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HEALTH TECHNOLOGY BRIEFING
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Ibrutinib in combination with venetoclax for chronic lymphocytic leukaemia or small lymphocytic lymphoma – first line

NIHRIO ID	24051	**NICE ID**	10222
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	647874

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Ibrutinib in combination with venetoclax is being developed for elderly and at risk patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). CLL and SLL are types of cancer in which too many white blood cells are produced, in SLL cells build up in the lymph nodes, in CLL the cancer cells can be found in the blood and bone marrow. As these cells develop abnormally, they are unable to function, fight infection and reduce the production of healthy blood cells. These diseases are chronic and develop slowly. Treatment is complex and depends on a number of factors, including the extent of disease, previous treatment, patient's age, symptoms and general state of health.

Ibrutinib is an oral drug that works against cancerous B lymphocytes, which are a type of white blood cells affected by these diseases. It does this by blocking an enzyme called Bruton's tyrosine kinase (BTK), which promotes survival of B lymphocytes. By blocking BTK, ibrutinib decreases the survival and migration of B lymphocytes, thereby delaying the progression of cancer. Venetoclax, attaches to a protein called BCL-2 that is present in high amounts in CLL cancer cells. By attaching BCL-2 and blocking its actions, venetoclax causes the death of cancer cells. If licensed, ibrutinib in combination with venetoclax will offer an additional first-line treatment option for elderly and at risk patients with CLL or SLL, potentially avoiding the use of chemotherapy.

PROPOSED INDICATION

First-line treatment of chronic lymphocytic leukaemia or small lymphocytic lymphoma.[1]

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 (Cys481) 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 Mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and CLL. By blocking BTK, ibrutinib is expected to slow down the migration of B lymphocytes and to induce cell death, thereby delaying or stopping the progression of the disease.[2]

Venetoclax (Venclyxto) is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax binds directly to the BCL homology 3 (BH3)-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death.[3]

In the phase III clinical trial (NCT03462719), participants will initially receive ibrutinib (420mg/day) for 3 cycles. Venetoclax dose ramp up (from 20 to 400mg over 5 weeks) will begin at cycle 4 and the combination of ibrutinib and venetoclax will be given for 12 cycles (each cycle is equivalent to 28 days).[1]

INNOVATION AND/OR ADVANTAGES

Ibrutinib with venetoclax is a new combination for the treatment of CLL/SLL.

Individually the drugs are licenced for CLL and it is hoped that based on preclinical models the combination will be synergistic as they have complementary clinical activity and no overlapping toxic effects. Ibrutinib results in mobilization of CLL cells from protective microenvironment niches where contact provides survival signals. Ibrutinib-mediated inhibition of BTK results in reduced levels of myeloid-cell leukaemia 1 (MCL1) protein, with an increase or no change in BCL2 levels. Venetoclax targets BCL2 to induce apoptosis, whereas MCL1 could protect from mitochondria-mediated cell death. A decrease in MCL1 levels by ibrutinib may lead to synergy when combined with venetoclax.[4]

In a phase II trial (NCT02756897) combined venetoclax and ibrutinib appeared to be an effective oral regimen for high-risk and older patients with CLL.[4] This combination also avoids the use of chemotherapy, and the treatment may not need to be continued indefinitely.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of ibrutinib and venetoclax is not currently licensed for any indication in the UK.

Ibrutinib is licensed for the treatment of adult patients with the following:[2]

- As a monotherapy for relapsed or refractory mantle cell lymphoma (MCL)
- As a monotherapy or in combination with obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL)
- As a monotherapy for previously treated Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy or in combination with rituximab in WM adult patients.
- As a monotherapy or in combination with bendamustine and rituximab (BR) for CLL previously treated with at least one prior therapy.

Venetoclax as monotherapy is indicated for the treatment of CLL in the presence of 17p deletion of TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor. It is licensed in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy and with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia.[3]

Very common adverse events (1 in 10 patients) of ibrutinib include: pneumonia, upper respiratory tract infection, skin infection, neutropenia, thrombocytopenia, headache, haemorrhage, bruising, hypertension, diarrhoea, vomiting, stomatitis, nausea, constipation, rash, arthralgia, muscle spasms, musculoskeletal pain, pyrexia and oedema peripheral.[2]

Very common adverse events (1 in 10 patients) of venetoclax include: pneumonia, upper respiratory tract infection, neutropenia, anaemia, lymphopenia, hyperkalaemia, hyperphosphatemia, hypocalcaemia, diarrhoea, vomiting, nausea, constipation and fatigue.[3]

Ibrutinib was designated EU orphan drug in 2012. This designation was reviewed and maintained in 2014 at the time of market authorization for the treatment of CLL.[6]

Ibrutinib in combination with venetoclax is in phase III trials for mantle-cell lymphoma and in phase II trials for Waldenstrom Macroglobulinemia, T-cell prolymphocytic leukemia and follicular lymphoma.[7]

PATIENT GROUP

DISEASE BACKGROUND

CLL is a type of non-Hodgkin lymphoma, a cancer in which the bone marrow makes too many lymphocytes (a type of white blood cell). In CLL, abnormal white blood cells develop from the lymphoid blood stem cells. These white blood cells are unable to function as normal lymphocytes and can accumulate in the blood and bone marrow, preventing the production of healthy blood cells, which can cause anaemia. As a chronic disease, CLL develops slowly over time.[8]

CLL is one of the most common types of leukaemia in adults. It is most common in those over 60 years old and rarely occurs in those under 40 years old.[9] Because CLL develops slowly, people often have no symptoms in the early stages. General symptoms of CLL include tiredness, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in the upper left abdomen), night sweats and weight loss.[9,10]

Various risk factors for CLL have been identified, including a family history of CLL, exposure to electromagnetic fields and radiation, the presence of a compromised immune system (HIV/AIDS patients or individuals on immunosuppressive medication) and exposure to certain hair dyes. CLL is also more common in men and people of Australian, American and European origin.[11]

Small lymphocytic lymphoma (SLL) is a different manifestation of the same disease as CLL hence it is similar to and treated in the same way as CLL. SLL develops when the body makes abnormal B-cells -lymphoma cells, which build up in lymph nodes. It shares similar symptoms with CLL including a painless swelling in the neck, armpit or groin.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, there were 3,157 new cases of CLL in the UK; just over 62% of which were in men. The European age-standardised incidence rate of CLL (ICD-10: C91.1) in England in 2017 was 6.1 per 100,000 population and for the UK, the European age-standardised incidence rate was 5.7 per 100,000 population.[13]

Hospital episode statistics for England 2018-19 recorded 22,642 admissions for CLL of B-cell type (ICD-10 code C91.1), and 23,606 finished consultant episodes resulting in 12,527 bed days and 20,179 day cases.[14]

In 2017, CLL accounted for less than 1% of cancer deaths in the UK. There were 565 CLL deaths in males, accounting for 60% of CLL deaths in the UK, and 382 CLL deaths in females accounting for 40% of deaths due to CLL in the UK. This equates to a European-age standardised mortality rate of 2.2 per 100,000 in males and 1.0 per 100,000 in females.[15]

No UK-wide statistics are available for CLL survival. Statistics are available for CLL diagnosed in England between 2008 and 2010. According to the National Cancer Intelligence Network, between 2008 and 2010, the five-year survival rates for CLL in England was 70% for men and 75% for women.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for CLL/SLL is complex and depends on a number of factors, including the extent of the disease, whether it has been treated before, and the patient's age, symptoms and general state of health. Patients whose CLL/SLL is not causing any symptoms or is getting worse only very slowly may not need treatment. Treatment for CLL/SLL is started only if symptoms become troublesome.[17]

CURRENT TREATMENT OPTIONS

The following first-line treatment recommendations have been made by NICE relevant to this group of CLL/SLL patients:[18]

- Venetoclax is recommended for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation when a B-cell receptor pathway inhibitor is unsuitable.
- Ibrutinib in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable

- Idelalisib monotherapy or in combination with rituximab, are recommended for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation.
- Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable.
- Bendamustine is recommended as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of CLL.

PLACE OF TECHNOLOGY

If licenced, ibrutinib in combination with venetoclax will provide and additional first line treatment option for adult patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma.

CLINICAL TRIAL INFORMATION

Trial	**GLOW,** NCT03462719, 2017-004699-77; A Randomized, Open-label, Phase 3 Study of the Combination of Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab for the First-line Treatment of Subjects With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). **Phase III – Active, not recruiting** **Location(s):** EU (inc UK) countries, United States, Canada and other countries. **Primary completion date:** February 2021
Trial design	Randomised, open label, parallel assignment.
Population	N = 211 (planned), diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma, aged > 65 or 18 to 64 years old with at least one of the following: • Cumulative Illness Rating Scale (CIRS) score > 6 • Creatinine clearance (CrCl) estimated less than (<) 70 millilitre per minute (mL/min) using Cockcroft-Gault equation.
Intervention(s)	Oral ibrutinib 420 mg/day for 15 cycles and venetoclax from cycle 4, increasing from 20 to 400mg over 5 weeks.
Comparator(s)	Chlorambucil 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6 and Obinutuzumab 1000 mg (IV) on Days 1, 8, and 15 of Cycle 1, and Day 1 of Cycles 2 to 6.
Outcome(s)	Primary outcome(s); • Progression-Free Survival (PFS) [Time Frame: From date of randomization to date of disease progression (PD) or death, whichever occurs first (Up to approximately 6 years)] See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

ESTIMATED COST

Ibrutinib is already marketed in the UK:[19]

- a pack of 28 x 140 mg, 28 x 280mg, 28 x 420mg, 28 x 560mg capsules cost £1430.80, £2861.60, £4292.40 and £5723.20 respectively.

Venetoclax is already marketed in the UK:[20]

- a pack of 14 x 10mg and 7 x 50mg tablets cost £59.87 and 149.67 respectively
- a pack of 7 x 100mg, 14 x 100mg and 112 x 100mg tablets cost £229.34, £598.68, and £4789.47 respectively.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- NICE technology appraisal guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal guidance. Obinutuzumab in combination with chlorambucil for treating untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE technology appraisal guidance. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011.
- NICE technology appraisal guidance. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE technology appraisal guidance. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

- London Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines. 2020.[21]
- British Journal of Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. 2018.[22]
- Current Oncology. Canadian evidence-based guideline for the first-line treatment of chronic lymphocytic leukaemia. 2018.[23]
- Blood Cancer Journal. Chronic lymphocytic leukaemia treatment algorithm 2018.[24]
- European Society for Medical Oncology. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[25]

ADDITIONAL INFORMATION

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