5.13 TAFASITAMAB, Powder for I.V. infusion 200 mg, Minjuvi®, Specialised Therapeutics Alim Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100, Authority Required, listing for tafasitamab in combination with lenalidomide and rituximab for the treatment of patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have had at least 1 prior systemic anti-CD20 therapy.

1.2 Listing was requested on the basis of a cost-utility analysis versus rituximab-based chemotherapy (R-CHEMO).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Relapsed and/or refractory follicular lymphoma
Intervention	Tafasitamab in combination with lenalidomide and rituximab
Comparator	Rituximab-based chemotherapy regimen
Outcomes	Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), time to next treatment (TTNT), duration of response (DOR), positron emission tomography (PET) complete response (CR) rate, patient-reported outcomes (PROs), safety
Clinical claim	In people with relapsed/refractory follicular lymphoma, tafasitamab in combination with lenalidomide and rituximab is more effective than rituximab-based chemotherapy with respect to efficacy and inferior with respect to safety

Source: Table 1, p2 of the submission.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: Not registered. The submission was made under the TGA/PBAC Parallel Process. The TGA evaluation was being conducted under Project Orbis in collaboration with the United States Food and Drug Administration (FDA). At the time of evaluation for PBAC consideration, the TGA notification letter at Milestone 2 and the draft PI were provided. The submission stated that the clinical evaluator's report is due 30th November 2025, the Delegate's overview is expected 6th January 2026, and the Delegate's decision is expected 20th March 2026.

2.2 The sponsor's proposed TGA indication is: [tafasitamab], in combination with rituximab and lenalidomide, is indicated for the treatment of adult patients with previously treated FL.

2.3 Tafasitamab was FDA-approved with lenalidomide and rituximab for adults with R/R FL on 18 June 2025 (FDA 2025[1]). The application was granted priority review, and tafasitamab received orphan drug designation for FL.

3 Requested listing

3.1 The restriction proposed in the submission is outlined below. Suggestions and additions proposed by the Secretariat and advised by the PBAC are added in italics and suggested deletions are crossed out with strikethrough.

Tafasitamab

Initial – Cycle 1 to 5 inclusive

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№. of Rpts**
TAFASITAMAB Injection	NEW (Public) NEW (Private) MP	1400 mg	~~11~~ *15*
Available brands			
Minjuvi (Tafasitamab 200mg *injection, 1* vial ~~powder for reconstitution~~)			
Concept ID (for internal Dept. use)	**Category / Program:** ☒ Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)		
	Prescriber type: ☒ Medical Practitioners		
	Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)		
	Prescribing rule level:		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*		
	Restriction Summary [new1] / Treatment of Concept: [new1A]		
	Episodicity: Relapsed and/or refractory		
	Severity: [blank]		
	Condition: Follicular lymphoma		
	Indication: Relapsed and/or refractory follicular lymphoma		
	Treatment Phase: ~~Treatment of relapse and/or refractory disease~~ Initial treatment (*Cycles 1 – 5 inclusive)*		
	Clinical criteria:		
	Treatment must be initiated in combination with lenalidomide and rituximab		
	AND		
	Clinical criteria:		

[1] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tafasitamab-cxix-relapsed-or-refractory-follicular-lymphoma#:~:text=On%20June%2018%2C%202025%2C%20the,be%20posted%20on%20Drugs@FDA.

	~~Patient must have relapsed or refractory or progressive disease after at least 1 prior systemic anti-CD20 therapy~~ *Patient must have undergone anti-CD20 therapy for this condition and experienced relapsed or refractory disease*
	AND
	~~**Clinical criteria:**~~
	~~The condition must been in need of treatment as determined by the medical practitioner~~
	~~**AND**~~
	Clinical criteria:
	The treatment must not exceed a total of 5 cycles *of treatment* under this restriction
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition.~~
	~~**Prescribing Instructions:**~~ ~~The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.~~
	Prescribing Instructions: *The treatment must not exceed a total of 12 cycles in a lifetime for this indication.*

Continuing treatment - Cycles 6 to 12 inclusive

MEDICINAL PRODUCT Form	***PBS item code***	**Dispensed Price Max Amt**	***Max. Amount***	***№. of Rpts***
TAFASITAMAB Injection	*NEW (Public)* *NEW (Private)* *MP*	Published price Public: $13,041.23 Private: $13,268.20 Effective price Public: $[redacted] Private: $[redacted]	*1400 mg*	*13*
Available brands				
Minjuvi *(Tafasitamab 200mg injection, 1 vial)*				

Concept ID *(for internal Dept. use)*	***Category / Program:*** ☒ *Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)*
	Prescriber type: ☒ *Medical Practitioners*
	Benefit type: ☒ *Authority Required (Telephone/Online PBS Authorities System)*
	Prescribing rule level:
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*
	Restriction Summary [new2] / Treatment of Concept: [new2A]
	Episodicity: *Relapsed and/or refractory*
	Severity: *[blank]*
	Condition: *Follicular lymphoma*
	Indication: *Relapsed and/or refractory follicular lymphoma*
	Treatment Phase: *Continuing treatment (Cycles 6 – 12 inclusive)*

	Clinical criteria:
	The treatment must be in combination with lenalidomide
	AND
	Clinical criteria:
	Patient must have previously received this drug as their most recent course of PBS-subsidised treatment for this condition.
	AND
	AND
	Clinical criteria:
	The treatment must not exceed a total of 7 cycles of treatment under this restriction
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	Prescribing Instructions: *The treatment must not exceed 12 cycles in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first.*

3.2 The submission proposed a Special Pricing Arrangement (SPA) with a published ex-manufacturer price (EMP) of $1,850 per 200 mg vial and an effective EMP of $[redacted] per 200 mg vial. The pre-PBAC response offered a reduced EMP of $[redacted] per 200 mg vial.

3.3 The intervention is tafasitamab in combination with lenalidomide and rituximab, given for 12 cycles of 28 days. The regimen includes:

- Tafasitamab administered at a dose of 12 mg/kg as an intravenous (IV) infusion on:
  - Days 1, 8, 15 and 22 of Cycles 1 to 3; and
  - Days 1 and 15 of Cycle 4 to 12.
- Lenalidomide 20mg orally once daily for days 1 to 21 of Cycles 1 to 12.
- Rituximab 375 mg/m^2 IV on:
  - Days 1, 8, 15 and 22 of Cycle 1; and
  - Day 1 of Cycles 2 to 5.

3.4 The submission requested a maximum of 11 repeats for its single treatment phase listing, stating that it would provide 3 months' worth of tafasitamab therapy. However, 11 repeats would only be sufficient for 3 months of treatment at the dosing schedule for cycles 1 to 3. To cover for the total duration of therapy (i.e. 12 cycles) and the requirement for concomitant rituximab for cycles 1 to 5 only, the Secretariat suggested separating the listing into two treatment phases: 'Initial treatment (Cycles 1 – 5 inclusive)' and 'Continuing treatment (Cycles 6 – 12 inclusive)', each with 15 and 13 repeats respectively.

3.5 The requested restriction was narrower than the requested TGA indication but was broader than the pivotal trial population from inMIND, specifically:

- The requested TGA indication was silent on the type of previous treatments, whereas the requested restriction and the inMIND inclusion criteria specified that patients must have had at least 1 prior systemic anti-CD20 therapy. The

ESC considered that in Australian clinical practice it would be very unlikely for patients to not have had anti-CD20 therapy in the first line setting.

- The requested restriction did not require documentation of CD19 and CD20 expression, whereas confirmed expressions of CD19 and CD20 were required for enrolment in the inMIND trial. The PBS restrictions for obinutuzumab for FL indications require patients to be CD20 positive. Patients are likely to have been tested for CD20 expression prior to first-line systemic therapy. The sponsor's Advisory Board clinicians considered that testing of CD19 expression is not routinely performed in Australian laboratories. CD19 is expressed in >90% of B-Cell lymphomas (Marshalek 2025). The ESC agreed with the submission that testing for the presence of CD19 is not routinely performed in Australia. The ESC advised that a requirement for the determination of CD19 status was not required in the restriction.
- The requested restriction was silent on performance status, whereas the inMIND trial excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status scores >2. The ESC agreed with the evaluation that it was reasonable for the restriction to be silent on performance status. Most people enrolled in the inMIND trial and in the Lymphoma and Related Diseases Registry (LaRDR) for Australian patients had ECOG scores of 0 or 1 (97.3% and 93.5%, respectively).
- The requested restriction states that the condition must be 'in need of treatment as determined by the medical practitioner', rather than providing direct criteria for treatment eligibility such as being symptomatic or the presence of Groupe d'Etude des Lymphones Folliculaires (GELF) or British National Lymphoma Investigation (BNLI) criteria, as is required in the obinutuzumab restriction. This was in line with clinical practice guidelines and the Sponsor's Advisory Board discussions, which acknowledged the heterogeneous nature of FL and promoted treatment decisions based on individual patient and disease characteristics (NCCN 2025, Dreyling 2021, Tobin 2024). The ESC considered that this was reasonable. The PBAC considered it would be redundant and thus unnecessary to include a criteria requiring the condition to be 'in need of treatment'.

3.6 Lenalidomide is neither TGA approved nor PBS listed for R/R FL. Given lenalidomide generics are available, the submission stated that the resources required to apply for TGA registration and PBS reimbursement of lenalidomide with rituximab in second-line FL would not be commercially viable. The FDA approved lenalidomide in combination with rituximab for R/R FL in 2019 (FDA 2019[2]). If the TGA approves the proposed indication for tafasitamab in combination with lenalidomide and rituximab, then lenalidomide could be considered TGA approved for R/R FL when used in this

[2] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/021880Orig1s057ltr.pdf

combination; however, lenalidomide would not be considered TGA approved for the lenalidomide and rituximab (R^2) regimen without tafasitamab.

3.7 To enable access to concomitant lenalidomide, the submission proposed a PBS restriction for lenalidomide (for use in combination with tafasitamab). This would be consistent with the PBAC's March 2015 consideration of bendamustine in mantle cell lymphoma, which was for use in combination with rituximab (Bendamustine Public Summary Document [PSD] March 2015 PBAC Meeting[3]). The requested listing for lenalidomide is presented in Table 2. Suggestions and additions advised by the PBAC are added in italics and suggested deletions are crossed out with strikethrough. The PBAC considered that the listing would also need to include strengths below 20 mg of lenalidomide, to allow for dose reductions.

Table 2: Essential elements of the requested listing for lenalidomide

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LENALIDOMIDE						
lenalidomide 20 mg capsule, 21	NEW (Public) NEW (Private) MP	$1266.69-$1315.57 published price[a]	1	21	~~3~~ 5	*Various brands*

Concept ID (for internal Dept. use)	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒ Medical Practitioners
	Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
	Authority type: ☒ *Complex Authority Required (CAR)*
	Prescribing rule level:
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
33337	***Administrative Advice:*** *Patients receiving lenalidomide under the PBS listing must be registered in the risk management program relevant for the brand of lenalidomide being prescribed and dispensed: Revlimid - i-access program; Lenalidomide Dr.Reddy's - Reddy-2-Assist Controlled Access Program; Lenalide - Juno Connected™; Lenalidomide Sandoz - MyCheckPoint Pregnancy Prevention Program; Lenalidomide Viatris - Viatris Care.*
28500 CAR	***Administrative Advice:*** *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
19967	**Caution:** This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.
	Restriction Summary [new3] / Treatment of Concept: [new3A]
	Episodicity: Relapsed and/or refractory

[3]https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/bendamustine-psd-march-2015.pdf

	Severity: [blank]
	Condition: Follicular lymphoma
New I1	**Indication:** Relapsed and/or refractory follicular lymphoma
	~~**Treatment Phase:** Treatment of relapse and/or refractory disease~~
New CC	**Clinical criteria:**
New CC	~~Treatment must be initiated in combination with tafasitamab and rituximab~~ *Patient must be undergoing concurrent treatment with tafasitamab and rituximab obtained through the PBS for Cycles 1 to 5; or*
New CC	*Patient must be undergoing concurrent treatment with tafasitamab obtained through the PBS for Cycles 6 to 12.*
	AND
28685	***Treatment* criteria:**
28684	~~The condition must have relapsed, be refractory to, or progressed following at least 1 prior systemic anti-CD20 therapy.~~
	AND
~~New CC~~	~~**Clinical criteria:**~~
~~New CC~~	~~The condition must been in need of treatment as determined by the medical practitioner~~
	~~**AND**~~
New CC	***Clinical criteria:***
New CC	*The treatment must not exceed 12 cycles in total, measured from the initial dose, or, must not extend beyond disease progression, whichever comes first.*
	~~**AND**~~
~~*21104*~~	~~**Clinical criteria:**~~
~~*21103*~~	~~Patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition.~~

Source: Table 15, p27 of the submission.

[a] DPMQ for multiple myeloma indications.

3.8 The submission requested a maximum quantity of 21 capsules with 3 repeats for the lenalidomide 20 mg strength. The Secretariat noted that the maximum quantity was consistent with the dosing schedule outlined in inMIND study; lenalidomide 20 mg orally once daily on days 1 to 21 of cycles 1 to 12. However, the Secretariat suggested amending the repeat quantity from 3 to 5, to provide sufficient supply for 6 months' worth of therapy based on 28-day cycles.

3.9 Overall, the submission requested the same restriction criteria as proposed for tafasitamab. Consistent with the suggestion for a two treatment phase listing for tafasitamab, the Secretariat suggested to amend the lenalidomide restrictions to include the following: 'Patient must be undergoing concurrent treatment with tafasitamab and rituximab obtained through the PBS for Cycles 1 to 5; or Patient must be undergoing concurrent treatment with tafasitamab obtained through the PBS for Cycles 6 to 12.' Further, to mimic existing PBS listings, the Secretariat suggested adding an administrative advice note pertaining to the various brands of lenalidomide: 'Patients receiving lenalidomide under the PBS listing must be registered in the risk management program relevant for the brand of lenalidomide being prescribed and dispensed: Revlimid - i-access program; Lenalidomide Dr.Reddy's - Reddy-2-Assist

Controlled Access Program; Lenalide - Juno ConnectedTM; Lenalidomide Sandoz - MyCheckPoint Pregnancy Prevention Program; Lenalidomide Viatris - Viatris Care.'

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 FL is the most common subtype of indolent non-Hodgkin Lymphoma (NHL), accounting for 15-25% of cases in Australia and New Zealand (Tobin 2024). The median age of onset is 60-65 years. Incidence of FL has risen globally in recent decades, and Australian data show an increase from 4.9 to 6.1 cases per 100,000 from 2011 to 2020, with a higher proportion of cases among men than women (AIHW 2024[4], Tobin 2024).

4.2 FL is a slow-dividing, slow-growing B-cell lymphoma that typically forms tumours in lymph nodes, although extra-nodal disease in the bone marrow is also commonly reported. Most patients with FL present with asymptomatic generalised painless enlarged lymph nodes (lymphadenopathy), which may wax and wane for several years (Jacobsen 2022). Approximately 20% of patients present with B-symptoms (night sweats, fever, weight loss). The disease course is variable. Median survival is over 20 years; however, 10-15% of patients with FL die within 5 years of diagnosis (Tobin 2024).

4.3 Pathologic grading is based on the number of centroblasts per high-power field (HPF). Grades 1, 2 and 3a FL are treated as indolent disease. Grade 3b FL is treated as aggressive disease. Staging of FL is made using The Lugano Classification staging system for NHL, which is a modification of the Ann Arbor staging system (Cheson 2014). Prognosis varies depending on patient and disease factors such as age, stage, haemoglobin level, serum lactate dehydrogenase (LDH) level, number of nodal sites, size of lymph nodes, bone marrow involvement and beta2-microglobulin level. The Follicular Lymphoma International Prognostic Index (FLIPI) criteria, developed in 2004 is a validated tool that stratifies patients into risk groups based on 5 criteria (age, Ann Arbor stage, serum LDH level and number of nodal sites) (Solal-Céligny 2004). Patients classified in the low, intermediate and high-risk groups have an estimated 5-year overall survival (OS) of 90.6% 77.6% and 52.5%, respectively, based on the FLIPI criteria (Solal-Céligny 2004).

4.4 Management of FL varies, depending on stage, tumour burden, toxicities, patient age, comorbidities and preferences (Tobin 2024). Patients with low tumour burden and asymptomatic disease do not require treatment and may be monitored on a 'watch and wait' basis (Tobin 2024). Patients with early stage (Lugano Stage I or II) FL may be treated with radiotherapy with a curative intent (Tobin 2024, Dreyling 2021). Patients with symptoms and/or high tumour burden are considered for systemic therapy

[4] AIHW. 2024. Cancer Data in Australia. Australian Institute of Health and Welfare. Available at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/about.

(Tobin 2024). FL also harbours a risk of histological transformation to a high-grade, aggressive lymphoma of 1-3% per year and up to 20% overall (Tobin 2024).

4.5 While FL is responsive to frontline therapy, advanced-stage FL remains incurable, and patients typically experience a chronic relapsing/remitting disease course, with shorter periods between subsequent therapies (Tobin 2024, Wästerlid 2024). First-line therapies usually consist of an anti-CD20 monoclonal antibody (mAb) such as rituximab or obinutuzumab, in combination with chemotherapy or as monotherapy. Responders to first-line therapy may receive anti-CD20 mAb maintenance therapy. For relapsed or refractory FL, the choice of treatment depends on clinical presentation, prior therapy, toxicity and performance status (Tobin 2024, Dreyling 2021). Patients with progression of disease within 24 months of first-line systemic therapy (POD24) have worse outcomes than those who experience disease progression more than 24 months after first-line therapy. Autologous stem cell transplantation (ASCT) may be considered in R/R FL, particularly for patients with POD24 (Tobin 2024). Patients who experience histological transformation to an aggressive lymphoma, such as diffuse large B-cell lymphoma (DLBCL), are treated with regimens recommended for transformed disease (NCCN 2025).

4.6 Tafasitamab is an Fc-enhanced mAb that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes, and on B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL) and FL. Tafasitamab mediates B-cell lysis via engagement of immune effector cells like natural killer cells, γδ T cells and phagocytes and direct induction of apoptosis.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated rituximab-based chemotherapy (R-CHEMO) as the main comparator. The main arguments provided in support of this nomination were:

- Lenalidomide is not TGA indicated or PBS subsidised for R/R FL, and as such, R^2, the comparator in the inMIND trial, was not a suitable comparator for PBS consideration. The extent of use of R^2 in Australia is unknown; however, the sponsor's Advisory Board outlined that some hospitals may fund it for select patients, and some patients may self-fund.
- The sponsor's Advisory Board outlined that R-CHEMO is the most frequently used second-line treatment for R/R FL, and the most commonly used regimen is R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone). R-CHOP-like regimens account for approximately 18% of second-line therapies in Australia (LaRDR Registry report). Table 3 summarises the second-line therapies received by Australian patients enrolled in the LaRDR registry.
- Second-line treatments are selected based on the treatment received in first-line, and the response to that treatment. Obinutuzumab-based chemotherapy

is the most frequently used first-line regimen in Australia, accounting for approximately 47% of treatments given post-PBS listing of obinutuzumab in 2018 (LaRDR Registry report). In patient's R/R to obinutuzumab, second-line therapies may include rituximab-based regimens. Rituximab-based regimens comprise approximately 34% of second-line therapies in Australia (LaRDR Registry report).

- Obinutuzumab and idelalisib were not considered relevant comparators by the submission because the requested population was not restricted to those with refractory disease within 6 months of completion of prior treatment. Additionally, idelalisib use is low due to toxicity. The evaluation considered this was reasonable, although some obinutuzumab with bendamustine (O-B) and idelalisib use may be substituted by the tafasitamab regimen.

Table 3: Second-line therapies received by Australian patients enrolled in the LaRDR Registry

Treatment protocol, (%)	Commenced second line before October 2018 (N=38) 'before obinutuzumab'	Commenced second line after October 2018 (N=50) 'after obinutuzumab'
Rituximab-based	28.9%	34.0%
Bendamustine-rituximab	2.6%	10.0%
R-CVP	0.0%	6.0%
R-CHOP-like	26.3%	18.0%
Obinutuzumab-based	2.6%	6.0%
O-CHOP-like	0.0%	4.0%
Bendamustine-obinutuzumab	2.6%	2.0%
Other chemotherapy-based therapies	57.9%	26.0%
Trial	5.3%	16.0%
Immunotherapy	5.3%	14.0%
Targeted therapies	0.0%	2.0%
CAR-T	0.0%	2.0%

Source: Table 11, p19 of the submission (original source: Table 1.4, LaRDR Registry report, Attachment 2.2 to the submission).
CAR-T = Chimeric Antigen Receptor T-cell therapy; LaRDR = Lymphoma and Related Diseases Registry; O-CHOP = Obinutuzumab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; R-CVP = Rituximab, Cyclophosphamide, Vincristine and Prednisone.

5.2 While comparing tafasitamab plus R^2 to placebo plus R^2 allowed for a blinded randomised trial, the evaluation noted that R^2 is not the most frequently used regimen in countries where R^2 is approved for use in FL. For example, in the United States of America (USA), where lenalidomide in combination with rituximab has been FDA-approved for previously treated FL since 2019, rituximab monotherapy (34%) and R-CHEMO (31%) remain the most commonly used therapies for second-line FL, with R^2 accounting for 6% of therapies given to patients in community facilities (Kambhampati 2024[5]). The evaluation considered that the comparative safety of R^2 versus R-CHEMO

[5] Swetha Kambhampati, Allison Dillon, Paul Cockrum, Syvart Dennen. Changes in Treatment Patterns over Time Among Real-World Patients with Follicular Lymphoma at Predominantly Community Facilities in the US. Blood 2024; 144 (Supplement 1): 3654. doi: https://doi.org/10.1182/blood-2024-203750

may be a factor contributing to the relatively low use of R^2 as: a higher proportion of serious adverse events (35% versus 29%), and study treatment discontinuations (11% versus 3%), dose reductions (36% versus 14%) and dose interruptions (59% versus 35%) were reported in the R^2 arm of REVELANCE compared to the R-CHEMO arm, respectively. The Pre-Sub-Committee Response (PSCR) stated that according to a CancerMPact Report (April 2025 commissioned by Incyte), R^2 was the most commonly used regimen in second-line since the approval of lenalidomide for relapsed FL in 2019. The PSCR also stated that R^2 is the comparator arm in multiple forthcoming registration trials in the R/R FL setting.

5.3 The submission nominated R-CHEMO, represented by R-CHOP, as the comparator. Additionally, other treatment options, such as chemotherapy-based regimens or immunotherapy, would be replaced. However, these were not captured in the trial nor considered in the economic analysis and financial estimates. The ESC considered the submission nominated comparator of R-CHEMO, represented by R-CHOP, was reasonable.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician advised that R^2 is currently the international standard of care for FL in both the first-line and second-line settings and noted that it is not currently available in Australia. The clinician outlined that R^2 offers efficacy comparable to R-CHEMO in the first-line setting and supported the submission argument that this evidence was likely a reasonable proxy for non-inferiority in the R/R FL setting. While the median time to next treatment for current first-line therapy is greater than 10 years, the clinician noted that once second-line treatment is required the prognosis for FL changes significantly. In Australia, patients requiring second-line treatment require repeated retreatment with R-CHEMO. The clinician considered that tafasitamab plus R^2 would provide a highly effective second-line option that increased the time to next treatment (TTNT), which was considered a more relevant endpoint for FL patients. The safety profile was described as comparable overall, with only a slight increase in diarrhoea. The clinician considered that prescribers would adjust lenalidomide dosing to manage toxicity, as tafasitamab itself would not add significant adverse effects. The clinician considered that approval of tafasitamab plus R^2 would reduce current concern that R^2 alone is not available on the PBS in this setting. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (34) and organisations (6) via the Office of Health Technology Assessment Consultation Hub. Health care professionals highlighted that R/R FL is an area of high unmet need with

the limitations of current PBS-subsidised options noted. Clinical need was noted to be particularly important in patients not fit for or unable to access ASCT. Health care professional input described tafasitamab plus R^2 as a treatment offering clinically significant improvements in progression free survival (PFS) and TTNT compared to R^2 alone. Tafasitamab plus R^2 was described as having a favourable safety profile compared to currently available treatments, especially for elderly or frail individuals with an increased risk of cardiac damage and neurotoxicity. Health care professional input outlined the benefits of improved duration of treatment efficacy on quality of life from both a physical and emotional perspective. Input described the lack of access to PBS subsidised non-chemotherapy options as a major gap in the treatment pathway.

6.3 Input from Rare Cancers Australia, Leukaemia Foundation and Lymphoma Australia all highlighted the unmet clinical need for new treatments in this area. The input described how currently available second- and third-line treatment options often involved the same types of chemoimmunotherapy regimens also offered in first-line treatment. Consumer organisations described the effectiveness of tafasitamab plus R^2 and how it offered a less invasive alternative for patients than ASCT or Chimeric Antigen Receptor T-cell (CAR-T) therapy. Consumer organisations also noted issues of equitable access with the cost of self-funding tafasitamab plus R^2 prohibitive for most consumers.

6.4 The PBAC noted the advice received from Australian Leukaemia & Lymphoma Group, Peter MacCallum Cancer Centre Lymphoma Group and the Haematology Society of Australia and New Zealand clarifying the likely use of tafasitamab plus R^2 in clinical practice. The input described the current unmet need given Australian patients do not have access to the R^2 which is internationally recognised as standard of care in this setting. Consistent with the input from health care professionals and consumer organisations these organisations highlighted the effectiveness of tafasitamab plus R^2 in treating R/R FL. The input noted that the preservation of CD19 expression at relapse post-tafasitamab (which targets CD19) should preserve third-line CAR-T availability if needed. Input from these health care professional organisations expected the uptake of tafasitamab plus R^2 to be high if recommended for PBS subsidy.

Clinical trials

6.5 No head-to-head trials comparing tafasitamab plus R^2 to R-CHEMO were available. The submission was based on one head-to-head randomised trial comparing tafasitamab plus R^2 and placebo plus R^2 in the R/R FL population: inMIND (NCT04680052). The submission also presented one head-to-head randomised trial comparing R^2 and R-CHEMO in first-line treatment of people with FL: RELEVANCE (NCT01650701). A claim of superior efficacy was made against the nominated comparator, R-CHEMO, based on outcomes of PFS, OS, positron emission tomography complete response (PET-CR) rate, and TTNT from inMIND against R^2. The acceptance of this claim also required the

acceptance of a non-inferiority claim between R^2 and R-CHEMO in R/R FL based on the first-line results of RELEVANCE.

6.6 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trials and key associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Tafasitamab vs R^2		
InMIND [NCT04680052]	A Phase 3, Randomised, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma Sehn, L. H., et al. (2024). Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma: results from a Phase 3 Study (inMIND). Sehn, L. H., et al. (2025). Outcomes from the Phase 3 inMIND study of tafasitamab plus lenalidomide and rituximab for patients with relapsed/refractory follicular lymphoma.	Clinical Study Report - interim analyses based on a data cut-off date of 23 February 2024 Blood 144: LBA-1. Presentation slides from International Conference on malignant Lymphoma (18th ICML) 2025, in Lugano, Switzerland (June 17-21, 2025).
R^2 vs R-CHEMO in first-line FL		
RELEVANCE [Trial NCT01650701]	Morschhauser, F., et al. (2022). Six-Year Results from RELEVANCE: Lenalidomide Plus Rituximab (R^2) Versus Rituximab Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma. Morschhauser, F., et al. (2018). Relevance: Phase III efficacy and safety study of lenalidomide plus rituximab (R^2) versus rituximab plus chemotherapy, followed by rituximab, in previously untreated follicular lymphoma.	Journal of Clinical Oncology **40**(28): 3239-3245. HemaSphere 2: 31-32.

Source: Table 27, pp50-51 of the submission.
FL = follicular lymphoma; R^2 = lenalidomide plus rituximab; R-CHEMO = rituximab-based chemotherapy; R/R = relapsed/refractory.

6.7 The key features of the direct randomised trials are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Tafasitamab + R^2 vs Placebo + R^2						
inMIND	548[a] Enrolled: Apr 2021 - NR Median OS follow-up[c] (months): T+R^2: 15.8 R^2: 14.6	R, MC, DB, P3, PC, PG	Low	CD19+ and CD20+ R/R[b] FL	PFS, PET-CR, OS, TTNT, HRQoL, safety	PFS, OS, TTNT, HRQoL (limited)
R^2 vs R-CHEMO in advanced untreated FL						
RELEVANCE	1030 Enrolled: Dec 2011 - Nov 2014 Median follow-up: 72 months	R, MC, OL, P3	Low	CD20+ grade 1-3a untreated FL	CR at 120 weeks, PFS, OS, safety	Not used

Source: Table 96, p176 of the submission, Morschhauser 2018, Morschhauser 2022.
CR = complete response; DB = double blind; FL = follicular lymphoma; HRQoL = health related quality of life; MZL = marginal zone lymphoma; MC = multi-centre; ND = not reported; OL = open label; OS = overall survival; P3 = phase 3; PC = placebo-controlled; PET = positron emission tomography; PFS = progression-free survival; PG = parallel group; R = randomised; R^2 = lenalidomide plus rituximab; R/R = relapsed/refractory; T = tafasitamab; TTNT=time to next treatment.
[a] FL cohort. inMIND also enrolled n=106 patients with MZL.
[b] Refractory to or relapsed after prior anti-CD20 monoclonal antibody therapy

[c] OS follow-up at Interim analysis data cut-off 23rd February, 2024.

6.8 The inMIND trial enrolled 548 patients with R/R FL and 106 patients with marginal zone lymphoma (MZL). The FL and MZL cohorts were randomised separately and reported separately a priori. Results from the FL cohort were used as the evidence base for the submission. Patients in the FL cohort were stratified by POD24 after initial diagnosis (yes or no), refractoriness to prior anti-CD20 monoclonal antibody therapy (yes or no) and the number of prior lines of therapy (<2 or ≥2), and randomised 1:1 to receive tafasitamab plus R^2 or placebo plus R^2.

6.9 The ESC noted important differences between inMIND and RELEVANCE:

- The inMIND population was R/R FL, whereas the RELEVANCE population had previously untreated FL.
- The R^2 regimen in RELEVANCE was not the same as the regimen used in the inMIND trial. The inMIND trial R^2 regimen included 12 * 28-day cycles of lenalidomide 20 mg (on days 1 to 21) plus rituximab, whereas RELEVANCE included a total of 18 * 28-day cycles of lenalidomide plus rituximab for those assessed as responders (complete response [CR] or partial response [PR]) after the first 6 cycles, with lenalidomide dose reduced to 10 mg for patients achieving CR.
- The inMIND trial did not include maintenance therapy, whereas patients in RELEVANCE received maintenance with rituximab as monotherapy every 8 weeks for 12 cycles (i.e., 6 doses for patients in the R^2 arm).

6.10 The ESC agreed with the evaluation that the overall evidence presented in the submission was considered to be of high risk of bias, despite the individual trials being RCTs. This was due to the need to use an unanchored comparison between trials of patients in different lines of therapy who received different regimens of the comparison treatment, as the incomplete network of trials identified in the R/R setting prevented the conduct of an anchored indirect comparison.

Comparative effectiveness

6.11 Table 6 summarises the key survival and time to event outcomes from the inMIND trial. The corresponding Kaplan-Meier curves are presented in Figure 1.

Table 6: Summary of time to event outcomes in inMIND (DCO 23rd February, 2024)

	Tafasitamab + R^2 N=273	Placebo + R^2 N=275	Absolute difference	HR (95% CI)
Progression-free survival (investigator assessed) – Primary trial outcome				
Events, n (%)	75 (27.5)	131 (47.6)	-	
Median PFS, months (95% CI)	22.37 (19.22, NE)	13.93 (11.53, 16.39)	8.44	**0.434 (0.324, 0.580)**, p<0.0001
PFS rate[a], % (95% CI)				-
6 months	92.4 (88.3, 95.1)	78.2 (72.7, 82.7)	14.2	-
12 months	79.0 (72.8, 84.0)	54.0 (47.1, 60.5)	25.0	-
2 years	41.7 (28.4, 54.6)	31.8 (23.6, 40.2)	9.9	-
Overall survival				
Deaths, n (%)	15 (5.5)	23 (8.4)	-	
Median months OS (95% CI)	NE (27.93, NE)	NE (NE, NE)	NE	0.587 (0.306, 1.128) p=0.1061
OS rate[a] (95% CI)				-
12 months	96.4 (92.8, 98.2)	93.7 (90.0, 96.1)	2.7	-
24 months	92.5 (87.0, 95.8)	85.5 (76.2, 91.4)	7.0	-
Time to first objective response				
Participants with objective response, n (%)[c]	228 (83.5)	199 (72.4)	-	-
Median time to first objective response, months (95% CI)	2.83 (1.0, 10.9)	2.83 (1.9, 11.4)	0.0	NR
Duration of response				
Number (%) of Responders	228 (83.5)	199 (72.4)		
Number (%) of responders with disease progression or death	53 (23.2)	78 (39.2)		
Median DOR (months) (95% CI)	21.19 (19.48, NE)	13.60 (12.42, 18.56)	7.59	**0.47 (0.33, 0.68)** p<0.0001
DOR rate (95% CI)				
6 months	91.5 (86.6, 94.6)	77.8 (70.9, 83.2)	13.7	-
12 months	76.3 (68.4, 82.4)	59.1 (50.3, 66.9)	17.2	-
2 years	39.5 (21.4, 57.1)	33.3 (20.5, 46.6)	6.2	-
Time to next treatment				
Events, n (%)	47 (17.2)	89 (32.4)		
Median TTNT[a], months (95% CI)	NE (NE, NE)	28.81 (20.73, NE)	NE	**0.447 (0.314, 0.638)** p<0.0001
PFS on next antilymphoma treatment				
Participants with events, n (n/N%)	27 (9.9)	43 (15.6)		
Median PFS[d], months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE	**0.556 (0.343, 0.902)** p=0.0158
PFS rate on next antilymphoma treatment (95% CI)				
6 months	98.5 (96.1, 99.4)	95.5 (92.2, 97.4)	3.0	-
12 months	92.8 (88.5, 95.6)	86.5 (81.4, 90.3)	6.3	-
2 years	85.3 (78.6, 90.0)	72.9 (62.5, 80.9)	12.4	-

Bold indicates statistically significant results.

Source: Table 53, p93, Table 54, p94 and Table 55, p96 of the submission and Table 28, p92 and Table 2.2.16.1, p1784 of the inMIND CSR.

CI = confidence interval; DCO = data cut-off; DOR = duration of response; HR = Hazard Ratio; KM = Kaplan-Meier; max = maximum; min = minimum; n = number of participants reporting data; N = total participants in group; NE = not evaluable; NR = not reported; OS = overall survival; R^2 = lenalidomide + rituximab; TTNT = time to next treatment.

[a] Estimated using the KM method.

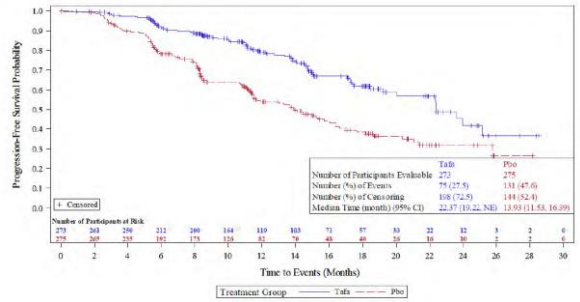
[b] The HR was estimated using a stratified Cox proportional hazards model.

[c] Time to objective response was defined as the time from the randomisation date to the date of first objective response (CR or PR).

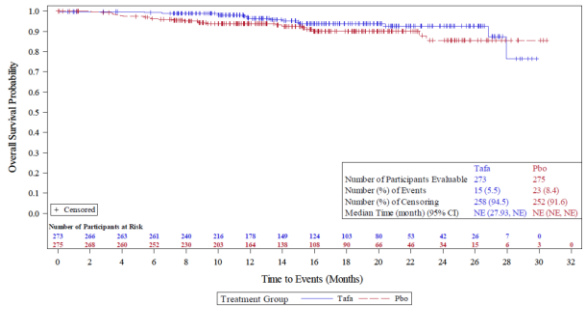
[d] PFS on next antilymphoma treatment defined as the time from randomisation to the time of second objective disease progression, or death from any cause, whichever first.

Figure 1: KM curves for time to event outcomes from the inMIND trial

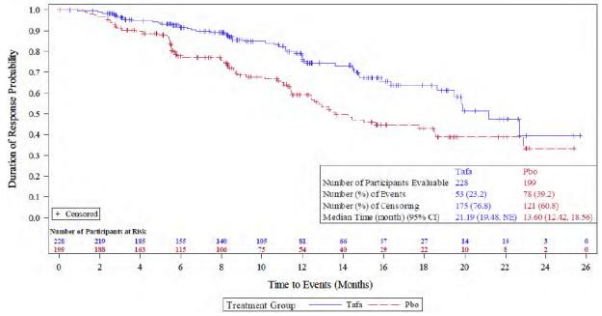
A. PFS



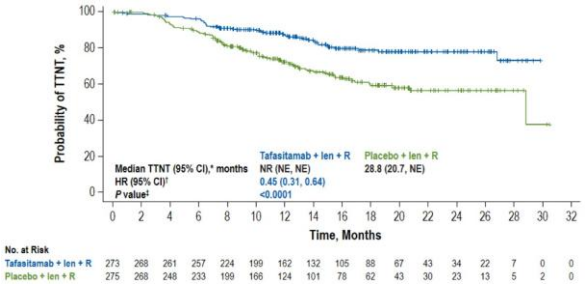
B. OS



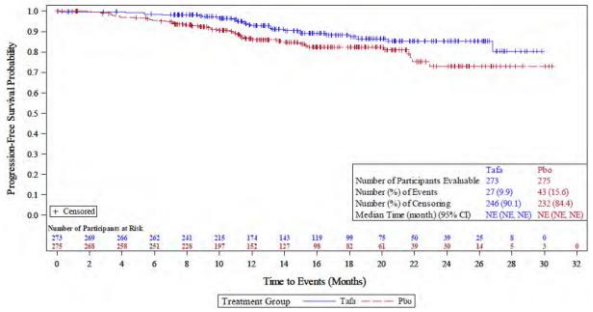
C. DOR



D. TTNT



E. PFS on next antilymphoma treatment



Source: A. Figure 10, p91 of the submission, B. Figure 4, p86 of the inMIND CSR, C. Figure 13, p99 of the submission, D. Figure 12, p95 of the submission (original source Sehn 2025) and E. Figure 7, p104 of the inMIND CSR.
CI = confidence interval; DOR = duration of response; FL = follicular lymphoma; HR = hazard ratio; len = lenalidomide; NE = not estimable; Pbo = Placebo + R^2; PFS = progression-free survival; OS = overall survival; R^2 = lenalidomide + rituximab; Tafa = tafasitamab + R^2; TTNT time to next treatment.

Note: PFS on next antilymphoma treatment defined as the time from randomisation to the time of second objective disease progression, or death from any cause, whichever first.

6.12 Tafasitamab plus R^2 was associated with a statistically significant PFS benefit, with a 56.6% reduction in risk of progressive disease (PD) or death, by investigator assessment, compared to placebo plus R^2. The Independent Review Committee (IRC) assessed fewer patients in both arms as having PD compared to investigators (5.8% fewer in the tafasitamab arm and 7.6% fewer in the placebo arm); however, the PFS hazard ratios (HRs) were similar (HR: 0.434 [95% Confidence Interval {CI} 0.324, 0.580] per investigator assessment versus HR: 0.407 [95% CI: 0.294, 0.563] per IRC).

6.13 OS remained immature at the time of evaluation, with a median OS follow-up of 15.0 months in the tafasitamab arm and 14.1 months in the placebo arm, with only 15 (5.5%) and 23 (8.4%) deaths for tafasitamab+R^2 and R^2, respectively, and median OS not reached in either arm. The point estimate of OS HR favoured patients in the tafasitamab arm; however, the result was not statistically significant (HR 0.587 [95% CI: 0.306, 1.128]). The 2-year estimates of OS rate were 92.5% of patients in the tafasitamab arm and 85.5% of patients in the placebo arm. Final analysis of OS is expected in August 2028.

6.14 There was no difference between study arms in the median time to first objective response. Duration of Response (DOR) per Investigator Assessment was 7.6 months longer for patients in the tafasitamab arm compared to the placebo arm (21.19 months [95% CI: 19.48, not estimable {NE}] versus 13.60 months [95% CI: 12.42, 18.56], respectively), with 53 (23.2%) responders in the tafasitamab arm and 78 (39.2%) responders in the placebo arm having disease progression or death. At 2 years, the DOR rate was 6.2% higher in the tafasitamab arm than in the placebo arm.

6.15 At data cut-off (DCO), 23rd February 2024, 226 (82.8%) of patients in the tafasitamab arm and 186 (67.6%) patients in the placebo arm were alive and had not initiated a new antilymphoma treatment, while 36 (13.2%) and 78 (28.4%) patients, respectively, had started a new antilymphoma treatment (based on censored participants). Patients in the tafasitamab arm had significantly longer TTNT compared to those in the placebo arm, with median TTNT not yet reached versus 28.81 months, respectively, and HR 0.45 (95% CI: 0.31, 0.64).

6.16 PFS on next antilymphoma treatment was measured from the time of randomisation and may be biased towards the tafasitamab arm due to the significantly longer TTNT in patients in that study arm. When considering only the participants who began a new antilymphoma treatment, both study arms had similar proportions of patients with second PFS events. Of the participants who started a new antilymphoma treatment, 13 (36.1%) participants in the tafasitamab arm had PD or started a subsequent antilymphoma therapy, and there were 3 deaths, compared to 28 (35.9%) and 4, respectively, in the placebo arm. It was unclear when these second PFS events occurred in relation to starting the new therapy. These results suggested that while tafasitamab plus R^2 may benefit patients by increasing time to first PFS and TTNT, this benefit may not be maintained after further lines of treatment.

6.17 Table 7 presents the PET-CR rate and overall response rate (ORR) from the inMIND trial.

Table 7: PET-CR rate and overall response rate from the inMIND trial (FL FDG-Avid set[e])

Variable	Tafasitamab + R^2 (N=251)	Placebo + R^2 (N=254)	Absolute difference	OR (95% CI)
PET-CR Rate				
Participants with post-baseline PET assessment[a], n (%)	201 (80.1)	205 (80.7)	-	-
Best metabolic response based on PET			-	
- CMR	124 (49.4)	101 (39.8)	-	-
- PMR	37 (14.7)	39 (15.4)	-	-
- No metabolic response / SD	19 (7.6)	12 (4.7)	-	-
- Progressive metabolic disease / PD	19 (7.6)	51 (20.1)	-	-
- NE	0 (0.0)	0 (0.0)	-	-
- PET scan after confirmed PD or start of new antilymphoma treatment	2 (0.8)	2 (0.8)	-	-
- Not assessed[b]	50 (19.9)	49 (19.3)	-	-
PET-CR rate (95% CI)[c]	49.4 (43.06, 55.76)	39.8 (33.70, 46.07)	9.6	**1.5 (1.04, 2.13)** p=0.0286
Best overall response per Lugano Classification, n (%)				
Complete Response (CR)	142 (52.0)	112 (40.7)	-	
Partial Response (PR)	86 (31.5)	87 (31.6)	-	
Stable Disease (SD)	28 (10.3)	46 (16.7)	-	
Progressive Disease (PD)	7 (2.6)	20 (7.3)	-	
Not Evaluable (NE)	2 (0.7)	0	-	
Not Done	8 (2.9)	10 (3.6)	-	
ORR[d] (95% CI)	83.5 (78.57, 87.72)	72.4 (66.67, 77.56)	11.1	**2.0 (1.30, 3.02)** p=0.0014

Bold type indicates statistical significance.

Source: Table 52, p92 of the submission (Original Source: inMIND CSR Table 2.2.1.1.).

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CMR = Complete Metabolic Response; CR = Complete Response; FDG = Fluorodeoxyglucose; FL= follicular lymphoma; NE = Not Evaluable; OR = Odds Ratio; PD = Progressive Disease; PET = Positron Emission Tomography; PMR = Partial Metabolic Response; R^2 = Lenalidomide + Rituximab; SD, Stable Disease.

[a] Percentages were calculated based on participants with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline.

[b] Not assessed includes participants who did not have a post-baseline PET scan.

[c] The PET-CR rate was defined as the proportion of participants who achieved a CMR at any time after the start of treatment as per Lugano Classification among the participants with a positive PET scan at baseline. Participants with no post-baseline assessment by PET or who did not achieve a CMR were classified as non-CR responders.

[d] ORR defined as the proportion of participants who achieved a CR or PR as determined per Lugano classification at any time during the study but before the first PD and before/at the start of a new anti-lymphoma treatment

[e] The fluorodeoxyglucose (FDG)-Avid Set (n=505: 92.2% of trial FL population) included all randomised participants with a PET scan at baseline with a resulting Deauville score of 4 or 5.

6.18 There was a statistically significant difference in investigator assessed PET-CR rate between the treatment groups, with an estimated odds ratio (OR) of 1.5 (95% CI: 1.04, 2.13). In the tafasitamab plus R^2 arm, 49.4% (n=124) patients achieved complete metabolic response compared to 39.8% (n=101) patients in the placebo + R^2 arm. A lower proportion of patients in the tafasitamab arm had progressive metabolic disease compared to those in the placebo arm (7.6% versus 20.1%).

6.19 The ORR was higher in the tafasitamab plus R^2 arm than in the placebo plus R^2 arm (ORR 83.5 [95% CI: 78.57, 87.72] versus 72.4 [95% CI: 66.67, 77.56]), with more patients in both arms achieving CR than PR (52.0% vs 31.5%, respectively in the tafasitamab arm compared to 40.7% vs 31.6%, respectively, in the placebo arm).

Patients in the tafasitamab arm had twice the odds of achieving an objective response (CR or PR) than those in the placebo arm (OR 2.0 [95% CI: 1.30, 3.02]).

6.20 No patients in the tafasitamab arm and n=9 (3.3%) patients in the placebo arm experienced transformation of FL into a more aggressive state. This was consistent with an annual transformation rate of 1 to 3% per annum reported in the literature (Tobin 2024). Longer term follow-up is necessary to determine whether the tafasitamab plus R^2 regimen reduces the rate of histological transformation to a clinically meaningful or statistically significant degree.

6.21 Table 8 summarises the patient-reported outcomes from the inMIND trial.

Table 8: Patient reported outcomes from the inMIND trial

	Tafasitamab + R^2 (N=273)		Placebo + R^2 (N=275)	
Timepoint	**N**	**Mean (SD)**	**N**	**Mean (SD)**
EORTC QLQ-C30 Global Health Status				
Baseline	266	68.6 (20.4)	266	68.6 (21.9)
End of treatment	186	67.7 (21.4)	186	67.5 (21.0)
Mean Change from Baseline (Mean % Change)	–	-0.5 (8.9)	–	-0.9 (8.1)
Mann-Whitney tests on Mean Change from Baseline	0.7639			
EQ-5D-5L VAS				
Baseline	264	72.5 (18.2)	264	73.6 (19.1)
End of treatment	186	73.7 (18.2)	186	72.5 (19.2)
Mean Change from Baseline (Mean % Change)	–	0.6 (5.7)	–	-1.7 (3.5)
Mann-Whitney tests on Mean Change from Baseline	0.3884			
FACT-Lym Total Score				
Baseline	259	24.0 (4.3)	263	24.3 (4.1)
End of treatment	184	23.5 (4.7)	183	23.2 (5.4)
Mean Change from Baseline (Mean % Change)	-	-0.3 (2.1)	-	-1.2 (-2.0)
Mann-Whitney tests on Mean Change from Baseline	0.3201			

Source: Table 60, p101, Table 61, p102 and Table 52, p103 of the submission.
EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol five Dimensions 5 Level; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; R^2 = Lenalidomide + Rituximab; SD = standard deviation; VAS = visual analogue scale.

6.22 Baseline scores for each health-related quality of life (HRQoL) instrument were similar across the treatment arms. There were no significant changes between baseline and the end of treatment assessment in any score or subscore reported for any of the instruments in either treatment arm.

Evidence for non-inferiority of R^2 and R-CHEMO

6.23 Given the lack of direct evidence to support the clinical comparison between tafasitamab plus R^2 and R-CHEMO regimens in patients with R/R FL in the second-line setting, the clinical therapeutic relativity of R^2 versus R-CHEMO in the first-line setting was used. To support extending the non-inferiority of R^2 and R-CHEMO to the second-line setting, the submission argued that there was consensus among haematology experts (per Advisory Board discussions) that non-inferiority of R^2 versus R-CHEMO (i.e. R-CHOP) in the first-line setting, can be a reasonable proxy for non-inferiority of R^2 versus rituximab-based chemotherapy limited to the R/R FL setting. The ESC noted the submission presented the RELEVANCE study, identified in the literature search, comparing R^2 versus R-CHEMO, consisting of R-CHOP (72%), rituximab plus

bendamustine (R-B) (23%), and rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP) (5%) in the first-line setting (Morschhauser 2018[6]).

6.24 Patients enrolled in RELEVANCE were younger than those enrolled in inMIND (median age 59 years compared to mean age 64, respectively) and similar to those enrolled in inMIND with respect to ECOG performance score, FL Grade and FLIPI score. However, patients in RELEVANCE had no prior systemic antilymphoma therapy, whereas patients enrolled in inMIND had had at least one prior therapy, including n=245 (45%) who had had at least 2 prior lines of therapy.

6.25 The ESC noted the R^2 regimen in RELEVANCE differed from that used in the inMIND trial. The RELEVANCE study design constituted three distinct treatment periods over a total of 120 weeks. The R^2 regimen for Treatment Period 1 consisted of lenalidomide 20mg daily on days 2 to 22 of each 28-day cycle, and rituximab 375 mg/m^2 of body surface area on days 1, 8, 15 and 22 of cycle 1 and then on day 1 of cycles 2 to 6. The dose of lenalidomide in Treatment Period 2 was dependent on the response assessment after the first 6 cycles: patients with CR then received lenalidomide 10mg daily for the remaining cycles; patients with PR received lenalidomide 20mg daily for 3 or 6 additional cycles until a CR was observed, then received lenalidomide 10mg daily for the remaining cycles (18 cycles total). Responders continued to receive rituximab every 8 weeks for a further 12 cycles in Treatment Period 3. Patients in the R-CHEMO arm received their R-CHEMO regimen in Treatment Period 1, with responders receiving rituximab maintenance therapy for Treatment Periods 2 and 3.

6.26 The key outcomes from RELEVANCE were CR, PFS, OS and safety. Table 9 presents efficacy results from RELEVANCE. Figure 2 presents survival curves for PFS and OS from RELEVANCE.

Table 9: Efficacy results from the RELEVANCE trial (IRC assessed)

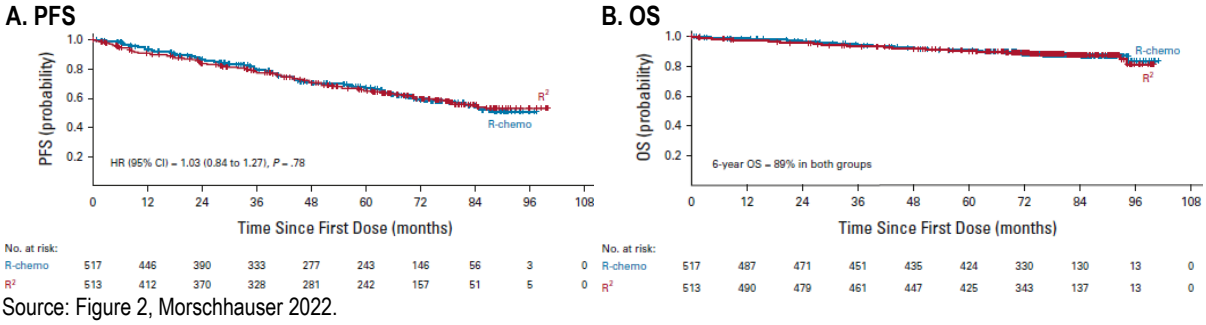
Outcome	R^2 (N = 513)	R-CHEMO (N = 517)	HR [95% CI]
Overall response at 6 years, n (%) [95% CI]	312 (61 [56–65])	336 (65 [61–69])	-
Complete response + complete response unconfirmed, n (%; 95% CI)	247 (48 [44–53])	274 (53 [49–57])	-
Complete response, n (%)	142 (28)	169 (33)	-
Complete response unconfirmed, n (%)	105 (20)	105 (20)	-
Partial response, n (%)	65 (13)	62 (12)	-
Stable disease, n (%)	2 (<1)	0	-
PD/death, n (%)	87 (17)	79 (15)	-
Not evaluated/not done/missing, n (%)	112 (22)	102 (20)	-
PFS, % (95% CI)			
PFS at 3 years	77 (72–80)	78 (74–82)	1.10 (0.85–1.43); p=0.48
PFS at 6 years	60 (55 to 64)	59 (54 to 64)	1.03 (0.84 to 1.27); p=0.78
OS, %			
OS at 3 years	94%	94%	1.16 (0.72-1.86)
OS at 6 years	89%	89%	1.00 (NR)

Source: Table 72, p122 of the submission. (Original sources: Morchhauser 2018, Morschhauser 2022)

[6] Morschhauser F, Fowler NH, Feugier P, et al. 2018. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med 379(10): 934-947. Available at: 10.1056/NEJMoa1805104.

CI = confidence interval; HR = hazard ratio; IRC = independent review committee; INV = investigator; NR = not reported; PD = progressive disease; PFS = progression-frees survival; R^2 = rituximab plus lenalidomide; R-CHEMO, rituximab plus chemotherapy.

Figure 2: PFS and OS from RELEVANCE



Source: Figure 2, Morschhauser 2022.
HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

6.27 The efficacy outcomes from the RELEVANCE trial support the trial conclusion that R^2 is non-inferior to R-CHEMO in first-line treatment of Grade 1-3a FL. It, however, remained unclear whether the non-inferiority conclusions from the first-line setting can be generalised to the R/R setting. It was unknown whether the differences in the R^2 regimen between RELEVANCE and inMIND protocol would impact the conclusion of non-inferiority between R^2 and R-CHEMO. Further, the ESC noted the complete and overall response rates with R^2 were higher in the second-line inMIND trial than in the first-line RELEVANCE trial (40.7% vs 28% complete response; 72% vs 61% overall response; respectively) which was unexpected given response rates are generally lower with each line of treatment. The ESC considered this highlighted the differences between the two trials (e.g. in terms of population, R^2 dose, duration of follow-up, and outcome reporting including confirmation of complete responses), contributing to the uncertainty regarding the claim of non-inferiority between R^2 and R-CHEMO.

6.28 The adverse events reported in the RELEVANCE trial were consistent with the known safety profiles of the regimens. A higher proportion of patients in the R^2 arm compared to R-CHEMO experienced a serious adverse event (SAE) (35% versus 29%), or a treatment-emergent adverse event (TEAE) leading to study treatment discontinuation (11% versus 3%), dose reduction (36% versus 14%) or dose interruption (59% versus 35%) (Morschhauser 2018). Patients in the R^2 arm reported higher proportions of cutaneous reactions (43% versus 24%), diarrhoea (37% versus 19%), rash (29% versus 8%), myalgia (14% versus 6%), peripheral oedema (14% versus 9%) and muscle spasms (13% versus 4%) than those on an R-CHEMO regimen, respectively. Patients in the R^2 arm reported lower proportions of patients with anaemia (66% versus 89%), nausea (20% versus 42%), vomiting (7% versus 19%), peripheral neuropathy (7% versus 16%), leukopenia (4% versus 10%), febrile neutropenia (2% versus 7%), alopecia (1% versus 9%) and Grade 3 or 4 neutropenia (32% versus 50%) than those on an R-CHEMO regimen.

Comparative harms

6.29 Table 10 presents the key safety data from the FL safety population of the inMIND trial.

Table 10: Summary of key adverse events from the inMIND trial

TEAE Category	Tafasitamab plus R² N=274 n with event (%)	Placebo plus R² N=272 n with event (%)	RD [95% CI][a]	RR [95% CI][a]
Any TEAE	272 (99.3)	270 (99.3)	0.00 [-0.01, 0.11]	1.00 [0.99, 1.01]
Serious TEAE	99 (36.1)	86 (31.6)	0.05 [-0.03, 0.13]	1.15 [0.91, 1.46]
Grade 3 or 4 TEAE	195 (71.2)	189 (69.5)	0.02 [-0.06, 0.09]	1.02 [0.92, 1.14]
Fatal TEAE	6 (2.2)	6 (2.2)	-0.00 [-0.02, 0.02]	0.99 [0.32, 3.04]
TEAE attributed to Tafasitamab/placebo				
Tafasitamab/placebo-related TEAE	202 (73.7)	179 (65.8)	0.08 [0.01, 0.16]	1.12 [1.01, 1.26]
Serious tafasitamab/placebo-related TEAE	29 (10.6)	32 (11.8)	-0.01 [-0.06, 0.04]	0.90 [0.56, 1.44]
Grade 3 or 4 tafasitamab/placebo-related TEAE	112 (40.9)	100 (36.8)	0.04 [-0.05, 0.12]	1.10 [0.89, 1.35]
Fatal tafasitamab/placebo-related TEAE	0 (0.0)	2 (0.7)	-0.01 [-0.02, 0.00]	NC
TEAE leading to permanent discontinuation of:				
Tafasitamab/placebo	30 (10.9)	18 (6.6)	0.04 [-0.00, 0.09]	1.65 [0.95, 2.90]
Lenalidomide	39 (14.2)	31 (11.4)	0.03 [-0.03, 0.08]	1.25 [0.80, 1.94]
Rituximab	8 (2.9)	8 (2.9)	-0.00 [-0.03, 003]	0.99 [0.38, 2.61]
TEAE leading to dose delay or dose interruption of:				
Tafasitamab/placebo	203 (74.1)	190 (69.9)	0.04 [-0.03, 0.12]	1.06 [0.96, 1.18]
Lenalidomide	210 (76.6)	197 (72.4)	0.04 [-0.03, 0.12]	1.06 [0.96, 1.17]
Rituximab	124 (45.3)	125 (46.0)	-0.01 [-0.09, 0.08]	0.98 [0.82, 1.18]
Most commonly reported TEAEs				
Grade 3 or 4 TEAE in ≥ 5% of participants in any group	195 (71.2)	189 (69.5)	0.02 [-0.06, 0.09]	1.02 [0.92, 1.14]
Neutropenia	109 (39.8)	102 (37.5)	0.02 [-0.06, 0.10]	1.06 [0.86, 1.31]
Pneumonia	23 (8.4)	14 (5.1)	0.03 [-0.01, 0.07]	1.63 [0.86. 3.10]
Thrombocytopenia	17 (6.2)	20 (7.4)	-0.01 [-0.05, 0.03]	0.84 [0.45, 1.58]
COVID-19	16 (5.8)	6 (2.2)	0.04 [0.00, 0.07]	2.64 [1.05, 6.66]
Neutrophil count decreased	16 (5.8)	18 (6.6)	-0.01 [-0.05, 0.03]	0.88 [0.46, 1.69]
Anaemia	12 (4.4)	16 (5.9)	-0.02 [-0.05, 0.02]	0.74 [0.36, 1.54]
Tafasitamab/placebo-related TEAEs in ≥ 5% of participants in any group	202 (73.7)	179 (65.8)	0.08 [0.01, 0.16]	1.12 [1.01, 1.26]
Neutropenia	90 (32.8)	78 (28.7)	0.04 [-0.04, 0.12]	1.15 [0.89, 1.47]
Fatigue	28 (10.2)	11 (4.0)	0.06 [0.02, 0.10]	2.53 [1.28, 4.97]
Thrombocytopenia	26 (9.5)	9 (3.3)	0.06 [0.02, 0.10]	2.87 [1.37, 6.01]
Diarrhoea	23 (8.4)	20 (7.4)	0.01 [-0.03, 0.06]	1.14 [0.64,2.03]
Infusion-related reaction	23 (8.4)	10 (3.7)	0.05 [0.01, 0.09]	2.28 [1.11, 4.71]
Pyrexia	18 (6.6)	13 (4.8)	0.02 [-0.02, 0.05]	1.37 [0.69, 2.75]
Constipation	19 (6.9)	13 (4.8)	0.02 [-0.02, 0.06]	1.45 [0.73, 2.88]
Anaemia	17 (6.2)	11 (4.0)	0.02 [-0.02, 0.06]	1.53 [0.73, 3.21]
Neutrophil count decreased	16 (5.8)	11 (4.0)	0.02 [-0.02, 0.05]	1.45 [0.69, 3.08]
Pneumonia	16 (5.8)	9 (3.3)	0.03 [-0.01, 0.06]	1.76 [0.79, 3.92]
COVID-19	15 (5.5)	14 (5.1)	0.00 [-0.03, 0.04]	1.06 [0.52, 2.16]
Nausea	14 (5.1)	14 (5.1)	-0.00 [-0.04, 0.04]	0.99 [0.48, 2.04]
Rash	14 (5.1)	15 (5.5)	-0.00 [-0.04, 0.03]	0.93 [0.46, 1.88]

Source: Table 63, p104 of the submission

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse event.

Note: It was unclear from the protocol and CSR how TEAEs were attributed to individual components of the regimens.

[a] Indicates results calculated during the evaluation.

6.30 Treatment-emergent adverse events (TEAEs) were reported by almost all participants in the trial. A slightly higher proportion of patients in the tafasitamab arm experienced a serious TEAE (36.1% versus 31.6% in the placebo arm), and the proportions of patients who experienced a Grade 3 or 4 TEAE, or a fatal TEAE were similar in both treatment arms. A slightly higher proportion of patients in the tafasitamab arm experienced a TEAE attributed to tafasitamab/placebo than in the placebo arm (73.7% versus 65.8%). No information was provided in the submission or the Clinical Study Report (CSR) relating to how TEAEs were attributed to tafasitamab/placebo, lenalidomide or rituximab. More patients in the tafasitamab arm had a TEAE leading to permanent discontinuation of tafasitamab (10.9% versus 6.6% in the placebo arm) or lenalidomide (14.2% versus 11.4% in the placebo arm). More patients in the tafasitamab arm had a dose delay or dose interruption of tafasitamab (74% versus 69.9% in the placebo arm) or lenalidomide (75.5% versus 72.4% in the placebo arm).

6.31 There were 6 fatal TEAEs in each study arm. In the tafasitamab arm, the fatal TEAEs were attributed to COVID-19 (n=2), sepsis, gastric adenocarcinoma, carcinoid tumour of the large intestine, and 'death'. In the placebo arm, the fatal TEAEs were attributed to cardiac failure, bronchopulmonary aspergillosis, COVID-19 pneumonia (n=2), pneumonia and sepsis. None of the fatal TEAEs in the tafasitamab arm were considered to be treatment-related.

6.32 Neutropenia was the most commonly reported Grade 3 or 4 TEAE, occurring in 39.8% of patients in the tafasitamab arm and 37.5% of patients in the placebo arm; however, only 0.7% and 1.1% of neutropenia TEAEs, respectively, were considered serious. The proportions of TEAEs considered tafasitamab/placebo related were largely similar across study arms. However, fatigue (10.2% versus 4.0%), thrombocytopenia (9.5% versus 3.3%) and infusion-related reaction (8.4% versus 3.7%) were more commonly reported in the tafasitamab arm (10.2% versus 4.0%) than in the placebo arm.

Benefits/harms

6.33 The unanchored comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of tafasitamab plus R^2 and R-CHEMO. Accordingly, a benefits/harms table has not been presented.

6.34 If the submission's assumption that R^2 and R-CHOP are non-inferior in terms of efficacy in the R/R setting is accepted, then, based on the results of the inMIND trial, for every 100 patients treated with tafasitamab plus R^2, after 2 years:

- Approximately 10 additional patients would be alive and progression-free.
- Patients who responded to treatment would have a 7.6 month longer duration of response.
- There would be no statistically significant benefit in OS.

6.35 The submission made a claim of inferior safety. However, considering the different R^2 regimens in the RELEVANCE and inMIND trials, and the different lines of therapy, it

was not possible to quantify the differences in harms due to the different adverse event (AE) profiles of the R^2 and R-CHOP regimens.

Clinical claim

6.36 The submission described tafasitamab plus lenalidomide and rituximab as superior in terms of effectiveness compared with rituximab-based chemotherapy and inferior in terms of safety compared to rituximab-based chemotherapy, but with an acceptable safety profile.

6.37 The evaluation considered the therapeutic conclusion was adequately supported by the clinical evidence presented; however, uncertainty remained regarding the magnitude of the benefit in the Australian setting due to the following:

- While the tafasitamab plus R^2 regimen demonstrated a clinically and statistically significant benefit compared to placebo plus R^2 in PFS, PET-CR rate, ORR, DOR and TTNT, its benefit over standard of care in Australia, including R-CHOP and other rituximab-based chemotherapy regimens, remains unknown.
- Lenalidomide was not TGA approved or PBS listed for FL. Although off-label use as part of the R^2 regimen may occur in Australia, it is likely limited.
- Non-inferiority of R^2 to R-CHEMO demonstrated in the RELEVANCE trial (first-line setting) may not be generalisable to the second-line setting. The ESC considered the assumption of non-inferiority conclusions from the first-line setting holding for the second-line setting was not unreasonable but was highly uncertain.
- The R^2 regimen used in the inMIND trial was different to that used in the RELEVANCE trial, and patients in RELEVANCE also received rituximab maintenance therapy.
- OS was immature at the time of evaluation. While the point estimate of OS HR favoured the tafasitamab arm, the result was not statistically significant (HR 0.587 [95% CI: 0.306, 1.128]), and interim results may not translate to a statistically significant result when longer term data becomes available.

Overall, the ESC considered that the claim of superior comparative effectiveness was highly uncertain but likely reasonable with the magnitude of benefit versus R-CHOP unknown.

6.38 The safety profiles of R^2 and R-CHEMO are different, with a higher proportion of patients in the R^2 arm of RELEVANCE reporting serious adverse events, treatment discontinuation and dose modifications than patients in the R-CHEMO arm. The ESC agreed with the evaluation that together with the safety data from the inMIND trial, where a higher proportion of patients in the tafasitamab plus R^2 arm experienced a serious TEAE compared to the placebo plus R^2 arm (36.1% versus 31.6%, respectively), this highlights the inferior safety of tafasitamab plus R^2 versus R-CHOP, though the differences are difficult to quantify from the available data. Further, the term “acceptable safety profile” was not considered informative.

6.39 The PBAC considered that the claim of superior comparative effectiveness was highly uncertain but likely reasonable.

6.40 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.41 The submission presented a stepped economic evaluation of tafasitamab plus R^2 versus R-CHEMO, based on the inMIND trial, and implementing a modelled evaluation. R-CHOP was used as a proxy for all R-CHEMO. Table 11 summarises the key aspects of the model presented in the submission.

Table 11: Summary of model structure, key inputs and rationale (based on the submission's model)

Component	Summary
Treatments	Tafasitamab in combination with rituximab and lenalidomide (R^2) versus R-CHOP.
Time horizon	20 years in the model base case versus a median of 14.1-15.8 months (for PFS, OS and TTNT) outcomes in inMIND. In similar contexts, the PBAC has advised shorter modelled time horizons (refer paragraph 6.45).
Outcomes	LYG and QALYs.
Methods used to generate results	Partitioned survival analysis. Health state allocations to PFS, PD (2L) and PD (3L+), dead were determined by KM data (PFS, TTNT and OS) from inMIND. OS data from inMIND were immature, with only 5.5% and 8.4% deaths for tafasitamab+R^2 and R^2, respectively. Median OS was not reached in either treatment group in the reported interim analysis.
Cycle length	28 days.
Allocation to health states	The model used the KM curves (PFS, OS and TTNT) to estimate the proportion of patients in each health state up to the truncation points. Beyond these points, parametric survival functions were fitted to the KM data to generate extrapolated estimates. The base case applied Criterion 2 from Gebski 2018 for determining the appropriate duration of KM data.
Extrapolation method	Parametric models were fitted to KM estimates from each treatment arm. Parametric extrapolations were selected based on goodness-of-fit metrics and visual inspection, for each treatment arm. The proportional hazards assumption was assessed using log-log survival plots and Schoenfeld residuals to determine whether independent or joint models were appropriate. **PFS**: lognormal / lognormal **OS**: exponential (jointly fitted) **TTD**: exponential / lognormal PFS= progression free survival; OS = overall survival; TTNT = time to next treatment; R^2 = rituximab and lenalidomide. Convergence was assumed not to occur within the modelled time horizon in the submission's base case analysis.
Health related quality of life	**Progression-free (PF) = 0.915** mapped from the EQ-5D-5L data from inMIND, using the published Australian algorithm Norman 2023. **Progressive disease PD (2L) utility = 0.895** derived from the difference in utility of 0.02 vs. PF, based on EQ-5D-5L data from inMIND, using Norman 2023. **Progressive disease PD (3L) utility = 0.779** derived using the difference in utility (0.116 vs. PD(2L)) from venetoclax PBAC model for CLL (July 2020). Overall, the utility values applied in the model were higher than those reported for FL patients in the literature and those used in previous PBAC submissions for FL.

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td>Drug costs</td><td>
• Assumed 5.1 vials of tafasitamab per dose based on mean patient weight from inMIND.
• The price of lenalidomide in the model was based on the PBS price for lenalidomide for multiple myeloma, since it is not PBS listed for FL.

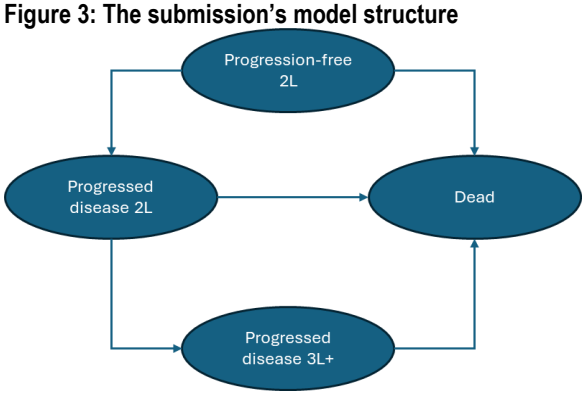
Units per course of treatment
<table>
<tr><th>Drug</th><th>Units per dose</th><th>Administrations per course</th><th>Source</th></tr>
<tr><td>tafasitamab</td><td>5.1 vials per dose*</td><td>23.1 doses</td><td>inMIND mean tafasitamab doses/course</td></tr>
<tr><td>lenalidomide</td><td>20 mg daily orally on Days 1 to 21 of Cycles 1 to 12</td><td>7.3 packs of 21 capsules each</td><td>inMIND actual dose intensity (3062.5mg) of lenalidomide in the tafasitamab+R^2 arm</td></tr>
<tr><td>rituximab (TAFA arm)</td><td rowspan="2">2.6x100mg vials and 1x500mg vials*</td><td>7.0 infusions</td><td>inMIND mean number of rituximab infusions in the tafasitamab+R^2 arm</td></tr>
<tr><td>rituximab (R-CHOP arm)</td><td>7.0 infusions</td><td>inMIND mean number of rituximab infusions in the tafasitamab+R^2 arm</td></tr>
<tr><td>CHOP</td><td>Prednisolone: 100 mg; Day 1 to 5 each cycle, doxorubicin: 50 mg/m2; Day 1 each cycle, vincristine: 1.4 mg/m2; Day 1 each cycle, and cyclophosphamide: 750 mg/m2; Day 1 each cycle</td><td>7.0 cycles</td><td>Based on eviQ guidelines. 7 cycles were within the 6-8 cycle range recommended by eviQ</td></tr>
</table>
*including wastage
eviQ protocol source: https://www.eviq.org.au/haematology-and-bmt/lymphoma/other-b-cell-lymphoma/3573-o-chop21-obinutuzumab-cyclophosphamide-doxor.
</td></tr>
<tr><td>Subsequent treatment costs</td><td>The majority of patients from inMIND did not receive any subsequent treatments on disease progression, with only 36/273 (13.2%) from TAFA+R^2 arm and 78/275 (28.4%) from placebo+R^2 arms initiating further antilymphoma treatments, which accounted for 76.6% (36/47) and 87.6% (78/89) of events in the two arms, respectively. The most common subsequent treatments included (CAR-T: 3.3%, R-B, 3.1% and R-CHOP: 1.6%). In the model, R-CHOP treatment was assumed to be a proxy for all 3L+ chemotherapy regimens on the PBS.</td></tr>
<tr><td>Terminal care costs</td><td>$27,525 was applied as a one-off cost upon transition to the dead health state for cancer-related deaths. The proportions of cancer-related deaths in each model arm (33.3% tafasitamab+R^2 and 73.9% R-CHOP) were based on the proportions of deaths occurring due to disease progression from inMIND. Terminal care costs should apply to both cancer-related as well as cancer-unrelated deaths (excluding sudden causes). The ICER was not very sensitive to inclusion of terminal care costs for all deaths.</td></tr>
</table>

Source: Table 82, p142 of the submission.

2L = second-line; 3L = third-line; CAR-T = chimeric antigen receptor T-cell therapy; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CLL = chronic lymphocytic leukaemia; FL = follicular lymphoma; KM = Kaplan-Meier; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R = relapsed/refractory; TAFA = tafasitamab; TTNT = time to next treatment.

6.42 The submission presented a partitioned survival analysis with four health states: progression-free [PF]; progressed disease (second-line setting) [PD 2L]; progressed disease (third-line plus setting) [PD 3L+]; and dead. The model included three survival curves, PF, OS and TTNT (time to next treatment). This approach of including an extra health state for progressed disease was reasonably justified in the submission by TTNT being an important objective linked to disease control and quality of life. A diagram of the model structure is presented in Figure 3.

Figure 3: The submission's model structure



Source: Figure 23 p156 of the submission.

6.43 All patients entered the model in the PF state and are at risk of progression or death each cycle. Patients who progress but stay on the same line of treatment move to the PD 2L health state, whereas those who progress and initiate the next line of treatment move to the PD 3L+ health state.

6.44 The economic model assumed a 20-year time horizon. The submission stated that the nominated duration was appropriate, given FL is a slow-progressing disease. The submission also argued that this was conservative compared to published economic models that had applied a lifetime horizon (Monga 2020; Oluwole 2024; Sun 2017).

6.45 In similar contexts, the PBAC has advised shorter modelled time horizons: 5 years for idelalisib for 3rd line FL (median trial follow up 9.7 months) (idelalisib PSD, November 2015 PBAC meeting), 10 years for venetoclax in previously untreated CLL (median trial follow up 29 months) (paragraph 6.45, venetoclax PSD, March 2020 PBAC Meeting) and a reduction from 15 years to 10 years for obinutuzumab for rituximab refractory FL (median trial follow up 24.1 months) (paragraph 6.34, obinutuzumab PSD, November 20156 PBAC meeting). Given the short trial follow-up (median 14.1-15.8 months for PFS, OS and TTNT in inMIND), the ESC agreed with the evaluation that a shorter model time horizon may be more appropriate to reduce uncertainty in long-term extrapolations, particularly given the immature OS data (with only 5.5% and 8.4% deaths for tafasitamab+R^2 and R^2 arms, respectively). The ESC noted that PBAC has advised shorter modelled time horizons in similar contexts and advised that a 10 year time horizon would be appropriate to account for uncertainty in long term outcomes for tafasitamab. The pre-PBAC response argued that the examples provided were not necessarily similar to the current submission with differences in the level of evidence provided and the approach taken to modelling OS potentially accounting for differences in time horizons. The pre-PBAC response presented a revised scenario with a 15 year time horizon.

6.46 The model used the KM data directly to estimate the proportion of patients in each health state up to the truncation points. Beyond these points, parametric survival functions were fitted to KM data to generate extrapolated estimates. The base case applied Criterion 2 from Gebski 2018 for determining the appropriate duration of KM

data. This criterion was originally developed to assess the reliability of KM estimates when the number of patients at risk becomes small, rather than to guide extrapolation in health economic models. It identifies the point at which survival estimates may become unstable due to sparse data, providing a statistical threshold for curtailing KM plots. In this model, Criterion 2 resulted in relatively long truncation points, with KM estimates for OS applied up to 24.5 months for the tafasitamab+R^2 arm and 24.9 months for the R-CHOP arm. While Criterion 2 of Gebski has been referenced in some PBAC submissions, the evaluation considered its application here may be inappropriate. The relatively short median follow-up in the inMIND trial (14.1–15.8 months) suggests that the KM data may not be sufficiently mature to support such extended durations. Using Criterion 2 of Gebski in this context risks overstating the reliability of the KM estimates and underrepresenting uncertainty in the extrapolated period. Applying median follow-up durations from the inMIND trial as truncation points increased the incremental cost effectiveness ratio (ICER) from a revised base case of $55,000 to < $75,000 /QALY to $75,000 to < $95,000/QALY. The ESC noted the submission also presented sensitivity analyses using KM data until the time points prior to failing Gebski Criterion 1 (2.5%) and Criterion 1 (5%) and that the number of months of follow-up varied from 21 to 27 across PFS, OS and time to next treatment outcomes across the three Gebski approaches. The ESC considered the use of Gebski criterion 2 was a source of uncertainty in the model, but noted the model was relatively insensitive to the choice of Gebski criteria (it either increased or decreased the ICER/QALY by [redacted]% depending on the criterion selected).

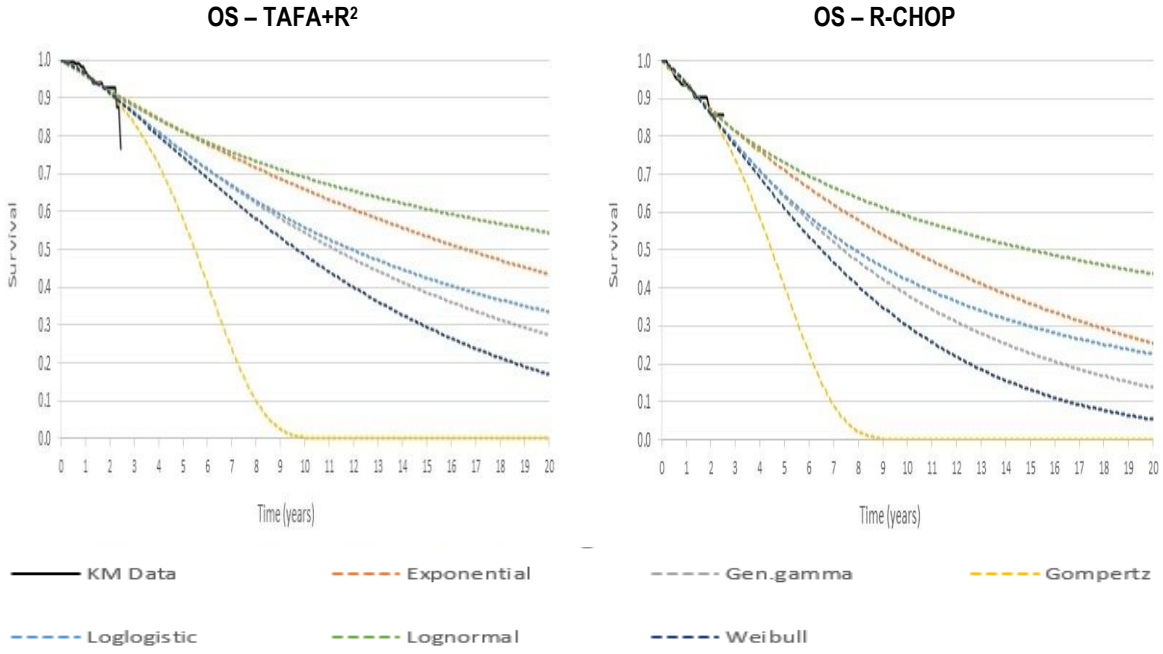
6.47 OS data used in the model from inMIND interim analysis were immature, with median OS not reached in either trial arm. The OS HR for tafasitamab plus R^2 versus R^2 from the inMIND trial was also not statistically significant: 0.587 (0.306, 1.128). The base case analysis did not model treatment effect waning, nor did it model curve or risk convergence for OS, PFS or TTNT. It was uncertain if the assumed survival benefit favouring tafasitamab would be realised as data mature. The ESC noted that, in the submission's base case, 73-77% of QALYs (and 5-44% of costs) were accrued in the extrapolated period. In a sensitivity analysis, when curve convergence was applied to survival estimates between Year 10 and 20, the ICER increased to $75,000 to < $95,000 per QALY gained (from a base case of $55,000 to < $75,000). Assuming curve convergence between Years 5 and 20 increased the ICER further to $115,000 to < $135,000 per QALY. Similarly, assuming risk convergence from Year 5 increased the ICER to $115,000 to < $135,000 per QALY.

6.48 In the venetoclax PBAC model for untreated CLL, from which the submission drew similarities with respect to health state utilities, the ESC considered that curve convergence from Year 5 (rather than risk convergence, noting curve convergence was more conservative in that case) for PFS, TTNT and time to initiation of subsequent treatment curves, would form an informative base case (Tables 9 and 12, venetoclax PSD, March 2020 PBAC Meeting). The PBAC had also previously recommended curve convergence for survival estimates within 10 years in the obinutuzumab model for stage II bulky or stage III/IV previously untreated follicular lymphoma (para 7.16,

obinutuzumab PSD, November 2017 PBAC Meeting). The PSCR argued that there are no PBS funded immunotherapies listed in later lines of therapy that would subsequently improve patient outcomes in the comparator arm and hence there was limited rationale for applying survival convergence. The ESC considered there was a high level of uncertainty around whether the survival benefit would persist as trial data mature and advised that either curve or risk convergence was appropriate to address this uncertainty. The pre-PBAC response presented a revised scenario which applied risk convergence from 10 years.

6.49 Model selection for extrapolation of KM data was based on goodness-of-fit statistics and visual inspection. Parametric functions for OS are presented in Figure 4. For OS, in the base case, the submission chose the jointly fitted exponential function (lowest BIC), claiming the exponential function to be the best fitting model (despite the loglogistic function reporting the lowest AIC). The ESC noted the ICER was sensitive to the chosen OS extrapolation function. Assuming the jointly estimated loglogistic function for OS data, the ICER increased to $75,000 to < $95,000 per QALY gained from a revised base case of $55,000 to < $75,000. Assuming the lognormal function, the ICER increased further to $95,000 to < $115,000 per QALY gained. The ICER was also sensitive to the assumption of independence instead of joint shape parameters for OS.

Figure 4: Extrapolations of OS for tafasitamab+R^2 (TAFA+R^2) and R-CHOP arms in the model



Source: pp.170-174 of the submission.
CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; OS=overall survival; R = rituximab; TAFA = tafasitamab.

6.50 For the PF health state in the base case, EQ-5D-5L data from the FL cohort in the inMIND trial were used with utilities calculated using Australian preference weights by Norman (2023), resulting in a utility of 0.915. The baseline value was applied to the PF state. The utility value of 0.915 suggests no difference in quality of life compared to the Australian general population, which may not be appropriate. It exceeds the population norm of 0.86 reported in Redwood (2024), based on a cross-sectional study conducted between July 2021 and August 2021. However, higher norms have been reported: Endo (2024) found a mean EQ-5D utility of 0.916 in Queensland adults (2022–2023), and McCaffrey (2016) reported 0.91 in South Australia (2013). The submission justified the PF utility on two grounds: (i) Redwood 2024 may underestimate utility due to COVID-19 impacts, citing Persson (2021) Swedish study, which reported a 0.06-0.07 VAS utility reduction after 10 months of pandemic restrictions; and (ii) patients with FL may experience quality of life similar to the general population while progression-free, given the disease's slow progression and QoL decline mainly in later therapy lines. However, these justifications imply that the model assumed PF utility to approximate or exceed Australian general population norms. The ESC agreed with the evaluation that the PF utility value was not reasonable given that even early FL symptoms (enlarged lymph nodes or fatigue) can affect QoL, let alone in a population with relapsed, refractory disease. Further, the ESC noted that the proposed population comprised patients who require treatment and considered this cohort would generally have a lower utility value than those patients who do not require treatment. When the PF utility was capped at 0.86 using the Redwood 2024 norm (while maintaining disutilities for PD states), the ICER increased to $75,000 to < $95,000 per QALY gained from a revised base case of $55,000 to < $75,000.

6.51 For the PD (2L) health state, the model applied a disutility of 0.02 associated with progression to PD (2L) from PF (based on EQ-5D-5L data from the inMIND trial, Norman 2023 weights), resulting in a utility of 0.895 for PD (2L). The disutility was derived from evaluation of EQ-5D-5L data as a function of PFS. The ESC considered that a disutility of 0.02 was unlikely to be clinically meaningful and considered the utility of 0.895 for PD (2L) was not plausible.

6.52 For the PD (3L+) health state, the model applied a utility decrement of 0.116 associated with progression from PD (2L) to PD (3L+), resulting in a utility of 0.779 for PD (3L+). Although it is generally preferable to source utilities for all health states from the same dataset, the submission argued that inMIND HRQoL data were insufficient post initiation of next antilymphoma treatment. The utility decrement of 0.116 between PD(2L) and PD(3L+), was based on differences between PD (0.776) and relapsed/refractory (R/R) (0.066) health states from the venetoclax PBAC July 2020 model for previously untreated CLL. The submission justified this by noting similarities in survival and clinical course between FL and CLL, both being indolent, relapsing remitting conditions.

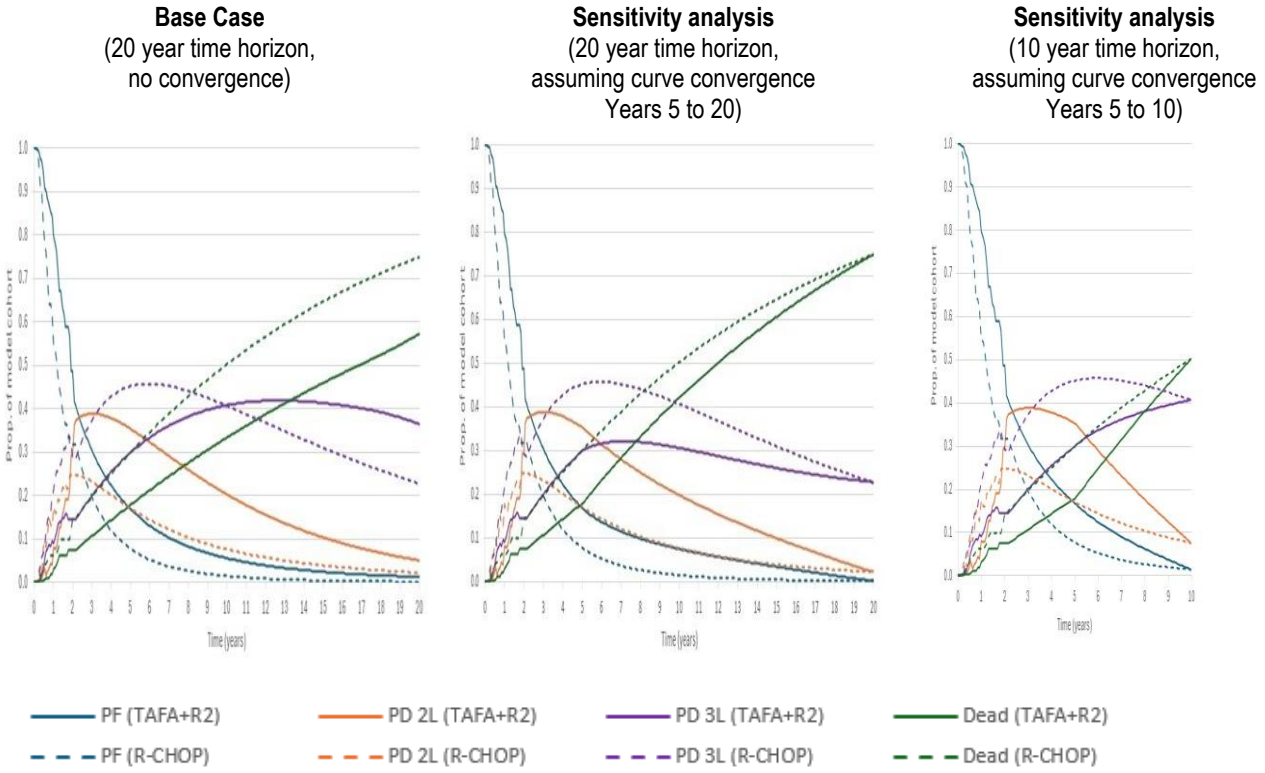
6.53 Overall, the utility values applied in the model were higher than those reported for FL patients in the literature and those used in previous PBAC submissions for FL. The most widely cited values (0.805 for PF and 0.618 for PD) originated from Wild (2006) and

Pettengell (2007), based on 222 FL patients from eight UK sites. These were applied in most published cost-effectiveness studies and PBAC submissions for FL. Using commonly cited utility values from Pettengell 2007 / Wild 2006 increased the ICER to $75,000 to < $95,000/QALY from a revised base case of $55,000 to < $75,000/QALY. The ESC considered that the trial-based utility values were implausibly high and advised that the use of alternative utility estimates from Wild (2006) would be more appropriate. The pre-PBAC response stated that the trial-based utility values do not exceed those of the general Australia population, but they were comparable and argued that trial-based utility values are generally preferred by the PBAC.

6.54 All subsequent FL treatments in the model were assumed to apply the cost of R-CHOP. Whilst CAR-T is recommended as 3rd line treatment in international guidelines, it is not reimbursed in Australia unless the FL has histologically transformed to DLBCL. Transformation of FL to more aggressive cancer histology (e.g., DLBCL) was low in inMIND and did not significantly differ between the tafasitamab+R^2 0 (0%) and R^2 arms 9 (3.3%).

6.55 Model Markov traces are presented in Figure 5, for the base case analysis with no convergence and sensitivity analyses applying OS, PFS and TTNT curve convergence from Year 5 to 20, and from Year 5 to 10 with a model duration of 10 years.

Figure 5: Markov traces base case and sensitivity analyses assuming curve convergence



Source: Figure 39B, p198 of the submission (Note: legend and line style for 'Dead' was adjusted during the evaluation for consistency across treatment groups); and constructed during the evaluation. Middle and right panel was generated during the evaluation using the submitted model by incorporating OS, PFS and TTNT curve convergence Years 5 to 20 and Years 5 to 10 (10-year model duration).

2L = 2nd-line; 3L = 3rd-line; OS=overall survival, PD= progressive disease; PF = progression-free; PFS = progression-free survival; R^2 = rituximab and lenalidomide; R-CHOP = rituximab, prednisolone, doxorubicin, vincristine and cyclophosphamide; TAFA = tafasitamab; TTNT = time to next treatment.

6.56 In the model base case (left panel), after 20 years, 57% and 75% of patients had died (accruing a total of 13.6 and 10.8 undiscounted life years over the model horizon, in the tafasitamab+R^2 and R-CHOP model arms, respectively, an increment of 2.8 undiscounted life years for the tafasitamab plus R^2 arm). Given the submission base case had assumed no curve or risk convergence, the Markov traces showed increasing divergence in the proportion dead (dark green lines) over 20 years, reflecting sustained OS benefit for tafasitamab+R^2. For the first 10 years, fewer tafasitamab+R^2 patients were in the 'dead' and PD (3L+) states. Beyond 10 years, the PD (3L+) curve for tafasitamab+R^2 (purple solid line) rose above R-CHOP (purple dashed line), indicating patients were assumed to remain alive in PD (3L+) rather than die.

6.57 In a sensitivity analysis assuming curve convergence from Year 5 to 20 (middle panel), the PD (3L+) curve for tafasitamab+R^2 remained below R-CHOP, as the proportion dead converged over time. Undiscounted life years decreased to 12.0 years for tafasitamab+R^2 and 10.8 for R-CHOP, with an estimated increment of 1.2

undiscounted life years for tafasitamab plus R^2. This scenario resulted in an ICER of $115,000 to < $135,000 per QALY gained, compared to the revised base case of $55,000 to < $75,000 . The ESC noted that if the model horizon was also reduced to 10 years whilst assuming curve convergence from Years 5 to 10, (right panel), total undiscounted life years further decreased to 7.8 and 7.2 years in the tafasitamab+R^2 and R-CHOP model arm, respectively, with an estimated increment of 0.6 undiscounted life years for tafasitamab plus R^2. In this scenario, the ICER increased further to $155,000 to < $255,000 per QALY gained.

6.58 The PBAC noted that the pre-PBAC response proposed a revised scenario with a 15 year time horizon and risk convergence from 10 years. In this revised scenario, after 15 years, 53% and 65% of patients had died in the tafasitamab+R^2 and R-CHOP model arms, respectively (difference of 12%) while the overall survival rates in the trial at 2 years were 93% and 86% respectively (difference of 7%). The PBAC considered that the modelled divergence in OS outcomes in the pre-PBAC response scenario was not adequately supported given the immaturity of the OS data. Under the scenario specified by the PBAC (15 year time horizon and risk convergence from 5 years) after 15 years, 59% and 65% of patients had died in the tafasitamab+R^2 and R-CHOP model arms, respectively (difference of 6%).

6.59 Table 12 presents the disaggregated summary of costs from the economic evaluation presented in the submission.

Table 12: Health care resource items: disaggregated summary of cost impacts (discounted) based on the submission's model

Resource use	tafasitamab+R^2	R-CHOP	Incremental cost	% of total incremental cost
Drug costs	**$**	**$6,472**	**$**	+ %
- Tafasitamab	$	$0	$	
- Lenalidomide	$9,500	$0	$	
- Rituximab	$3,204	$3,204	$	
- CHOP	$0	$3,267	-$	
Drug administration costs	$2,911	$882	$2,029	+ %
Health state costs[a]	$1,821	$1,547	$274	+ %
Adverse events	$2,097	1,835	$261	+ %
Costs of subsequent treatments	$4,116	$5,505	-$1,389	- %
Costs of terminal care	$3,595	$11,096	-$7,501	- %
Total Costs	**$**	**$27,338**	**$**	**%**

Source: Table 130, p205 of the submission.

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; R^2 = rituximab + lenalidomide; R = rituximab; TAFA = tafasitamab.

[a] Monitoring comprise of medical visits, laboratory tests and biopsies.

6.60 Tafasitamab costs were the largest contributor to incremental costs. The main cost offsets were terminal care costs, resulting from the large incremental benefit in overall survival under the base case assumption of no curve convergence. A one-off cost ($27,525) was applied on transition to the 'dead' health state for cancer-related deaths. The proportions of cancer-related deaths in each model arm (33.3% tafasitamab+R^2 and 73.9% R-CHOP) were based on the proportions of deaths occurring due to disease progression from inMIND. However, terminal care costs

should apply to both cancer-related and cancer-unrelated deaths (excluding sudden causes). The model was, however, not sensitive to this assumption.

6.61 Table 13 presents the disaggregated summary of health outcomes in the economic evaluation based on the model presented in the submission. Life-years and QALY gains in the base case were largely attributed to prolonging the time patients remained in the PD (2L) health state in the tafasitamab+R^2 arm.

Table 13: **Disaggregated summary of health outcomes[a] included in the economic evaluation (discounted) based on the submission's model**

Outcome	tafasitamab + R^2	R-CHOP	Increment
Life Years in PF	2.753	1.810	0.943
Life Years in PD (2L)	2.735	1.473	1.263
Life Years in PD (3L+)	4.024[a]	4.538	-0.514[a]
Total Life Years	**9.512[a]**	**7.821**	**1.691[a]**
QALYs in PF	2.519	1.656	0.863
QALYs in PD (2L)	2.448	1.318	1.130
QALYs in PD (3L+)	3.135[a]	3.535	-0.401[a]
Total QALYs	**8.102[a]**	**6.509**	**1.592[a]**

Source: Table 131, p205 of the submission.

2L =2nd-line; 3L = 3rd-line; PD= progressed disease; PF = progression-free; R^2 = rituximab + lenalidomide; R-CHOP = rituximab, prednisolone, doxorubicin, vincristine and cyclophosphamide; TAFA = tafasitamab.

[a] A cross-referencing error was identified during the evaluation in cell C27 of 'Inputs' worksheet of Tafasitamab EXCEL model for the duration of KM data for OS in the treatment arm, this was corrected to refer to cell G233 of 'Inputs' worksheet, instead of cell G234.

6.62 Table 14 presents a summary of the key drivers of the model.

Table 14: Key model drivers

Description	Method/Value	Impact based on the model presented in the submission Revised base case: $[redacted][1]/QALY gained[a].
Time horizon	In the base case, the model assumed a time horizon of 20 years. In similar settings, the PBAC had recommended shorter time horizons. The ESC considered a 10 year time horizon would be appropriate. The PBAC considered 15 year time horizon would be appropriate.	High, favoured TAFA. Reducing the time horizon to 10 years increased the ICER to $[redacted][2]/QALY gained.
OS, PFS and TTNT convergence	In the base case, the model assumed neither curve convergence nor risk convergence for OS, PFS or TTNT data. The ESC and PBAC agreed with the evaluation this may not be reasonable, given the immature data and, in particular, immature OS data presented, so the modelled divergence of OS curves in the base case may not be reasonable. Both the assumed survival benefit favouring TAFA and its durability were uncertain.	High, favoured TAFA. Assuming curve convergence between Years 5 and 20 increased the ICER to $[redacted][3]/QALY gained.
Utilities	PF 0.915; PD (2L) 0.895 PD (3L+) 0.779 For PF and PD (2L), the model applied EQ-5D-5L data from the inMIND trial, calculated using Australian preference weights by Norman 2023. For PD (3L+), the model applied disutility associated with progression from PD (2L) to PD (3L+), derived from the venetoclax PBAC July 2020 model for previously untreated CLL. Overall, the utility values applied in the model were higher than those reported for FL patients in the literature and those used in previous PBAC submissions for FL. The ESC considered the base case utility values were implausibly high and advised that alternative values should be used. While the PBAC agreed with ESC that the trial-based utilities appeared high, the Committee also acknowledged that the utility values reported by Wild (2006) were overly conservative.	Moderately high, favours TAFA. Assuming utilities of 0.81 for PF and 0.62 for both PD health states based on Wild 2006 increased the ICER to $[redacted][4]/QALY gained.
OS extrapolation	In the base case, the model assumed the exponential (joint) model, while the exponential function had the lowest BIC, the loglogistic function had the lowest AIC.	Moderate, favoured TAFA. Assuming the loglogistic (joint) model for OS extrapolations increased the ICER to $[redacted][4]/QALY gained.

Source: compiled during the evaluation.2L = second-line; 3L = third-line; CLL = chronic lymphocytic leukaemia; FL = follicular lymphoma; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression-free survival; R^2 = rituximab and lenalidomide; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TAFA = tafasitamab; TTNT = time to next treatment.

[a] A cross-referencing error was identified during the evaluation in cell C27 of 'Inputs' worksheet of Tafasitamab EXCEL model for the duration of KM data for OS in the treatment arm, this was corrected to refer to cell G233 of 'Inputs' worksheet, instead of cell G234.

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$135,000 to < $155,000*

[3] *$115,000 to < $135,000*

[4] *$75,000 to < $95,000*

6.63 Table 15 presents the results of the stepped economic evaluation based on the model presented in the submission. Steps 1 and 2 estimated outcomes over 24-months (2 years). From Step 3, results were reported over a 20-year time horizon.

Table 15: Results of the stepped economic evaluation (discounted) based on the submission's model

Step and component	Tafasitamab + R^2	R-CHOP	Increment
Step 1: trial-based costs and outcomes: time horizon of 24 months. Including drug costs and drug administration costs.			
Costs	$[redacted]	$7,354	$[redacted][b]
Progression-free life year (PFLY)	1.565	1.218	0.346
Incremental cost/ extra PFLY gained			$[redacted][b1]
Costs	$[redacted]	$7,354	$[redacted][b]
LYG	1.948	1.887	0.061
Incremental cost/extra LYG gained			$[redacted][b2]
Step 2: translation to QALYs (time horizon of 24 months)			
Costs	$[redacted]	$7,354	$[redacted][b]
QALYs	1.753	1.669	0.084
Incremental cost/QALY			$[redacted][b2]
Step 3: time horizon extended to 20 years			
Costs	$[redacted]	$7,354	$[redacted][b]
LYG	9.561	7.821	1.740
Incremental cost/extra LYG gained			$[redacted][b3]
Costs	$[redacted]	$7,354	$[redacted][b]
QALYs	8.139	6.509	1.630
Incremental cost/QALY			$[redacted][b3]
Step 4: inclusion of other healthcare resource use (subsequent treatment, health state, AEs and terminal care)			
Costs	$[redacted]	$27,338	$[redacted][4]
LYG	9.561	7.821	1.740
Incremental cost/extra LYG gained			$[redacted][3]
Costs	$[redacted]	$27,338	$[redacted]
QALYs	8.139	6.509	1.630
Incremental cost/extra QALY gained (base case in submission) [a]			**$[redacted][3]**
Costs	$[redacted][b]	$27,338[b]	$[redacted][b4]
LYG	9.512	7.821	1.691
Incremental cost/extra LYG gained			$[redacted][b3]
Costs	$[redacted][b]	$27,338[b]	$[redacted][b4]
QALYs	8.102	6.509	1.592
Incremental cost/extra QALY gained (revised base case)			**$[redacted][b3]**

Source: Table 129, p204 of the submission. QALY = quality adjusted life year.

PFLY = progression-free life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R^2 = rituximab + lenalidomide; TAFA = tafasitamab.

[a] A cross-referencing error was identified during the evaluation in cell C27 of 'Inputs' worksheet of Tafasitamab EXCEL model for the duration of KM data for OS in the treatment arm, this was corrected to refer to cell G233 of 'Inputs' worksheet, instead of cell G234.

[b] Indicates results generated and corrected during the evaluation i.e., the incremental cost reported in the submission was found to be incorrect for Steps 1 to 3.

The redacted values correspond to the following ranges:

[1] *$355,000 to < $455,000*

[2] *> $1,055,000*

[3] *$55,000 to < $75,000*

[4] *$115,000 to < $135,000*

6.64 The results of key univariate / multivariate sensitivity analyses (based on the model presented in the submission) are summarised in Table 16.

Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case (submission)	**$** [redacted]	**1.630**	**$** [redacted][1]	**-**
Revised base case (correcting cross-referencing error)[a]	**$** [redacted]	**1.592**	**$** [redacted][1]	**-**
Time horizon (base case 20 years)				
5 years	$ [redacted]	0.355	$ [redacted][2]	+ [redacted]%
10 years	$ [redacted]	0.846	$ [redacted][3]	+ [redacted]%
Discount rate (base case: 5%)				
0%	$ [redacted]	2.594	$ [redacted][4]	- [redacted]%
3.5%	$ [redacted]	1.826	$ [redacted][1]	- [redacted]%
Duration of KM data (base case: Criterion 2 of Gebski)				
Duration of KM data median follow-up from inMIND	$ [redacted]	1.416	$ [redacted][a5]	+ [redacted]%
Criterion 1 (2.5%) of Gebski	$ [redacted]	1.526	$ [redacted][5]	[redacted]%
Criterion 1 (5%) of Gebski	$ [redacted]	1.654	$ [redacted][1]	- [redacted]%
OS Extrapolations – parametric model function (base case jointly fitted exponential)				
OS parametric model jointly fitted lognormal	$ [redacted]	1.196	$ [redacted][6]	+ [redacted]%
OS parametric model jointly fitted loglogistic	$ [redacted]	1.395	$ [redacted][5]	+ [redacted]%
Assumptions about convergence (base case no convergence)				
Curve convergence between 10 and 20 years	$ [redacted]	1.238	$ [redacted][5]	+ [redacted]%
Curve convergence between 5 and 20 years	$ [redacted]	0.942	$ [redacted][7]	+ [redacted]%
Risk convergence from 10 years	$ [redacted]	1.370	$ [redacted][5]	+ [redacted]%
Risk convergence from 5 years	$ [redacted]	0.966	$ [redacted][7]	+ [redacted]%
Risk convergence from 3 years	$ [redacted]	0.688	$ [redacted][8]	+ [redacted]%
Utilities (base case: PF 0.915, PD (2L) 0.895 PD (3L+) 0.779)				
Assuming utilities of 0.81 for PF, 0.79 for PD (2L) and 0.674 for PD (3L+) by only changing utility for PF (maintaining disutilities of PD)	$ [redacted]	1.415	$ [redacted][5]	+ [redacted]%
Assuming utilities of 0.81 for PF and 0.77 for both PD health states based on GADOLIN	$ [redacted]	1.340	$ [redacted][5]	+ [redacted]%
Assuming utilities of 0.81 for PF and 0.62 for both PD health states based on Wild 2006	$ [redacted]	1.228	$ [redacted][5]	+ [redacted]%
Assuming utilities of 0.81 for PF and 0.62 for PD (2L) health states based on Wild 2006, and 0.504 for PD (3L+) assuming the same disutility versus PD (2L)	$ [redacted]	1.288	$ [redacted][5]	+ [redacted]%
Multivariate analyses				
OS, PFS and TTNT curve convergence between 5 and 20 years AND Assuming utilities of 0.81 for PF and 0.62 for PD (2L) health states based on Wild 2006, and 0.504 for PD (3L+) assuming the same disutility	$ [redacted]	0.883	$ [redacted][7]	+ [redacted]%
OS, PFS and TTNT curve convergence between 5 and 10 years AND	$ [redacted]	0.577	$ [redacted][8]	+ [redacted]%

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Time horizon of 10 years				
OS, PFS and TTNT curve convergence between 5 and 10 years AND Assuming utilities of 0.81 for PF and 0.62 for PD (2L) health states based on Wild 2006, and 0.504 for PD (3L+) assuming the same disutility AND Time horizon of 10 years	$[redacted]	0.568	$[redacted][8]	+[redacted]%
As above, but with risk convergence from Year 5 (rather than curve convergence)	$[redacted]	0.649	$[redacted][8]	+[redacted]%
OS, PFS and TTNT risk convergence from 5 years AND Time horizon of 15 years	$[redacted]	0.873	$[redacted][7]	+[redacted]%

Source: constructed during the evaluation; Tables 133-136, pp. 207-209 of the submission.

2L =2nd-line; 3L = 3rd-line; KM = Kaplan-Meier; OS = overall survival; PD= progressed disease; PF = progression-free; PFS = progression-free survival; R^2 = rituximab + lenalidomide; R-CHOP = rituximab, prednisolone, doxorubicin, vincristine and cyclophosphamide; QALY = quality adjusted life year; TTNT = time to next treatment.

[a] A cross-referencing error was identified during the evaluation in cell C27 of 'Inputs' worksheet of Tafasitamab EXCEL model for the duration of KM data for OS in the treatment arm, this was corrected to refer to cell G233 of 'Inputs' worksheet, instead of cell G234.

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*
[2] *$255,000 to < $355,000*
[3] *$135,000 to < $155,000*
[4] *$35,000 to < $45,000*
[5] *$75,000 to < $95,000*
[6] *$95,000 to < $115,000*
[7] *$115,000 to < $135,000*
[8] *$155,000 to < $255,000*

6.65 Multivariate sensitivity analyses demonstrated the combined effect of model drivers. In the submission's model, applying a 10-year time horizon, curve convergence (Years 5-10), and lower utility values, increased the ICER by [redacted]% to $155,000 to < $255,000 per QALY gained from a revised base case of $55,000 to < $75,000. This was primarily driven by the reduced QALY gain assumed in the extrapolated period. Noting that this multivariate sensitivity analysis incorporated utility values reported by Wild (2006), the ESC considered that this analysis was appropriate as a revised base case.

6.66 The pre-PBAC response argued that some of the inputs in the ESC multivariate analysis were particularly conservative and, when applied simultaneously overstated the overall uncertainty of the model results. The pre-PBAC response provided a revised scenario which shortened the time horizon to 15 years and applied risk convergence from 10 years. The pre-PBAC response noted that incorporating the reduced EMP offered in the response (see paragraph 3.2) along with the updated lenalidomide price (which was reduced as a result of the October 2025 price disclosure cycle) in the revised scenario would result in an ICER of $55,000 to < $75,000 per QALY gained with trial-based utilities and $75,000 to < $95,000 per QALY gained with literature utilities.

Drug cost/patient/course

6.67 Based on the price proposed in the submission, the average cost per patient per course on tafasitamab plus R^2 was $[redacted] for tafasitamab drug costs only, based on the effective price, assuming a mean number of 23.1 doses per treatment course. The average cost per patient per course was $[redacted] when the drug costs of R^2 (using lenalidomide's PBS price in multiple myeloma as a proxy) were combined with the drug costs of tafasitamab. The average cost per patient per course on R-CHOP was $6,472, based on 7 infusions per treatment course.

Table 17: Drug cost per patient (based on the price proposed in the submission)

	TAFA+R^2 Trial dose and duration	TAFA+R^2 Model	TAFA+R^2 Financial estimates	R^2 Trial dose and duration	R-CHOP Model	R-CHOP Financial estimates
Units per course	23.1 TAFA doses (mean)	23.1 TAFA doses[a]	23.1 TAFA doses[a]	7 infusions	7 infusions	7 infusions
Cost/patient/course: TAFA	-	$[redacted]	$[redacted]	-	-	-
Cost/patient/course: lenalidomide	-	$9,500	$9,500	-	-	-
Cost/patient/course: rituximab	-	$3,204	$3,204	-	$3,204	$3,204
Total Cost/patient/course	-	$[redacted]	$[redacted]	-	$6,472	$6,472

Source: compiled during the evaluation from economic and financial model assumptions.
R^2 = rituximab + lenalidomide; R-CHOP = rituximab, prednisolone, doxorubicin, vincristine and cyclophosphamide; TAFA = tafasitamab.
[a] TAFA dose of 12 mg/kg; assumed 76.93 weight based on mean weight and distribution in inMIND, hence calculated 5.1 TAFA vials (200 mg) per dose (including wastage) based on assumed weight and distribution.

6.68 The pre-PBAC response offered a reduced EMP of $[redacted] per 200 mg vial.

Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC. The submission adopted an epidemiological approach to estimate the financial implications of the requested tafasitamab plus R^2 PBS listing for treatment of R/R FL. A market share approach was not considered feasible as the PBS utilisation for all relevant comparators in the R/R FL setting could not be tracked. Table 18 summarises the data sources and parameter values used to estimate the utilisation and financial implications. The submission did not request a grandfathering clause and use in this setting was not considered in the financial implications.

Table 18: Key inputs for financial estimates

<table>
<tr><th>Data</th><th>Value</th><th>Source/comment</th></tr>
<tr><td colspan="3">Eligible population</td></tr>
<tr><td>Incidence of FL</td><td>1,209 in 2016 up to 2,014 in 2031 (Yr 6)</td><td>AIHW Cancer Data in Australia 2024: Table S11a.1: Blood cancer incidence (2016-2020 data). Extrapolated assuming linear market growth between 2020 and 2031.</td></tr>
<tr><td>Prevalence of FL</td><td>10-year prevalence 9,072 in 2016 to 11,958 in 2025</td><td>AIHW Cancer Data in Australia 2024: Table S11i.1: 10-year prevalence of blood cancers (2016-2020 data). The submission argued that 10-year prevalence estimates were most relevant given the indolent nature of FL. These data were linearly extrapolated to predict data for 2020 to 2026.
The evaluation considered that, as the prevalent population was generated from incident patients over time, there may be overlap between the incident and prevalent populations, leading to double-counting. Hence, the patient numbers may be overestimated. The PSCR argued that there was no double counting between incident and prevalent patients. The PSCR stated that the prevalent pool was specifically derived from incident cases occurring prior to the first year of the analysis (e.g. from the assumed time of listing). Whereas the incident patients are those diagnosed with R/R FL in a given year over the analysis period. The ESC considered that there may be a small degree of double counting in Year 1 but otherwise it was reasonable to accept the approach taken. The PBAC considered it was reasonable to accept the approach taken in this step.</td></tr>
<tr><td>Proportion of diagnosed FL patients receiving 1L treatment</td><td>69%</td><td>From Wasterlid 2024: 69% of 1,772 patients diagnosed with FL (in the Swedish Lymphoma register from 2007 to 2014, followed until 2020) received systemic first-line therapy.

The submission also presented estimates from other international studies (predominantly from US and Europe). These studies reported a range of 57% to 94%. The submission justified using the 69% estimate from Wasterlid 2024 in the base case, noting that it was close to the median across the international studies (excluding LaRDR).

<table>
<tr><th>Studies</th><th>% 1L</th><th>Median FU (yrs)</th></tr>
<tr><td>LarDR</td><td>57</td><td>2.1</td></tr>
<tr><td>Wasterlid 2024</td><td>69</td><td>6.8</td></tr>
<tr><td>Chihara 2025</td><td>62</td><td>4.8</td></tr>
<tr><td>Huntington 2022</td><td>64</td><td>2.8</td></tr>
<tr><td>Liu 2023</td><td>75</td><td>5.5</td></tr>
<tr><td>Batlevi 2020</td><td>85</td><td>8.3</td></tr>
<tr><td>Rajamaki 2023</td><td>94</td><td>5.8*</td></tr>
</table>
*used a 20-year simulation on the basis of retrospective data

The evaluation considered that this proportion was uncertain due to the use of a watch-and-wait approach in clinical practice. The LaRDR report provided the only Australian data source indicating that 57% of 1,182 patients newly diagnosed with FL (diagnosed at Australian sites between August 2016 and March 2025) received 1L active anti-lymphoma treatment. However, this estimate may also be unreliable, as patients who have progressed to later lines of therapy are likely to have a poorer prognosis, given the relatively short median follow-up of 2.1 years in the registry and the long natural history of FL. Consequently, 57% may be an under-estimate.
Overall, the PBAC considered the value used in the submission of 69% was reasonable.</td></tr>
</table>

<table>
<tr><th>Data</th><th>Value</th><th>Source/comment</th></tr>
<tr><td colspan="3">Eligible population</td></tr>
<tr><td>Proportion of 1L treatment patients progressing to R/R setting (2L)</td><td>40% over 10 years (20% first 2 years; 20% between 2-10 years)</td><td>From Wasterlid 2024.
The published studies identified through the literature search (see above) reported a range of 13% to 50%. The submission justified selecting the 40% estimate from Wasterlid 2024 in the base case, as this was close to the median value reported in published international studies (see below) (excluding LaRDR). The evaluation considered that this proportion was uncertain. Only 13% of 671 patients who received 1L treatment had received 2L treatment according to the LaRDR report. The PSCR stated that the LaRDR data only has a median follow up of 2.1 years from FL diagnosis and therefore was unlikely to capture the true proportion of 1L treated patients progressing to 2L treatment.
<table>
<tr><th>Studies</th><th>% 2L</th><th>Median follow up (yrs)</th></tr>
<tr><td>LaRDR</td><td>13</td><td>2.1</td></tr>
<tr><td>Wasterlid 2024</td><td>40</td><td>6.8</td></tr>
<tr><td>Huntington 2022</td><td>23</td><td>2.8</td></tr>
<tr><td>Rajamaki 2023</td><td>33</td><td>5.8</td></tr>
<tr><td>Chihara 2025</td><td>37</td><td>4.8</td></tr>
<tr><td>Liu 2023</td><td>44</td><td>5.5</td></tr>
<tr><td>Batlevi 2020</td><td>50</td><td>8.3</td></tr>
</table>

The PBAC noted that Wasterlid 2024 reported that 16% of patients treated in 2L had ‘first transformation’ as their treatment indication in 2L[7] but noted that other published studies have found higher rates of transformation in patients treated with bendamustine and rituximab (BR) first line[8] (which is commonly used in Australia but was only used in 16% of patients in 1L in Wasterlid 2024). The PBAC considered that the proportion of first-line treated patients who progress to the 2L setting was likely to be around 30%, but that, of these patients at least 16% would have transformed lymphoma (as reported in Wasterlid 2024) and thus not be eligible for tafasitamab (i.e. an overall rate of no higher than 30% * 84% = 25% over 10 years).</td></tr>
<tr><td colspan="3">Treatment utilisation</td></tr>
<tr><td>Incident patients: Uptake rate of TAFA + R2</td><td>[redacted]% Year 1
[redacted]% Year 2
[redacted]% Year 3 onwards</td><td>Assumptions. The evaluation considered that these estimates were uncertain, but likely overestimated given tafasitamab + R2 is only one treatment choice amongst many. The PBAC considered that the uptake rates in the incident population were overestimated and considered these should be revised to: [redacted]% in Year 1; [redacted]% in Year 2 and [redacted]% in Year 3 onwards.</td></tr>
</table>

[7] Based on Figure 3 of Wasterlid 2024.

[8] Rangel-Patiño J, et al. Rate of Transformation and Secondary Malignancies in Follicular Lymphoma Patients Treated with First-Line Bendamustine Rituximab and Rituximab Maintenance, Blood, Volume 144, Supplement 1, 2024, Page 2352. https://www.sciencedirect.com/science/article/pii/S0006497124050997

Data	Value	Source/comment
Eligible population		
Prevalent patients: Uptake rate of TAFA + R^2	[redacted]% Year 1 [redacted]% Year 2 [redacted]% Year 3 [redacted]% Year 4	Assumptions. (The submission assumed that a total of [redacted]% will uptake treatment over 4 years). The evaluation considered that these rates were likely overestimated, given that tafasitamab + R^2 is only one treatment choice amongst many. In addition, the evaluation raised the following concerns regarding the methodology applied: i. Double counting of patients: the financial model assumed that the same patients from the prevalent pool could initiate treatment more than once. Specifically, [redacted]% of the prevalent pool of 3,043 were assumed to uptake TAFA each year from Years 1 to 3, without accounting for the fact that patients treated earlier would no longer be eligible to initiate treatment again. A sensitivity analysis was conducted in which patients from the prevalent pool could not be re-treated. The PSCR argued the submission's approach was justified as it assumed the uptake rates ([redacted]% in Year 2, [redacted]% in Year 3 and [redacted]% in Year 4) applied to the whole eligible prevalent pool in Year 1 of 3,043 patients. The PSCR argued that the reason for this delayed uptake (delayed up to 4 years) was that these patients may have initiated a line of R/R therapy and would wait until a suitable time to initiate a subsequent line of therapy with tafasitamab + R^2, as the proposed restriction allows tafasitamab + R^2 to be used once per patient. ii. Changing eligibility over time: the model assumed [redacted]% uptake of the prevalent pool over four years. In practice, patients' clinical status may change over this period, rendering them ineligible for treatment. The evaluation considered that this assumption was therefore likely to have led to an overestimation of the financial impact. The ESC considered that while it was reasonable to assume delayed uptake in the prevalent patient population, the overall uptake rate in this group appeared high given the range of treatment options available in this condition. The pre-PBAC response argued that the assumed uptake rate was supported by the efficacy of the regimen and the lack of alternative options. The PBAC considered the uptake rate in the prevalent population was reasonable.
TAFA vials (200 mg)	5.1 per dose	As per assumptions and calculations in the modelled economic evaluation. This was reasonable.
Substituted PBS costs	R-CHOP	R-CHOP was used to represent all R based chemotherapy. This was reasonable.
Rituximab vials – per dose	2.6 x 100 mg 1 x 500 mg	As per assumptions and calculations in the modelled economic evaluation. This was reasonable.
TAFA+R^2 and R-CHOP units per treatment course	TAFA: 23.1 doses	inMIND mean TAFA doses/course. Based on the mean treatment duration of 263.5 days, 25 doses would actually be required (assuming full compliance). This was tested in sensitivity analysis.
	Lenalidomide: 7.3 packs	inMIND actual dose intensity of lenalidomide in TAFA+R^2 arm
	Rituximab (TAFA arm): 7.0 infusions	inMIND mean number of rituximab infusions in the TAFA+R^2 arm
	Rituximab (R-CHOP): 7.0 infusions	inMIND mean number of rituximab infusions in the TAFA+R^2 arm
	CHOP: 7.0 doses	

Source: pp.221-226 of the submission.

1L = first-line; 2L = second-line; CLL = chronic lymphocytic leukaemia; EFC = efficient funding of chemotherapy; FL = follicular lymphoma; LaRDR = Lymphoma and Related Diseases Registry; R^2 = rituximab and lenalidomide; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R = relapsed/refractory; TAFA = tafasitamab; TTNT = time to next treatment; AEMP = Australian ex-manufacturer price; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr=year.

6.70 Table 19 summarises the submission's calculation of the number of patients likely to receive tafasitamab plus R^2 therapy, number of scripts dispensed, and costs to the PBS/RPBS.

Table 19: Estimated total number of patients to be treated with tafasitamab + R^2 and costs to the PBS/RPBS (as estimated in the submission)

	Year 1 2026	Year 2 2027	Year 3 2028	Year 4 2029	Year 5 2030	Year 6 2031	Total
Incident patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Prevalent patients treated	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Number of patients treated	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][2]
Total scripts for TAFA[a]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][3]	[redacted][3]	[redacted][5]
Total scripts for lenalidomide	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][2]	[redacted][2]	[redacted][7]
Total scripts for rituximab	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][2]	[redacted][2]	[redacted][7]
Total scripts (TAFA+R^2)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][3]	[redacted][3]	[redacted][5]
Estimated financial implications of tafasitamab + R^2							
Cost to PBS/RPBS less copayments	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][10]
Estimated financial implications for R-CHOP							
Cost to PBS/RPBS less copayments[b]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][12]
Net financial implications							
Net cost to PBS/RPBS[b]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][10]
Net cost to MBS	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Net cost to PBS/RPBS/MBS[b]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][10]

Source: Tables 4-2 to 4-22, pp.166-178 of the submission.

R^2 = rituximab and lenalidomide; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TAFA = tafasitamab.

[a] Assuming 23.1 scripts per course per patient as estimated by the submission.

[b] Corrected during the evaluation. A number of errors and inconsistencies with the financial model and economic model were corrected and adjusted to be consistent with the economic model: i) cross-referencing errors in cells F304:G308 of 4c worksheet to cells D305:E329 of 4c worksheet (EFC mark ups) ii) typing error for price of rituximab per 500 mg vial ($216.18) in cell D313 of 4c worksheet and cell D312 in 3c worksheet iii) not considering vincristine pack size of 5 (1 mg) in cell D318 of 4c worksheet, and iv) adjustments to cyclophosphamide (3 vials of 500 mg) in cells E320: E321 of 4c worksheet to be consistent with the economic model.

The redacted values correspond to the following ranges:

[1] *< 500*
[2] *500 to < 5,000*
[3] *10,000 to < 20,000*
[4] *20,000 to < 30,000*
[5] *100,000 to < 200,000*
[6] *5,000 to < 10,000*
[7] *30,000 to < 40,000*
[8] *$100 million to < $200 million*
[9] *$50 million to < $60 million*
[10] *$500 million to < $600 million*
[11] *$0 to < $10 million*
[12] *$20 million to < $30 million*

6.71 The submission estimated that the net cost to the PBS/RPBS for the proposed listing of tafasitamab plus R^2 would be $500 million to < $600 million over the first six years of listing.

6.72 The evaluation and the ESC considered that the main uncertainties were:

- The proportions of patients diagnosed with FL receiving first and second-line treatment were uncertain due to data paucity for the Australian setting. The proportion of first-line patients progressing to second-line treatment was particularly lower in the LaRDR registry (13%) compared to the proportion

assumed in the submission (40%). The PSCR stated that the LaRDR data only has a median follow up of 2.1 years from FL diagnosis and therefore was unlikely to capture the true proportion of 1L treated patients progressing to 2L treatment. The ESC and PBAC agreed with the PSCR that the LaRDR data may be immature for this purpose. Overall, the ESC considered that the proportion of first-line treated patients who progress to the 2L setting was likely to be around 30% to 40% over ten years. The PBAC advised that the proportion of 1L treated patients progressing to R/R FL (40%) was likely overestimated by the submission as a significant proportion of patients will have transformed to DLBCL at progression and so would not be candidates for tafasitamab. The PBAC considered that the proportion of first-line treated patients who progress to the 2L setting was likely to be around 30%, but that, of these patients at least 16% would have transformed lymphoma (as reported in Wasterlid 2024) and thus not be eligible for tafasitamab (i.e. an overall rate of no higher than 30% * 84% = 25%).

- The evaluation and ESC considered that the assumed uptake of tafasitamab plus R^2 for both the incident and prevalent patient pool were uncertain; however, given that tafasitamab plus R^2 is only one treatment choice amongst many (including clinical trials, refer to Table 3), considered the uptake rates were likely overestimated. Additional safety concerns with tafasitamab may also limit uptake. The PBAC noted that the submission's assumed uptake rates in incident patients were: [redacted]% in Year 1; [redacted]% in Year 2; and [redacted]% from Year 3 onwards. The PBAC considered these should be revised to: [redacted]% in Year 1; [redacted]% in Year 2 and [redacted]% in Year 3 onwards. The PBAC considered the submission's estimated uptake rate in the prevalent population was reasonable.

Overall, the evaluation and the ESC considered that the financial estimates were likely overestimated.

6.73 The pre-PBAC response provided revised financial estimates which incorporated the price reduction offered in the response (see paragraph 3.2), and applying an updated lenalidomide price (i.e., post October 2025 price disclosure). The pre-PBAC response indicated that with these revised inputs the estimated financial impact to the PBS/RPBS would be between $30 million to < $40 million and $90 million to < $100 million per annum over the first six years of the analysis.

Quality Use of Medicines

6.74 No issues relating to quality use of medicines were identified in the submission.

Financial Management – Risk Sharing Arrangements

6.75 No specific risk-sharing arrangement (RSA) was proposed by the submission; however, the submission indicated that the sponsor was willing to enter into an RSA should it help to ensure early access for patients via a timely PBS listing.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for tafasitamab for use in combination with lenalidomide and rituximab for the treatment of patients with relapsed or refractory (R/R) follicular lymphoma (FL) as the TGA Delegate's Overview was not available at the time of PBAC consideration. However, the PBAC was of a mind to recommend the listing of tafasitamab on the basis of its assessment that an acceptable incremental cost-effectiveness ratio (ICER) could be achieved with a price reduction. The PBAC noted that the economic analysis used as the basis of its advice included amendments to the extent of benefit estimated beyond the period of follow-up in the trial. The PBAC considered the financial estimates to be overestimated and advised that adjustments to the financial model were required.

7.2 The PBAC welcomed input from health care professionals and organisations which highlighted the unmet clinical need for new treatments in this area, particularly for patients not fit for or unable to access autologous stem cell transplantation. The comments highlighted that time to next treatment (TTNT) is an important endpoint for people with FL; the PBAC acknowledged that an improvement in this outcome would make a meaningful difference to patients' quality of life. The PBAC also noted the input from the Australian Leukaemia & Lymphoma Group, the Peter MacCallum Cancer Centre Lymphoma Group and the Haematology Society of Australia and New Zealand that advised that the comparator used in the trial, lenalidomide and rituximab (R^2) is internationally recognised as standard of care in R/R FL but is not TGA registered, or PBS listed for this indication in Australia.

7.3 With respect to the proposed restriction, the PBAC proposed that:

- Separating the tafasitamab listing into an Initial treatment (Cycles 1 – 5 inclusive) and a Continuing treatment (Cycles 6 – 12 inclusive) listing was appropriate. The Committee considered that, as outlined in paragraph 3.4, the Initial treatment restriction should have 15 repeats and the Continuing treatment restriction should have 13 repeats.
- A Section 100 Efficient Chemotherapy Funding (EFC) Authority Required (Telephone/Online) listing would be appropriate for both tafasitamab treatment phases.
- Determination of CD19 and CD20 status was not required in the tafasitamab restriction. Similarly, the PBAC agreed with the ESC that reference to either Eastern Cooperative Oncology Group (ECOG) performance status or the Groupe d'Etude des Lymphones Folliculaires (GELF) or the British National Lymphoma Investigation (BNLI) criteria was not required in the restriction.
- Tafasitamab use should not exceed a total of 12 cycles for this indication in a lifetime.
- Completion of a total of 12 cycles of tafasitamab was permitted, even if a break in therapy or a need to cease one of the other components of the regimen was required.

- A Section 100 Highly Specialised Drug Program Authority Required (Telephone/Online) listing of lenalidomide was considered appropriate as outlined in Table 2. However, the Committee considered that the listing would also need to include strengths below 20 mg of lenalidomide, to allow for dose reductions.

7.4 The submission nominated rituximab-based chemotherapy (R-CHEMO) as the main comparator, reflecting the treatment most likely to be replaced, particularly R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone). The PBAC considered the submission nominated comparator of R-CHEMO, represented by R-CHOP, was reasonable.

7.5 The PBAC noted the clinical evidence for tafasitamab plus R^2 was based on the inMIND trial which compared this regimen versus placebo plus R^2 in the R/R FL population. The inMIND trial reported that tafasitamab plus R^2 was associated with a statistically significant progression free survival (PFS) benefit compared to placebo plus R^2 (HR: 0.43 [95% CI: 0.32, 0.58]). Median PFS, by investigator assessment, was 22.4 months in the tafasitamab arm plus R^2 and 13.9 months in the placebo plus R^2 arm. The PBAC noted that, while the point estimate of the overall survival (OS) hazard ratio favoured patients in the tafasitamab arm, the result was not statistically significant (HR: 0.59 [95% CI: 0.31, 1.13]) and the data were immature. A significant increase in time to next treatment (TTNT) for patients receiving tafasitamab plus R^2 compared to placebo plus R^2 was noted by the PBAC, with median TTNT not yet reached versus 28.8 months respectively, and HR 0.45 (95% CI: 0.31, 0.64).

7.6 The PBAC noted that no head-to-head trials comparing tafasitamab plus R^2 to the nominated comparator of R-CHEMO were available. Furthermore, no studies were available to support an anchored indirect comparison between tafasitamab plus R^2 and R-CHEMO in second-line FL. Instead, the submission presented data from the RELEVANCE trial to demonstrate non-inferiority between R^2 and R-CHEMO in first-line FL and argued that this non-inferiority would hold in the second-line setting. The PBAC considered that the efficacy outcomes from the RELEVANCE trial supported the assumption that R^2 is non-inferior to R-CHEMO in first-line treatment of Grade 1-3a FL. The PBAC agreed with the ESC that the assumption that the conclusion of non-inferiority in the first-line setting would hold for the second-line setting was not unreasonable but was highly uncertain. The PBAC considered that differences in the R^2 regimen used in the inMIND trial and that used in the RELEVANCE trial (see paragraph 6.25) further contributed to the uncertainty. Overall, the PBAC considered that the claim that tafasitamab plus R^2 has superior comparative effectiveness versus R-CHEMO was highly uncertain but likely reasonable. Further, the PBAC considered that the magnitude of benefit versus R-CHEMO was difficult to quantify.

7.7 The PBAC noted the safety profiles of R^2 and R-CHEMO are different, with the RELEVANCE trial showing a higher proportion of patients in the R^2 arm experiencing serious adverse events, treatment discontinuation and dose modifications than patients in the R-CHEMO arm. Similarly, the inMIND trial reported that 36.1% of patients receiving tafasitamab plus R^2 experienced a serious treatment-emergent

adverse event (TEAE) versus 31.6% in the placebo plus R^2 arm, alongside increased rates of treatment discontinuation and dose modifications. The PBAC considered that these findings collectively highlighted a less favourable safety profile for tafasitamab plus R^2 versus R-CHOP. As such, the PBAC considered that the claim of inferior comparative safety was reasonable.

7.8 The submission presented a stepped economic evaluation of tafasitamab plus R^2 versus R-CHEMO, based on the inMIND trial. The PBAC noted the concerns raised by the evaluation and ESC regarding the 20-year time horizon, the lack of either curve or risk convergence for OS, PFS or TTNT and the utility values used in the model. The PBAC noted that the ESC proposed a revised base case which applied a 10-year time horizon, curve convergence (Years 5-10), and utility values from Wild (2006). To account for some of the concerns raised by ESC, the pre-PBAC response provided a revised scenario with a 15-year time horizon and risk convergence from 10 years (along with a revised price for tafasitamab), which resulted in an ICER of around $55,000 to < $75,000/QALY using the trial-based utilities or $75,000 to < $95,000/QALY using literature-derived utilities. However, the PBAC noted that the pre-PBAC response scenario resulted in a large divergence in OS outcomes at 15 years (a survival difference between arms of 12% was modelled at 15 years, compared with a difference of 7% observed in the trial data at 2 years; refer to paragraph 6.58), which the Committee considered was not adequately supported given the immaturity of the OS data (with a trial follow-up of around 15 months for OS, and only 5.5% and 8.4% of deaths having occurred in the tafasitamab+R^2 and placebo+R^2 arms, respectively) and the lack of statistically significant OS gain. Thus, the PBAC considered that a 15-year time horizon and risk convergence from 5 years (rather than 10 years) would be more appropriate. The PBAC acknowledged the pre-PBAC response argument that concurrently reducing the time horizon and converging the treatment benefit account for the same uncertainty, however the PBAC considered that both changes were required given the substantial uncertainty associated with the long-term survival benefits given the immaturity of the OS data.

7.9 The PBAC noted the ESC considered the base case utilities were implausibly high and advised the use of utility values reported by Wild (2006). While the PBAC agreed that the trial-based utilities appeared high (given the values were similar to general Australian population norms), the Committee also acknowledged that the utility values reported by Wild (2006) were less reliable in this case. Overall, the PBAC advised that with the revisions to the model outlined above (i.e. 15 year time horizon and risk convergence from 5 years), the use of trial-based utility values was appropriate. The PBAC considered the cost-effectiveness analysis would be more reliable with these amendments to the extent of benefit estimated beyond the period of follow-up in the trial and advised that an ICER of up to $55,000 to < $75,000 per QALY gained would be acceptable. The PBAC considered this ICER was appropriate in the context of the uncertain magnitude of clinical benefit (given the immature trial data versus R^2 rather than R-CHOP), balanced against the clinical need in this population. The PBAC noted the price reduction offered in the pre-PBAC response and

considered that a further price reduction would be required to achieved cost-effectiveness based on the revised model.

7.10 The PBAC agreed with the ESC that the financial estimates were overestimated. The PBAC advised that the assumed proportion of 1L treated patients progressing to R/R FL (40% based on the Swedish Lymphoma Registry – Wasterlid [2024]) was likely too high as a significant proportion of patients will have transformed to DLBCL at progression and so would not be candidates for tafasitamab (refer to paragraph 6.72). The PBAC also considered the uptake rates were overestimated in the incident population and advised these rates should be reduced given the availability of other treatment options such as clinical trials (refer to paragraph 6.72). The PBAC noted that the financial estimates would also need to be revised to incorporate the price reduction required to achieve cost-effectiveness as outlined in paragraph 7.8.

7.11 The PBAC advised that an RSA would likely be required in the context of the significant cost of the listing, and to manage the risk associated with the uncertain script numbers (particularly noting uncertainties around uptake and the proportion of patients requiring treatment in second- and later-line FL).

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it was deferred.

Outcome:
Deferred

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.