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Ibrutinib in combination with obinutuzumab for the treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma in elderly – first line

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LAY SUMMARY

Chronic lymphocytic leukaemia (CLL) is a type of cancer in which too many white blood cells are produced. These develop abnormally and are unable to function and fight infection. They also prevent the production of other healthy blood cells. As the disease is chronic, it develops very slowly over time. Small lymphocytic lymphoma (SLL) is a different form of the same disease. Whereas CLL develops in the bone marrow, SLL cells are found in organs and tissues of the lymphatic system (a network of tissues and organs that help rid the body of toxins, waste and other unwanted materials). CLL/SLL is one of the most common leukaemias in adults, usually occurring above the age of 60 years. General symptoms include fatigue, frequent infections, and swollen lymph nodes.

The combination of ibrutinib (oral capsules) and obinutuzumab (intravenous injection) is being developed as a new treatment option for CLL/SLL in elderly patients. Both drugs act in different unique ways to improve the body's natural defence to fight the cancer cells and their combined effect may significantly reduce symptoms of the disease and increase survival.

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TARGET GROUP

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) (elderly) – first line

TECHNOLOGY

DESCRIPTION

Ibrutinib (Imbruvica) is a selective small molecule inhibitor of Bruton's Tyrosine Kinase (BTK), a signalling kinase expressed in B cells that functions downstream of the B cell antigen receptor (BCR). BTK, a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases, is required for B cell receptor signalling, plays a key role in B cell maturation, and is overexpressed in a number of B cell malignancies. The expression of BTK in tumour cells is associated with an increase in their proliferation and survival.[1,2] Ibrutinib binds to and irreversibly inhibits BTK activity, thereby decreasing survival and migration of B lymphocytes and delaying the progression of the cancer.

Obinutuzumab (Gazyvaro) is a monoclonal antibody that has been designed to recognize and attach to the protein CD20, which is found on the surface of B lymphocytes. In CLL and follicular lymphoma (FL), cancerous B lymphocytes multiply too quickly and replace the normal cells in the bone marrow and in lymph nodes. By attaching to CD20 on B lymphocytes, obinutuzumab makes the B lymphocytes a target for the body's immune system.[3]

In its phase III clinical trial ibrutinib is taken as 140mg hard gelatine capsules for oral administration three times daily and continuously (until evidence of progressive disease or no longer tolerated by the patient). Obinutuzumab is supplied as 1000mg/40ml solution in a single-use vial for intravenous (IV) administration and taken over 6 cycles: days 1 and 2 (100mg on day 1 and 900mg on day 2), 8 and 15 of cycle 1 followed by day 1 only on cycles 2-6.[4]

Ibrutinib is currently licensed in the EU for the treatment of:[2]

- Chronic lymphocytic leukaemia (*monotherapy or combination with bendamustine+rituximab*)
- Mantle cell lymphoma (*monotherapy*)
- Waldenstroem's macroglobulinaemia (*monotherapy*)

In the EU and globally, Ibrutinib is also in late clinical trials for the following indications:[1]

- Follicular lymphoma
- Non-Hodgkin lymphoma
- Diffuse large b cell lymphoma
- Graft Versus Host Disease
- Metastatic adenocarcinoma of the pancreas

Obinutuzumab is currently licensed in the EU for the treatment of:[3]

- Chronic lymphocytic leukaemia (*combination with chlorambucil*)
- Follicular lymphoma (*combination with bendamustine*)

Obinutuzumab is globally in late clinical trials for follicular lymphoma and Non-Hodgkin lymphoma.[6]

INNOVATION and/or ADVANTAGES

Ibrutinib (BTK inhibitor) in combination with obinutuzumab (anti-CD20 monoclonal antibody) is a promising new treatment option for elderly or unfit patients with CLL/SLL.[5]

DEVELOPER

Janssen-Cilag Ltd

AVAILABILITY, LAUNCH or MARKETING

Ibrutinib received an orphan drug designation from the EMA for CLL in April 2012.[1]

Obinutuzumab received an orphan drug designation from the EMA for CLL in October 2012.[6]

PATIENT GROUP

BACKGROUND

Chronic Lymphocytic Leukaemia (CLL) is a type of B lymphocyte cancer. In this type of cancer, abnormal white blood cells develop from blood stem cells. These leukaemia cells are unable to function as well as normal lymphocytes and can accumulate in the blood and bone marrow, preventing the production of healthy blood cells. As a chronic leukaemia, CLL develops slowly over time.[7] Diagnosis of CLL requires the presence of >5000 B lymphocytes/µL in the peripheral blood.[8]

Small lymphocytic lymphoma (SLL) and CLL are different forms of the same disease. They are treated in the same way, have a similar prognosis, and affect the same lymphocytes. Unlike CLL, however, cancer cells of SLL are found in organs and tissues of the lymphatic system, which is a network of fine vessels, glands and channels throughout the body. SLL is a low-grade form of Non-Hodgkin lymphoma.[9,10]

CLL/SLL is one of the most common leukaemias in adults. It is most common in those over 60 years old and rarely occurs in those under 40 years old.[11] Because CLL develops slowly, people often have no symptoms in early stages. General symptoms of CLL include: fatigue, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in upper left abdomen), night sweats and weight loss.[12]

Various risk factors and causes of CLL have been identified, including: certain medical conditions (pneumonia, sinusitis, shingles infection, autoimmune haemolytic anaemia, chronic osteoarthritis and prostatitis), exposure to electromagnetic radiation and the presence of a compromised immune system (HIV/AIDS patients or individuals on immunosuppressive medication).[13] Several genetic changes have also been identified and are regularly tested for as part of a CLL diagnosis. Deletions or mutations in these genes can change CLL prognosis and treatment. 30-50% people with CLL have a 13q deletion which results in an extremely slow developing type of CLL that may not require treatment for many years.[14]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of CLL in England was 6.3 per 100,000 population (2014); in the UK, the incidence of CLL was 6.0 per 100,000 (2014).[15]

For adults in England diagnosed with CLL, 66.5% of men and 72.5% women will survive >5 years after diagnosis.[16]

CLL (ICD-10 C91.1) accounted for less than 1% of cancer deaths in the UK (2014). In the UK (2014) there were 628 (61%) CLL deaths in males and 405 (39%) CLL deaths in females (male: female ratio of 16:10). This equates to a mortality rate of 2 per 100,000 in males and 1 per 100,000 in females.[17]

In 2015, there were 60,087 admissions for Lymphoid Leukaemia (ICD C91) in England, resulting in 68,028 bed days and 62,290 finished consultant episodes.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017
- NICE technology appraisal. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015
- NICE technology appraisal. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (TA344). June 2015
- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011
- NICE technology appraisal. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA202). October 2010
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2017 NHS Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P

CURRENT TREATMENT OPTIONS

Treatment options will vary mainly according to the stage of the cancer at diagnosis. There are 3 main stages of CLL:

- Stage A: Enlarged lymph glands in less than 3 areas and a high white blood cell count
- Stage B: Enlarged lymph glands in more than 3 areas and a high white blood cell count

- Stage C: Enlarged lymph glands or an enlarged spleen, high white blood cell count and low red blood cell/platelet count

Stage B and C are usually treated immediately; Stage A is only treated if symptoms occur or the disease appears to progress quickly. Treatment options for CLL can include:[19,20,21]

- First line therapy combinations (in treatment cycles of 28 days):
    - Fludarabine (oral) -Cyclophosphamide (oral) - Rituximab (IV) combination (FC-R)
    - Cyclophosphamide – doxorubicin – vincristine – prednisolone (CHOP)
    - Cyclophosphamide – doxorubicin – prednisolone (CAP)
    - Cyclophosphamide – vincristine – prednisolone (CVP)

- Second line therapy combinations (given to people who cannot have or for who the first line chemotherapy agents were ineffective – Stage C and refractory CLL):
    - Bendamustine – for those where fludarabine based treatment is inappropriate
    - Ibrutinib (alone) – for those with 17p deletion/TP53 mutation and for those where chemo-immunotherapy is unsuitable
    - Idelalisib-rituximab combination – for untreated CLL with 17p deletion/TP53 mutation
    - Obinutuzumab-chlorambucil combination - for untreated CLL with comorbidities which make full dose fludarabine based therapy and bendamustine based therapy unsuitable
    - Ofatumumab-chlorambucil combination - for untreated CLL if fludarabine based therapy or bendamustine is unsuitable

- Chemotherapy for relapsed/refractory CLL:
    - Ibrutinib (alone) – for CLL patients who received at least 1 prior therapy
    - Idelalisib-rituximab combination – for those with treated CLL which has relapsed within 24 months
    - Rituximab-fludarabine-cyclophosphamide combination – for relapsed/refractory CLL except when it is refractory to fludarabine (relapsed with 6 months treatment) or has been previously treated with rituximab
    - Fludarabine (alone) – for those where first line chemotherapy failed or who are intolerant of

- Stem cell transplants – high dose chemotherapy and radiotherapy followed by transplantation of stem cells from a genetically similar donor (allogenic)

- Radiotherapy – recommended in low doses (as CLL tends to be sensitive to radiotherapy) in those with much enlarged lymph nodes or spleen

Other treatment options intended for secondary effects of CLL and/or CLL treatment include:

- Immunoglobulin replacement therapy – to help prevent infections
- Antibiotic, antifungal and antiviral medications – to treat infections in CLL patients
- Granulocyte-colony stimulating factor (G-CSF) injections – to boost white blood counts
- Blood transfusions – to treat severe anaemia or bleeding and bruising problems

EFFICACY and SAFETY

Trial	iLLUMINATE, NCT02264574, EudraCT-2014-002069-31; Ibrutinib in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab
Sponsor	Pharmacyclics LLC
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA and other countries
Design	Randomised, active controlled

Participants	N=212
	Inclusion criteria:
	• Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria
	• Age ≥65 years OR if <65, must have at least one of the following criteria:
	  ○ Cumulative Illness Rating Score >6
	  ○ Creatinine clearance <70 mL/min (Cockcroft-Gault equation)
	  ○ Del 17p by FISH or TP53 mutation
	• Active disease meeting an IWCLL criteria for requiring treatment
	• Measurable nodal disease by CT (at least 1 lymph node >1.5 cm)
	• Adequate hematologic, hepatic and renal function
	• ECOG performance status of 0 to 2

Schedule	Patients receive ibrutinib 420mg daily (3x140mg capsules) taken orally and continuously (until evidence of progressive disease or no longer tolerated by the patient) in combination with obinutuzumab 1000 mg intravenously over 6 cycles: days 1+2 (100 mg on day 1 and 900 mg on day 2), 8 and 15 of cycle 1 followed by day 1 only on cycles 2-6
Follow-up	Not reported
Primary Outcomes	Progression Free Survival (PFS)
Secondary Outcomes	Overall Response Rate (ORR); Rate of minimal residual disease (MRD)-negative responses
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date October 2017. Estimated study completion date January 2020.

ESTIMATED COST and IMPACT

COST

Ibrutinib is already marketed individually in the UK as 90 x 140mg capsule pack (cost £4599) or 120 x 140mg capsule pack (cost £6132). This equates to £51.10 per capsule.[22]

Obinutuzumab is already marketed individually in the UK at £3312 per 1000mg vial (with the average dose set at 1000mg on day 1, 8 and 15 of treatment cycle 1 and 1000mg on day 1 of treatment cycle

2 to 6). Average cost for a treatment course is £26,496 (cycle 1 costs £9936 and cycle 2 to 6 cost £3312).[23]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Janssen-Cilag Ltd

UK PharmaScan ID number 644737.

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