NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Zanubrutinib for treating Waldenström's macroglobulinaemia [ID1427]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient expert	Patient expert	If the revised appraisal committee recommendations are ratified without further modification clinicians and patients will no doubt be very dissatisfied particularly since Ibrutinib is no longer available for relapsed or refractory WM on the NHS in England and Wales. I reiterate my earlier assertion that the cost of Zanubrutinib is the determining factor and the quickest way to achieve an improved outcome is for NICE to negotiate a mutually acceptable **interim** price with BeiGene until such time as BeiGene can provide updated evidential data over an extended period. Since the current evidential data is immature, it is not surprising that the NICE cost-effectiveness threshold calculations expressed in terms of ICER and QALY gained appear to be pessimistic. However, my understanding at the treatment centre I attend is that the on-going evidential data is particularly encouraging and will no doubt prove to be universally the case elsewhere. As a WM patient receiving treatment with Zanubrutinib since December 2017, via the BGB-3111- 302 clinical trial, extended in March 2022 for a further 5 years, renamed as BGB-3111-LTE1, I expect that by the time the proposed 3 year NICE review is reached new longer-term (minimum 7 years) data should enable Zanubrutinib to receive approval as a routine first-line treatment. Without my having the particular good fortune of joining this trial I would not have survived for very long after being withdrawn from chemoimmunotherapy options in March 2017 because of intolerance. Importantly since BeiGene did not submit any evidence for the initial treatment of WM with Zanubrutinib compared with alternative therapies in people for whom chemoimmunotherapy is unsuitable it has not been recommended for this group so they will be seriously disadvantaged. They	Thank you for these comments. Comment noted. The appraisal committee considered the immaturity of the data and the most suitable long-term extrapolations (FAD sections 3.4 and 3.9). The company have since provided cost-effectiveness evidence for people for whom

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			are living with a rare incurable lymphoma, are frail and will be denied access to what the clinical experts regard as a much preferred step-change in managing WM. Irrespective of whether BeiGene provided evidence for this group it prompts the question - would this potential situation be unlawful discrimination? The answer would appear to be 'Yes' since WM is clearly a cancerous disability. Furthermore, it is acknowledged that there is no reason to suppose that first-line treatment with Zanubrutinib would be less effect than if a patient had received one or more earlier treatments with either BR or DRC. In fact they are more likely to fair even better due to its better efficacy, better tolerance, lower toxicity with fewer side effects and hospital visits whilst also enjoying a much better quality experience. Like me I'm sure there will be others who will regard this as another example of a technical nicety thwarting a pragmatic approach to healthcare. In practice these proposed recommendations will also reduce clinician/patient choice by channelling more patients into starting treatment with DRC. **Why?** - no informed sensible patient will agree to starting treatment with BR when doing so would then probably mean having DRC next before state of the art treatment with Zanubrutinib is made available to them. Introduction of new drugs invariably have higher cost implications but also some identifiable cost savings and benefits. However, no attempt has been made to quantify either the significant cost savings of not having to administer chemoimmunotherapy or the possibility of freeing up human resources in an overstretched NHS. Also during the 7-years the £20-30K per QALY thresholds have been in use, inflation has increased by a multiplier of 1.19 equivalent to £23.8-35.7K per QALY, with current inflation expected to exceed 10%. **A significant fact and perhaps a review is overdue**. I suggest the overall cost-benefit analysis of introducing this new technology is more complex than usual and should include consideration of the above.	chemoimmunotherapy is unsuitable. The cost-effectiveness evidence and clinical factors for this group have been considered by the committee (FAD sections 3.11 and 3.15). The implications on the treatment pathway of the recommendation were considered by the committee for people with relapsed or refractory Waldenstrom's macroglobulinaemia who are able to tolerate chemoimmunotherapy (FAD section 3.19). When considering the cost-effectiveness of a new technology, the committee considers both the drug costs and also the associated healthcare resource costs or savings (such as costs or savings in how the drug is administered). When confidential discounts for the comparator treatments were included, the committee concluded that the ICER for zanubrutinib is

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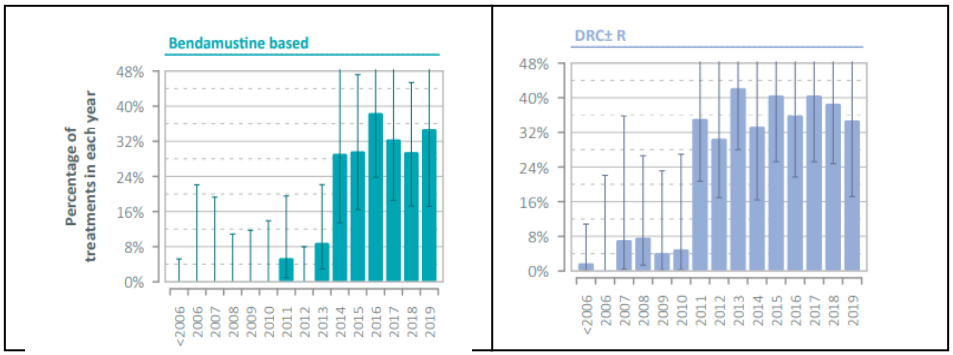
				only within what NICE usually considers cost-effective use after at least 1 treatment and when BR is also suitable (FAD section 3.18).
2	Patient organisation	WMUK and Lymphoma Science subgroup-NCRI (joint response	**We are concerned about the stipulation that: "in the absence of Zanubrutinib, the patient would otherwise be next treated with the combination of Bendamustine and Rituximab (BR)".** This will put patients who have already received BR at a potential disadvantage (approx. 50% of patients with WM in the UK receive BR as first line therapy (see data below from the 2nd Report of the Rory Morrison Registry (RMR) 2021, based on year treatment started) Rory-Morrison-Report-2021-2-11-21-Final-Version.pdf (wmuk.org.uk)  **1. DRC vs BR notes:** • Although considered equivalent in terms of efficacy and PFS, and in the absence of a head- • to-head comparison, DRC and BR are used in different ways. • **Treatment guidelines**- as seen in the treatment algorithm from the latest BCSH Guidelines for the Diagnosis and Management of WM- A British Society for Haematology Guideline (https://doi.org/10.1111/bjh.18036), there are specific clinical indications for the preference of BR over DRC, such as	Comments noted. The implications on the treatment pathway of the recommendation were considered by the committee for people with relapsed or refractory Waldenstrom's macroglobulinaemia (FAD section 3.19). The committee also acknowledged that disease- and patient- related factors can impact whether BR or DRC is used first-line, which in turn impacts the choice of second-line treatment (FAD section 3.1). Section 3.19 of the FAD notes that some people who have previously had BR may have retreatment. The committee considered the cost-effectiveness analyses for zanubrutinib vs a blended comparator (BR and DRC), and vs BR and DRC separately. The only ICER which was under £30,000 per QALY gained was from the comparison of zanubrutinib with BR (FAD section 3.15). Therefore zanubrutinib was only cost effective when compared with BR and the committee could not change its

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			hyperviscosity, cryoglobulinaemia, Al amyloidosis. The reason that BR is preferred in these circumstances is that it induces a more rapid response than DRC and can preserve organ function due to hyperviscosity (risk of stroke and other vascular events), Cryoglobulinaemia (risk of skin ulceration/ vasculitis/ renal failure/ progressive erve damage) and Al amyloidosis (deterioration of vital organ function, eps heart and kidneys). • Furthermore in the setting of high blood viscosity (more likely when the IgM paraprotein is ≥ 40g/L), recommended practice is to defer Rituximab for 2 cycles to avert an IgM flare, which can cause hyperviscosity syndrome necessitating weeks of plasma exchange (itself an expensive and scarce resource which requires wide-bore venous access with intendant risks). In this situation a brisk response to treatment is clinically needed, hence the choice of BR over DRC. If Rituximab is deferred in the setting of DRC, then there is unrealistic reliance on Cyclophosphamide to lower the disease burden until Rituximab can be introduced.	recommendation.

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			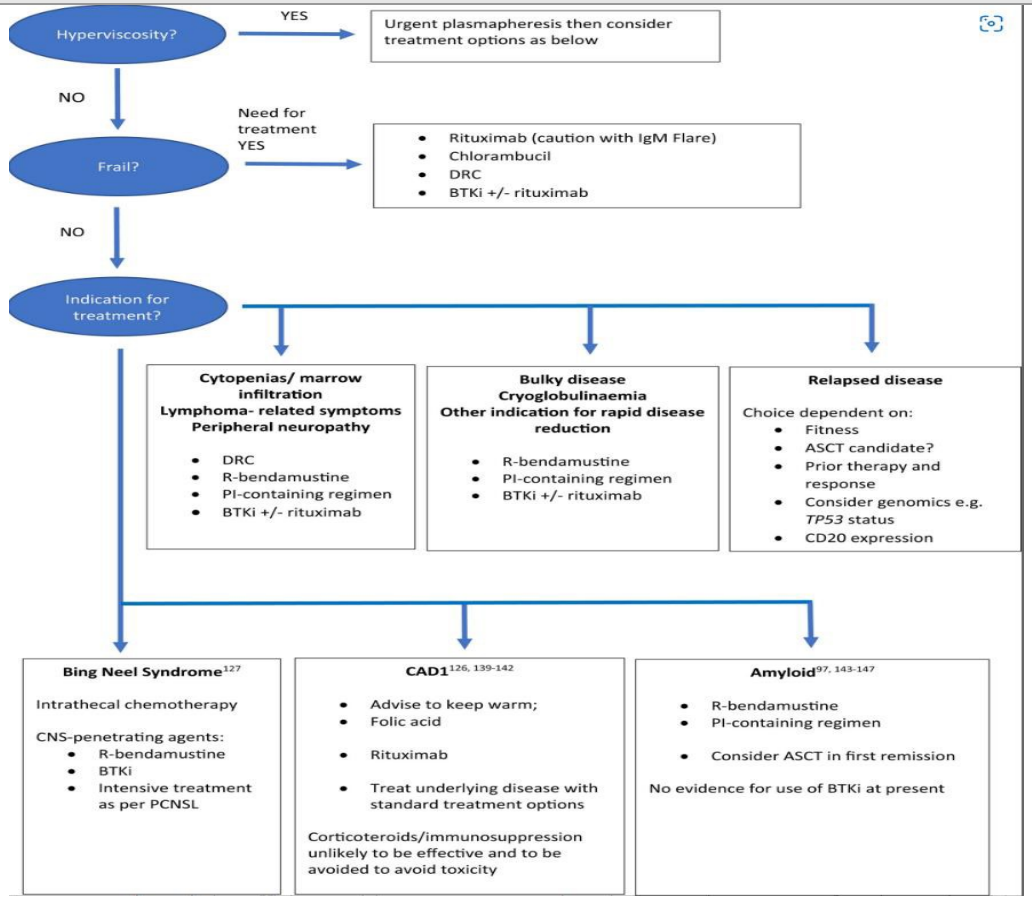 • **There is a risk that physicians will select front-line DRC in patients who would be better served by BR**, *to safeguard future access* to ZANU in those patients. **2. <u>Use of BR as second-line therapy</u>**	

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			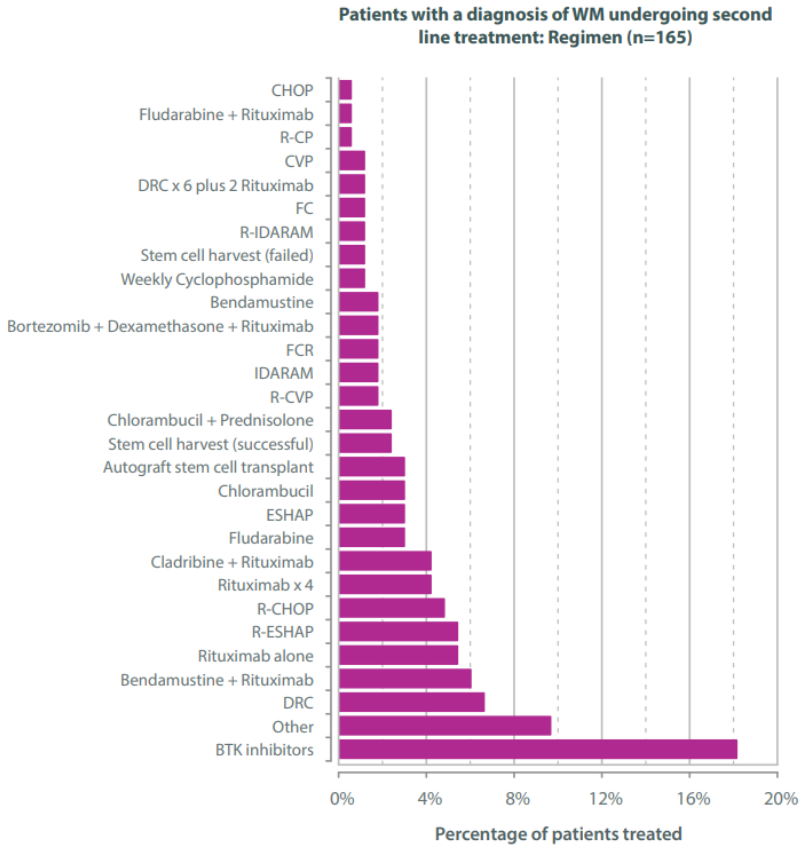 **As can be seen from the above graph from the 2nd Report of the RMR, BR is very rarely used as second-line therapy. This is likely due to the following reasons:** • While Ibrutnib was available on the CDF (2017-2022), its use in second and subsequent lines rose steadily due to the backlog of multiply-treated patients who had developed chemoresistance and physician and patient choice in seeking a less harsh therapy. • Patients with early treatment failure after BR are not candidates for BR re-treatment. Like all WM patient with relapsed disease, their prognosis is	

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			inferior. Since prognosis at relapse seems to be unrelated to previous treatment or time to progression (Does early disease progression predict survival after first line-treatment of Waldenström macroglobulinemia? - Labreuche - Hematological Oncology - Wiley Online Library), availability of effective treatment is a key prognostic factor. Prognosis is already worse for patients who are not candidates for BR re-treatment, and the current NICE criteria has worsened this further by also denying BR ineligible patients access to zanubrutinib. That is the real issue here – selected access will marginalise the WM population and increase the burden of unmet need • for those at highest risk. • Early progression of disease within 24 months of treatment (POD24) trends towards inferior survival. Although the relationship between POD24 and survival in WM is somewhat confounded, the 'POD24' time-point is useful to quantify the size of the BR treated subset that is unsuitable for BR re-treatment and zanubrutinib. The POD24 group accounted for 18% for 1L patients reported in a study at ASH 2021 (Kim et al, 2021). Half of these patients received BR. Thus, this 'BR ineligible group is ~10% of patients. Amended criteria to include this small subset of patients shouldn't have a major impact on the cost utility analysis. Kim et al ASH 2021.html • BR is a powerful treatment at front line; while the acute toxicities of bendamustine are not prominent, the drug seems to have a prolonged effect, probably immunological, leading to an increased risk of late infections (Bendamustine: A review of pharmacology, clinical use and immunological effects - PMC (nih.gov). This is of relevance in WM patients who frequently have a B cell deficiency from the outset. Due to the significant immunosuppression associated with BR, many physicians curtail BR doses when used at front-line or subsequent lines, to reduce the chance of damaging immunosuppression. Furthermore, the hypogammaglobulinaemia that can follow BR therapy can lead to use of intravenous immunoglobulin use spanning many months (IVIG itself is a resource that is expensive and in short supply globally).	

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			The following is an excerpt from the above publiction: “Bendamustine-induced lymphopenia, whether as monotherapy or in combination, has been widely reported in both hematological and non-hematological malignancies. Lymphopenia ranged from 5% in rituximab-refractory patients with iNHL to 75% of patients with grade 3–4 hematological toxicity receiving BR or even to 91% in patients treated for triple negative breast cancer. The latter group was characterized with pronounced decline in CD4+ cells, with 86% having grade 4 depressed CD4+ counts (<50/μl). In FL patients treated with bendamustine, marked reductions in CD3+ and CD3+CD4+ T cells were seen during induction with prolonged recovery during and after maintenance. Prolonged lymphopenia and low CD4+ T-cell counts, for at least 7–9 months were also observed in relapsed or refractory patients with iNHL and MCL. Recent population-based analysis by Martínez-Calle *et al* following BR treatment in patients with low grade lymphoproliferative disease revealed that median times to lymphocyte count recovery (≥1×109/l) and CD4+ recovery (≥0.2×109/l) were 26 and 24 months, respectively, and late recovery was associated with risk of serious infection”. • There appears to be an increased risk of second primary cancers following the use of Bendamustine in previously treated lymphoma Long-term outcomes, secondary malignancies, and stem cell collection following bendamustine in patients with previously treated non-Hodgkin lymphoma - PMC (nih.gov). See excerpt below: “With a **median follow-up of 8.9 years (95% C.I. 8.7-9.4)** years after study entry, 23 patients developed 25 cancers following bendamustine. Six patients developed MDS and 2 more developed AML, resulting in an annual incidence rate of 0.5%/person/year, and a **cumulative incidence rate of 6.2% (95% CI 3.1-12.2%) at the end of maximum follow up date**, adjusting for death from any cause as a competing event. The median time to **MDS/AML among subjects that developed MDS/AML following bendamustine** was 23 months (range 10-103). The median time to MDS/AML from the date of diagnosis was 89 months (range 33-226). One of the patients had a prior myeloid neoplasm and one had a prior germ cell tumor. Patients who developed MDS/AML had received a median of 5 therapies, including bendamustine, before developing the myeloid malignancy, which is the same	

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			as the median number of therapies received by the entire cohort. In univariate analysis, age at lymphoma diagnosis (P=0.44), lymphoma histology, total number of systemic regimens (P=0.44), or total dose of bendamustine (P=0.29) were associated with MDS/AML. Cytogenetics for each case were not available. Other cancers included non-melanoma skin cancer (n=6), adenocarcinoma (colon n=2; prostate n=2; lung n=2; breast n=1), squamous cell neck cancer (n=1), squamous cell anal cancer (n=1), hepatocellular carcinoma (n=1), and bladder cancer (n=1). None of these occurred in the 12 patients with a history of solid tumor before bendamustine administration". **For these reasons, the use of BR as second line therapy and more so after prior BR is likely to be very limited.** Many physicians would thus be unwilling to consider BR as second line therapy and hence feel unable to TICK Number 5 of the CDR Blueteq form and hence exclude patients from receiving Zanubrutinib. We acknowledge however, that some prior BR-exposed patients can be retreated with BR, albeit with the caveats outlined above. **We suggest we propose amended criteria for Zanubrutinib:** 1) patients who would otherwise be eligible for BR including those who have not previously received this treatment or received this > 2 years ago and did not experience significant toxicity 2) patients who experienced early treatment failure after BR for whom re-treatment is not recommended and novel therapy is needed. This includes BR treated patients who failed to achieve PR/CR, or experienced PD within 24 months, and/or developed significant toxicity.	
3	Patient organisation	WMUK and Lymphoma Science subgroup-NCRI (joint response	We are concerned about the absence of a recommendation for Zanubrutinib in first-line treatment for patients unsuitable for chemo-immunotherapy. We accept the limited evidence in this setting as well as the imprecise definition of 'unsuitable for chemoimmunotherapy'. In the absence of the opportunity to assess patients at front-line, the chance of seeking the answer to this question is slim. We would propose a consideration of a pre-defined setting in which front-line Zanubrutinib is permitted and data collection undertaken to enable a better understanding in this group.	Comment noted. The company have since provided cost-effectiveness evidence for people for whom chemoimmunotherapy is unsuitable. The cost-effectiveness evidence and clinical factors for this group have been considered by the committee (FAD sections 3.11 and 3.15).
4	Patient	BSH and	We are concerned that the recommendation of the use of zanubrutinib in	Comment noted. The committee

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	organisation	RCPath (joint response)	previously treated patients who would otherwise have been treated with rituximab and bendamustine may lead to inequity of access to zanubrutinib for patients with WM. This inequity may be due to 1. Patient related factors including age- choice of therapy takes into consideration the toxicity of the regimen as well as the efficacy. This is especially true in WM, where there is a high rate of patients dying of other causes rather than WM alone, and where evidence for treatment benefit is from multiple single arm phase 2 studies. Rituximab-and bendamustine will rarely be used as a treatment option due to toxicity concerns in more frailer patients or those with co-morbidities and thus this may prevent them from accessing a potentially important extra line of therapy for their WM that will not have the same associated toxicity. 2. Disease related factors which would mean that Rituximab bendamustine would be more likely to be used front-line and clinicians are less likely to use the same chemotherapy regimen again due to decreased efficacy on repeat usage and the concern about increased toxicity including the risks of secondary MDS. There are certain complications of WM that need to be taken into account when choosing therapy for patients, and how quickly the disease burden needs to be reduced, for example in those with bulky disease, cryoglobulinaemia or amyloid, the preference would be frontline, to use Rituximab and bendamustine to get more rapid reduction in disease burden to prevent long term complications or progression of disease on treatment. If this regimen is therefore used frontline, depending on length of time until disease progression, many clinicians would not consider using rituximab bendamustine again either if there was a short time until progression and thus likelihood of lack of efficacy or due to toxicity concerns in repeating bendamustine. 3. Clinician prescribing habits and patients already treated frontline with Rituximab bendamustine. As discussed above, there is no randomised data to indicate that there is a preferred chemoimmunotherapy option	acknowledged that disease- and patient- related factors can impact whether BR or DRC is used first-line, which in turn impacts the choice of second-line treatment (FAD section 3.1). The committee also considered that in people for whom there are no clinical considerations for which BR would be preferred, would be more likely to have the generally better tolerated DRC first-line (FAD section 3.19).

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			to use frontline and so both DRC and rituximab bendamustine are used as frontline regimens in patients with WM, sometimes the choice is dictated by patient related factors and sometimes disease related, but often it is simply clinician preference. Our concern is that if a clinician tends to prescribe rituximab-bendamustine frontline, then they are far more likely to prescribe an alternative chemoimmunotherapy regimen in the second line, this would therefore potentially lead to inequity of access to zanubrutinib that could potentially be geographical according to clinician/centre preference as to what is prescribed in the front line setting.	
5	Patient organisation	BSH and RCPath (joint response)	We are concerned that the lack of recommendation of the use of zanubrutinib in those unsuitable for chemoimmunotherapy prevents patients who cannot have chemoimmunotherapy from having a potentially effective oral therapy that would otherwise have led to an improvement in their quality of life. In patients who are unsuitable for chemoimmunotherapy, the goal of therapy is different in those who are more fit. Often life expectancy is likely to be shorter for other reasons such as their co-morbidities or frailty that makes them unsuitable for chemoimmunotherapy and thus the goal of the therapy is to lead to improvement in WM related symptoms with minimal toxicity. Not allowing these patients to access zanubrutinb (as they also would be definition not be eligible for it in the relapsed refractory setting if the current recommendation stays as it is) prevents them from having an effective therapy that we know from both trial and real world data can be well tolerated by elderly frail patients or those with co-morbidities.	The company have since provided cost-effectiveness evidence for people for whom chemoimmunotherapy is unsuitable. The cost-effectiveness evidence and clinical factors for this group have been considered by the committee (FAD sections 3.11 and 3.15).
6	Company	BeiGene	**Summary of the Company's position** The Company would like to thank the Committee for the opportunity to respond to the second Appraisal Consultation Document (ACD2).[1] The Company welcomes the recommendations made by the Committee for zanubrutinib as a treatment option for treating Waldenstrom's macroglobulinaemia (WM) in adults who have had at least 1 treatment, only if they would otherwise have treatment with bendamustine and rituximab (BR).	Comment noted. The cost-effectiveness evidence and clinical factors for this group have been considered by the committee (FAD sections 3.11 and 3.15).

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			The Company also welcomes the Committee's acknowledgement that: • The availability of an effective and well-tolerated oral treatment would be highly valued by people with WM and would address a significant unmet need. • Hazard ratios for progression-free and overall survival were low compared with those typically seen in cancer treatments, suggesting that zanubrutinib is a highly effective treatment and that zanubrutinib is more clinically effective than chemoimmunotherapy treatments in WM. • Some adjustment to post progression survival in the BR or dexamethasone, rituximab and cyclophosphamide (DRC) modelled arms may have been needed to account for the potential effect of follow-on treatments not available in the National Health Service (NHS), although the level of this adjustment was uncertain. The Company understands that the Committee was unable to make a recommendation for patients who are treatment naïve and unsuitable for chemoimmunotherapy following the second Appraisal Committee Meeting (ACM2). In response to this and to the statements made by the Committee in the ACD2, the Company would like to highlight further analyses presented in Comment 2 for patients who are treatment naïve and unsuitable for chemoimmunotherapy. These analyses take into the account the data available to the Company, and even with the paucity of data in WM, the analyses demonstrate that in addition to patients with relapsed/refractory disease, zanubrutinib is also a cost-effective therapy in patients who are treatment naïve and unsuitable for chemoimmunotherapy. When considering the Patient Access Scheme (PAS) for zanubrutinib ([redacted]% discount on the list price) and the evidence presented in Comment 2, zanubrutinib can be considered a cost-effective treatment option for treatment naïve patients who are unsuitable for chemoimmunotherapy, with all incremental cost-effectiveness ratios (ICERs) remaining comfortably under the £30,000 per quality-adjusted life-year (QALY) gained threshold (Table 1 and Table 2). Sensitivity analyses demonstrate that even when comparators are heavily discounted, zanubrutinib remains cost-effective. Probabilistic analysis demonstrates that the results are robust to parameter uncertainty	

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			with the mean ICER lying close to the deterministic ICER for all scenarios conducted.	
7	Company	BeiGene	**<u>Zanubrutinib is a cost-effective therapy in patients with WM who are treatment naïve and unsuitable for chemoimmunotherapy</u>** As stated in the first ACD, "*the committee concluded that BR and DRC represent the 2 most relevant comparators in this appraisal*".[2] This was reiterated in the second ACM where it was agreed that BR and DRC were the "*two treatments most commonly used"* and are "*key comparators for cost-effectiveness analysis".*[3] As presented in Table 1 of the Company's Technical Engagement response form, the United Kingdom (UK) 2021 Rory Morrison Registry report indicated that 85% of patients received either a bendamustine-based regimen (i.e., BR) or DRC between 2015 and 2020 in the first-line setting.[4] When considering the second-line setting, 77% of patients received either BR or DRC between 2017 and 2020.[5] Furthermore, clinical expert opinion obtained by the Company during this Technical Engagement stage supports the inclusion of BR and DRC as the two main treatments (aside from ibrutinib) within UK clinical practice for patients with WM. As such the Company is surprised that the Committee has introduced additional comparators (rituximab and chlorambucil monotherapies) within the ACD2, given that the following statements were made within ACD1 regarding the comparators within this appraisal: • "*The clinical experts said that rituximab or chlorambucil monotherapy would not work as quickly or have the same durability as standard combined chemoimmunotherapy regimens."* • *"Bendamustine and rituximab (BR) and dexamethasone, rituximab and cyclophosphamide (DRC) are the key comparators for zanubrutinib"* • *"While there is variation in the treatment pathway for people with Waldenstrom's macroglobulinaemia, particularly when it is relapsed or refractory, the committee concluded that BR and DRC represent the 2 most relevant comparators in this appraisal."*	Comment noted. The committee noted that for people for whom chemoimmunotherapy is unsuitable, BR and DRC are not treatment options. Whilst the committee acknowledged that neither chlorambucil nor rituximab were widely used, the committee considered these the relevant comparators because of their use in clinical practice (FAD section 3.1). The company's rationale for considering rituximab a more relevant comparator than chlorambucil is described in FAD section 3.7.

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			Neither rituximab monotherapy nor chlorambucil monotherapy are commonly used in clinical practice in the UK, as re-validated by clinical expert opinion sought by the Company following the second ACM. Nevertheless, data from the 2021 UK Rory Morrison registry show that rituximab is more widely used than chlorambucil in the front-line setting for the treatment for WM (11% vs 4%).[6] This is supported by the 2021 British Society for Haematology (BSH) WM guidelines, which describe chlorambucil monotherapy as having *"a very limited role"* in contemporary first-line therapy, whereas rituximab is noted to be *"generally well tolerated but associated with modest response rates".*[7] Concerns around the toxicity of chlorambucil monotherapy, which have grown in recent times with increased insight into varying treatment options, have limited its use in clinical practice, as more appropriate treatments have replaced older agents.[6] This was also validated by clinical expert opinion sought by the Company following the second ACM. In addition, based on clinical expert opinion, as chemotherapy-unsuitable patients are generally elderly, frailer, and have a worse prognosis than chemotherapy-suitable patients, the goal of treatment in this patient population is to maintain their quality of life and limit toxicities. Therefore, the use of chlorambucil in these patients would be counterproductive. A difference in the clinical efficacy between chlorambucil monotherapy and rituximab monotherapy has also been noted in trial data, with rituximab monotherapy demonstrating more favourable survival outcomes in the front-line setting for similar blood cancers. This is evidenced with a hazard ratio (HR) of 0.69 (95% CI: 0.51 - 0.91) for rituximab monotherapy when compared to chlorambucil monotherapy treated patients, in the treatment of chronic lymphocytic leukemia.[8] Further clinical evidence of superior efficacy of rituximab vs chlorambucil is provided by the matching-adjusted indirect comparison (MAIC) analyses conducted by the Company.[4] The progression-free survival HR for zanubrutinib relative to rituximab monotherapy is higher than that of zanubrutinib relative to chlorambucil monotherapy, with values of [redacted](95% CI [redacted] - [redacted]) and [redacted] (95% CI [redacted] - [redacted]), respectively. This indicates, indirectly, that patients treated with rituximab monotherapy were more likely to avoid disease progression and/or death than those treated with chlorambucil monotherapy.	

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			Regarding dosing plans and total costs for rituximab and chlorambucil monotherapies, little difference can be observed between the two treatments. As such, given that rituximab monotherapy is more widely used and is more clinically effective than chlorambucil monotherapy for the treatment of blood cancers, this justifies the inclusion of rituximab monotherapy as a comparator in the submission, in line with the UK 2021 Rory Morrison Registry data, clinical guidelines, and expert opinion sought by the Company. Therefore, the Company has conducted additional analyses to demonstrate the cost-effectiveness of zanubrutinib vs rituximab monotherapy in treatment-naïve, chemotherapy-unsuitable patients. Given the clinical inferiority of chlorambucil and higher level of toxicity than rituximab, this implies that if zanubrutinib is cost-effective relative to rituximab monotherapy, it will also be cost-effective relative to chlorambucil monotherapy. To perform this comparison, the Company has assumed the efficacy of zanubrutinib in the treatment naïve setting versus rituximab monotherapy can be obtained by applying the HRs derived from the Company's MAIC analysis (PFS HR [redacted] [95% CI [redacted] - [redacted]; OS [redacted] [95% CI [redacted] - [redacted]) to a baseline control arm within the model. This assumption is conservative given that the MAIC analyses included the full ASPEN ITT population of both patients with relapsed/refractory WM and treatment naïve patients who are unsuitable for chemoimmunotherapy (where "unsuitable" was defined as a physician determined status based on co-morbidities [renal, cardiac, infection, other] and risk factors [age]. Patient preference was not considered to meet the eligibility requirement for a treatment-naïve subject to be unsuitable for treatment with a standard chemoimmunotherapy regimen). As stated in the Technical Engagement Response, treatment naive patients historically experience better prognoses than relapsed/refractory patients, which conservatively suggests zanuburitinb is at least as effective in treatment naive patients compared to relapsed refractory setting. Evidence from the European chart review [5] and published literature confirm this statement, demonstrating decreasing PFS with each line of therapy whilst PFS and OS landmark rates in Castillo et al. 2021 (treatment-nave ibrutinib WM trial) were higher than in Treon et al. 2021 (R/R ibrutinib WM trial).[7,8] Evidence from ASPEN supports at least a comparable treatment effect for zanubrutinib across both treatment naïve patients and relapsed/refractory patients, with a similar proportion of	The committee considered the company's indirect comparisons (FAD section 3.7). The committee considered that the DRC data presented by the company was more suitable as a surrogate for rituximab compared to BR data (FAD section 3.11).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			patients achieving a very good partial response (VGPR) (treatment naïve – 26% vs. R/R – 29%).[9] This conservativeness of this assumption is further validated by clinical opinion and supported by the Committees comments from both ACDs that: • *"the assumption of equivalent efficacy by the company was likely to be a conservative one. This was based on the clinical experts' expectation that people having zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed or refractory. "– ACD1* [2] • "*people having zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed or refractory. So, the assumption of equivalent efficacy between first- and second-line treatment by the company may have been reasonable" – ACD2* [1] In addition, the Company has assumed that the efficacy and safety of rituximab monotherapy is equivalent to either the BR or DRC datasets within the submission, and that these datasets can act as a suitable baseline control arm within the model. This assumption can be considered conservative as highlighted in the ACD2, the Committee recognises that *"the comparators (monotherapy when chemoimmunotherapy is unsuitable) may be less effective than chemoimmunotherapy. This would increase the potential benefit of zanubrutinib compared with the comparators for this group".*[1] The assumption of increased potential benefit of zanubrutinib is further supported from results of the Company's MAIC which indicate that zanubrutinib is more effective versus rituximab monotherapy (PFS HR [redacted] [95% CI [redacted] – [redacted]; overall survival [OS] HR: [redacted] [95% CI [redacted] – [redacted]) than both BR combination therapy (PFS HR [redacted] [95% CI [redacted] – [redacted]; OS HR: [redacted] [95% CI [redacted] – [redacted]) and DRC combination therapy (PFS HR [redacted] [95% CI [redacted] – [redacted]; OS HR: [redacted] [95% CI [redacted] – [redacted]).[4] To reflect the cost of rituximab monotherapy, the company has removed the treatment acquisition and administration costs of bendamustine from the BR component of the model and the treatment acquisition and administration costs of dexamethasone/cyclophosphamide from the DRC component of the model, leaving only the costs of rituximab monotherapy within this analysis.	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>When considering the Company's preferred settings (Table 1) and assuming that rituximab monotherapy is equivalent to the BR dataset, zanubrutinib is associated with [redacted] additional costs and [redacted] additional QALY versus rituximab monotherapy, corresponding to an ICER of £21,341 per QALY gained. When considering the Company's preferred settings (Table 1) and assuming that rituximab monotherapy is equivalent to the DRC dataset, zanubrutinib is associated with [redacted] additional costs and [redacted] additional QALY versus rituximab monotherapy, corresponding to an ICER of £26,646 per QALY gained. The Company anticipates that rituximab monotherapy is heavily discounted, and as such has included scenarios assuming an 85% - 95% discount on the list price of rituximab monotherapy. Results show that even when rituximab monotherapy is provided at an extreme level of discount (95%) discount, the ICERs remain below £30,000 per QALY gained regardless of the dataset used as a proxy for rituximab monotherapy. Moreover, as stated previously, rituximab monotherapy is expected to be less effective than both BR and DRC and zanubrutinib is potentially more effective in treatment naïve patients than in patients with relapsed/refractory disease, therefore, these results can be considered highly conservative and the upper bound limit of the ICER.

Table 1: Cost-effectiveness results for zanubrutinib versus rituximab monotherapy using the BR dataset as proxy
<table>
<tr><th rowspan="2">#</th><th rowspan="2">Scenarios</th><th colspan="3">BR dataset</th></tr>
<tr><th>Inc. cost (£)</th><th>Inc. QALYs</th><th>ICER (£) vs. rituximab monotherapy</th></tr>
<tr><td>-</td><td colspan="4">Deterministic results</td></tr>
<tr><td>1</td><td>Company preferred settings
- [redacted]% PAS discount for zanubrutinib</td><td>[redacted]</td><td>[redacted]</td><td>£21,341</td></tr>
</table></td><td>The committee was not able recommend zanubrutinib for the population for whom chemoimmunotherapy is unsuitable because the ICER for zanubrutinib compared with rituximab was not below £30,000 per QALY gained (FAD sections 3.15 and 3.18).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row				NICE Response Please respond to each comment
				- Rituximab list price (primary and subsequent treatment) - Rituximab monotherapy efficacy and safety equalised to BR dataset - MAIC (i.e. PFS HR for zanubrutinib vs rituximab) - Ibrutinib excluded as a subsequent treatment (adjusted in costs and survival [[redacted] percentage point decrease at 6 years] in SoC)			
			2	**Scenario 2:** #1 plus ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£22,402
			3	**Scenario 3:** #1 plus ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 40% lower than	[redacted]	[redacted]	£23,968

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	zanubrutinib arms)			
4	**Scenario 4:** #1 plus assuming an 85% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,114
5	**Scenario 5:** #1 plus assuming an 90% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,277
6	**Scenario 6:** #1 plus assuming an 95% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,440
-	**Probabilistic results**			
7	Preferred settings (see #1)	[redacted]	[redacted]	£22,475

Abbreviations: BR, bendamustine plus rituximab; ICER, incremental cost-effectiveness ratio; Inc., incremental; ITT, intention-to-treat; MAIC, matched adjusted indirect comparison; PAS, Patient Access Scheme; QALY, quality-adjusted life-year; SoC, standard of care.

Table 2: Cost-effectiveness results for zanubrutinib versus rituximab monotherapy using the DRC dataset as proxy

#	Scenarios	DRC dataset		
		Inc. cost (£)	Inc. QALYs	ICER (£) vs. rituximab monotherapy
-	**Deterministic results**			
1	**Company preferred**	[redacted]	[redacted]	£26,646

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row				NICE Response Please respond to each comment
				settings - [redacted]% PAS discount for zanubrutinib - Rituximab list price (primary and subsequent treatment) - Rituximab monotherapy efficacy and safety equalised to DRC dataset - MAIC (i.e. PFS HR for zanubrutinib vs rituximab) - Ibrutinib excluded as a subsequent treatment (adjusted in costs and survival [[redacted] percentage point decrease at 6 years] in SoC)			
			2	**Scenario 2:** #1 plus ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£27,818
			3	**Scenario 3:** #1 plus ibrutinib subsequent	[redacted]	[redacted]	£29,608

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 40% lower than zanubrutinib arms)			
4	**Scenario 4:** #1 plus assuming an 85% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£29,455
5	**Scenario 5:** #1 plus assuming an 90% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£29,620
6	**Scenario 6:** #1 plus assuming an 95% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£29,785
-	**Probabilistic results**			
7	Preferred settings (see #1)	[redacted]	[redacted]	£28,165

Abbreviations: DRC, dexamethasone rituximab and cyclophosphamide; ICER, incremental cost-effectiveness ratio; Inc., incremental; ITT, intention-to-treat; MAIC, matched adjusted indirect comparison; PAS, Patient Access Scheme; QALY, quality-adjusted life-year; SoC, standard of care.

NICE National Institute for Health and Care Excellence

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 20 July 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BeiGene UK Ltd.

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NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	**Summary of the Company's position** The Company would like to thank the Committee for the opportunity to respond to the second Appraisal Consultation Document (ACD2).[1] The Company welcomes the recommendations made by the Committee for zanubrutinib as a treatment option for treating Waldenstrom's macroglobulinaemia (WM) in adults who have had at least 1 treatment, only if they would otherwise have treatment with bendamustine and rituximab (BR). The Company also welcomes the Committee's acknowledgement that: • The availability of an effective and well-tolerated oral treatment would be highly valued by people with WM and would address a significant unmet need. • Hazard ratios for progression-free and overall survival were low compared with those typically seen in cancer treatments, suggesting that zanubrutinib is a highly effective treatment and that zanubrutinib is more clinically effective than chemoimmunotherapy treatments in WM.

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	• Some adjustment to post progression survival in the BR or dexamethasone, rituximab and cyclophosphamide (DRC) modelled arms may have been needed to account for the potential effect of follow-on treatments not available in the National Health Service (NHS), although the level of this adjustment was uncertain. The Company understands that the Committee was unable to make a recommendation for patients who are treatment naïve and unsuitable for chemoimmunotherapy following the second Appraisal Committee Meeting (ACM2). In response to this and to the statements made by the Committee in the ACD2, the Company would like to highlight further analyses presented in Comment 2 for patients who are treatment naïve and unsuitable for chemoimmunotherapy. These analyses take into the account the data available to the Company, and even with the paucity of data in WM, the analyses demonstrate that in addition to patients with relapsed/refractory disease, zanubrutinib is also a cost-effective therapy in patients who are treatment naïve and unsuitable for chemoimmunotherapy. When considering the Patient Access Scheme (PAS) for zanubrutinib ([redacted]% discount on the list price) and the evidence presented in Comment 2, zanubrutinib can be considered a cost-effective treatment option for treatment naïve patients who are unsuitable for chemoimmunotherapy, with all incremental cost-effectiveness ratios (ICERs) remaining comfortably under the £30,000 per quality-adjusted life-year (QALY) gained threshold (Table 1 and Table *2*). Sensitivity analyses demonstrate that even when comparators are heavily discounted, zanubrutinib remains cost-effective. Probabilistic analysis demonstrates that the results are robust to parameter uncertainty with the mean ICER lying close to the deterministic ICER for all scenarios conducted.
2	**<u>Zanubrutinib is a cost-effective therapy in patients with WM who are treatment naïve and unsuitable for chemoimmunotherapy</u>**

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	As stated in the first ACD, "*the committee concluded that BR and DRC represent the 2 most relevant comparators in this appraisal*".[2] This was reiterated in the second ACM where it was agreed that BR and DRC were the "*two treatments most commonly used"* and are "*key comparators for cost-effectiveness analysis".*[3] As presented in Table 1 of the Company's Technical Engagement response form, the United Kingdom (UK) 2021 Rory Morrison Registry report indicated that 85% of patients received either a bendamustine-based regimen (i.e., BR) or DRC between 2015 and 2020 in the first-line setting.[4] When considering the second-line setting, 77% of patients received either BR or DRC between 2017 and 2020.[5] Furthermore, clinical expert opinion obtained by the Company during this Technical Engagement stage supports the inclusion of BR and DRC as the two main treatments (aside from ibrutinib) within UK clinical practice for patients with WM. As such the Company is surprised that the Committee has introduced additional comparators (rituximab and chlorambucil monotherapies) within the ACD2, given that the following statements were made within ACD1 regarding the comparators within this appraisal: • "*The clinical experts said that rituximab or chlorambucil monotherapy would not work as quickly or have the same durability as standard combined chemoimmunotherapy regimens."* • *"Bendamustine and rituximab (BR) and dexamethasone, rituximab and cyclophosphamide (DRC) are the key comparators for zanubrutinib"*

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

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	• *"While there is variation in the treatment pathway for people with Waldenstrom's macroglobulinaemia, particularly when it is relapsed or refractory, the committee concluded that BR and DRC represent the 2 most relevant comparators in this appraisal."* Neither rituximab monotherapy nor chlorambucil monotherapy are commonly used in clinical practice in the UK, as re-validated by clinical expert opinion sought by the Company following the second ACM. Nevertheless, data from the 2021 UK Rory Morrison registry show that rituximab is more widely used than chlorambucil in the front-line setting for the treatment for WM (11% vs 4%).[6] This is supported by the 2021 British Society for Haematology (BSH) WM guidelines, which describe chlorambucil monotherapy as having *"a very limited role"* in contemporary first-line therapy, whereas rituximab is noted to be *"generally well tolerated but associated with modest response rates".*[7] Concerns around the toxicity of chlorambucil monotherapy, which have grown in recent times with increased insight into varying treatment options, have limited its use in clinical practice, as more appropriate treatments have replaced older agents.[6] This was also validated by clinical expert opinion sought by the Company following the second ACM. In addition, based on clinical expert opinion, as chemotherapy-unsuitable patients are generally elderly, frailer, and have a worse prognosis than chemotherapy-suitable patients, the goal of treatment in this patient population is to maintain their quality of life and limit toxicities. Therefore, the use of chlorambucil in these patients would be counterproductive. A difference in the clinical efficacy between chlorambucil monotherapy and rituximab monotherapy has also been noted in trial data, with rituximab monotherapy demonstrating more favourable survival outcomes in the front-line setting for similar blood cancers. This is evidenced with a hazard ratio (HR) of 0.69 (95% CI: 0.51 - 0.91) for rituximab monotherapy when compared to chlorambucil monotherapy treated patients, in the treatment of chronic lymphocytic leukemia.[8]

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	Further clinical evidence of superior efficacy of rituximab vs chlorambucil is provided by the matching-adjusted indirect comparison (MAIC) analyses conducted by the Company.[4] The progression-free survival HR for zanubrutinib relative to rituximab monotherapy is higher than that of zanubrutinib relative to chlorambucil monotherapy, with values of [redacted] (95% CI [redacted] – [redacted]) and [redacted] (9% CI [redacted] – [redacted]), respectively. This indicates, indirectly, that patients treated with rituximab monotherapy were more likely to avoid disease progression and/or death than those treated with chlorambucil monotherapy. Regarding dosing plans and total costs for rituximab and chlorambucil monotherapies, little difference can be observed between the two treatments. As such, given that rituximab monotherapy is more widely used and is more clinically effective than chlorambucil monotherapy for the treatment of blood cancers, this justifies the inclusion of rituximab monotherapy as a comparator in the submission, in line with the UK 2021 Rory Morrison Registry data, clinical guidelines, and expert opinion sought by the Company. Therefore, the Company has conducted additional analyses to demonstrate the cost-effectiveness of zanubrutinib vs rituximab monotherapy in treatment-naïve, chemotherapy-unsuitable patients. Given the clinical inferiority of chlorambucil and higher level of toxicity than rituximab, this implies that if zanubrutinib is cost-effective relative to rituximab monotherapy, it will also be cost-effective relative to chlorambucil monotherapy. To perform this comparison, the Company has assumed the efficacy of zanubrutinib in the treatment naïve setting versus rituximab monotherapy can be obtained by applying the HRs derived from the Company's MAIC analysis (PFS HR [redacted] [95% CI [redacted] – [redacted]]; OS [redacted] [95% CI [redacted] – [redacted]]) to a baseline control arm within the model. This assumption is conservative given that the MAIC analyses included the full ASPEN ITT population of both patients with relapsed/refractory WM and treatment naïve patients who are unsuitable for chemoimmunotherapy (where "unsuitable" was defined as a

	physician determined status based on co-morbidities [renal, cardiac, infection, other] and risk factors [age]. Patient preference was not considered to meet the eligibility requirement for a treatment-naïve subject to be unsuitable for treatment with a standard chemoimmunotherapy regimen). As stated in the Technical Engagement Response, treatment naive patients historically experience better prognoses than relapsed/refractory patients, which conservatively suggests zanuburitinb is at least as effective in treatment naive patients compared to relapsed refractory setting. Evidence from the European chart review [5] and published literature confirm this statement, demonstrating decreasing PFS with each line of therapy whilst PFS and OS landmark rates in Castillo et al. 2021 (treatment-nave ibrutinib WM trial) were higher than in Treon et al. 2021 (R/R ibrutinib WM trial).[7,8] Evidence from ASPEN supports at least a comparable treatment effect for zanubrutinib across both treatment naïve patients and relapsed/refractory patients, with a similar proportion of patients achieving a very good partial response (VGPR) (treatment naïve – 26% vs. R/R – 29%).[9] This conservativeness of this assumption is further validated by clinical opinion and supported by the Committees comments from both ACDs that: • *"the assumption of equivalent efficacy by the company was likely to be a conservative one. This was based on the clinical experts' expectation that people having zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed or refractory. "– ACD1* [2] • "*people having zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed or refractory. So, the assumption of equivalent efficacy between first- and second-line treatment by the company may have been reasonable" – ACD2* [1] In addition, the Company has assumed that the efficacy and safety of rituximab monotherapy is equivalent to either the BR or DRC datasets within the submission, and that these datasets can act as a suitable baseline control arm within the model.

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	This assumption can be considered conservative as highlighted in the ACD2, the Committee recognises that *"the comparators (monotherapy when chemoimmunotherapy is unsuitable) may be less effective than chemoimmunotherapy. This would increase the potential benefit of zanubrutinib compared with the comparators for this group".*[1] The assumption of increased potential benefit of zanubrutinib is further supported from results of the Company's MAIC which indicate that zanubrutinib is more effective versus rituximab monotherapy [redacted] than both BR combination therapy [redacted] and DRC combination therapy [redacted].[4] To reflect the cost of rituximab monotherapy, the company has removed the treatment acquisition and administration costs of bendamustine from the BR component of the model and the treatment acquisition and administration costs of dexamethasone/cyclophosphamide from the DRC component of the model, leaving only the costs of rituximab monotherapy within this analysis. When considering the Company's preferred settings (Table 1) and assuming that rituximab monotherapy is equivalent to the BR dataset, zanubrutinib is associated with [redacted] additional costs and [redacted] additional QALY versus rituximab monotherapy, corresponding to an ICER of £21,341 per QALY gained. When considering the Company's preferred settings (Table 1) and assuming that rituximab monotherapy is equivalent to the DRC dataset, zanubrutinib is associated with [redacted] additional costs and [redacted] additional QALY versus rituximab monotherapy, corresponding to an ICER of £26,646 per QALY gained. The Company anticipates that rituximab monotherapy is heavily discounted, and as such has included scenarios assuming an 85% - 95% discount on the list price of rituximab monotherapy. Results show that even when rituximab monotherapy is provided at an extreme level of discount (95%) discount, the ICERs remain below £30,000

per QALY gained regardless of the dataset used as a proxy for rituximab monotherapy. Moreover, as stated previously, rituximab monotherapy is expected to be less effective than both BR and DRC and zanubrutinib is potentially more effective in treatment naïve patients than in patients with relapsed/refractory disease, therefore, these results can be considered highly conservative and the upper bound limit of the ICER.

Table 1: Cost-effectiveness results for zanubrutinib versus rituximab monotherapy using the BR dataset as proxy

#	Scenarios	BR dataset		
		Inc. cost (£)	Inc. QALYs	ICER (£) vs. rituximab monotherapy
-	**Deterministic results**			
1	**Company preferred settings** - [redacted]% PAS discount for zanubrutinib - Rituximab list price (primary and subsequent treatment) - Rituximab monotherapy efficacy and safety equalised to BR dataset - MAIC (i.e. PFS HR for zanubrutinib vs rituximab) - Ibrutinib excluded as a subsequent treatment (adjusted in costs and survival [redacted] percentage point decrease at 6 years] in SoC)	[redacted]	[redacted]	£21,341
2	**Scenario 2:** #1 plus ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£22,402

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3	**Scenario 3:** #1 plus ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm (equates to 40% lower than zanubrutinib arms)	[redacted]	[redacted]	£23,968
4	**Scenario 4:** #1 plus assuming an 85% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,114
5	**Scenario 5:** #1 plus assuming an 90% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,277
6	**Scenario 6:** #1 plus assuming an 95% discount on the price of rituximab monotherapy	[redacted]	[redacted]	£24,440
-	**Probabilistic results**			
7	Preferred settings (see #1)	[redacted]	[redacted]	£22,475

Abbreviations: BR, bendamustine plus rituximab; ICER, incremental cost-effectiveness ratio; Inc., incremental; ITT, intention-to-treat; MAIC, matched adjusted indirect comparison; PAS, Patient Access Scheme; QALY, quality-adjusted life-year; SoC, standard of care.

Table 2: Cost-effectiveness results for zanubrutinib versus rituximab monotherapy using the DRC dataset as proxy

#	Scenarios	DRC dataset		
		Inc. cost (£)	Inc. QALYs	ICER (£) vs. rituximab monotherapy
-	**Deterministic results**			
1	**Company preferred settings** - [redacted]% PAS discount for zanubrutinib	[redacted]	[redacted]	£26,646

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		- Rituximab list price (primary and subsequent treatment) - Rituximab monotherapy efficacy and safety equalised to DRC dataset - MAIC (i.e. PFS HR for zanubrutinib vs rituximab) - Ibrutinib excluded as a subsequent treatment (adjusted in costs and survival [percentage point decrease at 6 years] in SoC)			
	2	**Scenario 2:** #1 plus ibrutinib subsequent treatment costs excluded and percentage point decrease in survival at 6 years in SoC arm (equates to 45% lower than zanubrutinib arms)			£27,818
	3	**Scenario 3:** #1 plus ibrutinib subsequent treatment costs excluded and percentage point decrease in survival at 6 years in SoC arm (equates to 40% lower than zanubrutinib arms)			£29,608
	4	**Scenario 4:** #1 plus assuming an 85% discount on the price of rituximab monotherapy			£29,455
	5	**Scenario 5:** #1 plus assuming an 90% discount on the price of rituximab monotherapy			£29,620
	6	**Scenario 6:** #1 plus assuming an 95% discount on the price of rituximab monotherapy			£29,785
	-	**Probabilistic results**			
	7	Preferred settings (see #1)			£28,165
	Abbreviations: DRC, dexamethasone rituximab and cyclophosphamide; ICER, incremental cost-effectiveness ratio; Inc., incremental; ITT, intention-to-treat; MAIC, matched adjusted indirect comparison; PAS, Patient Access Scheme; QALY, quality-adjusted life-year; SoC, standard of care.				

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Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Shirley D'Sa: Medical Trustee, WMUK Charity** WMUK Homepage - WMUK **Kim Linton: NCRI Lymphoma Science subgroup** Lymphoma Science Subgroup - NCRI Dr Kim Linton Senior Lecturer and Honorary Consultant in Medical Oncology The Christie NHS Foundation Trust Wilmslow Road Manchester M20 4BX Kim.M.Linton@manchester.ac.uk

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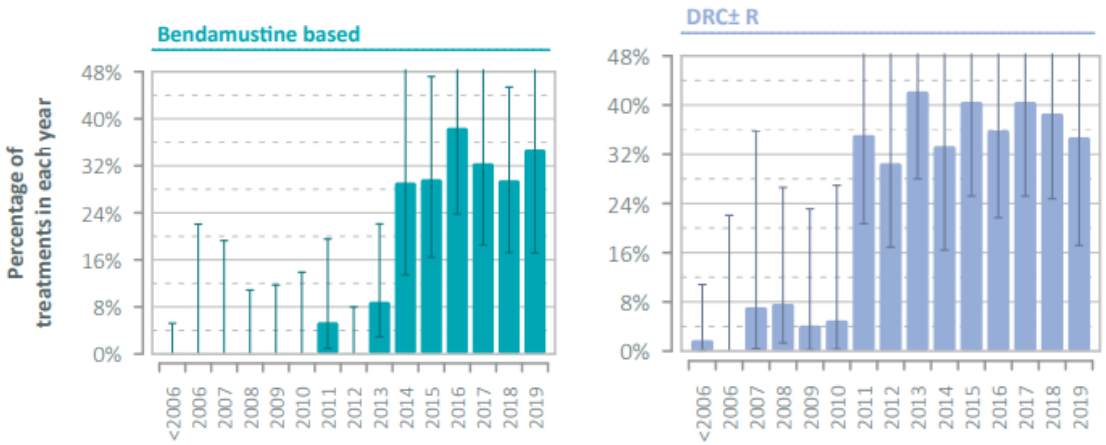
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Shirley D'Sa Consultant Haematologist & Associate Professor Clinic Lead, UCLH Centre for Waldenström and Related Conditions UCLH NHS Foundation Trust s.d'sa@nhs.net

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about the stipulation that: "in the absence of Zanubrutinib, the patient would otherwise be next treated with the combination of Bendamustine and Rituximab (BR)". This will put patients who have already received BR at a potential disadvantage (approx. 50% of patients with WM in the UK receive BR as first line therapy (see data below from the 2nd Report of the Rory Morrison Registry (RMR) 2021, based on year treatment started) Rory-Morrison-Report-2021-2-11-21-Final-Version.pdf (wmuk.org.uk)  1. DRC vs BR notes: • Although considered equivalent in terms of efficacy and PFS, and in the absence of a head-

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	to-head comparison, DRC and BR are used in different ways. • Treatment guidelines- as seen in the treatment algorithm from the latest BCSH Guidelines for the Diagnosis and Management of WM- A British Society for Haematology Guideline (https://doi.org/10.1111/bjh.18036), there are specific clinical indications for the preference of BR over DRC, such as *hyperviscosity, cryoglobulinaemia, Al amyloidosis*. The reason that BR is preferred in these circumstances is that it induces a more rapid response than DRC and can preserve organ function due to hyperviscosity (risk of stroke and other vascular events), Cryoglobulinaemia (risk of skin ulceration/ vasculitis/ renal failure/ progressive erve damage) and Al amyloidosis (deterioration of vital organ function, eps heart and kidneys). • Furthermore in the setting of high blood viscosity (more likely when the IgM paraprotein is ≥ 40g/L), recommended practice is to defer Rituximab for 2 cycles to avert an IgM flare, which can cause hyperviscosity syndrome necessitating weeks of plasma exchange (itself an expensive and scarce resource which requires wide-bore venous access with intendant risks). In this situation a brisk response to treatment is clinically needed, hence the choice of BR over DRC. If Rituximab is deferred in the setting of DRC, then there is unrealistic reliance on Cyclophosphamide to lower the disease burden until Rituximab can be introduced.

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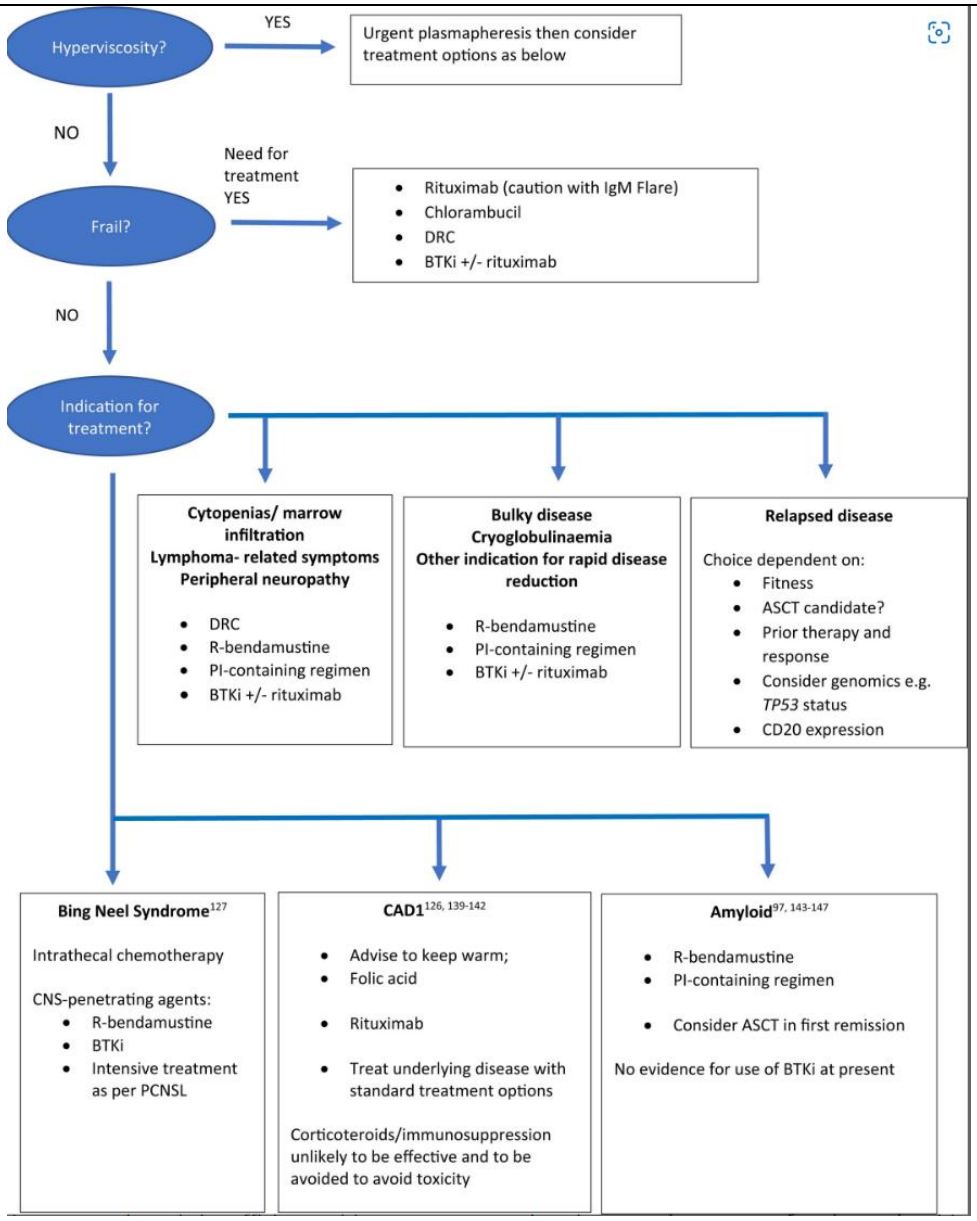

- There is a risk that physicians will select front-line DRC in patients who would be better served by BR, *to safeguard future access* to ZANU in those patients.

2. Use of BR as second-line therapy

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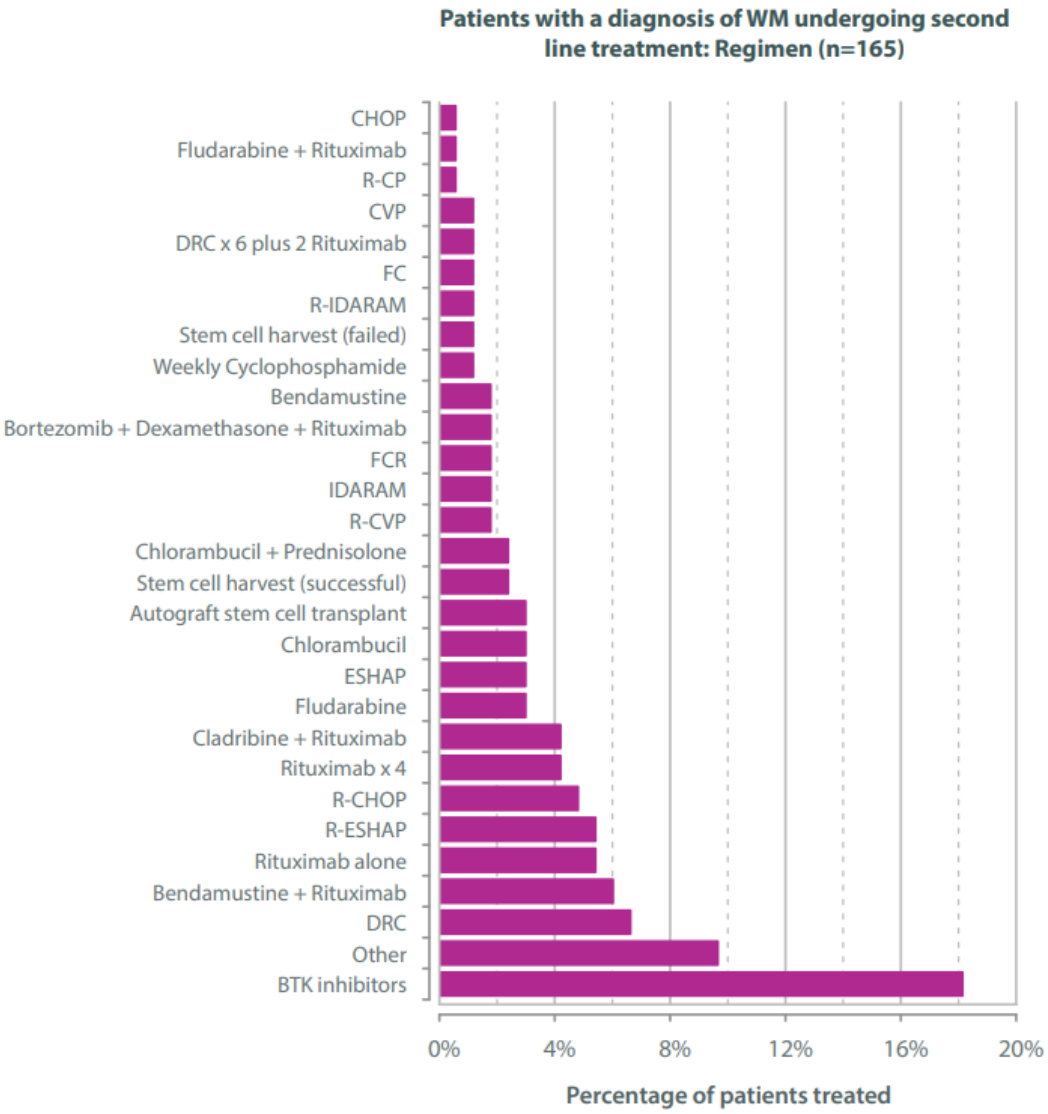

As can be seen from the above graph from the 2nd Report of the RMR, BR is very rarely used as second-line therapy. This is likely due to the following reasons:

- While Ibrutnib was available on the CDF (2017-2022), its use in second and subsequent lines rose steadily due to the backlog of multiply-treated patients who had developed chemoresistance and physician and patient choice in seeking a less harsh therapy.

- Patients with early treatment failure after BR are not candidates for BR re-treatment. Like all WM patient with relapsed disease, their prognosis is inferior. Since prognosis at relapse seems to be unrelated to previous treatment or time to progression (Does early disease progression predict survival after first line-treatment of Waldenström macroglobulinemia? - Labreuche - Hematological Oncology - Wiley Online Library), availability of effective treatment is a key prognostic factor. Prognosis is already worse for patients who are not candidates for BR re-treatment, and the current NICE criteria has worsened this further by also denying BR ineligible patients access to zanubrutinib. That is the real issue here – selected access will marginalise the WM population and increase the burden of unmet need

for those at highest risk.

- Early progression of disease within 24 months of treatment (POD24) trends towards inferior survival. Although the relationship between POD24 and survival in WM is somewhat confounded, the 'POD24' time-point is useful to quantify the size of the BR treated subset that is unsuitable for BR re-treatment and zanubrutinib. The POD24 group accounted for 18% for 1L patients reported in a study at ASH 2021 (Kim et al, 2021). Half of these patients received BR. Thus, this 'BR ineligible group is ~10% of patients. Amended criteria to include this small subset of patients shouldn't have a major impact on the cost utility analysis.

Kim et al ASH 2021.html

- BR is a powerful treatment at front line; while the acute toxicities of bendamustine are not prominent, the drug seems to have a prolonged effect, probably immunological, leading to an increased risk of late infections (Bendamustine: A review of pharmacology, clinical use and immunological effects - PMC (nih.gov). This is of relevance in WM patients who frequently have a B cell deficiency from the outset. Due to the significant immunosuppression associated with BR, many physicians curtail BR doses when used at front-line or subsequent lines, to reduce the chance of damaging immunosuppression. Furthermore, the hypogammaglobulinaemia that can follow BR therapy can lead to use of intravenous immunoglobulin use spanning many months (IVIG itself is a resource that is expensive and in short supply globally).

The following is an excerpt from the above publiction:

"Bendamustine-induced lymphopenia, whether as monotherapy or in combination, has been widely reported in both hematological and non-hematological malignancies. Lymphopenia ranged from 5% in rituximab-refractory patients with iNHL to 75% of patients with grade 3–4 hematological toxicity receiving BR or even to 91% in patients treated for triple negative breast cancer. The latter group was characterized with pronounced decline in $CD4^+$ cells, with 86% having grade 4 depressed $CD4^+$ counts (<50/µl). In FL patients treated with bendamustine, marked reductions in $CD3^+$ and $CD3^+CD4^+$ T cells were seen during induction with prolonged recovery during and after maintenance. Prolonged lymphopenia and low $CD4^+$ T-cell counts, for at least 7–9 months were also observed in relapsed or refractory patients with iNHL and MCL. Recent population-based analysis by Martínez-Calle *et al* following BR treatment in patients with low grade lymphoproliferative disease revealed that median times to lymphocyte count recovery ($\geq 1\times10^9$/l) and $CD4^+$ recovery ($\geq 0.2\times10^9$/l) were 26 and 24 months, respectively, and late recovery was associated with risk of serious infection".

- There appears to be an increased risk of second primary cancers following the use of Bendamustine in previously treated lymphoma Long-term outcomes, secondary malignancies, and stem cell collection following bendamustine in patients with previously treated non-Hodgkin lymphoma - PMC (nih.gov).

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	See excerpt below: "With a **median follow-up of 8.9 years (95% C.I. 8.7-9.4)** years after study entry, 23 patients developed 25 cancers following bendamustine. Six patients developed MDS and 2 more developed AML, resulting in an annual incidence rate of 0.5%/person/year, and a **cumulative incidence rate of 6.2% (95% CI 3.1-12.2%) at the end of maximum follow up date**, adjusting for death from any cause as a competing event. The median time to **MDS/AML among subjects that developed MDS/AML following bendamustine** was 23 months (range 10-103). The median time to MDS/AML from the date of diagnosis was 89 months (range 33-226). One of the patients had a prior myeloid neoplasm and one had a prior germ cell tumor. Patients who developed MDS/AML had received a median of 5 therapies, including bendamustine, before developing the myeloid malignancy, which is the same as the median number of therapies received by the entire cohort. In univariate analysis, age at lymphoma diagnosis (P=0.44), lymphoma histology, total number of systemic regimens (P=0.44), or total dose of bendamustine (P=0.29) were associated with MDS/AML. Cytogenetics for each case were not available. Other cancers included non-melanoma skin cancer (n=6), adenocarcinoma (colon n=2; prostate n=2; lung n=2; breast n=1), squamous cell neck cancer (n=1), squamous cell anal cancer (n=1), hepatocellular carcinoma (n=1), and bladder cancer (n=1). None of these occurred in the 12 patients with a history of solid tumor before bendamustine administration". For these reasons, the use of BR as second line therapy and more so after prior BR is likely to be very limited. Many physicians would thus be unwilling to consider BR as second line therapy and hence feel unable to TICK Number 5 of the CDR Blueteq form and hence exclude patients from receiving Zanubrutinib. We acknowledge however, that some prior BR-exposed patients can be retreated with BR, albeit with the caveats outlined above. <u>We suggest we propose amended criteria for Zanubrutinib:</u> 1) patients who would otherwise be eligible for BR including those who have not previously received this treatment or received this > 2 years ago and did not experience significant toxicity 2) patients who experienced early treatment failure after BR for whom re-treatment is not recommended and novel therapy is needed. This includes BR treated patients who failed to achieve PR/CR, or experienced PD within 24 months, and/or developed significant toxicity.
2	We are concerned about the absence of a recommendation for Zanubrutinib in first-line treatment for patients unsuitable for chemo-immunotherapy. We accept the limited evidence in this setting as well as the imprecise definition of 'unsuitable for chemo-immunotherapy'. In the absence of the opportunity to assess patients at front-line, the chance of seeking the answer to this question is slim. We would propose a consideration of a pre-defined setting in which front-line Zanubrutinib is permitted and data collection undertaken to enable a better understanding in this group.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] responding on behalf of BSH and RCPath Authors of recent BSH guidelines for the diagnosis and management of WM (BJH 2022) NCRI Lymphoma Network, and low grade lymphoma subgroup.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[nil]
Name of commentator person completing form:	[redacted] Haematology Consultant Royal Marsden Hospital

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the recommendation of the use of zanubrutinib in previously treated patients who would otherwise have been treated with rituximab and bendamustine may lead to inequity of access to zanubrutinib for patients with WM. This inequity may be due to 1. Patient related factors including age- choice of therapy takes into consideration the toxicity of the regimen as well as the efficacy. This is especially true in WM, where there is a high rate of patients dying of other causes rather than WM alone, and where evidence for treatment benefit is from multiple single arm phase 2 studies. Rituximab-and bendamustine will rarely be used as a treatment option due to toxicity concerns in more frailer patients or those with co-morbidities and thus this may prevent them from accessing a potentially important extra line of therapy for their WM that will not have the same associated toxicity. 2. Disease related factors which would mean that Rituximab bendamustine would be more likely to be used front-line and clinicians are less likely to use the same chemotherapy regimen again due to decreased efficacy on repeat usage and the concern about increased toxicity including the risks of secondary MDS. There are certain complications of WM that need to be taken into account when choosing therapy for patients, and how quickly the disease burden needs to be reduced, for example in those with bulky disease, cryoglobulinaemia or amyloid, the preference would be frontline, to use Rituximab and bendamustine to get more rapid reduction in disease burden to prevent long term complications or progression of disease on treatment. If this regimen is therefore used frontline, depending on length of time until disease progression, many clinicians would not consider using rituximab bendamustine again either if there was a short time until progression and thus likelihood of lack of efficacy or due to toxicity concerns in repeating bendamustine. 3. Clinician prescribing habits and patients already treated frontline with Rituximab bendamustine. As discussed above, there is no randomised data to indicate that there is a preferred chemoimmunotherapy option to use frontline and so both DRC and rituximab bendamustine are used as frontline regimens in patients with WM, sometimes the choice is dictated by patient related factors and sometimes disease related, but often it is simply clinician preference. Our concern is that if a clinician tends to prescribe rituximab-bendamustine frontline, then they are far more likely to prescribe an alternative chemoimmunotherapy regimen in the second line, this would therefore potentially lead to inequity of access to zanubrutinib that could potentially be geographical according to clinician/centre preference as to what is prescribed in the front line setting.
2	We are concerned that the lack of recommendation of the use of zanubrutinib in those unsuitable for chemoimmunotherapy prevents patients who cannot have chemoimmunotherapy from having a potentially effective oral therapy that would otherwise have led to an improvement in their quality of life. In patients who are unsuitable for chemoimmunotherapy, the goal of therapy is different in those who are more fit. Often life expectancy is likely to be shorter for other reasons such as their co-morbidities or frailty that makes them unsuitable for chemoimmunotherapy and thus the goal of the therapy is to lead to improvement in WM related symptoms with minimal toxicity. Not allowing these patients to

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	access zanubrutinb (as they also would be definition not be eligible for it in the relapsed refractory setting if the current recommendation stays as it is) prevents them from having an effective therapy that we know from both trial and real world data can be well tolerated by elderly frail patients or those with co-morbidities.
3	
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5	
6	

Insert extra rows as needed

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1	If the revised appraisal committee recommendations are ratified without further modification clinicians and patients will no doubt be very dissatisfied particularly since Ibrutinib is no longer available for relapsed or refractory WM on the NHS in England and Wales. I reiterate my earlier assertion that the cost of Zanubrutinib is the determining factor and the quickest way to achieve an improved outcome is for NICE to negotiate a mutually acceptable **interim** price with BeiGene until such time as BeiGene can provide updated evidential data over an extended period. Since the current evidential data is immature, it is not surprising that the NICE cost-effectiveness threshold calculations expressed in terms of ICER and QALY gained appear to be pessimistic. However, my understanding at the treatment centre I attend is that the on-going evidential data is particularly encouraging and will no doubt prove to be universally the case elsewhere. As a WM patient receiving treatment with Zanubrutinib since December 2017, via the BGB-3111- 302 clinical trial, extended in March 2022 for a further 5 years, renamed as BGB-3111-LTE1, I expect that by the time the proposed 3 year NICE review is reached new longer-term (minimum 7 years) data should enable Zanubrutinib to receive approval as a routine first-line treatment. Without my having the particular good fortune of joining this trial I would not have survived for very long after being withdrawn from chemoimmunotherapy options in March 2017 because of intolerance. Importantly since BeiGene did not submit any evidence for the initial treatment of WM with Zanubrutinib compared with alternative therapies in people for whom chemoimmunotherapy is unsuitable it has not been recommended for this group so they will be seriously disadvantaged. They are living with a rare incurable lymphoma, are frail and will be denied access to what the clinical experts regard as a much preferred step-change in managing WM. Irrespective of whether BeiGene provided evidence for this group it prompts the question - would this potential situation be unlawful discrimination? The answer would appear to be **'Yes'** since WM is clearly a cancerous disability. Furthermore, it is acknowledged that there is no reason to suppose that first-line treatment with Zanubrutinib would be less effect than if a patient had received one or more earlier treatments with either BR or DRC. In fact they are more likely to fair even better due to its better efficacy, better tolerance, lower toxicity with fewer side effects and hospital visits whilst also enjoying a much better quality experience. Like me I'm sure there will be others who will regard this as another example of a technical nicety thwarting a pragmatic approach to healthcare. In practice these proposed recommendations will also reduce clinician/patient choice by channelling more patients into starting treatment with DRC. **Why?** - no informed sensible patient will agree to starting treatment with BR when doing so would then probably mean having DRC next before state of the art treatment with Zanubrutinib is made available to them. Introduction of new drugs invariably have higher cost implications but also some identifiable

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 20 July 2022. Please submit via NICE Docs.

	cost savings and benefits. However, no attempt has been made to quantify either the significant cost savings of not having to administer chemoimmunotherapy or the possibility of freeing up human resources in an overstretched NHS. Also during the 7-years the £20-30K per QALY thresholds have been in use, inflation has increased by a multiplier of 1.19 equivalent to £23.8-35.7K per QALY, with current inflation expected to exceed 10%. **A significant fact and perhaps a review is overdue.** I suggest the overall cost-benefit analysis of introducing this new technology is more complex than usual and should include consideration of the above.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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ADDENDUM: Comments to company's ACD2 response

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Date completed	03/03/2022

Cost-effectiveness results for zanubrutinib versus rituximab monotherapy

The company conducted additional analyses to demonstrate the cost-effectiveness of zanubrutinib vs rituximab monotherapy in treatment-naïve, chemotherapy-unsuitable patients. The company argues that, given the clinical inferiority of chlorambucil and higher level of toxicity than rituximab, this implies that if zanubrutinib is cost-effective relative to rituximab monotherapy, it will also be cost-effective relative to chlorambucil monotherapy.

The company obtained the efficacy of zanubrutinib in the treatment naïve setting versus rituximab monotherapy by applying the HRs derived from the MAIC analysis (PFS HR [redacted] [95% CI [redacted]]; OS [redacted] [95% CI [redacted]]) to a baseline control arm within the model. In addition, the company assumed that the efficacy and safety of rituximab monotherapy is equivalent to either the BR or DRC datasets within the submission, and that these datasets can act as a suitable baseline control arm within the model. To reflect the cost of rituximab monotherapy, the company has removed the treatment acquisition and administration costs of bendamustine from the BR component of the model and the treatment acquisition and administration costs of dexamethasone/cyclophosphamide from the DRC component of the model.

ERG comment

The ERG appreciates the company's additional analyses to demonstrate the cost-effectiveness of zanubrutinib vs rituximab monotherapy in treatment-naïve, chemotherapy-unsuitable patients. However, the ERG still considers adjusting the survival of the comparator to reflect that ibutrinib cannot be included within the subsequent treatment pathway to be inappropriate.

Deterministic company's base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BR dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	21,341
Rituximab	[redacted]	[redacted]			
DRC dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	26,646
Rituximab	[redacted]	[redacted]			

Deterministic ERG base-case (company's base-case without OS adjustment)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BR dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	23,570
Rituximab	[redacted]	[redacted]			
DRC dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	34,084
Rituximab	[redacted]	[redacted]			

Probabilistic ERG base-case (company's base-case without OS adjustment)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BR dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	25,250
Rituximab	[redacted]	[redacted]			
DRC dataset					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	36,378
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	