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HEALTH TECHNOLOGY BRIEFING
NOVEMBER 2020

Imetelstat for Myelodysplastic syndrome

NIHRIO ID	12066	**NICE ID**	9552
Developer/Company	Geron Corporation	**UKPS ID**	

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

SUMMARY

Imetelstat is in clinical development for the treatment of relapsed/refractory low or intermediate-1 risk myelodysplastic syndrome (MDS) in transfusion-dependent patients, following erythropoiesis-stimulating agent (ESA) treatment. MDS are a group of disorders in which red blood cells, white blood cells, and platelets produced by the bone marrow do not grow and mature normally. MDS are long-term debilitating and life-threatening diseases. MDS patients may require repeated blood transfusions and currently have few treatment options.

Imetelstat sodium is an intravenously administered drug that works by blocking the activity of an enzyme called telomerase. Telomerase is involved in regulating cell growth and division. By blocking the activity of telomerase, this medicine is expected to stop the uncontrolled division of abnormal immature blood cells, therefore slowing the progression of MDS. If licensed, imetelstat will provide an additional treatment option for relapsed/refractory low or intermediate-1 risk MDS in transfusion-dependent patients, following ESA Treatment.

PROPOSED INDICATION

Treatment of transfusion dependent patients with low or intermediate-1 risk myelodysplastic syndrome (MDS) that is relapsed/refractory to erythropoiesis-stimulating agent (ESA) treatment.[1]

TECHNOLOGY

DESCRIPTION

Imetelstat (GRN163L) is a 13-mer N3'---P5' thio-phosphoramidate (NPS) oligonucleotide that has a covalently bound 5' palmitoyl (C16) lipid group. The proprietary nucleic acid backbone provides resistance to the effect of cellular nucleases, thus conferring improved stability in plasma and tissues, as well as significantly improved binding affinity to its target. The lipid group enhances cell permeability to increase potency and improve pharmacokinetic and pharmacodynamic properties. The compound has a long residence time in bone marrow, spleen, and liver. Imetelstat binds with high affinity to the template region of the RNA component of telomerase, resulting in direct, competitive inhibition of telomerase enzymatic activity, rather than elicit its effect through an antisense inhibition of protein translation. Imetelstat is administered by intravenous (IV) infusion.[2]

In the phase II/III clinical trial (NCT02598661) imetelstat will be administered as 2-hour IV infusion every 4 weeks at 7.5 mg/kg until disease progression, unacceptable toxicity, or withdrawal of consent, or lack of response.[1,3]

INNOVATION AND/OR ADVANTAGES

Patients with lower-risk myelodysplastic syndromes (MDS) who are dependent on red blood cell transfusions have limited options, especially if they are no longer responding to erythropoiesis-stimulating agents; new approaches are needed.[3,4]

Imetelstat is a novel, first-in-class telomerase inhibitor being developed in hematologic myeloid malignancies. Early clinical data suggest imetelstat may have disease-modifying activity through the suppression of malignant progenitor cell clone proliferation, which allows potential recovery of normal hematopoiesis.[5] Imetelstat targets cells with short telomeres and active telomerase, characteristics observed in MDS across all disease stages.[4]

In the phase II part of the current clinical trial (NCT02598661) treatment with imetelstat provided durable transfusion independence (TI) in heavily transfused non-del(5q) lower risk MDS relapsed/refractory to ESA treatment. Imetelstat achieved an 8-week TI rate of 42% for a median duration of 20 months, at the time, the longest reported with any agent in non-del 5q LR-MDS.[6] In the population of patients who were red blood cell transfusion–dependent, 29% achieved TI for more than 1 year and hematologic improvement (erythroid) was achieved by 68% of patients, lasting a median of 21 months.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Imetelstat does not currently have Marketing Authorisation in the EU/UK for any indication.

In July 2020 the EMA Committee for Orphan Medicinal Products (COMP) issued a positive opinion on the Company's application for orphan drug designation of imetelstat as a potential treatment for myelodysplastic syndromes (MDS).[5]

Imetelstat is also in phase III clinical development for Myelofibrosis and phase II trials for multiple myeloma, essential thrombocythemia or polycythemia vera, non-small cell lung cancer and locally recurrent or metastatic breast cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

MDS are a type of rare blood cancer where the body does not have enough healthy blood cells and the bone marrow functions abnormally and insufficient number of mature blood cells are produced.[8,9] Red blood cells, white blood cells, and platelets may all be affected by MDS, resulting in anaemia and increased risk of bleeding and infections.[10] As a result, individuals with MDS have abnormally low blood cell levels (low blood counts).[11] MDS mostly affects people 65 or older, but it can affect younger people too.[12]

The main types of MDS are MDS with single lineage dysplasia, MSD with multilineage dysplasia and MDS with excess blasts.[9] The most commonly used scoring is the Revised International Prognostic Scoring System (IPSS-R).[13] It 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.[14]

MDS affects patients' quality of life due to debilitating symptoms such as fatigue and dyspnoea. Treating patients with symptoms of MDS may require intravenous drug infusions, blood transfusions, and some may develop complications such as severe infections. The factors that may raise a person's risk of developing MDS include previous cancer therapy (including radiotherapy), and environmental toxins. MDS is more common in men and in smokers.[15] MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML). 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.[12]

The most common signs and symptoms of MDS include shortness of breath, weakness or feeling tired, easy bruising or bleeding which occurs due to thrombocytopenia, petechiae and leukopenia.[16,17]

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 is predominantly a disease of the elderly with an incidence of > 30 per 100,000 per year over the age of 70 years.[18]

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 is 6.7 among males and 3.0 among females in England.[19]

The Hospital Episodes Statistics for England in 2019-20, recorded 61,336 finished consultant episodes (FCE) for MDS (ICD10 code: D46), resulting in 59,794 hospital admissions and 52,892 day cases and 24,174 FCE bed days.[20]

The natural course of MDS is very variable, with survival ranging from a few weeks to several years. The median overall survival is 15-30 months at five years. Bone marrow failure (infection and haemorrhage) is the leading cause of death, with more patients dying before overt AML has occurred.[15] Previously reported 5-year overall survival rate for MDS within the EU was estimated at 31%.[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.[22] Treatments for MDS most often target slowing disease progression, managing symptoms, such as fatigue and preventing bleeding and infections.[23] The mainstay of treatment for 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.[12]

For people with low risk MDS, often a preferred approach is one of no active treatment or 'watchful waiting' and for some people, stem cell transplantation is a potentially curative treatment option. 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.[12]

CURRENT TREATMENT OPTIONS

According to European Society of Medical Oncology (ESMO) guidelines, for low or intermediate-1 risk MDS, second-line treatments currently used include anti-thymocyte globulin (ATG), hypomethylating agents (HMAs) and lenalidomide.[24]

PLACE OF TECHNOLOGY

If licenced, imetelstat will provide an additional treatment option for relapsed/refractory low or intermediate-1 risk MDS in transfusion-dependent patients, following ESA treatment.

CLINICAL TRIAL INFORMATION

Trial	**IMerge NCT02598661, 2015-002874-19; A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects With**

	IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) That is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment **Phase II/III - Recruiting** **Location(s):** **EU (inc UK), Canada, Israel, Republic of Korea, Russian Federation, United States** **Primary completion date: August 2022**
Trial design	Randomised, Parallel Assignment, Double Masking
Population	N = 225 (planned), adults with International Prognostic Scoring System (IPSS) low or intermediate-1 risk, non-del(5q) MDS, who are transfusion-dependent, are relapsed after or refractory to ESAs, and have not received treatment with lenalidomide or hypomethylating agents, aged 18 years and older.
Intervention(s)	Imetelstat will be administered at a starting dose of 7.5 milligram per kilogram (mg/kg) given intravenously every 4 weeks
Comparator(s)	Matching placebo to Imetelstat
Outcome(s)	Primary Outcome(s): • Percentage of participants without any red blood cell (RBC) transfusion during any consecutive 8 week period [Time Frame: During study (approximately 2 years)] See trial record for full list of other outcomes.
Results (efficacy)	Preliminary data from the phase II (open label) part of this trial was presented at the European Hematology Association (EHA) Annual Congress in June 2018. The data showed that the 13-patient initial cohort exhibited an increased rate and durability of transfusion independence compared to the overall trial population (8-week RBC-TI rate: 54% vs. 34%).[25]
Results (safety)	Preliminary data from the phase II (open label) part of this trial was presented at the European Hematology Association (EHA) Annual Congress in June 2018. This data showed that the AEs (mostly cytopenias) were predictable and reversible.[25]

Trial	**NCT01731951;** A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and Other Myeloid Malignancies **Phase II** - Completed **Location(s):** United States **Study completion date:** May 2018
Trial design	Randomised, Parallel Assignment, Open label
Population	N=81, primary myelofibrosis (PMF) or post-polycythemia vera/essential thrombocythemia myelofibrosis (Post-ET/PV MF), aged 18 years and older
Intervention(s)	Experimental arm G: Myelodysplastic syndromes (MDS)/ myeloproliferative neoplasm (MPN) or MDS participants with

	spliceosome mutations or ring sideroblasts will receive imetelstat, 7.5mg/kg on Day 1 of every 28-day cycle as long as they derive clinical benefit or until study end.
Comparator(s)	None
Outcome(s)	Primary Outcome(s): • MF patients: Overall response rate defined as a clinical improvement (CI), partial remission (PR), or complete remission (CR) according to the IWG-MRT consensus criteria [Time Frame: Up to 3 years] • MDS patients: Overall response rate according to the IWG response criteria in myelodysplasia [Time Frame: Up to 3 years] See trial record for full list of other outcomes.
Results (efficacy)	Imetelstat was found to be active in patients with myelofibrosis but also had the potential to cause clinically significant myelosuppression.[26]
Results (safety)	Treatment-related adverse events included grade 4 thrombocytopenia (in 18% of patients), grade 4 neutropenia (in 12%), grade 3 anaemia (in 30%), and grade 1 or 2 elevation in levels of total bilirubin (in 12%), alkaline phosphatase (in 21%), and aspartate aminotransferase (in 27%).[26]

ESTIMATED COST

The cost of imetelstat is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality. (TA322). September 2014.
- NICE Technology appraisal guidance. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE clinical guideline. Suspected cancer: recognition and referral (NG12). June 2015

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- London Cancer. Guidelines for the diagnosis and management of adult myelodysplastic Syndromes. 2015.[27]

- European Society of Medical Oncology. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[24]
- British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2013.[18]
- European LeukaemiaNet. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. 2013.[28]

ADDITIONAL INFORMATION

Geron Corporation did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision-making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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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