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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Ruxolitinib for chronic graft versus host disease (cGvHD)

NIHRIO ID	13739	**NICE ID**	10197
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	641953

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Ruxolitinib is in clinical development for chronic graft versus host disease (cGvHD). After a donor stem cell transplant, the donor's stem cells (the graft) may sometimes react against the host's own cells. This is called GVHD. cGvHD may happen more than three months after transplant. It can develop from acute GVHD or happen on its own. The symptoms depend on which parts of the body are affected. They may include skin changes, hair that grows slowly, feeling short of breath or wheezy, dry and swollen mouth and mouth ulcers, dry, gritty eyes, diarrhoea, stomach cramps, sickness and loss of appetite, vaginal narrowing and dryness, repeated infections, and muscle weakness and joint pain. Current standard treatment includes the use of steroids but this is often associated with significant side effects. Steroid resistance in GvHD may also develop which is difficult to treat and associated with a high mortality.

Ruxolitinib works by blocking the action of enzymes known as Janus kinases (JAKs), which are involved in the production and growth of blood cells and immune function. By blocking JAKs, ruxolitinib reduces the abnormal production of blood cells, thereby reducing the symptoms of the diseases. Ruxolitinib is administered as oral tablets and if licenced, will offer an additional therapy option for patients' steroid-refractory cGvHD after allogeneic hematopoietic stem cell transplantation.

PROPOSED INDICATION

Treatment of adults and adolescents ≥ 12 years with steroid-refractory chronic graft versus host disease (cGvHD) after allogeneic hematopoietic stem cell transplantation.[1,a]

TECHNOLOGY

DESCRIPTION

Ruxolitinib (Jakavi) is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.[2]

Ruxolitinib is currently in clinical development for the treatment of steroid-refractory cGvHD. In the phase III clinical trials (NCT03112603, REACH3), participants received either ruxolitinib 10 mg orally twice daily (BID) or best available therapy (BAT), with optional crossover to ruxolitinib after Cycle 6.[1,3]

INNOVATION AND/OR ADVANTAGES

The standard first line therapy of acute and chronic GvHD is the administration of steroids in conjunction with calcineurin inhibitors. However, prolonged and/or intensive steroid exposure is associated with a variety of side effects such as increased infection rates, myelopathy, and atrophy of the skin. Beyond the first line therapy, there is no standard defined so far. Steroid resistant acute/chronic GvHD is difficult to treat and associated with a high mortality. Common drugs and measures used in this situation have moderate success rates.[4]

Ruxolitinib is an inhibitor of Janus kinases 1/2 that has shown reduce the proliferation of t-effector cells and suppression of proinflammatory cytokine production showing their positive effects in experimental murine GvHD.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, ruxolitinib is licensed in the EU/UK for the treatment of: [2]

-disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis
-adults with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

The most frequently reported adverse drug reactions were thrombocytopenia, anaemia, neutropenia, urinary tract infections, bleeding, bruising, weight gain, dizziness, headache, raised aspartate aminotransferase, raised alanine aminotransferase, and hypercholesterolaemia, hypertriglyceridemia, and high blood pressure.[2,5]

[a] Information provided by Novartis Oncology on the UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Graft versus host disease (GvHD) is a possible complication of a bone marrow or stem cell transplant from another person. GvHD means the graft reacts against the host. The graft is the donated marrow or stem cells. The host is the person receiving the transplant. GvHD happens because the transplant affects the immune system. The donor's bone marrow or stem cells will contain some T cells. T cells are a type of white blood cell that helps fight infections. T cells attack and destroy cells they see as foreign, and potentially harmful such as viruses. Normally T cells don't attack its own body cells, because they recognise proteins on the cells called HLA (human leukocyte antigens). [6]

After a transplant, the bone marrow starts making new blood cells from the donor stem cells. These new blood cells have the donor's HLA pattern. They recognise the HLA pattern on the body cells as different (foreign) and may begin to attack some of them. The GvHD may affect different areas of the body. Most commonly it affects the skin, digestive system (including the bowel and stomach) or the liver.[6]

The GvHD can be classified to acute and chronic, based on when it starts after the transplant.

Acute GvHD (aGvHD) generally starts within 100 days of transplant but it can sometimes happen after this time. It usually happens about 2 to 3 weeks after the transplant when the new bone marrow begins to make blood cells. It can be mild or severe, and often starts with a rash on the palms of hands, the soles of the feet, the ears, and the face. The rash may be itchy or painful. It may also affect the mouth, the gut (digestive system) and the liver. This can cause diarrhoea, sickness, loss of appetite, and yellowing of the skin (jaundice).[6]

Chronic GvHD (cGvHD) starts more than 100 days after the transplant. A person is more likely to get it when acute GvHD has developed previously but it can happen even without having had aGvHD. It can be mild or severe, and for some people can go on for several months or even years. It may affect the skin, the gut, the liver, the mouth, the eyes, the lungs, the vagina, and the joints.[6]

CLINICAL NEED AND BURDEN OF DISEASE

The rate of cGvHD in adult allograft recipients ranges from 30-40% (1,592 patients, 2007-2012 cohort) and is 5-6% for extensive cGvHD (241 patients, 2007-2012 cohort) who will require second or subsequent lines of therapy. The rate of cGvHD amongst paediatric and adults allograft recipients was similar, the BSBMT Outcomes Register identified 154 cGvHD paediatric patient, whilst 22 patients have extensive cGvHD.[7]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The goal of any treatment is the effective control of GvHD whilst minimising the risk of toxicity and relapse. In many cases, patients are treated prophylactically where high probability of GvHD is present. Combination therapies are often required.[7] Treatment for GvHD depends on a number of factors and these include what type of GvHD the patient have and where patient have it.[8]

General treatment for cGvHD usually includes steroids. If these drugs do not control the GvHD, other treatments might be suggested to damp down the immune system. Some of these treatments depend on which part of the body is affected and include: tacrolimus, sirolimus, pentostatin, rituximab, imatinib, mycophenolate mofetil, and a special type of light therapy called extracorporeal photopheresis (ECP).[9]

The treatment for cGvHD of the skin includes keeping the skin clean and moisturising regularly. Patients should use unperfumed soaps and moisturising creams. Steroid creams or a cream called tracrolimus might be prescribed if the skin problems are just in small areas. Newer treatments being tried include halofuginone, etanercept and hydroxychloroquine.[9]

cGvHD might affect the gut anywhere from the mouth to the bowel. The treatment might include cleaning the mouth regularly, using of drip or tube feeding and anti-sickness drugs. cGvHD can also cause inflammation of the small air tubes in the lungs. This can cause shortness of breath, wheezing and a persistent cough. Patients probably need to take steroids long term, and antibiotics to stop the infections.[9]

cGvHD can make the eyes sore and dry. Artificial tears and steroid eye drops might be used to help keep the eyes moist and protect it from getting scratched. Besides that, the use of steroid cream can help to treat chronic vaginal GvHD.[9]

CURRENT TREATMENT OPTIONS

For patients with cGvHD:[7]
Where patients fail to show complete response (i.e. steroid-refractory cGvHD), have developed significant adverse effects to first-line treatments or are steroid-dependent, sirolimus is indicated. The following treatments are proposed to be added as second-line options (by organ/indication):
1. Refractory cGvHD: Pentostatin (1.5mg/m^2)
2. Skin, oral, liver and pulmonary cGvHD: ECP
3. Refractory cutaneous or musculoskeletal cGvHD: Rituximab
4. Refractory pulmonary or sclerodermatous cGvHD: Imatinib.

ECP should be the second line treatment of choice for skin, oral, liver and pulmonary cGvHD. Where patients show incomplete response to two different second-line options and/or have developed significant adverse effects, the following treatments are indicated third-line: mycophenolate mofetil, methotrexate and pulsed corticosteroids.

PLACE OF TECHNOLOGY

If licensed, ruxolitinib will offer a treatment option for patients with steroid-refractory cGvHD after allogeneic hematopoietic stem cell transplantation who currently have limited effective options.

CLINICAL TRIAL INFORMATION

Trial	REACH3, NCT03112603, INCB 18424-365; aged ≥12 years; ruxolitinib vs best available therapy (BAT); phase III
Sponsor	Incyte Corporation
Status	Ongoing

Source of Information	Trial registry,[1] Publication[3]
Location	EU countries (including the UK), USA, Canada and other countries
Design	Randomised, active-controlled, open-label, multi-center study
Participants	N=324 (planned); aged 12 years and older; have undergone Allogeneic Stem Cell Transplantation (alloSCT) from any donor source (matched unrelated donor, sibling, haploidentical) using bone marrow, peripheral blood stem cells, or cord blood; evident myeloid and platelet engraftment: Absolute neutrophil count (ANC) > 1000/mm^3 and platelet count > 25,000/ mm^3; participants with clinically diagnosed moderate to severe cGvHD according to National Institutes of Health (NIH) consensus criteria; participants currently receiving systemic or topical corticosteroids for the treatment of cGvHD for a duration of < 12 months prior to cycle 1 day 1 (if applicable), and have a confirmed diagnosis of steroid-refractory cGvHD defined per 2014 NIH consensus criteria irrespective of the concomitant use of a calcineurin inhibitor (CNI).
Schedule	Participants will be randomised to one of the treatment arms: - ruxolitinib tablet at a dose of 10 mg orally twice day (BID). - BAT. Patients may receive standard supportive care and cGVHD prophylaxis, such as corticosteroids and calcineurin inhibitors.
Follow-up	From baseline to end of study treatment, up to 36 months
Primary Outcomes	• Efficacy of ruxolitinib versus investigator's choice BAT in participants with moderate or severe SR-cGvHD assessed by overall response rate (ORR) at the cycle 7 day 1 visit [Time frame: cycle 7 day 1 (from baseline to day 168)]
Secondary Outcomes	• Rate of failure-free survival (FFS) [Time frame: from baseline to end of study treatment, up to 36 months] • Change in the modified Lee cGvHD symptom scale score [Time frame: cycle 7 day 1 (from baseline to day 168)] • Best overall response (BOR) [Time frame: from baseline to crossover or end of treatment up to 36 months] • ORR at end of cycle 3 [Time frame: cycle 4 day 1 (from baseline to day 84)] • Duration of response [Time frame: time from first response until GvHD progression or death, up to approximately 36 months] • Overall survival (OS) [Time frame: from the date of randomization to the date of death due to any cause up to approximately 36 months.] • Cumulative incidence of non-relapse mortality (NRM) [Time frame: months 1, 2, 6, 12, 18, and 24] • Percentage of participants with ≥ 50% reduction in daily corticosteroid dose at cycle 7 day 1 [Time frame: cycle 7 day 1 (from baseline to day 168)] • Percentage of participants successfully tapered off all corticosteroids at cycle 7 day 1 [Time frame: cycle 7 day 1 (from baseline to day 168)] • Cumulative incidence of malignancy relapse/recurrence (MR) [Time frame: At 3, 6, 12, 18, and 24 months] • Changes in Functional Assessment of Cancer therapy - Bone Marrow Transplantation (FACT-BMT) [Time frame: from baseline to end of treatment, up to 36 months] • Changes in EQ-5D [Time frame: from baseline to end of treatment, up to 36 months]

	• Incidence and severity of adverse events [Time frame: from baseline to 30-35 days after end of treatment, up to approximately 36 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as March 2020.

ESTIMATED COST

Ruxolitinib is already marketed in the UK. The NHS indicative price for ruxolitinib is:[10]

- A pack of 56 x 5 mg tablets costs £1428.00
- A pack of 56 x 10, 15 and 20 mg tablets costs £2856.00

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. NHS England: 16069/P. March 2017.

OTHER GUIDANCE

- Oxford University Hospitals. Diagnosis and management of acute graft versus host disease. 2018.[11]
- Digman FL. Diagnosis and management of chronic graft-versus-host disease. 2012.[12]

ADDITIONAL INFORMATION

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