Venetoclax (Venclyxto®) and obinutuzumab in patients with chronic lymphocytic leukaemia (CLL) and coexisting conditions

General information [1]

Drug description	Indication
a potent, selective inhibitor of B-cell lymphoma (BCL)-2 , an anti-apoptotic protein	pts with previously untreated CLL and coexisting conditions, a score of greater than 6 on the Cumulative Illness Rating Scale, or a calculated creatinine clearance of less than 70 ml per minute

Current treatment

Treatment options for CLL can include (first line therapy combinations) [2]:

- Fludarabine (oral) -Cyclophosphamide (oral) - Rituximab (IV) combination (FC-R)
  Venetoclax in patients with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable
- Ibrutinib in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable
- Idelalisib, in combination with rituximab, is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation.
- Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable
- Ofatumumab in combination with chlorambucil is recommended as an option for untreated CLL only if the person is ineligible for fludarabine-based therapy and bendamustine is not suitable and
- Bendamustine is recommended as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Regulatory status

EMA [3]

Approval status for this indication: positive CHMP opinion (2020-01-30)

Other indications: Venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. Venetoclax 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]

Approval status for this indication: approved (15.05.2019)

Other indications: Venetoclax is indicated:

- for the treatment of adult patients with CLL or SLL
- in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (accelerated approval)

Costs

14 Venclyxto® tablets 10 mg = € 72.93, 7 Venclyxto® tablets 50 mg = € 182.10, 7 Venclyxto® tablets 100 mg = 364.30, 14 Venclyxto® tablets 100 mg = € 732.38,
112 Venclyxto® tablets (4x28) = € 5,664.83 (ex-factory price each) [5]

CLL14 trial: The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a **5-week dose ramp-up** (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week) → € 2,816.47 (ramp-up), then **€ 5,664.82/month/cycle** (treatment duration was 12 months)

Study characteristics [1, 6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CLL14 NCT02242942 BO25323 EudraCT Number: 2014-001810-24	432	venetoclax–obinutuzumab	chlorambucil–obinutuzumab	PFS (investigator-assessed)	multinational, open-label, phase 3 trial	-	F. Hoffmann–La Roche and AbbVie	Link [1]

Efficacy (I vs. C)

PFS (investigator-assessed, at 24 months): 88.2% vs. 64.1% (HR 0.35; 95% CI, 0.23 to 0.53; p<0.001)

Safety (I vs. C)

Grade ≥3 AEs: n=167/212 (78.8%) vs. 164/214 (76.6%)

PFS (byICR, at 24 months): 88.6% vs. 63.7% (HR 0.33, 95% CI, 0.22 – 0.51, p <0.0001) **Median PFS** at updated efficacy analysis (data cut-off date 23 August 2019 and median follow-up of 40 months): not reached vs. 35.6 months (HR 0.31, 95% CI, 0.22-0.44) **36-month PFS estimate**: 81.9% (95% CI, 76.5-87.3) vs. 49.5% (95% CI,42.4-56.6) **MRD negativity in peripheral blood and bone marrow:** peripheral blood: 75.5% vs. 35.2%, p<0.001, bone marrow: 56.9% vs. 17.1%, p<0.001 **Overall response:** 84.7% vs. 71.3% (p<0.001) **Complete response:** 49.5% vs. 23.1% (p<0.001) **MRD negativity in pts with CR in peripheral blood and bone marrow:** peripheral blood: 42.1% vs. 14.4% (p<0.001); bone marrow: 33.8% vs. 10.6% (p<0.001) **MRD negativity rate at end of treatment**: peripheral blood: 76% vs. 35% (p<0.0001); bone marrow: 57% vs. 17% (p<0.0001) **OS, median:** not reached in either group	**SAEs[1]:** n=104/212 (49.1%) vs. 90/214 (42.1%) **Death[2]:** n=5/212(2.4%)[3] vs. 4/214 (1.9%) **Discontinuation[4]:** 16.0% vs. 15.4%

Risk of bias (study level)

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	no	no	unclear[5]	yes[6]	high

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Abbreviations: AE=adverse event, AML=acute myeloid leukaemia, BCL= B-cell lymphoma, CHMP=Committee for Medicinal Products for Human Use, CLL=chronic lymphocytic leukaemia, CR=complete remission, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, ICR=Independent Review Committee, IV=intravenous, MRD=minimal residual disease, n=number, SAE=serious adverse event, SLL= small lymphocytic lymphoma, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, pts=patients.

References:

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2. National Institute for Health Research (NIHR). Venetoclax in combination with obinutuzumab for the treatment of previously untreated chronic lymphocytic leukaemia –first line. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2017/12/11891-Venetoclax-and-obinutuzumab-for-CLL.pdf.
3. European Medicines Agency (EMA). Medicines. Venclyxto. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/venclyxto-0.
4. U.S. Food and Drug Administration (FDA). Venclexta. Label information [
5. Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/.
6. 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.

[1] pts with at least one serious AE
[2] grade 5 AE during treatment
[3] 2 pts received obinutuzumab only
[4] treatment discontinuation due to AE(s)
[5] QoL objectives (predefined in the study protocol): no results available
[6] Industry funded the study; the sponsors and the German CLL Study Group analyzed the data; third-party editing and administrative support was funded by the sponsor