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HEALTH TECHNOLOGY BRIEFING
MAY 2020

Rigosertib for myelodysplastic syndrome - second line

NIHRIO ID	5779	**NICE ID**	7408
Developer/Company	Oncova Therapeutics Inc.	**UKPS ID**	Not Available

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

SUMMARY

Rigosertib is in clinical development for the treatment of high-risk myelodysplastic syndrome (MDS) in patients who had progressed on, failed to respond to, or relapsed after previous treatment with azacitidine or decitabine. 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 can lead to severe anaemia, infections or bleeding and can result in leukaemia (cancer of the white blood cells). MDS patients may require repeated blood transfusions and currently have few treatment options.

Rigosertib is administered intravenously and has been designed to inhibit and block the activity of various proteins that suppresses the growth of cancer cells. If licensed, rigosertib will provide a treatment option for higher-risk MDS patients who had progressed on, failed to respond to, or relapsed after previous treatment with azacitidine or decitabine.

PROPOSED INDICATION

Second line treatment option for high-risk myelodysplatic syndrome (MDS) patients who had progressed on, failed to respond to, or relapsed after previous treatment with azacitidine or decitabine.[1]

TECHNOLOGY

DESCRIPTION

Rigosertib (Estybon, ON-01910.Na) is a small molecule inhibitor that has a new mechanism of action in inhibiting the activation of RAS as an oncogene-related product. Thus blocking the action of multi-kinases, including PI3K, and inhibits cellular signalling in cancer cells necessary for their survival and proliferation, thus killing cancer cells.[2] It is an anti-tumour agent that induces apoptosis and G2/M arrest via activation of the p53-mediated mitochondrial pathway. Rigosertib acts as a multi-kinase inhibitor to meliorate multiple dysregulated signalling transduction pathways in high-grade MDS.[3]

Rigosertib is currently in clinical development for the second line treatment of MDS. In the phase III clinical trial (INSPIRE; NCT02562443), patients will receive intravenous rigosertib 1800 mg/24 hr for 3 days every 2 weeks for first 8 cycles, then every 4 weeks in addition to best supportive care.[1] Details of the dosing regimens and administration schedule assessed are detailed in the clinical trial tables of this briefing.[1,4]

INNOVATION AND/OR ADVANTAGES

Due to the complexity and heterogeneity of the pathogenesis of MDS, therapeutic agents approved for MDS remain scarce. Decitabine and 5-azacitidine have shown therapeutic activity, although response rates are relatively low, and the resultant prolongation in survival was limited and unsatisfactory. Almost all patients who initially respond to hypomethylating agents (HMAs) become unresponsive in a short period or eventually progress into acute myeloid leukaemia. Thus, new agents should be developed to treat MDS.[3]

Rigosertib is a novel non-ATP competitive anticancer agent that inhibits mitotic progression and induces apoptosis in solid cancer cells and lymphoma cells, while it rarely affects normal cells.[3] In a phase II clinical trial, intravenous rigosertib was well tolerated and showed favourable clinical activity in patients with higher risk MDS.[3,5] Thus, rigosertib appears to be active and well tolerated in a setting in which therapeutic options are limited.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Rigosertib is in phase III clinical development for epidermolysis bullosa, non-small cell lung cancer respectively, squamous cell carcinoma, refractory anaemia with excess, chronic myelomonocytic leukaemia and cytopenia.[6]

Rigosertib has the following designation/awards;

- an orphan designation was granted by the European Commission to (E)-2,4,6-trimethoxystyryl-3-carboxymethylamino-4-methoxybenzyl-sulfone sodium salt in April 2012 for the treatment of MDS.[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 multileange dysplasia and MDS with excess blasts.[8] 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 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.[10]

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.[15,16]

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.[17]

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 6.7 among males and 3.0 among females in England.[18]

In England, in 2018-2019, there were 61,846 finished consultant episodes (FCE) for MDS (ICD-10 code: D46), resulting in 60,180 hospital admissions and 25,065 FCE bed days and 55,078 day cases.[19]

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.[20] 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.[10]

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. For patients with intermediate-2 or high risk MDS who are not eligible for haematopoietic stem cell transplantation anticancer drugs are recommended as a treatment option.[10]

CURRENT TREATMENT OPTIONS

According to European Society of Medical Oncology (ESMO) guidelines, for higher risk MDS patients who fail to respond to azacitidine or are primary refractory to HMAs, the recommended approach is to enrol such patients in a clinical trial with investigational agents and, if the patient has become eligible for allogeneic stem cell transplantation (alloSCT), proceed to transplant. At present, alloSCT is the only potentially curative treatment of higher risk MDS patients. However, co-morbidity, age, IPSS and IPSS-R score, cytogenetics, conditioning regimen and donor selection are predictors of post-transplant outcome and should be taken into account carefully during the decision process.[24]

PLACE OF TECHNOLOGY

If licensed, rigosertib will provide a second line treatment option for high-risk MDS patients who had progressed on, failed to respond to, or relapsed after previous treatment with azacitidine or decitabine.[1]

CLINICAL TRIAL INFORMATION

Trial	INSPIRE; NCT02562443, EudraCT-2015-001476-22; A Phase III, international, randomized, controlled study of rigosertib versus physician's choice of treatment in patients with myelodysplastic syndrome after failure of a hypomethylating agent **Phase III**- Ongoing **Location(s)**: EU (including UK), US, Canada and other countries
Trial design	Randomised, parallel assignment, open label

Population	n=360 (planned); MDS; at least one cytopenia; progression (according to 2006 IWG criteria) at any time after initiation of azacitidine or decitabine treatment or failure to achieve complete or partial response or haematological improvement; duration of prior HMA therapy ≤ 9 months and/or total ≤9 cycles of prior HMA therapy in ≤ 12 months
Intervention(s)	Rigosertib + best supportive care (BSC) • Patients will receive intravenous rigosertib 1800 mg/24 hr for 3 days every 2 weeks for first 8 cycles, then every 4 weeks thereafter + BSC
Comparator(s)	Physician's choice + BSC • Patients will receive Physician's choice of treatment or alternative treatment which may include any approved or standard-of-care therapy, based on frequently used treatment for MDS + BSC (azacitidine and/or decitabine)
Outcome(s)	Primary outcome: Overall survival of all randomized patients and overall survival of patients scored as IPSS-R very high risk. (Time frame: up to 30 months) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	ONTIME; NCT01241500; Phase III multicenter randomized controlled study to assess efficacy and safety of ON 01910.Na 72-Hr Continuous IV infusion in MDS patients with excess blasts relapsing after or refractory to or intolerant to azacitidine or decitabine **Phase III** **Location(s)**: EU (excluding UK) and United States
Trial design	Randomised, parallel assignment, open label
Population	n=299; MDS diagnosed confirmed with 6 weeks prior to entry according to WHO or French-American-British classification; at least one cytopenia; did not respond to, relapsed after, not eligible for, or opted not to do bone marrow transplantation
Intervention(s)	Rigosertib + BSC • Patients will receive rigosertib 1800 mg/24 hr as a continuous intravenous infusion for 72 hours every other week for the first 16 weeks then every 4 weeks afterwards and BSC
Comparator(s)	BSC
Outcome(s)	Primary outcome: Overall survival [Time frame: up to 18 months] See trial record for full list of other outcomes.
Results (efficacy)	As of Feb 2014, median overall survival was 8·2 months (95% CI 6·1-10·1) in the rigosertib group and 5·9 months (4·1 - 9·3) in the BSC group (hazard ratio 0·87, 95% CI 0·67-1·14; p=0·33).[25]
Results (safety)	The most common grade 3 or higher adverse events were anaemia (34 [18%] of 184 patients in the rigosertib group vs seven [8%] of 91 patients in the best supportive care group), thrombocytopenia (35 [19%] vs six [7%]),

	neutropenia (31 [17%] vs seven [8%]), febrile neutropenia (22 [12%] vs ten [11%]), and pneumonia (22 [12%] vs ten [11%]). 41 (22%) of 184 patients in the rigosertib group and 30 (33%) of 91 patients in the BSC group died due to adverse events and three deaths were attributed to rigosertib treatment.[25]

ESTIMATED COST

The cost of rigosertib is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality (TA322). September 2014, updated June 2019.
- 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

- No relevant guidance identified

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 Guideline for diagnosis, treatment and follow-up. 2014.[24]
- British Journal of Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2013.[17]

ADDITIONAL INFORMATION

Oncova Therapeutics Inc, 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.

REFERENCES

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