

**6.04 OBINUTUZUMAB,  
solution for I.V. infusion 1000 mg in 40 mL,  
Gazyva<sup>®</sup>,  
Roche Pty Ltd.**

**1 Purpose of Application**

1.1 Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (STREAMLINED) listing for obinutuzumab for the treatment of rituximab-refractory follicular lymphoma.

**2 Requested listing**

2.1 The requested restriction is provided below, including for use in combination with bendamustine for induction therapy, followed by obinutuzumab monotherapy as maintenance. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
OBINUTUZUMAB solution for i.v. infusion 1000 mg in 40 mL	1000 mg	7	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Gazyva Roche Products Australia Pty Ltd

<b>Category / Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	<i>Rituximab-refractory<sup>1</sup></i>
<b>Severity:</b>	<del>Refractory</del>
<b>Condition:</b>	CD20 positive follicular <i>B-cell non-Hodgkin's</i> lymphoma
<b>PBS Indication:</b>	<i>Rituximab-refractory follicular CD20 positive B-cell non-Hodgkin's lymphoma</i>
<b>Treatment phase:</b>	Re-induction treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

<sup>1</sup> The term “refractory” was changed to “rituximab-refractory” throughout the restriction table, per PBAC advice, November 2016.

Public Summary Document – November 2016 PBAC Meeting

<b>Clinical criteria:</b>	The treatment must be for re-induction treatment purposes only  AND  The condition must be refractory to treatment with rituximab for this condition  AND  <i>The treatment must be in combination with bendamustine</i>
<b>Prescriber Instructions</b>	<del>To be considered refractory to rituximab, the patient must have had no complete or partial response to a rituximab-containing treatment</del> OR <del>The patient must have had progressive disease while receiving a rituximab-containing treatment during either induction or maintenance therapy</del> OR <del>The patient must have had progressive disease within 6 months of completion of the last dose of a rituximab-containing treatment.</del>  <i>A 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.</i>  <i>The condition is considered rituximab-refractory if the patient experiences less than a partial response or progression of disease within 6 months after completion of a prior rituximab-containing regimen.</i>
<b>Administrative Advice</b>	<i>No increase in the maximum number of repeats may be authorised.</i>  <i>Special Pricing Arrangements apply.</i>

Name, Restriction, Manner of administration and form      Max. of Amount      No. of Rpts      Dispensed Price for Max. Amount      Proprietary Name and Manufacturer

OBINUTUZUMAB solution for i.v. infusion 1000 mg in 40 mL      1000 mg      5      \$ [REDACTED] (Published)  
\$ [REDACTED] (Effective)      Gazyva      Roche Products Australia Pty Ltd

<b>Category / Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	<i>Rituximab-refractory</i>
<b>Condition:</b>	<b>Refractory</b>
<b>PBS Indication:</b>	<i>Rituximab-refractory CD20 positive follicular B-cell non-Hodgkin's lymphoma</i>
<b>Treatment phase:</b>	Maintenance therapy
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised treatment with obinutuzumab for rituximab-refractory follicular lymphoma The treatment must be as monotherapy</p> <p>AND</p> <p>The treatment must be for maintenance therapy only</p> <p>AND</p> <p>Patient must have demonstrated a partial or complete response to the PBS- subsidised re-induction treatment</p> <p>AND</p> <p>Patient must not have progressive disease while receiving treatment with this drug</p> <p>AND</p> <p>Patient must not receive more than 12 doses or 2 years duration of treatment, whichever comes first, under this restriction</p>
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

- 2.2 The Pre-Sub-Committee Response (PSCR) (p5) claimed that the suggested wording for the maintenance therapy restriction was inconsistent with the GADOLIN trial and the patient population modelled in the economic evaluation, as it excluded patients with stable disease after induction therapy with obinutuzumab plus bendamustine from receiving obinutuzumab maintenance therapy. The ESC considered that patients with stable disease should be allowed access to obinutuzumab maintenance therapy.
- 2.3 The PBAC noted that unlike precedent examples of rituximab-based regimens where combination therapy increased response rates, no such incremental response was observed in the GADOLIN trial; rather, the major benefit observed related to the maintenance phase. The PBAC therefore considered that it was reasonable to follow the trial approach and allow access to obinutuzumab maintenance therapy for patients with stable, but not progressive, disease. The PBAC considered that the clinical criterion for maintenance therapy should be changed from “Patient must have demonstrated a partial or complete response to the PBS- subsidised re-induction treatment”, to “Patient must have demonstrated a partial or complete response, or stable disease, to the PBS- subsidised re-induction treatment”.
- 2.4 Obinutuzumab maintenance treatment is for a maximum of two years after an induction treatment of six months in combination with bendamustine. This maximum duration of treatment was included in the economic model.
- 2.5 The submission presented a cost-effectiveness analysis of obinutuzumab plus bendamustine compared with bendamustine monotherapy. Bendamustine monotherapy was used as a proxy for best supportive care.

### **3 Background**

- 3.1 TGA status: obinutuzumab was TGA approved on 26 August 2016. The approved indication is: '(Obinutuzumab) in combination with bendamustine, followed by (obinutuzumab) maintenance, is indicated for the treatment of patients with follicular lymphoma who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.'
- 3.2 Obinutuzumab is currently PBS-listed for use in the treatment of previously untreated chronic lymphocytic leukaemia in combination with chlorambucil.
- 3.3 Idelalisib was recommended for listing as monotherapy at the July 2016 PBAC meeting for patients with follicular lymphoma who are refractory to rituximab and to an alkylating agent.

### **4 Clinical place for the proposed therapy**

- 4.1 Follicular lymphoma is a commonly occurring form of non-Hodgkin's lymphoma characterised by tumour cell proliferation in a circular or follicular pattern within a lymph node. First-line treatment for patients is commonly rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or rituximab in combination with cyclophosphamide, vincristine and prednisone (R-CVP) followed by rituximab monotherapy as maintenance. Rituximab plus bendamustine was listed on the PBS on 1 August 2016 for first-line treatment in patients with indolent non-Hodgkin's lymphoma. The submission suggested that there are no options with proven benefit available on the PBS for patients who become refractory to rituximab-based regimens, and that currently these patients would receive best supportive care.
- 4.2 In the proposed clinical management algorithm, obinutuzumab in combination with bendamustine is to be used in adult patients with rituximab-refractory follicular lymphoma for re-induction. This is to be followed with obinutuzumab monotherapy for maintenance for a maximum of two years.

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

### **5 Comparator**

- 5.1 The submission nominated best supportive care as the comparator, with bendamustine monotherapy acting as proxy.
- 5.2 The ESC considered that it was uncertain whether best supportive care would be a reasonable comparator, as:
  - It is difficult to distinguish if patients with refractory follicular lymphoma would be genuinely refractory to rituximab or refractory to another component of rituximab combination therapy. In clinical practice, patients considered refractory to one rituximab based therapy will likely be switched to another rituximab based therapy. The PSCR (p1) and the Pre-PBAC response (p1) argued that the requested listing restricted obinutuzumab plus bendamustine to patients who

relapsed within six months of the last treatment with a rituximab-containing regimen, and that such patients are unlikely to be treated with additional rituximab-containing therapies. It was stated that further treatment with a rituximab-containing therapy should only be considered in patients who relapse after a remission of at least six months from the last rituximab-containing therapy. The PBAC noted the ESC's advice, however, considered that the re-use of rituximab as part of subsequent therapy in the patient population defined in the trial and in the proposed restriction, is undesirable and not recommended by international guidelines<sup>2</sup>. On this basis, the PBAC considered that best supportive care, such as non-rituximab containing palliative treatments, including chemotherapy, was the appropriate comparator.

- Idelalisib was recommended for listing for rituximab-refractory follicular lymphoma at the July 2016 PBAC meeting, and could also be a potential comparator. The PSCR (p2) argued that idelalisib was not a relevant comparator, on the basis that patients in the idelalisib trial were refractory to both rituximab and an alkylating agent and thus had more severe disease. The ESC considered that idelalisib may not be an appropriate main comparator, as patients need to be refractory to both rituximab and an alkylating agent to access PBS-subsidised idelalisib, and may therefore have more severe disease than the potential PBS population using obinutuzumab. The ESC noted the PSCR's statement (p2) that patients in the idelalisib trial (Study 101-09) had a median of four lines of prior treatment whereas patients in the GADOLIN trial had a median of two lines of prior treatment. The PBAC considered that idelalisib was an alternative comparator noting that 79.4% of participants in the GADOLIN trial were refractory to both rituximab and an alkylating agent (p158, GADOLIN CSR May 2015 update). However, the PBAC considered that consistent with the available clinical evidence, obinutuzumab plus bendamustine, if listed, would generally be used earlier in the treatment algorithm than idelalisib, primarily in patients with early progression or recurrence after regimens such as R-CHOP and R-CVP which are most commonly used in Australia. Hence, the PBAC did not consider idelalisib to be the appropriate main comparator.

- 5.3 The ESC considered that bendamustine was a reasonable proxy comparator, given the lack of available clinical data for best supportive care. The PBAC considered that bendamustine was a reasonable clinical proxy for best supportive care. However, the PBAC recalled its decision at the March 2015 meeting, that bendamustine was not cost-effective for the treatment of rituximab-refractory indolent non-Hodgkin's lymphoma and is not PBS-listed for this population (Bendamustine PSD, March 2015 PBAC meeting). On this basis, the PBAC considered that bendamustine was not an element of best supportive care in the Australian setting, and its cost should not be incorporated into the economic evaluation.

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

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<sup>2</sup> Annals of Oncology 25 (Supplement 3): iii76–iii82, 2014

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed input from individuals (24) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals were from patients who had previously received obinutuzumab and those who had not received obinutuzumab, but anticipated that they may need treatment in the future. The patients described the negative impacts of follicular lymphoma and stated that obinutuzumab represented an additional treatment option, which offered them hope for slowing disease progression and/or preventing disease relapse.

6.3 The PBAC noted the correspondence from the Leukaemia Foundation, which provided information on the impact of disease on life and quality of life, and feedback from patients on the benefits and side effects of obinutuzumab treatment, based on a survey of 123 people living with follicular lymphoma. The PBAC also noted the correspondence from Lymphoma Australia, which stated the clinical need for additional treatment options, particularly for the subset of patients with rituximab-refractory follicular lymphoma. The PBAC noted that the consumer comments were supportive of the PBS listing of obinutuzumab as requested by the submission.

### ***Clinical trials***

6.4 The submission was based on the GADOLIN trial, an open-label, head-to-head multicentre, Phase III randomised controlled trial comparing obinutuzumab plus bendamustine with bendamustine monotherapy (N=396 in September 2014 data cut; N=413 in May 2015 data cut) for rituximab-refractory non-Hodgkin's lymphoma, which included a sub-group of patients with follicular lymphoma.

6.5 Details of the trial presented in the submission are provided in the table below.

**Table 1: Trial and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
GADOLIN	Primary Clinical Study Report – GAO4753g/GO01297 – An open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with bendamustine + RO5072759 (GA101) in patients with rituximab-refractory, indolent non-Hodgkin's Lymphoma. Research Report Number 1051204.	July 2015
	Update Clinical Study Report – GAO4753g/GO01297 - An open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with bendamustine + RO5072759 (GA101) in patients with rituximab-refractory, indolent non-Hodgkin lymphoma. Research Report Number 1067639.	December, 2015
	Sehn LH, Chua N, Mayer J, <i>et al.</i> Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial	<i>Lancet Oncol</i> ; 2016; 17(8); 1081-1093

Source: Table B.2.3, p6 of Section B of the submission

6.6 The key features of the direct randomised trial are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>O-Benda vs. Benda</b>						
GADOLIN	396 <sup>a</sup>	R, MC, OL 21.9 months <sup>b</sup>	Low	Rituximab-refractory NHL	PFS, OS, safety, QoL	Yes – the FL subgroup

Benda = bendamustine; DB=double blind; FL = follicular lymphoma; NHL = non-Hodgkin lymphoma; MC=multi-centre; O-Benda = Obinutuzumab-bendamustine; OL=open label; OS=overall survival; QoL = quality of life; PFS=progression-free survival; R=randomised.

Source: compiled during the evaluation

<sup>a</sup> At the time of the first analysis (September 2014) 396 patients were enrolled. At the later data cut (May 2015) an additional 17 patients were enrolled increasing the total number of patients to 413.

<sup>b</sup> At the time of the first analysis (September 2014), median follow-up was 21.9 months for patients treated with obinutuzumab plus bendamustine. At the later data cut (May 2015), median follow-up for patients treated with obinutuzumab plus bendamustine was 25.3 months.

6.7 The results from the follicular lymphoma subgroup were used to inform the economic model.

### **Comparative effectiveness**

6.8 The submission provided the results of the intention to treat (ITT) population and two subgroups: follicular lymphoma and non-follicular lymphoma. The follicular lymphoma subgroup was pre-specified, and baseline characteristics were similar to the ITT population. Baseline characteristics were also similar between the obinutuzumab plus bendamustine treatment arm and the bendamustine monotherapy control arm for the follicular lymphoma subgroup.

6.9 The progression free survival (PFS) results from the GADOLIN trial for both the ITT population and the pre-specified subgroup of patients with follicular lymphoma is presented in Table 3. The Kaplan-Meier curves for PFS for the follicular lymphoma subgroup are presented in Figure 1.

**Table 3: Results of independently-assessed progression-free survival in the GADOLIN trial**

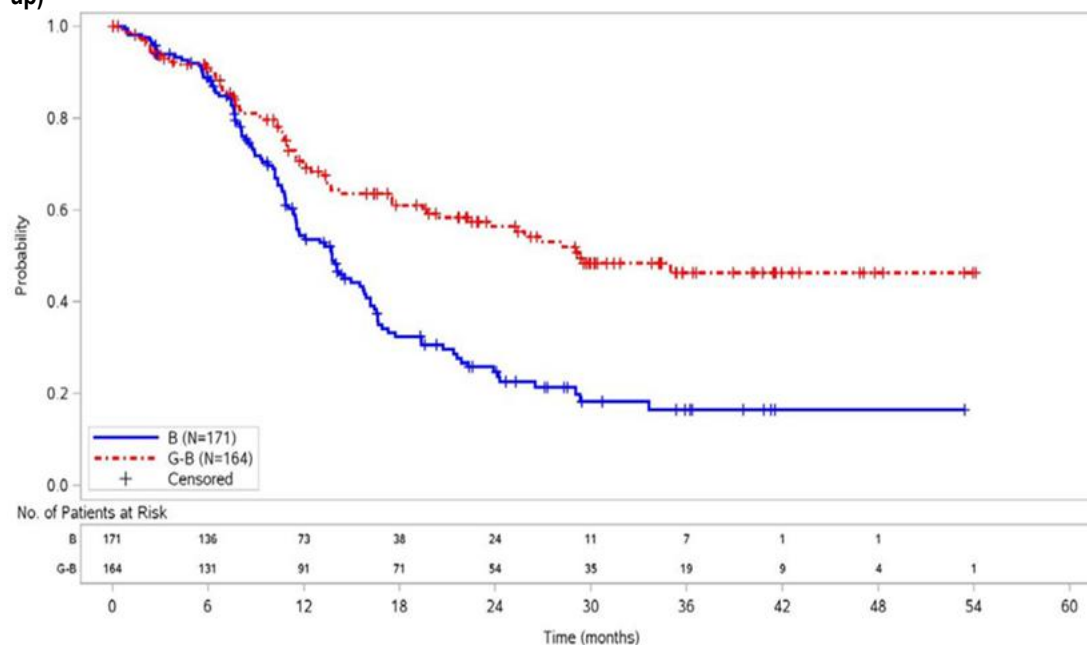
Drug	ITT		FL-subgroup	
	O-Benda	Benda	O-Benda	Benda
<b>1 September 2014 cut-off</b>				
N	194	202	155	166
Median follow-up (months)	21.9	20.3	N/A	N/A
Patients with events, n (%)	71 (36.6%)	104 (51.5%)	54 (34.8%)	90 (54.2%)
Disease progression	60 (30.9%)	95 (47.0%)	46 (29.7%)	83 (50.0%)
Deaths	11 (5.7%)	9 (4.5%)	8 (5.2%)	7 (4.2%)
Median PFS, months (95% CI)	NE (22.5, NE)	14.9 (12.8, 16.6)	NE (22.5, NE)	13.8 (11.4, 16.2)
Hazard ratio (95% CI) <sup>a</sup>	<b>0.55 (0.40, 0.74), p=0.0001</b>		<b>0.48 (0.34, 0.68), p&lt;0.0001</b>	
<b>1 May 2015 cut-off</b>				
N	204	209	164	171
Median follow-up (months)	25.3	24.5	24.1	24.1
Patients with events (n, %)	87 (42.6%)	125 (59.8%)	67 (40.9%)	108 (63.2%)
Disease progression	74 (36.3%)	115 (55.0%)	58 (35.3%)	100 (58.5%)
Deaths	13 (6.4%)	10 (4.8%)	9 (5.5%)	8 (4.7%)
Median PFS, months (95% CI)	29.2 (20.5, NE)	14.1 (11.7, 16.6)	29.2 (20.5, NE)	13.8 (11.5, 15.8)
Hazard ratio (95% CI) <sup>a</sup>	<b>0.53 (0.40, 0.70), p&lt;0.001</b>		<b>0.47 (0.34, 0.64), p&lt;0.0001</b>	

Source: Tables B.6.1, p27 and B.6.2, pp28-29 of Section B of the submission; extracted from Tables 23, p131; Table 38, p162; Table 43, p174; Table 47, p185; Table t\_ef\_tte\_strunstr\_pfsrad1\_marzl\_297\_IT, pp950-951; and t\_ef\_tte\_strunstr\_pfsrad1\_sml\_297\_IT, pp952-953 of the 1 September 2014 CSR. Table t\_sl\_c\_obst\_297\_IT p160; Table t\_ef\_tte\_strunstr\_pfsrad1\_297\_IT, pp161-162; Table t\_sl\_c\_obst\_foly\_297\_IT, p189 of the 1 May 2015 CSR and calculated during the evaluation.

Benda = bendamustine monotherapy; CI = Confidence Interval; FL = follicular lymphoma; ITT = intention-to-treat; N/A = not assessed; NE = not evaluable; O-Benda = obinutuzumab and bendamustine combination therapy; PFS = progression-free survival; **Bold** = statistically significant

<sup>a</sup> The analysis was stratified for lymphoma subtype, prior therapies and refractory type

**Figure 1: Progression-free survival, follicular lymphoma subgroup – 1 May 2015 cut-off (~24 month follow-up)**



Source: Figure B.6.1, p29 of Section B of the submission.  
 B = bendamustine; G-B = obinutuzumab plus bendamustine therapy

- 6.10 The ESC noted that patients in the follicular lymphoma subgroup were broadly balanced for disease characteristics at baseline between treatment arms, with a slight excess of bulky disease and a greater exposure to prior therapy in the bendamustine monotherapy control arm relative to the obinutuzumab plus bendamustine arm.
- 6.11 At the updated analysis (May 2015) the median follow-up was 24.1 months for obinutuzumab plus bendamustine and bendamustine monotherapy arms. Progression free survival was improved in both the ITT population and the subgroup of patients with follicular lymphoma. For the subgroup of patients with follicular lymphoma the median PFS was 29.2 months (95% confidence interval (CI): 20.5 to not estimable) for patients treated with obinutuzumab plus bendamustine and 13.8 months (95% CI: 11.5 to 15.8) for patients treated with bendamustine monotherapy (hazard ratio (HR): 0.47, 95% CI: 0.34 to 0.64). From the Kaplan-Meier curves it could be observed that the PFS started diverging after six months, which might be attributed to cessation of bendamustine monotherapy. The ESC noted that the investigator-assessed PFS, as a secondary outcome, was broadly consistent with the primary analysis with HRs of 0.48 (95% CI 0.35, 0.67;  $p < 0.0001$ ) and 0.47 (95% CI 0.35, 0.64;  $p < 0.0001$ ) for the September 2014 and May 2015 data cuts respectively.
- 6.12 For the subgroup of patients with non-follicular lymphoma, results were only presented at the first data cut-off (1 September 2014), which showed that PFS was not statistically significantly different between the two treatment groups. However, the number of patients with non-follicular lymphoma was small. There were only 39 patients in the obinutuzumab plus bendamustine arm and 35 patients in the bendamustine monotherapy arm in the non-follicular lymphoma subgroup; the median PFS was not reached in either arm. The submission did not present tests for interaction across the subgroups or provide a rationale for a difference in treatment effect between the non-follicular and follicular lymphoma subgroups. The Pre-PBAC response (p2) stated that the unstratified HR for independently-assessed PFS was 1.02 (95% CI: 0.53 to 1.96) in the non-follicular lymphoma subgroup versus 0.48 (95% CI: 0.35 to 0.65) in the follicular lymphoma subgroup (test for interaction  $p$ -value=0.05; 1 May 2015 clinical cut-off).
- 6.13 The PBAC noted that the follicular lymphoma subgroup was pre-specified in the trial protocol and represented the majority (81%) of the ITT population.
- 6.14 A fixed sequence testing procedure was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints for the primary analysis at the 1 September 2014 data cut-off. Analyses for the May 2015 cut-off were not adjusted for multiple statistical testing.
- 6.15 The overall survival (OS) in the ITT population and the follicular lymphoma subgroup is presented in Table 4. The Kaplan-Meier curves for OS in the obinutuzumab plus bendamustine and bendamustine monotherapy arms are presented in Figure 2.

**Table 4: Results of overall survival for patients in the GADOLIN trial (1 May 2015 cut-off)**

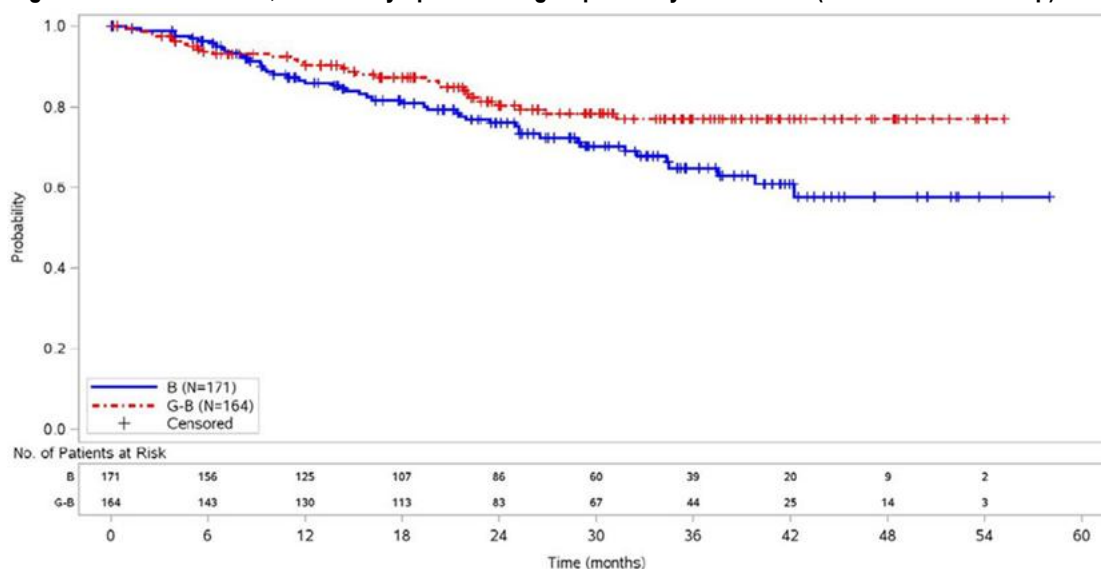
GADOLIN	ITT		FL-subgroup	
	O-Benda	Benda	O-Benda	Benda
<b>1 September 2014 cut-off</b>				
N	194	202	155	166
Median duration of follow-up (months)	21.9	20.3	N/A	N/A
Deaths, n (%)	34 (17.5%)	41 (20.3%)	25 (16.1%)	36 (21.7%)
Censored, n (%)	160 (82.5%)	161 (79.7%)	130 (83.9%)	130 (78.3%)
Median OS, months (95% CI)	NE (NE)	NE (39.8, NE)	NE (NE)	NE (39.8, NE)
Hazard ratio (95% CI) <sup>a</sup>	0.82 (0.52, 1.30), p=0.4017		0.71 (0.43, 1.19), p=0.1662	
<b>1 May 2015 cut-off</b>				
N	204	209	164	171
Median duration of follow-up (months)	25.3	24.5	24.1	24.1
Deaths, n (%)	42 (20.6%)	56 (26.8%)	30 (18.3%)	48 (28.1%)
Censored, n (%)	162 (79.4%)	153 (73.2%)	134 (81.7%)	123 (71.9%)
Median OS, months (95% CI)	NE (34.9, NE)	NE (25.3, NE)	NE (NE)	NE (42.2, NE)
Hazard ratio (95% CI) <sup>a</sup>	0.72 (0.48, 1.08) p = 0.114		0.62 (0.39, 0.98) p = 0.0379	

Source: Table B.6.1, p27, Table B.6.4, p32 of Section B of the submission and Table 35, p152, Table 42, p170 Table 47, p185 of the 1 September 2014 CSR and Tables t\_sl\_c\_obst\_297\_IT, p160; t\_ef\_tte\_strunstr\_os\_297\_IT, pp177-178; Table t\_sl\_c\_obst\_foly\_297\_IT, p189; and t\_ef\_tte\_strunstr\_os\_foly\_297\_IT, pp206-207 of the 1 May 2015 CSR.

Benda = bendamustine monotherapy; CI = Confidence Interval; FL = follicular lymphoma; ITT = intention to treat; N/A = not assessed; NE = not evaluable; O-Benda = obinutuzumab and bendamustine combination therapy; OS = overall survival

<sup>a</sup> The hazard ratios were not corrected for multiplicity, the analysis was stratified for lymphoma subtype, prior therapies and refractory type

**Figure 2: Overall survival, follicular lymphoma subgroup – 1 May 2015 cut-off (~24 months follow-up)**



Source: Figure B.6.2, p32 of Section B of the submission.  
B = bendamustine; G-B = obinutuzumab plus bendamustine

- 6.16 Overall survival data were immature at both the 1 September 2014 and 1 May 2015 cut-off dates. In the follicular lymphoma subgroup, the analysis at the latest data cut (median follow-up of 24.1 months) showed that obinutuzumab plus bendamustine was associated with a higher OS rate than bendamustine monotherapy (HR: 0.62; 95% CI: 0.39 to 0.98; without adjustment for multiplicity). The ESC noted that the

difference was non-significant after correcting for multiple comparisons. Median OS was not reached in either arm. The results of OS for the follicular lymphoma subgroup necessitated caution in interpretation, as the subgroup analyses were unadjusted for multiplicity at the updated 1 May 2015 data cut-off, and were based on immature survival data with the median OS not being reached in either treatment arm. The PBAC noted that the OS data were immature, but considered that an OS benefit was plausible.

### **Comparative harms**

- 6.17 Based on the follicular lymphoma subgroup, the most common Grade 3-5 adverse events that occurred with at least a five percent incidence in either of the treatment arms were neutropenia (32.3% versus 24.4% for obinutuzumab plus bendamustine vs. bendamustine monotherapy, respectively), thrombocytopenia (11.0% vs. 14.9%), anaemia (6.1% vs. 10.1%), febrile neutropenia (5.5% vs. 3.0%), infusion-related reactions (9.1% vs. 3.6%) and pneumonia (1.8% vs. 5.4%).
- 6.18 Patients treated in the obinutuzumab plus bendamustine arm in the follicular lymphoma subgroup were also at a greater risk of Grade 3-5 procedural complications (12.2% vs. 3.6%), all-grade cardiac events (12.2% vs. 5.4%) and all-grade musculoskeletal and connective tissue disorders (41.5% vs. 30.4%) when compared with bendamustine monotherapy. Grade 3-5 procedural complications included injury, poisoning and infusion-related events, and were driven by Grade 3-5 infusion-related reactions (9.1% vs. 3.6%).
- 6.19 Patients treated with obinutuzumab were more likely to experience Grade 3 or 4 cardiac events, with eight patients (4.9%) in the obinutuzumab arm versus two patients (1.2%) treated with bendamustine monotherapy. Neutropenia was also identified as a key safety event in the trial, with serious neutropenic events occurring more amongst patients treated with the obinutuzumab plus bendamustine compared to patients treated with bendamustine monotherapy (9.1% vs. 3.0%). An adverse event was classified as 'serious' if it was fatal, life-threatening, required inpatient hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was considered a significant medical event by the investigator.
- 6.20 Obinutuzumab has a warning in the Australian Product Information for progressive multifocal leukoencephalopathy. The PSCR (p3) stated that only [REDACTED] cases of progressive multifocal leukoencephalopathy have been reported out of approximately [REDACTED], [REDACTED] patients who have received obinutuzumab, with none of the cases occurring in patients treated for rituximab-refractory follicular lymphoma. The submission did not provide long-term safety data of obinutuzumab.

### **Benefits/harms**

- 6.21 A summary of the comparative benefits and harms for obinutuzumab plus bendamustine versus bendamustine monotherapy for the treatment of patients with rituximab-refractory follicular lymphoma is presented in Table 5.

**Table 5: Summary of comparative benefits and harms for obinutuzumab plus bendamustine versus best supportive care for the follicular subgroup in the GADOLIN trial (1 May 2015 cut-off)**

<b>Benefits</b>						
	<b>O-Benda N = 164</b>	<b>Benda N = 171</b>	<b>HR (95% CI)</b>			
<b>PFS</b>						
Patients with events, n (%)	67 (40.9%)	108 (63.2%)	-			
Median (mths) (95% CI)	29.2 (20.5, NE)	13.8 (11.5, 15.8)	<b>0.47 (0.34, 0.64), p&lt;0.0001</b>			
<b>OS</b>						
Died; n (%)	30 (18.3%)	48 (28.1%)				
Median (mths) (95% CI)	NE (NE)	NE (42.2, NE)	<b>0.62 (0.39, 0.98), p = 0.0379</b>			
<b>Harms</b>						
<b>Patients with events</b>	<b>O-Benda N = 164<sup>a</sup></b>	<b>Benda N = 168</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients<sup>b</sup></b>		<b>RD (95% CI)</b>
				<b>O-Benda</b>	<b>Benda</b>	
Grade 3-5 neutropenia	53/164	41/168	1.32 (0.94, 1.87)	32	24	7.9% (-1.8%, 17.6%)
Grade 3-5 febrile neutropenia	9/164	5/168	1.84 (0.63, 5.39)	5	3	2.5% (-1.8%, 6.8%)
Grade 3-5 Procedural complications	20/164	6/168	<b>3.42 (1.41, 8.29)</b>	12	4	<b>8.6% (2.9%, 14.4%)</b>
Grade 3-5 IRR	15/164	6/168	<b>2.56 (1.02, 6.44)</b>	9	4	<b>5.6% (0.3%, 10.8%)</b>
All-grade musculoskeletal events	68/164	51/168	<b>1.37(1.02, 1.83)</b>	41	30	<b>11.1% (0.9%, 21.4%)</b>
All-grade cardiac events	20/164	9/168	<b>2.28 (1.09, 4.85)</b>	12	5	<b>6.8% (0.8%, 12.9%)</b>

Source: Tables B.6.2, pp28-29, B.6.4, p32, B.6.11, pp40-42, B.6.12, p32 of Section B of the submission.

Benda = bendamustine; HR = hazard ratio; IRR = infusion-related reaction; NE = not evaluable; mths = months; O-Benda = obinutuzumab-bendamustine; RD = risk difference; RR = relative risk

**Bold** = statistically significant

<sup>a</sup> Calculated from safety population

<sup>b</sup> Median duration of follow-up 24.1 months

6.22 On the basis of the direct evidence presented by the submission (follicular lymphoma subgroup, May 2015 data cut-off), for every 100 patients treated with obinutuzumab plus bendamustine therapy in comparison with bendamustine monotherapy over a median duration of follow-up of approximately 24.1 months:

- Five more patients will experience a Grade 3-5 infusion-related reaction.
- Seven more patients will experience a cardiac event of any grade.

The PBAC considered that given the immature data, the median PFS results were not a reliable reflection of the true comparative effectiveness of treatment with obinutuzumab plus bendamustine compared to bendamustine monotherapy. The PBAC noted the rate at which patients treated with obinutuzumab plus bendamustine progressed was significantly lower than for patients treated with bendamustine alone, and that over a median duration of follow-up of approximately 24.1 months, 40.9% of patients treated with obinutuzumab plus bendamustine had progressed compared with 63.2% of patients treated with bendamustine alone.

### **Clinical claim**

6.23 The submission claimed that obinutuzumab plus bendamustine was superior in efficacy and no worse in comparative safety over bendamustine monotherapy (as a proxy for best supportive care) in patients with rituximab-refractory follicular lymphoma.

- 6.24 The claim of superior clinical efficacy might not be reasonable as although the benefit for OS was statistically significant at the longer follow-up, the statistical analyses presented were not robust. The ESC noted that the survival advantage favouring the obinutuzumab plus bendamustine arm was not statistically significant after adjusting for multiplicity.
- 6.25 The Pre-PBAC response (p2) provided examples of consumer comments describing the value of treatments that prolong PFS in follicular lymphoma. It argued that immature OS data was to be expected for indolent diseases such as follicular lymphoma, and that the claim of superior comparative effectiveness of obinutuzumab plus bendamustine over bendamustine monotherapy can be robustly supported by the PFS data from the GADOLIN trial.
- 6.26 The claim of comparable safety of obinutuzumab therapy over best supportive care might not be reasonable as:
- Patients treated with obinutuzumab plus bendamustine therapy were more likely to have Grade 3-5 procedural and infusion-related complications, along with all-grade cardiac and musculoskeletal events relative to bendamustine monotherapy.
  - Obinutuzumab has a warning in the Australian Product Information for progressive multifocal leukoencephalopathy.
- The Pre-PBAC response (p2) maintained that the safety profile of obinutuzumab plus bendamustine was comparable to bendamustine monotherapy and no worse than best supportive care in patients with rituximab-refractory follicular lymphoma, citing consumer comments as further evidence in support of this claim.
- 6.27 The PBAC considered that the claim of superior efficacy of obinutuzumab plus bendamustine over bendamustine monotherapy, was reasonable, based on the trial's primary endpoint, independently reviewed PFS. The PBAC agreed with the ESC that the submission did not provide adequate evidence of an OS benefit, but the PBAC considered that an OS benefit was likely to be observed with further follow-up. However, the PBAC considered that the magnitude of any OS benefit was highly uncertain, given the immaturity of the trial data presented. The PBAC further considered that with additional follow-up the difference between the treatment groups in PFS may reduce.
- 6.28 The PBAC considered that the data presented in the submission indicated that obinutuzumab, together with bendamustine and as monotherapy as maintenance, increased toxicity compared to bendamustine monotherapy. The PBAC noted the increased occurrence of musculoskeletal and cardiac events, infusion-related reactions and the trend toward increased Grade 3-5 neutropenia and febrile neutropenia (toxicities previously associated with obinutuzumab in patients with chronic lymphocytic leukaemia<sup>3</sup>).
- 6.29 The PBAC therefore considered that obinutuzumab plus bendamustine was of inferior safety compared with bendamustine monotherapy. However, the PBAC noted that obinutuzumab had a tolerable safety profile, and considered that it had an overall positive benefit-risk profile

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<sup>3</sup> Obinutuzumab PSD, March 2015 PBAC meeting

### Economic analysis

- 6.30 The submission presented a stepped cost-effectiveness analysis using the rituximab-refractory follicular lymphoma subgroup from the GADOLIN trial, with patients treated with bendamustine monotherapy serving as a proxy for best supportive care.
- 6.31 The economic evaluation was a Markov model with four health states, with all patients beginning in the progression-free health state. Patients in the progression-free states (with treatment or without treatment) would either remain progression-free, or transition to progressed disease or death. Patients with disease progression either transitioned to the death state, or remained in the progressed-disease state. A progression-free state for patients who have ceased treatment was included in the model to capture patients who remained progression-free after finishing therapy. The model structure and rationale is summarised in Table 6.

**Table 6: Summary of model structure and rationale**

Component	Summary
Time horizon	15 years in the model base case versus a median follow-up of 24.1 months in the GADOLIN trial.
Utility values used	PFS (on treatment): 0.82      PFS (off treatment): 0.81 Post-progression: 0.77      Death: 0.0
Outcomes	LYG and QALYs
Methods used to generate results	Markov model; cohort expected value analysis
Cycle length	7 days with half-cycle correction
Transition probabilities	Transition probabilities were based on KM curves from GADOLIN trial data, and parametric extrapolation was used to extrapolate transition probabilities beyond median trial follow-up.
Discount rate	5% for costs and outcomes

Source: compiled during the evaluation.

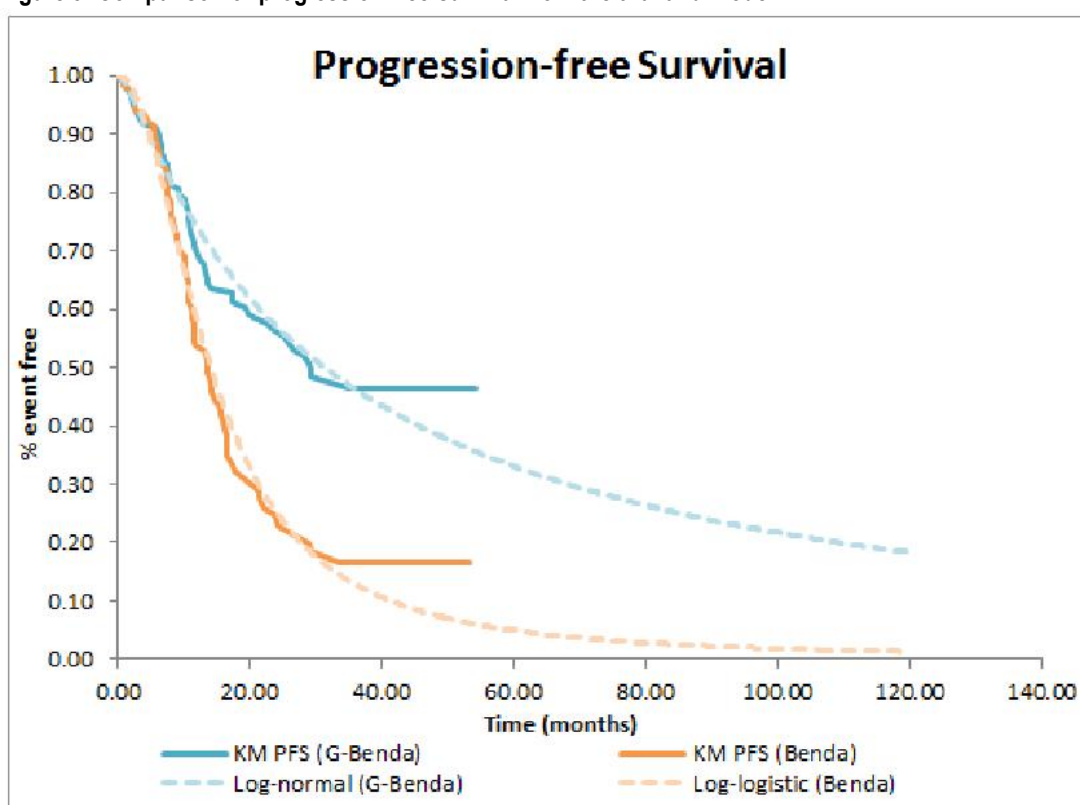
KM = Kaplan-Meier; LYG – life-years gained; QALYs = quality-adjusted life years

- 6.32 The submission used a time horizon of 15 years (extrapolated from a median 24.1 months of follow-up in the GADOLIN trial). This was justified based on the mean time of 4.25 years from an initial diagnosis of follicular lymphoma to the diagnosis of rituximab-refractory disease in the GADOLIN trial and the 20-year time horizon which was accepted by the PBAC in consideration of bendamustine for patients with previously untreated indolent non-Hodgkin's lymphoma (Bendamustine PSD, March 2015 PBAC meeting).
- 6.33 The submission noted the shorter, five-year time horizon used for the follicular lymphoma in the idelalisib PBAC submission, however did not consider this relevant because the idelalisib patient population had more severe disease being refractory to both rituximab and an alkylating agent and having had a median of four prior lines of treatment. A five-year time horizon was tested in sensitivity analyses during the evaluation.
- 6.34 The PBAC noted that 24% of patients enrolled in the GADOLIN trial had progressed within 6 months of completion of initial induction therapy with chemotherapy plus rituximab (p159, GADOLIN CSR May 2015 update). The PBAC further noted that after a median 24 months follow-up, 35% of patients receiving obinutuzumab plus bendamustine in the follicular lymphoma subgroup had experienced disease progression (Table 3) and 18% of patients had died (Table 5). The PBAC considered

that this indicated that the population in the GADOLIN trial had a relatively poor prognosis and thus reference to the 20 year time horizon used in the bendamustine submission may not be valid. On this basis, the PBAC considered that using a 10-year time horizon would be more appropriate in the base case analysis, and that a 15-year time horizon could be tested in a sensitivity analysis.

- 6.35 The ESC noted that the submission assumed a slightly lower utility for patients in the PFS health state who were off treatment (0.81), when compared with progression-free patients who remained on treatment (0.82). A rationale for this assumption was not provided in the submission. The Pre-PBAC response (p3) stated that the elicitation of preference weights was derived directly from patients in the GADOLIN trial; Australian tariffs were assigned to EQ-5D scores to derive utility values by health state, with a distinction between patients who were on versus off-treatment. The PBAC noted that the health state utilities were not a significant driver of the economic model.
- 6.36 A comparison of the PFS results from the trial with that modelled is presented in Figure 3.

Figure 3: Comparison of progression free survival from the trial and model



Source: "Graphs" worksheet from Economic Evaluation.xlsx in the submission

- 6.37 A log-normal distribution was fitted to the obinutuzumab plus bendamustine treatment arm, and a log-logistic distribution was fitted to the bendamustine monotherapy arm to extrapolate PFS beyond the median 24.1 months follow-up. The log-normal distribution for obinutuzumab plus bendamustine and log-logistic distribution for bendamustine alone were associated with the greatest level of fit

based on the Akaike Information Criteria. The ESC noted that more flexible parametric models were not tested. The extrapolations used resulted in 4.8% of patients in the bendamustine monotherapy arm remaining progression-free at 5 years compared to 32.6% of patients in the obinutuzumab plus bendamustine arm. At 15 years, 0.5% bendamustine monotherapy patients remained progression-free compared to 11.7% of obinutuzumab plus bendamustine patients. The ESC noted that the external validity of the extrapolation was not addressed by the submission. The Pre-PBAC response (p3) argued that the most appropriate approach to extrapolating PFS was undertaken in the economic model. The PBAC considered that it was biologically implausible that 4.8% of patients in the bendamustine monotherapy arm remained progression-free at 5 years compared to 32.6% of patients in the obinutuzumab plus bendamustine arm, as this assumed that the majority of the clinical benefit occurred after the cessation of obinutuzumab maintenance therapy at 2.5 years.

- 6.38 The PBAC also considered that the approach used to extrapolate PFS resulted in the benefit being overestimated. The PBAC noted that 29 of 164 patients (approximately 18%) in the obinutuzumab plus bendamustine arm were still receiving maintenance therapy at the time of the most recent data analysis<sup>4</sup>, and that the follow-up was insufficient to provide confidence about the PFS curve beyond the point of median follow-up. Further, the PFS curve for the obinutuzumab plus bendamustine arm may converge with that for the bendamustine monotherapy arm after all patients had completed maintenance. The PBAC considered that this created significant uncertainty regarding whether the fitted curve used to extrapolate the trial data would reliably predict PFS post cessation of obinutuzumab maintenance therapy.
- 6.39 The PBAC considered that a more plausible approach to extrapolating PFS would be to allow for more rapid convergence of the extrapolated PFS curves as the effect of obinutuzumab maintenance therapy waned. This may possibly be achieved by assuming no additional PFS benefit after cessation of obinutuzumab maintenance therapy, the rate of progression post cessation of obinutuzumab maintenance therapy to be the same as observed post cessation of bendamustine or by applying the observed rate of progression post rituximab maintenance therapy in the relapsed/refractory setting.
- 6.40 For OS, the submission modelled the transition probabilities separately for patients with progression-free disease and progressed disease. The ESC noted that separate estimation of pre- and post-progression survival rather than the usual aggregate estimation of OS was applied because the aggregate OS data were immature.
- 6.41 For the progression-free health state, the submission used a probability of dying based on the following parameters, selected on the basis of highest probability:
- The weekly probability of dying from the GADOLIN trial; or
  - The maximum age-and-gender specific background mortality observed in the

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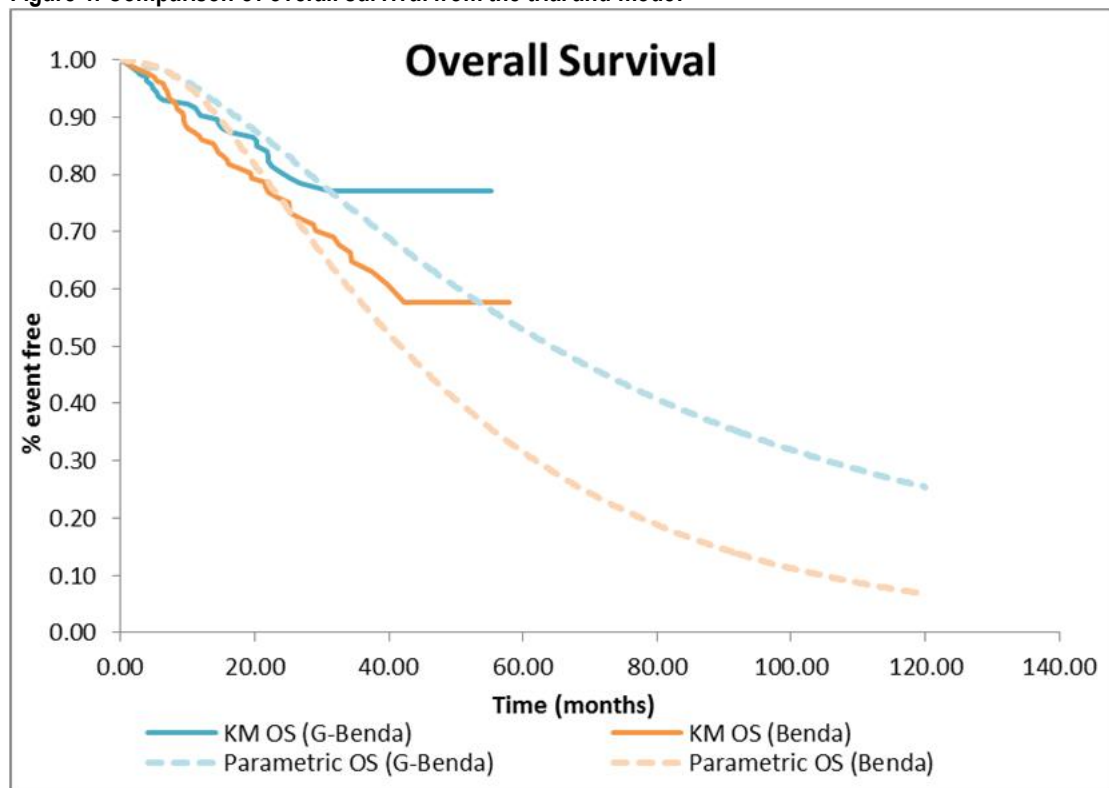
<sup>4</sup> Update Clinical Study Report – GAO4753g/GO01297 - An open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with bendamustine + RO5072759 (GA101) in patients with rituximab-refractory, indolent non-Hodgkin lymphoma. Research Report Number 1067639.

Australian population.

The methodology in modelling OS transition probabilities for patients in the progression-free health state was considered reasonable during the evaluation.

- 6.42 A constant probability of death based on an exponential model was used to estimate the OS for patients in the post-progression health state. The PBAC considered that the approach taken by the submission to use a pooled post-progression survival rate was reasonable for the base case, albeit it likely favoured the obinutuzumab arm.
- 6.43 The submission assumed that patients treated with obinutuzumab plus bendamustine would continue to benefit from treatment over the 15-year time horizon in the economic model, despite the maximum treatment duration of 2.5 years with obinutuzumab plus bendamustine therapy in the GADOLIN trial. The PBAC considered that the assumption of continued benefit from treatment over 15 years was not supported by data presented in the submission, or by prior experience with rituximab maintenance in the relapsed or refractory follicular lymphoma population. The PBAC therefore considered that the extrapolation method together with use of the 15 year time horizon significantly biased the results in favour of obinutuzumab, and resulted in the incremental cost effectiveness ratio (ICER) being underestimated. A comparison of the OS results from the trial with that modelled is presented in Figure 4.

Figure 4: Comparison of overall survival from the trial and model



Source: "Graphs" worksheet from Economic Evaluation.xlsx in the submission

- 6.44 The ESC noted that the model predicted 31.5% of patients in the bendamustine monotherapy arm remain alive at 5 years compared to 52.9% of patients in the obinutuzumab plus bendamustine arm. At 15 years, 1.7% bendamustine monotherapy patients remain alive compared to 14.5% of obinutuzumab plus bendamustine patients.
- 6.45 A summary of the key drivers of the economic model is presented in Table 7.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation of PFS	The selected parametric curves may have minimised the AIC but they did not necessarily best fit the end of the observed data for the obinutuzumab plus bendamustine arm. Other fitted curves provided more conservative gains in PFS. The PBAC considered that even if the most appropriate approach to extrapolating PFS was undertaken in the economic model, the trial data was too immature to reliably inform the rate of progression in the years post-cessation of obinutuzumab maintenance therapy.	High, favoured obinutuzumab
Extrapolation of survival for patients with progressed disease	- A constant probability of death was assumed for patients with progressed disease. - An exponential model was fitted to pooled post-progression survival from the GADOLIN trial. - No converging of OS over time, while maximum treatment duration was 2.5 years for obinutuzumab plus bendamustine and the model duration was 15 years. Survival difference at 15 years 0.128 (0.145 vs. 0.017).	High, favoured obinutuzumab
Health state utilities	PFS on treatment 0.823 PFS off treatment 0.807 Progression 0.770 General population utility aged 65 to 74 years: 0.8 – 0.82	Moderate, favoured obinutuzumab
Costs for health states	Health state costs were excluded from the economic model.	Unclear
Costs for further treatment	Costs for monitoring patients post-treatment were excluded from the economic model.	Unclear

Source: compiled during the evaluation

AIC = Akaike Information Criteria; OS = overall survival; PFS = progression free survival

6.46 The results of the cost-effectiveness analysis are presented in the table below.

Table 8: Results of the stepped economic evaluation

Step and component	O-Benda	BSC	Increment
<b>Step 1: trial-based costs and outcomes (maximum of 53.4 months)</b>			
Costs	\$	\$	\$
LYG			
QALY			
<b>Incremental cost/LYG gained</b>			\$
<b>Incremental cost/QALY</b>			\$
<b>Step 2: trial results and premodelling (extrapolation of PFS using parametric models)</b>			
Costs	\$	\$	\$
LYG			
QALY			
<b>Incremental cost/LYG</b>			\$
<b>Incremental cost/QALY</b>			\$
<b>Step 3: modelled evaluation (inclusion of MRU cost)</b>			
Costs	\$	\$	\$
LYG			
QALY			
<b>Incremental cost/LYG</b>			\$
<b>Incremental cost/QALY</b>			\$
<b>Step 4: modelled evaluation (inclusion of AE cost)</b>			
Costs	\$	\$	\$
LYG			
QALY			
<b>Incremental cost/LYG</b>			\$
<b>Incremental cost/QALY</b>			\$
<b>Step 5: modelled evaluation ( % discount on ex-manufacturer price of obinutuzumab)</b>			
Costs	\$	\$	\$
LYG			
QALY			
<b>Incremental cost/LYG</b>			\$
<b>Incremental cost/QALY</b>			\$

Source: Section D.5, pp17-20 of Section D of the submission and the Economic evaluation workbook.xlsx

AE= adverse event; LYG = life years gained; MRU = medical resource usage; O-Benda = obinutuzumab-bendamustine; PFS = progression-free survival; QALY = quality-adjusted life year; BSC = best supportive care

6.47 The submission estimated that obinutuzumab plus bendamustine therapy would result in a discounted ICER of \$45,000 - \$75,000 per quality-adjusted life year gained. The results from the economic model were uncertain and likely to be underestimated, due to the following assumptions:

- The extrapolation of PFS from a median follow-up of 24.1 months to the 15 year time horizon through fitting parametric models necessitated caution in interpretation of model results, as the external validity of the extrapolation was not evaluated in the submission.
- Survival benefits from obinutuzumab plus bendamustine were assumed to continue despite a maximum allowable treatment of 2.5 years.
- The PSCR (p4) maintained that the 15.4 month PFS gain (May 2015 cut-off) for patients treated with obinutuzumab plus bendamustine compared with bendamustine monotherapy was likely to translate into a sustained gain in OS. The PSCR also provided evidence in support of extended OS attributed to other anti-CD20 therapies over time, including one study comparing rituximab in

combination with fludarabine and cyclophosphamide compared with fludarabine plus cyclophosphamide only. The PBAC noted that the rituximab trial referred to in the PSCR was conducted in a population of patients receiving first-line treatment, and that a statistically significant difference in response rates had been observed at the end of induction. In contrast, patients in the GADOLIN trial had received prior treatments, and combination therapy did not induce a higher response rate. Further, in a trial of rituximab maintenance in relapsed or refractory lymphoma with mature follow-up data, convergence of PFS and OS curves occurred within three years after the cessation of maintenance therapy<sup>5</sup>.

- Costs associated with patients in different health states, treatment cessation and monitoring were not included in the model. The PSCR (p4) stated that the submission conservatively omitted such costs as they were not significant drivers of the model, and would bias the analysis against obinutuzumab plus bendamustine as these costs were incurred earlier in the control arm. The PBAC considered that it was inappropriate to apply the PBS cost of bendamustine in the economic model, given that it is not PBS-subsidised for rituximab-refractory follicular lymphoma, and noted it is more costly than PBS-subsidised best supportive care such as chemotherapy. Therefore, the PBAC considered that a more appropriate proxy for the cost of best supportive care would be CHOP.

6.48 The following table presents the sensitivity analysis presented in the submission, and additional analyses performed during the evaluation. The following sensitivity analyses were conducted during the evaluation:

- The impact of exponential, Weibull and Gompertz parametric models used in the extrapolation of PFS beyond median follow-up (ICERs in the range of \$45,000 - \$75,000 per QALY);
- The impact of including data from trial-based Kaplan-Meier curves up to the median follow-up of 24.1 months in the extrapolation of survival in the economic model (ICER in the range of \$45,000 - \$75,000 per QALY); and
- The impact of using a five-year time horizon and trial-based Kaplan-Meier curves up to median follow-up to model OS for patients with progressed disease (ICER in the range of \$105,000 - \$200,000 per QALY).

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<sup>5</sup> Van Oers et al, *J Clin Oncol*. 2010 June 10; 28(17): 2853–2858.

**Table 9: Results of key sensitivity analyses conducted during the evaluation.**

Univariate analyses	Δ Cost	Δ QALY	ICER
<b>Base case</b>	\$ [REDACTED]	[REDACTED]	\$ [REDACTED] <sup>a</sup>
Cost of BSC and PFS HR (Base case: bendamustine monotherapy and PFS HR = 1.0) Cost of BSC = \$30,135 PFS HR = [REDACTED]	(\$ [REDACTED])	[REDACTED]	(\$ [REDACTED])
Time horizon (base case: 15 years)			
5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Bendamustine price (base case: ex-manufacturer price)			
SAMEP price	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Parametric model used to extrapolate PFS beyond median follow-up (base case: log-normal for O-Benda, log-logistic for BSC)			
Exponential	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Weibull	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Gompertz	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Overall survival during trial period (base case: separate OS extrapolation models for PFS and PD) KM curves from the GADOLIN trial up to median 24.1 months follow-up, then extrapolation for PFS and PD applied.	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
<b>Multivariate</b>			
5 year time horizon and KM curve GADOLIN	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Section D.5, pp17-20 of Section D of the submission and the Economic evaluation workbook.xlsx

AE= adverse event; BSC = best supportive care; HR = hazard ratio; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; LYG = life years gained; MRU = medical resource usage; O-Benda = obinutuzumab-bendamustine; OS = overall survival; PD = Progressed disease; PFS = progression free survival; QALY = quality-adjusted life year; SAMEP = South Australian Medicines Evaluation Panel

<sup>a</sup> Values provided by submission were different and could not be verified. The values presented in parentheses were derived from the economic model during the evaluation, using the assumptions as presented in the submission.

6.49 The model was most sensitive to the time horizon. This was due to the assumed continued treatment benefit beyond the trial duration, while no costs occurred beyond 2.5 years. The following aspects were not tested in sensitivity analyses during evaluation:

- Converging of OS
- Costs for post-progression treatment, medical resource use in the health states (beyond the treatment period), death.

**Drug cost/patient/course: \$ [REDACTED] (obinutuzumab) plus \$ [REDACTED] (bendamustine)**

6.50 The drug costs per patient per course of obinutuzumab therapy was estimated using the following assumptions:

- A weighted price of obinutuzumab (\$ [REDACTED]) based on the dispensed price for maximum amount in the public and private settings (52.7% versus 47.3%), and a [REDACTED]% discount on the ex-manufacturer price.
- Assuming eight induction administrations (\$ [REDACTED]) and twelve maintenance administrations (\$ [REDACTED]).

6.51 Obinutuzumab is to be taken with bendamustine for a maximum of six cycles. The TGA-approved bendamustine dose for combination therapy is 90 mg/m<sup>2</sup>, and the actual dose in the GADOLIN trial was [REDACTED] mg per administration. This dose can be achieved through [REDACTED] 100 mg syringe and [REDACTED] 25 mg syringes of bendamustine (PBS items 10760H and 10763L). Further the public and private hospital setting split was also assumed to be 52.7% versus 47.3%. This would result in a weighted cost of \$ [REDACTED] per administration and \$ [REDACTED] for a full course.

6.52 This was compared to a cost of off-label use of bendamustine (120 mg/m<sup>2</sup>) for a maximum of six cycles as monotherapy. Based on the actual dose in the GADOLIN trial, the number of syringes needed were █ 100 mg syringes and █ 25 mg syringes for the first cycle and █ 100 mg syringes and █ 25 mg syringe for the second to the sixth cycle. Using a similar split for the public and private hospital setting the total cost would be \$█ for the full course. The PBAC considered that the appropriate cost for best supportive care to be applied in the economic model should be the cost of six cycles of CHOP, rather than the cost of bendamustine, which is not PBS-subsidised for rituximab-refractory follicular lymphoma.

**Estimated PBS usage & financial implications**

6.53 This submission was not considered by DUSC. An epidemiological approach was used to estimate the incidence of rituximab-refractory follicular lymphoma.

**Table 10: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated patients <sup>a</sup> Induction Maintenance <sup>b</sup>	█	█	█	█	█
Scripts <sup>c</sup>	█	█	█	█	█
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█
Net cost to MBS <sup>d</sup>	\$█	\$█	\$█	\$█	\$█
<b>Total net cost to PBS/RPBS/MBS</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>

Source: Table E.5.9, p24 of Section E of the submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical

<sup>a</sup> █ % uptake rate

<sup>b</sup> █ % of patients on induction will receive maintenance in first year, █ % will receive maintenance in second year and █ % will receive maintenance in third year

<sup>c</sup> █ scripts for induction, for maintenance: █ scripts in Year 1, █ scripts in Year 2 and █ scripts in Year 3

<sup>d</sup> █ % patient co-payment removed

6.54 The redacted table above shows that at year 5 the estimated number of patients (treated and maintenance) was less than 10,000 and the net cost to the PBS/RPBS would be \$10 - \$20 million. The net cost to the PBS/RPBS and the MBS over the first five years of listing was estimated to be \$60 - \$100 million. There was the potential for the number of eligible patients to be greater than the estimate in the submission, as:

- The submission only included the incidence population to estimate the number of patients with rituximab-refractory follicular lymphoma who might be eligible for treatment. The high rate of survival in patients with rituximab-refractory follicular lymphoma necessitated the consideration of the prevalent population. Using the Australian Institute of Health and Welfare (non-Hodgkin lymphoma prevalence) and the submission's assumptions (percentage of those patients having follicular lymphoma), there could be a potential prevalent pool of over 10,000 patients with follicular lymphoma in Australia, of whom some patients might be eligible to receive obinutuzumab plus bendamustine upon disease progression.
- The PSCR (p4) contended that the prevalent pool of patients with follicular lymphoma in Australia was considered in the financial estimates. The PSCR

stated that the prevalent pool of patients who would access obinutuzumab upon PBS listing was accounted for using █% of the incident follicular lymphoma patient population diagnosed four years prior in order to align with the mean number of years from initial diagnosis to a diagnosis of rituximab-refractory follicular lymphoma in the GADOLIN trial. The PSCR also noted that treatment caps have been proposed to mitigate risk of underestimating patient numbers.

- The ESC noted that the submission assumed that █% of patients in the incident population four years prior would inform prevalence. The █% estimate was based on expert opinion from seven haematologists and therefore is uncertain. The ESC considered that the submission's assumption was inappropriate, and might have underestimated the prevalent population of follicular lymphoma, of whom a certain percentage would be considered as rituximab-refractory.
- The sources used to estimate the percentage of patients with rituximab-refractory follicular lymphoma were the Sponsor's Haematology Advisory Board minutes and market research. Such sources might not be robust, and the estimated proportion of patients considered to progress rapidly or eventually might therefore be higher or lower.

### **Financial Management – Risk Sharing Arrangements**

- 6.55 A Risk Sharing Arrangement was provided by the submission, whereby a rebate by the sponsor to the Government would occur should expenditure exceed subsidisation caps based on a █% market uptake rate. The level of rebate is to be determined. Furthermore, the submission proposed a confidential Special Pricing Arrangement based on a █% reduction to the ex-manufacturer price of obinutuzumab. This effective price was included in the economic model and financial estimates.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend obinutuzumab for PBS listing for the treatment of rituximab-refractory follicular lymphoma, on the basis of uncertain cost-effectiveness and concerns about the plausibility of assumptions used in the economic model.
- 7.2 The PBAC noted the consumer comments and acknowledged that there was unmet clinical need for additional PBS-subsidised medicines for the treatment of rituximab-refractory follicular lymphoma.
- 7.3 The PBAC accepted best supportive care as the appropriate comparator, and considered that bendamustine efficacy was a reasonable proxy for that with best supportive care. However, as bendamustine was considered not cost-effective for the treatment of rituximab-refractory indolent non-Hodgkin's lymphoma at the March 2015 PBAC meeting and is not PBS-subsidised for this patient population, the PBAC considered that the cost of bendamustine could not be used as a proxy for the cost of best supportive care.
- 7.4 The PBAC considered that obinutuzumab plus bendamustine followed by obinutuzumab maintenance was of superior efficacy compared to bendamustine

monotherapy, on the basis of the GADOLIN trial's primary endpoint, PFS. However, the PBAC considered that with additional follow-up of the trial, the difference between the treatment groups in PFS may diminish. This is because data that are currently available are immature and are based on a median follow-up of approximately 24 months.

- 7.5 The PBAC noted that the submission did not provide adequate evidence of an OS benefit, however considered that obinutuzumab plus bendamustine followed by obinutuzumab maintenance was likely to demonstrate an OS benefit over bendamustine monotherapy with additional follow-up. The PBAC considered that the magnitude of any OS gain was highly uncertain due to the immaturity of the trial data presented in the submission.
- 7.6 The PBAC did not accept the submission's claim of non-inferior safety of obinutuzumab plus bendamustine compared to bendamustine monotherapy. The PBAC noted that obinutuzumab plus bendamustine followed by obinutuzumab maintenance was associated with increased rates of infusion-related reactions and musculoskeletal and cardiac events, compared to bendamustine monotherapy. Therefore, the PBAC considered that obinutuzumab plus bendamustine followed by obinutuzumab maintenance was of inferior safety compared to bendamustine monotherapy. However, the PBAC noted that obinutuzumab had an overall tolerable safety profile, and that the benefits of its use outweighed its toxicities.
- 7.7 The PBAC considered that the incremental cost per QALY gained of \$45,000 - \$75,000 for obinutuzumab plus bendamustine followed by obinutuzumab maintenance, over best supportive care, presented in the submission's base case analysis, was highly uncertain and was likely to be significantly underestimated due to several issues with the economic model, including:
- the significant uncertainty created as a result of extrapolating PFS from immature data, which likely biased the estimates in favour of obinutuzumab. The PBAC considered that the fitted parametric curve for the obinutuzumab plus bendamustine arm was unlikely to reliably predict PFS post cessation of obinutuzumab maintenance and in the trial approximately 18% of patients in the obinutuzumab plus bendamustine arm were still receiving obinutuzumab maintenance at the time of the most recent data analysis. The PBAC considered that it would have been more appropriate to allow for earlier convergence of the PFS curves, consistent with the waning of the obinutuzumab maintenance effect;
  - the submission used a 15-year time horizon, however, the PBAC considered that a 10-year time horizon was more appropriate given the relative poor prognosis of patients with follicular lymphoma that is refractor to rituximab;
  - the submission used the price of bendamustine as a proxy for the cost of best supportive care. However, bendamustine was previously not considered cost-effective for indolent non-Hodgkin's lymphoma (of which follicular lymphoma is a subset) in the rituximab-refractory setting and is not PBS-listed for this population (Bendamustine PSD, March 2015 PBAC meeting). Therefore, the PBAC considered that the cost of bendamustine should not be incorporated into the economic evaluation and that the cost for best supportive care would be more appropriately represented by a PBS-subsidised treatment that is currently used in Australian clinical practice to treat rituximab-refractory follicular lymphoma, e.g. 6 cycles of CHOP.

- 7.8 The PBAC noted the submission's offer of a risk share arrangement as means to mitigate uncertainties in the financial estimates, but that the level of rebate was not specified.
- 7.9 The PBAC considered that any resubmission should be a major submission to allow for evaluation of a revised economic model, which addresses the issues raised by the PBAC.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.