Ibrutinib (Imbruvica®) as a single agent or in combination with rituximab or obinutuzumab for the treatment of previously untreated chronic lymphocytic leukaemia (CLL)

General information

Drug description [1]	Indication [2]
Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK)	Ibrutinib as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL

Current treatment [3]

First line therapy combinations (in treatment cycles of 28 days):

- Fludarabine (oral) - Cyclophosphamide (oral) - Rituximab (IV) combination (FC-R)
- Cyclophosphamide – doxorubicin – vincristine – prednisolone (CHOP)
- Cyclophosphamide – doxorubicin – prednisolone (CAP)
- Cyclophosphamide – vincristine – prednisolone (CVP)

Regulatory status

EMA [2, 4]

Approval status for this indication: On 23 July 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imbruvica®. The CHMP adopted an extension to the existing indication as follows:

Imbruvica as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL.

Other indications:

- Ibrutinib as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- Ibrutinib as a single agent or in combination with bendamustine and rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- Ibrutinib as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib in combination with rituximab is indicated for the treatment of adult patients with WM.

✓ **Orphan status**: Imbruvica was designated an orphan medicine for CLL on 26 April 2012, MCL on 12 March 2013 and WM on 29 April 2014.

FDA [5, 6]

Approval status for this indication: On 21 April 2020, the FDA expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with CLL or small lymphocytic lymphoma (SLL).

Other indications: Ibrutinib is indicated for the treatment of adult patients with:

- MCL who have received at least one prior therapy (accelerated approval)
- CLL/ SLL
- CLL/SLL with 17p deletion
- WM
- Marginal zone lymphoma, who require systemic therapy and have received at least one prior anti-CD20-based therapy (accelerated approval)
- Chronic graft versus host disease after failure of one or more lines of systemic therapy

Costs

28 Imbruvica® tablets 420 mg = € 4,797.37 (ex-factory price) [7]

E1912 trial patients received ibrutinib at a daily dose of 420 mg [8] → costs for 28 days of ibrutinib treatment = € 4,797.37

Study characteristics[1] [8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
E1912 NCT02048813	529	Ibrutinib (420 mg per day) and rituximab for 6 cycles (after a single cycle of ibrutinib alone), followed by ibrutinib until disease progression	6 cycles of chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab	PFS	multicenter, open-label, randomized, phase 3 trial	-	National Cancer Institute and Pharmacyclics	Link

Efficacy (I vs. C) | **Safety** (I vs. C)

[1] Study results of a planned interim analysis of E1912

PFS at 3 years: 89.4% (95% CI, 86.0-93.0) vs. 72.9% (95% CI, 65.3-81.3); HR for progression or death 0.35; 95% CI, 0.22-0.56, p<0.001. PFS in a subgroup analysis involving **patients without IGHV mutation**: 90.7% vs. 62.5% at 3 years; HR for progression or death 0.26 (95% CI, 0.14-0.50). The 3-year PFS among **patients with IGHV** mutation was 87.7% vs. 88.0% in the chemoimmunotherapy group (HR for progression or death 0.44, 95% CI, 0.14-1.36) **OS**: higher in the ibrutinib– rituximab group than in the chemoimmunotherapy group (HR for death 0.17; 95% CI, 0.05-0.54, p<0.001). **OS at 3 years**: 98.8% (95% CI, 97.6-100) vs. 91.5% (95% CI, 86.2-97.0) **Overall response**: 95.8% (95% CI, 93.1-97.6) vs. 81.1% (95% CI, 74.5-86.6) **Complete response**: 17.2% (95% CI, 13.4-21.6) vs. 30.3% (95% CI, 23.6-37.7) **MRD-negative at 12 months** (ibrutinib-rituximab group): 8.3% (95% CI, 5.4-12.2)	**Grade ≥3 AEs**: n=282/352 (80.1%) vs. n=126/158 patients (79.7%) **Deaths:** n=4/352[2] (1.1%) vs. n=10/158[3] (6.3%) **Discontinuation[4]:** n=40/352 (11.4%) vs. 38/158 (24.1%)

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**
unclear	no	no, open-label	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AML=acute myeloid leukemia**,** C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, IGHV= immunoglobulin heavy-chain variable region, IV=intravenous, MCL=mantle cell lymphoma, MRD=minimal residual disease, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, SAE=serious adverse event, SLL=small lymphocytic lymphoma, WM=Waldenström's macroglobulinaemia.

References:

1. European Medicines Agency (EMA). Medicines. Imbruvica: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf.
2. European Medicines Agency (EMA). Medicines. Imbruvica: Pending EC decision [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imbruvica-0.
3. National Institute for Health Research (NIHR). Ibrutinib in combination with obinutuzumab for the treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma in elderly – first line.
4. European Medicines Agency (EMA). Medicines. Imbruvica. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica.
5. U.S. Food and Drug Administration (FDA). FDA approves ibrutinib plus rituximab for chronic lymphocytic leukemia [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ibrutinib-plus-rituximab-chronic-lymphocytic-leukemia.
6. U.S. Food and Drug Administration (FDA). Drugs@FDA. Imbruvica. Label Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205552s030,210563s006lblPI.pdf.
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online [Available from: https://warenverzeichnis.apoverlag.at/.
8. Shanafelt TD, XV Wang, Kay NE, Hanson CA, O'Brien S, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med 2019;381:432-43.

[2] 1 death due to CLL, 1 due to lung adenocarcinoma with respiratory failure, 1 due to acute respiratory failure, and 1 sudden death in a patient with history of atrial fibrillation
[3] 4 deaths due to CLL, 2 therapy-related, 1 due to lung cancer, 1 due to metastatic colon cancer, 1 due to drug overdose, and 1 due to infection
[4] Discontinuation due to AE(s)
[5] Reported results are interim analysis data; the E1912 trial is ongoing until 06/2026
[6] Partly industry-funded

9. Supplement to: Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med 2019;381:432-43. DOI: 10.1056/NEJMoa1817073.