

## 7.11 ZANUBRUTINIB, Capsule 80 mg, Brukinsa<sup>®</sup>, BeiGene Aus Pty Ltd

### 1 Purpose of submission

- 1.1 The Facilitated Resolution Pathway resubmission requested an Authority Required listing for zanubrutinib for the treatment of Waldenström macroglobulinaemia (WM) in two patient subpopulations: treatment-naïve (TN) patients who are unsuitable for chemo-immunotherapy and relapsed/refractory (R/R) patients who have received at least one prior therapy.
- 1.2 Listing was requested on the basis of cost-effectiveness analyses versus rituximab monotherapy (Rm) in the population of TN unsuitable for chemo-immunotherapy and bendamustine + rituximab (BR) in the R/R population.

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Patients with WM who have received at least one prior therapy or are unsuitable for chemo-immunotherapy as 1L treatment
Intervention	ZANU 160 mg (80 mg x2 capsules) orally twice daily or 320 mg once daily (80 mg x4 capsules)
Comparator	<b>TN WM patients unsuitable for chemo-immunotherapy:</b> Rituximab monotherapy is proposed as the main comparator for this patient group.  <b>R/R WM patients who have received at least one prior therapy:</b> Bendamustine in combination with rituximab is proposed as the most appropriate comparator in this patient group as a proxy for any treatment in the R/R setting.
Outcomes	Response rates, duration of response, progression-free survival, overall survival, frequency of adverse events
Clinical claim	<b>TN WM patients unsuitable for chemo-immunotherapy:</b> ZANU is superior in terms of effectiveness and safety compared with rituximab monotherapy.  <b>R/R WM patients who have received at least one prior therapy:</b> ZANU is superior in terms of effectiveness and safety compared with bendamustine in combination with rituximab.

Source: Table 1.2, p20 of the resubmission.

1L=first line, R/R=relapsed/refractory, TN=treatment naïve, WM=Waldenström macroglobulinaemia, ZANU=Zanubrutinib.

Blue shading represents information previously considered by the PBAC

### 2 Background

#### Registration status

- 2.1 Zanubrutinib was TGA-registered on 7 October 2021 for the treatment of adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.
- 2.2 Zanubrutinib is also TGA-registered for use in mantle cell lymphoma (MCL).

## Previous PBAC consideration

2.3 Zanubrutinib was previously considered by the PBAC in July 2021 for WM. The table below summarises the key matters from the previous PBAC consideration and how the resubmission addressed those concerns.

**Table 2: Summary of key matters of concern**

Component	Matter of concern	How the current resubmission addresses it
Restriction	The PBAC had previously considered (paragraph 7.3) the restriction should clearly define the TN population unsuitable for chemo-immunotherapy, by incorporating a CIRS score, where patients with a CIRS score of six or greater could be considered unsuitable for chemo-immunotherapy.	The resubmission added to the restriction: "Patient must be unsuitable for treatment with chemo-immunotherapy, defined by a CIRS of 6 or greater, if untreated (i.e., treatment-naïve) for this condition".
Clinical effectiveness	For the TN population (paragraph 7.6), the superiority claim was likely reasonable in terms of response outcomes, noting the ESC's advice that the magnitude of benefit was uncertain, and that response outcomes are unlikely to translate into survival outcomes. For the R/R population (paragraph 7.7), the MAIC results were uncertain, and superior effectiveness in terms of survival outcomes was not adequately supported by the data.	The resubmission maintained the importance of differences in response-based endpoints, and the plausibility of the link between these and survival outcomes. Castillo 2021 was added to support the use of response rates as surrogates for survival outcomes.
Base case economic model	The PBAC had previously considered (paragraph 7.14) that any resubmission should include a revised model that more accurately reflects the clinical course of WM and where the benefits of treatment are consistent with those expected. The PBAC noted (paragraph 7.16) - the structure should more accurately reflect the chronic relapsing nature of WM and the expected outcomes of treatment. - the inputs should be consistently applied for the treatment naïve and relapsed/refractory settings.	The revised model structure included one subsequent line of treatment. Subsequent treatment was based on TTNT data from iNOVATE with ITT data for IBRU+R used as a proxy for ZANU and ITT data for Rm as a proxy for both Rm (TN model) and BR (R/R model).  The resubmission updated its approach to extrapolation. Reduced model time horizon to 15 years (previously 20 years). Applied a [REDACTED]-month financial stopping rule for ZANU, to reduce cost of treatment in the model. Health state utilities were updated and based on treatment type and line of treatment, with utility decrements sourced from the literature.
Financial estimates and Risk-Sharing Arrangement	The PBAC (paragraph 7.15) had previously expressed concern that the financial impact of listing ZANU on the PBS was underestimated due to underestimates for the numbers of eligible patients and uptake, duration of treatment and inappropriate cost offsets for non-PBS subsidised treatments.	The financial analysis incorporated: <ul style="list-style-type: none"> <li>• Prevalent numbers of patients in Year 1</li> <li>• Increased uptake from Year 3</li> <li>• Removed non-PBS subsidised treatment</li> <li>• [REDACTED]-month financial stopping rule to cap Australian Government expenditure via a Risk Sharing Arrangement.</li> </ul>

Source: Zanubrutinib PBAC Public Summary Document, July 2021.

2L=second line, BR=bendamustine+rituximab, CIRS=Cumulative Illness Rating Scale, IBRU+R=ibrutinib+rituximab, MAIC=matching-adjusted indirect comparison, OS=overall survival, PFS=progression free survival, Rm=rituximab monotherapy, R/R=relapse/refractory, RSA=risk sharing arrangement, TN=treatment naïve, TTNT=time to next treatment, WM=Waldenström macroglobulinaemia, ZANU=zanubrutinib.

2.4 At the July 2021 meeting, the PBAC recommended the listing of zanubrutinib for the treatment of patients with relapsed or refractory (R/R) MCL who have received at least

one prior therapy and have a WHO performance status of 0 or 1. Listing was recommended on a cost-minimisation basis against ibrutinib.

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

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Zanubrutinib 80 mg capsule	1	120	5	\$11,672.21 published price \$ effective price	Brukinsa@ BeiGene Aus Pty Ltd
Category / Program:	GENERAL – General Schedule (Code GE)				
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners				
PBS Indication:	Waldenström macroglobulinaemia				
Treatment phase:	Initial and continuing				
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone				
Treatment criteria:	<b>Initial:</b> The treatment must be the sole PBS-subsidised therapy for this condition. <b>Continuing:</b> Patient must have previously received PBS-subsidised treatment with this drug for this condition.				
Clinical criteria:	Patient must have relapsed/refractory disease despite prior treatment, OR Patient must be unsuitable for treatment with chemo-immunotherapy, defined by a Cumulative Illness Rating Scale of 6 or greater, if untreated (i.e., treatment-naïve) for this condition, AND Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.				
-Administrative Advice:	Special Pricing Arrangements apply. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.				

Source: Tables 1.4, p21; Tables 1.9 to 1.11, pp39-40 of the resubmission.  
 Blue shading represents information previously considered by the PBAC

- 3.1 The ESC noted the requested restriction was appropriately updated to align with PBAC’s previous advice that chemo-immunotherapy unsuitability should be clearly defined as having a CIRS score of 6 or greater (paragraph 7.3, zanubrutinib public summary document [PSD], July 2021). This amendment was also applied to the previously presented grandfathering restriction.
- 3.2 The resubmission requested a Special Pricing Arrangement. The requested effective AEMP/DPMQ was reduced to \$/s (from \$/s in the July 2021 submission).
- 3.3 The requested restriction did not specify whether patients previously treated with a Bruton’s tyrosine kinase inhibitor (BTKi) would be eligible to receive zanubrutinib. The PBAC had previously agreed with the ESC that use of zanubrutinib should be restricted to patients untreated with a BTKi given the lack of evidence to support use in BTKi-treated patients; however, it would be appropriate to allow treatment in patients who are intolerant to another BTKi (paragraph 7.3, zanubrutinib PSD, July 2021).
- 3.4 The PBAC Secretariat had asked the PBAC to consider whether the listing should be restricted to patients with WHO status of 2 or less in line with the ASPEN trial population, and whether prior therapies should be further defined.

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

## 4 Population and disease

- 4.1 WM is a rare type of indolent non-Hodgkin lymphoma, with a distinct clinicopathology including both infiltration of the bone marrow by clonal small B-lymphocytes, plasmacytoid lymphocytes and plasma cells in the bone marrow (i.e., lymphoplasmacytic lymphoma, LPL), as well as IgM monoclonal gammopathy in blood (macroglobulinaemia).
- 4.2 The details of the population and disease were unchanged from the previous submission. Two subpopulations of patients with WM were proposed:
- TN patients unsuitable for chemo-immunotherapy. The resubmission proposed that patients would need to have a CIRS score of 6 or greater to be considered unsuitable for chemo-immunotherapy.
  - R/R patients who have received at least one prior therapy. After initial treatment, all WM patients eventually relapse and require additional treatments.
- 4.3 Zanubrutinib is a highly selective small-molecule inhibitor of BTK, which is part of the B-cell receptor signalling pathway and plays a central role in B-cell proliferation and survival. Zanubrutinib is equipotent against BTK compared to ibrutinib but has shown greater selectivity for BTK and fewer off-target effects in multiple in vitro enzymatic and cell-based assays (Tam et al., 2019).
- 4.4 The proposed total daily dose of zanubrutinib is 320 mg (four 80 mg capsules) taken orally once daily, or 160 mg (two 80 mg capsules) taken orally twice daily until disease progression or unacceptable toxicity. This indefinite treatment duration is an important difference from chemo-immunotherapy regimens, which are given as initial treatment with a fixed duration.
- 4.5 The clinical management algorithm for the intended use of zanubrutinib was unchanged from the previous submission and was based on Australian and international treatment guidelines for WM.

## 5 Comparator

- 5.1 The resubmission nominated separate comparators for each requested population: rituximab monotherapy (Rm) for TN patients unsuitable for chemo-immunotherapy and bendamustine + rituximab (BR) for the R/R population.
- 5.2 The PBAC had previously accepted the nominated comparators (paragraphs 7.4, 7.5, zanubrutinib, PSD July 2021). The PBAC had previously agreed with the ESC that zanubrutinib would primarily displace rather than replace alternative therapies given the disease is characterised by repeated cycles of disease stability followed by relapse (paragraph 7.5, zanubrutinib, PSD July 2021).

- 5.3 The resubmission identified ibrutinib as a near market comparator. The ESC acknowledged the unmet clinical need for effective treatments for WM noting that PBS subsidy for the treatment of WM has not been requested for ibrutinib despite TGA registration for use in WM.

## **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 the input from individuals (14), health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the symptoms associated with WM and the significant impact of these symptoms on daily life. Comments from patients who have received zanubrutinib described benefits in terms of reducing/eliminating symptoms associated with WM, improving quality of life, manageable side-effects of treatment compared to chemotherapy, convenience of an oral dosage form and ability to participate in activities of daily life.
- 6.3 The Australian patient support group for Waldenström's Macroglobulinemia (WMOzzies), Lymphoma Foundation, Leukaemia Foundation and Rare Cancers Australia supported listing zanubrutinib for the treatment of WM. The organisations noted that zanubrutinib was well tolerated and associated with fewer side effects compared to chemotherapy. The organisations considered that there was a high unmet need for treatments for WM, particularly for older patients who are not able to tolerate aggressive chemotherapy regimens.

### ***Clinical trials***

- 6.4 No new clinical trials were presented in the resubmission. An additional analysis of the overall response rate (ORR) in the matching-adjusted indirect comparison (MAIC) for the R/R population, previously presented in the July 2021 submission Pre-Sub-Committee Response (PSCR), was incorporated into the main clinical section.
- 6.5 The resubmission was based on the following evidence:
- For zanubrutinib – one open label RCT (ASPEN) with a direct comparison of zanubrutinib versus ibrutinib (Cohort 1) and a nonrandomised arm where patients received zanubrutinib (Cohort 2); one Phase 1/2 single arm study (Study AU-003).
  - For Rm in the TN population – one double-blind RCT (iINNOVATE) comparing ibrutinib+rituximab to placebo+rituximab, and one Phase 2 single arm study of Rm (Dimopoulos 2002).
  - For BR in the R/R population – two cohort studies (Tedeschi 2015 and Treon 2011).

6.6 A new publication including the final analysis results from iNNOVATE (Buske 2021) was identified, which was used in the economic model but not presented in the clinical section of the resubmission.

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title / Publication title	Publication date
<b>Zanubrutinib</b>		
ASPEN	A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM). Clinical Study Report BGB-3111-302 Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström's macroglobulinemia: the ASPEN study. Dimopoulos M, Garcia Sanz R, Lee HP, et al. Major responses in MYD88 wildtype (MYD88WT) Waldenström's macroglobulinemia (WM) patients treated with bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111). Dimopoulos M, Opat S, Lee HP, et al. Updated results of the ASPEN study from a cohort of patients with MYD88 wild-type Waldenström's macroglobulinemia.	18 May 2020  <i>Blood</i> 2020; 136(18): 2038-2050  <i>HemaSphere</i> 2019, 3(S1): 196. Abstract Book: 24th Congress of the European Hematology Association. <i>HemaSphere</i> 2020, 4(S1): 550. Abstract Book: 25th Congress of the European Hematology Association.
Study AU-003	A Phase 1, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients with B-Cell Lymphoid Malignancies. Clinical Study Report BGB-3111-AU-003. Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the phase 1 trial of patients with mantle cell lymphoma (MCL) treated with bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111).	15 June 2020  <i>Hematological Oncology</i> 2019; 37(S2): 245-247
<b>Rituximab-monootherapy</b>		
iNNOVATE	A Randomized, Double-Blind, Placebo- Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study.	21 June 2018  <i>New England Journal of Medicine</i> 2018; 378: 2399-2410 <i>Journal of Clinical Oncology</i> 4 October 2021. Epub ahead of print.
Dimopoulos 2002	A single-arm, prospective Phase 2 Study defining the activity of rituximab in patients with Waldenström's Macroglobulinemia. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab.	01 May 2002  <i>Journal of Clinical Oncology</i> 2002; 20(9): 2327-2333.
<b>Bendamustine-rituximab combination therapy</b>		
Tedeschi 2015	A single-arm retrospective study of patients with R/R WM who received BR combination as salvage therapy. Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström's macroglobulinemia	14 March 2015  <i>Leukemia &amp; Lymphoma</i> 2015; 56(9): 2637-2642.
Treon 2011	A single arm study of patients with R/R WM who received bendamustine-containing therapy. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine Therapy in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia	01 Feb 2011  <i>Clinical Lymphoma, Myeloma &amp; Leukemia</i> 2011; 11(1): 133-135

Source: Table 2.6, pp53-54 of the resubmission.

Blue shading represents information previously considered by the PBAC

6.7 Key features of the studies were summarised in Table 3 of the July 2021 PSD for zanubrutinib.

6.8 Based on the included studies (unchanged), the resubmission conducted separate indirect treatment comparisons (ITCs) in the two requested populations using data presented in Table 4 below.

**Table 4: Summary of the indirect treatment comparisons in the requested populations**

Requested population	TN	R/R
Main comparator	Rm	BR
Comparisons conducted by submission	<ol style="list-style-type: none"> <li>ITC (Bucher method) for <u>response outcomes and safety</u> using ZANU data (from ASPEN-Cohort 1) vs Rm (from iNNOVATE) via 'common' comparators: IBRU (ASPEN-Cohort 1)/ IBRU+R (iNNOVATE)</li> <li>Naïve ITC for <u>response outcomes</u> using ZANU data from (ASPEN Cohort 1 and Study AU-003) vs Rm data from (iNNOVATE and Dimopoulos 2002).</li> </ol>	<ol style="list-style-type: none"> <li>MAIC for <u>PFS, OS, ORR and safety</u> using ZANU data (from ASPEN-Cohort 1) vs BR (from Tedeschi 2015)</li> <li>Naïve ITC of <u>response outcomes</u> using ZANU data (from ASPEN Cohort 1 and Study AU-003) vs BR (from Tedeschi 2015 and Treon 2011).</li> </ol>
Populations compared in the clinical evaluation	ITT (a combination of TN and R/R), due to subgroup response results not reported for iNNOVATE	ITT and R/R populations
Population and results used in the economic model	ITT populations <ul style="list-style-type: none"> <li>ZANU (ASPEN Cohort 1)</li> <li>Rm PFS from iNNOVATE, OS also from iNNOVATE using data reported by Buske 2021 adjusted for treatment crossover.</li> </ul>	R/R populations <ul style="list-style-type: none"> <li>ZANU (ASPEN Cohort 1) adjusted PFS/OS from MAIC to match Tedeschi 2015</li> <li>BR (Tedeschi 2015) PFS and OS.</li> </ul>

Source: compiled during the evaluation

BR=bendamustine + rituximab, TN=treatment naïve, R=rituximab, R/R=relapsed refractory, ITC=indirect treatment comparison, MAIC=matching-adjusted indirect treatment comparison, Rm=rituximab monotherapy, PFS=progression-free survival, OS=overall survival. Blue shading represents information previously considered by the PBAC

## Comparative effectiveness

### Response outcomes

6.9 A summary of key response outcomes previously reported is presented in Table 5. The primary outcome of ASPEN was the proportion of patients achieving either very good partial response (VGPR) or CR (complete response); i.e., VGPR/CR.

Table 5: High quality response rates across the included studies (VGPR, CR and VGPR/CR)

Trial ID	R/R (%)	ZANU n/N (%)	IBRU n/N (%)	IBRU+R n/N (%)	Rm n/N (%)	BR n/N (%)	RD <sup>a</sup> (95%CI)	RR <sup>a,e</sup> (95% CI)
<b>VGPR</b>								
ASPEN Cohort 1 <sup>b</sup>	81.6	29/102 (28.4)	19/99 (19)	-	-	-	0.09 (-0.02, 0.20)	1.48 (0.89, 2.46) <sup>e</sup>
-TN subgroup		5/19 (26)	3/18 (17)	-	-	-	0.11 (-0.16, 0.36)	1.67 (0.46, 6.01)
-R/R subgroup		24/83 (29)	16/81 (20)	-	-	-	0.09 (-0.04, 0.22)	1.46 (0.84, 2.55)
ASPEN Cohort 2 <sup>a</sup>	82.1	7/26 (27)	-	-	-	-	NA	NA
-TN subgroup <sup>a</sup>		1/5 (20)	-	-	-	-		
-R/R subgroup <sup>a</sup>		6/21 (29)	-	-	-	-		
Study AU-003 <sup>d</sup>	67.1	32/73 (43.8)	-	-	-	-	NA	NA
-TN subgroup		8/24 (33)	-	-	-	-		
-R/R subgroup		24/49 (49)	-	-	-	-		
iNNOVATE	54.7	-	-	17/75 (23)	3/75 (4)	-	<b>0.19 (0.08, 0.29)</b>	<b>5.67 (1.73, 18.53)</b>
Dimopoulous 2002	44.4	-	-	-	NR	-	NA	NA
Tedeschi 2015	100	-	-	-	-	11/71 (15.5)	NA	NA
Treon 2011 <sup>c</sup>	100	-	-	-	-	5/24 (20.8)	NA	NA
<b>CR</b>								
ASPEN Cohort 1 <sup>b</sup>	81.6	0 (0)	0 (0)	-	-	-	0	0
ASPEN Cohort 2 <sup>a</sup>	82.1	0 (0)	-	-	-	-	NA	NA
Study AU-003 <sup>d</sup>	67.1	1/73 (1.4)	-	-	-	-	NA	NA
-TN subgroup	0	0	-	-	-	-	NA	NA
-R/R subgroup	100	1/49 (2)	-	-	-	-	NA	NA
iNNOVATE	54.7	-	-	2/75 (3)	1/75 (1)	-	NA	NA
Dimopoulous 2002	44.4	-	-	-	NR	-	NA	NA
Tedeschi 2015	100	-	-	-	-	5/71 (7)	NA	NA
Treon 2011 <sup>c</sup>	100	-	-	-	-	NR	NA	NA
<b>VGPR/CR</b>								
ASPEN Cohort 1 <sup>b</sup>	81.6	29/102 (28) <sup>f</sup>	19/99 (19) <sup>f</sup>	-	-	-	0.09 (-0.02, 0.21)	1.48 (0.89, 2.46) <sup>e</sup>
-TN subgroup		5/19 (26)	3/18 (17)	-	-	-	0.07 (-0.18, 0.32)	1.43 (0.40, 5.17)
-R/R subgroup		24/83 (29)	16/81 (19)	-	-	-	0.09 (-0.39, 0.22)	1.46 (0.84, 2.55)
ASPEN Cohort 2 <sup>a</sup>	82.1	7/26 (27)	-	-	-	-	NA	NA
-TN subgroup <sup>a</sup>		1/5 (20)	-	-	-	-		
-R/R subgroup <sup>a</sup>		6/21 (29)	-	-	-	-		
Study AU-003 <sup>d</sup>	67.1	33/73 (45.2)	-	-	-	-	NA	NA
-TN subgroup		8/24 (33.3)	-	-	-	-		
-R/R subgroup		25/49 (51.0)	-	-	-	-		
iNNOVATE	54.7	-	-	19/75 (26)	4/75 (5)	-	<b>0.2 (0.09, 0.31)</b>	<b>4.75 (1.69, 13.30)<sup>e</sup></b>
Dimopoulous 2002	44.4	-	-	-	NR	-	NA	NA
Tedeschi 2015	100	-	-	-	-	16/71 (22.5)	NA	NA
Treon 2011 <sup>c</sup>	100	-	-	-	-	5/24 (20.8)	NA	NA

**Bold** typography indicates statistically significant results. **Blue** shading represents information previously considered by the PBAC.

Source: Table 2.41, p97; Table 2.43, p100; Table 2.51, p112; Tables 2.61-2.64, pp129-132; Tables 2.71-2.72, pp139-140 of the July 2021 submission, iNNOVATE published report Figure 3A, Study AU-003 published report Trotman 2020 suppl Table S3, ASPEN published report Table 2.

CI=confidence interval, CR=complete response, n=number of participants with event, N=total participants in group, NA=not applicable, NR=not reported, RR=relative risk, VGPR=very good partial response, VGPR/CR=very good partial response or complete response.

<sup>a</sup> Results extracted and estimated (using STATA 14.0) during the July 2021 evaluation.

<sup>b</sup> Independent review committee assessment.

<sup>c</sup> 24 patients in Treon 2011 received Rm, 6 were treated with rituximab + ofatumumab.

<sup>d</sup> Pooled across all dosage arms (<320 mg qd, 160 mg bd and 320 mg bd, 95% received the proposed TGA dose).

<sup>e</sup> The July 2021 submission reported RR results as IBRU vs ZANU, these were re-estimated during the July 2021 evaluation to report as ZANU vs IBRU.

<sup>f</sup> Primary trial outcome.

6.10 The ESC had previously considered it was difficult to draw any definitive conclusions regarding VGPR/CR for each treatment due to differences between the studies, the relatively small number of patients achieving these outcomes, lack of data on duration of response across studies, and the immaturity of the data (paragraph 6.24, zanubrutinib, PSD, July 2021). In considering the resubmission, the ESC noted that this uncertainty remained in the absence of new clinical data.

### Survival outcomes

6.11 Results for progression-free survival (PFS) and overall survival (OS) from the zanubrutinib studies are summarised in Table 6 and Figure 1.

**Table 6: PFS and OS in ZANU trials (ASPEN and Study AU-003)**

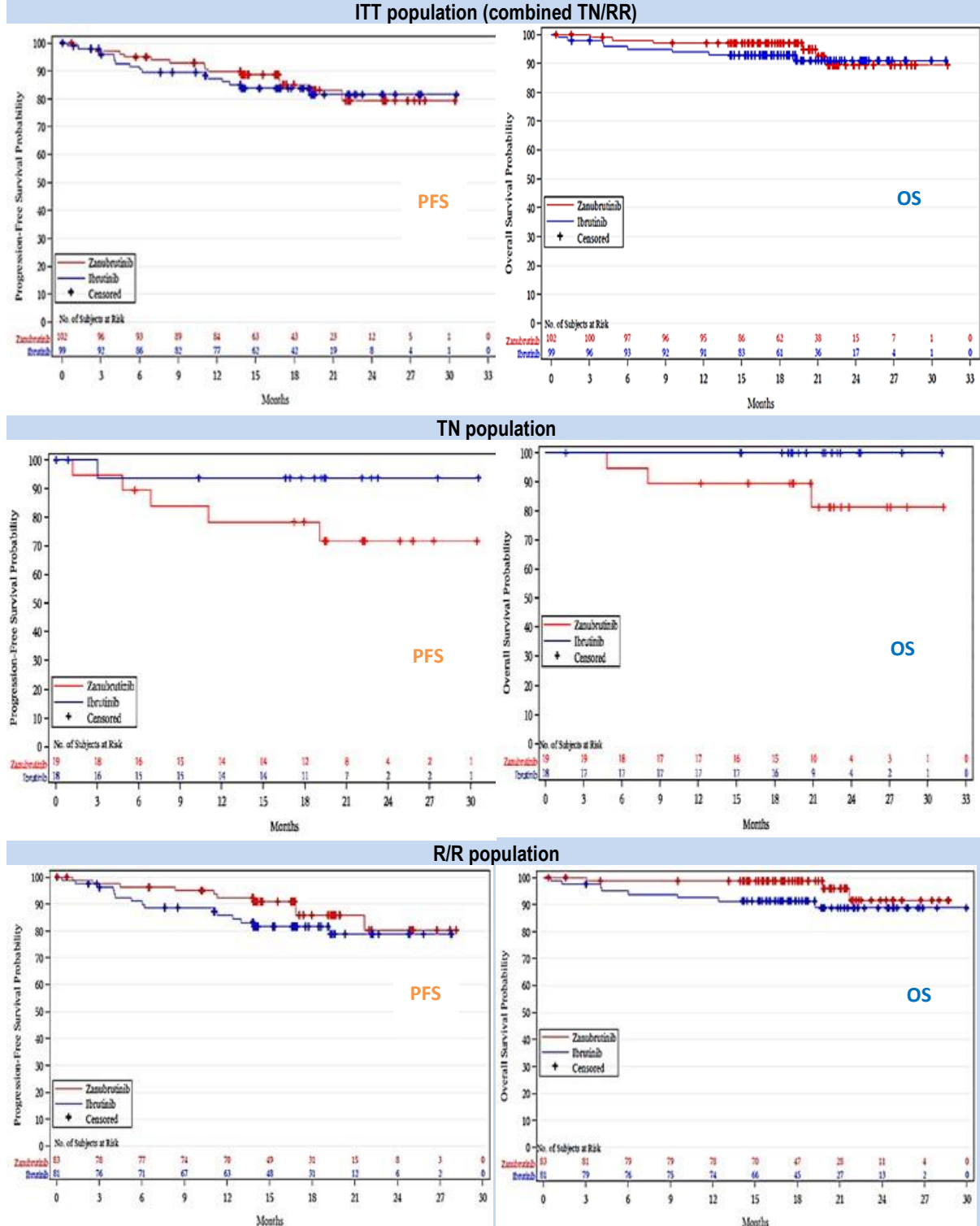
Trial ID	Outcomes	TN		R/R		Overall	
		ZANU	IBRU	ZANU	IBRU	ZANU	IBRU
<b>PFS</b>							
ASPEN Cohort 1	n/N with event (%)	5/19 (26.3)	1/18 (5.6)	10/83 (12.0)	15/81 (18.5)	15/102 (14.7)	16/99 (16.2)
ASPEN Cohort 2		2/5 (40.0)	-	7/21 (33.3)	-	9/26 (34.6)	-
StudyAU003		2/24 (8.3)	-	13/49 (26.5)	-	15/73 (20.5)	-
ASPEN	Median PFS, mths (95% CI)	NE (19.1, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
StudyAU003		NE (NE, NE)	-	NE (42.8, NE)	-	NE (NE, NE)	-
<b>OS</b>							
ASPEN Cohort 1	n/N with event (%)	3/19 (15.8)	0/18 (0)	3/83 (3.6)	8/81 (9.9)	6/102 (5.9)	8/99 (8.1)
ASPEN Cohort 2		1/5 (20.0)	-	2/21 (9.5)	-	3/26 (11.5)	-
StudyAU003		0/24 (0.0)	-	9/49 (18.4)	-	9/73 (12.3)	-
ASPEN	Median follow up, mths (95% CI)	22.4 (19.4, 23.8)	21.1 (19.3, 22.9)	18.7 (17.1, 20.3)	19.7 (17.9, 20.4)	19.5 (18.1, 20.8)	19.7 (18.7, 20.9)
StudyAU003		22.9 (21.8, 35.3)	-	37.3 (34.7, 44.1)	-	35.7 (27.2, 37.3)	-
ASPEN	Median OS, mths (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
StudyAU003		NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: Table 2.44, p100; Table 2.52, p114; Table 2.53, p114 of the July 2021 submission; Table 33, p125 and Table 39, p141 of the ASPEN CSR.

CI=confidence interval, IBRU=ibrutinib, NE=not estimable, OS=overall survival, PFS=progression-free survival, R/R=relapsed/refractory, TN=treatment naïve, ZANU=zanubrutinib.

Blue shading represents information previously considered by the PBAC.

Figure 1: KM plots of PFS and OS for ASPEN-Cohort 1



Source: Figure 2.14, p100, Figure 2.15, p101, Figure 2.18, p104, Figure 2.19, p104 of the July 2021 submission, Figure 14.2.1.5.4, p1658 of the ASPEN CSR.

ITT=intention to treat, KM=Kaplan–Meier, PFS=progression free survival, OS=overall survival.

Blue shading represents information previously considered by the PBAC.

- 6.12 After a median follow up of approximately 20 months, neither median PFS nor OS had been reached for any population or trial arm in ASPEN-Cohort 1.
- 6.13 PFS appeared numerically higher in those treated with zanubrutinib or ibrutinib than with Rm or BR (≈80% zanubrutinib or IBRU versus ≈40% Rm or ≈60% BR were event free at 30 months). However, these comparisons were uncertain due to differences across the studies and immature PFS data (particularly for ASPEN). The ESC considered PFS to be a clinically relevant measure in WM.
- 6.14 OS results from the included studies were also difficult to compare given data immaturity. The median OS was not reached in any study, with >90% still alive for zanubrutinib, IBRU and IBRU + R and Rm, and >72% still alive for BR at 30 months in Tedeschi 2015.
- 6.15 The resubmission included new data from iNNOVATE reported by Buske 2021 after a median follow up of 50 months. Buske 2021 reported both unadjusted OS and OS adjusted for crossover. OS adjusted for crossover (in 40% (n=35) of patients post progression from Rm to IBRU+R) was used in the economic model to represent Rm. Buske 2021 reported that median OS was calculated with adjustment for crossover patients using the two-stage accelerated failure time model (Latimer, 2014). However, Buske 2021 did not explain how this method was applied to the study population. Furthermore, given this was the only paper that presented OS results adjusted for crossover, it was unclear how comparable these results would be to OS data from zanubrutinib and other treatments. Therefore, the evaluation considered that the use of adjusted OS data to the model may have introduced further uncertainty to the results, especially when none of the treatment arms reached median OS. Despite the longer follow up, median OS was still not reached in either arm of iNNOVATE.
- 6.16 The ESC had previously noted that there appeared to be no difference between zanubrutinib and ibrutinib in the ITT and R/R population and that ibrutinib appeared to have better PFS and OS compared to zanubrutinib in the TN population. However, the ESC had noted that no reliable conclusions regarding survival outcomes could be drawn given the data were immature and observed differences were driven by a small number of events (paragraph 6.26, zanubrutinib PSD, July 2021). In reviewing the resubmission, the ESC considered that any difference in OS between treatments was unlikely to be observed in the clinical trial setting given patients with WM survive for a relatively long time due to the indolent nature of WM and given the rarity of WM. The ESC acknowledged that additional long-term trial data was unlikely to be forthcoming for WM. The pre-PBAC response (p1) maintained that a difference in the OS endpoint was not unreasonable based on the available evidence.

### **Quality of life outcomes**

- 6.17 ASPEN was the only study reporting quality of life (QoL) outcomes. There were no statistically significant differences between the two treatment arms for any of the QoL measures. However, zanubrutinib trended towards greater improvement in most

measures compared to ibrutinib, particularly when analysed over the first year on treatment in patients who achieved at least a VGPR.

- 6.18 The PBAC had previously considered comments from patients who had received zanubrutinib describing a range of benefits including improved QoL, the ability to work and live an active lifestyle and manageable side effects (paragraph 6.2, zanubrutinib PSD, July 2021).
- 6.19 PBAC representatives had also held a consumer hearing with representatives from the Australian patient support group for WM (WMozzies), prior to the July 2021 PBAC meeting. This was informed by a Rapid Consumer Evidence Brief prepared by the Consumer Evidence and Engagement Unit of the Department of Health, drawing on discussions held with WMozzies representatives concerning, among other matters, the experience of treatment with zanubrutinib. One perspective shared with the PBAC was that, although WM has a relapsing nature, it is the quality of life between relapsing periods that is greatly valued by those with the disease. WM makes people feel extremely tired and fatigued and the patient representatives had noted that zanubrutinib had given individuals back their energy, allowed them to feel like themselves again and to participate in activities. Patient representatives had noted that chemotherapy did not have the same benefits around quality of life and individuals continue to feel tired and unwell (paragraph 6.6, zanubrutinib PSD, July 2021).
- 6.20 The PBAC had previously considered that the consumer hearing with WMozzies was particularly valuable in highlighting the value of quality of life between relapsing periods of disease (paragraph 7.2, zanubrutinib PSD, July 2021).
- 6.21 A newly presented analysis of 302 WM patients in the global WhiMSICAL registry (Tohidi-Esfahani 2021) also indicated patients taking a BTKi had higher QoL scores (measured by EORTC QLQ-C30) with mean global score of  $80.1 \pm 16.2$  (n=44), compared to those not exposed to a BTKi who had been treated within 12 months: mean  $68.3 \pm 22.6$  (n=57, p=0.004). This was despite the BTKi cohort having undergone a median of two prior lines of treatment (IQR 1–4) compared to the non-BTKi cohort (median 1, IQR 1–2, p<0.001). This study did not provide patient characteristics for these two treatment groups separately. However, this same data when mapped to EQ-5D-3L utility values resulted in utility improvements of only 0.049 and 0.022 for BTKi versus non-BTKi agents in first line and second line treatments, respectively, suggesting a potentially smaller difference.

### ***Comparative harms***

- 6.22 No new safety data were presented in the resubmission. The PBAC had previously considered the claim of superior safety was not supported, especially when noting the duration of treatment with zanubrutinib will be substantially longer than with the comparator treatments (paragraph 7.8, zanubrutinib PSD, July 2021).

- 6.23 BTKis have a very different safety profile compared to either BR or Rm. For example, infusion-related adverse events occurred in more than half of patients given Rm in iNNOVATE (but none for zanubrutinib or ibrutinib since they were oral treatments), and IgM flares occurred in almost half of patients treated with Rm, which is a commonly reported AE for Rm, but were not reported for zanubrutinib or ibrutinib.
- 6.24 Conversely, BTKis are more likely to be associated with AEs such as atrial fibrillation and flutter (AF), neutropenia and major haemorrhage (although rates of major haemorrhage were equal in both arms of iNNOVATE). While zanubrutinib appeared to have reduced AF events compared to ibrutinib, it was associated with an increase in neutropenia (including grade 3-4 neutropenia) and reported similar incidence of all haemorrhage, including 12/207 (6% of total zanubrutinib patients from included studies) experiencing grade 3-4 major haemorrhage. The PSCR (p1) stated that BTKi therapy was associated with AEs that tend to occur early in treatment rather than later, and there are no longer-term toxicities which have been identified with extended zanubrutinib use. The PSCR noted that time-to-event data from ASPEN indicates that the incidence rates of many categories of AEs (major haemorrhage, AF, hypertension, neutropenia, pneumonia, diarrhoea) plateau after 24 months. The ESC considered that the potential for these AEs outside 24 months could not be excluded given the treatment duration with zanubrutinib. The ESC noted it is uncertain whether subsequent events were included in the ASPEN time-to-event curves. As AEs such as AF, hypertension, neutropenia, pneumonia, and diarrhoea would not necessarily result in permanent treatment discontinuation, patients previously inflicted may experience future events.

### ***Indirect treatment comparisons***

- 6.25 The ESC had previously noted there were considerable inconsistencies in the July 2021 submission's approach to the ITCs, with the comparisons in the TN population conducted only for response outcomes and the comparisons in the R/R population conducted for both response outcomes (using naïve ITC) and PFS/OS and ORR (using MAIC). The ITCs for the TN population were also based on data for the ITT population. The ESC had considered these inconsistencies hampered the interpretation of comparative outcomes (paragraph 6.36, zanubrutinib PSD, July 2021).

### **ITC zanubrutinib vs Rm**

- 6.26 The resubmission presented two ITCs (Table 7 and Table 8) comparing zanubrutinib and Rm via the Bucher method using commonly reported response outcomes and safety results from ASPEN and iNNOVATE, with ibrutinib/ibrutinib+rituximab arms as a 'common' reference. The ITT trial populations were used as iNNOVATE did not report separate response outcomes for TN or R/R. This may limit the applicability of the results to the TN population. These ITCs were unchanged from the July 2021 submission.

**Table 7: ITC response outcomes for zanubrutinib vs Rm (Bucher method) – a combined TN and R/R population (proxy for TN population)**

Outcomes	ASPEN			iNNOVATE			ITC (ZANU v Rm)* RR (95% CI) p value
	IBRU n/N (%)	ZANU n/N (%)	IBRU v ZANU RR (95%CI)	IBRU+R n/N (%)	Rm n/N (%)	IBRU+R v Rm RR (95%CI)	
MRR	77/99 (78)	79/102 (77)	1.00 (0.87, 1.17)	54/75 (72)	24/75 (32)	2.25 (1.57, 3.22)	2.24 (1.52, 3.3) p ≤ 0.0001
ORR	92/99 (93)	96/102 (94)	0.99 (0.92, 1.06)	69/75 (92)	35/75 (47)	1.97 (1.53, 2.53)	2.0 (1.54, 2.59) p ≤ 0.0001
VGPR	19/99 (19)	29/102 (28)	0.67 (0.41, 1.12)	17/75 (23)	3/75 (4)	5.67 (1.73, 18.53)	8.4 (2.31, 30.48) p = 0.0012
MR	15/99 (15)	17/102 (17)	0.91 (0.48, 1.72)	20/75 (27)	15/75 (20)	1.33 (0.741, 2.40)	1.47 (0.62, 3.49) p = 0.3865

Highlighted green cells represent the 'common' comparator arm. Blue shading represents information previously considered by the PBAC. Source: Table 2.61, p132 of the resubmission.

CI=confidence interval, IBRU=ibrutinib, IBRU+R=ibrutinib + rituximab, ITC=indirect treatment comparison, MR=minor response, MRR=major response rate (achieving partial response or better), ORR=overall response rate (achieving MR or better), Rm=rituximab monotherapy, RR=risk ratio, R/R=relapsed/refractory, TN=treatment naïve, VGPR=very good partial response, ZANU=zanubrutinib.

\* Indirect estimate of effect adjusted for the common reference. All numbers were rounded.

**Table 8: ITC safety outcomes for zanubrutinib vs Rm (Bucher method) – a combined TN and R/R population (proxy for TN population)**

Outcomes	ASPEN			iNNOVATE			ITC (ZANU vs Rm)* RR (95% CI) p value
	IBRU n/N (%)	ZANU n/N (%)	IBRU v ZANU RR (95% CI)	IBRU+R n/N (%)	Rm n/N (%)	IBRU+R vs Rm RR (95%CI)	
Hypertension	12/99 (12)	6/102 (6)	2.06 (0.81, 5.28)	10/75 (13)	3/75 (4)	3.33 (0.96, 11.63)	1.62 (0.34, 7.73) p=0.5467
AF	3/99 (3)	0/102 (0)	7.21 (0.38, 137.81)	9/75 (12)	1/75 (1)	9.0 (1.17, 69.29)	1.25 (0.03, 45.12) p=0.9036
Anaemia	5/99 (5)	5/102 (5)	1.03 (0.31, 3.45)	8/75 (11)	13/75 (17)	0.61 (0.27, 1.40)	0.6 (0.14, 2.57) p=0.4893
Neutropenia	8/99 (8)	16/102 (16)	0.51 (0.23, 1.15)	7/75 (9)	2/75 (3)	3.5 (0.75, 16.30)	6.79 (1.2, 38.52) p=0.0305
Pneumonia	7/99 (7)	1/102 (1)	7.21 (0.91, 57.56)	7/75 (9)	2/75 (3)	3.5 (0.75, 16.30)	0.49 (0.04, 6.44) p=0.5835
Thrombocytopenia	3/99 (3)	6/102 (6)	0.52 (0.13, 2.00)	0/75 (0)	4/75 (5)	0.11 (0.01, 2.03)	0.22 (0.01, 5.32) p=0.3482

Highlighted green cells represent the 'common' comparator arm. Blue shading represents information previously considered by the PBAC. Source: Table 2.62, p133 of the resubmission.

CI=confidence interval, IBRU=ibrutinib, IBRU+R=ibrutinib + rituximab, ITC=indirect treatment comparison, Rm=rituximab monotherapy, RR=risk ratio, R/R=relapsed/refractory, TN=treatment naïve, ZANU=zanubrutinib.

\* Indirect estimate of effect adjusted for the common reference. All numbers were rounded.

6.27 The PBAC had previously noted there were important differences between ASPEN and iNNOVATE impacting transitivity (paragraph 6.38, zanubrutinib PSD, July 2021).

6.28 The PBAC had stated the claim of superior effectiveness of zanubrutinib versus Rm based on the ITC of response outcomes may be reasonable, but this conclusion may not extend to survival outcomes given the submission did not present an ITC for PFS and OS, the survival data were immature, and response outcomes appeared to be poor surrogates for survival outcomes in WM. Also, given patients are likely to switch to alternate treatments following relapse, OS will also be influenced by subsequent treatments (paragraphs 6.41-6.42).

6.29 The ESC had previously considered it was difficult to assess comparative safety, given the considerable differences in safety profile between BTKis and Rm, the omission of important AEs from the ITC, potential safety implications associated with the addition of rituximab to ibrutinib, and the absence of direct comparative data (paragraph 2.43, zanubrutinib PSD, July 2021). The ESC maintained its previous consideration as the ITCs were unchanged from the previous submission.

**ITC zanubrutinib vs BR**

6.30 Given the lack of a common comparator linking zanubrutinib and BR, the resubmission presented two unanchored MAICs, for the ITT and RR populations, using individual patient-level data (IPD) for zanubrutinib from Cohort 1 of ASPEN matched to the population treated with BR in Tedeschi 2015. These were unchanged from the July 2021 submission.

6.31 The ESC had previously noted that unanchored MAICs can be more prone to uncertainty than anchored MAICs in that they do not use within-study randomised data and are prone to confounding due to unaccounted for differences in prognostic factors across single arms of different studies (paragraph 6.44, zanubrutinib PSD, July 2021).

6.32 The July 2021 submission had not included response outcomes in the MAIC. However, the previous PSQR presented a MAIC for ORR (i.e., achieving minor response or better) using investigator assessed outcomes from the ASPEN R/R analysis set versus Tedeschi 2015. This comparison was again included in the resubmission (Table 9).

**Table 9: MAIC of Overall Response Rate (ORR) using investigator assessed outcomes\***

	Before matching adjustment				After matching adjustment			
	ZANU (n=83)	BR (n=71)	OR (95% CI)	P-value	ZANU (n <sub>eff</sub> =46)	BR (n=71)	OR (95% CI)	P-value
ORR	78 (94.0%)	60 (84.5%)	2.86 (0.98, 9.48)	0.054	96.0%	60 (84.5%)	4.44 (1.22, 24.19)	0.022

Source: Table 2.69, p140 of the resubmission. Blue shading represents information previously considered by the PBAC.

\*Investigator assessed outcomes from ASPEN were utilised to be consistent with the likely method of assessment in Tedeschi et al 2015. ZANU=zanubrutinib, OR=odds ratio, ORR=overall response rate (achieving minor response or better).

6.33 The resubmission referred to Castillo 2021, which considered the relationship between attaining partial response or better (at 6 months) and PFS at 3 years in patients using ibrutinib.

6.34 The resubmission did not change previously presented PFS and OS results before and after matching adjustment (Table 10). As previously, the PFS values used in the MAIC were higher than reported for zanubrutinib-treated patients in Cohort 1 of ASPEN (event-free rates at 12 and 24 months were 89.7% and 79.4%, respectively).

**Table 10: PFS and OS event-free rates, ZANU (before and after matching adjustment) vs BR**

Outcomes	ZANU ASPEN Cohort 1 pre-matching (N=102)		MAIC: ZANU vs BR			
	PFS	OS	ZANU post-matching BR (N=50)		BR (N=71)	
PFS			OS	PFS	OS	PFS
12 months	94%	97%	94%	98%	79%	87%
24 months	85%	90%	81%	88%	59%	77%

Source: Table 2.69, p136 of the July 2021 submission. Blue shading represents information previously considered by the PBAC.

BR=bendamustine + rituximab, MAIC=matched-adjusted indirect comparison, OS=overall survival, PFS=progression-free survival, ZANU=zanubrutinib.

6.35 The PFS and OS HRs comparing zanubrutinib to BR pre-matching and post-matching are reported in Table 11, and KM curves before and after matching are presented in Figure 2 and Figure 3.

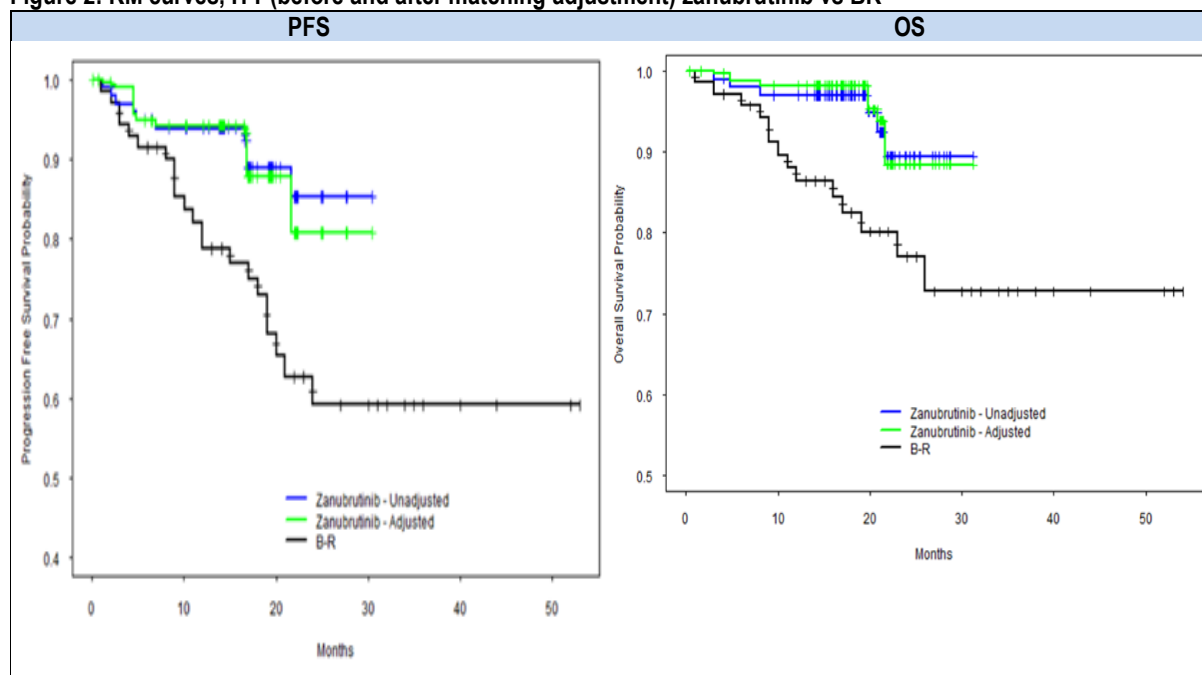
**Table 11: Hazard ratio ZANU (before and after matching adjustment) vs BR**

	HR (95% CI) ZANU vs BR	
	PFS	OS
<b>Pre-matching</b>	0.32 (0.15, 0.69)	0.31 (0.12, 0.80)
<b>Post-matching</b>	0.37 (0.15, 0.91)	0.29 (0.10, 0.85)

Source: p136 of the July 2021 submission.

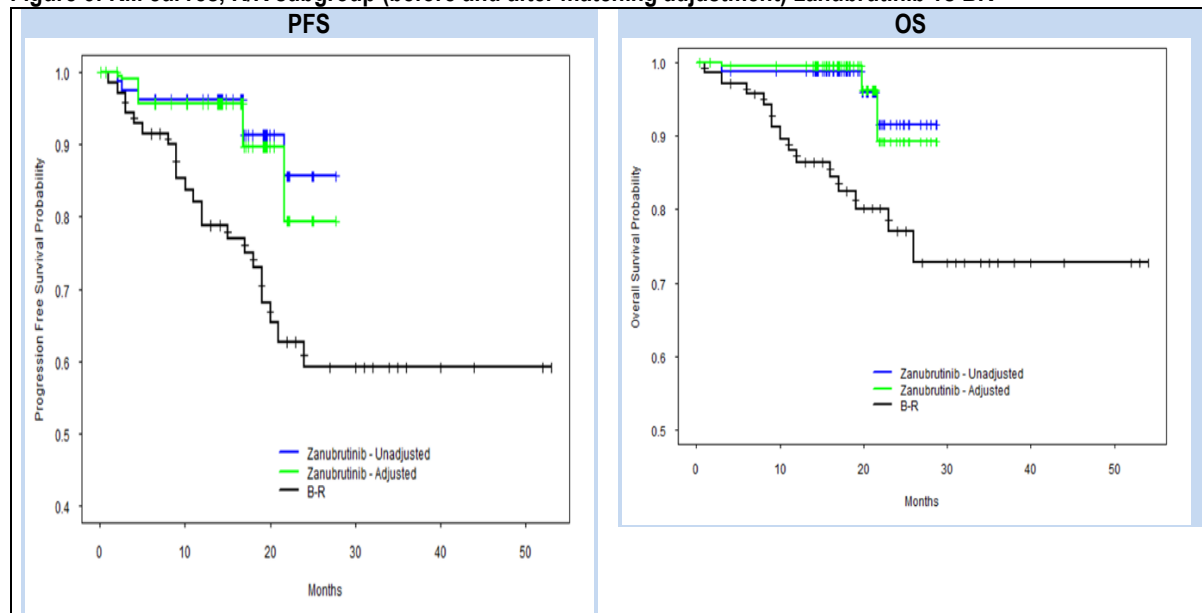
BR=bendamustine + rituximab, CI=confidence interval, HR=hazard ratio, OS=overall survival, PFS=progression-free survival, ZANU=zanubrutinib.

Figure 2: KM curves, ITT (before and after matching adjustment) zanubrutinib vs BR



Source: Figure 2.34, p137 and Figure 2.35, p137 of the July 2021 submission  
 BR=bendamustine+rituximab, KM=Kaplan-Meier, PFS=progression-free survival, ZANU=zanubrutinib.  
 NOTE: the Y axis for the submission's PFS and OS graphs do not start at zero with a different scale for PFS and OS.  
 Blue shading represents information previously considered by the PBAC.

Figure 3: KM curves, R/R subgroup (before and after matching adjustment) zanubrutinib vs BR



Source: Figure 2.36, p138 and Figure 2.37, p138 of the July 2021 submission.  
 BR=bendamustine + rituximab, KM=Kaplan-Meier, PFS=progression-free survival, R/R=relapsed/refractory, ZANU=zanubrutinib.  
 NOTE: the Y axis for the submission's PFS and OS graphs do not start at zero with a different scale for PFS and OS.  
 Blue shading represents information previously considered by the PBAC.

6.36 The resubmission again claimed superior efficacy of zanubrutinib to BR in R/R WM. While the data numerically favoured zanubrutinib, PFS and OS data from ASPEN were

premature with limited events for both PFS (15%) and OS (8%), creating uncertainty. The MAIC also could not adjust for a number of the identified differences in baseline characteristics between ASPEN-Cohort 1 and Tedeschi 2015, such as genetic profile, ECOG status, and serology at baseline, which are all known confounders for effectiveness.

- 6.37 Further, a lower than recommended dosing regimen was used in Tedeschi 2015 for 37% of patients receiving BR and the study included patients refractory to rituximab-based therapies, whereas patients with any prior exposure to BTKi treatments were excluded from ASPEN. Both factors may have reduced treatment efficacy in Tedeschi 2015.
- 6.38 The resubmission also conducted a MAIC for selected safety outcomes. The ESC had previously considered the comparative safety of zanubrutinib versus BR was difficult to assess due to the distinct safety profile of BTKis, omission of important AEs from the comparison and absence of direct comparative data. The ESC had considered that potential for considerable differences in patient characteristics and prognostic factors not adjusted for in the MAIC between zanubrutinib and BR introduced additional uncertainty to the interpretation of comparative safety results (paragraph 6.54, zanubrutinib PSD, July 2021). The ESC maintained its previous consideration as the MAIC was unchanged from the previous submission.

### **Benefits/harms**

- 6.39 The ITCs presented in the submission did not allow for a quantitative comparison of the benefits and harms of zanubrutinib and the proposed comparators (Rm and BR), except for the comparison of response rates versus Rm and ORR versus BR. The estimated effect size in these comparisons were associated with high uncertainty. Accordingly, a benefits/harms table was not presented. PFS and OS outcomes used in the modelled economic evaluation are presented in Figure 4.

### **Clinical claim**

- 6.40 The resubmission retained its previous claim and described zanubrutinib to have:
- superior effectiveness and safety compared to Rm in TN patients unsuitable for chemo-immunotherapy
  - superior effectiveness and safety compared to BR in R/R WM patients.
- 6.41 For the TN population, the PBAC had previously agreed with the ESC that the superiority claim was likely reasonable in terms of response outcomes, noting its advice that the magnitude of benefit was uncertain, and that response outcomes are unlikely to translate into survival outcomes. Nonetheless, the PBAC was certain of a response benefit, and given the substantial value of this outcome to patients in terms of improving quality of life and given lack of treatments available on the PBS, considered that zanubrutinib provided a high added therapeutic value in the treatment of WM (paragraph 7.6, zanubrutinib PSD, July 2021).

- 6.42 For the R/R population, the PBAC had previously considered that the MAIC results were uncertain, and that superior effectiveness in terms of survival outcomes was not adequately supported by the data. The PBAC further noted the sponsor's arguments in support of a positive correlation between response and survival outcomes but agreed with the ESC that given the indolent and relapsing nature of WM, response outcomes were unlikely to predict survival outcomes (paragraph 7.7, zanubrutinib PSD, July 2021).
- 6.43 In reviewing the resubmission, the ESC considered that the claim of superior efficacy was reasonable in terms of response outcomes however, the ESC remained uncertain of the survival benefit associated with zanubrutinib.
- 6.44 In terms of safety, the PBAC had previously considered the claim of superior safety was not supported, especially when noting the duration of treatment with zanubrutinib will be substantially longer than with the comparator treatments. The PBAC noted the safety profile for zanubrutinib appeared consistent with that for BTKis and as such, considered its safety profile to be manageable (paragraph 7.8, zanubrutinib PSD, July 2021). The ESC maintained that in the absence of comparative data, the uncertainty around the long-term comparative safety of zanubrutinib remains. The pre-PBAC Response (p2) noted that in an earlier phase 1/2 trial (Trotman et al. 2020) with a median follow up of 36 months, the proportion of patients treated with zanubrutinib experiencing an AE  $\geq$ Grade 3 (around 58%) was similar to that in ASPEN. On this basis, the sponsor considered that the observed safety data from ASPEN were representative of longer-term safety outcomes for WM patients treated with zanubrutinib.
- 6.45 The PBAC's views regarding the clinical claims were unchanged but, noting the additional context provided by Castillo (2021), considered that it was not unreasonable to accept the plausibility of some survival benefit, although it could not be reliably quantified.

### ***Economic analysis***

- 6.46 The July 2021 submission presented two separate partitioned survival analyses comparing zanubrutinib in the TN and R/R populations against nominated comparators. The PBAC had previously considered (paragraph 7.14, zanubrutinib PSD, July 2021) the economic models to be unreliable as they did not reflect the potential benefits of zanubrutinib, such as reduction in subsequent therapies and improved quality of life. Instead, the models were driven by large survival gains that were not well-supported by the data and considered clinically implausible. The PBAC had previously considered that any resubmission should include a revised model that more accurately reflected the clinical course of WM and where the benefits of treatment are consistent with those expected. The PBAC noted (paragraph 7.16, zanubrutinib PSD, July 2021) that:
- the structure should more accurately reflect the chronic relapsing nature of WM and the expected outcomes of treatment

- the inputs should be consistently applied for the treatment naïve and relapsed/refractory settings.
- 6.47 A Facilitated Resolution Pathway (FRP) workshop was held for zanubrutinib on 6 September 2021 to explore feasible options to address issues identified by the PBAC, with the following outcomes:
- **Structure:** it was considered that one subsequent line of treatment in each model was appropriate given paucity of data to support modelling any further lines of treatment.
  - **Subsequent therapy:** it was considered appropriate to model time to next therapy (TTNT) by parametrising the relationship with PFS.
  - **Time horizon:** there was a preference for a time horizon shorter than the 20 years given the frailty and advanced age of the patient population, especially within the TN chemo-immunotherapy unsuitable population where there are limited treatment options available.
  - **Duration of treatment:** the sponsor indicated it may consider applying a financial stopping rule in the form of a constrained duration of treatment.
  - **Utilities:** the preference for trial-based utilities where available was reiterated. Given the paucity of data in WM, it was considered that chronic lymphocytic leukaemia (CLL) represented an appropriate disease analogue to inform utility weights applied in the modelled health states.
  - **Extrapolation:** it was recommended that conservative assumptions are made in the revised model extrapolations.
- 6.48 The PSCR (p2) stated that the TN and R/R populations were modelled separately to reflect different treatment populations. The PSCR noted that the TN population in ASPEN were older and had a higher ECOG status at baseline on average compared to the R/R population. The PSCR also considered that utility scores from ASPEN (0.754 for TN patients versus 0.798 for R/R patients) suggested a lower baseline health status for TN patients. The ESC noted that the percentage of patients alive at the end of the 15-year time horizon for each model (51% for TN and 18% for R/R) was not consistent with TN patients having a poorer prognosis.
- 6.49 A summary of the models in the resubmission compared to the July 2021 submission is presented below.

**Table 12: Key components of the economic evaluation for the July 2021 submission and the resubmission.**

Component	July 2021 submission		Resubmission		Justification/comments
	TN model	R/R model	TN model	R/R model	
Type of analysis	Cost-utility analysis		No change		Appropriate
Outcomes	Life years gained (LYG), quality-adjusted life years gained (QALY)		No change		Appropriate

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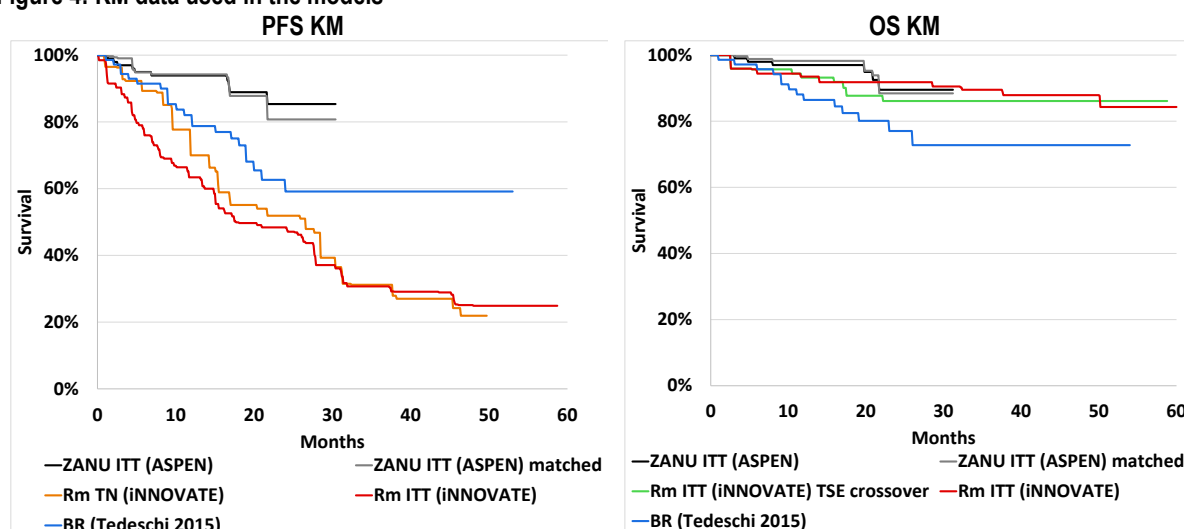
Component	July 2021 submission		Resubmission		Justification/comments
	TN model	R/R model	TN model	R/R model	
Methods used to generate results	Partitioned survival analysis		No change		Reasonable. While a Markov model may be a better fit for a relapsing-remitting disease, there is also limited data on the relationship between the health states or state transitions.
Health states	Three health states: • PFS • PD • Dead (absorbing state)	Three health states: • PFS • PD • Dead (absorbing state)	Five health states: • PF on treatment • PF off treatment • PDW • PDT • Dead (absorbing state)	Five health states: • PF on treatment • PF off treatment • PDW • PDT • Dead (absorbing state)	Time on treatment modelled separately (extrapolated KM data from ASPEN, treatment regimen for Rm and BR as described in iNNOVATE and Tedeschi 2015 respectively) TTNT based on hazard ratios between PFS and TTNT from iNNOVATE (IBRU+R proxy for ZANU, Rm proxy for RM and BR).
Cycle length	28 days, half cycle correction applied		No change		Appropriate
Time horizon	20 years vs 19.5 months follow up in ASPEN, 26.5 months in iNNOVATE, and 19 months in Tedeschi 2015.		15 years vs 19.5 months follow up in ASPEN, 50 months in iNNOVATE and 19 months in Tedeschi 2015.		The estimation of OS left 51% of patients alive at the end of the 15-year period in both arms of the TN model and 18% of patients alive in both arms of the R/R model. As survival was assumed to converge for ZANU and comparator in each model from year 10, the time horizon had less bearing on the ICER than in the July 2021 submission.

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Component	July 2021 submission		Resubmission		Justification/comments
	TN model	R/R model	TN model	R/R model	
Transition probabilities	<p><b>For ZANU:</b> based on ASPEN (ITT). <b>For Rm:</b> based on iNNOVATE Rm treatment arm for PFS and Tedeschi 2015 BR treatment arm for OS.</p>	<p><b>For ZANU:</b> based on ASPEN using a matched subset of the ITT populations. <b>For BR:</b> based on Tedeschi 2015.</p>	<p><b>For ZANU:</b> based on ASPEN (ITT) <b>For Rm:</b> based on iNNOVATE (ITT for PFS and OS adjusted for crossover from Buske 2021).</p>	<p><b>For ZANU:</b> ASPEN using a matched subset of the ITT populations and <b>For BR:</b> based on Tedeschi 2015.</p>	<p>PFS and OS data used in the models to extrapolate survival were very immature, particularly for ZANU OS, since few events have occurred in any of the treatment arms compared. The convergence eliminated some of the extreme survival gains from the previous models, particularly in the TN model where survival became similar for ZANU and Rm. A larger survival benefit for ZANU was assumed to year 10 versus the comparator, BR in the R/R model.</p> <p>Median follow up as a cut-off for the KM data resulted in a loss of the very limited data available and a large discrepancy between the commencement of the extrapolation between ZANU and Rm where Rm has an additional 30 months of follow up.</p>
	<p>In both models, PFS was modelled such that it could not exceed OS and the estimated PFS and OS could not exceed general population survival.</p> <p>Transition probabilities did not directly incorporate KM data but were entirely extrapolated.</p>	<p>In both models, PFS was modelled such that it could not exceed OS and the estimated PFS and OS could not exceed general population survival.</p> <p>KM data was used until median follow up followed by extrapolation.</p> <p>TTNT based on HRs from iNNOVATE (IBRU+R as proxy for ZANU, ITT Rm as proxy for BR (R/R model) and Rm (TN model)) applied to PFS.</p> <p>From year 5, linear convergence was applied to ZANU OS and from year 10, OS was assumed equal to the comparator arm in each model.</p> <p>A financial stopping rule of [REDACTED] months was implemented. After this point (adjusted to [REDACTED] months when accounting for treatment discontinuation) the sponsor would reimburse the Australian Government.</p>			



Figure 4: KM data used in the models



Source: compiled during the evaluation from Excel workbook 'Zanubrutinib\_WM\_NOV\_2021\_Resubmission\_S3\_Final\_Macros.xlsm'  
 BR=bendamustine + rituximab, KM=Kaplan-Meier, OS=overall survival, PFS=progression-free survival, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, TSE crossover=Two stage estimation treatment crossover adjustment, ZANU=zanubrutinib

6.52 KM data used in the models were similar (minor changes likely due to redigitisation) to the July 2021 submission except for Rm OS data from iINNOVATE, which were updated to more recently published data from Buske 2021, with up to 50 months of follow up compared to 26.5 months previously. The resubmission also chose to use OS adjusted for crossover (see discussion below); previously only unadjusted OS data were used in the models in any treatment arm.

### Extrapolations

6.53 A summary of extrapolations used in the economic models by treatment arm and survival curve is presented in Table 13. For the July 2021 submission, the PBAC had considered the approach to extrapolation inconsistent, impacting model validity (paragraph 7.10, zanubrutinib PSD, July 2021).

6.54 Compared to the July 2021 submission, the main changes in terms of extrapolation were:

- The revised models used KM data up to median follow-up, followed by extrapolations based on all available KM data. Previously, the models had relied entirely on extrapolated data (paragraph 7.10, zanubrutinib PSD, July 2021).
- The modelling of OS for Rm in the resubmission was based on an independent model of Rm OS from iINNOVATE, rather than assuming BR was a proxy for survival outcomes in these patients. Previously, use of BR data for Rm had introduced considerable uncertainty to the TN model (paragraph 6.74, zanubrutinib PSD, July 2021). The resubmission stated that proportional hazards were not considered because IPD data were not available from iINNOVATE, and a dependent extrapolation would not be significantly different from what was modelled given the choice of exponential function in the base case.

- Dependent modelling of BR OS data (in the R/R model) and choice of exponential function. The July 2021 submission had used independent modelling, which resulted in large OS gains for zanubrutinib; an independent Weibull extrapolation was chosen to estimate survival for the BR arm, this had the worst statistical fit of all functions (paragraphs 6.71, 6.72, zanubrutinib PSD, July 2021).
- Application of linear convergence of zanubrutinib OS to comparator arms, applied from Year 5 to Year 10 to equate the comparator arm OS from Year 10 onwards.
- A financial stopping rule of ■ months was implemented, after this point the sponsor would reimburse the Australian Government for expenditure on zanubrutinib. The ■-month rule was incorrectly implemented in the submitted models as a result of a coding error, which resulted in the financial stopping rule not being implemented until cycle 67 (i.e. the models costed for 65.5 months of treatment). Corrected base case ICERs were \$75,000 to < \$95,000 and \$55,000 to < \$75,000 per QALY gained in the TN and R/R models respectively, compared to \$95,000 to < \$115,000 and \$75,000 to < \$95,000 in the resubmission. Corrected results are presented throughout.

**Table 13: Summary of extrapolations used in the economic model by treatment arm and survival curve**

Model	Arm (source)	PFS	OS	Time on treatment	Time to next treatment
TN	ZANU (ITT ASPEN)	KM data to median follow up (18 mths ZANU, 50 mths Rm) followed by independent exponential extrapolation, restricted to not exceed OS.	KM data for 19.5 mths followed by independent exponential extrapolation, restricted to general population mortality to Year 5, then linear convergence to Rm OS to Year 10. Equal to Rm OS from Year 10.	KM data for 19.5 mths followed by independent exponential extrapolation restricted to not exceed OS.	PFS with 0.36 hazard ratio from iINNOVATE IBRU+R arm applied until Year 5, followed by PFS with 0.86 hazard ratio from Rm arm applied, restricted to not exceed OS.
	Rm (ITT iINNOVATE for PFS ITT iINNOVATE adjusted for crossover for OS)	exponential extrapolation, restricted to not exceed OS.	KM data for 50 mths followed by independent exponential extrapolation, restricted to general population mortality.	Fixed time on treatment assumed based on the planned dose in iINNOVATE.	PFS with 0.86 hazard ratio from iINNOVATE Rm arm applied, restricted to not exceed OS.
R/R	ZANU (ITT ASPEN matched to Tedeschi 2015)	KM data to median follow up (18 mths ZANU, 19 mths BR) followed by dependent exponential extrapolation, restricted to not exceed OS.	KM data for 19.5 mths followed by dependent exponential extrapolation, restricted to general population mortality to Year 5, then linear convergence to BR OS to Year 10. Equal to BR OS from Year 10.	KM data for 19.5 mths followed by independent exponential extrapolation restricted to not exceed OS.	PFS with 0.36 hazard ratio from iINNOVATE IBRU+R arm applied, until Year 5, followed by PFS with 0.86 hazard ratio from Rm arm applied, restricted to not exceed OS.
	BR (Tedeschi 2015)	exponential extrapolation, restricted to not exceed OS.	KM data for 50 mths followed by dependent exponential extrapolation, restricted to general population mortality.	Fixed time on treatment assumed based on the planned dose in Tedeschi 2015.	PFS with 0.86 hazard ratio from iINNOVATE Rm arm applied, to not exceed OS.

Source: Tables 3-17, 3-18, 3-33, 3-34 of the resubmission and compiled during the evaluation. Blue shading represents elements that were unchanged from the July 2021 submission.

BR=bendamustine + rituximab, IBRU+R=ibrutinib + rituximab OS=overall survival, PFS=progression-free survival, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, TTD=time to treatment discontinuation, ZANU=zanubrutinib

Note: ZANU (matched) arm included patients matched to those in Tedeschi 2015 using the MAIC described in Section 2.6.

6.55 As shown in Table 13, inconsistencies remained in the resubmission’s approach to extrapolation. The ESC noted some extrapolation issues were carried over from the July 2021 submission:

- ITT data (with a combination of TN and RR patients) from ASPEN and iINNOVATE were used to represent TN patients. Survival data from ASPEN indicated a lower PFS and OS in the TN versus ITT population (i.e. 70% vs 78% for zanubrutinib PFS, and 80% vs 88% for zanubrutinib OS at 24 months). It was unclear which data would best represent the TN chemo-immunotherapy unsuitable patients.
- In the R/R model, for zanubrutinib, ASPEN ITT data matched to Tedeschi 2015 was used. A number of the important differences between Tedeschi 2015 and ASPEN could not be adjusted for in the MAIC, affecting transitivity and potentially biasing the results against BR (see paragraph 6.36).

- Time on treatment for zanubrutinib was modelled using extrapolated KM data from ASPEN, whereas a fixed time on treatment was assumed for Rm and BR, based on the protocols from iNNOVATE and Tedeschi 2015. The models did not adjust for the patients who did not complete treatment with Rm or BR, even though these patients had contributed to the estimates of PFS and OS (likely with lower efficacy than those who received the recommended dosage). Total treatment costs for Rm and BR were adjusted for the proportion of patients in PFS in each cycle.
- 6.56 The ESC noted some new extrapolation issues were identified as arising from the resubmission:
- TTNT was based on the relationship between PFS and TTNT in iNNOVATE. IBRU+R ITT data was used as a proxy for zanubrutinib in both TN and R/R models and Rm ITT data was used as a proxy for Rm in the TN model and BR in the R/R model. It was unknown what effect the addition of Rm to ibrutinib treatment in iNNOVATE may have had on the relationship between PFS and TTNT, but it was likely to overestimate the TTNT for zanubrutinib (i.e. a BTKi used alone). Similarly, it was likely the addition of bendamustine would result in a different relationship between PFS and TTNT than Rm. Given BR is expected to be more effective than Rm, TTNT may be underestimated for BR.
  - KM data from the included studies were used until median follow up. This resulted in different lengths of KM data being used for each treatment arm, with a large discrepancy in the TN model where KM data for zanubrutinib was modelled to 18 or 19.5 months for PFS and OS respectively, out of a maximum 30.4 months of KM data, compared to 50 months (both PFS and OS) out of a maximum 58.8 months of KM data for Rm. A large amount of follow up for BR was also lost, as only 19 months out of a maximum 54 months of KM data were modelled directly. Furthermore, as the extrapolations were based on the total KM data available, an advantage was given to zanubrutinib OS since the extrapolation began where KM data exceeded the extrapolation curve. The implementation of convergence beyond Year 5, however, limited some of this advantage.
- 6.57 Choice of extrapolation followed the same logic as in the previous submission. For both PFS and OS, six parametric curves were fitted to the data (exponential, Gamma, Gompertz, log-logistic, log-normal, and Weibull). The Akaike information criterion (AIC) and Bayesian information criterion (BIC), along with visual inspection of the data, were used to assess goodness of fit and curve selection. Predictions in the unobserved period were considered for clinical plausibility when selecting the parametric curve. As with the July 2021 submission, given data were quite immature, it appeared that clinical plausibility was the overwhelming factor in extrapolation choice. PFS in the models was restricted by base case OS.

#### **Extrapolation for PFS**

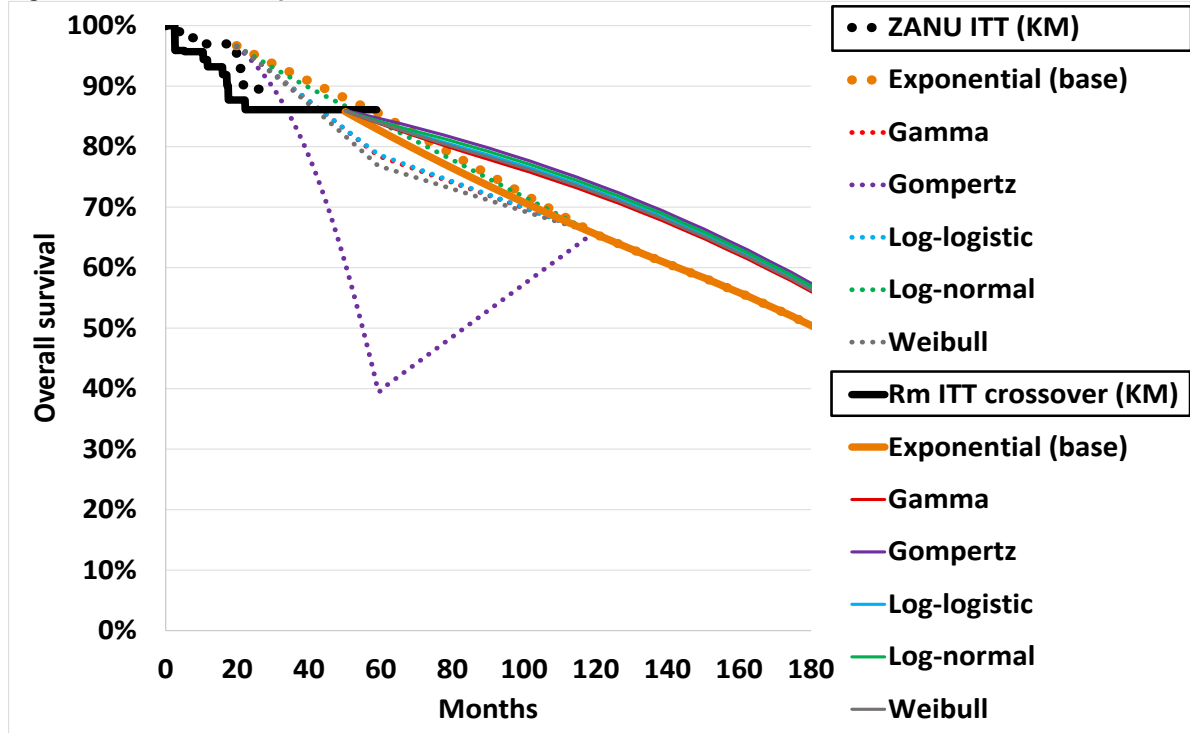
- 6.58 Unlike OS, PFS was not modelled to converge beyond Year 5 (only limited by base case OS). In the TN model this resulted in more than 30% of patients alive and progression

free at the end of the 15-year time horizon in the zanubrutinib arm. In comparison, no patients remained in PFS for Rm.

**Extrapolation for OS**

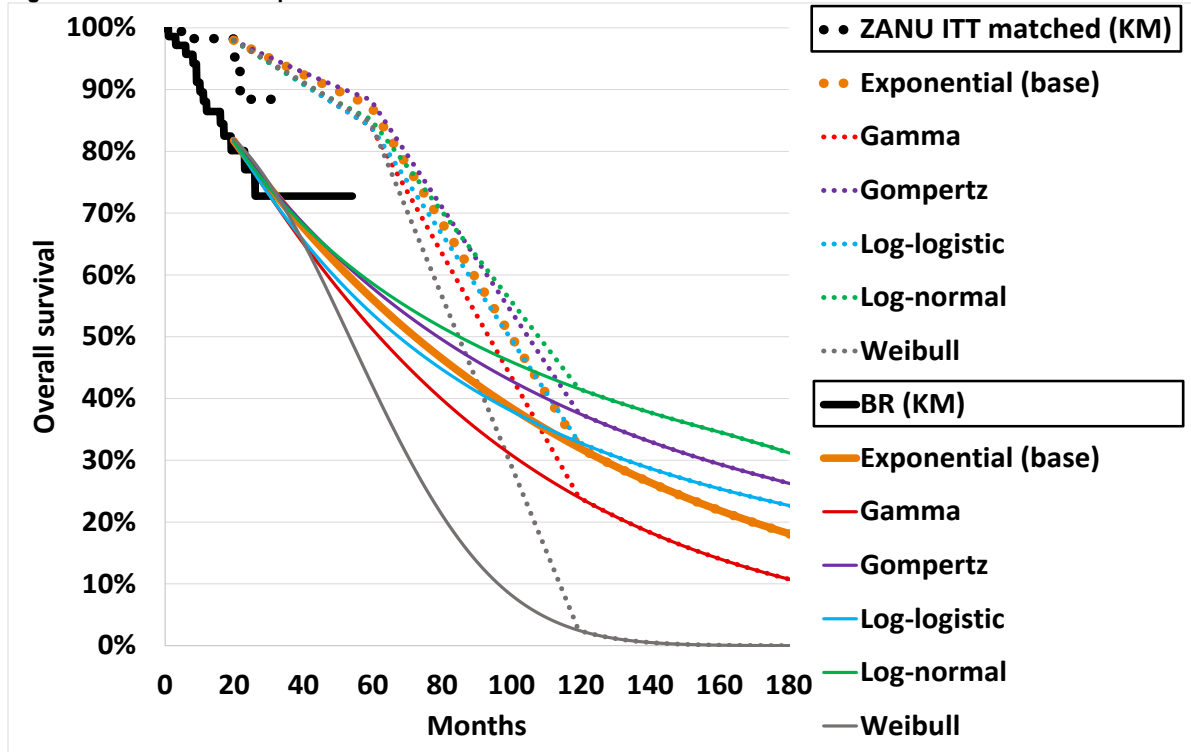
- 6.59 One change from the July 2021 submission was the use of recently published data from Buske 2021 (final analysis of iNNOVATE) to model Rm OS and the use of published KM data adjusted for crossover. While approximately 40% patients receiving Rm in iNNOVATE did switch to IBRU treatment post progression, Buske 2021 did not give enough detail on the crossover adjustment to determine how appropriate the adjustment was. The KM curves for the adjusted and unadjusted Rm OS data were not substantially different and most extrapolations of the KM data resulted in similar OS (a result of them being restricted by background mortality). The one notable difference was that the selected exponential curve for Rm OS (using data adjusted for treatment switching) predicted a lower survival for Rm than all other extrapolations, which favoured zanubrutinib.
- 6.60 The chosen extrapolation functions for OS in the resubmission produced the largest survival estimates for zanubrutinib up to Year 5 in both models (Figure 5 and Figure 6). The resubmission implemented linear convergence between Years 5 and 10. A sensitivity analysis with convergence commencing from 7.5 years was presented. Table 20 also presents sensitivity analyses conducted during the evaluation with no survival benefit after KM data cut off and a hazard rate convergence for OS from 30 months. The analyses had greater impact upon the R/R model ICER, because there was a greater difference between the OS extrapolations of zanubrutinib and BR than zanubrutinib and Rm. The PSCR (p2) maintained that it was reasonable to model an OS benefit for zanubrutinib based on the available data, noting that the OS benefit had been implemented in a conservative manner through convergence and a reduced time horizon.

Figure 5: Parametric extrapolations of OS for TN model



Notes: OS as modelled. Extrapolations include general population mortality and cannot exceed the OS base case. KM data used to median follow up, 19.5 months for ZANU, 50 months for Rm. ZANU extrapolations converge to base case Rm OS (exponential) from year 5. Source: compiled during the evaluation using Excel workbook 'Zanubrutinib\_WM\_NOV\_2021\_Resubmission\_S3\_Final\_Macros.xlsm' ITT=intention to treat, KM=Kaplan–Meier, OS=overall survival, Rm=rituximab monotherapy, TN=treatment naïve

Figure 6: Parametric extrapolations of OS for R/R model



Notes: OS as modelled. Extrapolations include general population mortality and cannot exceed the OS base case. KM data used to median follow up, 19.5 months for ZANU, 19 months for BR. ZANU extrapolations converge to BR OS from year 5. For dependent extrapolations, convergence maps to same function as would be modelled. For independent extrapolations, convergence is to exponential extrapolation of BR OS for demonstrative purposes.

Source: compiled during the evaluation using the Excel workbook 'Zanubrutinib\_WM\_NOV\_2021\_Resubmission\_S3\_Final\_Macros.xlsm'  
BR=bendamustine + rituximab, ITT=intention to treat, KM=Kaplan–Meier; OS=overall survival, R/R=relapsed/refractory, ZANU=zanubrutinib

### **Extrapolation for time on treatment**

6.61 Time on treatment for zanubrutinib was modelled using time to treatment discontinuation (TTD) KM data from ASPEN to 19.5 months followed by extrapolations to 15 years and restricted by OS. Unadjusted ITT data was used in the TN model and ITT data matched to Tedeschi 2015 was used in the R/R model. Based on statistical fit, the exponential function had the lowest AIC and BIC in both models and was chosen as a result. A stopping rule was implemented from 12 months for zanubrutinib, restricting the costs beyond this point. The ESC considered that in practice, the treatment duration on average may be substantially shorter than assumed in the model (average of 77-79 months, cost capped at 12 months) as most patients diagnosed with WM are elderly.

### **Extrapolation for time to next treatment**

6.62 With the inclusion of a subsequent line of treatment, the progressive disease state was split into two health states: progressed disease without treatment (PDW), and progressed disease requiring treatment (PDT). To capture the transition between these states, TTNT was estimated based upon the relationship between PFS and TTNT from iNNOVATE. A summary of the modelled TTNT is presented in Table 14 and Figure 7 below.

**Table 14: TTNT vs PFS HR estimates**

TTNT HR	Source	Use in model
0.86	Rm arm of iNNOVATE	Applied to PFS of Rm and BR Applied to PFS of ZANU from year 5
0.36	IBRU+R arm of iNNOVATE	Applied to PFS of ZANU to year 5

Source: Section 3.2.7.1.2, p176-177 of the resubmission

BR=bendamustine + rituximab, HR=hazard ratio, IBRU+R=ibrutinib + rituximab, PFS=progression free survival, Rm=rituximab monotherapy, ZANU=zanubrutinib

Figure 7: TTNT curves compared to PFS, OS

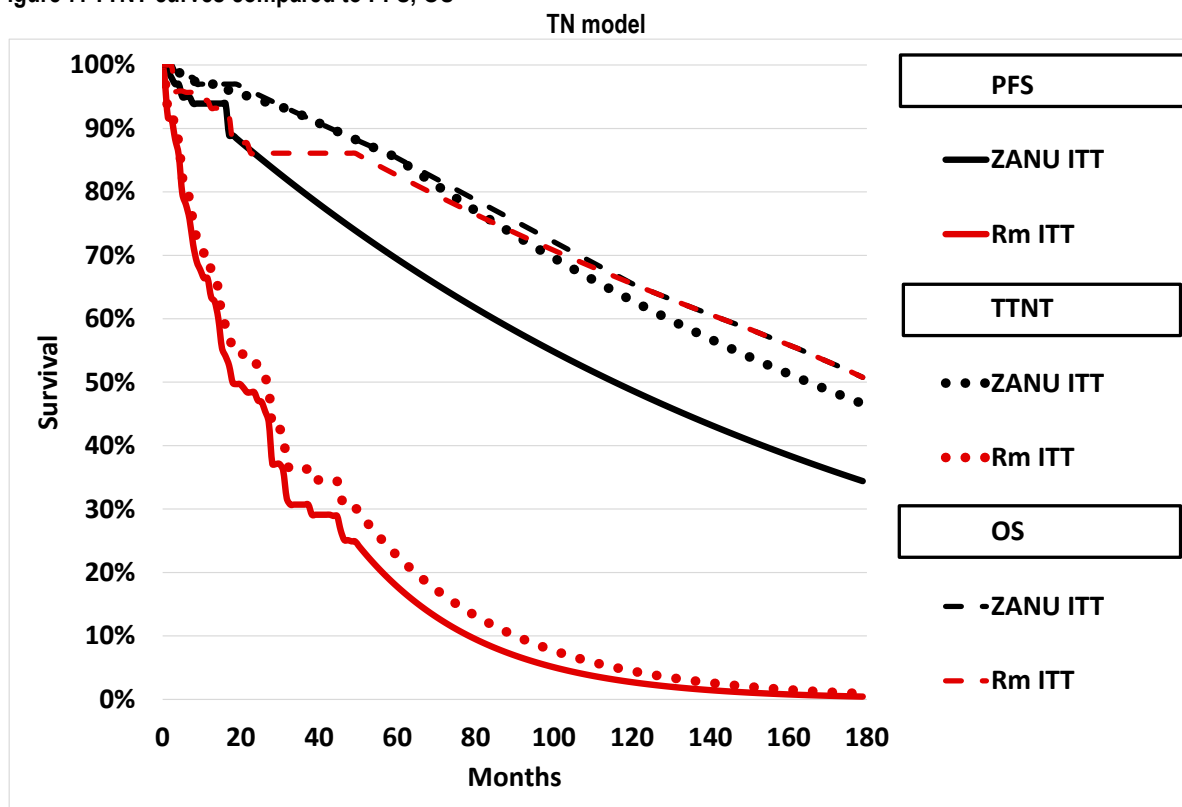


Figure 8: TTNT curves compared to PFS, OS

Notes: TTNT, PFS and OS as modelled. TTNT and PFS cannot exceed the OS base case. KM data used to median follow up, 18 months (PFS) to 19.5 months (OS) for ZANU, 19 months for BR, 50 months for Rm.

Source: compiled during the evaluation using the Excel workbook 'Zanubrutinib\_WM\_NOV\_2021\_Resubmission\_S3\_Final\_Macros.xlsm' BR=bendamustine + rituximab, ITT=intention to treat, KM=Kaplan–Meier; OS=overall survival, PFS=progression free survival, R/R=relapsed/refractory, Rm=rituximab monotherapy, TN=treatment naive, TTNT=time to next treatment, ZANU=zanubrutinib

6.63 The FRP workshop considered that the use of IBRU+R TTNT data as proxy for zanubrutinib could be reasonable if assessed for clinical plausibility. The evaluation considered that the clinical plausibility of IBRU+R TTNT data as proxy for zanubrutinib, and ITT Rm TTNT data as a proxy for Rm (TN) and BR (R/R), was not well justified, and may overestimate the effect of zanubrutinib while underestimating that for the comparator, particularly BR. If the comparator TTNT HRs were assumed equal to zanubrutinib (0.36), the ICERs increased to \$95,000 to < \$115,000 and \$75,000 to < \$95,000 per QALY gained in the TN and R/R models, respectively. TTNT was less influential on zanubrutinib as only a small proportion of patients were expected to experience disease progression. When the zanubrutinib TTNT HRs were assumed equal to the comparators (0.86), the ICERs increased to \$75,000 to < \$95,000 and \$55,000 to < \$75,000 per QALY gained in the TN and R/R models respectively.

#### Utilities

6.64 Health state utilities were revised for the resubmission to reflect the additional modelled health states. Relative decrements based on data from Kosmas 2015, were

applied to an anchor health state. Kosmas 2015 reported utilities for health states in CLL.

- 6.65 Utility data reported by ASPEN (divided into TN and R/R subgroups for each economic model and mapped to EQ-5D-3L) was assumed to represent PF on treatment and PF off treatment (the chosen anchor state), and zanubrutinib was assumed to have no treatment-related utility decrement. The evaluation considered it might have been more appropriate to assume some utility decrement from ongoing treatment with zanubrutinib compared to patients experiencing PF without treatment. While treatment with zanubrutinib may be expected to be associated with better quality of life than comparator treatments, the resubmission did not justify the magnitude of the expected utility benefit, nor why it would be equivalent to PF off treatment in the comparator arm. Treatment with zanubrutinib was associated with adverse events such as AF, neutropenia and major haemorrhage, however not all AEs were expected to have been captured given the short duration of the trials, and there may be repeated events or new events with longer term treatment.
- 6.66 A summary of the Kosmas 2015 utilities and the utilities applied in the economic evaluations is provided in Table 15 and Table 16 below.

**Table 15: Utility values from Kosmas 2015 used in the resubmission**

Health state in Kosmas 2015	TTO mean utility (95% CI)	Use in TN model	Use in R/R model
PFS 1L oral therapy	0.71 (0.67, 0.75)	Not used	N/A
PFS 1L IV therapy	0.67 (0.63, 0.71)	Absolute decrement from anchor state (0.15) for treatment with Rm	N/A
PFS 1L requiring hospital treatment more than once during each course of treatment	0.55 (0.50, 0.61)	Not used	N/A
PFS after therapy	0.82 (0.78, 0.85)	Anchor state for TN model	N/A
Progression after 1L (no treatment)	0.66 (0.62, 0.71)	Absolute decrement from anchor state (0.16) for PDW	N/A
PFS 2L therapy	0.55 (0.50, 0.60)	Absolute decrement from anchor state (0.27) for PDT	Absolute decrement from anchor state (0.16) for treatment with BR
PFS after 2L therapy	0.71 (0.66, 0.75)	Not modelled	Anchor state for R/R model
Progression after 2L	0.59 (0.55, 0.64)	Not modelled	Absolute decrement from anchor state (0.12) for PDW
Relapsed (progression after 3+ lines of treatment)	0.42 (0.37, 0.47)	Not modelled	Absolute decrement from anchor state (0.29) for PDT

Source: pp213-215 and pp249-250 of the resubmission and Kosmas CE, Shingler SL, Samanta K, Wiesner C, Moss PA, Becker U, Lloyd AJ. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. *Leuk Lymphoma*. 2015 May; 56(5): 1320-6.

1L=first line, 2L=second line, BR=bendamustine + rituximab, CI=confidence interval, IV=intravenous, N/A=not applicable, PDT=progressive disease requiring treatment, PDW=progressive disease without treatment, PFS=progression-free survival, R/R=relapsed/refractory, Rm=rituximab monotherapy, TN=treatment naive, TTO=time trade off, ZANU=zanubrutinib

**Table 16: Utility values applied in the economic evaluation**

Model	Health state	Utility value	Source	Previous submission	Source
TN	PF on treatment ZANU	0.754	Assumed equal to PF off treatment	0.791	ASPEN pooled pre-progression data mapped to EQ-5D-3L
	PF on treatment Rm	0.604	Decrement of 0.15 from PF off treatment		
	PF off treatment (anchor)	0.754	ASPEN TN pre-progression data mapped to EQ-5D-3L		
	PDW	0.594	Decrement of 0.16 from PF off treatment	0.691	Assumed decrement 0.10 from NHL studies
	PDT	0.484	Decrement of 0.27 from PF off treatment		
R/R	PF on treatment ZANU	0.798	Assumed equal to PF off treatment	0.791	ASPEN pooled pre-progression data mapped to EQ-5D-3L
	PF on treatment BR	0.638	Decrement of 0.16 from PF off treatment		
	PF off treatment (anchor)	0.798	ASPEN R/R pre-progression data mapped to EQ-5D-3L		
	PDW	0.678	Decrement of 0.12 from PF off treatment	0.691	Assumed decrement 0.10 from NHL studies
	PDT	0.508	Decrement of 0.29 from PF off treatment		

Note: The submission reported PFS utility value of 0.7908, but 0.791 was hardcoded into both the current and previous models

Source: p214 and p250 from resubmission, and pp155-156 of the July 2021 submission, Worksheet 'Utilities' in Excel workbook 'Section3\_CEM\_Zanubrutinib\_WM\_Final\_Rm\_PFS\_Toggle.xlsm'

EQ-5d=EuroQol 5-dimensions quality of life questionnaire; LS=least squared, NHL=non-Hodgkin lymphoma, PF =progression free, PDT=progressive disease requiring treatment, PDW=progressive disease without treatment.

- 6.67 Because the zanubrutinib arms accrued the majority of life years in PF on treatment and the comparators in progressive disease (either requiring or without treatment), it was the difference in utility between these health states that drove model results, particularly in the TN model, where modelled survival was similar between zanubrutinib and Rm.
- 6.68 Adverse events were unchanged from the July 2021 submission, with a one-off cost and utility decrement applied in the first cycle, except for major haemorrhage which was assumed to occur in 5.94% patients receiving zanubrutinib. Major haemorrhage was stated to incur both a one-off cost and disutility as per the other adverse events, but only the cost was incorporated into the submitted model. The evaluation updated the economic analysis to also include the disutility.

### Costs

- 6.69 The per cycle cost of zanubrutinib was based on the proposed DPMQ of \$ [REDACTED] for 120 x80 mg capsules, at a dose of 320 mg per day, every day until toxicity or disease progression, with dose intensity 97.6%. The resulting modelled dose was 312 mg per day.
- 6.70 Comparator drug and administration costs plus routine care costs were modelled as for the July 2021 submission but were updated to latest PBS/MBS prices. Like the July 2021 submission, the resubmission did not account for early discontinuation or dose reduction of rituximab or bendamustine, which would result in reduced costs in the comparator arms.
- 6.71 The model assumed 86% of patients in all arms that moved into progressive disease requiring treatment would receive subsequent treatment. Subsequent treatment costs were calculated as two courses of first-line comparator treatment, equivalent to 8.39 months of Rm in the TN model (\$4,447.07) and 10.6 months of BR in the R/R model (\$33,032.07).
- 6.72 A small cost was introduced in the resubmission for major haemorrhage at \$86.70 per episode, based on MBS item 13706. Major haemorrhage is more likely to be a hospitalisation cost. This substantially underestimated the true cost of treating major haemorrhage but was unlikely to have a large impact on the model results as AEs had little impact on the ICER.

### Results

- 6.73 Key drivers of the model are presented in Table 17 below.

**Table 17: Key drivers of the model – base case: TN \$ [redacted]<sup>1</sup>/QALY gained, R/R \$ [redacted]<sup>2</sup>/QALY gained**

Description	Method/Value	Impact
Time horizon	15 years vs 19.5 months follow up in ASPEN, 50 months in iNNOVATE and 19 months in Tedeschi 2015*	High, favoured ZANU. A reduction in the time horizon increased the ICER significantly, particularly in the TN model. Assuming a 10-year time horizon increased the ICERs to \$ [redacted] <sup>3</sup> per QALY gained in the TN model and \$ [redacted] <sup>2</sup> per QALY gained in the R/R model.
Health state utilities	Anchor state based on ASPEN, utility decrements for other states based on Kosmas 2015	High, favoured ZANU. Treatment with ZANU was not expected to accrue a utility decrement, unlike the comparator treatments. Furthermore, as more patients in the comparator arms were expected to progress and receive further treatment compared to ZANU, the difference in the utility between these health states drove the model, particularly the TN model where little survival benefit was estimated.
Treatment duration	No cost of treatment was applied beyond [redacted] months (based on proposed financial stopping rule)	High, favoured ZANU. The stopping rule mitigated the high cost of treatment associated with long treatment durations predicted by the model. Without the stopping rule, the ICERs increased to \$ [redacted] <sup>4</sup> and \$ [redacted] <sup>5</sup> per QALY gained in the TN and R/R models respectively.
Use of KM data	KM data was used until median follow up for each outcome, followed by extrapolations	Moderate, favoured ZANU, particularly as the KM data for OS for ZANU lay above the extrapolation curve when extrapolation commenced, such that both later and earlier cut-offs could result in moderately increased ICERs.
PFS extrapolation	Extrapolations of ASPEN, iNNOVATE and Tedeschi 2015 applied from median follow up in each study	Moderate, favoured ZANU. Majority of incremental LYs for ZANU versus Rm and BR were accrued in PF states, which have higher utilities. The data used in the resubmission to inform the extrapolations were uncertain, using ITT data (which included a proportion of R/R patients for ZANU and Rm in the TN model and a proportion of TN patients for ZANU in the R/R model). There were also differences between all the included studies affecting exchangeability and thus the reliability of the ITC results.
OS extrapolation	Extrapolations of ASPEN, iNNOVATE and Tedeschi 2015 applied from median follow up in each study. Linear convergence applied to ZANU OS from Year 5 and ZANU OS assumed equal to comparator from Year 10	High, favoured ZANU. Convergence from Year 5 mitigated some of the sustained survival benefits, but a survival benefit of ZANU versus the comparators was still assumed, particularly in the R/R model.  The survival data from included studies remained immature. This was more uncertain for OS than PFS.  The models were sensitive to an assumption of no survival gain, particularly for the R/R setting.
TTNT extrapolation	Based on the relationship between PFS and TTNT from iNNOVATE 0.36 ZANU Years 1-5 0.86 ZANU Year 5 onwards, Rm and BR Year 1 onwards	Moderate, favoured ZANU. A longer delay between progression and subsequent treatment resulted in more QALYs and fewer subsequent treatment costs in the ZANU arms of both models.

Source: compiled during the evaluation

\* Median follow-up reported

BR=bendamustine+rituximab, ICER=incremental cost-effectiveness ratio, ITT=intention to treat, KM=Kaplan–Meier, LY=life-year, OS=overall survival, PFS=progression-free survival, QALY=quality adjusted life year, R/R=relapsed/refractory, Rm=rituximab monotherapy TN=treatment naive, WM=Waldenström macroglobulinemia, Yr=year, ZANU=zanubrutinib

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$155,000 to < \$255,000

<sup>5</sup> \$135,000 to < \$155,000

6.74 Summary results for the economic analysis, and corresponding results from the July 2021 submission are presented below. Results were updated for the March 2022 resubmission during the evaluation to correct for a coding error with the financial stopping rule and to include the disutility for major haemorrhage, which the resubmission stated was included but had not been coded into the model.

Table 18: Results of the stepped economic evaluation TN model<sup>^</sup>

Model	July 2021 submission			Resubmission		
Step and component	ZANU	Rm	Increment	ZANU	Rm	Increment
<b>Step 1: Time horizon captures trial length (set to 3 years)</b>						
Costs	\$█	\$32,799	\$█	\$█	\$25,372	\$█
LYG	2.83	2.54	0.29	2.88	2.72	0.16
<b>Incremental cost/ LY gained</b>			<b>\$█<sup>1</sup></b>	<b>Incremental cost/LY gained</b>		
				<b>\$█<sup>2</sup></b>		
<b>Step 2: time horizon extended to 20 years</b>				<b>Step 2: Time horizon extended to 15 years</b>		
Costs	\$█	\$79,845	\$█	\$█	\$56,859	\$█
LYG	13.57	7.69	5.88	11.31	11.00	0.31
<b>Incremental cost/LY gained</b>			<b>\$█<sup>3</sup></b>	<b>Incremental cost/LY gained</b>		
				<b>\$█<sup>4</sup></b>		
<b>Step 3: discounting (5%) included</b>						
Costs	\$█	\$63,866	\$█	\$█	\$45,928	\$█
LYG	9.54	5.95	3.60	8.56	8.29	0.27
<b>Incremental cost/LY gained</b>			<b>\$█<sup>3</sup></b>	<b>Incremental cost/LY gained</b>		
				<b>\$█<sup>5</sup></b>		
<b>Step 4: utility weights applied</b>						
Costs	\$█	\$63,866	\$█	\$█	\$45,928	\$█
QALYs	7.37	4.32	3.04	6.19	4.64	1.55
<b>Incremental cost/QALY gained (base case)</b>			<b>\$█<sup>6</sup></b>	<b>Incremental cost/QALY gained</b>		
				<b>\$█<sup>7</sup></b>		
<b>Step 5: Financial stopping rule applied</b>						
Costs	-	-	-	\$█	\$45,928	\$█
QALYs	-	-	-	6.19	4.64	1.55
				<b>Incremental cost/ QALY gained (base case)</b>		
				<b>\$█<sup>6</sup></b>		

Source: Calculated during the evaluation and Table 3.8.2 of zanubrutinib commentary July 2021.

BR=bendamustine-rituximab, LY=life years, QALY=quality adjusted life years, Rm=rituximab monotherapy, ZANU=zanubrutinib

<sup>^</sup> March 2022 results recalculated to account for major haemorrhage disutility and financial stopping rule.

The redacted values correspond to the following ranges:

<sup>1</sup> \$355,000 to < \$455,000

<sup>2</sup> \$655,000 to < \$755,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$955,000 to < \$1,055,000

<sup>5</sup> \$855,000 to < \$955,000

<sup>6</sup> \$75,000 to < \$95,000

<sup>7</sup> \$155,000 to < \$255,000

Table 19: Results of the stepped economic evaluation R/R model<sup>^</sup>

Model	July 2021			Resubmission		
Step and component	ZANU (matched)	BR	Increment	ZANU (matched)	BR	Increment
<b>Step 1: Time horizon captures trial length (set to 3 years)</b>						
Costs	\$█	\$53,011	\$█	\$█	\$67,615	\$█
LYG	2.84	2.54	0.30	2.91	2.52	0.39
<b>Incremental cost/ LY gained</b>			<b>\$█<sup>1</sup></b>	<b>Incremental cost/ LY gained</b>		
<b>Step 2: time horizon extended to 20 years</b>			<b>Step 2: time horizon extended to 15 years</b>			
Costs	\$█	\$100,057	\$█	\$█	\$126,101	\$█
LYG	13.79	7.69	6.10	8.89	7.13	1.76
<b>Incremental cost/ LY gained</b>			<b>\$█<sup>3</sup></b>	<b>Incremental cost/ LY gained</b>		
<b>Step 3: discounting (5%) included</b>						
Costs	\$█	\$84,079	\$█	\$█	\$108,169	\$█
LYG	9.68	5.95	3.73	7.13	5.70	1.43
<b>Incremental cost/ LY gained</b>			<b>\$█<sup>4</sup></b>	<b>Incremental cost/ LY gained</b>		
<b>Step 4: utility weights applied</b>						
Costs	\$█	\$84,079	\$█	\$█	\$108,169	\$█
QALYs	7.42	4.52	2.90	5.58	4.07	1.51
<b>Incremental cost/ QALY gained (base case)</b>			<b>\$█<sup>6</sup></b>	<b>Incremental cost/ QALY gained</b>		
<b>Step 5: Financial stopping rule applied</b>						
Costs	-	-	-	\$█	\$108,169	\$█
QALYs	-	-	-	5.58	4.07	1.51
				<b>Incremental cost/QALY gained (base case)</b>		
				<b>\$█<sup>4</sup></b>		

Source: Calculated during the evaluation and Table 3.8.2 of zanubrutinib commentary July 2021

BR=bendamustine-rituximab, LY=life years, QALY=quality adjusted life years, Rm=rituximab monotherapy, ZANU=zanubrutinib

<sup>^</sup> March 2022 results recalculated to account for major haemorrhage disutility and financial stopping rule.

The redacted values correspond to the following ranges:

<sup>1</sup> \$255,000 to < \$355,000

<sup>2</sup> \$155,000 to < \$255,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$55,000 to < \$75,000

<sup>5</sup> \$135,000 to < \$155,000

<sup>6</sup> \$75,000 to < \$95,000

6.75 Key sensitivity analyses are summarised below.

Table 20: Results of model scenario analyses

Model	TN ZANU vs Rm			R/R ZANU (matched) vs BR		
	Incre Cost (\$)	Incre QALY	ICER (\$)	Incre Cost (\$)	Incre QALY	ICER (\$)
<b>Base case (corrected)<sup>^</sup></b>	█	1.548	█ <sup>1</sup>	█	1.513	█ <sup>2</sup>
Discounting (base 5% costs & QALYs)						
• Both 0%	█	2.108	█ <sup>2</sup>	█	1.927	█ <sup>2</sup>
• Both 3.5%	█	1.689	█ <sup>1</sup>	█	1.621	█ <sup>2</sup>
Time horizon (base 15 years)						
• 5 year	█	0.647	█ <sup>3</sup>	█	0.779	█ <sup>4</sup>
• 10 year	█	1.209	█ <sup>4</sup>	█	1.402	█ <sup>2</sup>
• 20 year	█	1.740	█ <sup>1</sup>	█	1.575	█ <sup>2</sup>
Start of extrapolation (base=median follow up)						
• KM data to 30 months (all arms)	█	1.573	█ <sup>1</sup>	█	1.367	█ <sup>2</sup>

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Model	TN ZANU vs Rm			R/R ZANU (matched) vs BR		
	Incre Cost (\$)	Incre QALY	ICER (\$)	Incre Cost (\$)	Incre QALY	ICER (\$)
<b>Analyses</b>						
<b>Base case (corrected)^</b>		1.548	█ <sup>1</sup>		1.513	█ <sup>2</sup>
• Extrapolation time 0		1.488	█ <sup>1</sup>		1.386	█ <sup>2</sup>
• KM cut off 10% data remaining		1.383	█ <sup>1</sup>		1.196	█ <sup>1</sup>
• KM cut off 20% data remaining		1.400	█ <sup>1</sup>		1.328	█ <sup>2</sup>
<b>OS convergence (base linear from year 5 to 10)</b>						
• Linear from 7.5 years to 10 years		1.568	█ <sup>1</sup>		1.754	█ <sup>5</sup>
• Comparator hazard rate from 30 months#		1.519	█ <sup>1</sup>		1.462	█ <sup>2</sup>
• No difference after KM (ZANU=Rm/BR)#		1.405	█ <sup>4</sup>		0.561	█ <sup>3</sup>
<b>TTNT HR (ZANU=0.36 to Yr 5 then 0.86, Rm/BR=0.86)</b>						
• HR=0.86 for ZANU, Rm and BR from Time 0#		1.447	█ <sup>1</sup>		1.422	█ <sup>2</sup>
• HR=0.36 for ZANU always (no hazard convergence)		1.567	█ <sup>1</sup>		1.514	█ <sup>2</sup>
• HR=1 (no delay to next treatment)		1.442	█ <sup>1</sup>		1.466	█ <sup>2</sup>
<b>Utilities (base anchor PF off treatment = PF on treatment with ZANU)</b>						
• Assume utility decrement with oral therapy for ZANU#		0.990	█ <sup>6</sup>		1.060	█ <sup>1</sup>
• PFS and PD utilities as in the July 2021 submission		0.651	█ <sup>3</sup>		1.219	█ <sup>1</sup>
• No difference between TN and R/R from ASPEN		1.558	█ <sup>1</sup>		1.505	█ <sup>2</sup>
• WhiMSICAL difference between treatments		1.513	█ <sup>1</sup>		1.453	█ <sup>2</sup>
• WhiMSICAL as on treatment utility adjusted by Kosmas 2015 (non-BTKi therapy anchor state) #		1.015	█ <sup>6</sup>		0.792	█ <sup>6</sup>
<b>ZANU financial stopping rule (cost cap) (base █ months)</b>						
• No stopping rule		1.548	█ <sup>3</sup>		1.513	█ <sup>7</sup>
• 38 months#		1.548	█ <sup>2</sup>		1.513	█ <sup>5</sup>
• 60 months#		1.548	█ <sup>4</sup>		1.513	█ <sup>1</sup>
<b>TTD extrapolation (ZANU exp TTD data)</b>						
• Set equal to PFS#		1.548	█ <sup>4</sup>		1.513	█ <sup>2</sup>
<b>Comparator in R/R model (base BR)</b>						
• DRC*#	N/A	N/A	N/A		1.513	█ <sup>1</sup>
<b>Subsequent treatment cost (86% pts, 2 lines of comparator)</b>						
• One subsequent line of treatment#		1.548	█ <sup>1</sup>		1.513	█ <sup>2</sup>
• 100% patients#		1.548	█ <sup>1</sup>		1.513	█ <sup>2</sup>
<b>Multivariate analyses (MA)</b>						
MA1: KM cut-off 10% data remaining, no survival difference after KM, DRC comparator in R/R model#		1.430	█ <sup>1</sup>		0.624	█ <sup>3</sup>
MA2: KM cut-off 10% data remaining, utility decrement with for ZANU, DRC comparator in R/R model#		0.813	█ <sup>3</sup>		0.700	█ <sup>3</sup>

Source: Tables 3-32, 3-47 of the resubmission and compiled during the evaluation. Results include corrected financial stopping rule duration and include disutility for major haemorrhage. The resubmission also presented alternative discounting scenarios, not presented here for brevity.

BR=bendamustine+rituximab, DRC=dexamethasone+rituximab+cyclophosphamide, exp=exponential, HR=hazard ratio, Incre=incremental, ICER=incremental cost-effectiveness ratio, Indep=independent, m=months, OS=overall survival, PFS=progression free survival,

QALY=quality adjusted life year, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, TTD=time to treatment discontinuation, vs=versus, y=years, ZANU=zanubrutinib.

\* assuming similar efficacy to BR but with lower cost, cost of DRC based on eviQ estimate for WM of \$1,490 per 21 day cycle for 6 cycles  
Source: <https://www.eviq.org.au/haematology-and-bmt/lymphoma/waldenstrom-macroglobulinaemia/1654-waldenstrom-macroglobulinaemia-drc-dexametha> Administration costs were reduced by 1/3 to reflect the 2 infusions per cycle compared to the 3 in BR. As with base case, 2 cycles of DRC assumed in subsequent treatment

^ Resulted recalculated to account for major haemorrhage disutility and financial stopping rule

# Conducted by the evaluation

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$155,000 to < \$255,000

<sup>4</sup> \$95,000 to < \$115,000

<sup>5</sup> \$45,000 to < \$55,000

<sup>6</sup> \$115,000 to < \$135,000

<sup>7</sup> \$135,000 to < \$155,000

6.76 Sensitivity analyses indicated that the model was most sensitive to time horizon, OS extrapolation (including KM data cut-off), utilities, comparator choice and the financial stopping rule. Multivariate analyses focusing on either survival or utility uncertainty (together with a later KM data cut-off and the more conservative DRC treatment costs replacing BR in the R/R model) supported the conclusions of the univariate sensitivity analyses i.e. for the TN model the ICER was relatively insensitive to cumulative changes in OS, but very sensitive to changes in the health state utilities, whereas for the R/R model the ICER was sensitive to both.

6.77 The ESC noted that overall, the uncertainties with the models were due to the paucity of data available for WM and these uncertainties were unlikely to be reduced substantially by any future clinical trial data or further adjustments to models.

### Drug cost/patient/month

Table 21: Summary cost per patient with zanubrutinib

	ASPEN	TN model	R/R model	Financials
Dose	312 mg per day <sup>a</sup>	312 mg per day <sup>a</sup>	312 mg per day <sup>a</sup>	312 mg per day <sup>a</sup>
Total dose per month	9,510 mg	9,510 mg	9,510 mg	9,510 mg
Time on treatment per patient (months) as reported in the submission	NR (median not reached)	36.90	36.51	
Time on treatment per patient (months) calculated from model during evaluation	N/A	37.45	37.05	N/A
Total cost of treatment per patient	N/A	\$ <sup>b</sup>	\$ <sup>b</sup>	\$ <sup>b</sup>
Cost of treatment per patient per month	N/A	\$ <sup>b</sup>	\$ <sup>b</sup>	\$ <sup>b</sup>

Source: Tables 3-28 and 3-43 of resubmission and compiled during the evaluation.

Notes: Submission and model time on treatment could not be matched for the 'with financial stopping rule' applied. Results presented here use values calculated from the model. Costs and time on treatment are undiscounted.

<sup>a</sup> 320 mg at dose intensity 97.6%

<sup>b</sup> includes [redacted] month financial stopping rule. Model costs include corrected implementation of the stopping rule.

AE=adverse event, BR=bendamustine + rituximab, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, ZANU=zanubrutinib.

### Estimated PBS usage & financial implications

6.78 Like the July 2021 submission, the resubmission used an epidemiological approach to estimate the financial impact of listing zanubrutinib. For the July 2021 submission, the

PBAC had expressed concern that the financial impact of listing zanubrutinib on the PBS was underestimated due to underestimates for the numbers of eligible patients and uptake, duration of treatment and inappropriate cost offsets for non-PBS subsidised treatments (paragraph 7.15, zanubrutinib PSD, July 2021).

- 6.79 The PBAC had agreed with the consumer hearing comments that uptake for zanubrutinib would be high, particularly in the relapsed/refractory setting, as patients and clinicians would prefer to limit treatment with cytotoxic chemotherapy (paragraph 7.15, zanubrutinib PSD, July 2021).
- 6.80 The resubmission made the following changes compared to the July 2021 submission:
- Prevalent population calculated for second line or later (2L+) use in Year 1 increased from < 500 in the July 2021 submission to < 500.
  - Treatment duration was adjusted to account for the financial stopping rule proposed by the sponsor (| months). However, with financial stopping rule applied, the treatment duration in the economic models was ~37 months as this accounted for discontinuations. The financial estimates were adjusted in the pre-PBAC response to account for discontinuations, as per the ESC's advice that the estimates and model should be consistent.
  - Uptake rate in Years 4-6 increased to |% (previously |%).
  - Cost offsets for non-PBS listed treatments were removed. Treatment cost offsets now included in the resubmission were filgrastim (associated with neutropenia treatment), cyclophosphamide (5% IV and 14% oral R/R regimens), and chlorambucil (16% TN regimens). Filgrastim is available on the PBS for chemotherapy-induced neutropenia.
  - MBS item 13706 (\$86.70) was proposed as the cost for bleeding events, which were previously not included. Likely a substantial underestimate.
- 6.81 The parameters and data sources applied in the financial analysis are presented in the table below.

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Table 22: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	July 2021	Source	Comment
<b>Eligible population</b>				
Incident patients (1L)	No change	Yr 1: 1 Yr 2: 1 Yr 3: 1 Yr 4: 1 Yr 5: 1 Yr 6: 1	Estimated using a WM incidence rate of 0.37 per 100,000 (AIHW 2017, Code C88 stated). This was then applied to projected population based on ABS statistics and adjusted for PBS eligibility: - % treated (70-80%) - sponsor's market research (increased over time) - % unsuitable for CIT (30%) - sponsor's market research	Verifiable data sources and calculations were reasonable. WM incidence could not be verified, AIHW Code C88 refers to immunoproliferative cancers but does not specify WM subset.  Grandfathered patients were updated in the pre-PBAC response.
Incident patients (2L+)	Yr 1: [redacted] <sup>a1</sup> Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	Estimated using a WM incidence rate of 0.37 per 100,000 (AIHW 2017, Code C88 stated). Incidence was then applied to projected population from 2 years prior to year of interest based on ABS statistics and adjusted for PBS eligibility, from Year 2 onwards. For Year 1, the resubmission used a prevalence rate of 1.22 per 100,000 (assumed 1.5% of 5-year prevalence of NHL, AIHW 2021, Code C82-86) and adjusted for PBS eligibility and then removed grandfathered ([redacted]) patients. PBS eligibility: - % treated (70-80%) - sponsor's market research - % progress 2L (62%) - sponsor's market research - % survive to 2L (90%) - Castillo et al. 2015 - % BTKi naïve (80%) - sponsor's market research	
Total patients eligible to initiate treatment	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	Incident patients 1L and 2L+ combined	Reasonable. Year 2 estimate was previously 52 in the July 2021 submission.
Grandfathered	Yr 1: [redacted]	[redacted]	Estimated by sponsor	Updated in pre-PBAC response.

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Data	Value	July 2021	Source	Comment
<b>Treatment utilisation</b>				
Uptake rate (1L and 2L+)	Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4-6: █ %	█ % █ % █ % █ %	Uptake (█-█ %) - sponsor's market research to year 3 (increase over time) Years 4-6 assumed patient preference for oral therapy	Reasonable, though given the indolent nature of the disease, patients are likely to cycle through all available treatments during their lifetimes. Therefore, patients might choose an alternative treatment initially but go on to ZANU as a later line.
Number initiating treatment	Yr 1: █ Yr 2: █ Yr 3: █ Yr 4: █ Yr 5: █ Yr 6: █	█ █ █ █ █ █	Total eligible multiplied by uptake rate plus 100% of grandfathered patients	Calculations were arithmetically correct.
Scripts dispensed	Yr 1: █ Yr 2: █ Yr 3: █ Yr 4: █ Yr 5: █ Yr 6: █	█ █ █ █ █ █	Incident patient months based on an assumed time on treatment of █ months, multiplied by 11.89 scripts per year (1 script=1 pack of 120 capsules, 4 capsules per day) 100% compliance was assumed	The time on treatment was based on financial stopping rule. Grandfathered patients were assumed to have received 6 months of treatment prior to financial analysis
Subsequent treatments	Not costed	Not costed	Subsequent treatment was not discussed in the financial estimates section.	ZANU represents an additional line of therapy, i.e. may displace rather than replace other treatments. The costs of these treatments are expected to accrue following ZANU treatment, but their exclusion is largely consistent with the economic evaluation in that virtually no patients prior to Year 5 were expected to receive subsequent treatment after zanubrutinib in either model.

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Data	Value	July 2021	Source	Comment
<b>Costs</b>				
ZANU	\$█ per 30-day supply	\$█ per 28-day supply	DPMQ (effective) set equal to effective price in MCL. 120x 80 mg capsules equal a 30-day supply when 97.6% dose intensity assumed	The resubmission assumed a compliance of 84% for all substituted therapies, the source of this estimate is unknown as it was not discussed in the resubmission.
Filgrastim	No changes to values	\$642.41	PBS codes 5742F, 6291D SC daily for up to 2 weeks per episode. Total 14 doses. 13.9% ZANU pts expected to receive for neutropenia, compliance 84%, scripts/yr 0.59	Price used for filgrastim was based on PBS items 5741E and 6126K (1 mL injections) rather than the nominated 0.5 mL injections (5742F and 6291D) with DPMQ \$345.08. Only subsidised for use with chemotherapy.
Cyclophosphamide (oral)		\$155.65	PBS code 1266P 100 mg/m <sup>2</sup> twice daily (average dose <sup>b</sup> 200 mg) for 5 days every 4 weeks for 6 cycles, for total 30 doses of 8 tabs/dose. 14% R/R pts received oral cyclophosphamide. Compliance 84%, scripts/yr 4.03.	Average dose was calculated using an average BSA of 1.86 m <sup>2</sup> for all substituted treatments, but the effective BSA used was 2 m <sup>2</sup> (doses rounded up).
Cyclophosphamide (IV)		\$187.20	PBS codes 4327R, 7226H 250 mg/m <sup>2</sup> (average dose <sup>b</sup> : 500 mg) for 3 days every 4 weeks for 6 cycles. Total 18 doses. 5% of R/R pts, compliance 84%, scripts/yr 15.12.	
Chlorambucil		\$135.30	PBS code 1163F 8 mg/m <sup>2</sup> for 10 days every 4 weeks for a maximum 12 cycles. Total 120 doses. 16% 1L pts, compliance 84%, scripts/year 8.06	
R/PBS split		97.41%: 2.59%	Based on existing PBS Item statistics for bendamustine for indolent non-Hodgkin's lymphoma Jan 2020-Dec 2020	
Public/ private split		28.6%: 71.4%		
Patient copayment		\$22.20 PBS \$6.15 RPBS	Average copay was based on the current weighted mean copayment of bendamustine for non-Hodgkin's lymphoma	Reasonable.
MBS costs	\$36.00 per episode of Grade 3-4 neutropenia  \$138.72 per episode of major haemorrhage	\$36.00 per episode of Grade 3-4 neutropenia  NA	MBS: 119 (80% fee) specialty consultant physician minor attendance for patients experiencing Grade 3-4 neutropenia, from ASPEN (13.9%).  MBS 13706 (80% fee) administration of blood or bone marrow already collected for patients experiencing major haemorrhage, from ASPEN (5.94%). 2 services assumed (\$69.36 x2=\$138.72, 80% fee)	The resubmission used the ASPEN data as annual incidence of neutropenia and major haemorrhage while receiving treatment. This differed from the economic evaluation where they were assumed to occur once per patient. Other adverse events were not included.  Cost of major haemorrhage appeared low, but likely to be a hospitalisation cost.  The submission also did not estimate a reduction in administration costs (all comparators are provided intravenously, whereas ZANU is an oral therapy).  The PBAC considered that the impact of these inconsistencies was relatively minor and balanced across treatments.

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1L=first-line treatment, 2L=second-line treatment, BTKi=Bruton's tyrosine Kinase inhibitor, copay(s)=copayment(s), CIT=chemo-immunotherapy, DPMQ=dispensed price for maximum quantity, R/R=relapsed/refractory, TN=treatment naïve, TTD=time to treatment discontinuation, yr=year, ZANU=zanubrutinib

Source: Tables 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7, 4-8, 4-13, 4-14, 4-21 of the resubmission and Table 4.1.1 of the July 2021 commentary.

<sup>a</sup> Australian population in 2020 x 1.22/100000=316 prevalent WM x eligibility criteria = < 500 eligible patients - < 500 grandfathered = < 500

<sup>b</sup> Based on the submission's assumed average patient body surface area of 1.86 m<sup>2</sup> used to calculate the quantity administered for chemo-immunotherapies.

Blue shading represents information previously considered by the PBAC

*The redacted values correspond to the following ranges:*

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5000

6.82 The net cost to the PBS/RPBS was estimated to be approximately \$50 million to < \$60 million over the first 6 years of listing (increased from \$30 million to < \$40 million in the July 2021 submission).

**Table 23: Estimation of use and financial impact of the proposed medicine**

	2022	2023	2024	2025	2026	2027
<b>Estimation of number of treated patients</b>						
<b>1L WM</b>						
Incident WM population	1	1	1	1	1	1
Total 1L patients eligible	1	1	1	1	1	1
Total 1L patients treated with ZANU	1	1	1	1	1	1
<b>R/R WM (pts diagnosed 2yrs prior)</b>						
Incident WM	-	1	1	1	1	1
Prevalent WM	316					
Total 2L+ patients eligible	1	1	1	1	1	1
Total 2L+ patients treated with ZANU	1	1	1	1	1	1
<b>Grandfathered</b>						
Total patients initiate ZANU	1	1	1	1	1	1
Total patients initiate ZANU July 2021	1	1	1	1	1	1
Total patients treated ZANU	1	1	1	1	1	1
Total patients treated ZANU July 2021	1	1	1	1	1	1
<b>Estimated number of ZANU scripts (PBS/RPBS)</b>						
1L	1	1	2	2	2	2
2L+	1	2	2	2	2	2
Grandfathered	2	2	2	1	1	1
<b>Total ZANU scripts</b>	2	2	2	2	2	2
<b>Total ZANU scripts July 2021</b>	2	2	2	2	2	2
<b>Estimated effective cost of ZANU to PBS/RPBS (less copay)</b>						
Net cost ZANU (\$)	3	3	3	4	3	4
Net cost ZANU July 2021 (\$)	3	3	3	3	3	3
<b>Estimation financial implications for currently listed treatments</b>						
<b>Total cost offset to PBS/RPBS (\$)</b>	-3	-3	-3	-3	-3	-3
<b>Total cost offset to PBS/RPBS July 2021 (\$)</b>	-3	-3	-3	-3	-3	-3
<b>Estimated financial implications for the PBS/RPBS and the health budget</b>						
Net cost PBS/RPBS (\$)	3	3	3	4	3	4
Net cost PBS/RPBS July 2021 (\$)	3	3	3	3	3	3
Net cost to MBS (\$)	3	3	3	3	3	3
Net cost to MBS (item 119) July 2021 (\$)	3	3	3	3	3	3
<b>Net cost to government</b>						
<b>March 2022 (\$)</b>	3	3	3	4	3	4
<b>July 2021 (\$)</b>	3	3	3	3	3	3
<b>Sensitivity analyses</b>						
<b>ZANU discontinuation per models (\$)</b>	3	3	3	3	3	3
<b>Without financial stopping rule (\$)</b>	3	3	3	4	4	4

Source: Tables 4-2, 4-9, 4-12, 4-15, 4-16, 4-17, 4-19, 4-20, 4-22, 4-23 of resubmission and compiled during the evaluation.

Note: cost of bendamustine was incorrectly used for oral cyclophosphamide and costs have been updated to correct for this.

1L=first-line treatment, 2L= second-line treatment, GF=grandfathered, R/R=relapsed/refractory, TN=treatment naïve, ZANU=zanubrutinib

\* Australian population in 2020 x 1.22/100000=316 prevalent WM x eligibility criteria= < 500 eligible patients - <500 grandfathered = < 500

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5000

<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> \$10 to < \$20 million

- 6.83 The PSCR (p3) clarified the source of the WM incident rate of 0.37 per 100,000 and the source of the proportion of patients with NHL who have WM (stated to be 1-2% in model). The PSCR noted the AIHW 2017 data shows the incidence of Non-Hodgkin Lymphoma in Australia to be 19.8 per 100,000 (Cancer data in Australia, Cancer summary data visualisation - Australian Institute of Health and Welfare (aihw.gov.au)) and WM accounts for 1-2% of the NHL cases according to Lymphoma Australia. The PSCR stated that using this information, the incidence of WM in Australia can be calculated to be 0.39 per 100,000 (2% of 19.8). The ESC noted it was unknown where Lymphoma Australia sourced the estimate of 1-2%. The ESC further noted the upper end of the range (2%) was used to inform the financial estimates.
- 6.84 The PSCR (p3) informed that as of 25 January 2022, a total of < 500 WM patients have initiated on the early access program. The pre-PBAC Response (p2) provided an update that as of February 2022, a total of 50 WM patients have initiated on the early access program. The pre-PBAC Response estimated that there will be < 500 enrolled patients by 1 September 2022, a potential listing date for zanubrutinib, based on the observed uptake to date. The pre-PBAC response noted that this was reflected in its revised financial estimates.
- 6.85 The financial estimates are uncertain:
- Time on treatment is fixed at a cost for | months per patient, which is likely an overestimate. This did not account for patients who discontinue treatment earlier (the economic models estimate ~37 months of treatment per patient when the financial stopping rule is in place). The ESC considered the duration of treatment should be consistent between the models and financial estimates noting that an overestimate in the financial estimates would mean that that a Risk Sharing Arrangement (RSA) would not result in a cost-effective price per patient as proposed in the submission. As stated above, the pre-PBAC response revised the estimates to apply treatment durations consistent with the economic model.
  - The submission estimated an increase in treatment from |% to |% over the course of 6 years, but with limited treatment options, it is likely that eventually all patients will receive zanubrutinib (i.e. if they do not receive it first or second line, they may receive it as a later line of treatment).
  - R/R patients may be underestimated. As per the financial estimates in the July 2021 submission, patients who did not progress 2 years after diagnosis, did not progress at all. As WM is characterised by patients relapsing and remitting over time, it is likely that eventually nearly all patients will go on to a second line of treatment.
  - The financial estimates only included patients who are BTKi-naïve (80%). The requested restriction did not limit use based on prior BTKi use. Given the lack of clinical evidence to support retreatment, the PBAC had previously considered that

zanubrutinib should be restricted to patients untreated with a BTKi (except those who had been intolerant to another BTKi) (paragraph 7.3, zanubrutinib PSD, July 2021).

- Zanubrutinib has a different safety profile to currently available treatments, and management of these (e.g. major haemorrhages) was costed to be low (\$138.72 per episode of major haemorrhage based on MBS item 13706). Major haemorrhage is more likely to be a hospitalisation cost. There are also potential AEs of discontinuing treatment that may result in additional healthcare costs. However, the cost per patient of major haemorrhage and neutropenia may be overestimated as the MBS costs were applied annually, which differed from the economic model where they were applied once per patient. Although there were inconsistencies in the MBS costs associated with AEs and administration, the PBAC considered that their impact was relatively minor and likely balanced across treatments.

- 6.86 Sensitivity analyses indicated the financial estimates were most sensitive to variations to the number of patients receiving zanubrutinib and duration of zanubrutinib treatment. If treatment duration occurred as predicted in the economic analysis with the financial stopping rule in place (37.1-37.5 months), the total net cost to Government would be \$40 million to < \$50 million over 6 years (a reduction of 16.3%). Without the stopping rule in place, treatment duration was assumed to be 77.0-79.3 months (from the economic analysis), and total net cost to Government would be \$60 million to < \$70 million over 6 years (an increase of 26.1%).

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

- 6.87 The PBAC had noted the treatment duration is uncertain given the limited follow-up in the clinical trials compared with the expected long time on treatment and foreshadowed that this risk could potentially be managed with an RSA (paragraph 7.15, zanubrutinib, July 2021).
- 6.88 The resubmission proposed a [REDACTED]-month financial stopping rule to cap Australian Government expenditure based on the financial estimates, with a rebate payable to the Australian government for expenditure above the estimated use. This proposal would require such an RSA to continue indefinitely in order to ensure that expenditure beyond the initial [REDACTED] months ([REDACTED] years) of listing is capped at this treatment duration. The ESC noted that the usefulness of an RSA in managing expenditure would be dependent on the certainty of the estimated number of patients and average treatment duration.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of zanubrutinib for the treatment of Waldenström macroglobulinemia (WM) in treatment-naïve (TN) patients who are unsuitable for chemo-immunotherapy and in relapsed/refractory (R/R) patients who have received at least one prior chemo-immunotherapy. The PBAC is satisfied that zanubrutinib

provides, for some patients, a significant improvement in efficacy over rituximab monotherapy (Rm) and bendamustine and rituximab (BR) in the TN and R/R populations respectively.

7.2 The PBAC again acknowledged there was a high and urgent unmet need for effective treatments for WM on the PBS. The PBAC also recognised the sponsor's participation in the Facilitated Resolution Pathway workshop, and efforts to address outstanding issues raised at the PBAC meeting and discussed at the workshop. In the context of limited clinical data for a rare disease, the PBAC considered that the resubmission's revised model was sufficiently reliable for decision making, and that the listing would be cost-effective with an incremental cost-effectiveness ratio (ICER) of less than \$45,000 to < \$55,000/QALY for the base case analysis for the R/R population. The PBAC noted the corresponding ICER for the TN population would be higher (\$55,000 to < \$75,000/QALY) and considered this to be acceptable noting that it was subject to less uncertainty as it relied on a smaller gain in overall survival (OS).

7.3 In terms of the restriction, the PBAC recommended:

- unsuitability for chemo-immunotherapy be defined as having a CIRS score of 6 or greater (in line with PBAC's previous advice and as proposed in the resubmission);
- use should be restricted to BTKi-naïve patients or patients who are intolerant to another BTKi (in line with PBAC's previous advice);
- R/R patients must have relapsed after 'prior chemo-immunotherapy' (not just 'prior therapy' as proposed in the original submission and the resubmission);
- use should be limited to patients with a WHO score of 2 or less, consistent with ASPEN and Study AU-003; and
- grandfathering provisions should apply for 12 months from the date of PBS listing.

7.4 The PBAC's views regarding the comparator, clinical place in therapy and the clinical trials were unchanged from its July 2021 consideration. No new clinical trials were available. In terms of comparative effectiveness, the PBAC noted some further analyses and arguments were presented including Buske 2021 with the final data analysis from iNNOVATE, Tohidi-Esfahani 2021 with an analysis of QoL from the WhiMSICAL registry, and Castillo 2021, which considered the relationship between response and progression-free survival outcomes in WM patients treated with ibrutinib. The PBAC remained confident that zanubrutinib would have superior response outcomes to the comparator regimens, and although the precise magnitude was uncertain, these outcomes were patient-relevant, and meant that zanubrutinib offered high added therapeutic value for WM. The PBAC had been concerned that the survival gains claimed in the previous submission were inadequately supported but noting the additional context provided by Castillo 2021, and more importantly, that the gains modelled in the revised economic evaluation were substantially more

conservative, the PBAC considered that it was not unreasonable to accept the plausibility of some survival benefit, although it could not be reliably quantified. Furthermore, the PBAC recognised that given the rarity of WM and its indolent nature, additional evidence demonstrating a survival gain were unlikely to be forthcoming. The PBAC remained of the view that the superior safety claim had not been adequately supported.

- 7.5 The PBAC noted the revisions to the economic models had broadly addressed the PBAC's outstanding issues and were aligned with the FRP workshop outcomes (in terms of several aspects of the model structure, time horizon, extrapolations and utilities). Nonetheless, some inconsistencies and uncertainties remained, particularly the continued modelling of a survival benefit, but as noted above, the PBAC acknowledged that this had been implemented in a more conservative manner than in the July 2021 submission. The PBAC considered a plausible range for the ICER for the treatment naïve population was \$75,000 to < \$95,000/QALY (resubmission corrected base case) to \$95,000 to < \$115,000/QALY (with removal of the OS gain beyond the KM data) and for the R/R population was \$55,000 to < \$75,000/QALY to \$155,000 to < \$255,000/QALY. The PBAC considered the upper estimate for the R/R population was unacceptably high, but that zanubrutinib could be cost-effective with an ICER of less than \$45,000 to < \$55,000/QALY for the base case analysis for the R/R population. The PBAC noted the corresponding ICER for the TN population would be higher (\$55,000 to < \$75,000/QALY) and considered this to be acceptable noting that it was subject to less uncertainty as it relied on a smaller gain in OS.
- 7.6 The PBAC recognised the challenges of using an RSA to achieve cost-effectiveness as the estimated number of patients treated must be reached in order for the RSA to constrain the cost per patient. However, in this case, the PBAC considered it was unlikely that the patient numbers had been overestimated and thus considered, provided the expenditure caps were based on the average (not maximum) treatment durations from the economic models and the rebate for use above the expenditure caps was 10%, that a cost-effective price would likely be achieved using an RSA.
- 7.7 The PBAC noted that the resubmission had revised the financial estimates in terms of the prevalent patient population, uptake, PBS cost offsets and costs of bleeding events (paragraph 6.80). The pre-PBAC response had further updated the estimated number of grandfathered patients and the treatment durations (37.5 and 37.1 months in the TN and R/R populations), in response to the ESC's advice that the treatment durations in the economic evaluation and financial estimates should be consistent. Overall, the PBAC considered that the financial estimates informed by the patient numbers in the resubmission and average treatment durations from the economic model were a reasonable basis for an RSA.
- 7.8 The PBAC advised that zanubrutinib is not suitable for prescribing by nurse practitioners.
- 7.9 The PBAC recommended that the Early Supply Rule should apply.

7.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for zanubrutinib:

- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of the highly valued patient-relevant response outcomes.
- b) The treatment is expected to address a high and urgent unmet clinical need because there are no subsidised therapies for WM, which is a seriously debilitating condition in terms of quality of life.
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	NEW	1	120	5	Brukinsa
		Max.qty (packs) multiplier = 1 Repeat increases: nil			
<b>Restriction Summary [new 1] / Treatment of Concept: [new 2]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities immediate assessment					
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative advice:</b> Special Pricing Arrangements apply.					
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					
<b>Episodicity:</b> [blank]					
<b>Severity:</b> [blank]					
<b>Condition:</b> Waldenström macroglobulinaemia					
<b>Indication:</b> Waldenström macroglobulinaemia					
<b>Treatment Phase:</b> Initial					
<b>Clinical criteria:</b>					
The condition must have relapsed or be refractory to at least one prior chemo-immunotherapy; or					
Patient must be unsuitable for treatment with chemo-immunotherapy, defined by a Cumulative Illness Rating Scale of 6 or greater, if untreated (i.e., treatment-naïve) for this condition					

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	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be untreated with a Bruton's tyrosine kinase inhibitor for this condition; or
	Patient must have developed intolerance to another Bruton's tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this condition
<b>Restriction Summary [new 3] / Treatment of Concept: [new 4]</b>	
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities immediate assessment
	<b>Indication:</b> Waldenström macroglobulinaemia
	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	<b>Clinical criteria:</b>
	Patient must have received treatment with this drug for this indication prior to [insert listing date here]
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must have relapsed or been refractory to at least one prior chemo-immunotherapy, prior to having initiated non-PBS subsidised treatment with this drug for this condition; or
	Patient must have been unsuitable for treatment with chemo-immunotherapy, defined by a Cumulative Illness Rating Scale of 6 or greater, if untreated (i.e., treatment-naïve) for this condition prior to initiating non-PBS subsidised treatment with this drug
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had a World Health Organisation (WHO) performance status of no greater than 2 prior to initiating non-PBS subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving non-PBS-subsidised treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have been untreated with a Bruton's tyrosine kinase inhibitor for this condition prior to initiating non-PBS subsidised treatment with this drug; or
	Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when non-PBS subsidised treatment was initiated for this condition
	<b>Prescribing Instructions:</b> A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once.
	<b>Administrative advice:</b> This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
<b>Restriction Summary [new 5] / Treatment of Concept: [new 6]</b>	
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners

<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities immediate assessment
<b>Indication:</b> Waldenström macroglobulinaemia
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## 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.