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HEALTH TECHNOLOGY BRIEFING
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Magrolimab in addition to azacitidine for myelodysplastic syndromes - First-line

NIHRIO ID	29679	**NICE ID**	10609
Developer/Company	Gilead Sciences Ltd	**UKPS ID**	662212

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Magrolimab in addition to azacitidine is in clinical development for the treatment of myelodysplastic syndromes (MDS) in adults. MDS are a group of disorders in which the red blood cells, white blood cells and platelets produced by the bone marrow do not mature normally. Patients with myelodysplastic syndromes can develop tiredness or weakness due to anaemia (low red blood cell counts), infections due to low white blood cell counts, and bruising or abnormal bleeding due to low platelet counts. MDS are long-term debilitating and life-threatening diseases because they can lead to severe anaemia, infections or bleeding, and can result in leukaemia.

Magrolimab is a monoclonal antibody designed to recognise and attach to a protein called CD47 that is widely found on the surface of the abnormal cells seen in MDS. By binding to CD47, magrolimab is thought to help the immune system detect and kill the abnormal blood cells. Azacitidine is an analogue of cytidine which is part of the fundamental genetic material of cells (DNA and RNA). Azacitidine is already approved for MDS and the addition of Magrolimab may provide synergistic efficacy and safety. If licenced the combination of magrolimab and azacitidine could provide a first line treatment option for MDS patients who have few therapeutic options available.

PROPOSED INDICATION

Treatment-naïve adult patients with intermediate/high/very high risk myelodysplastic syndromes (MDS).[1]

TECHNOLOGY

DESCRIPTION

Magrolimab (also referred to as 5F9, Hu5F9-G4), is a humanized IgG4 monoclonal antibody which has high affinity for human CD47 resulting in its blockade, enhancing the phagocytosis of cancer cells by macrophages. Azacitidine is an analogue of cytidine that synergizes with magrolimab to enhance phagocytosis.[2-4]

Magrolimab in addition to azacitidine is currently being evaluated in previously untreated participants with intermediate/high/very high risk myelodysplastic syndrome (MDS) in the phase III clinical trial (NCT04313881). Patients receive the following magrolimab and azacitadine dosing regimens:[1]
Magrolimab:

- Cycle 1: 1mg/kg priming dose on Days 1 and 4; 15 mg/kg on Day 8; and 30 mg/kg on Days 11, 15, and 22
- Cycle 2: weekly doses of 30 mg/kg on Days 1, 8, 15, and 22
- Cycle 3 and onward: 30 mg/kg every 2 weeks on Days 1 and 15

Azacitidine: 75 mg/m^2 on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each cycle.

INNOVATION AND/OR ADVANTAGES

There are currently few therapeutic options for the treatment of MDS in the UK, with high risk MDS particularly limited in curative treatments.[5]

Magrolimab is a novel immunotherapy that blocks a key macrophage checkpoint. Azacitidine is an antineoplastic agent that is believed to exert its effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. A phase 1b study of magrolimab in addition to azacitidine for MDS demonstrated positive efficacy and safety results.[2,3]

Magrolimab may offer benefits over current options, with the ability to target leukemia stem cells (LSC), preventing acute myeloid leukemia (AML) development in MDS patients.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Magrolimab is not licensed for any other cancer indications in the EU/UK.

Magrolimab has the following regulatory designations/awards:

- EMA PRIME designation for MDS in October 2020;[6]
- EU Orphan drug designation for MDS in June 2020;[7]
- FDA Breakthrough Therapy Designation for the treatment of MDS in September 2020.[8]

Magrolimab in addition to azacitidine is also in a phase 3 clinical trial for acute myeloid leukemia and in phase 2 trials for myeloid malignancies.[9]

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.[10] MDS can affect people of any age, but is most common in adults aged 70 to 80 years.[5]

The main types of MDS are MDS with single lineage dysplasia, MSD with multilineage dysplasia and MDS with excess blasts.[5] 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.[10] HR-MDS is generally progressive in nature and can transform into acute myeloid leukemia (AML).[11]

HR-MDS can develop into AML if the number of blast cells in the blood rises above 20%.[12] 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.[13]

Some people with MDS 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:[14]

- 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.[15] The factors that may raise a person's risk of developing MDS include previous cancer therapy (including radiotherapy) and exposure to the chemical benzene.[13,14]

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.[16] 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.[17]

The natural course of MDS is variable, with survival ranging from a few weeks to several years. The 5-year overall survival rate for MDS within the EU is estimated at 31% and the risk of progression to AML is 25-35% at five years.[18,19]

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 61,336 finished consultant episodes (FCE) for MDS (ICD-10 code C46), resulting in 59,794 hospital admissions and 24,174 FCE bed days and 52,892 day cases.[20] At the time of EU Orphan designation, myelodysplastic syndromes affected less than 2 in 10,000 people in the EU. This was equivalent to a total of fewer than 104,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000.[7]

In 2019 there were 1,126 deaths registered with MDS as the final underlying cause in England and Wales.[21]

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.[22] 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.[13,16] People with low risk MDS may be observed without treatment, also called 'watchful waiting'.[13] The only way to potentially cure MDS is to have intensive treatment with an allogeneic stem cell transplant from a donor; however, it is not suitable for the majority of patients.[22] 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.[13,16] 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.[16]

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 intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS).[23]

PLACE OF TECHNOLOGY

If licenced, the addition of magrolimab to azacitidine could provide a first line treatment option for MDS patients who have few therapeutic options available.

CLINICAL TRIAL INFORMATION

Trial	**ENHANCE;** NCT04313881, 2020-004287-26; A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination With Azacitidine Versus Azacitidine Plus Placebo in Treatment-naïve Patients With Higher Risk Myelodysplastic Syndrome **Phase III** - Recruiting **Location(s):** Australia, New Zeland, United States and United Kingdom **Primary completion date:** August 2022
Trial design	Randomized, parallel assignment, double-blinded

Population	N = 520 (planned), previously untreated individuals with intermediate to very high-risk Myelodysplastic Syndrome (MDS), aged 18 years and older
Intervention(s)	Magrolimab administered intravenously and azacitidine administered either subcutaneously (SB) or intravenously (IV) according to region-specific drug labelling.
Comparator(s)	Administered either subcutaneously or intravenously according to region-specific drug labelling and placebo to match magrolimab administered intravenously
Outcome(s)	Primary Outcome Measures : - Proportion of Participants with Complete Remission (CR) [Time Frame: Up to 24 months] - Overall Survival (OS) [Time Frame: Up to 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**5F9005; NCT03248479; A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination With Azacitidine in Patients With Hematological Malignancies** Phase Ib - Recruiting Location(s): United States and United Kingdom Primary completion date: August 2021
Trial design	Non-randomized, parallel assignment, open label
Population	N = 287 (planned), individuals with AML or intermediate to very high-risk Myelodysplastic Syndrome (MDS), aged 18 years and older
Intervention(s)	• Magrolimab monotherapy administered intravenously • Magrolimab administered intravenously and azacitidine administered either subcutaneously (SB) or intravenously (IV) according to region-specific drug labelling.
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures : 1. Percentage of Participant Experiencing Adverse Events [Time Frame: First dose date up to 4 years] 2. Complete Remission (CR) Rate For Participants With AML [Time Frame: Up to 4 years] 3. RBC Transfusion Independence Rate for Participants with Low-Risk MDS [Time Frame: Up to 8 weeks] 4. Complete Remission Rate for Participants with MDS [Time Frame: Up to 4 years] 5. Duration of Complete Remission (DCR) in Participants with AML and MDS [Time Frame: Up to 4 years] See trial record for full list of other outcomes.
Results (efficacy)	The MDS patient data were reported at the European Hematology Association conference in 2020, with 91% of evaluable patients with MDS showing evidence of an objective response and 42% of patients achieving complete

	remission (CR). The CR figure rose to 56% after six months of therapy indicating the response is both durable and typically deepens over time.[24]
Results (safety)	-

ESTIMATED COST

The cost of magrolimab is not yet known.

Azacitidine 100mg powder for suspension for injection vials is available for £321.00, £272.85, £230.00, £220.00 or £321.00 depending on supplier.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal (proposed). Pevonedistat with azacitidine for untreated myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (GID-TA10767). Expected publication date: TBC.
- 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

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

OTHER GUIDANCE

- London Cancer. Guidelines for the Diagnosis and Management of Adult Myelodysplastic Syndromes. 2015.[26]
- European Society for Medical Oncology. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[27]
- British Journal of Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2013.[16]

ADDITIONAL INFORMATION

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