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Venetoclax in combination with obinutuzumab for the treatment of previously untreated chronic lymphocytic leukaemia – 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 white blood cells 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. CLL is one of the most common leukaemia in adults, usually occurring above the age of 60 years. General symptoms include fatigue, frequent infections, and swollen lymph nodes.

Venetoclax is a drug that attaches to a protein in the body called Bcl-2. This protein presents in high amounts in CLL cancer cells, where it helps the cancer cells survive for longer in the body and makes them resistant to cancer medicines. Venetoclax causes the death of cancer cells and thereby slows the progression of the disease. In combination with obinutuzumab the body's immune system gets strengthened. If licenced, venetoclax with obinutuzumab will offer an additional treatment option for patients with previously untreated CLL.

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TARGET GROUP

Chronic lymphocytic leukaemia (CLL) (previously untreated, with comorbidities) – first line; in combination with obinutuzumab

TECHNOLOGY

DESCRIPTION

Venetoclax (Venclyxto) is a selective small molecule inhibitor of B-cell lymphoma 2 (Bcl-2), an anti-apoptotic protein that helps the cancer cells survive for longer in the body and makes them resistant to cancer medicines. Bcl-2 is overexpressed in around 95% of people with chronic lymphocytic leukaemia (CLL) and is present in high amounts in CLL cancer cells. The active substance in venetoclax attaches to Bcl-2. By attaching to Bcl-2 and blocking its actions, venetoclax causes the death of cancer cells and thereby slows the progression of the disease.[1]

Obinutuzumab (Gazyvaro) is a monoclonal antibody that has been designed to recognise and attach to the protein CD20, which is found on the surface of B lymphocytes.[2] CD20 is thought to be involved in B-cell activation, regulation of B-cell growth, and transmembrane calcium flux.[3] 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.[2]

In the phase III clinical trial (NCT02242942), venetoclax is taken as oral tablet 20 mg daily during cycle 1, day 22-28; 50 mg daily during cycle 2, day 1-7; 100 mg daily during cycle 2, day 8-14; 200 mg daily during cycle 2, day 15-21; 400 mg daily during cycle 2, day 22-28 and on day 1-28 for all subsequent cycles until the end of cycle 12. Obinutuzumab is given as intravenous (IV) infusion 100 mg or 1000 mg, depending on splitting rules, at cycle 1, day 1 (if 100 mg was received on day 1, 900 mg will be administered on cycle 1, day 2); 1000 mg at cycle 1, day 8 and day 15; 1000 mg at day 1 for all subsequent cycles until the end of cycle 6.[4]

Venetoclax is currently marketed in the EU for the treatment of relapsed/refractory CLL. In the EU and globally venetoclax is also in development for the following indications:[5]

- Diffuse large b-cell lymphoma
- Relapsed/refractory multiple myeloma
- Follicular lymphoma
- Waldenstrom's macroglobulinemia
- Untreated and relapsed/refractory chronic lymphocytic leukaemia
- Acute myeloid leukaemia
- Chronic myeloid leukaemia
- Myelodysplastic syndrome
- Mantle cell lymphoma

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

- Previously untreated chronic lymphocytic leukaemia (*combination with chlorambucil*)
- Follicular lymphoma:

- In combination with chemotherapy in patients with previously untreated advanced follicular lymphoma
- In combination with bendamustine in patients whose disease has not responded or whose cancer has progressed during or up to 6 months after treatment with the medicine rituximab.

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

The combination of venetoclax with obinutuzumab is not currently licenced for any indication in the EU.

INNOVATION and/or ADVANTAGES

Results demonstrated that venetoclax could be safely combined with obinutuzumab, even in patients with comorbidities and at increased risk of tumour lysis syndrome (TLS) due to renal impairment.[7] Therefore, if licensed, venetoclax in combination with obinutuzumab will offer an additional treatment option for patients with previously untreated CLL and comorbidities.

DEVELOPER

AbbVie Ltd, Genentech

AVAILABILITY, LAUNCH or MARKETING

Venetoclax received Orphan Drug Designation for the treatment of CLL by the EMA in December 2012.[8]

Obinutuzumab received Orphan Drug Designation for the treatment of CLL by the EMA in October 2012.[9]

PATIENT GROUP

BACKGROUND

Chronic Lymphocytic Leukaemia (CLL) is a type of B lymphocyte cancer. B lymphocytes are a type of white blood cells (leukocytes). 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.[10]

CLL 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 accounted for less than 1% of cancer deaths in the UK (2014). In the UK in 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 1.2 per 100,000 in females.[17]

In 2015, there were 60,087 admissions for Lymphoid Leukaemia (ICD-10 C91.1) in England, resulting in 68,028 bed days and 62,290 finished consultant episodes.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Venetoclax for chronic lymphocytic leukaemia (ID944). Expected Nov 2017
- 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

OTHER GUIDANCE

Eichhorst B, Robak T, Montserrat et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology (2015) 26:5, 78-84

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Oscier D, Dearden C, Eren E et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. British Journal of Haematology (2012) 159:5, 541-564

Follows G et al. Interim statement from the BCSH CLL Guidelines Panel. http://www.b-s-h.org.uk/media/13488/interim-statement-cll-guidelines-version6.pdf

CURRENT TREATMENT OPTIONS

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

- 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:[19,20,21,22,23,24]

- First line therapy combinations:
    - Fludarabine (oral) -Cyclophosphamide (oral) - Rituximab (IV) combination (FC-R) Venetoclax in patients with a 17p deletion or TP53 mutation and 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, in combination with rituximab, is 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 chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable
    - Ofatumumab in combination with chlorambucil is recommended as an option for untreated chronic lymphoytic leukaemia only if the person is ineligible for fludarabine-based therapy and bendamustine is not suitable and
    - Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

- Relapsed/refractory CLL:
    - Bendamustine – for those where fludarabine based treatment is inappropriate
    - Ibrutinib (alone) – for those who have had at least 1 prior therapy or for those with 17p deletion/TP53 mutation and in whom chemo-immunotherapy is unsuitable
    - Idelalisib-rituximab combination – for CLL patients who disease has relapsed within 24months

- Venetoclax in patients:
  - with a 17p deletion or TP53 mutation and whose disease has progressed after a B-cell receptor pathway inhibitor or
  - without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor and

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

- Radiotherapy –should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy. Low doses of external beam radiotherapy (2 × 2 Gy) can be highly effective in this situation and a higher dose (30 Gy in 2–3 Gy fractions) may be required in patients with transformed aggressive disease or those known to have a *TP53* abnormality

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	NCT02242942, EudraCT-2014-001810-24; obinutuzumab + venetoclax versus obinutuzumab + chlorambucil; phase III
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[4], Global Data[25]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, controlled, parallel assignment, open label
Participants	N=445; 18 years and older; documented previously untreated CLL according to the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria, CLL requiring treatment according to IWCLL criteria, total cumulative illness rating scale (CIRS score) greater than (>) 6, adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia is due to marrow involvement of CLL, adequate liver function, life expectancy > 6 months, agreement to use highly effective contraceptive methods per protocol;
Schedule	Randomised to: Venetoclax, oral tablet: 20 mg daily during Cycle 1, Day 22-28; 50 mg daily during Cycle 2, Day 1-7; 100 mg daily during Cycle 2, Day 8-14; 200 mg daily during Cycle 2, Day 15-21; 400 mg daily during Cycle 2, Day 22-28 and on Day 1-28 for all subsequent cycles until the end of Cycle 12. Obinutuzumab, IV infusion: 100 mg or 1000 mg, depending on splitting rules, at Cycle 1, Day 1 (if 100 mg was received on Day 1, 900 mg will be administered on

	Cycle 1, Day 2); 1000 mg at Cycle 1, Day 8 and Day 15; 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6
Follow-up	Follow-up period up to 5 years
Primary Outcomes	Progression-Free Survival (PFS) based on investigator assessment (using IWCLL criteria), defined as the time from randomisation to the first occurrence of progression, relapse or death from any cause
Secondary Outcomes	• PFS Based on Institutional Review Committee (IRC)-Assessments, Defined as the Time From Randomization to the First Occurrence of Progression or Relapse or Death From any Cause • Percentage of Participants with an Overall Response of Complete Response (CR), CR with Incomplete Bone marrow Recovery (CRi), or Partial Response (PR), as Determined by the Investigator at Completion of Treatment According to IWCLL Criteria • Percentage of Participants With Minimal Residual Disease (MRD) Negativity as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment • Percentage of Participants With OR at Completion of Combination Treatment Response Assessment • Percentage of Participants With MRD Negativity, as Measured by ASO-PCR at Completion of Combination Treatment Response Assessment • Overall Survival • Duration of Objective Response • Percentage of Participants By Best Response Achieved • Event-Free Survival • Time to Next Anti-Leukemic Treatment • Percentage of Participants With Adverse Events Assessed According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 • Percentage of Participants With Human-Anti-Human Antibodies • Percentage of Participants With Adverse Events of Special Interest • Apparent Clearance of obinutuzumab • Apparent Clearance of venetoclax • Apparent Volume of Distribution of obinutuzumab • Apparent Volume of Distribution of venetoclax • Number of CD19 + CD5+ Cells • Number of CD19 + CD5- Cells • Change From Baseline in M.D. Anderson Symptom Inventory (MDASI) score • Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30) • Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date November 2018. Estimated study completion date September 2021.

ESTIMATED COST and IMPACT

COST

A 112-pack of 100 mg tablets (which is enough for 28 days of 400 mg treatment, used at week 5 onward) costs £4,789.47 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.[26] The cost of obinutuzumab is stated as £3,312 (excluding VAT) per 1,000 mg vial.[27]

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

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