SMC2522

tafasitamab powder for concentrate for solution for infusion (Minjuvi®)

Incyte Pharmaceuticals Limited

07 April 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

tafasitamab (Minjuvi®) is not recommended for use within NHSScotland.

Indication Under Review: 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).

In an open-label, uncontrolled, phase II study in patients with relapsed or refractory DLBCL who were ineligible for ASCT, tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy was associated with an objective response rate of 60%.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tafasitamab is a fragment crystallisable(Fc)-enhanced monoclonal antibody that targets and binds to the CD19 antigen on B lymphocytes causing B-cell lysis through the engagement of immune effector cells such as natural killer cells and phagocytes and the direct induction of cell death. The Fc modification causes enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis compared with the unmodified antibody.[1, 2]

The recommended dose of tafasitamab is 12mg per kg body weight administered as an intravenous infusion in 28 day cycles according to the schedule in the Summary of Product Characteristics (SPC). In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 25mg daily on days 1 to 21 of each cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide SPC.

1.2. Disease background

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma and accounts for up to 58% of all cases. Approximately 5,500 people are diagnosed with the disease in the UK each year; the incidence increases with age with most people aged over 65 years. Risk factors include a family history of lymphoma, autoimmune disease, human immunodeficiency virus infection, hepatitis C viral seropositivity, a high body mass as a young adult and some occupational exposures. Approximately half of newly diagnosed patients with DLBCL receive curative treatment. However, the disease is aggressive and approximately 30% of cases relapse and 10% to 15% are refractory to first-line therapy. The prognosis is poor for patients who are ineligible for autologous stem cell transplant (ASCT) or have refractory disease after any line of treatment with a median overall survival of 6 to 11 months and 6.1 to 7.1 months respectively.[2-4]

1.3. Treatment pathway and relevant comparators

Guidelines recommend salvage chemotherapy followed by high dose chemotherapy and ASCT for fit patients who relapse following first line therapy, however most patients are ineligible because of age or co-morbidities. Selected patients who relapse following ASCT may receive an allogenic stem cell transplant. In transplant ineligible patients, the aim of treatment is to induce disease control and remission for as long as possible to prolong survival. Treatment options include off-label platinum and/or gemcitabine salvage chemotherapy; however, there is no optimal regimen. Other options include entry into clinical studies or palliative care.[2, 3] Since the publication of these guidelines, polatuzumab vedotin in combination with bendamustine and rituximab has been licenced and approved by SMC on an interim basis for the treatment of adult patients with relapsed or refractory DLBCL who are not candidates for haematopoietic stem cell transplant (SMC2282). Chimeric antigen receptor (CAR)-Tcell therapies, axicabtagene ciloleucel and tisagenecleucel, are also licensed and approved by SMC for relapsed or refractory DLBCL, after two or more lines of systemic therapy (SMC2189 and SMC2200). In clinical practice, their use is limited by the complex and timely manufacturing process, patient tolerability of the conditioning regimen and risk of adverse events.[2] Clinical experts consulted by SMC indicated that polatuzumab vedotin plus bendamustine and rituximab is currently the predominant treatment for the indication under

review and that gemcitabine or etoposide chemotherapy regimens may also be used for some patients. These are likely to represent the most relevant comparators for this submission.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Tafasitamab has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Eligibility for a PACE meeting

Tafasitamab meets SMC end of life and orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the indication under review is from the L-MIND study as described in table 2.1.[5, 6]

Table 2.1. Overview of relevant studies

Criteria	L-MIND[5, 6]
Study Design	Multicentre, open-label, single-arm, phase II study
Eligible Patients	• Adult patients with histologically confirmed DLBCL. • Measurable disease at baseline. • Relapsed and/or refractory disease according to International Working Group (IWG) response criteria following at least one but no more than three systemic treatments including at least one anti-CD20 therapy. • Ineligible for high dose chemotherapy and ASCT. • Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
Treatments	Intravenous (IV) tafasitamab plus oral lenalidomide for up to twelve 28-day cycles, followed by tafasitamab monotherapy until disease progression or unacceptable toxicity. Tafasitamab 12mg/kg was administered by IV infusion on days 1, 8, 15 and 22 of cycles one to three (an additional loading dose was administered on day 4 of cycle one). From cycle four, tafasitamab was administered on days 1 and 15 of each cycle. Lenalidomide 25mg orally was self-administered on days 1 to 21 of each 28-day cycle
Primary outcome	Objective response rate, defined as the proportion of patients with a complete or partial response as assessed by an independent review committee (IRC) according to the 2007 International Working Group response criteria for malignant lymphoma
Secondary outcomes	Duration of response, progression free survival and overall survival
Statistical analysis	Efficacy analysis were conducted in the full analysis set (all patients who had received at least one dose of both tafasitamab and lenalidomide). Descriptive statistics only.

The primary analysis for the L-MIND study was conducted after a median of 13.2 months follow-up (data cut-off: 30 November 2018). An objective response was achieved by 60% of patients in the full analysis set (FAS). The submitting company provided updated results from a planned interim analysis conducted after at least 35 months of follow-up for all patients (data cut-off: 30 October 2020). The results from both data-cuts have been presented in table 2.2.[5, 6]

Table 2.2: Primary and selected secondary outcomes in the FAS of the L-MIND study[2, 5-7]

L-MIND FAS	Tafasitamab plus lenalidomide (n=80)	
Data cut-off	30 November 2018	30 October 2020
Primary outcome: objective response rate as assessed by IRC		
ORR, % (n)	60% (48)	58% (46)
Complete response, % (n)	42% (34)	40% (32)
Partial response, % (n)	18% (14)	18% (14)
Selected secondary outcomes		
Median duration of response[A]	21.7 months	43.9 months
Median PFS[B] follow-up	17.3 months	33.9 months
PFS events, n	39	42
Median PFS	12.1 months	11.6 months
KM estimated PFS at 18 months	46%	*
KM estimated PFS at 36 months	Not reported	*
Median OS follow-up	19.6 months	42.7 months
Deaths, n	29	*
Median OS	Not reached	33.5 months
KM estimated OS at 18 months	64%	*
KM estimated OS at 36 months	Not reported	*

FAS=full analysis set; IRC=independent review committee; KM=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival. [A]Kaplan-Meier estimated in the 48 patients who achieved an objective response. [B]PFS was assessed by IRC. *Kaplan-Meier estimates for PFS and OS were considered confidential by the company.

Subgroup analysis for objective response rate (ORR) based on age, gender, primary refractory disease and refractoriness to last prior therapy were generally consistent with the primary analysis and the updated analysis (data cut-off October2020).[2, 5, 7] At the November 2018 data-cut, the ORR was lower in patients with International Prognostic Index (IPI) intermediate to high risk and high risk disease (n=40; ORR: 50%), germinal centre B cell phenotype of origin (n=37; ORR: 49%) and at least two lines of prior therapy (n=40; ORR: 50%).

At the October 2020 data cut-off, compared with the FAS, the median PFS and overall survival were lower in the subgroups of patients with primary refractory disease, rituximab refractory disease and refractoriness to last prior therapy.[6]

*Other data were also assessed but remain confidential.**

2.2. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing tafasitamab and lenalidomide with polatuzumab vedotin, bendamustine and rituximab and chemotherapy regimens, the submitting company presented indirect treatment comparisons. The results included in table 2.3 have been used to inform the economic base case unless otherwise specified.

Table 2.3. Summary of indirect treatment comparison

Criteria	Overview
Design	Five unanchored matching adjusted indirect comparisons (MAICs) and a retrospective observational matched cohort study (RE-MIND2)[8, 9]
Population	Patients with relapsed or refractory DLBCL who are not eligible to receive ASCT
Comparators	Tafasitamab and lenalidomide (TAFA+LEN), polatuzumab, bendamustine and rituximab (POLA+BR), rituximab, gemcitabine and oxaliplatin (R-GemOx) and bendamustine and rituximab (BR).
Studies included	L-MIND[6] (TAFA-LEN); GO29365[10-12] (POLA+BR and BR); NCT01118845 [13], NCT00831597 [14] (BR); RE-MIND2[9] (R-GemOx and BR)
Outcomes	Overall survival, progression free survival (PFS) and independent review committee assessed progression free survival (IRC-PFS)
Results	<u>TAFA+LEN versus POLA+BR (Results from MAIC)</u> As the proportional hazard assumption was not satisfied, a time varying HR splitting at 4 months was used to inform the economic base case. From 4 months to the end of follow-up the evidence suggested that TAFA+LEN was superior to POLA+BR for overall survival and there was no evidence of a difference between treatments for IRC-PFS. • 0 to 4 months: overall survival: HR 1.82 (95% CI: 0.58 to 5.65); IRC-PFS: 1.42 (95% CI: 0.65 to 3.09) • 4 months to follow-up: overall survival: HR 0.41 (95% CI: 0.19 to 0.90); IRC-PFS HR 0.39 (95% CI: 0.14 to 1.06). <u>TAFA+LEN versus BR (results from MAIC)</u> Using a constant hazard ratio for overall survival and IRC-PFS the evidence suggests TAFA+LEN is superior to BR. • Overall survival: HR 0.39 (95% CI: 0.29 to 0.53); IRC-PFS (using pooled MAIC estimates) HR 0.39 (95% CI: 0.18 to 0.82) <u>TAFA-LEN versus R-GemOx (results from RE-MIND2)</u> The evidence suggests that TAFA-LEN is superior to R-GemOx for overall survival and PFS. • Overall survival HR: 0.47 (95% CI: 0.31 to 0.71); PFS: 0.43 (95% CI: 0.29 to 0.65) ** The constant hazard ratio for overall survival and IRC-PFS for the comparison between TAFA+LEN versus POLA-BR were considered confidential by the company.*
Company conclusion	The company concluded that statistically significant improvements in overall survival were seen in the MAIC with TAFA+LEN versus POLA+BR from 4 months to the end of follow up using a piecewise constant HR with splitting at the 4-month timepoint. From comparison with RE-MIND2, they concluded that clinically relevant, significant benefits were seen in overall survival in the TAFA+LEN cohort compared with the R-GemOx cohort and this was supported by a clinically relevant benefit in PFS.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Overall, the safety profile of tafasitamab was considered clinically manageable andmore safety data will be collected in the post marketing setting..[2] In the L-MIND study at data cut-off 30 November 2018, 37% (30/80) of patients had completed 12 cycles of tafasitamab and lenalidomide and 35% were still receiving tafasitamab monotherapy. The median duration of exposure to combination therapy or lenalidomide was 6.2 months and to tafasitamab 4.1 months. All patients experienced a treatment-emergent adverse event (AE) and 51% (41/81) of all patients reported a serious AE; serious adverse events that were considered to be treatment-related

occurred in 19% of patients. Combination study treatment was discontinued in 12%of patients due to AEs, and 25% discontinued one or both medicines due to AEs.[5]

The most frequently reported treatment-emergent AEs of any grade with an incidence ≥20% were: neutropenia (49%), all rash (36%), anaemia (35%), diarrhoea (33%), thrombocytopenia (31%), asthenia (24%), cough (22%), peripheral oedema (22%), pyrexia (21%) and decreased appetite (20%).[5] Adverse events of special interest associated with tafasitamab included infections, neutropenia and infusion-related reactions. Infections or infestations were reported in 73% of patients and were considered serious in 26%. Neutropenia occurred more frequently in patients receiving tafasitamab in combination with lenalidomide (49%) compared with the monotherapy extension phase (28%); the majority of neutropenic events (39/40; 98%) on combination therapy were grade 3 or higher. Most patients required granulocyte colony stimulating factor and neutrophil counts returned to baseline within one week in 81% (32/39). Infusion related-reactions were reported by 6.2% of patients; most were low-grade and manageable. See the SPC for further safety information.[1, 2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the L-MIND study, treatment with tafasitamab plus lenalidomide followed by tafasitamab monotherapy was associated with an IRC assessed ORR of 60% at the primary analysis after a median follow-up of 13.2 months; the median duration of response was 21.7 months and 42% of patients achieved a complete response. At a subsequent planned data-cut (October 2020) after all patients had at least 35 months follow-up, the ORR was 58%, median duration of response was 43.9 months and 40% achieved a complete response.[5, 6]

4.2. Key uncertainties

- L-MIND was a non-randomised single-arm study and therefore there are no controlled or direct data comparing efficacy and safety of tafasitamab plus lenalidomide with relevant comparators such as polatuzumab vedotin plus bendamustine and rituximab or salvage chemotherapy regimens. As part of the GB conditional marketing authorisation, the company will conduct an additional single-arm, open-label study of tafasitamab plus lenalidomide in patients with relapsed or refractory DLBCL (FIRM-MIND; NCT05429268[15]). However no further controlled or comparative studies with tafasitamab plus lenalidomide in the population under review have been planned.[15, 16]

- There were a number of limitations that affected the validity and robustness of the MAIC which included the unanchored designs with data derived mainly from relatively small single-arm studies and the sample sizes further decreased after matching. There were some prognostic variables that could not be matched and heterogeneity in study design that may have affected the relative effect estimates. The piecewise splitting approach of the HR at 4 months for the comparison between tafasitamab and lenalidomide and polatuzumab vedotin, bendamustine and rituximab could limit the accuracy of data applied in the economic evaluation, potentially exaggerating the survival advantage of

polatuzumab vedotin, bendamustine and rituximab in the short term and overestimating the long-term hazard. Limitations for the matched cohort study, RE-MIND2, include heterogeneity in study design which may confound survival estimates and the potential for treatment selection bias when using data from a retrospective real-world observational study. Due to these limitations the company's conclusions for the MAICs and comparisons with RE-MIND2 are highly uncertain.

- As L-MIND was a small study and tafasitamab can be used for any line of treatment in patients with relapsed or refractory disease, it is unclear if the study population accurately reflects patients who may receive treatment in Scottish clinical practice. Subgroup results for the primary outcome were generally consistent with the FAS including those refractory to rituximab or to last prior treatment. The ORR was slightly lower in patients with an IPI intermediate to high risk, germinal centre B cell phenotype of origin and at least two lines of prior therapy and survival outcomes were shorter in the subgroups of patients with refractory disease.[5, 6] However, L-MIND was not designed to detect differences between subgroups and patient numbers were low in some groups, therefore results should be interpreted with caution.
- In L-MIND, the majority (93%) of patients had received one or two prior lines of therapy, 80% did not have bulky disease and most patients (92%) had an ECOG performance status of 0 or 1.[5] The generalisability of study results to patients with poorer prognostic characteristics is uncertain.
- L-MIND had an open-label study design, which could introduce potential bias for subjective safety and efficacy outcomes. This risk was minimised for the primary outcome, which was assessed by IRC and according to IWG response criteria.
- As no formal statistical hypothesis was tested, the aim of the study was mainly exploratory and the resulting data are uncontrolled.[2]
- The study did not include health related quality of life outcomes and therefore the impact that tafasitamab and lenalidomide has on patients' quality of life is unknown.

4.3. GB conditional marketing authorisation specific obligations

The MHRA specific obligations are unlikely to address the key uncertainties in the clinical evidence presented; namely the lack of direct evidence with a relevant comparator in the population under review.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that tafasitamab plus lenalidomide could provide an additional treatment option that may be suitable for selected patients. It is likely to be used as per the licensed indication and may be considered at different points in the treatment pathway depending on individual patient characteristics, eligibility for alternative therapeutic options, and previous treatments received.

4.5. Service implications

The introduction of tafasitamab plus lenalidomide is likely to require additional clinical and pharmacy resource to prepare, administer and to monitor and treat adverse events, particularly as tafasitamab monotherapy is continued until unacceptable toxicity or disease progression. The ease of administration associated with the oral formulation of lenalidomide may be advantageous to some patients. Patient numbers are expected to be low.

5. Patient and clinician engagement PACE

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of tafasitamab, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Diffuse large B-cell lymphoma (DLBCL) is a rare and aggressive disease. Many patients relapse or are refractory to first line treatment and around half of these are unsuitable for ASCT; the prognosis for this patient population is poor. The symptom burden associated with the disease and first line chemotherapy is high and has a profound effect on the physical and psychological wellbeing of the patient.

- There is an unmet need for further treatments for patients with relapsed or refractory DLBCL who are ineligible for ASCT, particularly if they can be sequenced with current therapies or they provide an option for patients unsuitable for existing treatments. The introduction of tafasitamab plus lenalidomide would provide an additional treatment that could potentially improve response rates and survival outcomes for a proportion of patients.

- The availability of this treatment could improve the symptom burden and allow patients to spend more quality time with their family and friends, which may lead to improvements in quality of life. Additional hospital visits are likely to be required for administration tafasitamab; however, these can be conducted in the outpatient setting.

- Although the safety profile of tafasitamab plus lenalidomide appears relatively tolerable, it is associated with adverse events and some patients may experience serious adverse events that require hospital admission. Patients may be may be prepared to tolerate toxicities to achieve the potential benefit with treatment.

- As tafasitamab is continued until disease progression or unacceptable toxicity, additional capacity in haematology day units will be required and there may be workload implications for staff to prepare and administer the medicine and to monitor and treat adverse events.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years,

including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (45 years)
Population	Patients with relapsed or refractory DLBCL ineligible for ASCT, in line with the marketing authorisation for tafasitamab with lenalidomide (TAFA+LEN) and the patient population enrolled in the L-MIND study.
Comparators	TAFA+LEN is compared against the following three comparators: polatuzumab vedotin plus bendamustine and rituximab (POLA+BR), gemcitabine and oxaliplatin plus rituximab (R-GemOx), and bendamustine plus rituximab (BR). Clinical experts consulted by the SMC considered POLA+BR the preferred treatment for this indication and one that could be displaced, but could also be given as an additional line of therapy.
Model description	The economic analysis used a partitioned survival model with three health states (progression free, progressed, and death), applying a four-week cycle length, with patients entering the model at a median age of 69.3 years. The model adopts an NHS Scotland and social care perspective.
Clinical data	The primary source of clinical data for TAFA+LEN in the economic model was the L-MIND study, based on results from the 30th October 2020 data cut (representing 42.7 months follow-up for overall survival). In the absence of direct evidence, efficacy data for comparators were generated from two key sources: RE-MIND2[9, 17], where 1:1 nearest neighbour matching (using propensity scores) of subsets of patients from L-MIND vs. retrospective real-world patients[18, 19] on comparator therapies was performed, and a MAIC against available clinical trial data (Mounier et al. 2013[20] for R-GemOx, GO29365[10, 11] for POLA+BR, and GO29365[10, 11] & Ohmachi et al 2013[13] for BR). RE-MIND2 was selected in the base-case for R-GemOx, as there was poor overlap of the patient populations in L-MIND and the Mounier et al. 2013 study. The MAIC was selected for POLA+BR and BR in the base-case analysis.
Extrapolation	To estimate long-term efficacy of the intervention, data from the L-MIND clinical study report were extrapolated by fitting parametric curves for overall survival (OS) and PFS with TAFA+LEN and for time to treatment discontinuation (TTD) of TAFA (the TTD KM estimates were used directly for LEN), with the best fitting curve selected based on statistical fit, visual fit and clinical expert validation. In each case, a log-normal distribution was chosen in the base case. Independent log-normal distributions (fitted to the RE-MIND2 data) were also chosen to extrapolate OS and PFS for R-GemOx in the base case. The KM curve from Re-MIND 2 was used for TTD of R-GemOx. Time-varying OS and PFS HRs from the MAIC were used for POLA+BR, with a 4-month split applied in the base case, while constant HRs from the MAIC were used for BR. TTD of POLA+BR and BR was modelled by

	exponential distributions fitted to the median treatment durations from TA649. OS does not appear to have been capped by general population background mortality in the model.
Quality of life	Health related quality of life (HRQoL) data were not collected in the L-MIND trial. Instead, the base case utility values were sourced from the National Institute for Health and Care Excellence (NICE) appraisal for axicabtagene ciloleucel (TA559): the estimates were 0.72 for PFS and 0.65 for PD. The estimates were based on a population receiving CAR-T and so may not be generalisable to the L-MIND population. However clinical experts in Scotland consulted by the company indicated that the values were reasonable given their use in prior technology appraisals (such as SMC2282 and the NICE TA649). Alternative values from NICE TA567 (0.83 for PFS, 0.71 for PD) were explored in a scenario analysis. QoL loss from subsequent CAR-T therapy was included resulting in a quality-adjusted life year (QALY) loss of 0.0083 per patient receiving CAR-T (Lin et al. 2019[21]). Exclusion of CAR-T as a subsequent treatment was explored in a scenario analysis. QoL loss related to AEs was applied as a one-off QALY loss
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, co-medication, monitoring, health-state specific disease management, subsequent treatments, adverse events and terminal care. The proportions of patients receiving subsequent treatment were based on the full analysis set for RE-MIND2, except for CAR-T where the proportions were estimated using the matched RE-MIND2 patient population. This method resulted in no patients on TAFA+LEN receiving subsequent CAR-T, compared with 5.1%, 4.0% and 4.1% of patients following treatment with POLA+BR, BR and R-GemOx respectively.
PAS	A PAS was submitted by the company, with a discount offered on the list price for tafasitamab. The company estimated a price discount for lenalidomide due to the availability of generic versions. Discounts for generic versions cannot be considered for decision making, so the price with PAS of the branded lenalidomide treatment (Revlimid®) was used. PAS discounts are in place for polatuzumab vedotin, rituximab and (subsequent treatment) tisagenlecleucel, which were included in the results used for decision-making.

6.2. Results

The results presented do not take account of the PAS for comparator medicines or the PAS for tafasitamab but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for comparator medicines due to commercial confidentiality and competition law issues.

The base case results using list prices are presented in Table 6.2. The total costs for TAFA+LEN were higher than those for the comparators, primarily due to the higher medicine acquisition costs. The costs of disease management with TAFA+LEN were also higher. Most of the QALY gains associated with TAFA+LEN were accrued in the progression free health state.

Table 6.2. Base-case CE Results (list price)

Intervention	Total costs	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	£421,021	5.04	3.23	--	--	--	--
POLA+BR	£145,875	2.20	1.42	£275,146	2.84	1.80	£152,442
BR	£68,331	1.59	1.02	£352,690	3.45	2.20	£160,144
R-GemOx	£63,375	1.82	1.16	£357,646	3.22	2.06	£173,486

Abbreviations: BR = bendamustine and rituximab; CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis, the ICER was very sensitive to variation in the OS hazard ratio after 4-months for the comparison vs POLA+BR and to the log-normal parameters for TTD of TAFA for the comparisons vs BR and vs R-GemOx. A range of scenario analyses were performed, with the most plausible scenarios and those with increased uncertainty presented in Table 6.3.

Table 6.3 Key scenario analyses results (list price)

Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
-	Base-Case	£152,442	£160,144	£173,486
1	25-year time horizon	£151,792	£159,722	£173,157
2	Apply constant MAIC HRs for OS & PFS	£256,513	£160,144	£184,821
3	OS parametric model for TAFA+LEN and R-GemOx: Generalized gamma	£148,354	£154,501	£166,060
4	PFS parametric model for TAFA+LEN and R-GemOx: Generalized gamma	£142,753	£148,962	£156,487
5	RE-MIND2 survival data for POLA+BR & BR (lognormal for OS & PFS, TTD KM data)	£119,729	£163,412	£173,486
6	Exclude CAR-T as a subsequent treatment	£160,163	£165,334	£179,172
7	6.2% patients require maintenance co-medications for TAFA+LEN	£153,217	£160,779	£174,164
8	Utility of 0.83 for PFS and 0.71 for PD based on NICE TA567	£133,474	£140,138	£151,419
2, 7	Apply constant MAIC HRs for OS & PFS and 6.2% require maintenance co-medications alongside TAFA+LEN	£257,871	£160,779	£174,164

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; POLA+BR = polatuzumab

vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = Tafasitamab + lenalidomide; TTD = time to treatment discontinuation

6.4. Key strengths

The cost-effectiveness model informing the pharmaco-economic evaluation was well-built and allowed a wide range of sensitivity/scenario analyses to be performed. Appropriate sources were selected to inform the model parameters and reasonable methods were used for the indirect treatment comparisons. The structure of the model was appropriate and systematic literature reviews were conducted to identify previous publications reporting economic evidence or HRQoL data for patients with DLBCL.

6.5. Key uncertainties

The main weaknesses of the economic analysis were:

- The lack of direct evidence comparing the efficacy of TAFA+LEN against the comparators. While two reasonable methods were adopted to estimate comparative efficacy data, neither approach was deemed appropriate for all of the comparators; the MAIC was not selected for R-GemOx in the base-case as there was poor overlap of the patient populations in L-MIND and the Mounier et al. 2013 study, while the RE-MIND2 analysis resulted in more pessimistic survival predictions for POLA+BR and BR. Less than 50% of the 81 patients in the L-MIND population were matched against patients receiving POLA+BR in the RE-MIND2 post-hoc analyses. The use of the MAIC for the comparisons against POLA+BR and BR required the assumption of proportional hazards (albeit with different HRs before and after 4 months in base-case).
- A time-varying HR was used for the comparison against POLA+BR, with a structural break at month 4. Comparing the extrapolated OS curve for POLA+BR against the reported estimates, this approach appears to exaggerate the survival advantage of POLA+BR in the short term while overestimating the long-term hazard. Overall, this would overestimate the incremental life-years gained in the comparison against POLA+BR and so lead to an optimistic cost-effectiveness estimate for this comparison. A scenario with constant HRs for OS and PFS has been explored (scenario 2).
- A different method was used for estimating the proportions of patients receiving CAR-T than for the subsequent treatments, which resulted 5.1%, 4.0% and 4.1% of patients receiving CAR-T following POLA+BR, BR and R-GemOx, respectively, but none following TAFA+LEN. Given the high cost of CAR-T treatment, this significantly reduces the incremental costs of TAFA+LEN vs the comparators. A scenario excluding CAR-T for all patients (scenario 6) has been explored. The proportions receiving subsequent CAR-T in the full analysis set for RE-MIND2 were requested and provided: these were 2.2%, 1.0% and 1.3% for POLA+BR, BR and R-GemOx, but 0% for TAFA+LEN. At least one patient received CAR-T after disease progression in L-MIND.
- 0% of patients were assumed to receive co-medications alongside TAFA+LEN after week 4, which likely underestimates the total costs of TAFA+LEN. In the L-MIND study, patients would not receive co-medications only at the discretion of the investigator and in the

absence of infusion-related reactions. 6.2% of patients experienced infusion related reactions in the L-MIND study. A scenario with 6.2% of patients receiving co-medications alongside TAFA+LEN (scenario 7) has been explored.

7. Conclusion

The Committee considered the benefits of tafasitamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as tafasitamab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept tafasitamab for use in NHSScotland.

8. Guidelines and Protocols

European Society for Medical Oncology (ESMO) published: Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2015.[3]

9. Additional Information

9.1. Product availability date

31 May 2022

9.2. Summary of product characteristics

Tafasitamab 200mg powder for concentrate for solution for infusion (Minjuvi®) SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Tafasitamab	12mg/kg given via intravenous infusion on: Day 1, 4, 8, 15 and 22 of cycle 1 Day 1, 8, 15 and 22 of cycle 2 and 3 Day 1 and 15 of cycle 4 onwards	Year 1 153,019 Year 2 onwards 91,650
Lenalidomide	25mg orally on days 1 to 21 of each cycle for up to 12 cycles	

Costs from eMC Dictionary of Medicines and Devices Browser on 09/01/23. Costs calculated using the full cost of vials assuming wastage based on a 70kg adult. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 59 patients eligible for treatment with tafasitamab plus lenalidomide in each year. The estimated uptake rate was 10% in year 1 and 30% in year 5. This resulted in six patients estimated to receive treatment in year 1 rising to 18 patients in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

References

1. Incyte Biosciences UK Ltd. Tafasitamab 200mg powder for concentrate for solution for infusion (Minjuvi®). Summary of product characteristics. Electronic Medicines Compendium. Available at: https://www.medicines.org.uk/emc/product/13003 Last updated: 30 May 2022. [cited.
2. The European Medicines Agency (EMA) European Public Assessment Report. Tafasitamab (Minjuvi®). 24/06/2021 EMA/426468/2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/minjuvi-epar-public-assessment-report_en.pdf.
3. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A*, et al.* Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116-25.
4. Cancer Research UK. Diffuse large B cell lymphoma. Last reviewed: 24 November 2020. Available at: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma
5. Salles G, Duell J, González Barca E, Tournilhac O, Jurczak W, Liberati AM*, et al.* Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020. Epub 2020/06/05.
6. Duell J, Maddocks KJ, González-Barca E, Jurczak W, Liberati AM, De Vos S*, et al.* Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2021. Epub 2021/07/02.
7. MorphoSys A. G. Clinical Study Report Addendum 3.0. A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of Lenalidomide Combined with MOR00208 in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma (R-R DLBCL) L-MIND. March 2021 Data on file.
8. Cordoba R, Prawitz T, Westley T, Sharma A, Ambarkhane S, Kapetanakis V*, et al.* Tafasitamab Plus Lenalidomide Versus 3 Rituximab-Based Treatments for Non-Transplant Eligible Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Matching-Adjusted Indirect Comparison. Adv Ther. 2022;39(6):2668-87. Epub 2022/04/12.
9. Nowakowski GS, Yoon DH, Peters A, Mondello P, Joffe E, Fleury I*, et al.* Improved Efficacy of Tafasitamab plus Lenalidomide versus Systemic Therapies for Relapsed/Refractory DLBCL: RE-MIND2, an Observational Retrospective Matched Cohort Study. Clin Cancer Res. 2022:Of1-of15. Epub 2022/06/09.
10. Sehn LH, Herrera AF, Matasar MJ, Kamdar M, Assouline S, Hertzberg M*, et al.* Polatuzumab vedotin (Pola) plus bendamustine (B) with rituximab (R) or obinutuzumab (G) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): updated results of a phase (Ph) Ib/II study. Blood. 2018;132(Supplement 1):1683-.
11. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M*, et al.* Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155-65. Epub 2019/11/06.
12. Food and Drug Administration (FDA) Statistical Review and Evaluation: Polatuzumab vedotin (Polivy). 19 August 2019.
13. Ohmachi K, Niitsu N, Uchida T, Kim SJ, Ando K, Takahashi N*, et al.* Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2013;31(17):2103-9. Epub 2013/05/08.
14. Vacirca JL, Acs PI, Tabbara IA, Rosen PJ, Lee P, Lynam E. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol. 2014;93(3):403-9. Epub 2013/08/21.

15. ClinicalTrials.gov. Study to Evaluate the Safety and Efficacy of Tafasitamab Plus Lenalidomide in Participants With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (firmMIND). NCT05429268. Available at: https://clinicaltrials.gov/ct2/show/NCT05429268. [cited.
16. Medicines & Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Tafasitamab 200mg powder for concentrate for solution for infusion (Minjuvi®). PLGB 42338/0016. October 2021. Available at: https://mhraproducts4853.blob.core.windows.net/docs/404563a9932987de10c0a84b19bdcf600d19fa61.
17. MorphoSys AG. Data on File. Study Report: An Observational Retrospective Cohort Study of Systemic Therapies for Relapsed or Refractory Diffuse Large B-cell Lymphoma (R/R DLBCL), to Compare Outcomes to Those from Tafasitamab + Lenalidomide in the L-MIND Study (RE-MIND2). 2021. p. 1–257.
18. Northend M, Wilson W, Osborne W, Fox CP, Davies AJ, El-Sharkawi D*, et al.* Results of a United Kingdom real-world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory DLBCL. Blood Adv. 2022;6(9):2920-6. Epub 2022/01/13.
19. Ionescu-Ittu R, Shang A, Velde NV, Guerin A, Lin Y, Shi L*, et al.* Second-line rituximab-bendamustine versus rituximab-gemcitabine-oxaliplatin in diffuse large B-cell lymphoma in the real world. J Comp Eff Res. 2019;8(13):1067-75. Epub 2019/08/28.
20. Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas RO*, et al.* Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica. 2013;98(11):1726-31. Epub 2013/06/12.
21. Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. J Clin Oncol. 2019;37(24):2105-19. Epub 2019/06/04.

This assessment is based on data submitted by the applicant company up to and including 17 February 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment

process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.