NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Pevonedistat in addition to azacitidine for Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia and Low Blast Acute Myeloid Leukemia – first-line

NIHRIO ID	12063	**NICE ID**	10380
Developer/Company	Takeda UK Ltd	**UKPS ID**	649537

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pevonedistat in addition to azacitidine is being investigated for the treatment of higher-risk myelodysplastic syndromes (HR-MDS), chronic myelomonocytic leukemia (CMML) and low-blast acute myeloid leukemia (LB-AML). MDS is a group of long-term debilitating and life-threatening malignant blood disorders in which the bone marrow does not produce enough healthy blood cells. In CMML, the bone marrow produces too many abnormal and immature monocytes which do not work properly. MDS and CMML can lead to severe anaemia, infections or bleeding and result in cancer of the white blood cells (acute myeloid leukemia). There is a high unmet need for transplant-ineligible patients who lack treatment options.

Pevonedistat, administered by IV infusion, blocks the activity of an enzyme in the body called NEDD8-activating enzyme (NAE). NAE is involved in the growth and spread of cancer cells. By blocking NAE in patients with AML, pevonedistat is expected to prevent the degradation of certain proteins affecting key pathways including DNA repair, the cell cycle, and cell survival, thereby preventing the development and worsening of cancer. Chemotherapy drugs, such as azacitidine, work in different ways to stop the growth of cancer cells. If licensed, pevonedistat in addition to azacitidine would offer an additional first-line treatment option for adults with HR-MDS, CMML, or LB-AML.

PROPOSED INDICATION

Pevonedistat in addition to azacitidine for first line treatment in higher-risk myelodysplastic syndromes (HR-MDS), chronic myelomonocytic leukemia (CMML) and low-blast acute myeloid leukemia (LB-AML).[a]

TECHNOLOGY

DESCRIPTION

Pevonedistat (TAK-924/MLN4924) is a small molecule inhibitor of NEDD8 (Neural precursor cell expressed, developmentally down-regulated 8) activating enzyme (NAE) with potential antineoplastic activity. Pevonedistat binds to and inhibits NAE.[1] By inhibiting NAE in the neddylation pathway, pevonedistat prevents degradation of certain proteins affecting key pathways including DNA repair, the cell cycle, and cell survival, thereby interfering with protein homeostasis and leading to cancer cell death.[a]

NAE is an essential component of the NEDD8 conjugation pathway that controls the activity of the cullin-RING E3 subtype of ubiquitin ligases, thereby regulating the turnover of a subset of proteins upstream of the proteasome. Substrates of cullin-RING ligases (CRLs) have important roles in cellular processes associated with cancer cell growth and survival pathways. Pevonedistat disrupts CLRs-mediated protein turnover leading to apoptotic death in human tumour cells by the deregulation of S-phase DNA synthesis.[2]

Pevonedistat in combination with azacitidine is currently in clinical development for the treatment of HR-MDS, CMML and LB-AML. In the phase III trial (PANTHER, NCT03268954), patients receive azacitidine 75 mg/m^2, intravenously or subcutaneously (per investigator's choice), on days 1 to 5, days 8 and 9 and pevonedistat 20 mg/m^2, 60 (±10) minute infusion, intravenously, on days 1, 3, and 5 in 28-day treatment cycles.[3] Patients, including those who achieve a complete response, may receive study treatment until they experience unacceptable toxicity, relapse, transformation to AML (for patients with HR-MDS or CMML), or progressive disease (for patients with LB-AML), the sponsor terminates the study, or discontinuation due to other reasons. [a]

INNOVATION AND/OR ADVANTAGES

Pevonedistat is a first-in-class NAE inhibitor in AML and MDS.[4] The combination of azacitidine and pevonedistat were shown to result in significantly increased DNA-damage and cell death compared to single agent alone, as measured by Western Blotting and a fluorescence activated cell sorter (FACS) analysis of cell cycle distributions. Thus pevonedistat and azacitidine can combine to produce synergistic antitumour activity in pre-clinical models of AML. Coupled with their non-overlapping clinical toxicities, these data suggest the potential for future combination studies in clinical trials.[5]

Results from a global phase II clinical trial (NCT02610777) show that the combination of pevonedistat and azacitidine is a highly active, promising therapeutic approach and suggest benefit in the HR-MDS subgroup across multiple clinically meaningful endpoints, including overall survival (OS), event-free survival (EFS), complete remission (CR), overall response rate (ORR), the duration of response and transfusion independence, with a safety profile similar to azacitidine alone.[6,7]

[a] Information provided by Takeda UK Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pevonedistat does not currently have Marketing Authorisation in the EU/UK for any indication. Pevonedistat was granted an EU orphan designation for the treatment of myelodysplastic syndromes (December 2018) and acute myeloid leukaemia (July 2019).[8,9]

Pevonedistat in combination with azacitidine is currently in phase II and III clinical development for several indications, including relapsed or refractory AML, atypical chronic myeloid leukemia (BCR-ABL1 negative) and chronic eosinophilic leukemia.[10]

In July 2020, Takeda Ltd announced that pevonedistat was granted Breakthrough Therapy Designation by US FDA for the treatment of patients with HR-MDS.[11]

PATIENT GROUP

DISEASE BACKGROUND

Myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affects quality of life due to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with blood transfusions, and complications such as severe infections.[12] MDS can affect people of any age, but is most common in adults aged 70 to 80 years.[13]

The main types of MDS are MDS with single lineage dysplasia, MSD with multilineage dysplasia and MDS with excess blasts.[13] The Revised International Prognostic Scoring System (IPSS-R) classifies prognosis as very low-risk, low-risk, intermediate-risk, high-risk or very high-risk based on blood cell levels, cytogenetic factors and number of immature cells (blasts) in the bone marrow and blood.[12] High risk (HR)-MDS is generally progressive in nature and can transform into AML.[14]

The WHO system, which divides MDS into eight subgroups, does not class chronic myelomonocytic leukemia (CMML) as a type of MDS, but rather within a new category of myelodysplastic-myeloproliferative overlap syndromes.[15] A myeloproliferative disorder is a condition where there are too many blood cells made. In CMML, the bone marrow produces too many abnormal monocytes which are not fully developed to work properly.[16]

Both HR-MDS and CMML can develop into an AML if the number of blast cells in the blood rises above 20%.[16] AML is a rapidly growing cancer of the blood and bone marrow, with a poor prognosis if left untreated. Around 30% of patients with MDS progress to AML.[17] AML can be referred to as acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia.[18] Low-blood AML (LB-AML) (with 20-30% bone marrow blasts) is characterized by peculiar features, has increased frequency in elderly individuals and after cytotoxic treatment for a different primary disease (therapy-related), poor-risk cytogenetics, lower white blood cell counts, and less frequent mutations of *NPM1* and *FLT3* genes.[19]

Some people with myelodysplastic syndromes and CMML do not have any symptoms at all, or symptoms tend to be mild at first and get worse slowly. The symptoms are caused by a drop in the number of blood cells and could include:[16,20]

- tiredness and sometimes breathlessness because of a low red blood cell count (anaemia)

- frequent infections because of a low white blood cell count
- bleeding (such as nosebleeds) or bruising easily because of a low platelet count

Some may experience pain or discomfort in the abdomen from an enlarged spleen.[20] The factors that may raise a person's risk of developing MDS include previous cancer therapy (including radiotherapy) and environmental toxins.[17]

In addition to the MDS and CMML symptoms above, patients with AML may also experience general weakness, a high temperature, weight loss, pain in bones or joints, swollen lymph nodes, and pale skin.[21]

CLINICAL NEED AND BURDEN OF DISEASE

MDS are a rare group of blood disorders with an approximated incidence of 4 per 100,000 per year, but are predominantly diseases of the elderly with an incidence of > 30 per 100,000 per year over the age of 70 years.[22] In 2017, there were 2,385 registrations of newly diagnosed cases of MDS (ICD-10 code: D46) and the direct age-standardised rate per 100,000 population of newly diagnosed cases was 6.7 among males and 3.0 among females in England.[23]

The natural course of MDS is variable, with survival ranging from a few weeks to several years. For patients who have had MDS for 5 years, the median overall survival time is 15-30 months and the risk of progression to AML is 25-35%.[24] Previously reported 5-year overall survival rate for MDS within the EU was estimated at 31%.[25] The median survival for CMML is 20 months, range 7–60 months.[22] Between 15 and 30 out of every 100 people with CMML (between 15 to 30%) transform into AML.[16]

In 2017, there were 4,102 registrations of newly diagnosed cases of AML (ICD-10 code: C92) and the direct age-standardised rate per 100,000 population of newly diagnosed cases was 0.2 among males and 0.1 among females in England.[23] More than 40 out of 100 (40%) of new cases are in people aged 75 and over.[26] Generally with AML, around 20 out of 100 people (around 20%) will survive their leukaemia for 5 years or more after their diagnosis.[27]

The 2018-2019 Hospital Episodes Statistics for England recorded a total of 61,846 finished consultant episodes (FCE) for MDS, resulting in 60,180 hospital admissions and 25,065 FCE bed days and 55,078 day cases. The FCE for AML was 57,796, resulting in 53,891 hospital admissions, 130,391 FCE bed days and 45,349 day cases.[28]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The type of treatment depends on the type of MDS, risk group and other health conditions of the patient. The aim of treatment is to get the number and type of blood cells in the bloodstream back to normal.[29] Central to the management of MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, low-dose standard chemotherapy or immunosuppressive therapies are used for some patients.[17,22]

People with low risk MDS and CMML patients without (or with only mild asymptomatic) cytopenias or major signs of myeloproliferation may be observed without treatment, also called 'watchful waiting'.[17,26,30] The only way to potentially cure MDS and CMML is to have intensive treatment with an allogeneic stem cell transplant from a donor; however, it is not

suitable for the majority of patients.[16,29] For patients who are transplant ineligible, there is a lack of treatment options and there is a high unmet need.

Many patients become red blood cell transfusion dependent, particularly those with low or intermediate-1 risk MDS. A major goal of treatment is then to achieve transfusion independence and a number of treatments can be used to reduce or eliminate the transfusion need for MDS patients. For patients with intermediate-2 or high risk MDS who are not eligible for haematopoietic stem cell transplantation anticancer drugs, such as azacitidine, intensive chemotherapy or oral low dose melphalan are recommended as a treatment options.[17,22] Hypomethylating agents, such as azacitidine offer an alternative to intensive treatment approaches in high risk MDS. They do not offer a cure but, by modifying the disease, may offer a survival benefit and are well tolerated in the elderly and those with comorbidities.[22]

The main treatment for AML is chemotherapy. Other treatments include radiotherapy, growth factors, stem cell or bone marrow transplants, and targeted cancer drugs.[26] MDS and CMML patients with high risk of developing AML are likely to receive chemotherapy similar to that used to treat AML.[29,31]

CURRENT TREATMENT OPTIONS

According to NICE, azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have:[32]

- Intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder
- AML with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification

PLACE OF TECHNOLOGY

If licensed, pevonedistat in addition to azacitidine would offer an additional first-line treatment option for adults with HR-MDS, CMML, or LB-AML.

CLINICAL TRIAL INFORMATION

Trial	**PANTHER; NCT03268954; EudraCT 2017-000318-40; Pevonedistat-3001;** A Phase 3, Randomized, Controlled, Open-label, Clinical Study of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia **Phase III –** Active, not recruiting **Location(s):** EU (incl UK), USA, Canada and other countries **Primary completion date:** Nov 2020
Trial design	Randomised (1:1 randomised allocation to treatment), parallel assignment, open label
Population	N=454 (actual), adults with morphologically confirmed diagnosis of myelodysplastic syndromes (MDS) or nonproliferative chronic myelomonocytic leukemia (CMML) (i.e., with white blood cell [WBC] <13,000/µL) or low-blast

	acute myelogenous leukemia (AML) based on FAB or WHO classification; aged 18 years and older
Intervention(s)	Pevonedistat 20 mg/m^2 (intravenous) and azacitidine 75 mg/m^2 (intravenous or subcutaneous [per investigator's choice]) combination
Comparator(s)	Azacitidine 75 mg/m^2 (intravenously or subcutaneously [per investigator's choice])
Outcome(s)	Primary outcome: Event-Free Survival (EFS) [Time frame: from randomization until transformation to acute myeloid leukemia in patients with MDS or CMML, or death due to any cause : up to 6 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02610777; EudraCT 2015-000221-37; Pevonedistat-2001; A Phase 2, Randomized, Controlled, Open-Label, Clinical Study of the Efficacy and Safety of Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia and Low-Blast Acute Myelogenous Leukemia **Phase II –** Active, not recruiting **Location(s):** EU (not incl UK), USA, Canada and Israel **Primary completion date:** Sep 2019
Trial design	Randomised (1:1 randomised allocation to treatment), parallel assignment, open label
Population	N=120 (actual); adults with Morphologically confirmed diagnosis of MDS or nonproliferative CMML (that is, with white blood cells [WBC] <20,000 per microliter [/mcL]) or low blast AML; aged 18 years and older
Intervention(s)	Pevonedistat 20 mg/m^2 (intravenous) and azacitidine 75 mg/m^2 (intravenous or subcutaneous [per investigator's choice]) combination
Comparator(s)	Azacitidine 75 mg/m^2 (intravenous or subcutaneous [per investigator's choice])
Outcome(s)	Primary outcome: Overall Survival (OS) [Time frame: from randomization until death up to 44 months] See trial record for full list of other outcomes
Results (efficacy)	Although not statistically significant, pevonedistat and azacitidine combination (P+A) increased OS, EFS (AML transformation or death), and response rates vs azacitidine (A) alone, particularly in patients with higher-risk MDS.[6] • In the intention-to-treat (ITT) population (n = 120), median OS was numerically longer with P+A vs A: 21.8 vs 19.0 mos (HR 0.80; 95% CI 0.51–1.26; *P* = 0.334; median follow-up 21.4 vs 19.0 mos).

	• EFS in the ITT population trended longer in the P+A arm vs. A alone with a median of 21.0 mos. vs. 16.6 mos (HR 0.65; 95% CI 0.41–1.02; *P* = 0.060) • Overall response rate (ORR) in the ITT response evaluable patients was 71% vs. 60% for P+A and A, respectively • Subgroup analyses median OS with P+A vs A in higher-risk MDS patients (n = 67) of 23.9 vs 19.1 mos (HR 0.70; 95% CI 0.39–1.27; *P* = 0.240) and in LB-AML patients (n = 36) of 23.6 vs 16.0 mos (HR 0.49; 95% CI 0.22–1.11; *P* = 0.081). • EFS was significantly longer in the higher-risk MDS arm (median 20.2 vs 14.8 mos; HR 0.54; 95% CI 0.29–1.00; *P* = 0.045). • In HR-MDS CR rate was 52% vs 27% in the P+A arm vs. A alone (*P* = 0.05)
Results (safety)	The safety profile of pevonedistat combined with azacitidine was similar to azacitidine alone, and did not lead to increased myelosuppression.[7] • Grade ≥3 adverse events were reported in 90% vs 87% of P+A vs A pts; the most common were neutropenia (333% vs 27%), febrile neutropenia (26% vs 29%), anaemia (19% vs 27%), thrombocytopenia (19% vs 23%), decreased neutrophil count (21% vs 10%), and pneumonia (12% vs. 10%).[6,7] • On-study deaths occurred in 9% of P+A pts vs 16% of A pts.[6]

ESTIMATED COST

The cost of pevonedistat is not yet known.

Azacitidine is already marketed in the UK. The NHS indicative price of azacitidine is £321 for a 100-mg vial (excluding VAT).[33] Generic versions of azacitidine have become available in 2020 in the UK and therefore the price of azacitidine to the NHS is subject to change.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Glasdegib with chemotherapy for untreated acute myeloid leukaemia (GID-TA10314). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Guadecitabine for untreated acute myeloid leukaemia (GID-TA10325). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Talacotuzumab for untreated acute myeloid leukaemia (GID-TA10249). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (GID-TA10478). Expected date of issue to be confirmed.
- NICE technology appraisal. Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia (TA552). December 2018.

- NICE technology appraisal. Gemtuzumab ozogamicin for untreated acute myeloid leukaemia (TA545). November 2018.
- NICE technology appraisal. Midostaurin for untreated acute myeloid leukaemia (TA523). June. 2018.
- 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.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia, Version 3.2019. 2019.[34]
- European Hematology Association and the European LeukemiaNet. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults. 2018.[30]
- London Cancer. Guidelines for the Diagnosis and Management of Adult Myelodysplastic Syndromes. 2015.[35]
- European Society for Medical Oncology. Myelodysplastic syndromes: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2014.[24]
- British Journal of Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2013.[22]

ADDITIONAL INFORMATION

REFERENCES

1 National Cancer Institute (NCI). *NCI drug dictionary: pevonedistat*. 2020. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/pevonedistat [Accessed 13 August 2020].

2 Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature*. 2009 2009/04/01;458(7239):732-6. Available from: https://doi.org/10.1038/nature07884.

3 ClinicalTrials.gov. *Pevonedistat Plus Azacitidine Versus Single-Agent Azacitidine as First-Line Treatment for Participants With Higher-Risk Myelodysplastic Syndromes (HR MDS), Chronic Myelomonocytic Leukemia (CMML), or Low-Blast Acute Myelogenous Leukemia (AML) (PANTHER). Trial ID: NCT03268954*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03268954 [Accessed 13 August 2020].

4 Swords RT, Coutre S, Maris MB, Zeidner JF, Foran JM, Cruz J, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood*. 2018;131(13):1415-24. Available from: https://doi.org/10.1182/blood-2017-09-805895.

5 Smith PG, Traore T, Grossman S, Narayanan U, Carew JS, Lublinksky A, et al. Azacitidine/Decitabine Synergism with the NEDD8-Activating Enzyme Inhibitor MLN4924 in

Pre-Clinical AML Models. *Blood*. 2011;118(21):578-. Available from: https://doi.org/10.1182/blood.V118.21.578.578.

6 Ades L, Watts JM, Radinoff A, Arnan M, Cerrano M, Lopez PF, et al. Phase II study of pevonedistat (P) + azacitidine (A) versus A in patients (pts) with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (LB AML) (NCT02610777). *Journal of Clinical Oncology*. 2020;38(15_suppl):7506-. Available from: https://doi.org/10.1200/JCO.2020.38.15_suppl.7506.

7 Takeda Pharmaceutical Company Limited. *Takeda Announces Compelling Data from the Phase 2 Trial of Pevonedistat Plus Azacitidine in Patients with Higher-Risk MDS*. 2020. Available from: https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-compelling-data-from-the-phase-2-trial-of-pevonedistat-plus-azacitidine-in-patients-with-higher-risk-mds/ [Accessed 13 August 2020].

8 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Pevonedistat for the treatment of acute myeloid leukaemia*. Committee for Orphan Medicinal Products; 2019. Report No.: EMADOC-628903358-1130. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/19/2186-public-summary-opinion-orphan-designation-pevonedistat-treatment-acute-myeloid-leukaemia_en.pdf [Accessed 13 August 2020].

9 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Pevonedistat for the treatment of myelodysplastic syndromes*. Committee for Orphan Medicinal Products; 2019. Report No.: EMA/806417/2018. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/18/2120-public-summary-opinion-orphan-designation-pevonedistat-treatment-myelodysplastic-syndromes_en.pdf [Accessed 13 August 2020].

10 ClinicalTrials.gov. *Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Pevonedistat, azacitidine | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&intr=Pevonedistat%2C+azacitidine&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=f&phase=1&phase=2 [Accessed 13 August 2020].

11 Takeda Pharmaceutical Company Limited. *Takeda Announces U.S. FDA Breakthrough Therapy Designation Granted for Pevonedistat for the Treatment of Patients with Higher-Risk Myelodysplastic Syndromes (HR-MDS)*. 2020. Available from: https://bit.ly/39IYsDS [Accessed 19 August 2020].

12 National Institute for Health and Care Excellence (NICE). *Final scope for the appraisal of luspatercept for treating anaemia caused by myelodysplastic syndromes*. 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10508/documents/final-scope [Accessed 13 August 2020].

13 National Health Service (NHS). *Myelodysplastic syndrome (myelodysplasia)*. 2018. Available from: https://www.nhs.uk/conditions/myelodysplasia/ [Accessed 13 August 2020].

14 Ma Y, Shen J, Wang L-X. Successful treatment of high-risk myelodysplastic syndrome with decitabine-based chemotherapy followed by haploidentical lymphocyte infusion: A case report and literature review. *Medicine*. 2018;97(16):e0434-e. Available from: https://doi.org/10.1097/MD.0000000000010434.

15 National Institute for Health and Care Excellence (NICE). *Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia: Final Scope*. 2009. Available from: https://www.nice.org.uk/guidance/ta218/documents/myelodysplastic-syndromes-azacitidine-final-scope2 [Accessed 13 August 2020].

16 Cancer Research UK (CRUK). *What is chronic myelomonocytic leukaemia (CMML)?* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/chronic-myelomonocytic-leukaemia-cmml/what-is-cmml [Accessed 13 August 2020].

17 National Institute for Health and Care Excellence (NICE). *Final scope for the appraisal of lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality*. 2012. Available from: https://www.nice.org.uk/guidance/ta322/documents/myelodysplastic-syndrome-deletion-5q-lenalidomide-final-scope2 [Accessed 13 August 2020].

18 National Cancer Institute (NCI). *Adult Acute Myeloid Leukemia Treatment (PDQ®)–Patient Version*. 2020. Available from: https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq#:~:text=It%20is%20the%20most%20common,leukemia%2C%20and%20acute%20nonlymphocytic%20leukemia. [Accessed 13 August 2020].

19 De Bellis E, Fianchi, L., Buccisano, F., Criscuolo, M., Maurillo, L., Cicconi, L., Brescini, M., Del Principe, M. I., Di Veroli, A., Venditti, A., Lo-Coco, F., Voso, M. T. TREATMENT OF LOW-BLAST COUNT AML USING HYPOMETHYLATING AGENTS. *Mediterranean Journal of Hematology and Infectious Diseases*. 2017 1 July 2017;9(1):e2017045. Available from: https://doi.org/10.4084/mjhid.2017.045.

20 Cancer Research UK (CRUK). *What are myelodysplastic syndromes (MDS)?* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/myelodysplastic-syndromes/what-is-mds [Accessed 13 August 2020].

21 Cancer Research UK (CRUK). *Acute myeloid leukaemia (AML): Symptoms.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/symptoms [Accessed 08 September 2020].

22 Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, et al. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. *British Journal of Haematology*. 2014;164(4):503-25. Available from: https://doi.org/10.1111/bjh.12694.

23 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2017*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 13 August 2020].

24 Fenaux P, Haase D, Sanz GF, Santini V, Buske C. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up &#x2020. *Annals of Oncology*. 2014;25:iii57-iii69. Available from: https://doi.org/10.1093/annonc/mdu180.

25 Maynadié M, De Angelis R, Marcos-Gragera R, Visser O, Allemani C, Tereanu C, et al. Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study. *Haematologica*. 2013;98(2):230-8. Available from: https://doi.org/10.3324/haematol.2012.064014.

26 Cancer Research UK (CRUK). *What is acute myeloid leukaemia (AML)?* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/about-acute-myeloid-leukaemia [Accessed 13 August 2020].

27 Cancer Research UK (CRUK). *Acute myeloid leukaemia (AML): Survival.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/survival#:~:text=The%20statistics%20below%20are%20for,or%20more%20after%20their%20diagnosis. [Accessed 08 September 2020].

28 Office for National Statistics. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis*. 2018-19. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 13 August 2020].

29 Cancer Research UK (CRUK). *Tests and treatment for myelodysplastic syndrome (MDS).* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/myelodysplastic-syndromes/treatment [Accessed 14 August 2020].

30 Itzykson R, Fenaux P, Bowen D, Cross NCP, Cortes J, De Witte T, et al. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults: Recommendations From the European Hematology Association and the European LeukemiaNet. *HemaSphere*. 2018;2(6):e150. Available from: https://doi.org/10.1097/hs9.0000000000000150.

31 Cancer Research UK (CRUK). *Tests and treatment for chronic myelomonocytic leukaemia (CMML).* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/chronic-myelomonocytic-leukaemia-cmml/tests-treatment [Accessed 08 September 2020].

32 National Institute for Health and Care Excellence (NICE). *Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218)*. Last Update Date: February 2014. Available from: https://www.nice.org.uk/guidance/ta218/chapter/1-Guidance [Accessed 14 August 2020].

33 British National Formulary (BNF). *Medical forms: Azacitidine.* Available from: https://bnf.nice.org.uk/medicinal-forms/azacitidine.html [Accessed 08 September 2020].

34 Tallman MS, Wang ES, Altman JK, Appelbaum FR, Bhatt VR, Bixby D, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2019;17(6):721. Available from: https://doi.org/10.6004/jnccn.2019.0028.

35 London Cancer. *Guidelines for the Diagnosis and Management of Adult Myelodysplastic Syndromes* Last Update Date: Available from: http://www.londoncancer.org/media/111759/myelodysplastic-syndromes-london-cancer-guidelines-2015.pdf [Accessed 08 Septemeber 2020].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.