# Single Technology Appraisal

# Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

# Committee Papers

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**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

**Contents:**

The following documents are made available to stakeholders:



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**Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Thursday 19 June 2025. 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.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>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): | Sanofi |

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| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | N/A |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | Sanofi welcomes the opportunity to comment on the draft guidance for isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of newly diagnosed multiple myeloma (NDMM) in patients ineligible for stem cell transplant. We are committed to working collaboratively with NICE to address the committee's questions. Our goal is to ensure that NHS patients have access to this innovative therapy. |

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**Conducting an NMA using the SWOG S0777 study to inform the cost-effectiveness analyses**

Section 3.4 of the draft guidance states:
"*The committee concluded that it would like the company to present results from an NMA using the SWOG S0777 study with randomisation preserved. It added that this should be done using both the intention-to-treat (ITT) population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population. It concluded that these results should be used to inform the cost-effectiveness estimates*."

We acknowledge that our initial submission only considered the non-randomised subgroup of patients aged ≥65 years as a proxy for transplant ineligibility in the SWOG S0777 trial to conduct the NMA. In response to the committee's request to preserve randomisation, we have now updated our analysis to include both the "no intent to transplant" subgroup and the intention-to-treat (ITT) population. Below, we provide:

1. NMA method
2. Results
3. A methodological assessment of the different populations
4. Base-case and implementation in the model

1. Method

Standard proportional hazard NMA was carried out using a Bayesian approach to capture the uncertainty in model parameters while preserving correlation between treatment effects. Relative treatment effects were estimated using Markov chain Monte Carlo (MCMC) methods and NMA methods were consistent with NICE DSU TSDs 2–4. The NMA was conducted using the evidence network presented in Figure 21 of the company submission. The NMA was updated to incorporate the final OS analysis data from the MAIA trial. The NMA was run to generate results using 2 populations in SWOG S0777:
- the intention-to-treat (ITT) population
- the "no intent to transplant" subgroup (stratification factor)

2. Results

Results from the different indirect treatment comparisons for IsaVRd versus DRd are summarised in Table 1 below.

**Table 1: Indirect treatment comparison - IsaVRd vs DRd: PFS and OS results**

| ITC method | PFS (HR, 95% CI) | OS (HR, 95% CI) |
|---|---|---|
| **MAIC** | [redacted] | [redacted] |
| **NMA - No intent to transplant** | [redacted] | [redacted] |
| **NMA - ITT** | [redacted] | [redacted] |

Among the different analyses, the NMA using the "no intent to transplant" subgroup has the lowest risk of bias. This analysis suggests a more favourable treatment effect for IsaVRd compared with DRd, with hazard ratios of [redacted] for PFS and [redacted] for OS. The PFS estimate aligns closely with that obtained from the MAIC, while the OS estimate is numerically lower than both the MAIC and other NMA populations. Although the hazard ratios for both PFS and OS are not statistically significant, this is expected given large number of nodes in the network needed to include all comparators. Nonetheless, the results suggest a clinically meaningful benefit in both progression-free and overall survival.

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3. Methodological assessment of the randomised populations in SWOG S0777

3.1. NMA - ITT Population

Using the ITT population introduces substantial bias due to meaningful differences in baseline characteristics compared to the transplant-ineligible population enrolled in IMROZ. A comparison of baseline characteristics identified as treatment effect modifiers and ranked by order of importance is summarised below.

**Table 2: Comparison of baseline characteristics between SWOG S0777 and IMROZ (ITT populations)**

| Characteristic | SWOG S0777 Trial (n=471) | IMROZ Trial (n=465) | Difference |
|---|---|---|---|
| **Median Age** | 63 years | 72 years | +9 years |
| **Frailty** | Not reported | Not reported | NA |
| **ISS Stage III** | 34% (155/460)*** | 26.9% (120/465) | –6.1% |
| **High-Risk Cytogenetics** | 33% (out of 316 patients)** | 16.6% (74/446) | –16.4% |
| **ECOG Performance Status >1** | 12% (53/441)*** | 11.0% (49/446) | –1% |
| **LDH ≥ 190 U/L** | 36% (163/454)*** | 12.7% (56/446) | -23.3% |
| **Renal impairment: eGFR<60 ml min 1.73 m2** | Not reported | 28.7% (128/446) | NA |
| **Chromosomal Abnormality 1q21+** | Not reported | 37.0% (165/446) | NA |
| **MM Type (IgG)** | Not reported | 64.6% (286/446) | NA |
| **Transplant Rate*** | 35% (161/460)*** | 0% | –35% |

* Not pre-identified as a treatment effect modifier but instead creates confounding with the treatment effect in the trial
** SWOG S0777 First data cut
*** SWOG S0777 Second data cut

Key differences include:

- Age: IMROZ enrolled an older, transplant-ineligible population (median age 72), while SWOG S0777 included a younger, broader population (median age 63), many of whom were transplant-eligible. The median age in IMROZ exceeds the interquartile range in SWOG (VRd: 56 to 70; Rd: 56 to 71), indicating that the populations are very different. Age was identified by clinicians as the most important treatment effect modifier.

- Frailty: Although not reported in SWOG S0777, frailty is expected to differ substantially. The inclusion of transplant-eligible patients in the ITT population, with 35% proceeding to transplant, suggests that patients in SWOG were significantly fitter (with likely negligible to low frailty) than those in IMROZ, which exclusively enrolled transplant-ineligible patients.

- High-risk cytogenetics: IMROZ included 16.6% of patients with high-risk cytogenetics, compared to 33% in SWOG. This difference limits the comparability of treatment effects between the two trials.

- LDH ≥ 190 U/L: High LDH levels were seen in 36% of patients in SWOG S0777, compared with only 12.7% in IMROZ. This large difference suggests that patients in SWOG may have had more aggressive disease, making comparisons with IMROZ more difficult.

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|---|---|
| | - Transplant confounding: A critical limitation of the SWOG ITT population is that 35% of patients received an autologous stem cell transplant. This introduces a major source of confounding, as the treatment effect observed reflects not only the effect of VRd vs Rd but also the known benefit of a transplant (VRd + ASCT vs Rd + ASCT). In contrast, IMROZ exclusively enrolled patients who were transplant ineligible based on clinical criteria.<br><br>ECOG performance status and ISS stage were broadly similar between trials, with ECOG >1 reported in 14% of SWOG and 11.3% of IMROZ, and ISS Stage III in 34% and 26.9% respectively. Unreported characteristics in SWOG S0777 such as renal impairment, chromosomal abnormality 1q21+, and MM type (IgG) limit the ability to interpret comparability.<br><br>To conclude, using the SWOG ITT population in a network meta-analysis to inform outcomes in the transplant-ineligible setting would introduce significant bias and reduce the validity of the comparison. The treatment effect in the ITT population is confounded by a meaningful proportion of post-randomisation transplant. The population also differs substantially from IMROZ in terms of treatment effect modifiers such as age, cytogenetics, and—though not directly measured—frailty and renal function. As a result, the assumption of transitivity, which requires that treatment effect modifiers be similarly distributed across trials, is not met.<br><br>Clinical experts have confirmed that the treatment effect observed in the SWOG ITT population is not applicable to the transplant-ineligible population represented in IMROZ. Therefore, the ITT population from SWOG is not considered a reliable proxy for the transplant-ineligible population in the NMA.<br><br>3.2. NMA – No intent to transplant subgroup<br><br>Among the randomised populations in SWOG S0777, the “no intent to transplant” subgroup represents a more appropriate proxy for the transplant-ineligible population than the ITT population. However, it is important to clarify the distinction between “no intent to transplant” and "transplant ineligibility". “No intent” is a designation recorded at baseline, which may reflect patient preferences or other non-clinical factors. In contrast, transplant ineligibility is based on objective clinical criteria such as age, comorbidities, and performance status. Therefore, while the “no intent” group likely includes all transplant-ineligible patients, it also encompasses a proportion of transplant-eligible patients who chose not to receive a transplant.<br><br>The inclusion of some transplant-eligible patients in the “no intent” group may result in differences in treatment effect modifiers such as age, frailty, and renal function, which are common determinants of transplant eligibility. Because of this heterogeneity, the use of this subgroup in the NMA has initially been discouraged. Moreover, baseline characteristics for this subgroup are not reported, meaning that potential differences with a transplant-ineligible population cannot be assessed. Nonetheless, the absence of transplant intent implies a closer clinical resemblance to the IMROZ cohort than the broader ITT population. Any remaining differences are expected to arise from the unknown proportion of transplant-eligible patients with no intent to transplant.<br><br>The “no intent” subgroup has methodological advantages over the full ITT population. Patients in this group were not likely to proceed to transplant, as they represent the subset of transplant-eligible patients who had no intent to undergo transplant. This reduces the risk of confounding in the treatment effect from post-randomisation transplant, which is a key limitation of the ITT population. |

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| | In summary, while not a perfect match, the "no intent to transplant" subgroup is a more clinically and methodologically appropriate population than the full ITT cohort in SWOG S0777. While differences may remain due to the inclusion of some transplant eligible patients, this subgroup is expected to be closer in terms of treatment effect modifiers and avoids confounding from post-randomisation transplant, thereby better supporting the validity of a network meta-analysis.<br><br>4. Base case and implementation in the model<br>As requested by committee we have presented results from an NMA using the SWOG S0777 study with randomisation preserved, using both the ITT population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population. Between these two populations, only the no intent-to-transplant subgroup is clinically and methodologically appropriate for estimating the relative treatment effect of IsaVRd versus DRd in the transplant-ineligible population.<br><br>The committee stated that the NMA using the no intent-to-transplant subgroup as a proxy, would result in a conservative estimate. Therefore, in order to align with the committee's preference to use the most conservative approach, we have utilised the MAIC to inform our base case. While it does not preserve randomisation, the MAIC adjusts for key treatment effect modifiers and provides a more conservative estimate of the treatment effect for both PFS and OS.<br><br>We acknowledge the concerns raised about the complexity of the time-varying parametric MAIC approach and the EAG's recommendation, which stated that there is not enough evidence to support the non-proportional hazards assumption. As a result, the updated base case uses a constant HR MAIC anchored to the DRd curves from the MAIA trial. This method has the advantage of estimating a Cox proportional hazard ratio limited to the IMROZ follow-up period (68 months) for both IsaVRd and DRd.<br><br>To ensure that all available data are used, the maximum follow-up available for DRd is used to inform the absolute survival curves — approximately 100 months for OS and 75 months for PFS. Scenario analyses using the parametric MAIC were conducted.<br><br>In addition, scenario analyses were conducted using parametric MAICs, including one using 68 months of follow-up for IsaVRd and full follow-up for DRd, and another using 60 months of follow-up for IsaVRd. In terms of ICER impact, the constant HR MAIC sits between these scenarios (approximately +/- [redacted] QALYs), with only modest variation in cost-effectiveness outcomes. Based on this, and in line with expert comments during the first committee meeting, we recommend the constant HR MAIC as the most appropriate and robust approach for the base case, as it makes full use of the available evidence.<br><br>In contrast, the NMA increases QALY estimates by approximately [redacted] QALYs and [redacted] QALYs when using the no intent-to-transplant subgroup and the ITT population, respectively, compared with the constant HR MAIC. |
| 2 | **Addressing the committee's request for clarification as to whether the observed differences in TTD and PFS are clinically justified**<br><br>Section 3.13 of the draft guidance states:<br>"*The committee considered that there were many areas of uncertainty (see section 3.11) and would like to see clarification on whether the inconsistencies in the modelling of TTD and PFS are clinically justified and would be expected in NHS practice*."<br><br>We would like to provide further clarification and new supporting evidence to address this concern. |

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1) Longer PFS

The longer PFS observed for IsaVRd compared to DRd is supported by significantly higher rates of minimal residual disease negativity (MRD–). A MAIC was conducted to explore MRD negativity rates at a sensitivity threshold of $10^{-5}$ between IsaVRd (IMROZ) and MAIA (DRd). The analysis demonstrated that IsaVRd significantly increased the odds of achieving MRD–, with an odds ratio of [redacted].

MRD negativity and increasingly, sustained MRD negativity beyond 12 months, is a well-established surrogate for PFS and OS in multiple myeloma. The higher MRD– rates observed with IsaVRd supports the PFS benefit and the validity of the modelled treatment effect.

**Table 3: Unadjusted and adjusted Odds Ratio for MRD negativity between IsaVRd and DRd**

| Method | Odds Ratio (95% CI) |
|---|---|
| **Unadjusted OR** | 2.94 (2.12 to 4.08) |
| **MAIC adjusted OR** | [redacted] |
| **MAIC adjusted bootstrap median OR (percentile CI)** | [redacted] |

2) Equivalent TTD

Despite the PFS benefit, the MAIC on time-to-discontinuation (TTD) estimated a hazard ratio of [redacted], indicating no difference in treatment duration between IsaVRd and DRd.

The results are supported by:

- **Comparable maintenance tolerability**: Both regimens share the same maintenance components i.e. treat until progression or unacceptable AEs—anti-CD38 monoclonal antibody, lenalidomide, and dexamethasone—resulting in comparable tolerability. As noted by the EAG, the adverse event profile of DRd appears to be less favourable than that of IsaVRd. This would suggest that TTD for IsaVRd could be longer than for DRd. However, the slightly fitter population in IMROZ compared to MAIA likely contributes to this interpretation. After adjustment, the tolerability profiles during the maintenance phase are expected to be similar, as indicated by the MAIC on TTD. This is consistent with clinical expert opinion.
- **Impact of intensive induction**: The more intensive induction phase with bortezomib could lead to higher early discontinuation in IsaVRd treated patients compared to DRd in clinical practice.
- **Discontinuation largely unrelated to progression**: Treatment discontinuation was predominantly driven by factors other than disease progression, which accounted for only 27.5% of discontinuations in the IsaVRd arm of IMROZ. In total, 72.5% of patients discontinued treatment for reasons unrelated to progression—most notably adverse events (43.5%) and patient withdrawal, primarily due to tolerability issues (16.7%). Additional reasons included poor compliance to protocol (4.3%) and other factors such as investigator decision or mutual agreement (8.0%). Therefore, the MAIC on TTD mainly adjusts for treatment discontinuation due to AE and supports the similar tolerability profile of IsaRd and DRd.
- **Higher MRD– rates may support treatment discontinuation**: The MAIC on MRD– showed a significantly higher proportion of patients achieving MRD– with IsaVRd than with DRd. In IMROZ, 58.1% of patients treated with IsaVRd achieved MRD–, and 46.7% achieved sustained MRD negativity for at least 12 months. As a result, patients are more

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|---|---|
| | likely to achieve sustained MRD– and may choose to discontinue treatment before progression.<br>- **Mature TTD data with long follow-up**: With six years of follow-up and the median reached, there is no reason to expect that the relationship – overlap of TTD curves – will change after the observed data.<br>- **Minimal change after adjustment**: Before adjustment, the TTD curves from IMROZ and MAIA were already closely aligned, with an unadjusted HR of [redacted]. The MAIC adjustment brought the curves slightly closer, but the change was minimal, indicating that the observed overlap between the two curves was not artificially driven by the adjustment process. This further supports the robustness of the TTD comparison.<br>- **MAIC selected for clinical plausibility**: The MAIC was selected in the company's base case because it produced clinically plausible results for OS and PFS, reinforcing the reliability of the analysis for TTD.<br><br>To conclude, the statistically significant PFS benefit observed with IsaVRd is supported by deeper responses and higher MRD– rates, reinforcing the validity of the modelled treatment effect. While PFS improves, the MAIC shows that TTD remains equivalent between IsaVRd and DRd—a finding that is clinically plausible given the similar tolerability profile of isatuximab and daratumumab and the backbone agents in clinical practice. Treatment discontinuation in IMROZ was largely unrelated to disease progression, further supporting the MAIC findings, with both arms reaching median TTD and follow-up extending to approximately six years, during which the curves did not separate. Additionally, expert clinical opinion confirms that some patients may remain off treatment for extended periods—potentially years—following deep and durable responses, further supporting the real-world plausibility of the modelling assumptions.<br><br>Because TTD is modelled to be equivalent—partly due to the similar tolerability profile—the base case applies the same adverse event costs and disutilities for IsaVRd as for DRd. |
| 3 | **Adopting the committee's preference for the appropriate reference curve**<br><br>Section 3.7 of the draft guidance states:<br>"*The committee concluded that its preferred method to model OS and PFS for Isa-Bor-Len-Dex and comparators would be to apply the hazard ratio generated from an NMA to an appropriate reference curve, such as Dar-Len-Dex OS and PFS curves from MAIA or Dar-Len-Dex SACT data*."<br><br>We acknowledge the committee's request to anchor HRs to DRd curves. We note that survival curves from DRd in SACT were not publicly available or accessible within the timelines of this appraisal. Therefore, we used the DRd curves from the MAIA trial as the reference for anchoring HRs.<br><br>Accordingly, the committee's preferred distributions for DRd extrapolation in the DRd TA (TA917) were selected for the reference curves: generalised gamma for OS, gamma for PFS, and Gompertz for TTD.<br>We also present a comparison of survival for IsaVRd and DRd from the previous base case and the current base case anchored to DRd. The current DRd-anchored survival projections are more conservative and more closely aligned with clinical expert expectations. |

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|---|---|
| | **Table 4: Overall survival rates in the model – IsaVRd**<br>\| \| **10 years** \| **15 years** \| **20 years** \|<br>\| **Initial base-case** \| 52.40% \| 35.40% \| 17.70% \|<br>\| **Current base-case, anchored to DRd** \| [redacted] \| [redacted] \| [redacted] \|<br>\| **Clinician estimates %, (95% CI)** \| 45% (35% to 55%) Max: 60% \| 24% (15% to 33%) Max: 35% \| 11% (5% to 17%) Max: 20% \|<br><br>**Table 5: Progression-free survival rates in the model – IsaVRd**<br>\| \| **10 years** \| **15 years** \| **20 years** \|<br>\| **Initial base-case** \| 40.2% \| 25.2% \| 12.6% \|<br>\| **Current base-case, anchored to DRd** \| [redacted] \| [redacted] \| [redacted] \|<br>\| **Clinician estimates %, (95% CI)** \| 28% (23% to 33%) Max: 40% \| 11% (2% to 16%) Max: 20% \| 2% (0% to 6%) Max: 10% \| |
| 4 | **Addressing the Committee's request for evidence supporting an OS benefit**<br><br>Section 3.8 of the draft guidance states:<br>"*The EAG noted that the available clinical-effectiveness evidence was not sufficient to support the assumption that people having Isa-Bor-Len-Dex live longer than people having Dar-Len-Dex. [...] The committee agreed with the EAG that it had not yet seen sufficient clinical evidence to support an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex*."<br><br>We would like to provide further clarification and new supporting evidence to address this concern:<br>- The NMA using the "no intent to transplant" subgroup from SWOG S0777 estimated a HR for overall survival of [redacted] for IsaVRd versus DRd. While not statistically significant, the point estimate is consistent with a clinically meaningful OS benefit.<br>- This is further supported by evidence from SWOG S0777, where the addition of bortezomib to Rd significantly improved OS in both the "no intent to transplant" subgroup (HR: 0.583; 95% CI: 0.371 to 0.917; p=0.0134) and the intention-to-treat population (HR: 0.709; 95% CI: 0.536 to 0.938; p=0.0114). These results confirm that bortezomib improves survival when added to Rd, providing a clear rationale for expecting an OS benefit when bortezomib is added to IsaRd in comparison to DRd.<br>- The survival benefit is likely driven by the deeper responses induced by bortezomib. IsaVRd appears to significantly improve MRD– rates compared with DRd. In IMROZ, 58.1% of patients treated with IsaVRd achieved MRD–, and 46.7% achieved sustained MRD negativity for at least 12 months—highlighting the depth and durability of response. MRD– is a well-established surrogate for both PFS and OS in multiple myeloma, and sustained MRD– is recognised as a predictor of long-term survival. These findings provide biological plausibility for an OS benefit with IsaVRd. |
| 5 | **Updating subsequent treatments to reflect regimens available in NHS practice**<br><br>It has been highlighted by the EAG that the costs of subsequent treatments did not include selinexor-bortezomib-dexamethasone (SVd) in the original submission. Teclistamab is also now available in the NHS. Therefore, the model has been updated to include SVd at second and third line, and teclistamab at fourth line. |

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<table>
<tr><td></td><td>
The updated treatment distributions are based on estimates provided by two clinical experts. The revised proportions for IsaVRd and DRd are shown in the table below.<br><br>
Table 6: Subsequent treatment distribution after IsaVRd and DRd in NHS
<table>
<tr><th>Line of Therapy</th><th>Regimen</th><th>IsaVRd</th><th>DRd</th></tr>
<tr><td rowspan="4">2L</td><td>Kd</td><td>27.5%</td><td>27.5%</td></tr>
<tr><td>Vd</td><td>17.5%</td><td>17.5%</td></tr>
<tr><td>VCd</td><td>30.0%</td><td>25.0%</td></tr>
<tr><td>SVd</td><td>25.0%</td><td>30.0%</td></tr>
<tr><td rowspan="3">3L</td><td>PanVd</td><td>20.0%</td><td>20.0%</td></tr>
<tr><td>CTd</td><td>65.0%</td><td>65.0%</td></tr>
<tr><td>SVd</td><td>15.0%</td><td>15.0%</td></tr>
<tr><td rowspan="3">4L</td><td>Pd</td><td>27.5%</td><td>27.5%</td></tr>
<tr><td>PanVd</td><td>2.5%</td><td>2.5%</td></tr>
<tr><td>Teclistamab</td><td>70.0%</td><td>70.0%</td></tr>
</table>
</td></tr>
<tr><td>6</td><td>
Selecting a starting age that reflects the NHS population<br><br>
Section 3.6 of the draft guidance states:<br>
“It also recalled that the starting age used in the model, based on the age in IMROZ, was younger than would be expected in NHS clinical practice (see section 3.3). So, it requested that the model be updated to include a starting age reflecting the NHS population and based on an appropriate source. Its preference was people having Dar-Len-Dex in Systemic AntiCancer Therapy (SACT) data.”<br><br>
Data on transplant eligibility are not collected in SACT, therefore no data on patient’s age are available specifically for the transplant-ineligible population. Similarly, the median age of patients initiating DarLenDex in NHS practice is not reported in the published literature. However, a retrospective study of 200 transplant-ineligible NDMM patients in the UK treated with standard of care between 2009 and 2018 reported a median age of 75 years (DOI: 10.3324/haematol.2019.240762).<br><br>
Based on this, the base-case analysis has been updated to use a starting age of 75 years, in line with the committee’s request to reflect NHS clinical practice. Patients initiating IsaVRd are expected to be among the fitter subset of the transplant-ineligible population, and therefore their age is expected to be lower than 75 years in clinical practice. This has been validated by clinical experts.
</td></tr>
<tr><td>7</td><td>
Selecting the most appropriate post-progression utility values<br><br>
Section 3.10 of the draft guidance states:<br>
“The committee noted that the company had included utility values from the study by Hatswell et al. (2019) as a scenario in the model. The committee agreed that the post-progression utility value from TA587 was low. This was because, at the time of that evaluation, fewer treatment options were available post-progression, which is not reflective of the current treatment pathway. So, the committee concluded that it was not appropriate to use utility values from TA587. It would prefer to use post-progression utility values from IMROZ, or treatment-independent progressed-disease utility values derived by applying a decrement based on Hatswell et al. to the IMROZ PFS utility value.”
</td></tr>
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<table>
<tr><td></td><td>
We acknowledge the committee's preference and have adopted an approach aligned with this recommendation. Specifically, we refer to the Bayesian meta-regression using EQ-5D data from Hatswell et al. (2019), which reports utility values by line of treatment: 0.620 for first-line, 0.590 for second-line, 0.578 for third-line, and 0.479 for fourth-line and beyond. The decrement between first- and second-line treatment is 0.030, followed by 0.012 between second- and third-line, and 0.099 between third-line and fourth-line and beyond.<br><br>
As the model includes a single post-progression survival (PPS) health state that aggregates all subsequent lines of therapy, applying multiple line-specific decrements would require assumptions about the time spent in each line of treatment that differ by comparator. Therefore, to ensure comparability across treatment arms we apply only the decrement between first- and second-line treatment. Few patients are also expected to reach 4L after IsaVRd and DRd.<br><br>
Applying the 0.030 decrement to the IMROZ PFS utility values results in the following post-progression utility values:<br><br>
<table>
<tr><td></td><td>IsaVRd</td><td>DRd</td><td>Rd</td><td>VMP</td><td>VCd</td></tr>
<tr><td>PFS</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PPS (Hatswell decrement between 1L and 2L)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
<br>
We therefore recommend applying the decrement from Hatswell to the IMROZ PFS utility values, rather than using the PPS utility value directly from IMROZ, which may overestimate quality of life in the post-progression setting. Using IMROZ utility value has a minimal impact on the QALYs ([redacted])
</td></tr>
<tr><td>8</td><td>
We present the company's updated base case at list price and associated scenario analyses.<br><br>
Base Case Assumptions:<br>
- OS and PFS: Estimated using a constant hazard ratio (HR) from the MAIC, anchored to DRd reference curves from the MAIA trial (Gamma for PFS, Generalised Gamma for OS), in line with the committee's preferred distributions in the DRd TA.<br>
- TTD, Adverse Events, and Disutilities: Assumed equivalent to DRd. For TTD, the Gompertz distribution was selected, in line with the committee's preferred distributions in the DRd TA.<br>
- Utility Values: Based on the Hatswell decrement applied to IMROZ PFS utilities.<br>
- Subsequent Treatments: Updated to reflect NHS clinical practice, including SVd and teclistamab.<br>
- Starting Age: 75 years.<br><br>
<table>
<tr><td></td><td colspan="2">Incremental</td><td rowspan="2">ICER</td><td rowspan="2">NMB</td></tr>
<tr><td></td><td>Cost</td><td>QALYs</td></tr>
<tr><td>ACM2 Company's base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>1. IMROZ age</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2. IMROZ PPS utility</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>3. Subsequent treatments: without SVd and Teclistamab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>4. NMA SWOG ≥ 65 years old</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>5. NMA SWOG ITT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>6. NMA SWOG No intent to transplant</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>7. pMAIC 68 months IMROZ/100 months DRd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
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| | | | | | |
|---|---|---|---|---|---|
| | **8. pMAIC 60 months IMROZ/100 months DRd** | [redacted] | [redacted] | [redacted] | [redacted] |

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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 draft guidance 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.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Myeloma UK |

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**Disclosure**
Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]
Please state:

- the name of the company
- the amount
- the purpose of funding including whether it related to a product mentioned in the stakeholder list
- whether it is ongoing or has ceased.

We have received funding from the manufacturer of the technology (Johnson & Johnson) in the last 12 months.

In 2024, 4% of Myeloma UK's income came from pharmaceutical companies.

The table below shows the 2024 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, honoraria, or sponsorship events.

| | Core grant | Research / Project | Consultancy/ Honoraria | Events | Total |
|---|---|---|---|---|---|
| Akt Health Communications Ltd | | | 240 | | 240 |
| Alexion Pharma UK Ltd | | 10000 | | | 10000 |
| The Binding Site Ltd | 25000 | | | | 25000 |
| Bristol-Myers Squibb Pharmaceuticals Ltd | 10000 | | | | 10,000 |
| Gilead Sciences | | 19000 | | | 19,000 |
| GlaxoSmithKline UK Limited | | | 700 | | 700 |
| ITECHO Health Ltd | | 1500 | | | 6600 |
| Johnson & Johnson / Janssen-Cilag Ltd | 19400 | | 200 | 13990 | 33590 |
| Kyowa Kirin Ltd | | 5000 | | | 5000 |
| Menarini Stemline UK Limited | | | 1844 | 3423 | 5267 |
| Pfizer Limited | | 9391 | 73448 | | 73448 |
| Oxford Biomedica UK Limited | 5000 | - | | | 5000 |
| Sebia | | | | 11192 | 11,192 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | Sanofi | | | 720 | 33,990 | 34710 |
| | Takeda | 20000 | | 880 | 15389 | 36269 |
| | Totals | 79400 | 59891 | 4344 | 77984 | 221,619 |

| | |
|---|---|
| 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**<br><br>Insert each comment in a new row.<br>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 | Myeloma UK is very disappointed that NICE did not recommend isatuximab plus bortezomib, lenalidomide and dexamethasone for newly diagnosed myeloma patients who are not eligible for high-dose therapy and stem cell transplantation (HDT-SCT) for routine commissioning.<br><br>This treatment is a significant advance for HDT-SCT ineligible patients. It delivers responses which are deeper the current standard of care and comparable to the depth of responses HDT-SCT eligible patient achieve. |
| 2 | **We believe the differences between the time to treatment discontinuation and progression-free survival are clinically plausible and consistent with available evidence**<br><br>Firstly, the main difference between IsaVRD and the main comparator (daratumumab with lenalidomide and dexamethasone (DRD)) is the addition of bortezomib. Therefore, the progression-free survival (PFS) benefit is largely driven by the bortezomib. Bortezomib is typically given for a fixed number of cycles, with patients remaining in remission long after their treatment has stopped. The sustained benefit of bortezomib is shown in the SWOG S0777 trial (1), which compared VRD to RD. The only difference between the trial arms was the induction phase, where patients randomised to the VRD arm got bortezomib for eight 21-day cycles. The trial demonstrates a significant progression-free survival benefit with the addition of bortezomib.<br><br>Secondly, IsaVRD delivers very deep responses and high levels of sustained minimal residual disease (MRD) negativity. In the IMROZ trial (2), 74.7% of patients who had IsaVRD achieved a complete response or better, with 58.1% of the intention-to-treat population reaching MRD-negative status and 46.8% having sustained MRD negativity for 12 months or more. These |

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|---|---|
| | responses are deeper than those observed for DRD in the MAIA trial, where only 32.1% of patients reached MRD-negative status, and 18.8% had sustained MRD-negative status for 12 months or more (3). It is well established that MRD negativity is associated with improved PFS and overall survival, with the FDA Oncologic Drugs Advisory Committee approving the use of MRD as a validated surrogate endpoint for myeloma in 2024. The difference in the depth of response further supports the extended PFS benefit observed.<br><br>Finally, there are many reasons that patients discontinue treatment – the treatment stops working, the side effects aren't manageable, regular hospital visits aren't manageable, or they don't want to be on treatment when they feel they don't have to. In the most recent publication for the IMROZ trial (2), 138 patients had discontinued treatment with IsaVRD, and only 38 (28%) of these patients had discontinued treatment due to progressive disease. (60 discontinued treatments due to adverse events, 6 due to poor compliance, 23 due to patient request and 11 for other reasons.) The low number of patients discontinuing treatment due to disease progression further supports the plausibility of the PFS benefit observed.<br><br>References<br>1. Durie, B.G., et.al. 2020. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood cancer journal*, *10*(5), p.53.<br>2. Facon, T., et. al. 2024. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *New England Journal of Medicine*, *391*(17), pp.1597-1609.<br>3. Facon, T., et. al. 2025. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. *Leukemia*, pp.1-9. |
| | **We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival.**<br><br>As shown in the committee meeting IsaVRD delivers longer remission times than the current standard of care.<br><br>In the IMROZ trial, 63% of patients who received IsaVRD were still in remission after 5 years (60 months).<br><br>Given that the current 5-year survival rate for myeloma is 55% this length of remission is highly significant for myeloma patients.<br><br>Having a long remission is very important for patients and their families. Patients describe remission as "*stability*", a time when "*life is more normal*" or "*they can more or less ignore the fact they have myeloma*".<br><br>Relapse has a massive impact on the quality of lives of patients. It is hugely disruptive to patients and their families, and a significant source of stress and anxiety. Relapse completely disrupts the lives of patients and their families, symptoms (e.g., pain, fatigue), hospital visits and tests and uncertainty about the future increases. Switching treatments means adjusting to different side effects and new routines for hospital visits/treatment administration.<br><br>***"Whilst I know Myeloma is a relapsing cancer, I was actually quite shocked that I had relapsed. Having been in remission for over 4 years I had convinced myself I was*** |

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| | |
|---|---|
| | ***cured. So, it took me some time to come to terms with the fact it was back. Emotionally this was quite tough."***<br><br>***"Unfortunately, I've switched treatment 3 times now and I think how you adjust depends on a number of factors: primarily what the new treatment is and how you experience the side effects but also, how well prepared you are for any potential side effects (and how well your team helps you to manage these)."***<br><br>***"Relapse is upsetting, devastating in fact and I always worry about what the next treatment will be like, particularly whether it will work and what impact the side effects might have on my QOL. "***<br><br>This period of instability typically lasts between 2-3 months due to the time needed to test and confirm relapse, book and consent patients for treatment and for patients to respond and adjust to the new treatment. During this time, the patient's health often deteriorates.<br><br>We believe the true QOL benefit of a long remission isn't reflected in the IMROZ QOL data. Firstly, the trial QOL data doesn't capture the impact a long remission has on carers and families whose lives are also disrupted by relapse.<br><br>Secondly, in the IMROZ trial, investigators collected QoL data during the active treatment period and then 30 and 90 days after the last study treatment administration. Therefore, the QoL data only captures the impact of relapse for patients who discontinued treatment due to disease progression. |
| 3 | **IsaVRD gives patients who are on the borderline of eligibility for HDT-SCT access to a kinder treatment option with comparable response rates.**<br><br>The high level of sustained MRD negativity means that, if approved, IsaVRD would give patients for whom stem cell transplant is unsuitable access to a quadruplet treatment that delivers the depth of responses which are comparable to those reached following HDT-SCT.<br><br>If approved, IsaVRD gives patients who are on the borderline between transplant eligibility and ineligibility access to a treatment that delivers comparable results without having to balance the mortality risk and high side effect burden of having HDT-SCT.<br><br>HDT-SCT is a very intensive treatment which has severe side effects, with patients spending 2-3 weeks in hospital and needing 3-6 months to recover. It is well established that side effect burden and recovery time are higher for less-fit patients and those with comorbidities.<br><br>There are also patients for whom HDT-SCT is not a viable option due to caring responsibilities or limited or stretched support networks.<br><br>***"When they brought-up stem cell transplantation, I thought about my friend who was also diagnosed with myeloma. He had a SCT, and it was very grim. He took a long time to recover fully. I wanted to get treatment over and done with. Also, for me being 75/76 benefits didn't outweigh the risks. If you only have 4-5-6 years on average, I didn't want to spend one of those years in hospital, in recovery."***<br><br>***"When my mum was diagnosed, we had to decide between a stem cell transplant and standard chemotherapy early on. The transplant was only available in London, which brought up a lot of worries. We were trying to figure out how we'd manage the travel, who would support her while she was there, and how it would affect her emotionally. On top of*** |

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| | ***that, because of her age and the stage of her myeloma, there was a real risk it wouldn't work. Even if it did, we were told it might only give her one more year—five years instead of four with chemo.***<br>***And as a carer, those choices don't leave you—you carry the weight of them long after the moment has passed. I still wonder if we made the right call. "*** |
| 4 | **IsaVRD could increase access to maintenance in genetically and clinically high-risk patients.**<br><br>In current clinical practice, it is estimated that approximately 20% of patients get a bortezomib-based regimen at diagnosis. Clinical experts at the committee meeting highlighted that this is mainly patients with genetically high-risk myeloma or with severe kidney impairment. However, bortezomib-based regimens are fixed-duration treatments with no maintenance.<br><br>The BSH guideline recommends the use of bortezomib-based regimens for treating high-risk myeloma patients.<br><br>Bortezomib is the treatment of choice for patients with kidney impairment due to tolerability and speed of response. For many patients, kidney function improves following treatment and means they are more likely to tolerate other drugs.<br><br>IsaVRD gives high-risk patients and those with renal impairment access to both bortezomib and maintenance giving them the best chance for deep responses, long remission times and improved overall survival.<br><br>References<br>Sive, J., et. al. 2021. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *British journal of haematology*, *193*(2). |
| 5 | **We are concerned that the Committee did not fully consider the significant patient benefit of increased depth of response.**<br><br>IsaVRD delivers very deep responses and high levels of sustained MRD negativity. In the IMROZ trial, 74.7% of patients who had IsaVRD achieved a complete response or better with 58.1% of the intention to treat population reaching MRD negative status and 46.8% having a sustained MRD negativity for 12 months of more.<br><br>Reaching a MRD negativity has a significant positive impact on the mental wellbeing myeloma. Knowing that you have had the deepest response possible and that your cancer is undetectable / you are cancer-free is completely different to knowing it is there but controlled.<br><br>Having no detectable signs of cancer often gives patients and their families an increased feeling of freedom, hope and optimism for the future. The risk of relapse or infection risk feels lower. This means patients are more likely to plan for the future and increase social activities and engagements.<br><br>The full QoL impact of achieving MRD negativity won't be picked up in the anxiety or depression utility scores. The utility scores also do not take into account the anxiety partners and family experience. It is also important to note that the anxiety related to potential relapse is cyclical and linked to monthly blood tests or changes in health (e.g. a new pain). |

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| | |
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| 6 | **We are concerned that the Committee did not fully consider the importance of a long and durable first remission.**<br><br>The first remission is often the deepest, longest remission and the period when a patient's quality of life is highest.<br><br>Myeloma is a relapsing and remitting cancer where each additional line of treatment is associated with worse outcomes; remission times decrease, and side effects increase.<br><br>Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities.<br><br>First remission is therefore widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed.<br><br>It is also important to take into account that a significant number of patients will not receive subsequent treatment.<br><br>References<br>Fonseca, R., et.al. 2023. Impact of disease progression, line of therapy, and response on health-related quality of life in multiple myeloma: a systematic literature review. *Clinical Lymphoma Myeloma and Leukemia*, *23*(6), pp.426-437. |
| | **We are concerned that the Committee did not fully consider the significant patient benefit of receiving a quadruplet.**<br><br>Quadruplets are considered the most effective treatments for myeloma. The complementary mechanisms of action work together to treat the biologically distinct subclones present in myeloma.<br><br>Quadruplets also provide more flexibility to mitigate and manage side effects. There are four drugs to work with. If a patient experiences side effects due to one of the drugs, its dose can be easily adjusted. However, with monotherapies and doublets severe side effects, often leads to treatment discontinuation, which is devastating for patients. |

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], ON BEHALF OF THE UK MYELOMA SOCIETY |

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| 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], CONSULTANT HAEMATOLOGIST AND EXECUTIVE MEMBER, UK MYELOMA SOCIETY |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>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 | Section 3.8 OS benefit. The committee raised concerns about the survival benefit of Isatuximab |

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| | plus bortezomib, lenalidomide and dexamethasone compared to Daratumumab lenalidomide dexamethasone.<br>It is clinically plausible that there is a survival benefit due to the addition of a proteosome inhibitor to an anti-CD38/IMID backbone (quadruplet vs triplet induction therapy).<br>There is likely to be an excess mortality in the IMROZ trial as this was conducted during the COVID pandemic. COVID positive results were reported for a number patients who died whilst participating in the IMROZ trial. Whilst we are unable to be certain, it is likely that COVID was contributory to their deaths. Myeloma patients had a very high mortality from COVID during this period (around 50%, Cook et al BJ Haem 2020). The MAIA study was not performed in the COVID pandemic, so this issue did not affect the Daratumumab lenalidomide dexamethasone comparator. |
| 2 | Section 3.9 Time to treatment discontinuation (TTD). The committee raised concerns about why the PFS was longer than TTD in the IMROZ trial.<br>This would fit with clinical experience. There are a number of reasons why patients will stop treatment (such as side effects or patient preference) at a time when they are in remission and will continue to remain in the this state for a while. As stated in the committee the depth of response (complete response/MRD negativity) is thought to be greater for a quadruplet than a triplet therapy.<br>Isatuximab plus bortezomib, lenalidomide and dexamethasone would be expected to have more side effects than Daratumumab lenalidomide dexamethasone, due to the addition of bortezomib that can cause neurotoxicity and other side effects. |
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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**Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]**

**Draft guidance comments form**

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- 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 draft guidance document, please submit these separately.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Johnson & Johnson |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | In relation the MAIA study the draft guidance states, *"Survival data from this trial was available for up to 100 months of follow-up"*.<br><br>However, as at the time of the final OS analysis, the median follow-up for overall survival in MAIA was 89.3 months[1] |

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| | [1.] Facon et al. – poster at EHA 2024 |
| 2 | The draft guidance states, *"No COVID-19-related deaths were recorded in MAIA because it was done before the pandemic".*<br><br>This is factually inaccurate. Whilst the MAIA trial completed study enrolment in January 2017 and conducted its primary analysis before the pandemic, it was impacted towards the end of its follow-up with deaths attributed to COVID-19 recorded across both treatment arms. |
| 3 | The draft guidance states the Company, *"modelled time to treatment discontinuation (TTD) for Isa-Bor-Len-Dex to be shorter than for Dar-Len-Dex".*<br><br>This appears inconsistent with the IMROZ and MAIA trial data which reported median treatment duration for Isa-Bor-Len-Dex of 53.2 months[2] and 47.5 months for Dar-Len-Dex[3]. After excluding patients >80 years to align with the inclusion criteria in IMROZ, the median treatment duration for Dar-Len-Dex in MAIA was [redacted] months [redacted].<br><br>[2.] Facon et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma; The New England Journal of Medicine; 2024<br><br>[3.] Facon et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. Leukemia. 2025 |
| 4 | Johnson & Johnson note that the drug administration costs used in the Company model assumed NHS reference cost code SB12Z (Deliver simple parenteral chemotherapy at first attendance) for first and subsequent doses of drugs administered as a subcutaneous (SC) injection. This significantly overestimates the attributable cost to the NHS and is inconsistent with recent multiple myeloma appraisals (e.g. TA917, TA763, TA897 and TA1015) which have used N10AF (Specialist Nursing, Cancer Related, Adult, Face to face) for SC administration costs.<br><br>In the context of the comparison of Isa-Bor-Len-Dex with Dar-Len-Dex, it is not plausible that the administration costs associated with daratumumab SC delivery would be similar to IV administration costs for isatuximab (e.g. £394 for SC cost using SB12Z and £430 for IV subsequent therapy cost using SB15Z) when considering daratumumab is given as a 3-5 minute injection versus a 75 minute infusion for isatuximab with an initial infusion length of >3 hours.[4,5]<br><br>[4.] Mateos et al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA; Journal of Clinical Oncology. 2019<br>[5.] https://www.medicines.org.uk/emc/product/14817/smpc#gref |
| 5 | The draft guidance states, *"the model assumed that the adverse events profile of Dar-Len-Dex is less favourable than that of Isa-Bor-Len-Dex".*<br><br>The modelling for adverse events (AEs) seems counterintuitive given the addition of a fourth agent (isatuximab), and considering increased exposure associated with 11 additional intravenous (IV) administrations for isatuximab (47 total administrations)[5] versus subcutaneous (SC) daratumumab (36 total administrations)[6] in the first two years after initiation of first-line treatment.<br><br>[6.] https://www.medicines.org.uk/emc/product/11488/smpc#gref |

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- 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.
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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Sanofi |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | Sanofi welcomes the opportunity to comment on the draft guidance for isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of newly diagnosed multiple myeloma (NDMM) in patients ineligible for stem cell transplant. We are committed to working collaboratively with NICE to address the committee's questions. Our goal is to ensure that NHS patients have access to this innovative therapy. |

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## Draft guidance comments form

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**Conducting an NMA using the SWOG S0777 study to inform the cost-effectiveness analyses**

Section 3.4 of the draft guidance states:
"*The committee concluded that it would like the company to present results from an NMA using the SWOG S0777 study with randomisation preserved. It added that this should be done using both the intention-to-treat (ITT) population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population. It concluded that these results should be used to inform the cost-effectiveness estimates*."

We acknowledge that our initial submission only considered the non-randomised subgroup of patients aged ≥65 years as a proxy for transplant ineligibility in the SWOG S0777 trial to conduct the NMA. In response to the committee's request to preserve randomisation, we have now updated our analysis to include both the "no intent to transplant" subgroup and the intention-to-treat (ITT) population. Below, we provide:

1. NMA method
2. Results
3. A methodological assessment of the different populations
4. Base-case and implementation in the model

1. Method

Standard proportional hazard NMA was carried out using a Bayesian approach to capture the uncertainty in model parameters while preserving correlation between treatment effects. Relative treatment effects were estimated using Markov chain Monte Carlo (MCMC) methods and NMA methods were consistent with NICE DSU TSDs 2–4. The NMA was conducted using the evidence network presented in Figure 21 of the company submission. The NMA was updated to incorporate the final OS analysis data from the MAIA trial. The NMA was run to generate results using 2 populations in SWOG S0777:
- the intention-to-treat (ITT) population
- the "no intent to transplant" subgroup (stratification factor)

2. Results

Results from the different indirect treatment comparisons for IsaVRd versus DRd are summarised in Table 1 below.

**Table 1: Indirect treatment comparison - IsaVRd vs DRd: PFS and OS results**

| ITC method | PFS (HR, 95% CI) | OS (HR, 95% CI) |
|---|---|---|
| **MAIC** | [redacted] | [redacted] |
| **NMA - No intent to transplant** | [redacted] | [redacted] |
| **NMA - ITT** | [redacted] | [redacted] |

Among the different analyses, the NMA using the "no intent to transplant" subgroup has the lowest risk of bias. This analysis suggests a more favourable treatment effect for IsaVRd compared with DRd, with hazard ratios of [redacted] for PFS and [redacted] for OS. The PFS estimate aligns closely with that obtained from the MAIC, while the OS estimate is numerically lower than both the MAIC and other NMA populations. Although the hazard ratios for both PFS and OS are not statistically significant, this is expected given large number of nodes in the network needed to include all comparators. Nonetheless, the results suggest a clinically meaningful benefit in both progression-free and overall survival.

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3. Methodological assessment of the randomised populations in SWOG S0777

3.1. NMA - ITT Population

Using the ITT population introduces substantial bias due to meaningful differences in baseline characteristics compared to the transplant-ineligible population enrolled in IMROZ. A comparison of baseline characteristics identified as treatment effect modifiers and ranked by order of importance is summarised below.

**Table 2: Comparison of baseline characteristics between SWOG S0777 and IMROZ (ITT populations)**

| Characteristic | SWOG S0777 Trial (n=471) | IMROZ Trial (n=465) | Difference |
|---|---|---|---|
| **Median Age** | 63 years | 72 years | +9 years |
| **Frailty** | Not reported | Not reported | NA |
| **ISS Stage III** | 34% (155/460)*** | 26.9% (120/465) | –6.1% |
| **High-Risk Cytogenetics** | 33% (out of 316 patients)** | 16.6% (74/446) | –16.4% |
| **ECOG Performance Status >1** | 12% (53/441)*** | 11.0% (49/446) | –1% |
| **LDH ≥ 190 U/L** | 36% (163/454)*** | 12.7% (56/446) | -23.3% |
| **Renal impairment: eGFR<60 ml min 1.73 m2** | Not reported | 28.7% (128/446) | NA |
| **Chromosomal Abnormality 1q21+** | Not reported | 37.0% (165/446) | NA |
| **MM Type (IgG)** | Not reported | 64.6% (286/446) | NA |
| **Transplant Rate*** | 35% (161/460)*** | 0% | –35% |

* Not pre-identified as a treatment effect modifier but instead creates confounding with the treatment effect in the trial
** SWOG S0777 First data cut
*** SWOG S0777 Second data cut

Key differences include:

- Age: IMROZ enrolled an older, transplant-ineligible population (median age 72), while SWOG S0777 included a younger, broader population (median age 63), many of whom were transplant-eligible. The median age in IMROZ exceeds the interquartile range in SWOG (VRd: 56 to 70; Rd: 56 to 71), indicating that the populations are very different. Age was identified by clinicians as the most important treatment effect modifier.

- Frailty: Although not reported in SWOG S0777, frailty is expected to differ substantially. The inclusion of transplant-eligible patients in the ITT population, with 35% proceeding to transplant, suggests that patients in SWOG were significantly fitter (with likely negligible to low frailty) than those in IMROZ, which exclusively enrolled transplant-ineligible patients.

- High-risk cytogenetics: IMROZ included 16.6% of patients with high-risk cytogenetics, compared to 33% in SWOG. This difference limits the comparability of treatment effects between the two trials.

- LDH ≥ 190 U/L: High LDH levels were seen in 36% of patients in SWOG S0777, compared with only 12.7% in IMROZ. This large difference suggests that patients in SWOG may have had more aggressive disease, making comparisons with IMROZ more difficult.

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| | - Transplant confounding: A critical limitation of the SWOG ITT population is that 35% of patients received an autologous stem cell transplant. This introduces a major source of confounding, as the treatment effect observed reflects not only the effect of VRd vs Rd but also the known benefit of a transplant (VRd + ASCT vs Rd + ASCT). In contrast, IMROZ exclusively enrolled patients who were transplant ineligible based on clinical criteria.<br><br>ECOG performance status and ISS stage were broadly similar between trials, with ECOG >1 reported in 14% of SWOG and 11.3% of IMROZ, and ISS Stage III in 34% and 26.9% respectively. Unreported characteristics in SWOG S0777 such as renal impairment, chromosomal abnormality 1q21+, and MM type (IgG) limit the ability to interpret comparability.<br><br>To conclude, using the SWOG ITT population in a network meta-analysis to inform outcomes in the transplant-ineligible setting would introduce significant bias and reduce the validity of the comparison. The treatment effect in the ITT population is confounded by a meaningful proportion of post-randomisation transplant. The population also differs substantially from IMROZ in terms of treatment effect modifiers such as age, cytogenetics, and—though not directly measured—frailty and renal function. As a result, the assumption of transitivity, which requires that treatment effect modifiers be similarly distributed across trials, is not met.<br><br>Clinical experts have confirmed that the treatment effect observed in the SWOG ITT population is not applicable to the transplant-ineligible population represented in IMROZ. Therefore, the ITT population from SWOG is not considered a reliable proxy for the transplant-ineligible population in the NMA.<br><br>3.2. NMA – No intent to transplant subgroup<br><br>Among the randomised populations in SWOG S0777, the “no intent to transplant” subgroup represents a more appropriate proxy for the transplant-ineligible population than the ITT population. However, it is important to clarify the distinction between “no intent to transplant” and "transplant ineligibility". “No intent” is a designation recorded at baseline, which may reflect patient preferences or other non-clinical factors. In contrast, transplant ineligibility is based on objective clinical criteria such as age, comorbidities, and performance status. Therefore, while the “no intent” group likely includes all transplant-ineligible patients, it also encompasses a proportion of transplant-eligible patients who chose not to receive a transplant.<br><br>The inclusion of some transplant-eligible patients in the “no intent” group may result in differences in treatment effect modifiers such as age, frailty, and renal function, which are common determinants of transplant eligibility. Because of this heterogeneity, the use of this subgroup in the NMA has initially been discouraged. Moreover, baseline characteristics for this subgroup are not reported, meaning that potential differences with a transplant-ineligible population cannot be assessed. Nonetheless, the absence of transplant intent implies a closer clinical resemblance to the IMROZ cohort than the broader ITT population. Any remaining differences are expected to arise from the unknown proportion of transplant-eligible patients with no intent to transplant.<br><br>The “no intent” subgroup has methodological advantages over the full ITT population. Patients in this group were not likely to proceed to transplant, as they represent the subset of transplant-eligible patients who had no intent to undergo transplant. This reduces the risk of confounding in the treatment effect from post-randomisation transplant, which is a key limitation of the ITT population. |

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| | In summary, while not a perfect match, the "no intent to transplant" subgroup is a more clinically and methodologically appropriate population than the full ITT cohort in SWOG S0777. While differences may remain due to the inclusion of some transplant eligible patients, this subgroup is expected to be closer in terms of treatment effect modifiers and avoids confounding from post-randomisation transplant, thereby better supporting the validity of a network meta-analysis.<br><br>4. Base case and implementation in the model<br><br>As requested by committee we have presented results from an NMA using the SWOG S0777 study with randomisation preserved, using both the ITT population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population. Between these two populations, only the no intent-to-transplant subgroup is clinically and methodologically appropriate for estimating the relative treatment effect of IsaVRd versus DRd in the transplant-ineligible population.<br><br>The committee stated that the NMA using the no intent-to-transplant subgroup as a proxy, would result in a conservative estimate. Therefore, in order to align with the committee's preference to use the most conservative approach, we have utilised the MAIC to inform our base case. While it does not preserve randomisation, the MAIC adjusts for key treatment effect modifiers and provides a more conservative estimate of the treatment effect for both PFS and OS.<br><br>We acknowledge the concerns raised about the complexity of the time-varying parametric MAIC approach and the EAG's recommendation, which stated that there is not enough evidence to support the non-proportional hazards assumption. As a result, the updated base case uses a constant HR MAIC anchored to the DRd curves from the MAIA trial. This method has the advantage of estimating a Cox proportional hazard ratio limited to the IMROZ follow-up period (68 months) for both IsaVRd and DRd.<br><br>To ensure that all available data are used, the maximum follow-up available for DRd is used to inform the absolute survival curves — approximately 100 months for OS and 75 months for PFS. Scenario analyses using the parametric MAIC were conducted.<br><br>In addition, scenario analyses were conducted using parametric MAICs, including one using 68 months of follow-up for IsaVRd and full follow-up for DRd, and another using 60 months of follow-up for IsaVRd. In terms of ICER impact, the constant HR MAIC sits between these scenarios (approximately +/- [redacted] QALYs), with only modest variation in cost-effectiveness outcomes. Based on this, and in line with expert comments during the first committee meeting, we recommend the constant HR MAIC as the most appropriate and robust approach for the base case, as it makes full use of the available evidence.<br><br>In contrast, the NMA increases QALY estimates by approximately [redacted] QALYs and [redacted] QALYs when using the no intent-to-transplant subgroup and the ITT population, respectively, compared with the constant HR MAIC. |
| EAG response | The EAG agrees with the company that the SWOG SO777 trial and IMROZ trial ITT populations differ substantially and that using data from these two trials in an NMA will not produce meaningful estimates of the treatment effectiveness of IsaVRd relative to comparators.<br><br>The EAG agrees with the company that, in theory, the 'no intent' subgroup is a more suitable population to use in an NMA than the ITT population. In practice, however, the difference in definition between 'no intent' and 'transplant ineligible', potentially results in confounding that cannot be quantified or understood in terms of the direction of any resultant bias. More importantly, the absence of trial baseline characteristics for the transplant ineligible (or 'no intent') |

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|---|---|
| | populations means that it is not possible to compare the severity of disease of the transplant ineligible (or 'no intent') SWOG SO777 trial and IMROZ trial populations.<br><br>Whilst the NICE AC may have been correct to conclude that a 'no intent' subgroup analysis could generate conservative results, the inability to be able to analyse differences between SWOG SO777 trial and IMROZ trial patient characteristics in the 'no intent' subgroup, coupled with the clear difference in SWOG SO777 trial and IMROZ trial ITT patient baseline characteristics means that the EAG considers that results from the NMAs requested by the NICE AC and performed by the company should not be used to inform decision making; results from the company's original (non-time varying) MAIC analysis are more robust.<br><br>Finally, the EAG considers that it is not appropriate to use the final MAIA data cut in the NMA or MAIC. The extra MAIA trial data suggest a changing OS hazard ratio over time (worsening for DRd); this not only means that the OS hazard ratio is not proportional, but also that the OS hazard ratio may worsen for the IMROZ trial as more data are collected. |
| 2 | **Addressing the committee's request for clarification as to whether the observed differences in TTD and PFS are clinically justified**<br><br>Section 3.13 of the draft guidance states:<br>"*The committee considered that there were many areas of uncertainty (see section 3.11) and would like to see clarification on whether the inconsistencies in the modelling of TTD and PFS are clinically justified and would be expected in NHS practice*."<br><br>We would like to provide further clarification and new supporting evidence to address this concern.<br><br>1) Longer PFS<br><br>The longer PFS observed for IsaVRd compared to DRd is supported by significantly higher rates of minimal residual disease negativity (MRD–). A MAIC was conducted to explore MRD negativity rates at a sensitivity threshold of $10^{-5}$ between IsaVRd (IMROZ) and MAIA (DRd). The analysis demonstrated that IsaVRd significantly increased the odds of achieving MRD–, with an odds ratio of [redacted].<br><br>MRD negativity and increasingly, sustained MRD negativity beyond 12 months, is a well-established surrogate for PFS and OS in multiple myeloma. The higher MRD– rates observed with IsaVRd supports the PFS benefit and the validity of the modelled treatment effect.<br><br>**Table 3: Unadjusted and adjusted Odds Ratio for MRD negativity between IsaVRd and DRd**<br>**Method** \| **Odds Ratio (95% CI)**<br>**Unadjusted OR** \| 2.94 (2.12 to 4.08)<br>**MAIC adjusted OR** \| [redacted]<br>**MAIC adjusted bootstrap median OR (percentile CI)** \| [redacted]<br><br>2) Equivalent TTD<br><br>Despite the PFS benefit, the MAIC on time-to-discontinuation (TTD) estimated a hazard ratio of [redacted], indicating no difference in treatment duration between IsaVRd and DRd.<br><br>The results are supported by:<br><br>- **Comparable maintenance tolerability**: Both regimens share the same maintenance components i.e. treat until progression or unacceptable AEs—anti-CD38 monoclonal |

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**Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]**

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| | |
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| | antibody, lenalidomide, and dexamethasone—resulting in comparable tolerability. As noted by the EAG, the adverse event profile of DRd appears to be less favourable than that of IsaVRd. This would suggest that TTD for IsaVRd could be longer than for DRd. However, the slightly fitter population in IMROZ compared to MAIA likely contributes to this interpretation. After adjustment, the tolerability profiles during the maintenance phase are expected to be similar, as indicated by the MAIC on TTD. This is consistent with clinical expert opinion.<br>- **Impact of intensive induction**: The more intensive induction phase with bortezomib could lead to higher early discontinuation in IsaVRd treated patients compared to DRd in clinical practice.<br>- **Discontinuation largely unrelated to progression**: Treatment discontinuation was predominantly driven by factors other than disease progression, which accounted for only 27.5% of discontinuations in the IsaVRd arm of IMROZ. In total, 72.5% of patients discontinued treatment for reasons unrelated to progression—most notably adverse events (43.5%) and patient withdrawal, primarily due to tolerability issues (16.7%). Additional reasons included poor compliance to protocol (4.3%) and other factors such as investigator decision or mutual agreement (8.0%). Therefore, the MAIC on TTD mainly adjusts for treatment discontinuation due to AE and supports the similar tolerability profile of IsaRd and DRd.<br>- **Higher MRD– rates may support treatment discontinuation**: The MAIC on MRD– showed a significantly higher proportion of patients achieving MRD– with IsaVRd than with DRd. In IMROZ, 58.1% of patients treated with IsaVRd achieved MRD–, and 46.7% achieved sustained MRD negativity for at least 12 months. As a result, patients are more likely to achieve sustained MRD– and may choose to discontinue treatment before progression.<br>- **Mature TTD data with long follow-up**: With six years of follow-up and the median reached, there is no reason to expect that the relationship – overlap of TTD curves – will change after the observed data.<br>- **Minimal change after adjustment**: Before adjustment, the TTD curves from IMROZ and MAIA were already closely aligned, with an unadjusted HR of [redacted]. The MAIC adjustment brought the curves slightly closer, but the change was minimal, indicating that the observed overlap between the two curves was not artificially driven by the adjustment process. This further supports the robustness of the TTD comparison.<br>- **MAIC selected for clinical plausibility**: The MAIC was selected in the company's base case because it produced clinically plausible results for OS and PFS, reinforcing the reliability of the analysis for TTD.<br><br>To conclude, the statistically significant PFS benefit observed with IsaVRd is supported by deeper responses and higher MRD– rates, reinforcing the validity of the modelled treatment effect. While PFS improves, the MAIC shows that TTD remains equivalent between IsaVRd and DRd—a finding that is clinically plausible given the similar tolerability profile of isatuximab and daratumumab and the backbone agents in clinical practice. Treatment discontinuation in IMROZ was largely unrelated to disease progression, further supporting the MAIC findings, with both arms reaching median TTD and follow-up extending to approximately six years, during which the curves did not separate. Additionally, expert clinical opinion confirms that some patients may remain off treatment for extended periods—potentially years—following deep and durable responses, further supporting the real-world plausibility of the modelling assumptions. |

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<table>
<tr><td></td><td>Because TTD is modelled to be equivalent—partly due to the similar tolerability profile—the base case applies the same adverse event costs and disutilities for IsaVRd as for DRd.</td></tr>
<tr><td>EAG comment</td><td>The EAG remains concerned that the prolonged PFS benefit that occurs after patients have stopped treatment with IsaVRd may not be reasonable but accepts that the company has provided some potentially plausible reasons to explain why this is occurring. The EAG considers that IMROZ trial data showing time to next treatment may have been informative as these data; these data may have provided evidence that prolonged PFS was not due to receiving subsequent therapy prior to progression.</td></tr>
<tr><td>3</td><td>Adopting the committee’s preference for the appropriate reference curve<br><br>Section 3.7 of the draft guidance states:<br>"The committee concluded that its preferred method to model OS and PFS for Isa-Bor-Len-Dex and comparators would be to apply the hazard ratio generated from an NMA to an appropriate reference curve, such as Dar-Len-Dex OS and PFS curves from MAIA or Dar-Len-Dex SACT data."<br><br>We acknowledge the committee’s request to anchor HRs to DRd curves. We note that survival curves from DRd in SACT were not publicly available or accessible within the timelines of this appraisal. Therefore, we used the DRd curves from the MAIA trial as the reference for anchoring HRs.<br><br>Accordingly, the committee’s preferred distributions for DRd extrapolation in the DRd TA (TA917) were selected for the reference curves: generalised gamma for OS, gamma for PFS, and Gompertz for TTD.<br>We also present a comparison of survival for IsaVRd and DRd from the previous base case and the current base case anchored to DRd. The current DRd-anchored survival projections are more conservative and more closely aligned with clinical expert expectations.<br><br>Table 4: Overall survival rates in the model – IsaVRd
<table>
<tr><th></th><th>10 years</th><th>15 years</th><th>20 years</th></tr>
<tr><td>Initial base-case</td><td>52.40%</td><td>35.40%</td><td>17.70%</td></tr>
<tr><td>Current base-case, anchored to DRd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Clinician estimates %, (95% CI)</td><td>45% (35% to 55%)<br>Max: 60%</td><td>24% (15% to 33%)<br>Max: 35%</td><td>11% (5% to 17%)<br>Max: 20%</td></tr>
</table>
Table 5: Progression-free survival rates in the model – IsaVRd
<table>
<tr><th></th><th>10 years</th><th>15 years</th><th>20 years</th></tr>
<tr><td>Initial base-case</td><td>40.2%</td><td>25.2%</td><td>12.6%</td></tr>
<tr><td>Current base-case, anchored to DRd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Clinician estimates %, (95% CI)</td><td>28% (23% to 33%)<br>Max: 40%</td><td>11% (2% to 16%)<br>Max: 20%</td><td>2% (0% to 6%)<br>Max: 10%</td></tr>
</table></td></tr>
<tr><td>EAG comment</td><td>The EAG notes that, compared with the initial base case, the new company base case 10, 15 and 20 year OS and PFS rates are more in line with clinician estimates. The decision to anchor to MAIA trial DRd or IMROZ trial IsaVRd PFS and OS data should be made based on an</td></tr>
</table>

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| | |
|---|---|
| | assessment of whether it is the MAIA trial population or the IMROZ trial population that is the most similar to the NHS population. |
| 4 | **Addressing the Committee's request for evidence supporting an OS benefit**<br><br>Section 3.8 of the draft guidance states:<br>"*The EAG noted that the available clinical-effectiveness evidence was not sufficient to support the assumption that people having Isa-Bor-Len-Dex live longer than people having Dar-Len-Dex. [...] The committee agreed with the EAG that it had not yet seen sufficient clinical evidence to support an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex*."<br><br>We would like to provide further clarification and new supporting evidence to address this concern:<br>- The NMA using the "no intent to transplant" subgroup from SWOG S0777 estimated a HR for overall survival of [redacted] for IsaVRd versus DRd. While not statistically significant, the point estimate is consistent with a clinically meaningful OS benefit.<br><br>- This is further supported by evidence from SWOG S0777, where the addition of bortezomib to Rd significantly improved OS in both the "no intent to transplant" subgroup (HR: 0.583; 95% CI: 0.371 to 0.917; p=0.0134) and the intention-to-treat population (HR: 0.709; 95% CI: 0.536 to 0.938; p=0.0114). These results confirm that bortezomib improves survival when added to Rd, providing a clear rationale for expecting an OS benefit when bortezomib is added to IsaRd in comparison to DRd.<br><br>- The survival benefit is likely driven by the deeper responses induced by bortezomib. IsaVRd appears to significantly improve MRD– rates compared with DRd. In IMROZ, 58.1% of patients treated with IsaVRd achieved MRD–, and 46.7% achieved sustained MRD negativity for at least 12 months—highlighting the depth and durability of response. MRD– is a well-established surrogate for both PFS and OS in multiple myeloma, and sustained MRD– is recognised as a predictor of long-term survival. These findings provide biological plausibility for an OS benefit with IsaVRd. |
| EAG comment | The EAG considers the 'no intent' NMA performed by the company is confounded and insufficiently robust to evidence a survival gain.<br><br>The addition of bortezomib to Rd improving OS does not mean that a transitivity argument holds that adding bortezomib to IsaRd improves OS.<br><br>The EAG is unable to confirm whether there is a causal link between MRD negativity and outcomes. In the IMROZ trial, the impact of MRD negativity on patients continuing IsaVRd treatment is unknown; further, it is not known if MRD negativity is routinely tested in NHS practice. Both these factors could influence the generalisability of IMROZ trial IsaVRd data to NHS practice. |
| 5 | **Updating subsequent treatments to reflect regimens available in NHS practice**<br><br>It has been highlighted by the EAG that the costs of subsequent treatments did not include selinexor-bortezomib-dexamethasone (SVd) in the original submission. Teclistamab is also now available in the NHS. Therefore, the model has been updated to include SVd at second and third line, and teclistamab at fourth line.<br><br>The updated treatment distributions are based on estimates provided by two clinical experts. The revised proportions for IsaVRd and DRd are shown in the table below.<br><br>**Table 6: Subsequent treatment distribution after IsaVRd and DRd in NHS** |

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| | |
|---|---|
| | <table><tr><th>Line of Therapy</th><th>Regimen</th><th>IsaVRd</th><th>DRd</th></tr><tr><td rowspan="4">2L</td><td>Kd</td><td>27.5%</td><td>27.5%</td></tr><tr><td>Vd</td><td>17.5%</td><td>17.5%</td></tr><tr><td>VCd</td><td>30.0%</td><td>25.0%</td></tr><tr><td>SVd</td><td>25.0%</td><td>30.0%</td></tr><tr><td rowspan="3">3L</td><td>PanVd</td><td>20.0%</td><td>20.0%</td></tr><tr><td>CTd</td><td>65.0%</td><td>65.0%</td></tr><tr><td>SVd</td><td>15.0%</td><td>15.0%</td></tr><tr><td rowspan="3">4L</td><td>Pd</td><td>27.5%</td><td>27.5%</td></tr><tr><td>PanVd</td><td>2.5%</td><td>2.5%</td></tr><tr><td>Teclistamab</td><td>70.0%</td><td>70.0%</td></tr></table> |
| EAG Comment | It is not clear if the benefits of treatment with SVd and teclistamab have been included in the company model; the EAG considers that if benefits are not included then costs should not be included.<br><br>It is not clear why the proportions of patients receiving second-line treatment with SVd would be higher for patients treated with DRd versus IsaVRd. |
| 6 | **Selecting a starting age that reflects the NHS population**<br><br>Section 3.6 of the draft guidance states:<br>"*It also recalled that the starting age used in the model, based on the age in IMROZ, was younger than would be expected in NHS clinical practice (see section 3.3). So, it requested that the model be updated to include a starting age reflecting the NHS population and based on an appropriate source. Its preference was people having Dar-Len-Dex in Systemic AntiCancer Therapy (SACT) data.*"<br><br>Data on transplant eligibility are not collected in SACT, therefore no data on patient's age are available specifically for the transplant-ineligible population. Similarly, the median age of patients initiating DarLenDex in NHS practice is not reported in the published literature. However, a retrospective study of 200 transplant-ineligible NDMM patients in the UK treated with standard of care between 2009 and 2018 reported a median age of 75 years (DOI: 10.3324/haematol.2019.240762).<br><br>Based on this, the base-case analysis has been updated to use a starting age of 75 years, in line with the committee's request to reflect NHS clinical practice. Patients initiating IsaVRd are expected to be among the fitter subset of the transplant-ineligible population, and therefore their age is expected to be lower than 75 years in clinical practice. This has been validated by clinical experts. |
| EAG comment | The EAG considers that, unless clinical trial data can be adjusted to produce effectiveness estimates for the starting age used in the company model, it is methodologically inappropriate to have a starting age in the company model that differs from the clinical trial starting age. |
| 7 | **Selecting the most appropriate post-progression utility values**<br><br>Section 3.10 of the draft guidance states:<br>"*The committee noted that the company had included utility values from the study by Hatswell et al. (2019) as a scenario in the model. The committee agreed that the post-progression utility value from TA587 was low. This was because, at the time of that evaluation, fewer treatment options were available post-progression, which is not reflective of the current treatment pathway. So, the* |

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<table>
<tr><td></td><td>committee concluded that it was not appropriate to use utility values from TA587. It would prefer to use post-progression utility values from IMROZ, or treatment-independent progressed-disease utility values derived by applying a decrement based on Hatswell et al. to the IMROZ PFS utility value."<br><br>We acknowledge the committee's preference and have adopted an approach aligned with this recommendation. Specifically, we refer to the Bayesian meta-regression using EQ-5D data from Hatswell et al. (2019), which reports utility values by line of treatment: 0.620 for first-line, 0.590 for second-line, 0.578 for third-line, and 0.479 for fourth-line and beyond. The decrement between first- and second-line treatment is 0.030, followed by 0.012 between second- and third-line, and 0.099 between third-line and fourth-line and beyond.<br><br>As the model includes a single post-progression survival (PPS) health state that aggregates all subsequent lines of therapy, applying multiple line-specific decrements would require assumptions about the time spent in each line of treatment that differ by comparator. Therefore, to ensure comparability across treatment arms we apply only the decrement between first- and second-line treatment. Few patients are also expected to reach 4L after IsaVRd and DRd.<br><br>Applying the 0.030 decrement to the IMROZ PFS utility values results in the following post-progression utility values:<br><br>
<table>
<tr><td></td><td>IsaVRd</td><td>DRd</td><td>Rd</td><td>VMP</td><td>VCd</td></tr>
<tr><td>PFS</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PPS (Hatswell decrement between 1L and 2L)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
<br>We therefore recommend applying the decrement from Hatswell to the IMROZ PFS utility values, rather than using the PPS utility value directly from IMROZ, which may overestimate quality of life in the post-progression setting. Using IMROZ utility value has a minimal impact on the QALYs (-[redacted])</td></tr>
<tr><td>EAG comment</td><td>The EAG considers that the company approach is reasonable.</td></tr>
<tr><td>8</td><td>We present the company's updated base case and associated scenario analyses.<br><br>Base Case Assumptions:<br>- OS and PFS: Estimated using a constant hazard ratio (HR) from the MAIC, anchored to DRd reference curves from the MAIA trial (Gamma for PFS, Generalised Gamma for OS), in line with the committee's preferred distributions in the DRd TA.<br>- TTD, Adverse Events, and Disutilities: Assumed equivalent to DRd. For TTD, the Gompertz distribution was selected, in line with the committee's preferred distributions in the DRd TA.<br>- Utility Values: Based on the Hatswell decrement applied to IMROZ PFS utilities.<br>- Subsequent Treatments: Updated to reflect NHS clinical practice, including SVd and teclistamab.<br>- Starting Age: 75 years.<br><br>
<table>
<tr><td></td><td colspan="2">Incremental</td><td></td><td></td></tr>
<tr><td></td><td>Cost</td><td>QALYs</td><td>ICER</td><td>NMB</td></tr>
<tr><td>ACM2 Company's base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>1. IMROZ age</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2. IMROZ PPS utility</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

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| | **3. Subsequent treatments: without SVd and Teclistamab** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **4. NMA SWOG ≥ 65 years old** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **5. NMA SWOG ITT** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **6. NMA SWOG No intent to transplant** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **7. pMAIC 68 months IMROZ/100 months DRd** | [redacted] | [redacted] | [redacted] | [redacted] |
| | **8. pMAIC 60 months IMROZ/100 months DRd** | [redacted] | [redacted] | [redacted] | [redacted] |

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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 draft guidance 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.

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>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): | Johnson & Johnson |

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| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | N/A |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | In relation the MAIA study the draft guidance states, *"Survival data from this trial was available for up to 100 months of follow-up"*.<br><br>However, as at the time of the final OS analysis, the median follow-up for overall survival in MAIA was 89.3 months[1] |

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| | |
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| | [1.] Facon et al. – poster at EHA 2024 |
| EAG comment | None |
| 2 | The draft guidance states, *"No COVID-19-related deaths were recorded in MAIA because it was done before the pandemic".*<br><br>This is factually inaccurate. Whilst the MAIA trial completed study enrolment in January 2017 and conducted its primary analysis before the pandemic, it was impacted towards the end of its follow-up with deaths attributed to COVID-19 recorded across both treatment arms. |
| EAG comment | None |
| 3 | The draft guidance states the Company, *"modelled time to treatment discontinuation (TTD) for Isa-Bor-Len-Dex to be shorter than for Dar-Len-Dex"*.<br><br>This appears inconsistent with the IMROZ and MAIA trial data which reported median treatment duration for Isa-Bor-Len-Dex of 53.2 months[2] and 47.5 months for Dar-Len-Dex[3]. After excluding patients >80 years to align with the inclusion criteria in IMROZ, the median treatment duration for Dar-Len-Dex in MAIA was [redacted] months [redacted].<br><br>[2.] Facon et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma; The New England Journal of Medicine; 2024<br><br>[3.] Facon et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. Leukemia. 2025 |
| EAG comment | The available evidence suggests that there may be minimal difference in treatment duration between IsaVRd and DRd. |
| 4 | Johnson & Johnson note that the drug administration costs used in the Company model assumed NHS reference cost code SB12Z (Deliver simple parenteral chemotherapy at first attendance) for first and subsequent doses of drugs administered as a subcutaneous (SC) injection. This significantly overestimates the attributable cost to the NHS and is inconsistent with recent multiple myeloma appraisals (e.g. TA917, TA763, TA897 and TA1015) which have used N10AF (Specialist Nursing, Cancer Related, Adult, Face to face) for SC administration costs.<br><br>In the context of the comparison of Isa-Bor-Len-Dex with Dar-Len-Dex, it is not plausible that the administration costs associated with daratumumab SC delivery would be similar to IV administration costs for isatuximab (e.g. £394 for SC cost using SB12Z and £430 for IV subsequent therapy cost using SB15Z) when considering daratumumab is given as a 3-5 minute injection versus a 75 minute infusion for isatuximab with an initial infusion length of >3 hours.[4,5]<br><br>[4.] Mateos et al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA; Journal of Clinical Oncology. 2019<br>[5.] https://www.medicines.org.uk/emc/product/14817/smpc#gref |
| EAG comment | The 2023/2024 N10AF cost is £109. The EAG has run a scenario using this N10AF cost to highlight the impact on cost effectiveness results. |
| 5 | The draft guidance states, *"the model assumed that the adverse events profile of Dar-Len-Dex is less favourable than that of Isa-Bor-Len-Dex"*.<br><br>The modelling for adverse events (AEs) seems counterintuitive given the addition of a fourth agent (isatuximab), and considering increased exposure associated with 11 additional intravenous (IV) administrations for isatuximab (47 total administrations)[5] versus subcutaneous (SC) daratumumab (36 total administrations)[6] in the first two years after initiation of first-line treatment.<br><br>[6.] https://www.medicines.org.uk/emc/product/11488/smpc#gref |

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NICE National Institute for Health and Care Excellence

**Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on Thursday 19 June 2025. Please submit via NICE Docs.

| | |
|---|---|
| EAG comment | None |

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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