Tafasitamab (Minjuvi®/Monjuvi®) for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem-cell transplant (ASCT)

General information

Drug description [1]	Indication [2]
Tafasitamab (Minjuvi®/Monjuvi®, MOR208, previously XmAb5574) is an Fc-enhanced, humanised, anti-CD19 monoclonal antibody, which mediates antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and exerts direct cytotoxicity.	Tafasitamab (Minjuvi®/Monjuvi®) is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

Current treatment [3]

- The most commonly used salvage treatment regimens for relapsed or refractory DLBCL include:
  - R-GDP – rituximab with gemcitabine, dexamethasone and cisplatin
  - R-DHAP – rituximab with dexamethasone, high-dose cytarabine and cisplatin
  - R-ICE – rituximab with ifosfamide, carboplatin and etoposide.
- For adults whose DLBCL is relapsed or refractory after 2 or more systemic therapies NICE recommends:
  - Tisagenlecleucel
  - Axicabtagene ciloleucel

Regulatory status

EMA [2]	FDA [4]
Approval status for this indication: On 24 June 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Minjuvi®. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 26/08/2021 <u>The full indication is:</u> Minjuvi® is indicated in combination with lenalidomide followed by Minjuvi® monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT. ✓ **Orphan status** ✓ **Medicine is under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1] **Other indications:** none	**Approval status for this indication**: On 31 July 2020, the FDA granted accelerated approval to tafasitamab-cxix (Monjuvi®), indicated in combination with lenalidomide for adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are not eligible for ASCT. ✓ **Indication approved under accelerated approval** based on overall response rate ✓ **Priority review, fast track, breakthrough, and orphan product designation** **Other indications:** none

Costs

Minjuvi® powder for concentrate for solution for infusion 200 mg = € 782.00 [5]

Warnings and precautions [6]

- **Infusion-related reactions**
  - Monitor patients frequently during infusion. Interrupt or discontinue infusion based on severity.
- **Myelosuppression**

[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.

- Monitor complete blood counts. Manage using dose modifications and growth factor support.
- Interrupt or discontinue Monjuvi® based on severity.

❖ **Infections**
- Bacterial, fungal and viral infections can occur during and following Monjuvi®.
- Monitor patients for infections.

❖ **Embryo-foetal toxicity**
- May cause foetal harm.
- Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.

Recommended premedications [6]

❖ Administer premedications 30 minutes to 2 hours prior to starting Monjuvi® infusion to minimise infusion-related reactions.
❖ Premedications may include acetaminophen, histamine H1 receptor antagonists, histamine H2 receptor antagonists, and/or glucocorticosteroids.
❖ For patients not experiencing infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions.
❖ If a patient experiences an infusion-related reaction, administer premedications before each subsequent infusion.

Study characteristics [1, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
L-MIND NCT02399085	81	coadministered tafasitamab (12 mg/kg IV) and oral lenalidomide (25 mg/day) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy	-	proportion of patients with an objective response (complete or partial response according to the 2007 International Working Group response criteria)	multicentre, open-label, single-arm, phase 2 study	-	MorphoSys	[1]

Efficacy (n=80)

Patients treated with tafasitamab plus lenalidomide:
Objective response (complete + partial response): n=48/80 (60%); 95% CI, 48–71
Complete response: n=34/80 (43%)
Partial response: n=14/80 (18%)
Median time to initial response (partial or complete): 2.0 months (IQR 1.9–3.1)
Disease control: n=59/80 (74%; 95% CI, 63–83)
PET-confirmed complete response: 30/34 (88%; 95% CI, 73–97)
7 patients had diffuse large B-cell lymphoma arising from a previous indolent lymphoma. All seven of these patients responded to the tafasitamab plus lenalidomide treatment; n=2/7 (29%) had a complete response and n=5/7 (71%) had a partial response; the 2 patients who had a complete response as best response were still in remission at data cut-off.
Median duration of response in the 48 patients who achieved an objective response: 21.7 months (95% CI, 21.7-not reached)

Safety (n=81)

TEAEs of any grade: n=81/81 (100%)
AEs of grade 3 or 4 before lenalidomide discontinuation: n=56/80 (70%)
AEs of grade 3 or 4 after lenalidomide discontinuation: n=15/51 (29%)
SAEs: n=41/81 (51%)
SAEs suspected to be treatment-related by the investigators: n=15/81 (19%)
Infusion-related reactions (all grade 1): n=5/81 (6%)
Death: n=30/81 (37%)[2]
TEAEs leading to death: n=4/30 (13%)[3]

[2] 8 patients died during study treatment and 22 patients died post-treatment; 77% of the 30 deaths were related to lymphoma progression and 23% were unrelated to disease progression.
[3] The investigators did not consider any of these 4 TEAEs to be related to study treatment.

PFS event after initially having an objective response: n=13/48 (27%)
Proportion of patients with a response lasting 12 months: 72% (95% CI, 55–83)
Median duration of response among the 34 patients with a complete response: not reached; patients with a PFS event after initially having a complete response: 9%; the proportion of patients with a response lasting 12 months and 18 months was the same at 93% (95% CI, 75–98).
Median duration of response for the 18% with a partial response: 4.4 months (95% CI, 2.0–9.1); n=10/14 (71%) had a PFS event after initially having a partial response.
PFS event (disease progression or death): n=39/80 (49%)
Median PFS (at a median follow-up of 17.3 months): 12.1 months (95% CI, 5.7-not reached)
12-month PFS: 50% (95% CI, 38–61)
18-month PFS: 46% (95% CI, 33–57)
Median PFS after discontinuation of lenalidomide: 12.7 months (95% CI, 2.3-not reached)
Median time to progression: 16.2 months (95% CI, 7.4-not reached), with disease progression events occurring in 44%
Median time to next treatment: 15.4 months (95% CI, 7.6-not reached); 54% of patients received subsequent treatment
At a median follow-up of 19.6 months: 36% of patients had died
Median overall survival: not reached (95% CI, 18.3-not reached); 74% of patients were alive at 12 months and 64% of patients were alive at 18 months; 38% remained in remission at data cut-off.

Long-term analysis (updated efficacy analysis with ≥35 months follow up; data cut-off 30 October 2020) [9]:
Objective response rate (complete response + partial response): n=46/80 (57.5%), 95%CI, 45.9–68.5
Complete response: n=32/80 (40.0%)
Partial response: n=14/80 (17.5%)
Median duration of response: 43.9 months (95% CI, 26.1–not reached)
Median PFS: 11.6 months (95% CI, 6.3–45.7)
Median OS: 33.5 months (95% CI, 18.3–NR)

Median overall duration of response (CR+PR): 43.9 (95% CI, 26.1-NR)
Median OS (after a median follow-up time of 42.7 months): 31.6 months (95% CI, 18.3-NR) [10]

Risk of bias - study level (case series) [11]

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	yes	yes	yes	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	yes	no	yes	yes	unclear[4]	yes
Overall risk of bias: moderate risk								

[4] Primary analysis data; L-MIND trial is currently ongoing. Estimated study completion date is 11/2022.

Abbreviations: AE=adverse event, AJ=adjustment, ASCT=autologous stem-cell transplant, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DLBCL=diffuse large B-cell lymphoma, 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, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NR=not reached, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAEs=treatment-emergent adverse events

References:

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