. There are generally two groups that fall into this:

- Younger, fitter, suitable for a stem cell transplant. If they respond well, they will get an allogeneic stem cell transplant.
- Older, frailer patients who are not suitable for a transplant. They will receive gilteritinib therapy for as long as it is providing some benefit before moving onto palliative care treatments.

Children

There is currently no data available on the efficacy and safety of gilteritinib in children below 18 years of age, but trials are ongoing. However, patients who are six months to less than 18 years of age with one of the following:

- Relapsed or refractory AML and a FLT3-ITD mutation

OR

- Newly-diagnosed AML with a FLT3-ITD mutation

can receive gilteritinib via a paediatric investigation plan.

A paediatric investigation plan is an agreement between the European Medicines Agency (EMA) and the pharmaceutical company for drugs that are still under investigation in clinical trials, but are considered to be of benefit to children.

Patients should receive gilteritinib until it is

Who receives gilteritinib? (cont.)

no longer of benefit to them or they experience unacceptable side effects. As the response to gilteritinib can be delayed, treatment may initially need to be continued for up to six months to allow time for a clinical response to occur.

If you would like more information about adult or childhood acute myeloid leukaemia (AML) you can download our booklets from our website at **www.leukaemiacare.org.uk**.

How is gilteritinib given?

Gilteritinib can be given as a treatment on its own and is available as tablets to be taken by mouth once daily. It can be ingested with or without food and should be taken at approximately the same time every day. When doses are missed or not taken at the right time, the dose should be taken as soon as possible on the same day. The normal schedule can be resumed the following day. In the event of vomiting following taking the daily dose, patients should not take another dose but should return to the normal schedule the following day.

Blood tests assessing liver and kidney function, as well as the level of creatine phosphokinase, must be performed prior to starting treatment with gilteritinib, on day 15 of the first treatment cycle, and monthly thereafter for the duration of treatment. High levels of creatine phosphokinase may indicate muscle tissue, heart or brain injury.

In addition to the blood tests, an electrocardiogram (ECG) needs to be completed before starting gilteritinib treatment, on day 8 and day 15 of the first cycle of treatment, and before starting the following three months of treatment.

You will be required to read and sign a consent form summarising the receipt of verbal and written information in relation to your AML treatment and potential side effects of gilteritinib.

What are the side effects of gilteritinib?

As is common with the majority of drugs, gilteritinib may cause side effects. The most common side effects are shown below.

Common side effects

- Dizziness
- Cough
- Shortness of breath
- Oedema, i.e. fluid retention in the body, most commonly the legs
- Abnormal physical weakness or lack of energy
- Nausea, diarrhoea or constipation
- Fatigue
- Muscle and joint pain
- Low blood pressure
- Increased levels of the liver and muscle enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and creatine phosphokinase)

It is important to report side effects to your doctor or nurse so that they can be managed and treated effectively. This may include reducing the dosage to help alleviate some of the side effects you are experiencing.

Fertility, pregnancy and breastfeeding

Fertility and contraception

Pregnancy testing seven days prior to initiating treatment with gilteritinib is recommended for women who potentially could be pregnant. Additionally, effective contraception (methods that result in less than 1% pregnancy rates) is recommended during treatment and for six

months after treatment.

Examples of effective contraceptives include:

- Contraceptive implant
- Intrauterine system, or IUS
- Intrauterine device, or IUD, also called the coil
- Female sterilisation
- Male sterilisation or vasectomy

The effect of gilteritinib on the effectiveness of hormonal contraceptives is unknown, and therefore women using hormonal contraceptives should add a barrier method of contraception (such as a male or female condom) if they or their male partner are undergoing treatment. Men are advised to use effective contraception while receiving treatment and for four months following the last dose.

Pregnancy

As it is possible that gilteritinib can harm the baby when taken by pregnant women, it is not recommended during pregnancy and in women who potentially could be pregnant from not using effective contraception.

Breastfeeding

Because of the potential harm to breastfeeding children, breastfeeding should be discontinued during treatment with gilteritinib, and for at least two months after the last dose.

What happens if gilteritinib doesn't work for me?

If your AML has not gone into remission following your treatment with gilteritinib, or you have relapsed after achieving remission with gilteritinib, your consultant will discuss what other treatments are available for you, and to help you decide on the next course of action. Knowledge of your type of AML, your physical condition and any new treatments which may help you will guide your consultant's next treatment.

Patients with AML and a FLT3-ITD or FLT3-TKD gene mutation are prone to being refractory to treatment (i.e. a relapse before treatment course is finished, even though there was an initial response) or relapsing after remission. This is one of the main reasons that second-generation tyrosine kinase inhibitors were developed.

However, as is the case with other FLT3 inhibitors, patients with AML may not respond to treatment to gilteritinib, or may develop resistance to it after an initial response. In patients whose AML progresses despite treatment, new mutations have been observed, and these mutations are linked to the resistance of the patients to the FLT3 inhibitors.

Studies of intensive chemotherapy or less toxic drugs such as azacitidine or low dose cytarabine combined with gilteritinib are underway and results to date are encouraging. Gilteritinib is also being studied in combination with intensive chemotherapy in patients with newly-diagnosed AML who have FLT3 mutations.

Otherwise, patients may sometimes be considered for other

intensive chemotherapy if fit enough, or they may be considered for entry into a clinical trial (including other possible FLT3 inhibitors or novel therapies).

In any event, including having no further treatment, the best supportive care which includes blood product transfusions, antibiotics and granulocyte colony-stimulating factor (GCSF) is always available. Granulocyte colony-stimulating factor is a blood growth factor that stimulates the bone marrow to produce more of the white blood cells called neutrophils which fight infections.

Glossary

Acute leukaemia

Leukaemia which progresses rapidly and is generally aggressive. There are two main types: acute lymphoblastic leukaemia and acute myeloid leukaemia.

Acute lymphoblastic leukaemia (ALL)

A leukaemia in which lymphocytes start multiplying uncontrollably in the bone marrow, resulting in high numbers of abnormal, immature lymphocytes. Lymphocytes are a type of white blood cell involved in the immune response.

Acute myeloid leukaemia (AML)

A rapid and aggressive cancer of the myeloid cells in the bone marrow.

Alanine aminotransferase (ALT)

An enzyme found mainly in the liver and kidney. Elevated levels of ALT indicate liver damage from hepatitis, infection, cirrhosis or liver cancer.

Alkaline phosphatase (ALP)

An enzyme found in large amounts in the liver and bones. Smaller amounts are found in the intestines and in the placenta of pregnant women. Each of the body parts makes a different form of ALP. Increased levels of ALP generally indicate liver or bone damage.

Amino acids

Organic molecules which are the building blocks for making proteins.

Antibiotic

A drug used to treat or prevent bacterial infections.

Aspartate aminotransferase (AST)

An enzyme found primarily in the liver and heart, but also in many other tissues including the muscle, red blood cells, pancreas,

kidney and brain. Damage to these organs releases this enzyme, resulting in elevated AST levels in the blood. Serum levels of AST generally match the extent of damage.

Barrier contraception

A contraceptive method acting as a barrier to keep the sperm from fertilising the woman's egg. Examples include the male and female condoms, the diaphragm and the cap. Some barrier methods also protect against sexually transmitted infections.

Blood cancer

A cancer of blood cells from the bone marrow or lymphatic system. There are three main types of blood cancer:

- Leukaemia begins in the bone marrow and is classified according to the type of blood cell it affects (either myeloid or lymphoid) and whether it grows quickly (acute) or slowly (chronic).
- Lymphoma starts in the lymphocyte white blood cells within the lymphatic system.
- Myeloma is a cancer of the plasma cells and starts in the bone marrow. Plasma cells are a type of white blood cell that makes antibodies.

Blood cells

Cells present in the blood and bone marrow which include red blood cells, white blood cells and platelets. These three types of blood cell make up 45% of the blood volume, with the remaining 55% being plasma, the liquid component of blood.

Chemoimmunotherapy

Chemotherapy to which an immunotherapy drug has been added.

Chemotherapy

Drugs that work in different ways to stop the growth of cancer cells,

Glossary (cont.)

either by killing the cells or by stopping them from dividing.

Chromosomes

Thread-like structures which carry the genes, and are located in the nuclei of every cell in the body. There are 46 chromosomes (23 pairs) in humans.

Complete haematological remission

Complete remission has occurred when:

- Blood cell counts have returned to normal
- Less than 5% of abnormal, leukaemia cells are still present in the bone marrow

Complete molecular remission

Complete remission with no leukaemia cells anywhere in the body (i.e. no minimal residual disease).

Creatine phosphokinase

An enzyme present in several body tissues, but mainly the muscles and the brain that is required for muscle and brain function. High levels of creatine phosphokinase generally indicates muscle or heart muscle injury.

Cytarabine

An antimetabolite drug which works by disrupting the DNA of cancer cells, thereby slowing or stopping their growth.

DNA (deoxyribonucleic acid)

Thread-like chain of amino acids found in the nucleus of each cell in the body which carries genetic instructions used in the growth, development and functioning of the individual's cells.

DNA methyl-transferase 3A (DNMT3A)

An enzyme that adds a methyl group to various parts of the DNA to modify information passed on by the parent to the child such as cellular

diversity and embryonic development.

Electrocardiogram (ECG)

A test that measures the electrical activity of the heartbeat. With each beat, an electrical impulse (or "wave") travels through the heart, causing the muscle to squeeze and pump blood from the heart. An ECG will show any heart abnormalities.

Enzyme

The substance produced by the body to help bring about a specific biochemical reaction.

Fatigue

Tiredness and weakness rendering the patient unable to work or perform usual activities.

First-generation drug

The original drug developed within a new class of drug.

FLT3 (FMS-like tyrosine kinase 3) mutation

The mutation in a gene called FLT3 which is responsible for AML leukaemia.

Genes

Genes are made up of DNA which stores the genetic information required to make human proteins.

Granulocytes

A group of white blood cells, which have granular bodies in their cytoplasm. They include the neutrophils, eosinophils and basophils white blood cells, all of which protect the body from bacteria, allergens and inflammation.

Hypomethylating agents

A drug that inhibits the DNA methyltransferase enzyme, which prevents DNA from producing the proteins required for the normal development of AML cells.

Glossary (cont.)

Leukaemia

A group of cancers that usually begin in the bone marrow and result in high numbers of abnormal blood cells. These cells are not fully developed and are called blasts or leukaemia cells. Depending on the type of blood cell involved, there are different types of leukaemia with varying characteristics, such as being acute (develop quickly) or chronic (develop slowly).

Lymphoedema

A condition that causes swelling in the body's tissues affecting any part of the body, but usually develops in the arms or legs. It develops when the lymphatic system is blocked or does not work properly.

Mutation (gene)

The permanent alteration in the DNA sequence of a gene, so that it differs from what is found in most people.

Neutrophils

White blood cells involved in fighting inflammation and infection, specifically bacterial infections.

Nucleophosmin 1 (NPM1)

A protein which is essential for the normal function of cells. One of the functions of NPM1 is being a tumour suppressor which is why when there is a mutation in the gene responsible for the protein, it is involved in a number of cancers including leukaemia.

Oedema

The excess fluid in an area of the body which usually causes swelling of the area.

Paediatric patients

Patients from birth up to the age of 18.

Platelets

One of the types of blood cells which help to stop

bleeding.

Prognosis

An indication of how well a patient is expected to respond to treatment based on their individual characteristics at the time of diagnosis or other timepoint in the disease.

Proliferation

A rapid increase, for example in the number of cells.

Pulmonary oedema

Excess fluid in the lungs.

Red blood cells

Small blood cells that contain haemoglobin and carry oxygen and other substances to all tissues of the body.

Refractory

A condition for which treatment does not result in a remission. However, the condition may be stable.

Relapse

Relapse occurs when a patient initially responds to treatment, but after six months or more, the response stops. This is also sometimes called a recurrence.

Runt-related transcription factor (RUNX1)

Also known as acute myeloid leukaemia 1 protein (AML1), this protein has a major role in how the stem cells in the bone marrow develop and is involved in the development of AML.

Second-generation drug

Related to the first-generation drugs, second-generation drugs are often developed to resolve issues identified with the first-generation drug for example to decrease side effects or increase the efficacy of the drug.

Stem cell

The most basic cell in the

Glossary (cont.)

body that has the ability to develop into any of the body's specialised cell types, from muscle cells to brain cells. However, what makes these stem cells reproduce uncontrollably, as in cancer, is thought to be linked to chromosome abnormalities.

Target therapy

Drugs that specifically interrupt the leukaemia cells from growing in the body. However, these drugs do not also harm the body's healthy cells the way conventional drugs do.

Toxicity

Harmful effect.

Tumour suppressor 53 (TP53)

The activity of the TP53 suppressor protein prevents the formation of tumours. However, when a person inherits only one active version of the TP53 gene from their parents, they are predisposed to developing cancer in a variety of tissues in early adulthood.

Tyrosine kinase

An enzyme which can switch 'on' and 'off' many of the functions of the body's cells. Cells have receptors for tyrosine kinases present in their membranes enabling tyrosine kinases to play a major role in the activation of the cells processes.

Tyrosine kinase inhibitors

Drugs that inhibit the tyrosine kinase enzyme which controls the function of a cell. Tyrosine kinase inhibitors can switch 'off' tyrosine kinase enzymes that are permanently active due to a mutation.

Tyrosine kinase receptors

Receptors present in the membranes of all of the body's cells which can be

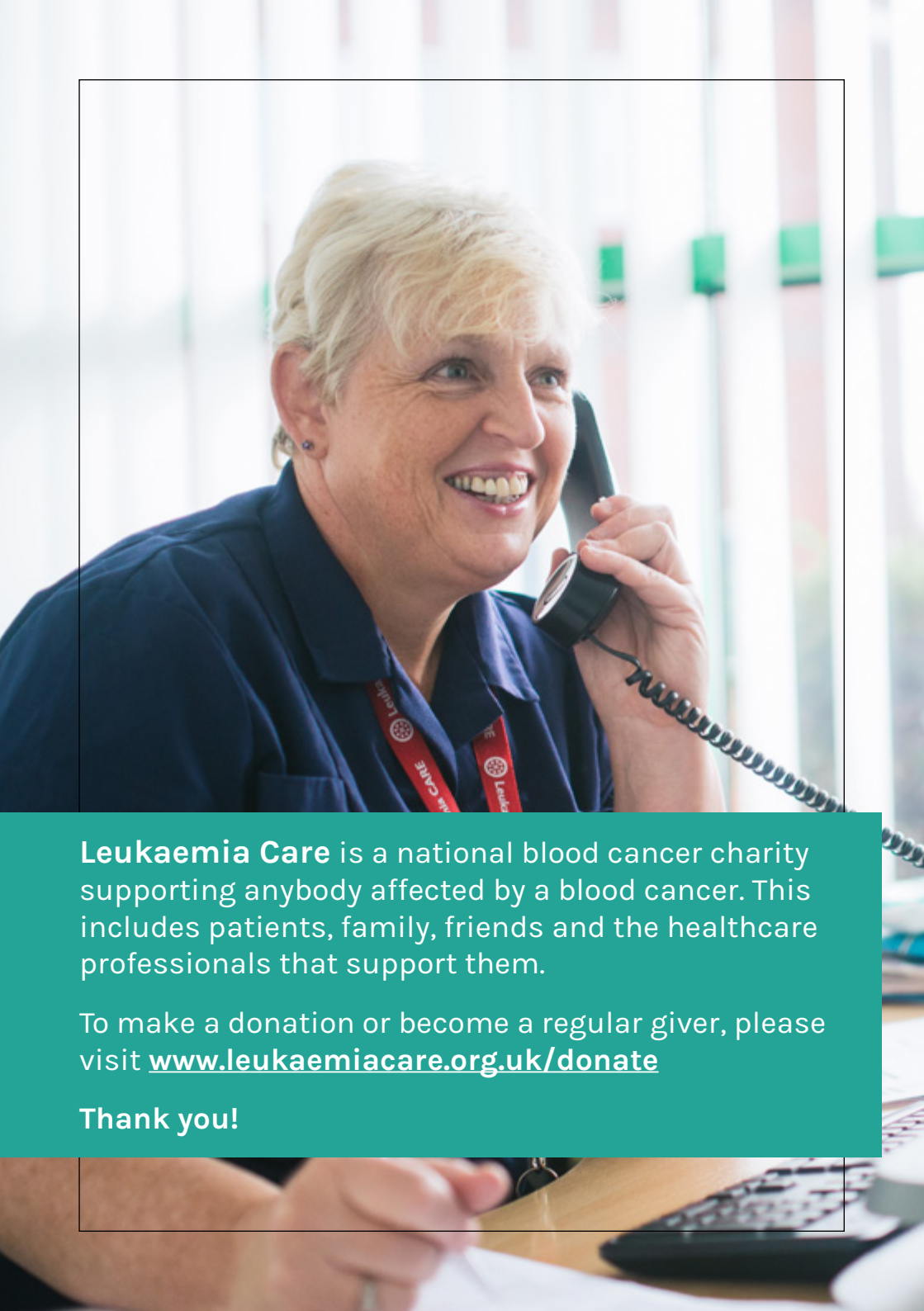
activated by the tyrosine kinase enzyme.

Venetoclax

Venetoclax is an inhibitor of the B-cell lymphoma-2 protein (BCL2) which regulates the natural death of cells in the body. Mutations in the genes responsible for BCL2 cells prevent the natural death of cells thereby extending survival of cells. Venetoclax attaches itself to these BCL2 cancer cells, blocking their actions and causing them to die.

White blood cells

White blood cells are one of the types of cells found in the blood and bone marrow, along with red blood cells and platelets. White blood cells create an immune response against both infectious disease and foreign invaders. Granulocyte white blood cells include the neutrophils (protect against bacterial infections and inflammation), eosinophils (protect against parasites and allergens) and basophils (create the inflammatory reactions during an immune response). Other white blood cells include the lymphocytes (recognise bacteria, viruses and toxins, to which they produce antibodies) and monocytes (clear infection products from the body).



Leukaemia Care is a national blood cancer charity supporting anybody affected by a blood cancer. This includes patients, family, friends and the healthcare professionals that support them.

To make a donation or become a regular giver, please visit **www.leukaemiacare.org.uk/donate**

Thank you!

Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

There are a number of organisations, including ourselves, who provide expert advice and information.

Leukaemia Care

We are a charity dedicated to supporting anyone affected by the diagnosis of any blood cancer. We provide emotional support through a range of support services including a helpline, patient and carer conferences, support group, informative website, one-to-one buddy service and high-quality patient information. We also have a nurse on our help line for any medical queries relating to your diagnosis.

Helpline: **08088 010 444**
www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

Blood Cancer UK

Blood Cancer UK is the leading charity into the research of blood cancers. They offer support to patients, their family and friends through patient services.

0808 2080 888
www.bloodcancer.org.uk

Cancer Research UK

Cancer Research UK is a leading charity dedicated to cancer research.

0808 800 4040
www.cancerresearchuk.org

Macmillan

Macmillan provides free practical, medical and financial support for people facing cancer.

0808 808 0000
www.macmillan.org.uk

Maggie's Centres

Maggie's offers free practical, emotional and social support to people with cancer and their families and friends.

0300 123 1801
www.maggiescentres.org

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444
www.adviceguide.org.uk

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

support@leukaemiacare.org.uk

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Leukaemia Care is registered as a charity in England and Wales (no.1183890) and Scotland (no. SC049802).
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Leukaemia Care
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