Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING JANUARY 2019

Idasanutlin in addition to cytarabine for relapsed or refractory acute myeloid leukaemia

NIHRIO ID	11985	**NICE ID**	9763
Developer/Company	Roche Products Ltd	**UKPS ID**	645121

Licensing and market availability plans	Currently in phase III trial

SUMMARY

Idasanutlin in addition to cytarabine is in development for the treatment of relapse or refractory Acute Myeloid Leukaemia (AML). AML is a type of cancer that causes the bone marrow (the soft inner part of the bones where new blood cells are made) to produce excess immature white blood cells. The term acute means that it can develop fairly quickly and becomes increasingly more severe. If left untreated it would cause death within a few weeks or months. It is most common in people aged 60 years and over. Symptoms of AML may include weakness, fatigue, shortness of breath, recurrent infections, prolonged bleeding and unintended weight loss. Some risk factors, such as exposure to radiation, smoking, exposure to benzene, cancer treatments or blood or genetic disorders, may increase a person's risk of developing AML.

The most common treatment option for AML is chemotherapy to kill the cancerous cells. Idasanutlin in addition to cytarabine is a new treatment option that has shown promising clinical activity in acute leukaemia. Idasanutlin acts by blocking the activity of a protein known as MDM2 that is frequently found in AML. Blocking the activity of MDM2 can result in promoting cancer cells death. Idasanutlin is taken orally. If licenced, idasanutlin in addition to cytarabine would offer a new treatment option for patients with relapsed or refractory AML.

PROPOSED INDICATION

Relapsed or refractory acute myeloid leukaemia (AML).[a]

TECHNOLOGY

DESCRIPTION

Idasanutlin (RG7388) is a second-generation, nutlin-class, orally bioavailable, selective mouse double minute 2 homolog (MDM2) antagonist. MDM2 is an important negative regulator of the p53 tumour suppressor and is expressed at high levels in a large proportion of AML.[1] Idasanutlin exhibits single-nanomolar binding affinity for MDM2 and an average half maximal inhibitory concentration (IC_{50}) of 40 nM in antiproliferative cell-based assays among wild-type p53 cancer lines.[2] Wild-type p53 is expressed in over 80 % of AML cases; thus, inhibition of the interaction between MDM2 and p53 can re-establish the p53 pathway in AML cells resulting in cell cycle arrest and induction of apoptosis.[1]

Idasanutlin is in clinical development for patients with refractory or relapsed AML[3]. In the phase III clinical trial (MIRROS; NCT02545283), idasanutlin is administered orally at a dose of 300mg twice daily (in cycle 1) or once daily (in cycles 2 and 3) in addition to intravenous (IV) infusion of cytarabine, 1 gram per square meter (g/m^2) for five days of every treatment cycle (treatment cycle length is 28 days).[3]

INNOVATION AND/OR ADVANTAGES

Idasanutlin has shown promising clinical activity in acute leukaemias by enhancing the activity of the tumour suppressor, p53, through antagonism of MDM2. In combination with different anticancer drugs, it showed synergism in cancer cellular lines.[4,5] The results from phase 1/1b study evaluating idasanutlin (as monotherapy or in combination with cytarabine) in relapsed or refractory AML patients showed that the MDM2 protein expression in leukemic blasts and stem cells are associated with idasanutlin-induced complete remission in patients with AML.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Idasanutlin does not currently have Marketing Authorisation in the EU/UK for any indication.
Idasanutlin is in phase II clinical development for :[6]

- Non-Hodgkin Lymphoma
- Follicular Lymphoma
- Polycythemia Vera

Idasanutlin was granted an orphan designation in the EU in in August 2014 for the treatment of acute myeloid leukaemia.[7]

PATIENT GROUP

DISEASE BACKGROUND

[a] Information provided by Roche Products Ltd.

Leukaemia is cancer of the white blood cells. Acute myeloid leukaemia (AML) refers to a group of blood and bone marrow cancers. This disorder is characterised by incomplete maturation of blood cells and reduced production of other normal haematopoietic stem cells.[8]

In AML, blood cancer starts mainly from young white blood cells called granulocytes or monocytes. In less common types of AML, too many immature platelets or immature red blood cells are produced. The word acute means that the leukaemia can develop fairly quickly. The leukaemic cells can eventually spread to other parts of the body including the lymph nodes and the spleen.[8,9]

The causes of AML are unknown and in most cases it is unclear why leukaemia develops. However, there are a number of risk factors that may increase a person's risk of developing AML, such as exposure to radiation, smoking, exposure to benzene, cancer treatments, blood or genetic disorders.

Most symptoms of AML are due to the effects of the leukaemia cells in the bone marrow and include looking very pale and feeling very tired, becoming breathless easily, having various infections in a short period of time, unusual bleeding and blood spots or rashes on the skin.[10]

In patients younger than 60 years, treatment of AML typically consists of cytotoxic chemotherapy with a general cure rate of 35–40% depending on the cytogenetic classification while similar outcome can be observed in only 5–15% of older patients, primarily because of their inability to tolerate intensive treatment and their generally higher risk disease features.[11]

Treatment outcomes in older patients who are unable to receive intensive chemotherapy are extremely poor, with a median survival of 5–10 months. For the majority of treated AML patients who achieve remission, relapse will occur within 3 years of the initial diagnosis. Hence, the prognosis for AML patients following disease relapse is poor and the treatment options are unsatisfactory.[11]

CLINICAL NEED AND BURDEN OF DISEASE

European age standardised incidence rates of AML in England and Wales in 2015 were 5.3 and 5.4 per 100,000 respectively and accounts for less than 1% of all new cancer cases in the UK.[12]

In England in 2016, there were 3,715 registrations of newly diagnosed cases of myeloid leukaemia (ICD 10 code C92).[13] AML incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK, the peak rate of AML cases is 85-89 years of age (based on 2013-2015 data). In the UK, 56% of AML cases are in males, and 44% are in females. [12]

The company has estimated a UK patient population size of 2,556 and an estimated eligible patient population of 779.[b]

In the UK in 2016, there were 2,601 deaths from AML.[14].Five-year relative survival for AML in men in England (14%) is similar to the average for Europe (15%). Five-year relative survival for AML in women in England (16%) is below the average for Europe (18%).[15]

In England in 2017-2018, there were 47,446 finished consultant episodes (FCE) for acute myeloblastic leukaemia (ICD 10: C92.0) , 44,245 hospital admissions and 118,428 FCE bed days.[16]

AML relapse affects about 50% of all patients who achieved remission after initial treatment, and can occur several months to several years after treatment. However, every patient carries the risk of relapse, and the majority of relapses occur within two to three years of initial treatment.[17]

[b] Information provided by Roche Products Ltd on UK PharmaScan

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Chemotherapy is the main treatment for AML although bone marrow or stem cell transplant may also be offered.[18]
NICE recommend azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have AML with 20–30% blasts and multilineage dysplasia. Azacitidine is not recommended, within its marketing authorisation, for treating AML with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.[19]

CURRENT TREATMENT OPTIONS

Chemotherapy for AML has two phases - induction and consolidation:[10]

- Induction: the aim of induction is to achieve complete remission (CR). The standard induction chemotherapy regimen is the combination of an anthracycline, usually daunorubicin, given for 3 days with continuous infusion of cytarabine for 7 days (3+7).
- Consolidation: consolidation is designed to eliminate residual leukaemia cells that persist after induction. The standard consolidation regimen is intermediate or high dose cytarabine.

Patients might also be given etoposide, daunorubicin, fludarabine, or idarubicin.[18]
After achievement of CR, all patients will eventually relapse without further treatment, and therefore consolidation treatment is essential provided that patients have adequate organ function.[10]

However, recent European LeukemiaNet (ELN) recommendations state that treatment of patients with relapse AML requires a balance assessment of the likely benefit of further therapy versus the potential complications associated with salvage chemotherapy but no specific salvage regimen has emerged as the standard.[20]

PLACE OF TECHNOLOGY

If licensed, idasanutlin in addition to cytarabine will offer an additional treatment option for patients with AML whose condition has become refractory to treatments or has relapsed after prior treatments.

CLINICAL TRIAL INFORMATION

Trial	MIRROS, NCT02545283, **WO29519**; idasanutlin in addition to cytarabine versus cytarabine in addition to placebo; phase III
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU(incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, double-blind
Participants	N=440 (planned); aged 18 years and older; documented/confirmed first/second refractory/relapsed AML using World Health Organization classification, except acute promyelocytic leukaemia; no more than 2 prior induction regimens (excluding prior hematopoietic stem cell transplant) in their first line treatment and one must have included cytarabine with an anthracycline (or

	anthracenedione); Eastern Cooperative Oncology Group performance status of 0 to 1; adequate hepatic and renal function; white blood cell (WBC) count at randomization less than or equal to (</=) 50000 cells per cubic millimetre (/mm^3).
Schedule	Randomised to: • Oral idasanutlin,300 mg twice daily (in Cycle 1) or once daily (in Cycles 2 and 3) in addition to cytarabine, 1 gram per square meter (g/m^2) intravenous (IV) infusion for 5 days of every treatment cycle for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRi), up to 28 additional days are allowed for blood count recovery, if needed. • Placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or CRi, up to 28 additional days are allowed for blood count recovery, if needed.
Follow-up	3 cycles (treatment cycle length=28 days); 5 days of treatment followed by 23 days of rest. Cycle 1: induction therapy; cycle 2 and 3: consolidation therapy for responding participants.
Primary Outcomes	Overall Survival in TP53 wild type (WT) population [Time Frame: Baseline up to approximately 3.5 years]
Secondary Outcomes	• Overall Survival in the overall population [Time Frame: Baseline up to approximately 3.5 years] • Percentage of participants in complete remission (CR) at the end of induction according to Hematologic Malignancy Response Assessment (HMRA) in TP53 WT Population [Time Frame: At the end of induction (up to Day 56)] • Percentage of participants in incomplete platelet count recover (CRp) at the end of induction according to HMRA in TP53 WT population [Time Frame: At the end of induction (up to Day 56)] • Percentage of participants with Overall Remission at the end of induction according to HMRA in TP53 WT population [Time Frame: At the end of induction (up to Day 56)] • EFS according to HMRA in TP53 WT population [Time Frame: Baseline up to treatment failure, relapse or death from any cause (up to approximately 3.5 years)] • LFS according to HMRA in TP53 WT population [Time Frame: Date of remission to date of relapse or death (up to approximately 3.5 years)] • Percentage of participants undergoing HSCT following response, in TP53 WT population [Time Frame: Baseline up to approximately 3.5 years]

	• Percentage of participants in CR at the end of induction according to HMRA in overall population [Time Frame: At the end of induction (up to Day 56)] • Percentage of participants in CRp at the end of induction according to HMRA in overall population [Time Frame: At the end of induction (up to Day 56)] • Percentage of participants with Overall Remission at the End of Infusion According to HMRA in Overall Population [Time Frame: At the end of induction (up to Day 56)] • EFS According to HMRA in Overall Population [Time Frame: Baseline up to treatment failure, relapse or death from any cause (up to approximately 3.5 years)] • LFS According to HMRA in Overall Population [Time Frame: Date of remission to date of relapse or death (up to approximately 3.5 years)] • Percentage of Participants Undergoing HSCT Following Response, in Overall Population [Time Frame: Baseline up to approximately 3.5 years] • Apparent Clearance (CL/F) of Idasanutlin [Time Frame: Cycle 1: Predose (0 hour [Hr]), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Apparent Volume of Distribution (Vd/F) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Maximum Concentration Observed (Cmax) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Steady-State Concentration (C trough) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Area Under the Concentration-Time Curve (AUC) During One Dosing Interval (AUCtau) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]

	• AUC from Time Zero to 24 Hours Post Dose (AUC0-24) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Half-Life (t 1/2) of Idasanutlin [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)] • Total Clearance (CL) of Cytarabine [Time Frame: Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)] • Volume of Distribution (Vd) of Cytarabine [Time Frame: Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)] • Percentage of Participants with Adverse Events [Time Frame: Baseline up to approximately 3.5 years] • Change from Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Score [Time Frame: Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)] • Change from Baseline in EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire Score [Time Frame: Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as December 2019. Study completion date reported as May 2021.

ESTIMATED COST

The cost of idasanutlin is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ivosidenib for treating relapsed or refractory IDH1-positive acute myeloid leukaemia (ID1548). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Quizartinib for treating relapsed or refractory acute myeloid leukaemia (ID1325). Expected date of issue to be confirmed.
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Clofarabine for refractory or relapsed acute myeloid leukaemia (AML) as a bridge to stem cell transplantation (all ages). 170080P. November 2018.
- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P. February 2017.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All ages): Revised. B04/P/a. January 2015.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

OTHER GUIDANCE

- Alberta Health Services. Clinical Practice Guidelines, Acute Myeloid Leukemia. 2017.[21]
- NHS. Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 2016.[22]
- European Society for Medical Oncology (ESMO). Acute Myeloblastic Leukaemia in Adult Patients: ESMO Clinical Practice Guidelines. 2013.[23]
- British Society for Haematology. Guidelines on the management of acute myeloid leukaemia in adults. 2006.[24]

REFERENCES

1 Lehmann C, Friess T, Birzele F, Kiialainen A, Dangl M. Superior anti-tumor activity of the MDM2 antagonist idasanutlin and the Bcl-2 inhibitor venetoclax in p53 wild-type acute myeloid leukemia models. *Journal of hematology & oncology*. 2016;9(1):50-. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27353420.

2 Glenn KJ, Yu LJ, Reddy MB, Fretland AJ, Parrott N, Hussain S, et al. Investigating the effect of autoinduction in cynomolgus monkeys of a novel anticancer MDM2 antagonist, idasanutlin, and relevance to humans. *Xenobiotica*. 2016 2016/08/02;46(8):667-76. Available from: https://doi.org/10.3109/00498254.2015.1110761.

3 ClinicalTrials.gov. *A Study of Idasanutlin With Cytarabine Versus Cytarabine Plus Placebo in Participants With Relapsed or Refractory Acute Myeloid Leukemia (AML) (MIRROS).* Available from: https://clinicaltrials.gov/ct2/show/NCT02545283 [Accessed 10 December 2018]

4 Gras J. Idasanutlin. MDM2 (Hdm2) inhibitor, Treatment of acute myeloid leukemia, Hematological cancer therapy. *Drugs of the Future*. 2018;43(2):87. Available from: https://journals.prous.com/journals/servlet/xmlxsl/pk_journals.xml_summary_pr?p_JournalId=2&p_RefId=2743593&p_IsPs=N.

5 Reis B, Jukofsky L, Chen G, Martinelli G, Zhong H, So V, et al. Clinical Response to Idasanutlin (RG7388) in Acute Myeloid Leukemia Patients Is Associated with Pre-Treatment MDM2 Protein Expression in Leukemic Blasts and Leukemic Stem Cells. *Blood*. 2015;126(23):2580-. Available from: http://www.bloodjournal.org/content/126/23/2580.

6 ClinicalTrials.gov. *Idasanutlin.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=Idasanutlin&titles=&outc=&spons=roche&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 15 January 2019]

7 European Medicines Agency. *Public summary of opinion on orphan designation.* Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141328 [Accessed 15 January 2019]

8 National Organization for Rare Disorders. *Acute Myeloid Leukemia (AML).* Available from: https://rarediseases.org/physician-guide/acute-myeloid-leukemia-aml/ [Accessed 12 December 2018]

9 Cancer Research UK. *Acute Myeloid Leukaemia.* Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/about-acute-myeloid-leukaemia [Accessed 12 December 2018]

10 Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *The Lancet*. 2013 2013/02/09/;381(9865):484-95. Available from: http://www.sciencedirect.com/science/article/pii/S0140673612617279.

11 Ravandi F, Gojo I, Patnaik MM, Minden MD, Kantarjian H, Johnson-Levonas AO, et al. A phase I trial of the human double minute 2 inhibitor (MK-8242) in patients with refractory/recurrent acute myelogenous leukemia (AML). *Leukemia Research*. 2016 2016/09/01/;48:92-100. Available from: http://www.sciencedirect.com/science/article/pii/S0145212616301552.

12 Cancer Research UK. *Acute myeloid leukaemia (AML) incidence statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence#heading-Two [Accessed 13 December 2018]

13 Office for National Statistics. *Cancer registration statistics, England.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 13 December 2018]

14 Cancer Research UK. *Acute myeloid leukaemia (AML) mortality statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/mortality [Accessed 15 January 2019]

15 Cancer Research UK. *Acute myeloid leukaemia (AML) survival statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/survival#heading-Zero [Accessed 15 January 2019]

16 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 17 December 2018]

17 Leukaemiacare. *Relapse in Acute Myeloid Leukaemia (AML).* Available from: https://www.leukaemiacare.org.uk/wp-content/uploads/Relapse-in-Acute-Myeloid-Leukaemia-AML-Web-Version.pdf [Accessed 12 December 2018]

18 Cancer Research UK. *Chemotherapy for acute myeloid leukaemia (AML).* Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/treating-aml/chemotherapy/chemotherapy-for-aml [Accessed 12 December 2018]

19 National Institute of Health and Care Excellence. *Myeloid leukaemia.* Available from: https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers#path=view%3A/pathways/blood-and-bone-marrow-cancers/myeloid-leukaemia.xml&content=view-index [Accessed 13 December 2018]

20 Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-47. Available from: http://www.bloodjournal.org/content/bloodjournal/129/4/424.full.pdf.

21 Alberta Health Services. *Clinical Practice Guideline, Acute Myeloid Leukemia.* Available from: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe006-aml.pdf [Accessed 13 December 2018]

22 NHS. *Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML* Available from: http://www.yhscn.nhs.uk/media/PDFs/cancer/Haem%20docs/SYR%20Network%20Guidelines%20new%20version%20AML.pdf [Accessed 13 December 2018]

23 Fey MF, Buske C, on behalf of the ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2013;24(suppl_6):vi138-vi43. Available from: http://dx.doi.org/10.1093/annonc/mdt320.

24 Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, Craddock C, et al. Guidelines on the management of acute myeloid leukaemia in adults. *British Journal of Haematology*. 2006;135(4):450-74. Available from: https://doi.org/10.1111/j.1365-2141.2006.06314.x.

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