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HEALTH TECHNOLOGY BRIEFING
MARCH 2020

Ibrutinib for chronic Graft versus Host Disease

NIHRIO ID	13345	**NICE ID**	9653
Developer/Company	Janssen-Cilag	**UKPS ID**	643042

Licensing and market availability plans	Currently in Phase III trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Ibrutinib 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 Graft versus Host Disease (GvHD). cGvHD may happen more than three months after transplant. 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.

Ibrutinib belongs to class of drugs called Bruton's Tyrosine Kinase (BTK) inhibitors that work against defective B lymphocytes, which are a type of white blood cells affected by these diseases. Earlier studies have demonstrated that ibrutinib works by blocking the BTK signalling pathway, resulting in reduced production of the defective blood cells in GvHD and some other types of blood cancers. Ibrutinib is available as tablets and taken orally. If licensed, ibrutinib will offer an additional first line treatment option for cGvHD which may improve patients' quality of life by helping reduce the dose of steroids used and reduce the severity of GvHD symptoms.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Treatment of chronic graft versus host disease (cGvHD) – first line.[a]

TECHNOLOGY

DESCRIPTION

Ibrutinib (Imbruvica) is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia (CLL). BTK's pivotal role in signalling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib effectively inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.[2]

Ibrutinib in addition to corticosteroids is currently in development (NCT02959944) for the treatment of cGvHD in patients aged 12 years and older with new onset, moderate or severe condition.{ClinicalTrials.gov, 2016 #19} Ibrutinib can be taken orally in tablets available at the following dosages: 140/280/420/560mg.[a]

INNOVATION AND/OR ADVANTAGES

The standard first line therapy of acute and chronic GvHD is the administration of steroids in conjunction with calcineurin inhibitors. Prolonged and/or intensive steroid exposition is associated with a variety of side effects such as increased infection rates, myelopathy, and atrophy of the skin. In the UK there is not a recommended alternative for the first line treatment of patients with chronic GvHD and so it remains an area of unmet need.

A previous phase II trial (NCT02195869) evaluated the safety and efficacy of ibrutinib in patients with active cGVHD with inadequate response to corticosteroid-containing therapies. Forty-two patients who had failed 1 to 3 prior treatments received ibrutinib (420 mg) daily until cGVHD progression. The primary efficacy end point was cGVHD response based on 2005 National Institutes of Health criteria. At a median follow-up of 13.9 months, best overall response was 67%; 71% of responders showed a sustained response for $\geqslant$20 weeks. Responses were observed across involved organs evaluated. Most patients with multiple cGVHD organ involvement had a multiorgan response. Median corticosteroid dose in responders decreased from 0.29 mg/kg per day at baseline to 0.12 mg/kg per day at week 49; 5 responders discontinued corticosteroids. The most common adverse events were fatigue, diarrhoea, muscle spasms, nausea, and bruising. Plasma levels of soluble factors associated with inflammation, fibrosis, and cGVHD significantly decreased over time with ibrutinib. According to experts, ibrutinib's side effects outweigh the impact of the cGvHD symptoms since these side effects are manageable.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ibrutinib is licensed in the EU/UK as a monotherapy or in combination with other cancer medicines for the following indications:[2]

[a] Information provided by Janssen in UK PharmaScan

- Mantle cell lymphoma (MCL): as monotherapy is indicated for the treatment of adult patients with relapsed or refractory MCL.
- Waldenström's macroglobulinaemia (WM): as monotherapy is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib in combination with rituximab is indicated for the treatment of adult patients with WM.
- CLL: as a monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL.
- CLL: as a monotherapy or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who received at least one prior therapy.

The most common side effects of ibrutinib (which may affect more than 1 in 5 people) are diarrhoea, neutropenia, musculoskeletal pain, haemorrhage, bruising, rash, nausea and fever. The most serious side effects are neutropenia alone or with fever, pneumonia and thrombocytopenia.[5]

Ibrutinib was approved by the Food Drug Administration (FDA) for the first-line treatment of cGvHD in August 2017.[4]

Ibrutinib received an orphan designation from the European Medicines Agency (EU/3/16/1780) for the treatment of graft versus host disease in 2016.

Ibrutinib as a monotherapy or in combination is at phase III development for a range of conditions including pancreatic adenocarcinoma, mature B-cell NHL, follicular lymphoma, relapsed of refractory diffuse large B-cell lymphoma, indolent NHL.

PATIENT GROUP

DISEASE BACKGROUND

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 us fight infections. T cells attack and destroy cells they see as foreign, and potentially harmful such as viruses. Normally T cells do not attack own body cells, because they recognise proteins on the cells called HLA (human leukocyte antigens) which are inherited. Apart from identical twins, HLA is unique to each person.[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] Patients frequently have erythematous rash, enteritis, or hepatic involvement characterized by transaminase elevation or hyperbilirubinemia at initial presentation and intermittently afterward during the course of the disease.

Manifestations of chronic GvHD (cGvHD) have a wide range of severity and impact on quality of life after haematopoietic cell transplantation (HCT). 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 allograft recipients shows similar incidence compared to adults, and the BSBMT in the 2007-2012 paediatric patient cohort, 154 patients have cGvHD, while 22 patients have extensive cGvHD.[7]

The company has estimated the UK patient population range susceptible to receive this treatment is between 1 per 50,000 and 25 per 100,000 people.[b]

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]

Optimal treatment of chronic GvHD requires a multidisciplinary team approach that includes transplantation specialists, a primary health care provider, organ-specific consultants, nurses, and ancillary services such as social services, vocational specialists, patient and family support groups, and systems.

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. Severity of the disease is established as mild/moderate or severe using the National Institutes of Health (NIH) response criteria.

CURRENT TREATMENT OPTIONS

Treatments 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 tacrolimus 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]

[b] Information provided by Janssen in UK PharmaScan

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]

PLACE OF TECHNOLOGY

If licensed, ibrutinib will offer an additional first line treatment option for patients with cGvHD.

CLINICAL TRIAL INFORMATION

Trial	**INTEGRATE, NCT02959944; Ibrutinib in Combination With Corticosteroids Versus Placebo in Combination With Corticosteroids in Subjects With New Onset Chronic Graft Versus Host Disease (cGVHD)** ; **Phase III** **Location(s):** USA, Canada, , EU (not UK) and countries in Asia. ,
Trial design	Randomised, multi-centre, trial.
Status	Ongoing.
Population	N=186; 12 years and older; child, adult, older adult; new onset moderate or severe cGVHD as defined by the 2014 NIH Consensus Development Project Criteria; need for systemic treatment with corticosteroids for cGVHD; previous systemic treatment for cGVHD (including extracorporeal photopheresis [ECP]); May be receiving other immunosuppressants for the prophylaxis or treatment of acute GVHD but if the subject is receiving prednisone for prophylaxis or treatment of acute GVHD it must be at or below 0.5 mg/kg/d; Karnofsky or Lansky (subjects <16 years) performance status ≥60
Intervention(s):	Ibrutinib (with prednisone), administered orally, daily
Comparator(s):	Matched placebo.
Outcome(s):	Primary outcome: • Response rate at 48 weeks, defined by the NIH Consensus Development Project Criteria (2014) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Ibrutinib is already marketed in the UK: a pack of 90 x 140 mg and 120 x 140mg capsules costs £4,599 and £6,132 respectively.[10]

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. 16069/P. March 2017.

OTHER GUIDANCE

- National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. 2015.
- NIH Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. The 2014 Pathology Working Group Report. 2015.
- Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. 2015.
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ADDITIONAL INFORMATION

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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.