Future Treatments in Acute Myeloid Leukaemia (AML)

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

The main treatment for acute myeloid leukaemia (AML) is chemotherapy, including targeted therapy where cancer drugs attack specific components of the leukaemia cells. This might be followed by a stem cell transplant. Surgery and radiation therapy may be used in special circumstances. New therapies are being developed and investigated every day. Several of these new drugs for the treatment of AML are described in this booklet.

If you need specific advice or have any questions about this treatment, please contact your medical team or Clinical Nurse Specialist (CNS).

Booklet compiled by our Patient Information Writer, Isabelle Leach and peer reviewed by a medical professional who is specialised in leukaemia, Dr Emmanouil Nikolousis. We are also grateful to a leukaemia patient, Julie Quigley, for her valuable contribution as a 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 - 10.00pm on weekdays and 9.30am - 12.30pm on Saturdays. If you need someone to talk to, call **08088 010 444**

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**, over the phone on **08088 010 444** or via LiveChat.

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.

Patient and carer conferences

Our nationwide conferences provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support.

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**, as well as speak to one of our care advisers on our online support service, LiveChat (9am-5pm weekdays).

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 quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals. To subscribe go to **www.leukaemiacare.org.uk/communication-preferences/**

Drug approvals and recommendations

Information on when new drugs are approved by the European Medicines Agency (EMA), the medicines regulatory authority for Europe, are available on the EMA website under the Human Medicines tab. A European Public Assessment Report (EPAR) for each drug that is approved is provided on the website, together with its Summary of Product Characteristics (SPC), which details everything that is available on the drug.

If a drug is not on the website, then it is being developed and investigated by the sponsor pharmaceutical company (e.g. Daiichi Sankyo in the case of quizartinib which is not yet approved in Europe; for more information, go to the quizartinib section in this booklet starting on page 18). To find out more on the stage of development of a drug that is not approved, two websites are very helpful:

1. The Sponsor pharmaceutical company website provides regular press releases (e.g. **https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006846.html**). Preliminary trial results, strategies on submission for drug approval, and Orphan Designation on the company's drugs are often shared.

2. ClinicalTrial.gov (**https://clinicaltrials.gov**) is a website database of approximately 276,190 clinical trials studies in over 204 countries. The phases of the studies and their estimated completion dates will indicate the stage of development of the drug. Phase 1 and 2 trials investigate how the drug behaves in healthy volunteers and which are the best doses to use. Phase 3 clinical trials investigate the efficacy and safety of the drug in large numbers of patients with the disease. Positive results in a Phase 3 trial will allow the sponsor pharmaceutical company to submit for approval to the EMA.

The National Institute for Health and Care Excellence (NICE) issues recommendation guidelines based on the best available evidence of which drugs work and what their costs are. Decisions on which topics to develop guidelines on, and in what order, are based on suggestions by commissioners and professional organisations, and organisations for people using services, their families and carers. The final decision is made in conjunction with NHS England and the Department of Health and Public Health. Published guidelines are available on the NICE website at **https://www.nice.org.uk/guidance/published?type=cg**. Checks on whether a guideline needs updating is usually undertaken by NICE every two years and is always undertaken at least every four years from the date of guideline publication. A list of the guidance in the various stages of development with estimated completion dates are available on the NICE website at **https://www.nice.org.uk/guidance/**

Clofarabine

What is clofarabine?

Clofarabine (developed by Genzyme) is a type of chemotherapy drug known as a DNA synthesis inhibitor, which stops cancer cells making DNA, thereby preventing them from growing and multiplying.

Clofarabine is indicated for the treatment of children and adults up to 21 years of age with relapsed or refractory acute lymphoblastic leukaemia (ALL), who have received at least two previous regimens.

Clofarabine was approved for the treatment of relapsed or refractory ALL by the Food and Drug Administration (FDA) on 28 December 2004 and is marketed under the name of Clolar®. It was approved for the same indication in Europe, Australia and New Zealand on 29 May 2006, and is marketed as Evoltra®.

In addition, clofarabine is also being investigated as a treatment for:

- Older patients with AML who cannot have high dose treatment with a stem cell transplant
- Patients with myelodysplastic syndrome (MDS) which is a group of conditions where the bone marrow does not make enough normal blood cells

The bone marrow of patients with MDS makes blood cells which are not fully developed and do not work normally. The cause is not known, but exposure to the chemical benzene (present in petrol and cigarette smoke) or treatment with radiotherapy or chemotherapy have been implicated. Patients with MDS are commonly aged between 65 to 70 years, with only 20% being younger than 50 years old.

Who receives clofarabine?

Clofarabine is approved for the treatment of children and adolescents (1 to 18 years of age) and adults up to 21 years of age with relapsed or refractory acute lymphoblastic leukaemia when at least two other types of treatment have failed. There is no experience

of the safety and efficacy of clofarabine for children less than one year of age or adults greater than 21 years of age.

Clofarabine should not be given to patients with the following:

- Known hypersensitivity reaction to the constituents of clofarabine (clofarabine, sodium chloride and water for injections)
- Severe renal and hepatic impairment
- Pregnant or breast-feeding women

How is clofarabine administered?

Clofarabine is available as a single-use vial containing 20mg of clofarabine in 20mL of normal saline. It is administered by intravenous infusion.

1. For the first cycle, the recommended paediatric dose of 52mg/m^2 is administered as an intravenous infusion over two hours every day for five consecutive days.
2. The cycle is then repeated every two to six weeks as soon as the number of blood cells return to normal. Dosage used is based on the patient's body surface area, calculated using the actual height and weight before the start of each cycle.

Extra fluids are given through the drip to prevent the build-up of uric acid which occurs as the cancer cells are broken down by clofarabine. Medications to prevent nausea and vomiting will be given if required. Liver and kidney function will be monitored during the five days of clofarabine infusion. Clofarabine, like fludarabine, will require the administration of irradiated blood products for up to one year after receiving clofarabine (and this will be indefinite if the patient undergoes stem cell transplantation).

What are the side effects of clofarabine?

The most common side effects reported in more than 10% of patients during clinical trials with with clofarabine were:

Clofarabine (cont.)

- Nausea
- Vomiting
- Febrile (feverish) neutropenia
- Headache
- Rash
- Diarrhoea
- Itching (pruritus)
- High temperature (pyrexia)
- Palmar-plantar erythrodysaesthesia syndrome (reddening, swelling, numbness and skin peeling on palms of the hands and soles of the feet)
- Fatigue
- Anxiety
- Mucosal membrane inflammation (areas that produce mucus to filter out bacteria swell up)
- Flushing

What trials have there been for clofarabine?

Four Phase 3 clinical trials of clofarabine in patients with AML are ongoing. All these trials are sponsored by Genzyme, a Sanofi company. No expanded access trials, which enable patients who cannot participate in a clinical trial to gain access to a medical product not yet approved by the regulatory authority, are available for clofarabine at present.

More details of the criteria that patients need to have to take part in the trials, and locations of the centres for the clinical trials can be found at **https://clinicaltrials.gov**

Phase 3 trials of clofarabine for the treatment of patients with AML

NCT00703820

- **Title of trial:** Clofarabine plus Cytarabine versus Conventional Induction Therapy and a Study of Natural Killer Cell Transplantation in Newly Diagnosed Acute Myeloid Leukaemia
- **Status of trial:** Active, not recruiting
- **Enrolment/estimated enrolment:** 324 patients
- **Study start date:** 4 August

2008

- **Estimated study completion date:** June 2020

NCT00317642

- **Title of trial:** A Study of Clofarabine and Cytarabine for Older Patients with Relapsed or Refractory Acute Myelogenous Leukaemia (AML), (CLASSIC I)
- **Status of trial:** Completed, results available
- **Enrolment/estimated enrolment:** 326 patients
- **Study start date:** 1 August 2006
- **Estimated study completion date:** January 2012

NCT02085408

- **Title of trial:** Clofarabine or Daunorubicin Hydrochloride and Cytarabine Followed by Decitabine or Observation in Treating Older Patients with Newly Diagnosed Acute Myeloid Leukaemia
- **Status of trial:** Active, not recruiting
- **Enrolment/estimated enrolment:** 727 patients
- **Study start date:** 28 December 2010
- **Estimated study completion date:** September 2018

NCT01471444

- **Title of trial:** Fludarabine-IV Busulfan ± Clofarabine and Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS)
- **Status of trial:** Active, not recruiting
- **Enrolment/estimated enrolment:** 250 patients
- **Study start date:** 2 November 2011
- **Estimated study completion date:** November 2020

Gilteritinib

What is gilteritinib?

Gilteritinib (manufactured by Astellas) is a cancer drug which is being investigated for the treatment of patients with relapsed or refractory AML.

Tyrosine kinase receptors are receptors present in the membranes of all of the body's cells, and they carry information to and from complex cell networks such as the bone marrow, amongst others. FMS-like tyrosine kinase 3 (FLT3) is a member of the class 3 receptor tyrosine kinase family, and mutations in the FLT3 gene are known to be involved in the development of AML. FLT3s mutations are found in approximately one third of all patients with AML, and these mutations are associated with relapsed and refractory cases of AML.

Gilteritinib is known to inhibit both FLT3 mutations involved in AML and it is being developed for treatment of patients with relapsed or refractory AML who have these mutations. These two FLT3 mutations are FLT3-ITD and FLT3-TKD:

1. FLT3-ITD is a FLT3 mutation that includes an internal tandem duplication (ITD) which is a small doubling up of amino acids in the membrane of the receptor. Amino acids are the building block for proteins.
2. FLT3-TKD is a point mutation in a single amino acid in the tyrosine kinase domain (TKD).

The FLT3-ITD mutations are present in the AML cells of 20% to 30% of newly diagnosed patients and point mutations in the tyrosine kinase domain are present in 7% of patients.

In October 2017, the FDA granted gilteritinib Fast Track Designation for the treatment of adult patients with FLT3 mutation-positive relapsed or refractory AML. This Fast Track program enables Astellas to accelerate the development, review, and approval of gilteritinib for the treatment of AML.

In January 2018, gilteritinib was granted Orphan Designation for the treatment of AML by the European Commission. Orphan Designation is given to drugs that may be of significant benefit

to patients with rare conditions (affecting less than 5 in 10,000 people). This status makes it easier for a drug to be approved, and the company developing it receives scientific advice and funding.

On 23 March 2018, a new drug application for marketing approval of gilteritinib in Japan was submitted by Astellas Pharma Inc for the treatment of adult patients with FLT3 mutation-positive relapsed or refractory AML. On 29 March 2018, Astellas also submitted new drug application for approval of gilteritinib in the same patient population to the FDA.

Who receives gilteritinib?

Currently, gilteritinib is being investigated in adults with FLT3 mutation-positive relapsed or refractory AML. There is no experience of the safety and efficacy of gilteritinib for those under 18 years of age.

Gilteritinib is known to inhibit two of the FLT3 mutations (FLT3-ITD and FLT3-TKD) and is being developed for treatment of patients with relapsed or refractory AML who have these mutations.

How is gilteritinib administered?

A dose-finding, first-in-human trial of gilteritinib which investigated oral daily doses of gilteritinib ranging from 20mg to 450mg in 252 patients with relapsed or refractory acute myeloid leukaemia showed that gilteritinib 120mg gave the best combination of activity against AML (consistent FLT3 inhibition) and a good safety profile. Based on this data, gilteritinib 120mg once daily is being tested in Phase 3 trials.

In the ongoing Phase 3 ADMIRAL study, which compares gilteritinib with salvage chemotherapy (chemotherapy given to a patient when other options are exhausted) in 371 adult patients with FLT3-positive relapse/ refractory AML, gilteritinib 120mg is administered orally once daily.

What are the side effects of gilteritinib?

Early experience of the safety of

Gilteritinib (cont.)

gilteritinib comes from a first-in-human trial of 252 patients with relapsed or refractory acute myeloid leukaemia. The three most common side effects that patients experienced with gilteritinib were diarrhoea (37% of patients), anaemia (34%) and fatigue (33%). Other side effects included abnormal liver enzyme tests, pneumonia, acute renal failure and pyrexia (high temperature).

What trials have there been for gilteritinib?

Gilteritinib is currently being investigated in large numbers of patients (Phase 3 trials) and is showing consistent inhibition of FLT3 mutations in patients with relapsed or refractory AML, as well as being well tolerated by these patients.

The new drug applications submitted in Japan and the US for gilteritinib are based on data from the ongoing Phase 3 ADMIRAL study (NCT02421939), which is comparing gilteritinib with salvage chemotherapy in adult patients with FLT3-positive relapse/refractory AML. The study which started in October 2015 has recruited 371 patients and is estimated to be completed by November 2020.

Six other Phase 3 clinical trials of gilteritinib in patients with AML are also ongoing. All these trials are sponsored by Astellas Pharma Global Development, Inc. Two expanded access trials are available alongside the other trials.

More details of the criteria that patients need to have to take part in the trials and locations of the centres for the clinical trials can be found at **https://clinicaltrials.gov**

Phase 3 and expanded access trials of gilteritinib for the treatment of patients with AML

NCT02752035

- **Title of trial:** A Study of ASP2215 (Gilteritinib) by Itself, ASP2215 Combined with Azacitidine or Azacitidine by Itself to Treat Adult Patients who have

Recently Been Diagnosed with Acute Myeloid Leukaemia with a FLT3 Gene Mutation and who Cannot Receive Standard Chemotherapy

- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 540 patients
- **Study start date:** 1 August 2016
- **Estimated study completion date:** March 2022

NCT02957262

- **Title of trial:** A Study of ASP2215 (Gilteritinib), Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FMS-like Tyrosine Kinase 3 (FLT3/ITD) Acute Myeloid Leukaemia (AML) in First Complete Remission
- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 354 patients
- **Study start date:** 10 January 2017
- **Estimated study completion date:** March 2024

NCT02997202

- **Title of trial:** A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukaemia (AML)
- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 346 patients
- **Study start date:** 7 June 2017
- **Estimated study completion date:** August 2024

NCT03182244

- **Title of trial:** A Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukaemia (AML) with FLT3 Mutation
- **Status of trial:** Recruiting

Gilteritinib (cont.)

- **Enrolment/estimated enrolment:** 318 patients
- **Study start date:** 15 January 2018
- **Estimated study completion date:** June 2020

NCT02421939

- **Title of trial:** A Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukaemia (AML) with FMS-like Tyrosine Kinase (FLT3) Mutation (ADMIRAL trial)
- **Status of trial:** Active, not recruiting
- **Enrolment/estimated enrolment:** 371 patients
- **Study start date:** 20 October 2015
- **Estimated study completion date:** February 2020

If you wish to have further information on AML, please view our collection of patient information booklets that are available on our website at **www.leukaemiacare.org.uk**

Quizartinib

What is quizartinib?

Quizartinib (developed by Daiichi Sankyo) is a selective FLT3 receptor tyrosine kinase inhibitor that is being investigated for the treatment of adult patients with relapsed/refractory AML.

Quizartinib has shown promising activity against leukaemia in relapsed and refractory patients in a large Phase 2 study. It is currently being investigated in two international Phase 3 trials for the treatment of AML with FLT3-ITD mutations for relapsed/refractory patients (QuANTUM-R trial) and newly-diagnosed patients (QuANTUM-First trial).

Results from the QuANTUM-R trial will form the basis of worldwide regulatory submissions for quizartinib in AML leukaemia.

Quizartinib has been granted Fast Track Designation by the FDA for the treatment of relapsed/refractory AML. It has also been granted Orphan Drug Designation by the FDA and EMA for the treatment of AML.

Who receives quizartinib?

Quizartinib is an investigational agent that is not currently approved for any indication in any country. Safety and efficacy have not been established.

Patients with a FLT3-ITD mutation AML have a lower overall survival rate and an increased rate of relapse compared with patients with AML but without this mutation. Therefore, Daiichi Sankyo are investigating quizartinib for the treatment of relapsed/refractory AML in patients with FLT3-ITD mutations in their international QuANTUM-R Phase 3 trial. These patients will be the first to receive quizartinib once it is approved.

How is quizartinib administered?

In Phase 1 and 2 trials, quizartinib has been administered as an oral solution once daily. In a Phase 1 dose-finding trial, the maximum tolerated dose of quizartinib was determined as 60mg daily. Increases in the QT interval on the ECG tracing, which may lead to

heart rhythm disturbances, were noticed at the maximum tolerated dose of 60mg daily.

To prevent the occurrence of any heart rhythm disturbances, the starting dose of quizartinib in the QuANTUM-R Phase 3 trial will be 30mg daily until the QT interval on the ECG has been checked, and then the doses will be increased to 60mg daily.

What are the side effects of quizartinib?

The most common side effects reported in patients during Phase 1 and 2 clinical trials with quizartinib were:

- Febrile neutropenia (decrease in numbers of neutrophils, which are white blood cells involved in fighting disease, together with a temperature)
- Neutropenia (decrease in numbers of neutrophils which are white blood cells involved in fighting disease)
- Anaemia (low level of red blood cells and haemoglobin which is carried by the red blood cells)
- Thrombocytopenia (decrease in the levels of platelets, which are small blood cells that help the body form clots to stop bleeding)
- Increased QT interval on the ECG tracing (this may lead to heart rhythm disturbances)
- Leukopenia (decrease in numbers of all white blood cells)
- Pneumonia

What trials have there been for quizartinib?

Quizartinib has shown promising results in relapsed/refractory patients in a large Phase 2 study. It is currently being studied in two large Phase 3 studies (QuANTUM-R and QuANTUM-First), which are detailed below.

QuANTUM-R

This trial is due to end in July 2019 and the results will be used to support worldwide submissions for the approval of quizartinib in the treatment of AML leukaemia.

Quizartinib (cont.)

The trial compares quizartinib with salvage chemotherapy in patients with AML who are FLT3-ITD positive.

Preliminary results from the global QuANTUM-R Phase 3 trial were released by Daiichi Sankyo in May 2018. The QuANTUM-R Phase 3 trial showed that quizartinib significantly prolonged overall survival compared with salvage chemotherapy in patients with FLT3-ITD mutation-positive relapsed or refractory AML. Safety was consistent with that observed in Phase 2 trials of quizartinib.

QuANTUM-First

This trial is still recruiting patients and is due to be completed in November 2020. Details of recruitment can be found at **https://quantumfirststudy.com/**

The trial compares quizartinib and chemotherapy with placebo and chemotherapy in newly diagnosed patients with FLT3-ITD mutation-positive AML. The two treatments will be compared for effectiveness as induction/consolidation therapy and maintenance therapy.

More details of the criteria that patients need to have to take part in the trials, and locations of the centres for the clinical trials, can be found at **https://clinicaltrials.gov**

Phase 3 trials of quizartinib for the treatment of patients with AML

NCT02039726

- **Title of trial:** (QuANTUM-R): An Open-label Study of Quizartinib Monotherapy vs Salvage Chemotherapy in Acute Myeloid Leukemia (AML) Subjects who are FLT3-ITD Positive
- **Status of trial:** Active, not recruiting
- **Enrolment/estimated enrolment:** 367 patients
- **Study start date:** April 2014
- **Estimated study completion date:** July 2019

NCT02668653

- **Title of trial:** Quizartinib with Standard of Care Chemotherapy and as Maintenance Therapy in Patients with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukaemia (AML) (QuANTUM-First)
- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 536 patients
- **Study start date:** September 2016
- **Estimated study completion date:** November 2020

Leukaemia Care offers nationwide support groups for people affected by a diagnosis of a blood or lymphatic cancer. Visit **www.leukaemiacare.org.uk**, or call **08088 010 444**, to find out more and to find a group near you.

Venetoclax

What is venetoclax?

Venetoclax (marketed as Venclyxto® in Europe and Venclexta® in the US by AbbVie/Genentech) is a B-cell lymphoma-2 (BCL2) inhibitor. BCL2 cells are found in high numbers among chronic lymphocytic leukaemia (CLL) cancer cells. Venetoclax attaches itself to these BCL2 cancer cells, blocking their actions and causing them to die.

On 6 December 2012, venetoclax was designated an Orphan Drug because of the low number of patients with CLL.

On 5 December 2016, venetoclax received conditional approval for the treatment of CLL for:

- Patients with 17p deletion or TP53 mutations who are unsuitable for, or have failed treatment with, a B-cell receptor pathway inhibitor.
- Patients without 17p deletion or TP53 mutations who have failed treatment with both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

The approval is conditional to the European Medicines Agency reviewing any additional data as and when it is available.

On 8 June 2018, the FDA in the US granted regular approval to venetoclax for patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

Who receives venetoclax?

Venetoclax is conditionally indicated for the treatment of CLL.

There is no experience of the safety and efficacy of venetoclax for children.

Patients with AML

Although there is currently no indication for venetoclax in the treatment of AML, early Phase 1 and 2 trials are investigating the combination of venetoclax with decitabine or azacitidine in the treatment of elderly patients with AML.

A Phase 1b trial in 57 elderly

patients with AML (median age of 75 years), for whom intensive chemotherapy was not an option, reported that 61% of patients receiving the combination of drugs achieved complete remission or complete remission with incomplete marrow recovery. Moreover, nine of the patients went on to receive stem cell transplants while in remission, suggesting that venetoclax with decitabine or azacitidine may be a step forward to achieving cure. It is also shown that patients with the IDH2 mutation can have a better response to venetoclax.

On their own, decitabine or azacitidine do not achieve a cure (less than 30% remission); however, when combined with venetoclax, which has a low toxicity profile, the results are greatly improved. Large Phase 3 trials are needed to confirm these results.

Similar results have been reported when combining venetoclax and cytarabine in 71 patients ≥65 years with previously untreated AML. Results showed that 62% of patients receiving the combination of drugs achieved complete remission or complete remission with incomplete marrow recovery. Based on this trial, enrolment has begun in a Phase 3 trial to confirm these results in a greater number of patients.

How is venetoclax administered?

Venetoclax is available in film-coated tablets containing either venetoclax 10mg, 50mg or 100mg. The tablets are administered orally once daily according to the following dosing schedule. They should be swallowed whole, with a meal and water.

The starting dose is venetoclax 20mg once daily for seven days. The dose is then gradually increased over a period of five weeks up to the recommended daily dose of 400mg as shown on the next page:

Venetoclax (cont.)

Week	Venetoclax Daily Dose
One	20mg
Two	50mg
Three	100mg
Four	200mg
Five and onwards	400mg

This five-week dose-titration schedule is designed to reduce the size of the tumour gradually and decrease the risk of tumour lysis syndrome, which is when tumour cells release their contents into the bloodstream leading to metabolic disturbances which can progress to clinical toxic effects, including kidney (renal) problems, heart rate disturbances, seizures, and death due to multi-organ failure.

The risk of tumour lysis syndrome is greater with a rapid decrease of a large tumour, and if the patient has poor renal function or any other serious diseases. Before treatment with venetoclax is started by an experienced cancer physician, assessment of the tumour (X-ray and computed tomography scan) and blood chemistry (potassium, uric acid, phosphorus, calcium and creatinine) levels will be performed, and any abnormalities corrected to decrease risk of tumour lysis syndrome.

What are the side effects of venetoclax?

The most common side effects reported in more than 20% of patients during clinical trials with venetoclax for the treatment of CLL include:

- Diarrhoea
- Nausea
- Vomiting
- Constipation
- Fatigue
- Anaemia (low level of red cells and haemoglobin which red cells carry)
- Neutropenia (decrease in numbers of neutrophils which are white blood cells involved in fighting disease)
- Thrombocytopenia (decrease

in the levels of platelets, which are small blood cells that help the body form clots to stop bleeding)

- Upper respiratory tract infections
- Hyperphosphataemia (abnormally high levels of phosphate in the blood)

What trials have there been for venetoclax?

Venetoclax is currently being investigated in two large Phase 3 trials for the treatment of patients with AML who are ineligible for standard induction, and in patients with AML who are ineligible for intensive chemotherapy. Both trials are sponsored by AbbVie. An expanded access trial (NCT03123029) is available alongside these trials.

In the first trial (NCT02993523), venetoclax combined with azacitidine is being compared with azacitidine alone in treatment-naïve patients with AML (those who have never had treatment) who cannot have standard induction therapy. The study is estimated to be completed in August 2020.

In the second trial (NCT03069352), venetoclax combined with low dose cytarabine is being compared with low dose cytarabine alone in treatment-naïve patients with AML who are ineligible for intensive chemotherapy. The study is estimated to be completed in November 2019.

More details of the criteria that patients need to have to take part in the trials, and locations of the centres for the clinical trials, can be found at **https://clinicaltrials.gov**

Phase 3 and expanded access trials of venetoclax for the treatment of patients with AML

NCT02993523

- **Title of trial:** A Study of Venetoclax in Combination with Azacitidine versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukaemia

Venetoclax (cont.)

who are Ineligible for Standard Induction Therapy

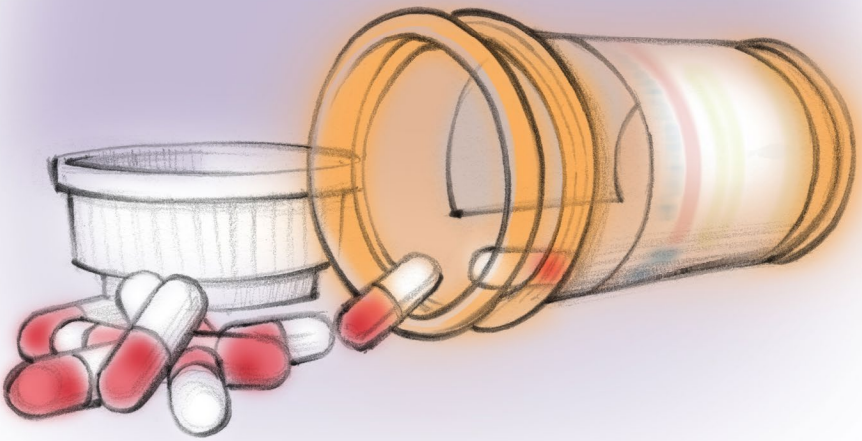
- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 400 patients
- **Study start date:** 3 April 2017
- **Estimated study completion date:** 5 August 2020

NCT03069352

- **Title of trial:** A Study of Venetoclax in Combination with Low Dose Cytarabine versus Low Dose Cytarabine Alone in Treatment Naïve Patients with Acute Myeloid Leukaemia who are Ineligible for Intensive Chemotherapy
- **Status of trial:** Recruiting
- **Enrolment/estimated enrolment:** 175 patients
- **Study start date:** 23 May 2017
- **Estimated study completion date:** 25 November 2019

NCT03123029

- **Title of trial:** Expanded Access to Venetoclax
- **Status of trial:** Expanded access available
- **Enrolment/estimated enrolment:** N/A
- **Study start date:** N/A
- **Estimated study completion date:** N/A



Vyxeos

What is Vyxeos?

Vyxeos® is the registered name for the combination of two cancer drugs (daunorubicin and cytarabine) which has been formulated for intravenous injection. Daunorubicin and cytarabine are already licensed for the treatment of patients with AML, and both act by damaging the DNA of cancer cells in the blood stream and bone marrow.

Vyxeos is being investigated by Jazz Pharmaceuticals for the treatment of adult patients with two types of newly diagnosed AML:

1. Therapy-related AML (t-AML) – This is a recognised illness which occurs as a complication of a patient having had cytotoxic and/or radiation therapy.
2. AML with myelodysplasia related changes (AML-MRC) – Patients who have previously had other types of blood disorders have AML with myelodysplasia related changes.

On 3 August 2017, the FDA granted Vyxeos approval for the treatment of adults with newly diagnosed t-AML or AML-MRC. This is the first FDA-approved treatment specifically for these conditions. The approval was based on preliminary data from Study CLTR0310301 which is being conducted in 309 patients (aged 60-75 years) with newly-diagnosed t-AML or AML-MRC.

Who receives Vyxeos?

Vyxeos is approved for the treatment of adults with newly diagnosed t-AML or AML-MRC. There is no experience of the safety and efficacy of Vyxeos for those below 18 years of age.

Vyxeos should not be given to patients with the following:

- Known hypersensitivity reaction to daunorubicin and cytarabine
- Impaired cardiovascular function
- Severe renal and hepatic impairment
- Very low blood cell counts which may lead to haemorrhage

- Pregnant or breast-feeding women

How is Vyxeos administered?

Vyxeos is administered in a liposome, which is a small ball-like structure made from a thin cell membrane that combines the doses of daunorubicin and cytarabine and is formulated for intravenous infusion.

The aim of administering Vyxeos is to achieve remission when all the leukaemia cells in the blood or bone marrow are removed and the normal bone marrow develops again.

To bring about or induce remission, patients receive an induction cycle of Vyxeos. Occasionally, the first induction chemotherapy does not destroy all the leukaemia cells and a second induction cycle may be required.

- For the first induction cycle, the recommended dose of Vyxeos is combined daunorubicin 44mg/m^2 (mg of drug per meter of body surface area of the patient) and cytarabine 100mg/m^2 in a liposome by intravenous infusion over 90 minutes on days one, three and five of the cycle.
- If required, the same dose can be given on days one and three of a second induction cycle.

For the first induction cycle of the treatment, administration of Vyxeos by intravenous infusion commonly requires a stay in a hospital of three to five weeks, depending upon whether remission can be achieved and how well side effects can be tolerated. Patients typically receive the entire treatment cycle during their stay in hospital. In some cases, the intravenous infusions which are on days one, three and five of the cycle can be administered in an outpatient infusion centre allowing the patient to go home afterwards. However, the patient must be admitted to the hospital after the completion of all the infusions for the remainder of the induction cycle as they will have very low

Vyxeos (cont.)

blood cell counts that require special monitoring.

Your consultant will often perform a bone marrow biopsy 14 to 21 days after starting your treatment and, according to the results of the biopsy, you can proceed to consolidation chemotherapy for the next cycle of treatment.

Once patients are in remission, they receive consolidation chemotherapy with the aim of eliminating any leukaemia cells that are still present after induction chemotherapy, as this will help reduce the risk of the leukaemia returning. Consolidation chemotherapy is given between five to eight weeks after the last induction cycle and once blood cell counts have reverted to normal.

- The recommended dose for each consolidation cycle is combined daunorubicin 29mg/m^2 and cytarabine 65mg/m^2 in a liposome via intravenous infusion over 90 minutes on days one and three.
- A second consolidation therapy cycle may be required as the same dose as the first consolidation therapy cycle.

Consolidation therapy can be given in an outpatient infusion centre, allowing the patients to return home when therapy is finished.

In total, the duration of therapy may last between four to six months, depending upon how you respond to the treatment, how well you tolerate it, the number of consolidation chemotherapy cycles required, and the availability of a stem cell transplant.

What are the side effects of Vyxeos?

The most common side effects which occurred in more than 25% of patients during clinical trials with Vyxeos were:

- Haemorrhage events
- Febrile (feverish) neutropenia
- Rash
- Oedema (build-up of fluid in the body)
- Nausea
- Mucositis

- Diarrhoea
- Constipation
- Musculoskeletal pain
- Fatigue
- Abdominal pain
- Dyspnoea (difficult or laboured breathing)
- Headache
- Cough
- Decreased appetite
- Arrhythmia (abnormal heart rhythms)
- Pneumonia
- Bacteraemia (infection of the blood)
- Chills
- Sleep disorders
- Vomiting

What trials have there been for Vyxeos?

There are currently no ongoing, or planned Phase 3 trials of Vyxeos for the treatment of patients with a diagnosis of AML.

The Phase 3 trial (NCT01696084) which provided the preliminary data that led to the approval of Vyxeos for the treatment of adult patients with newly diagnosed t-AML or AML-MRC, is still ongoing. The study started in November 2012 and is due to be completed by November 2019. FDA approval was achieved on the strength of data on overall survival, which was 9.56 months for patients who received Vyxeos and 5.95 months for patients daunorubicin and cytarabine in separate infusions.

A Phase 4 trial (NCT03526926) titled 'A Post-Marketing Observational Study of VYXEOS to Assess the Incidence of Infusion-Related Reactions in Adult Patients' is due to start soon. Jazz Pharmaceuticals plan to recruit 50 patients, and they estimate that the trial will be completed by January 2019.

More details of the criteria that patients need to have to take part in the trials and locations of the centres for the clinical trials can be found at **https://clinicaltrials.gov**

Glossary

Acute Myeloid Leukaemia (AML)

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young white blood cells called granulocytes or monocytes in the bone marrow.

Amino acids

Organic molecules which are the building blocks for making proteins.

Blast cells

Immature cells found in the bone marrow. They are not fully developed and therefore do not carry any particular function within the body. In normal humans, up to 5% of the cells found in the bone marrow are blast cells.

Chemotherapy

A form of cancer treatment that uses one or more anticancer drugs as part of a standardised chemotherapy regime.

Clinical trial

A medical research study involving patients with the aim of improving treatments and their side effects. You will always be informed if your treatment is part of a trial.

ClinicalTrials.gov

ClinicalTrials.gov is a database of trials and includes details of 276,190 research studies in all 50 states and in 204 countries.

Cytotoxic drugs

Drugs that are toxic to cancer cells and prevent their growth and replication.

Deoxyribonucleic Acid (DNA)

A molecule that carries the genetic instructions used in the growth development, functioning and reproduction of all living organisms.

Generic drug

A pharmaceutical drug that is the equivalent to a brand name product in dosage, strength, route of administration, quality and performance and intended use.

Mutation

The changing of the structure of a gene, resulting in a variant form which may be transmitted to subsequent generations, caused by the alteration of single base units in DNA, or the deletion,

insertion, or rearrangement of larger sections of genes or chromosomes.

Myelodysplasia

Myelodysplastic syndrome is a group of conditions where the bone marrow does not make enough normal blood cells. The blood cells made are not fully developed and not able to work normally. These blood cells include red blood cells which supply oxygen to the body's tissues, white blood cells which fight infection and platelets which help blood clot.

Palmar-plantar erythrodysaesthesia syndrome

Reddening, swelling, numbness and desquamation (skin sloughing or peeling) on palms of the hands and soles of the feet (and, occasionally, on the knees, elbows, and elsewhere), chemotherapy-induced.

Phase 3 trial

A Phase 3 trial is a large clinical trial (more than 100 patients) that collects information on a drug's safety and effectiveness using different populations and different dosages and by using the drug in combination with other drugs.

Phase 4 trial

Phase 4 trials are conducted once a drug has been granted a license to find out more about a drug's side effects, its long-term risks and benefits, or how well it works when it's used more widely.

Platelets

A disc-shaped element in the blood that assists in blood clotting. During normal blood clotting, the platelets clump together (aggregate).

Red Blood Cell

The blood cell that carries oxygen. Red cells contain haemoglobin, which permits them to transport oxygen (and carbon dioxide).

Relapse

The return of a disease or the signs and symptoms of a disease after a period of improvement.

Remission

A period of time when the illness is less severe or is not affecting someone.

Glossary (cont.)

Refractory disease

Refractory describes a disease or condition which does not respond to attempted forms of treatment. A cancer is said to be refractory when it does not respond to (or is resistant to) cancer treatment.

Salvage chemotherapy

Chemotherapy given to a patient when other options are exhausted.

Targeted therapy

Drugs that specifically interrupt the ability of the leukaemia to grow in the body. These drugs do not simultaneously harm healthy tissue the way conventional chemotherapy agents do.

Tyrosine Kinase Inhibitor (TKI)

A drug which blocks the action of a tyrosine kinase (a particular type of enzyme in the cell). In CML it works mainly by blocking the activity of the BCR-ABL protein.

White blood cell

One of the cells the body makes to help fight infections. There are several types of white blood cells. The two most common types are the lymphocytes and neutrophils.

Tell us what you think!

If you would like to give us some feedback about this patient information booklet, please hover over the code to the right using your phone or tablet's camera. Click the link as it appears and this will take you to a short web form to fill in.

Suitable for Android, iPhone 7 and above.

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

Bloodwise

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

020 7504 2200
www.bloodwise.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

Leukaemia Care,
One Birch Court,
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Registered charity
259483 and SC039207

Leukaemia Care
YOUR Blood Cancer Charity

Health & care information you can trust
The Information Standard Certified Member