Mosunetuzumab (Lunsumio®) as monotherapy for the treatment of relapsed or refractory follicular lymphoma (FL)

General information [1]

Drug description	Indication
Mosunetuzumab (Lunsumio®) is a bispecific monoclonal antibody which simultaneously binds to CD20 on B cells and CD3 on T cells, thereby inducing the death of malignant B cells.	Mosunetuzumab (Lunsumio®) as monotherapy is indicated for the treatment of adult patients with relapsed or refractory FL who have received at least two prior systemic therapies.

Current treatment [2]

- The NICE recommendation for treating relapsed or refractory FL that has progressed up to 6 months post treatment or did not respond to rituximab or a rituximab containing regimen or recommends that obinutuzumab with bendamustine be administered followed by obinutuzumab maintenance.
- According to ESMO guidelines, in early relapses of asymptomatic cases in FL, a non-cross-resistant scheme is the preferred treatment (e.g. bendamustine after CHOP or vice versa).
- In symptomatic cases with low tumour burden, rituximab monotherapy may be applied.
- In later relapses, monotherapy is a well established option with palliative intent, survival can be achieved long-term.

Regulatory status

EMA [1, 3]	FDA [4]
Approval status for this indication: On 22 April 2022, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Lunsumio®. Lunsumio® was reviewed under EMA's accelerated assessment programme. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 03/06/2022 The full indication is: ❖ Lunsumio® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory FL who have received at least two prior systemic therapies **Other indications**: none ✓ **Medicine received a conditional marketing authorisation**[1] ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 14 July, 2020, the FDA granted breakthrough therapy designation to mosunetuzumab for the treatment of adult patients with relapsed or refractory FL who have received at least two prior systemic therapies. UPDATE [5] : The FDA has accepted the submission of a biologics license application for mosunetuzumab (Lunsumio®) and granted it priority review for the treatment of adults with relapsed or refractory FL who have received at least 2 prior systemic therapies. **Other indications**: none

Costs [6]

Lunsumio® concentrate for solution for infusion 1 mg/ml = € 244.00 (ex-factory price)
Lunsumio® concentrate for solution for infusion 30 mg/30ml = € 7,327.00 (ex-factory price)

Posology [7]

- Lunsumio® must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, in a setting with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS).
- **Prophylaxis and premedication:**

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- Lunsumio® should be administered to well-hydrated patients.
- Patients requiring premedication:
    - Cycles 1 and 2: all patients.
    - Cycles 3 and beyond: patients who experienced any grade CRS with previous dose.
- Intravenous corticosteroids:
    - Dexamethasone 20 mg or methylprednisolone 80 mg (complete at least 1 hour prior to Lunsumio® infusion).
- Anti-histamine: 50-100 mg:
    - Diphenhydramine hydrochloride or equivalent oral or intravenous anti-histamine (at least 30 minutes prior to Lunsumio® infusion.

Anti-pyretic: 500-1000 mg paracetamol (at least 30 minutes prior to Lunsumio® infusion.

Special warnings and precautions for use [7]

❖ **Traceability**
- In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

❖ **CRS**
- CRS, including life-threatening reactions, have occurred in patients receiving Lunsumio®.
- Signs and symptoms included pyrexia, chills, hypotension, tachycardia, hypoxia, and headache.
- Infusion related reactions may be clinically indistinguishable from manifestations of CRS. CRS events occurred predominantly in cycle 1 and were mainly associated with Day 1 and Day 15 dose administrations.
- Patients should be premedicated with corticosteroids, antipyretics and antihistamines at least through cycle 2.
- Patients must receive adequate hydration prior to the administration of Lunsumio®.
- Patients should be monitored for signs or symptoms of CRS. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. Physicians should institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated.

❖ **Serious infections**
- Serious infections such as pneumonia, bacteraemia, and sepsis or septic shock have occurred in patients receiving Lunsumio®, some of which were life-threatening or fatal events.
- Febrile neutropenia was observed in patients after receiving Lunsumio® infusion.
- Lunsumio® should not be administered in the presence of active infections. Caution should be exercised when considering the use of Lunsumio® in patients with a history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus), with underlying conditions that may predispose to infections or who have had significant prior immunosuppressive treatment.
- Patients should be administered prophylactic antibacterial, antiviral and/or antifungal medicinal products, as appropriate.
- Patients should be monitored for signs and symptoms of infection, before and after Lunsumio® administration, and treated appropriately.
- In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines.

❖ **Tumour flare**
- Tumour flare has been reported in patients treated with Lunsumio®.
- Manifestations included new or worsening pleural effusions, localised pain and swelling at the sites of lymphoma lesions and tumour inflammation. Consistent with the mechanism of action of Lunsumio®, tumour flare is likely due to the influx of T-cells into tumour sites following Lunsumio® administration.
- There are no specific risk factors for tumour flare that have been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ.
- Patients treated with Lunsumio® should be monitored and evaluated for tumour flare at critical anatomical sites.

❖ **Tumour lysis syndrome (TLS)**
- TLS has been reported in patients receiving Lunsumio®.
- Patients must have adequate hydration prior to the administration of Lunsumio®. Patients should be administered prophylactic anti-hyperuricemic therapy (e.g allopurinol, rasburicase), as appropriate. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

❖ **Immunisation**
- Live and/or live-attenuated vaccines should not be given concurrently with Lunsumio®. Studies have not been conducted in patients who recently received live vaccines.

❖ **Patient card**

The prescriber must discuss the risks of Lunsumio® therapy with the patient. The patient should be provided with the patient card and instructed to carry it at all times. The patient card describes the common signs and symptoms of CRS, and provides instructions on when a patient should seek medical attention.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
NCT02500407, GO29781	Group A (n=33) Group B (n=197)	mosunetuzumab IV in 3-week cycles, at full dose in cycle 1 day 1 (group A) or with ascending (step-up) doses during cycle 1 on days 1, 8, and 15 (group B), for 8 or 17 cycles on the basis of tumour response[2]	-	safety, tolerability, pharmacokinetics, and to determine the recommended phase II dose, maximum tolerated dose, and dose-limiting toxicities	**ongoing[3],** phase I and Ib multicenter, open-label, dose-escalation, and expansion study	-	Genentech, Inc.	[10]

Efficacy

Group B patients with aggressive B-NHL (n=129)

Best ORR: 34.9%
CR rate: 19.4%
Median DOR for all responders and complete responders: 7.6 (95% CI, 5.6-22.8) and 22.8 (95% CI, 7.6-NE) months, respectively.
Median time to first response:1.4 months (range, 1.1-13.8)
Median PFS across all dose levels: 1.4 months (95% CI, 1.4-2.9)

Group B patients with indolent B-NHL (n=68)

ORR: 66.2%
CR rate: 48.5%
Median DOR for all and complete responders: 16.8 (95% CI, 11.7-NE) and 20.4 (95% CI, 16.0-NE) months, respectively.
Median time to first response: 2.6 months (range, 1.2-7.5)
Median PFS across all dose levels: 11.8 months (95% CI, 8.4-NE)

ORR in patients with indolent (n=4) or aggressive NHL (n=15) and **prior CAR-T therapy**: 36.8%; **CRs**: 26.3%
CR rates in patients with FL refractory to both a prior anti-CD20 antibody and alkylating agent (55.9%) and in those with progressive disease within 24 months of starting first-line therapy (54.5%).

PK and exposure-response relationships

- The mosunetuzumab concentration increased in an approx. dose-proportional manner over the dose range of 0.05-60 mg.

Safety

Group A, safety population (n=33)

Any AE: 32/33 (97.0)
Treatment-related AEs: 24/33 (72.7%)
Serious AEs (not including grade 5 malignant neoplasm progression): 7/33 (21.2%)
Treatment-related serious AEs: 2/33 (6.1%)
Grade 5 (fatal) AEs (not including grade 5 malignant neoplasm progression): 1/33 (3.0%)
Any AE leading to mosunetuzumab discontinuation: 1/33 (3.0%)
Treatment-related AE leading to mosunetuzumab treatment discontinuation: 1/33 (3.0%)

Group B, safety population (n=197)

Treatment-related AEs: 146/197 (74.1%)
Serious AEs (not including grade 5 malignant neoplasm progression): 69/197 (35.0%)
Treatment-related serious AEs: 36/197 (18.3%)
Grade 5 (fatal) AEs (not including grade 5 malignant neoplasm progression): 3/197 (1.5%)

[2] Doses up to 2.8 mg and 60 mg were assessed in groups A and B, respectively; maximum tolerated dose was not exceeded.
[3] NCT02500407 is currently ongoing; estimated study completion date is 03/2023.

- The apparent half-life was approximately 6-11 days.
- The PK profile of IV mosunetuzumab was described by a two-compartment PK model with time-dependent clearance.
- The estimated serum clearance was approximately 1 L/d at baseline and reduced to an average steady state of approximately 0.5 L/d over a transitional half-life of 21 days; this is higher than the expected range for a typical immunoglobulin G1 antibody, indicating a potential impact of target-mediated drug disposition.
- Exposure-response analyses indicated positive relationships between PK exposure (CD20 RO% and AUC averaged over the initial 42 days of treatment for aggressive and indolent NHL, respectively) and CR rates or ORRs.
- Observed CR rates and ORRs in the top exposure quartiles were 35% (n=12/34) and 56% (n=19/34), respectively, in patients with aggressive NHL, and 65% (n=13/20) and 75% (n=15/20), respectively, in patients with indolent NHL.
- In group A, there was a trend for an increase in grade ≥2 CRS with maximal RO% over the initial 42 days of treatment (RO_{max} days 0-42), which was largely mitigated when using cycle 1 step-up dosing, resulting in a broader therapeutic index.

Pharmacodynamics

- Mosunetuzumab treatment induced T-cell activation in peripheral blood.
- Patients experiencing CRS had a trend for higher interleukin-6 peak induction, which was observed primarily after day 1 dosing.

UPDATE: Efficacy in patients with relapsed or refractory FL (clinical cut-off: 27 August 2021, median observation time 18.3 months, n=90) [3]

CR: 60%
ORR: 80.0%
PR: 20.0%
Median DOR: 22.8 months (9.7, NR)
Median duration of complete response: NR

Any AE leading to mosunetuzumab treatment discontinuation: 11/197 (5.6%)
Treatment-related AE leading to mosunetuzumab treatment discontinuation: 7/197 (3.6%)

Group B, prior CAR-T therapy (n=19)
Any AE: 19/19 (100.0%)
Treatment-related AEs: 13/19 (68.4%)
Serious AEs (not including grade 5 malignant neoplasm progression): 12/19 (63.2%)
Treatment-related serious AEs: 5/19 (26.3%)
Grade 5 (fatal) AEs (not including grade 5 malignant neoplasm progression): 1/19 (5.3%)
Any AE leading to mosunetuzumab discontinuation: 1/19 (5.3%)
Treatment-related AE leading to mosunetuzumab treatment discontinuation: 0

Risk of bias - study level (case series) [12]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	unclear	yes	partial	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	partial	unclear	no	yes	unclear	yes
Overall risk of bias: moderate								

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Abbreviations: AE=adverse event, AJ=adjustment, AUC=Area under the concentration-time curve, NHL=B-cell non Hodgkin lymphoma, C=comparator, CAR-T=chimeric antigen receptor T cell, CHMP=Committee for Medicinal Products for Human Use, CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone, CI=confidence interval, CR=complete response, CRS=cytokine release syndrome, DOR=duration of response, EMA=European Medicines Agency, ESMO-MCBS=

European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FL=follicular lymphoma, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NE=not estimable, NHL=non-Hodgkin lymphoma, NICE=National Institute for Health and Care Excellence, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PK=pharmacokinetics, PM=preliminary grade, QoL=quality of life, RO=average CD20 receptor occupancy, SAE=serious adverse event, ST=standard treatment, TLS=tumour lysis syndrome

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