Venetoclax (Venclyxto®) in combination with a hypomethylating agent for the treatment of patients with newly diagnosed acute myeloid leukaemia (AML)

General information

Drug description [1]	Indication [2]
Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein.	Venetoclax in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Current treatment [3]

- Chemotherapy for AML is in two phases:
  - Induction: usually the patient is given two or more different chemotherapy drugs in cycles of treatment; the 2 main drugs are cytarabine and daunorubicin.
  - Consolidation: Combinations of chemotherapy can be used in this phase, including amsacrine, high dose cytarabine, etoposide, daunorubicin, fludarabine, idarubicin; some patients have high dose chemotherapy and then a bone marrow or stem cell transplant.

Regulatory status

EMA [2]

Approval status for this indication: On 22 April 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Venclyxto®.

The CHMP adopted a new indication as follows:

- Venclyxto® in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Other indications:

- Venclyxto® in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- Venclyxto® in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- Venclyxto® monotherapy is indicated 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 chemoimmunotherapy and a B-cell receptor pathway inhibitor.

✓ **Medicine under additional monitoring**

FDA [4, 5]

Approval status for this indication: On 16 October 2020, the FDA granted regular approval to venetoclax (Venclexta®) in combination with azacitidine, decitabine, or low-dose cytarabine (LDAC) for newly-diagnosed AML in adults 75 years or older, or who have comorbidities precluding intensive induction chemotherapy.

- ✓ Venetoclax was initially granted accelerated approval for this indication in November 2018.
- ✓ FDA granted this application priority review, breakthrough designation, and orphan drug designation.

Other indications: Venclexta® is indicated:

- for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL).

Costs

112 Venclyxto® tablets 100 mg = € 4,980.00 (ex-factory price) [6]

According to the VIALE-A dosing regimen (patients received 400 mg of Venetoclax orally, once daily) [7], **28 days of venetoclax treatment** = **€ 4,980.00.**

Warnings and precautions [4]

- **Tumour Lysis Syndrome (TLS):** Anticipate TLS; assess risk in all patients. Pre-medicate with anti-hyperuricemic and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases.
- **Neutropenia:** Monitor blood counts. Interrupt dosing and resume at the same or reduced dose. Consider supportive care measures.
- **Infections:** Monitor for signs and symptoms of infection and treat promptly. Withhold for Grade 3 and 4 infections until resolution and resume at the same or reduced dose.
- **Immunization:** Do not administer live attenuated vaccines prior to, during, or after treatment with Venclexta® until B-cell recovery.
- **Embryo-Foetal Toxicity**: May cause embryo-foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.
- Treatment of patients with **multiple myeloma** with Venclexta® in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Study characteristics [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
VIALE-A NCT02993523	431	**azacitidine** (75 mg per m^2 of BSA subcutaneously or IV on days 1 through 7 every 28-day cycle) + **Venetoclax** orally, once daily (target dose, 400 mg)	**azacitidine** (75 mg per m2 of BSA subcutaneously or IV on days 1 through 7 every 28-day cycle) + matching **placebo**	OS	multicentre, randomized, double-blind, placebo-controlled, phase 3 trial	-	AbbVie and Genentech	[7]

Efficacy (I vs. C)

Survival outcomes:

Median OS: 14.7 months vs. 9.6 months (HR for death 0.66; 95% CI, 0.52-0.85; p<0.001)
Composite complete remission: 66.4% (95% CI, 60.6-71.9) vs. 28.3% (95% CI, 21.1-36.6); p<0.001
Composite complete remission before the initiation of cycle 2: 43.4% (95% CI, 37.5-49.3) vs. 7.6% (95% CI, 3.8-13.2); p<0.001
Median time to first response (either complete remission or complete remission with incomplete hematologic recovery): 1.3 months vs. 2.8 months
Median duration of composite complete remission: 17.5 months vs.13.4 months
Complete remission: 36.7% vs. 17.9% of the patients; p<0.001
Duration of complete remission: 17.5 months vs. 13.3 months
Median time to first response: 1.0 month vs. 2.6 months
Duration of response: 17.8 months vs. 13.9 months
Red-cell transfusion independence: 59.8% vs. 35.2%; p<0.001
Platelet transfusion independence: 68.5% vs. 49.7%; p<0.001

Median OS among patients with de novo AML (i.e., in those with no history of myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukemogenic agents): 14.1 (95% CI, 10.7-19.3) months vs. 9.6 (95% CI, 6.8-13.0) months; HR 0.67; 95% CI, 0.51-0.90
Median OS among patients with secondary AML: 16.4 months (95% CI, 9.7-24.4)vs. 10.6 months (95% CI, 4.9-13.2); HR 0.56; 95% CI, 0.35-0.91
Median OS among patients with an intermediate cytogenetic risk: 20.8 months (95% CI, 16.4-NR) vs. 12.4 months (95% CI, 9.1-15.8); HR for death 0.57; 95% CI, 0.41-0.79
Median OS among patients with a poor cytogenetic risk: 7.6 months (95% CI, 5.3-9.9) vs. 6.0 months (95% CI, 3.6-10.7); HR 0.78; 95% CI, 0.54-1.1
Median event-free survival: 9.8 months (95% CI, 8.4-11.8) vs. 7.0 months (95% CI, 5.6-9.5); HR for death 0.63; 95% CI, 0.50-0.80; p<0.001)

QoL:

No differences were observed between the two treatment groups with respect to QoL measures.

Safety (I vs. C)

Adverse events:

Grade ≥3 AEs: n=279/283 (99%) vs. n=139/144 (97%)
SAEs: n=235/283 (83%) vs. n=105/144 (73%)
Mortality at 30 days: n=21/283 (7%) vs. n=9/144 (6%)
Discontinuation: 24% vs. 20%

Causes of death:

Total number of patient death: n=161/286 (56%) vs. n=109/145 (75%)
Due to disease progression: n=78/286 (27%) vs. n=64/145 (44%)
Not due to disease progression: n=77/286 (27%) vs. n=36/145 (25%)
Unknown: n=6/286 (2%) vs. n=9/145 (6%)

Risk of bias (study level) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[1]	yes[2]	unclear

First published: 05/2021
Last updated: 08/2021

Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, BCL=B-cell lymphoma, BSA=body-surface area, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final

[1] VIALE-A trial is ongoing until 05/2021
[2] The sponsors, provided financial support for the trial and participated in the design, trial conduct, analysis, and interpretation of the data. The first draft of the manuscript was written by the first author and a medical writer employed by the sponsor, with input from all the authors.

magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, LDAC=low-dose cytarabine, n=number, MG=median gain, n=number of patients, NR=not reached, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SLL=small lymphocytic lymphoma, ST=standard treatment, TLS=tumor lysis syndrome

References:

1. European Medicines Agency (EMA). Venclyxto: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Medicines. Venclyxto. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/venclyxto-1].
3. National Institute for Health Research (NIHR). Venetoclax in combination with a hypomethylating agent or low dose cytarabine for newly diagnosed acute myeloid leukaemia. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/11/13670-Venetoclax-for-AML-V1.0-OCT18-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). Venclexta. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208573s023lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA grants regular approval to venetoclax in combination for untreated acute myeloid leukemia. [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-regular-approval-venetoclax-combination-untreated-acute-myeloid-leukemia].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;383:617-29. [Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2012971].
8. Supplement to: DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617-29.
9. Protocol for: DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617-29.
10. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy (Viale-a). [Available from: https://clinicaltrials.gov/ct2/show/NCT02993523].
11. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].