Duvelisib (Copiktra®) for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) and refractory follicular lymphoma (FL)

General information [1]

Drug description	Indication
Duvelisib is an anti-neoplastic agent which acts by inhibiting phosphatidylinositol 3-kinase p110δ (PI3K-δ) and PI3K-γ. These enzymes are involved in the proliferation and survival of malignant B-cell lines and primary CLL tumour cells, and in immunological pathways in the tumour microenvironment of malignant B cells.	Duvelisib is intended for the treatment of adult patients with relapsed or refractory CLL and refractory FL.

Current treatment

❖ Drug therapies and treatments that can be used to treat relapsed or refractory CLL include [2]:

- Ibrutinib alone
- Venetoclax alone or with rituximab
- Duvelisib
- Idelalisib with rituximab
- Ofatumumab
- Combinations of ibrutinib or venetoclax with anti-CD20 antibodies
- Allogeneic stem cell transplantation
- Alemtuzumab alone or in combination
- Clinical trials.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 25 March 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Copiktra®, intended for the treatment of adult patients with relapsed or refractory CLL and refractory FL. **UPDATE**: Date of issue of marketing authorisation valid throughout the European Union; 19/05/2021 [4] The full indication is: Copiktra® is indicated for the treatment of adult patients with: ❖ relapsed or refractory CLL after at least two prior therapies. ❖ FL is refractory to at least two prior systemic therapies. **Other indications**: none ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 24 September 2018, the FDA granted regular approval to duvelisib (Copiktra®) for adult patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) after at least two prior therapies. In addition, duvelisib received accelerated approval for adult patients with relapsed or refractory FL after at least two prior systemic therapies. **Other indications**: none ✓ **Priority review**

Costs

Currently no cost information available.

Warning: Fatal and serious toxicities [5]

❖ **Fatal and/or serious infections** occurred in 31% of Copkitra®-treated patients. Monitor for signs and symptoms of infection. Withhold Copiktra® if infection is suspected.
❖ **Fatal and/or serious diarrhoea or colitis** occurred in 18% of Copiktra®-treated patients. Monitor for the development of severe diarrhoea or colitis. Withhold Copiktra®.
❖ **Fatal and/or serious cutaneous reactions** occurred in 5% of Copiktra®-treated patients. Withhold Copiktra®.
❖ **Fatal and/or serious pneumonitis** occurred in 5% of Copiktra®-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold Copiktra®.

Study characteristics: DUO trial [6, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DUO, Study IPI-145-07 NCT02004522	319	oral duvelisib 25 mg twice daily (n=160)	ofatumumab IV (n=159)	PFS[1]	global, multicentre, randomized, open-label, phase 3 trial	-	Verastem Oncology and Infinity Pharmaceuticals Inc.	[6]

Efficacy (I vs. C)	**Safety** (I vs. C)
Median PFS by blinded IRC review was significantly longer for the duvelisib arm compared with the ofatumumab arm: 13.3 months vs. 9.9 months, HR 0.52, p<0.0001 **Improvement in PFS:** 17.6 months vs. 9.7 months, HR 0.40, p<0.0001 **Median PFS by IRC in the subset of patients with del(17p)/TP53 mutations:** 12.7 months vs. 9.0 months for ofatumumab, HR 0.40, p=0.0002, with an **estimated probability of being progression-free at 6 months and 12 months** of 73% and 55% vs. 63% and 30%. **Median PFS by investigator assessment in patients with del(17p)/TP53 mutations:** 13.8 months vs. 9.5 months, HR 0.41, p=0.0003 with an **estimated probability of being progression-free at 6 months and 12 months** of 77% and 66% vs. 53% and 33%. Duvelisib maintained a favourable odds ratio relative to ofatumumab for all subgroups analysed. **ORR per IRC response assessment** for duvelisib was significantly higher compared with ofatumumab: 73.8% vs. 45.3%, p<0.0001 **PRs**: 72.5% vs. 44.7% **Lymph node response by IRC assessment:** 85.0% (95% CI, 79.5-90.5) vs. 15.7% (95% CI, 10.1-21.4); p<0.0001 **Median OS:** not reached on either treatment arm with a **12-month probability of survival** of 86% (HR 0.99; 95%CI, 0.65-1.50) for both treatments **PROs and QoL [8]:** ❖ Comprehensive analysis of PRO scores showed that duvelisib patients reported consistently better health-related QoL over time as compared to ofatumumab patients in the subset of patients receiving ≥ 2 prior therapies. ❖ The magnitude of differences was generally smaller in the ITT population vs. the subset of patients who received 2 or more prior therapies and the differences were generally not statistically significant.	**Any AEs grade ≥3**: n=138/158 (87%) vs. n=75/155 (48%) **SAEs in ≥2% of patients:** n=115/158 (73%) vs. n=50/155 (32%) **Any AE leading to death[2]:** n=19/158 (12%) vs. n=7/155 (5%) **Discontinuation[3]:** n=55/158 (35%) vs. n=6/155 (4%) **Crossed over to study IPI-145-12 to receive opposite treatment:** n=8/158 (5%) vs. n=89/155 (57%)

Study characteristics: DUO crossover extension study [9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
DUO crossover extension study, IPI-145-12, NCT02049515	90	Duvelisib 25 mg twice daily in 28-day cycles until PD, intolerance, death, or study withdrawal[4]	-	ORR per investigator	open-label, two-arm, non-randomised, phase III study	-	SecuraBio	[9] (crossover extension study)

Efficacy (I vs. C)	**Safety** (I vs. C)
ORR (investigator-assessed) with duvelisib treatment after crossover: n=69/90 (77%) **ORR in the subset of patients with del(17p) and/or TP53 mutations**: n=20/26 (77%) **PR (in all patients)**: n=55/90 (61%) **PR (in patients with del(17p) and/or TP53 mutations**: n=15/26 58% **Median time to response**: 2.6 months (range 1.5–10.7 months) **Median duration of response**: 14.9 months (95% CI, 9.0–18.6 months) for the total patient population and 11.3 months (95% CI, 5.1–21.2 months) for the subset of patients with del(17p) and/or TP53 mutations. 73% of patients, who were refractory to ofatumumab**, achieved a response** after crossing over to duvelisib, with the majority of these responses being **PRs** (63%).	**Any TEAE grade ≥3**: n=80/90 (89%) **Any serious TEAE**: n=67/90 (74%) **TEAEs leading to death**: n=12/90 (13%) **Treatment discontinuation[5]**: n=47/90 (52%)

[1] PFS was defined as time from randomization to first documentation of progressive disease as determined by an IRC or death attributable to any cause.
[2] There were 19 fatal AEs on the duvelisib arm, 4 of which were assessed by investigators as related to study drug: staphylococcal pneumonia (n =2) and sepsis and general health deterioration (n=1 each). On the ofatumumab arm, 7 patients had fatal AEs, although none were attributed to ofatumumab treatment.
[3] Discontinuation due to AE(s).
[4] Patients who exhibited radiographically confirmed PD by central review in the DUO trial had the option to subsequently receive the other study treatment (duvelisib or ofatumumab).
[5] Treatment discontinuation due to TEAEs.

90% of response-evaluable patients had **>50% reduction in target nodal lesions.** 82% of patients experienced **redistribution lymphocytosis,** which occurred early, with a median time to onset of 1.1 weeks (range, 0.7–89.7 weeks) and a median duration of 15.1 weeks (range, 1.1–127 weeks). Median time to **resolution of first lymphocytosis**: 14.6 weeks (range, 2–87.3 weeks). Estimated probability of being **progression-free at 6 months and 12 months** (in all patients): 88% and 64% **Median OS** in patients who received duvelisib after crossover (n=90): 43 months, with an estimated probability of survival at 6 and 12 months of 91% and 82%, respectively.	

Risk of bias (study level) [11]: DUO trial					
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, open-label	unclear[6]	yes[7]	unclear
					First published: 04/2021 **Last updated**: 07/2021

Abbreviations: AE=adverse event, AJ=adjustment, 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 magnitude of clinical benefit grade, FL=follicular lymphoma, HR=hazard ratio, I=intervention, Int.=intention, IRC=independent review committee, ITT=intention-to-treat, MG=median gain, n=number of patients, ORR=overall response rate, OS=overall survival, PD=progressive disease, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response/remission, PROs=patient-reported outcomes, QoL=quality of life, SAE=serious adverse event, SLL=small lymphocytic lymphoma, ST=standard treatment, TEAE=treatment-emergent adverse events

References:

1. European Medicines Agency (EMA). Medicines. Sarclisa. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/sarclisa-0].
2. Leukemia & Lymphoma Society. Relapsed and refractory CLL. [Available from: https://www.lls.org/leukemia/chronic-lymphocytic-leukemia/treatment/relapsed-and-refractory].
3. U.S. Food and Drug Administration (FDA). Sarclisa. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf].
4. European Medicines Agency (EMA). Medicines. Sarclisa. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/copiktra].
5. U.S. Food and Drug Administration (FDA). Copiktra. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211155s001lbl.pdf].
6. Flinn IW, Hillmen P, Montillo M, Nagy Z, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood 2018;132(23):2446-2455. [Available from: https://doi.org/10.1182/blood-2018-05-850461].
7. U.S. National Library of Medicine, ClinicalTrials.gov. A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL (DUO). [Available from: https://clinicaltrials.gov/ct2/show/NCT02004522].
8. Zinzani P, et al. PATIENT-REPORTED OUTCOMES AND QUALITY OF LIFE IN DUO: A RANDOMIZED TRIAL OF DUVELISIB VS. OFATUMUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA. [Available from: https://library.ehaweb.org/eha/2020/eha25th/294217/p.zinzani.patient-reported.outcomes.and.quality.of.life.in.duo.a.randomized.html].
9. Davids MS, Kuss BJ, Hillmen P, Montillo M, et al. Efficacy and Safety of Duvelisib Following Disease Progression on Ofatumumab in Patients with Relapsed/Refractory CLL or SLL in the DUO Crossover Extension Study. Clin Cancer Res 2020;26:2096–103. [Available from: https://clincancerres.aacrjournals.org/content/26/9/2096.long].
10. U.S. National Library of Medicine, ClinicalTrials.gov. A Phase 3 Extension Study of Duvelisib and Ofatumumab in Patients With CLL/SLL Previously Enrolled in Study IPI-145-07. [Available from: https://clinicaltrials.gov/ct2/show/NCT02049515].

[6] DUO-trial is ongoing until 06/2021.
[7] Industry-funded.

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].