Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING OCTOBER 2018

Venetoclax in combination with bortezomib and dexamethasone for relapsed multiple myeloma - second line and beyond

NIHRIO ID	12975	**NICE ID**	9777
Developer/Company	AbbVie Ltd	**UKPS ID**	644705

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Venetoclax is being developed as an enteric coated tablet to be given in combination with bortezomib and dexamethasone for the treatment of relapsed multiple myeloma (MM). MM is a blood cancer that arises from the plasma cells in the bone marrow. Normal plasma cells have a role in fighting infections through the production of antibodies. The abnormal plasma cells multiply and spread within the bone marrow, releasing a large amount of a single type of antibody that has no useful function. Symptoms of MM include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections. MM usually cannot be cured, thus further treatment is needed when the cancer comes back (a relapse).

Venetoclax acts by blocking a protein called B-cell lymphoma (BCL)-2 that mediates the survival of MM cells. Bortezomib and dexamethasone are currently used to treat MM and it is hypothesised that both working via different mechanisms can improve sensitivity to Venetoclax in relapsed MM. The combination of venetoclax, bortezomib, and dexamethasone will offer an additional treatment option for patients with relapsed MM in patients who have received at least one, but no more than three, prior lines of therapy.

PROPOSED INDICATION

Relapsed multiple myeloma – second line and beyond.[a]

TECHNOLOGY

DESCRIPTION

Venetoclax (Venclyxto, ABT-199) is a potent, selective, orally bioavailable small-molecular inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein.[1,2] Overexpression of BCL-2 and myeloid leukaemia cell differentiation protein (MCL-1) plays a part in the pathogenesis of multiple myeloma (MM), also it is hypothesised that high levels of MCL-1 may cause resistance to BCL-2 inhibition.[b] Venetoclax binds directly to the 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. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[2]

Venetoclax is being developed as an enteric coated tablet to be given in combination with bortezomib and dexamethasone for the treatment of relapse MM in patients who have received at least one, but no more than three, prior lines of therapy.[a]

In the phase III clinical trial (NCT02755597), participants received (in cycles 1-8): venetoclax 800mg orally every day once daily on days 1 - 21 plus bortezomib 1.3mg/m2 by subcutaneous injection on days 1, 4, 8 & 11 and dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11 & 12. In cycles 9 and beyond patients received venetoclax 800mg orally every day on days 1 - 35 plus bortezomib 1.3mg/m2 by subcutaneous injection on days 1, 8, 15 & 22 and dexamethasone orally 20 mg on Days 1, 2, 8, 9, 15, 16, 22 & 23.[3]

INNOVATION AND/OR ADVANTAGES

It was indicated that venetoclax is the first BCL-2 inhibitor to show activity in MM. It is an engineered small molecule that was uniquely designed to fit the exact pocket of the protein.[4] Targeting of MCL-1 genetically or pharmacologically in vitro and in vivo induced apoptosis of human MM cell lines. Xenograft models that coexpressed BCL-XL or MCL-1 with BCL-2 were resistant to venetoclax. This resistance was mitigated by combining venetoclax with bortezomib.[1] Venetoclax blocks BCL-2 whilst bortezomib upregulates NOXA which is a protein that neutralises MCL-1 therefore improving sensitivity to Venetoclax.[b] Dexamethasone, a steroid commonly used in MM treatment, can upregulate the expression of the proapoptotic molecule BIM and increase its binding to BCL-2, which also results in increased sensitivity to venetoclax. Thus, targeting BCL-2 and MCL-1 function to induce apoptosis through the combination of venetoclax, bortezomib, and dexamethasone is a compelling approach to treat MM.[1]

[a] Information provided by company on UK PharmaScan
[b] Information provided by company

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Venetoclax monotherapy is already licensed in the UK for the treatment of:[2]

- Chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
- CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Very common (frequency more than 10%) adverse events associated with venetoclax are upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, diarrhoea, vomiting, nausea, constipation, and fatigue.[2]

Venetoclax is in phase III stage of development for various subgroups of patients with chronic lymphocytic leukaemia, acute myeloid leukaemia, and small lymphocytic lymphoma.[5]

Venetoclax is in phase II stage of development for various groups of patients with:[6]

- Chronic lymphocytic leukaemia,
- Acute myelogenous leukaemia,
- Mantle cell lymphoma,
- Waldenström macroglobulinemia,
- Non-hodgkin's lymphoma,
- Acute lymphoblastic leukaemia,
- Follicular lymphoma

PATIENT GROUP

DISEASE BACKGROUND

MM is a blood cancer arising from plasma cells (a type of white blood cell made in the bone marrow). Plasma cells form part of the immune system. Normal plasma cells produce antibodies, also called immunoglobulins, to help fight infection. MM develops when DNA is damaged during the development of a plasma cell. This abnormal cell then starts to multiply and spread within the bone marrow. The abnormal plasma cells release a large amount of a single type of antibody – known as paraprotein – which has no useful function.[7]

Unlike many cancers, MM does not exist as a lump or tumour. Most of the medical problems related to MM are caused by the build-up of abnormal plasma cells in the bone marrow and the presence of the paraprotein in the body. MM is called so because the cancer often affects several areas of the body, such as the spine, skull, pelvis and ribs.[7,8] In the early stages, MM may not cause any symptoms. Eventually, MM causes a wide range of problems, including a persistent dull ache or areas of tenderness in the bones, weak bones that break easily, tiredness, weakness and shortness of breath caused by anaemia, repeated infections, and kidney problems. Less commonly, MM may cause bruising and unusual bleeding such as frequent nosebleeds, bleeding gums and heavy periods.[8]

Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course.[9]

The cause of MM is still unknown. There are some factors that are linked to higher risk of MM such as having a condition called monoclonal gammopathy of unknown significance (MGUS), male gender, older age (60 years and over), black people, family history of MM or MGUS, and

overweight/obesity.[8,10]

MM disease-related events and subsequent disability may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Age standardised incidence rate of MM in England in 2015 was 9.3 per 100,000. In 2015, MM was the 19th most common cancer in the UK with 4,920 new cases in England and Wales (2,835 male and 2,085 female). MM incidence is strongly linked to age, with almost half (45%) of new cases diagnosed in the UK between 2013-2015 presenting in persons aged 75 years and older. MM incidence rates are projected to rise by 11% in the UK between 2014 and 2035, from 11.12 per 100,000 to 12.38 per 100,000.[12] In 2016-17 NHS England reported 140,645 finished consultant episodes (FCEs) and 136,025 admissions under ICD code C90.0 (multiple myeloma) resulting in 90,685 FCE bed day.[13]

Based on data from 2010-2011, almost half of patients with MM in England and Wales now survive their disease for at least 5 years with a third surviving for 10 years or more.[14] Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), and the adoption of haematopoietic stem cell transplantation.[15]

In the UK, there were around 3,000 myeloma deaths every year, that's more than 8 every day (2014-2016).[14] In 2017 in England there were 2,756 registered deaths due to multiple myeloma and malignant plasma cell neoplasms ICD 10 code: C90.[16]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

A multidisciplinary team will discuss the best treatment option for the patient.[17] Treatment for MM can often help to control symptoms and improve quality of life. However, MM is incurable and relapsed MM needs additional treatment. The initial treatment for MM may be either non-intensive (for older or less fit patients) or intensive (for younger or fitter patients). Both non-intensive and intensive treatments involve taking a combination of anti-myeloma medicines. But intensive treatment involves higher doses and is followed by a stem cell transplant. The medicines usually include a chemotherapy medicine, a steroid medicine, and either thalidomide or bortezomib. High doses of chemotherapy medication affect healthy bone marrow, so a stem cell transplant will be needed to allow the bone marrow to recover.[8]

Further treatment is needed if MM returns. Treatment for relapses is similar to initial treatment, although non-intensive treatment is often preferred. A small group of people may benefit from a second course of high-dose treatment and a second stem cell transplant. Treatment depends on the individual situation, such as how long they were in remission for, what treatment they had and their current level of health and fitness. If MM was in remission for longer than 18 months after initial treatment, the patient might have the same combination of drugs again. If the MM relapses in under 18 months the doctor may suggest a different type of treatment.[17]

CURRENT TREATMENT OPTIONS

Treatment options for relapsed and refractory MM which include the novel agents thalidomide, bortezomib and lenalidomide as single-agents or in combination with dexamethasone have shown significant activity in patients with relapsed MM and are generally well tolerated. These agents have set the stage for the development of the next-generation immunomodulatory drugs (IMiDs) and the proteasome inhibitors (PIs) (i.e. pomalidomide and carfilzomib in relapsed and/or refractory disease). In general, doublet or triplet regimens are preferred above single agents for optimal effect.[18]

NICE guidelines recommend the following treatments for relapsed MM:

- First relapse treatment include:[19]
  - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib
  - Bortezomib monotherapy – only after one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation
- Subsequent relapse treatment include:[19]
  - Lenalidomide in combination with dexamethasone – two or more prior therapies
  - Ixazomib in combination with lenalidomide and dexamethasone, through the Cancer Drugs Fund (CDF) after two or more prior therapies.
  - Panobinostat in combination with bortezomib and dexamethasone – relapsed and/or refractory, at least two prior therapies including bortezomib and an immunomodulatory agent
  - Pomalidomide in combination with low-dose dexamethasone – third or subsequent relapse; three previous treatments including both bortezomib and an immunomodulatory agent
  - Daratumumab monotherapy as 4th line therapy through the CDF
- Second autologous stem cell transplant – suitability determined by response to first transplant, number of prior treatments, overall health and fitness, and ranking on RISS system[19]

PLACE OF TECHNOLOGY

Venetoclax in combination with bortezomib, and dexamethasone will offer an additional treatment option for patients with relapsed MM in patients who have received at least one, but no more than three, prior lines of therapy.

CLINICAL TRIAL INFORMATION

Trial	NCT02755597, **M14-031, EudraCT 2015-004411-20; venetoclax vs placebo, both in combination with bortezomib and dexamethasone; phase III**
Sponsor	AbbVie
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, parallel assignment, double blind
Participants	n=291; aged 18-99 years; MM; relapsed or progressive on or after any regimen or who are refractory to the most recent line of therapy; have received prior treatment with at least one, but no more than three, prior lines of therapy for MM; measurable disease at screening; Eastern Cooperative Oncology Group (ECOG) performance score less than or equal to 2.
Schedule	Participants were randomised to one of two treatment arms: 1. Experimental arm: Cycles 1-8: venetoclax 800mg orally every day on days 1 - 21 plus bortezomib 1.3mg/m2 subcutaneously on days 1, 4, 8 & 11 and dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11 & 12. Cycles 9 and beyond: venetoclax 800mg orally every day on days 1 - 35 plus bortezomib 1.3mg/m2 subcutaneously on days 1, 8, 15 & 22 and dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22 & 23. 2. Placebo comparator arm: Cycles 1-8: placebo (to match venetoclax 100mg tablet) 800mg orally every day on days 1 - 21 plus bortezomib 1.3mg/m2 subcutaneously on days 1, 4, 8 & 11 and dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11 & 12 Cycles 9 and beyond: placebo (to match venetoclax 100mg tablet) 800mg orally every day on days 1 - 35 plus bortezomib 1.3mg/m2 subcutaneously on days 1, 8, 15 & 22 and dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22 & 23
Follow-up	Follow-up 3 years
Primary Outcomes	Progression-free survival (PFS) [Time frame: measured at subject's baseline (prior to subject's first dose) and at day 1 of every cycle thereafter for up to 3 years following the last subject first dose.]
Secondary Outcomes	• Brief Pain Inventory - Short Form [BPI-SF] - Worst Pain [Time Frame: Starting with Cycle 1 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days), collected on Day 1 of every other cycle and the Treatment Completion Visit (TCV) while participant is on treatment (approximately 2 years)] • Duration of Response (DOR) [Time Frame: Measured at subject's initial response and at Day 1 of every Cycle thereafter for up to 3 years following the last subject first dose] • PFS in subjects with high B-cell lymphoma 2 (BCL-2) expression [Time Frame: Measured at subject's baseline (prior to subject's first dose) and at Day 1 of every Cycle thereafter for up to 3 years following the last subject first dose] • Minimal Residual Disease (MRD) status [Time Frame: Measured from baseline up to the time of suspected CR/stringent complete response (sCR)

	with an expected average of 6 months] • Objective Response Rate (ORR) [Time Frame: Measured at subject's baseline (prior to subject's first dose) and at Day 1 of every Cycle thereafter for up to 3 years following the last subject first dose] • Patient Reported Outcomes Measurement Information System - (PROMIS) [Time Frame: Starting with Cycle 1 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days), collect on Day 1 of every other cycle and the Treatment Completion Visit (TCV) while participant is on treatment (approximately 2 years)] • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) - Physical Functioning [Time Frame: Starting with Cycle 1 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days), collect on Day 1 of every other cycle and the Treatment Completion Visit (TCV) while participant is on treatment (approximately 2 years)] • Overall survival (OS) [Time Frame: Measured up to 6 years after the first subject is randomized] • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) - Global Health Status [Time Frame: Starting with Cycle 1 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days), collect on Day 1 of every other cycle and the Treatment Completion Visit (TCV) while participant is on treatment (approximately 2 years)] • Very Good Partial Response (VGPR) or better response rate. [Time Frame: Measured at subject's baseline (prior to subject's first dose) and at Day 1 of every Cycle thereafter for up to 3 years following the last subject first dose] • Time to disease progression (TTP) [Time Frame: Measured at subject's baseline (prior to subject's first dose) and at Day 1 of every Cycle thereafter for up to 3 years following the last subject first dose]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as April 2020.

ESTIMATED COST

Venetoclax is already marketed in the UK; a pack of 112 x 100 mg tablets costs £4789.47.[20]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies (ID1467). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Multiple myeloma (one prior therapy) - vorinostat (with bortezomib) (ID501). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for previously treated multiple myeloma (ID1139). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pomalidomide in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1358). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma (ID974). Expected October 2018.
- NICE technology appraisal in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected October 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dezamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Daratumumab with lenalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA454). July 2017.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). April 2014.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE diagnostic guidance in development. Multiple myeloma and related disorders - Freelite assays (and alternative technologies identified during scoping) for diagnosis in primary care

(GID-DT28). Expected date of issue to be confirmed.

- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

OTHER GUIDANCE

- The UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017[17]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017[21]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015[22]
- The Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014[23]
- The European Myeloma Network. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014[24]

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NB: 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.