NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Novartis
   - UK Myeloma Forum
   - Royal College of Nursing
   - Janssen

   'No comment' response received from the Department of Health

3. **Addendum to ACD response** from Novartis

4. **Evidence Review Group critique of the company ACD response prepared** by PenTAG

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Panobinostat for treating multiple myeloma after at least 2 previous treatments

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Novartis	*The company provided comments and new evidence incorporating time-dependent hazard ratios derived using the matching adjusted indirect comparison method after independently fitting parametric curves to the Pano-Bort-Dex and Len-Dex data (Not reproduced here). Please see FAD section 3.24 to 3.27 for a summary.*	Comments noted. The Committee considered the comments and new evidence presented incorporating time-dependent hazard ratios. The Committee concluded that the use of time-dependent hazard ratios based on the matching adjusted indirect comparison was acceptable in its decision- making (see FAD section 4.6).
Novartis	*The company provided comments and new evidence incorporating an updated patient access scheme, comprising a confidential simple discount on the list price of panobinostat (Not reproduced here). Please see FAD section 3.24 to 3.27 for a summary.*	Comments noted. The Committee considered all of the new evidence available including the main comparison of panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone, and the additional comparison of panobinostat plus bortezomib and dexamethasone compared with bortezomib plus dexamethasone which included the updated patient access scheme (see FAD section 3.24 to 3.27). The Committee considered that this analysis was not required for its decision making because the company had provided a new indirect comparison with the relevant comparator (lenalidomide plus dexamethasone). The Committee agreed that the new cost-effectiveness analyses provided by the company for the comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone were relevant to its decision making (see FAD section 4.6 and 4.7).
Novartis	*The company provided comments and new evidence incorporating new final overall survival data from the PANORAMA-1 trial. (Not reproduced here). Please see FAD*	Comments noted. The Committee considered the comments and new evidence incorporating new

Consultee	Comment [sic]	Response
	section 3.24 to 3.27 for a summary.	final overall survival data. The Committee accepted that the results from the PANORAMA-1 trial used in the post hoc subgroup analysis demonstrated that panobinostat plus bortezomib and dexamethasone was clinically more effective than bortezomib plus dexamethasone based on the interim and final overall survival data (see FAD section 4.3).
Novartis	*The company provided comments and new evidence incorporating a comparison of Pano-Bort-Dex with Bort-Dex for patients with relapsed and/or refractory multiple myeloma who have had at least 2 prior regimens including bortezomib and an immunomodulatory agent (Not reproduced here). Please see FAD section 3.24 for a summary.*	Comments noted. The Committee considered the comparison with Bort-Dex. However, the Committee considered that this analysis was not required for its decision making because the company had provided a new indirect comparison with the relevant comparator (lenalidomide plus dexamethasone). The Committee therefore considered that bortezomib plus dexamethasone was not the appropriate comparator and agreed not to consider this comparison further (see FAD section 4.7).
Royal College of Nursing	The RCN welcomed the opportunity to review this document. The comments below reflect the views of our reviewers in response to the questions on which comments were requested: i) **Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with multiple myeloma. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. Comment noted. The Committee heard from the clinical experts that the pathway of treatment is heterogeneous and people could have either thalidomide or bortezomib, plus an alkylating agent and a corticosteroid, as first-line treatment. This may be followed by bortezomib and then lenalidomide. The Committee also heard from the clinical experts that almost all patients have bortezomib by subcutaneous rather than intravenous administration. The Committee also heard from the clinical experts that panobinostat plus bortezomib and dexamethasone would likely fit

Consultee	Comment [sic]	Response
		in the treatment pathway at the same point as lenalidomide plus dexamethasone (see FAD section 4.1).
	iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The appraisal committee seems to have adopted a comprehensive approach to this work. There are no other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted. Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme (see FAD section 1.1)
	Iv) **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**	
	v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. See NICE Equality impact assessment for panobinostat.
UK Myeloma Forum	We are writing on behalf of the UK myeloma forum that represents Haematologist in	

Consultee	Comment [sic]	Response
	the UK with an interest in myeloma. We are disappointed with the ACD for Panobinostat for treating multiple myeloma in people who have received at least one prior therapy because we feel that panobinostat when used in combination with bortezomib and dexamethasone has clinical utility in patients with relapsed myeloma. The initial pre-clinical studies showed a synergy for this combination of drugs based on their inhibition of distinct pathways of protein degradation that are critical for the survival of myeloma plasma cells. Subsequently clinical efficacy was clearly demonstrated in the phase 3 PANORAMA 1 study that compared panobinostat/bortezomib/dexamethasone to bortezomib/dexamethasone with meaningful improvements in response and duration of response. The TA was complicated by the drug company involved choosing the comparator lenalidomide and dexamethasone for their health economic model. The reasons for choosing the comparator lenalidomide/dexamethasone were not entirely clear but clearly involved a concern that (re-treatment with) bortezomib/dexamethasone would no longer be available for patients in the UK as a treatment at relapse. The patient group who received 1-4 prior lines in the Phase 3 studies of lenalidomide/dexamethasone are not comparable to the patient cohort in the PANORAMA study, as they had had less exposure to novel drugs such as bortezomib, and treatment pathways have changed considerably in the last 10 years. The use of these subgroups in the health economic model therefore led to uncertainty and did not, in our view, produce a model that was adequate to the task. We feel that the comparator should have been bortezomib/dexamethasone as it made any health economic analysis much more straightforward and robust (given it would be comparing arms of the PANORAMA trial) and also we feel that access to	Comment noted. Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme (see FAD section 1.1) Comment noted. The Committee heard from the clinical experts that panobinostat plus bortezomib and dexamethasone would likely fit in the treatment pathway at the same point as lenalidomide plus dexamethasone (that is, after bortezomib and dexamethasone), and so the Committee considered that lenalidomide plus dexamethasone was the most appropriate comparator to panobinostat plus bortezomib and dexamethasone in this appraisal. (see FAD section 4.1). Comment noted. The Committee considered the cost-effectiveness analysis comparing panobinostat plus bortezomib and dexamethasone with bortezomib plus dexamethasone. However, the

Consultee	Comment [sic]	Response
	bortezomib/dexamethasone at relapse, although currently threatened is an established treatment for myeloma. Failure to gain access to panobinostat in this setting will undoubtedly negatively impact on patient outcomes.	Committee considered that this analysis was not required for its decision making because the company had provided a new indirect comparison with the relevant comparator (lenalidomide plus dexamethasone). The Committee therefore considered that bortezomib plus dexamethasone was not the appropriate comparator and agreed not to consider this comparison further (see FAD section 4.7).

Comments received from commentators

Commentator	Comment [sic]	Response
Janssen	• Janssen welcome NICE's acknowledgement that retreatment with bortezomib is part of established UK clinical practice. We note that established practice, based on previous criteria of the National Cancer Drugs Fund (NCDF), is to retreat with bortezomib only those patients who have had at least a prior partial response to bortezomib for at least 6 months. Evidence for bortezomib retreatment comes from a number of studies including RETRIEVE and 22 others included in a large meta-analysis by Knopf et al (Petrucci 2013, Knopf 2014). We also wish to highlight that the NHS England National Chemotherapy Algorithm for Multiple Myeloma is not yet published in its final version. Therefore, we do not believe it is appropriate to prejudge how recent changes to the NCDF for myeloma treatments including bortezomib, lenalidomide and pomalidomide will be incorporated into the final version.	Comment noted. The Committee heard from the clinical experts that the pathway of treatment is heterogeneous and people could have either thalidomide or bortezomib, plus an alkylating agent and a corticosteroid, as first-line treatment. This may be followed by bortezomib and then lenalidomide. The Committee also heard from the clinical experts that almost all patients have bortezomib by subcutaneous rather than intravenous administration. The Committee also heard from the clinical experts that panobinostat plus bortezomib and dexamethasone would likely fit in the treatment pathway at the same point as lenalidomide plus dexamethasone (see FAD section 4.1).
	• It is not clear if further analysis will be considered by the Committee to assess the clinical and cost effectiveness of panobinostat in combination with bortezomib and dexamethasone (PAN/BTZ/DEX) vs bortezomib and dexamethasone (BTZ/DEX) in the subgroup of PANORAMA-1 who received ≥2	Comment noted. The Committee considered the comments and new evidence submitted by the company which included new evidence regarding the comparison of panobinostat plus bortezomib and dexamethasone with bortezomib plus dexamethasone (see FAD section 3.24). The

Commentator	Comment [sic]	Response
	prior treatments including bortezomib and an immunomodulatory therapy (IMiD). However, we wish to highlight that the adjustments made to the economic model analysing the full trial population to adapt the use of BTZ/DEX as applied in the trial to UK practice (ie. reducing maximum treatment duration) may not have taken full account of the expected improvement in the tolerability profile of BTZ/DEX. As the ERG has highlighted in its report, the trial-based utilities of PAN/BTZ/DEX may be overestimated compared to BTZ/DEX as the poorer tolerability profile for PAN/BTZ/DEX may not have been fully captured. The magnitude of the overestimation could be larger still when considering the extended treatment duration of BTZ/DEX in the trial vs routine practice. It is also unclear to what extent the PANORAMA-1 study will reflect the use of bortezomib retreatment in patients with prior response as in UK clinical practice, as noted above. • Janssen note that the Velcade Response Scheme (VRS) relates to TA129 – bortezomib for the treatment of progressive multiple myeloma in people who are at first relapse. Whilst the VRS is not referred to within the ACD and may therefore be irrelevant to the current recommendation, we note that this is mentioned on slide 3 (cost effectiveness analysis presentation) presented at the first Appraisal Committee meeting (18.08.15). This slide notes the 'bortezomib PAS' as being included in the company assumptions for the subgroup analysis of patients who received ≥2 prior treatments that was discussed during the meeting. **References** Knopf K, et al. Meta-Analysis of the Efficacy and Safety of Bortezomib Re-Treatment in Patients With Multiple Myeloma Clinical Lymphoma, Myeloma & Leukemia, 2014 14 (5): 380-8 Petrucci MT, Giraldo P, Corradini P, Teixeira A, Dimopoulos MA, Blau IW, et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol 2013 Mar;160(5):649-59.	Committee recalled that the PANORAMA-1 trial included a comparison of panobinostat plus bortezomib and dexamethasone with bortezomib plus dexamethasone, providing trial data for this comparison in the population included in the marketing authorisation for panobinostat. However, the Committee considered that this analysis was not required for its decision making because the company had provided a new indirect comparison with the relevant comparator (lenalidomide plus dexamethasone). The Committee therefore considered that bortezomib plus dexamethasone was not the appropriate comparator and agreed not to consider this comparison further. (see FAD section 4.7). Comment noted. The patient access scheme for bortezomib was not included in the company's analyses because it only applies to bortezomib monotherapy in people whose multiple myeloma has relapsed for the first time after having one treatment (see NICE technology appraisal guidance on bortezomib for relapsed multiple myeloma) (see FAD sections 3.17 and 3.24).

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Manufacturer's response to the ACD

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Abbreviations

ACD	appraisal consultation document
AIC	Akaike information criterion
ASCT	autologous stem cell transplantation
ASH	American Society of Hematology
BIC	Bayesian information criterion
BSC	best supportive care
BTZ	bortezomib
CDF	Cancer Drug Fund
CI	confidence interval
DEX	dexamethasone
EMA	European Medicines Agency
ERG	Evidence Review Group
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drug
ISS	International Staging System
ITT	intention-to-treat
LEN	lenalidomide
LLoT	last line of treatment
LY	life year
MAIC	matching adjusted indirect treatment comparison
MM	multiple myeloma
MRU	medical resource utilisation
NICE	National Institute for Health and Care Excellence
OS	overall survival
PANO	panobinostat
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazard
POM	pomalidomide
QALY	quality-adjusted life years
rrMM	relapsed/refractory MM
STA	Single Technology Appraisal
THAL	thalidomide
TTP	time to progression

1 Response

In this document, and the related Addendum, Novartis responds to the challenges raised by the Evidence Review Group (ERG), at the first Appraisal Committee meeting, and in the appraisal consultation document (ACD). Novartis considers that the analyses presented can address these challenges and serve to reduce the clinical and economic uncertainties.

1.1 Overview of further analyses

Section 2 describes an alternative method for determining the relative efficacy of the panobinostat regimen (PANO/BTZ/DEX) versus lenalidomide plus dexamethasone (LEN/DEX), the current standard of care in the patient population corresponding to the panobinostat licensed indication (ie patients who have received at least two prior treatments including an immunomodulatory drug (IMiD) and bortezomib (BTZ). It addresses the concerns of the ERG as well as the explicit requests in the ACD to maintain a sufficient effective patient number (ACD, Section 3.27 and 4.8) as well as to apply independently fitted survival curves to the two arms (ACD, Section 4.7 and 4.8)[a]. The updated method is matching only to those significant baseline prognostic factors which predict survival and applies time dependent HRs, i.e. avoiding the use of constant hazards. The updated method described in this current document is populated with the interim PANORAMA-1 OS data.

Section 3 describes a new direct comparison of PANO/BTZ/DEX versus BTZ/DEX, and is in response to the explicit suggestion of the AC (ACD, Section 4.4 and 4.10) that such an analysis should have been provided in our original submission for the subgroup of interest. The analysis described here is based directly on data from PANORAMA-1 but for the subgroup of patients corresponding to the panobinostat licensed indication. Furthermore, only patients who had responded to prior treatment with BTZ were included, in line with the former requirements of the Cancer Drug Fund (CDF) for use of BTZ. This additional direct comparison model is populated with the final PANORAMA-1 OS data described in the Addendum to the Manufacturer's Response to the ACD. Novartis maintains its view that BTZ in combination with DEX is not an appropriate comparator in current UK clinical practice following the CDF delisting of BTZ earlier this year. However, Novartis acknowledges that this direct comparison provides valuable additional information regarding the economic analysis of PANO/BTZ/DEX and may assist the Appraisal Committee in making its decision.

In the Addendum to the Manufacturer's Response to the ACD the final OS data is presented. The indirect treatment comparison method as described in this current document, together with a direct comparison against BTZ/DEX as requested by the AC and the ACD – populated with the final OS data from PANORAMA-1 and assuming the higher discount – is also presented in the Addendum.

[a] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

We believe that these two documents with the final OS data and the two CE analyses (i.e. indirect against LEN/DEX and direct against BTZ/DEX) will aid the AC to make an informed decision on the efficacy of Panobinostat.

Sensitivity analysis is also provided with removing subsequent active treatments as suggested in the ACD (ACD, Section 4.12).

1.2 End of Life criteria

In light of the final OS data presented in Appendix 1 of the Addendum to the Manufacturer's Response to the ACD, Novartis reiterates its view that panobinostat in combination with BTZ and DEX meets the End of Life criteria for the following reasons:

- A retrospective audit performed by the Haematological Malignancy Research Network (HMRN)[1] in relation to a cohort of 1645 patients with multiple myeloma (MM) diagnosed between September 2004 and August 2011 suggests that OS for patients receiving third-line therapy is 1.1 years (95% confidence interval [CI]: 0.8-1.4) from the start of the third line regimen for patients who receive LEN/DEX as third-line therapy, in line with the related NICE Guidance (TA171). This subgroup specific additional information is provided to address the life expectancy of patients having lenalidomide plus dexamethasone after 2 previous treatments in England (ACD, Section 4.16).
- The final OS data from the PANORAMA-1 trial shows a numerical benefit of [redacted] months for PANO/BTZ/DEX vs BTZ/DEX in the EMA labelled population.[b] This addresses concerns raised regarding the additional survival benefit of PANO/BTZ/DEX (ACD, Section 4.17). This trial data represents the only available direct survival comparison of PANO/BTZ/DEX against a current standard of care treatment. However, the *modelled* OS benefit of PANO/BTZ/DEX vs LEN/DEX is 2.52 months.
- Novartis assumes the eligible patient population to be around 930[c] in England and Wales in the following setting: patients who have received at least two prior treatments including an IMiD and BTZ. This addresses the request for eligible population data for the subgroup in line with the EMA licence (ACD, Section 4.18).

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[b] Shared in the Addendum together with further analysis populated with the final OS data from PANORAMA-1 trial assuming a higher offered discount

[c]

Annual incidence: 3,138; calculated based on a total population of 58,112,666 for 2016 and an incidence rate of 5,4/100,000; Source: Office of National Statistics and Cancer Research UK;

Treatment rate: 70.4%; Source: Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0;

3-year survival rate: 52.7%; 3-year survival rate is used as a proxy for patients eligible for 3rd line treatment; Source: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Multiple-Myeloma/

Proportion of patient having received ≥2 prior lines including an IMiD and BTZ: 54.5%; Source: Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0. However, based on expert inputs this proportion is assumed to be around **80%** in most centres.

1.3 Cost effectiveness result

Results for the cost-effectiveness analysis comparing PANO/BTZ/DEX with LEN/DEX is summarised below in Table 1 and also in

Table 12.

Table 1 Summary of base case cost effectiveness results comparing PANO/BTZ/DEX with a) LEN/DEX and b) BTZ/DEX with PAS

a)

With PAS[d]	**Total**			**Incremental versus LEN/DEX**			**ICER vs LEN/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£146,310	2.29	1.52	£3,262	0.18	0.106	£30,701	£17,833
LEN/DEX	£143,048	2.10	1.41					

Time dependent HRs derived using MAIC method applied to subpopulation (2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year

b)

With PAS[e]	**Total**			**Incremental versus BTZ/DEX**			**ICER vs BTZ/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£137,447	2.491	1.652	£5,891	0.245	0.172	£34,333	£24,095
BTZ/DEX	£131,555	2.247	1.480					

Direct comparison based on the PANORAMA-1 trial using data for the subpopulations with at least 2 prior lines of treatment including an IMiD and BTZ including only those responding to the prior BTZ.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year..

[d] A simple discount of [redacted]%

[e] A simple discount of [redacted]%

2 Cost-effectiveness of PANO/BTZ/DEX versus LEN/DEX using time dependent HRs derived using MAIC method applied to the subpopulation of patients having received 2–3 prior lines of therapy, populated with interim OS data from the PANORAMA-1 trial

2.1 Assessment of the suitability of survival models used for the health economic model

Please note that a similar comparison against LEN/DEX, populated with the final OS data from PANORAMA-1 trial and assuming a higher discount is presented in the Addendum to the Manufacturer's Response to the ACD.

2.1.1 Overview of the approach

The sections below describe an assessment of the survival models used to derive hazard ratios (HRs) of progression-free survival (PFS) and OS for the health economic model comparing PANO/BTZ/DEX versus LEN/DEX. HRs were used to link the efficacy of LEN/DEX to the efficacy of PANO/BTZ/DEX in patients who had received at least 2 prior regimens including BTZ and an IMiD (European Medicines Agency (EMA) label population).

Using HRs in the health economic model, instead of directly comparing LEN/DEX with PANO/BTZ/DEX, was necessary because trial results (ie, efficacy data, Kaplan–Meier curves and patient characteristics) have not been published for LEN/DEX in the patient population corresponding to the EMA label for panobinostat. Trial results for LEN/DEX have only been published for the intent-to-treat population of the pivotal trials, as well as for patients having received one prior line of treatment and for patients having received 2–3 prior lines of treatment.[3]

HRs were derived by comparing the efficacy (ie, PFS and OS) of LEN/DEX and PANO/BTZ/DEX in patients who received 2–3 prior lines of treatment, using the Matching Indirect Treatment Comparison (MAIC) method. To perform a fair comparison of LEN/DEX versus PANO/BTZ/DEX, the following adjustments for differences in trial design (ie patient selection and baseline characteristics) were made for PANO/BTZ/DEX:

- Exclusion of patients who had received LEN treatment before initiation of PANO/BTZ/DEX
- After exclusion of patients with prior LEN treatment, the remaining patients were matched on time since diagnosis (4.1 years) and β2-microglobulin level (proportion of patients with β2-microglobulin > 2.5 mg/L: 74.5%).

It is important to emphasize that the information utilized to derive the HRs (ie, published Kaplan–Meier curves and baseline characteristics for LEN/DEX in patients having received 2–3 prior lines of

treatment, adjusted patient population of PANO/BTZ/DEX) was not used directly in the health economic model. Instead, the derived HRs were used to generate PFS and OS data for LEN/DEX in a hypothetical patient population reflecting the panobinostat EMA label setting assuming that the same relationship would be observed between LEN/DEX and PANO/BTZ/DEX in the EMA label setting as observed in patients who have received 2–3 prior lines of therapy.

2.1.2 Using the MAIC method to match the two trial subpopulation for PFS and OS

In line with the recommendations of the ERG report and the ACD (ACD, 3.27, 3.29 and 4.7) published by the National Institute for Health and Care excellence (NICE) for the economic evaluation, we have used the MAIC method to derive HRs based on data for the subpopulation having received 2–3 prior lines of treatment as this method provides the most appropriate approach for deriving the relative efficacies of LEN/DEX versus PANO/BTZ/DEX. The choice of this method is based on the following arguments.

1. The MAIC method attempts to take into account relevant baseline characteristics. This is considered important because:
    a. Clinicians suggest that one of the most relevant factors regarding the choice of therapy for patients with relapsed/refractory MM (rrMM) is the mechanism of action; hence those with prior use of LEN/DEX have been excluded from the data set.
    b. Exploratory analysis of data from the MM-009/-010 studies showed that the number of prior therapies and baseline ß2-microglobulin levels (specifically having a baseline level of > 2.5mg/L) were the only two significant predictors for time to progression (TTP), while the use of prior thalidomide (THAL) or BTZ did not impact the TTP outcome.[3] A similar analysis for OS suggests that baseline International Staging System (ISS) score in addition to the number of prior therapies and baseline ß2-microglobulin levels are significant predictors for OS.[4] However baseline ISS score has *not* been reported for the subgroup with 2–3 prior lines of treatment from the MM-009/MM-010 trials.
    c. The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, patients in the PANO/BTZ/DEX group who had received prior LEN/DEX were excluded from the analysis set, ie from the subgroup of patients having received 2–3 prior lines of treatment. Exclusion of a subgroup of patients in this manner is possible using the MAIC method.
2. The MAIC methodology allows adjustment for a limited number of patient characteristics. The MAIC method can therefore be used in cohorts with smaller sample sizes without sacrificing the final effective sample size and avoids distortion of the comparison.

a. If adjustment was made for all available patient characteristics, the effective patient number in the PANO/BTZ/DEX cohort would decrease to 23. Such concern addressed in the ACD (ACD, Section 3.27 and 3.29).

b. However, adjusting for only the four most important patient characteristics means that the effective patient number remains 140 out of the total subgroup population of 188 (ie patients who had received 2–3 prior lines in the PANORAMA-1 trial).

3. The PFS and OS HRs derived using the MAIC methodology seem to be clinically plausible in light of the efficacy data available for PANO/BTZ/DEX and LEN/DEX for the Intention-to-treat (ITT) cohorts and the subgroups of patients who have received 2–3 prior lines of treatment, when acknowledging the differences in the patient characteristics between the two trials (ie PANORAMA-1 and pooled data for MM-009/MM-010), as summarised in Table 2.

Table 2 Summary of median PFS and OS for PANO/BTZ/DEX and LEN/DEX for patients who have received 2−3 prior therapies in PANORAMA-1 and MM-009/-010

Parameter	**PANO/BTZ/DEX 2–3 prior lines subgroup**		**LEN/DEX 2–3 prior lines subgroup**	
	n	**Median (95% CI), months**	**n**	**Median, months**
PFS	188	11.33 (9.36 – 13.70)	220	9.5
OS	188	33.31 (29.70 – NE)	220	35.8

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

Data on file;[5] Stadtmauer et al 2009[3]

2.1.3 Treatment discontinuation – LEN/DEX

While PFS and OS for LEN/DEX and PANO/BTZ/DEX can be compared using an indirect treatment comparison (MAIC method), comparison of treatment duration using these methods is not feasible because LEN/DEX is given continuously until disease progression. Instead, a method based on the published median PFS and the median treatment duration for the subgroup of patients who had received 2–3 prior lines of treatment (9.5 and 9.2 months, respectively) was used. In particular, it was assumed that the risk of treatment discontinuation is 3.3% (9.5/9.2) higher than the risk of PFS in each model cycle. Treatment discontinuation was therefore estimated by multiplying the rate of progression or pre-progression death by 3.3%.

Please note that in the original submission the probability of treatment discontinuation for LEN/DEX was falsely calculated based on the median PFS and treatment duration related to the full population, instead of the 2-3 prior lines subgroup.

2.1.4 Post progression treatment mix

Disease progression is implemented through patients moving from the two pre-progression health states to the post-progression health state, corresponding to fourth-line therapy. Fourth-line therapy can be: a) pomalidomide plus DEX (POM/DEX) together with further supportive care (medical

resource utilisation, MRU)[f,6] b) other active treatments together with further supportive care, or c) supportive care alone. Patients finally move to the death health state. The modelled fourth-line treatment options are referred to as last line of treatment (LLoT).

The proportion of patients receiving any active treatment in the post-progression health state was based on the interim data from the PANORAMA-1 trial. This assumes that 31.5% of patients receive POM/DEX followed by MRU[g], 45.5% receive other active treatments in line with the retrospective analysis published by Gooding *et al* in 2013[6] followed by MRU and the remaining 23% receive best supportive care (MRU) alone. Since such data has not been published for patients receiving LEN/DEX, we assume patients in the LEN/DEX arm receive similar post-progression therapies and in similar proportions to those reported for PANO/BTZ/DEX.

To address the request of the ACD (ACD, Section 4.12) sensitivity analysis is provided to analyse the effect of removing subsequent active treatments.

2.1.5 Matching the two subpopulations (with 2–3 prior lines of treatment) with selected patient characteristics only

This section addresses the concerns raised in both the ERG report and the ACD on the reliability of the MAIC due to low statistical power after matching (ACD, Section 3.27 and 3.29).

To adjust for differences between the trials in terms of patient and disease characteristics at baseline, the matching algorithm proposed by Signorovitch *et al.*[7] was used. In particular, individual patient-level data from the PANORAMA-1 trial were reweighted such that the selected average/median baseline characteristics matched those reported from the MM-009/MM-010 trials. (This was performed for the subgroup of patients who had received 2–3 prior lines of therapy.) The matching ensures that treatment outcomes are comparable across balanced trial populations to the extent of the considered baseline characteristics. Ideally, matching should be based on clinically relevant risk factors that impact on the relative treatment effects.

Exploratory analysis of data from the MM-009/-010 studies showed that the number of prior therapies and baseline ß2-microglobulin levels (specifically having a baseline level of > 2.5mg/L) were the only two significant predictors for TTP, while the use of prior THAL or BTZ did not impact the TTP outcome.[3] A similar analysis for OS suggests that baseline ISS score in addition to the number of prior therapies and baseline ß2-microglobulin levels are significant predictors for OS. [4] Duration of MM (ie time since diagnosis) was also identified as a predictor for TTP and OS and was therefore also included as a matching criterion. However as baseline ISS scores were not reported in the 2–3 prior lines subgroup analysis of the MM-009/MM-010 trials, this characteristic had to be excluded from the matching process. The MM-009/MM-010 trials also excluded patients who had previously

[f] Medical-resource utilisation incorporates clinical attendance, inpatient admissions, transfusions, supportive therapy, blood tests as described by Gooding *et al.* 20136. Gooding S, Lau I-J, Sheikh M *et al.* Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre *Blood* 2013;122:Abstract 1727.

[g] MRU, medical resource utilisation

received LEN. Therefore, to match the patient selection criteria, patients in the PANO/BTZ/DEX group who had received prior LEN/DEX were also excluded from the analysis set, ie the patient subgroup with 2–3 prior lines of treatment.

Selected baseline patient characteristics before and after the adjustment of the PANORAMA-1 trial data are presented in Table 3. The effective sample size (computed as the square of the summed weights divided by the sum of the squared weights) in the PANORAMA-1 trial decreased from 142 to 138 (97.2 %) in the subgroup analysis (patients with 2–3 prior lines of treatment). However the weighted number of patients (ie sum of patient weights) was 140 (98.6%). (Patients with prior use of LEN-based treatment were excluded from the PANORAMA-1 dataset.)

Table 3 Baseline patient characteristics used in the matching adjusted indirect treatment comparison, before and after adjustment for the subpopulations with 2–3 prior lines of treatment

Baseline characteristics, proportion of patients	**LEN/DEX (n = 220)**	**PANO/BTZ/DEX unadjusted[a] (n = 142)**	**PANO/BTZ/DEX adjusted (n = 140)**
Patient with prior LEN based regimen	0%	0%	0%
Patient with 2–3 prior lines of treatment	100%	100%	100%
Patients with median time since diagnosis > 49.2 months	50%	47.2%	50%
Patients with serum ß2-microglobulin > 2.5 mg/L	74.5%	67.6%	74.5%

[a]The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 188). All patients had complete information on the covariates.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat.

Stadtmauer *et al.* 2009.[155]

2.2 PFS assessment using the updated MAIC method

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7) as well as the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8).

Results of the MAIC indicated that in terms of PFS, the efficacy of PANO/BTZ/DEX was better to that of LEN/DEX in both patient populations analysed (Figure 1 and Table 4).

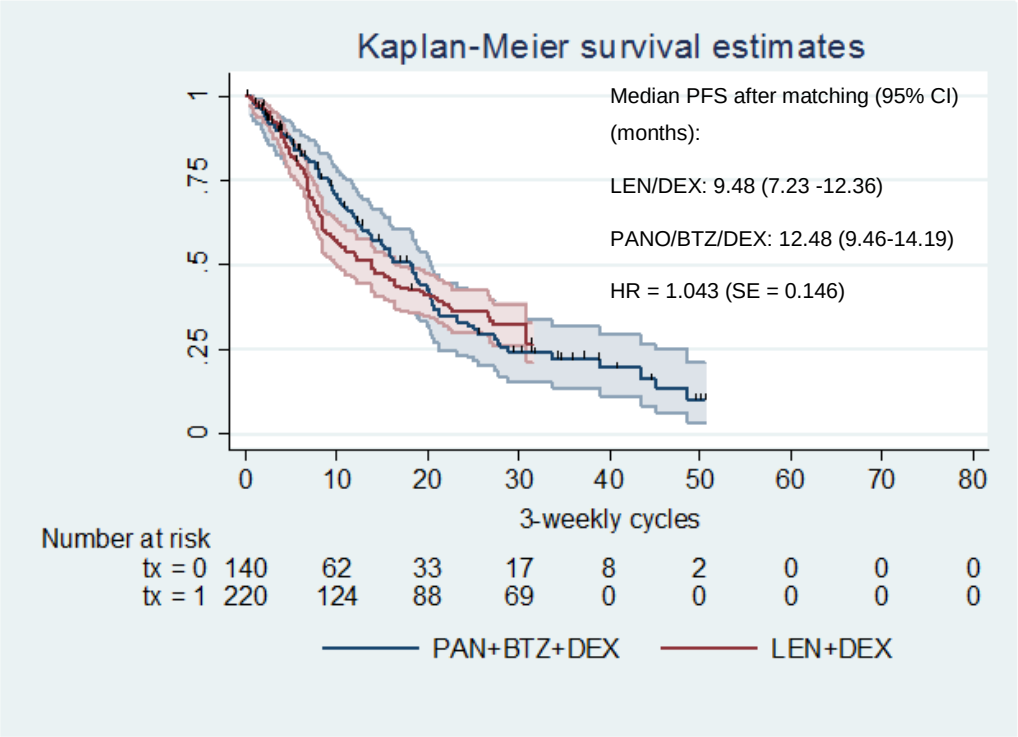
Table 4 PFS HR and median PFS for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment

	HR	**SE**	**95% CI**	**Median PANO/BTZ/DEX**	**Median LEN/DEX**
PFS	1.043	0.146	0.783 – 1.388	12.48	9.48

				(9.46 – 14.19)	(7.23 – 12.36)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; SE, standard error of the log hazard ratio.

Figure 1 Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment



Notes:

N = 220 for LEN/DEX, N = 140 for PANO/BTZ/DEX (refers to the weighted sample size)

PANO/BTZ/DEX: patients with 2–3 prior lines of treatment, no prior LEN treatment, matched to LEN/DEX against β2-microglobulin and time from diagnosis

LEN/DEX: patients with 2–3 prior lines of treatment[3]

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; LEN, lenalidomide; MAIC, MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PFS, progression-free survival.

2.2.1 Testing for the proportional hazard assumption

At first, a constant (time independent) hazard ratio (HR = 1.043) was used to determine the PFS of LEN/DEX (relative to PANO/BTZ/DEX) in the economic model. However the use of a constant HR implicitly assumes that the proportional hazard (PH) assumption of the Cox regression model based on which the HR was estimated is satisfied. To test whether the proportional hazard assumption is satisfied, three types of assessments were carried out as summarised in Table 5.

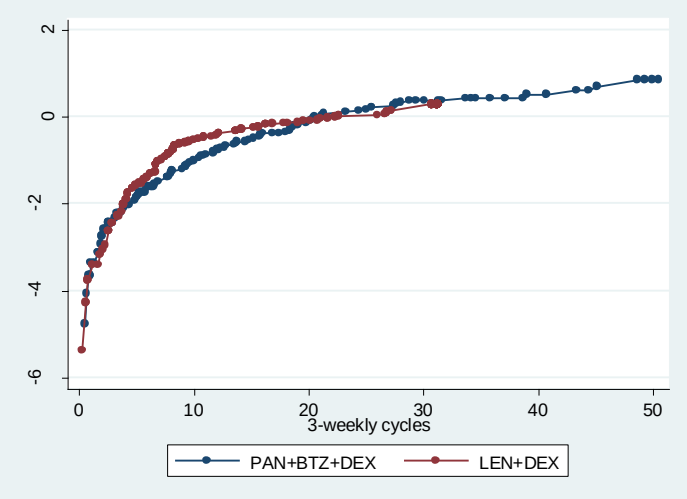
Table 5 Overview of tests used to assess the proportional hazard assumption

Test	Interpretation	Comment
Visual inspection of the log-cumulative hazard plot	Log of minus cumulative hazard versus survival time graph should result in parallel curves if the predictor is proportional.	Interpreting plots is subjective. In general, one can conclude PH unless a distinct pattern of non-parallelism (e.g., crossing) is seen. Intertwined lines with no distinct pattern may simply indicate no difference between groups.
Visual inspection of the Schoenfeld residuals	Schoenfeld residuals for the treatment covariate versus time should result in a flat line.	Systematic departures from a horizontal line are indicative of non-proportional hazards.
Statistical test based on the scaled Schoenfeld residuals	Testing the time dependent covariates is equivalent to testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time.	Called the Therneau and Grambsch test. A non-zero slope is an indication of a violation of the PH assumption.

PH, proportional hazard

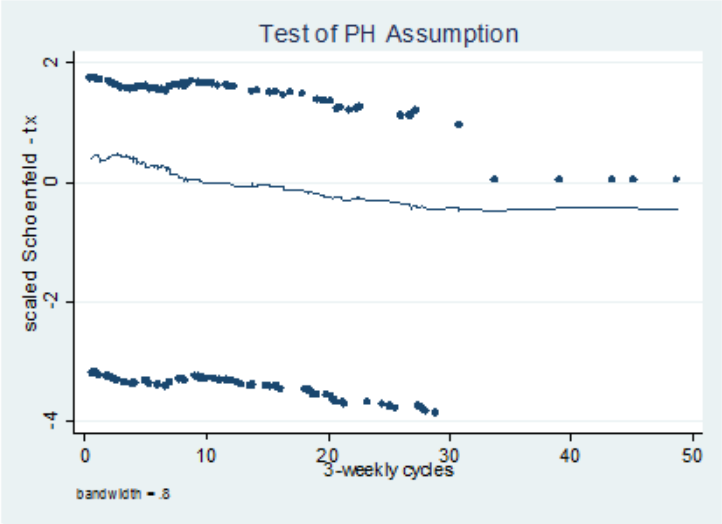
The results of the assessment of the PH assumption indicate that the proportional hazard assumption is not satisfied therefore a constant HR cannot be applied. The log-cumulative hazards plot suggests that the hazard of PFS is larger for LEN/DEX than for PANO/BTZ/DEX at the beginning of the treatments (suggested by the diverging curves during approximately the first 10 cycles), then the trend changes and the hazard of PFS becomes lower for LEN/DEX than for PANO/BTZ/DEX (suggested by the converging curves between approximately the next 10 cycles), while the hazards seem to be very similar after approximately 20–25 cycles (Figure 2). The Schoenfeld residuals plot also suggests the violation of the PH assumption because the residuals do not follow a straight line (Figure 3). Finally, the Therneau and Grambsch test indicates a P value of less than 0.05 (Table 6).

Figure 2 Log (-cumulative hazards) versus time for PFS



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 3 Schoenfeld residuals versus time for PFS



PFS, progression-free survival; PH, proportional hazard.

Table 6 Therneau and Grambsch test result for PFS

	rho	chi2	Degrees of freedom	Prob>chi2 (P value)
treatment	–0.13003	3.97	1	0.0464

PFS, progression-free survival

2.2.2 Application of time-dependent HRs of PFS to address non-proportional hazards

As an alternative to the constant HR approach, a time-varying HR approach was also developed to address the issue of non-proportional hazards. In this approach, a fully parametric survival model was fitted on the LEN/DEX simulated patient-level data and on the matched PANO/BTZ/DEX patient-level data, separately. Five different distributions (exponential, Weibull, log-logistic, lognormal, and Gompertz) were assessed and the best fitting regression model was selected. For each treatment, the best fitting regression model implied a certain hazard rate profile (i.e., hazard rate of PFS for each 3-weekly cycle).

The ratio of the two rates in each 3-weekly cycle then yielded a HR profile that was not constant but changed over the 3-weekly cycles (hence the name time-varying HR)[h]. Because for LEN/DEX, PFS

[h] Modelled PFS was used to derive the 3-weekly hazard rates using the following formula:

PFS(t) = exp(-H(t))

H(t) = - ln(PFS(t))

h(t) = H(t+1) – H(t)

where PFS(t) is the modelled progression-free survival at time 't', H(t) is the cumulative hazard function at time t, h(t) is the hazard rate at time 't'. The hazard ratio at time t, HR(t), was derived as the ratio of the treatment-specific hazard rates at time 't'.

data were available only until approximately 30 cycles, beyond this point, based on visual assessment of the log–cumulative hazard plot, the HR of PFS between LEN/DEX and PANO/BTZ/DEX was assumed to be one.

Table 7 presents the Akaike information criterion/ Bayesian information criterion (AIC/BIC) values for LEN/DEX and PANO/BTZ/DEX. For LEN/DEX, the lognormal distribution resulted in the best model fit, whereas for PANO/BTZ/DEX the Weibull distribution yielded the best fit. Figure 4 presents the Kaplan–Meier estimates and the model predictions. According to visual assessment, these models indeed fit the Kaplan–Meier curves well. The log-normal distribution implied a unimodal hazard profile for LEN/DEX whereas the Weibull model implied an increasing hazard profile for PANO/BTZ/DEX. The ratio of these profiles (not surprisingly) did not result in a constant HR (depicted in Figure 5) but in a reversed U-shape HR profile.

Figure 6 presents the PFS curve for PANO/BTZ/DEX in the population corresponding to the licensed indication (ie, used in the health economic model) and the implied PFS curve for LEN/DEX using the time dependent HR approach described above.

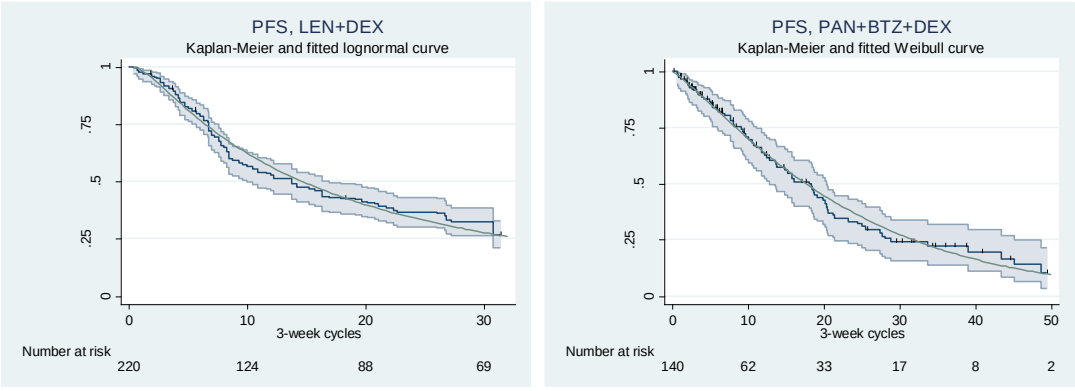
Table 7 AIC/BIC values for the PFS models for LEN/DEX and PANO/BTZ/DEX

	LEN/DEX		**PANO/BTZ/DEX (matched)**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	639.6038	642.9975	277.5292	280.485
Weibull	641.1437	647.931	***276.5625***	***282.4741***
Log-logistic	629.571	636.3582	277.2262	283.1379
Log-normal	***627.28***	***634.0672***	280.209	286.1207
Gompertz	640.6507	647.4379	278.5276	284.4392

The best fitting model selected for the base case analysis is shown in bold italic

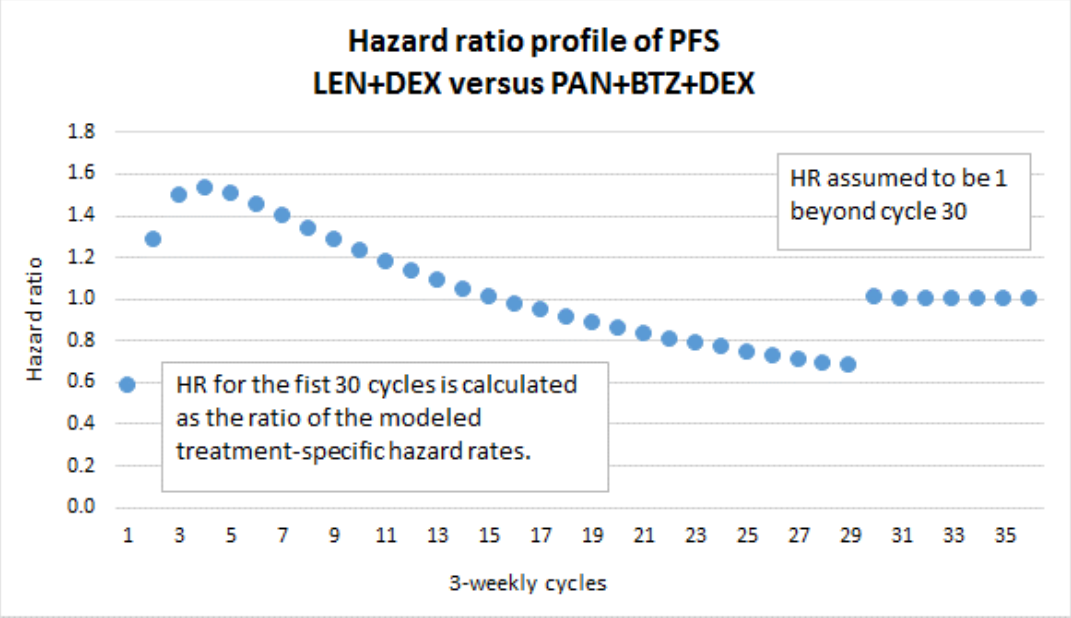
AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 4 Kaplan–Meier estimates of PFS and modelled curves



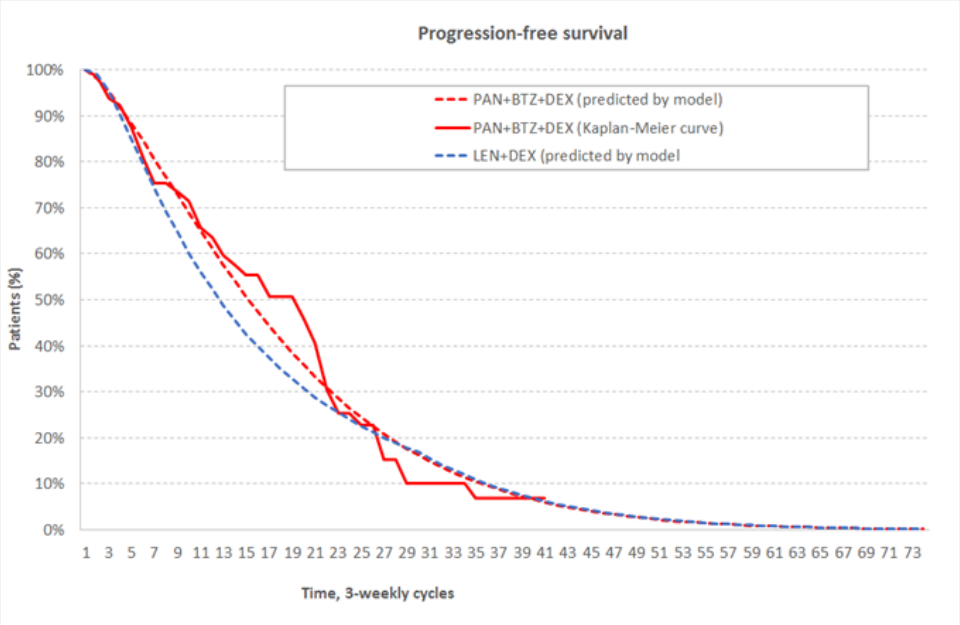
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 5 Hazard ratio profile – time-dependent hazard ratio scenario



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 6 Progression-free survival estimates in the health economic model for the subpopulation having received least 2 prior lines of therapies including an IMiD and BTZ derived via the MAIC method using time dependent HRs



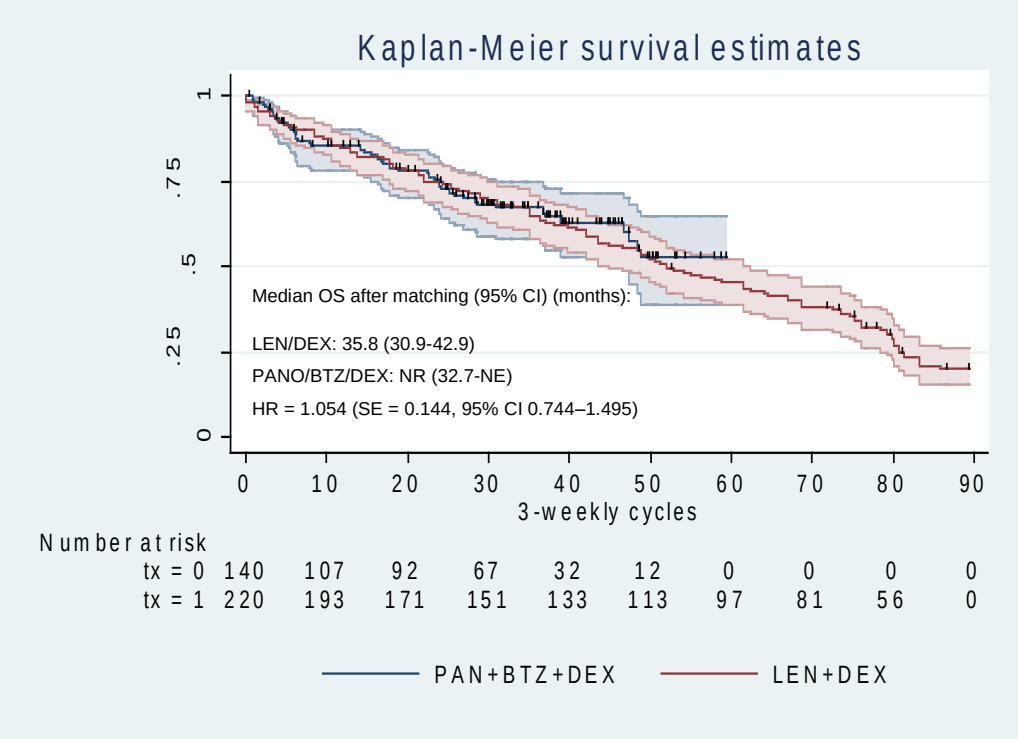
BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat;

2.3 OS assessment using the updated MAIC method

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7) as well as the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8)[i].

Results of the MAIC indicated that in terms of OS, the efficacy of PANO/BTZ/DEX was similar to that of LEN/DEX in both patient populations analysed (Figure 7 and Table 8). Figure 7 shows the Kaplan–Meier curves for PANO/BTZ/DEX and LEN/DEX. The data suggests an increasing OS benefit for PANO/BTZ/DEX beyond 35–40 cycles (3-week cycles).

Figure 7 OS Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment



Notes: NE, not estimable; NR, not reached.

N = 220 for LEN/DEX, N = 140 for PANO/BTZ/DEX (refers to the weighted sample size)

PANO/BTZ/DEX: patients with 2–3 prior lines of treatment, no prior LEN treatment, matched to LEN/DEX against β2-microglobulin and time from diagnosis

LEN/DEX: patients with 2–3 prior lines of treatment[3]

[i] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PANO, panobinostat.

Table 8 OS HRs and median OS for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with two to three prior lines of treatment

	HR	SE	95% CI	Median PANO/BTZ/DEX	Median LEN/DEX
Final OS	1.054	0.178	0.744 – 1.495	NR (32.7 – NE)	35.8 (30.9 – 42.9)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PANO, panobinostat; SE, standard error of the log hazard ratio; NE, not estimable; NR, not reached.

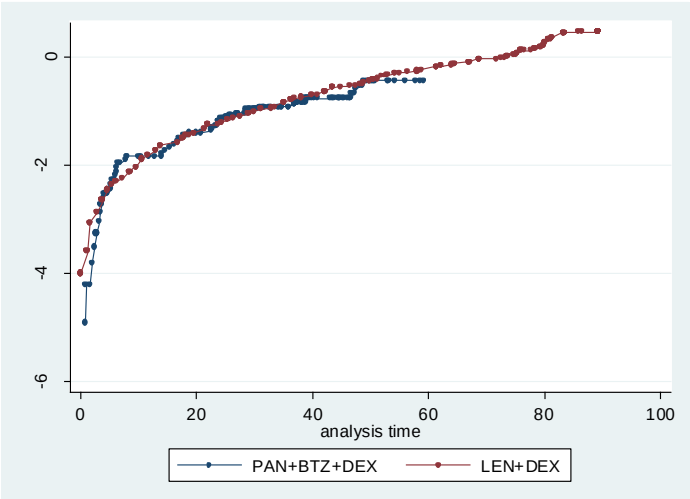
2.3.1 Testing for the proportional hazard assumption

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7).

The same PH assessments were carried out for OS as for PFS and were performed using the final OS data.

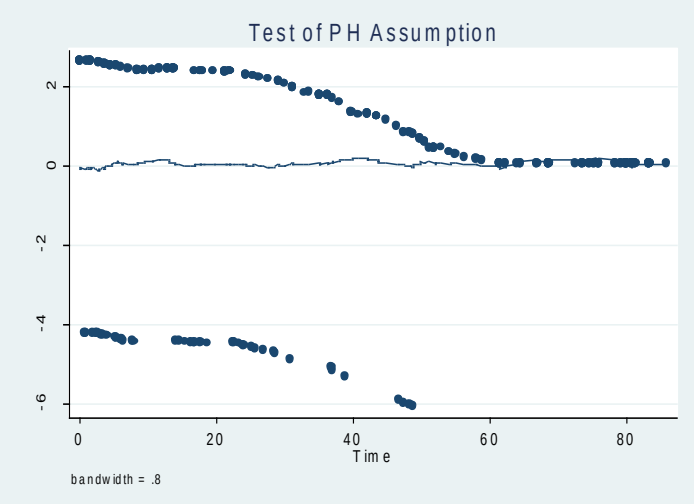
The results of the assessment of the PH assumption indicate that the PH assumption is not fully satisfied therefore a constant HR cannot be applied. The log-cumulative hazard plot suggests that the hazard of death for LEN/DEX is very similar to the hazard of death for PANO/BTZ/DEX for the first 35–40 cycles (Figure 8). However, after that point the log-cumulative hazard curves start to diverge which is an indication of higher mortality rates for LEN/DEX than for PANO/BTZ/DEX. The Schoenfeld residuals plot seems to confirm this by exhibiting a fairly straight line for the first 35–40 cycles and a seemingly stable line at a higher level afterwards (Figure 9). The Therneau and Grambsch test indicates that we cannot reject the null hypothesis (PH assumption, P value = 0.908) (Table 9).

Figure 8 Log (-cumulative hazards) versus time for OS



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat.

Figure 9 Schoenfeld residuals versus time for OS



OS, overall survival; PH, proportional hazard.

Table 9 Therneau and Grambsch test result for OS

Data cut-off	rho	chi2	Degrees of freedom	Prob>chi2 (P value)
Final OS data	0.00792	0.01	1	0.9080

OS, overall survival.

2.3.2 Application of time-dependent OS HR as an alternative to the constant OS HR

This section address the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8)[j]*.*

An indication of non-proportional hazards was seen in the log-cumulative hazard curves. Therefore, as an alternative to the constant HR approach, a time-varying HR approach was explored using the OS data.

In this approach, a Cox model was set up in which the HR formula yielded constant HRs for different time intervals. This approach was considered to be a fair reflection of the data given the visual assessment of the log-cumulative hazard curves, which suggested a constant (close to 1) HR for the first 35–40 cycles and a constant (larger than 1) HR for the period after that. A constant HR for the period after the first 35–40 cycles was considered to be appropriate because the treatment-specific log-cumulative hazards indicated a stable diverging pattern.

[j] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

Because the exact cut-off point is difficult to determine and may be arbitrary assigned by simple visual assessment of the curves, we assessed 6 Cox models with different cut-off time points defined between cycles 35–40. The AIC/BIC values were obtained and compared to help decide which Cox model had the best fit and are presented in Table 10.

Using a cut-off at the 39th cycle yielded the best model fit. Table 11 below presents the estimated HRs.

Table 10 Model fit a different cut-off time points

Cut-off point	**AIC**	**BIC**
35th cycle	2231.3	2239.072
36th cycle	2231.3	2239.072
37th cycle	2231.144	2238.916
38th cycle	2231.294	2239.06
39th cycle	***2230.885***	***2238.657***
40th cycle	2231.12	2238.893

The best fitting model selected for the base case analysis is shown in bold italic

AIC, Akaike information criterion; BIC, Bayesian information criterion

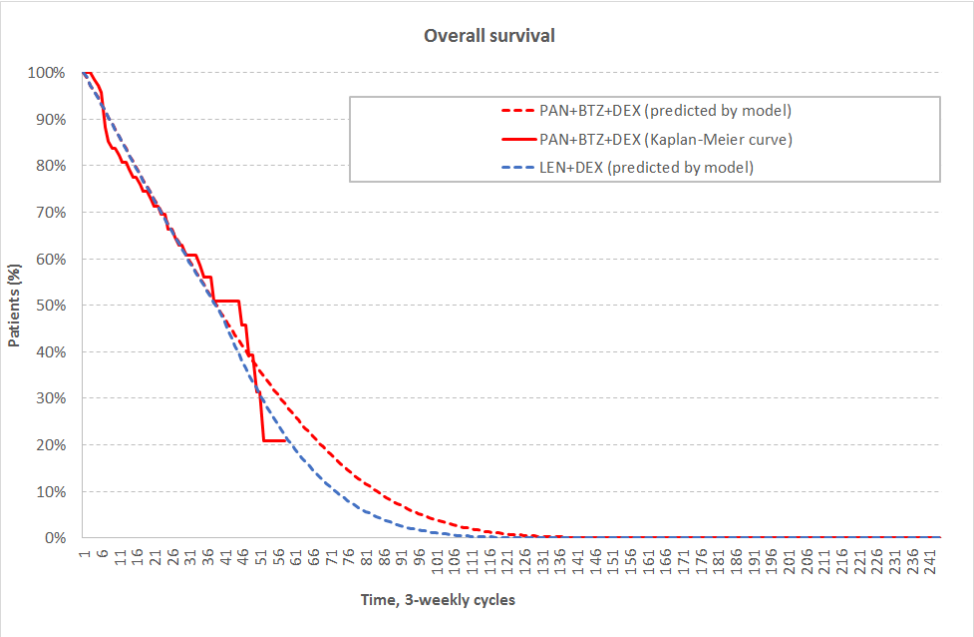
Table 11 Estimated hazard ratios using the 39th cycle as the cut-off time point

Time (no. of cycles)	**OS HR**	**SE**	**z**	**P>z**	**95% CI**
< 39th cycle	1.008	0.190	0.04	0.967	0.697 - 1.458
≥ 39th cycle	1.498	0.943	0.64	0.521	0.436 – 5.147

HR, hazard ratio; OS, overall survival; SE, standard error of the log hazard ratio.

Figure 10 presents the OS curves for PANO/BTZ/DEX in the licensed indication (ie, used in the health economic model) and the implied OS curve for LEN/DEX using the time dependent HR approach.

Figure 10 Overall survival estimates in the health economic model for the subpopulation having received at least 2 prior lines of therapies including an IMiD and BTZ derived via the MAIC method using time dependent HRs



BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat.

Technical note:

The hazard ratio formula included the function of the following form g(t), which took on the value 1 if t was greater than some specified value of t, called t0, and took on the value 0 if t was less than or equal to t0. In the best fitting model t0 was 39 cycles.

The hazard function was expressed as follows: $h(t,X)= h0(t)\times\exp(\beta x+\delta xg(t))$

where h(t,X) is the hazard rate at time t and risk factors X, h0(t) is the unspecified baseline hazard rate, and $\exp(\beta x+\delta xg(t))$ is the hazard ratio given risk factor x. In the present case x = 1 was referring to LEN/DEX treatment.

This specification of the hazard function yielded two hazard ratios:

$t \geq 39$: $HR = \exp(\beta+\delta g(t)))$

$t < 39$: $HR = \exp(\beta)$.

2.4 Results of the cost-effectiveness analysis

Please note that a similar comparison against LEN/DEX, populated with the final OS data from PANORAMA-1 trial and assuming a higher discount is presented in the Addendum to the Manufacturer's Response to the ACD.

2.4.1 Base case − incremental cost-effectiveness analysis

Results for the cost-effectiveness analysis using the most plausible method to derive HRs for PANO/BTZ/DEX versus LEN/DEX are summarised in Table 12.

Although the base case (ie using the HRs from the subgroup population derived using the MAIC method with time dependent HRs) indicates gains in quality-adjusted life year (QALY) and life-year (LY) for PANO/BTZ/DEX over LEN/DEX, these gains are relatively low. Furthermore, the published evidence suggests that one cannot distinguish between PANO/BTZ/DEX and LEN/DEX in this subpopulation in terms of efficacy and that the determining factor will be the cost of the PANO/BTZ/DEX combination. It should also be noted that, because of these small incremental QALYs, the incremental cost-effectiveness ratios (ICERs) are volatile and specifically sensitive to the incremental cost, ie the cost of the treatment.

Table 12 Summary of base case results using the MAIC method (discounted) with PAS

With PAS[k]	**Total**			**Incremental versus LEN/DEX**			**ICER vs LEN/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£146,310	2.29	1.52	£3,262	0.183	0.106	£17,883	£30,701
LEN/DEX	£143,048	2.10	1.41					

Time dependent HRs derived using MAIC method applied to subpopulation (patients having received two to three prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[k] A simple discount of [redacted]%

2.4.2 Clinical outcomes from the model

Comparing the model results with the clinical outcomes from PANORAMA-1 for PANO/BTZ/DEX in the subpopulation of patients who have received at least two prior therapies, including BTZ and an IMiD, reveals the following as summarised in Table 13:

- The model underestimates median PFS by 2.23 months and hence the treatment-related cost and/or the savings associated with the treatment-free interval after stopping PANO/BTZ/DEX.
- The model underestimates median OS by 4.4 months and hence the post-progression cost associated with PANO/BTZ/DEX. However, it also underestimates the post- progression QALY benefit.
- The model overestimates the median treatment duration by 0.92 months and hence the cost associated with PANO/BTZ/DEX.

Table 13 Summary of model results compared with clinical data

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT)	**Model results**
Median PFS (PANO/BTZ/DEX)	12.5 months	10.27 months
Median OS (PANO/BTZ/DEX)	30.56 months	26.2 months
Median treatment duration (PANO/BTZ/DEX)	4.5 months	5.42 months
Proportion of patients experiencing AEs (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Einsele et al 2015[8]

The validity of the methodology is further supported by comparison of the model results for LEN/DEX with the efficacy results from the pooled dataset of the MM-009/MM-010 trials for LEN/DEX in the subpopulation of patients who have received 2–3 prior therapies.[3] Table 14 compares the model results (using each of the possible indirect treatment comparison methodologies) with the trial data.

It is worth noting that the model estimates the PFS and OS associated with LEN/DEX for the subpopulation with *2–3 prior lines of treatment including an IMiD and BTZ* whereas the LEN/DEX trial data presented below are for patients who have received 2–3 prior lines of treatment but not necessarily including prior BTZ or prior treatment with an IMiD.

Table 14 Summary of model results (median) for LEN/DEX compared with clinical data (median)

	ITC method	PFS (undiscounted values)			OS (undiscounted values)		
		HR[1]	Median, months		HR[1]	Median, months	
			Per model[l]	Per trial[m]		Per model[v]	Per trial[w]
Patient population			2-3 prior lines incl. IMID & BTZ	2-3 prior lines (MM-009/010)		2-3 prior lines incl. IMID & BTZ	2-3 prior lines (MM-009/010)
	MAIC	Time dependent[n]	8.88	9.5	Time dependent[o]	26.2	35.8

[1]HR for LEN/DEX versus PANO/BTZ/DEX

ITC, Indirect Treatment Comparison; BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Stadtmauer et al 2009;[3] Einsele et al 2015[8]

2.4.3 Disaggregated results for the base case

Table 15, Table 16 and

[l] Estimated by the model for the subpopulation with 2–3 prior lines of treatment including an IMiD and BTZ

[m] Reported by Stadtmauer *et al* based on the retrospective analysis of MM-009/MM-010 on the subpopulation with 2–3 prior lines of treatment

[n] For cycle specific PFS HRs see Section 3.2.2

[o] OS HR < 39th cycle = 1.01; OS HR ≥ 39 cycle = 1.50

Table 17 provide an overview of the undiscounted and discounted QALYs, costs and resource use costs that the model predicts for each health state when applying the base case MAIC methodology to derive the HRs for LEN/DEX versus PANO/BTZ/DEX. Results show that PANO/BTZ/DEX is associated with a decrement in QALY during the pre-progression on treatment phase and a corresponding gain in QALY during the pre-progression off treatment phase so that overall there is little difference in the QALYs between the two treatments.

PANO/BTZ/DEX is associated with cost saving in the pre-progression health state and is associated with additional costs only in the post-progression health state. This is due to the longer post-progression survival assumed by the indirect treatment comparison.

The OS data available for LEN/DEX and PANO/BTZ/DEX in the subpopulation with 2–3 prior lines of treatment are 35.8 months vs 33.31 months respectively. From this aspect, assuming a positive incremental cost associated with the post-progression survival is conservative and increases the ICER associated with PANO/BTZ/DEX from a dominant position[p].

Table 15 Summary of QALY gain by health state using the MAIC method (discounted)

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	0.33	0.62	–0.29	0.29	42.65%
B: Pre-progression, off treatment	0.34	0.02	0.32	0.32	47.06%
C: Post progression	0.85	0.78	0.07	0.07	10.29%
D: Death	0	0	0.00	0.00	0%
Total	1.52	1.41	0.11	0.68	100%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

Table 16 Summary of cost by health state using the MAIC method (discounted): with PAS[q]

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on	£[redacted]	£45,286	–£[redacted]	£[redacted]	[redacted] %

[p] Assuming the QALY benefit associated with the pre-progression health states would remain 0.034 for PANO/BTZ/DEX over LEN/DEX

[q] A simple discount of [redacted]%

treatment					
B: Pre-progression, off treatment	£441	£21	£420	£420	2.73%
C: Post-progression	£[redacted]	£96,594	£[redacted]	£[redacted]	[redacted] %
D: Death	£1,139	£1,146	–£8	£8	0.05%
Total	£146,310	£143,048	£3,262	£15,400	100%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme.

Table 17 Summary of predicted resource cost use by category of cost using the MAIC method (discounted): with PAS[r]

Item	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£[redacted]	£40,180	-£[redacted]	£[redacted]	[redacted] %
Tests and monitoring (on treatment)	£907	£4,913	–£4,006	£4,006	23.18%
Tests and monitoring (No treatment)	£441	£21	£420	£420	2.43%
Last line of treatment	£[redacted]	£96,594	£[redacted]	£[redacted]	[redacted] %
AEs	£1,134	£193	£941	£941	5.44%
Terminal care	£1,139	£1,146	–£8	£8	0.05%
Total	£146,310	£143,048	£3,262	£17,282	100%

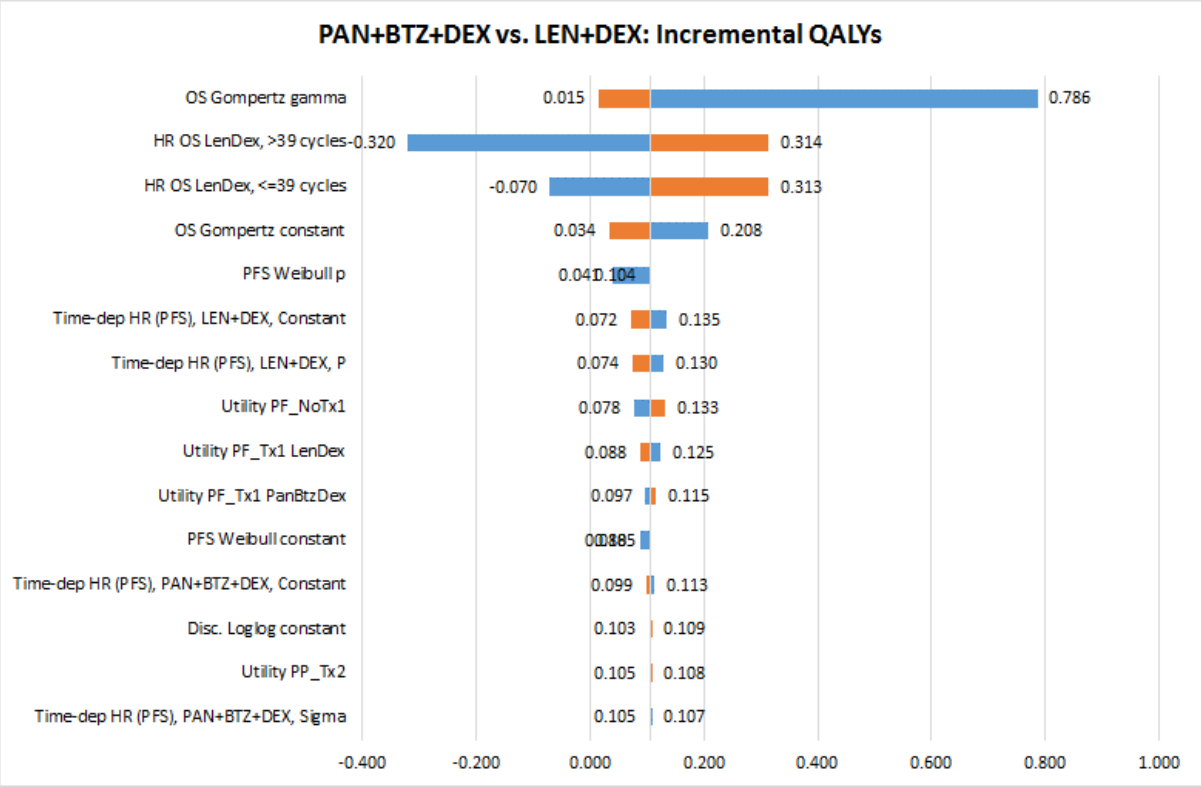
AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme.

[r] A simple discount of [redacted]%

2.4.4 Deterministic sensitivity analyses results

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie the deterministic) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. Tornado plots were generated for costs and QALYs, separately, and for the ICER, and rank parameters from highest to lowest based on the magnitude of the result impact (see Figure 11, Figure 12 and Figure 13).

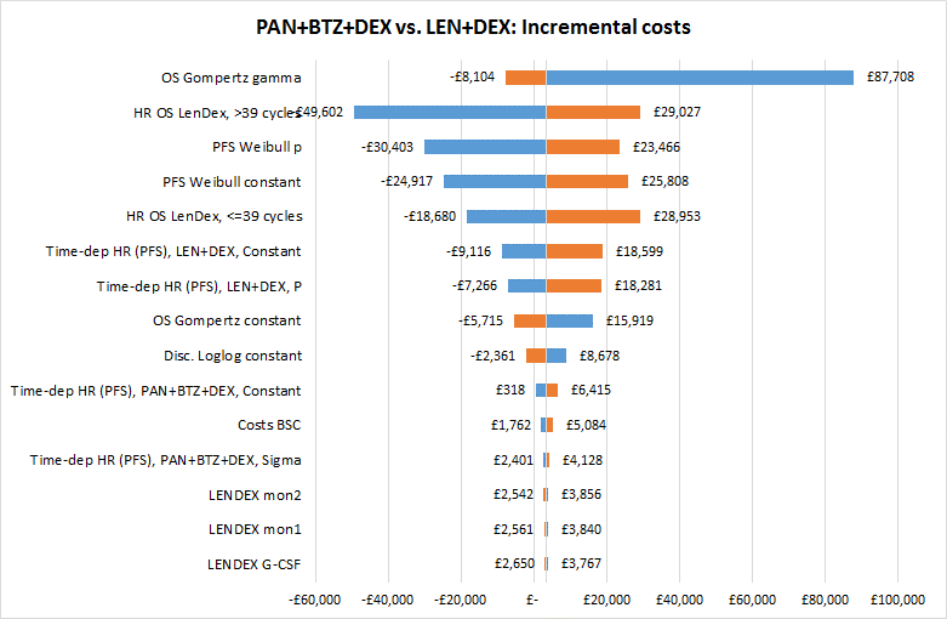
Figure 11 Tornado diagram of incremental QALYs for PANO/BTZ/DEX versus LEN/DEX: updated MAIC (discounted)



Orange bars indicate upper limit; Blue bars indicate lower limit.

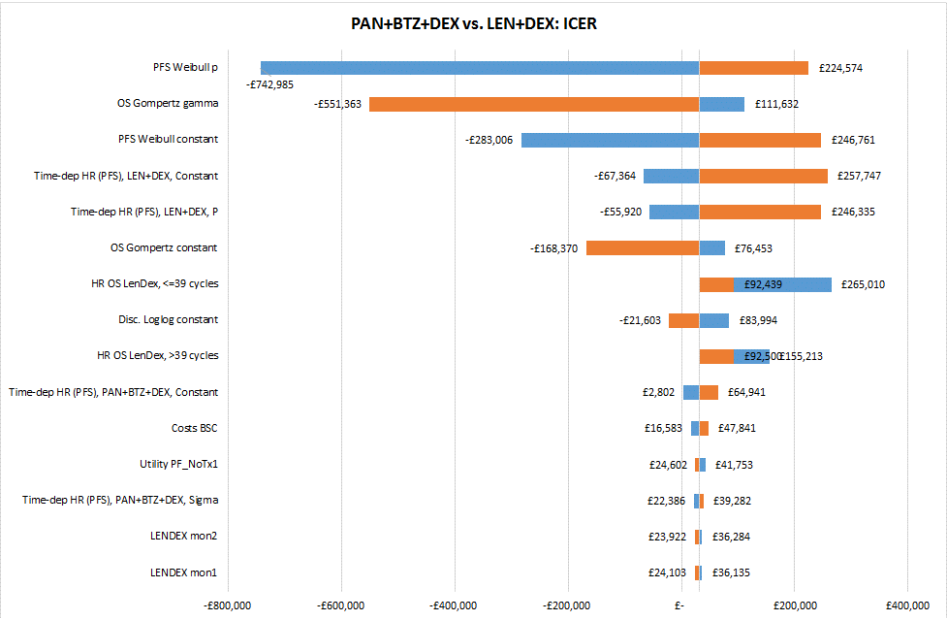
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

Figure 12 **Tornado diagram of incremental costs for PANO/BTZ/DEX versus LEN/DEX: base case (discounted) with PAS**[s]



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

Figure 13 Tornado diagram of ICERs for PANO/BTZ/DEX versus LEN/DEX: base case (discounted): with PAS[t]



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

[s] A simple discount of [redacted]%

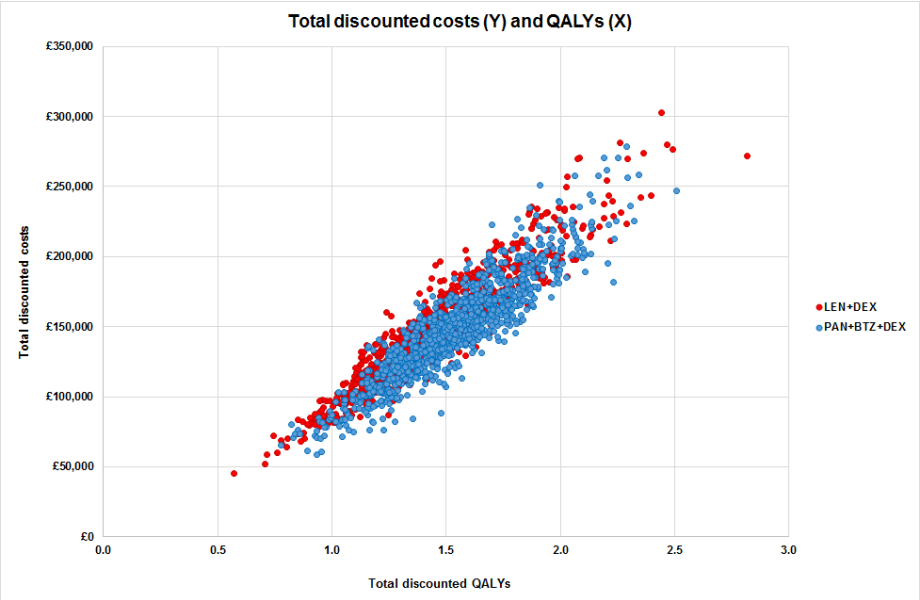
[t] A simple discount of [redacted]%

2.4.5 Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in Figure **14** (scatter plot of total QALYs and costs),

Figure **15** (scatter plot of incremental QALYs and costs). The probabilistic sensitivity analysis was run using the MAIC method and deriving HRs from the subpopulation (2–3 prior lines of therapy).

Figure 14 **Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): updated MAIC (discounted): with PAS**[u]

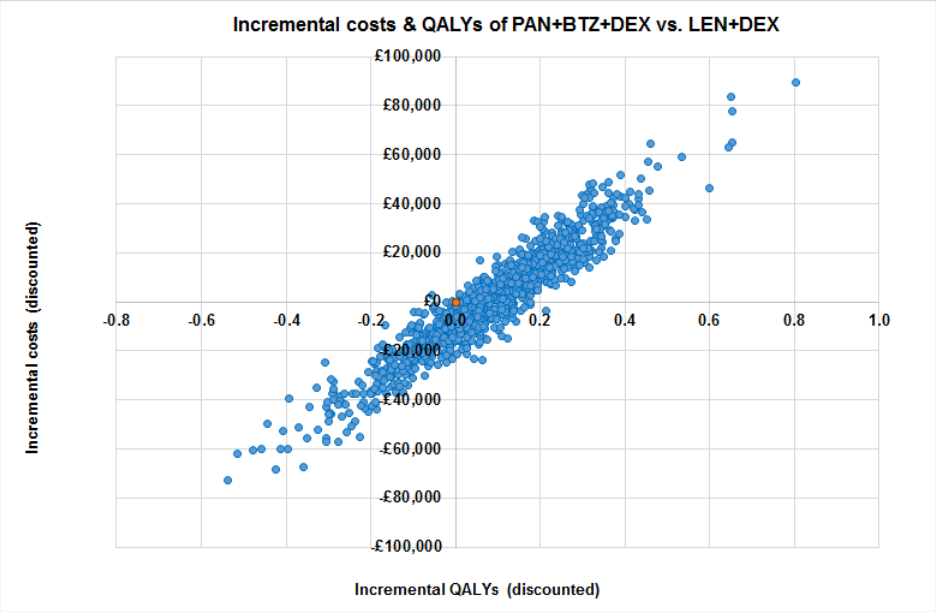


Base case, ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[u] A simple discount of [redacted]%

Figure 15 **Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): base case (discounted): with PAS**[v]



Base case: ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes, presented in Table 18.

Table 18 The probabilistic sensitivity analysis and 95% CIs around key model outcomes for the base case (discounted): with PAS[w]

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£146,310 (£83,067 to £235,359)	£3,262 (–£44,193 to £45,879)	1.52 (1.02 to 2.13)	0.11 (–0.31 to 0.43)	£30,701
LEN/DEX	£143,048 (£82,631 to £241,707)		1.42 (0.94 to 2.19)		

Base case, ie using the 'MAIC' method to derive HRs from the subpopulation (patients who had received 2–3 prior lines)

[v] A simple discount of [redacted]%

[w] A simple discount of [redacted]%

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probability of PANO/BTZ/DEX being cost effective at certain threshold is summarized in Table 19.

Table 19 **The probability of PANO/BTZ/DEX being cost effective versus LEN/DEX according to willingness to pay threshold: with PAS**[x]

WTP threshold	PANO/BTZ/DEX	LEN/DEX
£20,000 / QALY	45.5%	54.5%
£30,000 / QALY	47.5%	52.5%
£50,000 / QALY	54.6%	45.4%

2.4.6 Scenario analysis

The results of the scenario analyses using the updated MAIC method to derive time-dependent HRs from data for the subpopulation (ie 2–3 prior lines) are presented in Table 20.

Table 20 **Scenario analyses with PAS**[y]

Scenario	Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Base case	**£3,262**	**0.106**	**0.183**	**£30,701**	**£17,833**
Discount rate of 5% for both costs and effects	£2,666	0.099	0.172	£26,810	£15,476
Time horizon, 5 years	-£169	0.079	0.140	Dominant	Dominant
Time horizon, 10 years	£3,262	0.106	0.183	£30,700	£17,832
OS, Weibull	£11,302	0.171	0.284	£66,082	£39,776
OS, Kaplan–Meier + Gompertz	£2,139	0.097	0.169	£22,000	£12,670
PFS, Gompertz	£3,095	0.106	0.183	£29,329	£16,903
PFS, exponential	£2,782	0.108	0.182	£25,864	£15,267
Time to discontinuation, Kaplan–Meier estimates	£3,028	0.106	0.183	£28,487	£16,553
Assuming no	£3,262	0.103	0.183	£31,735	£17,832

[x] A simple discount of [redacted]%

[y] A simple discount of [redacted]%

disutility associated with LEN/DEX					
Assuming no active treatment in the post-progression health state[z]	**-£1,397**	**0.106**	**0.183**	**Dominant**	**Dominant**
Different methodologies used to derive HRs for PFS and OS for LEN/DEX versus PANO/BTZ/DEX					
Naïve comparison[2]	-£17,500	-0.038	-0.048	Cost saving	Cost saving
Unadjusted Cox	-£2,984	0.052	0.102	dominant	dominant
Threshold analyses (ie non time dependent, constant PFS and OS HRs for LEN/DEX vs PANO/BTZ/DEX)					
HR = 0.8	-£29,241	-0.242	-0.333	Cost saving	Cost saving
HR = 0.9	-£18,813	-0.121	-0.154	Cost saving	Cost saving
HR = 1	-£9,559	-0.016	0.000	Cost saving	dominant
HR = 1.1	-£1,299	0.074	0.134	dominant	dominant
HR = 1.2	£6,116	0.154	0.252	£39,748	£24,302

[2]Note in the case when both the incremental cost and the incremental QALY are negative (ie cost saving but less utility), the higher the ICER the more cost effective the treatment.

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; QALY, quality-adjusted life year.

[z] As requested by the AC (ACD, Section 4.12)

3 Cost effectiveness of PANO/BTZ/DEX versus BTZ/DEX in patients who have received at least 2 prior lines of treatment including an IMiD and BTZ and responded to the prior BTZ – populated with the interim OS data from PANORAMA-1

Although there are no explicit reimbursement channels to support access to BTZ/DEX in patients with at least 2 prior lines of treatment including an IMiD and BTZ (and who have responded to prior BTZ therapy), a full cost effectiveness analysis has been performed upon the request at the first NICE Appraisal Committee meeting and the ACD (Section 4.4 and 4.10 and Summary Pages 26, 27).

Please note that a similar comparison against BTZ/DEX, populated with the final OS data from PANORAMA-1 trial and assuming a higher discount is presented in the Addendum to the Manufacturer's Response to the ACD.

3.1 Methods

3.1.1 Patient population and corresponding efficacy and safety data

The patient population considered corresponded to patients from PANORAMA-1 who had received at least 2 prior lines of treatment including an IMiD and BTZ-based regimen and had response to prior BTZ. The number of patients included is:

- PANO/BTZ/DEX: n = 72
- BTZ/DEX: n = 72

Table 21 summarises the efficacy data for the patient population from PANORAMA-1 used for the indirect comparison with BTZ/DEX and compares the data with those for patients corresponding to the EMA licensed indication. Similarly, Table 22 summarizes the safety data from PANORAMA-1 for these two patient populations.

Table 21 Summary of the efficacy data from PANORAMA-1 for the population corresponding to the EMA label and the subgroup used for the direct comparison against BTZ/DEX

	EMA label population, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD		**Population for direct comparison with BTZ/DEX, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD *excluding* those with no response to the prior BTZ**	
	PANO/ BTZ/DEX N = 73/72	**PBO/ BTZ/DEX N = 74/73**	**PANO/ BTZ/DEX N = 72/71**	**PBO/ BTZ/DEX N = 72/71**

Median PFS, months HR (95% CI)	12.5 0.47 (0.32 to 0.72)	4.7	12.48 0.48 (0.32 to 0.73)	4.86
Median OS (**interim analysis**), months HR (95% CI)	30.46 0.76 (0.48 to 1.21)	19.52	30.46 0.81 (0.51 to 1.29)	19.88
ORR, % (95% CI)	58.9 (46.8 to 70.3)	39.2 (28.0 to 51.2)	59.7 (47.50 to 71.12)	38.89 (27.62 to 51.11)
CR/nCR, % (95% CI)	21.9 (13.1 to 33.1)	8.1 (3.0 to 16.8)	22.22 (13.27 to 33.56)	8.33 (3.12 to 17.26)
Median duration of response, months	11.99 (9.69 to 13.37)	6.97 (4.86 to 13.40)	11.99 (9.69 to 13.37)	6.97 (4.86 to 13.40)
Median TTP	12.68 (8.34 to 14.19)	4.99 (3.75 to 6.80)	12.68 (8.34 to 14.19)	4.86 (3.71 to 6.80)
On-treatment deaths, %	6.9	6.8	N/A	N/A

BTZ, bortezomib; CI, confidence interval; CR, complete response; nCR, near complete response; DEX, dexamethasone; EMA, European Medicines Agency; HR, hazard ratio; IMiD, immunomodulatory drug; ORR, overall/objective response rate; OS, overall survival; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; TTP, time to progression

Table 22 Incidence of on-treatment deaths and grade 3/4 adverse events in PANORAMA-1 for the population corresponding to the EMA label and the subgroup used for the direct comparison against BTZ/DEX

Incidence, %	**EMA label population, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD**		**Population for direct comparison with BTZ/DEX, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD *excluding* those with no response to the prior BTZ**	
	PANO/ BTZ/DEX N = 73/72	**PBO/ BTZ/DEX N = 74/73**	**PANO/ BTZ/DEX N = 72/71**	**PBO/ BTZ/DEX N = 72/71**
On-treatment deaths, %	6.9	6.8	N/A	N/A
Thrombocytopenia	68	44	46 (65%)	35 (49%)
Infections (pneumonia)	19.4	16.4	13 (18%)	12 (17%)
Infections (sepsis)	2.8	6.8	0 (0%)	2 (3%)
Diarrhoea	33.3	15.1	54 (76%)	34 (48%)
Asthenia/fatigue	26.4	13.7	Asht or fatig: 33 (46%) Fatig: 33 (46%) Asht: 16 (23%)	Asht or fatig: 25 (35%) Fatig 25 (35%) Asth: 11 (15%)

Haemorrhage	2.8	2.7	N/A	N/A
Neutropenia	31.9	9.6	25 (35%)	10 (14%)

BTZ, bortezomib; DEX, dexamethasone; EMA, European Medicines Agency; IMiD, immunomodulatory drug; LEN, lenalidomide; PANO, panobinostat; PBO, placebo.

3.1.2 Clinical parameters for PANO/BTZ/DEX and BTZ/DEX

Clinical parameters for PANO/BTZ/DEX and BTZ/DEX were derived from patient-level data for the relevant patient populations from PANORAMA-1 using a similar approach to that described in the original submission (section 5.3.2).

3.1.2.1 Risk of progression or death

The risk of experiencing a PFS event (ie either progression or death) in a given cycle was estimated using patient-level data from the PANORAMA-1 trial. Time since randomisation until progression or death (ie an event) or censoring was considered as exposure time. Table 23 provides descriptive statistics for the derived time to PFS event dataset.

Table 23 Descriptive statistics on the derived PFS dataset

Variable	**Characteristic**	**PANO/BTZ/DEX N = 72**	**BTZ/DEX N = 72**
Time to PFS event	No. of events – n	44	53
	No. of censored – n	28	19

Notes: event corresponds to patients who progressed or died; censored corresponds to patients who were censored for PFS (i.e., those who have not progressed, or died at the date of the analysis cut-off, or if patients received any further anti-cancer therapy).

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level PFS data to smooth and extrapolate PFS curves beyond the trial period and to derive the transition probabilities. The regression models were compared using the AIC, BIC values, and by visually assessing model fit. The best fitting models were selected for smoothing and extrapolating the PFS data. Table 24 summarise the AIC/BIC statistics for the PFS models. Based on the AIC and BIC statistics, clinical plausibility as well as visual assessment, the Weibull distribution was judged to provide the best model (Figure 16).

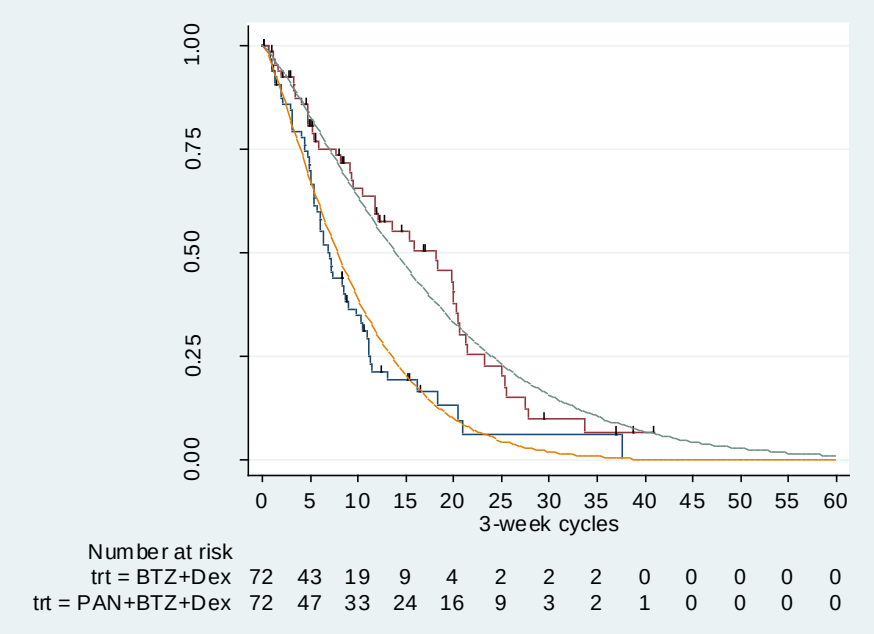
Table 24 AIC and BIC statistics of the PFS models

Model	AIC	BIC
Exponential	325.7219	331.6615
Weibull	***319.1743***	***328.0837***
Lognormal	322.8553	331.7648
Loglogistic	320.0477	328.9571
Gompertz	323.9435	332.8529

Note: best fitting model selected for the base case analysis in italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 16 Progression-free survival: Kaplan–Meier curve and fitted Weibull model



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

3.1.2.2 Risk of treatment discontinuation

Risk of treatment discontinuation was determined from the median duration of treatment for the two treatment groups. Data were analysed for patients corresponding to the safety set (ie, patients who received at least 1 dose of study drug):

- PANO/BTZ/DEX: n = 71
- BTZ/DEX: n = 71

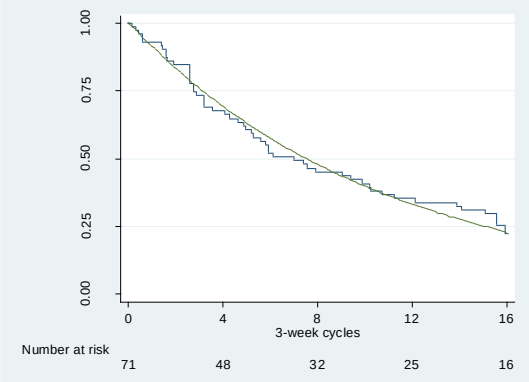
The median treatment duration was

- PANO/BTZ/DEX: 4.83 months (7.00 model cycles)
- BTZ/DEX: 4.80 months (6.95 model cycles).

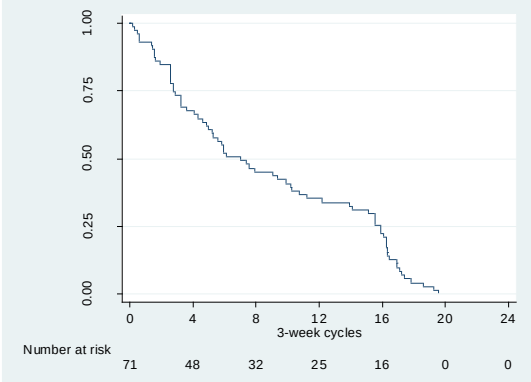
Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth the time to treatment discontinuation curves and to derive the transition probabilities. Curves were smoothed until 48 weeks, at which point the proportion of patients on treatment dropped sharply (see Figure 17). Beyond 48 weeks of treatment duration, treatment discontinuation rates were not smoothed. AIC/BIC statistics for the models are summarised in Table 25. The exponential model was considered to provide the best fit for PANO/BTZ/DEX and the Gompertz model was considered to provide the best fit for the BTZ/DEX.

Figure 17 Kaplan–Meier curve and fitted models for the proportion of patients without treatment discontinuation

a) PANO/BTZ/DEX

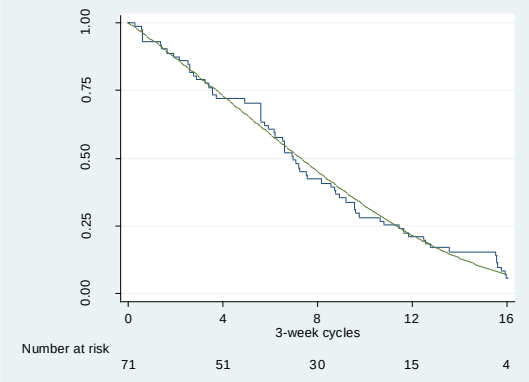


Kaplan–Meier and fitted curve (until cycle 16)

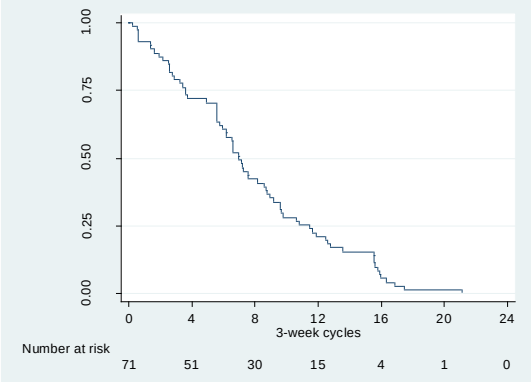


Complete Kaplan–Meier curve

b) BTZ/DEX



Kaplan–Meier and fitted curve (until cycle 16)



Complete Kaplan–Meier curve

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Table 25. AIC and BIC statistics of the treatment discontinuation models

	PANO/BTZ/DEX		**BTZ/DEX**	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	***218.0568***	***220.319***	193.0992	195.3619
Weibull	220.0373	224.5627	183.727	188.2524
Lognormal	221.8601	226.3855	200.6948	205.2201
Loglogistic	220.5865	225.1118	195.6549	200.1802
Gompertz	220.0558	224.5812	***181.3976***	***185.9229***

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

3.1.2.3 Probability of death

The risk of death in a given cycle was estimated using patient-level data from the PANORAMA-1 trial. Table 26 provides descriptive statistics for the derived time to death dataset.

Table 26. Descriptive statistics on the derived OS dataset (interim OS)

Variable	Characteristic	PANO/BTZ/DEX N = 72	PBO/BTZ/DEX N = 72
Time to death	No. of OS events, n	33	39
	No. of censored, n	39	33

Notes: OS event corresponds to a patient who died; censored corresponds to a patient alive at last contact

BTZ, bortezomib; DEX, dexamethasone; OS, overall survival; PANO, panobinostat; PBO, placebo.

3.1.2.3.1 Approach

OS for PANO/BTZ/DEX and PBO/BTZ/DEX was modelled and extrapolated by fitting a regression (survival) model on each of the treatment arms separately, ie not introducing a treatment effect parameter in the survival model, to prevent imposing restrictive assumptions (e.g. proportional hazards) on the risk profiles.

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth and extrapolate the OS curves. The regression models were compared along the AIC and BIC values, visually assessed model fit, and clinical plausibility[aa]. The Weibull model was selected for the base case analysis. Figure 18 presents the Kaplan–Meier and modelled OS curves; **Error! Reference source not found. Table 27** summarizes the AIC and BIC values calculated for the various regression models.

Table 27 AIC and BIC statistics for the OS models (interim OS)

a) (PANO/BTZ/DEX)

	Full PANORAMA 1 population	
Model	**AIC**	**BIC**
Exponential	155.4229	157.6996
Weibull	***155.9171***	***160.4704***
Lognormal*	155.0214	159.5748
Loglogistic*	156.4851	161.0384
Gompertz	156.1568	160.7101

Note: best fitting model selected for the base case analysis is shown in bold italics; * yields clinically implausible extrapolations therefore not shown in the model. AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

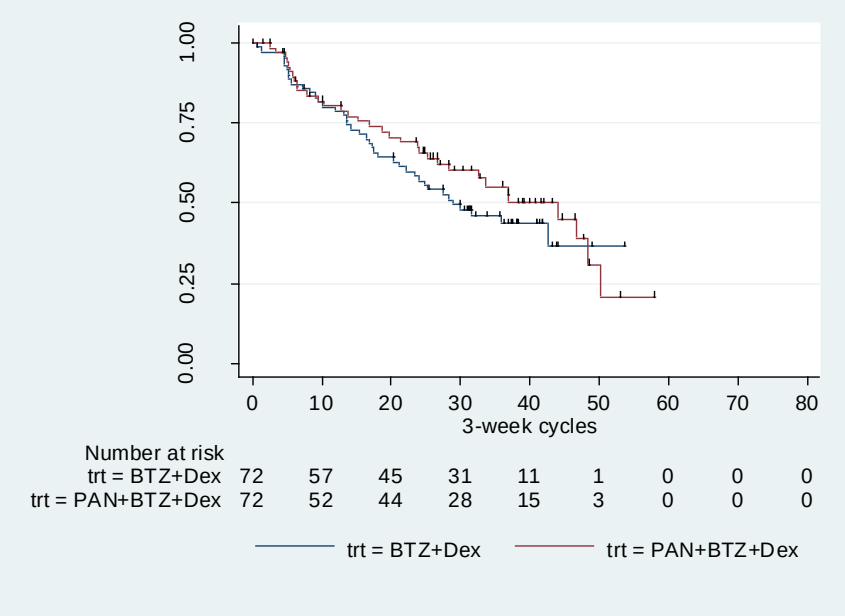
[aa] The Weibull and Gompertz models imply increasing mortality risk in the long run. From a clinical perspective, the prediction of constant (implied by an exponential model) or decreasing mortality rates over the lifetime (implied by a log-logistic or lognormal model) is unlikely to be plausible; modelling increasing mortality may be more appropriate. Therefore, the Weibull and the Gompertz models were preferred prior to model fitting and the best fitting model used for the base case analysis was selected from these two.

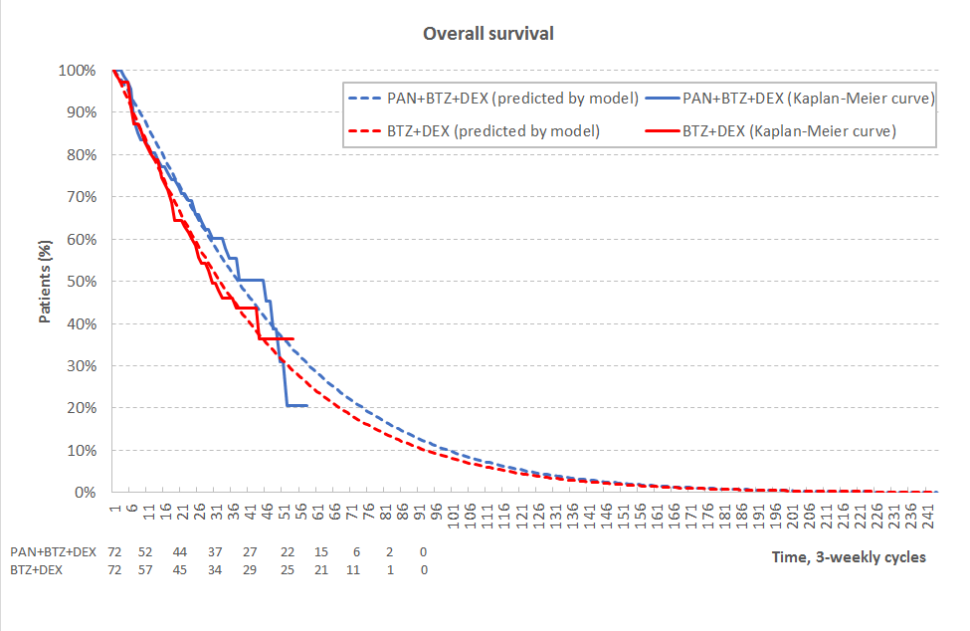
b) PBO/BTZ/DEX

	Full PANORAMA 1 population	
Model	**AIC**	**BIC**
Exponential	181.826	184.1026
Weibull	***183.2748***	***187.8282***
Lognormal*	182.803	187.3564
Loglogistic*	182.1812	186.7346
Gompertz	183.8151	188.3684

Note: best fitting model selected for the base case analysis is shown in bold italics; * yields clinically implausible extrapolations therefore not shown in the model. AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 18 Kaplan–Meier curve and fitted Weibull overall survival model (interim OS)





BTZ, bortezomib; DEX, dexamethasone; KM, Kaplan–Meier; PANO, panobinostat

3.2 Results

3.2.1 Base case − incremental cost-effectiveness analysis

Results for the cost-effectiveness analysis comparing PANO/BTZ/DEX versus BTZ/DEX are summarised in Table 28. Results are generated using the interim OS data from PANORAMA-1. Please note that results based on the final OS data from PANORAMA-1 with the higher discount are presented in the Addendum to the Manufacturer's response to the ACD.

Table 28 Summary of base case results (discounted): with PAS (interim OS)

With PAS[bb]	**Total**			**Incremental versus BTZ/DEX**			**ICER vs BTZ/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£137,447	2.491	1.652	£5,891	0.245	0.172	£34,333	£24,095
BTZ/DEX	£131,555	2.247	1.480					

Direct comparison based on the PANORAMA-1 trial using data for the subpopulations with at least 2 prior lines of treatment including an IMiD and BTZ including only those responding to the prior BTZ.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year..

3.2.2 Clinical outcomes from the model

Comparing the model results with the clinical outcomes from PANORAMA-1 for PANO/BTZ/DEX and BTZ/DEX in the subpopulation of patients who have received at least two prior therapies, including BTZ and an IMiD, and had a response to the prior BTZ based regimen reveals the following as summarised in **BTZ/DEX**:

- The model overestimates the median PFS by 0.5 months and hence the pre-progression QALY benefit.
- The model overestimates the median OS by 2.1 months and hence the post-progression QALY benefit and cost associated to it.
- The model overestimates the median treatment duration by 0.6 months and hence the cost associated with PANO/BTZ/DEX.

Table 29:

PANO/BTZ/DEX:

[bb] A simple discount of [redacted]%

- The model underestimates median PFS by 2.9 months and hence the pre-progression QALY benefit.
- The model underestimates the median OS, hence underestimates the post progression QALY and cost associated to it.
- The model overestimates the median treatment duration by 0.57 months and hence the cost associated with PANO/BTZ/DEX.

BTZ/DEX:

- The model overestimates the median PFS by 0.5 months and hence the pre-progression QALY benefit.
- The model overestimates the median OS by 2.1 months and hence the post-progression QALY benefit and cost associated to it.
- The model overestimates the median treatment duration by 0.6 months and hence the cost associated with PANO/BTZ/DEX.

Table 29 Summary of model results compared with clinical data for a) PANO/BTZ/DEX and b) BTZ/DEX (interim OS)

a)

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT and response to prior BTZ)	**Model results**
Median PFS (PANO/BTZ/DEX)	12.5 months	9.6 months
Median OS (PANO/BTZ/DEX)	30.5 months	25.5 months
Median treatment duration (PANO/BTZ/DEX)	4.83 months	5.4 months
Proportion of patients experiencing AEs (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

b)

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT and response to prior BTZ)	**Model results**
Median PFS (BTZ/DEX)	4.9 months	5.4 months
Median OS (BTZ/DEX)	19.9 months	22.0 months
Median treatment duration (BTZ/DEX)	4.80 months	5.4 months
Proportion of patients experiencing AEs (BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Disaggregated results for the base case

Table **30**, PANO/BTZ/DEX is associated with greater costs during the pre-progression on treatment state and these are off-set by reduced costs during the post-progression and a longer off-treatment period, with the result that overall, PANO/BTZ/DEX is associated with a cost-saving compared with BTZ/DEX (Table 31). Consistent with this, as shown in

Table **32**, PANO/BTZ/DEX is associated with greater drug costs compared with BTZ/DEX but this is off-set by reduced costs associated with the last line of treatment as well as the longer off-treatment period.

Table 31 and

Table 32 provide an overview of the discounted QALYs, costs and resource use costs that the model predicts for each health state for the two arms.

Results show that, compared with BTZ/DEX, PANO/BTZ/DEX is associated with a similar gain in QALY during the pre-progression on treatment phase and a considerably greater gain in QALY during the pre-progression off treatment phase which offsets smaller gain in QALY observed with PANO/BTZ/DEX in the post-progression phase (

Table **30**). Overall there is a small incremental gain in QALY for PANO/BTZ/DEX over BTZ/DEX.

Table 30 Summary of QALY gain by health state (interim OS)

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	0.33	0.32	0.02	0.02	5.1%
B: Pre-progression, off treatment	0.35	0.08	0.27	0.27	69.23%
C: Post progression	0.97	1.08	-0.11	0.11	28.2%
D: Death	0	0	0.00	0.00	0%
Total	1.71	1.65	0.07	0.39	100%

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; QALY, quality-adjusted life year.

PANO/BTZ/DEX is associated with greater costs during the pre-progression on treatment state and these are off-set by reduced costs during the post-progression and a longer off-treatment period, with the result that overall, PANO/BTZ/DEX is associated with a cost-saving compared with BTZ/DEX (Table 31). Consistent with this, as shown in

Table **32**, PANO/BTZ/DEX is associated with greater drug costs compared with BTZ/DEX but this is off-set by reduced costs associated with the last line of treatment as well as the longer off-treatment period.

Table 31 Summary of cost by health state: with PAS[cc] (interim OS)

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	£[redacted]	£13,980	£[redacted]	£[redacted]	[redacted] %
B: Pre-progression, off treatment	£447	£102	£345	£345	0.75%
C: Post-progression	£[redacted]	£116,332	–£[redacted]	£[redacted]	[redacted] %
D: Death	£1,130	£1,140	-£10	£10	0.02%
Total	£137,447	£131,555	£5,891	£45,750	100%

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PAS, Patient Access Scheme.

Table 32 Summary of predicted resource use by category of cost: with PAS[dd] (interim OS)

Item	Cost intervention (PANO/BTZ/DEX)	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£[redacted]	£12,341	£[redacted]	£[redacted]	[redacted] %
Tests and monitoring (on treatment)	£2,054	£1,639	£415	£415	0.90%
Tests and monitoring (No treatment)	£447	£102	£345	£345	0.75%
Last line of treatment	£[redacted]	£116,332	–£[redacted]	£[redacted]	[redacted] %

[cc] A simple discount of [redacted]%

[dd] A simple discount of [redacted]%

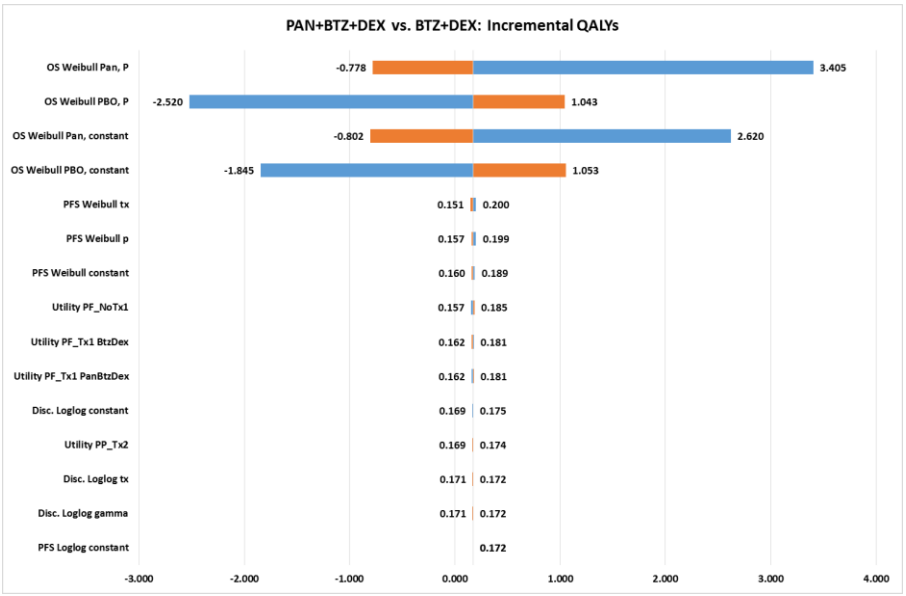
AEs	£1,141	£816	£326	£326	0.70%
Terminal care	£1,130	£1,140	-£10	£10	0.02%
Total	£137,447	£131,555	£5,891	£46,076	100%

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme.

3.2.3 Deterministic sensitivity analyses results

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie the deterministic) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. Tornado plots were generated for costs and QALYs, separately (Figure 19 and Figure 20), and for the ICER (Figure 21). In the plots, parameters are ranked from highest to lowest based on the magnitude of the result impact.

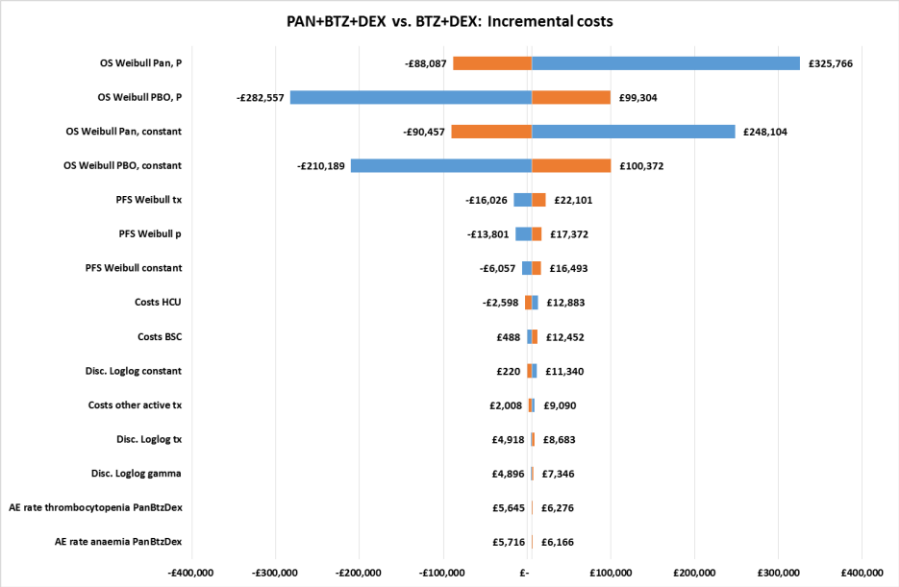
Figure 19 Tornado diagram of incremental QALYs for PANO/BTZ/DEX versus BTZ/DEX (discounted) (interim OS)



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; QALY, quality-adjusted life years.

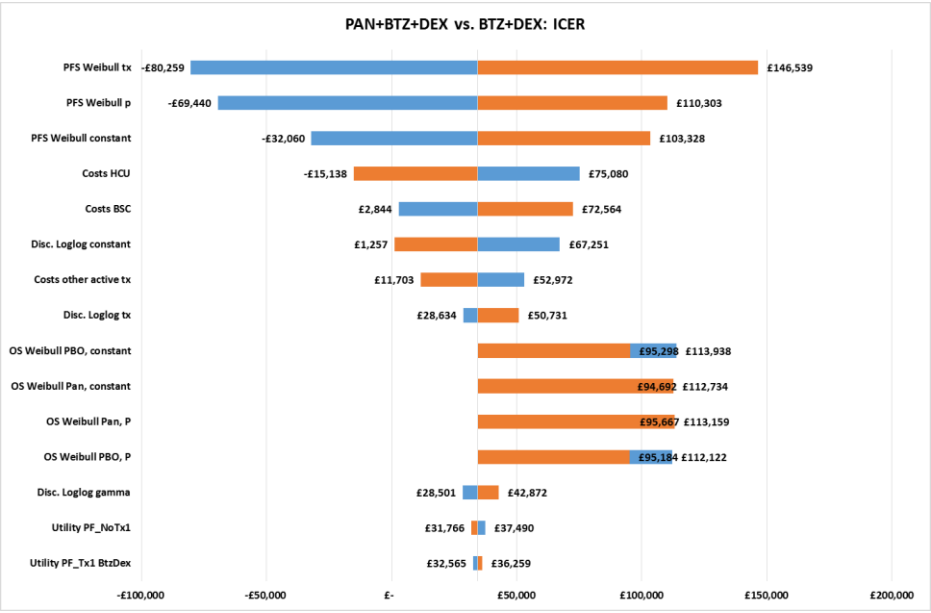
Figure 20 Tornado diagram of incremental costs for PANO/BTZ/DEX versus BTZ/DEX) (discounted): with PAS[ee] (interim OS)



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme.

Figure 21 Tornado diagram of ICERs for PANO/BTZ/DEX versus LBTZ/DEX(discounted): with PAS[ff] (interim OS)



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; LEN lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

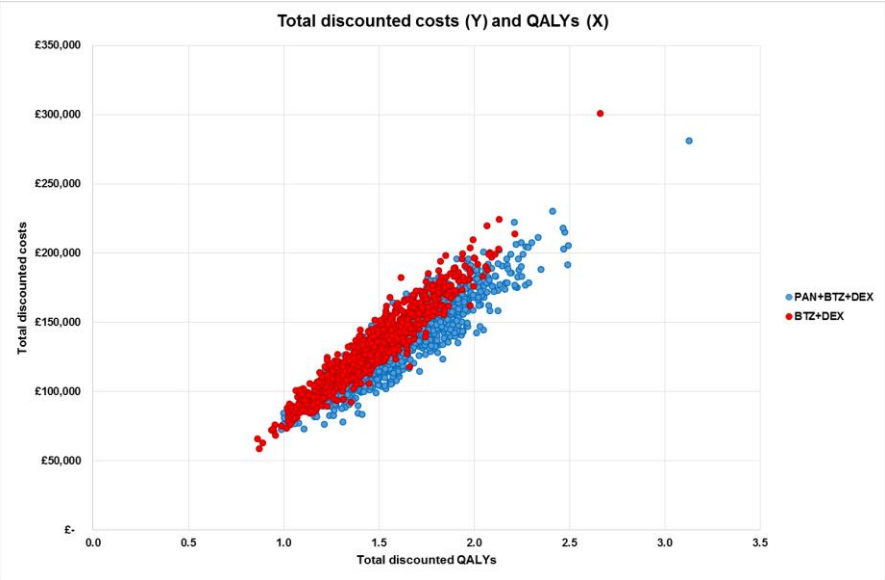
[ee] A simple discount of [redacted]%

[ff] A simple discount of [redacted]%

3.2.4 Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in **Figure 22** (scatter plot of total QALYs and costs), **Figure 23** (scatter plot of incremental QALYs and costs).

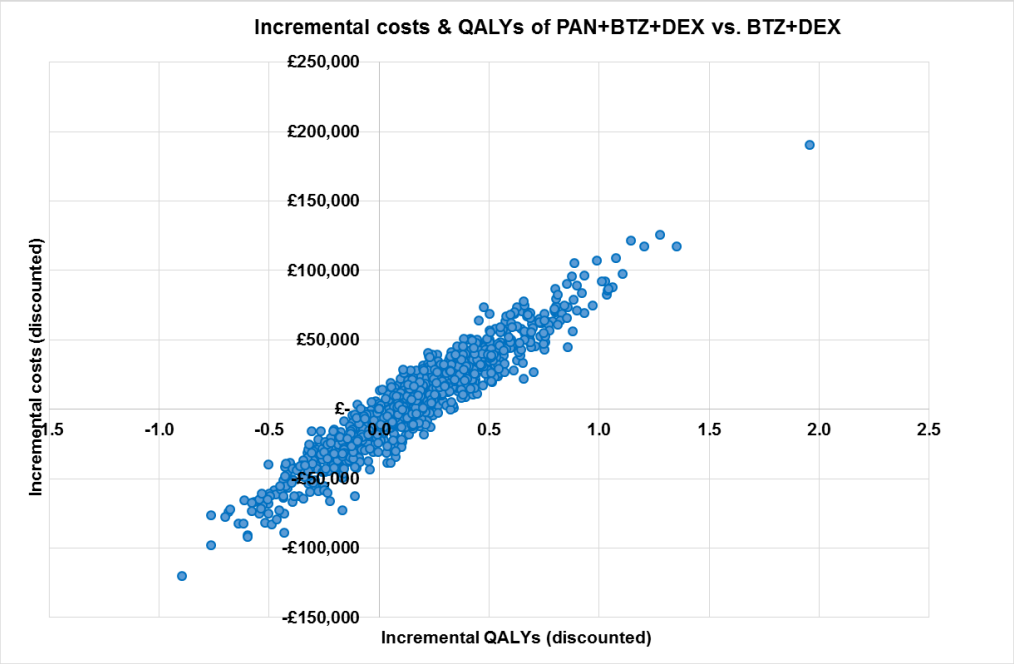
Figure 22 Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and BTZ/DEX (probabilistic sensitivity analysis): discounted analysis with PAS[gg] (interim OS)



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[gg] A simple discount of [redacted]%

Figure 23 Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): discounted analysis: with PAS[hh] (interim OS)



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes, which are presented in Table 33.

Table 33 The probabilistic sensitivity analysis and 95% CIs around key model outcomes for the base case (discounted): with PAS[ii] (interim OS)

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£137,447 (£89,572 to £191,063)	£5,891 (-£66,744 to £74,932)	1.652 (1.21 to 2.21)	0.172 (–0.49 to 0.86)	£34,333
BTZ/DEX	£131,555 (£85,360 to £186,999)		1.480 (1.06 to 1.94)		

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probability of PANO/BTZ/DEX being cost effective at certain willingness to pay threshold is summarised in Table 34.

[hh] A simple discount of [redacted]%

[ii] A simple discount of [redacted]%

Table 34 The probability of PANO/BTZ/DEX being cost effective according to willingness to pay thresholds: with PAS[jj] (interim OS)

WTP threshold	PANO/BTZ/DEX	BTZ/DEX
£20,000 / QALY	67.8%	32.2%
£30,000 / QALY	69.8%	30.2%
£50,000 / QALY	75.5%	24.5%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

3.2.5 Scenario analysis

The results of the scenario analyses are presented in Table 35.

Table 35 Scenario analyses for PANO/BTZ/DEX versus BTZ/DEX: with PAS[kk] (interim OS)

Scenario	Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Base case	**£5,891**	**0.172**	**0.245**	**£34,333**	**£24,095**
Discount rate of 5% for both costs and effects	£5,903	0.165	0.235	£35,819	£25,155
Time horizon, 5 years	£4,743	0.150	0.211	£31,572	£22,461
Time horizon, 10 years	£5,925	0.171	0.244	£34,582	£24,274
PFS, Loglogistic	-£1,362	0.198	0.267	dominant	dominant
PFS, Lognormal	£1,833	0.180	0.248	£10,181	£7,403
PFS, Gompertz	£7,448	0.170	0.245	£43,795	£30,460
PFS, exponential	£3,133	0.176	0.245	£17,780	£12,815
PFS, KM+Weibull	£8,015	0.169	0.245	£47,362	£32,779
Time to discontinuation, Kaplan–Meier estimates	£6,392	0.171	0.245	£37,310	£26,144
OS, Gompertz	£22	0.117	0.159	£184	£135
OS, Exponential	£16,415	0.287	0.424	£57,280	£38,700
OS, KM+Weibull	-£16,660	-0.049	-0.100	£340,543[ll]	£166,516

[2] Please note that in the case when both the incremental cost and the incremental QALY are negative (ie cost saving but less utility), the higher the ICER the more cost effective the treatment still could be.

[jj] A simple discount of [redacted]%

[kk] A simple discount of [redacted]%

[ll] Please note that in this case a significant cost saving (-£16,660) is associated with a small QALY loss (18 quality adjusted days)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; OS, overall survival; PANO, panobinostat; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year.

4 References

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We are writing on behalf of the UK myeloma forum that represents Haematologist in the UK with an interest in myeloma.

We are disappointed with the ACD for Panobinostat for treating multiple myeloma in people who have received at least one prior therapy because we feel that panobinostat when used in combination with bortezomib and dexamethasone has clinical utility in patients with relapsed myeloma. The initial pre-clinical studies showed a synergy for this combination of drugs based on their inhibition of distinct pathways of protein degradation that are critical for the survival of myeloma plasma cells. Subsequently clinical efficacy was clearly demonstrated in the phase 3 PANORAMA 1 study that compared panobinostat/bortezomib/dexamethasone to bortezomib/dexamethasone with meaningful improvements in response and duration of response.

The TA was complicated by the drug company involved choosing the comparator lenalidomide and dexamethasone for their health economic model. The reasons for choosing the comparator lenalidomide/dexamethasone were not entirely clear but clearly involved a concern that (re-treatment with) bortezomib/dexamethasone would no longer be available for patients in the UK as a treatment at relapse. The patient group who received 1-4 prior lines in the Phase 3 studies of lenalidomide/dexamethasone are not comparable to the patient cohort in the PANORAMA study, as they had had less exposure to novel drugs such as bortezomib, and treatment pathways have changed considerably in the last 10 years. The use of these subgroups in the health economic model therefore led to uncertainty and did not, in our view, produce a model that was adequate to the task.

We feel that the comparator should have been bortezomib/dexamethasone as it made any health economic analysis much more straightforward and robust (given it would be comparing arms of the PANORAMA trial) and also we feel that access to bortezomib/dexamethasone at relapse, although currently threatened is an established treatment for myeloma. Failure to gain access to panobinostat in this setting will undoubtedly negatively impact on patient outcomes.

National Institute for Health and Care Excellence

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Panobinostat for treating multiple myeloma in people who have received at least one prior therapy.

Nurses caring for people with multiple myeloma reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The RCN welcomed the opportunity to review this document. The comments below reflect the views of our reviewers in response to the questions on which comments were requested:

i) **Has the relevant evidence has been taken into account?**

The evidence considered seems comprehensive.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with multiple myeloma. The preliminary views on resource impact and implications should be in line with established standard clinical practice.

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

The appraisal committee seems to have adopted a comprehensive approach to this work. There are no other comments to add.

The RCN would welcome guidance to the NHS on the use of this health technology.

iv) **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?**

We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.

Janssen's response to the Appraisal Consultation Document (ACD) for panobinostat for treating multiple myeloma after at least 2 previous treatments

Please find below Janssen's comments on the above ACD.

- Janssen welcome NICE's acknowledgement that retreatment with bortezomib is part of established UK clinical practice. We note that established practice, based on previous criteria of the National Cancer Drugs Fund (NCDF), is to retreat with bortezomib only those patients who have had at least a prior partial response to bortezomib for at least 6 months. Evidence for bortezomib retreatment comes from a number of studies including RETRIEVE and 22 others included in a large meta-analysis by Knopf et al (Petrucci 2013, Knopf 2014). We also wish to highlight that the NHS England National Chemotherapy Algorithm for Multiple Myeloma is not yet published in its final version. Therefore, we do not believe it is appropriate to prejudge how recent changes to the NCDF for myeloma treatments including bortezomib, lenalidomide and pomalidomide will be incorporated into the final version.

- It is not clear if further analysis will be considered by the Committee to assess the clinical and cost effectiveness of panobinostat in combination with bortezomib and dexamethasone (PAN/BTZ/DEX) vs bortezomib and dexamethasone (BTZ/DEX) in the subgroup of PANORAMA-1 who received ≥2 prior treatments including bortezomib and an immunomodulatory therapy (IMiD). However, we wish to highlight that the adjustments made to the economic model analysing the full trial population to adapt the use of BTZ/DEX as applied in the trial to UK practice (ie. reducing maximum treatment duration) may not have taken full account of the expected improvement in the tolerability profile of BTZ/DEX. As the ERG has highlighted in its report, the trial-based utilities of PAN/BTZ/DEX may be overestimated compared to BTZ/DEX as the poorer tolerability profile for PAN/BTZ/DEX may not have been fully captured. The magnitude of the overestimation could be larger still when considering the extended treatment duration of BTZ/DEX in the trial vs routine practice. It is also unclear to what extent the PANORAMA-1 study will reflect the use of bortezomib retreatment in patients with prior response as in UK clinical practice, as noted above.

- Janssen note that the Velcade Response Scheme (VRS) relates to TA129 – bortezomib for the treatment of progressive multiple myeloma in people who are at first relapse. Whilst the VRS is not referred to within the ACD and may therefore be irrelevant to the current recommendation, we note that this is mentioned on slide 3 (cost effectiveness analysis presentation) presented at the first Appraisal Committee meeting (18.08.15). This slide notes the 'bortezomib PAS' as being included in the company assumptions for the subgroup analysis of patients who received ≥2 prior treatments that was discussed during the meeting.

References

Knopf K, et al. Meta-Analysis of the Efficacy and Safety of Bortezomib Re-Treatment in Patients With Multiple Myeloma Clinical Lymphoma, Myeloma & Leukemia, 2014 14 (5): 380-8

Petrucci MT, Giraldo P, Corradini P, Teixeira A, Dimopoulos MA, Blau IW, et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol 2013 Mar;160(5):649-59.

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Addendum to the Manufacturer's Response to the ACD

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Abbreviations

ACD	appraisal consultation document
AIC	Akaike information criterion
ASCT	autologous stem cell transplantation
ASH	American Society of Hematology
BIC	Bayesian information criterion
BSC	best supportive care
BTZ	bortezomib
CDF	Cancer Drug Fund
CI	confidence interval
DEX	dexamethasone
EMA	European Medicines Agency
ERG	Evidence Review Group
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drug
ISS	International Staging System
ITT	intention-to-treat
LEN	lenalidomide
LLoT	last line of treatment
LY	life year
MAIC	matching adjusted indirect treatment comparison
MM	multiple myeloma
MRU	medical resource utilisation
NICE	National Institute for Health and Care Excellence
OS	overall survival
PANO	panobinostat
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazard
POM	pomalidomide
QALY	quality-adjusted life years
rrMM	relapsed/refractory MM
STA	Single Technology Appraisal
THAL	thalidomide
TTP	time to progression

1 Response

In this document, and the related appendices, Novartis responds to the challenges raised by the Evidence Review Group (ERG), at the first Appraisal Committee meeting, and in the appraisal consultation document (ACD). Novartis considers that the analyses presented can address these challenges and serve to reduce the clinical and economic uncertainties.

1.1 Overview of further analyses

Appendix 1 provides the final overall survival (OS) data from the PANORAMA-1 trial which is to be published in December 2015 at the 57th American Society of Hematology (ASH) Congress. Please note that this information is marked as Academic in Confidence.

Appendix 2 describes an alternative method for determining the relative efficacy of the panobinostat regimen (PANO/BTZ/DEX) versus lenalidomide plus dexamethasone (LEN/DEX), the current standard of care in the patient population corresponding to the panobinostat licensed indication (ie patients who have received at least two prior treatments including an immunomodulatory drug (IMiD) and bortezomib (BTZ). It addresses the concerns of the ERG as well as the explicit requests in the ACD to maintain a sufficient effective patient number (ACD, Section 3.27 and 4.8) as well as to apply independently fitted survival curves to the two arms (ACD, Section 4.7 and 4.8)[a]. The updated method is matching only to those significant baseline prognostic factors which predict survival and applies time dependent HRs, i.e. avoiding the use of constant hazards. The updated method is populated with the final PANORAMA-1 OS data described in Appendix 1. The results of the cost-effectiveness analysis using these data are also presented. Sensitivity analysis is provided with removing subsequent active treatments as suggested in the ACD (ACD, Section 4.12).

Appendix 3 describes a new direct comparison of PANO/BTZ/DEX versus BTZ/DEX, and is in response to the explicit suggestion of the AC (ACD, Section 4.4 and 4.10) that such an analysis should have been provided in our original submission for the subgroup of interest. The analysis described here is based directly on data from PANORAMA-1 but for the subgroup of patients corresponding to the panobinostat licensed indication. Furthermore, only patients who had responded to prior treatment with BTZ were included, in line with the former requirements of the Cancer Drug Fund (CDF) for use of BTZ. This additional direct comparison model is populated with the final PANORAMA-1 OS data described in Appendix 1. Novartis maintains its view that BTZ in combination with DEX is not an appropriate comparator in current UK clinical practice following the CDF delisting of BTZ earlier this year. However, Novartis acknowledges that this direct comparison provides valuable additional information regarding the economic analysis of PANO/BTZ/DEX and may assist the Appraisal Committee in making its decision.

[a] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

Novartis has informed the Department of Health that it is increasing the level of discount for panobinostat from [redacted]% to [redacted]%. The cost-effectiveness analyses described here are presented with a PAS of [redacted]%.

1.2 End of Life criteria

In light of the final OS data presented in Appendix 1, Novartis reiterates its view that panobinostat in combination with BTZ and DEX meets the End of Life criteria for the following reasons:

- A retrospective audit performed by the Haematological Malignancy Research Network (HMRN)[1] in relation to a cohort of 1645 patients with multiple myeloma (MM) diagnosed between September 2004 and August 2011 suggests that OS for patients receiving third-line therapy is 1.1 years (95% confidence interval [CI]: 0.8-1.4) from the start of the third line regimen for patients who receive LEN/DEX as third-line therapy, in line with the related NICE Guidance (TA171). This subgroup specific additional information is provided to address the life expectancy of patients having lenalidomide plus dexamethasone after 2 previous treatments in England (ACD, Section 4.16).
- The final OS data from the PANORAMA-1 trial shows a numerical benefit of [redacted] months for PANO/BTZ/DEX vs BTZ/DEX in the EMA labelled population. This addresses concerns raised regarding the additional survival benefit of PANO/BTZ/DEX (ACD, Section 4.17). This trial data represents the only available direct survival comparison of PANO/BTZ/DEX against a current standard of care treatment. However, the *modelled* OS benefit of PANO/BTZ/DEX vs LEN/DEX is 2.52 months.
- Novartis assumes the eligible patient population to be around 930[b] in England and Wales in the following setting: patients who have received at least two prior treatments including an IMiD and BTZ. This addresses the request for eligible population data for the subgroup in line with the EMA licence (ACD, Section 4.18).

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b

Annual incidence: 3,138; calculated based on a total population of 58,112,666 for 2016 and an incidence rate of 5,4/100,000; Source: Office of National Statistics and Cancer Research UK;

Treatment rate: 70.4%; Source: Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0;

3-year survival rate: 52.7%; 3-year survival rate is used as a proxy for patients eligible for 3rd line treatment; Source: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Multiple-Myeloma/

Proportion of patient having received ≥2 prior lines including an IMiD and BTZ: 54.5%; Source: Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0. However, based on expert inputs this proportion is assumed to be around **80%** in most centres.

1.3 Cost effectiveness results

Results for the cost-effectiveness analysis populated with final OS data from PANORAMA-1 comparing PANO/BTZ/DEX with a) LEN/DEX and b) BTZ/DEX are summarised below in

Table 12.

Table 1 Summary of base case cost effectiveness results comparing PANO/BTZ/DEX with a) LEN/DEX and b) BTZ/DEX *with* PAS

a)

With PAS[c]	**Total**			**Incremental versus LEN/DEX**			**ICER vs LEN/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£141,707	2.40	1.59	£1,425	0.210	0.124	£6,783	£11,527
LEN/DEX	£140,281	2.19	1.47					

Time dependent HRs derived using MAIC method applied to subpopulation (2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

b)

With PAS[d]	**Total**			**Incremental versus BTZ/DEX**			**ICER vs BTZ/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£140,388	2.585	1.712	–£8,909	0.080	0.066	Dominant	Dominant
BTZ/DEX	£149,297	2.505	1.646					

Direct comparison based on the PANORAMA-1 trial using data for the subpopulations with at least 2 prior lines of treatment including an IMiD and BTZ including only those responding to the prior BTZ.

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IMiD, immunomodulatory drug; LYG, life years gained; PANO, panobinostat; QALY, quality y-adjusted life year.

[c] A simple discount of [redacted]%

[d] A simple discount of [redacted] %

2 Appendix 1: Final analysis of overall survival from the phase 3 PANORAMA-1 trial of PANO/BTZ/DEX vs. BTZ/DEX

The following data will be presented at the 57th Annual meeting of the American Society of Hematology in December 2015.[2]

2.1 Methods

As of 29 June 2015, the 415 events required to conduct the final analysis of OS were observed. Kaplan–Meier estimations of OS were performed for the entire treatment population (N = 768) and for the following two subgroups: patients who had received prior BTZ and an IMiD (n = 193), and patients who had received at least 2 prior regimens including BTZ and an IMiD (n = 147).

2.2 Results

Median OS was numerically higher for the PANO/BTZ/DEX arm for all prior treatment subgroups, with the greatest difference being among the most heavily pre-treated subgroup of patients, those who had received at least 2 prior regimens including BTZ and an IMiD. The median OS for the patients who received at least 2 prior lines including BTZ and an IMiD was [redacted] months (95% CI, [redacted] – [redacted]) in the PANO/BTZ/DEX arm vs [redacted] months (95% CI, [redacted] – [redacted]) for BTZ/DEX (Figure 1).

A higher percentage of patients on the BTZ/DEX arm received post-study therapy compared with the PANO/BTZ/DEX arm which may have confounded the OS results. In patients who had received at least 2 prior regimens including BTZ and an IMiD the proportion of patients receiving post-study therapy was [redacted] % in the PANO/BTZ/DEX arm and [redacted] % in the BTZ/DEX arm.

Figure 1 OS for Patients who had received at least 2 prior regimens including BTZ and an IMiD in PANORAMA-1

3 Appendix 2 Cost-effectiveness of PANO/BTZ/DEX versus LEN/DEX using time dependent HRs derived using MAIC method applied to the subpopulation of patients having received 2–3 prior lines of therapy

3.1 Assessment of the suitability of survival models used for the health economic model

3.1.1 Overview of the approach

The sections below describe an assessment of the survival models used to derive hazard ratios (HRs) of progression-free survival (PFS) and OS for the health economic model comparing PANO/BTZ/DEX versus LEN/DEX. HRs were used to link the efficacy of LEN/DEX to the efficacy of PANO/BTZ/DEX in patients who had received at least 2 prior regimens including BTZ and an IMiD (European Medicines Agency (EMA) label population).

Using HRs in the health economic model, instead of directly comparing LEN/DEX with PANO/BTZ/DEX, was necessary because trial results (ie, efficacy data, Kaplan–Meier curves and patient characteristics) have not been published for LEN/DEX in the patient population corresponding to the EMA label for panobinostat. Trial results for LEN/DEX have only been published for the intent-to-treat population of the pivotal trials, as well as for patients having received one prior line of treatment and for patients having received 2–3 prior lines of treatment.[3]

HRs were derived by comparing the efficacy (ie, PFS and OS) of LEN/DEX and PANO/BTZ/DEX in patients who received 2–3 prior lines of treatment, using the Matching Indirect Treatment Comparison (MAIC) method. To perform a fair comparison of LEN/DEX versus PANO/BTZ/DEX, the following adjustments for differences in trial design (ie patient selection and baseline characteristics) were made for PANO/BTZ/DEX:

- Exclusion of patients who had received LEN treatment before initiation of PANO/BTZ/DEX
- After exclusion of patients with prior LEN treatment, the remaining patients were matched on time since diagnosis (4.1 years) and β2-microglobulin level (proportion of patients with β2-microglobulin > 2.5 mg/L: 74.5%).

It is important to emphasize that the information utilized to derive the HRs (ie, published Kaplan–Meier curves and baseline characteristics for LEN/DEX in patients having received 2–3 prior lines of treatment, adjusted patient population of PANO/BTZ/DEX) was not used directly in the health economic model. Instead, the derived HRs were used to generate PFS and OS data for LEN/DEX in a hypothetical patient population reflecting the panobinostat EMA label setting assuming that the same relationship would be observed between LEN/DEX and PANO/BTZ/DEX in the EMA label setting as observed in patients who have received 2–3 prior lines of therapy.

3.1.2 Using the MAIC method to match the two trial subpopulation for PFS and OS

In line with the recommendations of the ERG report and the ACD (ACD, 3.27, 3.29 and 4.7) published by the National Institute for Health and Care excellence (NICE) for the economic evaluation, we have used the MAIC method to derive HRs based on data for the subpopulation having received 2–3 prior lines of treatment as this method provides the most appropriate approach for deriving the relative efficacies of LEN/DEX versus PANO/BTZ/DEX. The choice of this method is based on the following arguments.

1. The MAIC method attempts to take into account relevant baseline characteristics. This is considered important because:
    a. Clinicians suggest that one of the most relevant factors regarding the choice of therapy for patients with relapsed/refractory MM (rrMM) is the mechanism of action; hence those with prior use of LEN/DEX have been excluded from the data set.
    b. Exploratory analysis of data from the MM-009/-010 studies showed that the number of prior therapies and baseline ß2-microglobulin levels (specifically having a baseline level of > 2.5mg/L) were the only two significant predictors for time to progression (TTP), while the use of prior thalidomide (THAL) or BTZ did not impact the TTP outcome.[3] A similar analysis for OS suggests that baseline International Staging System (ISS) score in addition to the number of prior therapies and baseline ß2-microglobulin levels are significant predictors for OS.[4] However baseline ISS score has *not* been reported for the subgroup with 2–3 prior lines of treatment from the MM-009/MM-010 trials.
    c. The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, patients in the PANO/BTZ/DEX group who had received prior LEN/DEX were excluded from the analysis set, ie from the subgroup of patients having received 2–3 prior lines of treatment. Exclusion of a subgroup of patients in this manner is possible using the MAIC method.
2. The MAIC methodology allows adjustment for a limited number of patient characteristics. The MAIC method can therefore be used in cohorts with smaller sample sizes without sacrificing the final effective sample size and avoids distortion of the comparison.
    a. If adjustment was made for all available patient characteristics, the effective patient number in the PANO/BTZ/DEX cohort would decrease to 23. Such concern addressed in the ACD (ACD, Section 3.27 and 3.29).
    b. However, adjusting for only the four most important patient characteristics means that the effective patient number remains 140 out of the total subgroup population of 188 (ie patients who had received 2–3 prior lines in the PANORAMA-1 trial).

3. The PFS and OS HRs derived using the MAIC methodology seem to be clinically plausible in light of the efficacy data available for PANO/BTZ/DEX and LEN/DEX for the Intention-to-treat (ITT) cohorts and the subgroups of patients who have received 2–3 prior lines of treatment, when acknowledging the differences in the patient characteristics between the two trials (ie PANORAMA-1 and pooled data for MM-009/MM-010), as summarised in Table 2.

Table 2 Summary of median PFS and OS for PANO/BTZ/DEX and LEN/DEX for patients who have received 2−3 prior therapies in PANORAMA-1 and MM-009/-010

Parameter	PANO/BTZ/DEX 2–3 prior lines subgroup		LEN/DEX 2–3 prior lines subgroup	
	n	Median (95% CI), months	n	Median, months
PFS	188	11.33 (9.36 – 13.70)	220	10.6
OS	188	[redacted]	220	35.8

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

Data on file;[5] Stadtmauer et al 2009[3]

3.1.3 Treatment discontinuation – LEN/DEX

While PFS and OS for LEN/DEX and PANO/BTZ/DEX can be compared using an indirect treatment comparison (MAIC method), comparison of treatment duration using these methods is not feasible because LEN/DEX is given continuously until disease progression. Instead, a method based on the published median PFS and the median treatment duration for the subgroup of patients who had received 2–3 prior lines of treatment (9.5 and 9.2 months, respectively) was used. In particular, it was assumed that the risk of treatment discontinuation is 3.3% (9.5/9.2) higher than the risk of PFS in each model cycle. Treatment discontinuation was therefore estimated by multiplying the rate of progression or pre-progression death by 3.3%.

Please note that in the original submission the probability of treatment discontinuation for LEN/DEX was falsely calculated based on the median PFS and treatment duration related to the full population, instead of the 2-3 prior lines subgroup.

3.1.4 Post progression treatment mix

Disease progression is implemented through patients moving from the two pre-progression health states to the post-progression health state, corresponding to fourth-line therapy. Fourth-line therapy can be: a) pomalidomide plus DEX (POM/DEX) together with further supportive care (medical resource utilisation, MRU)[e],[6] b) other active treatments together with further supportive care, or c) supportive care alone. Patients finally move to the death health state. The modelled fourth-line treatment options are referred to as last line of treatment (LLoT).

[e] Medical-resource utilisation incorporates clinical attendance, inpatient admissions, transfusions, supportive therapy, blood tests as described by Gooding *et al.* 20136. Gooding S, Lau I-J, Sheikh M *et al.* Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre *Blood* 2013;122:Abstract 1727.

The proportion of patients receiving any active treatment in the post-progression health state has been updated based on the final data from the PANORAMA-1 trial. This assumes that 31.5% of patients receive POM/DEX followed by MRU[f], 4.1% receive other active treatments in line with the retrospective analysis published by Gooding *et al* in 2013[6] followed by MRU and the remaining 64.4% receive best supportive care (MRU) alone. Since such data has not been published for patients receiving LEN/DEX, we assume patients in the LEN/DEX arm receive similar post-progression therapies and in similar proportions to those reported for PANO/BTZ/DEX.

To address the request of the ACD (ACD, Section 4.12) sensitivity analysis is provided to analyse the effect of removing subsequent active treatments.

3.1.5 Matching the two subpopulations (with 2–3 prior lines of treatment) with selected patient characteristics only

This section addresses the concerns raised in both the ERG report and the ACD on the reliability of the MAIC due to low statistical power after matching (ACD, Section 3.27 and 3.29).

To adjust for differences between the trials in terms of patient and disease characteristics at baseline, the matching algorithm proposed by Signorovitch *et al.*[7] was used. In particular, individual patient-level data from the PANORAMA-1 trial were reweighted such that the selected average/median baseline characteristics matched those reported from the MM-009/MM-010 trials. (This was performed for the subgroup of patients who had received 2–3 prior lines of therapy.) The matching ensures that treatment outcomes are comparable across balanced trial populations to the extent of the considered baseline characteristics. Ideally, matching should be based on clinically relevant risk factors that impact on the relative treatment effects.

Exploratory analysis of data from the MM-009/-010 studies showed that the number of prior therapies and baseline ß2-microglobulin levels (specifically having a baseline level of > 2.5mg/L) were the only two significant predictors for TTP, while the use of prior THAL or BTZ did not impact the TTP outcome.[3] A similar analysis for OS suggests that baseline ISS score in addition to the number of prior therapies and baseline ß2-microglobulin levels are significant predictors for OS. [4] Duration of MM (ie time since diagnosis) was also identified as a predictor for TTP and OS and was therefore also included as a matching criterion. However as baseline ISS scores were not reported in the 2–3 prior lines subgroup analysis of the MM-009/MM-010 trials, this characteristic had to be excluded from the matching process. The MM-009/MM-010 trials also excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, patients in the PANO/BTZ/DEX group who had received prior LEN/DEX were also excluded from the analysis set, ie the patient subgroup with 2–3 prior lines of treatment.

Selected baseline patient characteristics before and after the adjustment of the PANORAMA-1 trial data are presented in Table 3. The effective sample size (computed as the square of the summed weights divided by the sum of the squared weights) in the PANORAMA-1 trial decreased from 142 to

[f] MRU, medical resource utilisation

138 (97.2 %) in the subgroup analysis (patients with 2–3 prior lines of treatment). However the weighted number of patients (ie sum of patient weights) was 140 (98.6%). (Patients with prior use of LEN-based treatment were excluded from the PANORAMA-1 dataset.)

Table 3 Baseline patient characteristics used in the matching adjusted indirect treatment comparison, before and after adjustment for the subpopulations with 2–3 prior lines of treatment

Baseline characteristics, proportion of patients	LEN/DEX (n = 220)	PANO/BTZ/DEX unadjusted[a] (n = 142)	PANO/BTZ/DEX adjusted (n = 140)
Patient with prior LEN based regimen	0%	0%	0%
Patient with 2–3 prior lines of treatment	100%	100%	100%
Patients with median time since diagnosis > 49.2 months	50%	47.2%	50%
Patients with serum ß2-microglobulin > 2.5 mg/L	74.5%	67.6%	74.5%

[a]The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 188). All patients had complete information on the covariates.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat.

Stadtmauer *et al.* 2009.[155]

3.2 PFS assessment using the updated MAIC method

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7) as well as the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8).

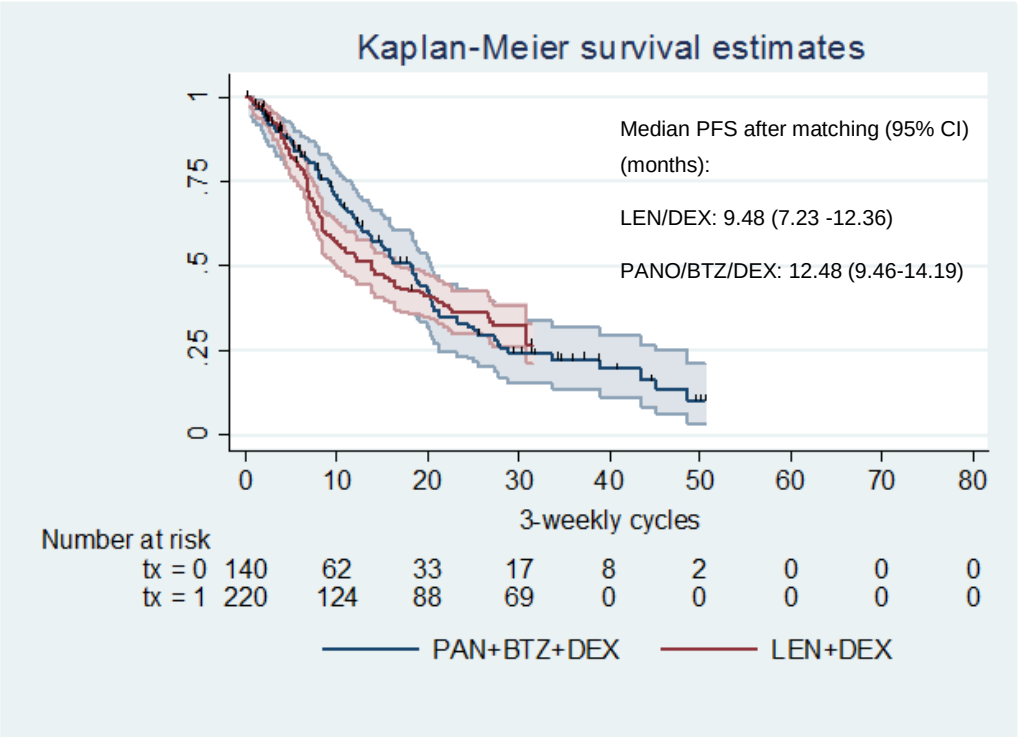
Results of the MAIC indicated that in terms of PFS, the efficacy of PANO/BTZ/DEX was better to that of LEN/DEX in both patient populations analysed (Figure 2 and Table 4).

Table 4 PFS HR and median PFS for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment

	HR	SE	95% CI	Median PANO/BTZ/DEX	Median LEN/DEX
PFS	1.043	0.146	0.783 – 1.388	12.48 (9.46 – 14.19)	9.48 (7.23 – 12.36)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; SE, standard error of the log hazard ratio.

Figure 2 Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment



Notes:

N = 220 for LEN/DEX, N = 140 for PANO/BTZ/DEX (refers to the weighted sample size)

PANO/BTZ/DEX: patients with 2–3 prior lines of treatment, no prior LEN treatment, matched to LEN/DEX against β2-microglobulin and time from diagnosis

LEN/DEX: patients with 2–3 prior lines of treatment[3]

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; LEN, lenalidomide; MAIC, MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PFS, progression-free survival.

3.2.1 Testing for the proportional hazard assumption

At first, a constant (time independent) hazard ratio (HR = 1.043) was used to determine the PFS of LEN/DEX (relative to PANO/BTZ/DEX) in the economic model. However the use of a constant HR implicitly assumes that the proportional hazard (PH) assumption of the Cox regression model based on which the HR was estimated is satisfied. To test whether the proportional hazard assumption is satisfied, three types of assessments were carried out as summarised in Table 5.

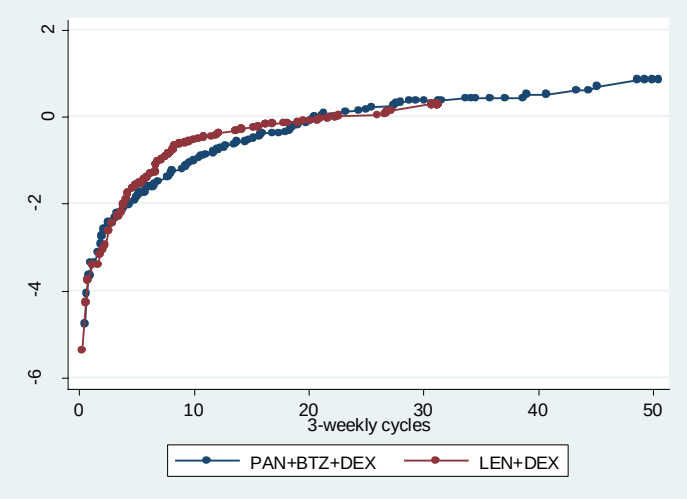
Table 5 Overview of tests used to assess the proportional hazard assumption

Test	Interpretation	Comment
Visual inspection of the log-cumulative hazard plot	Log of minus cumulative hazard versus survival time graph should result in parallel curves if the predictor is proportional.	Interpreting plots is subjective. In general, one can conclude PH unless a distinct pattern of non-parallelism (e.g., crossing) is seen. Intertwined lines with no distinct pattern may simply indicate no difference between groups.
Visual inspection of the Schoenfeld residuals	Schoenfeld residuals for the treatment covariate versus time should result in a flat line.	Systematic departures from a horizontal line are indicative of non-proportional hazards.
Statistical test based on the scaled Schoenfeld residuals	Testing the time dependent covariates is equivalent to testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time.	Called the Therneau and Grambsch test. A non-zero slope is an indication of a violation of the PH assumption.

PH, proportional hazard

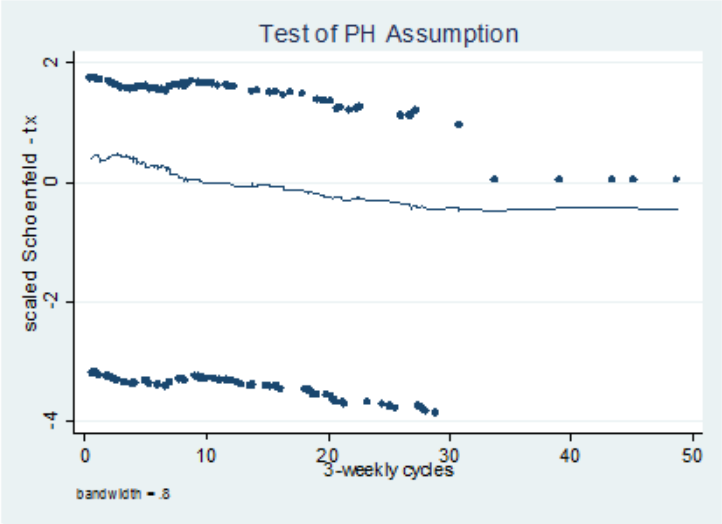
The results of the assessment of the PH assumption indicate that the proportional hazard assumption is not satisfied therefore a constant HR cannot be applied. The log-cumulative hazards plot suggests that the hazard of PFS is larger for LEN/DEX than for PANO/BTZ/DEX at the beginning of the treatments (suggested by the diverging curves during approximately the first 10 cycles), then the trend changes and the hazard of PFS becomes lower for LEN/DEX than for PANO/BTZ/DEX (suggested by the converging curves between approximately the next 10 cycles), while the hazards seem to be very similar after approximately 20–25 cycles (Figure 3). The Schoenfeld residuals plot also suggests the violation of the PH assumption because the residuals do not follow a straight line (Figure 4). Finally, the Therneau and Grambsch test indicates a P value of less than 0.05 (Table 6).

Figure 3 Log (-cumulative hazards) versus time for PFS



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 4 Schoenfeld residuals versus time for PFS



PFS, progression-free survival; PH, proportional hazard.

Table 6 Therneau and Grambsch test result for PFS

	rho	chi2	Degrees of freedom	Prob>chi2 (P value)
treatment	–0.13003	3.97	1	0.0464

PFS, progression-free survival

3.2.2 Application of time-dependent HRs of PFS to address non-proportional hazards

As an alternative to the constant HR approach, a time-varying HR approach was also developed to address the issue of non-proportional hazards. In this approach, a fully parametric survival model was fitted on the LEN/DEX simulated patient-level data and on the matched PANO/BTZ/DEX patient-level data, separately. Five different distributions (exponential, Weibull, log-logistic, lognormal, and Gompertz) were assessed and the best fitting regression model was selected. For each treatment, the best fitting regression model implied a certain hazard rate profile (i.e., hazard rate of PFS for each 3-weekly cycle).

The ratio of the two rates in each 3-weekly cycle then yielded a HR profile that was not constant but changed over the 3-weekly cycles (hence the name time-varying HR)[g]. Because for LEN/DEX, PFS

[g] Modelled PFS was used to derive the 3-weekly hazard rates using the following formula:

PFS(t) = exp(-H(t))

H(t) = - ln(PFS(t))

h(t) = H(t+1) – H(t)

where PFS(t) is the modelled progression-free survival at time 't', H(t) is the cumulative hazard function at time t, h(t) is the hazard rate at time 't'. The hazard ratio at time t, HR(t), was derived as the ratio of the treatment-specific hazard rates at time 't'.

data were available only until approximately 30 cycles, beyond this point, based on visual assessment of the log–cumulative hazard plot, the HR of PFS between LEN/DEX and PANO/BTZ/DEX was assumed to be one.

Table 7 presents the Akaike information criterion/ Bayesian information criterion (AIC/BIC) values for LEN/DEX and PANO/BTZ/DEX. For LEN/DEX, the lognormal distribution resulted in the best model fit, whereas for PANO/BTZ/DEX the Weibull distribution yielded the best fit. Figure 5 presents the Kaplan–Meier estimates and the model predictions. According to visual assessment, these models indeed fit the Kaplan–Meier curves well. The log-normal distribution implied a unimodal hazard profile for LEN/DEX whereas the Weibull model implied an increasing hazard profile for PANO/BTZ/DEX. The ratio of these profiles (not surprisingly) did not result in a constant HR (depicted in Figure 6) but in a reversed U-shape HR profile.

Figure 7 presents the PFS curve for PANO/BTZ/DEX in the population corresponding to the licensed indication (ie, used in the health economic model) and the implied PFS curve for LEN/DEX using the time dependent HR approach described above.

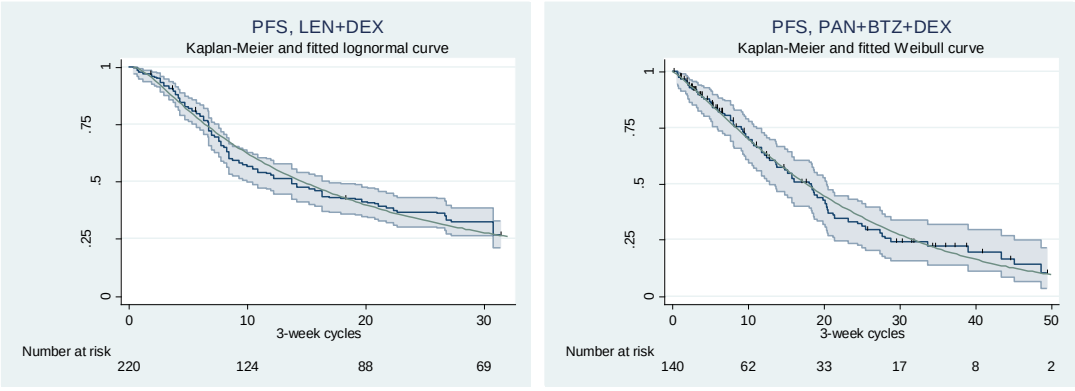
Table 7 AIC/BIC values for the PFS models for LEN/DEX and PANO/BTZ/DEX

	LEN/DEX		**PANO/BTZ/DEX (matched)**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	639.6038	642.9975	277.5292	280.485
Weibull	641.1437	647.931	***276.5625***	***282.4741***
Log-logistic	629.571	636.3582	277.2262	283.1379
Log-normal	***627.28***	***634.0672***	280.209	286.1207
Gompertz	640.6507	647.4379	278.5276	284.4392

The best fitting model selected for the base case analysis is shown in bold italic

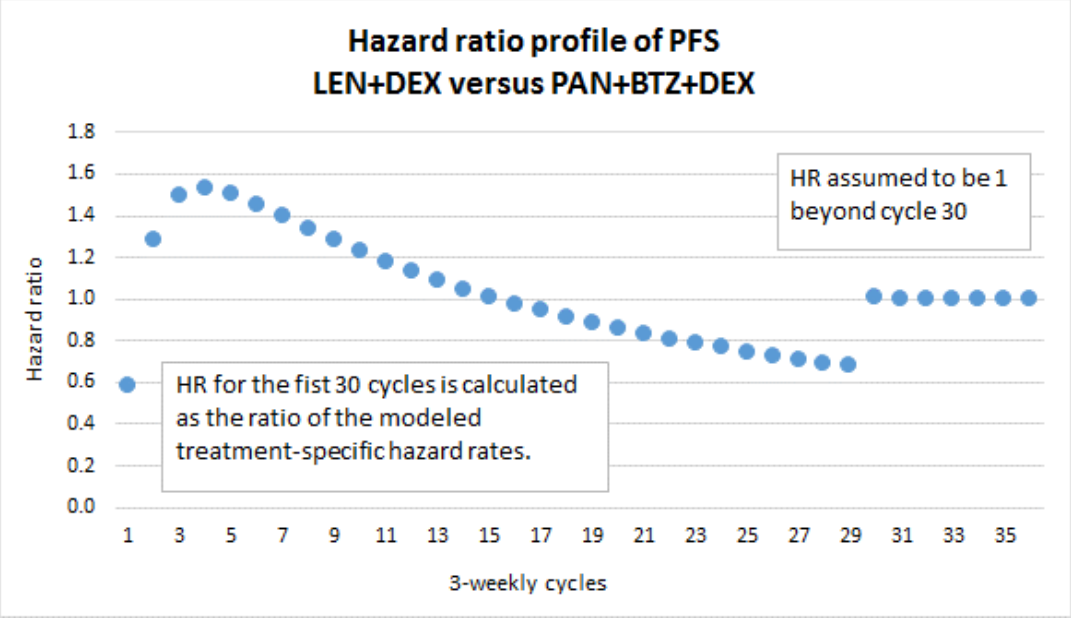
AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 5 Kaplan–Meier estimates of PFS and modelled curves



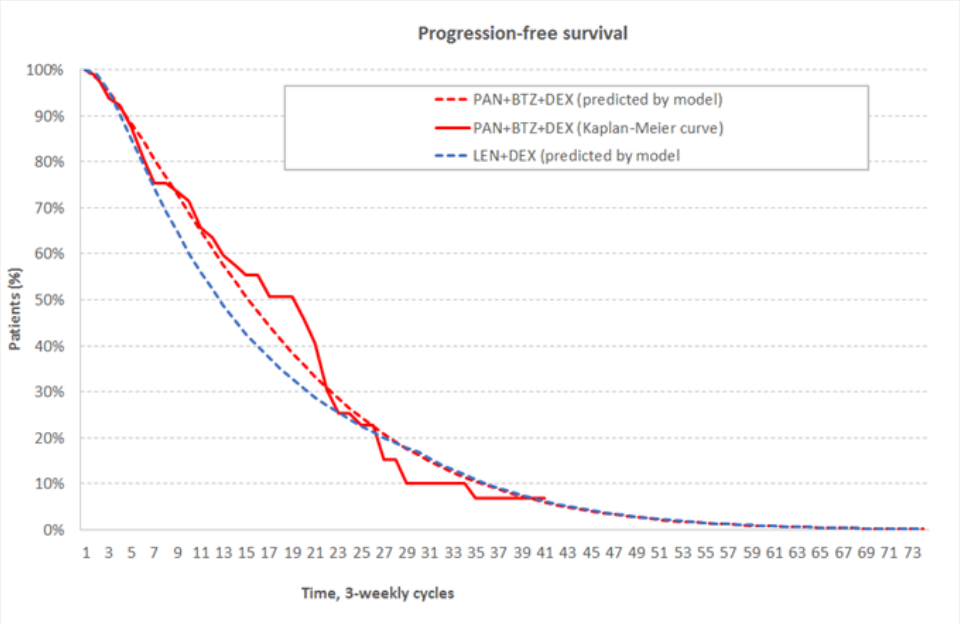
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 6 Hazard ratio profile – time-dependent hazard ratio scenario



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Figure 7 Progression-free survival estimates in the health economic model for the subpopulation having received least 2 prior lines of therapies including an IMiD and BTZ derived via the MAIC method using time dependent HRs



BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat;

3.3 OS assessment using the updated MAIC method

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7) as well as the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8)[h].

Results of the MAIC indicated that in terms of OS, the efficacy of PANO/BTZ/DEX was similar to that of LEN/DEX in both patient populations analysed (Figure 8 and Table 8). Figure 8 shows the Kaplan–Meier curves for PANO/BTZ/DEX and LEN/DEX. The data suggests an increasing OS benefit for PANO/BTZ/DEX beyond 35–40 cycles (3-week cycles).

Figure 8 OS Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with 2–3 prior lines of treatment

Notes:

N = 220 for LEN/DEX, N = 140 for PANO/BTZ/DEX (refers to the weighted sample size)

PANO/BTZ/DEX: patients with 2–3 prior lines of treatment, no prior LEN treatment, matched to LEN/DEX against β2-microglobulin and time from diagnosis

LEN/DEX: patients with 2–3 prior lines of treatment[3]

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PANO, panobinostat.

[h] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

Table 8 OS HRs and median OS for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the subpopulation with two to three prior lines of treatment

	HR	SE	95% CI	Median PANO/BTZ/DEX	Median LEN/DEX
Final OS	1.171	0.144	0.883 – 1.553	42.0 (33.6 – 55.2)	35.8 (30.9 – 42.9)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PANO, panobinostat; SE, standard error of the log hazard ratio.

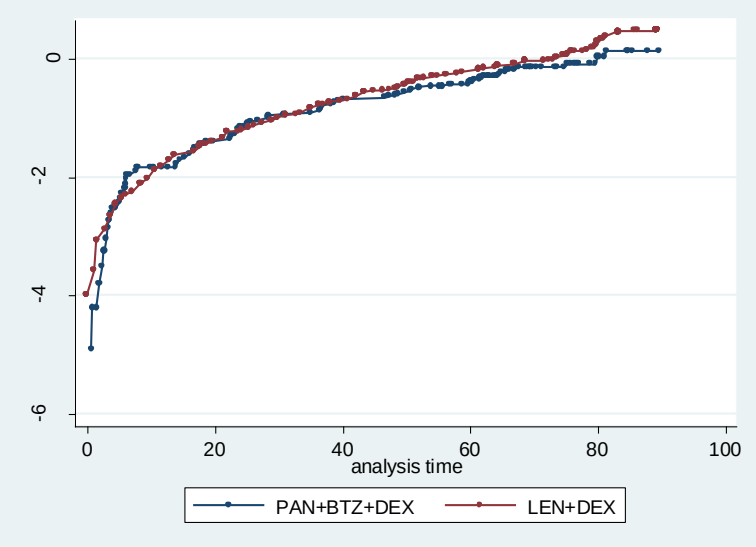
3.3.1 Testing for the proportional hazard assumption

This section address the concern over the proportional hazard assumption in the method applied in the original submission (ERG report; ACD, Section 4.7).

The same PH assessments were carried out for OS as for PFS and were performed using the final OS data.

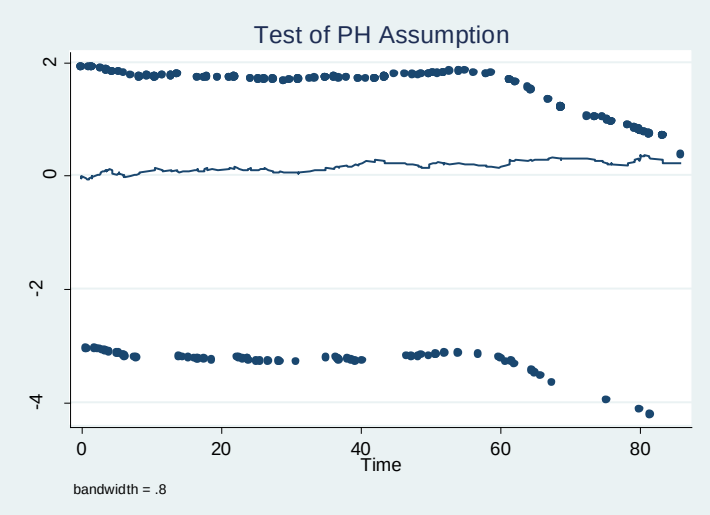
The results of the assessment of the PH assumption indicate that the PH assumption is not fully satisfied therefore a constant HR cannot be applied. The log-cumulative hazard plot suggests that the hazard of death for LEN/DEX is very similar to the hazard of death for PANO/BTZ/DEX for the first 35–40 cycles (Figure 9). However, after that point the log-cumulative hazard curves start to diverge which is an indication of higher mortality rates for LEN/DEX than for PANO/BTZ/DEX. The Schoenfeld residuals plot seems to confirm this by exhibiting a fairly straight line for the first 35–40 cycles and a seemingly stable line at a higher level afterwards (Figure 10). The Therneau and Grambsch test indicates that we cannot reject the null hypothesis (PH assumption, P value = 0.4027) (Table 9).

Figure 9 Log (-cumulative hazards) versus time for OS



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat.

Figure 10 Schoenfeld residuals versus time for OS



OS, overall survival; PH, proportional hazard.

Table 9 Therneau and Grambsch test result for OS

Data cut-off	rho	chi2	Degrees of freedom	Prob>chi2 (P value)
Final OS data	0.05460	0.70	1	0.4027

OS, overall survival.

3.3.2 Application of time-dependent OS HR as an alternative to the constant OS HR

This section address the explicit request by the AC for survival curves fitted independently (ACD, Section 4.8 and 4.8)[i]*.*

A clear indication of non-proportional hazards was seen in the log-cumulative hazard curves. Therefore, as an alternative to the constant HR approach, a time-varying HR approach was explored using the OS data.

In this approach, a Cox model was set up in which the HR formula yielded constant HRs for different time intervals. This approach was considered to be a fair reflection of the data given the visual assessment of the log-cumulative hazard curves, which suggested a constant (close to 1) HR for the first 35–40 cycles and a constant (larger than 1) HR for the period after that. A constant HR for the period after the first 35–40 cycles was considered to be appropriate because the treatment-specific log-cumulative hazards indicated a stable diverging pattern.

Because the exact cut-off point is difficult to determine and may be arbitrary assigned by simple visual assessment of the curves, we assessed 6 Cox models with different cut-off time points defined

[i] Given that no data on LEN/DEX has been published in the EMA licensed indication, fitting independent (or any) parametric figures was not an option. Instead, time-dependent HRs were calculated based on the comparison of a less restricted dataset, i.e. patients with 2-3 prior lines to make the two arms independent from each other (i.e. no constant HRs) in the actual CE model.

between cycles 35–40. The AIC/BIC values were obtained and compared to help decide which Cox model had the best fit and are presented in Table 10.

Using a cut-off at the 39th cycle yielded the best model fit. Table 11 below presents the estimated HRs.

Table 10 Model fit a different cut-off time points

Cut-off point	AIC	BIC
35th cycle	2518.687	2526.459
36th cycle	2518.416	2526.188
37th cycle	2517.666	2525.438
38th cycle	2518.057	2525.829
39th cycle	***2517.066***	***2524.839***
40th cycle	2517.151	2524.923

The best fitting model selected for the base case analysis is shown in bold italic

AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 11 Estimated hazard ratios using the 39th cycle as the cut-off time point

Time (no. of cycles)	OS HR	SE	z	P>z	95% CI
< 39th cycle	0.99	0.181	-0.05	0.961	0.69 - 1.42
≥ 39th cycle	1.52	0.458	1.38	0.167	0.84 - 2.74

HR, hazard ratio; OS, overall survival; SE, standard error of the log hazard ratio.

Figure 11 presents the OS curves for PANO/BTZ/DEX in the licensed indication (ie, used in the health economic model) and the implied OS curve for LEN/DEX using the time dependent HR approach.

Figure 11 Overall survival estimates in the health economic model for the subpopulation having received at least 2 prior lines of therapies including an IMiD and BTZ derived via the MAIC method using time dependent HRs

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat.

Technical note:

The hazard ratio formula included the function of the following form g(t), which took on the value 1 if t was greater than some specified value of t, called t0, and took on the value 0 if t was less than or equal to t0. In the best fitting model t0 was 39 cycles.

The hazard function was expressed as follows: $h(t,X)= h0(t)\times\exp(\beta x+\delta xg(t))$

where h(t,X) is the hazard rate at time t and risk factors X, h0(t) is the unspecified baseline hazard rate, and $\exp(\beta x+\delta xg(t))$ is the hazard ratio given risk factor x. In the present case x = 1 was referring to LEN/DEX treatment.

This specification of the hazard function yielded two hazard ratios:

$t \geq 39$: $HR = \exp(\beta+\delta g(t)))$

$t < 39$: $HR = \exp(\beta)$.

3.4 Results of the cost-effectiveness analysis

3.4.1 Base case − incremental cost-effectiveness analysis

Results for the cost-effectiveness analysis using the most plausible method to derive HRs for PANO/BTZ/DEX versus LEN/DEX are summarised in Table 12.

Although the base case (ie using the HRs from the subgroup population derived using the MAIC method with time dependent HRs) indicates gains in quality-adjusted life year (QALY) and life-year (LY) for PANO/BTZ/DEX over LEN/DEX, these gains are relatively low. Furthermore, the published evidence suggests that one cannot distinguish between PANO/BTZ/DEX and LEN/DEX in this subpopulation in terms of efficacy and that the determining factor will be the cost of the PANO/BTZ/DEX combination. It should also be noted that, because of these small incremental QALYs, the incremental cost-effectiveness ratios (ICERs) are volatile and specifically sensitive to the incremental cost, ie the cost of the treatment.

Table 12 Summary of base case results using the MAIC method (discounted) with PAS

With PAS[j]	**Total**			**Incremental versus LEN/DEX**			**ICER vs LEN/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/ DEX	£141,707	2.40	1.59	£1,425	0.210	0.124	£6,783	£11,527
LEN/DEX	£140,281	2.19	1.47					

Time dependent HRs derived using MAIC method applied to subpopulation (patients having received two to three prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PAS, Patient Access Scheme; PANO, panobinostat; QALY, quality-adjusted life year.

[j] A simple discount of [redacted]%

3.4.2 Clinical outcomes from the model

Comparing the model results with the clinical outcomes from PANORAMA-1 for PANO/BTZ/DEX in the subpopulation of patients who have received at least two prior therapies, including BTZ and an IMiD, reveals the following as summarised in Table 13:

- The model underestimates median PFS by 2.23 months and hence the treatment-related cost and/or the savings associated with the treatment-free interval after stopping PANO/BTZ/DEX.
- The model overestimates median OS by [redacted] months and hence the post-progression cost associated with PANO/BTZ/DEX. It also overestimates the post- progression QALY benefit, although to a lesser extent since this state (post- progression) is associated with lower utility values in general.
- The model overestimates the median treatment duration and hence the cost associated with PANO/BTZ/DEX.

Table 13 Summary of model results compared with clinical data

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT)	**Model results**
Median PFS (PANO/BTZ/DEX)	12.5 months	10.27 months
Median OS (PANO/BTZ/DEX)	[redacted] months	26.88 months
Median treatment duration (PANO/BTZ/DEX)	4.5 months	5.42 months
Proportion of patients experiencing AEs (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Einsele et al 2015[8]

The validity of the methodology is further supported by comparison of the model results for LEN/DEX with the efficacy results from the pooled dataset of the MM-009/MM-010 trials for LEN/DEX in the subpopulation of patients who have received 2–3 prior therapies.[3]

Table 14 compares the model results (using each of the possible indirect treatment comparison methodologies) with the trial data.

It is worth noting that the model estimates the PFS and OS associated with LEN/DEX for the subpopulation with *2–3 prior lines of treatment including an IMiD and BTZ* whereas the LEN/DEX trial data presented below are for patients who have received 2–3 prior lines of treatment but not necessarily including prior BTZ or prior treatment with an IMiD.

Table 14 Summary of model results (median) for LEN/DEX compared with clinical data (median)

	ITC method	PFS (undiscounted values)			OS (undiscounted values)		
		HR[1]	Median, months		HR[1]	Median, months	
			Per model[k]	Per trial[l]		Per model[v]	Per trial[w]
Patient population			2-3 prior lines incl. IMID & BTZ	2-3 prior lines (MM-009/010)		2-3 prior lines incl. IMID & BTZ	2-3 prior lines (MM-009/010)
	MAIC	Time dependent[m]	8.88	9.5	Time dependent[n]	26.88	35.8

[1]HR for LEN/DEX versus PANO/BTZ/DEX

ITC, Indirect Treatment Comparison; BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Stadtmauer et al 2009;[3] Einsele et al 2015[8]

3.4.3 Disaggregated results for the base case

Table 15,

Table 16 and Table 17 provide an overview of the undiscounted and discounted QALYs, costs and resource use costs that the model predicts for each health state when applying the base case MAIC methodology to derive the HRs for LEN/DEX versus PANO/BTZ/DEX. Results show that PANO/BTZ/DEX is associated with a decrement in QALY during the pre-progression on treatment phase and a corresponding gain in QALY during the pre-progression off treatment phase so that overall there is little difference in the QALYs between the two treatments.

PANO/BTZ/DEX is associated with cost saving in the pre-progression health state and is associated with additional costs only in the post-progression health state. This is due to the longer post-progression survival assumed by the indirect treatment comparison.

The OS data available for LEN/DEX and PANO/BTZ/DEX in the subpopulation with 2–3 prior lines of treatment are 35.8 months vs [redacted] months respectively. From this aspect, assuming a positive

[k] Estimated by the model for the subpopulation with 2–3 prior lines of treatment including an IMiD and BTZ

[l] Reported by Stadtmauer *et al* based on the retrospective analysis of MM-009/MM-010 on the subpopulation with 2–3 prior lines of treatment

[m] For cycle specific PFS HRs see Section 3.2.2

[n] OS HR < 39th cycle = 0.99; OS HR ≥ 39 cycle = 1.517

incremental cost associated with the post-progression survival is conservative and increases the ICER associated with PANO/BTZ/DEX from a dominant position[o].

Table 15 Summary of QALY gain by health state using the MAIC method (discounted)

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	0.33	0.62	–0.29	0.29	41.43%
B: Pre-progression, off treatment	0.34	0.02	0.32	0.32	45.71%
C: Post progression	0.92	0.83	0.09	0.09	12.86%
D: Death	0	0	0.00	0.00	0%
Total	1.59	1.47	0.124	0.7	100%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

Table 16 Summary of cost by health state using the MAIC method (discounted): with PAS[p]

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	£[redacted]	£45,286	–£[redacted]	£[redacted]	[redacted] %
B: Pre-progression, off treatment	£441	£21	£420	£420	2.00%
C: Post-progression	£[redacted]	£93,831	£[redacted]	£[redacted]	[redacted] %
D: Death	£1,134	£1,143	–£9	£9	0.04%
Total	£141,707	£140,281	£1,425	£20,975	100%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme.

[o] Assuming the QALY benefit associated with the pre-progression health states would remain 0.034 for PANO/BTZ/DEX over LEN/DEX

[p] A simple discount of [redacted]%

Table 17 Summary of predicted resource cost use by category of cost using the MAIC method (discounted): with PAS[q]

Item	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£[redacted]	£40,180	–£[redacted]	£[redacted]	[redacted] %
Tests and monitoring (on treatment)	£907	£4,913	–£4,006	£4,006	18.68%
Tests and monitoring (No treatment)	£441	£21	£420	£420	1.96%
Last line of treatment	£[redacted]	£93,831	£[redacted]	£[redacted]	[redacted] %
AEs	£1,134	£193	£941	£941	4.39%
Terminal care	£1,134	£1,143	–£9	£9	0.04%
Total	£141,707	£140,281	£1,425	£21,441	100%

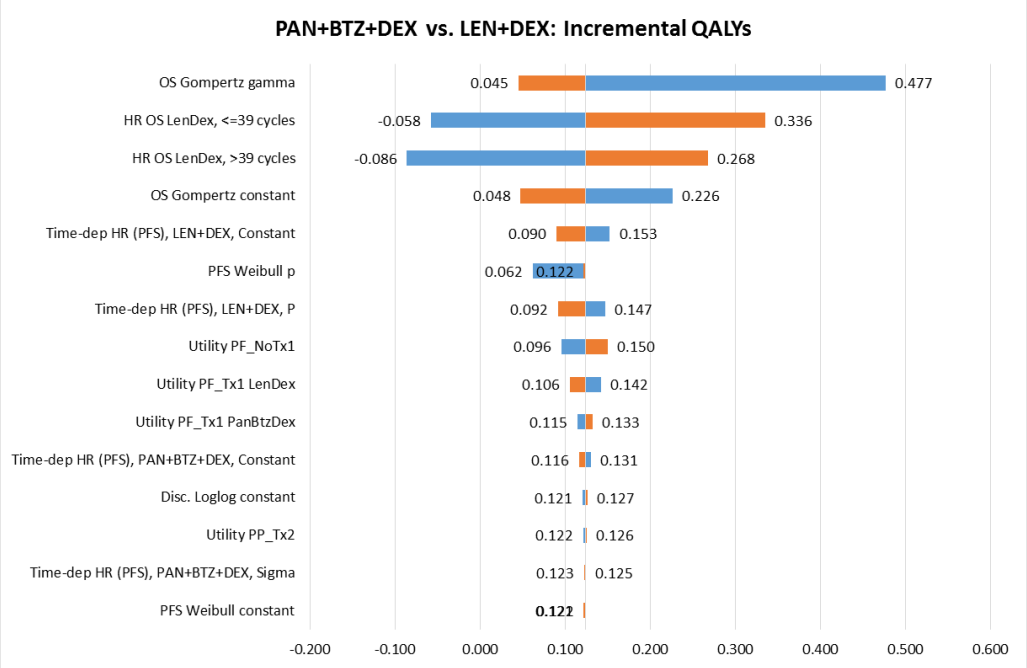
AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme.

[q] A simple discount of [redacted]%

3.4.4 Deterministic sensitivity analyses results

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie the deterministic) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. Tornado plots were generated for costs and QALYs, separately, and for the ICER, and rank parameters from highest to lowest based on the magnitude of the result impact (see Figure 12, Figure 13 and Figure 14).

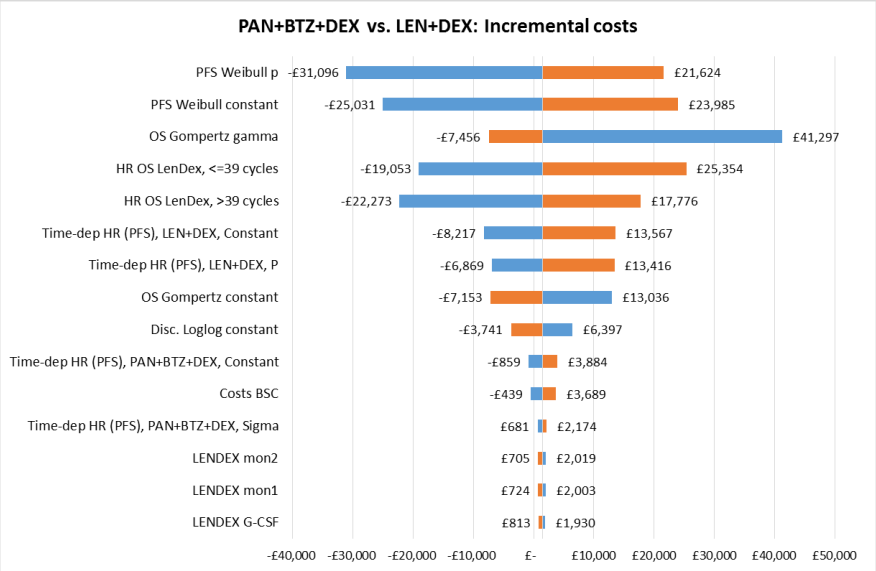
Figure 12 Tornado diagram of incremental QALYs for PANO/BTZ/DEX versus LEN/DEX: updated MAIC (discounted)



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

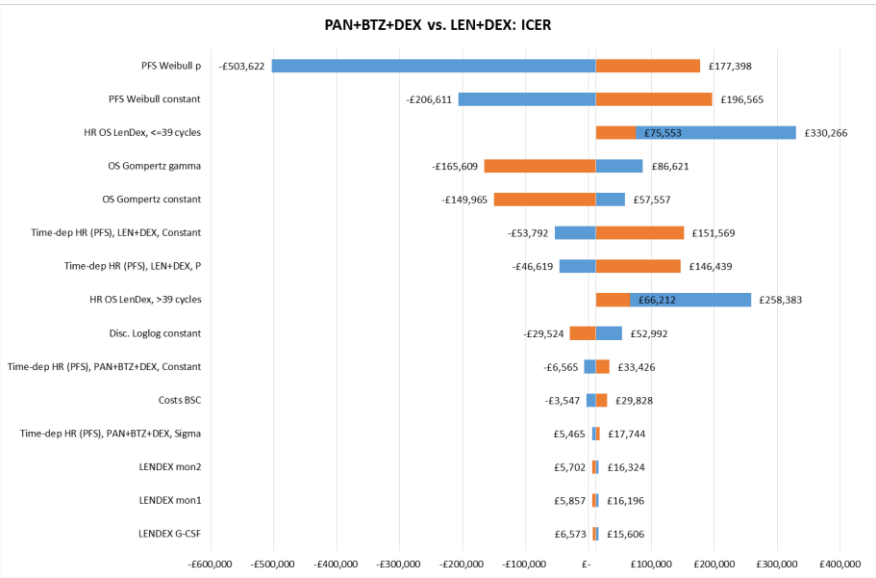
Figure 13 Tornado diagram of incremental costs for PANO/BTZ/DEX versus LEN/DEX: base case (discounted): with PAS[r]



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

Figure 14 Tornado diagram of ICERs for PANO/BTZ/DEX versus LEN/DEX: base case (discounted): with PAS[s]



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

[r] A simple discount of [redacted]%

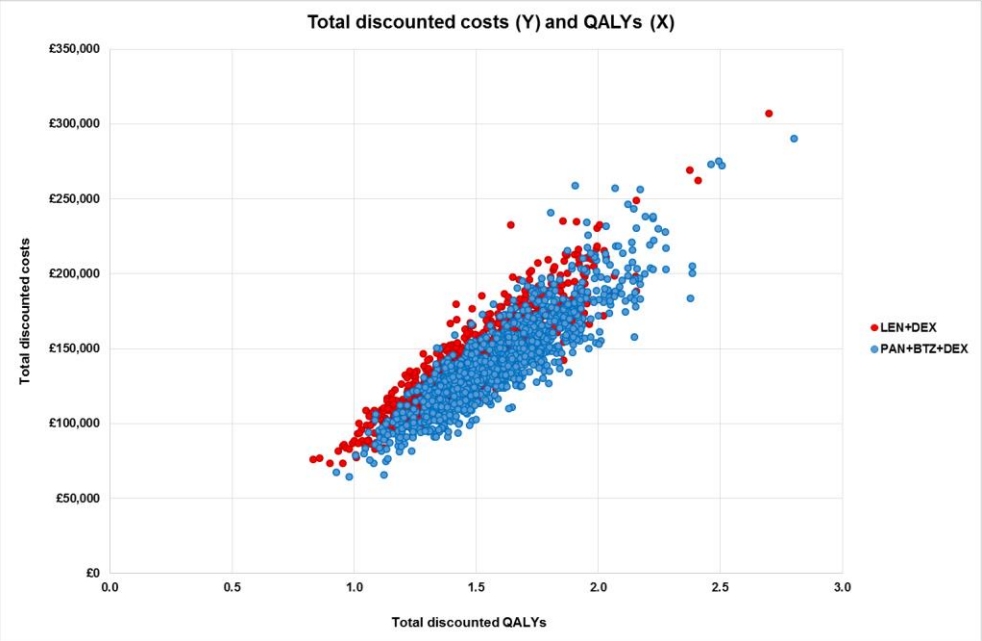
[s] A simple discount of [redacted]%

3.4.5 Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in Figure 15 (scatter plot of total QALYs and costs),

Figure 16 (scatter plot of incremental QALYs and costs). The probabilistic sensitivity analysis was run using the MAIC method and deriving HRs from the subpopulation (2–3 prior lines of therapy).

Figure 15 Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): updated MAIC (discounted): with PAS[t]

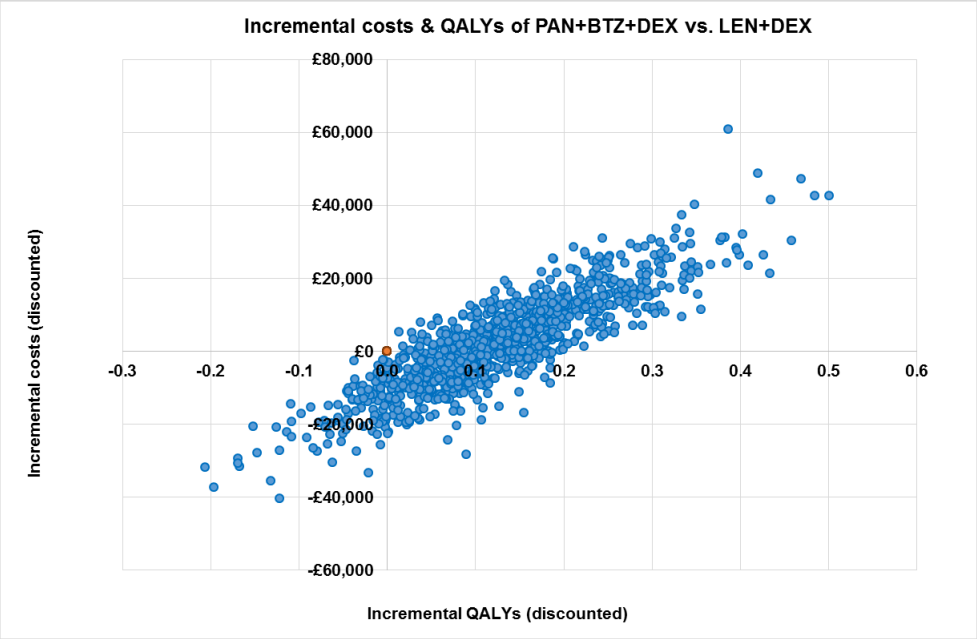


Base case, ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[t] A simple discount of [redacted]%

Figure 16 Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): base case (discounted): with PAS[u]



Base case: ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes, presented in Table 18.

Table 18 The probabilistic sensitivity analysis and 95% CIs around key model outcomes for the base case (discounted) with PAS[v]

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£141,707 (£90,611 to £217,477)	£1,426 (–£22,152 to £28,3175)	1.59 (1.13 to 2.15)	0.12 (–0.06 to 0.34)	£11,883
LEN/DEX	£140,281 (£92,398 to £204,776)		1.47 (1.06 to 1.94)		

Base case, ie using the 'MAIC' method to derive HRs from the subpopulation (patients who had received 2–3 prior lines)

[u] A simple discount of [redacted] %

[v] A simple discount of [redacted] %

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probability of PANO/BTZ/DEX being cost effective at certain threshold is summarized in Table 19.

Table 19 The probability of PANO/BTZ/DEX being cost effective versus LEN/DEX according to willingness to pay threshold: with PAS[w]

WTP threshold	PANO/BTZ/DEX	LEN/DEX
£20,000 / QALY	49.9%	50.1%
£30,000 / QALY	55.6%	44.3%
£50,000 / QALY	67.6%	32.4%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

3.4.6 Scenario analysis

The results of the scenario analyses using the updated MAIC method to derive time-dependent HRs from data for the subpopulation (ie 2–3 prior lines) are presented in Table 20.

Table 20 Scenario analyses with PAS[x]

Scenario	Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Base case	£1,425	0.124	0.210	£11,527	£6,783
Discount rate of 5% for both costs and effects	£694	0.115	0.196	£6,040	£3,533
Time horizon, 5 years	–£4,123	0.075	0.134	dominant	dominant
Time horizon, 10 years	£1,415	0.124	0.210	£11,449	£6,737
OS, Weibull	£5,263	0.158	0.263	£33,385	£19,994
OS, Kaplan–Meier + Gompertz	£2,361	0.132	0.223	£17,891	£10,582
PFS, Gompertz	£1,185	0.123	0.210	£9,641	£5,636
PFS, exponential	£1,140	0.125	0.210	£9,090	£5,426
Time to discontinuation, Kaplan–Meier estimates	£1,197	0.124	0.210	£9,677	£5,697
Assuming no disutility associated with LEN/DEX	£1,425	0.120	0.210	£11,589	£6,783
Assuming no active treatment in the post-	**-£3,363**	**0.124**	**0.210**	**dominant**	**dominant**

[w] A simple discount of [redacted] %

[x] A simple discount of [redacted] %

progression health state[y]					
Different methodologies used to derive HRs for PFS and OS for LEN/DEX versus PANO/BTZ/DEX					
Naïve comparison[2]	–£19,783	–0.042	–0.054	Cost saving	Cost saving
Unadjusted Cox	£5,249	0.155	0.263	£33,794	£19,939
Threshold analyses (ie non time dependent, constant PFS and OS HRs for LEN/DEX vs PANO/BTZ/DEX)					
HR = 0.8[2]	-£34,277	-0.271	-0.378	Cost saving	Cost saving
HR = 0.9[2]	-£22,695	-0.133	-0.174	Cost saving	Cost saving
HR = 1[2]	-£12,556	-0.016	0.000	Cost saving	Cost saving
HR = 1.1	-£3,607	0.085	0.150	Dominant	Dominant
HR = 1.2	£4,349	0.173	0.282	£25,103	£15,425

[2]Note, in the case when both the incremental cost and the incremental QALY are negative (ie cost saving but less utility), the higher the ICER the more cost effective the treatment still could be.

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; QALY, quality-adjusted life year.

[y] As requested by the AC (ACD, Section 4.12)

4 Appendix 3 Cost effectiveness of PANO/BTZ/DEX versus BTZ/DEX in patients who have received at least 2 prior lines of treatment including an IMiD and BTZ

Although there are no explicit reimbursement channels to support access to BTZ/DEX in patients with at least 2 prior lines of treatment including an IMiD and BTZ (and who have responded to prior BTZ therapy), a full cost effectiveness analysis has been performed upon the request at the first NICE Appraisal Committee meeting and the ACD (Section 4.4 and 4.10 and Summary Pages 26, 27).

4.1 Methods

4.1.1 Patient population and corresponding efficacy and safety data

The patient population considered corresponded to patients from PANORAMA-1 who had received at least 2 prior lines of treatment including an IMiD and BTZ-based regimen and had response to prior BTZ. The number of patients included is:

- PANO/BTZ/DEX: n = 72
- BTZ/DEX: n = 72

Table 21 summarises the efficacy data for the patient population from PANORAMA-1 used for the indirect comparison with BTZ/DEX and compares the data with those for patients corresponding to the EMA licensed indication. Similarly, Table 22 summarizes the safety data from PANORAMA-1 for these two patient populations.

Table 21 Summary of the efficacy data from PANORAMA-1 for the population corresponding to the EMA label and the subgroup used for the direct comparison against BTZ/DEX

	EMA label population, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD		**Population for direct comparison with BTZ/DEX, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD *excluding* those with no response to the prior BTZ**	
	PANO/ BTZ/DEX N = 73/72	**PBO/ BTZ/DEX N = 74/73**	**PANO/ BTZ/DEX N = 72/71**	**PBO/ BTZ/DEX N = 72/71**
Median PFS, months HR (95% CI)	12.5 0.47 (0.32 to 0.72)	4.7	12.48 0.48 (0.32 to 0.73)	4.86
Median OS (final analysis), months HR (95% CI)	[redacted] [redacted] ([redacted] to [redacted])	[redacted]	[redacted] [redacted] ([redacted] to [redacted])	[redacted]
ORR, % (95% CI)	58.9 (46.8 to 70.3)	39.2 (28.0 to 51.2)	59.7 (47.50 to 71.12)	38.89 (27.62 to 51.11)

CR/nCR, % (95% CI)	21.9 (13.1 to 33.1)	8.1 (3.0 to 16.8)	22.22 (13.27 to 33.56)	8.33 (3.12 to 17.26)
Median duration of response, months	11.99 (9.69 to 13.37)	6.97 (4.86 to 13.40)	11.99 (9.69 to 13.37)	6.97 (4.86 to 13.40)
Median TTP	12.68 (8.34 to 14.19)	4.99 (3.75 to 6.80)	12.68 (8.34 to 14.19)	4.86 (3.71 to 6.80)
On-treatment deaths, %	6.9	6.8	N/A	N/A

BTZ, bortezomib; CI, confidence interval; CR, complete response; nCR, near complete response; DEX, dexamethasone; EMA, European Medicines Agency; HR, hazard ratio; IMiD, immunomodulatory drug; ORR, overall/objective response rate; OS, overall survival; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; TTP, time to progression

Table 22 Incidence of on-treatment deaths and grade 3/4 adverse events in PANORAMA-1 for the population corresponding to the EMA label and the subgroup used for the direct comparison against BTZ/DEX

Incidence, %	**EMA label population, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD**		**Population for direct comparison with BTZ/DEX, ie patients having received ≥ 2 prior regimens, including BTZ and an IMiD *excluding* those with no response to the prior BTZ**	
	PANO/ BTZ/DEX N = 73/72	**PBO/ BTZ/DEX N = 74/73**	**PANO/ BTZ/DEX N = 72/71**	**PBO/ BTZ/DEX N = 72/71**
On-treatment deaths, %	6.9	6.8	N/A	N/A
Thrombocytopenia	68	44	46 (65%)	35 (49%)
Infections (pneumonia)	19.4	16.4	13 (18%)	12 (17%)
Infections (sepsis)	2.8	6.8	0 (0%)	2 (3%)
Diarrhoea	33.3	15.1	54 (76%)	34 (48%)
Asthenia/fatigue	26.4	13.7	Asht or fatig: 33 (46%) Fatig: 33 (46%) Asht: 16 (23%)	Asht or fatig: 25 (35%) Fatig 25 (35%) Asth: 11 (15%)
Haemorrhage	2.8	2.7	N/A	N/A
Neutropenia	31.9	9.6	25 (35%)	10 (14%)

BTZ, bortezomib; DEX, dexamethasone; EMA, European Medicines Agency; IMiD, immunomodulatory drug; LEN, lenalidomide; PANO, panobinostat; PBO, placebo.

4.1.2 Clinical parameters for PANO/BTZ/DEX and BTZ/DEX

Clinical parameters for PANO/BTZ/DEX and BTZ/DEX were derived from patient-level data for the relevant patient populations from PANORAMA-1 using a similar approach to that described in the original submission (section 5.3.2).

4.1.2.1 Risk of progression or death

The risk of experiencing a PFS event (ie either progression or death) in a given cycle was estimated using patient-level data from the PANORAMA-1 trial. Time since randomisation until progression or death (ie an event) or censoring was considered as exposure time. Table 23 provides descriptive statistics for the derived time to PFS event dataset.

Table 23 Descriptive statistics on the derived PFS dataset

Variable	**Characteristic**	**PANO/BTZ/DEX N = 72**	**BTZ/DEX N = 72**
Time to PFS event	No. of events – n	44	53
	No. of censored – n	28	19

Notes: event corresponds to patients who progressed or died; censored corresponds to patients who were censored for PFS (i.e., those who have not progressed, or died at the date of the analysis cut-off, or if patients received any further anti-cancer therapy).

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level PFS data to smooth and extrapolate PFS curves beyond the trial period and to derive the transition probabilities. The regression models were compared using the AIC, BIC values, and by visually assessing model fit. The best fitting models were selected for smoothing and extrapolating the PFS data. Table 24 summarise the AIC/BIC statistics for the PFS models. Based on the AIC and BIC statistics, clinical plausibility as well as visual assessment, the Weibull distribution was judged to provide the best model (Figure 17).

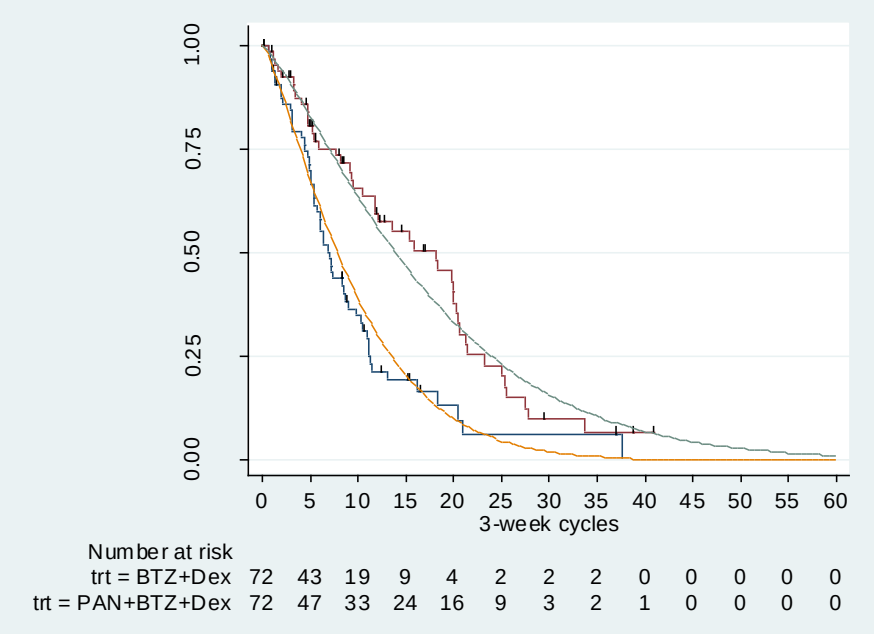
Table 24 AIC and BIC statistics of the PFS models

Model	**AIC**	**BIC**
Exponential	325.7219	331.6615
Weibull	***319.1743***	***328.0837***
Lognormal	322.8553	331.7648
Loglogistic	320.0477	328.9571
Gompertz	323.9435	332.8529

Note: best fitting model selected for the base case analysis in italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 17 Progression-free survival: Kaplan–Meier curve and fitted Weibull model



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

4.1.2.2 Risk of treatment discontinuation

Risk of treatment discontinuation was determined from the median duration of treatment for the two treatment groups. Data were analysed for patients corresponding to the safety set (ie, patients who received at least 1 dose of study drug):

- PANO/BTZ/DEX: n = 71
- BTZ/DEX: n = 71

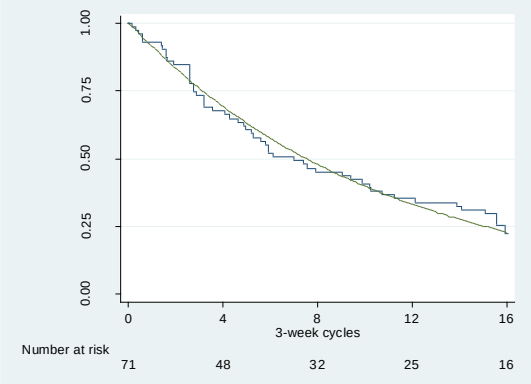
The median treatment duration was

- PANO/BTZ/DEX: 4.83 months (7.00 model cycles)
- BTZ/DEX: 4.80 months (6.95 model cycles).

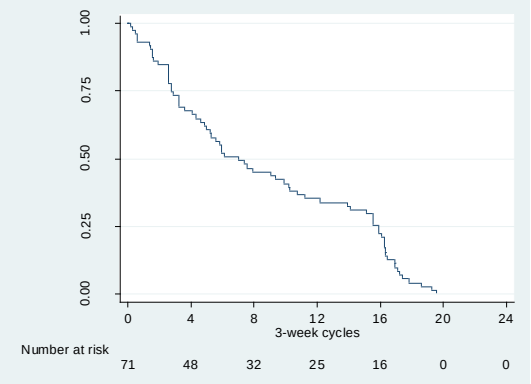
Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth the time to treatment discontinuation curves and to derive the transition probabilities. Curves were smoothed until 48 weeks, at which point the proportion of patients on treatment dropped sharply (see Figure 18). Beyond 48 weeks of treatment duration, treatment discontinuation rates were not smoothed. AIC/BIC statistics for the models are summarised in Table 25. The exponential model was considered to provide the best fit for PANO/BTZ/DEX and the Gompertz model was considered to provide the best fit for the BTZ/DEX.

Figure 18 Kaplan–Meier curve and fitted models for the proportion of patients without treatment discontinuation

a) PANO/BTZ/DEX

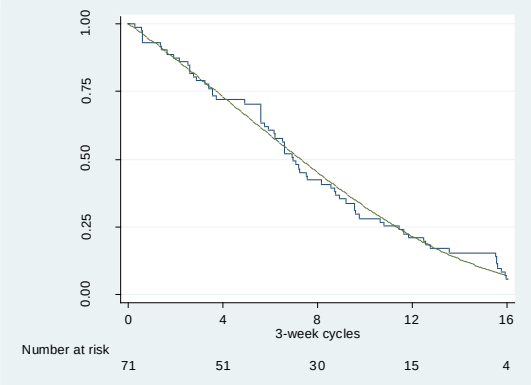


Kaplan–Meier and fitted curve (until cycle 16)

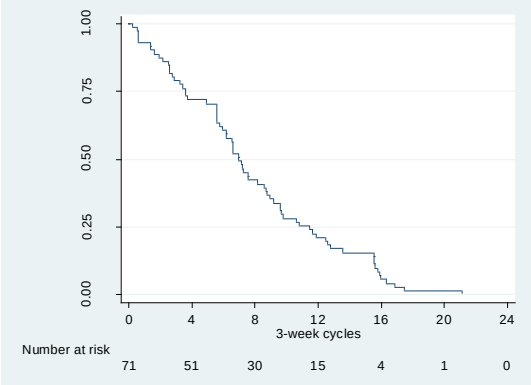


Complete Kaplan–Meier curve

b) BTZ/DEX



Kaplan–Meier and fitted curve (until cycle 16)



Complete Kaplan–Meier curve

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Table 25. AIC and BIC statistics of the treatment discontinuation models

	PANO/BTZ/DEX		**BTZ/DEX**	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	***218.0568***	***220.319***	193.0992	195.3619
Weibull	220.0373	224.5627	183.727	188.2524
Lognormal	221.8601	226.3855	200.6948	205.2201
Loglogistic	220.5865	225.1118	195.6549	200.1802
Gompertz	220.0558	224.5812	***181.3976***	***185.9229***

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

4.1.2.3 Probability of death

The risk of death in a given cycle was estimated using patient-level data from the PANORAMA-1 trial. Table 26 provides descriptive statistics for the derived time to death dataset.

Table 26. Descriptive statistics on the derived OS dataset

Variable	Characteristic	PANO/BTZ/DEX N = 72	PBO/BTZ/DEX N = 72
Time to death	No. of OS events, n	[redacted]	[redacted]
	No. of censored, n	[redacted]	[redacted]

Notes: OS event corresponds to a patient who died; censored corresponds to a patient alive at last contact

BTZ, bortezomib; DEX, dexamethasone; OS, overall survival; PANO, panobinostat; PBO, placebo.

Four modelling approaches were considered:

1. Using an appropriate regression (survival) model estimated for PANO/BTZ/DEX and BTZ/DEX jointly, ie introducing a treatment effect parameter in the survival model. Extrapolated OS is determined by the survival model directly.
2. Using the Kaplan–Meier estimates for treatment cycles for which observed survival is available from the PANORAMA-1 trial and extrapolating survival beyond that using the risk of death implied by the OS model defined in approach 1.
3. Using a two-part model, in which the OS for PANO/BTZ/DEX and BTZ/DEX are modelled separately:
    - OS for PANO/BTZ/DEX is modelled by a regression model
    - OS for BTZ/DEX is modelled by a regression model for the first 55 treatment cycles and modelled by using the risk of death estimated for PANO/BTZ/DEX for treatment cycles > 55
4. Using a two-part model, in which PANO/BTZ/DEX and BTZ/DEX are modelled separately:
    - PANO/BTZ/DEX is modelled by a regression model for the first 55 cycles
    - BTZ/DEX is modelled by a regression model for the first 55 cycles
    - OS for both PANO/BTZ/DEX and BTZ/DEX are modelled by using the risk of death estimated for patients who survived until cycle 55. No difference between the treatment arms are modelled.

Two-part models refer to modelling OS separately for two sections of follow-up time: for the first 55 cycles and for later cycles.

For approach 3 and 4, cycle 55 was chosen as the cut-off point because the Kaplan–Meier survival curves crossed at this point and because it was considered that no robust extrapolation could be prepared for the individual treatment arms due to the low patient numbers.

4.1.2.3.1 Approach 1:

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth and extrapolate the OS curves. The regression models were compared along the AIC and BIC values, visually assessed model fit, and clinical plausibility[z]. The Weibull model was selected for the base case analysis. Figure 19 presents the Kaplan–Meier and modelled OS curves; **Error! Reference source not found.** summarizes the AIC and BIC values calculated for the various regression models.

Table 27 AIC and BIC statistics for the OS models using approach 1

	Full PANORAMA 1 population	
Model	**AIC**	**BIC**
Exponential	396.7025	402.642
Weibull	***398.0029***	***406.9124***
Lognormal	395.8692	404.7787
Loglogistic	396.2355	405.145
Gompertz	398.6978	407.6072

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 19 Kaplan–Meier curve and fitted Weibull overall survival model derived using approach 1

[z] The Weibull and Gompertz models imply increasing mortality risk in the long run. From a clinical perspective, the prediction of constant (implied by an exponential model) or decreasing mortality rates over the lifetime (implied by a log-logistic or lognormal model) is unlikely to be plausible; modelling increasing mortality may be more appropriate. Therefore, the Weibull and the Gompertz models were preferred prior to model fitting and the best fitting model used for the base case analysis was selected from these two.

BTZ, bortezomib; DEX, dexamethasone; KM, Kaplan–Meier; PANO, panobinostat

Assessment of approach 1: The modelled and extrapolated OS curve for BTZ/DEX always appears above the curve for PANO/BTZ/DEX because the Weibull model implies PHs. However, this does not seem to be plausible given that the Kaplan–Meier curves estimated from the PANORAMA-1 trial crossed and indicated an OS benefit for PANO/BTZ/DEX versus BTZ/DEX for the first 55 cycles.

4.1.2.3.2 Approach 2:

This approach used the Kaplan–Meier estimates for treatment cycles for which observed survival is available (ie 85 cycles for PANO/BTZ/DEX and 82 cycles for BTZ/DEX) from the PANORAMA-1 trial and extrapolated survival beyond that point using the risk of death implied by the Weibull OS model defined in approach 1. The resulting survival curves are given in Figure 20.

Figure 20 Survival curves derived using approach 2

BTZ, bortezomib; DEX, dexamethasone; KM, Kaplan–Meier; PANO, panobinostat.

Assessment of approach 2: While using the Kaplan–Meier estimates is an unbiased representation of the OS profiles, it does not seem to be clinically relevant because after 55 cycles there are very few patients in the risk set; the survival advantage of BTZ/DEX is likely to be due to random chance and thus exaggerated.

4.1.2.3.3 Approach 3:

This approach uses a two-part model in which OS curves for PANO/BTZ/DEX and BTZ/DEX are modelled separately.

OS for PANO/BTZ/DEX is modelled and extrapolated by a regression model. Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth and extrapolate the OS curves. The regression models were compared using the AIC and BIC values (Table 28), and were visually assessed for model fit and clinical plausibility (Figure 21).

Table 28 AIC and BIC statistics for the PANO/BTZ/DEX model using approach 3

Model	AIC	BIC
Exponential	181.1335	183.4102
Weibull	***180.0968***	***184.6501***
Lognormal	182.0577	186.611
Loglogistic	183.0684	187.6217
Gompertz	180.3852	184.9385

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

OS for BTZ/DEX is modelled by a regression model for the first 55 treatment cycles (see Table 29 for AIC and BIC values) and modelled by using the risk of death estimated for PANO/BTZ/DEX for treatment cycles beyond cycle 55. The survival curve is shown in Figure 21.

Table 29 AIC and BIC statistics for the BTZ/DEX model (≤ 55 cycles) using approach 3

Model	AIC	BIC
Exponential	205.277	207.5536
Weibull	207.2767	211.83
Lognormal	204.5515	209.1048
Loglogistic	***204.366***	***208.919***
Gompertz	206.2824	210.8358

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone.

Figure 21 Survival curves derived using approach 3

BTZ, bortezomib; DEX, dexamethasone; KM, Kaplan–Meier; PANO, panobinostat.

Assessment of approach 3: Modelled and extrapolated survival seems clinically plausible although the extrapolated part may somewhat under-predict the true survival.

4.1.2.3.4 Approach 4:

This approach used a two-part model in which the OS for PANO/BTZ/DEX and BTZ/DEX are modelled separately. In this approach:

- OS for PANO/BTZ/DEX is modelled and extrapolated by a regression model. The same survival estimates are used for the first 55 cycles as for approach 3.
- OS for BTZ/DEX is modelled and extrapolated by a regression model. The same survival estimates are used for the first 55 cycles as for approach 3.
- OS for both PANO/BTZ/DEX and BTZ/DEX are modelled by using the risk of death estimated for patients who survived until cycle 55. No difference between the treatment arms was modelled (see Figure 22).

Figure 22 Kaplan–Meier survival estimates for PANO/BTZ/DEX and BTZ/DEX based on the risk of death for patients who survived until cycle 55 (approach 4)

Note: time 0 corresponds to cycle 56

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

AIC/BIC statistics for the OS model are summarized in Table 30 and the survival curve is shown in

Figure 23. The Weibull model was considered to provide the best model fit.

Table 30. AIC and BIC statistics for the OS model (> 55 cycles) derived using approach 4

Model	AIC	BIC
Exponential	68.42914	71.85628
Weibull	***70.42239***	***75.56311***
Lognormal	70.23806	75.37878
Loglogistic	70.34238	75.48309
Gompertz	70.42363	75.56435

Note: best fitting model selected for the base case analysis is shown in bold italics

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 23 Overall survival curve derived using approach 4

BTZ, bortezomib; DEX, dexamethasone; KM, Kaplan–Meier; PANO, panobinostat.

Assessment of approach 4: Modelled and extrapolated survival seems clinically plausible. The extrapolated part seems more clinically plausible than that derived using approach 3. This approach was selected as the base case for the modelling. The results detailed below are based on applying this approach. Scenario analysis is provided for all four approaches described above.

4.2 Results

4.2.1 Base case − incremental cost-effectiveness analysis

Results for the cost-effectiveness analysis comparing PANO/BTZ/DEX versus BTZ/DEX are summarised in Table 31 using approach 4 (discussed in section 4.1.2.3.4) for determining the probability of death as the base case.

Table 31 Summary of base case results (discounted): with PAS

With PAS[aa]	**Total**			**Incremental versus BTZ/DEX**			**ICER vs BTZ/DEX**	
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**Cost per LYs gained, £**	**Cost per QALYs gained, £**
PANO/BTZ/DEX	£140,388	2.585	1.712	–£8,909	0.080	0.066	Dominant	Dominant
LEN/DEX	£149,297	2.505	1.646					

Direct comparison based on the PANORAMA-1 trial using data for the subpopulations with at least 2 prior lines of treatment including an IMiD and BTZ including only those responding to the prior BTZ.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year..

4.2.2 Clinical outcomes from the model

Comparing the model results with the clinical outcomes from PANORAMA-1 for PANO/BTZ/DEX and BTZ/DEX in the subpopulation of patients who have received at least two prior therapies, including BTZ and an IMiD, and had a response to the prior BTZ based regimen reveals the following as summarised in BTZ/DEX:

- The model overestimates the median PFS by 0.5 months and hence the pre-progression QALY benefit.
- The model overestimates the median OS by 2.1 months and hence the post-progression QALY benefit and cost associated to it.
- The model overestimates the median treatment duration by 0.6 months and hence the cost associated with PANO/BTZ/DEX.

Table 32:

PANO/BTZ/DEX:

- The model underestimates median PFS by 2.9 months and hence the pre-progression QALY benefit.

[aa] A simple discount of [redacted]%

- The model accurately estimates the median OS.
- The model overestimates the median treatment duration by 0.57 months and hence the cost associated with PANO/BTZ/DEX.

BTZ/DEX:

- The model overestimates the median PFS by 0.5 months and hence the pre-progression QALY benefit.
- The model overestimates the median OS by 2.1 months and hence the post-progression QALY benefit and cost associated to it.
- The model overestimates the median treatment duration by 0.6 months and hence the cost associated with PANO/BTZ/DEX.

Table 32 Summary of model results compared with clinical data for a) PANO/BTZ/DEX and b) BTZ/DEX

a)

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT and response to prior BTZ)	**Model results**
Median PFS (PANO/BTZ/DEX)	12.5 months	9.6 months
Median OS (PANO/BTZ/DEX)	[redacted] months	25.5 months
Median treatment duration (PANO/BTZ/DEX)	4.83 months	5.4 months
Proportion of patients experiencing AEs (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

b)

Outcome	**Clinical trial results** (Prior IMiD, BTZ and ≥ 2 LoT and response to prior BTZ)	**Model results**
Median PFS (BTZ/DEX)	4.9 months	5.4 months
Median OS (BTZ/DEX)	[redacted] months	22.0 months
Median treatment duration (BTZ/DEX)	4.80 months	5.4 months
Proportion of patients experiencing AEs (BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

4.2.3 Disaggregated results for the base case

Table 33, PANO/BTZ/DEX is associated with greater costs during the pre-progression on treatment state and these are off-set by reduced costs during the post-progression, with the result that overall, PANO/BTZ/DEX is associated with a cost-saving compared with BTZ/DEX (Table 34). Consistent with this, as shown in

Table 35, PANO/BTZ/DEX is associated with greater drug costs compared with BTZ/DEX but this is off-set by reduced costs associated with the last line of treatment.

Table 34 and

Table 35 provide an overview of the discounted QALYs, costs and resource use costs that the model predicts for each health state when applying approach 4 described in section 4.1.2.3.4 to extrapolate OS data for the two arms.

Results show that, compared with BTZ/DEX, PANO/BTZ/DEX is associated with a similar gain in QALY during the pre-progression on treatment phase and a considerably greater gain in QALY during the pre-progression off treatment phase which offsets smaller gain in QALY observed with PANO/BTZ/DEX in the post-progression phase (

Table 33). Overall there is a small incremental gain in QALY for PANO/BTZ/DEX over BTZ/DEX.

Table 33 Summary of QALY gain by health state (probability of death based on approach 4) (discounted)

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	0.33	0.32	0.02	0.02	3.92%
B: Pre-progression, off treatment	0.35	0.08	0.27	0.27	52.94%
C: Post progression	1.03	1.25	-0.22	0.22	43.14%
D: Death	0	0	0.00	0.00	0%
Total	1.71	1.65	0.07	0.51	100%

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; QALY, quality-adjusted life year.

PANO/BTZ/DEX is associated with greater costs during the pre-progression on treatment state and these are off-set by reduced costs during the post-progression, with the result that overall, PANO/BTZ/DEX is associated with a cost-saving compared with BTZ/DEX (Table 34). Consistent with this, as shown in

Table 35, PANO/BTZ/DEX is associated with greater drug costs compared with BTZ/DEX but this is off-set by reduced costs associated with the last line of treatment.

Table 34 Summary of cost by health state (probability of death based on approach 4) (discounted): with PAS[bb]

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
A: Pre-progression, on treatment	£[redacted]	£13,980	£[redacted]	£[redacted]	[redacted] %
B: Pre-progression, off treatment	£447	£102	£345	£345	0.63%
C: Post-progression	£[redacted]	£134,085	–£[redacted]	£[redacted]	[redacted] %
D: Death	£1,126	£1,129	–£3	£3	0.00%
Total	£140,388	£149,297	–£8,909	£54,518	100%

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PAS, Patient Access Scheme.

Table 35 Summary of predicted resource use by category of cost (probability of death based on approach 4) (discounted): with PAS[cc]

Item	Cost intervention (PANO/BTZ/DEX)	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£[redacted]	£12,341	£[redacted]	£[redacted]	[redacted] %
Tests and monitoring (on treatment)	£2,054	£1,639	£415	£415	0.76%
Tests and	£447	£102	£345	£345	0.63%

[bb] A simple discount of [redacted] %

[cc] A simple discount of [redacted] %

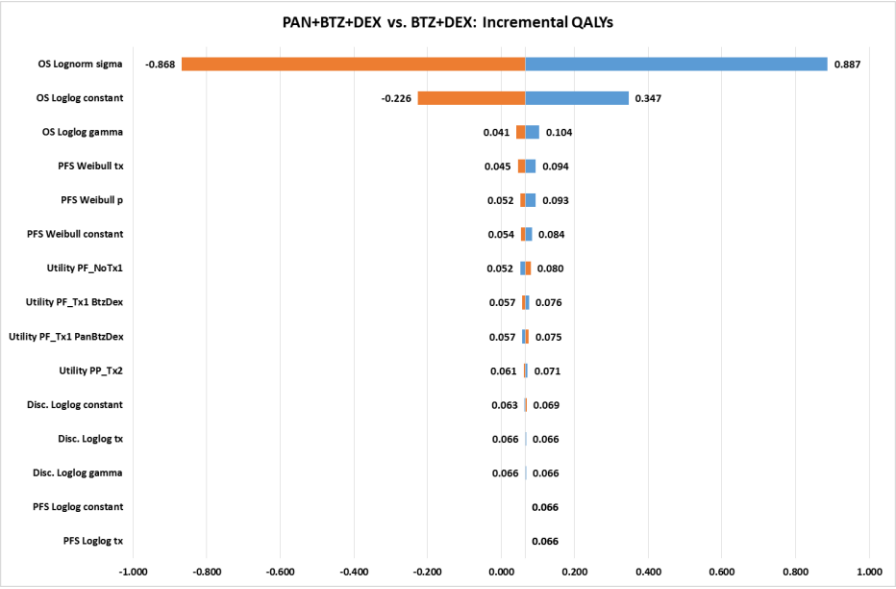
monitoring (No treatment)					
Last line of treatment	£[redacted]	£134,085	–£[redacted]	£[redacted]	[redacted] %
AEs	£1,141	£816	£326	£326	0.59%
Terminal care	£1,126	£1,129	–£3	£3	0.00%
Total	£140,388	£149,297	–£8,909	54,844£	100%

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme.

4.2.4 Deterministic sensitivity analyses results

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie the deterministic) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. Tornado plots were generated for costs and QALYs, separately (Figure 24 and Figure 25), and for the ICER (Figure 26). In the plots, parameters are ranked from highest to lowest based on the magnitude of the result impact.

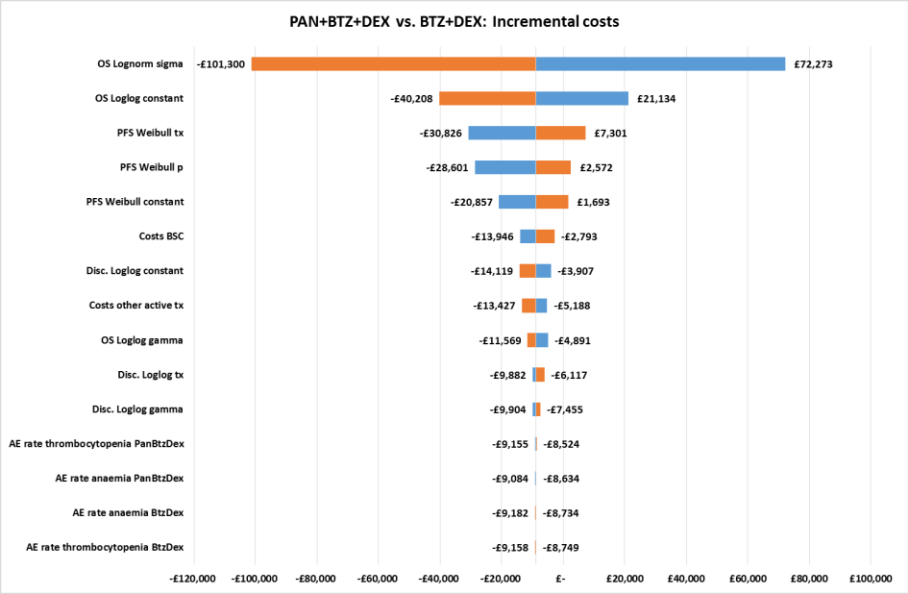
Figure 24 Tornado diagram of incremental QALYs for PANO/BTZ/DEX versus BTZ/DEX (probability of death based on approach 4) (discounted)



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; QALY, quality-adjusted life years.

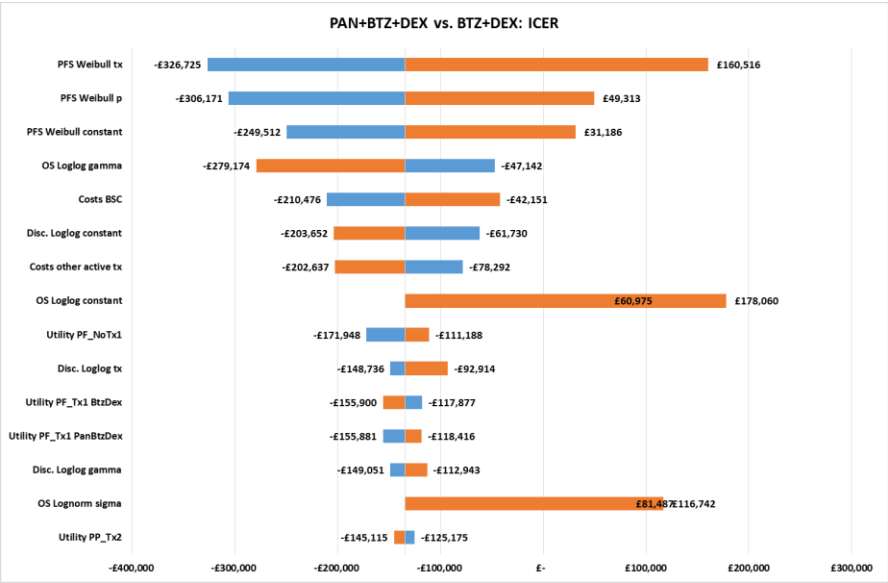
Figure 25 Tornado diagram of incremental costs for PANO/BTZ/DEX versus BTZ/DEX (probability of death based on approach 4) (discounted): with PAS[dd]



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme.

Figure 26 Tornado diagram of ICERs for PANO/BTZ/DEX versus LBTZ/DEX: (probability of death based on approach 4) (discounted): with PAS[ee]



Orange bars indicate upper limit; Blue bars indicate lower limit.

BTZ, bortezomib; DEX, dexamethasone; LEN lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme.

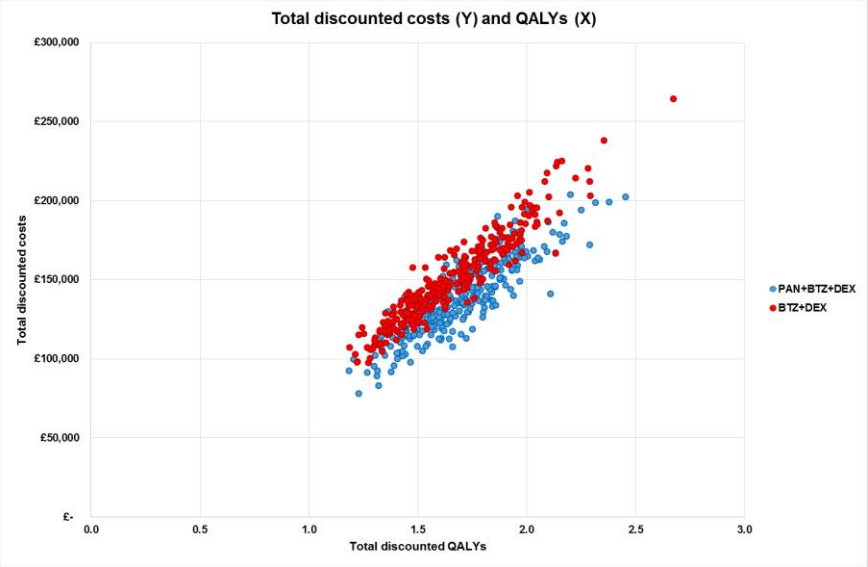
[dd] A simple discount of [redacted] %

[ee] A simple discount of [redacted] %

4.2.5 Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in Figure 27 (scatter plot of total QALYs and costs), Figure 28 (scatter plot of incremental QALYs and costs). Probabilistic sensitivity analysis is run using Approach 4 described in section 4.1.2.3.4 for the OS extrapolation.

Figure 27 Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and BTZ/DEX (probabilistic sensitivity analysis): probability of death based on approach 4, discounted analysis with PAS[ff]

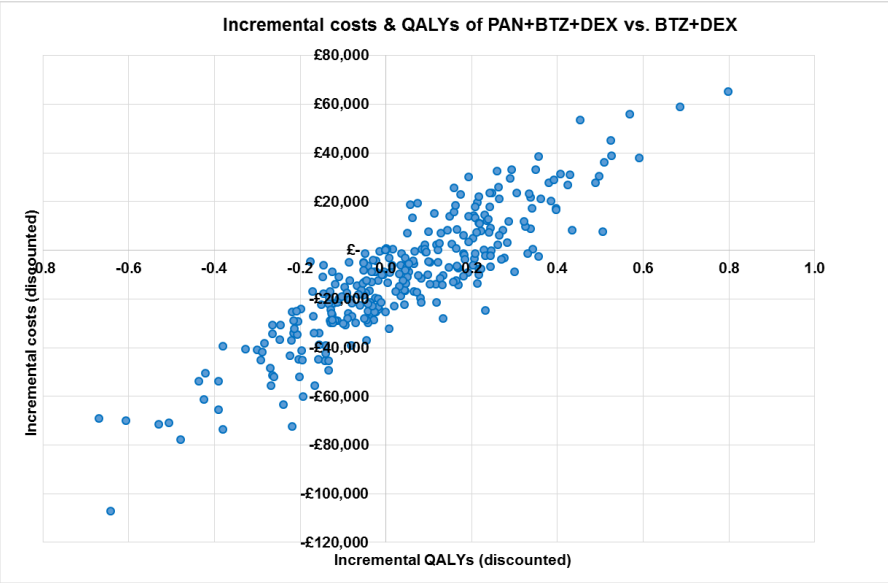


Base case, ie using probability of death based on approach 4

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[ff] A simple discount of [redacted] %

Figure 28 Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): probability of death based on approach 4, discounted analysis: with PAS[gg]



Base case: probability of death based on approach 4

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes, which are presented in Table 36.

Table 36 The probabilistic sensitivity analysis and 95% CIs around key model outcomes for the base case (discounted): with PAS[hh]

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£140,388 (£95,337 to £186,646)	–£8,909 (–£45,145 to £23,372)	1.712 (1.34 to 2.29)	0.066 (–0.24 to 0.33)	Dominant
BTZ/DEX	£149,297 (£108,477 to £212,030)		1.646 (1.28 to 2.18)		

Base case: probability of death based on approach 4

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

[gg] A simple discount of [redacted] %

[hh] A simple discount of [redacted] %

The probability of PANO/BTZ/DEX being cost effective at certain willingness to pay threshold is summarised in Table 37.

Table 37 The probability of PANO/BTZ/DEX being cost effective according to willingness to pay thresholds: with PAS[ii]

WTP threshold	PANO/BTZ/DEX	LEN/DEX
£20,000 / QALY	74.7%	25.3%
£30,000 / QALY	77.0%	23.0%
£50,000 / QALY	80.0%	20.0%

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

4.2.6 Scenario analysis

The results of the scenario analyses using the probability of death based on approach 4 are presented in Table 38.

Table 38 Scenario analyses for PANO/BTZ/DEX versus BTZ/DEX: with PAS[jj]

Scenario	Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Base case	**-£8,909**	**0.066**	**0.080**	**dominant**	**dominant**
Discount rate of 5% for both costs and effects	-£8,093	0.066	0.081	dominant	dominant
Time horizon, 5 years	-£6,074	0.077	0.097	dominant	dominant
Time horizon, 10 years	-£8,571	0.068	0.082	dominant	dominant
PFS, Loglogistic	-£16,851	0.086	0.091	dominant	dominant
PFS, Lognormal	-£13,136	0.073	0.080	dominant	dominant
PFS, Gompertz	-£7,352	0.065	0.080	dominant	dominant
PFS, exponential	-£11,667	0.071	0.080	dominant	dominant
PFS, KM estimates	-£6,785	0.064	0.080	dominant	dominant
Time to discontinuation, Kaplan–Meier estimates	-£8,443	0.066	0.080	dominant	dominant
Different approaches used to extrapolate OS KM curves (see Section 4.1.2.3 for details)					
Approach 1	-£26,100	-0.098	-0.177	£265,402[kk]	£147,234

[ii] A simple discount of [redacted] %

[jj] A simple discount of [redacted] %

[kk] Please note that in this case a significant cost saving (-£26,100) is associated with a small QALY loss (35 quality adjusted days)

Approach 2	-£38,126	-0.214	-0.358	£178,169[II]	£106,507
Approach 3	-£7,480	0.072	0.088	dominant	dominant

[2] Please note that in the case when both the incremental cost and the incremental QALY are negative (ie cost saving but less utility), the higher the ICER the more cost effective the treatment still could be.

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; OS, overall survival; PANO, panobinostat; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year.

[II] Please note that in this case a significant cost saving (-£38,126) is associated with a small QALY loss (78 quality adjusted days)

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Panobinostat (Farydak®) for treating multiple myeloma in people who have received at least one prior therapy

A critique of the of the ACD response and addendum documents from Novartis

Report commissioned by:

NHS R&D HTA Programme

On behalf of:

NICE

Produced by:

Optimity Advisors
Peninsula Technology Assessment Group (PenTAG)

Although Optimity Advisors are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Adeline Durand: Contributed to project management, the critique of the company's ACD response and addendum, report writing and editing.
Ketevan Rtveladze: Contributed to the critique of the company's submission, report writing and editing.
Clive Pritchard: Contributed to the critique of the company's submission, report writing and editing.
Chris Cooper: Commented on the searches provided by the company and contributed to report writing.
Ruben Mujica-Mota: Contributed to the critique of the company's submission and commented on drafts of the report and is the guarantor of the report from PenTAG.

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AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplantation
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criterion
BNF	British National Formulary
BTZ	bortezomib
CF	Cognitive Functioning
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CSR	Clinical Study Report
CTD	cyclophosphamide, thalidomide and dexamethasone
DAC	deacetylases
DEX	dexamethasone
DOX	doxorubicin
EBMT	European Group for Blood and Bone Marrow Transplant
ECG,	electrocardiogram
EF	Emotional Functioning
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	5-dimension EuroQol questionnaire
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Status
GOG	Gynecologic Oncology Group
HDAC	histone deacetylase
HERC	Health Economics Research Centre
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQL	health-related quality of life
HSP	heat shock protein
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IRC	Independent Review Committee
LEN	lenalidomide
LLoT	last line of treatment
MAIC	matching adjusted indirect treatment comparison
mEBMT	modified European Group for Blood and Bone Marrow Transplant
MGUS	monoclonal gammopathy of undetermined significance

MM	multiple myeloma
MR	minimal response
MRU	Medical Resource Utilisation
NCDF	National Cancer Drugs Fund
nCR	near-complete response
NICE	National Institute for Health and Care Excellence
Ntx	Neurotoxicity
ODAC	Oncologic Drugs Advisory Committee
ORR	overall/objective response rate
OS	overall survival
PANO	panobinostat
PANORAMA	PANobinostat ORAl in multiple MyelomA
PAS	Patient Access Scheme
PBO	placebo
PF	Physical Functioning
PFS	progression-free survival
PI	proteasome inhibitor
POM	pomalidomide
PR	partial response
QALY	quality-adjusted life years
QLQ-C30	Quality of Life Questionnaire-core 30
QLQ-MY20	EORTC MM-specific module
QTcF	QT interval corrected for heart rate by use of Fridericia's QT formula
RCT	randomised controlled trial
RF	Role Functioning
rrMM	relapsed/refractory MM
SD	standard deviation
SF	Social Functioning
SMC	Scottish Medicines Consortium
STA	Single Technology Appraisal
TA	Technology Appraisal
TFI	treatment-free interval
THAL	thalidomide
TTP	time to progression
VBA	Visual Basic for Applications

1. Summary

The text cited directly from Novartis' response to the ACD is presented with quotation marks in italic and cross referenced. Note that the specific sections/pages of the ACD response and addendum referred to by the ERG in this report apply to either the Novartis response to the ACD response using interim OS data and a [redacted]% PAS or the Addendum to the ACD Novartis response using final OS data and a [redacted]% PAS.

The original submission from Novartis considered the use of panobinostat (Farydak®) in combination with bortezomib and dexamethasone for people with multiple myeloma who have received at least 1 prior therapy (PANO/BTZ/DEX). The comparator considered was bortezomib and dexamethasone (placebo/BTZ/DEX). Novartis also considered the use of PANO/BTZ/DEX triplet for patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including immunomodulatory drug (IMiD) and BTZ based regimens in line with marketing authorisation. The comparator for this analysis was lenalidomide in combination with dexamethasone (LEN/DEX).

Novartis' response to the ACD includes cost-effectiveness results for the PANO/BTZ/DEX versus LEN/DEX comparison and also for the PANO/BTZ/DEX versus BTZ/DEX comparison based on:

- Interim overall survival (OS) from PANORAMA-1
- [redacted]% discount on the price of panobinostat
- A different distribution of fourth-line treatment costs based on updated data from PANORAMA-1 (31.5% on POM/DEX, 4.1% on other active treatments and 64.4% on BSC)

The addendum reports the same comparison but assuming:

- Final overall survival (OS) from PANORAMA-1
- [redacted]% discount on the price of panobinostat
- A different distribution of fourth-line treatment costs based on updated data from PANORAMA-1 (31.5% on POM/DEX, 4.1% on other active treatments and 64.4% on BSC)

Having considered Novartis' revised submission, the ERG view for the comparison of PANO/BTZ/DEX versus LEN/DEX in patients with at least two prior lines of treatment including an IMiD and BTZ is that:

- The new ICER of £11,527 presented in this updated analysis for the comparison of PANO/BTZ/DEX versus LEN/DEX is a deterministic figure and as such does not account properly for the uncertainty in base case model parameters. This ICER is based on results presented by the company in the revised submission give rise to non-linearities, which result in an expected ICER above £20,000 per QALY gained. This probabilistic estimate is reasonably valid and more robust than the original figures submitted by Novartis to NICE for this appraisal.
- The matching-adjusted indirect comparison (MAIC) method used by Novartis to select a LEN/DEX comparator group (from the MM-009 and MM-010 trials) with comparable baseline characteristics to the PANO/BTZ/DEX group (from the PANORAMA-1 trial) is unlikely to produce valid comparisons since it only used two baseline variables to match patient groups: time since

diagnosis and β2-microglobulin level. The company argues that these were the only statistically significant predictors of PFS from the MM trials.

The ERG considered this to be an area of uncertainty and the Advisory Committee may wish to consider if these characteristics are the only significant predictor of PFS.

- The validity of comparative effectiveness analysis using this matching method is more questionable in relation to survival outcomes, as these are likely to be affected by differential use of subsequent lines of treatment across the two source trials (PANORAMA-1 and MM trials). The company assumed that the relative frequency of treatments given after patient progression was the same in the two treatment arms.

Having considered Novartis' revised submission the ERG view for the comparison of PANO/BTZ/DEX versus BTZ/DEX is that:

- Based on the outcomes of a sample of n=72 in each arm (which excludes three patients who had shown no response to BTZ), Novartis presents substantial evidence that the up to week 61 PANO/BTZ/DEX results in improved OS and PFS than BTZ/DEX. However, the company did not present evidence of baseline covariate balance across the two arms in the subgroup of interest, which leaves open the possibility that randomisation may have resulted in differences across arms in observed confounders. Furthermore, the company does not report any adjustment for baseline covariate imbalance in the analysis of the key effectiveness outcomes. There is less clarity about the evidence on the incidence of AEs and their quality of life implications.

- The company presented a range of time to event statistical analysis to project treatment duration, PFS and OS outcomes beyond the observed period. The largest source of uncertainty for cost-effectiveness analysis was the extrapolation of patient survival beyond cycle 61, because of the small number of observations available for analysis at this point (n=16 in the PANO triple therapy arm and n=21 in the BTZ/DEX arm), and because the survival curve of PANO/BTZ/DEX, which had an initial survival advantage over the comparator, crossed only once the survival curve of LEN/DEX, at week 55. Despite the range of sensitivity analyses presented by the company, all had in common an extrapolation of observed survival curve differences, and thus ignored the plausible scenario where no survival differences after week 55, or at least 61, would occur. These analyses in addition to a sensitivity analysis that excluded the cost of active therapies post-progression would have provided a comprehensive assessment of uncertainty.

- In spite of the limitations the comparative effectiveness analysis between PANO/BTZ/DEX vs. BTZ/DEX in patients with at least 2 prior therapies including BTZ and IMiD (excluding patients with no prior response to BTZ) is based on a higher quality of evidence than the indirect comparison for the PANO triplet therapy vs. LEN/DEX.

2. Introduction

The original submission from Novartis considered in the Appendix 17 of the submission the use of PANO/BTZ/DEX triplet for patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including immunomodulatory drug (IMiD) and BTZ based regimens. The comparator for this analysis was lenalidomide in combination with dexamethasone (LEN/DEX).
Following the NICE appraisal consultation process in August 2015, Novartis have submitted additional analyses using either interim or final PANORAMA-1 OS data.

This document is a critique of the additional evidence and the revised cost-effectiveness models submitted by Novartis as a response to the concerns highlighted by the Committee in the ACD.

3. Update overall survival analysis from the phase 3 PANORAMA-1 trial of PANO/BTZ/DEX vs. BTZ/DEX

Novartis presented the final analysis of OS data which required 415 deaths of the entire trial population to be recorded.

The results presented are only for the subgroup of interest i.e. patients who had received at least 2 prior regimens including BTZ and an IMiD.

Table 1: Overall survival for patients who had received at least 2 prior regimens including BTZ and an IMiD in PANORAMA-1

	Prior IMiD plus BTZ and ≥ 2 prior lines of treatment	
	PANO/BTZ/DEX ***N = 73***	***PBO/BTZ/DEX*** ***N = 74***
Median OS, months (95% CI)	[redacted]	[redacted]

Figure 1: Kaplan–Meier curve for overall survival in the PANORAMA-1 for patients who had received at least 2 prior regimens including BTZ and an IMiD

The percentage of patients on the BTZ/DEX arm who received post-study therapy was [redacted]% and [redacted]% in the PANO/BTZ/DEX arm for patients who had received at least 2 prior regimens including BTZ and an IMiD.

4. Critique of the cost-effectiveness of PANO/BTZ/DEX versus LEN/DEX using time dependent HRs derived using MAIC method applied to the subpopulation of patients having received 2–3 prior lines of therapy

4.1. Survival models

4.1.1. Matching-adjusted Indirect Comparison (MAIC) method

Novartis presented an updated survival analysis using a different method for determining the relative efficacy of the panobinostat regimen (PANO/BTZ/DEX) versus LEN/DEX, in patients with at least two prior treatments. It seeks to address "the concerns of the ERG as well as the explicit requests in the ACD to maintain a sufficient effective patient number (ACD, Section 3.27 and 4.8) as well as to apply independently fitted survival curves to the two arms (ACD, Section 4.7 and 4.8)". The updated method matches only on the basis of those significant baseline prognostic factors which predict survival and applies time dependent HRs, i.e. avoiding the use of constant hazards. The updated method is populated with the final PANORAMA-1 OS data described in Appendix 1 of Novartis' response to the ACD. New cost-effectiveness analysis using these data are also presented, including sensitivity analysis "removing subsequent active treatments as suggested in the ACD (ACD, Section 4.12)."

Similarly to the results presented in their original submission when using the MAIC approach, Novartis matches the two groups on a sample from PANO/BTZ/DEX arm. This was done in two steps: first, excluding patients who had received LEN treatment before initiation of PANO/BTZ/DEX (to mirror the MM-009 and MM-010 trials, which were the source of LEN/DEX arm and excluded patients with history of LEN treatment), and then matching the remaining patients on the baseline variables of time since diagnosis (4.1 years) and β2-microglobulin level (proportion of patients with β2-microglobulin > 2.5 mg/L: 74.5%). The justification given by Novartis for this choice of matching covariates was the evidence from the MM-009 and MM-010 trial that these variables were β2-microglobulin level and the number of prior therapies were the only statistically significant predictors of PFS, while these two baseline variables and the International Staging System (ISS) score were significant predictors of OS. However, according to a report on the MM trials, significant predictors of OS also included a high baseline percentage of plasma cells (Dimopoulos et al. 2009).

Novartis notes that "*It is important to emphasize that the information utilized to derive the HRs (ie, published Kaplan–Meier curves and baseline characteristics for LEN/DEX in patients having received 2–3 prior lines of treatment, adjusted patient population of PANO/BTZ/DEX) was not used directly in the health economic model. Instead, the derived HRs were used to generate PFS and OS data for LEN/DEX in a hypothetical patient population reflecting the panobinostat EMA label setting assuming that the same relationship would be observed between LEN/DEX and PANO/BTZ/DEX in the EMA label setting (patients with at least two prior lines of therapy including IMiD and BTZ) as observed in patients who have received 2–3 prior lines of therapy*."

The company argues that matching on more patient characteristics could have been performed but refers to the committee's comments about the small effective sample size that resulted from such extended matching in their original analyses (n=23), to justify using the effective sample size of their more limited matching n=140 (from the 188 patients who had received 2–3 prior lines in the PANORAMA-1 trial).

It is stated that *"PFS and OS HRs derived using the MAIC methodology seem to be clinically plausible in light of the efficacy data available for PANO/BTZ/DEX and LEN/DEX for the Intention-to-treat (ITT) cohorts and the subgroups of patients who have received 2–3 prior lines of treatment, when acknowledging the differences in the patient characteristics between the two trials (ie PANORAMA-1 and pooled data for MM-009/MM-010), as summarised in* Table 2 ***Error! Reference source not found.**."*

Table 2: Summary of median PFS and OS for PANO/BTZ/DEX and LEN/DEX for patients who have received 2–3 prior therapies in PANORAMA-1 and MM-009/-010

Parameter	PANO/BTZ/DEX 2–3 prior lines subgroup			LEN/DEX 2–3 prior lines subgroup	
	n	Final OS data Median (95% CI), months	Interim OS data Median (95% CI), months	n	Median, months
PFS	188	11.33 (9.36 – 13.70)	11.33 (9.36 – 13.70)	220	10.6
OS	188	[redacted]	[redacted]	220	35.8

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

Stadtmauer et al 2009

Source: Novartis' addendum

It is not clear to the ERG why the results depart from the results presented in the original submission. For patients with 2 to 3 lines of treatment (48.3% of the study population), median PFS was reported as 11.30 months for n = 188 patients (see Table 19 of the ERG report) instead of 11.33 months here.

The MAIC method is limited to only two patient characteristics considered by the Company to be the only statistically significant predictors of PFS in order to keep an effective sample size. However the ERG considered this to be an area of uncertainty since there are observed and unobserved confounding factors between the populations considered within these different trials and it may be useful for the Committee to consider if these characteristics are the only significant predictors of survival from a clinical point of view.

4.1.2. Treatment discontinuation

The company also revised the rate of treatment discontinuation that is used for LEN/DEX in the economic analysis. It argued that "comparison of treatment duration using these methods [MAIC] is not feasible because LEN/DEX is given continuously until disease progression." Instead, the company used the ratio of the median time to disease progression (9.5 months) to the median time to discontinuation (9.2), of 1.033, in the subgroup of patients with 2-3 prior lines of treatments, to derive an estimate of excess risk (3.3%) from the risk of disease progression in each model cycle.

4.1.3. Post-progression mix

In the original submission, the post-progression active treatment mix was taken from the study of Gooding et al. (2013) where 31.5% receive POM/DEX and 45.5% receive other active treatment. Novartis has updated these proportions in the new evidence submitted based on the final data from PANORAMA-1.

As patients progress in the new model, the new proportion of patients receiving POM/DEX followed by MRU is 31.5%, 4.1% receive other active treatments and 64.4% receive supportive care alone.

The company assumed patients in the LEN/DEX arm receive similar post-progression therapies and in similar proportions to those reported for PANO/BTZ/DEX. The company state that this was assumed to apply to both treatment arms of the model since such data has not been published for patients receiving LEN/DEX. **It must be borne in mind that this equalising assumption is limited to the cost side of the analysis; the effectiveness (QALY) side of the comparison is unaffected by it and represents a potential source of bias that the matching method would be unlikely to address** (the company does not present data on the frequency of active treatment vs best supportive care alone in the LEN/DEX sample).

Table 3: Distribution of treatments in 4th line

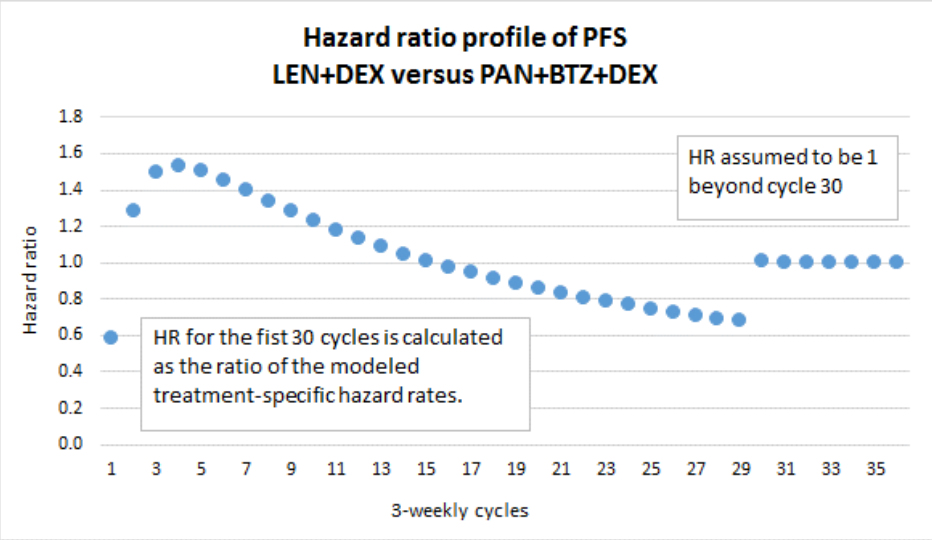
	Original submission	Updated analysis
POM+DEX	31.5%	31.5%
Other active treatment	45.5%	4.1%
BSC	23.0%	64.4%

Using the treatment mix from the original analysis increases the ICER to £19,617 per QALY gained, instead of £11,527 with the updated post-progression treatment mix

4.2. PFS assessment

In comparison with the original submission by Novartis, the addendum presents statistical tests of the proportional hazards assumption of the time to progression or death (progression free survival) analysis comparing the two arms and implemented by the MAIC method. The results of their tests confirm that the Cox proportional hazard assumption is not valid in the matched patient sample and, therefore, that the analysis should allow for the ratio of risks of progression or death to vary across the two arms. Novartis thus implemented this by estimating five different parametric models to fit the time to progression or death data separately for each arm and selecting their preferred model based on goodness of fit statistics (Bayes Information Criteria and Akaike Information Criteria). Novartis then estimated the ratio of progression/death risk between PANO/BTZ/DEX and LEN/DEX by the ratio of the estimated hazards of their respective best-fitting models in each 3-week cycle, thus allowing a varying pattern of this relative risk over time since the start of treatment.

Figure 1 Hazard ratio profile – time-dependent hazard ratio scenario



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Source: Novartis' response to the ACD

The result of these analyses was that the estimated HR used to populate the economic model exhibited an inverted U-shape with a peak early on after the start of treatment as shown in Figure 1, at around the time of the 4th 3-week cycle of treatment (i.e. at 12 weeks). This was a consequence of the best fitting model for the LEN/DEX data being the log-normal, which is characterised by a higher hazard (risk of progression or death) in the early period that gradually declines with time, whereas the model adopted by the company as best fitting the PANO/BTZ/DEX data **was the Weibull**, which had a rising hazard over time. It is noteworthy that the Weibull did not appear to fit the data significantly better than the exponential time-to-event model, which is characterised by its constant hazard, and that in fact the latter was a better fit according to one statistic (the Bayesian Information Criteria; see Table 4 below).

Table 4: AIC/BIC values for the PFS models for LEN/DEX and PANO/BTZ/DEX

	LEN/DEX		PANO/BTZ/DEX (matched)	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	639.6038	642.9975	277.5292	280.485
Weibull	641.1437	647.931	***276.5625***	***282.4741***
Log-logistic	629.571	636.3582	277.2262	283.1379
Log-normal	***627.28***	***634.0672***	280.209	286.1207
Gompertz	640.6507	647.4379	278.5276	284.4392

The best fitting model selected for the base case analysis is shown in bold italic

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival.

Source: Novartis' response to the ACD

The ERG consider this analysis to be a useful addition over the original analysis given the evidence that the relative magnitude of risks of progression or death between the two treatment arms is not proportionally constant. However, the way in which the company interpreted the results to populate their economic analyses is questionable for three main reasons.

First, the matching patient sample from the PANO/BTZ/DEX arm of PANORAMA-1 used for these analyses was selected to match only two patient characteristics, which, while preserving sample size for statistical power relative to matching on a larger number of potentially relevant predictor variables, **may increase the risk of biased estimates of effect due to observed confounders (in addition to confounding due to unobserved factors**). The Company did not provide a table of summary baseline patient characteristics for each arm to allow the committee to appreciate the extent to which potentially relevant factors of PFS, other than simply those on which matching was based, may have been unevenly distributed across PANO/BTX/DEX and LEN/DEX arms.

Second, the statistical analysis presented by Novartis suggests that the **Weibull model is not necessarily superior to the exponential model** for estimating the risk of progression or death under the PANO/BTZ/DEX arm. This has the implication that the HR (the ratio of the progression or death risk under LEN/DEX to the risk under PANO/BTZ/DEX) peaks earlier on after the start of treatment when using the Weibull model than when using the exponential. This is a source of structural uncertainty for the cost-effectiveness results due to its interaction with discounting but the company did not provide an adequate sensitivity analysis of it (i.e. it present deterministic 'scenario analyses' see section 4.4.4 below, but no probabilistic analysis).

Third, the model adopted a risk of treatment discontinuation for LEN/DEX proportional to its estimated risk of progression or death, imputed from the ratio of median time to progression or death and median time to treatment discontinuation. This assumption implies in turn that the risk of treatment discontinuation followed the same log-normal pattern of higher discontinuation risk in the early period that was followed by the time to progression or death in the new analyses by Novartis for LEN/DEX. Whether this is compatible with the available evidence reported for the MM-009/MM-010 trials was not discussed by Novartis.

4.3. OS assessment

Similarly to the PFS analysis just described, Novartis tested the proportional hazards assumption in the OS data from the LEN/DEX and the matched PANO/BTZ/DEX (final data) arms. Diagnostic tests based on visual inspection suggested that the "hazard of death for LEN/DEX is very similar to the hazard of death for PANO/BTZ/DEX for the first 35–40 cycles (Figure 9 of the Novartis' response to the ACD). However, after that point the log-cumulative hazard curves start to diverge which is an indication of higher mortality rates for LEN/DEX than for PANO/BTZ/DEX.". A similar interpretation was given of the visual inspection of the pattern of Schonfeld residuals over time, despite favourable results of statistical tests of the proportional hazard assumption based on such pattern (perhaps recognising that the test has limited ability of detecting violations of such assumption with nonlinear time patterns). Novartis then fitted a cox survival model with death hazards that varied between the initial 35-40 cycle and the subsequent periods. In order to identify the 'break point' time in the HR, the model used goodness of fit statistics to identify the best fitting of a set of such cox models that varied only in terms of the time of break between 35 and 40 weeks, and chose the model with HR change at the 39 cycle. At such point, the HR for LEN/DEX relative to PANO/BTZ/DEX changed from 0.99 (95% CI: 0.69 to 1.42) to 1.52 (0.84 to 2.74).

Table 5: Estimated hazard ratios using the 39th cycle as the cut-off time point

Time (no. of cycles)	OS HR	SE	z	P>z	95% CI

< 39th cycle	0.99	0.181	-0.05	0.961	0.69 - 1.42
≥ 39th cycle	1.52	0.458	1.38	0.167	0.84 - 2.74

HR, hazard ratio; OS, overall survival; SE, standard error of the log hazard ratio.

Source: Novartis' addendum

The new analysis relaxes the constant proportional hazards assumption, however two limitations remain in this analysis.

First, the matching method is unlikely to have properly adjusted for confounders, especially in relation to the subsequent treatments received by patients in the PANORAMA-1 and the MM-009/MM010 trials. **This is important because there is high uncertainty regarding the HR estimate of 1.52 used by Novartis** in the economic model due to the possibility of it being driven by differences in subsequent treatments given after the progression across the two arms in those trials. Further, it is noted that the matching for confounding did not include the baseline information on high baseline percentage of plasma cells, which was found to be significant predictor of survival in the MM-009/MM010 trials (Dimapoulos et al. 2009), nor the ISS score also a significant predictor in the same trials, which was unavailable to the Novartis analysts. Novartis did not provide a sensitivity analysis of the ICER with a reduced survival effect in order to account for the probable bias in the survival advantage estimated for PANO/BTZ/DEX.

The second limitation is related to the first, in that Novartis states that it followed the recommendation by the Appraisal Committee to investigate the effect of excluding the costs of active subsequent lines of treatment. This sensitivity analysis was performed on the cost side only omitting any adjustments on the effectiveness, survival and QALY side. This suggests that any such sensitivity analysis is potentially inconsistent.

4.4. Results of the cost-effectiveness analysis

4.4.1. Base case results

Base case inputs of the model are presented in Table 12 of Novartis' response to the ACD. The ERG present Novartis' base case results in Table 6 below. The base case analysis is based on a cost of 20mg capsule of PANO set at [redacted] with a discount of [redacted]% according to the new PAS submitted by Novartis to the Department of Health.

The results of the analysis are presented based on relative effectiveness estimates using the MAIC method with PAS.

Novartis results are presented under the assumption that Bortezomib is administered subcutaneously as considered appropriate in the ACD. Additionally, Novartis has implemented the following changes based on information provided by the clinical experts consulted by the ERG and accepted by the Committee:

- Lymphopenia set at a zero instead of £167; and
- Specialist visit frequency every 2nd cycle instead of every cycle.

Similarly to the original submission, the small difference in QALYs between the two therapies suggests that it is difficult to establish a statistical difference in effectiveness between PANO/BTZ/DEX and LEN/DEX in this population and makes the incremental analysis results very volatile.

Table 6: Summary of base case results using the MAIC method (discounted) with PAS

With PAS	Total			Incremental vs LEN/DEX			ICER vs LEN/DEX	
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Cost per LYs gained, £	Cost per QALYs gained, £
PANO/BTZ/DEX	£141,707	2.40	1.59	£1,425	0.210	0.124	£6,783	£11,527
LEN/DEX	£140,281	2.19	1.47					

Time dependent HRs derived using MAIC method applied to subpopulation (patients having received two to three prior lines)
BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PAS, Patient Access Scheme; PANO, panobinostat; QALY, quality-adjusted life year.
Source: Novartis' addendum

Previous cost-effectiveness results

The tables below report the cost-effectiveness results according to the original Novartis analysis comparing PANO/BTZ/DEX in those who have received at least 2 prior lines of therapy including an IMiD and bortezomib, and under the ERG's preferred assumptions, which were accepted by the Committee in the ACD.

Table 7: Novartis results, [redacted] PAS, hazard ratios (HRs) based on unadjusted Cox and interim overall survival (OS)

	PANO/BTZ/DEX	LEN/DEX	Incremental
Costs	£147,308	£147,632	-£324
Life years	2.288	2.216	0.072
QALYs	1.521	1.469	0.052
Cost per QALY			dominant

Source: ERG critique to the first PAS

Table 8: ERG preferred approach, [redacted] PAS, interim OS, HRs based on MAIC applied to subpopulation

	PANO/BTZ/DEX	LEN/DEX	Incremental
Costs	£146,310	£120,108	£26,202
Life years	2.288	1.827	0.461
QALYs	1.521	1.237	0.28
Cost per QALY			£92,306

Source: ERG critique to the first PAS

It should be noted that the observed median OS for PANO triplet therapy in PANORAMA-1 trial has increased since the interim results; it was reported as 33.31 and it is now [redacted] months in patients having received 2 to 3 prior lines of treatment (as reported in Table 2 of the Novartis' addendum using the interim and the final OS data, respectively). However, the modelled life years for PANO/BTZ/DEX in

patients having received 2 to 3 prior lines of treatment including BTZ and an IMiD have increased in the new analysis compared to the original submission 2.40 years vs. 2.29 years (28.8 month vs. 27.5 months). This is expected to be due, at least partly, to the different statistical models used to estimate survival differences between the two treatment arms in the MAIC: in the original analysis Novartis adopted a cox proportional hazards model with constant hazards; in the new submission, OS is modelled using a cox proportional hazards model with a hazard ratio that varies between the period before and the period after cycle 39.

The observed final median OS for patients in the population for which Panobinostat has a positive opinion i.e. patients who have received at least 2 prior lines including BTZ and an IMiD is lower, [redacted] months, than the one reported for patients having received 2 to 3 prior lines of treatment only and this figure is lower than survival in the interim analysis.

Novartis also presented the clinical outcomes of the model compared with the interim and final clinical outcomes from PANORAMA-1 for PANO/BTZ/DEX in the subpopulation of patients who have received at **least two prior therapies, including BTZ and an IMiD**. It shows that the model underestimates the PFS by 2.23 months and overestimates the OS by [redacted] months compared to the final trial outcomes. It also shows that the model overestimates the median treatment duration by 0.92 months and hence the cost of PANO/BTZ/DEX. The summary of model results vs. the clinical data is presented in Table 9 below.

Table 9: Summary of model results vs. the (final OS) clinical data

Outcome	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)*	*Original submission model result*	*New model result*
Median PFS (PANO/BTZ/DEX)	*12.5 months*	*12.0 months*	*10.27 months*
Median OS (PANO/BTZ/DEX)	[redacted] *months*	*26.2 months*	*26.88 months*
Median treatment duration (PANO/BTZ/DEX)	*4.5 months*	*5.5 months*	*5.42 months*
Proportion of patients experiencing adverse events (PANO/BTZ/DEX)	*Rates obtained from trial*	*Rates obtained from trial*	*Rates obtained from trial*

BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

Source: Adapted from Novartis' addendum

It is not clear to the ERG why the modelled median OS for the PANO/BTZ/DEX have increased compared to the original submission when the median OS in the final OS data used in the updated analysis are lower than the median OS in the interim data which was used in the original analysis; i.e. [redacted] instead of 30.56 months.

Similarly the company compared the model results for LEN/DEX with the respective arm in the MM-009 and MM-010 trials involving 2-3 prior lines of treatment. The model reportedly underestimated median PFS by 0.62 months and OS by [redacted] months. It is noted that these comparisons with observed clinical data of the PANO/BTZ/DEX and LEN/DEX model results may lend support to their generalisability but have no bearing on the validity of the model comparison with PANO/BTZ/DEX.

The disaggregated QALYs and costs for the disease states determined by the PFS and OS results are presented in the Novartis' response to the ACD in Tables 15, 16 and 17. Novartis reports that "*Results show that PANO/BTZ/DEX is associated with a decrement in QALY during the pre-progression on treatment phase and a corresponding gain in QALY during the pre-progression off treatment phase so that overall there is little difference in the QALYs between the two treatments*." Still, there is a gain in QALYs of 0.03 attributable to the period before progression. In the model results for the pre-progression period, PANO/BTZ/DEX is cost saving relative to LEN/DEX.

Novartis argues that given the comparative data available on median OS for the 2-3 prior lines of therapy showing that LEN/DEX has a survival advantage of 1.17 months, the survival advantage of PANO arm in the model results in a conservative ICER because costs in this period transform PANO/BTZ/DEX from a cost-saving intervention to one having additional costs and additional QALYs (which increase from 0.03 to 0.12 per patient). In the Novartis base case model, for a given mean PFS, a longer mean OS is associated with higher ICERs, since the period post progression is lengthened and is associated with costs accumulating at a faster rate than QALYs.

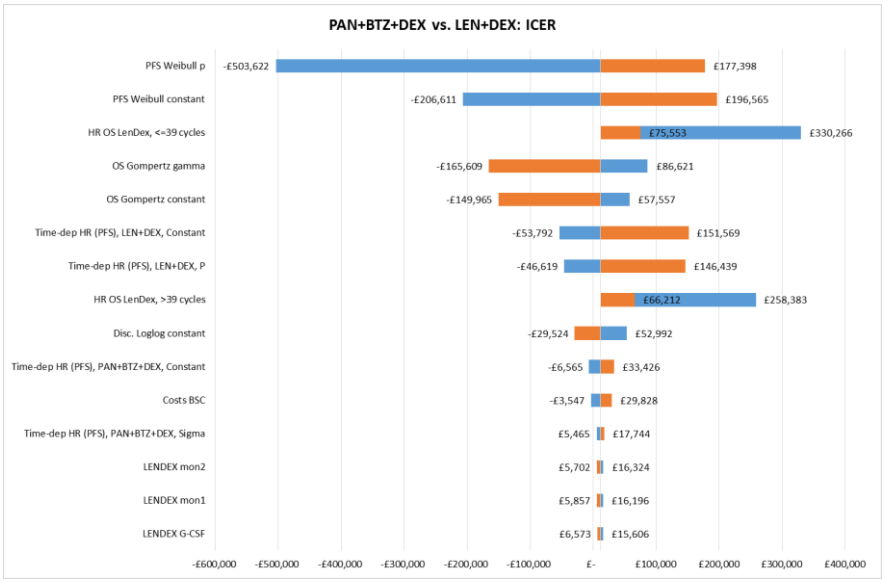
It should be noted that the efficacy data (i.e. HRs for LEN/DEX vs. PANO/BTZ/DEX) are coming from the subpopulation of patients who have received 2 to 3 prior line of treatment which is wider than the population of the subgroup analysis which considered people patients who received two or three prior lines of therapy including an **IMiD and BTZ.** It is unclear therefore whether the effectiveness data included in the subgroup analysis are appropriate for the patient group of interest.

4.4.2. Deterministic sensitivity analyses results

In the deterministic sensitivity analysis, ranges of cost per QALY results were obtained by varying input parameters one at a time between the upper and lower bounds of the 95% confidence interval. If the confidence interval was not reported, upper and lower limits for the sensitivity analysis were generated by adding or subtracting two times 20% of the mean.

The upper and lower confidence limits of PFS statistical model gave cost per QALY estimates ranging from -£503,622 (a 4269% reduction compared with the base case) to £177,398 (a 1439% increase on the base case). This result suggests that the ICER is very sensitive to PFS parameter values. However, the new analysis does not describe the details of these univariate analyses, and since the only descriptors available were the labels in the Tornado diagrams the meaning of some of these analysis was unclear (The titles of the graphs also appear inconsistent across these analyses; Figures 12-14).The Tornado diagram is presented in the Figure 2 below:

Figure 2: Tornado diagram of ICERs for PANO/BTZ/DEX versus LEN/DEX: base case (discounted): with PAS



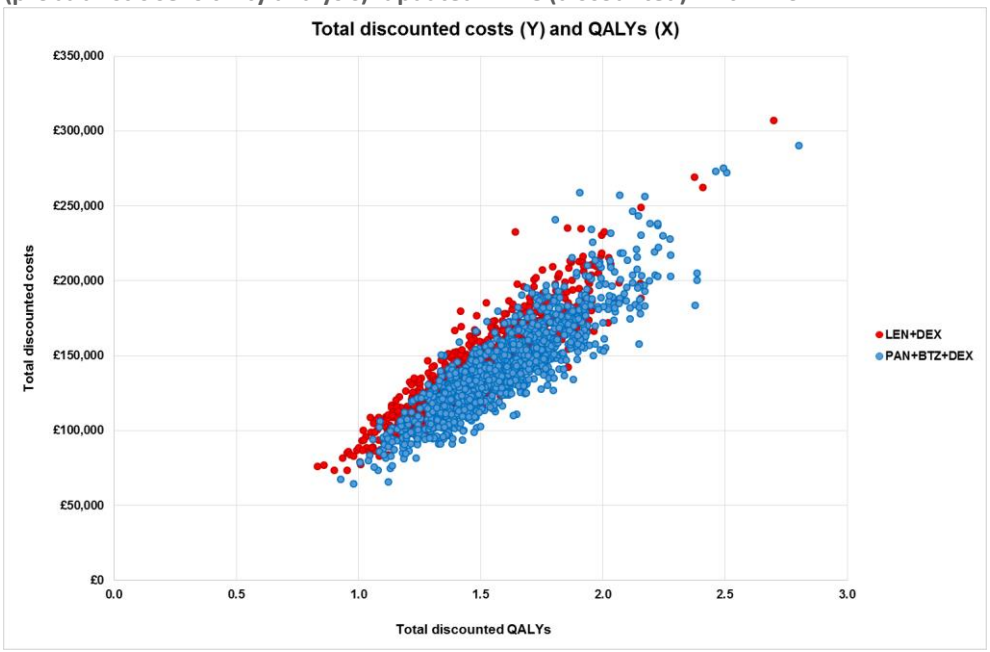
Orange bars indicate upper limit; Blue bars indicate lower limit.

Source: Novartis' addendum

4.4.3. Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in Figure 3 (scatter plot of total QALYs and costs), Figure 4 (scatter plot of incremental QALYs and costs). The probabilistic sensitivity analysis was run using the MAIC method and deriving HRs from the subpopulation (2–3 prior lines of therapy).

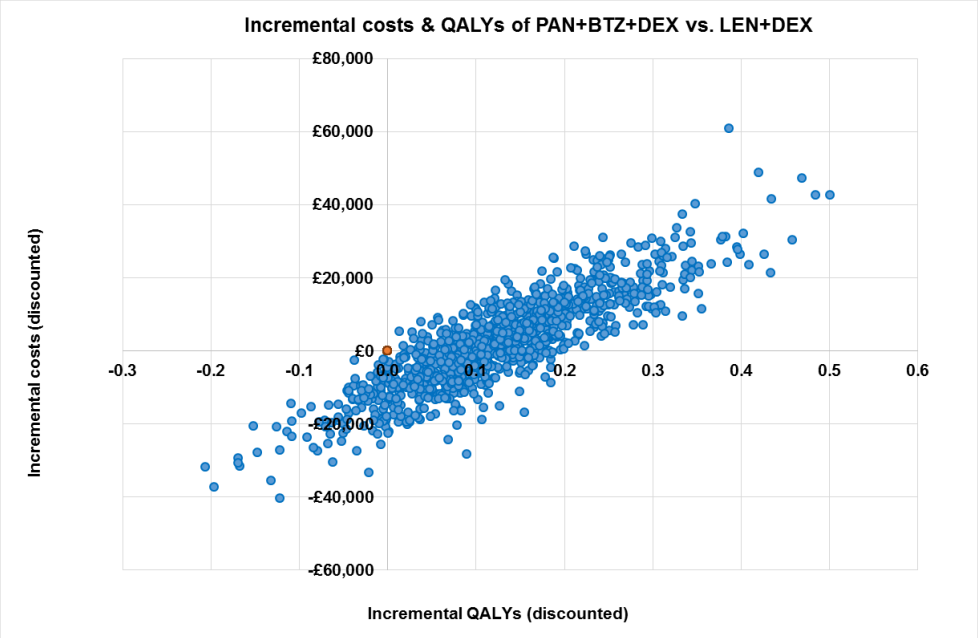
Figure 3 Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): updated MAIC (discounted): with PAS



Base case, ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Figure 4 Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis): base case (discounted): with PAS



Base case: ie using the 'MAIC' method to derive time dependent HRs from the subpopulation (patients who had received 2–3 prior lines)

Source: Novartis' addendum

The PSA resulted in the following 95% CIs around key model outcomes presented in Table 10 below:

Table 10: CI around key model outcomes

	Cost	*Incremental cost*	*QALYs*	*Incremental QALY*	*ICER (QALY)*
PANO/BTZ/DEX	£141,707 (£90,611 to £217,477)	*£1,426 (–£22,152 to £28,3175)*	*1.59 (1.13 to 2.15))*	*0.12 (–0.06 to 0.34*	£11,883
LEN/DEX	£140,281 (£92,398 to £204,776)		*1.47 (1.06 to 1.94)*		

Base case, ie using the 'MAIC' method to derive HRs from the subpopulation (patients who had received 2–3 prior lines)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Source: Novartis' addendum

The probabilistic results presented are similar to the deterministic results, however when the ERG repeated the PSA on a number of occasions in the Company's model, the ICERs obtained were between £20,000 and £25,000. This implies that the true ICER may be higher than the determinist ICER of £11,527 per QALY gained. Indeed, the ERGs calculated ICER is consistent with Novartis' result in Addendum Table 19 on the Addendum which says that the probability of PANO/BTZ/DEX being cost-

effective versus LEN/DEX at the £20,000 willingness to pay threshold for a QALY is 49.9%. These results suggest that Novartis model comparison between PANO/BTZ/DEX and LEN/DEX exhibit nonlinear relationships between model inputs and outputs (likely arising from the modelling of non-proportional hazard ratios for PFS; see section 4.2 above) that render deterministic ICERs inadequate and the base case probabilistic ICER the correct value on which to base NICE Appraisal Committee discussions about PANO/BTZ/DEX cost-effectiveness.

4.4.4. Scenario analysis

Here, the ERG list the assumptions of scenario analysis that were made by Novartis in the cost-effectiveness model:

- A discount rate of 5%, rather than 3.5%, was used;
- Time horizons of 5 and 10 years were used instead of 25 years;
- PFS for PANO/BTZS/DEX was modelled with the Gompertz and exponential parametric functions instead of the Weibull model;
- OS for PANO/BTZS/DEX was modelled with the Weibull and the Kaplan-Meier + Gompertz parametric functions (instead of the Weibull model);
- Time to discontinuation was based on Kaplan-Meier estimates rather than a loglogistic model;
- Assuming no disutility associated with LEN/DEX

It should be noted that the results presented for the use of Kaplan-Meier + Gompertz for OS in table 20 of the addendum were incorrect with higher results. We have updated it in Table 11 below.

Modelling the PFS of PANO/BTZ/DEX with parametric functions other than the Weibull function (as done in the base case model) provides lower ICERs in all cases, however the biggest impact on the ICER was observed when modelling OS with a Weibull function, resulting in increasing the ICER by 189%, at £33,385. This cost-effectiveness result is less favourable for the company. Except when using the Weibull function for modelling OS, all the ICER remained below £20,000 per QALY in all scenarios. However it must be noted that these are all deterministic analyses and as such underestimate the ICER of PANO/BTZ/DEX.

Table 11: Scenario analyses

Scenario	Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Base case	***£1,425***	***0.124***	***0.210***	***£11,527***	***£6,783***
Discount rate of 5% for both costs and effects	*£694*	*0.115*	*0.196*	*£6,040*	*£3,533*
Time horizon, 5 years	*–£4,123*	*0.075*	*0.134*	*dominant*	*dominant*
Time horizon, 10 years	*£1,415*	*0.124*	*0.210*	*£11,449*	*£6,737*
OS, Weibull	*£5,263*	*0.158*	*0.263*	*£33,385*	*£19,994*
OS, Kaplan–Meier + Gompertz	***–£393***	***0.108***	***0.185***	***dominant***	***dominant***
PFS, Gompertz	*£1,185*	*0.123*	*0.210*	*£9,641*	*£5,636*
PFS, exponential	*£1,140*	*0.125*	*0.210*	*£9,090*	*£5,426*
Time to discontinuation, Kaplan–Meier estimates	*£1,197*	*0.124*	*0.210*	*£9,677*	*£5,697*

Assuming no disutility associated with LEN/DEX	*£1,425*	*0.120*	*0.210*	*£11,589*	*£6,783*
Assuming no active treatment in the post-progression health state[1]	***-£3,363***	***0.124***	***0.210***	***dominant***	***dominant***
Different methodologies used to derive HRs for PFS and OS for LEN/DEX versus PANO/BTZ/DEX					
Naïve comparison[2]	*–£19,783*	*–0.042*	*–0.054*	*Cost saving*	*Cost saving*
Unadjusted Cox	*£5,249*	*0.155*	*0.263*	*£33,794*	*£19,939*
Threshold analyses (ie non time dependent, constant PFS and OS HRs for LEN/DEX vs PANO/BTZ/DEX)					
HR = 0.8[2]	*-£34,277*	*-0.271*	*-0.378*	*Cost saving*	*Cost saving*
HR = 0.9[2]	*-£22,695*	*-0.133*	*-0.174*	*Cost saving*	*Cost saving*
HR = 1[2]	*-£12,556*	*-0.016*	*0.000*	*Cost saving*	*Cost saving*
HR = 1.1	*-£3,607*	*0.085*	*0.150*	*Dominant*	*Dominant*
HR = 1.2	*£4,349*	*0.173*	*0.282*	*£25,103*	*£15,425*

Source: Novartis' addendum

4.4.5. Conclusion

The ERG have verified the manufacturer's new deterministic base case result when using the final OS data. The ICER presented was £11,527 per QALY gained for the PANO/BTZ/DEX versus LEN/DEX comparison when applying the new PAS with a simple discount of [redacted]%. This is a much lower ICER than the one presented in the original analysis.

However, the probabilistic simulations run by the ERG using the manufacturer's model tended to give less favourable results for PANO/BTZ/DEX than the deterministic analysis. In contrast with the deterministic ICER that Novartis presents as the base case estimate for cost-effectiveness analysis, the probabilistic results adequately account for uncertainty in estimated parameter values. The correct ICER is therefore calculated to be equal to above £20,000 in the base case.

The company's submission presents a number of scenario analysis, the results of which have been verified by the ERG. All those results are below £20,000 except when modelling OS with a Weibull function, resulting in increasing the ICER at £33,385. These numbers are underestimated as they are all deterministic.

The ERG is more confident with the new ICER presented in this updated analysis for the PANO/BTZ/DEX versus LEN/DEX comparison when applying the new PAS. However there are still some concerns regarding the risks resulting in biased comparisons due to unadjusted observed confounders in the PANO/BTZ/DEX vs LEN/DEX indirect comparison from which the relative effectiveness parameters and progression free survival and overall survival profiles that populated the cost-effectiveness model were derived. In addition, the use of the Weibull model is not necessarily superior to the exponential model for estimating PFS risk under the PANO/BTZ/DEX and the effect of this structural uncertainty on the probabilistic ICER was not investigated by Novartis.

There are some uncertainties regarding the HR estimate of 1.52 for overall survival. In response to the Committee's advice, the company have tested for and rejected the proportional hazard assumption

and used a different indirect comparison method. The new estimate may still be flawed because the matching method is limited to two patient characteristics: time since diagnosis and β2-microglobulin level. **The Advisory Committee may wish to consider if these characteristics are the only significant predictor of survival.**

In the new survival analysis, the differences between the two arms will only occur in effect in the second period from the 39th cycle which means that by that time, the more likely survival is to be impacted by the 4th line of Treatment. As noted above, there will be differences in the post-progression treatments given to patients between PANROAMA-1 trial and the MM-009/MM010, which the MAIC method is unlikely to properly adjust for. In this regard, the Novartis model assumed post-progression therapies given in similar proportions across arms to adjust for costs, but there is no a priori reason why this is a valid assumption.

5. Critique of the cost-effectiveness of PANO/BTZ/DEX versus BTZ/DEX in patients who have received at least 2 prior lines of treatment including an IMiD and BTZ

5.1. Methods

Novartis presented a new comparison between PANO/BTZ/DEX versus BTZ/DEX for the population defined in the marketing authorisation of patients with relapsed and/or refractory multiple myeloma who have received at least two prior standard therapies, including BTZ and an IMiD. They used either the interim OS from PANORAMA-1 and a [redacted]% discount on the price of panobinostat in their response to the ACD, or a new comparison using either the interim overall survival (OS) from PANORAMA-1 and a [redacted]% discount on the price of panobinostat in their addendum. Table 21 of the company's ACD response say 'Median OS (final analysis)' but the ERG assume the results presented are the interim data.
Additionally these are direct comparisons using the two treatment arms from the PANORAMA-1 trial contrary to what the company said in their response to the ACD and their addendum (Section 4.1.1).

It is noted that no comparative table of descriptive baseline characteristics are presented for the two PANORAMA-1 trial arms in the subgroup of patients analysed. This leaves open the question of whether randomisation in the subgroup of interest achieved balance in potential confounders across the two treatments for the subgroup of interest. This is important because any observable confounding would have affected the effectiveness and cost-effectiveness as the time to event and survival analyses did not control for any differences in baseline characteristics between the groups.

5.1.1. Efficacy and safety data

Novartis compare efficacy and safety results for the population defined in the marketing authorisation and the population used in their direct comparison which excludes patients with no response to the prior BTZ. The ERG consider this method to be appropriate in order to reflect current clinical practice. Only one patient and two patients did not respond in the PANO/BTZ/DEX and BTZ/DEX arms, respectively, therefore the efficacy data are very similar between the two populations.

Regarding safety data, the ERG is not clear why the results are so different. Novartis presented the incidence and % for the population used within the direct comparison but only the incidence for the population defined in the marketing authorisation. The ERG present the results in the table below:

	EMA label population, i.e. patients having received ≥ 2 prior regimens, including BTZ and an IMiD		Population for direct comparison with BTZ/DEX, i.e. patients having received ≥ 2 prior regimens, including BTZ and an IMiD *excluding* those with no response to the prior BTZ	
	PANO/BTZ/DEX	PBO/BTZ/DEX	PANO/BTZ/DEX	PBO/BTZ/DEX

	N = 73/72	N = 74/73	N = 72/71	N = 72/71
On-treatment deaths, %	6.9 (10%)	6.8 (9%)	N/A	N/A
Thrombocytopenia	68 (94%)	44 (61%)	46 (65%)	35 (49%)
Infections (pneumonia)	19.4 (27%)	16.4 (23%)	13 (18%)	12 (17%)
Infections (sepsis)	2.8 (4%)	6.8 (9%)	0 (0%)	2 (3%)
Diarrhoea	33.3 (46%)	15.1 (21%)	54 (76%)	34 (48%)
Asthenia/fatigue	26.4 (37%)	13.7 (19%)	Asht or fatig: 33 (46%) Fatig: 33 (46%) Asht: 16 (23%)	Asht or fatig: 25 (35%) Fatig 25 (35%) Asth: 11 (15%)
Haemorrhage	2.8 (4%)	2.7 (4%)	N/A	N/A
Neutropenia	31.9 (44%)	9.6 (13%)	25 (35%)	10 (14%)

Source: Adapted from Novartis' addendum

5.1.2. Clinical parameters

5.1.2.1. Risk of progression or death

On the basis of the AIC and BIC statistic, clinical plausibility and visual inspection, the Weibull model was selected as the best fit for PFS. The company only provided the AIC and BIC statistics for one arm and it is not clear to the ERG which arm. Therefore the ERG cannot give an opinion on the choice of parametric model. As the company only show the fitted Weibull curve, the ERG cannot verify the company judgement based on visual inspection.

The ERG is generally concerned that the company have not implemented a stopping rule at the end of cycle 4 to evaluate patients' response and at the end of cycle 8 to reflect UK clinical practice.

5.1.2.2. Risk of treatment discontinuation

On the basis of the AIC and BIC statistic, clinical plausibility and visual inspection, the Gompertz distribution was selected for the BTZ/DEX responders and the exponential distribution for PANO/ BTZ/DEX.

5.1.2.3. Risk of death

The OS analysis explored four different approaches, which varied between a fitting a single equation to the time to death data from the patient subgroup in both treatments of PANORAMA-1 and estimating the relative effect (hazard ratio) using a treatment indicator covariate in the fitted equation (Approach 1); using the non-parametric Kaplan-Meier estimates for the available follow-up in each arm and extrapolating beyond the respective end of follow-up dates using the predicted mortality risks from the model in approach 1 (Approach 2); separate curve fitting for each arm and extrapolating BTZ/DEX arms survival beyond the 55 cycle using the curve fitted to PANO/BTZ/DEX (Approach 3); and by a separate curve fitting up to cycle 55 in both arms, and extrapolating using the risk of death estimated from a

single curve fitted to patients from both groups who were alive at cycle 55 (Approach 4). Approach 4 was considered to be more clinically plausible since it preserved Kaplan-Meier survival curve crossing at cycle 55 and used the best fitting among the survival curves that increased in risk over time (Weibull). The base case analysis was based on Approach 4 and the results of all other approaches were presented as sensitivity analyses.

Approach 1 used the Weibull function, which as recognised by Novartis implied the constant proportional hazards (PH) assumption throughout the observed period. The PH assumption was unlikely to be met given the crossing of survival curves at cycle 55. Clearly Approach 2 represented a more flexible approach to model the observed survival period, although gains in statistical efficiency and convenience in populating a model are obtained by the two-part survival model approaches (Approach 3 and Approach 4).

The ERG confirmed that the excel model provided by Novartis used the approach 4 as described in the addendum.

5.2. Results of the cost-effectiveness analysis

5.2.1. Deterministic results

5.2.1.1. Base case

Since PANO/BTZ/DEX produced more total QALYs and lower total costs than BTZ/DEX it was dominant.

Table 12: Summary of base case results (discounted): with PAS

With PAS	Total			Incremental vs LEN/DEX			ICER vs LEN/DEX	
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Cost per LYs gained, £	Cost per QALYs gained, £
PANO/BTZ/DEX	£140,388	2.585	1.712	–£8,909	0.080	0.066	Dominant	Dominant
LEN/DEX	£149,297	2.505	1.646					

Direct comparison based on the PANORAMA-1 trial using data for the subpopulations with at least 2 prior lines of treatment including an IMiD and BTZ including only those responding to the prior BTZ.

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; PAS, Patient Access Scheme; QALY, quality-adjusted life year..

Source: Novartis' addendum

The disaggregated PFS and OS results are also presented in the Novartis' addendum in Tables 33, 34 and 35. In terms of QALYs, PANO/BTZ/DEX had higher QALYs in the pre-progression period of 0.29, 0.27 of which were due to the period off treatment. In contrast it resulted in 0.22 less QALYs as BTZ/DEX patients spent longer periods in the post-progression phase. As discussed in the critique of the original Novartis submission, the ability of the analysis to have captured acute AEs impact on quality of life is questionable, since health related quality of life measurements were made at a fixed point in each cycle, thus likely missing the effects of adverse events emerging and resolving within the intervening periods.

Table 35 of the addendum shows that savings occur in the PANO/BTZ/DEX arm post-progression period. The results show that while PANO/BTZ/DEX is associated with increased costs in the pre-progression phase, of £[redacted] and reduced costs by £[redacted] in the post-progression phase relative to BTZ/DEX, thus resulting in an overall cost-saving intervention. The bulk of the excess costs in the pre-progression phase are due to the drug acquisition costs, whilst the reduction in costs is influenced by the estimated mean survival advantage with PANO/BTZ/DEX, which after 55 weeks starts to diminish due to the survival curves crossing. This is a in important future of the analysis, because as evidenced by the cost-effectiveness analysis of PANO/BTZ/DEX vs. LEN/DEX, a longer post-progression period in the model is associated with costs that accumulate at a more rapid pace than that of QALYs, thus resulting in higher ICERs.

5.2.1.2. Deterministic sensitivity analysis

In the deterministic sensitivity analysis, ranges of cost per QALY results were obtained by varying input parameters one at a time between the upper and lower bounds of the 95% confidence interval. If the confidence interval was not reported, upper and lower limits for the sensitivity analysis were generated by adding or subtracting two times 20% of the mean.

The upper and lower confidence limits of PFS gave cost per QALY estimates ranging from -£326,725 to £160,516. This result confirms that the ICER is very volatile.

5.2.1.3. Scenario analysis

Here, the ERG list the assumptions of scenario analysis that were made by Novartis in the cost-effectiveness model:

- A discount rate of 5%, rather than 3.5%, was used;
- Time horizons of 5 and 10 years were used instead of 25 years;
- PFS for PANO/BTZS/DEX was modelled with the loglogistic, lognormal, Gompertz, exponential parametric functions and Kaplan-Meier instead of the Weibull model;
- Time to discontinuation was based on Kaplan-Meier estimates rather than a loglogistic model;
- OS for PANO/BTZS/DEX was modelled using approach 1, 2 and 3

In all cases, the ICER was dominant expect when using the approach 1 and 2 for OS modelling which showed the biggest on the incremental LYs and QLAYs and gave positive ICERs both above £100,00 per QALY gained.

The analysis of structural uncertainty was limited to exploring the four approaches to analyse survival, which through its effect on the duration of the post-progression phase is the most influential parameter in the model. This is a weakness of the analysis because of the small number (n=15 in PANO arm and n=21 in BTZ arm) of patients on which survival evidence is based from two cycles after cycle 55, the point at which the survival curve of PANO/BTZ/DEX crosses the survival curve of BTZ/DEX from above. In these circumstances it would have been appropriate to perform a sensitivity analysis assuming that no differences in survival remain after cycle 61, instead of extrapolating the observed differences indefinitely using the survival curves fitted to the data.

5.2.2. Probabilistic sensitivity analyses results

The results of the multivariate probabilistic sensitivity analysis of 1000 simulations are presented in Figure 27 (scatter plot of total QALYs and costs) and Figure 28 (scatter plot of incremental QALYs and costs) in Novartis addendum.

The probabilistic results presented are similar to the deterministic results. The ERG repeated the PSA on a number of occasions in the Company's model and the ICERs obtained were all dominant.

5.2.3. Conclusion

The ERG have verified the manufacturer's new deterministic base case result when using the final OS data. The ICER presented was dominant for the PANO/BTZ/DEX versus BTZ/DEX comparison when applying the new PAS with a simple discount of [redacted]%

The results of the probabilistic analysis are similar to those of the deterministic analysis.

The company's submission presents a number of scenario analysis, the results of which have been verified by the ERG. All those results are dominant except when modelling OS using the approach 1 and 2 as describe by the company.

However, the effectiveness evidence presented by Novartis presented some limitations. There was no documentation of the comparative distribution of baseline characteristics between treatment arms. Since the sample size was relatively small (n=72 in each arm), it is quite possible that the randomisation device used in PANORAMA-1, the source of the effectiveness data, may not have achieved covariate balance across the two trial arms. This potential confounding issue is particularly important given that the time to event analyses undertaken by Novartis were unadjusted for baseline characteristics.

The analysis of structural uncertainty was limited to exploring the four approaches to analyse survival, which through its effect on the duration of the post-progression phase is the most influential parameter in the model. This is a weakness of the analysis because of the small number (n=15 in PANO arm and n=21 in BTZ arm) of patients from cycle 61, just two cycles after the point at which the survival curve of PANO/BTZ/DEX crosses the survival curve of BTZ/DEX from above. In these circumstances it would have been appropriate to perform a sensitivity analysis assuming that no differences in survival remain after cycle 61, instead of extrapolating the observed differences indefinitely using the survival curves fitted to the data. It is noted that the company did not perform the corresponding analysis that Novartis performed in response to the recommendation by the ACD for the PANO/BTX/DEX vs. LEN/DEX comparison to the comparison of the former with BTZ/DEX, whereby the costs of active treatment post-progression were omitted from the analysis.

Other areas of uncertainty remain in terms of the effect of PANO/BTZ/DEX on health related quality of life associated with the incidence of acute AEs, which might not have been adequately measured in the PANORAMA-1 trials from which the evidence of relative effectiveness for the triple therapy relative to BTZ/DEX was obtained for the Novartis cost-effectiveness model.

In spite of this the evidence suggesting PANO/BTZ/DEX is cost-effective relative to BTZ/DEX in patients with at least two prior lines of therapy including an IMiD and BTZ in patients who responded to prior BTZ is of higher quality than the comparative evidence for PANO/BTZ/DEX vs. LEN/DEX in patients with at least two prior therapies including an IMiD and BTZ.

6. References

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