

Single Technology Appraisal

**Zanubrutinib for treating Waldenstrom's
macroglobulinaemia [ID1427]**

Committee Papers

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:

- 1. Comments on the Appraisal Consultation Document from BeiGene**
- 2. Consultee and commentator comments on the Appraisal Consultation Document** from:
 - a. Janssen
 - b. WMUK
- 3. Comments on the Appraisal Consultation Document from experts:**
 - a. Ronald Presswood – patient expert, nominated by WMUK
- 4. Evidence Review Group critique of company comments on the ACD**

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

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

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| | <p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> • 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? <p>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:</p> <ul style="list-style-type: none"> • 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. <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p> |
| <p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p> | <p>BeiGene UK Ltd.</p> |

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| <p>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p> | <p>None</p> |
| <p>Name of commentator person completing form:</p> | <p>██████████</p> |
| <p>Comment number</p> | <p>Comments</p> |
| <p>1</p> | <p>Summary of the Company's position</p> <p>The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD). The Company welcomes the Committee's acknowledgement that:</p> <ul style="list-style-type: none"> • The availability of an effective and well-tolerated oral therapy such as zanubrutinib, would be highly valued by people with Waldenström's macroglobulinemia and would address a significant unmet need. • Zanubrutinib is more clinically effective than chemoimmunotherapy treatments and the hazard ratios for progression-free survival (PFS) and overall survival (OS) are low compared to those typically seen with cancer treatments. • The extrapolated PFS and OS estimates for zanubrutinib are clinically plausible and appropriate for decision making. Moreover, in the absence of clinical evidence, there should be no treatment effect cut-off as assuming zanubrutinib suddenly stops working after 5 years is clinically implausible. |

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Furthermore, the Company accepts the Committee's decision to use the matching-adjusted indirect comparison (MAIC) rather than the simulated treatment comparison (STC) but is pleased the Committee recognises the substantial overlap in the confidence intervals, demonstrating consistency in the results generated by both methods.

The Company respects the Committee's decision to not approve zanubrutinib following the first Appraisal Committee Meeting (ACM). In response to this decision, the Company would like to highlight the following key points for consideration by the Committee:

- The patient access scheme (PAS) simple discount has been submitted to NHS England in response to this ACD. A simple discount of ██████% has been agreed with NHS England. This equates to a price of £█████ per 120 pack of 80 mg tablets of zanubrutinib.
- Dexamethasone rituximab and cyclophosphamide (DRC)/ bendamustine plus rituximab (BR) survival should be adjusted to reflect that ibrutinib cannot be included within the subsequent treatment pathway (as detailed in Comment 2).

In addition, the Company noted one factual inaccuracy within the ACD; this is detailed in comment 3.

When considering the revised PAS and evidence presented in Comment 2, zanubrutinib can be considered a cost-effective treatment option for patients with Waldenström's macroglobulinaemia, with all incremental cost-effectiveness ratios (ICERs) remaining comfortably under the £30,000 per quality-adjusted life-year (QALY) gained threshold (Table 1). Probabilistic analysis demonstrates that the results are robust to parameter uncertainty with the mean ICER lying close to the deterministic ICER for the Company's revised base-case.

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Within the ICER versus standard of care (SoC), the base-case split of BR:DRC (49%:51%) still represents the Company's preferred assumptions. The split is based on recorded treatment data from the 2021 Rory Morrison Registry Report.¹ This assumption was validated by two leading UK clinicians in Waldenström's macroglobulinaemia, who both confirmed during the recent NICE ACM for zanubrutinib that it was clinically realistic to assume approximately equal usage of BR and DRC, and that this reflects standard of care in UK clinical practice.² However, to mitigate any uncertainty in the ICER resulting from variability in clinical practice in the UK, the Company conducted two additional scenarios analyses which vary the weighting of BR:DRC to account for the potential variability in the usage of the two treatments across centres in the UK. Clinical expert opinion sought by the Company following the ACM indicated that it was reasonable to assume that the usage of BR and DRC may vary between 40-60%. In both these scenarios, the ICER remained comfortably below £30,000 per QALY gained, and hence should address the uncertainty in the ICER as a result of variability in current SoC practices across the UK.

Table 1. Cost-effectiveness scenario analyses for zanubrutinib PAS price versus SoC

| # | Scenarios | Inc. cost (£) | Inc. QALYs | ICER (£) vs. SoC |
|-------------------------------|--|---------------|------------|------------------|
| <i>Deterministic analysis</i> | | | | |
| 1 | Company revised base-case¹ - ██████ % PAS discount for zanubrutinib - 49%:51% BR:DRC | ██████ | ██████ | 25,045 |

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|---|--|--|------------|------------|--------|
| | | <ul style="list-style-type: none"> - MAIC - Ibrutinib excluded (adjusted in costs and survival [REDACTED] percentage point decrease at 6 years] in SoC) - DRC OS curve = dependent Gamma - No treatment waning | | | |
| 2 | | Scenario 1: #1 plus STC methodology for ITC | [REDACTED] | [REDACTED] | 24,822 |
| 3 | | Scenario 2: #1 plus ibrutinib subsequent treatment costs excluded and [REDACTED] percentage point decrease in survival at 6 years in SoC arm (equates to 55% lower than zanubrutinib arms) | [REDACTED] | [REDACTED] | 26,849 |
| 4 | | Scenario 3: #1 plus Odds k=1 curve for DRC OS | [REDACTED] | [REDACTED] | 24,921 |
| 5 | | Scenario 4: #1 plus 40%:60% BR:DRC split for SoC | [REDACTED] | [REDACTED] | 25,724 |
| 6 | | Scenario 5: #1 plus 60%:40% BR:DRC split for SoC | [REDACTED] | [REDACTED] | 24,151 |
| Probabilistic analysis | | | | | |
| 8 | | Company revised base case ¹ | [REDACTED] | [REDACTED] | 26,316 |
| <p>Abbreviations: BR, bendamustine plus rituximab; DRC, dexamethasone rituximab and cyclophosphamide; ICER, incremental cost-effectiveness ratio; Inc., incremental; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; OS, overall survival; PAS, Patient Access</p> | | | | | |

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| | Scheme; QALY, quality-adjusted life-year; SoC, standard of care; STC, simulated treatment comparison. 1. Please refer to Table 2, Appendix 1 for model settings. |
| 2 | <p><u>Removing the ibrutinib subsequent costs in the DRC/BR arms should be balanced by an adjustment in the DRC/BR OS to prevent bias against zanubrutinib</u></p> <p>The Company acknowledges that despite the established use of ibrutinib for the treatment of relapsed/refractory (R/R) Waldenström’s macroglobulinaemia patients in the UK, it cannot be included in the treatment pathway given that it is not routinely commissioned by NICE having recently received a negative Final Appraisal Document from NICE following a CDF review of appraisal TA491.³ Hence, the Company accepts the Committee’s decision to remove subsequent treatment costs of ibrutinib in their preferred base-case assumptions.</p> <p>In the original Company submission, clinical experts validated OS extrapolations for DRC and BR based on the assumption that 72% would receive ibrutinib as a subsequent treatment. In Study 118E, ibrutinib was shown to be effective at delaying progression and extending survival.⁴ Accordingly, the Company believes the removal of ibrutinib subsequent treatment costs should be balanced by an adjustment in DRC/BR OS curves. Moreover, within this appraisal in response to the Company’s Technical Engagement evidence submission, the Evidence Review Group (ERG) acknowledged the difficulties arising from removing ibrutinib from the model and noted not excluding the benefits of subsequent ibrutinib use (i.e. survival benefit) and only the costs of ibrutinib subsequent treatment following progression on BR or DRC would result in a higher ICER for zanubrutinib.⁵</p> |

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ERG clinical experts in the ibrutinib Cancer Drugs Fund (CDF) review of TA491 (ID 3778) indicated that at 6 years, the survival probability of a patient in the Physician's Choice treatment arm for R/R Waldenström's macroglobulinaemia would be half of that of a patient receiving ibrutinib (50% less survival at 6 years).⁶

Within this appraisal for zanubrutinib, the Committee's preferred base-case assumptions estimates that ██████% patients receiving zanubrutinib are alive at 6 years whereas in the SoC arm ██████% of patient are alive at 6 years. This equates to an ██████% reduction in survival (1-██████), notably much lower than the proposed 50% reduction by the ERG clinical experts in the ibrutinib CDF review of TA491 (ID 3778). The difference between zanubrutinib and SoC is expected to be at a minimum the same as the difference between ibrutinib and Physician's choice, given that the ASPEN trial has demonstrated comparable efficacy and an improved tolerability profile (as acknowledged by the NICE Committee during the ACM for zanubrutinib on the 12th April 2022²) compared to ibrutinib.

To prevent bias against zanubrutinib and in alignment with ERG clinical expert opinion in the ibrutinib CDF review of TA491 (ID 3778), the Company have implemented an adjustment in the DRC and BR OS curves such that the curves are 50% lower than the zanubrutinib curves are 6 years in their revised base-case (adjusted OS at 6 years = ██████%). This equates to an absolute decrease of ██████ percentage points in the SoC OS curves prior to adjustment (██████ – ██████). This adjustment was validated by UK clinical experts who agreed that it was clinically plausible that in the absence of ibrutinib subsequent treatment, at 6 years the SoC survival would be 50% less than the survival for zanubrutinib. Furthermore, they agreed that the resulting total life years for SoC (██████ years [undiscounted]) over the model time horizon was clinically plausible in the absence of ibrutinib subsequent treatment.

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| | As a result of this adjustment, coupled with the revised PAS discount, zanubrutinib is associated with £ [REDACTED] additional costs and [REDACTED] additional QALYs, corresponding to an ICER of £25,045 per QALY gained. | | | | | | | |
|---|---|---|-----------|--|---|---|--|--|
| 3 | The Company note one factual inaccuracy in the draft ACD, as detailed in the table below. | | | | | | | |
| <table border="1"> <thead> <tr> <th data-bbox="526 552 1055 587">Location</th> <th data-bbox="1064 552 1592 587">Suggested change</th> <th data-bbox="1601 552 2130 587">Rationale</th> </tr> </thead> <tbody> <tr> <td data-bbox="526 587 1055 1024"> Draft ACD page 6-7 <ul style="list-style-type: none"> “187 people with relapsed or refractory Waldenstrom's macroglobulinaemia who had had 1 or more previous treatments” “42 people who had not had any previous treatment and for whom chemoimmunotherapy was unsuitable.” </td> <td data-bbox="1064 587 1592 1024"> <ul style="list-style-type: none"> “192 people with relapsed or refractory Waldenstrom's macroglobulinaemia who had had 1 or more previous treatments” “37 people who had not had any previous treatment and for whom chemoimmunotherapy was unsuitable.” </td> <td data-bbox="1601 587 2130 1024"> Typographical error – incorrect numbers reported. </td> </tr> </tbody> </table> | Location | Suggested change | Rationale | Draft ACD page 6-7 <ul style="list-style-type: none"> “187 people with relapsed or refractory Waldenstrom's macroglobulinaemia who had had 1 or more previous treatments” “42 people who had not had any previous treatment and for whom chemoimmunotherapy was unsuitable.” | <ul style="list-style-type: none"> “192 people with relapsed or refractory Waldenstrom's macroglobulinaemia who had had 1 or more previous treatments” “37 people who had not had any previous treatment and for whom chemoimmunotherapy was unsuitable.” | Typographical error – incorrect numbers reported. | | |
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References

1. The Rory Morrison Registry. *Second UK Waldenström's Macroglobulinaemia Registry Report 2021*. <https://wmuk.org.uk/resource/the-rory-morrison-wmuk-registry-report-2021/> (2021).
2. NICE. Appraisal Committee Meeting: Zanubrutinib for Waldenström's macroglobulinaemia - Lead team presentation. (2022).
3. NICE. Final appraisal document - Ibrutinib for treating Waldenstrom's macroglobulinaemia. (2022).
4. Treon, S. P. *et al.* Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia. *J Clin Oncol* **39**, 565–575 (2021).
5. NICE. Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427] Appraisal Committee Papers - 1st Committee meeting. (2022).
6. NICE. Ibrutinib for treating Waldenström's macroglobulinaemia CDF review TA491 - Appraisal Committee Meeting. (2021).

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Appendix 1 – Company preferred base case settings

Table 2: Summary of Company preferred base case settings

| Setting | Base case | Scenario |
|--------------------------------|--|---|
| ITC method | MAIC | Scenario 1: STC |
| Ibrutinib subsequent treatment | - 100% removal of ibrutinib costs from the SoC arm. - █████ percentage point decrease in survival at 6 years (compared to the original curves) for the SoC arm. | Scenario 2 - 100% removal of ibrutinib costs from the SoC arm. - █████ percentage point decrease in survival at 6 years (compared to the original curves) for the SoC arm. |
| OS curve for DRC | Dependent Gamma curve | Scenario 3: Odds k=1 curve |
| Treatment waning | Not applied | N/A |
| BR:DRC split | 49% = BR 51% = DRC | Scenario 4 - 40% = BR - 60% = DRC Scenario 5 - 60% = BR - 40% = DRC |

Abbreviations: BR, bendamustine plus rituximab; DRC, dexamethasone rituximab and cyclophosphamide; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; N/A, not applicable; OS, overall survival; SoC, standard of care; STC, simulated treatment comparison.

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| <p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p> | <p>Janssen-Cilag</p> |
| <p>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p> | <p>None</p> |
| <p>Name of commentator person completing form:</p> | <p>*****</p> |
| <p>Comment number</p> | <p>Comments</p> |
| <p>1</p> | <p>Front line patients that are unsuitable for chemo-immunotherapy</p> <ul style="list-style-type: none"> • Janssen notes that for the group of first-line (1L) patients unsuitable for chemo- |

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| | <p>immunotherapy, no comparison was presented that compared zanubrutinib with the appropriate comparators, namely chlorambucil or rituximab monotherapy, and therefore there is no evidence for zanubrutinib relative clinical benefit in this trial population.</p> <ul style="list-style-type: none"> Ibrutinib has demonstrated an efficacy benefit in 1L Waldenström’s macroglobulinaemia (WM) patients vs rituximab monotherapy (one of the appropriate comparators for 1L chemo unsuitable patients) in the phase 3 iNNOVATE trial. Given ibrutinib and zanubrutinib belong to the same class of drugs, Janssen agrees with the clinical experts that in clinical practice patients receiving zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed/refractory (RR). Additionally, there are precedents in other Non-Hodgkin lymphomas, specifically in chronic lymphocytic leukaemia (CLL), where, despite the lack of robust evidence for comparative clinical benefit in the “high risk” (HR) CLL population with 17p deletion or TP53 mutation, the NICE recommendation for treatment of CLL RR patients with ibrutinib was extended to the HR CLL population, a small group of patients with high unmet need (TAG 429), which is similar to the chemo-unsuitable 1L patients in WM. Ibrutinib WM clinical data as well as precedents in CLL could be considered by the Committee as additional supportive information on the clinical benefit of zanubrutinib in 1L WM patients unsuitable for chemo-immunotherapy. |
| 2 | <p>Indirect comparison</p> <ul style="list-style-type: none"> Janssen notes there are limitations to both the matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) approaches to modelling the comparative benefit of zanubrutinib vs bendamustine and rituximab (BR) and dexamethasone, rituximab and cyclophosphamide (DRC). The Committee also noted in Section 3.5 that <i>“the hazard ratios for progression-free and overall survival were low compared to those typically seen in cancer treatment, suggesting that zanubrutinib is a highly effective treatment”</i>. For reference, in the ibrutinib CDF review (ID3778), where comparator efficacy was derived from an indirect treatment comparison (ITC) based on comparator data from an observational retrospective chart review in WM patients, the ITC hazard ratio for progression-free survival (PFS) was 0.25. This estimate of ibrutinib relative clinical benefit vs standard of care in the RR population also aligned with the iNNOVATE PFS hazard ratio for ibrutinib in combination with rituximab vs rituximab, of 0.25, which was even lower (0.22) in the RR subgroup. The magnitude of the results for ibrutinib relative PFS benefit gives credibility to the low hazard ratios generated by both the zanubrutinib STC and MAIC. The results from the MAIC may in fact be deemed conservative. |

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- 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.
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Comments on the ACD received from WMUK

| | |
|---|------|
| Name | |
| Role | |
| Organisation | WMUK |
| Comments on the ACD: | |
| <p>Whilst WMUK are unable to comment on the long-term effectiveness of Zanubrutinib, we can comment that patients overwhelmingly prefer an oral treatment due to the better quality of life and lack of side effects in comparison to chemotherapy.</p> <p>Zanubrutinib enables patients to live well with WM, leading as fulfilling and normal lives as possible due to the convenience of an oral treatment they can take at home and far fewer side effects than the standard treatment of chemotherapy.</p> <p>Zanubrutinib also minimises hospital visits, trips which are often arduous and only made possible by relying on a network of family and friends.</p> <p>WM currently has no alternative oral treatments available and is solely treated by options which are hospital based.</p> <p>Patients describe Zanubrutinib as a 'game changer', 'step change' treatment which has an immediate effect on their well being and ability to return to their normal lives. This is important as increasingly younger WM patients with families and working lives are recognised as part of the WM demographic.</p> | |

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| | 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 | <p>Having read the relevant evidential documentation prior to the meeting and listened to the subsequent presentation and contributions at the Appraisal committee first stage meeting I anticipated that Zanubrutinib would not be recommended for treating WM in adults either after at least 1 therapy or as a first-line treatment when chemoimmunotherapy is unsuitable.</p> <p>In particular I understand the technical nicety that Zanubrutinib should not have been compared with Ibrutinib, nevertheless, the fact remains that Zanubrutinib has demonstrated that it is more clinically effective than chemoimmunotherapy options with lower toxicity and is superior to the first generation Bruton tyrosine kinase (BTK) inhibitor Ibrutinib and importantly is regarded as a step-change in managing WM.</p> <p>It is also acknowledged that from a patient and clinician perspective the availability of an effective and well-tolerated oral therapy is highly valued and addresses a significant unmet need. However, 78 years on since WM was first identified, it appears that an excellent opportunity to change the routine outcome for patients could be missed unless a more pragmatic approach is taken at the second stage meeting in order to reach a successful conclusion for all stakeholders.</p> <p>Having stressed that the NICE cost-effectiveness threshold expressed in terms of incremental cost-effectiveness ratios (ICERs) and the resulting quality-adjusted life years (QALYs) gained is paramount, it is significant that no attempt has been made to establish what associated cost savings would ensue from using the new technology. One clinical expert expressed the view that there would be no additional associated costs or training needs using Zanubrutinib and also postulated that it was more likely that cost savings would accrue but importantly free-up human resources in an already overstretched NHS.</p> <p>The price of Zanubrutinib used for the ICER evaluation was not clarified by what, if any, quantity threshold this related to. Given that commercial negotiations of this type are ultimately influenced significantly by an overall anticipated usage one would reasonably expect the pricing structure to be tiered so that when the purchase quantity increases the price decreases accordingly.</p> <p>To-date, the majority of WM patients having had or still receiving either BTK inhibitor have only done so after having previously endured the detrimental and traumatic consequences of undergoing chemoimmunotherapy. Therefore it is not unrealistic to postulate that if they had received these as a first-line option their overall clinical and life-quality outcomes would have been no different and could have been even better.</p> <p>Since price has clearly been the determining factor for the negative recommendation by the Appraisal committee the obvious way forward for a satisfactory outcome would be for NICE to specify precisely what the initial price for Zanubrutinib would need to be and give BeiGene the option of deciding whether to accommodate this or lose a significant UK market opportunity.</p> |

Zanubrutinib for treating Waldenstrom's macroglobulinaemia [ID1427]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 26 May 2022. Please submit via NICE Docs.

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

Zanubrutinib for Waldenström's macroglobulinaemia [ID1427]

ADDENDUM: Critique to the company's ACD response

| | |
|--------------------------|--|
| Produced by | Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University |
| Authors | Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK Ben Wijnen, Health Economist, Maastricht UMC, the Netherlands Sabine Grimm, Health Economist, Maastricht UMC Jeremy Howick, Systematic Reviewer, KSR Ltd Nigel Armstrong, Health Economist, KSR Ltd Willem Witlox, Health Economist, Maastricht UMC Thomas Otten, Health Economist, Maastricht UMC Kate Misso, Information Specialist, KSR Ltd Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University |
| Correspondence to | Rob Riemsma, Kleijnen Systematic Reviews Ltd Unit 6, Escrick Business Park Riccall Road, Escrick York, YO19 6FD United Kingdom |
| Date completed | 03/03/2022 |

•Dexamethasone rituximab and cyclophosphamide (DRC)/ bendamustine plus rituximab (BR) survival should be adjusted to reflect that ibrutinib cannot be included within the subsequent treatment pathway.

In its ACD response, the company accepts the committee's decision to remove subsequent treatment costs of ibrutinib in their preferred base-case assumptions, but states that removing the ibrutinib subsequent costs in the DRC/BR arms should be balanced by an adjustment in the DRC/BR OS to prevent bias against zanubrutinib. ERG clinical experts in the ibrutinib Cancer Drugs Fund (CDF) review of TA491 (ID 3778) indicated that at 6 years, the survival probability of a patient in the Physician's Choice treatment arm for R/R Waldenström's macroglobulinaemia would be half of that of a patient receiving ibrutinib (50% less survival at 6 years). In line with this, the company implemented an adjustment in the DRC and BR OS curves such that the curves are 50% lower than the zanubrutinib curves are 6 years in their revised base-case (adjusted OS at 6 years = ████████). This equates to an absolute decrease of ████████ percentage points in the SoC OS curves prior to adjustment (██████).

The ERG considers adjusting the survival of DRC and BR to reflect that ibrutinib cannot be included within the subsequent treatment pathway to be inappropriate. BR and DRC patients have likely not received ibrutinib at all (i.e. the DRC and BR survival curves do likely not include any ibrutinib effect) based on the following considerations:

- Ibrutinib received marketing authorisation in 2014.
- For DRC, the study of Dimopoulos et al. (2016) included patients between November 2002 and April 2006. Hence, as ibrutinib was not available yet, it was not possible for those patients to receive subsequent ibrutinib.
- For BR, the study of Tedeschi et al. (2015) was submitted in 2014. Although the authors do not state in which period the data were collected, it is very unlikely that those patients were subsequently treated with ibrutinib.
- Lastly, subsequent ibrutinib use in the model was not informed based on the before mentioned studies but was based on the UK WMUK Rory Morrison Registry which included patients up to the year 2018.

In the original company submission, clinical experts validated OS extrapolations for DRC and BR based on the assumption that 72% would receive ibrutinib as a subsequent treatment. The ERG therefore considers that the only potential bias that could have occurred would be related to the curve choice. This could be resolved by selecting less optimistic OS curves for DRC and BR. It should, however, be noted that the second least optimistic OS curve for BR is currently selected and the difference with the least optimistic OS curve (gamma) is minor.

In addition, the ERG questions whether aligning with assumptions from the CDF review of TA491 is appropriate, as this review is still ongoing and hence it is unclear whether the committee will accept these assumptions.

Although the ERG considers the OS adjustment to be arbitrary, it can confirm that its current implementation in the economic model appears to be correct (i.e. resulting in DRC and BR OS curves that are 50% lower than the zanubrutinib curves at 6 years).