Health Technology Briefing
November 2021

Venetoclax with dexamethasone for previously treated relapsed/refractory multiple myeloma

Company/Developer	AbbVie

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 20474	NICE ID: 10518	UKPS ID: 647043

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Venetoclax with dexamethasone is currently in clinical development for the treatment of patients with multiple myeloma (MM). MM, also known as myeloma, is a type of bone marrow cancer. Bone marrow is the spongy tissue at the centre of some bones that produces the body's blood cells. It is called MM as the cancer often affects several areas of the body, such as the spine, skull, pelvis and ribs. MM is currently incurable, and patients tend to go into remission and relapse several times, often needing new or different kinds of treatment than previously received when relapse occurs, therefore, there is a need for new treatments.

Venetoclax is a type of targeted therapy drug called a BCL2 inhibitor (blocker). BCL2 is a protein some cancer cells make too much of. It prevents the cancer cells from dying, so they continue to grow. Venetoclax blocks the BCL2 protein and helps destroy the cancer cells. It is administered orally. As MM is an incurable malignancy, new approaches to treatment are needed. If licensed, venetoclax with dexamethasone will be an additional treatment option for those with relapsed or refractory MM that have already received other types of therapy.

Proposed Indication

Treatment of patients with previously treated relapsed/refractory multiple myeloma.

Technology

Description

Venetoclax (Venclyxto, ABT-199, GDC-0199) is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukaemia (CLL) cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. 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 permeabilisation (MOMP), caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[1]

Venetoclax in addition to dexamethasone is currently in clinical development for the treatment of patients previously treated relapsed/refractory MM. In the phase III clinical trial (NCT03539744) subjects receive venetoclax administered orally once daily plus dexamethasone administered orally once every week for each 28-day cycle, or comparator (pomalidomide and dexamethasone).[2]

Key Innovation

As MM is an incurable malignancy, new approaches to treatment are needed.[3] Venetoclax is a BCL-2 inhibitor.[4] It is an engineered small molecule that was uniquely designed to fit the exact pocket of the protein. In the MM setting, we know that high expression of BCL2 is common and is also a mechanism of cell survival. Venetoclax directly inhibits BCL2 function. It induces cell death in myeloma cell lines and primary tumour samples.[4,5] 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.[6] Thus, venetoclax in combination with dexamethasone could offer a promising treatment option to patients who are unresponsive to other treatments.

Regulatory & Development Status

Venetoclax has a marketing authorisation in the EU/UK for the following indications:[1]

- in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
- in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy
- as monotherapy for the treatment of CLL 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, or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor
- in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

Venetoclax was granted orphan drug status in the EU in 2016 for treatment of MM (EU/3/16/1767).[7]

Venetoclax plus dexamethasone is also in phase II clinical trials for treatment of acute lymphoblastic leukaemia (ALL) and chronic myelogenous leukaemia .[8]

Patient Group

Disease Area and Clinical Need

MM is a type of bone marrow cancer that is characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, and immunosuppression, as well as osteolysis and end-organ damage.[9,10] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[11] The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities. MM is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS).[9] t(11;14) is the most common chromosome translocation in MM, but a consensus of clinicopathological features and impact on survival is yet to be reached.[12] Additional risk factors for MM include age, gender, and ethnicity. The risk of MM increases with age with most people diagnosed in their mid-60s. Men are more likely to develop the disease than women and MM is twice as common in black populations compared with white people.[13] In early stages, MM may not cause any symptoms or complications and can be diagnosed by routine blood or urine tests. Eventually, myeloma causes a wide range of problems, which can include bone fracture, tenderness or pain, anaemia, fatigue, kidney problems or infections or less commonly bruising and unusual bleeding.[9]

In 2016, MM was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[14] In England, in 2017, there were 5,034 newly diagnosed cases of MM and malignant plasma cell neoplasms (ICD-10: C90). Incidence is strongly linked to age, with the highest rates in people ages 70 to 89 years.[15]Over the last decade, incidence rates have increased by a seventh (to 15%), represented by an increase in males by 15% and in females by 12%. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[14] Approximately, 20% of myeloma patients will exhibit *t* (11;14).[4] In England, in 2019-21 there were 107,457 finished consultant episodes and 103,209 hospital admissions with a primary diagnosis of MM and malignant plasma cell neoplasms (ICD-10 code: C90.0), resulting in 66,906 bed days and 92,219 day cases.[16] Almost half (52.3%) of people diagnosed with MM in England and Wales survive their disease for 5 years or more, with a third surviving for 10 years or more. In England and Wales in 2020, there were 2,881 registrations of death where MM was recorded as the underlying cause.[17]

Recommended Treatment Options

NICE guidelines recommends the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[18]

- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
- Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after three previous therapies.
- Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory MM patients after three previous therapies.
- Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after two or three previous therapies.

Clinical Trial Information

Trial	NCT03539744; 2017-003838-88; A Phase 3, Multicenter, Randomized, Open Label Study of Venetoclax and Dexamethasone Compared With Pomalidomide and Dexamethasone in Subjects With t(11;14)-Positive Relapsed or Refractory Multiple Myeloma **Phase III** - Recruiting **Location(s):** 9 EU countries, UK, Canada, United States and other countries. **Primary completion date:** June 2022
Trial Design	Randomised, parallel assignment, open label
Population	N = 244; adults aged 18 years and older; participants with MM positive for t(11;14) who have received at least 2 prior lines of therapy (two consecutive cycles of lenalidomide; two consecutive cycles of a proteasome inhibitor)
Intervention(s)	Orally administered venetoclax plus oral dexamethasone
Comparator(s)	Orally administered pomalidomide plus oral dexamethasone
Outcome(s)	Primary Outcome: Progression-Free Survival (PFS) Time Frame: Up to approximately 43 months from first randomization See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Venetoclax is already marketed in the UK for the treatment of chronic lymphocytic leukaemia (as a monotherapy or combination treatment with rituximab); a 112-pack of 100 mg tablets costs £4,789.47 (excluding VAT).[19]

The NHS indicative price for dexamethasone is £64.82 for a pack of 30 x 500mg tablets.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected date of issue: October 2022.
- NICE technology appraisal in development. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma (ID3862). Expected date of issue: June 2022
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA658). November 2020.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.

- NICE technology appraisal. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). April 2019
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P/a
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT)(All Ages): Revised. 2015. B04/P/a.
- 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. 2013/14. NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

Other Guidance

- European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma. 2021.[21]
- The International Myeloma Working Group (IMWG). Treatment of relapsed and refractory multiple myeloma: recommendations from the IMWG. 2021[22]
- NCCN Guidelines Insights: Multiple Myeloma, Version 3. 2018.[23]
- NHS England. NHS manual for prescribed specialist services. Chapter 29: blood and marrow transplantation services (adults and children). 2018/2019.[24]
- 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.[25]
- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[26]
- NHS England. National chemotherapy algorithms - multiple myeloma. 2015.[27]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015.[28]

Additional Information

References

1 Electronic medicines compendium (emc). *Venclyxto 10 mg film-coated tablets.* 2021. Available from: https://www.medicines.org.uk/emc/product/2267 [Accessed 14 October 2021].

2 Clinicaltrials.gov. *A Study of Venetoclax and Dexamethasone Compared With Pomalidomide and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma*. *Trial ID*. 2018. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03539744 [Accessed 14 October 2021].

3 Sonneveld, P., Broijl A. *Treatment of relapsed and refractory multiple myeloma*. Haematologica. 2016;101(4):396-406. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5004403/

4 Vaxman, I., Sidiqi M. H., Gertz M. *Venetoclax for the treatment of multiple myeloma*. Expert Review of Hematology. 2018 2018/12/02;11(12):915-20. Available from: https://doi.org/10.1080/17474086.2018.1548931

5 The ASCO post. *Two Studies Show Potential of Venetoclax as Single Agent and in Combination for Myeloma.* 2017. Available from: https://ascopost.com/issues/april-25-2017/two-studies-show-potential-of-venetoclax-as-single-agent-and-in-combination-for-myeloma/ [Accessed 14 October 2021].

6 Moreau, P., Chanan-Khan A., Roberts A. W., Agarwal A. B., Facon T., Kumar S., et al. *Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM*. Blood. 2017 Nov 30;130(22):2392-400. Available from: https://pubmed.ncbi.nlm.nih.gov/28847998/

7 European Medicines Agency (EMA). *Public summary of opinion on orphan designation (EMA/623817/2016)*. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/16/1767-public-summary-positive-opinion-orphan-designation-venetoclax-treatment-multiple-myeloma_en.pdf [Accessed 14 October 2021].

8 Clinicaltrials.gov. *venetoclax plus Dexamethasone | Phase 2, 3.* 2021. Available from: https://clinicaltrials.gov/ct2/results?term=venetoclax+plus+Dexamethasone&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 15 October 2021].

9 Hipp, S., Tai Y. T., Blanset D., Deegen P., Wahl J., Thomas O., et al. *A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo*. Leukemia. 2017 Aug;31(8):1743-51. Available from: https://pubmed.ncbi.nlm.nih.gov/28025583/

10 NHS. *Overview Multiple myeloma.* 2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/ [Accessed 14 October 2021].

11 National Institute of Health and Care Excellence (NICE). *Multiple Myeloma.* 2021. Available from: https://cks.nice.org.uk/topics/multiple-myeloma/#!backgroundSub [Accessed 14 October 2021].

12 An, G., Xu Y., Shi L., Zou D., Deng S., Sui W., et al. *t(11;14) multiple myeloma: a subtype associated with distinct immunological features, immunophenotypic characteristics but divergent outcome*. Leuk Res. 2013 Oct;37(10):1251-7. Available from: https://pubmed.ncbi.nlm.nih.gov/23927993/

13 MayoClinic. *Multiple myeloma.* 2021. Available from: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378 [Accessed 14 October 2021].

14 Cancer Research UK. *Myeloma statistics.* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed 14 October 2021].

15 Office for National Statistics (ONS). *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 14 October 2021].

16 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 14 October 2021].

17 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality.* 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset/current [Accessed 14 October 2021].

18 National Institute for Health and Care Excellence (NICE). *Myeloma overview.* 2021. Available from: https://pathways.nice.org.uk/pathways/myeloma [Accessed 14 October 2021].

19 National Cancer Institute of Health and Care Excellence, N. *Venetoclax.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/venetoclax.html [Accessed 14 October 2021].

20 National Institute For Health and Care Excellence (NICE). *Dexamethasone.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/dexamethasone.html [Accessed 14 October 2021].

21 Bruno, B., Wäsch R., Engelhardt M., Gay F., Giaccone L., D'Agostino M., et al. *European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma*. Haematologica. 2021 Aug 1;106(8):2054-65. Available from: 10.3324/haematol.2020.276402

22 Lancet, T. *Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group* (*E105-E118)*. Last Update Date: Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30756-7/fulltext#%20 [Accessed 16 November 2021].

23 Kumar, S. K., Callander N. S., Alsina M., Atanackovic D., Biermann J. S., Castillo J., et al. *NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018*. J Natl Compr Canc Netw. 2018 Jan;16(1):11-20. Available from: https://pubmed.ncbi.nlm.nih.gov/29295877/

24 England, N. *Manual for Prescribed Specialised Services 2018/19* (*5)*. Last Update Date: Available from: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual.pdf [Accessed 14 October].

25 Snowden, J. A., Greenfield D. M., Bird J. M., Boland E., Bowcock S., Fisher A., et al. *Guidelines for screening and management of late and long-term consequences of myeloma and its treatment*. Br J Haematol. 2017 Mar;176(6):888-907. Available from: https://pubmed.ncbi.nlm.nih.gov/28107574/

26 Dimopoulos, M. A., Moreau P., Terpos E., Mateos M. V., Zweegman S., Cook G., et al. *Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†)*. Ann Oncol. 2021 Mar;32(3):309-22. Available from: https://pubmed.ncbi.nlm.nih.gov/33549387/

27 England, N. *National chemotherapy algorithms - multiple myeloma* Last Update Date: Available from: https://www.google.com/search?q=NHS+England.+National+chemotherapy+algorithms+-+multiple+myeloma.+2015&rlz=1C1GCEB_enGB959GB959&sxsrf=AOaemvLOD6Qbbu3UEGRMhG2dSrC-I3Wzlw%3A1637070135075&ei=N7WTYejNA9uR9u8PiMOX6AU&oq=NHS+England.+National+chemotherapy+algorithms+-+multiple+myeloma.+2015&gs_lcp=Cgdnd3Mtd2l6EANKBAhBGABQAFgAYP0EaABwAHgAgAFHiAFHkgEBMZgBAKABAcABAQ&sclient=gws-wiz&ved=0ahUKEwioxf2-gZ30AhXbiP0HHYjhBV0Q4dUDCA4&uact=5 [Accessed 16 November 2021].

28 Palumbo, A., Avet-Loiseau H., Oliva S., Lokhorst H. M., Goldschmidt H., Rosinol L., et al. *Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group*. Journal of Clinical Oncology. 2015 2015/09/10;33(26):2863-9. Available from: https://doi.org/10.1200/JCO.2015.61.2267 [Accessed 16 November 2021].

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