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HEALTH TECHNOLOGY BRIEFING
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Venetoclax in addition to ibrutinib for relapsed mantle cell lymphoma – second-line and beyond

NIHRIO ID	18313	**NICE ID**	10040
Developer/Company	AbbVie Ltd	**UKPS ID**	645219

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Venetoclax in addition to ibrutinib is being developed for the treatment of patients with relapsed mantle cell lymphoma (MCL). MCL is a rare type of non-Hodgkin lymphoma that usually behaves like a fast-growing lymphoma. It develops when B-cells, white blood cells that fight infection, become abnormal. The abnormal B-cells usually build up in lymph nodes, but they can affect other parts of the body. MCL often responds well to frontline chemotherapy but the responses are not durable and often of relatively short duration. Once MCL has entered the relapsed/refractory stage, it becomes more difficult to treat and patients deteriorate at an increasing pace.

Venetoclax is expected to work by blocking proteins called BCL-2. These proteins prevent the natural process that leads to cell death (apoptosis). BCL-2 proteins can be found in high levels in cancer cells. By blocking the action of these proteins, the medicine is expected to make cancer cells more responsive to the natural process that causes their death, and this can slow down the growth of the cancer. When combined with ibrutinib, which blocks the action of an enzyme known as Bruton's tyrosine Kinase (BTK), the effect is synergistic. If licensed, venetoclax in combination with ibrutinib taken orally will offer additional second-line and beyond treatment options for adults with relapsed MCL.

PROPOSED INDICATION

Treatment of adults patients with relapsed mantle cell lymphoma (MCL) in combination with ibrutinib.[1,a]

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 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 in addition to ibrutinib is currently in clinical development for the treatment of relapsed mantle cell lymphoma (MCL). In the phase III clinical trial (NCT03112174; SYMPATICO), subjects receive either ibrutinib and venetoclax or matched placebo administered orally once daily until clinical disease progression or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Venetoclax is a potent, selective inhibitor of BCL-2.[2] Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell–receptor pathway, which is often co-opted by B-cell cancers with resultant excessive growth signaling. Preclinical models indicate that dual inhibition of BTK and BCL2 is synergistic. Ibrutinib and venetoclax affect different critical pathways in the malignant B cell and have overlapping toxic effects that are generally minor, thus allowing for the development of an oral combination therapy with the potential for improved efficacy.[3]

In a phase II clinical trial (NCT02471391), a study involving historical controls, dual targeting of BTK and BCL2 with ibrutinib and venetoclax was consistent with improved outcomes in patients with MCL who had been predicted to have poor outcomes with current therapy.[3,4] Additionally, overall response rate (ORR) by positron emission tomography (PET) of 71%, with attainment of minimal residual disease (MRD) negativity was reported. At the time of primary endpoint analysis (median follow up 15.9 months), median progression free survival, duration of response, time to progression and overall survival had not been reached.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Venetoclax has a marketing authorisation in the EU/UK for the following indications:[6]

- 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

[a] Information provided by AbbVie Ltd on UK PharmaScan

- 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.

The most common adverse reactions (occurs in ≥1/10 patients) of venetoclax include: pneumonia, upper respiratory tract infection, neutropenia, anaemia, lymphopenia, hyperkalaemia, hyperphosphataemia, hypocalcaemia, diarrhoea, vomiting, nausea, constipation and fatigue.[2]

In the EU, the medicinal product venetoclax was granted an orphan designation for the treatment of MCL in December 2017.[7]

Venetoclax in combination with ibrutinib is currently in phase II and III clinical development for CLL, BTK and PLCG2 gene mutations, follicular lymphoma, and Waldenstrom macroglobulinemia.[8]

PATIENT GROUP

DISEASE BACKGROUND

MCL is a rare type of non-Hodgkin lymphoma (NHL) that usually behaves like a high-grade lymphoma.[9,10] It develops when B-cells (also called B-lymphocytes) become abnormal. The abnormal B-cells (lymphoma cells) usually build up in lymph nodes, but they can affect other parts of the body. The causes of MCL are mostly unknown.[10]

The most common signs of MCL is painless swelling in neck, armpit or groin caused by lymphoma cells building up in the lymph nodes. Other symptoms include drenching night sweats, high temperatures with no obvious cause, unexplained weight loss. Sometimes other areas of the body may be affected, such as the spleen, bowel, or bone marrow. Depending on where the lymphoma spreads to, this can cause symptoms such as: loss of appetite, diarrhoea, sickness (nausea), anaemia and bruising or bleeding easily.[10] Rarely, MCL spreads to the brain and spinal cord (the central nervous system or CNS), called secondary CNS lymphoma. This causes symptoms such as headaches, dizziness and confusion.[9]

MCL relapses at some time after treatment in most people. Sometimes, MCL is refractory (does not respond) to the first-line treatment. MCL patients can relapse several times and different treatment may be recommended each time.[9]

CLINICAL NEED AND BURDEN OF DISEASE

NHL the 6th most common type of cancer in adults (not counting non melanoma skin cancer) in the UK.[11] There were 12,065 (ICD-10 code C82-85) new cases of NHL in England in 2017.[12]

MCL represents 5%–7% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000 recently.[13] About 500 people are diagnosed with MCL each year in the UK.[9] It mainly occurs in people over the age of 60 and is more common in men than women (3:1 ratio).[10,14] Regional data from the north east of England collected between 2010 and 2016 indicates that the relative 5-year survival for MCL is 41.9% in the UK.[15] Hospital admissions data for England in 2018-2019 recorded 8,035 finished consultant episodes (FCE) for MCL (ICD-10 code C83.1), 7,657 hospital admissions and 8,763 FCE bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A team of specialist, called a multidisciplinary team, will meet to discuss the best possible treatment. The aim of treatment is to get rid of as much of the lymphoma as possible.[10]

Treatment for mantle cell lymphoma can be similar to treatment for other types of NHL. Treatment can sometimes get rid of the lymphoma completely. But unfortunately it can come back fairly soon afterwards. Treatment options include:[17,18]

- Chemotherapy and immunotherapy
- Steroids
- Radiotherapy for people with localised stage I or II mantle cell lymphoma,
- Stem cell transplant
- Less intensive treatment such as bortezomib (a targeted cancer drug), chlorambucil (a chemotherapy drug), ibrutinib.

'Watch and wait' (observation without therapy) may be considered until disease progression for people with clinically non-progressive mantle cell lymphoma who are asymptomatic and for whom radiotherapy is not suitable.[18]

CURRENT TREATMENT OPTIONS

There is no accepted standard of care for treating relapsed or refractory MCL in people who have received at least two previous lines of therapy.[14] According to NICE recommendations, the current treatment option for relapsed or refractory MCL in adults is ibrutinib, only if:[19]

- they have had only 1 previous line of therapy and
- the company provides ibrutinib with the discount agreed in the commercial access agreement with NHS England.

A range of chemotherapy regimens are used such as, R-BAC (rituximab, bendamustine and cytarabine), rituximab plus bendamustine, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone) and single-agent cytarabine. Allogeneic haemopoietic stem-cell transplantation is a potentially curative treatment in patients for whom it is suitable.[14] In cases of early relapses or in refractory cases, newer targeted approaches (ibrutinib, lenalidomide) should be strongly considered. Temsirolimus and bortezomib have been shown to be effective but should preferably be applied in combination with chemotherapy.[13]

PLACE OF TECHNOLOGY

If licensed, venetoclax in addition to ibrutinib would offer additional second-line and beyond treatment options for adults with relapsed MCL.

CLINICAL TRIAL INFORMATION

Trial	**SYMPATICO;** NCT03112174**;** Phase 3 Study of Ibrutinib in Combination With Venetoclax in Subjects With Mantle Cell Lymphoma **Phase III –** Recruiting **Location(s):** EU (incl UK), USA, Canada, Australia and Republic of Korea **Primary completion date:** March 2022

Trial design	Randomized, parallel assignment, double-blinded
Population	N=362 (planned); subjects with relapsed MCL; aged 18 years and over
Intervention(s)	Combination of venetoclax and ibrutinib administered orally once daily
Comparator(s)	Matched oral placebo
Outcome(s)	Primary outcomes: • Occurrence of Tumour Lysis Syndrome [Time frame: approximately 3 months after last subject enrolled into safety run-in portion] • Occurrence of Dose Limiting Toxicities [Time frame: approximately 3 months after last subject enrolled into safety run-in portion] • Progression-free Survival [Time frame: approximately 1 year after last subject has stopped treatment with study drug(s)] • Complete Response [Time frame: approximately 1 year after last subject has stopped treatment with study drug(s)]
Results (efficacy)	-
Results (safety)	-

Trial	**OAsIs;** NCT02558816; EudraCT 2014-003740-13; **RC14_0048;** A Phase I/II Trial of Obinutuzumab, ABT-199 (GDC-0199) Plus Ibrutinib in Relapsed / Refractory Mantle Cell Lymphoma Patients **Phase I/II –** Active, not recruiting **Location(s):** France and UK **Primary completion date:** April 2019
Trial design	Non-randomized, single group assignment, open label
Population	N=48; subjects with relapsed/refractory MCL; aged 18 yrs and over for French patients and 16 yrs and over for UK patients
Intervention(s)	Step A: 9 patients receive the combination of Ibrutinib + Obinutuzumab (GA101) Step B: 24 patients receive the combination of Ibrutinib + Obinutuzumab + Venetoclax Step C: 15 untreated patients receive the combination of Ibrutinib + Obinutuzumab + Venetoclax
Comparator(s)	No comparator
Outcome(s)	Primary outcomes: • Step A: occurrence of unacceptable toxicity of the combination of Obinutuzumab and Ibrutinib during the first cycle of treatment [Time Frame: week 4] • Step B: occurrence of unacceptable toxicity (definition p3) of the combination of Obinutuzumab and Ibrutinib plus Venetoclax during the cycle 2 in terms of Dose-Limiting Toxicities (DLTs) [Time Frame: At the end of cycle 2 (each cycle is 28 days)] • Step C: occurrence of unacceptable toxicity of the combination of Obinutuzumab and Ibrutinib and

	Venetoclax at the end of the cycle 2 [Time Frame: At the end of cycle 2 (each cycle is 28 days)] See trial record for full list of other outcomes
Results (efficacy)	Results of Step C:[20] • All (n=15) patients are in response, including complete response/unconfirmed complete response (CR/uCR) in 7 cases, at end of cycle 2 according to Cheson 99 criteria. • At the end of Cycle 3, 8 patients (others are ongoing) were minimal residual disease (MRD) negative in bone marrow (BM), including the P53mut patient. • Seven patients completed 6 cycles, all reached CR according to Lugano criteria (6 in CR/Cru according to Cheson criteria) and were MRD neg, including the P53mut patient. • At date of last monitoring (Jul 2019), no disease progression is reported and all patients remain under the planned treatment.
Results (safety)	Results of Step C:[20] • During the first three months of treatment, non-hematological grade 3-4 adverse events (AEs) were hepatobiliary disorders (n=4; 3 patients with raised γ-glutamyltransferase -grade 3-, alanine -grade 3- and aspartate -grade 4- aminotransferase and one with biological cytolysis - grade 4) and rash (n=1; grade 3). • Hematological grade 3-4 AEs were lymphocytosis (n=1; grade 3) and neutropenia (n=1; grade 4).

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).[21]

Ibrutinib already marketed in the UK. The NHS indicative price is as follows:[22]

- a pack of 28 × 140 mg tablets costs £1,430.80
- a pack of 28 × 280 mg tablets costs £2,861.60
- a pack of 28 x 420 mg tablets costs £4,292.40
- a pack of 28 x 560 mg tablets costs £5,723.20

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. KTE-X19 for treating relapsed or refractory mantle cell lymphoma (GID-TA10312). Expected January 2021.
- NICE technology appraisal. Ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502). January 2018.

- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

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

- British Society for Haematology. Guideline for the management of mantle cell lymphoma. May 2018.[23]
- European Society for Medical Oncology (ESMO). Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. May 2017.[13]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Study of Ibrutinib Combined With Venetoclax in Subjects With Mantle Cell Lymphoma (SYMPATICO). Trial ID: NCT03112174*. 2017. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03112174 [Accessed 20 July 2020].

2 Electronic medicines compendium (emc). *Venclyxto 10 mg film-coated tablets*. 2020. Available from: https://www.medicines.org.uk/emc/product/2267 [Accessed 20 July 2020].

3 Tam CS, Anderson MA, Pott C, Agarwal R, Handunnetti S, Hicks RJ, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. *New England Journal of Medicine*. 2018;378(13):1211-23. Available from: https://doi.org/10.1056/NEJMoa1715519.

4 ClinicalTrials.gov. *ABT-199 & Ibrutinib in Mantle Cell Lymphoma (AIM). Trial ID: NCT02471391*. 2015. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02471391 [Accessed 20 July 2020].

5 Handunnetti SM, Anderson MA, Burbury K, Hicks RJ, Birbirsa B, Bressel M, et al. Three Year Update of the Phase II ABT-199 (Venetoclax) and Ibrutinib in Mantle Cell Lymphoma (AIM) Study. *Blood*. 2019;134(Supplement_1):756. Available from: https://doi.org/10.1182/blood-2019-126619.

6 Electronic medicines compendium (emc). *Venclyxto 10 mg gilm-coated tablets: Therapeutic indications*. 2020. Available from: https://www.medicines.org.uk/emc/product/2267#INDICATIONS [Accessed 17 August 2020].

7 European Medicines Agency (EMA). *EU/3/17/1954*. 2018. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171954 [Accessed 28 July 2020].

8 ClinicalTrials.gov. *Search for venetoclax, ibrutinib | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=venetoclax%2C+ibrutinib&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 17 August 2020].

9 Lymphoma Action. *Mantle cell lymphoma.* Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/mantle-cell-lymphoma [Accessed 20 July 2020].

10 Macmillan Cancer Support. *Mantle cell lymphoma overview*. Available from: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/mantle-cell-lymphoma [Accessed 20 July 2020].

11 Cancer Research UK (CRUK). *What is non-Hodgkin lymphoma?* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/about [Accessed 22 July 2020].

12 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

13 European Society for Medical Oncology (ESMO. *Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up* Last Update Date: May 2017. Available from: https://www.annalsofoncology.org/article/S0923-7534(19)42151-0/pdf [Accessed 23 July 2020].

14 National Insitute for Health and Care Excellence (NICE). *KTE-X19 for treating relapsed or refractory mantle cell lymphoma [ID1313]: Final scope document*. 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10312/documents/final-scope [Accessed 22 July 2020].

15 Haematological Malignancy Research Network (HMRN). *HMRN - Survival - Mantle Cell Lymphoma.* Available from: https://www.hmrn.org/statistics/survival [Accessed 10 August 2020].

16 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 24 July 2020].

17 Cancer Research UK (CRUK). *Mantle cell lymphoma.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell [Accessed 22 July 2020].

18 National Insititute for Health and Care Excellence (NICE). *Non-Hodgkin's lymphoma: diagnosis and management | 1.5 Management of mantle cell lymphoma (NG52)*. Last Update Date: 20 July 2016. Available from: https://www.nice.org.uk/guidance/NG52/chapter/Recommendations#management-of-mantle-cell-lymphoma [Accessed 17 August 2020].

19 National insitute for Health and Care Excellence (NICE). *NICE Pathway: Treating mantle cell lymphoma.* Available from: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma/treating-mantle-cell-lymphoma#content=view-node%3Anodes-relapsed-or-refractory-disease [Accessed 20 July 2020].

20 Le Gouill S, Morschhauser F, Bouabdallah K, Cartron G, Casasnovas O, Gastinne T, et al. Ibrutinib, Venetoclax Plus Obinutuzumab in Newly Diagnosed Mantle Cell Lymphoma Patients. *Blood*. 2019;134(Supplement_1):1530-. Available from: https://doi.org/10.1182/blood-2019-125681.

21 British National Formulary (BNF). *Medical forms: VENETOCLAX.* Available from: https://bnf.nice.org.uk/medicinal-forms/venetoclax.html [Accessed 28 July 2020].

22 British National Formulary (BNF). *Medical Forms: IBRUTINIB.* Available from: https://bnf.nice.org.uk/medicinal-forms/ibrutinib.html [Accessed 17 August 2020].

23 British Society for Haematology. Guideline for the management of mantle cell lymphoma. 2018 16 May 2018. Available from: https://doi.org/https://doi.org/10.1111/bjh.15283.

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