National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: April 2017

Ibutinib with Venetoclax and Obinutuzumab for the treatment of Chronic Lymphocytic Leukaemia patients with TP53 deletion and/or mutation

NIHRIO (HSRIC) ID: 12792

LAY SUMMARY

Chronic Lymphocytic Leukaemia (CLL) is a type of slow developing type of white blood cell cancer. It is most common in those above 60 years old and rarely occurs in people below 40 years old. Some people with CLL have genetic changes in a gene (TP53) which is responsible for production of Tumour Protein 53; a protein which suppresses cancer. CLL patients with genetic changes to the TP53 gene have shorter survival times and often don't respond to existing treatments options.

The GIVe chemotherapy regime involves giving CLL patients 3 different chemotherapy drugs (Ibrutinib, Venetoclax and Obinutuzumab) together as part of a six month treatment programme. Each of these drugs is licensed and given individually to treat CLL, however to date they have not been used in combination. If the GIVe chemotherapy regime was licenced in the UK it could provide a new treatment option to CLL patients with genetic TP53 changes. This sub-group of CLL patients currently have limited treatment options.

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.

TARGET GROUP

Chronic Lymphocytic Leukaemia with TP53 deletion and/or mutation; previously untreated; first line

TECHNOLOGY

DESCRIPTION

Ibrutinib; (CRA-032765; ibrutinib (capsule); ibrutinib (tablet); Imbruvica; JNJ-54179060; PCI-32765) is an orally active, small molecule, selective Bruton's Kinase (Btk) inhibitor developed originally for the treatment of B-cell lymphomas but also licenced and in clinical trials for a variety of other conditions. Ibrutinib works by irreversibly blocking cell signals by specifically blocking Bruton's tyrosine kinase (Btk) involved in the pathway which aids cancer cell survival and growth. Blocking this pathway promotes the death of the cell, preventing it from dividing and the cancer growing.[1]

Venetoclax tablets (RG-7601, ABT-199, GDC-0199; Veclexta, Venclyxto) is a selective Bcl inhibitor. Bcl-2 is a protein which regulates apoptosis (programmed cell death). Cancer cells can overexpress this protein, making the cancer cells resistant to standard chemotherapy. Venetoclax inhibits Bcl-2 allowing cancer cells to undergo apoptosis.[2] Venetoclax is administered orally at a starting dose of 20mg once daily for 7 days and gradually increasing over the next 5 weeks up to the recommended dose of 400mg as follows: 50mg daily in week 2, 100mg daily in week 3, 200mg daily in week 4 and 400mg daily in week 5.[3]

Obinutuzumab (Gazyva, afutuzumab, Antibodies GlycArt, Anticancers GlyArt, GA-101, GA-301, GA-401, GA-501, Gazyvaro, R-7159, RG-7195, RO-5072759) is a third generation anti-CD20 therapeutic antibody which uses GlycoMab technology for glycosylation which increases antibody-dependant cellular toxicity. [4] This results in lysis of B-lymphocytes. [5] Obinutuzumab is administered intravenous (IV) infusion in 6 treatment cycles of 28 days followed by a maintenance dose of 1000mg every 2 months for 2 years or until disease progression. 1000mg Obinutuzumab is administered on day 1, 8 and 15 of cycle 1 and 1000mg. Obinutuzumab is administered on day 1 of cycles 2-6 of treatment.[6]

Venetoclax and Ibrutinib can inhibit the growth of cancer cells by blocking enzymes required for cell growth. Whilst Obinutuzumab, which is a monoclonal antibodies, targets certain cells to try and block cancer growth in a different way. Given the alternative mechanisms of action Venetoclax together with Obinutuzumab and Ibrutinib may be a better treatment for chronic lymphocytic leukaemia.

Ibrutinib, Venetoclax and Obinutuzumab are currently licenced individually for a variety of indications, which have been summarised below.

Ibrutinib has been licenced for the use the following indications in the EU:

- Chronic Lymphocytic Leukaemia; adults with previously untreated or received 1 prior therapy
- Mantle Cell Lymphoma (MCL); adult patients with relapsed/refractory MCL with at least 1 prior treatment
- Waldenstrom's Hypergammaglobulinaemia (WM); adults with WM who received at least 1 prior treatment or first line for patients unsuitable for chemo-immunotherapy

Venetoclax combined with Obinutuzumab has been licenced for use in Chronic Lymphocytic Leukaemia in the EU.

Ibrutinib, Venetoclax and Obinutuzumab combination are not currently licenced for use in combination for the treatment of CLL, but the combination is currently in phase III trials.

Recognised common adverse events (AEs) (>10%) of Ibrutinib in the currently licenced indications include: Infections (incl. Pneumonia, Upper respiratory Tract Infections, Sinusitis and skin infections), Neutropenia, Thrombocytopenia, Headache, Haemorrhage, Bruising, Diarrhoea, Vomiting, Stomatitis, Nausea, Constipation, Rash, Arthralgia, Muscle spasm, Musculoskeletal pain, Pyrexia (fever) and Peripheral oedema. [7] Recognised common AEs (>10%) of Venetoclax are Upper Respiratory Tract Infections, Neutropenia, Anaemia, Hyperphosphatemia, Diarrhoea, Vomiting, Nausea, Constipation and Fatigue. [8] Recognised common AEs (>10%) of Obinutuzumab are Upper Respiratory Tract Infections, Sinusitis, Neutropenia, Thrombocytopenia, Anaemia, Cough, Diarrhoea, Constipation, Arthralgia, Pyrexia, Asthenia, Infusion related reactions.[9]

Ibrutinib, Venetoclax and Obinutuzumab are currently in phase III clinical trials individually and in combination.

INNOVATION and/or ADVANTAGES

If licensed, Ibrutinib + Venetoclax + Obinutuzumab (GIVe) chemotherapy regime will offer an additional treatment option for patients with CLL with TP53 deletion and/or mutation, a CLL patient subgroup with limited existing treatment options.

DEVELOPER

AbbVie

AVAILABILITY, LAUNCH or MARKETING

Each of the drugs in the GIVe regime, Ibrutinib, Venetoclax and Obinutuzumab are licenced and launched individually but not currently in combination. Ibrutinib is designated orphan drug status in the EU and USA and Breakthrough Therapy and US Fast Track status by the FDA. Venetoclax is designated orphan drug status in the EU and USA and Breakthrough Therapy and US Fast Track status by the FDA. Obinutuzumab is a designated orphan drug in the EU and USA and designated Breakthrough Therapy by the FDA.

Regarding the combination of these drugs, the GIVe regime, is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Chronic Lymphocytic Leukaemia (CLL) is a type of B-lymphocyte (white blood cell) cancer. In this type of cancer, abnormal white blood cells develop from blood stem cells. These leukaemia cells are unable to function and fight infection as well as normal lymphocytes and can accumulate in the blood and bone marrow, preventing the production of healthy blood cells (white blood cells, red blood cells and platelets). 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 >60years old and rarely occurs in those <40 years old.[11] Because CLL develops slowly, people often have no symptoms in the 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 the presence of certain medical conditions (pneumonia, sinusitis, shingles infection, autoimmune haemolytic anaemia, chronic osteoarthritis and prostatitis), exposure to electromagnetic radiation and people with low immunity (people with HIV/AIDS or on immunosuppressive medication).[13] Several genetic changes have also been identified which are regularly tested for as part of 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 slowly developing type of CLL which may not require treatment for many years. <10% people have deletion of the TP53 gene.[14] TP53 mutation/deletion in CLL is associated with advanced stage disease, refractory disease and poor clinical outcomes (with a shorter overall survival and progression free survival and reduced time till first treatment compared to CLL patients without TP53 mutation/deletion). There are limited treatment options available to CLL patients with TP53 mutation/deletion as patients are often resistant to standard chemotherapy regimes. Allogenic stem cell transplantation, a potentially curative treatment option in CLL, may be recommended in this patient segment however it is often inappropriate due to patient age, comorbidities and risk of transplantation related mortality.[15]

CLINICAL NEED and BURDEN OF DISEASE

For England, the incidence of CLL was 6.3 per 100,000 population in 2014 and for the UK the incidence of CLL was 6.0 per 100,000 in 2014.[16]

In adults in England diagnosed with CLL, 66.5% of men and 72.5% women will survive >5 years after diagnosis.[17]

CLL (ICD-10 C91.1) accounted for <1% cancer deaths in the UK in 2014. In total 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 per 100,000 in females.[18]

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.[19]

Deletions within the short arm of chromosome 17 (17p13) are common genetic changes seen in CLL patients. Mutations in TP53 (located on 17p13) occurs in 80% of CLL patients with 17p13 deletions while TP53 mutations without 17p13 deletions are more infrequent, occurring in 4 to 5% CLL cases. Approximately 5 to 7% of all CLL patients have TP53 deletion on diagnosis. In addition, 25 to 40% of those with advanced refractory disease have TP53 deletions. TP53 deletions and mutations are associated with reduced p53 protein function and poorer CLL prognosis outcomes. However there are no specific population size estimates for patients with TP53 deletion or mutations from available published sources.[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE Technology appraisal guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE Technology appraisal guidance. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (TA 344). June 2015.
- NICE Technology appraisal guidance. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA202). October 2010.
- NICE Technology appraisal guidance. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010.

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 (e.g. neck, armpit and groin) 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 and Stage A is only treated if symptoms appear or the disease appears to progress quickly.

There are several treatment options available to those with advanced CLL (for those with stage B and C) which are usually comprised of chemotherapy agents, targeted therapies (usually monoclonal antibodies targeting a specific molecule) and steroids in combination or alone:[21-23]

- 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 – recommended as first line treatment for those where fludarabine based treatment is inappropriate
    - Ibrutinib (alone) – recommended for those with 17p deletion/TP53 mutation and for those where chemo-immunotherapy is unsuitable
    - Idelalisib-rituximab combination – recommended for untreated CLL with 17p deletion/TP53 mutation

    - Obinutuzumab-chlorambucil combination - recommended for untreated CLL with comorbidities which make full dose fludarabine based therapy unsuitable and bendamustine based therapy is unsuitable.
    - Ofatumumab-chlorambucil combination - recommended for untreated CLL if fludarabine based therapy or bendamustine is unsuitable
- Chemotherapy for relapsed/refractory CLL:
    - Ibrutinib (alone) – recommended for CLL patients who received at least 1 prior therapy
    - Idelalisib-rituximab combination – recommended for those with treated CLL which has relapsed within 24 months.
    - Rituximab-fludarabine-cyclophosphamide combination – recommended 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) – recommended for those where first line chemotherapy are failed or intolerant of.
    - Ofatumumab (alone) – not recommended for those whose CLL is refractory to fludarabine and alemtuzumab.
- 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 very enlarged lymph nodes or spleen.
- Antibiotic, Antifungal and Antiviral medications – recommended to treat infections in CLL patients.[23]
- Blood transfusions – recommended for treatment of severe anaemia or bleeding and bruising problems which occur as a result of low red blood cells or platelet counts due to CLL.
- Immunoglobulin Replacement Therapy – transfusion of antibodies from donated blood to the CLL patient to help prevent infections.
- Granulocyte-colony stimulating factor (G-CSF) injections – recommended to boost the numbers of white blood cells in CLL patients.

EFFICACY and SAFETY		
Trial	Ibrutinib plus Venetoclax plus Obinutuzumab (GIVe regime), NCT02758665, eUDRAct Number: 2015-004606-41, CLL2 GIVe, TrialTroveID-277980; Chronic Lymphocytic Leukaemia; TP53 deletion (17p) and/or mutation; Ibrutinib plus Venetoclax plus Obinutuzumab; phase II clinical trial	Ibrutinib plus Venetoclax plus Obinutuzumab (GIVe regime), NCT02950051, CLL13, EudraCT Number 2015-004936-36, GAIA, HOVON 140 CLL, TrialTroveID-289671; Chronic Lymphocytic Leukaemia; TP53 deletion (17p) and/or mutation; Ibrutinib plus Venetoclax plus Obinutuzumab vs Standard chemotherapy vs Rituximab plus Ve-Netoclax vs Venetoclax plus Obinutuzumab; phase III clinical trial
Sponsor	German CLL Study Group – GCLLSG; Johnson & Johnson; Janssen-Cilag; Roche	CLL Study Group – GCLLSG; Swiss Group for Clinical Cancer Research – SAKK; University of Cologne Germany
Status	Ongoing	Ongoing

Source of Information	trial registry[24]	trial registry[25]
Location	Germany	Austria, Belgium, Denmark, Finland, Germany, Ireland, Israel, Netherlands, Norway, Sweden and Switzerland
Design	Single arm, uncontrolled study	Randomised, active-controlled
Participants	N=40 (planned); aged>18 years; Chronic Lymphocytic Leukaemia; with TP53 deletion (17p-) and/or mutation; previously untreated	N= 920 (planned); >18 years; Chronic Lymphocytic Leukaemia; with TP53 deletion (17p-) and/or mutation; previously untreated
Schedule	Participants received in combination: Ibrutinib: 420mg orally per day Venetoclax: Taken orally in cycles of 28 days: -Cycle 1: (day 22 to 28): 20mg (2x 10mg tablets) -Cycle 2: (day 1 to 7): 50mg (1x50mg tablet), (day 8 to 14) 100mg (1x 100mg tablet), (day 15 to 21) 200mg (2x 100mg tablets), (day 22 to 28) 400mg (4x 100mg tablets) Cycle 3 to12: (day 1 to 28) 400mg (4x 100mg) Obinutuzumab: taken Intravenously in cycles of 28 days -Cycle 1: (day 1) 100mg, (day 2) 900mg, (day 8 + 15) 1000mg -Cycle 2 to 6: 1000mg	4 different intervention arms with different chemotherapy regimens run in parallel delivered in 6 cycles (28 days each) 1. Standard Chemotherapy (SCIT): a) <65 years: Fludarabine + Cyclophosphamide+ Rituximab (FCR) for 6 cycles Cycle 1 to 6: Fludarabine (IV 25mg/m^2 day 1 to 3) + Cyclophosphamide (IV 250mg/m^2 day 1 to 3) + Rituximab (IV 375mg/m^2 on cycle 1 day 0, 500mg/m^2 on cycle 2 to 6 day 1). b) >65 years: Bendamustine + Rituximab (BR) for 6 cycles Cycle 1 to 6: Bendamustine (IV 90mg/m^2 day 1 to 2) + (IV 375mg/m^2 on cycle 1 day 0, 500mg/m^2 on cycle 2 to 6 day 1). 2. Rituximab + Venetoclax (RVe regime): 6 cycles of Rituximab + Venetoclax (RVe) followed by 6 cycles of Venetoclax alone. Cycle 1 to 6: Rituximab (IV 375mg/m^2 on cycle 1 day 0, 500mg/m^2 on cycle 2 to 6 day 1) + Venetoclax (ramp up until final dose is reached). Cycle 7 to 12: Venetoclax alone (ramp up until final dose is reached). 3.Obinutuzumab + Venetoclax (GVe regime): 6 cycles Obinutuzumab + Venetoclax (GVe) followed by 6 cycles Venetoclax alone

		a) Venetoclax Cycle 1: 20mg (2x 10mg tablets) orally, day 22 to 28; Cycle 3 to 12: 400mg (4x 100mg tablets) day 1 to 28 b) Obinutuzumab Cycle 1: 100mg Obinutuzumab IV day 1, 900mg Obinutuzumab orally day 2, 1000mg day 8 +15 Cycle 2 to 6: 1000mg Obinutuzumab IV day 1 4.Ibrutinib + Venetoclax + Obinutuzumab (GIVe regime): 6 cycles of Ibrutinib + Venetoclax + Obinutuzumab followed by 6 cycles of Ibrutinib + Venetoclax. a) Ibrutinib: Cycles 1 to 12: 420mg orally days 1 to 28 Cycles 13 to 36: 420mg orally days 1 to 28 b) Venetoclax: Cycle 1: 20mg (2x 10mg tablets) orally, days 22 to 28 Cycle 2: 50mg (1x 50mg tablet) orally, days 1 to 7, 100mg (1x 100mg tablet) orally days 8 to 14, 200mg (2x 100mg tablets) days 15 to 21, 400mg (4x100mg tablets) days 22 to 28. Cycle 3 to 12: 400mg (4x100mg tablets) days 1 to 28 c) Obinutuzumab: Cycle 1: 100mg intravenously (day 1), 900mg intravenously (day 1), 1000mg intravenously (day 8 and 15) Cycle 2 to 6: 1000mg (day 1)
Follow up	Active treatment for 12 cycles (28 days each)	Active treatment for up to 12 cycles (28 days each).
Primary Outcomes	Complete Response Rate (CR)	Efficacy of the GIVe regime vs. standard chemimmunotherapy (SCIT) using: -Progression Free Survival (PFS) -Minimal Residual Disease (MRD)
Secondary Outcomes	Proportion of patients free of disease progression (up to 336 days) after 12 cycles of therapy, Overall response rate (up to 1176), Progression Free Survival, Event Free Survival, Overall	Comparison of GIVe regime vs standard chemimmunotherapy (SCIT) -MRD at different time points: month 2, 9, 13 and 15 -MRD levels in bone marrow

	Survival, Duration of response, Time to next CLL treatment, Treatment free survival, Subsequent treatment for CLL, Adverse Events, Adverse events off special interest, evidence of Richter's transformation, Exploratory evaluation of baseline markers and clinical outcome parameters. No quality of life measurement included in trial outcomes.	-PFS: comparing RVe and GVe regimes against standard chemimmumotherapy - Overall Response Rate (ORR) at 3,9,13 and 15 - Event free survival - Overall Survival - Duration of response in patients with: complete response (CR), CR with incomplete recovery of bone marrow (CRi), partial response (PR). - Adverse Events - Adverse Events of special interest - Health related Quality of Life - Time from randomisation to first occurrence of progression/relapse/death (from any cause)
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Not Reported	Not Reported

ESTIMATED COST and IMPACT

COST

Ibrutinib is already marketed individually in the UK at 90 x 140mg capsule pack cost £4599/a pack or 120 x 140mg capsule pack cost £6132. This equates to £51.10 per capsule.[26]

Venetoclax is already marketed individually in the UK at 112 x 100mg capsule pack cost £4,790 (with dosage usually 400mg/day). Average cost for the first years treatment course is £58,752.23 and for year two onwards is £41,127.[27]

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).[28]

There is currently no cost estimate for the combination therapy.

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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