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Newcastle University

Health Technology Briefing
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Venetoclax in combination with azacitidine for myelodysplastic syndrome

Company/Developer	AbbVie

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 13262	NICE TSID: 11877	UKPS ID: 668739

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Venetoclax in combination with azacitidine is currently in clinical development for the treatment of myelodysplastic syndrome (MDS) in newly diagnosed higher-risk adults. MDS occurs when the blood-forming cells in the bone marrow (inner part of the bone that creates blood cells) become abnormal, leading to low numbers of one or more types of blood cells. These abnormal blood cells in MDS, either stay in the bone marrow or are destroyed before they get into the bloodstream. As the condition develops, the bone marrow becomes full. The immature blood cells then spill out into the bloodstream. The low numbers of normal blood cells in the bloodstream eventually cause symptoms such as reduced blood cell count (anaemia), feeling weak, tired, and breathless during activity, and repeated infections. High-risk MDS has the highest potential of developing acute myeloid leukaemia. There are currently limited treatment options for patients with high-risk MSD therefore there is a need to increase the treatment options available to this group of patients. Venetoclax blocks proteins BCL-2, which aid cancer cell growth/survival. By blocking this protein, it can kill and slow down the growth of cancer cells. Venetoclax is taken orally as a tablet, once daily. Venetoclax may delay this progression and thereby increase survival.

If licensed, venetoclax in combination with azacitidine will offer an additional treatment option for high-risk MDS patients who have limited effective therapies available and may increase the survival rate in this group of patients.

Proposed Indication

Treatment of adults with newly diagnosed higher risk-myelodysplastic syndrome (MDS).[1,2]

Technology

Description

Venetoclax (Venclyxto) 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) and acute myeloid leukaemia (AML) 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 permeabilization (MOMP), caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[3]

Venetoclax in addition to azacitidine is currently in phase III clinical development for the treatment of adults with newly diagnosed higher risk MSD. In the phase III trial (NCT04401748) participants received oral venetoclax once daily for 14 days, in combination with subcutaneous or intravenous azacitidine for 7 days of the first 9 days, of each 28 day cycle or a matched placebo.[2]

Key Innovation

Venetoclax is a potential new treatment for MDS. The high-risk MDS population has the highest potential of developing AML with a median survival of 0·8–1·6 years.[4] There is therefore a need to delay progression to AML and improve survival. If licensed, venetoclax will offer an additional treatment option for high-risk MDS patients who currently have few effective therapies available.

Regulatory & Development Status

Venetoclax has Marketing Authorisation in UK/Europe for the following indications:[5]

- treatment of adult patients with previously treated CLL as monotherapy especially in patients with genetic changes (17p deletion or TP53 mutation) who cannot be treated with medicines known as B-cell receptor pathway inhibitors (ibrutinib and idelalisib) or if these medicines have stopped working or patients who do not have these genetic changes, after treatments with chemotherapy combined with immunotherapy as well as a B-cell receptor pathway inhibitor have both not worked.
- treatment of adult patients with previously treated CLL in combination with rituximab.
- treatment of adult patients with untreated CLL in combination with obinutuzumab.
- treatment of patients with AML used in combination with either azacitidine or decitabinein in adults who cannot have intensive chemotherapy.
- venetoclax in combination with a hypomethylating agent or low dose cytarabine is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.[6]

Venetoclax in combination with azacitidine is currently in Phase II and III trials for the treatment of:[7]

- high-risk MDS in newly diagnosed adults.
- AML and MDS after a relapse in adult patients.

- AML in newly diagnosed adult patients.
- myelodysplastic/myeloproliferative neoplasms in adults.
- -cell acute lymphoblastic leukaemia in newly diagnosed patients 15 years and above.
- relapsed/refractory acute lymphoblastic leukaemia.
- AML after allogenic stem cell transplantation in adolescents and adults
- high-risk recurrent/refractory MDS in adults.
- advanced breakpoint cluster region protein (BCR)-ABL negative myeloproliferative neoplasms.
- NPMI-mutated AML in adults with molecular relapse/progression.
- AML in treatment naïve adults ineligible for standard induction therapy.
- AML as maintenance therapy in adult patients in remission.
- therapy related or secondary MDS in adult patients.
- AML/MDS in MRD positive post allo-HSCT adult patients.
- relapsed/refractory high-risk MDS or chronic myelomonocytic leukaemia in adult patients.

On 14 October 2016, orphan designation (EU/3/16/1767) was granted by the European Commission to AbbVie Ltd for venetoclax for the treatment of multiple myeloma.[8]

Patient Group

Disease Area and Clinical Need

MDS is a type of rare blood cancer where there is insufficient healthy blood cells. It is also known as myelodysplasia.[9] Myelodysplastic syndromes get their name from myelo, meaning bone marrow, and dysplasia, meaning abnormal growth. The bone marrow doesn't make enough normal blood cells. The blood cells it does make are not fully developed and not able to work normally.[10] The low numbers of normal blood cells in the bloodstream eventually cause symptoms including feeling weak and tired because of a lack of red blood cells (anaemia), becoming breathless when you are active because of a lack of red blood cells (anaemia), having repeated infections because of a low number of white blood cells, bruising or bleeding because of a low number of platelets.[11] Myelodysplastic syndromes can occur in people of any age but are most common in people over 70 years old.[10] In some, but not all, MDS may develop into AML. Some types of MDS have a higher risk of transforming into AML than others. Transformation might happen after a few months for some types of MDS but after several years for others.[10] MDS is divided into different risk groups, based on how quickly or slowly MDS may develop and the risk of it developing into leukaemia, with the risk group determining the best treatment to give patients.[12] Risk is determined via the revised International Prognostic Scoring System (IPSS-R). It divides MDS into 5 risk group, which are very low risk, low risk, intermediate risk, high-risk, and very high-risk.[13]

The incidence of MDS is 4–5 per 100,000, but it increases with age such that the incidence is 30 per 100,000 in those aged over 70; and 40 per 100,000 in those aged over 80. Some 10% of MDS are secondary, most often due to radiotherapy or chemotherapy for cancer; with increasing numbers of patients surviving chemotherapy, the incidence of therapy related MDS may also be set to increase.[14] In 2017, there were 2,385 registrations of newly diagnosed cases of MDS (ICD-10 code: D46) and the direct age-standardised rate per 100,000 population of newly diagnosed cases was 6.7 among males and 3.0 among females in England.[15] In England, in 2021-2022, there were 55,383 finished consultant episodes (FCE) for MDS (ICD-10 code: D46), resulting in 53,972 hospital admissions and 19,795 FCE bed days and 50,721 day cases.[16]

Recommended Treatment Options

For the treatment of MDS the National Institute for Health and Care Excellence (NICE) recommends:

- azacitidine for adults who are not eligible for haematopoietic stem cell transplantation and have intermediate-2 and high-risk MDS according to the IPSS. Or if the patient chronic myelomonocytic leukaemia with 10-29% marrow blasts without myeloproliferative disorder.[17]
- lenalidomide is recommended as an option, within its marketing authorisation, that is for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Only if the company provides it according to the commercial arrangement.[18]

Further treatment recommendations from the National Health Service include:[9]

- supportive treatments such as Injections of growth factor medicines (erythropoietin or G-CSF), blood transfusion, medicines to remove excess iron in the blood, or antibiotics for treatment of infections.
- chemotherapy is sometimes given to patients that have a type of MDS that increases the risk of AML.
- immunosuppressant medicines, such as anti-thymocyte globulins (ATGs) and ciclosporin, can be used to suppress the immune system and can sometimes help improve blood count.
- a stem cell transplant (also called a bone marrow transplant) is given after chemotherapy. It can sometimes cure MDS but isn't suitable for everyone.

Clinical Trial Information	
Trial	M15-531. NCT02942290; 2016-001657-41 A phase 1b dose escalation study evaluating the safety and pharmacokinetics of venetoclax in combination with azacitidine in subjects with treatment-naïve higher-risk MDS **Phase Ib -** Active, not recruiting **Locations**: Three EU countries, UK, United states, Canada and Australia **Primary completion date** - June 2024
Trial Design	An open-label, non-randomised, dose-finding study
Population	N = 129 (estimated) adult participants with untreated higher-risk MDS
Intervention(s)	Venetoclax oral tablet combined with azacitadine injection taken subcutaneously or intravenously
Comparator(s)	None
Outcome(s)	• Recommended phase 2 dose (RPTD) and dosing schedule of venetoclax in combination with azacitidine [Time Frame: Measured from day 1 until day 28 per dose level]. • The RPTD of venetoclax [co-administered venetoclax and azacitidine] will be determined during the dose escalation phase of the study. RPTD will be determined using available safety and pharmacokinetics data [upon completion of the dose escalation phase]. See trial record for full list of other outcomes

Results (efficacy)	At data cut-off, December 31, 2019, 57 patients had received Ven+Aza, with a median follow-up of 13.0 months (95% confidence interval [CI] 11.3, 15.6 months). The Overall Response Rate was 77%, including complete remission (CR) and marrow CR (mCR) achieved by 42% and 35% of patients (of whom 40% achieved mCR + haematological improvement), respectively; none achieved partial remission. Median overall survival was not reached (95% CI 16.2 months, not estimable). Median duration of response was 14.8 months (95% CI 12.9 months, not estimable). Median progression-free survival was 17.5 months (14.5, not estimable). Of the patients who received the RP2D of Ven 400 mg for 14 days/28-day cycle in combination with Aza, physical functioning, was maintained through 48 weeks of treatment. In addition, clinically meaningful improvement in fatigue and dyspnoea, was achieved by the beginning of Cycle 5 and was maintained through Week 48. (Cycle 13)[19,20]
Results (safety)	All patients experienced ≥1 adverse event (AE), the most common being constipation (54%), neutropenia (51%), and nausea (51%). Grade ≥3 AEs were experienced by 97% of patients, with neutropenia (51%), febrile neutropenia (46%), and thrombocytopenia (30%) the most common. Febrile neutropenia was the most common serious AE (42%). The 30-day mortality rate was 2%.[19,20]

Trial	**VERONA.** NCT04401748; 2020-000744-55 A randomized, double-blind, phase 3 study evaluating the safety and efficacy of venetoclax in combination with azacitidine in patients newly diagnosed with higher-risk MDS (Higher-Risk) **Phase III –** Active, not recruiting **Locations**: 10 EU countries, UK, United States, Canada, and others **Primary completion date** - February 14, 2025
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 525 (actual) newly diagnosed adult participants with higher risk MDS
Intervention(s)	Venetoclax once daily (QD) (Days 1-14) in combination with AZA QD (7 days of the first 9 days) of each 28-day cycle
Comparator(s)	Matched placebo
Outcome(s)	• Complete Remission (CR) [Time Frame: Up To 36 Months] • Overall survival (OS) [Time Frame: Up To 5 Years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Venetoclax is already marketed in the UK as a monotherapy for AML and CLL, and in combination with Obinutuzumab or rituximab for the treatment of adult patients with CLL; a unit of 112 tablets of venetoclax 100mg costs £4,789.47, a unit of 7 tablets of venetoclax 50mg costs £149.67, and a unit of 14 tablets of venetoclax 10mg costs £59.87.[21]

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality. (TA322). September 2014, last updated: June 2019
- NICE Technology appraisal guidance. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. (TA218). March 2011

NHS England (Policy/Commissioning) Guidance

- Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised Reference: NHS England B04/P/a
- Clinical Commissioning Policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias Reference: NHS England: 16070/P
- Clinical commissioning policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias (all ages)

Other Guidance

- Pan-London Haemato-Oncology Clinical Guidelines.2020[22]
- British Society for Haematology guidelines for the management of adult myelodysplastic syndromes 2021[23]
- Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2021[24]

Additional Information

References

1 ClinicalTrials.gov. *A Study Evaluating Venetoclax in Combination With Azacitidine in Participants With Treatment-Naïve Higher-Risk Myelodysplastic Syndromes (MDS). Trial ID: NCT02942290*. 2016. Status: Active. Available from: https://clinicaltrials.gov/ct2/show/NCT02942290 [Accessed 9 February 2023].

2 ClinicalTrials.gov. *Study Of Venetoclax Tablet With Intravenous or Subcutaneous Azacitidine to Assess Change in Disease Activity In Adult Participants With Newly Diagnosed Higher-Risk Myelodysplastic Syndrome (Verona). Trial ID: NCT04401748*. 2020. Status: Active. Available from: https://clinicaltrials.gov/ct2/show/NCT04401748 [Accessed 9 Febuary 2023].

3 Electronic Medicines Compedium. *Venclyxto 50 mg film-coated tablets* Available from: https://www.medicines.org.uk/emc/product/10475/smpc [Accessed 9 February 2023].

4 Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-65. Available from: https://doi.org/10.1182/blood-2012-03-420489.

5 European Medicines Agency. *Venclyxto*. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto [Accessed 9 February 2023].

6 Electronic Medicines Compedium G. *Venclyxto 10 mg film-coated tablets (Great Britain)*. Available from: https://www.medicines.org.uk/emc/product/2267/smpc#gref [Accessed 6th April 2023].

7 ClinicalTrials.gov. *Search of Venetoclax plus Azacitidine,Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies, completed.* Status: Phase 2,3. Available from: https://clinicaltrials.gov/ct2/results?term=venetoclax+plus+Azacitidine&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 23 March 2023].

8 European Medicines Agency. *Orphan designation for the treatment of multiple myeloma.* . Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161767#:~:text=On%2014%20October%202016%2C%20orphan%20designation%20%28EU%2F3%2F16%2F1767%29%20was,GmbH%20%26%20Co.%20KG%2C%20Germany%2C%20in%20May%202018. [Accessed 18th April 2023].

9 National Health Service (NHS). *Myelodysplastic syndrome (myelodysplasia)*. 2021. Available from: https://www.nhs.uk/conditions/myelodysplasia/ [Accessed 9 February 2023].

10 Cancer Research UK. *What are myelodysplastic syndromes (MDS)?* Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/myelodysplastic-syndromes/what-is-mds [Accessed 9 February 2023].

11 Macmillan Cancer Support. *Myelodysplasia (MDS)*. 2022. Available from: https://www.macmillan.org.uk/cancer-information-and-support/blood-cancer/myelodysplasia-mds [Accessed 13 February 2023].

12 Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Ossa JEA, Nannya Y, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evidence*. 2022;1(7):EVIDoa2200008. Available from: https://doi.org/doi:10.1056/EVIDoa2200008.

13 Greenberg PL, Stone RM, Al-Kali A, Bennett JM, Borate U, Brunner AM, et al. NCCN Guidelines® Insights: Myelodysplastic Syndromes, Version 3.2022: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2022;20(2):106-17. https://jnccn.org/view/journals/jnccn/20/2/article-p106.xml.

14 Neukirchen J, Schoonen WM, Strupp C, Gattermann N, Aul C, Haas R, et al. Incidence and prevalence of myelodysplastic syndromes: data from the Düsseldorf MDS-registry. *Leukemia research*. 2011;35(12):1591-6.

15 Office for National Statistics (ONS). *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 28 February 2023].

16 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 31 January 2023].

17 National Institute of Health and Care excellence NICE. *Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia.Technology appraisal guidance [TA218].* 2011. Available from: https://www.nice.org.uk/guidance/ta218/resources/myelodysplastic-syndromes-azacitidine-mds-uk-patient-support-group [Accessed 02 March 2023].

18 National Institute of Health and Care excellence NICE. *Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality.Technology appraisal guidance [TA322].* 2014. Available from: https://www.nice.org.uk/guidance/ta322 [Accessed 02 March 2023].

19 Jacqueline S. Garcia et al. *Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study*. 2020. Available from: https://ash.confex.com/ash/2020/webprogram/Paper139492.html [Accessed 24 March 2023].

20 Wei AH, Garcia JS, Borate U, Fong CY, Baer MR, Nowak D, et al. MDS-158: Updated Safety and Efficacy of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Treatment-Naïve, Higher-Risk Myelodysplastic Syndromes: Phase 1b Results. *Clinical Lymphoma Myeloma and Leukemia*. 2021;21:S343. https://pubmed.ncbi.nlm.nih.gov/21708407/.

21 British National Formulary (BNF). *Venetoclax Medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/venetoclax/medicinal-forms/ [Accessed 15 February 2023].

22 Pan-London Haemato-Oncology Clinical Guidelines. *Acute Leukaemias and Myeloid Neoplasms Part 5: Myelodysplastic Syndromes.* . 2020. Available from: https://www.kingshealthpartners.org/assets/000/003/347/Pan_London_MDS_Guideline_Jan_2020_original.pdf [Accessed 02 March 2023].

23 Killick SB, Ingram W, Culligan D, Enright H, Kell J, Payne EM, et al. British Society for Haematology guidelines for the management of adult myelodysplastic syndromes. *British Journal of Haematology*. 2021;194(2):267-81. https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.17612.

24 Fenaux P, Haase D, Santini V, Sanz GF, Platzbecker U, Mey U. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(2):142-56. https://pubmed.ncbi.nlm.nih.gov/33221366/.

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