Moxetumomab pasudotox (Lumoxiti®) for the treatment of patients with relapsed or refractory hairy cell leukaemia (HCL): Withdrawal of the marketing authorisation in the European Union

General information [1]

Drug description	Indication
Moxetumomab pasudotox, an antineoplastic agent, is a CD22-targeted immunotoxin designed to direct the cytotoxic action of the truncated Pseudomonas exotoxin to cells which express the CD22 receptor.	Moxetumomab pasudotox as monotherapy is indicated for the treatment of adult patients with relapsed or refractory HCL after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

Current treatment [2]

- ❖ Drug therapy that can be used to treat relapsed or refractory HCL includes:
  - Cladribine
  - Interferon-alfa
  - Rituximab
  - Moxetumomab pasudotox-tdfk.
- ❖ Some other therapies for relapsed or refractory HCL include:
  - Splenectomy in case of significantly enlarged spleen and no response to, or relapse after, treatment with cladribine, pentostatin, rituximab and BL22
  - In case of no response to chemotherapy or other therapies, an allogeneic stem cell transplantation (ASCT) might be considered
  - Participation in a clinical trial.

Regulatory status

EMA	FDA [3, 4]
Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation under exceptional circumstances for Lumoxiti. **UPDATE**: On 23 July 2021, the European Commission **withdrew** the marketing authorisation for Lumoxiti® (moxetumomab pasudotox) in the European Union. The withdrawal was at the request of the marketing authorisation holder, AstraZeneca AB, which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons. Lumoxiti® was granted marketing authorisation in the EU on 8 February 2021 for treatment of adult patients with relapsed or refractory HCL after receiving at least two prior systemic therapies. The marketing authorisation was initially valid for a 5-year period. The product had not been marketed in the EU [5].	**Approval status for this indication**: On 13 September 2018, the FDA approved moxetumomab pasudotox-tdfk (Lumoxiti®), a CD22-directed cytotoxin indicated for adult patients with relapsed or refractory HCL who received at least two prior systemic therapies, including treatment with a PNA. **Limitations of Use**: not recommended in patients with severe renal impairment (CrCl ≤ 29 mL/min). **Other indications**: none

Costs

Currently no cost information available.

Premedication [6]

- ❖ Premedication is required 30-90 minutes prior to each Lumoxiti® infusion with an oral antihistamine (e.g. hydroxyzine or diphenhydramine), an antipyretic (e.g. paracetamol), and a histamine-2 receptor antagonist (e.g. ranitidine, famotidine, or cimetidine).

Warning [4, 6]

- ❖ **Capillary leak syndrome (CLS),** including life-threatening cases, occurred in patients receiving moxetumomab pasudotox.
  - Patients who experience grade 2 or higher CLS should receive appropriate supportive measures including treatment with oral or intravenous corticosteroids, with monitoring of weight, albumin levels, and blood pressure until resolution.
- ❖ **Haemolytic Uremic Syndrome (HUS),** including life-threatening cases, occurred in patients receiving moxetumomab pasudotox.
  - Patients who experience grade 2 or higher HUS should receive appropriate supportive measures and fluid replacement, with monitoring of blood chemistry, complete blood counts, and renal function (including monitoring of serum creatinine and/or eGFR) until resolution.

Study characteristics [4, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
Study 1053 NCT01829711	80	moxetumomab pasudotox 40 µg/kg IV on days 1, 3, and 5 every 28 days for ≤6 cycles	-	durable complete response	pivotal, multicenter, single-arm open-label study	CD22	MedImmune	[7]

Efficacy

Median haemoglobin, neutrophil count, and platelet count: improved rapidly during treatment. Hematologic remission in about one month: achieved in 80% of patients (n=64/80); median 1.1 months, 95% CI, 1.0-1.2).
Durable complete response rate (at a median follow-up of 16.7 months; 2.1-48.8): 30% (n=24/80; 95% CI, 20.3-41.3)
Objective response rate: 75% (n=60/80; 95% CI, 64.1-84.0) based on BICR. **Complete response rate**: 41% (n=33/80; 95% CI, 30.4-52.8). 33 patients achieved CR, including elimination of leukemic cells in bone marrow by morphologic assessment; significant (>90%) reductions in bone marrow involvement were also observed in 29.6% of patients achieving PR (n=8/27). **Average spleen size**: decreased during treatment, and among patients with baseline splenomegaly (17 cm or larger), 6 (42.9%) resolved to 14 cm or smaller.
Most (n=28/33) CRs were achieved at the end of treatment disease assessment; 5 patients achieved CR at disease assessment 6 after the end of treatment.
Median duration of hematologic remission from CR, median duration of CR, and median PFS: not reached.
6 patients relapsed from CR as of the data cut-off; 4 had asymptomatic relapse with only reappearance of hairy cells in the bone marrow with normal haematological counts and 2 had loss of hematologic remission. Among complete responders, 27 (85%) patients achieved **minimal residual disease negativity** as assessed by immunohistochemistry.
Median duration of CR for minimal residual disease-positive patients: 5.9 months.
Median duration of CR for minimal residual disease-negative patients: not reached.

UPDATE (at the time of **final analysis** - cut-off date of 29 April 2019 - the median follow-up was 24.6 months) [6]:
Durable CR: 36%, 95% CI, 26-48
CR with HR ≥360 days: 33%, 95% CI, 22-44
Best overall response:
CR[1]: 41%, 95% CI, 30-53
OR rate: 75%, 95% CI, 64-84
Partial response[2]: 34%
Stable disease[3]: 15%
Median duration of response, months (range): 66.7 (0+ to 66.7)
Of the 33 patients who achieved IRC-assessed CR, 82% were MRD-negative and 89.7% who achieved a durable CR were MRD-negative. The median duration of CR was 12.0 months for MRD-positive patients (n = 6) and 62.8 months for MRD-negative patients (n = 27).

Safety

AEs (not including serious AEs): n=77/80 (96.25%)
SAEs: n=28/80 (35%)
Death[4]: n=3
Discontinuation[5]: n=12/80 (15%)

HUS occurred in 8.8% of patients, including grade 3 in 5.0% and grade 4 in 1.3%.

CLS occurred in 8.8% of patients, the majority were grade 2. There were 2.5% grade 4 events.

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**
no	no	no, open-label	yes	yes[6]	high

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[1] CR defined as clearing of the bone marrow of hairy cells by routine haematoxylin & eosin stain, radiologic resolution of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission.
[2] Partial response defined as ≥ 50% decrease or normalisation (<500/mm3) in peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission.
[3] Stable disease defined as ≥ 50% decrease of peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission or 50% improvement over baseline for haematologic parameters if not meeting haematologic remission criteria.
[4] 3 deaths occurred on study due to pneumonia, septic shock, and sepsis syndrome and underlying HCL; none were considered treatment related.
[5] Adverse reactions resulting in permanent discontinuation.
[6] The study and manuscript were funded by the sponsor. Employees of the sponsor were involved in the study design, the collection, analysis, and interpretation of data, the review of the manuscript, and the decision to submit for publication.

Abbreviations: AE=adverse event, AJ=adjustment, ASCT=allogeneic stem cell transplantation, BICR=blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLS=capillary leak syndrome, CR=complete response, CrCl=creatinine clearance, eGFR=estimated glomerular filtration rate, 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, HCL=hairy cell leukaemia, HR=haematologic remission, , HUS=haemolytic uremic syndrome, I=intervention, Int.=intention, IV=intravenously, n=number, MG=median gain, MRD=minimal residual disease, n=number of patients, OR=overall response, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PNA=purine nucleoside analogue, PR=partial response, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

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