Single Technology Appraisal

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Johnson & Johnson Innovative Medicine**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Blood Cancer UK
   b. Myeloma UK
   c. Myeloma UK – HMRN data
   d. Pfizer

3. **External Assessment Group critique of company comments on the Draft Guidance**

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

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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. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Johnson & Johnson Innovative Medicine

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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.	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 Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive Summary	**Executive summary** Johnson and Johnson Innovative Medicine (J&J IM) is surprised and very concerned that the recommendation of teclistamab for treating relapsed and refractory multiple myeloma (RRMM) after three or more treatments is restricted to patients who would otherwise receive pomalidomide plus dexamethasone (PomDex). This restriction is surprising given that at no point in the appraisal thus far, including the first committee meeting, was the need for evidence in patients who would otherwise be treated with pomalidomide raised or requested. This decision is concerning as it will prevent access to teclistamab in patients who currently face a severe unmet need for an effective treatment option and would derive substantial clinical benefit from teclistamab. J&J IM appreciates the opportunity to participate in the consultation for this guidance and would like to highlight the following points: **NICE's draft recommendation for teclistamab excludes a small population of patients who would not normally be treated with pomalidomide; we consider these are patients who have previously received treatment with pomalidomide (Pom-exposed). These patients are desperately in need of effective treatment options as they near the end of their terminal illness. They face an extremely high unmet need, and removal of this restriction would**

represent a low risk for decision making as this patient population is relatively small based on the current RRMM treatment pathway in the UK, with numbers expected to rapidly diminish over time as innovative therapies such as teclistamab replace treatment with pomalidomide plus dexamethasone.

- By the time patients are eligible for teclistamab (i.e., in the fourth-line setting and beyond [4L+]), they will have relapsed or failed to respond to multiple lines of treatment. The symptomatic and emotional burden of MM intensifies with each subsequent treatment and relapse, meaning that there is a significant unmet need in triple-class exposed (TCE) patients for an alternative, efficacious treatment to improve their quality of life.[1, 2] The Committee recognised the substantial impact MM has on survival and quality of life in the draft guidance document (DGD), acknowledging the unmet need for effective treatments for people who have already received several treatments.[3] In particular, J&J IM were encouraged by the following wording in the DGD which highlights the potential for teclistamab to address this unmet need: *"the committee concluded that teclistamab is an innovative medicine that could provide a novel treatment option for people with relapsed and refractory multiple myeloma".*[3] PomDex is the most commonly used treatment option in this setting, and so for the majority of patients with TCE RRMM who would otherwise be offered PomDex (i.e., Pom-naïve patients), the draft positive recommendation for teclistamab now represents a substantial step-change in the treatment paradigm, offering the potential for improved disease control and patient HRQoL, and ultimately, prolonged survival.

- The restriction of teclistamab to patients who would otherwise be offered PomDex, however, means that a limited population of Pom-exposed patients are excluded from being able to access teclistamab. This includes patients who have already received and progressed on PomDex in the 4L setting, as well as the historical cohort of patients who received and progressed on isatuximab with pomalidomide and dexamethasone (IsaPomDex) in the 4L setting whilst it was available via the Cancer Drugs Fund. This population is small, with only 1% of RRMM patients ever reaching 5th line therapy.[4] Furthermore, the UK real world (RW) TCE cohort study showed that of the 645 patients with TCE RRMM and an ECOG PS of 0-1 who received PomDex, only 27.9% went on to receive a subsequent treatment. Based on the current treatment pathway, Pom-exposure will diminish over time, as more effective therapies such as teclistamab replace the use of PomDex at 4th (and 5th) line, while IsaPomDex has recently received a negative recommendation by NICE, meaning patients can no longer become Pom-exposed via IsaPomDex.[5]

- While the Pom-exposed patient population is small, they face a critical unmet need for effective treatment options. In the UK RW TCE cohort study, the majority of Pom-exposed patients who received subsequent treatment were treated with panobinostat in combination with bortezomib and dexamethasone (PanoBorDex) (N=112; 62.2%), which concurs with UK clinical expert advice that PanoBorDex is the most relevant comparator for Pom-exposed patients with 4L+ RRMM. The outcomes for patients receiving PanoBorDex are extremely poor, with a median OS of 6.31 months (95% CI: 4.63, 7.92) and median TTNT of 4.83 months (95% CI: 3.55, 6.87). Thus, delays to the availability of teclistamab in this population will inevitably mean that many patients will unfortunately die. In the absence of any other effective treatment options, and it is imperative that teclistamab is made available as quickly is possible.

- UK clinical experts consulted also highlighted that a small number of patients who are penta-refractory may now receive treatment with selinexor in combination with dexamethasone (SelDex) following the recent NICE recommendation (TA970)[6] (see Comment 1).

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- It is notable that, to be able to receive treatment with either PanoBorDex or SelDex patients must be bortezomib-sensitive, or penta-refractory, respectively. For patients who are bortezomib-refractory but not penta-refractory (for example, patients who receive DaraBorDex in the 2L setting, who are likely to be bortezomib-refractory and will be unable to access carfilzomib to become penta-refractory), there are no further treatment options in UK clinical practice, underlining the unmet need in this patient population.
- J&J IM is therefore committed to working with NICE to ensure that teclistamab is able to receive approval within its full licensed indication through the National Health Service (NHS), irrespective of which treatment patients would have otherwise received. Such a recommendation will ensure that all eligible TCE RRMM patients can access teclistamab and therefore are able to benefit from its improved efficacy versus all existing recommended treatment options in this setting. **Removal of the restricted recommendation for teclistamab would address a substantial unmet need for patients facing extremely poor prognoses, whilst representing a low risk for decision making, given the relatively small and diminishing prevalence of pomalidomide exposure in the current pathway.**

Restriction of a recommendation to patients who would only otherwise be offered a comparator is inconsistent with NICE precedent.

- Where there is a single most relevant comparator or defined 'most relevant' comparator for a given evaluation, NICE has not typically applied a restricted recommendation to patients who would otherwise receive that comparator. Thus, J&J IM considers that a restricted recommendation for teclistamab contradicts precedent established in prior NICE evaluations.
- Specifically, of the 13 most recent prior NICE evaluations conducted in patients with RRMM, 11 did not impose a restriction to patients who would otherwise be offered the comparator. Many of these appraisals - including TA695, TA870 and TA970 - all evaluated the clinical and cost-effectiveness of a single comparator considered to be the most relevant, and although the NICE final scope for the three evaluations specified multiple comparators, no restricted recommendations were issued.[6-8] Only 2 appraisals included a restriction based on either a specific prior treatment or the comparator that a patient would otherwise receive (TA897 and TA974). In both of these appraisals, multiple comparators were identified as relevant.[9, 10] The restriction in TA897 was only made because no indirect treatment comparison (ITC) was presented versus a comparator which *was identified* as a relevant comparator, whilst the restriction in TA974 was made because the intervention did not demonstrate cost-effectiveness versus the relevant treatment.
- Thus, J&J IM considers that it is unprecedented, and inappropriate, for NICE to restrict a recommendation for teclistamab to patients who would be offered PomDex when this comparator was identified and confirmed to be the only relevant comparator for this evaluation by both the EAG and the NICE committee in the public discussion.[11]

Teclistamab is clinically and cost-effective against PanoBorDex, which is the main comparator to teclistamab in Pom-exposed patients.

- J&J IM maintains the position that it is inappropriate to restrict a NICE recommendation to the only comparator identified as relevant during the appraisal process. Nonetheless, J&J IM notes the Committee's concern that it *has not seen evidence of teclistamab's clinical and cost effectiveness in people that have had pomalidomide + dexamethasone.* Thus, to further inform the appraisal of teclistamab within its full licensed population, this response

presents the following additional evidence to support the clinical and cost-effectiveness of teclistamab in patients who have been exposed to PomDex:

- The UK RW TCE study indicates that the majority (62.2%) of Pom-exposed patients subsequently received PanoBorDex as their next treatment. This was supported by feedback received from UK clinical experts who indicated that the most appropriate comparator to teclistamab in Pom-exposed patients is PanoBorDex (see Comment 1).
- Subgroup analyses from the MajesTEC-1 trial demonstrate that efficacy outcomes for Pom-exposed patients receiving teclistamab are highly consistent with the intention-to-treat (ITT) population of the trial (see Comment 2).
- An unanchored matching-adjusted indirect comparison (MAIC) was conducted between teclistamab (MajesTEC-1) versus PanoBorDex (UK RW TCE cohort study) in Pom-exposed patients. The results demonstrate that treatment with teclistamab is associated with a statistically significant 54% reduction in the risk of disease progression (HR: 0.46; 95% CI: 0.26, 0.84; p-value=0.0106) and a statistically significant 59% reduction in the risk of death (HR: 0.41; 95% CI: 0.22, 0.74; p-value=0.0030) versus PanoBorDex. A sensitivity analysis conducted resulted in similar outcomes for teclistamab versus PanoBorDex, supporting the robustness of the MAIC results (see Comment 3).
- At PAS price, the probabilistic results of the cost-effectiveness analysis showed that teclistamab was a cost-effective use of NHS resources when compared to PanoBorDex at a WTP threshold of £30,000/QALY, with an ICER of £[redacted] and a positive incremental net health benefit of [redacted]. Teclistamab had a [redacted]% probability of being cost-effective at a WTP threshold of £30,000/QALY. These results include the application of the 1.7x severity modifier with a proportional QALY shortfall of [redacted]%, highlighting the severe unmet need faced by the Pom-exposed patient population (see Comment 3).

Teclistamab is also clinically and cost-effective against SelDex, another treatment which may be received in a subset of Pom-exposed RRMM patients who are penta-refractory.

- UK clinical experts consulted also highlighted that patients who are penta-refractory may now receive treatment with selinexor in combination with dexamethasone (SelDex) following the recent NICE recommendation (TA970).[6] (see Comment 1).
- The results of an unanchored MAIC between teclistamab, using the MajesTEC-1 trial, versus SelDex, using the STORM trial, demonstrate that treatment with teclistamab results in a 39% reduction in the risk of disease progression (HR: 0.61; 95% CI: 0.33, 1.13) and a statistically significant 45% reduction in the risk of death (HR: 0.55; 95% CI: 0.33, 0.93) versus SelDex (see Comment 4).[12]
- At PAS price, the probabilistic results of the cost-effectiveness analysis showed that teclistamab was a cost-effective use of NHS resources when compared to SelDex at a WTP threshold of £30,000/QALY, with an ICER of £[redacted] and a positive incremental net health benefit of [redacted]. Teclistamab had a [redacted]% probability of being cost-effective at a WTP threshold of £30,000/QALY. These results include the application of the 1.7x severity modifier with a proportional QALY shortfall of [redacted]%, highlighting the severe unmet need faced by the Pom-exposed patient population (see Comment 4).

Conclusions

Following the draft positive recommendation for teclistamab and the additional evidence presented in this DGD response, the clinical and cost-effectiveness of teclistamab within its full marketing authorisation i.e., in RRMM after at least 3 prior therapies including an immunomodulatory agent (IMiD), proteasome inhibitor (PI) and anti-CD38 monoclonal antibody

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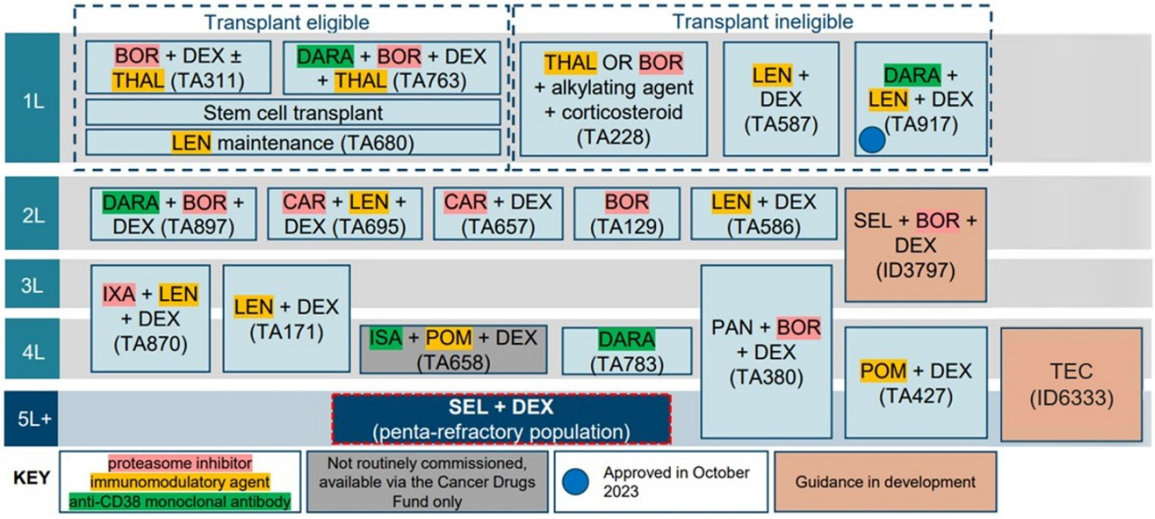
	(mAb), has been demonstrated versus PanoBorDex, the most relevant comparator in this setting, as well as SelDex, following its recent recommendation in TA970.[6] It is critical that this additional evidence is interpreted alongside the extremely high unmet need faced by Pom-exposed patients with 4L+ RRMM. Furthermore, the number of Pom-exposed patients is expected to diminish over time, as described previously, and therefore the reimbursement of teclistamab in this population represents a low risk to decision-making. Accordingly, J&J IM considers there is no clear rationale for the recommendation for teclistamab to be restricted to patients who would otherwise receive pomalidomide. Currently, this restriction is denying patients who face a substantial, severe unmet need (demonstrated via teclistamab qualifying for a 1.7 x severity modifier in this population) the opportunity to receive an effective treatment option at the end of their terminal illness. J&J IM consider that teclistamab should therefore be recommended in line with its full marketing authorisation, as illustrated in Figure 1, which would allow all patients with 4L+ TCE RRMM to be able to benefit from teclistamab, regardless of prior exposure to pomalidomide. **Figure 1: Summary of the anticipated UK RRMM treatment pathway**  Figure adapted from NICE TA970. **Abbreviations:** BOR: bortezomib; CAR: carfilzomib; DAR: daratumumab; DEX: dexamethasone; ISA: isatuximab; IXA: ixazomib; LEN: lenalidomide; PAN: panobinostat; POM: pomalidomide; SEL: selinexor: TEC: teclistamab; THAL: thalidomide.
Comment 1	**UK clinical experts indicated that PanoBorDex represents the most appropriate comparator to teclistamab for pom-exposed 4L+ RRMM patients. SelDex could also represent a comparator treatment for patients who are penta-refractory.** • As previously detailed in the executive summary to this response, the UK RW TCE cohort study was used to determine the most appropriate comparator to teclistamab for Pom-exposed patients. Of the N=645 patients with an ECOG PS of 0-1 who received PomDex, only 27.9% (n=180) of patients went on to receive a subsequent treatment. Of these, the majority of patients (N=112; 62.2%) received subsequent treatment with PanoBorDex. J&J sought additional clinical validation from UK clinical experts in MM, who confirmed that in this setting, PanoBorDex would represent the most commonly used treatment-option for Pom-exposed patients. The outcomes for patients receiving PanoBorDex are extremely poor, with a median OS of 6.31 months (95% CI: 4.63, 7.92) and median TTNT of 4.83 months (95% CI: 3.55, 6.87), highlighting that, in the absence of teclistamab, there is a critical unmet need for more effective treatment options.

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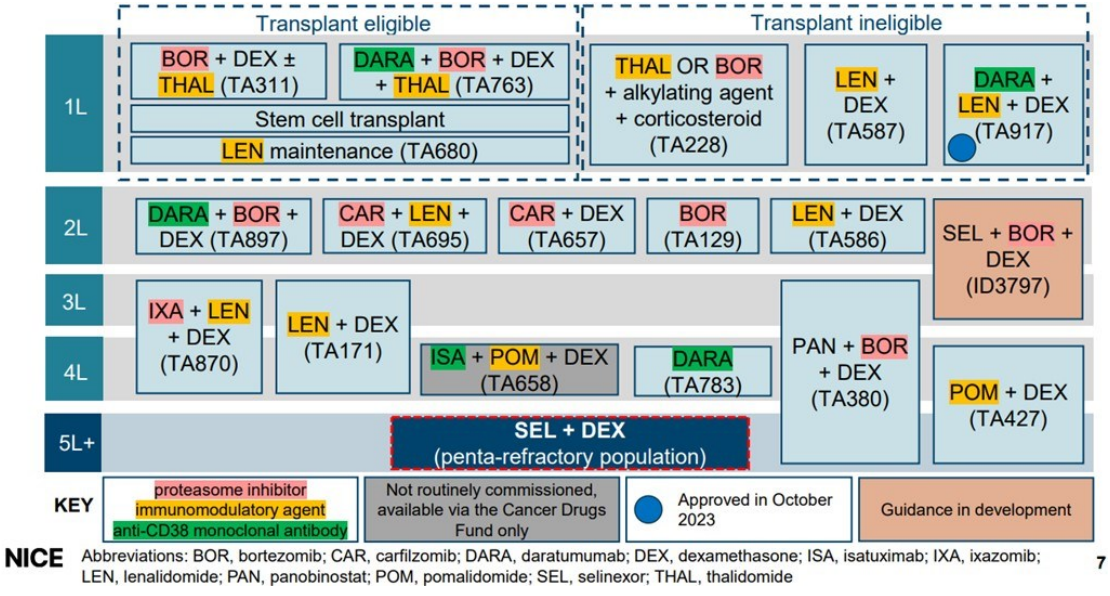
	• UK clinical experts also acknowledged the availability of SelDex. This treatment was only recently recommended by NICE in May 2024 for patients with penta-refractory MM, after at least four prior therapies (TA970)[6], and as such, was not previously listed in the scope for the teclistamab appraisal. The experts noted that a few patients may receive SelDex, however that only a limited subset of patients would fulfil the criteria of being penta-refractory, due to the need for patients to have received two distinct proteasome inhibitors based on the current treatment algorithm for RRMM.[13, 14] Clinical experts did not consider any other active treatments to represent relevant comparators in this setting. • Finally, UK clinical experts confirmed that best supportive care (BSC) does not represent a relevant comparator to teclistamab for Pom-exposed patients. Clinicians highlighted that patients receiving BSC would be treated with palliative intent. The idea of palliation is to provide a patient with a symptom-controlled death, making them as comfortable as possible at the end of their journey with their disease, which is different to an active treatment where the intention is to provide the patient with a period of progression-free survival. Patients treated with palliative care would not be eligible for active treatment with either teclistamab, or PanoBorDex or SelDex, meaning BSC is not a relevant comparator for this patient population. This clinical feedback is aligned with the RRMM treatment pathway presented as part of the recent NICE appraisal committee meeting for SelDex (TA970) (Figure 2), which demonstrates that other that PomDex, PanoBorDex and SelDex represent the only two treatments recommended by NICE for patients with 5L+ RRMM. **Figure 2: Summary of the UK RRMM treatment pathway presented as part of the NICE appraisal committee meeting for SelDex (TA970)**  In summary, PanoBorDex is considered to represent the primary comparator to teclistamab in patients who would not be able to receive treatment with PomDex. SelDex is considered a supplementary comparator for a small subset of patients, for completeness.
Comment 2	**Subgroup analyses of MajesTEC-1 trial data demonstrate that there is no evidence that pomalidomide-exposed patients have substantially different outcomes to the ITT population**

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In the original Company submission, the efficacy of teclistamab was informed by results from the MajesTEC-1 trial (August 2023 data cut off [DCO]), reported for the ITT population. When considering prior treatments received by patients, the trial population is comprised of two distinct subgroups: the 'Pomalidomide-Naïve' (Pom-Naïve) population and the 'Pomalidomide-Exposed' (Pom-Exposed) population. Considering the treated analysis set (N=165 patients), 139 (84.2%) patients had received prior pomalidomide and 26 (15.8%) patients had received no prior pomalidomide. As shown by Figure 3, receipt of prior pomalidomide was generally indicative of a higher number of lines of therapy being received by patients.

Figure 3: Distribution of lines of therapy received by the 'Pomalidomide-Naïve' and 'Pomalidomide-Exposed' populations

Footnote: Purple bars indicate the pomalidomide-exposed population, while red bars indicate the pomalidomide-naïve population. **Abbreviations:** PRLINES: prior lines of therapy; PRIOR_POMA: prior pomalidomide.

The following post-hoc subgroup analyses were conducted by J&J IM to explore the impact of prior exposure to pomalidomide on efficacy outcomes in patients treaFIted with teclistamab in the MajesTEC-1 trial. Efficacy outcomes explored were progression free survival (PFS), overall survival (OS) and time to next treatment (TTNT).

Results

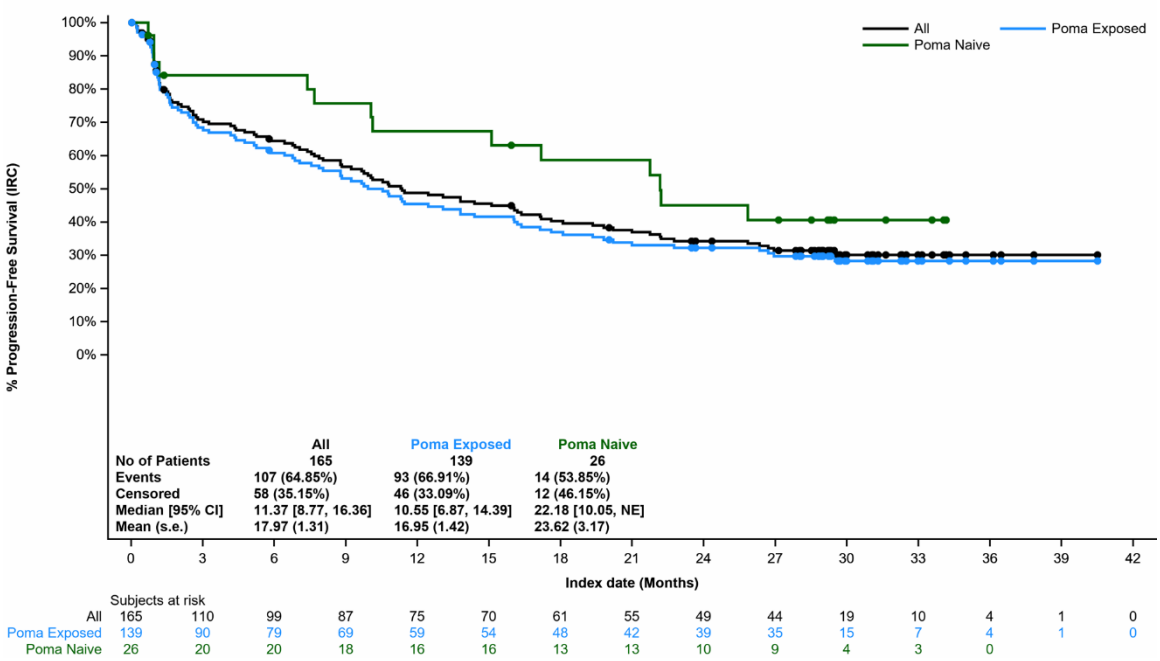
KM curves for PFS, OS and TTNT for the 'Pomalidomide-Naïve', 'Pomalidomide-Exposed' and the ITT population of the MajesTEC-1 trial are provided in Figure 4, Figure 5 and Figure 6, respectively. In general, outcomes are numerically better in the 'Pomalidomide-Naïve' than the 'Pomalidomide-Exposed' populations, although confidence intervals overlap in each case.

PFS

As shown in Figure 4, PFS was nominally higher in the 'Pom-Naïve' subgroup (median PFS: 22.18 months [95% CI: 10.05, not estimable [NE]]) when compared to the 'Pom-Exposed'

subgroup (median PFS: 10.55 [95% CI: 6.87, 14.39]). This effect is likely attributable in part to the increased number of prior therapy lines in the 'Pom-Exposed' subgroup, which was a more heavily pre-treated population. PFS KM curves for the 'Pom-Exposed' subgroup and ITT population are highly consistent, with the ITT population achieving a median PFS of 11.37 months (95% CI: 8.77, 16.36). This is likely owing to the fact that the majority of patients in the ITT population had received prior treatment with pomalidomide (139/165 [84.2%]).

Figure 4: Subgroup analysis for PFS (August 2023 DCO)



Abbreviations: CI: confidence interval; DCO: data cut off; IRC: independent review committee; PFS: progression free survival.

OS and TTNT

As shown by Figure 5, trends in OS and TTNT were highly aligned to those observed in the subgroup analysis for PFS:

- OS was nominally higher in the 'Pom-Naïve' subgroup, with median OS not reached (95% CI: 18.27, NE) at the August 2023 DCO, versus in the 'Pom-Exposed' subgroup which achieved a median OS of 18.10 months (95% CI: 12.22, 29.11). OS for the ITT population was similar to the 'Pom-Exposed' subgroup with a median OS of 22.21 months (95% CI: 15.08, 29.86).
- TTNT for the 'Pom-Exposed' subgroup (median TTNT: 11.30 months [95% CI: 7.85, 14.98]) and the ITT population (median TTNT: 12.58 months [95% CI: 8.71, 17.38]) were closely aligned. TTNT for the 'Pom-Naïve' subgroup (Figure 6) was extended versus the ITT and Pom-Exposed subgroup, with a median TTNT of 24.21 months (95% CI: 10.38, NE).

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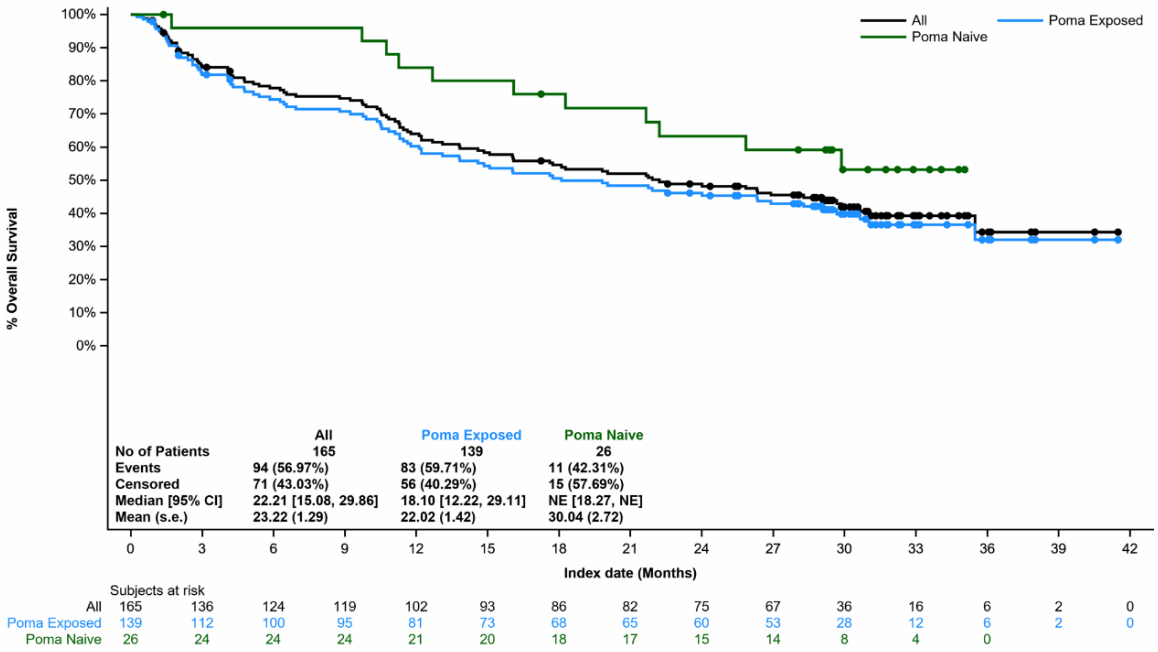
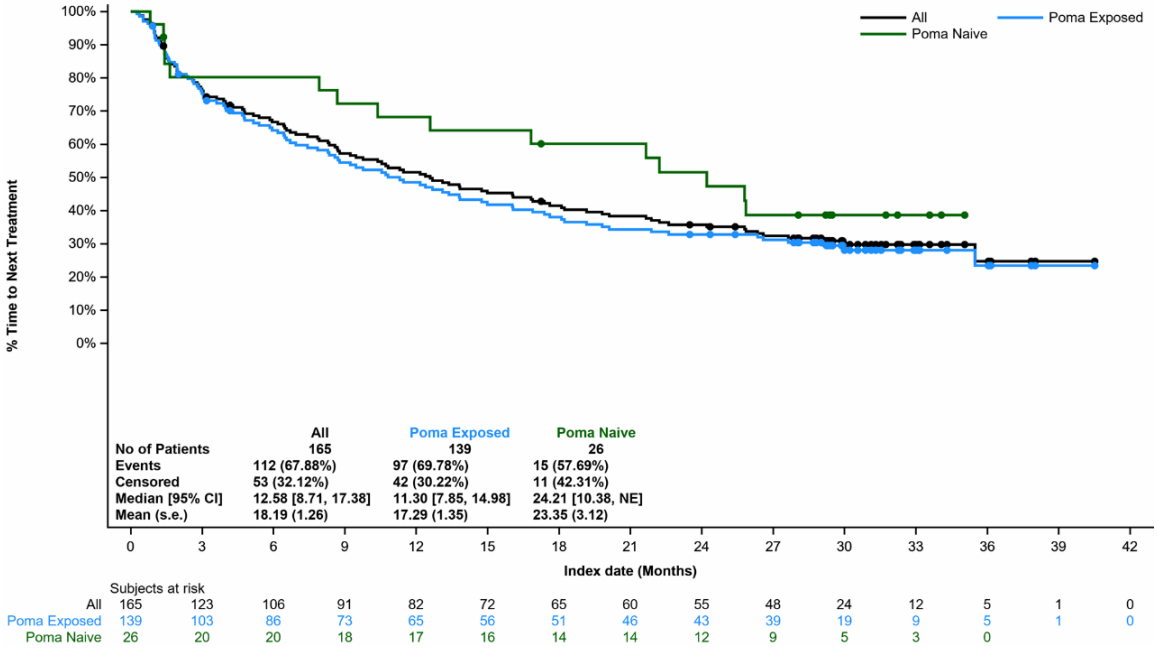
Figure 5: Subgroup analysis for OS (August 2023 DCO)



Abbreviations: CI: confidence interval; DCO: data cut off; PFS: progression free survival.

Figure 6: Subgroup analysis for TTNT (August 2023 DCO)



Abbreviations: CI: confidence interval; DCO: data cut off; TTNT: time to next treatment.

Overall, the results of the subgroup analyses demonstrate that efficacy outcomes (PFS, OS, TTNT) for patients receiving teclistamab in the MajesTEC-1 trial were highly consistent between the 'Pom-Exposed' and the ITT populations.

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Comment 3	Indirect evidence demonstrates that teclistamab produces statistically significant and clinically meaningful improvements in TTNT (proxy for PFS) and OS versus PanoBorDex, in Pom-exposed patients with TCE RRMM. Cost-effectiveness results demonstrate that teclistamab is a cost-effective use of NHS resources in UK clinical practice versus PanoBorDex, in this patient population. ***Assessment of clinical effectiveness*** The clinical systematic literature review (SLR) presented in Section B.2.1 of the Company submission did not identify any studies investigating PanoBorDex as a treatment specifically in patients with triple-class exposed RRMM. The clinical SLR did identify the PANORAMA-1 trial (NCT01023308), the key evidence based used to inform NICE's decision making for PanoBorDex for patients with MM following at least 2 prior therapies (TA380).[15, 16] However, this trial recruited patients who had received between just 1 and 3 prior lines of therapy, meaning that no patient enrolled had received PanoBorDex after 4 prior lines of therapy. Furthermore, patients were not required to be specifically TCE, and were unlikely to have been exposed to PomDex; pomalidomide therapy was approved by the Food and Drug Administration (FDA) in 2013 while the PANORAMA-1 trial ran from 2009–2015.[17, 18] As such, the PANORAMA-1 trial was not considered appropriate to inform the clinical effectiveness of PanoBorDex in the pom-exposed TCE RRMM population. Instead, the UK RW TCE cohort study, which was also used to inform the ITC for teclistamab versus PomDex presented in the Company submission (Section B.2.9), was considered to be the best source of evidence of PanoBorDex in the Pom-exposed patient population of relevance to this evaluation. In brief, the UK RW TCE cohort study is a registry study using NHS England's (NHSE's) cancer and linked datasets available through the NCRAS database. Further information on the UK RW TCE cohort study is provided in Section B.2.9 of the Company submission. The UK RW TCE cohort study analysed the survival outcomes of TCE RRMM patients treated within NHS and as such, this study was considered the most appropriate data source to inform the efficacy evidence for PanoBorDex in the ITC. Specifically, efficacy estimates for PanoBorDex were informed by a sub-population of the UK RW TCE cohort who had received PanoBorDex subsequent to treatment with PomDex at the index line (i.e., pom-exposed patients, n=112). To align with the inclusion criteria of the MajesTEC-1 trial, only patients who also had an Eastern Cooperative Oncology Group (ECOG) score between 0–1 were considered for the comparative assessment (n=83). To best address the present decision problem and to better align with the patients selected for comparison in the UK RW TCE cohort, only the Pom-exposed population in the MajesTEC-1 trial was used for comparative evaluation of the clinical and cost-effectiveness of teclistamab in the Pom-exposed TCE RRMM population. ***MAIC methodology*** As noted above, clinical efficacy inputs for teclistamab in the ITC were informed by data from the Pom-exposed subpopulation from the latest (August 2023) DCO of the MajesTEC-1 trial (N=139). Clinical efficacy inputs for PanoBorDex were informed by data from the latest (March 2023) DCO of the UK RW TCE cohort study in a sub-population of patients received PanoBorDex subsequent to treatment with pomalidomide at the index line (i.e., Pom-exposed) and who also had an ECOG score 0–1 (n=83). Due to time constraints, anonymised individual patient level data (IPD) could not be released during the time of the consultation period and therefore, only aggregate data were available from the PanoBorDex cohort of the UK RW TCE cohort study. In absence of IPD and with MajesTEC-1 being a single-arm trial, an unanchored MAIC was conducted to evaluate the clinical effectiveness of teclistamab vs PanoBorDex in pom-exposed TCE RRMM patients. Outcomes assessed in the unanchored MAIC were OS and TTNT (used as a proxy for PFS, in the absence of sufficient data in the UK RW TCE cohort study for defining disease progression).[19]

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For the MAIC, IPD from the Pom-exposed sub-population in the MajesTEC-1 trial were used to reweight each patient to adjust for imbalances in the identified baseline characteristics that had prognostic significance. A logistic propensity score model was used for reweighting, with regression parameters estimated by the method-of moments approach. The purpose of reweighting was to ensure that the means (or alternatively, proportions) and standard deviations of covariates from the relevant population in MajesTEC-1 were more closely aligned to those of the PanoBorDex-treated, Pom-exposed sub-population of the UK RW TCE cohort study.

Covariates matched during the MAIC were identified through a combination of literature review searches and input from clinical experts. The covariates were then ranked in order of importance. The greatest number of covariates possible were balanced, whilst maintaining a sufficiently large effective sample size of the MajesTEC-1 patient population. It should be noted that the covariates adjusted in each ITC (versus PomDex, PanoBorDex and SelDex) were also dependent on the level of reporting on the covariate for each relevant population in the UK RW TCE cohort study (for PanoBorDex) or the STORM trial (for SelDex, described below in Comment 4), leading to slight differences in the total number of covariates adjusted for in each analysis. Further details on the identification and selection of prognostic factors for adjustment are provided in Appendix B.

In the base case analysis, 6 covariates were adjusted for, including 3 priority variables; refractory status, presence of extramedullary disease, and number of prior LOTs in addition to years since MM diagnosis, age and ECOG status. Similar to the ITC for teclistamab versus PomDex presented in the Company submission, the two remaining priority variables; cytogenic profile and R-ISS stage were not adjusted for in the base case analysis as they were not reported for the population of interest in the UK RW TCE cohort study, (the Pom-exposed, PanoBorDex-treated patient population). Baseline characteristics of the MajesTEC-1 patient population before and after matching are presented in Appendix B; results indicate that the populations were well-matched following adjustment.

A sensitivity analysis (SA1) in which all available prognostic factors reported in the population of interest in the UK RW TCE cohort study were adjusted for was also conducted. This sensitivity analysis adjusted for the same covariates included in the base case MAIC as well as three additional non-priority covariates; prior autologous HCT, race and sex. Given that the sensitivity analyses resulted in a low ESS for the teclistamab treatment arm, and that the three additional covariates adjusted for were not considered as high priority versus the covariates already adjusted for in the base case analysis (see Appendix B; Table 2) the results of this sensitivity analysis were not considered appropriate for informing the cost-effectiveness analysis. The results of this sensitivity analysis are however provided in Table 1 below, for completeness.

MAIC results

KM curves presenting results of the base-case MAICs for teclistamab versus PanoBorDex for TTNT (as proxy for PFS) and OS are presented in Figure 7 and Figure 8, respectively.[19]

The base case analysis demonstrates that teclistamab is associated with a statistically significant 54% reduction in the risk of progression (adjusted HR: 0.46; 95% CI: 0.26, 0.84; p-value: 0.0106) versus PanoBorDex, and a statistically significant 59% reduction in the risk of death (adjusted HR: 0.41; 95% CI: 0.22, 0.74; p-value: 0.0030) versus PanoBorDex. These results correspond to an adjusted median PFS and OS for teclistamab of 10.7 and 20.6 months, respectively, versus 4.8 and 6.3 months for PanoBorDex.

The results of SA1 were consistent with the base case analysis, providing confidence that the base-case results are robust to the number of covariates adjusted for. It is, however, acknowledged that the sensitivity analyses may be less reliable owing to the reduced ESS associated with the teclistamab arm (Table 1).

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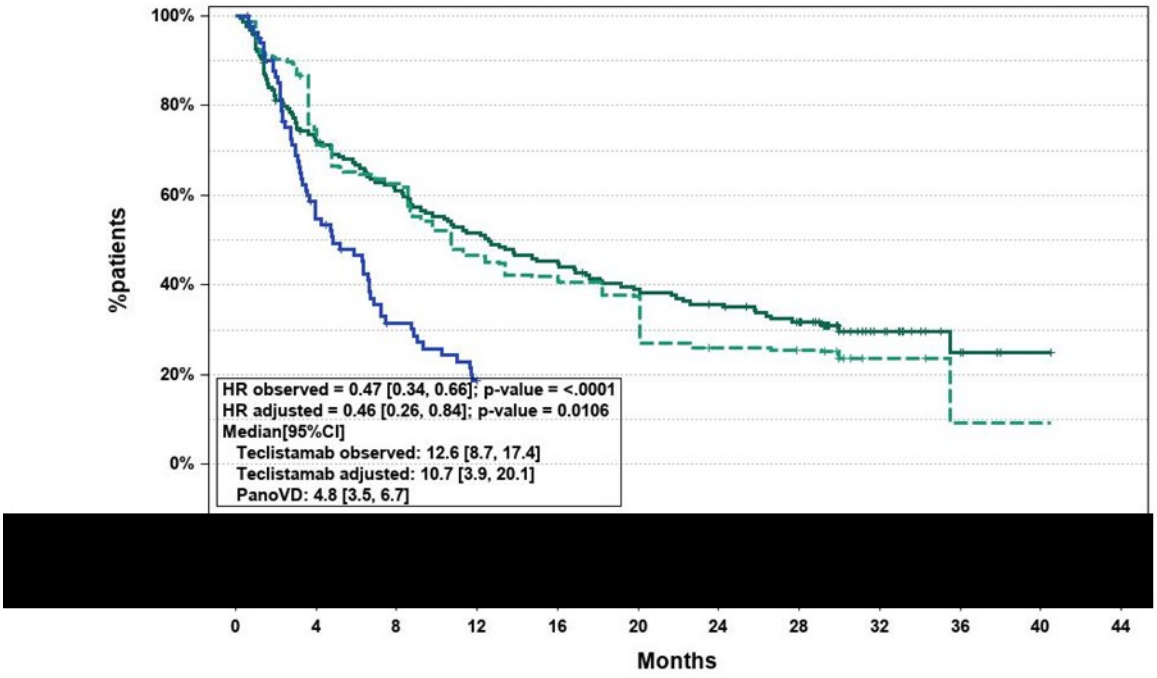
Table 1: Summary of the MAIC results between teclistamab versus PanoBorDex

ITC Results for Teclistamab versus PanoBorDex	PFS (using TTNT as a proxy)		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted[a] (N=139)	0.51 (0.36, 0.72)	0.0001	0.46 (0.32, 0.66)	<0.0001
Base case (ESS=[redacted])	0.46 (0.26, 0.84)	0.0106	0.41 (0.22, 0.74)	0.0030
SA 1 (ESS=[redacted])	0.44 (0.23, 0.81	0.0095	0.41 (0.21, 0.79)	0.0082

Footnote: a Unadjusted comparison between the Pom-exposed patient population in MajesTEC-1 and the PanoBorDex population of the UK RW TCE cohort study.
Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; ITC: indirect treatment comparison; MAIC: matching adjusted indirect comparison; OS: overall survival; PanoBorDex: Panobinostat, bortezomib and dexamethasone; PFS: progression-free survival; SA: sensitivity analysis; TTNT: time to next treatment.

Figure 7: PFS KM curve (based on TTNT as a proxy) for teclistamab versus PanoBorDex (base case ITC)



Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; PFS: progression free survival.

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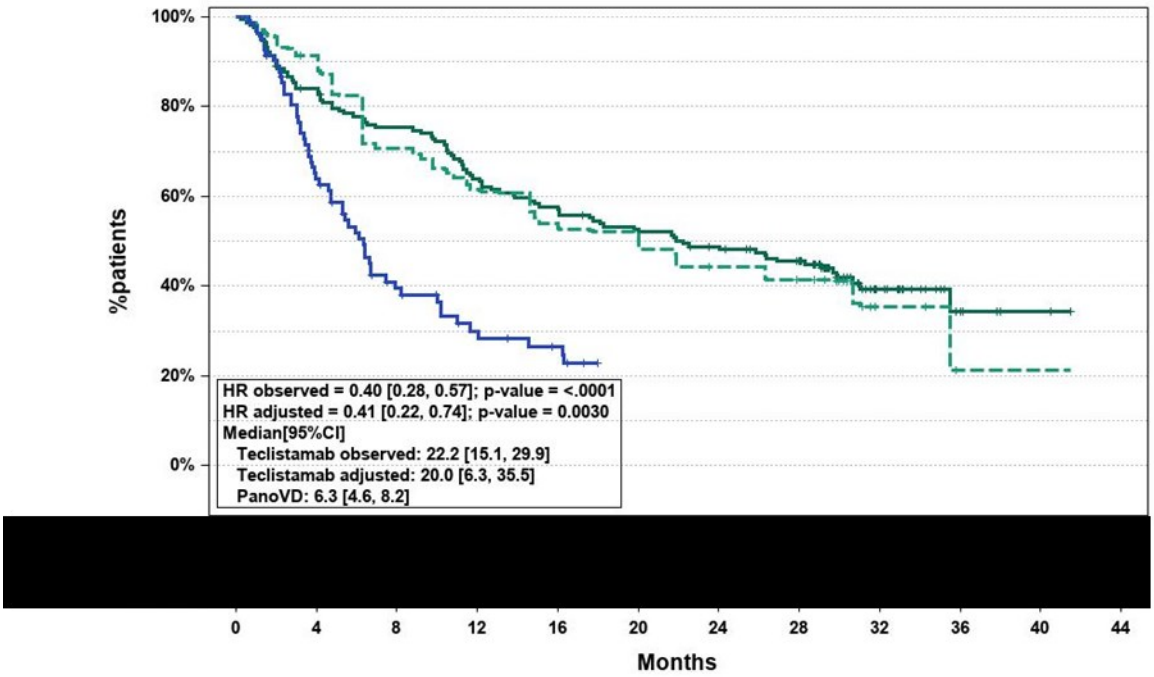
Figure 8: OS KM curve for teclistamab versus PanoBorDex (base case ITC)



Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival.

Assessment of cost-effectiveness

Based on the results of the ITC, a cost-effectiveness analysis for teclistamab versus PanoBorDex was conducted.

The clinical efficacy of teclistamab and PanoBorDex was based on extrapolation of the MAIC-weighted OS and TTNT KM data from MajesTEC-1, and the OS and TTNT KM data for PanoBorDex from the UK RW TCE cohort study, as detailed above. Utility values for teclistamab were aligned with the Committee's preferred base case. In the absence of available utility data from the UK RW TCE cohort study, utility values for PanoBorDex were informed by the accepted utility values for SelDex in TA790, as these were deemed to represent the best proxy for patients with 5L+ RRMM. As PanoBorDex is associated with toxicity concerns which are likely to impact on patient HRQoL (see Appendix C.5), this is likely to be a conservative assumption. Therefore, AE disutilities were also considered.

Full details of the cost-effectiveness analysis, including all relevant model inputs, are provided in Appendix C.

The results showed that treatment with teclistamab is associated with a cost-effective ICER of £[redacted] and a positive NHB of [redacted] (at PAS price) at a willingness-to-pay threshold of £30,000/QALY. Full results of the cost-effectiveness analysis are presented in Appendix D.

These results demonstrate that teclistamab represents a cost-effective use of NHS resources for Pom-exposed patients versus PanoBorDex. It should be noted that these results include the application of the 1.7x severity modifier, with a high proportional QALY shortfall of [redacted]%. The highest 1.7x severity modifier was met in [redacted]% of simulations, underlining the severe unmet need in this patient population which can be addressed by the recommendation of teclistamab within its full licensed indication.

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	The substantial difference in survival outcomes between teclistamab (median OS 20.0 months) and PanoBorDex (median OS 6.3 months) indicates that teclistamab would have been a strong candidate for End of Life criteria under older NICE methods. Whilst we acknowledge that these methods no longer apply, we consider this to be illustrative of the relevance of the 1.7 severity modifier and the high unmet need amongst this patient population. Therefore, we would deem it appropriate for NICE to use the flexibilities available to them when interpreting this evidence.
Comment 4	**Additional indirect evidence demonstrates that teclistamab is associated with improved efficacy versus SelDex for patients with 4L+ RRMM who would not be eligible to receive PomDex**. **Furthermore, economic results demonstrate that teclistamab represents a cost-effective use of NHS resources in UK clinical practice versus SelDex, in this patient population.** ***Assessment of clinical effectiveness*** It should be noted that SelDex was not listed in the NICE final scope for this appraisal.[11] However, J&J IM acknowledge that disease management of MM is a rapidly-evolving space, with SelDex recently recommended by NICE in the RRMM setting after 4 or more prior therapies (TA970).[6] Therefore, for completeness, additional comparative (clinical and economic) evidence for teclistamab versus SelDex is provided to further inform NICE's decision making on the restricted recommendation for teclistamab. As detailed in Section B.2.1 of the Company submission, the clinical SLR identified the pivotal STORM trial for SelDex the clinical evidence of which was used to inform the positive recommendation for SelDex (TA970).[6] This trial included patients with penta-refractory RRMM, meaning that patients must be refractory to two proteosome inhibitors (PIs), two immunomodulatory imide drugs (IMiDs) and an anti-CD38 monoclonal antibody (mAb). In order to fulfil the two prior IMiDs criteria, patients in this trial are almost guaranteed to have received prior pomalidomide. Indeed, the Chari *et al.* 2019 publication reporting results from the STORM trial indicated that 117/122 (96%) of the intention-to-treat (ITT) trial population l had received prior carfilzomib, pomalidomide and daratumumab.[12] As such, the STORM trial was selected to inform efficacy estimates for SelDex in the MAIC versus teclistamab. While the STORM trial highly likely included patients who received prior pomalidomide, it should be noted that results from the STORM trial were not reported specifically for a Pom-exposed subpopulation. However, due to the penta-refractory nature of all patients in the STORM trial, results are likely highly representative of a Pom-exposed patient population. As noted below, additional exclusion criteria were applied to the MajesTEC-1 trial to better align baseline characteristics of the patient population in this trial to the population in the STORM trial, but this could not be performed for receipt of prior pomalidomide given the data were not available from aggregate data from the STORM trial. ***MAIC methodology*** Data from the ITT population in the latest (August 2023) DCO of the MajesTEC-1 trial was used to inform the clinical efficacy of teclistamab in the indirect evidence. Individual patient level data (IPD) were available from the MajesTEC-1 trial, however only aggregate data were available from the STORM trial. As such, to adjust for any discrepancies in baseline characteristics between trial populations which may potentially influence results, a MAIC was conducted. As both the MajesTEC-1 and STORM trials were single-arm trials, no common comparator arm was available to facilitate an anchored comparison, and as such, an unanchored MAIC was conducted.[19] Prior to MAIC adjustment, additional eligibility criteria were applied to patients in the MajesTEC-1 trial to ensure closer alignment with the patient population in the STORM trial. This included

	excluding patients who were not TCE as well as those who were not penta-exposed. Patients who were refractory to daratumumab or to their last line of therapy were also excluded (Appendix E). For the MAIC, IPD from the ITT population in the MajesTEC-1 trial were reweighted so that its summary statistics more closely aligned to those of the ITT population of the SelDex trial. Covariates used during the matching process were identified through literature review and clinical expert input and were ranked in order of importance, considering the prognostic strength of the factors and the degree of imbalance between the populations. The greatest number of covariates possible were balanced, whilst maintaining a sufficiently large effective sample size of the MajesTEC-1 patient population. The approach for the identification and selection of prognostic factors is generally aligned with the approach taken for the ITC for teclistamab versus PanoBorDex, above, with further details provided in Appendix B. Covariates adjusted for in the base case were: refractory status, cytogenetic profile, international staging system/revised international staging system (ISS/R-ISS) stage, presence of extramedullary disease and the number of prior lines of therapy received. Further information on the matching process as well as a summary of MajesTEC-1 baseline characteristics pre- and post-matching, is provided in Appendix E; results indicated that populations were well-matched after adjustment. In line with the MAICs presented above versus PanoBorDex, key outcomes investigated were PFS and OS with results presented below. For completeness, duration of response (DOR), objective response rate (ORR) and proportion of patients achieving a complete response (CR) were also investigated and results are provided in Appendix E. ***Results*** KM curves presenting results of the MAICs for teclistamab versus SelDex for PFS and OS are presented in Figure 9 and Figure 10 respectively.[19] The MAIC results indicate that treatment with teclistamab is associated with a 39% reduction in the risk of progression (adjusted HR: 0.61; 95% CI: 0.33, 1.13; p-value: 0.1164) versus SelDex, and a statistically significant 45% reduction in the risk of death (adjusted HR: 0.55; 95% CI: 0.33, 0.93; p-value: 0.0265) versus SelDex. These results correspond to a median PFS and OS for teclistamab of 9.7 and 18.1 months, respectively, versus 3.7 months and 8.6 months for SelDex. Overall, the MAIC results strongly support statistically significant improved efficacy of teclistamab versus SelDex in a predominantly Pom-exposed RRMM patient population in terms of delaying disease progression and ultimately death.

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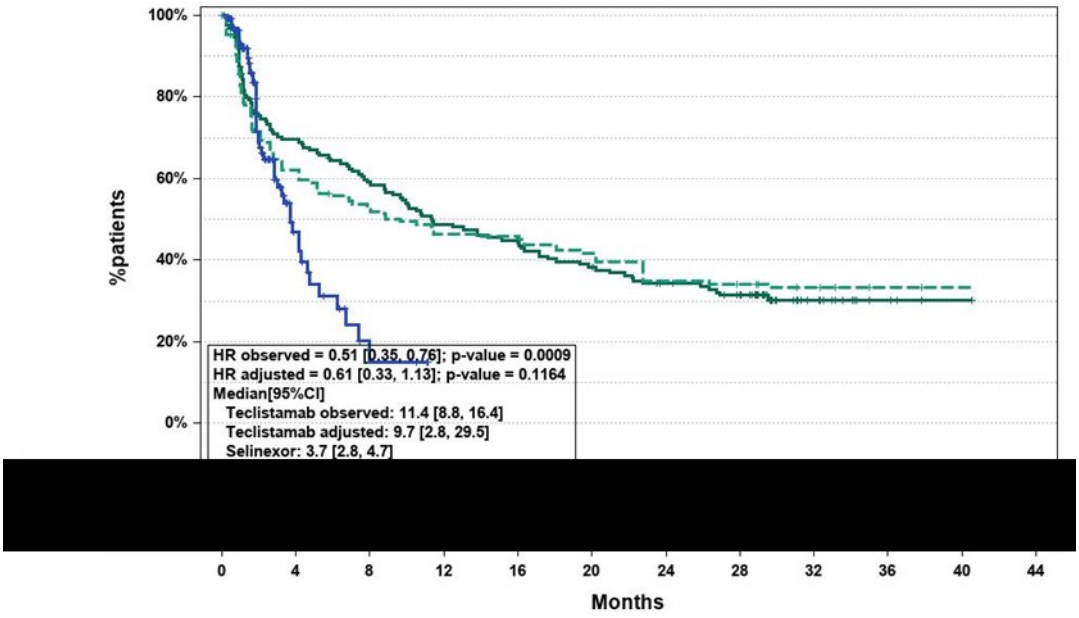
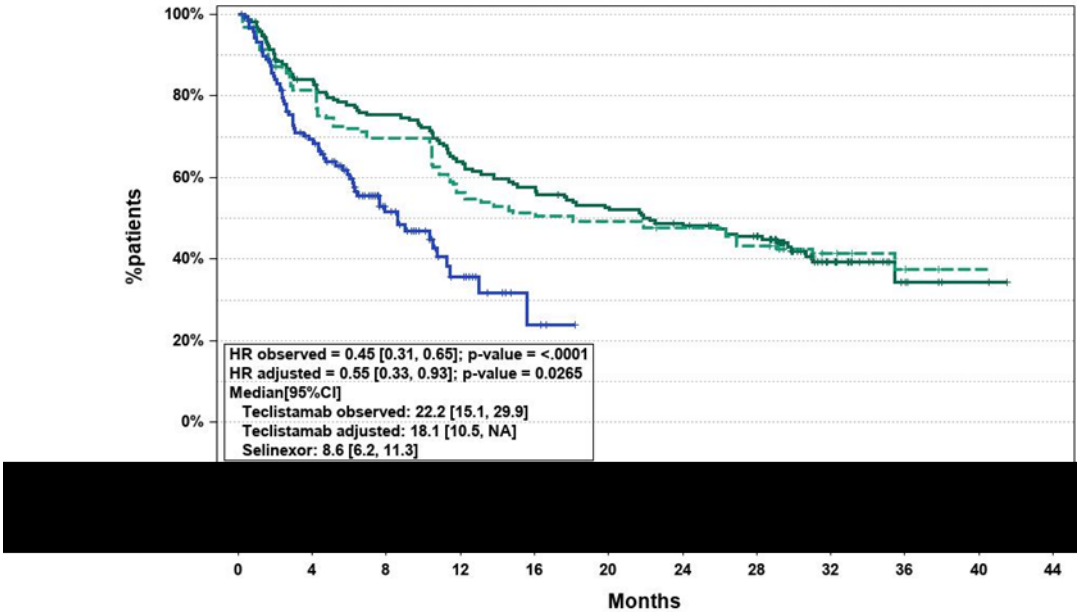
Figure 9: PFS KM curve for teclistamab versus SelDex



Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; PFS: progression free survival.
Source: J&J IM Data on File. MajesTEC-1 RRMM MAIC versus SelDex ITC Report. 2024.

Figure 10: OS KM curve for teclistamab versus SelDex



Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival.
Source: J&J IM Data on File. MajesTEC-1 RRMM MAIC versus SelDex ITC Report. 2024.

Assessment of cost-effectiveness

The cost-effectiveness analysis for teclistamab versus SelDex indicated that treatment with teclistamab is associated with a positive incremental NHB of [redacted] (at PAS price) at a willingness-to-pay threshold of £30,000/QALY. Results of the cost-effectiveness analysis are presented in

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	Appendix G, with supplementary information on the modelling inputs and approaches used provided in Appendix **F**. These results demonstrate that teclistamab represents a cost-effective use of NHS resources versus SelDex. Of note, teclistamab had a [redacted]% probability of being cost-effective at a WTP threshold of £30,000/QALY. These results include the application of a 1.7x severity modifier, with a proportional QALY shortfall of [redacted]%, which highlights the exceptionally high unmet need in this patient population which can be addressed by the recommendation of teclistamab within its full licensed indication. It is worth noting the substantial difference in survival outcomes between teclistamab (median OS 18.1 months) and SelDex (median OS 8.6 months) indicates that teclistamab would have been again a strong candidate for End of Life criteria under older NICE methods. Whilst we acknowledge that these methods no longer apply, we consider this to be illustrative of the relevance of the 1.7 severity modifier and the high unmet need amongst this patient population. Therefore, we would deem it appropriate for NICE to use the flexibilities available to them when interpreting this evidence

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Appendix A: Committee-preferred assumptions applied in the cost-effectiveness analysis

In recognition of the evaluation committee's preferred assumptions, the additional cost-effectiveness analyses submitted as part of this response document apply all of the Committee's preferred assumptions outlined in the DGD, where relevant, to the new comparisons versus PanoBorDex and SelDex.[3] These assumptions include:

- Modelling OS, PFS and TTD for teclistamab by the fixing selected curves to the midpoint of the range provided for the clinical expert's most likely values
- Using a log-normal distribution to extrapolate TTD for the teclistamab arm
- Using treatment-specific utility values
- Switching teclistamab from once weekly to once every other week starting at 52 weeks, then using the MajesTEC-1 data
- Basing the proportion of patients receiving IVIG on MajesTEC-1 data and duration set at 9 doses of IVIG
- Using a teclistamab drug wastage assumption of 28.8%, as estimated by NHS England
- Using the updated approach to inform teclistamab skipped doses without adjustment for monthly and bi-monthly regimens, to align with the SmPC for teclistamab

Full details of any new modelling inputs or approaches required to develop the economic analyses between teclistamab and PanoBorDex and teclistamab and SelDex are detailed in Appendix C and Appendix F, respectively. Cost-effectiveness results are detailed in Appendix D (teclistamab vs PanoBorDex) and Appendix G (teclistamab vs SelDex).

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Appendix B: Additional information for the ITC for teclistamab versus PanoBorDex[19]

MAIC methodology

Identification and rank ordering of prognostic factors

Imbalances in baseline patient characteristics between the UK RW TCE cohort (pom-exposed, PanoBorDex patients) and MajesTEC-1 (Pom-exposed patients) that are prognostic for the outcomes of interest can lead to biased comparative efficacy estimates if left unadjusted. The steps undertaken for identifying and rank-ordering prognostic factors requiring adjustment in the current analysis are outlined below.

1. Prior to conducting MAIC, a pool of potential prognostic variables was identified by consulting studies from a literature review of clinical outcomes in triple-class exposed RRMM patients, as well as input from clinical experts.

2. Clinical experts were consulted to provide input on the most important factors that should be adjusted for in the analyses. Analyses that adjusted for these 'priority variables' where available in the UK RW TCE cohort study) were considered the base case analyses for each outcome.

3. The remaining factors were judged to be of lesser importance and adjusted for as a sensitivity analysis. These factors were ranked in order of importance considering both prognostic strength and degree of imbalance between the study populations and refined based on clinical input. The prognostic strength of a factor was assessed by univariate regression using MajesTEC-1 data. Population differences between MajesTEC-1 and the UK RW TCE cohort (pomalidomide-exposed, PanoBorDex patients) were assessed using standardised mean differences (SMDs) (where an SMD between 0 and 0.1 was considered a small difference, an SMD >0.1 and ≤0.2 was a moderate difference, and an SMD of >0.2 was a substantial difference).

Unanchored MAIC method

Given the lack of a common comparator, an unanchored MAIC was conducted to estimate the relative treatment effect of teclistamab versus PanoBorDex by leveraging IPD from MajesTEC-1 and aggregate data from the UK RW TCE cohort study (pom-exposed, PanoBorDex patients).

The observed MajesTEC-1 population (n=165) was first restricted to match the eligibility criteria and distribution of prognostic factors in the UK RW TCE cohort study (pom-exposed, PanoBorDex patients). That is, patients from MajesTEC-1 were removed from the IPD set if they would not have satisfied the eligibility criteria used in the UK RW TCE cohort study (pom-exposed, PanoBorDex patients) related to the requirement to have previously received pomalidomide (n=139). The remaining patients were reweighted to adjust for imbalances in the identified baseline characteristics of prognostic significance. A logistic propensity score model was estimated that included the identified covariates, which is equivalent to the model on the log of the individual weights: $\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_i$, where $\boldsymbol{X}_i$ was the covariate vector for the i[th] individual; and where the regression parameters, $\boldsymbol{\alpha}_1$, were estimated by a method-of-moments. The weighting methodology guarantees a close balance of covariates between the MajesTEC-1 and the UK RW TCE cohort study (pom-exposed, PanoBorDex patients) populations. That is, after reweighting patients, the means (or proportions) and standard deviations of covariates from MajesTEC-1 were as closely matched to those in the UK RW TCE cohort study (pom-exposed, PanoBorDex patients).

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Estimating indirect treatment effects

Following matching of the MajesTEC-1 population to the UK RW TCE cohort (pom-exposed, PanoBorDex patients), the comparative efficacy of teclistamab versus PanoBorDex was determined for the OS and TTNT. Estimates of the comparative efficacy of teclistamab versus PanoBorDex were derived as the difference between (a) an estimate of the outcome of interest in a population similar to patients in the UK RW TCE cohort (pom-exposed, PanoBorDex patients) study, had they received teclistamab, and (b) the estimated outcome with based on summary-level data from the UK RW TCE cohort (pom-exposed, PanoBorDex patients) study.

Time to event endpoints: For TTNT and OS, pseudo-IPD representing the patients in the UK RW TCE cohort study (pom-exposed, PanoBorDex patients) were derived by digitizing Kaplan–Meier curves and applying the Guyot method. A dataset combining weighted IPD from MajesTEC-1 and pseudo-IPD simulated for the UK RW TCE cohort study (pom-exposed, PanoBorDex patients) (setting weights for pseudo-observations equal to 1), was then used to estimate hazard ratios (HRs) and their 95% CIs using a weighted Cox proportional hazards model. Robust standard errors were estimated using the sandwich estimator.

All analyses were conducted using SAS 9.4 based on the methods developed by Signorovitch et al, and as implemented by the NICE Evidence Synthesis Technical Support Document Series.

Effective sample size (ESS)

The effective sample size (ESS) was calculated to reflect the impact of weighting on the available information in the IPD: $ESS = (\sum w_i)^2/(\sum w_i^2)$, where w_i, $i = 1, \ldots N$, are the patient weights. A low ESS compared to the original sample size N indicates extreme patient weights due to large imbalances in patient populations prior to reweighting.

Adjustment of baseline characteristics

A summary of the prognostic factors available for adjustment in the PanoBorDex cohort of the UK RW TCE cohort study is provided in Table 2. As data for the PanoBorDex cohort were only available in the form of aggregate data as opposed to individual patient data, a small number of additional covariates were available for adjustment when compared to the previous IPTW ITC between teclistamab and PomDex – namely, race, sex and extramedullary disease.

As previously detailed in Comment 3 of the DGD response, in the base case MAIC, six variables were adjusted for – the five variables included as part of the IPTW ITC between teclistamab and PomDex (refractory status, number of prior LOTs, years since MM diagnosis, age and ECOG PS), as well as the presence of extramedullary disease, as this was an additional 'priority' covariable available for adjustment for the PanoBorDex population of the UK RW TCE cohort study compared to the original IPTW ITC versus PomDex. These six covariates therefore formed the base case, 6-variable MAIC between teclistamab and PanoBorDex. A sensitivity analysis (SA) MAIC was also explored, in which all available covariates in the UK RW TCE cohort study were adjusted for. The results of the sensitivity analysis are summarised in this appendix for completeness, but have not been used to inform the cost-effectiveness for teclistamab versus PanoBorDex given that the additional covariates adjusted for were not considered to be as relevant for adjustment when compared to the base case, and this analysis reduced the ESS of the teclistamab treatment arm further (Table 3).

Baseline characteristics for the MajesTEC-1 trial (Pom-exposed population) and the UK RW TCE cohort population (Pom-exposed, PanoBorDex-treated) before and after matching to prognostic variables in the base case 6-variable MAIC, and the SA MAIC, are provided in Table 3. As shown in Table 3, the MajesTEC-1 and UK RW TCE cohort populations were very well-matched following adjustment. The distribution of MAIC weights in the base case analysis is shown in Figure 11.

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Table 2: Prognostic factors identified and available for the MajesTEC-1 trial and UK RW TCE cohort study (patients receiving PanoBorDex)

Rank	Prognostic Factor	Available in MajesTEC-1?	Available in UK RW TCE cohort study? (Pom-exposed patients receiving PanoBorDex)
Priority	Refractory status	Yes	Yes
Priority	Cytogenetic profile	Yes	No
Priority	R-ISS stage	Yes	No
Priority	Presence of extramedullary disease	Yes	Yes
Priority	Number of prior lines of therapy	Yes	Yes
Non-priority: 6	Years since MM diagnosis	Yes	Yes
Non-priority: 7	Age (years)	Yes	Yes
Non-priority: 9	Prior autologous HCT	Yes	Yes
Non-priority: 8	ECOG status	Yes	Yes
Non-priority: 10	Race	Yes	Yes
Non-priority: 11	Sex	Yes	Yes
Non-priority: 12	Type of MM	Yes	No
Non-priority: 13	Creatinine clearance	Yes	No
Non-priority: 14	Percentage bone marrow plasma cells	Yes	No
Non-priority: 15	Time since discontinuation of last treatment	Yes	No

Abbreviations: ECOG: Eastern Cooperative Oncology Group; HCT: hematopoietic cell transplantation; LOTs: lines of therapy; MM: multiple myeloma; R-ISS, revised International Staging System

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Table 3: Baseline Characteristics between UK RW TCE cohort study (PanoBorDex) and MajesTEC-1, before and after adjustment

Category	Adjusted for in	Unadjusted Comparison			Base Case 6-variable MAIC	SA MAIC
		UK RW TCE cohort study (PanoBorDex) N=83	MajesTEC-1 (observed) N=165	MajesTEC-1 (Pom-exposed) N=139	MajesTEC-1 (Pom-exposed) N (ESS)=[redacted]	MajesTEC-1 (Pom-exposed) N (ESS)=[redacted]
Refractory status						
Non triple-refractory (%)	Base case, SA	41	22	19	41	41
Triple or quad refractory (%)		47	47	45	47	47
Penta-refractory (%)		12	30	36	12	12
Presence of extramedullary disease						
Yes (%)	Base case, SA	2	17	17	2	2
Number of prior lines of therapy						
4 (%)	Base case, SA	30	21	20	30	30
5 (%)		49	21	24	49	49
≥6 (%)		21	32	35	21	21
Years since MM diagnosis						
Median	Base case, SA	5.5	6	6.2	5.2	5.5
Age (years)						
Median	Base case, SA	71.5	64	64	71	72
<65 (%)		31	52	56	31	31
ECOG status						
0 (%)	Base case, SA	23	33	32	23	23
1 or 2 (%)		77	67	68	77	77

Abbreviations: ASCT: Autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IMiD, immunomodulatory drug; LOTs, lines of therapy; MM: multiple myeloma; RW: real-world; SA: sensitivity analysis; TCE: triple class exposed.

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Figure 11 Distribution of MAIC Weights for the base case analysis

Abbreviations: ESS: effective sample size ; MAIC: matching-adjusted indirect comparison.

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Appendix C: Clinical parameters and healthcare cost and resource use inputs informing the cost-effectiveness estimates for PanoBorDex

This appendix summarises the additional model inputs used in the cost-effectiveness analysis for teclistamab versus PanoBorDex. Wherever possible, the cost-effectiveness analysis is aligned with the Committee's preferred base case inputs and assumptions from the economic analysis between teclistamab and PomDex. Changes that have been made to the Company's base case since ACM1, to align with the Committee's preferred base case, are outlined in Appendix A.

A summary of new modelling inputs and approaches for the cost-effectiveness analysis for teclistamab versus PanoBorDex in a population of Pom-exposed patients are detailed in the sections below.

Modelling of PFS (using TTNT as a proxy), OS and TTD was informed by extrapolation of the MAIC-weighted data from MajesTEC-1 for teclistamab (matched to the PanoBorDex cohort of the UK RW TCE cohort study using the 6-variable MAIC detailed in Appendix B), and the UK RW TCE cohort study for PanoBorDex.

Wherever possible, the approach to extrapolation was consistent with the approaches used in the Committee's preferred base case. For teclistamab, the best statistically fitting curves were selected for each endpoint, and were similarly calibrated to align with the UK clinical expert estimates of survival at 10 and 15 years. For PanoBorDex, curves were selected based on consideration of statistical fit to the data from the UK RW TCE cohort study, as well as long-term plausibility, based on estimated estimates of survival for PanoBorDex provided by UK clinical experts as part of this response, as detailed in the sections below.

Other relevant modelling inputs for PanoBorDex were informed by the UK RW TCE cohort study where possible. Where required, and appropriate, other inputs were sourced from prior NICE appraisals relevant to this indication, including TA380 (for PanoBorDex) and TA970 (SelDex, as the most recent NICE appraisal modelling a 5L+ RRMM patient population).[6, 15]

Appendix C.1: Modelled baseline characteristics

Baseline characteristics used to inform the economic analysis between teclistamab and PanoBorDex were updated to align with the MAIC-weighted baseline characteristics in MajesTEC-1 from the 6-variable MAIC (Table 4).

Table 4: Summary of baseline characteristics used in the economic analysis between teclistamab and PanoBorDex

Characteristics	Pom-Exposed TCE RRMM Population	Source
Age (mean)	68.93	MajesTEC-1 (MAIC-weighted using the 6-variable approach to align with the Pom-exposed UK RW TCE cohort study population receiving PanoBorDex)
Proportion of female	49.3%	
Body weight (mean)	71.54 kg	
Body surface area (mean)	1.80 m²	

Abbreviations: MAIC: matching-adjusted indirect comparison; PanoBorDex: panobinostat, bortezomib and dexamethasone; TCE: triple-class exposed; UK: United Kingdom

Appendix C.2: Clinical efficacy - PFS

Teclistamab PFS

A summary of the statistical fit of each of the teclistamab PFS extrapolations (using TTNT as a proxy) is provided in Table 5. Similarly to the MajesTEC-1 data used in the original CS base case, the lognormal PFS extrapolation provided the best statistical fit to the MAIC-weighted data from MajesTEC-1. As such, in line with the Committee's preferred base case, the lognormal extrapolation for teclistamab PFS was calibrated to align with the UK clinical

expert estimates of survival for teclistamab at 10 and 15 years. A summary of these landmark estimates is provided in Table 6.

Figure 12: Teclistamab PFS (using TTNT as a proxy) extrapolations (MajesTEC-1, 6-variable MAIC-weighted data versus PanoBorDex in the UK RW TCE cohort study)

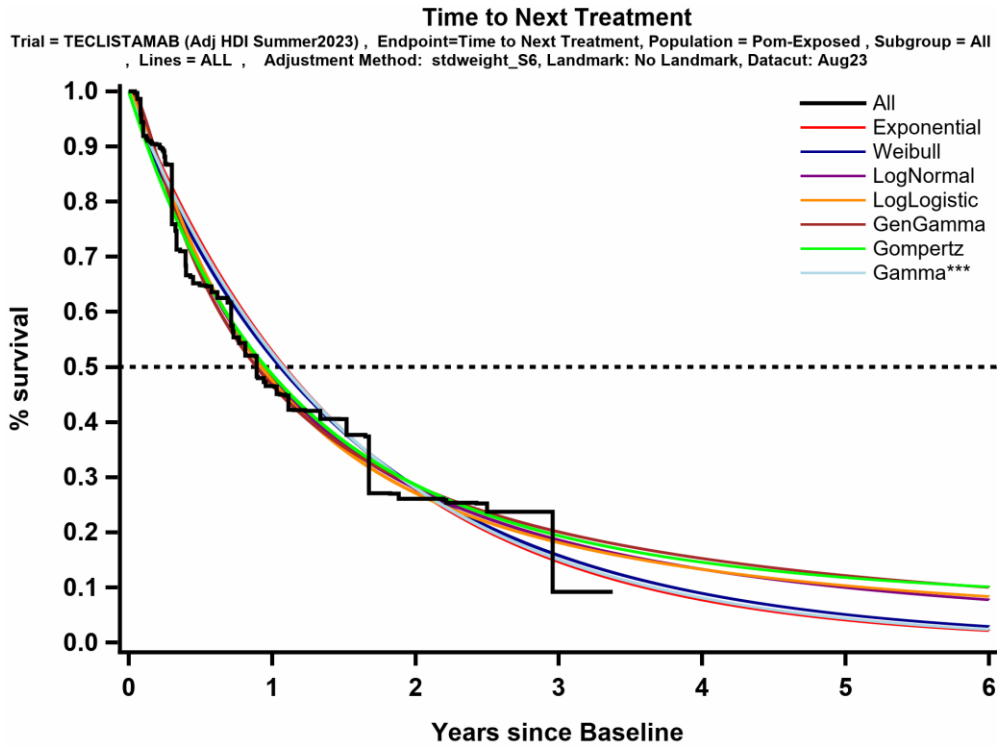

Table 5: Goodness-of-fit statistics for teclistamab PFS (using TTNT as a proxy) extrapolations (MajesTEC-1 6-variable MAIC versus PanoBorDex in the UK RW TCE cohort study)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	1558.1	1564.0	6	6
Exponential	1556.7	1559.7	5	4
Lognormal	1546.4	1552.3	1	1
Loglogistic	1549.7	1555.6	3	2
Gompertz	1554.0	1559.9	4	5
Gamma	1558.7	1564.5	7	7
Generalised gamma	1547.4	1556.3	2	3

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; PanoBorDex: Panobinostat, bortezomib and dexamethasone; PFS: progression-free survival; RW: real-world; TCE: triple-class exposed; TTNT: time to next treatment.

Table 6: Modelled landmark estimates of teclistamab PFS

Parametric curve	5-year PFS (%)	10-year PFS (%)	15-year PFS (%)
Clinical expert estimates			
Clinical expert estimates	7–20	2–8	0–2

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Landmark estimates of PFS for base case extrapolation			
Calibrated log-normal	10.04	5.02	1.01

Abbreviations: PFS: progression-free survival.

PanoBorDex PFS

A summary of the statistical fit of each of the PanoBorDex PFS extrapolations (using TTNT as a proxy) is provided in Table 7. The lognormal provided the best statistical fit to the UK RW TCE cohort study data, followed by the Generalised gamma.

A summary of the landmark estimates of PanoBorDex PFS at 5, 10 and 15 years compared to UK clinical expert estimates of expected survival with PanoBorDex is provided in Table 8. These show that the lognormal extrapolation is generally clinically plausible, although the extrapolation may be slightly optimistic at 10 and 15 years by predicting that a very small proportion of patients would still be progression-free for longer than 10 years.

As the lognormal provided suitable visual fit, best statistical fit and was clinically plausible, the lognormal was selected to model PFS for PanoBorDex, and there was no rationale for any further calibration.

Figure 13: PanoBorDex PFS (using TTNT as a proxy) extrapolations (based on the UK RW TCE cohort study)

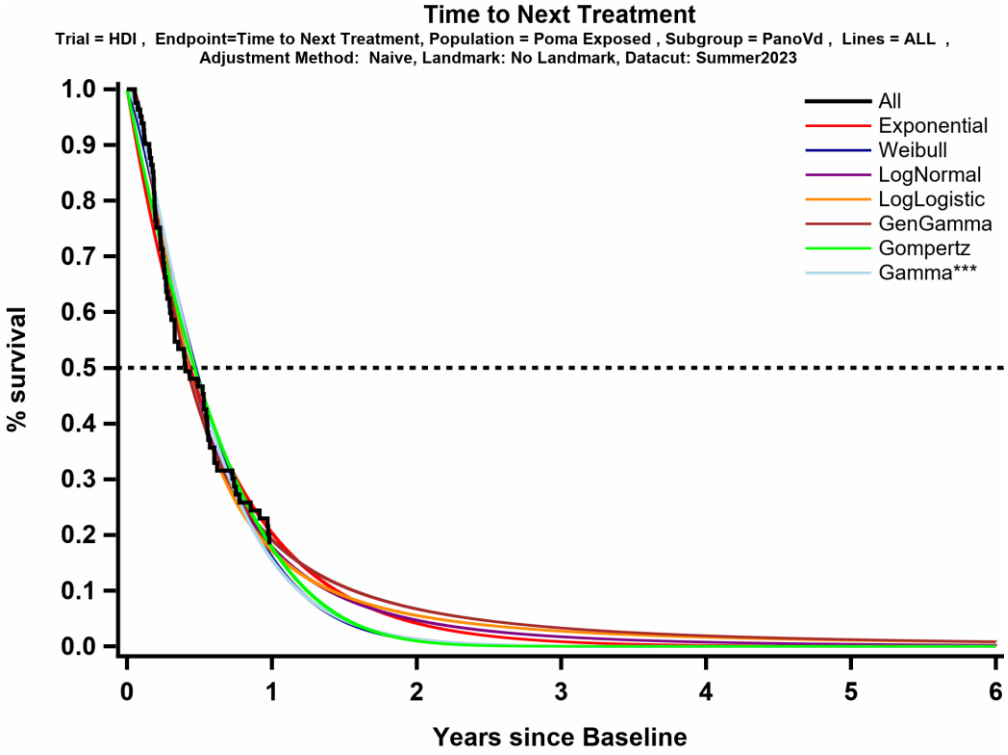

Table 7: Goodness-of-fit statistics for PanoBorDex PFS extrapolations (based on the UK RW TCE cohort study)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	796.2	801.1	5	5
Exponential	800.0	802.4	6	6
Lognormal	788.3	793.2	1	1

Loglogistic	790.4	795.3	3	2
Gompertz	800.7	805.6	7	7
Gamma	794.0	798.9	4	4
Generalised gamma	789.7	796.9	2	3

Table 8: Modelled landmark estimates of PanoBorDex PFS

Parametric curve	5-year PFS (%)	10-year PFS (%)	15-year PFS (%)
Clinical expert estimates			
Clinical expert estimates[a]	0 (0–1)	0 (0-0)	0 (0-0)
Landmark estimates of PFS for base case extrapolation			
Log-normal	0.39%	0.03%	0.01%

[a] The mean value of most likely estimates provided by two clinical experts, presented alongside the overall range estimated by the experts for this value.
Abbreviations: PanoBorDex: Panobinostat, bortezomib and dexamethasone; PFS: progression-free survival.

Appendix C.3: Clinical efficacy – OS

Teclistamab OS

A summary of the statistical fit of each of the teclistamab OS extrapolations is provided in Table 9. Similar to the MajesTEC-1 data used in the original CS base case, the lognormal provided the best statistical fit to the MAIC-weighted OS data from MajesTEC-1. As such, in line with the Committee's preferred base case, the lognormal extrapolation for OS was fitted to the MAIC-weighted and subsequent-treatment adjusted OS KM data from MajesTEC-1, and calibrated to align with the UK clinical expert estimates of survival for teclistamab at 10 and 15 years. A summary of the resulting landmark estimates of OS is provided in Table 10.

Figure 14: Teclistamab OS extrapolations (MajesTEC-1, 6-variable MAIC-weighted data versus PanoBorDex in the UK RW TCE cohort study)

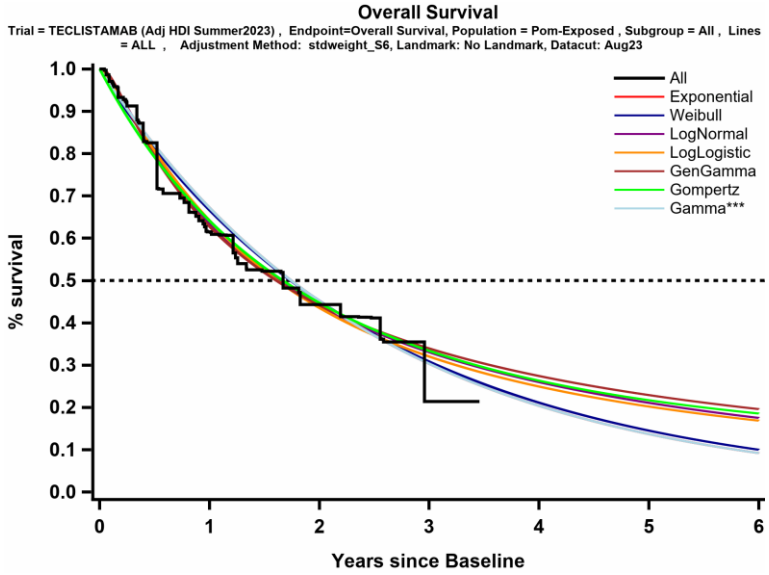

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Table 9: Goodness-of-fit statistics for teclistamab OS extrapolations (MajesTEC-1 6-variable MAIC versus PanoBorDex in the UK RW TCE cohort study)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	1345.9	1351.7	6	6
Exponential	1344.0	1346.9	4	2
Lognormal	1338.6	1344.5	1	1
Loglogistic	1341.3	1347.1	3	3
Gompertz	1344.0	1349.8	4	5
Gamma	1346.0	1351.8	7	7
Generalised gamma	1340.2	1349.0	2	4

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; OS: overall survival; PanoBorDex: Panobinostat, bortezomib and dexamethasone; RW: real-world; TCE: triple-class exposed.

Table 10: Modelled landmark estimates of teclistamab OS

Parametric curve	5-year OS (%)	10-year OS (%)	15-year OS (%)
Clinical expert estimates			
Clinical expert estimates	12–30	5–15	1–5
Landmark estimates of OS for base case extrapolation			
Calibrated Log-Normal	19.31%	10.05%	3.03%

Abbreviations: OS: overall survival.

PanoBorDex OS

A summary of the statistical fit of each of the PanoBorDex OS extrapolations is provided in Table 11. The lognormal provided the best statistical fit to the observed data, closely followed by the Generalised Gamma extrapolation.

A summary of the resulting landmark estimates of PanoBorDex OS at 5, 10 and 15 years compared to UK clinical expert estimates of survival is provided in Table 12. In addition to good visual fit (Figure 15), these show that the lognormal extrapolation is plausible at 5, 10 and 15 years, falling within the range of the most likely estimates of OS predicted by the clinical experts at each time point. As such, the lognormal was selected in the base case for PanoBorDex OS, and there was no rationale for any further calibration of the OS extrapolation.

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Figure 15: PanoBorDex OS extrapolations (based on the UK RW TCE cohort study)

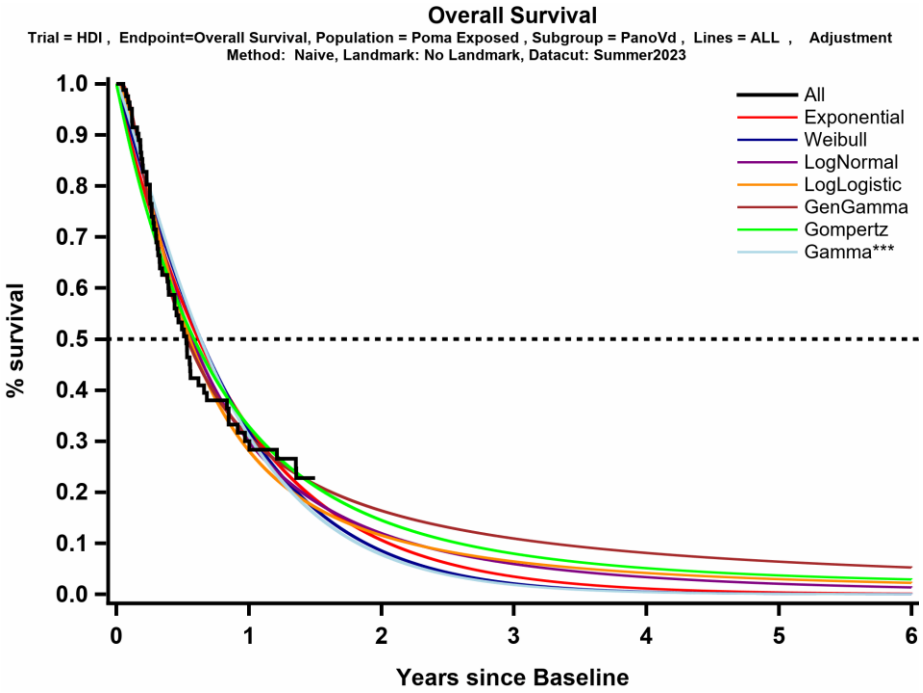

Table 11: Goodness-of-fit statistics for PanoBorDex OS extrapolations (based on the UK RW TCE cohort study)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	776.7	781.6	6	6
Exponential	775.6	778.0	5	4
Lognormal	765.5	770.4	2	1
Loglogistic	767.5	772.3	3	3
Gompertz	776.8	781.6	7	6
Gamma	775.4	780.2	4	5
Generalised gamma	764.6	771.8	1	2

Table 12: Landmark estimates of OS for PanoBorDex

Parametric curve	5-year OS (%)	10-year OS (%)	15-year OS (%)
Clinical expert estimates			
Clinical expert estimates[a]	4 (0–10)	0 (0–1)	0 (0–1)
Landmark estimates of OS for base case extrapolation			
Lognormal extrapolation	2.09%	0.36%	0.11%

[a] The mean value of most likely estimates provided by two clinical experts, presented alongside the overall range estimated by the experts for this value.
Abbreviations: OS: overall survival; PanoBorDex: panobinostat, bortezomib and dexamethasone.

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Appendix C.4: Clinical efficacy - TTD

A summary of the statistical fit of each of the teclistamab TTD extrapolations is provided in Table 13 below. Similarly to the MajesTEC-1 data used in the original CS base case, the lognormal and Generalised gamma extrapolations provide the best statistical fit to the MAIC-weighted data from MajesTEC-1.

To align with the Committee's preferred approach to modelling TTD for teclistamab, the lognormal was fitted to the MAIC-weighted data from MajesTEC-1 and was calibrated to align with the UK clinical expert estimates of TTD for teclistamab at 10 and 15 years (as shown in Table 14).

Figure 16: Teclistamab TTD extrapolations (MajesTEC-1, 6-variable MAIC-weighted data versus PanoBorDex in the UK RW TCE cohort study)

Table 13: Goodness-of-fit statistics for teclistamab TTD extrapolations (MajesTEC-1, 6-variable MAIC-weighted data versus PanoBorDex in the UK RW TCE cohort study)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	1576.2	1582.0	5	6
Exponential	1577.2	1580.2	6	5
Lognormal	1562.8	1568.6	2	1
Loglogistic	1567.6	1573.5	3	3
Gompertz	1570.2	1576.0	4	4
Gamma	1577.7	1583.6	7	7
Generalised gamma	1562.2	1571.0	1	2

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Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; PanoBorDex: Panobinostat, bortezomib and dexamethasone; RW: real-world; TCE: triple-class exposed; TTD: time to treatment discontinuation.

Table 14: Modelled landmark estimates of teclistamab TTD

Parametric curve	5-year TTD (%)	10-year TTD (%)	15-year TTD (%)
Clinical expert estimates			
Clinical expert estimates	4–20	1–5	0–2
Landmark survival for selected base case extrapolation			
Calibrated log-normal	[redacted]	[redacted]	[redacted]

Abbreviations: TTD: time to treatment discontinuation.

Time to treatment discontinuation: PanoBorDex

TTD data for PanoBorDex were not available from the UK RW TCE cohort study. Therefore, in line with the approach taken for modelling TTD for PomDex in the original CS, TTD for PanoBorDex was modelled by taking the HR between teclistamab PFS and teclistamab TTD, and then applying this ratio to the PanoBorDex PFS extrapolation to derive a TTD extrapolation for PanoBorDex. It should be noted that while a full extrapolation was applied to TTD for PanoBorDex, when the costs were calculated in the CEM, drug costs were only applied up to 48 weeks of PanoBorDex treatment to align with the SmPC.

Appendix C.5: Health state utility values

In line with the Committee's preferred base case, utility values were modelled to be treatment-dependent between teclistamab and PanoBorDex. For teclistamab, the utility values were modelled to be time-dependent, and were based on ITT data from the MajesTEC-1 trial.

No utility data were collected as part of the UK RW TCE cohort study, making it necessary to source values from the published literature to inform the treatment-dependent utility values for PanoBorDex in the economic analysis. The only relevant utilities for PanoBorDex identified in the utilities SLR were those from the PANORAMA-1 trial, where utility values of 0.679 (pre-progression, on treatment), 0.720 (pre-progression, off treatment) and 0.640 were reported. However, the use of utility values from PANORAMA-1 was not considered to be clinically plausible for the following reasons:

- These utility values are higher than the utility values used for PomDex (PFS: 0.610; PD: 0.570), and the PD utility of 0.64 is higher than the PD utility value for teclistamab from MajesTEC-1 (PD: [redacted]). As such, the PANORAMA-1 utilities lack face validity, and likely substantially overestimate HRQoL for the Pom-exposed population of patients with 5L+ RRMM who would receive PanoBorDex in current UK clinical practice and who are the focus of this economic analysis. Patients in PANORAMA-1 were only required to have received 2 prior lines of treatment and were not TCE, representing a much less heavily pre-treated patient population. As previously detailed in the CS, Section B.1.3.3, for patients with MM, HRQoL significantly deteriorates with each relapse and subsequent line of treatment.[20, 21]

- The toxicity profile associated with PanoBorDex is accepted to be substantially worse compared to PomDex. When PomDex was compared to PanoBorDex as part of NICE TA427, the final appraisal document noted that PanoBorDex is associated with an adverse toxicity profile which is particularly problematic in patients who have already had multiple therapies, including severe gastrointestinal problems that can severely affect daily activities. This was reiterated in Myeloma UK's submission as part of TA427, which highlighted that PomDex has a less severe side-effect profile than PanoBorDex.[22]

Therefore, it was not considered appropriate to use utilities from PANORAMA-1 for the PanoBorDex arm in base case.

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The recent NICE appraisal for SelDex was considered as an alternative source of utility data. Whilst TA970 did not include PanoBorDex specifically, it does report utility values for a population of patients with 5L+ RRMM, which is a closer reflection and therefore better proxy for the Pom-exposed population of patients with 5L+ RRMM of relevance to this economic analysis. The economic analysis in TA970 considered PF and PD utility values of 0.589 and 0.535, respectively, which appear to be clinically plausible and valid – these utilities are similar, but slightly lower than the corresponding PF and PD utilities of 0.610 and 0.570 associated with PomDex. It would be expected that utility for PanoBorDex would be decreased compared to PomDex, given the later line use with PanoBorDex.

As such, the utility values from TA970 were used to inform health state utility values for PanoBorDex in the base case economic analysis, as detailed in Table 15.

As detailed below, AE disutilities were also applied to both teclistamab and PanoBorDex in this economic analysis, in order to ensure that the potential impact of AEs on HRQoL were fully captured.

Table 15: Utility data for patients receiving PanoBorDex

Health state	PanoBorDex Health State Utility (SE)
Progression free	0.589 (0.020)
Progressed disease	0.535 (0.107)

Abbreviations: PanoBorDex: Panobinostat, bortezomib and dexamethasone; SE: standard error.
Source: TA970, Page 91 of the Committee Papers.[6]

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Appendix C.6: Healthcare resource use

Adverse events

In line with the (accepted) approach outlined in the Company submission, Grade ≥3 AEs that had occurred in at least 5% of patients for either teclistamab or PanoBorDex were included in the economic model.

Also in line with the Committee's preferred base case, AEs for teclistamab were sourced from the MajesTEC-1 trial – in general these are aligned with the AEs modelled for the economic analysis between teclistamab and PomDex, with some slight differences, as a result of some AEs which did not occur at >5% for PomDex, but do so for PanoBorDex, or vice versa.

The UK RW TCE cohort study did not report on AE data for PanoBorDex, meaning AEs had to be sourced from the published literature. AEs were therefore sourced from the PANORAMA-1 trial, in line with NICE TA380 for PanoBorDex. As previously detailed, it is acknowledged that patients in PANORAMA-1 were only required to have received 2 prior lines of treatment and were not TCE. However, as patients in PANORAMA-1 were less heavily pre-treated than the population of relevance to this submission, these AEs may underestimate the true toxicity profile associated with PanoBorDex, and therefore represents a conservative approach (positive uncertainty).

The incidence of AEs for teclistamab and PanoBorDex used in the model are presented in Table 16. Three new AEs are included based on the PanoBorDex cohort that were not previously modelled in the CEM, namely: diarrhoea, hypokalaemia, and hyponatraemia (as per TA380).

In the Committee's preferred base case between teclistamab and PomDex, AE disutilities were excluded, as the EAG considered that the MajesTEC-1 utility values may already capture the HRQoL of AEs associated with teclistamab, and therefore inclusion of AE disutilities could represent double counting. However, the utility values for PanoBorDex are taken from the STORM trial, as a proxy for 5L+ RRMM patients, as detailed above. As these patients were receiving SelDex, it is unlikely that these reflect the substantial toxicity profile that is associated with PanoBorDex. As part of NICE TA970, the clinical expert submission highlighted that SelDex is generally well-tolerated, with a manageable side effect profile (and see Appendix C.5: Health state utility values). In contrast, as highlighted previously in NICE TA427, PanoBorDex is associated with a substantial toxicity profile that is particularly problematic, including severe gastrointestinal problems that can severely impact daily living.

Given this, the use of the STORM utility values for a patient population receiving SelDex is unlikely to capture the true HRQoL impact of AEs associated with PanoBorDex – as such, AE disutilities are applied in the model to ensure that the HRQoL impact associated with PanoBorDex is fully captured. For consistency, AE disutilities are also included for teclistamab in this economic analysis – as the EAG highlighted in their report, the MajesTEC-1 health state utility values may already capture the disutility associated with AEs for teclistamab, so this is likely to represent a conservative assumption. A summary of the duration and disutility associated with each of the new AEs in the CEM is summarised in Table 17 below. The disutilities associated with all other AEs were aligned with Table 51 in the original Company Submission, Document B. The costs associated with each of these AEs is detailed in Table 18 below. The costs of all other AEs were aligned with the Committee's preferred base case.

Table 16: Incidence of AEs included in the model for patients receiving teclistamab and PanoBorDex

Adverse event	Teclistamab	PanoBorDex
Anaemia	37.6%	22.2%
Asthenia and fatigue	[redacted]	30.6%
CRS, Grade 1-2	71.5%	0.0%
CRS, Grade 3+	0.6%	0.0%
Diarrhoea	[redacted]	33.3%

Hypertension	[redacted]	0.0%
Hypokalaemia	[redacted]	20.8%
Hyponatraemia	[redacted]	6.9%
Hypophosphatemia	[redacted]	0.0%
Leukopenia	9.1%	0.0%
Lymphopenia	34.5%	12.5%
Neurotoxicity, Grade 1-2	[redacted]	0.0%
Neurotoxicity, Grade 3+	[redacted]	0.0%
Neutropenia	65.5%	31.9%
Pneumonia	[redacted]	13.9%
Thrombocytopenia	23.0%	59.7%

Abbreviations: AE: adverse event: CRS: cytokine release syndrome.
Source: NICE TA380, Page 326 of the Committee Papers.

Table 17: Summary of AE duration and disutility inputs for the additional adverse events included in the model for PanoBorDex

Adverse event	Utility decrement	Decrement Source	Duration of AE (days)	Duration sources	Overall QALY loss per AE
Diarrhoea	-0.1030	Lloyd 2006[23]	[redacted]	MajesTEC-1 (August 2023 DCO)	[redacted]
Hypokalaemia	-0.2000	TA510 (clinical opinion)[24]	[redacted]		[redacted]
Hyponatraemia	-0.2000	Assumed equal to hypokalaemia NICE TA510)[24]	[redacted]		[redacted]

Abbreviations: AE: adverse event; PanoBorDex: panobinostat plus bortezomib and dexamethasone; QALY: quality-adjusted life year.

Table 18: Costs associated with additional adverse events included in the model for PanoBorDex

Adverse event	Cost (£)	Source
Diarrhoea	761.63	TA380, price adjusted to 2022/2023 using the NHS cost inflation index.
Hypokalaemia	1,831.29	National Schedule of NHS Costs 2021-22, KC05: Weighted Average of Non-Elective Admissions
Hyponatraemia	1,525.00	National Schedule of NHS Costs 2021-22, Total HRGs. Currency code KC05J – KC05N (based on TA970)

Drug acquisition, administration and co-medication costs

Drug acquisition costs for PanoBorDex are presented in Table 19. In line with the approach taken to modelling PomDex, as no data on dose intensity were available from the UK RW TCE cohort study, dose intensity for PanoBorDex was based on the previous NICE appraisal for PanoBorDex (TA380). Based on the data from PANORAMA-1, panobinostat, bortezomib and dexamethasone were associated with a relative dose intensity of 80.7%, 75.7% and 87.5%, respectively, as detailed in Table 19 below.

Bortezomib was assumed to be administered via SC infusion, as J&J IM understands that there is little to no IV use of bortezomib in clinical practice – the cost of each SC administration was aligned with administration cost used for SC administration of teclistamab in the committee preferred base case.

No pre- or co-medication costs were modelled for PanoBorDex.

Table 19: Drug acquisition costs for PanoBorDex

Regimen	Regimen description	Capsule strength (mg)	Pack size	Pack cost	Relative Dose Intensity
Panobinostat	Oral	10.0	6	3,492.00	80.7%
		15.0	6	3,492.00	80.7%
		20.0	6	4,656.00	80.7%
Bortezomib	SC	3.5	1	48.59	75.8%
Dexamethasone	Oral	2.0	50	2.62	87.5%
		2.0	100	8.86	87.5%
		4.0	50	35.95	87.5%
		4.0	100	169.40	87.5%
		8.0	50	30.00	87.5%

Abbreviations: PanoBorDex: panobinostat, bortezomib and dexamethasome; SC: subcutaneous.
Source: List prices for each treatment are sourced from the BNF. Relative dose intensities were based on TA380.

Appendix C.7: Subsequent treatments

The approach to modelling subsequent treatments was aligned with the Committee's preferred base case, except the specific distributions of subsequent treatments has been updated to be derived from the PanoBorDex cohort of the UK RW TCE cohort study (reweighted to remove any treatments that did not reflect current UK clinical practice) to reflect the Pom-exposed population of relevance to this economic analysis.

A summary of the subsequent treatment distributions following either teclistamab or PanoBorDex is provided in Table 20 below.

Table 20: Summary of subsequent treatment distributions following either teclistamab or PanoBorDex

Treatment	Teclistamab	PanoBorDex
Melphalan + Thalidomide	31.6%	31.6%
Cyclophosphamide + Thalidomide	21.1%	21.1%
Melphalan	15.8%	15.8%
Bendamustine + Thalidomide	15.8%	15.8%
Bortezomib + Dexamethasone	5.3%	5.3%
Bortezomib + Cyclophosphamide + Dexamethasone	5.3%	5.3%
Bortezomib + Panobinostat + Dexamethasone	0.0%	0.0%
Cyclophosphamide + Dexamethasone	0.0%	0.0%
Cyclophosphamide + Pomalidomide + Dexamethasone	0.0%	0.0%
Bendamustine	0.0%	0.0%

Abbreviations: PanoBorDex: Panobinostat, bortezomib and dexamethasone.

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Appendix C.8: Severity Modifier

The severity modifier for Pom-exposed patients with 5L+ RRMM who would receive PanoBorDex was calculated in line with the approaches detailed in Section B.3.6 of the original Company submission. The total QALYs for the current MM population in the UK was based on the results of the base case economic analysis versus PanoBorDex (i.e. using utility values for PF and PD from the PanoBorDex base case), as shown in Table 21.

The STORM trial was considered to represent the most appropriate source for the population characteristics and utility values to inform the severity modifier calculation in the economic analyses versus PanoBorDex and SelDex, as a contemporary source of published evidence providing information on the characteristics of patients with 5L+ RRMM.

The use of the STORM trial is supported by clinical expert opinion provided as part of NICE TA970, which indicated that the STORM trial was broadly generalisable to people that they treated in UK clinical practice. The clinicians highlighted that the only people with penta-refractory MM considered for treatment in the fifth-line setting or later will likely be younger and have a better ECOG PS than people not considered for treatment. This is aligned with clinical expert feedback obtained as part of this submission.[6] As detailed in the Company submission, Section B.2.3.3, when the clinicians compared the average age of patients in MajesTEC-1 (64 years) versus the age of patients in the UK RW TCE cohort study (71 years, includes a historical cohort), the experts indicated that the mean age in MajesTEC-1 (64 years) was generalisable to UK clinical practice, highlighting older or frailer patients typically do not receive four or more lines of treatment, and that a younger subset of patients likely make up a large proportion of the patients who are eligible for fourth line treatment. This trend is likely to continue further down the RRMM pathway, where the patients fit enough to continue receiving further treatments after each line of therapy are likely to represent a younger and fitter subset of the overall TCE RRMM population.

As such, the population characteristics in the STORM trial, as detailed in Table 21 below, were considered to represent the most appropriate proxy for the 5L+ Pom-exposed RRMM population in UK clinical practice.

The results shown in Table 22, demonstrate that teclistamab is eligible for a 1.7x severity modifier when compared to PanoBorDex based on a proportional QALY shortfall of [redacted]. As detailed in Appendix D, the probabilistic results indicate that [redacted]% of the PSA iterations would meet the 95% threshold for the 1.7x severity modifier, underlining the extremely poor prognosis faced by Pom-exposed patients, who have run out of effective treatment options and face the end of their terminal illness.

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Table 21: Summary features of QALY shortfall analysis

Factor	Value
Starting age (mean)	64.5
Proportion of female patients (%)	39.5%
Health state utility: PF	0.589
Health state utility: PD	0.535

Abbreviations: PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year

Table 22: Summary of QALY shortfall analysis versus PanoBorDex

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	[redacted]	[redacted]	1.7x

Abbreviations: QALY: quality-adjusted life year.

Appendix D: Cost-effectiveness results for teclistamab versus PanoBorDex

Probabilistic and deterministic cost-effectiveness results for teclistamab versus PanoBorDex are presented in Table 23 and Table 24, respectively (teclistamab PAS price), and Table 25 and Table 26, respectively (teclistamab list price). J&J IM acknowledges that a confidential simple PAS discount is also available for panobinostat, however, as this price is confidential and therefore not publicly available, it was excluded from ICER calculations.

At PAS price, the probabilistic results showed that teclistamab was a cost-effective use of NHS resources when compared to PanoBorDex at a WTP threshold of £30,000/QALY, with an ICER of £[redacted] and a positive incremental net health benefit of [redacted]. Teclistamab had a [redacted]% probability of being cost-effective at a WTP threshold of £30,000/QALY.

These results were underpinned by substantial improvements in life years gained (LYG) ([redacted]) and quality-adjusted life years (QALYs) ([redacted]; including the 1.7x severity modifier) for teclistamab versus PanoBorDex. The extremely high proportional QALY shortfall of [redacted]%, with [redacted]% of the PSA simulations meeting the threshold for the 1.7x severity modifier, underlines the severe unmet need currently faced by Pom-exposed patients in UK clinical practice. Overall, the cost-effectiveness results highlight the substantial improvements in both quality and length of life that teclistamab will be able to offer to this patient population, who are otherwise close to dying from their terminal illness.

Table 23: Probabilistic cost-effectiveness results for teclistamab versus PanoBorDex (teclistamab PAS price; 1.7x severity modifier applied, 200 iterations)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 24: Deterministic cost-effectiveness results for teclistamab versus PanoBorDex (teclistamab PAS price; 1.7x severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000

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Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 25: Probabilistic cost-effectiveness results for teclistamab versus PanoBorDex (teclistamab list price; with severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]					
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 26: Deterministic cost-effectiveness results for teclistamab versus PanoBorDex (teclistamab list price; with severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Appendix E: Additional information for the ITC for teclistamab versus SelDex[25]

MAIC methodology

Identification and rank ordering of prognostic factors

Imbalances in baseline patient characteristics between STORM and MajesTEC-1 that are prognostic for the outcomes of interest can lead to biased comparative efficacy estimates if left unadjusted. The steps undertaken for identifying and rank-ordering prognostic factors requiring adjustment in the current analysis are outlined below.

1. Prior to conducting MAIC, a pool of potential prognostic variables was identified by consulting studies from a literature review of clinical outcomes in triple-class exposed RRMM patients, as well as input from clinical experts.

2. Clinical experts were consulted to provide input on the most important factors that should be adjusted for in the analyses. Analyses that adjusted for all of these top-ranked variables were considered the base case analyses for each outcome.

3. The remaining factors were judged to be of lesser importance and adjusted for as a sensitivity analysis. These factors were ranked in order of importance considering both prognostic strength and degree of imbalance between the study populations and refined based on clinical input. The prognostic strength of a factor was assessed by univariate regression using MajesTEC-1 data. Population differences between MajesTEC-1 and STORM were assessed using standardized mean differences (SMDs) (where an SMD between 0 and 0.1 was considered a small difference, an SMD >0.1 and ≤0.2 was a moderate difference, and an SMD of >0.2 was a substantial difference).

4. This evidence-informed rank ordered list was presented to and validated by clinical experts. The ranking was updated as required until a consensus was reached on the final rank-ordered list of factors. This final ranking could be applied across all outcomes of interest thereby providing consistency across all analyses.

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Unanchored MAIC method
Given the lack of a common comparator, an unanchored MAIC was conducted to estimate the relative treatment effect of teclistamab versus SelDex by leveraging IPD from MajesTEC-1 and published aggregate data from STORM.

The MajesTEC-1 population was adjusted to match the eligibility criteria and distribution of prognostic factors in STORM. That is, patients from MajesTEC-1 were removed from the IPD set if they would not have satisfied the eligibility criteria used in STORM. The remaining patients were reweighted to adjust for imbalances in the identified baseline characteristics of prognostic significance. A logistic propensity score model was estimated that included the identified covariates, which is equivalent to the model on the log of the individual weights: $\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_i$, where $\boldsymbol{X}_i$ was the covariate vector for the i[th] individual; and where the regression parameters, $\boldsymbol{\alpha}_1$, were estimated by a method-of-moments. The weighting methodology guarantees a close balance of covariates between the MajesTEC-1 and STORM populations. That is, after reweighting patients, the means (or proportions) and standard deviations of covariates from MajesTEC-1 were almost exactly equal to those published in STORM.

Estimating indirect treatment effects
Following matching of the MajesTEC-1 population to the STORM population, the comparative efficacy of teclistamab versus SelDex was determined for the following outcomes: ORR, ≥CR rate, DoR, OS, and PFS. Estimates of the comparative efficacy of teclistamab versus SelDex were derived as the difference between (a) an estimate of the outcome of interest in a population similar to patients in STORM, had they received teclistamab, and (b) the estimated outcome with SelDex based on published summary-level data from STORM.

Binary endpoints: For binary endpoints (i.e., ORR and ≥CR rate), estimates were derived by fitting an intercept-only generalized linear model with MAIC adjustment weights. The logit link function was used. Weights were based on a generalized method-of-moments propensity score model to ensure a close balancing of covariates. An estimate of the log odds ratio (OR) and its 95% confidence interval (CI) for teclistamab versus SelDex was then derived. Furthermore, response-rate ratios (RRs) were calculated as the ratio of response rates for teclistamab versus SelDex.

Time to event endpoints: For PFS and OS, pseudo-IPD representing the patients in STORM were derived by digitizing published Kaplan–Meier curves and applying the Guyot method. For DoR, pseudo-IPD were derived by digitizing a bar graph displaying the response duration for each patient. A dataset combining weighted IPD from MajesTEC-1 and pseudo-IPD simulated for STORM Part 2 (setting weights for pseudo-observations equal to 1), was then used to estimate hazard ratios (HRs) and their 95% CIs using a weighted Cox proportional hazards model. Robust standard errors were estimated using the sandwich estimator.

All analyses were conducted using SAS 9.4 based on the methods developed by Signorovitch et al, and as implemented by the NICE Synthesis Technical Support Document Series.

Effective sample size
The effective sample size (ESS) was calculated to reflect the impact of weighting on the available information in the IPD: $ESS = (\sum w_i)^2 / (\sum w_i^2)$, where w_i, $i = 1, \ldots N$, are the patient weights. A low ESS compared to the original sample size N indicates extreme patient weights due to large imbalances in patient populations prior to reweighting.

Adjustment of baseline characteristics
To account for differences in eligibility criteria surrounding refractory status and treatment history and more closely align the MajesTEC-1 and STORM patient populations, patients from MajesTEC-1 who did not fulfil the following criteria were excluded:

- Patients who were not penta-exposed
- Patients who were not TCE refractory
- Patients who were refractory to daratumumab
- Patients who were not refractory to their last line of therapy

Application of this eligibility criteria reduced the sample size of the patient population in the MajesTEC-1 trial from N=165 to N=80 patients; 85 patients were excluded (Table 28).

As noted in Comment 4 of the response document, prognostic factors were identified through the approach outlined in Appendix B, and were ranked in order of importance, considering the prognostic strength of the factors and the degree of imbalance between populations. The final ranked list of prognostic factors is provided in Table 27.

In the base case analysis, the optimal number of prognostic covariates were adjusted for, considering the balance between patient populations and the resulting ESS of the teclistamab patient population. Ultimately, all five covariates identified as priority prognostic factors were adjusted for in the base case analysis: refractory status, cytogenic risk, R-ISS stage, presence of extramedullary disease and number of prior lines of treatment received. The ESS of the MajesTEC-1 patient population following adjustment was N=[redacted].

Baseline characteristics of the ITT population of the teclistamab treatment arm of the MajesTEC-1 trial before and after matching are presented in Table 28. Following adjustment, proportions or median values for the adjusted covariates were exactly matched between trials, indicating a well-balanced population.

Table 27: Ranking of prognostic factors for the MAIC comparing teclistamab versus SelDex

Rank	Prognostic factor	Adjusted for in the base case analysis?
Priority	Refractory status	Yes
Priority	Cytogenic profile	Yes
Priority	ISS/R-ISS stage	Yes
Priority	Presence of extramedullary disease	Yes
Priority	Number of prior lines of therapy	Yes
Non-priority	Years since MM diagnosis	No
Non-priority	Age (years)	No
Non-priority	Prior autologous HCT	No
Non-priority	ECOG status	No
Non-priority	Race	No
Non-priority	Sex	No
Non-priority	Type of multiple myeloma	No
Non-priority	Creatinine clearance	No
Non-priority	Percentage of bone marrow plasma cells	No
Non-priority	Time since discontinuation of last treatment	No

Abbreviations: ECOG: Eastern Cooperative Oncology Group; HCT: haematopoietic cell transplantation; ISS/R-ISS: international staging system/revised international staging system; MM: multiple myeloma.

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Table 28: Baseline characteristics of the teclistamab patient population before and after matching

Characteristic	SelDex (STORM trial; Chari et al. 2019) (N=122)	Teclistamab (MajesTEC-1 trial, August 2023 DCO) Unadjusted		Teclistamab (MajesTEC-1 trial, August 2023 DCO) Adjusted[a]
		Total (N=165)	Following exclusion (N=80)	Base case ESS=[redacted]
Penta-refractory (%)	68	30	53	68
High cytogenic risk (%)	44	23	23	44
R-ISS stage 1 (%)	17	29	28	17
R-ISS stage 2 (%)	64	63	64	64
R-ISS stage 3 (%)	19	8	9	19
Extramedullary disease (%)	22	17	18	22
Prior lines of treatment (median)	7	5	5	7
Time from diagnosis (median, years)	6.6	6	5.9	6.7
Age <65 years (%)	49	52	55	49
Age 65≤n≤75 (%)	36	36	33	40
Age >75 years (%)	15	12	13	11
Prior autologous HCT (%)	84	82	84	83
ECOG score 0 (%)	31	33	34	34
ECOG score 1 or 2 (%)	69	67	66	66
White (%)	70	81	73	75
Black (%)	17	13	20	17
Other (%)	13	6	8	8
Male (%)	58	58	55	54
Immunoglobin subtype IgA or IgM (%)	15	19	16	18
Creatinine clearance (mL/min) <60	32	27	24	26
Creatinine clearance (mL/min) ≥60	68	73	76	74
Mean percentage of bone marrow plasma cells	27	25	26	31
Time since discontinuation of last treatment	4.1	5.3	5	5

[a] Grey cells indicate characteristics not adjusted for in the base-case MAIC analyses.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; HCT: haematopoietic cell transplantation; Ig: immunoglobulin; R-ISS: revised international staging system.

Additional results

Additional results for teclistamab versus SelDex, in terms of ORR, DOR, and the proportion of patients achieving CR, are presented in Figure 17 and Figure 18.

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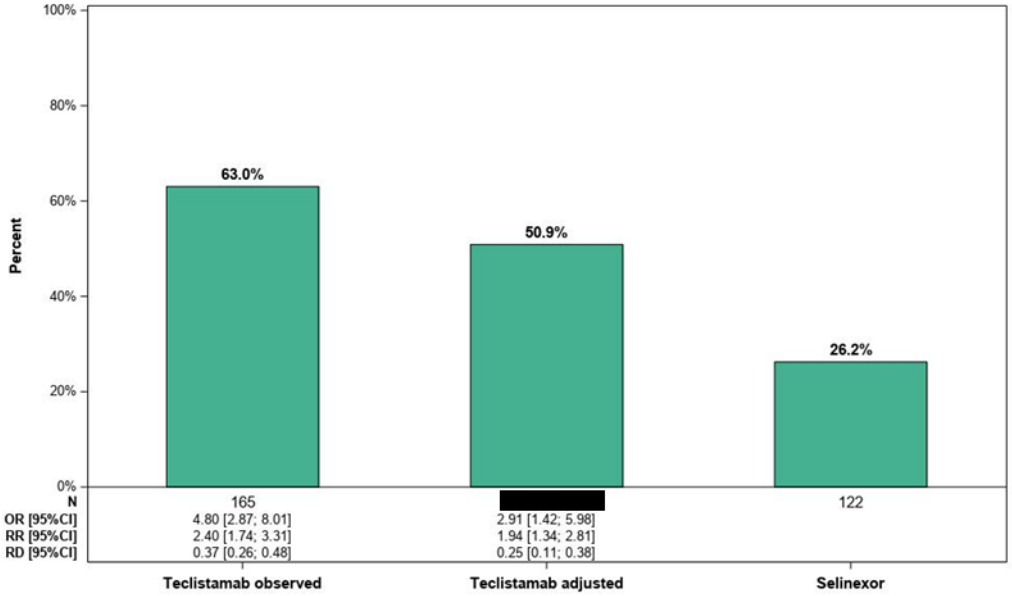
Overall, treatment with teclistamab resulted in a statistically significant 2.9 times higher odds of achieving response versus SelDex, corresponding to 50.9% of patients and 26.2% of patients achieving ORR in the teclistamab and SelDex patient populations, respectively. Results for DOR indicate the statistically significant, improved ability of teclistamab to prolong response versus SelDex (adjusted HR: 0.06; 95% CI: 0.03, 0.14; p-value<0.0001). Additionally, patients receiving teclistamab were 38 times more likely [OR: 38.69, 95% CI: 8.33, 179.62]); to achieve a CR (39.2% of patients) versus SelDex (1.6% of patients); this result was statistically significant.

As previously noted in the CS an SLR conducted in 2022 to identify data on the relationship between HRQoL and clinical response concluded that deeper responses result in improved HRQoL in patients with MM.[26] Therefore, this improvement in depth of response observed for teclistamab versus SelDex is expected to have translate to improvements in HRQoL.

Figure 17: ORR for teclistamab versus SelDex



Abbreviations: OR: odds ratio; ORR: objective response rate; RD: risk difference: RR: relative risk.

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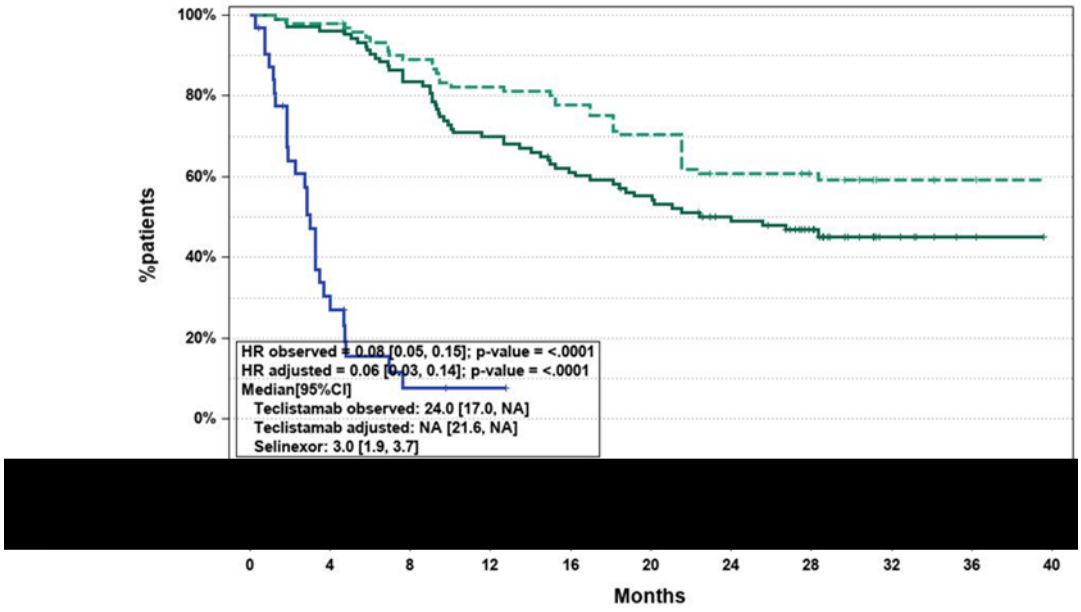
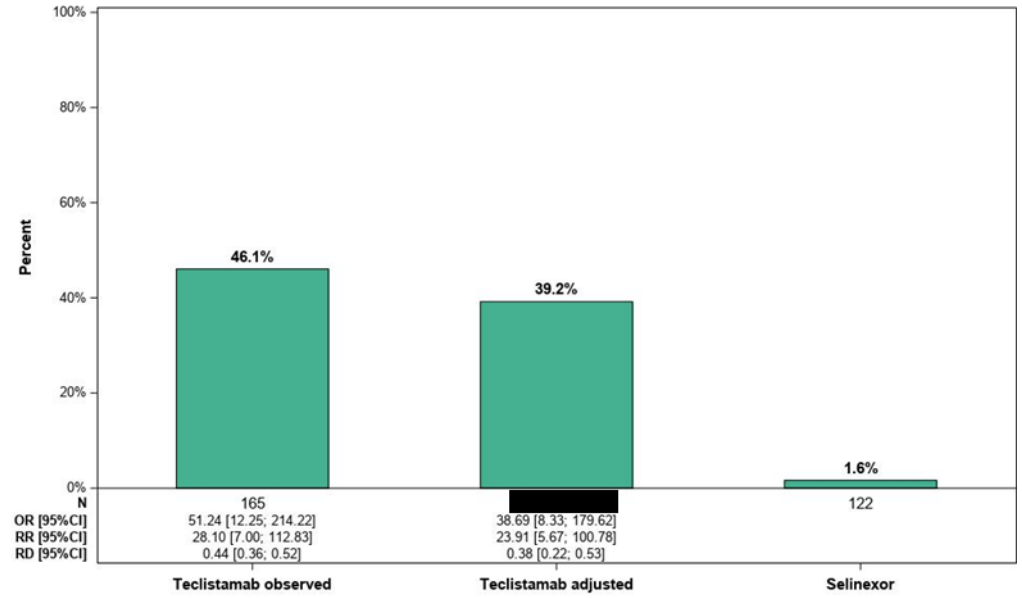
Figure 18: DOR for teclistamab versus SelDex



Abbreviations: DOR: duration of response; HR: hazard ratio; KM: Kaplan-Meier.

Figure 19: Proportion of patients achieving CR for teclistamab versus SelDex



Abbreviations: CR: complete response; OR: odds ratio; RD: risk difference: RR: relative risk.

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Appendix F: Clinical parameters and healthcare cost and resource use inputs informing the supplementary cost-effectiveness estimates for SelDex

This appendix summarises the additional model inputs used in the cost-effectiveness analysis for teclistamab versus SelDex. Wherever possible, the cost-effectiveness analysis is aligned with the Committee's preferred base case inputs and assumption from the economic analysis between teclistamab and PomDex. Changes that have been made to the Company's base case since ACM1, to align with the Committee's preferred base case, are outlined in Appendix A.

A summary of new modelling inputs and approaches for the cost-effectiveness analysis for teclistamab versus SelDex in a population of Pom-exposed patients are detailed in the sections below.

Modelling of PFS, OS and TTD were informed by extrapolation of the MAIC-weighted data from MajesTEC-1 for teclistamab (matched to STORM, as detailed in Appendix E), and the STORM clinical trial for SelDex.

Wherever possible, the approach to extrapolation was consistent with the approaches used in the Committee's preferred base case:

- For teclistamab, the best statistically fitting curves were selected for each endpoint, and were similarly calibrated to align with the UK clinical expert estimates of survival at 10 and 15 years.
- For SelDex, curves were selected based on consideration of statistical fit to the data from the STORM trial, as well as long-term plausibility, based on clinical expert estimates of long-term survival published as part of NICE TA970.[6]

Other relevant modelling inputs for SelDex were informed by the STORM trial, and NICE evaluation TA970.

Appendix F.1: Modelled baseline characteristics

Baseline characteristics used to inform the economic analysis between teclistamab and SelDex were updated to align with the weighted baseline characteristics from the MAIC between MajesTEC-1 and STORM (Table 29**Table *4***).

Table 29: Summary of baseline characteristics used in the economic analysis between teclistamab and SelDex

Characteristics	Pom-Exposed TCE RRMM Population	Source
Age (mean)	64.96	MajesTEC-1, MAIC-weighted to the STORM trial (as outlined in Section 4 of the response and Appendix E)
Proportion of female	46.5%	
Body weight (mean)	72.88 kg	
Body surface area (mean)	1.83 m^2	

Abbreviations: MAIC: matching-adjusted indirect comparison; PanoBorDex: panobinostat, bortezomib and dexamethasone; RRMM: relapsed refractory multiple myeloma; SelDex: selinexor with dexamethasone; TCE: triple-class exposed; UK: United Kingdom

Appendix F.2: Clinical efficacy - PFS

Teclistamab PFS

Unlike the comparisons versus PomDex and PanoBorDex, PFS data for SelDex were available from the STORM trial. As such, PFS data (as assessed by independent review committee [IRC]) was used to inform PFS for teclistamab in this economic analysis, rather than using TTNT data as a proxy.

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A summary of the statistical fit of each of the teclistamab PFS extrapolations is provided in Table 30. Overall, the generalised gamma, lognormal and Gompertz PFS extrapolations provided the best statistical fits to the MAIC-weighted data from MajesTEC-1. In line with the Committee's preferred base case for teclistamab PFS in the CS, the lognormal extrapolation for teclistamab PFS was selected and calibrated after 5 years to align with the UK clinical expert estimates of survival for teclistamab at 10 and 15 years – while the generalised gamma provides a better visual and statistical fit in this analysis, the generalised gamma also estimates higher teclistamab PFS compared to the lognormal, so the use of the lognormal was still considered to represent the most appropriate extrapolation. A summary of these landmark estimates is provided in Table 31.

Figure 20: Teclistamab PFS (based on MajesTEC-1; MAIC-weighted to STORM trial data)

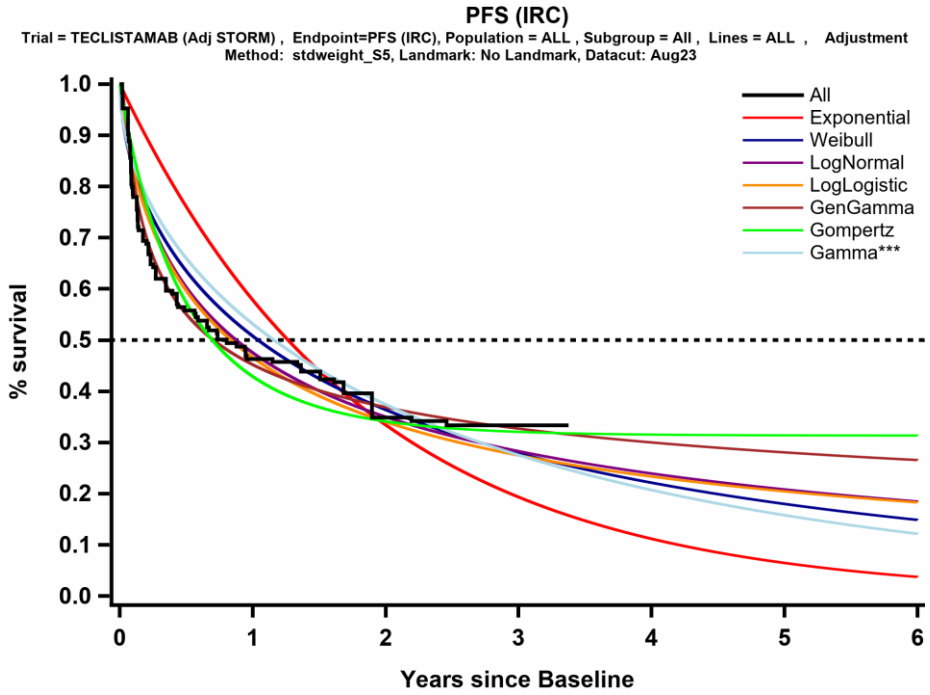

Table 30: Goodness-of-fit statistics for teclistamab PFS extrapolations (based on MajesTEC-1; MAIC-weighted to STORM trial data)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	700.9	705.6	5	5
Exponential	724.5	726.9	7	7
Lognormal	691.4	696.1	2	2
Loglogistic	695	699.8	4	4
Gompertz	694.7	699.4	3	3
Gamma	704.6	709.4	6	6
Generalised gamma	685.7	692.9	1	1

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; RW: real-world; TCE: triple-class exposed.

Table 31: Modelled landmark estimates of teclistamab PFS

Parametric curve	5-year PFS (%)	10-year PFS (%)	15-year PFS (%)
Clinical expert estimates			

Clinical expert estimates	7–20	2–8	0–2
Landmark estimates of PFS for calibrated lognormal and generalised gamma			
Calibrated lognormal	20.9	5	1
Calibrated generalised gamma	26.6	4.8	1

Abbreviations: PFS: progression-free survival.

SelDex PFS

A summary of the statistical fit of each of the SelDex PFS extrapolations is provided in Table 32. The lognormal extrapolation provided the best statistical fit to the STORM clinical trial data. Furthermore, this extrapolation was selected for SelDex PFS in prior NICE evaluation TA970, which was supported by clinical opinion stating that all PFS extrapolations provided similar estimates, whereby less <1% of patients remained progression free at two years. As such, in this case, the lognormal extrapolation, which provides a 2-year PFS estimate for SelDex of 1.8%, may be slightly conservative (Table 33). However, this was considered the most appropriate for modelling SelDex PFS in the base case.

A summary of the landmark estimates of SelDex PFS at 1, 2 and 5 years is additionally provided in Table 33.

Figure 21: SelDex PFS extrapolations (STORM trial data)

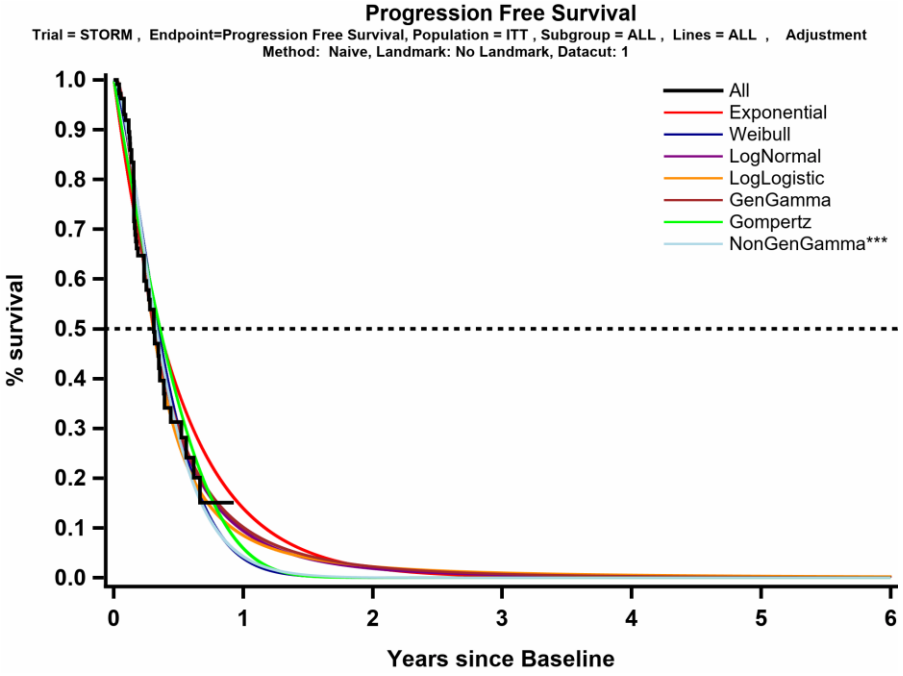

Table 32: Goodness-of-fit statistics for SelDex PFS extrapolations (STORM trial data)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	590.9	596.5	5	5
Exponential	599.3	602.1	7	6
Lognormal	583.4	589	1	1
Loglogistic	583.8	589.4	2	2

Gompertz	599.1	604.7	6	7
Gamma	587.8	593.4	4	3
Generalised gamma	585.3	593.8	3	4

Abbreviations: PFS: progression-free survival; SelDex: selinexor with dexamethasone.

Table 33: Modelled landmark estimates of SelDex PFS

Parametric curve	1-year PFS (%)	2-year PFS (%)	5-year PFS (%)
Landmark estimates of PFS for base case extrapolation			
Lognormal	9.7	1.8	0.1

Abbreviations: PFS: progression-free survival; SelDex: selinexor with dexamethasone.

Appendix F.3: Clinical efficacy – OS

Teclistamab OS

A summary of the statistical fit of each of the teclistamab OS extrapolations is provided in Table 34. Similarly to the MajesTEC-1 data used in the original CS base case, the lognormal provided the best statistical fit to the MAIC-weighted OS data from MajesTEC-1. In line with the Committee's preferred base case for teclistamab OS in the CS, the lognormal extrapolation for OS was fitted to the MAIC-weighted and subsequent-treatment adjusted OS KM data from MajesTEC-1, and calibrated to align with the UK clinical expert estimates of survival for teclistamab at 5, 10 and 15 years. A summary of the resulting landmark estimates of OS is provided in Table 35.

Figure 22: Teclistamab OS (based on MajesTEC-1; MAIC-weighted to STORM trial data)

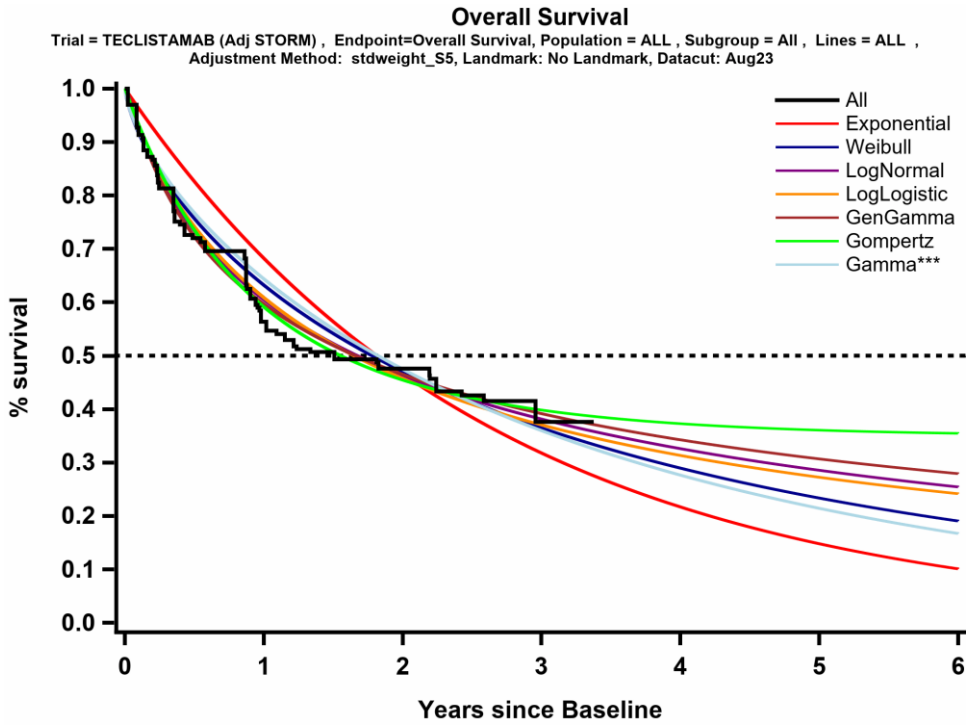

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Table 34: Goodness-of-fit statistics for teclistamab OS extrapolations (based onMajesTEC-1; MAIC-weighted to STORM trial data)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	705.4	710.1	5	4/5
Exponential	710.6	713	7	7
Lognormal	701.3	706.1	1	1
Loglogistic	702.8	707.6	3	3
Gompertz	702	706.8	2	2
Gamma	706.6	711.3	6	6
Generalised gamma	703	710.1	4	4/5

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; OS: overall survival; RW: real-world; TCE: triple-class exposed.

Table 35: Modelled landmark estimates of teclistamab OS

Parametric curve	5-year OS (%)	10-year OS (%)	15-year OS (%)
Clinical expert estimates			
Clinical expert estimates	12–30	5–15	1–5
Landmark estimates of OS for base case extrapolation			
Calibrated Lognormal	26.6	10.1	3.0

Abbreviations: OS: overall survival.

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SelDex OS

A summary of the statistical fit of each of the SelDex OS extrapolations is provided in Table 36. The lognormal provided the best statistical fit to the observed data, followed by the Generalised Gamma extrapolation. However, the lognormal, generalised gamma and loglogistic extrapolations resulted in a proportion of patients remaining alive at 5 years (6.2%, 9.8% and 6.7%, respectively) that contradict clinical opinion obtained during TA970 in which clinical experts predicted that <5% of patients would remain alive at 5 years following treatment with SelDex.[6] As such, the three curves predicting survival rates of >5% for SelDex at 5 years were excluded from consideration from the base case, as they lacked clinical plausibility.

The remaining four curves were associated with similar visual (Figure 23) and statistical fits (all within 2 AIC points and 5 BIC points) and 5-year estimates of survival. Of the remaining four extrapolations, the Weibull curve was selected, to align with the same type of extrapolation preferred by the Committee for modelling SelDex as part of NICE TA970. With a 5-year OS of 0%, the Weibull extrapolation can be considered clinically plausible based on the clinical expert estimates provided in TA970.[6]

Figure 23: SelDex OS extrapolations (STORM trial data)

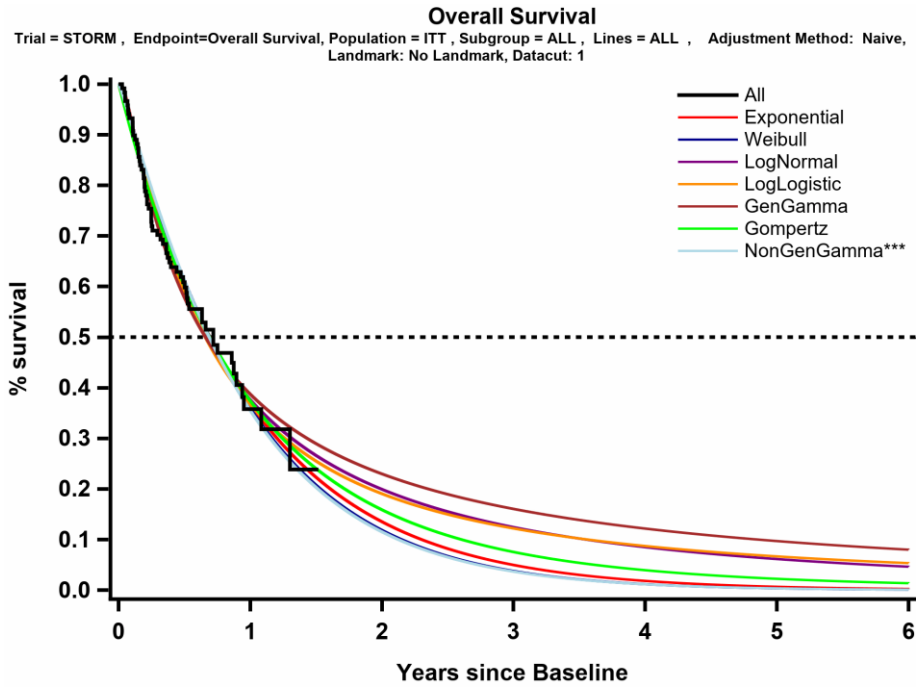

Table 36: Goodness-of-fit statistics for SelDex OS extrapolations (based onMajesTEC-1; MAIC-weighted to STORM trial data)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	873.1	878.7	6	6
Exponential	871.4	874.2	4	2
Lognormal	867.8	873.4	1	1
Loglogistic	870.6	876.2	3	3
Gompertz	873.3	878.9	7	7
Gamma	872.8	878.4	5	5

Generalised gamma	869.3	877.8	2	4

Abbreviations: OS: overall survival; SelDex: selinexor with dexamethasone.

Table 37: Landmark estimates of OS for SelDex

Parametric curve	1-year OS (%)	2-year OS (%)	5-year OS (%)
Landmark estimates of OS for base case extrapolation			
Weibull	36.4	12.0	0.00

Abbreviations: OS: overall survival; SelDex: selinexor with dexamethasone.

Appendix F.4: Clinical efficacy - TTD

A summary of the statistical fit of each of the teclistamab TTD extrapolations is provided in Table 38 below. Similarly to the MajesTEC-1 data used in the original CS base case, the lognormal and Generalised gamma extrapolations provide the best statistical fit to the MAIC-weighted data from MajesTEC-1.

To align with the Committee's preferred approach to modelling TTD for teclistamab in the CS, the lognormal was fitted to the MAIC-weighted data from MajesTEC-1 and was calibrated to align with the UK clinical expert estimates of TTD for teclistamab at 10 and 15 years (as shown in Table 39).

Figure 24: Teclistamab TTD (based on MajesTEC-1; MAIC-weighted to STORM trial data)

Table 38: Goodness-of-fit statistics for teclistamab TTD extrapolations (based on MajesTEC-1; MAIC-weighted to STORM trial data)

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	819	823.8	5	5
Exponential	843.4	845.8	7	7
Lognormal	806.4	811.2	2	2

Loglogistic	810.2	814.9	4	4
Gompertz	808.1	812.9	3	3
Gamma	824	828.8	6	6
Generalised gamma	797.6	804.8	1	1

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; MAIC: matching-adjusted indirect comparison; RW: real-world; TCE: triple-class exposed; TTD: time to treatment discontinuation.

Table 39: Modelled landmark estimates of teclistamab TTD

Parametric curve	5-year TTD (%)	10-year TTD (%)	15-year TTD (%)
Clinical expert estimates			
Clinical expert estimates	4–20	1–5	0–2
Landmark survival for selected base case extrapolation			
Calibrated lognormal	[redacted]	[redacted]	[redacted]

Abbreviations: TTD: time to treatment discontinuation.

Time to treatment discontinuation: SelDex

TTD data for SelDex were not available from the STORM trial. Therefore, in line with the approach taken for modelling TTD for PomDex in the original CS, TTD for SelDex was modelled by taking the HR between teclistamab PFS and teclistamab TTD, and then applying this ratio to the SelDex PFS extrapolation to derive a TTD extrapolation for SelDex. The resulting landmark estimates of TTD are presented in Table 40.

Table 40: Modelled landmark estimates of SelDex TTD

Parametric curve	1-year TTD (%)	2-year TTD (%)	5-year TTD (%)
Median and landmark survival for selected extrapolation			
Selected extrapolation	[redacted]	[redacted]	[redacted]

Abbreviations: SelDex: selinexor with dexamethasone; TTD: time to treatment discontinuation.

Appendix F.5: Health state utility values

In line with the Committee's preferred base case, utility values were modelled to be treatment-dependent between teclistamab and SelDex. For teclistamab, the utility values were modelled to be time-dependent, and were based on data from the MajesTEC-1 trial. As previously detailed in Appendix C for PanoBorDex, utility values from the STORM trial are reported in NICE TA970 for SelDex, and these were used in the Committee's preferred base case for modelling SelDex in the economic analysis conducted as part of NICE TA970. As such, these utility values were also considered to represent the most appropriate treatment-dependent utility values to apply to SelDex in the economic model.

These are summarised in Table 41, below.

Table 41: Utility data for patients receiving SelDex

Health state	SelDex Health State Utility (SE)
Progression free	0.589 (0.020)
Progressed disease	0.535 (0.107)

Abbreviations: SelDex: Selinexor and dexamethasone; SE: Standard Error.
Source: TA970, Page 91 of the Committee Papers.[6]

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Appendix F.6: Healthcare resource use

Adverse events

In line with the approach outlined in the CS, Grade ≥3 AEs that had occurred in at least 5% of patients for either teclistamab (in MajesTEC-1) or SelDex (based on STORM) were included in the economic model, as summarised in Table 42.

As with the comparison between teclistamab and PanoBorDex, this means that there are some slight differences in the AEs modelled in the economic analysis for teclistamab, as a result of some AEs which did not occur at >5% for PomDex, but do so for SelDex, or vice versa.

Three new AEs are included based on the SelDex cohort that were not previously modelled in the CEM: diarrhoea, hypokalaemia, and hyponatraemia; this is consistent with the additional AEs added for the PanoBorDex arm. The costs associated with each of these AEs is detailed in Table 43 below. The costs of all other AEs were aligned with the Committee's preferred base case in TA970. In line with the committee's preferred base case,

Table 42: Incidence of AEs included in the model for patients receiving teclistamab and SelDex

Adverse event	Teclistamab	SelDex
Anaemia	37.6%	45.1%
Asthenia and fatigue	[redacted]	27.0%
CRS, Grade 1-2	71.5%	0.0%
CRS, Grade 3+	0.6%	0.0%
Decreased appetite	[redacted]	6.6%
Diarrhoea	[redacted]	7.4%
Hyperglycaemia	[redacted]	6.6%
Hypertension	[redacted]	0.0%
Hypokalaemia	[redacted]	6.6%
Hyponatraemia	[redacted]	22.1%
Hypophosphatemia	[redacted]	0.0%
Leukopenia	9.1%	14.8%
Lymphopenia	34.5%	11.5%
Nausea	0.6%	9.8%
Neurotoxicity, Grade 1-2	[redacted]	0.0%
Neurotoxicity, Grade 3+	[redacted]	0.0%
Neutropenia	65.5%	22.1%
Pneumonia	[redacted]	9.0%
Sepsis	[redacted]	7.4%
Thrombocytopenia	23.0%	62.3%

Abbreviations: AE: adverse event: CRS: cytokine release syndrome.
Source: NICE TA380, Page 326 of the Committee Papers.

Table 43: Costs associated with additional adverse events included in the model for SelDex

Adverse event	Cost (£)	Source
Decreased appetite	1,844.00	National Schedule of NHS Costs 2021-22, Weighted Average of FD10A-FD10M (Non-Malignant Gastrointestinal Tract Disorders with Multiple

		Interventions, with CC Score 8+, 5-7, 3-4, 0-2, 9+, 5-8, 3-4, 0-2, 11+, 6-10, 3-5, 0-2) (in line with TA970)
Diarrhoea	761.63	TA380, price adjusted to 2022/2023 using the NHS cost inflation index.
Hyperglycaemia	1,533.00	NHS code KB02G, KB02H, KB02J, KB02K, Diabetes with Hyperglycaemic Disorders (in line with TA970)
Hypokalaemia	1,831.29	National Schedule of NHS Costs 2021-22, KC05: Weighted Average of Non-Elective Admissions
Hyponatraemia	1,525.00	National Schedule of NHS Costs 2021-22, Total HRGs. Currency code KC05J – KC05N (in line with TA970)
Nausea	1,844.00	National Schedule of NHS Costs 2021-22, Weighted Average of FD10A-FD10M (Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 8+, 5-7, 3-4, 0-2, 9+, 5-8, 3-4, 0-2, 11+, 6-10, 3-5, 0-2) (in line with TA970)
Sepsis	4,408.00	National Schedule of NHS Costs 2021-22, WH07D Infections or Other Complications of Procedures, with Single Intervention, with CC (in line with TA970)

Drug acquisition, administration and co-medication costs

Drug acquisition costs for SelDex are presented in Table 44. Dose intensity for SelDex was sourced from TA970, with a relative dose intensity of 98.4% for Selinexor and 100% for dexamethasone, respectively.

In line with TA970, all patients receiving SelDex were also assumed to receive concomitant treatment with the 5-hydroxytryptamine (5-HT3) antagonist ondansetron, which was modelled at a cost of £0.46 per administration of SelDex, based on the BNF.

Table 44: Drug acquisition costs for SelDex.

Regimen	Regimen description	Capsule strength (mg)	Pack size	Pack cost	Relative Dose Intensity
Selinexor	Oral	20.0	20	9,200.00	98.4%
Dexamethasone	Oral	2.0	50	2.62	100%
		2.0	100	8.86	100%
		4.0	50	35.95	100%
		4.0	100	169.40	100%
		8.0	50	30.00	100%

Abbreviations: SelDex: Selinexor and dexamethasone.
Source: List prices for each treatment are sourced from the BNF.

Appendix F.7: Subsequent treatments

The approach to modelling subsequent treatments was aligned with the approach used in TA970, the recent NICE evaluation for SelDex, except for the proportions of patients receiving teclistamab who receive subsequent treatments, which is based on the MajesTEC-1 trial.

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A total of 70% of patients receiving teclistamab were assumed to receive subsequent treatment (based on MajesTEC-1) and 65% of patients receiving SelDex were assumed to receive subsequent treatment (based on TA970). The duration of receiving subsequent treatments (13.43 weeks, for both treatment arms) and the distribution of subsequent treatments received (100% cyclophosphamide and dexamethasone [CycloDex], for both treatment arms) were based on TA970.[6]

A summary of the subsequent treatments following either teclistamab or SelDex is provided in Table 45 below.

Table 45: Summary of subsequent treatment distributions following either teclistamab or SelDex

Treatment	Teclistamab	SelDex
Cyclophosphamide + Dexamethasone	100%	100%

Abbreviations: CycloDex: cyclophosphamide and dexamethasone; SelDex: Selinexor and dexamethasone.
Source: NICE TA970. 2024.[6]

Appendix F.8: Severity Modifier

The severity modifier for SelDex was calculated in line with the methods used for PanoBorDex, as detailed in Appendix C.8. The total QALYs for the current MM population in the UK were based on the results of the base case economic analysis versus SelDex (i.e. using utility values for PF and PD from the SelDex base case), as shown in Table 46.

The results, as shown in Table 49, demonstrate that teclistamab is eligible for a 1.7x severity modifier when compared to SelDex based on a proportional QALY shortfall of [redacted]%. As detailed in Appendix G, the probabilistic results indicate that [redacted]% of the PSA iterations would meet the 95% threshold for the 1.7x severity modifier, underlining the extremely poor prognosis faced by Pom-exposed patients, who have run out of effective treatment options and face the end of their terminal illness.

Table 46: Summary features of QALY shortfall analysis

Factor	Value
Starting age (mean)	64.5
Proportion of female patients (%)	39.5%
Health state utility: PF	0.589
Health state utility: PD	0.535

Abbreviations: PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year

Table 47: Summary of QALY shortfall analysis versus SelDex

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	[redacted]	[redacted]	1.7x

Abbreviations: QALY: quality-adjusted life year.

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Appendix G: Cost-effectiveness results for teclistamab versus SelDex

Probabilistic and deterministic cost-effectiveness results for teclistamab versus SelDex are presented in Table 48 and Table 49, respectively (teclistamab PAS price), and Table 50 and Table 51, respectively (teclistamab list price). J&J IM acknowledges that a confidential simple PAS discount is also available for selinexor, however, as this price is confidential and therefore not publicly available, it was excluded from ICER calculations.

At PAS price, the probabilistic results showed that teclistamab was a cost-effective use of NHS resources when compared to SelDex at a WTP threshold of £30,000/QALY, with an ICER of £[redacted] and a positive incremental net health benefit of [redacted]. Teclistamab had a [redacted]% probability of being cost-effective at a WTP threshold of £30,000/QALY.

These results were underpinned by substantial improvements in life years gained (LYG) ([redacted]) and quality-adjusted life years (QALYs) ([redacted]; including the 1.7x severity modifier) for teclistamab versus PanoBorDex. The extremely high proportional QALY shortfall of [redacted]%, with [redacted]% of the PSA simulations meeting the threshold for the 1.7x severity modifier, underlines the severe unmet need currently faced by Pom-exposed patients in UK clinical practice. Overall, the cost-effectiveness results highlight the substantial improvements in both quality and length of life that teclistamab will be able to offer to this patient population, who are otherwise close to dying from their terminal illness.

Table 48: Probabilistic cost-effectiveness results for teclistamab versus SelDex (teclistamab PAS price; 1.7x severity modifier applied, 200 iterations)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SelDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SelDex: Selinexor and dexamethasone.

Table 49: Deterministic cost-effectiveness results for teclistamab versus SelDex (teclistamab PAS price; 1.7x severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SelDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PanoBorDex: panobinostat in combination with bortezomib and dexamethasone; QALYs: quality-adjusted life years; SelDex: selinexor with dexamethasone.

Table 50: Probabilistic cost-effectiveness results for teclistamab versus SelDex (teclistamab list price; with 1.7x severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SelDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SelDex: Selinexor and dexamethasone.

Table 51: Deterministic cost-effectiveness results for teclistamab versus SelDex(teclistamab list price; 1.7x severity modifier applied)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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SelDex																								

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SelDex: Selinexor and dexamethasone.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Blood Cancer 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 Johnson & Johnson and Bristol Myers Squibb Pharmaceuticals **Johnson & Johnson:** • £91,290 for the Blood Cancer Action Plan • £240 for a Haematology Study Day • £180 for a CAR-T Patient Advocacy Group stakeholder meeting **Bristol Myers Squibb Pharmaceuticals** • £466,192 for Increasing awareness and access to clinical trials for ethnic minority communities. • £35,000 for the Blood Cancer Action Plan
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** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1.	Whilst we welcome the positive recommendation of Teclistamab for relapsed or refractory triple class-exposed myeloma patients, we are disappointed and deeply concerned with the decision to restrict access for a specific subgroup of patients.

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NICE National Institute for Health and Care Excellence

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333]

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2.	We appreciate the committee's decision following the uncertainties brought to light. However, we are equally concerned that a novel treatment for a triple-class exposed group will not reach a subgroup of patients who may benefit from it. We hope an agreement can be reached in a way that doesn't impede access to this potentially beneficial treatment for patients who have previously received pomalidomide plus dexamethasone (PomDex).
3.	We have spoken to individuals who, after having very little success with PomDex, received Teclistamab and have been able to achieve remission. The decision to restrict access would mean those who have been exposed to PomDex would be robbed of the opportunity to benefit from this new treatment. We believe this decision to be unjust and unethical. If it is possible for patients to benefit from Teclistamab post exposure to PomDex, it seems unreasonable to limit access for this group of patients who have been eagerly awaiting the approval of novel treatments, like Teclistamab, as it may be their only lifeline.
4.	Triple-class exposed relapsed or refractory myeloma patients, including those who have been treated with PomDex, should be given as many treatment options as possible. In the absence of other novel therapies on the NHS, they should be given access to Teclistamab as it may be their best and only chance at achieving positive results this far down their treatment pathway.
5.	PomDex exposed patients will be experiencing high clinical and emotional burdens and suffering from the difficulties associated with steroid treatments including a deterioration in their quality of life. They could therefore benefit, in more ways than one, from access to Teclistamab. This group of patients deserve an effective, steroid-free monotherapy such as Teclistamab with its tolerable safety profile.
6.	As Teclistamab becomes available for other triple-class exposed myeloma patients, those who are PomDex exposed and face poor prognosis should not be unjustly left behind. We fear that the high unmet clinical needs of PomDex-exposed patients will remain if the decision to restrict access in this population becomes finalised.
7.	We reiterate the following key messages from our previous submission and would ask that these be reconsidered sufficiently, with pomalidomide-exposed patients in mind, before the final decision is reached: • As patients progress through subsequent treatments in the relapsed/refractory setting, many experience intensified side effects and higher physical and psychological burden. • People living with myeloma, including those who have been treated with PomDex, understand that even if they achieve remission, myeloma is not curable and will return at an unknown point in the future. Therefore, the knowledge that new novel treatments, like Teclistamab, is being reviewed has been a source of reassurance and hope for them and their families. • Some patients we spoke to explained that combination treatments (such as Pomalidomide and Dexamethasone) were not successful in controlling disease but have made them feel 'very delicate'. They described going through the 'ordeals of several rounds of treatments with only some short-term success.'

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	• There are huge unmet needs for this heavily pre-treated and difficult-to-treat patient population. Currently, people with triple-class refractory myeloma face poor outcomes. Their hopes are placed on the potential access to newer therapies such as Teclistamab. • People with myeloma have expressed that amongst the most important aspects of treatment for them are maximal disease control for significant periods of time, with minimal symptoms and side effects. If this can be achieved using Teclistamab for pomalidomide exposed patients, the restriction on this recommendation should be appropriately reconsidered. • As this group of patients would be triple class exposed, the likelihood of their disease responding positively to the remaining alternative options is very small. This leaves an increasing group of people bearing heavy physical and mental burdens, significantly reduced health related quality of life, heightened anxieties, and poorer outcomes. • Teclistamab's potential to markedly improve physical functioning and overall health is welcomed by many who would benefit from it.
9.	We strongly urge NICE to reconsider the decision to restrict access and push for wider access to PomDex exposed patients. If Teclistamab gives this group a better chance at longer-term success than the alternative, it should be considered instead of defaulting to a restriction that could remove this option entirely from a group of patients who otherwise face very poor outcomes.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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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

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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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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 (Janssen/Johnson and Johnson) in the last 12 months.

The table below shows the 2023 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

	Core grant	Research / Project	Donation	Consultancy/ Honoraria	Events	Total
AbbVie Ltd	-	10,000	-	870	-	10,870
Alexion Pharma UK Ltd	-	7,500	-	-	-	7,500
Amgen Ltd	-	20,000	-	-	-	20,000
The Binding Site Ltd	20,000	-	-	437	-	20,437
Bristol-Myers Squibb Pharmaceuticals Ltd	15,000	-	-	-	-	15,000
GlaxoSmithKline UK Limited	-	20,026	-	-	-	20,026
ITECHO Health Ltd	-	6,600	-	-	-	6,600
Janssen-Cilag Ltd	-	15,907	-	260	9,093	25,260
Menarini Stemline UK Limited	-	7,000	-	-	-	7,000
Pfizer Limited	-	-	-	73,448	-	73,448
Stemline Therapeutics Switzerland GmbH	-	-	-	1,451	-	1,451
Sanofi	-	-	-	-	27,990	27,990
Takeda UK	30,000	-	-	-	29,681	59,681
	65,000	**87,033**	**-**	**76,466**	**66,764**	295,263

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None

Name of commentator person completing form:

Caroline Donoghue

Comment number	**Comments**
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	We welcome NICE's decision to approve teclistamab for relapsed and refractory myeloma patients. It is a highly effective treatment that will extend and improve myeloma patients' lives.
2	**We believe that NICE's decision to restrict the use of teclistamab is unfair and unreasonable.** The decision to recommend teclistamab only as an alternative to pomalidomide plus dexamethasone' is unclear, insufficiently explained and inconsistent with previous appraisals. In the last five years (August 2019-August 2024), NICE appraised and published guidance for ten myeloma-specific HTAs. Four of these appraisals were reappraisals following initial approvals through the Cancer Drugs Fund. Of the ten appraisals conducted, five resulted in an optimised recommendation. None of these optimised recommendations restricted the use of treatments under review as an alternative to a comparator. All of the restrictions applied to these treatments are related to the treatments that patients had already had (number of treatment lines or type of drug e.g. anti-CD38) rather than the type of treatments they have not had. For example, in TA974 (selinexor, bortezomib and dexamethasone), selinexor was compared to panobinostat in the third-line setting. The appraisal did not result in eligibility restrictions, which required the appraised technology to be used only when panobinostat was offered as an alternative. Therefore, we are concerned that this decision doesn't accurately reflect the evidence presented and believe the restriction is unfair and unreasonable.
3	**We believe that the restriction applied to teclistamab is unreasonable because pomalidomide is the only relevant comparator for the licenced indication.** Myeloma is a complex and highly individual cancer with a varied and rapidly evolving treatment pathway. As a result, the current patient population is very varied with the number and type, of previous treatments received dependent on when they were diagnosed and when they relapsed. It can also be influenced by the number and type of clinical trials and free of charge schemes that are available. Whilst other treatments are used at fifth, sixth and seventh line, it is highly challenging to gather sufficient data to appraise new treatments across multiple lines when there is no real standard of care, and the patient cohort is heterogenous and small. For the patient population (triple class exposed patients) in scope for this appraisal it gets even harder. The treatments available to patients at fifth, six or seventh line are often clinical trials or salvage/last chance drugs which are used whenever a patient runs out of more effective, more tolerable options. These treatments are old and therefore there is very limited data on their efficacy in triple class exposed patients. The heterogeneity of triple class exposed myeloma patients is highlighted in the data from the HMRN dataset attached which includes triple classed exposed myeloma patients diagnosed between 2004-2019 and who started fourth line treatment in 2017 (after pomalidomide was approved). In this data, most patient became triple class exposed at either fourth or fifth line.

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	The data also shows that pomalidomide is the preferred treatment for patients who become triple-class exposed and that pomalidomide is widely used across 4th, 5th, 6th and 7th lines. Therefore, pomalidomide is a relevant comparator at all lines. We believe comparing teclistamab to pomalidomide is sufficient to justify approval for the full licenced indication.
4	**We believe the restriction applied to teclistamab is unreasonable and unnecessary given the predominant use of teclistamab in the myeloma pathway.** The decision to only recommend teclistamab as an alternative to pomalidomide exclusively impacts triple-class exposed myeloma patients who are currently getting pomalidomide or have already had pomalidomide and who will be fit enough to get teclistamab as their next line of treatment. This a small and finite group of patients. Clinicians will choose to use teclistamab as early as they can in the pathway, therefore the number of pomalidomide exposed patients who could benefit from the treatment will significantly reduce over time. Furthermore, data suggests that only 15% of patients will get four lines of treatment and 1% five or more. (Yong. et.al. 2016). Therefore, the number of people who are triple-class exposed and would go on to get teclistamab after receiving pomalidomide at fourth or fifth line will be very small and insignificant when compared to the number of triple-class exposed, pom-naïve patients who will get teclistamab at fourth line now and in the future. As a result, we believe the restriction is unnecessary, resulting in a significant and unacceptable inequality for a small cohort of myeloma patients. Ref: Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.
5	**We are concerned that the proposed recommendation excludes myeloma patients with the highest unmet need.** All patients who have already been exposed to pomalidomide will not be eligible for teclistamab due to the proposed restriction. Teclistamab could give these patients the chance of reaching complete response and significantly extending their life. It also gives them a kinder treatment option without high dose dexamethasone. The life expectancy for triple-class and pomalidomide exposed patients is typically less than < 6 months. On publication of the guidance Myeloma UK received several emails and calls from this group of patients worried about their future and their prospects beyond their current treatment. ***'Basically, this is close to a death sentence for me…… there aren't many people like me. I don't understand why it should be denied to the very people with no options left.'***

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	"Obviously teclistamab was a huge beacon of hope for me and it's unavailability to me feels like a death-sentence." ***"I am currently on 4th line treatment of Isatuximab, Pomalidomide and Dexamethasone (IPD). My kappa light chains have just begun to rise, albeit currently still at a low level (27). I am anxious about the next line of treatment that may be necessary. I have read about the excellent results that bi-specific antibody have given to people in my situation in the USA. My haematological consultant, has said that they would be the obvious next treatment to have if available. I am writing therefore to ask if you can urgently reconsider the restrictions on use of bi-specific antibodies for people like me."***
6	**We believe NICE's decision to restrict the use of teclistamab will unfairly impact patients whose treatment was impacted by the pandemic.** During the COVID-19 pandemic (March 2020-September 2023) pomalidomide was approved as an interim treatment for second- and third-line myeloma patients to reduce the need for chemotherapy and reduce admissions and risk of neutropenia. With the current restriction patients in this cohort will not be eligible for teclistamab. We don't believe this was considered when the restriction was applied. We believe it is unfair for patient in this cohort to miss out on a potentially effective treatment.
7	**We are concerned that patient evidence submitted and presented was not considered when applying the restriction to the use of teclistamab.** In our submission and the committee meeting we highlighted that teclistamab was a highly effective treatment for multiply relapsed and refractory patients. We emphasised the need for treatments with new mechanisms of action to overcome treatment resistance, highlighting that this need gets more significant with every relapse. We discussed how treatments like teclistamab, which deliver high response rates at later lines gave patients hope that there would be an effective option when they relapse. This is particularly true for patients at 5th line and beyond because there aren't really any effective options. The treatment options at this stage are either palliative care or older drugs that have significant toxicity and low response rates with most patients only achieving partial responses. We also shared perspectives from patients who were lucky enough to get teclistamab through clinical trials or compassionate use, showing the benefit the treatment can deliver for refractory myeloma patients. We also highlighted that teclistamab had the potential to transform the myeloma pathway changing the belief that relapse leads to worse response rates and remission times. The need for better treatments and the benefit teclistamab delivers is relevant to all triple class exposed and triple class refractory patients whether they have had pomalidomide or not. We believe based on this evidence that there should have been flexibility when assessing a treatment indicated across multiple lines in a complex and dynamic treatment pathway.
8	**We are concerned that NICE did not consider the negative impact of their decision to restrict the use teclistamab would have on clinical trials access and uptake in England.** There are 11 myeloma clinical trials actively recruiting in England that include pomalidomide containing combinations in at least one of the trial arms. Nine of these trials are recruiting patients at earlier lines.

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	We believe the current restriction will discourage clinical recommendation and patients wishing to join these trials and future trials as they will be concerned that joining the trial will lead to them missing out on a highly effective myeloma treatment. The NICE statement on clinical trial participation and subsequent access to drugs approved by NICE, is cited by clinicians and industry as being unclear. Furthermore, most patients are not aware of this statement. As such, there will be considerable hesitation about joining trials with pomalidomide containing regimens because there will be concerns about jeopardising access to teclistamab. This could have significant impact on trial recruitment, UK life sciences and myeloma treatment innovation.

Insert extra rows as needed

Checklist for submitting comments

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Started Fourth-line treatment from 2017 onwards

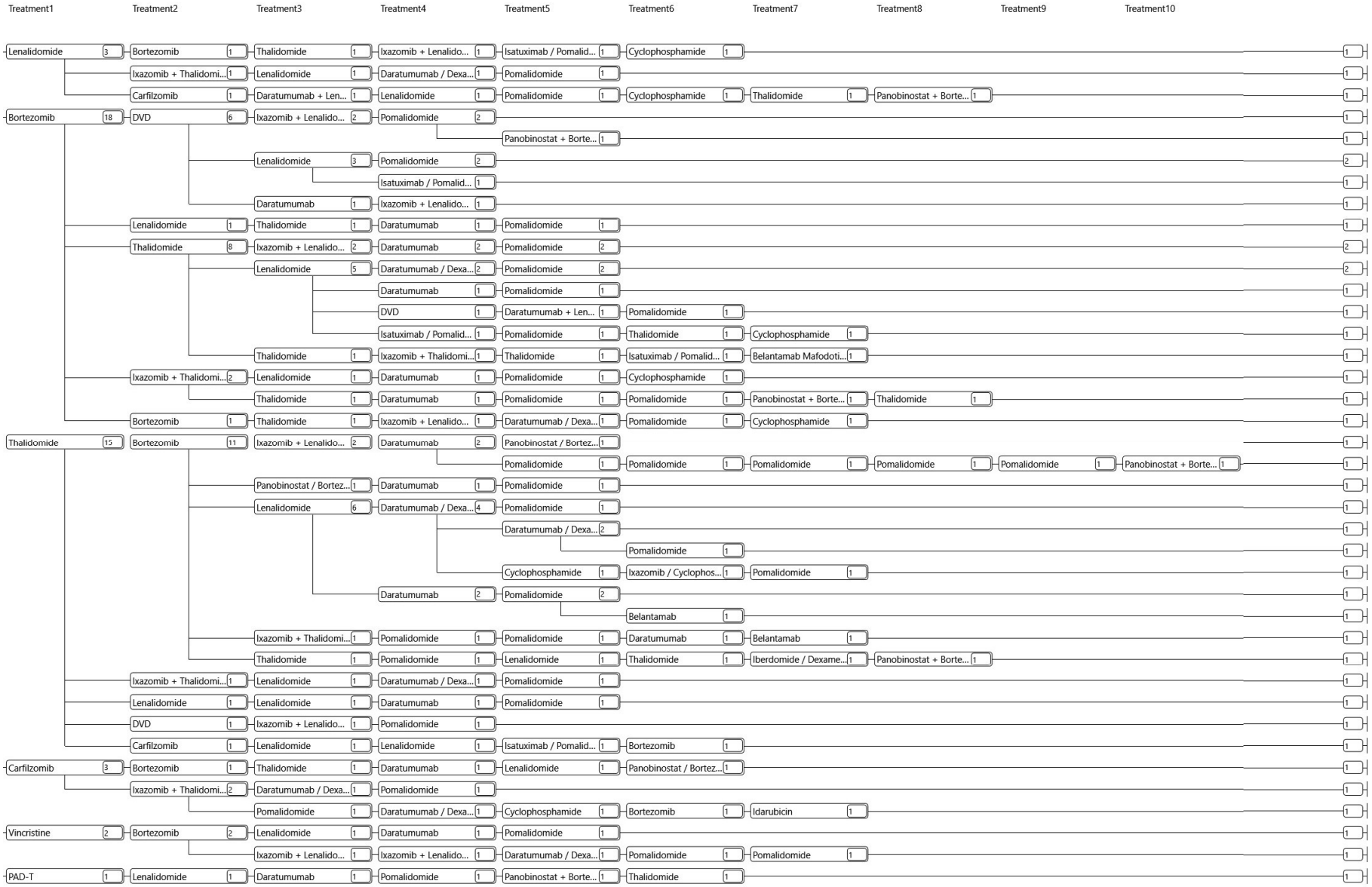
In total, 42 patients were identified who had received an immunomodulatory agent, a proteasome inhibitor, an anti-CD38 antibody (eligibility criteria) and they started Fourth-line treatment from 2017 onwards when pomalidomide was available (Table 3). Subjects are counted as many times at they received a treatment i.e. a patient who received 5th and 6th line after reaching the eligibility criteria their information will be included in the 5th and 6th line columns.

Table 1 Myeloma patients diagnosed 2004 to 2019 followed up to 2023 by treatment line: Haematological Malignancy Research Network

		Treatment line n (%)				
		4th Line	**5th Line**	**6th Line**	**7th Line**	**8th Line**
Total		**10**	**28**	**16**	**10**	**4**
No previous treatment with pomalidomide		10 (100)	24 (85.7)	6 (37.5)	1 (10.0)	0
Previous treatment with pomalidomide		0	4 (14.3)	10 (62.5)	9 (90.0)	4 (100)
Median age at start of treatment line years (IQR)	No previous treatment with pomalidomide	69.7 (64.3 - 76.0)	69.8 (65.7 - 73.3)	72.0 (48.4 - 76.2)	72.8 (72.8 - 72.8)	-
	Previous treatment with pomalidomide	-	68.0 (62.4 - 73.5)	70.4 (68.8 - 75.8)	69.1 (60.6 - 76.1)	69.7 (63.7 - 70.0)
Median time since diagnosis (years) (IQR)	No previous treatment with pomalidomide	4.9 (3.5 - 6.7)	4.9 (2.7 - 8.5)	5.2 (3.3 - 8.9)	6.2 (6.2 - 6.2)	-
	Previous treatment with pomalidomide	-	5.3 (4.8 - 7.8)	6.2 (5.2 - 9.4)	7.5 (6.0 - 8.3)	7.4 (5.6 - 8.4)
Median time since start of first-line chemotherapy (years) (IQR)	No previous treatment with pomalidomide	4.1 (3.5 - 5.5)	4.9 (2.7 - 8.5)	5.2 (3.3 - 8.8)	6.1 (6.1 - 6.1)	-
	Previous treatment with pomalidomide	-	5.3 (4.7 - 5.9)	5.9 (5.1 - 7.2)	6.5 (5.9 - 7.9)	7.3 (5.5 - 8.3)
Median year of previous treatment line (range)	No previous treatment with pomalidomide	2021 (2014 - 2022)	2019 (2017 - 2021)	2018.5 (2018 - 2020)	2019 (2019 - 2019)	-
	Previous treatment with pomalidomide		2020 (2018 - 2021)	2020 (2017 - 2021)	2020 (2017 - 2021)	2020 (2017 - 2021)
Treatment Regimen:						
Belantamab		-	-	1 (6.3)	2 (20.0)	-
Bortezomib / Dexamethasone		-	-	1 (6.3)	-	-
CTD		-	-	-	-	1 (25.0)
CTDa		-	-	-	1 (10.0)	-
Cyclophosphamide		-	-	1 (6.3)	-	-
Cyclophosphamide / Dexamethasone		-	2 (7.1)	2 (12.5)	1 (10.0)	-
Cyclophosphamide / Prednisolone		-	-	-	1 (10.0)	-
Daratumumab / Dexamethasone		-	2 (7.1)	-	-	-
Daratumumab / Lenalidomide / Dexamethasone		-	1 (3.6)	-	-	-
Iberdomide / Dexamethasone		-	-	-	-	-
Ixazomib / Cyclophosphamide / Dexamethasone		-	-	1 (6.3)	-	-
Isatuximab / Pomalidomide / Dexamethasone		1 (10.0)	-	-	-	-
Lenalidomide / Dexamethasone		1 (10.0)	1 (3.6)	-	-	-
Lenalidomide / Ixazomib / Dexamethasone		1 (10.0)	-	-	-	-
MPT		-	-	1 (6.3)	-	-
PAD		-	-	1 (6.3)	-	-
Panobinostat / Bortezomib		-	1 (3.6)	1 (6.3)	-	-
Panobinostat / Bortezomib / Dexamethasone		-	2 (7.1)	-	1 (10.0)	2 (50.0)
Pomalidomide			2 (7.1)			
Pomalidomide / Cyclophosphamide / Dexamethasone		1 (10.0)	1 (3.6)	2 (12.5)	-	1 (25.0)
Pomalidomide / Dexamethasone		6 (60.0)	16 (57.1)	4 (25.0)	3 (30.0)	-
TIDE		-	-	1 (6.3)	-	-

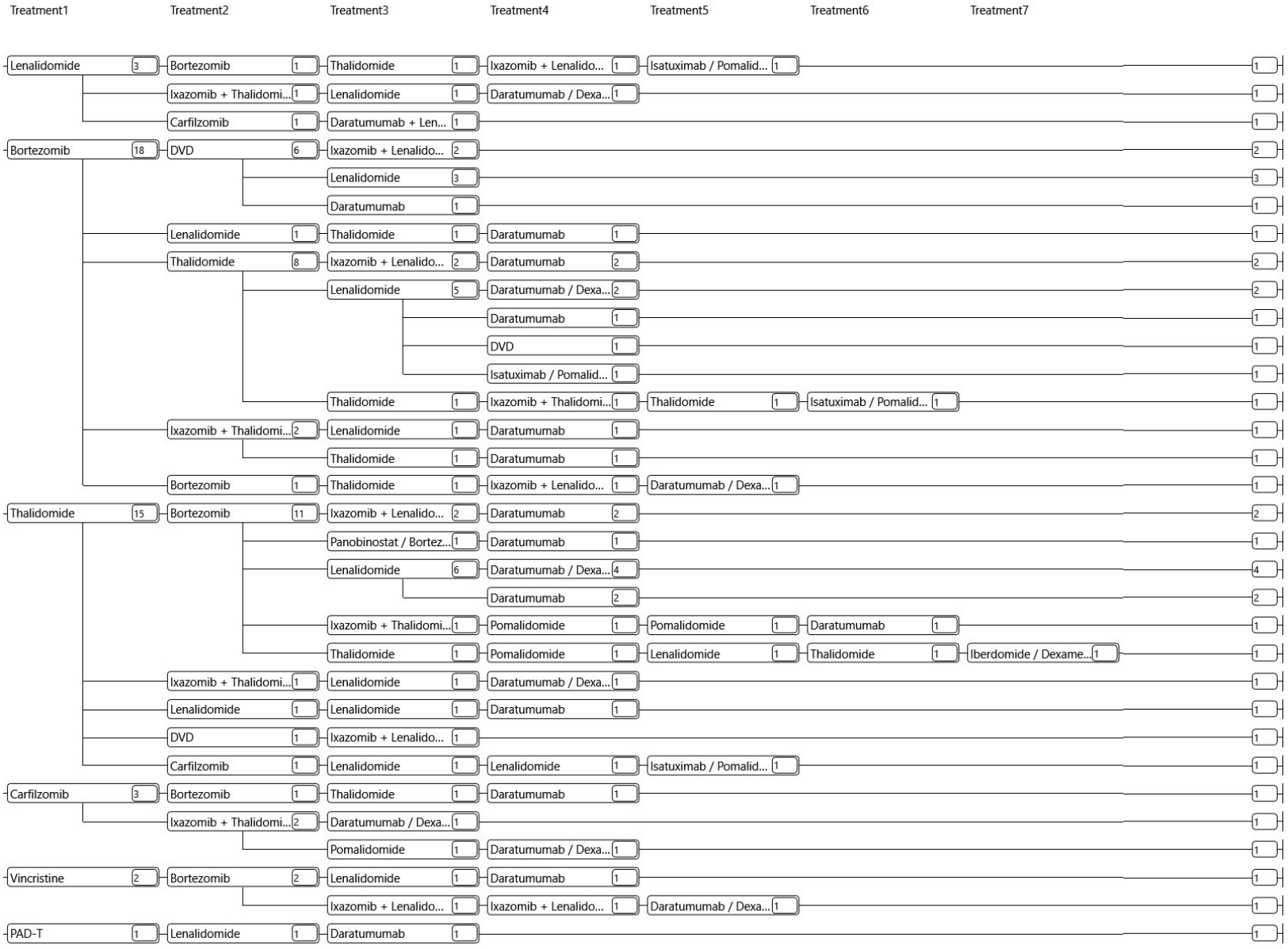
Z-DEX	-	-	-	1 (10.0)	-

Figure 1 Complete treatment[1] pathway for patients meeting criteria[2] and started Fourth-line treatment from 2017 onwards



[1] Grouped using main regimen agent(s). [2] Received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody

Figure 2 Treatment[1] history for patients prior to criteria completion[2] where Fourth-line treatment started from 2017 onwards



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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. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer Ltd.

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NICE National Institute for Health and Care Excellence

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 13 August 2024. Please submit via NICE Docs.

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.	Pfizer Ltd holds a marketing authorisation in the UK for a similar Bi Specific Antibody, elranatamab.
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** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The teclistimab treatment recommendation is inconsistent with elranatamab (ID4026) based on line of treatment (LOT): the recommendations are not aligned across these two current appraisals despite the same approach to the decision problem. We ask that

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	NICE and the committee provides clarity and ensure consistency in decision-making on this point. It is unclear why the recommendations within Draft Guidance for teclistamab (ID6333) and elranatamab (ID4026) differs from each other when the medicines are both bispecific antibody treatments being evaluated for the same disease and patient population with the same comparator. The wording in this appraisal recommendation (ID6333) refers to "3 or more treatments" whereas the elranatamab appraisal recommendation refers to "3 or more lines of treatment". We assume this is due to. a) Inconsistent decision-making across committees, or b) That "number of treatments" and "lines of treatment" are incorrectly considered interchangeable by NICE In the case of a) We ask that NICE and the committee provides clarity and ensure consistency in decision-making on this point. Pfizer emphasises the importance of ensuring guidance is clear and clinically meaningful in practice and does not create clinical ambiguity and uncertainty by using different terminology where no difference is intended. If b) We argue that these terms are not interchangeable. There are several combination treatments (including immune mediated inflammatory disease (IMiD), protease inhibitor (PI) and anti-CD38 monoclonal antibody (mAb) classes of treatments) being used across, and increasingly earlier, in the treatment pathway. This has changed the onset of refractoriness whereby patients are exposed and refractory to these (multiple) therapies earlier in the treatment pathway, and this trend is expected to continue. Therefore, patients receive multiple "treatments" in early lines of therapy in combination and therefore the onset of exposure and refractoriness to those treatments also moves earlier in the treatment pathway. For example, a patient having received 3 LOT increasingly receive multiple combinations of treatments making a recommendation based on LOT irrelevant to clinical decision making. Patients' ineligible today based on LOT, might quickly become eligible per licensed indication, as this "shift" continues over time as more patients become TCE RRMM earlier in the pathway. We ask that the committee, consider whether these terms are in fact interchangeable and provide clarity on how the recommendation should be interpreted given the evidence.
2	
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Insert extra rows as needed

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the 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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EAG RESPONSE TO COMPANY RESPONSE TO NICE DRAFT GUIDANCE

1.1 Introduction

In response to NICE Draft Guidance, the company raised concerns about the NICE proposal to restrict teclistamab to the population who would otherwise receive pomalidomide with dexamethasone (PomDex).

The External Assessment Group (EAG) has undertaken a pragmatic, targeted assessment of the additional evidence provided by the company.

1.2 Choice of relevant comparator

The focus of the original company submission (CS) was on the ≥3 line setting. However, as PomDex is only available in the ≥4 line setting, the company has focused on active comparators that are available to patients in the ≥5 line setting, i.e., panobinostat in combination with bortezomib and dexamethasone (PanBorDex) and selinexor in combination with dexamethasone (SelDex).

PanBorDex

In the original teclistamab CS, the company explained that:

> *PanBorDex was historically used in patients with RRMM after three prior therapies, but is no longer used due to ongoing toxicity concerns. This view was supported by clinical experts in TA658, TA783 and as part of a NICE ACD for TA10568 (belantamab mafodotin) where clinicians stated that "PanBorDex is rarely used in clinical practice*" (CS, Table 1).

Recent clinical advice to NICE[1] was that clinicians would not risk treating patients with multiple myeloma that was refractory to two proteasome inhibitors (PI) with a third PI (i.e. bortezomib, as part of PanBorDex) due to toxicity and limited efficacy concerns. At least 70.3% of the MajesTEC-1 trial population had previously been treated with two PIs (CS, Table 8).

The EAG therefore considers that PanBorDex is not a relevant comparator to teclistamab for the triple class exposed (TCE) population who were also pomalidomide-exposed.

SelDex

NICE SelDex TA970 Final Guidance[1] was published in May 2024. To receive SelDex, patients must have received >4 lines of treatment and be penta-refractory (i.e., must be refractory to

two PIs, two immunomodulatory imide drugs (IMiDs) and an anti-CD38 monoclonal antibody (mAb). Clinical advice to the company was that few patients are penta-refractory.

Best supportive care

In the NHS, PomDex is only recommended as an option for patients who have had ≥3 previous treatments (TA427[2] recommendation). Therefore, PomDex-exposed NHS patients should all have had ≥4 lines of treatment. The NICE TA970 AC[1] concluded that standard of care for NHS patients who had received ≥4 lines of treatment was best supportive care (BSC). Therefore, the EAG considers that the most appropriate comparator to teclistamab for PomDex-exposed NHS patients who have had ≥4 lines of treatment is BSC, or SelDex if patients are penta-refractory.

The company has not provided any clinical or cost effectiveness evidence for the comparison of teclistamab versus BSC. However, the NICE TA970 AC[1] determined that, compared with BSC, SelDex is a cost effective option for NHS patients. As SelDex is considered cost effective versus BSC, if teclistamab is cost effective versus SelDex, then teclistamab is also cost effective versus BSC.

1.3 EAG summary and critique of teclistamab versus SelDex clinical effectiveness evidence

Due to the absence of a common comparator, the company conducted unanchored matching-adjusted indirect comparisons (MAICs) to estimate the relative treatment effects of teclistamab (MajesTEC-1 trial August 2023 DCO, IPD) versus SelDex (aggregate STORM trial data). The MajesTEC-1 trial population was adjusted to match STORM trial eligibility criteria and distribution of prognostic factors. The covariates adjusted for in the base case were refractory status, cytogenetic profile, international staging system/revised international staging system (ISS/R-ISS) stage, presence of extramedullary disease and the number of prior lines of therapy received.

Key outcomes were progression-free survival (PFS) and overall survival (OS). PFS results numerically favour teclistamab but are not statistically significant (adjusted hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.33 to 1.13; p-value: 0.1164). OS MAIC results statistically significantly favour teclistamab (adjusted HR: 0.55; 95% CI: 0.33 to 0.93; p-value: 0.0265).

1.3.1 EAG critique of company MAIC

- The EAG considers that company MAIC methods were appropriate and agrees with the company that the populations were well matched after adjusting. However, following adjustment, the MajesTEC-1 trial effective sample size was only N=[redacted] ([redacted] MajesTEC-1 trial patients were excluded).

- It is not clear from the provided information whether all the MajesTEC-1 trial patients who provided the data that informed the unanchored MAICs had been previously treated with PomDex.
- Due to the absence of a common comparator, the company was only able to carry out unanchored MAICs. The company unanchored MAIC point estimates are associated with wide confidence intervals, reflecting the uncertainty around the relative effectiveness of teclistamab and SelDex.
- It is not known whether the proportional hazards (PH) assumptions hold. When using Cox PH models to compare time to event outcomes, violation of the PH assumption can lead to biased results and incorrect inferences.

1.4 EAG critique of teclistamab versus SelDex cost effectiveness evidence

1.4.1 Company model parameters: teclistamab

Comparison, at 5 years, of model PFS, OS and time to treatment discontinuation (TTD) estimates and clinician estimates suggests that:

- teclistamab PFS is above the upper bound of clinician estimates (modelled PFS of 20.9% versus clinician estimates of 20% at the upper bound with a 13.5% midpoint estimate).
- teclistamab OS is above the mid-point of clinician estimates (modelled OS of 26.6% versus clinician estimates of 30% at the upper bound with a 21% midpoint estimate).
- teclistamab TTD is above the mid-point of clinician estimates (modelled TTD of [redacted]% versus a midpoint of 12% and upper bound of 20%)

None of the alternative parametric distributions considered by the company to generate teclistamab PFS or OS estimates were a better fit to the MajesTEC-1 trial MAIC adjusted teclistamab K-M data whilst also generating 5-year estimates that were closer to the midpoint of clinician estimates than the parametric distributions used by the company.

The EAG considers that, at 5 years, compared with clinician estimates, the distributions chosen by the company may slightly overestimate patient benefit (PFS and OS) and costs (TTD) for patients treated with teclistamab. If the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained is not close to the cost effectiveness threshold, the EAG considers that it is unlikely that the overestimations would affect cost effectiveness conclusions.

1.4.2 Company model parameter values: SelDex

Comparison of company model PFS, OS and TTD estimates with TA970[1] K-M data is provided in Table 1.

Table 1 Comparison of company model PFS, OS and TTD estimates with TA970 SelDex data

Time point	Company model	TA970	EAG
Progression-free survival			
1 year	9.7%	3.12%	3.98%
Overall survival			
1 year	36%	37.99%	-
2 years	12%	16.12%	-
Time to treatment discontinuation			
1 year	[redacted]	0.75%	[redacted]

EAG=External Assessment Group; OS=overall survival; PFS=progression-free survival; SelDex=selinexor in combination with dexamethasone; TTD=time to treatment discontinuation

The EAG considers that:

- The company's PFS estimate at 1 year (generated using a log normal distribution) appears very optimistic (9.7%). The Weibull distribution provides a closer match (3.98%) to the TA970[1] 1 year PFS estimate (3.12%) than the distribution used by the company.
- The company OS estimates appear pessimistic; however, survival for this population is low so the impact of the potential underestimate is probably small. None of the alternative parametric distributions that did not have implausible long tails provided a closer fit to TA970[1] data.
- The company used adjusted PFS as a proxy for TTD leading to 1 year TTD estimates that were much higher than TA970[1] TTD data. Using a Weibull distribution to generate PFS estimates reduces 1 year TTD to [redacted]%.

1.4.3 Utility values

The SelDex progressed disease (PD) value is lower than the teclistamab PD utility value. The EAG has therefore reduced the teclistamab PD utility value to match the SelDex PD utility value.

1.4.4 Severity modifier

The EAG considers that it is appropriate to use a severity modifier of 1.7 for the comparison of teclistamab versus SelDex.

1.4.5 Other model parameters

The EAG is satisfied that the company approaches to modelling subsequent therapies, relative dose intensity and adverse events were appropriate.

1.5 Summary of EAG revisions to the company model

The company base case cost effectiveness results presented in the company response to NICE Draft Guidance do not match the base case cost effectiveness results generated by the company model. The EAG revisions have been made to the base case cost effectiveness results generated by the company model.

The EAG has made two revisions to the company base case analysis:

- PFS estimates for patients treated with SelDex are generated using a Weibull distribution
- the PD utility value for patients treated with teclistamab is reduced to 0.535 to match the TA970[1] PD utility value for patients treated with SelDex

Deterministic cost effectiveness results, generated using list prices, for the comparison of teclistamab versus SelDex are presented in Table 2. Deterministic and probabilistic cost effectiveness results generated using confidential prices will be provided in a confidential appendix.

Table 2 Deterministic cost effectiveness results for teclistamab versus SelDex (list prices for teclistamab and SelDex)

Technology	Teclistamab		SelDex		Incremental		ICER (£/QALY)	Change from base case
	Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs (x 1.7)		
A. Company base case (company response)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
B. Company base case (company model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) Use Weibull distribution to generate SelDex PFS estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Reduce teclistamab PD health state utility values to match SelDex PD utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C. EAG revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PD=progressed disease; PFS=progression-free survival; QALYs=quality adjusted life years; SelDex=selinexor in combination with dexamethasone

2 REFERENCES

1. National Institute for Health and Care Excellence. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments. Technology appraisal guidance. TA970. Published 8 May 2024; Available from: https://www.nice.org.uk/guidance/ta970. Accessed 19 August 2024.
2. National Institute for Health and Care Excellence. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. Technology appraisal guidance. TA427. Published 11 January 2017; Available from: https://www.nice.org.uk/guidance/ta427. Accessed 19 August 2024.