

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

### 1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required listing for the treatment of Waldenström macroglobulinaemia (WM) in two patient subpopulations: (i) treatment-naïve (TN) patients who are 'unsuitable' for chemo-immunotherapy and (ii) 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 TN unsuitable for chemo-immunotherapy population, and versus bendamustine + rituximab (BR) in the R/R population.

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

| Component      | Description                                                                                                                                                                                                                                                                                       |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population     | Patients with WM who have received at least one prior therapy or who are unsuitable for chemo-immunotherapy as 1L treatment.                                                                                                                                                                      |
| Intervention   | Zanubrutinib 160 mg orally twice daily (80 mg x2 capsules) or 320 mg once daily (80 mg x4 capsules).                                                                                                                                                                                              |
| Comparator     | <b>TN patients unsuitable for chemo-immunotherapy:</b> Rituximab monotherapy (Rm) as main comparator.<br><b>R/R patients who have received at least one prior therapy:</b> Bendamustine in combination with rituximab (BR) as main comparator, 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 patients unsuitable for chemo-immunotherapy:</b><br>Zanubrutinib is superior in terms of effectiveness and safety compared with Rm.<br><b>R/R patients who have received at least one prior therapy:</b><br>Zanubrutinib is superior in terms of effectiveness and safety compared with BR. |

Source: Table 1.1, p19 of the submission.

1L=first line, BR=bendamustine-rituximab, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, WM=Waldenström macroglobulinaemia.

### 2 Background

#### Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA clinical evaluator's report (CER, 1st round) and TGA Delegate's Overview were available. The TGA Delegate was yet to indicate a proposed decision on the registration of zanubrutinib. The TGA Delegate noted that the pivotal study (ASPEN) did not meet its primary endpoint of superiority over ibrutinib for very good partial response (VGPR)/complete response (CR) though the results for key and secondary endpoints were numerically similar, and considered this raised uncertainty around the interpretation of results, in particular, whether they have met the threshold for

supporting full registration in the setting of a rare disease (TGA Delegate’s Overview). However, the TGA Delegate considered if the results for zanubrutinib were considered in isolation of the comparator arm of ASPEN, taking into account the rarity of the condition and the clinical value of alternatives to ibrutinib, there may be a place for zanubrutinib in the landscape of WM treatment (TGA Delegate’s Overview).

- 2.2 The proposed TGA indication is: “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”.
- 2.3 Zanubrutinib has been submitted for approval in WM to the European Medicines Agency (EMA) and Food and Drug Administration (FDA), and was approved for the treatment of WM by Health Canada on 1 March 2021.
- 2.4 TGA registration for use in Mantel Cell Lymphoma (MCL) was also requested for zanubrutinib, with a submission to the July 2021 PBAC meeting (item 5.13 refers).

### 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<br>80 mg capsule                     | 1                        | 120                      | 5              | \$11,672.21 published<br>\$ [REDACTED] effective | Brukina®<br>BeiGene Aus Pty Ltd   |

|                               |                                                                                                                                                                                     |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Category / Program:</b>    | GENERAL – General Schedule (Code GE)                                                                                                                                                |
| <b>Prescriber type:</b>       | <input checked="" type="checkbox"/> Medical Practitioners                                                                                                                           |
| <b>PBS Indication:</b>        | Waldenström’s macroglobulinaemia                                                                                                                                                    |
| <b>Restriction:</b>           | <input checked="" type="checkbox"/> Authority Required – Telephone                                                                                                                  |
| <b>Administrative Advice:</b> | Special Pricing Arrangements apply.<br>No increase in the maximum quantity or number of units may be authorised.<br>No increase in the maximum number of repeats may be authorised. |

|                            |                                                                                                                                                                                                         |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Treatment phase:</b>    | Initial                                                                                                                                                                                                 |
| <b>Treatment criteria:</b> | The treatment must be the sole PBS-subsidised therapy for this condition.                                                                                                                               |
| <b>Clinical criteria:</b>  | Patient must have relapsed/refractory disease despite prior treatment, or<br>Patient must be unsuitable for treatment with chemo-immunotherapy if untreated (i.e., treatment-naïve) for this condition. |

|                            |                                                                                                                                                                                                                     |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Treatment phase:</b>    | Continuing                                                                                                                                                                                                          |
| <b>Treatment criteria:</b> | Patient must have previously received PBS-subsidised treatment with this drug for this condition.                                                                                                                   |
| <b>Clinical criteria:</b>  | The treatment must be the sole PBS-subsidised therapy for this condition,<br>AND<br>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition. |

Source: Table 1.7, p36; Table 1.8 and 1.10, pp37-38 of the submission.

- 3.1 The submission also sought transitioning arrangements (i.e. a ‘Grandfather’ listing), as the sponsor anticipated establishing an early access program following TGA approval.

- 3.2 The requested restrictions would allow Bruton's tyrosine kinase inhibitor (BTKi)-treated patients (e.g. ibrutinib treated patients) to receive zanubrutinib. The zanubrutinib trials excluded BTKi-treated patients and in the financial estimates, only patients who have not had ibrutinib were assumed to receive zanubrutinib. The ESC considered that use of zanubrutinib should be restricted to patients untreated with a BTKi given the lack of evidence for zanubrutinib in BTKi-treated patients.
- 3.3 The requested PBS indication was consistent with the proposed TGA indication. However, neither of these defined which patients may be 'unsuitable' for chemo-immunotherapy in order to use zanubrutinib as a first-line (1L) treatment. The submission's intended TN population was patients who are unsuitable due to frailty, risk factors, or contraindications. The ASPEN trial for zanubrutinib defined unsuitability as the presence of documented comorbidities or risk factors, and the sponsor's clinician survey based unsuitability on a total cumulative illness rating scale (CIRS) score of greater than 6, similar to the scoring system used to characterise patients unsuitable for chemo-immunotherapy in chronic lymphocytic leukaemia (CLL) for idelalisib or obinutuzumab on PBS. The ESC considered that unsuitability based on a CIRS score could be used to define the eligible TN patient population, noting that there would be very few patients not able to receive some form of chemo-immunotherapy as there are mild, well tolerated therapies (e.g. chlorambucil + rituximab) for frailer patients. The pre-PBAC response agreed with this approach.

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

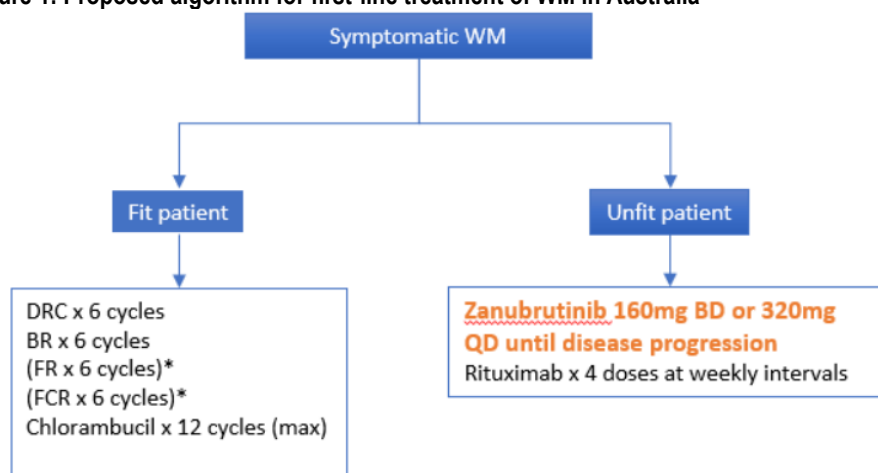
## 4 Population and disease

- 4.1 WM is a rare type of indolent non-Hodgkin's lymphoma (iNHL), 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). The diagnosis of WM is based on the histopathological confirmation of bone marrow infiltration by LPL and the detection of any amount of monoclonal IgM protein.
- 4.2 The pathogenic gene variant MYD88<sup>L265P</sup> is present in >90% of cases of WM (Treon et al 2012, Varettoni et al 2017). A second set of pathogenic gene variants with prognostic significance, found at chemokine receptor 4 (CXCR4<sup>WHIM</sup>) are seen in approximately 30% to 40% of cases (Hunter et al 2014, Xu et al 2016). These genetic alterations are intricately linked, but have opposing effects on the efficacy of BTK-targeting agents; MYD88<sup>L265P</sup> improves response to BTKis, whereas CXCR4<sup>WHIM</sup> confers resistance. However, neither of these tests are conducted routinely in Australian clinical practice.
- 4.3 Approximately one quarter of patients will not have symptoms at diagnosis (smouldering/asymptomatic WM). For those with symptoms, the most common are weakness, severe fatigue, bleeding from the nose or gums, weight loss, and bruises or

other skin lesions. High levels of IgM can lead to hyperviscosity syndrome (approx. 15% of patients), in which the blood becomes abnormally thick (Taulikar and Tam 2016). Symptoms of this syndrome include visual problems (e.g., blurring or loss of vision) and neurological problems (e.g., headache, dizziness, vertigo). Bone marrow infiltration can lead to anaemia and thrombocytopenia, and some patients may present with fever, night sweats and/or unexplained weight loss.

- 4.4 Given a lack of evidence that treatment of asymptomatic patients provides a survival benefit when compared with treatment at the time symptoms develop, patients are only treated once symptomatic, or if they present severe cytopenia or macroglobulinaemia. WM is not yet curable, but with modern therapies it has become an indolent disease with a median survival over 10 years (Buske et al 2018, Brandefors et al 2018). Many patients will die of causes other than WM, especially those diagnosed in older age. However, this is a heterogeneous group and outcomes are variable.
- 4.5 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).
- 4.6 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.
- 4.7 The submission suggested that patients in Australia receive either Rm (if unfit), or a chemo-immunotherapy regimen (DRC (dexamethasone+rituximab+cyclophosphamide), BR (bendamustine+ rituximab) for transplant eligible patients, fludarabine+rituximab (FR), fludarabine+cyclophosphamide+rituximab (FRC) or chlorambucil (for the frail and/or elderly)). Fludarabine should be avoided or used with caution in frontline treatment in transplant-eligible patients due to stem cell toxicity. In the R/R setting, the choice of subsequent treatment depends on prior success to previous rituximab-based regimen, with either a repeat or alternate rituximab-based regimen (if >3 years since last rituximab based treatment), or alternate rituximab-based treatment (if between 1-3 years), or clinical trial (if <12 months). The submission positioned zanubrutinib as an option for patients in 1L treatment if they are unfit for chemo-immunotherapy or as an alternative agent in the R/R setting.
- 4.8 The proposed clinical management algorithms were based on the submission's combination of Australian (Taulikar and Tam 2016) and international treatment guidelines (ESMO 2018, NCCN V1.2017, IWWM-8 2016) for WM, and are shown in the figures below.

Figure 1: Proposed algorithm for first-line treatment of WM in Australia

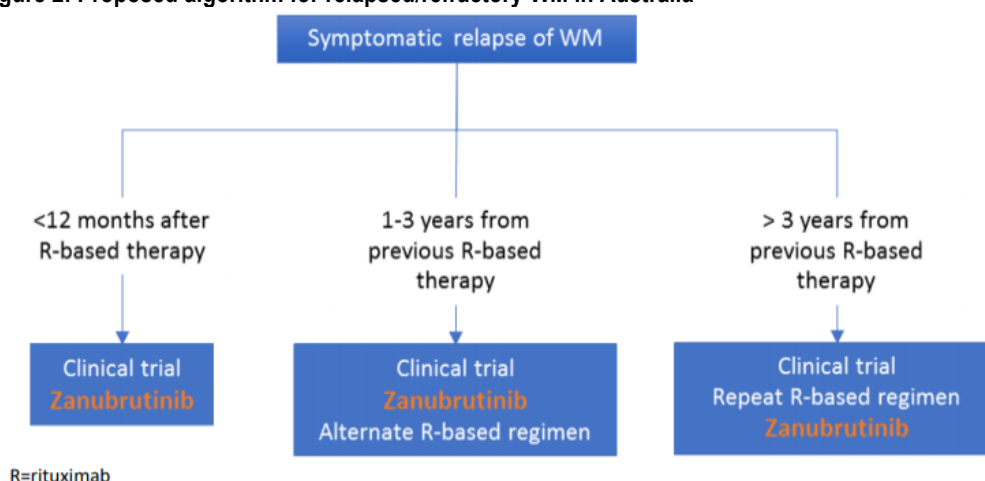


Source: Figure 1.4, p33 of the submission.

\* Fludarabine should be avoided or used with caution

BR=bendamustine+rituximab, DRC=dexamethasone, rituximab and cyclophosphamide, FR= fludarabine+rituximab, FCR= fludarabine, cyclophosphamide and rituximab, WM=Waldenström macroglobulinaemia.

Figure 2: Proposed algorithm for relapsed/refractory WM in Australia



R=rituximab

Source: Figure 1.6, p34 of the submission.

R=rituximab, WM=Waldenström macroglobulinaemia.

4.9 All the therapy combinations in the R/R clinical management algorithm included rituximab, as it is the chemotherapy backbone which confers resistance not the rituximab. In R/R patients, high dose chemotherapy followed by autologous stem cell transplant (ASCT) is another option in a small proportion of patients with good fitness, but this was not depicted in the submission's algorithms. Chemotherapy alone is also recommended as an option in the R/R population by the ESMO guidelines but is rarely used in practice in Australia. Bortezomib is suggested as an option by the Australian guidelines for TN patients with high IgM, although it is contraindicated for patients with unresolved neuropathy. Australian guidelines recommend patients with indolent relapse of WM can be observed without active therapy. Currently patients who meet criteria for treatment at relapse will be treated with chemo-rituximab with

consideration of change of chemotherapy backbone if time in first remission is short or toxicity is a consideration.

- 4.10 The PBAC noted that NCCN Guidelines Version 1.2022 WM/Lymphoplasmacytic Lymphoma (LPL) were recently updated to include zanubrutinib as a preferred regimen for the primary therapy of WM/LPL along with BR, bortezomib/dexamethasone/rituximab, ibrutinib ± rituximab, and DRC. Zanubrutinib was also added as a preferred regimen for previously treated WM/LPL.

## **5 Comparator**

- 5.1 The submission nominated separate comparators for each requested population: Rm for TN patients unsuitable for chemo-immunotherapy and BR for the R/R population.
- 5.2 For the TN population, the submission argued that Rm was the most appropriate comparator because it was:
- Listed in the Australian Clinical Practice Guidelines for WM as a 1L therapy suitable in patients unable to tolerate chemo-immunotherapy (Talaullikar and Tam 2016);
  - Prescribed by Australian haematologists in clinical practice at the highest rates compared to other 1L therapies in patients who are ineligible/ who would not be appropriately treated with standard PBS-listed chemo-immunotherapy, based on the sponsor's clinician survey performed in Australia (n=26); and
  - The second most used front-line therapy after BR in the international WhiMSICAL registry data.
- 5.3 The sponsor's clinician survey indicated that other therapies used in this setting were: obinutuzumab monotherapy, chlorambucil monotherapy, rituximab+chlorambucil, and ibrutinib. Rm is not PBS-subsidised for use in patients with WM (only in combination with chemotherapy, for previously untreated or R/R CD20 positive lymphoid cancer), neither is obinutuzumab monotherapy or ibrutinib. Chlorambucil is a chemotherapy, so does not fit the indication of use in patients who are chemo-immunotherapy 'unsuitable'. In the financial estimates, based on results from the clinician survey for the TN population, zanubrutinib was assumed to substitute for PBS items related to Rm, chlorambucil monotherapy, and rituximab+chlorambucil.
- 5.4 The only therapy recommended for use in TN patients unable to tolerate chemo-immunotherapy in the Australian guidelines is Rm. The European guidelines (ESMO) also recommend single-agent chemotherapy (e.g. chlorambucil or fludarabine) as well as bortezomib+rituximab for patients considered "medically non-fit", although these patients are not described as "unsuitable to chemo-immunotherapy". In addition, Australian and IWWM-8 guidelines recommend Rm should be avoided for the subset of patients with high IgM due to the risk of "IgM flare" and recommend plasmapheresis in patients with IgM >4 g/L before planned rituximab therapy. The ESC considered that Rm was an appropriate comparator for this patient population. The ESC considered that although not PBS listed for use in WM, Rm was likely still used in

clinical practice in TN patients who may not tolerate standard chemo-immunotherapy. The ESC also considered that rituximab and bendamustine, rituximab, cyclophosphamide and prednisolone (R-CP) and rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) were appropriate comparators, noting these therapies are often given with dose reductions in this patient population.

5.5 The submission nominated BR combination therapy as the main comparator for the R/R population, using it as proxy for any treatment in this setting, arguing that:

- Current evidence suggests that BR is the most common treatment used (aside from the non-PBS listed ibrutinib). The submission stated that the sponsor's clinician survey indicated that ibrutinib monotherapy was received by 32% of patients, followed by BR at 25%, DRC at 14%, and FCR (fludarabine+ cyclophosphamide +rituximab) at 5%, although these percentages could not be verified from the survey results presented. The ESC noted that DRC is the recommended treatment in Australian treatment guidelines and generally has a more tolerable safety profile than BR, and hence considered it would be widely used in clinical practice.
- BR is considered relatively effective and safe compared to other second-line options that are available through the PBS.

5.6 The choice of BR as the main comparator in the R/R setting may be reasonable; however, the evaluator and ESC raised several issues:

- The international WhIMSICAL WM patient registry demonstrated a large variety of treatments in WM with considerable variation persisting despite comprehensive treatment guidelines. Therefore, any of the TGA-approved treatments for WM could be used in the R/R setting. While BR, Rm and ibrutinib were the most commonly used 2L treatments in WhIMSICAL, the frequency of use depended on the 1L treatment used, with a much lower likelihood of retreatment if BR was used in 1L. If a patient received BR in 1L, the most common 2L treatments were either ibrutinib or DRC. The sponsor's clinician survey also indicated that 44% of patients who progress on a non-BTKi are prescribed a BTKi (i.e., ibrutinib) in 2L.
- The Australian WM treatment guidelines state that any of the front-line regimens can be used for re-treatment provided the patient has maintained a response for >2 years. These guidelines also note that in clinical trials, BR was found to be superior to R-CHOP, with reduced toxicity and faster onset of action compared to DRC as initial therapy (Talaoulikar and Tam 2016). The ESC considered that patients and clinicians would likely use an oral BTKi over standard chemotherapy in the R/R setting even if a good prior response was achieved with standard chemotherapy.
- Given all patients with WM will ultimately relapse after an initial response to therapy, it may be more appropriate to expect that all patients will eventually cycle through all of the available treatments, so zanubrutinib would delay rather than substitute for other therapies. The ESC agreed with the evaluation that

zanubrutinib would likely displace rather than replace alternative therapies for most patients given the chronic nature of WM.

- While BR is PBS listed for treatment of iNHL, combination treatment, specifically with bendamustine is not listed for use in the R/R setting. For this reason, the Australian-based consensus-driven cancer treatment protocols and information (eviQ) recommends DRC for symptomatic R/R WM (although dexamethasone IV is also not listed on the PBS). No randomised studies have compared DRC with BR, however two retrospective studies suggest similar overall response rates with a non-significant trend towards more rapid achievement of best response with BR. Progression free survival (PFS) and overall survival (OS) were not statistically significantly different between BR and DRC; however, for PFS, there was a trend favouring BR in both studies (log rank  $p=0.10$  in Castillo et al 2018 and  $p=0.08$  in Paludo et al 2018, respectively). DRC is less costly compared to BR. The ESC considered DRC was also a relevant comparator.
- The financial estimates assumed substitution of zanubrutinib for PBS items for BR, DRC (rituximab and cyclophosphamide components) and FRC in the R/R setting. Given bendamustine is not PBS listed for use in the R/R setting, application of a cost offset would be inappropriate when estimating the net PBS cost.

- 5.7 The submission appropriately identified ibrutinib as a near market comparator. The submission stated that ibrutinib has become standard management for WM overseas, but can only be obtained via compassionate access in Australia for WM. There has not been an application to the PBAC for this indication. The submission presented the ASPEN study, a Phase 3 trial comparing zanubrutinib and ibrutinib.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician noted that as WM progresses, there is an increased risk of infections, systemic symptoms, and bone marrow failure, which can have a substantial impact on quality of life. The clinician noted the two main chemo-immunotherapy regimens used in Australia are bendamustine+rituximab and dexamethasone+rituximab+cyclophosphamide and that many patients will initially respond to treatment, but would ultimately relapse given there is currently no cure for WM. The clinician highlighted the increased risk of adverse effects associated with repeated chemotherapy treatment such as myelodysplasia, myelosuppression and infections and indicated that most clinicians would prefer to limit treat chemotherapy treatment to 1L due to these effects. The clinician noted that while ibrutinib has a better toxicity profile compared to chemotherapy, it is associated with important adverse effects such as atrial fibrillation and bleeding, which are thought to be due to off-target binding to other tyrosine

kinases. The clinician noted that zanubrutinib has high selectivity for BTK and exhibits less off-target inhibition than ibrutinib and considered the results from ASPEN indicated that zanubrutinib had a better safety profile compared to ibrutinib. The clinician indicated the most suitable treatment for a patient was largely determined based on clinical judgement. However, the clinician considered the CIRS score could be used to identify patients unsuitable for chemo-immunotherapy. The clinician considered that if zanubrutinib was PBS-listed, it would be commonly used in the R/R setting, but there would be limited use in TN patients who are fit, as these patients generally respond well to chemo-immunotherapy.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (15), health care professionals (4) and organisations (4) via the Consumer Comments facility on the PBS website. The comments highlighted the significant impact of the disease on daily life. Many of the comments were from patients who had received zanubrutinib through compassionate access or a clinical trial. The comments from patients who had received zanubrutinib described a range of benefits including improved quality of life, the ability to work and live an active lifestyle and manageable side effects.
- 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 the high unmet need for treatments for WM, particularly for older patients who are not able to tolerate aggressive chemotherapy regimens. The organisations highlighted the tolerable safety profile of zanubrutinib noting that patients treated with zanubrutinib experienced few side effects.
- 6.4 The PBAC noted the advice received from three haematologists from research centres and hospitals across Australia that zanubrutinib has a favourable safety profile compared to ibrutinib, particularly in terms of cardiovascular toxicity, bleeding, and diarrhoea. The haematologists also noted the Australian-led international WhiMSICAL study which captured patient-derived quality of life scores reported superior QoL scores of patients receiving a BTKi compared to those who had received conventional chemotherapy.
- 6.5 A form of consumer hearing was also held with representatives from the Australian patient support group for WM (WMozzies), prior to the 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 the population to have access to treatment, current challenges with existing therapies and experience of zanubrutinib.
- 6.6 The following is a summary of the perspectives presented to PBAC representatives:
- There are currently limited treatment options for patients with WM, and available treatment options have high toxicity. The side effects of zanubrutinib were

considered relatively minor (e.g. bruising), and there was some suggestion of reduced side effects compared with ibrutinib (in terms of diarrhoea and atrial fibrillation, which were noted in international patient forums).

- Given that WM is a rare condition, the PBS restriction should ideally allow the broadest access possible, including those previously treated with a BTKi. It was considered likely that BTKi options such as zanubrutinib would be preferred to chemotherapy for both tolerability and oral formulation. Uptake was expected to be high.
- 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 representatives noted that zanubrutinib had given individuals back their energy, allowed them to feel like themselves again and to participate in activities. It was noted that chemotherapy does not have the same benefits around quality of life and individuals continue to feel tired and unwell.
- In terms of long-term outcomes, representatives noted that the submission did not include long-term data, but explained that several WMozzies members had been treated with zanubrutinib for three to six years and remained stable, with similar experiences reported overseas.

### ***Clinical studies***

6.7 The submission presented comparisons between zanubrutinib versus each of the two nominated comparators, Rm and BR:

- An indirect treatment comparison (ITC) of response and safety outcomes for zanubrutinib (ASPEN-Cohort 1) versus Rm (iNNOVATE), with ibrutinib (ASPEN-Cohort 1)/ ibrutinib+R (iNNOVATE) as the 'common' reference;
- A naïve pooled ITC of response outcomes, for zanubrutinib (ASPEN-Cohort 1 and Study AU-003) versus Rm (iNNOVATE and Dimopoulos 2002);
- Matching-adjusted indirect treatment comparisons (MAICs) of PFS, OS and safety, for zanubrutinib (ASPEN-Cohort 1) versus BR (Tedeschi 2015); and
- A naïve pooled ITC of response outcomes, for zanubrutinib (ASPEN-Cohort 1 and Study AU-003) versus BR (Tedeschi 2015 and Treon 2011).

6.8 Details of the studies presented in the submission are provided in the table below.

Table 2: Studies and associated reports presented in the submission

| 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<br>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.                                                | 18 May 2020<br><br><i>Blood</i> 2020, 136: 2038-50                                                            |
|                                                   | Major responses in MYD88 wildtype (MYD88WT) Waldenström's macroglobulinemia (WM) patients treated with bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111).                                                                                                                                                                                                                                                                                              | June 2019.<br>HemaSphere. Conference: 24th Congress of the EHA. Netherlands. 3 (Supplement 1) (pp 196), 2019. |
|                                                   | Updated results of the ASPEN study from a cohort of patients with MYD88 wild-type Waldenström's macroglobulinemia.                                                                                                                                                                                                                                                                                                                                                  | June 2020.<br>HemaSphere. Conference: 25th Congress of the EHA. 4 (Supplement 1) (pp 550), 2020.              |
| 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.<br>Tam C.S., 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<br><br><i>Hematological Oncology</i> 2019, 37(S2): 245-247                                       |
| <b>Rituximab-monotherapy</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.<br>Dimopoulos M.A, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia.                                                                                                                                                               | 21 June 2018<br><br><i>N Engl J Med</i> 2018, 378: 2399-2410                                                  |
| Dimopoulos 2002                                   | A single-arm, prospective Phase 2 Study defining the activity of rituximab in patients with Waldenström's Macroglobulinemia.<br>Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab.                                                                                                                                                                                                                               | 01 May 2002<br><br><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.<br>Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström's macroglobulinaemia.                                                                                                                                                                                           | 14 March 2015<br><br><i>Leuk Lymphoma</i> 2015, 56(9): 2637-42                                                |
| Treon 2011                                        | A single arm study of patients with R/R WM who received bendamustine-containing therapy.<br>Treon SP, Hanzis C, Tripsas C, et al. Bendamustine Therapy in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia.                                                                                                                                                                                                                                     | 01 Feb 2011<br><br><i>Clinical Lymphoma, Myeloma &amp; Leukemia</i> 2011, 11(1): 133-135                      |

Source: Table 2.6, pp51-52 of the submission.

6.9 The key features of the studies are summarised in the table below.

**Table 3: Key features of the included studies**

| Trial                       | N                    | Treatments               | Design/ duration                                    | Risk of bias | Patient population                                                                                                                                                                                | Key Outcomes      | Use in modelled evaluation                              |
|-----------------------------|----------------------|--------------------------|-----------------------------------------------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------|
| ZANU                        |                      |                          |                                                     |              |                                                                                                                                                                                                   |                   |                                                         |
| ASPEN-Cohort 1              | 201                  | ZANU v. IBRU             | P3, R, OL, MC (12 countries incl Aust)/ 19.47mths   | High         | R/R or TN WM unsuitable for CIT (due to comorbidities or risk factors). ASPEN Patients in Cohort 1 had confirmed MYD88 <sup>L265P</sup> , patients in Cohort 2 did not have this genetic variant. | CR, VGPR, PFS, OS | PFS/OS (ITT) for TN pop'n<br>PFS/OS (R/R) for R/R pop'n |
| ASPEN-Cohort 2 <sup>f</sup> | 26                   | ZANU                     | As for ASPEN-Cohort 1 but single arm only.          | High         |                                                                                                                                                                                                   |                   | No                                                      |
| Study AU-003                | 78 [73] <sup>b</sup> | ZANU                     | P1/2, MC (6 countries incl Aust), OL/ 30mths        | High         |                                                                                                                                                                                                   |                   | No                                                      |
| Rm                          |                      |                          |                                                     |              |                                                                                                                                                                                                   |                   |                                                         |
| iNNOVATE <sup>g</sup>       | 150                  | Rm v. IBRU+ Rm           | P3, R, DB, MC (9 countries incl Aust)/ 26.5mths     | Low          | R/R or TN WM                                                                                                                                                                                      | CR, VGPR, PFS, OS | PFS (ITT) for TN pop'n                                  |
| Dimopoulos 2002             | 27                   | Rm                       | P2, MC (Greece) <sup>a</sup> OL/ 15.7mth            | High         |                                                                                                                                                                                                   | CR, OS            | No                                                      |
| BR                          |                      |                          |                                                     |              |                                                                                                                                                                                                   |                   |                                                         |
| Tedeschi 2015               | 71                   | BR                       | Coh <sup>c</sup> , MC (Italy) <sup>a</sup> / 19mths | High         | RR WM                                                                                                                                                                                             | CR, VGPR, PFS, OS | PFS/OS for R/R pop'n<br>OS for TN pop'n                 |
| Treon 2011                  | 30 <sup>e</sup>      | BR (n=24)<br>B+OFA (n=6) | Retro Coh <sup>d</sup> , SC (USA) / 17.5mths        | High         |                                                                                                                                                                                                   | CR, PFS           | No                                                      |

Source: Compiled from the CSR/publications during the evaluation

Aust=Australia, BR=bendamustine+rituximab, CIT=chemo-immunotherapy, CR=complete response, DB=double blind, MC=multi-centre, Mths=months, OFA=ofatumumab, OL=open label, OS=overall survival, P=phase, PFS=progression-free survival, pop'n=population, R=randomised, Retro=retrospective study, R/R=relapse/refractory, SC=single centre, VGPR=very good partial response, ZANU=zanubrutinib, Rm=rituximab monotherapy, USA=United States of America, WM= Waldenström macroglobulinaemia.

<sup>a</sup> Estimate based on authors' affiliations.

<sup>b</sup> 73 in WM Efficacy Evaluable Set (i.e., received  $\geq 1$  dose of ZANU, had baseline IgM or M-paraprotein  $\geq 5$  g/L, and no prior exposure to a BTKi).

<sup>c</sup> Patients were prospectively identified. Consecutive patients with R/R receiving BR were recruited and had consented prior to treatment. The analysis was however conducted retrospectively (p2638 of Tedeschi 2015).

<sup>d</sup> Patients were retrospectively identified via chart review.

<sup>e</sup> 6/30 (20%) of patients in Treon 2011 who were refractory to rituximab received bendamustine alone or bendamustine plus ofatumumab. Results were not reported separately for these patients.

<sup>f</sup> Results were only reported for 26 out of 28 included patients.

<sup>g</sup> A conference abstract of the 5-year follow-up results was identified during the evaluation (Buske et al., 2020). Updated PFS data was presented in the evaluation.

6.10 Overall, with the exception of iNNOVATE, the studies had a high risk of bias due to either a lack of blinding, lack of randomisation or the retrospective analyses conducted. For ASPEN, while the primary response outcome was assessed by an independent review committee (IRC) blinded to treatment assignment, other response outcomes were based on investigators' assessment, which could have biased the findings.

- 6.11 The submission did not present results for zanubrutinib from Cohort 2 of ASPEN, as it had only a single arm. ASPEN-Cohort 2 recruited patients without the MYD88<sup>L265P</sup> genetic variant, who are less likely to respond to BTKi treatment. Given the submission included single-arm studies and the requested PBS population would also include these patients, their results are informative and thus were extracted and summarised during the evaluation.
- 6.12 Reporting of eligibility criteria and patient baseline characteristics were limited for the non-randomised studies. Based on available information, there were a number of important differences across the studies, including: i) a lower proportion of TN patients in ASPEN vs iNNOVATE (18.4% vs 45.3%), which may be due to inclusion of TN patients suitable for chemo-immunotherapy in iNNOVATE, which may have in turn led to improved outcomes in iNNOVATE; ii) a higher proportion of patients with favourable genetic profile (MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup>), predicting better response to BTKi, in ASPEN-Cohort 1 compared to iNNOVATE (approx. 72%-90% vs 44.6%); iii) the addition of rituximab to ibrutinib in iNNOVATE, which may have improved the treatment effect of ibrutinib in patients with a less favourable genetic profile; and iv) rituximab-refractory patients were excluded from iNNOVATE but were included in Tedeschi 2015 and Treon 2011, this is important as results from Tedeschi 2015 were used in the model as a proxy for the Rm arm instead of results from iNNOVATE (see *Economic analysis*), which is likely to favour zanubrutinib. The ESC considered it was difficult to determine the overall impact of these differences on the comparisons between studies.
- 6.13 All studies used the recommended doses of treatments, except for Tedeschi 2015 where a proportion of patients received a lower dose of bendamustine, with 22/71 (31%) patients treated at a dose of 70 mg/m<sup>2</sup> and 4/71 (6%) at a dose of 50 mg/m<sup>2</sup>. Study analyses were not stratified by dosing regimen, so the lower dosage may have impacted the treatment effect.
- 6.14 The methods used to assess response were reasonably consistent across the studies. All studies adopted the response criteria from the Sixth International Workshop on WM (IWWM-6), except for Treon 2011, which followed the Third International Workshop on WM (IWWM-3) criteria, and Dimopoulos 2002, which did not report on the method used but was published before both the IWWM-3 and IWWM-6. Key differences between IWWM-3 and IWWM-6 include the addition of VGPR as a new category of response in IWWM-6, along with more sensitive IgM quantification methods and more thorough assessments of the bone marrow, which could have an impact on response rates and disease progression.

## **Comparative effectiveness**

### **Response outcomes**

- 6.15 The primary outcome of ASPEN was the proportion of patients achieving either VGPR or CR (VGPR/CR). The submission's ITCs for response outcomes were based on results for VGPR/CR, ORR (i.e., achieving MR or better) and MRR (i.e., achieving PR or better).
- 6.16 The submission noted that PFS and OS endpoints from ASPEN were not mature at the time of submission, thus disease response rates were presented as meaningful surrogates of effectiveness. However, as the submission did not address the requirements outlined in the PBAC Guidelines for translating comparative treatment effects of proposed surrogate measures to target clinical outcomes, this claim was unsupported (Appendix 5, PBAC Guidelines v5.0, 2016). The Pre-Sub-Committee Response (PSCR) noted that patients who achieve a PR or VGPR demonstrated a longer PFS and time to next treatment compared with those who had minor response or stable disease (Paludo et al 2018), and a multivariate analysis of ibrutinib in WM showed that partial response or better at six months was significantly associated with superior PFS (Castillo et al 2021). The PSCR considered these data supported a relationship between response outcomes and survival outcomes in WM and claimed that these findings were also consistent with the well-established relationship between depth of response, prolonged disease control and OS in multiple myeloma, another disease associated with gammopathy (Lonial & Anderson 2014). The ESC considered it was inappropriate to use evidence from multiple myeloma to support a relationship between response and survival outcomes for WM as multiple myeloma and WM are distinct diseases with different clinical manifestations. The ESC considered that response outcomes were likely a poor surrogate for survival outcomes in WM given the indolent nature of the disease.
- 6.17 A summary of key response outcomes is presented in Table 4. Further response outcomes (PR, MR, ORR, MRR) were presented in the Commentary.

Table 4: 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 <sup>b</sup> Cohort 1 | 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 <sup>b</sup> Cohort 1 | 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.

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 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 evaluation.

<sup>b</sup> Independent review committee (IRC) assessment.

<sup>c</sup> 24 patients in Treon 2011 received Rm, 6 were treated with R+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 submission reported RR results as IBRU vs ZANU, these were re-estimated during the evaluation to report as ZANU vs IBRU.

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

- 6.18 Overall, there were no notable differences between the treatments with respect to high quality response rates (VGPR, CR and VGPR/CR) except for Rm, which had a lower proportion of patients with high quality response rates compared to other treatments. Very few patients achieved CR with any treatment, so no comparisons could be made. Similarly, few patients achieved a VGPR. In iNNOVATE, statistically significantly more patients treated with ibrutinib+R attained a VGPR versus Rm (23% vs 4%, RD 0.19, 95% CI: 0.08, 0.29). Given very few patients achieved CR, the results for VGPR/CR were almost identical to those for VGPR. The ESC considered that the low number of patients achieving CR across the studies was consistent with CR rates for WM observed in clinical practice.
- 6.19 Results for other response outcomes PR, ORR and MRR appeared to support similar conclusions; that is, no notable differences, with the exception of Rm, which showed lower response rates.
- 6.20 Some further observations in relation to the results included that:
- The proportions of responders to zanubrutinib were similar across the ITT/TN/RR populations; however, this similarity did not appear to carry through to survival outcomes (see below), suggesting that response may not be a good surrogate outcome for survival.
  - The addition of rituximab to ibrutinib may have to an extent, counterbalanced the negative effect of unfavourable genetic variants on response outcomes for ibrutinib, compensating for a lower proportion of patients with the most favourable genetic profile in iNNOVATE versus ASPEN. Despite noted trial differences, the proportion of responders in the 'common' reference arm ibrutinib+R in iNNOVATE and ibrutinib from ASPEN-Cohort 1 were similar (23% vs 17-20%), suggesting the nomination of ibrutinib/ibrutinib+R as 'common' comparator for response outcomes in the ITC was potentially reasonable.
- 6.21 There were limited data across the studies for duration of response, time to response and time to treatment discontinuation.
- 6.22 In ASPEN, median duration of VGPR/CR was not estimable, and duration of major response at 24 months was similar for zanubrutinib and ibrutinib patients (85.2% vs 81.6%). Median time to VGPR/CR was shorter in zanubrutinib than ibrutinib (4.80 vs 7.39 months), but median time to major response was equal in both treatment arms (2.83 months). Time to treatment discontinuation (TTD) was longer in zanubrutinib-treated patients than in those given ibrutinib (9.22 vs 5.52 months).
- 6.23 iNNOVATE did not include data on time to response or duration of response, but reported time to next treatment, which was significantly higher in ibrutinib+R than in the Rm treatment arm (HR=0.1, 95% CI: 0.04, 0.23). The median time to the next treatment was 18.1 months in Rm patients and not estimable in those receiving ibrutinib+R.

- 6.24 The ESC considered it was difficult to draw any definitive conclusions regarding VGPR/CR for each treatment due to differences between the studies (as described in paragraph 6.12), the relatively small number of patients achieving these outcomes, lack of data on duration of response across studies, and the immaturity of the data.

### Survival outcomes

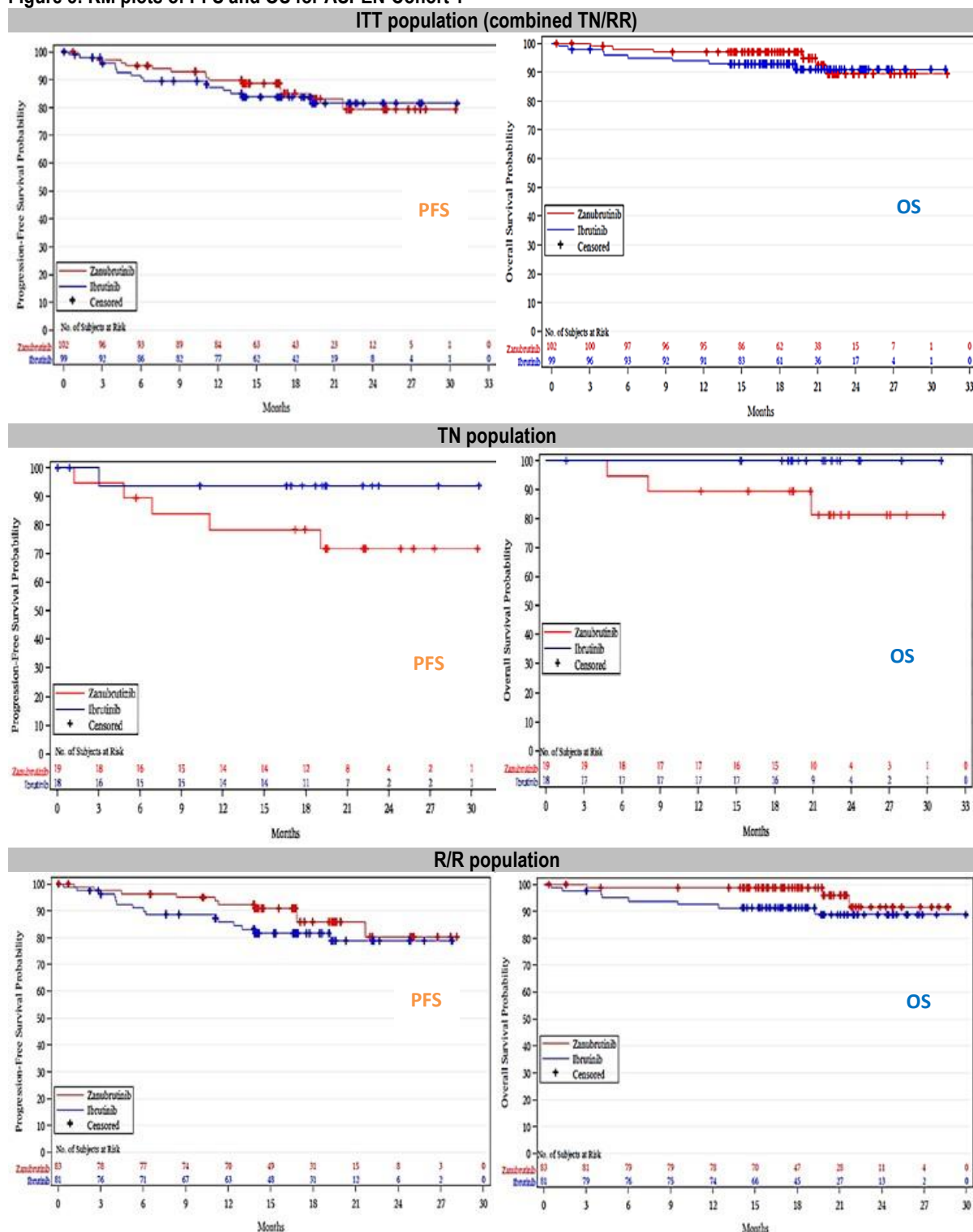
- 6.25 Results for PFS and OS from the zanubrutinib studies are summarised in Table 5 and Figure 3.

**Table 5: PFS and OS in ZANU trials (ASPEN and Study AU-003)**

| Trial ID       | Outcomes                        | TN                |                  | R/R               |                   | Overall           |                   |
|----------------|---------------------------------|-------------------|------------------|-------------------|-------------------|-------------------|-------------------|
|                |                                 | ZANU              | IBRU             | ZANU              | IBRU              | ZANU              | IBRU              |
| PFS            |                                 |                   |                  |                   |                   |                   |                   |
| 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)       | -                 |
| OS             |                                 |                   |                  |                   |                   |                   |                   |
| 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 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=relapse/refractory, TN=treatment-naïve, ZANU=zanubrutinib.

Figure 3: 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 submission, Figure 14.2.1.5.4, p1658 of the ASPEN CSR. Abbreviations: ITT=intention to treat, KM=Kaplan-Meier, PFS=progression free survival, OS=overall survival.

6.26 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. The ESC 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 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.

- 6.27 The submission did not present survival outcomes for the remaining included studies. Results from these studies (plus comparable results from zanubrutinib) were summarised during the evaluation.
- 6.28 The PFS results appeared numerically higher in those treated with zanubrutinib or ibrutinib than Rm or BR ( $\approx 80\%$  for zanubrutinib and ibrutinib vs  $\approx 40\%$  for Rm and  $\approx 60\%$  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).
- 6.29 The 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, ibrutinib and ibrutinib+R and Rm, and  $>72\%$  still alive for BR at 30 months in Tedeschi 2015. There was also significant crossover post-progression from Rm to ibrutinib+R (40%) in iNOVATE, making the comparison problematic.

### ***Quality of Life***

- 6.30 ASPEN was the only study reporting quality of life (QoL) outcomes (measured using the EQ-5D-5L and EORTC QLQ-C30 questionnaires). 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 VGPR.

### ***Comparative harms***

- 6.31 A summary of key adverse events is presented in Table 6.

Table 6: Summary of key adverse events in the studies

| AEs n (%)                                            | Study AU-003 | ASPEN                     |                          |                          | iNNOVATE       |                | Tedeschi 2015 |
|------------------------------------------------------|--------------|---------------------------|--------------------------|--------------------------|----------------|----------------|---------------|
|                                                      | ZANU<br>N=78 | ZANU<br>Cohort 1<br>N=101 | ZANU<br>Cohort 2<br>N=28 | IBRU<br>Cohort 1<br>N=98 | IBRU+R<br>N=75 | Rm<br>N=75     | BR<br>N=71    |
| <b>Patients ≥1 AE</b>                                | 78 (100.0)   | 98 (97.0)                 | 24 (85.7)                | 97 (99.0)                | -              | -              | NR            |
| <b>Most common AEs of interest in either group</b>   |              |                           |                          |                          |                |                |               |
| Infusion-related reactions                           | -            | -                         | -                        | -                        | 32 (43)        | 44 (59)        | 5 (7)         |
| Atrial fibrillation and flutter (any grade)          | -            | <b>2 (2.0)</b>            | -                        | <b>15 (15.3)</b>         | -              | -              | -             |
| All haemorrhage                                      | 49 (62.8)    | 49 (48.5)                 | 11 (39)                  | 58 (59.2)                | -              | -              | -             |
| Arthralgia                                           | -            | -                         | -                        | -                        | <b>18 (24)</b> | <b>8 (11)</b>  | -             |
| Anaemia                                              | -            | -                         | 6 (21)                   | -                        | 14 (19)        | 22 (29)        | -             |
| Fatigue                                              | -            | -                         | 4 (14)                   | -                        | <b>10 (13)</b> | <b>20 (27)</b> | -             |
| IgM Flare                                            | -            | -                         | -                        | -                        | <b>6 (8)</b>   | <b>35 (47)</b> | -             |
| Neutropenia                                          | 11 (14.1)    | <b>25 (24.8)</b>          | 5 (18)                   | <b>12 (12.2)</b>         | -              | -              | -             |
| Upper respiratory tract infection                    | 40 (51.3)    | 24 (23.8)                 | 6 (21)                   | 28 (28.6)                | -              | -              | -             |
| Diarrhoea                                            | 15 (19.2)    | 21 (20.8)                 | 8 (29)                   | 31 (31.6)                | <b>21 (28)</b> | <b>11 (15)</b> | -             |
| Contusion                                            | 25 (32.1)    | 13 (12.9)                 | 6 (21)                   | 23 (23.5)                | -              | -              | -             |
| Muscle spasms                                        | -            | <b>10 (9.9)</b>           | 4 (14)                   | <b>23 (23.5)</b>         | -              | -              | -             |
| Urinary tract infection                              | 15 (19.2)    | -                         | 4 (14)                   | -                        | -              | -              | -             |
| Cough                                                | 18 (23.1)    | -                         | 5 (18)                   | -                        | -              | -              | -             |
| Any Grade 3 or higher                                | 45 (59.0)    | 59 (58.4)                 | 18 (64)                  | 62 (63.3)                | 45 (60)        | 46 (61)        | -             |
| <b>Most common Grade 3 or higher in either group</b> |              |                           |                          |                          |                |                |               |
| Neutropenia                                          | 9 (11.5)     | 16 (15.8)                 | 3 (11)                   | 8 (8.2)                  | 7 (9)          | 2 (3)          | 25 (35.2)     |
| Hypertension                                         | 3 (3.8)      | 6 (5.9)                   | 3 (11)                   | 11 (11.2)                | <b>10 (13)</b> | <b>3 (4)</b>   | -             |
| Thrombocytopenia                                     | 1 (1.3)      | 6 (5.9)                   | 2 (7)                    | 3 (3.1)                  | <b>0</b>       | <b>4 (5)</b>   | -             |
| Anaemia                                              | 7 (9.0)      | 5 (5.0)                   | 3 (11)                   | 5 (5.1)                  | 8 (11)         | 13 (17)        | -             |
| Pneumonia                                            | 3 (3.8)      | <b>1 (1.0)</b>            | 2 (7)                    | <b>7 (7.1)</b>           | 7 (9)          | 2 (3)          | 4 (5.6)       |
| Atrial fibrillation and flutter                      | -            | <b>0 (0.0)</b>            | -                        | <b>4 (4.1)</b>           | <b>9 (12)</b>  | <b>1 (1)</b>   | -             |
| Major haemorrhage                                    | 4 (5.1)      | 6 (5.9)                   | 2 (7)                    | 9 (9.2)                  | 3 (4)          | 3 (4)          | -             |
| Cellulitis                                           | 4 (5.1)      | -                         | -                        | -                        | -              | -              | -             |
| Basal cell carcinoma                                 | 4 (5.1)      | -                         | -                        | -                        | -              | -              | -             |
| Infusion related reaction                            | -            | -                         | -                        | -                        | <b>1 (1)</b>   | <b>12 (16)</b> | -             |
| <b>Patients ≥ 1 TRAE</b>                             | 59 (75.6)    | 80 (79.2)                 | -                        | 84 (85.7)                | -              | -              | -             |
| <b>Most common treatment-emergent AE (TEAE)</b>      |              |                           |                          |                          |                |                |               |
| Neutropenia                                          | 8 (10.3)     | <b>22 (21.8)</b>          | 5 (18)                   | <b>11 (11.2)</b>         | -              |                | -             |
| Diarrhoea                                            | 5 (6.4)      | <b>11 (10.9)</b>          | 8 (29)                   | <b>23 (23.5)</b>         |                |                | -             |
| Fatigue                                              | -            | 11 (10.9)                 | 4 (14)                   | 9 (9.2)                  |                |                | -             |
| Contusion                                            | 19 (24.4)    | <b>10 (9.9)</b>           | 6 (21)                   | <b>22 (22.4)</b>         |                |                | -             |
| Epistaxis                                            | -            | 7 (6.9)                   | -                        | 14 (14.3)                |                |                | -             |
| Patients with any TE SAE                             | -            | 40 (39.6)                 | 11 (39)                  | 40 (40.8)                | 32 (43)        | 25 (33)        | -             |
| TE SAE ≥ Grade 3                                     | 39 (50.0)    | 59 (58.4)                 | -                        | 62 (63.3)                | -              | -              | -             |
| TR TE SAE                                            | -            | 16 (15.8)                 | -                        | 20 (20.4)                | -              | -              | -             |
| AE leading to treatment discontinuation              | 11 (14.1)    | 4 (4.0)                   | 2 (7.1)                  | 9 (9.2)                  | -              | -              | 10 (14)       |
| AE leading to death                                  | 5 (6.4)      | 1 (1.0)                   | 0 (0)                    | 4 (4.1)                  | -              | -              | 1 (1.4)       |
| AE Leading to dose reduction                         | 7 (9.0)      | 14 (13.9)                 | 2 (7.1)                  | 23 (23.5)                | -              | -              | -             |
| Patients with ≥ 1 AE of special interest             | 76 (97.4)    | 86 (85.1)                 | -                        | 81 (82.7)                | -              | -              | -             |

**Bold** typography indicates statistically significant differences between trial treatment arms, conducted during evaluation using STATA16.

Source: Table 2.55, pp120-121; Table 2.58, p123, Table 2.59, pp125-126; Table 34 and Table 35, pp115-116 Study AU003 CSR; iNNOVATE and Tedeschi 2015 publications.

AE=adverse event, BR=bendamustine+rituximab, CI=confidence interval, IBRU=ibrutinib, n=number of participants reporting data, N=total participants, ZANU=zanubrutinib, TEAE=treatment emergent adverse event, TE SAE=treatment emergent severe adverse event, TR=Treatment related.

- 6.32 The safety profile of BTKis is very different compared to either BR or Rm. For example, infusion-related adverse events occurred in more than half of patients treated with Rm in iNNOVATE (but none for zanubrutinib or ibrutinib since they are oral treatments), and IgM flares, a commonly reported AE for Rm, occurred in almost half of patients treated with Rm, but were not reported for zanubrutinib or ibrutinib.
- 6.33 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, see paragraph below). 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 patients (6% of total zanubrutinib patients from included studies) experiencing grade 3-4 major haemorrhage. The ESC considered that the safety profile for BTKis was generally manageable.
- 6.34 It is unclear how the addition of rituximab to ibrutinib affected the safety profile of the individual drugs. It is possible that rituximab may have resulted in increased AEs; for example, anaemia rates in the ibrutinib+R arm of iNNOVATE are double those seen in the ibrutinib arm of ASPEN (11% vs 5%, respectively) and are closer to those in the Rm arm of iNNOVATE (17%). Similarly, the rate of Grade  $\geq 3$  AF for ibrutinib+R was much greater than that for ibrutinib alone and Rm (12% vs 4% and 1%, respectively). Conversely, rates of major haemorrhage were equal in the ibrutinib+R and Rm arms (4%) of iNNOVATE and much higher in the ibrutinib monotherapy arm of ASPEN (9.2%). The possibility of other toxicity interactions in patients treated with ibrutinib+R remains a source of bias and may impact the safety results in the ITC given ibrutinib/ibrutinib+R was the common comparator.
- 6.35 The submission did not present safety results for zanubrutinib-treated patients in ASPEN-Cohort 2. These patients were more likely to discontinue treatment because of AEs compared to zanubrutinib patients in Cohort 1 and they reported higher rates of diarrhoea, contusion, and muscle spasms. They also experienced more Grade  $\geq 3$  AEs (64% vs 58%) and had higher rates in all of the most common Grade  $\geq 3$  AEs (except for neutropenia) compared to zanubrutinib patients in Cohort 1. While in Cohort 1 some AEs were lower in zanubrutinib than in ibrutinib, these differences were minimal between zanubrutinib patients in Cohort 2 and ibrutinib.

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

- 6.36 The ESC noted there were considerable inconsistencies in the submission's approach to the ITCs, with the comparisons in the TN population conducted only for response outcomes (i.e., MRR, ORR, VGPR, MR) and the comparisons in the R/R population conducted for both response outcomes (using naïve ITC) and PFS/OS (using MAIC). Furthermore, despite no PFS/OS comparison in the ITC for the TN population, the modelled economic evaluation (a partitioned survival model) was entirely based on those outcomes. The ITCs for the TN population were also based on data for the ITT

population (see paragraph 6.39 below). The modelled economic evaluation for the TN population applied PFS data for Rm from iNNOVATE but OS data from Tedeschi 2015 for BR (as proxy for OS for Rm, see *Economic analysis* for further discussion). The ESC considered these inconsistencies hampered the interpretation of comparative outcomes.

### ITC zanubrutinib vs Rm

6.37 The submission presented an ITC comparing zanubrutinib and Rm via the Bucher method using commonly reported response outcomes and safety results between ASPEN and iNNOVATE, using ibrutinib/ibrutinib+R arms as a ‘common’ reference. The ITT trial populations were used as iNNOVATE did not report separate response outcomes for TN or R/R subgroups. This may limit the applicability to the TN population.

6.38 As discussed above (see paragraph 6.12), there were important differences between ASPEN and iNNOVATE impacting transitivity.

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

| Outcomes | ASPEN           |                 |                           | iNNOVATE          |               |                           | ITC (ZANU v Rm)*                |
|----------|-----------------|-----------------|---------------------------|-------------------|---------------|---------------------------|---------------------------------|
|          | IBRU<br>n/N (%) | ZANU<br>n/N (%) | IBRU v ZANU<br>RR (95%CI) | IBRU+R<br>n/N (%) | Rm<br>n/N (%) | IBRU+R v Rm<br>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)<br>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)<br>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)<br>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)<br>p = 0.3865 |

Highlighted cells represent the ‘common’ comparator arm.

Source: Table 2.61, p129 of the submission.

CI=confidence interval, IBRU=ibrutinib, ITC=indirect treatment comparison, MR=minor response, MRR=major response rate, ORR=overall response rate, Rm=rituximab monotherapy, RR=risk ratio, VGPR=very good partial response, ZANU=zanubrutinib.

\* Indirect estimate of effect adjusted for the common reference, numbers have been rounded.

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

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

Highlighted cells represent the 'common' comparator arm.

Source: Table 2.62, p130 of the submission.

CI=confidence interval, IBRU=ibrutinib, ITC=indirect treatment comparison, Rm=rituximab monotherapy, RR=risk ratio, ZANU=zanubrutinib.

\* Indirect estimate of effect adjusted for the common reference.

- 6.39 The results of the ITC may not be applicable to the requested TN population since the combined TN/RR population was used as proxy for the TN population. However, use of the ITT instead of the TN population may have had minimal impact on the ITC as the reported response outcomes for zanubrutinib appeared to be reasonably consistent in the ITT/TN/RR populations for MRR, ORR, VGPR and MR.
- 6.40 Overall, the submission concluded that the ITCs supported a clinical claim of superior efficacy of zanubrutinib compared to Rm. Despite the caveats noted, this claim may be reasonable in terms of response outcomes given iNOVATE found ibrutinib+R to be superior to Rm and ASPEN found zanubrutinib to be likely noninferior to ibrutinib, and the size of the effect difference between ibrutinib+R and Rm was reasonably large in iNOVATE.
- 6.41 This conclusion however 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 appear 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.
- 6.42 The submission's ITC for commonly reported safety outcomes in ASPEN and iNOVATE using ibrutinib/ibrutinib+R as common comparator was not considered informative by the evaluation because of the very different safety profile of Rm (see paragraphs 6.32 and 6.33). Also, the ibrutinib+R combination appeared to be different to the AE profile of ibrutinib monotherapy.
- 6.43 The submission did not discuss other important and severe AEs for zanubrutinib in the ITC such as Grade 3 major haemorrhage, which occurred in approximately 6% of patients treated with zanubrutinib. The submission also did not discuss the implications of the difference in duration of treatment between the two regimens,

given zanubrutinib is an indefinite-duration therapy. As WM is an indolent cancer, there is a potential for increased long-term toxicity compared with Rm, which was not investigated by the included studies due to their limited follow-up. The ESC 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.

### ITC zanubrutinib vs BR

- 6.44 Given the lack of a common comparator linking zanubrutinib and BR, the submission conducted 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. The ESC 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.

**Table 9: Pairwise MAIC\* presented in the submission**

|   | ZANU population (ASPEN)             | Comparator population (Tedeschi 2015) | Outcomes compared               |
|---|-------------------------------------|---------------------------------------|---------------------------------|
| 1 | 102 patients with WM (ITT Analysis) | 71 R/R patients in the trial for BR   | PFS, OS, common safety outcomes |
| 2 | 83 patients in the R/R subgroup     | 71 R/R patients in the trial for BR   | PFS, OS, common safety outcomes |

Source: Table 2.65, p134 of the submission.

BR=bendamustine rituximab; ITT=intent-to-treat; MAIC=matching-adjusted indirect comparison; R/R=relapsed or refractory.

\* Note that the results presented in the MAIC analyses are derived from ad-hoc/post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the included trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.45 The matching algorithm proposed by Signorovitch et al. (2012) was used to adjust for differences in baseline patient and disease characteristics between the studies. The matching variables considered for inclusion in the MAIC are presented in Table 10. Only some of these variables were reported in Tedeschi 2015.

**Table 10: Matching variables considered in the MAIC**

| Matching variables                                               | Reported in Tedeschi 2015 |
|------------------------------------------------------------------|---------------------------|
| Age ( $\leq 75$ vs $> 75$ years)                                 | median (range)*           |
| Number of prior therapies (0–3 vs $> 3$ lines; 1–3 vs 3 lines)   | median (range)*           |
| ECOG performance status (0–1 vs $> 1$ )                          | No                        |
| MYD88/CXCR4 mutation status                                      | No                        |
| IgM concentration ( $\leq 40$ vs $> 40$ g/L)                     | median (range)*           |
| $\beta 2$ -microglobulin concentration ( $\leq 3$ vs $> 3$ mg/L) | No                        |
| Platelet count ( $\leq 100$ vs $> 100 \times 10^9/L$ )           | No                        |
| Haemoglobin concentration ( $\leq 110$ vs $> 110$ g/L)           | No                        |
| Presence of extramedullary disease                               | Yes                       |
| IPSSWM risk categories                                           | Yes (low, medium, high)   |

Source: p134 of the submission

\*median values used to estimate the proportion of patients with these variables

- 6.46 It was unclear why the submission did not use IRC-assessed data, as investigator-assessed outcomes are more likely to be biased. The proportion of extramedullary

disease based on investigator assessments was lower than the IRC-assessed values (61.8% vs 79.4%, p79 ASPEN CSR).

- 6.47 The submission did not justify why response outcomes were not included in the MAIC, but were instead analysed using naïve ITC. The PSCR presented a MAIC for ORR using investigator assessed outcomes from the ASPEN R/R analysis set versus Tedeschi et al. 2015 (see below). The PSCR claimed there were no differences in the MAIC results when using IRC or investigator assessed outcomes when considering ORR.

**Table 11: 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   |

\*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

- 6.48 The ESC considered it was unclear why MAICs were not performed for the primary outcomes in ASPEN (VGPR/CR), which the submission had suggested were indicative of higher effectiveness.
- 6.49 The submission presented PFS and OS results before and after matching adjustment (Table 12). 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). The submission did not explain this discrepancy.

**Table 12: 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             |     |           |     |
|----------|------------------------------------------|-----|------------------------------|-----|-----------|-----|
|          |                                          |     | ZANU post-matching BR (N=50) |     | BR (N=71) |     |
|          | PFS                                      | OS  | PFS                          | OS  | PFS       | OS  |
| 12m      | 94%                                      | 97% | 94%                          | 98% | 79%       | 87% |
| 24m      | 85%                                      | 90% | 81%                          | 88% | 59%       | 77% |

Source: Table 2.69, p136 of the submission.

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

- 6.50 The PFS and OS HRs comparing zanubrutinib to BR pre-matching and post-matching are reported in Table 13, and KM curves before and after matching are presented in Figure 4 and Figure 5.

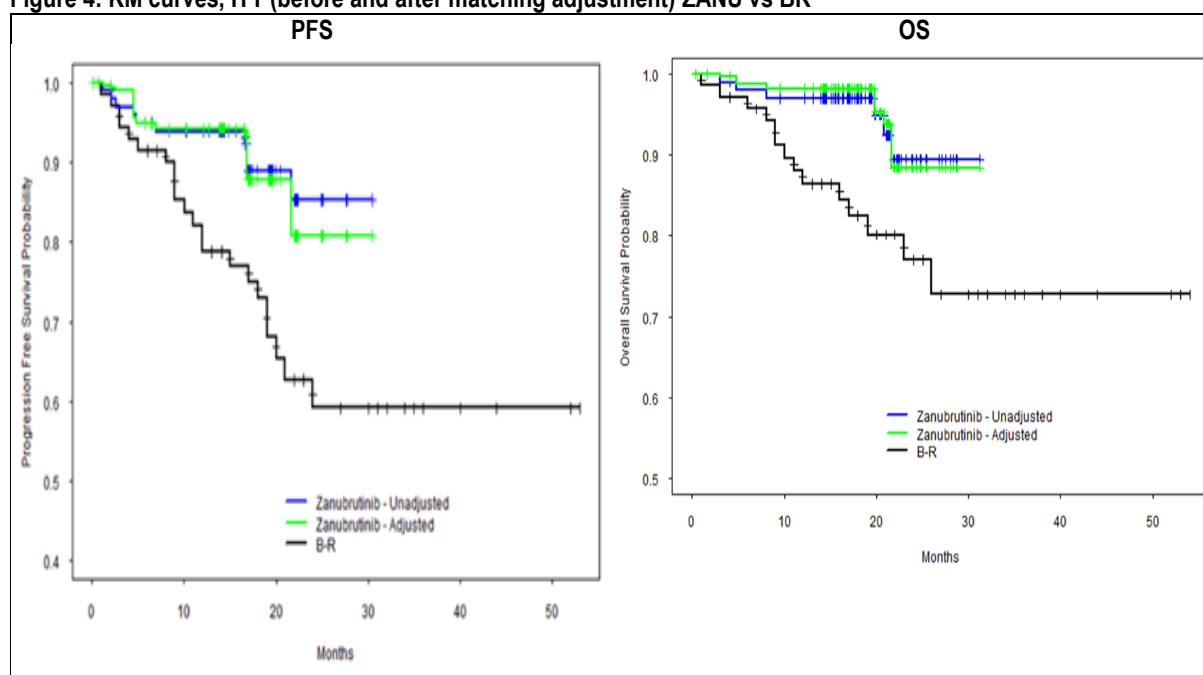
**Table 13: Hazard ratio ZANU (before and after matching adjustment) vs BR**

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

Source: p136 of the submission.

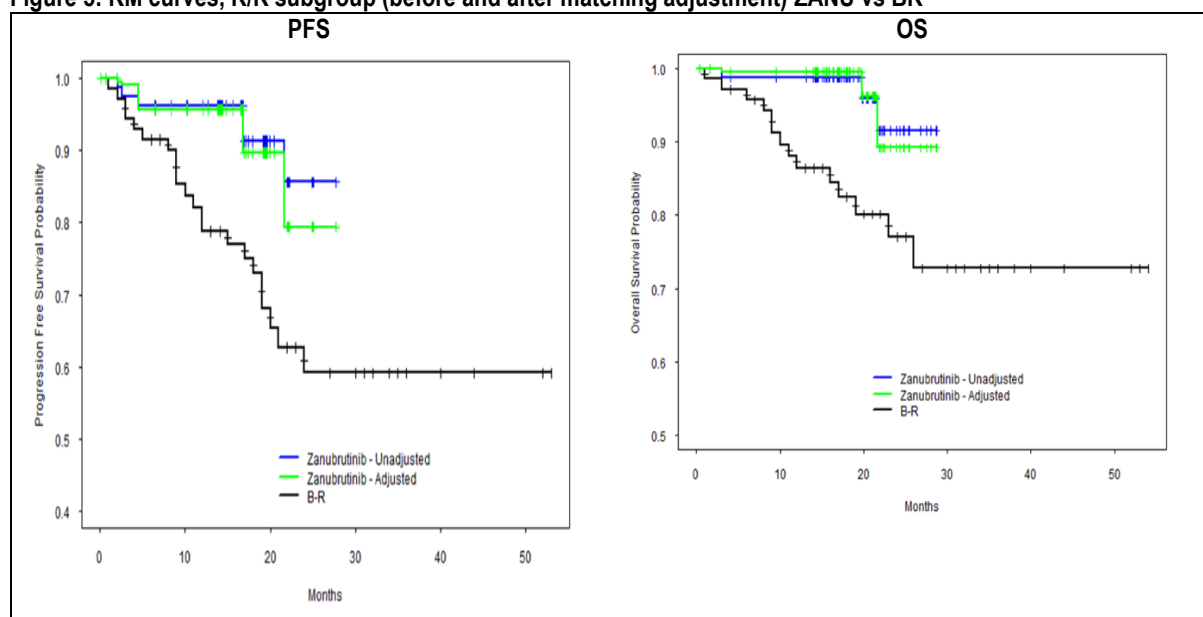
BR=bendamustine+rituximab, CI=confidence interval, HR=hazard ratio, OS=overall survival, PFS=progression-free survival, ZANU=zanubrutinib.

**Figure 4: KM curves, ITT (before and after matching adjustment) ZANU vs BR**



Source: Figure 2.34, p137 and Figure 2.35, p137 of the 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.

**Figure 5: KM curves, R/R subgroup (before and after matching adjustment) ZANU vs BR**



Source: Figure 2.36, p138 and Figure 2.37, p138 of the submission.  
 BR=bendamustine+rituximab, KM=Kaplan-Meier, PFS=progression-free survival, R/R=relapsed or 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.

6.51 The submission 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%), which added to the uncertainty of the claim. 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. 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 of these factors may have reduced treatment efficacy in Tedeschi 2015.

6.52 The submission also conducted a MAIC for selected safety outcomes (Table 14).

**Table 14: AEs grade  $\geq 3$  occurring in  $\geq 5\%$  of patients, ZANU (before and after matching adjustment) vs BR**

| Outcomes            | ZANU pre-matching (N=102) | MAIC of ZANU vs BR           |           |
|---------------------|---------------------------|------------------------------|-----------|
|                     |                           | ZANU post-matching BR (N=50) | BR (N=71) |
| Anaemia, %          | 5.0                       | 3.6                          | NR        |
| Hypertension, %     | 5.9                       | 9.5                          | NR        |
| Neutropenia, %      | 15.8                      | 17.5                         | 35.2      |
| Pneumonia, %        | 1.0                       | 1.5                          | 5.6       |
| Thrombocytopenia, % | 5.9                       | 5.2                          | NR        |

Source: Table 2.70, p138 of the submission.

AEs=adverse events, BR=bendamustine+rituximab, MAIC=matched-adjusted indirect comparison, ZANU=zanubrutinib.

6.53 Results showed that zanubrutinib was associated with lower rates of neutropenia and pneumonia compared to BR. Anaemia and thrombocytopenia were recorded in 3% of the BR courses, but Tedeschi 2015 did not report rates per patient. BR and zanubrutinib have very different safety profiles, while BR was associated with a higher rate of neutropenia, zanubrutinib patients experienced Grade  $\geq 3$  AEs that were not reported in Tedeschi 2015, such as hypertension, anaemia, thrombocytopenia and major haemorrhage. These events are more difficult to manage and potentially concerning given zanubrutinib is an indefinite-duration treatment likely to be taken by patients long-term.

6.54 One key difference between the evidence for zanubrutinib and BR was the study design. ASPEN was a randomised trial with a very specific eligibility criteria, whereas Tedeschi 2015 was a retrospective cohort analysis which did not specify inclusion criteria beyond a diagnosis of R/R WM and treatment with BR. In particular, there were no restrictions on previous treatments, surgery, malignancies or comorbidities, as was the case in ASPEN. Therefore, it is possible that some patients in Tedeschi 2015 may not have been eligible for inclusion in ASPEN. As with the ITC of safety outcomes for zanubrutinib and Rm, the ESC 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 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.

## **Benefits/harms**

- 6.55 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. The estimated effect size in this comparison was associated with high uncertainty. Accordingly, a benefits/harms table was not been presented.

## **Clinical claim**

- 6.56 The submission described zanubrutinib as:
- superior in terms of effectiveness and safety compared to Rm in TN patients unsuitable for chemo-immunotherapy, and
  - superior in terms of effectiveness and safety compared to BR in R/R WM patients.
- 6.57 Overall, the ESC considered these claims were not adequately supported due to the following:
- For zanubrutinib versus Rm, while the claim of superior effectiveness may be reasonable for response outcomes, the magnitude of the effect was uncertain. Furthermore, the same conclusion cannot be extended to survival outcomes given the lack of ITC for PFS and OS and mature survival data. This is important as differences across studies, particularly patient baseline characteristics, are more likely to impact on survival than response rates, and response rates are considered poor surrogates for survival in WM.
  - For zanubrutinib versus BR, response rates were not compared in the MAICs (though the data was available). The PFS and OS data from ASPEN were immature, with limited events for both PFS (15%) and OS (8%), creating uncertainty. Further, the reported differences in PFS and OS between zanubrutinib and BR may be due to differences in baseline characteristics between ASPEN-Cohort 1 and Tedeschi 2015, such as genetic profile, ECOG status and serology, which are all known confounders for effectiveness and could not be adjusted for in the MAICs. Tedeschi 2015 also recruited patients who were refractory to rituximab and included 37% of patients who received a suboptimal dose of BR. Both factors could bias the results against BR.
  - The safety profiles of zanubrutinib, Rm and BR are substantially different, thus the submission's ITCs of commonly reported AEs were not informative. For example, Grade 3 $\geq$  neutropenia occurred in 15.8% of zanubrutinib patients, while IgM flares were common (47%) in the Rm arm of iNOVATE; but these AEs were not included in the ITCs for safety outcomes as they were not common between all treatments. The claim of superior safety for zanubrutinib vs BR was based on the higher proportion of Grade  $\geq$ 3 neutropenia and pneumonia with BR, but ASPEN reported other Grade  $\geq$ 3 AEs such as hypertension, anaemia, thrombocytopenia and major haemorrhage that were not reported in Tedeschi 2015. The submission also did

not discuss other important and severe AEs for zanubrutinib such as Grade  $\geq 3$  major haemorrhage, which occurred in approximately 6% of patients treated with zanubrutinib. The PSCR maintained the claim of superior safety over Rm. The PSCR considered that addition of rituximab to one of the 'common' comparator arms likely biased the ITC results in favour of Rm. The PSCR noted that while the incidence of Grade  $\geq 3$  major haemorrhage was higher in ASPEN than iNOVATE, it resolved in 5 out of the 6 who experienced this AE. The PSCR also noted that clinicians generally consider neutropenia to be manageable through safety monitoring, use of granulocyte colony-stimulating factor (G-CSF) and dose reductions and it claimed that ability to manage AEs associated with zanubrutinib is shown by the low rate of treatment discontinuation in the zanubrutinib arm of ASPEN (4.0%). The PSCR noted that Rm-specific AEs such as IgM flares are associated with several symptoms that are detrimental to patient QoL such as significant risk of opportunistic and repeated infections. The PSCR argued that given the slow resolution time of transient IgM increases, the detrimental effects of IgM flare represent an issue of ongoing management for patients and clinicians. The PSCR also maintained the claim of superior safety over BR, noting BR was associated with a higher rate of treatment discontinuation compared with zanubrutinib when ASPEN and Study AU-003 safety results were pooled.

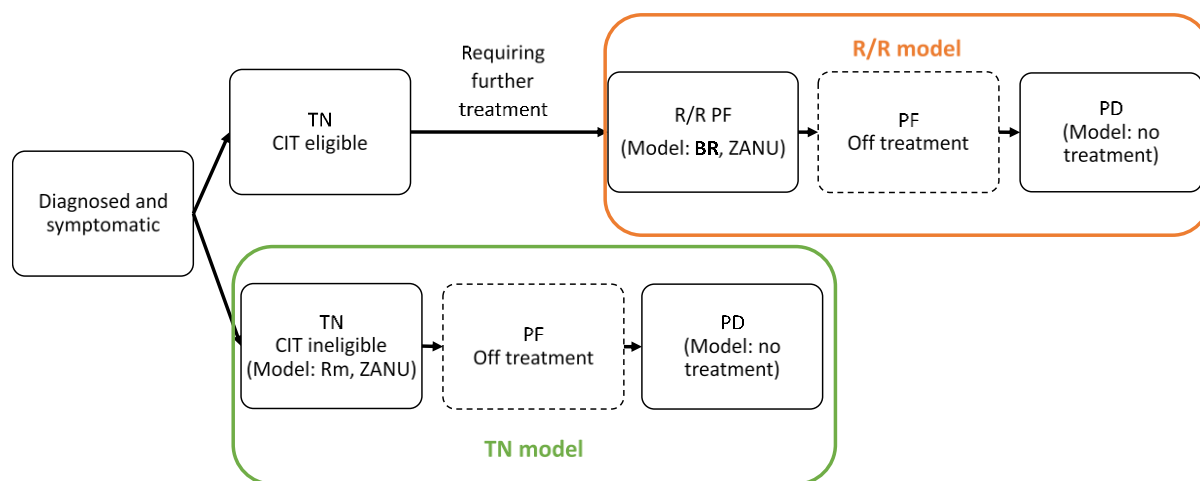
- The submission also did not discuss the implications of the difference in treatment duration between zanubrutinib and chemo-immunotherapy regimens. Given zanubrutinib is an indefinite-duration therapy, there is potential for increased long-term toxicity compared with BR or Rm, which was not investigated by the included studies due to their limited follow-up. The PSCR stated that BTKis are associated with AEs that tend to occur early in treatment rather than later, and that no longer-term toxicities have been identified with extended zanubrutinib use. The PSCR presented data from ASPEN showing that the incidence rates of many categories of AEs plateau after 24 months. The ESC considered that in the absence of comparative data, the uncertainty around the long-term comparative safety of zanubrutinib remained.
- 6.58 The submission also claimed improved effectiveness and superior safety compared to ibrutinib (as a near future comparator). The ESC considered the claim had been a prudent inclusion in the submission as it related to a potential near market comparator, but the ESC noted that it was not relevant for PBAC decision-making regarding zanubrutinib at the present time.
- 6.59 For the TN population, the PBAC considered that the claim of superior comparative effectiveness was reasonable in terms of response outcomes. The PBAC noted that response outcomes were not compared for the R/R population. The PBAC considered the available clinical data did not adequately support a claim of superior comparative effectiveness for zanubrutinib in terms of survival outcomes in either the TN or R/R population.

- 6.60 The PBAC considered it was difficult to assess the comparative safety of zanubrutinib given the different adverse event profile of zanubrutinib compared to Rm and BR. It considered that the evidence presented did not adequately support a claim of superior safety.

***Economic analysis***

- 6.61 The submission presented two separate economic evaluations comparing zanubrutinib to Rm in TN chemo-immunotherapy-unsuitable WM patients; and zanubrutinib to BR in R/R WM patients (herein referred to as TN and R/R models respectively). Data from three studies were used to populate the model: ASPEN-Cohort 1 (herein ASPEN) for zanubrutinib PFS, OS and TTD; iNNOVATE for Rm PFS; and Tedeschi 2015 for BR PFS and OS. BR OS data from Tedeschi 2015 was also used as a proxy for Rm OS (discussed further below).
- 6.62 The type of economic evaluation presented was a cost-utility analysis using partitioned survival analyses with three health states: alive without progression (PFS), alive following progression (PD), and dead. A visualisation was produced during the evaluation depicting where the two economic models fit in the patient treatment pathway.

Figure 6: Simplified treatment pathway



Source: compiled during the evaluation.

CIT=chemo-immunotherapy, PD=progressed disease, PF=progression free, R/R=relapsed/refractory, TN=treatment naïve.

Note: While not explicitly stated, patients in the model can be in PF with or without treatment. Subsequent lines of treatment are not modelled outside of the first treatment in each model. Patients in R/R can enter the R/R model at any line of treatment after first line. Patients can remain in any state for multiple cycles. Patients can die in any health state.

6.63 The submission's modelling inherently assumed there is no link between first and subsequent lines of therapy. Chemo-immunotherapy unsuitable patients entered the TN model and received one line of therapy. Separately, patients with at least one prior therapy entered the R/R model and received one line of treatment. While the structure selection may be driven by the lack of data for any longer-term health state transitions or efficacy in subsequent treatments, a partitioned survival structure with just one line of treatment does not reflect the relapse-remitting nature of WM. The PSCR accepted that patients may cycle through all relevant treatments over the entire disease course of WM. The PSCR stated that subsequent therapy costs were included in the economic evaluation and that the clinical effect of subsequent therapies was accounted for through the use of overall survival from the clinical studies. The ESC noted subsequent treatments were not explicitly modelled in the economic evaluation, and considered that the follow-up durations of the included studies were unlikely to capture any effects of downstream treatments.

6.64 A summary of the model is presented below.

Table 15: Summary of model structure, key inputs and rationale

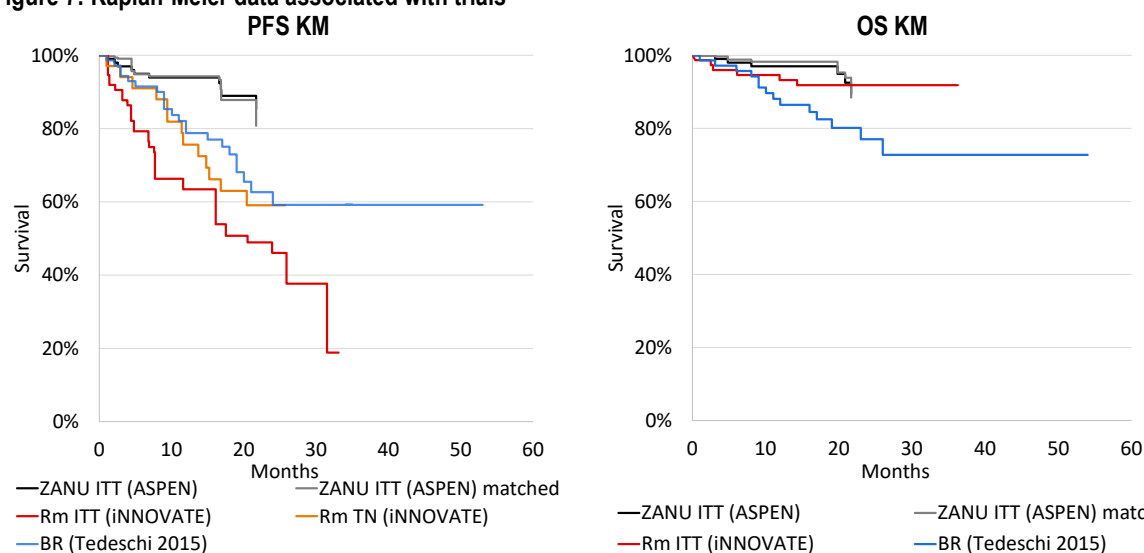
| Component                        | Description                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                               | Justification/comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  | TN model                                                                                                                                                                                                                                                                                                                                                                     | R/R model                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Type of analysis                 | Cost-utility analysis                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                               | Appropriate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Outcomes                         | Life years gained, quality-adjusted life years gained                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                               | Appropriate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Methods used to generate results | Partitioned survival analysis                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                               | While a Markov model may be a better fit for a relapse-remitting disease, there was limited data to inform the relationship between potential health states or state transitions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Health states                    | Three health states:<br>• PFS<br>• PD<br>• Dead (absorbing state)                                                                                                                                                                                                                                                                                                            | Three health states:<br>• PFS<br>• PD<br>• 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).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Cycle length                     | 28 days, half cycle correction applied                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                               | Appropriate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Time horizon                     | 20 years vs median follow up of 19.5 months in ASPEN, 26.5 months in iNNOVATE, and 19 months in Tedeschi 2015.                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                               | The estimation of OS left 33% of patients alive at the end of the 20-year period in the ZANU arms of both models. These patients therefore accrued all the benefits of longer OS without terminal care costs which would be accrued by everyone eventually (on death). There was also no long-term evidence of a sustained survival benefit for ZANU versus the two comparators.                                                                                                                                                                                                                                                                                                        |
| Allocation to health states      | Based on independent parametric extrapolations of PFS and OS KM curves from ASPEN (ITT population) for ZANU, and data from iNNOVATE Rm treatment arm for PFS and Tedeschi 2015 BR treatment for OS for Rm.                                                                                                                                                                   | Based on parametric extrapolations of PFS and OS KM curves from ASPEN using a matched subset of the ITT populations for ZANU and Tedeschi 2015 for BR.<br><br>PFS extrapolations were modelled jointly. OS was extrapolated with a different parametric extrapolation for each treatment arm. | PFS and OS data used in the model to extrapolate survival were very immature, particularly for ZANU OS since few events had occurred in any of the treatment arms, thus any comparison of OS would be highly uncertain, magnified by extrapolating the data to 20 years. The TN model was based on data for the ITT population for ZANU rather than data for TN patients. For Rm, the OS data was based on OS data for BR from Tedeschi 2015 for R/R patients, which included patients who were refractory to rituximab. Differences in the relationship between PFS and OS across arms may also be a result of the differences in the studies informing estimates particularly for Rm. |
|                                  | 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.                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Utility values                   | – The submission estimated utilities for the PFS health state from EQ-5D-5L data collected during ASPEN until study discontinuation, but was focused on pre-progression utility.<br>– PD utility decrement of 0.1 based on NICE TAs of IBRU (TA502 and TA429)<br>– Adverse event disutilities were modelled separately using values reported in the NICE TA491 (IBRU for WM) |                                                                                                                                                                                                                                                                                               | Utilities did not account for treatment or level of response in patients. The model slightly favoured the comparator arms.<br>Utilities were based on the UK value set. PD disutility was not based on WM or ZANU data and therefore may not be representative of PD for WM.<br>AEs were captured as one-off events in the model. As ZANU is an initial and maintenance drug, not all AEs were captured in ASPEN.                                                                                                                                                                                                                                                                       |
| Software package                 | Excel 2010                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                               | Appropriate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

Source: Compiled during the evaluation based on data presented on pp148, 151-152 and Tables 3.7 and 3.12 in the submission.

AE=adverse event, BR=bendamustine plus rituximab, EQ-5D-5L=EuroQoL 5-dimension 5-level quality of life questionnaire, IBRU=ibrutinib, KM=Kaplan-Meier, OS=overall survival, PD=progressive disease, PFS=progression free survival, Rm=rituximab monotherapy, ZANU=zanubrutinib.

6.65 Instead of applying KM data followed by extrapolated data, the model was entirely based on modelled data for both PFS and OS. PFS and OS KM data from ASPEN, iNNOVATE and Tedeschi 2015 were used to select the best fitting parametric functions. To assist with model validation, KM data from the included study arms were sought from the sponsor during the evaluation and replotted in Figure 7 below. The reproduced KM curves for zanubrutinib (both matched and unmatched) were not identical to those presented in the submission. The reason for this discrepancy was unclear as other plots matched those in the submission. A correction was also made by the sponsor during evaluation to change the Rm PFS to be based on ITT data from iNNOVATE, rather than data from the TN subgroup. A summary of the KM data and the extrapolation in the model is presented in Table 16 below. The ESC considered that the disparity between the outcomes which formed the basis of the submission's superiority claim and those modelled in the economic evaluation added to the overall uncertainty associated with the results of the economic evaluation.

**Figure 7: Kaplan-Meier data associated with trials**



Source: compiled during the evaluation using: 'Digitized KM and re-created IPD\_Tedeschi 2015\_forBeiGene\_2021Apr6\_CEPL\_Rm\_Dimopolous 2018\_2021Apr8.xlsx', 'INV PFS\_wt\_BR.xlsx' and 'OS\_wt\_BR.xlsx' obtained from the sponsor during the evaluation.

BR=bendamustine+rituximab, KM=Kaplan-Meier, OS=overall survival, PFS=progression free survival, Rm=rituximab monotherapy, R/R=relapsed/refractory, TN=treatment naïve, ZANU=zanubrutinib.

**Table 16: Summary of extrapolations used in the economic model by treatment arm and survival curve**

| Model | Arm (source)                                | PFS                                                                     | OS                                                                                       | Time on treatment                                                          |
|-------|---------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| TN    | ZANU (ITT ASPEN)                            | <u>Independent</u> exponential extrapolation, restricted to be below OS | <u>Independent</u> exponential extrapolation, restricted to general population mortality | ASPEN TTD extrapolation restricted to be below OS                          |
|       | Rm (ITT iNNOVATE for PFS Same as BR for OS) |                                                                         | Same as BR OS                                                                            | Fixed time on treatment assumed based on the planned dose in iNNOVATE      |
| R/R   | ZANU (ITT ASPEN matched to Tedeschi 2015)   | <u>Dependent</u> exponential extrapolation, restricted to be below OS   | <u>Independent</u> exponential extrapolation, restricted to general population mortality | ASPEN TTD extrapolation restricted to be below OS                          |
|       | BR (Tedeschi 2015)                          |                                                                         | <u>Independent</u> Weibull extrapolation, restricted to general population mortality     | Fixed time on treatment assumed based on the planned dose in Tedeschi 2015 |

Source: Tables 3.12 and 3.24 from the submission and compiled during the evaluation

BR=bendamustine+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.

#### 6.66 There were significant inconsistencies in the submission's approach to extrapolation:

- ITT data (with a combination of TN and R/R patients) from ASPEN and iNNOVATE were used to represent TN patients, thus the overall model validity in the TN population was questionable.
- Furthermore, in the TN model, OS data for Rm were actually based on BR from the R/R model, further affecting validity. In addition, BR data was derived from Tedeschi 2015, where 18% of patients were rituximab-refractory and, therefore, would not be treated with rituximab.
- ITT data matched to Tedeschi 2015 was used in the R/R model. A number of important differences between Tedeschi 2015 and ASPEN could not be adjusted for in the MAIC (see paragraph 6.51), affecting transitivity and potentially biasing the results against BR.
- Modelling of PFS and OS in the TN model did not consider an assessment of proportional hazards and the two treatment arms were fitted independently to parametric functions. Conversely, in the R/R model, a proportional hazard test was considered important. As proportional hazards could not be rejected for either PFS or OS, PFS was modelled dependently (where the zanubrutinib and BR were jointly fitted to parametric functions with treatment as covariate) however, OS was still modelled independently. The submission did not justify this inconsistent approach. In general, independent PFS extrapolations seemed reasonable. Due to data paucity, it was not possible during the evaluation to test the proportional hazard assumption for the TN model.
- 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 dose).

- The KM data used for parametric extrapolations were based on investigator-assessed PFS. There was potential for bias compared to IRC data given investigators were not blinded to treatment assignment and assessment of disease progression was somewhat subjective.
- 6.67 The ESC noted that the uncertainties around interpretation of comparative effectiveness of zanubrutinib would also be issues for the interpretation of the results of the economic analyses. The ESC considered that uncertainty in the economic analyses was further increased by the reliance on modelled data only and inconsistencies between approaches taken for each extrapolation.
- 6.68 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. The submission stated that predictions in the unobserved period were considered for clinical plausibility when selecting the parametric curve. Given data were quite immature, it appeared that clinical plausibility was the main factor in extrapolation choice.
- 6.69 Due to limited KM data relative to model duration, all parametric functions appeared to fit the KM data initially while large variations were seen in the tail end of the distributions. Even seemingly minor changes in KM data, for example using ASPEN ITT data versus ASPEN ITT data matched to Tedeschi 2015 for zanubrutinib, or swapping between jointly fitted versus independently fitted curves, led to wide variations in terms of longer term predictions, further highlighting the uncertainty in the extrapolations.

#### **Extrapolation of PFS**

- 6.70 The exponential distribution was chosen on the above basis as the most appropriate fit for PFS in all treatment arms of both models. The only distinction was that in the R/R model, extrapolation for zanubrutinib was based on a dependent function with BR rather than independent functions.

#### **Extrapolation of OS**

- 6.71 The extrapolations for OS were unreliable. Based on AIC, BIC, visual inspection and clinical plausibility, independent exponential extrapolations for zanubrutinib were chosen in both the TN and R/R models. These produced the largest survival estimates of any extrapolation, with WM mortality matching general population mortality from about year 10 until model end. In both the TN and R/R models, more than 33% of patients were alive at the end of the 20-year time horizon, compared to less than 10% in the comparator arms. The pre-PBAC response maintained that an overall survival gain for zanubrutinib was plausible. The pre-PBAC response argued that in the context of the limited evidence, the exponential distribution was the most appropriate on the

basis that it required the fewest parameters to be specified and therefore was associated with the fewest assumptions beyond the observed trial data.

- 6.72 An independent Weibull extrapolation was chosen to estimate survival for the BR arm based on clinical plausibility. This had the worst statistical fit of all the curves (highest AIC, BIC) and the second most conservative estimate of survival. The independent exponential function had the lowest AIC and BIC and would have given similar but slightly improved survival for BR compared to the Weibull distribution. No justification was presented in the submission as to why this was less clinically plausible. Other independent extrapolations of zanubrutinib and BR produced very different estimates of OS.
- 6.73 The submission also used BR data from the R/R model to substitute for Rm data in the TN model, arguing that extrapolated OS, based on Rm data from the iNNOVATE ITT population did not produced clinically plausible results. This was not appropriate (see paragraph below). Further, the evaluation noted a discrepancy in the parameters for Rm OS extrapolation in the model where they did not match those for BR (with the exception of the exponential function) and were also different to the extrapolations based on iNNOVATE data.
- 6.74 Using BR data for Rm introduced considerable uncertainty to the model. The KM OS curve for zanubrutinib crossed that for Rm but not BR, suggesting that using BR to represent Rm likely underestimated patient survival in the Rm arm, potentially favouring zanubrutinib. It could be argued that TN patients in iNNOVATE may have been fitter than TN patients in ASPEN. Within iNNOVATE, 40% of Rm patients also received ibrutinib post-Rm, which may have improved their survival. However, this was reflective of current and emerging clinical practice where many patients appear to be accessing BTKi as second-line therapy via clinical trials or compassionate access. It also highlighted that if all patients are likely to cycle through the same treatments across their disease course, it may be unreasonable to explore a difference in OS, particularly when data informing OS is immature but generally showing no difference. A sensitivity analysis assuming no difference in OS between zanubrutinib and Rm increased the ICER significantly to \$455,000 to < \$555,000/QALY gained from a base case of \$75,000 to < \$95,000 (see Table 19). The ESC considered that the modelled survival benefit was the main source of uncertainty in the economic model and was poorly supported by the data.

#### **Extrapolation of time on treatment**

- 6.75 Time on treatment for zanubrutinib was extrapolated using limited TTD KM data from ASPEN. The extrapolations were based on unadjusted ITT data in the TN model and ITT data matched to Tedeschi 2015 in the R/R model. Visually, all extrapolations fitted the KM data well, but large variations were seen in the tail end of the distributions. Based on statistical fit, the exponential function was chosen with an estimated average treatment duration of 7 years in the base case. This is however uncertain given the small differences in the TTD KM data between the matched and unmatched groups for

zanubrutinib resulted in large differences in extrapolations, particularly for the Gompertz distribution where the average treatment durations varied from 7.3 years to 5.1 years based on unmatched data and matched data respectively.

## Utilities

- 6.76 Health state utility for patients in the PFS state in both models, irrespective of treatment received, was assumed to be 0.791. This was based on EQ-5D-5L results from ASPEN that were first mapped to EQ-5D-3L and then regressed based on patient characteristics. For the PD health state, an assumption was made to apply a disutility of 0.1 to the PFS health state utility based on data for ibrutinib in CLL. Disutilities were also applied for Grade 3 or above AEs based on assumed AE rates from the clinical studies. While some discrepancies were detected with respect to the assumed AE rates, with some important Grade 3 or above AEs omitted for zanubrutinib and comparators, modelled AEs and their associated disutilities had minimal impact on the cost-effectiveness results. Changes to the health state utilities had a moderate effect on the model results, however they were overshadowed by survival gains.

## Costs

- 6.77 For zanubrutinib, the per cycle cost of treatment was based on the effective AEMP of \$ [REDACTED] for 120 capsules, which provides for 30 days of treatment at a dose of 320 mg per day (4x80 mg capsules) to be taken until either intolerable toxicity or disease progression, with an assumed dose intensity of 97.6%. The cost of zanubrutinib should be based on the requested effective DPMQ of \$ [REDACTED] rather than AEMP and model results were updated to reflect this. However, given the relatively small difference, this error had minimal impact on the model results.
- 6.78 For the comparators, the per cycle cost of Rm was based on an assumed price of \$1,093.25 per 500 mg vial and the recommended dose of 375 mg/m<sup>2</sup> administered weekly for two 4-week blocks with a 12-week break in between for Rm and once every 4 weeks for 6 cycles (i.e., total 24 weeks) for BR. The assumed price for rituximab 500 mg vial could not be verified, based on the PBS listing (items 4614W, 7257Y) the DPMA should be \$1,327.26 for 700 mg (1x500 mg vial plus 2x100 mg vials). The per cycle cost of bendamustine was based on the weighted average PBS price of \$1,745.54 per 2x100 mg vials at a dose of 90 mg/m<sup>2</sup>, administered for 2 days every four weeks for 6 cycles (24 weeks). For both Rm and BR, dosing was based on the mean body weight of 1.86 m<sup>2</sup> from ASPEN. Neither comparator is PBS listed in its respective setting.
- 6.79 Terminal care cost was a significant driver of costs in the comparator arms, due to shorter mean survival and fewer patients alive at the end of the time horizon (<10% compared to >30% in the zanubrutinib arms). Terminal care/end of life costs were taken from Goldsbury et al., 2018, based on final year of cancer treatment, and inflated to 2020 costs. These costs were applied in the cycle in which a patient's death

occurred. However, a scenario analysis assuming all patients would accrue this cost by model end did not significantly impact the ICER (3% increase).

## Results

6.80 Key drivers of the model are summarised 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            | 20 years vs 19.5 months follow up in ASPEN, 26.5 months in iNNOVATE and 19 months in Tedeschi 2015.*                                                                                                                   | Favoured ZANU. A reduction in the time horizon increased the ICER significantly, assuming a 10-year time horizon increased the ICERs to >\$ [redacted] <sup>3</sup> per QALY gained in both the TN and R/R models.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Use of KM data          | Used to fit parametric functions for PFS/OS and TTD but was not directly used in the model. OS KM data from iNNOVATE was not used to fit the parametric functions for Rm in the TN model, but was based on BR KM data. | Favoured ZANU, particularly as the KM data for OS for ZANU and Rm (based on ITT data from ASPEN for ZANU and ITT data from iNNOVATE for Rm) were observed to cross (see Figure 7). A sensitivity analysis using KM data to 30 months followed by extrapolation increased the ICER substantially in the TN model to >\$ [redacted] <sup>3</sup> per QALY gained.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| PFS extrapolation       | Extrapolations of ASPEN, iNNOVATE and Tedeschi 2015 applied from cycle 1 of the model.                                                                                                                                 | Favoured ZANU. 155.8% and 87.2% of incremental LYs for ZANU versus Rm and BR respectively were accrued in PFS, which had a higher utility. The data used to inform the extrapolation were uncertain, using mixed TN and R/R data in both models. There were also significant differences between all the included studies affecting exchangeability and thus results of any ITCs were considered uncertain.                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| OS benefit              | Extrapolations based on immature OS KM data from ASPEN and Tedeschi 2015 and applied from cycle 1 of the model.                                                                                                        | ZANU was assumed to have a sustained survival benefit over comparators. This assumption strongly favoured ZANU.<br><br>The survival data from included studies were immature. While this was problematic/uncertain for PFS (see points above), it was even more uncertain for OS where there were even fewer events and observed OS for ZANU and Rm crosses at around 20 months, suggesting potentially no difference in OS. OS extrapolation for Rm was also based on the extrapolation for BR from the R/R population.<br><br>When no difference in survival (since all patients are likely to eventually cycle through the same treatments over time due to the relapse-remitting nature of WM) is assumed, the ICER increased significantly to \$ [redacted] <sup>4</sup> and \$ [redacted] <sup>5</sup> per QALY gained in the TN and R/R models. |
| ZANU treatment duration | Extrapolations of ASPEN TTD KM data and applied from cycle 1 of the model                                                                                                                                              | Based on the extrapolations, average treatment duration with ZANU was 7 years in the base case. This resulted in a high total cost for ZANU which drove incremental costs in the model, however, the approach still likely favoured ZANU as extrapolated TTD was always below PFS.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Source: compiled during the evaluation

BR=bendamustine+rituximab, ICER=incremental cost effectiveness ratio, ITC=indirect treatment comparison, 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 naïve, TTD=time to discontinuation, WM=Waldenström macroglobulinaemia, ZANU=zanubrutinib.

\* Median follow-up reported

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> \$455,000 to < \$555,000<sup>5</sup> \$655,000 to < \$755,000

6.81 Summary results of the cost-effectiveness model are presented below.

Table 18: Results of the stepped economic evaluation

| Model                                                             | Treatment naïve |          |                            | Relapse/refractory |           |                            |
|-------------------------------------------------------------------|-----------------|----------|----------------------------|--------------------|-----------|----------------------------|
| Step and component                                                | ZANU            | Rm       | Increment                  | ZANU (matched)     | BR        | Increment                  |
| Step 1: Time horizon captures trial length (model set to 3 years) |                 |          |                            |                    |           |                            |
| Costs                                                             | \$ [REDACTED]   | \$32,799 | \$ [REDACTED]              | \$ [REDACTED]      | \$53,011  | \$ [REDACTED]              |
| LYG                                                               | 2.83            | 2.54     | 0.29                       | 2.84               | 2.54      | 0.30                       |
| Incremental cost/extra LY gained                                  |                 |          | \$ [REDACTED] <sup>1</sup> |                    |           | \$ [REDACTED] <sup>1</sup> |
| Step 2: Time horizon extended to 20 years                         |                 |          |                            |                    |           |                            |
| Costs                                                             | \$ [REDACTED]   | \$79,845 | \$ [REDACTED]              | \$ [REDACTED]      | \$100,057 | \$ [REDACTED]              |
| LYG                                                               | 13.57           | 7.69     | 5.88                       | 13.79              | 7.69      | 6.10                       |
| Incremental cost/extra LY gained                                  |                 |          | \$ [REDACTED] <sup>2</sup> |                    |           | \$ [REDACTED] <sup>3</sup> |
| Step 3: Discounting (5%) included                                 |                 |          |                            |                    |           |                            |
| Costs                                                             | \$ [REDACTED]   | \$63,866 | \$ [REDACTED]              | \$ [REDACTED]      | \$84,079  | \$ [REDACTED]              |
| LYG                                                               | 9.54            | 5.95     | 3.60                       | 9.68               | 5.95      | 3.73                       |
| Incremental cost/extra LY gained                                  |                 |          | \$ [REDACTED] <sup>2</sup> |                    |           | \$ [REDACTED] <sup>2</sup> |
| Step 4: Utility weights applied                                   |                 |          |                            |                    |           |                            |
| Costs                                                             | \$ [REDACTED]   | \$63,866 | \$ [REDACTED]              | \$ [REDACTED]      | \$84,079  | \$ [REDACTED]              |
| QALYs                                                             | 7.37            | 4.32     | 3.04                       | 7.42               | 4.52      | 2.90                       |
| Incremental cost/extra QALY gained (base case)                    |                 |          | \$ [REDACTED] <sup>4</sup> |                    |           | \$ [REDACTED] <sup>4</sup> |

Source: Calculated during the evaluation using Excel model 'Section3\_CEM\_Zanubrutinib\_WM\_Final\_Rm\_PFS\_Toggle.xlsm'

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

The redacted values correspond to the following ranges:

<sup>1</sup> \$255,000 to < \$355,000<sup>2</sup> \$55,000 to < \$75,000<sup>3</sup> \$45,000 to < \$55,000<sup>4</sup> \$75,000 to < \$95,000

6.82 Average treatment with zanubrutinib in the model was 7.0 years in the base case, with benefits of zanubrutinib assumed to extend beyond treatment to incremental undiscounted Life Years (LYs) of 7.69 and 6.10 years in the TN and R/R models respectively. There is a lack of long-term data supporting both the extended treatment duration and size of the LYs gain. The ESC considered the ICERs to be highly uncertain noting that the modelled benefits in LYs gained were essentially based entirely on assumptions as the available clinical data did not adequately support an incremental survival benefit. Overall, the ESC considered that the ICERs were unlikely informative of the true cost-effectiveness of zanubrutinib in each treatment setting.

6.83 Key sensitivity analyses are summarised below.

**Table 19: Results of sensitivity analyses**

| Model                                                                                                                 | TN ZANU vs Rm |            |                            | R/R ZANU (matched) vs BR |            |                             |
|-----------------------------------------------------------------------------------------------------------------------|---------------|------------|----------------------------|--------------------------|------------|-----------------------------|
| Analyses                                                                                                              | Incre cost    | Incre QALY | ICER                       | Incre cost               | Incre QALY | ICER                        |
| <b>Base case (corrected)</b>                                                                                          | \$ [REDACTED] | 3.04       | \$ [REDACTED] <sup>1</sup> | \$ [REDACTED]            | 2.90       | \$ [REDACTED] <sup>1</sup>  |
| Time horizon (base 20 years)                                                                                          |               |            |                            |                          |            |                             |
| • In trial (3 year, KM data to 30m)                                                                                   | \$ [REDACTED] | 0.12       | \$ [REDACTED] <sup>2</sup> | \$ [REDACTED]            | 0.25       | \$ [REDACTED] <sup>3</sup>  |
| • 5 year                                                                                                              | \$ [REDACTED] | 0.64       | \$ [REDACTED] <sup>4</sup> | \$ [REDACTED]            | 0.55       | \$ [REDACTED] <sup>4</sup>  |
| • 10 year                                                                                                             | \$ [REDACTED] | 1.65       | \$ [REDACTED] <sup>5</sup> | \$ [REDACTED]            | 1.52       | \$ [REDACTED] <sup>5</sup>  |
| • 15 year                                                                                                             | \$ [REDACTED] | 2.51       | \$ [REDACTED] <sup>6</sup> | \$ [REDACTED]            | 2.37       | \$ [REDACTED] <sup>1</sup>  |
| • 30 year                                                                                                             | \$ [REDACTED] | 3.33       | \$ [REDACTED] <sup>1</sup> | \$ [REDACTED]            | 3.19       | \$ [REDACTED] <sup>1</sup>  |
| Start of extrapolation (base=cycle 0)                                                                                 |               |            |                            |                          |            |                             |
| • KM data to 30 months                                                                                                | \$ [REDACTED] | 2.27       | \$ [REDACTED] <sup>5</sup> | \$ [REDACTED]            | 2.83       | \$ [REDACTED] <sup>1</sup>  |
| OS extrapolation (base: ZANU exp, Rm= BR Weibull)                                                                     |               |            |                            |                          |            |                             |
| • No diff in survival (Rm/BR OS=ZANU OS)                                                                              | \$ [REDACTED] | 0.56       | \$ [REDACTED] <sup>7</sup> | \$ [REDACTED]            | 0.33       | \$ [REDACTED] <sup>8</sup>  |
| • No survival benefit off treatment <sup>a</sup>                                                                      | \$ [REDACTED] | 1.76       | \$ [REDACTED] <sup>9</sup> | \$ [REDACTED]            | 1.56       | \$ [REDACTED] <sup>9</sup>  |
| OS extrapolation R/R (base: ZANU exp, BR Weibull)                                                                     |               |            |                            |                          |            |                             |
| • Dependent Weibull                                                                                                   |               |            |                            | \$ [REDACTED]            | 2.89       | \$ [REDACTED] <sup>1</sup>  |
| • Dependent gamma                                                                                                     | N/A           | N/A        | N/A                        | \$ [REDACTED]            | 2.81       | \$ [REDACTED] <sup>1</sup>  |
| • Independent Weibull (ZANU and BR)                                                                                   |               |            |                            | \$ [REDACTED]            | -0.98      | ZANU dominated              |
| • Independent gamma (ZANU and BR)                                                                                     |               |            |                            | \$ [REDACTED]            | 0.11       | \$ [REDACTED] <sup>10</sup> |
| Convergence from Year 10 (no restriction on TTD): comparator HR used for both arms from Year 10 (base no convergence) |               |            |                            |                          |            |                             |
| • PFS                                                                                                                 | \$ [REDACTED] | 2.93       | \$ [REDACTED] <sup>1</sup> | \$ [REDACTED]            | 2.85       | \$ [REDACTED] <sup>1</sup>  |
| • OS                                                                                                                  | \$ [REDACTED] | 2.62       | \$ [REDACTED] <sup>6</sup> | \$ [REDACTED]            | 2.47       | \$ [REDACTED] <sup>6</sup>  |
| • PFS and OS                                                                                                          | \$ [REDACTED] | 2.50       | \$ [REDACTED] <sup>6</sup> | \$ [REDACTED]            | 2.41       | \$ [REDACTED] <sup>6</sup>  |
| Convergence from Year 5                                                                                               |               |            |                            |                          |            |                             |
| • PFS and OS (no restriction on TTD)                                                                                  | \$ [REDACTED] | 1.54       | \$ [REDACTED] <sup>4</sup> | \$ [REDACTED]            | 1.48       | \$ [REDACTED] <sup>4</sup>  |
| • PFS and OS (TTD<PFS)                                                                                                | \$ [REDACTED] | 1.54       | \$ [REDACTED] <sup>9</sup> | \$ [REDACTED]            | 1.48       | \$ [REDACTED] <sup>4</sup>  |
| TTD extrapolation (ZANU exp TTD data)                                                                                 |               |            |                            |                          |            |                             |
| • Gompertz                                                                                                            | \$ [REDACTED] | 3.04       | \$ [REDACTED] <sup>1</sup> | \$ [REDACTED]            | 2.90       | \$ [REDACTED] <sup>11</sup> |
| • Set equal to PFS                                                                                                    | \$ [REDACTED] | 3.04       | \$ [REDACTED] <sup>5</sup> | \$ [REDACTED]            | 2.90       | \$ [REDACTED] <sup>6</sup>  |
| Clinical stopping rule from 10 years (base no rule)                                                                   | \$ [REDACTED] | 2.50       | \$ [REDACTED] <sup>1</sup> | \$ [REDACTED]            | 2.41       | \$ [REDACTED] <sup>1</sup>  |
| Comparator in R/R model (base BR)                                                                                     |               |            |                            |                          |            |                             |
| • DRC*                                                                                                                | N/A           | N/A        | N/A                        | \$ [REDACTED]            | 2.90       | \$ [REDACTED] <sup>1</sup>  |

Source: Tables 3.22, 3.35 of the submission and compiled during the evaluation.

BR=bendamustine+rituximab, DRC= dexamethasone, rituximab, cyclophosphamide, exp=exponential, HR=hazard ratio, Incre=incremental, ICER=incremental cost-effectiveness ratio, m=months, OS=overall survival, PFS=progression free survival, QALY=quality adjusted life year, Rm=rituximab monotherapy, R/R=relapse/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.

<sup>^</sup>ZANU OS estimated as weighted average on % patients on treatment x OS based on ASPEN + % patients on treatment x OS based on Tedeschi 2015. This does not account for the uncertainty of the time on treatment extrapolation.

The redacted values correspond to the following ranges:

- <sup>1</sup> \$75,000 to < \$95,000
- <sup>2</sup> \$855,000 to < \$955,000
- <sup>3</sup> \$255,000 to < \$355,000
- <sup>4</sup> \$155,000 to < \$255,000
- <sup>5</sup> \$115,000 to < \$135,000
- <sup>6</sup> \$95,000 to < \$115,000
- <sup>7</sup> \$455,000 to < \$555,000
- <sup>8</sup> \$755,000 to < \$855,000
- <sup>9</sup> \$135,000 to < \$155,000
- <sup>10</sup> > \$1,055,000
- <sup>11</sup> \$55,000 to < \$75,000

6.84 Sensitivity analyses indicated that the model was most sensitive to time horizon, use of KM data, the inclusion of the large OS gain and duration of treatment effect. The ESC noted that the ICERs increased substantially when KM data (up to 30 months) was used in the model, different OS extrapolations were applied, the time horizon was reduced from 20 years, no survival benefit between arms was assumed and no survival benefit following discontinuation of zanubrutinib was assumed. The ESC considered it was difficult to determine the most clinically plausible extrapolations given the current limited data, and as such the ESC considered it would have been more appropriate to assume no sustained survival benefit following zanubrutinib treatment discontinuation.

6.85 While the ESC considered DRC was also a relevant comparator in the R/R setting with a lower cost and similar efficacy compared to BR (see paragraph 5.6), the ESC also noted that using the cost of DRC in place of BR in the model had a relatively minor impact on the ICER.

### Drug cost/patient/course

Table 20: Drug cost per patient for proposed and comparator drugs

|                                                         | ZANU         | Rm (TN)                                          | ZANU matched | BR (R/R)   |
|---------------------------------------------------------|--------------|--------------------------------------------------|--------------|------------|
| Time on treatment per pt (months) in submission         | 86.04        | 4.24                                             | 84.24        | 5.27       |
| Time on treatment per pt (months) calculated from model | 84.98        | 1.70<br>(4.24 incl. treatment break)             | 82.56        | 5.27       |
| Total cost of treatment per pt (inc admin and AE costs) | \$[REDACTED] | \$10,662                                         | \$[REDACTED] | \$30,874   |
| Cost of treatment per pt per month                      | \$[REDACTED] | \$6,275.95<br>(\$2,513.07 incl. treatment break) | \$[REDACTED] | \$5,853.79 |

Notes: Submission and model time on treatment could not be matched. Results presented here use values calculated from the model. Total cost of treatment was recalculated to include admin and AE costs. Costs and time on treatment are undiscounted

Source: Compiled during the evaluation from Excel workbook 'Section3\_CEM\_Zanubrutinib\_WM\_Final\_Rm\_PFS\_Toggle.xlsm'

AE=adverse event, BR=bendamustine+rituximab, PD=progressive disease, PFS=progression free survival, Rm=rituximab monotherapy, R/R=relapse/refractory, TN=treatment naïve, ZANU=zanubrutinib

***Estimated PBS usage & financial implications***

- 6.86 This submission was not considered by DUSC.
- 6.87 The submission used an epidemiological approach to estimate the financial implications of listing, for first- and subsequent lines of therapy. However, patients were identified using an incident approach, and this may not be appropriate given there would be an existing pool of patients who would like to initiate treatment with zanubrutinib. Furthermore, as the model assumed that only incident patients from two years prior would be considered, use in the R/R setting was potentially underestimated, since patients diagnosed more than two years previously may also wish to initiate zanubrutinib.
- 6.88 Key inputs applied in the financial analysis are presented below. The submission assumed substitution of zanubrutinib for PBS items for Rm, chlorambucil monotherapy and rituximab+chlorambucil in the TN chemo-immunotherapy ineligible population; and for BR, DRC and FRC in the R/R population. The submission also included costs for filgrastim to manage neutropenia in a proportion of patients receiving zanubrutinib. Costs for dexamethasone IV (part of DRC) were not included in the estimates as it is not currently listed on the PBS, which was reasonable. A number of small discrepancies were detected between the drug prices used in the financial estimates and prices according to the PBS Schedule, however these discrepancies were unlikely to significantly impact the results. An issue with the financial analysis was the inclusion of non-PBS listed treatments (i.e. Rm, bendamustine) as PBS cost offsets for zanubrutinib. While non-PBS treatments may be the most appropriate comparators, their costs cannot be included as PBS cost offsets.

Public Summary Document – July 2021 PBAC Meeting

Table 21: Data sources and parameter values applied in the utilisation and financial estimates

| Data                         | Value                                                          | Source                                                                                                                                                                                                                                                                                                                                                                                                                                    | Comment                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Eligible population</b>   |                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                        |
| Incident patients (1L)       | Yr 1: █<br>Yr 2: █<br>Yr 3: █<br>Yr 4: █<br>Yr 5: █<br>Yr 6: █ | Estimated using a WM incidence rate of 0.37 per 100,000 (AIHW Code C88 stated). This was then applied to projected population based on ABS statistics and adjusted for PBS eligibility:<br>- % treated (70-80%)- sponsor's market research (increased over time)<br>- % unsuitable for CIT (30%)- sponsor's market research                                                                                                               | Data sources and calculations were reasonable. However, WM incidence could not be verified. AIHW Code C88 refers to immunoproliferative cancers, but does not specify WM subset.                                                                                                                                                                                       |
| Incident patients (2L+)      | Yr 1: █<br>Yr 2: █<br>Yr 3: █<br>Yr 4: █<br>Yr 5: █<br>Yr 6: █ | Estimated using a WM incidence rate of 0.37 per 100,000 (AIHW Code C88 stated). This was then applied to projected population from 2 years prior to year of interest based on ABS statistics and adjusted for PBS eligibility:<br>- % treated (70-80%)- sponsor's market research<br>- % progress 2L (62%)- sponsor's market research<br>- % survive to 2L (90%)- Castillo et al. 2015<br>- % BTKi naïve (80%)- sponsor's market research | The requested restriction did not limit use of ZANU to 2L treatment and patients with WM tend to have a slow progressing disease suggesting numbers of patients with R/R using an incidence approach may be underestimated, particularly in the first year. Adopting of the AIHW 5-year prevalence data results in a larger R/R population (73 eligible pts in Year 1) |
| Grandfathered                | Yr 1: █                                                        | Estimated by sponsor                                                                                                                                                                                                                                                                                                                                                                                                                      | This number could not be verified                                                                                                                                                                                                                                                                                                                                      |
| <b>Treatment utilisation</b> |                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                        |
| Uptake rate (1L and 2L+)     | Yr 1: █%<br>Yr 2: █%<br>Yr 3-6: █%                             | Uptake (█-█%)- sponsor's market research (increase over time)                                                                                                                                                                                                                                                                                                                                                                             | The uptake for ZANU was likely to be underestimated. Given the indolent nature of the disease, patients are likely to cycle through many treatments during their lifetimes.                                                                                                                                                                                            |
| Scripts dispensed            | Yr 1: █<br>Yr 2: █<br>Yr 3: █<br>Yr 4: █<br>Yr 5: █<br>Yr 6: █ | Incident patient months based on an assumed average time on treatment of 50.4 months, multiplied by 10.23 scripts per year<br>Grandfathered patients expected to have received 6 months of treatment prior to PBS listing<br>84% compliance was assumed                                                                                                                                                                                   | The time on treatment was based on the average time on treatment when the model was restricted to a 6-year time horizon (50.1 months for R/R pts, 50.7 months for TN pts). Time on treatment should be calculated as expected for patient lifetime (using 20-year time horizon in the model, average time on treatment is 85.9 months)                                 |
| Subsequent treatments        | Not costed                                                     | Subsequent treatment was not discussed in the financial estimates section of the submission.                                                                                                                                                                                                                                                                                                                                              | The availability of ZANU represents an additional line of therapy; i.e. displace rather than replace other treatments. The costs of these treatments are expected to accrue following ZANU treatment.                                                                                                                                                                  |
| <b>Costs</b>                 |                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                        |
| ZANU                         | \$█ per 28 day supply                                          | DPMQ (effective)                                                                                                                                                                                                                                                                                                                                                                                                                          | Discrepancies were noted between drug costs used in the economic evaluation and the financial estimates section of the submission.                                                                                                                                                                                                                                     |

Public Summary Document – July 2021 PBAC Meeting

| Data                    | Value                                        | Source                                                                                                                                                                                                                                     | Comment                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Filgrastim              | \$642.41 <sup>a</sup>                        | 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                                                                         | The submission assumed a compliance of 84% for all substituted therapies, the source of this estimate is unknown as it was not discussed in the submission.                                                                                                                                                                                                                                                       |
| BENDA                   | \$1745.54 <sup>a</sup>                       | PBS codes 10760H, 10763L, 90 mg/m <sup>2</sup> (average dose <sup>c</sup> 180 mg) for 2 days, every 4 weeks for 6 cycles. Total doses 12. 25% R/R pts receive BENDA, compliance 84%.                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Cyclophosphamide (oral) | \$155.65                                     | PBS code 1266P 100 mg/m <sup>2</sup> twice daily (average dose <sup>c</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. | Price used for filgrastim was based on PBS items 5741E (1 mL injections) rather than the nominated 0.5ml injections (5742E and 6291D) with DPMQ \$345.08.                                                                                                                                                                                                                                                         |
| Cyclophosphamide (IV)   | \$187.20                                     | PBS codes 4327R, 7226H 250 mg/m <sup>2</sup> (average dose <sup>c</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.                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Rituximab               | \$1685.82 <sup>a</sup>                       | PBS codes 4614W, 7257Y 375 mg/m <sup>2</sup> (average dose <sup>c</sup> 750 mg) once a week for 4 weeks (1L) or every 4 weeks for 6 cycles (R/R). Average <sup>b</sup> total 5.18 doses. 47.7% pts, compliance 84%, scripts/yr 4.35        | Average dose was calculated using an average BSA of 2 m <sup>2</sup> for all substituted treatments, this differed to the economic evaluation in Section 3, where a BSA of 1.86 m <sup>2</sup> was used.                                                                                                                                                                                                          |
| Fludarabine             | \$179.11 <sup>a</sup>                        | PBS codes 4393F, 7233Q 25 mg/m <sup>2</sup> (average dose <sup>c</sup> 50 mg) for 3 days every 4 weeks for 6 cycles. Total 18 doses. 5% R/R pts, compliance 84%, script/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                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                   |
| MBS costs               | \$36.00 per episode of Grade 3-4 neutropenia | MBS: 119 (80% fee) specialty consultant physician minor attendance for patients experiencing Grade 3-4 neutropenia from ASPEN (13.9%).                                                                                                     | The submission did not account for other adverse events (BTKis are associate with bleeding events), nor the possibility that ASPEN underestimates the total number of patients who experience an adverse event (median TTD was not reached in the trial). The submission also did not estimate a reduction in administration costs (all comparators are provided intravenously, whereas ZANU is an oral therapy). |

Source: Tables 4.2, 4.4, 4.5, 4.6, 4.7, 4.10, 4.11 and Section 4.3.2 of the submission, with additional numbers from Excel model 'Section4\_Zanubrutinib\_WM.xlsx'

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

<sup>a</sup>Weighted average cost assuming 28.6% public hospital 71.4% private hospital split based on bendamustine PBS usage.

<sup>b</sup>Weighted by treated 1L vs 2L patients.

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

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

6.89 The net cost to PBS/RPBS was estimated to be approximately \$30 million to < \$40 million over the first six years of listing (Table 22). The PBAC considered that the financial estimates may be underestimated due to:

- The number of patients was likely underestimated, particularly in the first year. The submission used incidence data from two years prior to estimate the number of R/R patients, but R/R patients are not limited to second line use (they may also use zanubrutinib in later lines of therapy). Prevalence data from 2015 suggested the number of prevalent patients may be higher. In the financial estimates, if patients did not progress two years after diagnosis, they 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.
- Potential underestimate for zanubrutinib uptake. The submission estimated an increase in uptake from 70% to 80% over the course of the 6 years, but with limited treatment options, it is likely that eventually nearly 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). The ESC considered that the uptake of zanubrutinib would likely be high, particularly in the R/R population as patients would likely prefer an oral therapy over infusible chemotherapy even if there was a good prior response with chemotherapy.
- Time on treatment (50.4 months) was based on a restricted time horizon (6 years), whereas the base case economic model estimated a longer time on treatment (85.9 months for TN patients, 83.5 months for R/R patients) based on a 20-year time horizon. The submission presented a sensitivity analysis where time on treatment was increased to 86.4 months, which increased the total net cost to \$40 million to < \$50 million.
- As WM is an indolent disease, it is likely that zanubrutinib will displace rather than replace treatments. Therefore, patients are likely to receive currently available treatments after discontinuing zanubrutinib, and the savings from avoiding these treatments are overestimated. Furthermore, the submission estimated the cost of currently listed treatments based on clinician reported usage. However, several of these treatments (Rm, BR, DRC) are not subsidised by the PBS, in combination or individually, or are restricted to patient populations different from those in the submission. The ESC noted this slightly overestimated the potential savings, where the total net cost over 6 years increased to approximately \$30 million to < \$40 million if the treatments were restricted to their PBS listings. The PSCR noted if patients go on to receive subsequent treatments after progression, this is beyond the 6-year duration of the estimates. The ESC considered that the financial estimates should be interpreted in the context that some patients will accrue costs for subsequent treatments within the 6-year time frame, with others accruing these costs beyond 6 years. Further, the ESC considered that as per all the

extrapolations presented in the economic model, the estimated treatment duration for zanubrutinib was highly uncertain.

- Zanubrutinib has a different safety profile to currently available treatments, and management of these (e.g., major haemorrhages) was not accounted for. There was also no long-term data on AEs in zanubrutinib patients and there may be AEs related to treatment discontinuation that lead to additional healthcare costs.
- The requested restriction required TN patients to be 'unsuitable' for chemo-immunotherapy but did not specify what makes them ineligible. There is potential for use outside the target PBS population (see paragraph 3.3). The requested restriction also did not restrict access to patients who are BTKi-naïve. While there is guidance recommending that retreatment with ibrutinib is not appropriate, there are currently no recommendations for retreatment with zanubrutinib or zanubrutinib following ibrutinib.

6.90 Sensitivity analyses conducted during the evaluation indicated the financial estimates were sensitive to most variables, particularly those related to number of patients receiving zanubrutinib and duration of zanubrutinib treatment.

Table 22: 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 2 yrs prior)</b>                                                                      |       |       |       |       |       |       |
| Incident WM                                                                                                    | 1     | 1     | 1     | 1     | 1     | 1     |
| Total 2L+ patients eligible                                                                                    | 1     | 1     | 1     | 1     | 1     | 1     |
| Total 2L+ patients treated with ZANU                                                                           | 1     | 1     | 1     | 1     | 1     | 1     |
| Grandfathered                                                                                                  | 1     | 1     | 1     | 1     | 1     | 1     |
| Total patients initiate ZANU                                                                                   | 1     | 1     | 1     | 1     | 1     | 1     |
| Total patients treated ZANU                                                                                    | 1     | 1     | 1     | 1     | 1     | 1     |
| <b>Estimated number of ZANU scripts (PBS/RPBS)</b>                                                             |       |       |       |       |       |       |
| 1L                                                                                                             | 1     | 1     | 2     | 2     | 2     | 2     |
| 2L+                                                                                                            | 1     | 1     | 2     | 2     | 2     | 2     |
| Grandfathered                                                                                                  | 1     | 1     | 1     | 1     | 1     | 1     |
| Total ZANU scripts                                                                                             | 2     | 2     | 2     | 2     | 2     | 2     |
| <b>Estimated effective cost of ZANU to PBS/RPBS (less copay)</b>                                               | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  |
| <b>Estimation changes in use and financial impact of currently listed treatments</b>                           |       |       |       |       |       |       |
| Total number of patients who would have been treated with comparators displaced by PBS listing of ZANU (1L+2L) | 1     | 1     | 1     | 1     | 1     | 1     |
| <b>Changes in scripts for substituted therapies</b>                                                            |       |       |       |       |       |       |
| BENDA scripts                                                                                                  | 1     | 1     | 1     | 1     | 1     | 1     |
| RITUXIMAB scripts                                                                                              | 1     | 1     | 1     | 1     | 1     | 1     |
| CYCLOPHOSPHAMIDE IV scripts                                                                                    | 1     | 1     | 1     | 1     | 1     | 1     |
| CYCLOPHOSPHAMIDE oral scripts                                                                                  | 1     | 1     | 1     | 1     | 1     | 1     |
| FLUDARABINE scripts                                                                                            | 1     | 1     | 1     | 1     | 1     | 1     |
| CHLORAMBUCIL scripts                                                                                           | 1     | 1     | 1     | 1     | 1     | 1     |
| Total number of reduced scripts                                                                                | 1     | 1     | 1     | 2     | 2     | 2     |
| FILGRASTIM scripts                                                                                             | 1     | 1     | 1     | 1     | 1     | 1     |
| <b>Total cost offset to PBS/RPBS (less copay)</b>                                                              | -\$ 3 | -\$ 3 | -\$ 3 | -\$ 3 | -\$ 3 | -\$ 3 |
| <b>Estimated financial implications for the PBS/RPBS and the health budget</b>                                 |       |       |       |       |       |       |
| Net change in scripts 1L+2L+GF                                                                                 | 1     | 2     | 2     | 2     | 2     | 2     |
| Net cost PBS/RPBS                                                                                              | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  |
| Net cost to MBS (item 119)                                                                                     | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  |
| <b>Net cost to Government</b>                                                                                  | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  | \$ 3  |

Source: Tables 4.4, 4.5, 4.6, 4.9, 4.13, 4.16, 4.17, 4.19, 4.20 of submission and compiled during the evaluation

1L=first-line treatment, 2L= second-line treatment, BENDA=bendamustine, copay=copayments, GF=grandfathered, R/R=relapse/refractory, TN=treatment naïve, ZANU=zanubrutinib

The redacted values correspond to the following ranges:

1 &lt; 500

2 500 to &lt; 5,000

3 \$0 to &lt; \$10 million

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

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

- 6.91 The pre-PBAC response acknowledged the uncertainty around the financial estimates. The pre-PBAC response indicated that the sponsor was willing to enter a Risk Sharing Arrangement.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of zanubrutinib for the treatment of adult patients with Waldenström macroglobulinaemia (WM). The PBAC acknowledged the meaningful consumer support and engagement with this submission, including a consumer hearing with patient group representatives held prior to the PBAC meeting. The PBAC recognised that there are no treatments on the PBS specifically for WM and considered that zanubrutinib offered, for some patients, high added therapeutic value in terms of tolerability, response outcomes and quality of life. However, the PBAC did not have a reliable basis to determine a cost-effective price for zanubrutinib as the economic model did not reflect the expected treatment outcomes of improved quality of life and reduced need for subsequent therapies, including chemotherapy, but instead was based on projected large gains in overall survival, which were not supported by the clinical data and were considered clinically implausible. The PBAC considered the estimated use and financial impact to be underestimated.
- 7.2 The PBAC noted the consumer comments describing an improvement in quality of life following treatment with zanubrutinib, its tolerable safety profile, and the toxicity associated with currently available chemo-immunotherapies. The PBAC acknowledged there was a high clinical need for effective treatments for the proposed patient population, particularly for patients who are unable to tolerate chemo-immunotherapy. The PBAC considered that the consumer hearing with WMozzies was particularly valuable in highlighting the value of quality of life between relapsing periods of disease.
- 7.3 The PBAC considered that the restriction should clearly define the treatment naïve population unsuitable for chemo-immunotherapy, by incorporating a CIRS score. Patients with a CIRS score of six or greater could be considered unsuitable for chemo-immunotherapy, similar to the current ibrutinib PBS listing for CLL/SLL. The PBAC 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, the PBAC considered it would be appropriate to allow treatment in patients who are intolerant to another BTKi.
- 7.4 The PBAC accepted the nominated comparator of rituximab monotherapy for the treatment naïve population, noting that the listing is for patients unsuitable for chemo-immunotherapy, although also acknowledged that chemo-immunotherapy may be used in this patient population with dose reductions.

- 7.5 The PBAC accepted bendamustine+rituximab as an appropriate comparator for the relapsed/refractory population. The PBAC considered that dexamethasone+rituximab+cyclophosphamide (DRC) would also be an appropriate comparator noting it is recommended in Australian treatment guidelines and is considered to have similar efficacy, but a lower cost compared to bendamustine+rituximab. The PBAC considered that a blended comparator of bendamustine+rituximab and DRC would likely be more representative of current clinical practice however, accepted that bendamustine+rituximab would likely be a reasonable proxy for both treatments. The PBAC 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.
- 7.6 For the treatment naïve population, the submission's claim of superior effectiveness compared to rituximab monotherapy was based on an indirect treatment comparison (ITC) of response outcomes for zanubrutinib from ASPEN with those for rituximab monotherapy from INNOVATE, with ibrutinib/ibrutinib+rituximab arms as a 'common' reference. The PBAC noted there were a number of important differences between trials (see paragraph 6.12), and agreed with the ESC that it was difficult to determine the overall impact these differences may have had on the ITC. The PBAC 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.
- 7.7 For the relapsed/refractory population, the submission's claim of superior effectiveness compared to bendamustine+rituximab was based on unanchored matching-adjusted indirect comparisons (MAICs) using the data from ASPEN (for the ITT and relapsed/refractory populations) and from Tedeschi 2015 (for relapsed/refractory population treated with bendamustine+rituximab). The PBAC noted the resulting HRs for PFS and OS from the MAICs favoured zanubrutinib numerically. However, the PBAC noted the survival data were immature, and there were differences in patient characteristics between ASPEN and Tedeschi 2015, which could not be adjusted for in the MAICs due to a number of these characteristics not being reported in Tedeschi 2015. On this basis, the PBAC 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 noted the MAIC presented in the PSCR indicated a benefit for zanubrutinib in terms of overall response rate outcomes, but considered MAICs for the primary outcomes in ASPEN (VGPR/CR) would also be informative (particularly in view of the high value of response outcomes to patients in terms of improving quality of life). 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.

- 7.8 For treatment naïve patients, superior safety was claimed based on an ITC of ASPEN and iNNOVATE; for relapsed/refractory patients, superior safety was claimed based on a MAIC of ASPEN and Tedeschi 2015. The PBAC considered it was difficult to interpret the comparisons due to: substantial differences in the adverse event profile between zanubrutinib and rituximab or bendamustine; the addition of rituximab to the 'common' reference arm of the comparison between zanubrutinib and rituximab monotherapy; and differences in patient characteristics not adjusted for in the MAIC between zanubrutinib and bendamustine+rituximab. However, the PBAC noted the safety profile for zanubrutinib appeared consistent with that for BTKis and as such, considered its safety profile to be manageable. The PBAC noted the consumer comments indicated zanubrutinib was more tolerable compared to chemotherapy, which is expected with a non-cytotoxic treatment. Overall, the PBAC 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.
- 7.9 In terms of the economic evaluation, the PBAC noted the submission presented two separate partitioned survival analyses comparing each population against the nominated comparators. The PBAC noted that patients in the models received only one line of therapy and because the models were separate, there was no link between first and subsequent lines of therapy. Therefore, the PBAC considered the model structure did not adequately reflect the lifetime experience of most patients with WM, who would cycle through multiple available treatments following treatment relapse with intervening periods of stabilised disease.
- 7.10 The PBAC noted the modelled gain in PFS and OS was based entirely on extrapolated data. The PBAC considered the modelled survival benefits to be uncertain due to the following:
- There were inconsistencies in the submission's approach to extrapolation, which impacted model validity (see paragraph 6.66).
  - There was limited KM data to validate the parametric functions selected. While all functions appeared to fit the KM data, there were large variations observed between the tail ends of the distributions.
  - The model structure did not allow for effects of subsequent treatments on survival outcomes to be captured.
  - The PFS and OS data used in the model to extrapolate survival were immature, particularly for OS since very few deaths had occurred in any of the included trials.
  - The model was highly sensitive to the estimated survival benefit for zanubrutinib, and increased substantially when i) KM data was used in the model, ii) no overall

survival benefit between arms was assumed and iii) no overall survival benefit following discontinuation of zanubrutinib was assumed.

- 7.11 The PBAC noted the modelled incremental gain in life years (undiscounted) for zanubrutinib in the treatment naïve and relapsed/refractory populations was 5.88 and 6.10 respectively, and more than 33% patients receiving zanubrutinib remained alive at the end of the 20-year time horizon in both models. The PBAC considered this was not clinically plausible noting the median age of patients with WM is around 70 years.
- 7.12 The PBAC noted the utility value for the PFS health state was based on EQ-5D-5L results from ASPEN that were first mapped to EQ-5D-3L and then regressed based on patient characteristics. The PBAC noted the model applied the same utility value for treatment naïve and relapsed/refractory patients in the PFS health state irrespective of treatment administered. The PBAC considered this approach potentially underestimated the utility benefit associated with zanubrutinib.
- 7.13 In the model, the time on treatment for zanubrutinib was extrapolated using data from ASPEN and the estimated treatment duration varied substantially depending on the extrapolation function chosen as well as whether the matched or unmatched zanubrutinib data were used. The PBAC noted the expected treatment duration was long, seven years in the base case analysis, and the model results were sensitive to treatment duration. The PBAC further noted with a seven year treatment duration, the cost per patient for zanubrutinib was approximately \$[REDACTED]-\$[REDACTED], and noted that this cost was high in comparison to other treatments for indolent diseases and did not reflect a cost-effective price given the benefits observed in the trials, and those expected over the longer term.
- 7.14 Overall, the PBAC considered the economic model was unreliable as it did not reflect the expected treatment outcomes of improved quality of life and reduced need for subsequent therapies, including chemotherapy, but instead was based on projected large gains in overall survival, which were not supported by the clinical data and were considered clinically implausible. The PBAC considered 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.
- 7.15 The PBAC noted that an epidemiological approach was used to estimate the financial impact of listing zanubrutinib. The PBAC agreed with the evaluation that the impact was likely underestimated, noting the number of patients receiving zanubrutinib (due to underestimating the number of eligible patients and uptake) and the duration of treatment were likely underestimated (see paragraph 6.90). The PBAC 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. The PBAC noted the discrepancy between time on treatment in the economic analysis (85.9 months for treatment naïve patients and 83.5 months for relapsed/refractory patients) compared to the financial estimates (50.4 months). The PBAC considered that PBS cost-offsets for bendamustine and

rituximab monotherapy were inappropriate given these therapies are not PBS subsidised. The PBAC 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.

- 7.16 The PBAC considered zanubrutinib addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies. However, the PBAC considered a number of issues remained outstanding. Before a resubmission for zanubrutinib is made, the PBAC would like to offer the sponsor a solution-focussed workshop with one or more members of the PBAC, to explore feasible options to address the following issues:
- The structure of the economic model(s): the structure should more accurately reflect the chronic relapsing nature of WM and the expected outcomes of treatment.
  - The inputs for the economic model(s): the inputs should be consistently applied for the treatment naïve and relapsed/refractory settings.
  - The inputs for the financial estimates, including the likely number of eligible patients, the uptake and treatment duration.
- 7.17 The workshop agenda would be based on the issues for resolution outlined above. Should the sponsor accept this offer, a facilitated resolution pathway may be acceptable for the resubmission (as defined in the *Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme*). It should be noted that any advice provided by members of the PBAC, the sponsor or the department in a workshop is in no way binding on the PBAC, the Department, sponsor, evaluation groups or sub-committees of the PBAC. If this option is not acceptable to the sponsor, a standard re-entry pathway is available.
- 7.18 The PBAC noted that this submission is eligible for an independent review.

**Outcome:**

Not recommended

## **8 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.

## **9      10 Sponsor's Comment**

Beigene welcomes the opportunity to participate in a solution-focussed workshop to make zanubrutinib available on the PBS for patients with WM as soon as possible.