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SMC2542

mosunetuzumab concentrate for solution for infusion (Lunsumio®)

Roche Products Ltd

04 August 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 orphan medicine process

mosunetuzumab (Lunsumio®) is not recommended for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

In a single arm, open label, phase II study, treatment with mosunetuzumab was associated with a complete response rate of 60% in a cohort of patients with relapsed or refractory FL who had received at least two prior therapies.

The submitting company's justification of the treatment 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 Medicine Consortium

1. Clinical Context

1.1. Medicine background

Mosunetuzumab is a bispecific monoclonal antibody and conditional agonist that targets and causes B-cell cell lysis and apoptosis when simultaneously bound to CD20 on B-cells and CD3 on T-cells.[1, 2]

The recommended dose of mosunetuzumab is 1mg on day 1, 2mg on day 8 and 60mg on day 15 of cycle 1, 60mg on day 1 of cycle 2 and 30mg on day 1 of cycle 3 and beyond. Each cycle is 21 days and treatment is administered via intravenous (IV) infusion. Unless unacceptable toxicity or disease progression is experienced, mosunetuzumab is administered for 8 cycles for patients who achieve a complete response (CR). For patients who achieve a partial response (PR) or have stable disease (SD) in response to treatment with mosunetuzumab after 8 cycles, an additional 9 cycles of treatment (17 cycles total) should be administered. See the Summary of product characteristics (SPC) for further information.[1]

1.2. Disease background

Follicular lymphoma (FL) is an incurable, an indolent non-Hodgkin's lymphoma. Although the disease is heterogeneous, for many people it is chronic with spontaneous episodes of relapse and a relatively long overall survival. Common symptoms include painless swelling of lymph nodes in the neck, armpit or groin, fatigue, frequent infections, unexplained weight loss, night sweats or fevers; however, because of the indolent nature of the disease, many patients are asymptomatic. After increasing numbers of relapses the disease free intervals and duration of response become shorter and the risk of refractoriness to treatment increases. The median progression free survival (PFS) for patients who have received two prior therapies is approximately 1 year and median overall survival ranges from approximately 5 to 9 years.[2-5]

1.3. Treatment pathway and relevant comparators

For patients with relapsed FL, there is no standard treatment and options depend on patient fitness and choice, prior therapy, refractory status and stage at relapse. For early systemic relapse, <6 months since last rituximab, options include, obinutuzumab plus bendamustine followed by obinutuzumab maintenance or, an anthracycline may be added. If relapse occurs >6 months since last rituximab, retreatment with the same rituximab chemotherapy regimen may be considered if the initial remission was prolonged; if the remission was shorter (typically <2 years) or the initial regimen was poorly tolerated an alternative rituximab chemotherapy regimen may be considered. Chemotherapy regimens used in combination with rituximab include cyclophosphamide, vincristine and prednisolone (R-CVP), bendamustine or cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). Rituximab plus lenalidomide is an alternative option for previously treated patients and may be appropriate for selected patients who tolerate chemotherapy poorly. Eligible patients may also be considered for autologous stem cell transplant or entry into available clinical trials. Idelalisib can be used for patient's refractory to two prior treatment lines; however, clinical experts advised that use in Scotland has declined due to potential side effects. Chimeric antigen receptor T-cell (CAR-T) treatments have been licensed for relapsed or refractory FL. Tisagenlecleucel (licensed after two or more prior therapies) is not recommended by SMC in the

absence of a submission by the holder of the marketing authorisation (SMC2566). Axicabtagene ciloleucel was recently licensed for use after three or more treatment lines.[3, 4] The submitting company consider the most relevant comparators for this submission are rituximab plus lenalidomide and rituximab plus chemotherapy using rituximab plus bendamustine as a proxy.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option
Mosunetuzumab has a conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Eligibility for a PACE meeting
Mosunetuzumab meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety for mosunetuzumab for the indication under review is from a relevant cohort of 90 patients from GO29781.[2, 6]

Table 2.1. Overview of relevant studies

Criteria	Relevant cohort of GO29781 (n=90)[2, 6]
Study design	Multicentre, open-label, phase I/II study.
Eligible patients	Patients aged ≥18 years with histologically confirmed grade 1-3a FL that had relapsed or was refractory to two or more previous lines of therapy including an anti-CD20 therapy and an alkylating agent. At least one bi-dimensionally measurable lesion (with largest dimension >1.5cm for nodal lesions, or >1.0cm for extranodal lesions by) and an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1.
Treatments	All patients received the licensed dose of intravenous mosunetuzumab in 21 day cycles. Patients who achieved a complete response (CR) after cycle 8 did not receive further treatment but continued to be monitored. Patients who achieved a partial response or had stable disease after cycle 8 continued treatment for up to 17 cycles unless they experienced disease progression or unacceptable toxicity.
Randomisation	All patients (n=90) received mosunetuzumab.
Primary outcome	CR rate assessed by independent review facility (IRF) according to the international working group (IWG) standard non-Hodgkin's lymphoma response criteria.
Secondary outcomes	Objective response rate, duration of response, progression-free survival and overall survival.
Statistical analysis	Efficacy analyses were performed in the intention-to-treat population that included all enrolled patients. The primary analysis was planned for approximately 6 months after the last patients received their first dose of mosunetuzumab. The study cohort was powered to detect a 14% difference between mosunetuzumab and a pre-specified historical control CR rate of 14% (that is, from 14% to 28%). The historical control CR rate is based on a phase II study of copanlisib, a PI3K inhibitor. All other statistics are descriptive.

At the primary analysis (data cut-off: 15 March 2021), treatment with mosunetuzumab was associated with a CR rate of 58%. Statistical significance compared with the historical control CR rate of 14% (for copanlisib) was demonstrated. As the data were immature at the primary analysis,

results from two later data cuts have been provided by the company to support this submission. The cost-effectiveness and indirect treatment comparison are informed by the January 2022 data-cut.[2, 6-8] Details of the primary and selected secondary outcomes have been presented in Table 2.1 for the August 2021 data cut. The later data cut is considered confidential by the company.

Table 2.1: Primary and selected secondary outcomes in the relevant cohort from GO29781[2, 6, 7]

	Mosunetuzumab (n=90[A])
Data cut-off	**27 August 2021**
Median follow-up	18.3 months
Response outcomes per independent review committee	
ORR, % (n/N)	80% (72/90)
CR, %	60%
PR, %	20%
SD, %	7.8%
Median DOR	22.8 months
KM estimated ORR at 18 months	57%
Median duration of CR	NE
KM estimated CR at 18 months	64%
Time to event outcomes per independent review committee	
PFS events	42
Median PFS	17.9 months
KM estimated PFS at 12 months	58%
KM estimated PFS at 18 months	47%
Deaths	8
Median overall survival	NE
KM estimated OS at 12 months	93%
KM estimated OS at 18 months	NE
CR=complete response; KM=Kaplan-Meier; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PR=partial response; SD=stable disease. [A]Two patients were on retreatment and have been excluded from the analyses.	

As CR rates were high, only 11 patients with a PR or SD continued treatment beyond cycle 8. Of these, 4 patients experienced a deepening of response (PR to CR in 3 patients and SD to PR in 1 patient), 5 patients maintained their PR or SD response and 1 patient progressed.[2]

2.2. Health-related quality of life outcomes

Patient reported outcomes were assessed using physical functioning and fatigue scores from the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) questionnaire, Functional Assessment of Cancer Therapy- Lymphoma (FACT-Lym) subscale and EuroQol-5 dimensions-5 levels (EQ-5D-5L) utility index and visual analogue score (VAS). Compliance rates were high, between 70% and 80% at scheduled assessments. In general, scores were maintained from baseline to cycle 8 with minimal fluctuation between cycles.[2]

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

In the absence of direct comparative evidence the company performed indirect treatment comparisons. These compared mosunetuzumab with rituximab plus lenalidomide and rituximab plus bendamustine (used to represent rituximab plus chemotherapy).

Table 2.2: Summary of indirect treatment comparison

Criteria	Overview
Design	• Unanchored matched-adjusted indirect treatment comparison (MAIC) for the comparison of mosunetuzumab versus rituximab plus lenalidomide. • Propensity score (PS) analysis for the comparison of mosunetuzumab versus rituximab plus bendamustine.
Population	Patients with relapsed or refractory FL who had received ≥2 prior systemic therapies
Comparators	Rituximab plus lenalidomide and rituximab plus bendamustine
Studies included	GO29781[6, 7], AUGMENT[9], CONTRALTO[10], GO29365[11]
Outcomes	Objective response rate (ORR), complete response (CR), progression-free survival (PFS), overall survival and discontinuation due to adverse events
Results	The company consider that the results of the indirect comparison are confidential. For the overall survival and PFS outcomes, the company conclude that there is numerical evidence favouring mosunetuzumab compared to rituximab plus bendamustine but not compared to rituximab plus lenalidomide. For the response-related outcomes, they conclude that there is numerical evidence favouring mosunetuzumab compared to rituximab plus lenalidomide but not compared to rituximab plus bendamustine.

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

3. Summary of Safety Evidence

The regulator concluded that mosunetuzumab generally has a manageable safety profile in the population under review; they considered the most important concerns to be associated with cytokine release syndrome, tumour flare and serious infections.[2]

At the August 2021 data cut-off, in the cohort of 90 patients from study GO29781 that were relevant to the licensed indication, the median number of cycles was 8. A treatment-emergent adverse event (AE) was reported by all patients and these were considered treatment-related in 92%. Patients reporting a grade 3 or 4 treatment-related adverse event (TRAE) were 51%, patients with a reported serious TRAE were 33%, patients with a dose modification due to TRAEs were 5.6% and patients discontinuing therapy due to a TRAE were 2.2%. The most frequently reported treatment-emergent AEs of any grade with an incidence ≥20% were: cytokine release syndrome (44% per American Society for Transplantation and Cellular Therapy [ASTCT] 2019 criteria and 46% per Lee 2014 criteria), fatigue (37%), headache (31%), neutropenia/neutrophil count decreased (28%), pyrexia (29%), hypophosphatemia (27%) and pruritus (21%). These safety data were supported by additional analysis in a larger population (n=218) of patients with non-Hodgkin's lymphoma, further details can be found in the SPC.[1, 2, 6]

Cytokine release syndrome was the most frequent serious AE (requiring hospitalisation) and affected up to 23% (21/90) of patients at data cut-off 15 March 2021; common symptoms included pyrexia, chills, hypotension, tachycardia, hypoxia and headache. Most events had a maximum severity of grade 1 (26%) or 2 (17%) and occurred in cycle 1 after day 1 (23%) or day 15 (36%). Corticosteroids, paracetamol and antihistamines were used to manage symptoms however, 18% of patients with an event (per ASTCT 2019) required treatment with tocilizumab alone or in combination with corticosteroids, 22% required oxygen administration and 5% required vasopressors. Tumour flare events occurred in 3.3% (3/90) of patients, these presented as one grade 2 pleural effusion and two grade 3 tumour flares; these resolved within a median of 5 days. Patients should be monitored for tumour flare at critical anatomical sites. Other adverse events of special interest include haematological, neurological, hepatic and infections. Refer to the SPC for further safety information.[1, 2, 6]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Mosunetuzumab is the first bispecific antibody licensed for the treatment of FL and has a novel mechanism of action.
- In the GO29781 study, treatment with mosunetuzumab was associated with a CR rate of 60% at the August 2021 data cut off which was considered relevant and clinically meaningful by the regulator. This was supported by secondary outcomes which indicated a high ORR (80%) with a durable response.[2, 6]

4.2. Key uncertainties

- Evidence is from a cohort of 90 patients from an open-label, single arm-study GO29781.[2, 6] This is associated with a number of limitations including a lack of direct comparative evidence versus alternative treatment options, potential bias of subjective outcomes limiting interpretability of results and a small sample size which increases uncertainty of the results.
- In the absence of direct comparative evidence, the submitting company conducted indirect treatment comparisons, which were associated with a number of limitations affecting the credibility of the results. The MAIC, which compared mosunetuzumab with rituximab plus lenalidomide, was unanchored due to a lack of common control. There were differences between the studies in follow-up and populations with approximately half of patients in the lenalidomide plus rituximab study receiving second line treatment and none refractory to rituximab compared with all patients in the mosunetuzumab study having treatment at third line or later and 79% refractory to rituximab. There was a considerable reduction in effective sample size (most likely due to excessive matching) indicative of differences between the studies and potentially questions if the studies were comparable enough for matching. In the PS analysis, which compared mosunetuzumab with rituximab plus bendamustine, a large number of parameters were included in the modelling approaches, which far exceeds the recommended ratio. This is likely the reason for the high weights

assigned to some patients. Furthermore, a number of different matching techniques have been tested for in the PS analysis, however, the overall approach lacks strategy and the final choice of approach lacks justification. Again, effective sample sizes were small with wide confidence intervals. Due to these limitations, the results of the MAIC and the PS analysis are highly uncertain.

- Superiority of mosunetuzumab was tested against a historical CR rate based on the results of a phase II study of copanlisib. However, this medicine is not licensed for use in the UK for FL and Scottish clinicians in general indicated that an alternative PI3K inhibitor, idelalisib is either no longer or less commonly used in practice compared with other treatments in the third line and beyond setting. The submitting company considered that the most relevant comparators for this submission are rituximab plus lenalidomide and rituximab plus bendamustine. Some clinical experts highlighted that obinutuzumab plus bendamustine may also represent a third line option. However, it is not often used in the third-line setting.
- Survival data are immature and it is uncertain if favourable response rates will translate into a survival benefit in the longer term.[7]
- In GO29781, patients that achieved a CR received 8 cycles of mosunetuzumab and those with a PR or SD received up to 17 cycles. As the CR rates were high, only 11 patients continued treatment beyond cycle 8 and therefore the evidence in patients who received up to 17 cycles is limited.[2]
- There may be some generalisability issues. Evidence is available for patients with grade 1 to 3A disease and there are no data in patients with grade 3B disease, management and treatment of these patients may follow a different approach. Patients with an ECOG PS ≥2 were excluded from the study and there is no evidence for mosunetuzumab in these less fit patients. In the relevant FL cohort of GO29781, most patients (62%) had received more than three previous lines of therapy and therefore may be more heavily pre-treated compared with patients receiving mosunetuzumab as a third line option.

4.3. GB conditional marketing authorisation specific obligations

- Provide results from study GO42909, a randomised, open-label, multicentre study evaluating mosunetuzumab in combination with lenalidomide in comparison to rituximab in combination with lenalidomide in patients with FL after at least one line of systemic therapy. Due 31 March 2026.[12]

The MHRA specific obligations are unlikely to address the key uncertainties in the clinical evidence presented for this indication as study GO42909 will evaluate mosunetuzumab in combination with lenalidomide and not mosunetuzumab monotherapy. Furthermore, the study population will have received at least one prior therapy and it is unknown what proportion will have received at least two prior therapies to match the current indication under review.

4.4. Clinical expert input

Clinical experts consulted by SMC generally considered mosunetuzumab to be a therapeutic advance because of the response rates reported in study GO29781 and novel mechanism of action

not used before in patients with FL. They considered that it could provide an additional treatment option for some patients who had relapsed following at least two prior lines of therapy.

4.5. Service implications

Mosunetuzumab is required to be given in a setting with appropriate medical support to manage severe reactions such as cytokine release syndrome.[1] This is likely to have service implications and could restrict the location where treatment can be given to larger cancer centres with critical care facilities available. Additional clinical capacity may be required to prescribe, prepare and administer treatment and to monitor for adverse events. As administration is via IV infusion additional day unit capacity will also be required, particularly for the step up dosing associated with the first treatment cycle.

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

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 mosunetuzumab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Follicular lymphoma is an incurable condition characterised by relapses that become more frequent and difficult to treat. There is no standard of care for patients who have received two prior systemic therapies with treatment choice dependent on response to previous therapies and patient health. Patients who have relapsed quickly or after a stem cell transplant or who have disease that is refectory, have limited effective treatment options and an unmet need for an increased range of effective therapies with acceptable tolerability.
- Mosunetuzumab was associated with high rates of response that were durable in a population of heavily pre-treated patients, many of whom were refractory to existing therapies (including anti-CD20 antibodies and alkylating agents).
- By inducing a sustained remission, mosunetuzumab would give the patient and their family an extended period when the patient is well and their disease controlled, allowing them to be involved more in family, work and social activities. This may relieve some of their anxiety. Some families are aware of mosunetuzmab and its novel mechanism of action and for them accessing this treatment may provide reassurance that the patient has optimum treatment. For some, the extended remission may provide hope of a bridge to a time when additional new therapies become available.
- Mosunetuzumab is associated with cytokine release syndrome and neurotoxicity. Some patients reported that they are happy to risk these to gain the benefits of this novel therapy. There is established clinical expertise in the management of medicines associated with these types of 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

A summary description of the economic analysis performed is provided in Table 6.1

Table 6.1 Description of economic analysis

	Overview
Analysis type	Cost utility
Time horizon	Lifetime (40 years)
Population	Adult patients with relapsed or refractory Grade 1-3a FL who have received at least two prior systemic therapies
Comparators	Rituximab + lenalidomide, rituximab + bendamustine (as a proxy for R-chemotherapy).
Model description	The model was structured as a three-state partitioned survival model featuring the states of PFS, progressed disease (PD) and death. Model cycle length was 1 week, and half cycle correction was applied.
Clinical data	The main source of clinical data for mosunetuzumab was the single arm phase I/II open label GO29781 study for estimation of PFS and overall survival (January 2022 data cut), with indirect treatment comparisons providing comparator PFS and overall survival estimates (unadjusted MAIC for comparison with rituximab plus lenalidomide, PS analysis for the comparison with rituximab plus bendamustine). Individual level patient data were available for both treatment arms in order to perform the indirect comparison with rituximab plus bendamustine, but only for mosunetuzumab for the comparison with rituximab plus lenalidomide.
Extrapolation	Parametric functions were fitted to the PFS and overall survival study data for mosunetuzumab with the Weibull applied in the base case for both outcomes for the comparison with rituximab plus lenalidomide. Separate functions were fitted to the rituximab plus lenalidomide comparator data with the log-normal and Weibull used for PFS and overall survival. For the comparison with rituximab plus bendamustine, the log-normal and exponential functions were fitted to the study data to extrapolate PFS and overall survival outcomes for mosunetuzumab respectively, and the same functions were fitted for the rituximab plus bendamustine arm PFS and overall survival outcomes extrapolation. Time on treatment (ToT) for mosunetuzumab was represented by the observed duration in the GO29781 study with treatment stopped at 17 cycles (approximately 12 months), or capped at disease progression. No extrapolation was performed. For comparators, ToT was set at base case modelled PFS as no direct data were available on duration, but capped at a specified maximum number of cycles where relevant. An assumption was made of no treatment waning due to patients finishing treatment at or within 12 months.
Quality of life	Age adjusted utilities were estimated based on analysis of EQ 5D-5L observations in GO29781 (n=83), mapped to the EQ-5D-3L version utilities, to produce estimates of

	0.804 and 0.747 for PFS and PD states respectively. Alternative health state utilities from a study in patients with FL used in prior appraisals were applied in scenario analysis (0.81 and 0.62 for PFS and PD respectively).[13] Specific disutilities for adverse events were not applied.
Costs and resource use	Medicine acquisition and administration costs have been estimated for mosunetuzumab and comparators. Doses and duration for mosunetuzumab were in line with the GO29781 study protocol, and based on BNF recommendations for comparators and subsequent therapies. Use of post progression subsequent therapies were estimated based on clinical expert opinion. Re-treatment with rituximab plus lenalidomide was assumed to not be possible, which led to lower subsequent therapy costs in the rituximab plus lenalidomide comparator arm compared to mosunetuzumab and rituximab plus bendamustine arms. Disease management resource use (for example clinic visits, tests and scans) pre and post progression were derived from a prior NICE technology appraisal[14] and clinical expert opinion. Costs were estimated for adverse events of grade 3 or more in >2% of the trial population, and a one-off cost for terminal care from a published source was included.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of mosunetuzumab. A PAS discounted price exists for lenalidomide which was taken into account as a comparator and subsequent therapy in the assessment of the cost-effectiveness of mosunetuzumab versus rituximab plus lenalidomide .

6.2. Results

The base case results (applying mosunetuzumab PAS) show mosunetuzumab was dominated by rituximab plus lenalidomide, with fewer quality-adjusted life years (QALYs) and an incremental cost (Table 6.2). The QALY loss versus rituximab plus lenalidomide is related to lower estimated life years and QALYs gained in the post progression state, offsetting life year and QALY gains in PFS state for mosunetuzumab. Incremental costs for mosunetuzumab were driven by higher drug administration, disease management and subsequent therapy costs.

The results presented do not take account of the PAS for lenalidomide 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 lenalidomide due to commercial confidentiality and competition law issues.

For the comparison with rituximab plus bendamustine an incremental cost-effectiveness ratio (ICER) of £37,821/QALY gained is estimated with mosunetuzumab PAS applied (Table 6.2), with health outcomes driven by QALY gains in the PFS state for mosunetuzumab, and incremental costs driven by higher medicine acquisition costs, but also additional drug administration, disease management and subsequent therapy costs.

Table 6.2 Base case results with mosunetuzumab PAS price

Comparison	ICER (£/QALYs)
mosunetuzumab vs rituximab + lenalidomide	dominated
mosunetuzumab vs rituximab + bendamustine	£37,821

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PAS, patient access scheme

6.3. Sensitivity analyses

In one way sensitivity analysis the utility for the PFS health state was the most sensitive variable for comparisons with rituximab plus lenalidomide and rituximab plus bendamustine. However, a scenario analysis applying health state utilities from a published source (of 0.81 and 0.62 for PFS and PD states respectively) used in prior FL technology appraisals[13] had only a modest impact on the results (Table 6.3). A scenario was explored by the company applying the log-logistic parametric function to the mosunetuzumab overall survival data in the comparisons with rituximab plus lenalidomide and rituximab plus bendamustine. This produced more optimistic overall survival estimates stated by the company to be in line with expectations for mosunetuzumab based on later (July 2022) GO29781 data cuts, resulting in an ICER estimate for the comparison with rituximab plus lenalidomide of £72,347 with mosunetuzumab PAS applied (Table 6.3). This scenario resulted in an ICER estimate of £29,490 for the comparison with rituximab plus bendamustine (Table 6.3). Requested scenario analysis relating to shorter time horizon, assuming no survival benefit, and for the comparison with rituximab and bendamustine only using the Weibull function for extrapolation of mosunetuzumab overall survival, all resulted in higher ICERs (Table 6.3)

Table 6.3 Key scenario analyses with mosunetuzumab PAS

Scenario	Scenario description	ICER (£/QALY)
mosunetuzumab vs R-Len		
1	Log-logistic for mosunetuzumab OS	£72,347
2	Wild et al utilities[13](0.81 PFS, 0.62 PD)	Dominated
3	Time horizon 20 years	Dominated
4	No survival benefit assumed	£585,864
mosunetuzumab vs RB		
1	Log-logistic for mosunetuzumab OS	£29,490
2	Wild et al utilities[13](0.81 PFS, 0.62 PD)	£36,926
3	Time horizon 20 years	£45,714
4	No survival benefit assumed	£203,383
5	Weibull for OS extrapolation for both treatment arms	£68,833

6	R-CHOP medicine and admin costs (in place of RB medicine cost)	£38,894

Abbreviations: R-Len, rituximab + lenalidomide; RB, rituximab + bendamustine; OS, overall survival; QALYs, Quality Adjusted Life Years; PFS, Progression Free Survival; PD, Progressive Disease; ICER, incremental cost-effectiveness ratio

6.4. Key strengths

- Rituximab plus lenalidomide represents a relevant comparator after more than 2 prior therapies. SMC clinical experts considered rituximab plus bendamustine to have generally similar efficacy and safety to rituximab plus chemotherapy regimens, so appears reasonable to use as a proxy comparator for rituximab plus chemotherapy.
- Individual patient data are available for the indirect comparison of mosunetuzumab with rituximab plus bendamustine for use in the economic analysis.
- The handling of subsequent therapies in the economic analysis appears reasonable. The assumption that there can be no re-treatment with rituximab plus lenalidomide is reasonable in the base case, based on clinical expert opinion, but if there was any re-use in clinical practice this would modestly improve the cost-effectiveness results for mosunetuzumab in the comparison with rituximab plus lenalidomide.

6.5. Key uncertainties

- Mosunetuzumab cannot be considered to be cost-effective compared to rituximab plus lenalidomide, and has highly uncertain cost-effectiveness compared to rituximab plus bendamustine. The base case estimates a QALY loss and higher incremental costs for mosunetuzumab in the comparison with rituximab plus lenalidomide, or a high ICER when a more optimistic (but potentially plausible) mosunetuzumab overall survival extrapolation is applied in scenario analysis. For the rituximab plus bendamustine comparison the wide confidence intervals in the indirect treatment comparison for PFS and overall survival means that it is not possible to robustly conclude a PFS or life year benefit for mosunetuzumab. If no life year or QALY benefit can be ascertained then the appropriate analysis could be a cost-minimisation analysis, although even this is uncertain based on the ITC evidence (see bullet below).
- There is no direct clinical evidence against the comparators included in the economic analysis, so the relative PFS and overall survival evidence in the economic analysis is based on indirect treatment comparisons that have major limitations as expressed in section 4.2 above. The clinical data available for mosunetuzumab are very limited from a single arm study and overall survival outcomes are immature. Due to the mosunetuzumab clinical evidence and ITC weaknesses the relative life year and QALY estimates for mosunetuzumab and comparators are highly uncertain to the extent that it is difficult to ascertain whether there is a survival (or QALY) benefit (or loss) for mosunetuzumab in either comparison (there may be some biases unfavourable for mosunetuzumab for the rituximab plus lenalidomide comparison, and PFS/overall survival outcomes inconsistent with complete response results). Scenarios assuming no survival benefit for mosunetuzumab or applying

plausible extrapolations with less optimistic survival benefit estimates for mosunetuzumab (versus rituximab plus bendamustine) resulted in high ICERs (Table 6.3)

- There are uncertainties associated with the choice of extrapolation, in particular for overall survival, which impacts on the cost-effectiveness results. Also, there is inherent uncertainty associated with long extrapolation of outcomes beyond the trial data, which can be explored by assuming a shorter time horizon. Adopting a 20 year time horizon resulted in higher ICERs.
- Due to separate ITC approaches versus each comparator the life year and QALY estimates for mosunetuzumab differed (7.12 QALYs and 7.26 QALYs in the rituximab plus lenalidomide and rituximab plus bendamustine comparison respectively) and the cost estimates for mosunetuzumab also differed between comparisons. This increases the uncertainty over the separate cost-effectiveness results for each comparison.
- There are limitations with the sources used for health state utility values in the base case and scenario analyses, and the utilities may be high for both PFS and PD states. However the difference in PFS and PD utilities derived from GO29781 EQ 5D observations appear reasonable for use in the base case.
- As rituximab plus bendamustine is a proxy for rituximab plus chemotherapy assuming the costs for the latter in the economic analysis is appropriate. An analysis assuming R-CHOP costs for the rituximab plus bendamustine comparator results in a small increase in the ICER (Table 6.3).

7. Conclusion

The Committee considered the benefits of mosunetuzumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as mosunetuzumab 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 mosunetuzumab for use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology published 'The investigation and management of follicular lymphoma' in 2020.

The European Society of Medical Oncology published 'Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' in 2020.

9. Additional Information

9.1. Product availability date

04 October 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
Mosunetuzumab	**Administered via intravenous infusion** **Cycle 1: 1mg on day 1, 2mg on day 8 and 60mg on day 15** **Cycle 2: 60mg on day 1** **Cycle 3 onwards: 30mg on day 1**	**Initial 8 cycles 66,660** **Each additional cycle 6,600**

Costs from BNF online on 09.05.23. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

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

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

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This assessment is based on data submitted by the applicant company up to and including 16 June 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.