Venetoclax for chronic lymphocytic leukaemia with 17p deletion or TP53 mutation

LAY SUMMARY

Chronic lymphocytic leukaemia is a cancer that affects white blood cells called lymphocytes. It causes the body to make large numbers of abnormal lymphocytes that do not work properly and build up in the lymph nodes (glands) and bone marrow. Chronic lymphocytic leukaemia usually affects older people and usually develops slowly. However, the disease develops more quickly and is harder to treat in patients when the lymphocyte cells have certain mutations in their genes called 17p deletion or TP53 mutation.

Venetoclax is a new drug for patients with chronic lymphocytic leukaemia with the 17p deletion or TP53 mutation, and it is given as a tablet once a day.

If venetoclax is licensed for use in the UK, it could be a new treatment option for patients with chronic lymphocytic leukaemia that may reduce symptoms of the disease and increase survival.

NIHR HSRIC ID: 11210
TARGET GROUP

- Chronic lymphocytic leukaemia (CLL): with 17p deletion or TP53 mutation — monotherapy.

TECHNOLOGY

DESCRIPTION

Venetoclax (ABT-199, GDC-0199) is a novel small molecule that is designed to selectively inhibit the function of the Bcl-2 family protein. Bcl-2 proteins are central regulators of apoptosis which are expressed at high levels in non-Hodgkin lymphoma, CLL and in other B-cell neoplasms, leading to treatment resistant malignancies. In clinical trials, venetoclax dosing was increased in a step-wise lead-in period (up to 5 weeks) to a final treatment dose of 400mg orally once daily.

Venetoclax does not currently have marketing authorisation in the EU for any indication.

Venetoclax is currently in phase III clinical trials for CLL as a combination therapy. It is also in phase II clinical trials for acute myeloid leukaemia and non-Hodgkin lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, venetoclax will offer an additional treatment option for patients with chronic lymphocytic leukaemia who have 17p deletion or TP53 mutation, a group who are more likely to experience progressive and treatment resistant disease.

DEVELOPER

AbbVie Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Phase II clinical trials.

PATIENT GROUP

BACKGROUND

CLL is characterised by the accumulation of resting malignant B cells in peripheral blood and the presence of proliferating malignant B cells in the lymph nodes, spleen and bone marrow. The progressive accumulation of monoclonal B lymphocytes leads to leucocytosis, lymphadenopathy, hepatosplenomegaly, anaemia, thrombocytopenia, neutropenia, bone marrow failure, recurrent infections and systemic symptoms (fatigue, weight loss, night sweats).

CLL is an extremely heterogeneous disease clinically, with some patients never requiring treatment. Whilst around 80% of patients are asymptomatic at diagnosis the majority will require treatment at some point, and as no current treatment option is curative, patients who are treated will eventually relapse. There is no good evidence that exposure to chemicals or
radiation, diet, cigarette smoking, viral infections or autoimmune diseases are risk factors for the development of CLL. However, there is an increase in both lymphoid malignancies, including CLL, and subclinical monoclonal B-cell expansion in first and second degree relatives of patients with CLL. The incidence of second malignancies is increased in both treated and untreated CLL\(^7\).

Deletion of 17p is the strongest independent adverse prognostic factor for survival, and is associated with the shortest median treatment-free survival in patients with CLL\(^8\). The 17p deletion mutation is a genomic alteration in which a part of chromosome 17 is absent\(^9\). This deletion involves the loss of the \(TP53\) tumour suppressor gene. Defects in p53 pathway impair correct DNA repair and apoptosis and result in increased genomic instability and abnormal cell proliferation. In various cancer types, p53 protein is most often inactivated due to mutation in the \(TP53\) gene accompanied by deletion of the other allele (locus 17p.13.1)\(^10\). The 17p deletion is found in 5-7% of CLL cases in early stages, rising to 25-40% of patients with advanced refractory disease. \(TP53\) gene encodes the key transcriptional factor acting in response to genotoxic stress. In CLL, \(TP53\) defects have been observed in 5-10% patients at diagnosis, with an increased frequency in progressive and chemo-refractory disease\(^9\). The median life expectancy for CLL patients with 17p deletion is less than 2-3 years\(^9\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adults, accounting for around 51% of all leukaemias and an estimated 4,100 new diagnoses in England in 2013\(^11\). Approximately 75% of patients diagnosed with CLL are over the age of 60\(^12\), with incidence in men twice that of women\(^13\).

CLL is usually initially treatable, but there are no curative treatments for CLL, and the majority of patients will eventually relapse\(^14,15\). Survival in the early stages of the disease is likely to be 10 years or more, however survival for people diagnosed at an advanced stage is around 1-3 years\(^12\). The 5-year survival rates for all stages of CLL are 40% and 50% for males and females respectively\(^12\). In 2013-14, there were 30,275 hospital admissions due to CLL (ICD-10 C91.1) in England, accounting for 31,071 finished consultant episodes and 16,078 bed days\(^16\). There were 1,071 deaths registered in England and Wales during 2012\(^17\).

Approximately 5-10% of people with CLL have ‘high-risk’ disease characterised by the presence of 17p deletion or \(TP53\) mutation which influences the rate of cell growth and is associated with resistance to treatment\(^18\). The population likely to be eligible to receive venetoclax could not easily be estimated from available routine published sources.
RELEVANT GUIDANCE

NICE Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

CLL usually develops very slowly and often does not require treatment for many months or years. For active disease, the choice of treatment is dependent on fitness, co-morbidities and whether there is a high risk disease. Treatment options for CLL include:

- Chemotherapy – FCR (fludarabine, cyclophosphamide and rituximab), chlorambucil or bendamustine.
- Alemtuzumab in combination with pulsed high dose glucocorticoids is the treatment of choice in high risk CLL outside of clinical trials.
- Ofatumumab (not recommended by NICE).
- Monoclonal anti-CD20 antibodies.

\(^a\) Information provided by company.
Radiotherapy.
Splenectomy — removal of enlarged spleen.
Allogenic stem cell transplant should be considered as consolidation therapy for all fit patients with high risk CLL.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01889186, M13-82, EudraCT 2012-004027-20; ABT-199; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AbbVie Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial Registry²⁵.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl. UK), USA, Canada, Australia.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=150 (planned; n=100 in the main cohort and n=50 in the safety expansion cohort); over 18 years old. Diagnosis of CLL that meets published 2008 Modified International Workshop for Chronic Lymphocytic Leukaemia National Cancer Institute-Working Group (IWCLL NCI-WG) criteria; 17p deletion; indication for treatment according to the 2008 Modified IWCLL NCI WG guidelines; clinically measurable disease; refractory or relapsed after at least one prior line of therapy or previously untreated CLL; adequate bone marrow function, adequate coagulation, renal, and hepatic function. Subject excluded if received previous allogeneic stem cell transplant, developed Richter’s transformation, has prolymphocytic leukaemia or has active and uncontrolled autoimmune cytopenias.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Subjects receive ABT-199 400mg administered orally once daily following a step-wise lead-in dose escalation period (up to 5 weeks).</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Treatment continued until disease progression or no longer tolerated by patient due to toxicity.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Main cohort; overall response rate (ORR). Safety expansion cohort; adverse events; change in physical exam findings, including vital signs (temperature, weight, blood pressure, heart rate); change in clinical laboratory test results (chemistry, haematology, urinalysis, viral serologies); change in cardiac assessment findings.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Main cohort; complete remission; partial remission; duration of overall response; progression-free survival; time to progression; overall survival; % subjects who move on to stem cell transplant; event free survival; time to first response; time to 50% reduction in absolute lymphocyte count. Safety expansion cohort; ORR and efficacy endpoints. Exploratory endpoints include EQ5D-5L²⁶, EQ5D-VAS²⁷, EORTC²⁸ QLQ-C30²¹ and QLQ-CLL16.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Estimated results publishing in December 2015.</td>
</tr>
</tbody>
</table>

ESTIMATED COST and IMPACT

COST

The cost of venetoclax is not yet known.

²⁵ EuroQol 5-dimension.
²⁶ EuroQol visual analogue scale.
²⁷ European Organisation for Research and Treatment of Cancer.
²⁸ Quality of life questionnaires.
## 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

---

### REFERENCES

5. NIHR Horizon Scanning Centre. Ofatumumab (Arzerra) for relapsed chronic lymphocytic leukaemia. University of Birmingham, November 2013. [www.hsc.nihr.ac.uk/](http://www.hsc.nihr.ac.uk/)


