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

Erratum

Report commissioned by:

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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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Declaration of competing interest of the authors

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 submission, report writing and editing.
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Contents

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the location of the change in the original ERG report and the nature of the change.

Page no.	Change
2	The ERG added an acknowledgement.
14	The ERG marked the OS HR in the subgroup of people who had at least 2 prior lines of treatment using Naïve comparison, Unadjusted Cox, and MAIC methods as CIC in Section 1.2.
15	As above
15	Novartis has requested a text around indirect method (MAIC) to be changed. The text has been amended for clarity.
25	Novartis has requested a text around the use of BTZ based regimen in the 3rd line to be changed. The ERG had amended the text and added a paragraph: **"According to the reimbursement algorithm, if a patient has BTZ at induction, then either LEN (NCDF funded) or BTZ (TA129) can be used in the 2nd line. If BTZ is used as 2nd line, then the patient would receive LEN/DEX (TA171). The combination of PANO/BTZ/DEX can then be used instead (as 3rd line). According to our clinical expert, a medical decision could be made to use BTZ in 3rd line therapy after BTZ/DEX induction and LEN as 2nd line, which goes beyond the reimbursement decision. Then the combination of PANO/BTZ/DEX could be used instead as 3rd line."**
27	Novartis has requested a text around the number of patients eligible for PANO use to be changed. The company pointed out the section of the submission where the calculation was presented. The text has been amended accordingly.
32	Novartis has requested a text around the literature searches to be changed as the literature search was within the 6 months limit in line with the guidance. The text has been amended.
52	Novartis clarified that the number patients analysed for the PFS was cited incorrectly in their submission. The ERG has changed the text: "The ERG **was** not clear why the results for PFS **were** only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm. **Following the Factual Error Check, Novartis clarified that PFS analysis was actually conducted for the full analysis set i.e. 387 and 377 for the treatment arm and control arm, respectively."**
56	As above. Sentence has been deleted: **"Once again, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm"**.
91	The company requested the text to be amended around HRQL data use in the analysis. The text has been amended accordingly.
92	Novartis has requested a text around indirect method (MAIC) to be changed. The text has been amended for clarity.
123	Marking added to median age at diagnosis is 73.1 years in Section 5.2.3.1
142	Figure 31 label d) and e) relabelled as a) and b).

143	As above
144	Novartis stated that using the undiscounted figures instead of the discounted when comparing with reported KM figures could be more accurate. The ERG has changed the text accordingly.
151	Table 68: The Median treatment duration of the subpopulation of patients who had received at least two prior lines of treatment including thalidomide only and bortezomib based regimen should be 4.8 months. Additionally, the source should say: Adapted from Appendix 17 Table 28
172	Novartis pointed out that Table 88 and 90 showed incorrect data. These tables have been amended accordingly.
173	As above
174	Probabilistic results added Table 94 in Section 7.4.2.4 and wording "**The ERG ran a PSA with these new parameters. The probabilistic ICER £[redacted]. The 95% CIs around key model outcomes are presented in Table 94 below:"**

1. Summary

The text cited directly from the submission by Novartis (hereafter referred to as "the submission") is presented with quotation marks in italic and cross referenced. Note that the specific sections/pages of the submission referred to by the ERG in this report apply to v0.2 of the submission. In addition, the ERG reviewed the economic analysis presented in the Appendix 17 of the submission.

Given the nature of the STA process, the ERG was bound to time constraints. Most of the initial review process was dedicated to finding the methodological and logical errors in the submission and its' Appendix 17. Some updated figures were submitted by the company during the clarification stage.

1.1. Scope of the submission

The 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 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).

1.2. Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence of the submission is based on the PANORAMA-1 trial that is a phase 3, multicentre, randomised, double-blind, placebo-controlled study in patients with rrMM who have received between one and three prior treatment regimens. In this trial patients received either the triplet therapy PANO/BTZ/DEX or BTZ/DEX. The primary efficacy endpoint of the trial was progression free survival. An extension of 3.9 months was demonstrated (according to investigator assessment). The secondary efficacy endpoints include overall survival, response rate, response duration and time to progression. No mature overall survival results are presented in the submission.

The clinical effectiveness evidence for patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen relies on indirect comparison of the PANORAMA-1 trial (the intervention arm) and the pooled data from MM-009 and MM-010 trials for LEN/DEX. The indirect treatment methodology used to estimate the relative effectiveness between PANO/BTZ/DEX and LEN/DEX treatments was the Unadjusted Cox regression. The hazard ratios generated were 1.061 and 1.075 for progression free survival and overall survival, respectively; no confidence intervals were estimated by the company. The company also provided the results of indirect comparisons using naïve comparisons

(HR 1.190 and 0.959 for PFS and OS, respectively), and the matching adjusted indirect comparison method (HR 1.108 and 1.413 for PFS and OS, respectively, which, **compared with the other methods, made a more comprehensive adjustmen**t for baseline differences across treatment groups.

1.3. Summary of submitted cost effectiveness evidence

The cost-effectiveness systematic review of the literature undertaken by Novartis identified 14 studies. The quality assessment was carried out for only six studies out of 14. They compared effectiveness and cost-effectiveness of various treatment options for relapsed or relapsed and refractory multiple myeloma. The modelling approaches of these studies informed the structure of their model.

Novartis developed two cost-utility models as decision analytic semi-Markov model. The structure of the model for the economic analysis of the full PANORAMA-1 trial population (i.e. people who have received at least one prior therapy) includes two pre-progression health states, two post-progression health states and the death health state.
The model for the economic analysis of the subgroup of people who have received at least two prior therapies including IMiD and BTZ regimen includes two pre-progression health states, one post-progression health state and the death health state.

Both models are reported to capture the three key aspects of multiple myeloma that are affected by disease progression and the effects of treatment, namely survival, health related quality of life and costs.

Novartis model produced an ICER for PANO/BTZ/DEX triplet compared to BTZ/DEX of £79,025 cost per QALY gained for the full trial sample analysis of people who have received at least one prior therapy. The probability of PANO/BTZ/DEX being cost-effective at the £30,000 threshold was 0%.

In the subgroup of those patients with ≥2 prior therapies, including IMiD and BTZ, the ICER of PANO/BTZ/DEX vs LEN/DEX was £[redacted] and £[redacted] per QALY gained for subcutaneous and intravenous BTZ administration, respectively

1.4. Commentary on the robustness of submitted evidence

1.4.1. Strengths

- The economic models comparing PANO/BTZ/DEX with BTZ/DEX, in the full trial population, and PANO/BTZ/DEX with LEN/DEX in subgroup of people who had at least 2 prior lines for treatment

that THAL induction is based on a trial, but in practice, most people will receive BTZ/DEX as induction treatment. This, however, contradicts the company's claim based on BCSH guidance that many UK patients receive THAL based therapy at induction (page 38).

Following the induction, patients who are eligible go through high dose chemotherapy (ASCT). Following the ASCT, patients who have a relapse of typically 18 months – 2 years can receive ASCT again. Patients who have a shorter remission or are no longer suitable for ASCT for any other reasons will receive LEN/DEX treatment, which is the relapse setting.

Moreover, the company note that usage of PANO along with bortezomib (BTZ) and dexamethasone (DEX) provides another treatment option for MM. The ERG sought the views of an expert on use of different medications on different lines. It was explained that if a patient had THAL at the 1st line and then relapsed, BTZ/DEX could be used in the 2nd line. The combination of PANO/BTZ/DEX could be then be used instead if superior to BTZ/DEX (as2nd line). If the patient had BTZ at induction, then LEN in the 2nd line can be used (NCDF funded).

According to the reimbursement algorithm, if a patient has BTZ at induction, then either LEN (NCDF funded) or BTZ (TA129) can be used in the 2nd line. If BTZ is used as 2nd line, then the patient would receive LEN/DEX (TA171). The combination of PANO/BTZ/DEX can then be used instead (as 3rd line). According to our clinical expert, a medical decision could be made to use BTZ in 3rd line therapy after BTZ/DEX induction and LEN as 2nd line, which goes beyond the reimbursement decision. Then the combination of PANO/BTZ/DEX could be used instead as 3rd line.

who have received between one and three prior treatment regimens". However, the following section 4.3.2 describes the inclusion criteria of the PANORAMA-1 trial as "*patients with relapsed or relapsed and refractory MM who had received one to three previous treatments".* Also in Section 5.1.1 on page 136 the company mention "*a systematic review was performed in August 2013 to identify economic evidence relating to second-line therapy of patients with rrMM"*. This occurs in several instances throughout the submission.

Therefore the ERG is generally concerned with the confusion that this creates for the PANO indication. The ERG believe that rrMM makes reference to the subgroup analysis of patients who had received at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (the Appendix 17 of the submission).

Our clinical expert however, pointed to the fact that when clinicians talk of rrMM they typically mean relapsed, relapsed and refractory and primary refractory MM as defined in the paper published in Rajkumar et al.[1]

Novartis may also confuse the reader on page 11 of the Appendix 17 of the submission where they analyse the patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen which state that the "*economic analysis presented in this Appendix considers patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a bortezomib based regimen".*

The company also note that approximately 1300 patients in England and Wales would be eligible to receive PANO annually **– a title of the paragraph 2 on page 41. The figure is calculated from the HMRN data and equals to 1348 patients. The detailed calculation is only presented later on in Section 6 of the submission.**

The company state that there is a lack of epidemiological data specific to patients with rrMM, but that figures are available for the number of people with MM. Based on CRUK figure, there were 4039 diagnoses in England in 2011 (4792 diagnoses in the UK). Again, it is not really clear why Novartis refer to rrMM population that is defined as the group that had two prior lines of treatment.

Novartis also stated that 37% of patients with MM in England survived cancer for 5 years or more[2]. However, the ERG found more up-to-date figures. Net 5 year survival in England and Wales was 47%[3]. The company cite "*5 year or more survival*" in England in the period of 2005-09 that is 37% from the .

[1] Rajkumar SV, Harousseau JL, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Blood 2015:117;15:4691-5.

[2] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/ (Accessed 17 June 2014).

[3] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero (Accessed 9 July 2015).

The brand name Farydak (sometimes spelt Faridak) was omitted in the company literature searches. The ERG clarified the rationale for this omission and the company replied that the omission has not impacted on the identification of relevant studies. The ERG ran scoping searches to test this point and reached a similar conclusion.

Within the submission, the company observe the paucity of mature trial data and, we note, is aware of further data that is now available to them. In view of additional data being available the ERG asked the company to update their literature searches. The company declined to do so.

In principal, the search syntax and search protocol was adequate to meet the requirements of this submission. We note, however, that the literature searches are now seven months old.

4.1.1.2 Indirect and mixed treatment comparisons

Separate searches for indirect and/or mixed treatment comparators were not undertaken for this submission. The ERG notes however that the range of comparators used in the literature searching is broader than required in the scope.

4.1.1.3 AEs

Separate searches for AEs were not undertaken for this submission. The ERG clarified the rationale for this decision and the company responded that they were aware of all the AE data for PANO.

Given the noted AE profile, the ERG would still have preferred that separate searches were conducted to look beyond one study which has driven this submission.

4.1.1.4 HRQL

Systematic searches were undertaken to identify utility and health related quality of life data. In total, two searches were made.

Search one (2003-2013) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)

Search two (2013-2014) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)
3. (terms for thalidomide or bortezomib or lenalidomide or pomalidomide or carfilzomib or ixazomib or panobinostat)

Literature searches were carried out in MEDLINE, MEDLINE in Process and EMBASE all via OVID. The searches were limited to human-only populations and to studies published in English.

One of the main commentary of the ERG is the use of terms relapsed and relapsed and refractory multiple myeloma. The ERG is generally concerned with the confusion that this creates for the PANO indication. The ERG believe that rrMM makes reference to the subgroup population analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

Additionally, according to the final NICE scope, time to next treatment was one of the outcomes to be analysed. However, Novartis do not give a valid explanation why it was excluded.

The ERG is generally concerned with absence of stopping rule that is the UK practice at cycle 4. As noted before, this rule was not implemented in the PANORAMA-1 trial and patients continued treatment up to cycle 12. Moreover, as noted by the company "*there is a notable difference between the way bortezomib was administered in PANORAMA-1 compared with current UK practice"*. Patients do not continue BTZ treatment beyond cycle 8 in the UK. Although this was implemented in the modelling approach as the model allows for 10% of the population to continue treatment beyond cycle 8 (this is further discussed in Section 5.1.2).

4.2 Summary of submitted evidence

The company present the analysis of the efficacy outcomes from PANORAMA-1 trial at the data cut-off of 10 September 2013 and OS data at the data cut-off of 18 August 2014. On page 135 they state that the further trial data would become available in May/June 2015.

The ERG sought clarification information on final trial data. Novartis stated the final OS data is planned to be published in December at the 57th ASH Congress, should the required number of events happened in time for data submission.

4.2.1 Progression free survival

The company present the PFS results as the primary outcome from PANORAMA-1.

In Table 11 we report the results at the data cut-off of 10 September 2013 as per investigator assessment, as per independent review, as well as the multivariate Cox model analysis. As noted in Section 4.1.5, the ERG has clarified that final PFS analysis was performed at the first data cut off (September 2013) since 467 PFS events were recorded at that time.

The ERG **was** not clear why the results for PFS **were** only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm. **Following the Factual Error Check, Novartis clarified that PFS analysis was actually conducted for the full analysis set i.e. 387 and 377 for the treatment arm and control arm, respectively.**

Subgroup	Event, %	Median PFS (95% CI), months	Cox model HR (95% CI), Log-rank p value
PANO/BTZ/DEX	*54.5*	*12.25 (9.46 to 14.62)*	*0.66 (0.50 to 0.86)*
PBO/BTZ/DEX	*70.7*	*8.54 (7.72 to 10.41)*	
Two or three prior lines of therapy			
PANO/BTZ/DEX	*52.6*	*11.99 (9.46 to 13.70)*	*0.64 (0.50 to 0.83)*
PBO/BTZ/DEX	*66.2*	*7.62 (6.01 to 8.67)*	
Prior BTZ use			
PANO/BTZ/DEX	*58.0*	*11.04 (8.34 to 13.70)*	*0.58 (0.44 to 0.77)*
PBO/BTZ/DEX	*68.9*	*7.56 (5.88 to 7.89)*	
No prior BTZ use			
PANO/BTZ/DEX	*50.0*	*12.48 (10.18 to 14.16)*	*0.68 (0.53 to 0.87)*
PBO/BTZ/DEX	*67.8*	*8.64 (7.98 to 10.84)*	

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

Source: Submission Table 15

Additionally an analysis of PFS results according to baseline characteristics. In most pre-specified subgroups considered PFS results favoured for the PANO group versus (vs.) the control group. It should be noted that the CI of the HR are crossing 1 for the subgroups: other ethnic origin, no previous use of IMiD drugs, Americas as geographical regions, pooled regions, normal risk of cytogenetic. However, none of the p values of the pre-specified subgroups considered are statically significant.

4.2.2 Response

The overall response rate is relatively similar for patients treated with PANO/BTZ/DEX vs. placebo/BTZ/DEX: 60.7% and 54.6%; p = 0.09. However, the proportion of patients achieving a CR or nCR was approximately two-fold higher in the PANO/BTZ/DEX group than in the placebo/BTZ/DEX group: 27.6% vs. 15.7%; p = 0.00006.

Results from a landmark analysis of data from PANORAMA-1 showed that patients achieving CR/nCR had a longer median PFS compared to patients achieving PR in both treatment groups for each time point evaluated.

Table 14: Landmark analysis for PFS response according to response status in the PANORAMA-1

Landmark time and treatment group	Number of patients		Median PFS after landmark time, months		HR (95% CI)
	with CR/nCR	with PR	Patients with CR/nCR	Patients with PR	
6 weeks					
PANO/BTZ/DEX	*12*	*57*	*NE*	*12.55*	*0.33 (0.12 to 0.89)*
PBO/BTZ/DEX	*3*	*57*	*15.80*	*10.18*	*0.85 (0.19 to 3.90)*
12 weeks					
PANO/BTZ/DEX	*49*	*107*	*16.49*	*10.32*	*0.40 (0.25 to 0.65)*
PBO/BTZ/DEX	*23*	*122*	*14.13*	*9.69*	*0.62 (0.36 to 1.07)*

The use of the terms relapsed, and relapsed and refractory multiple myeloma create some confusion. The ERG is generally concerned with the impact that this may have when considering the evidence provided for the different PANO indications.

The ERG is also concerned with the efficacy data used for the control arm since the use of BTZ does not correspond with that recommended in NICE guidance and will impact on the clinical outcomes from the model. Firstly, there is no 4-cycle stopping rule for the BTZ/DEX arm in the PANORAMA-1 trial as per recommended in the NICE TA129 guidance. Secondly, patients continued treatment up to cycle 16 instead of cycle 8 as per BTZ label. This would have an impact on the clinical outcomes from the model.

The HRQL was not measured in PANORAMA-1 trial during TFI therefore it was necessary **to extrapolate from the last cycle of treatment (full trial sample analysis) or use the utility reported in Acaster et al. (subgroup analysis)**.

Critique on efficacy outcomes:

- There are also a few issues with the reported PFS and OS. Different numbers were observed by investigator and independent review and Novartis do not provide an explanation to this. Additionally, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm as they claim that final PFS was observed;
- The company also present a summary of sensitivity analysis around PFS, but no details on parameter change were presented;
- Importantly, no mature OS data for the PANORAMA-1 trial have been reported in this submission.

Novartis present three subgroup population in the submission, but does not make a reference to the third group until the later stage where the indirect and mixed comparison methods are discussed, which serves as a basis for subgroup analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

One of the weaknesses of the clinical effectiveness evidence for the PNAO vs. LEN comparison is that there is no direct trial-based comparison between Len and the primary comparators defined in the scope, therefore the submission relies on indirect comparison.

Critique on the indirect and mixed treatment comparisons (Section 4.10):

- This section appears in the submission without any explanation of how it relates to the effectiveness and cost-effectiveness of PANO in relation to the main incremental analysis for the population of interest. It could be interpreted as indicating that BTZ/DEX is an inappropriate comparator of PANO/BTZ/DEX for some patients who have received at least one prior therapy. This warrants further discussion given that the authorised indication for PANO has yet to be determined;
- Novartis compare results of the duration of exposure and TTP/PFS reported from various trials with different comparators, however the ERG would like to insist that there might be many confounding

factors between the populations considered within these different trials therefore a direct comparison is not appropriate;

- Generally, the methods of indirect and mixed comparisons are poorly described. Novartis do not give many details on the methods used. The ERG is concerned with absence of the WinBUGS files as the company claimed that is what they have used for the common comparison method;
- A number tables in the section on indirect and mixed comparisons have errors and statistical significance is no systematically presented;
- Most importantly, all the evidence arising from these studies is likely to be affected by confounding, whether it is from observed differences across trials and trial arms in baseline characteristics, or unmeasured confounding. **Analyses unadjusted or partially adjusted** for baseline differences are likely to be biased (including the analyses using individual patient data, which also invalidly assume proportional hazards) **and those based on the MAIC method** suffer from low statistical power (as evidenced by the effective sample sizes).

starting ages in the model given that, in the UK, nearly 60% of patients are estimated to be diagnosed at the age of 70 or older and the median age at diagnosis is **73.1** years. This compares with a starting age in the model of 62.1 years.

5.2.3.2 Clinical effectiveness data

Most of the effectiveness data for the full trial sample analysis in the economic model was drawn from PANORAMA-1. The one exception is that progression data for those receiving LEN/DEX after failure to the initial treatment came from MM-009 and MM-010 as data for progression in patients receiving subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial.

The health states between which patients move in the model were defined in terms of progression or non-progression of illness. The risk of progression or death in a given cycle was modelled by fitting survival functions to Kaplan-Meier plots of patient level PFS data. Because the risk of progression and the risk of death were both required by the model, the proportion of patients who progressed relative to those who had a PFS event (death or disease progression) was estimated for each cycle by a logistic regression. The model appears to follow the structure set out in the, as we have described in Section 5.1.2.2, although a more intuitive explanation of how the health states presented in Figure 37 in the submission correspond to the labels used in the excel model.

A similar survival analysis approach was adopted to the risk of treatment discontinuation. The modelled survival functions appeared to be implemented appropriately and transition probabilities similarly derived from the survival functions using standard methods.[4]

The fitting of survival functions to the observed data has not been replicated as part of this critique as the ERG have not had access to patient-level data from PANORAMA-1, MM-009 or MM010. Neither have the ERG replicated the results of the indirect treatment comparisons analysis. However, the following section makes some observations on the differences between the modelled survival estimates used in the cost-effectiveness calculations and the survival observed in PANORAMA-1.

In Section 7, we explored the impact on the ICER if patients were not required to discontinue BTZ therapy despite having less than minimal response at cycle 4, as per PANORAMA-1 trial, in order to reflect the efficacy used in the control arm of the model.

5.2.3.3 Mortality data

Modelled survival in the cost-effectiveness analysis should mimic the observed survival in PANORAMA-1 as all the mortality data in the full trial sample model, including for patients who proceed to LEN/DEX after PANO/BTZ/DEX or BTZ/DEX (although data on progression in this group was not collected as part of PANORAMA-1 and is based on MM-009 and MM-010 studies), is drawn from the trial.

The ERG noted that the modelled mean survival in the PANO group was greater than the median survival reported by PANORAMA-1 at the 18th August 2014 interim analysis (mean of 42.84 vs. median of 38.24 months) but that the reverse was true fort the PBO group (mean of 33.56 vs. a median of 35.38 months).

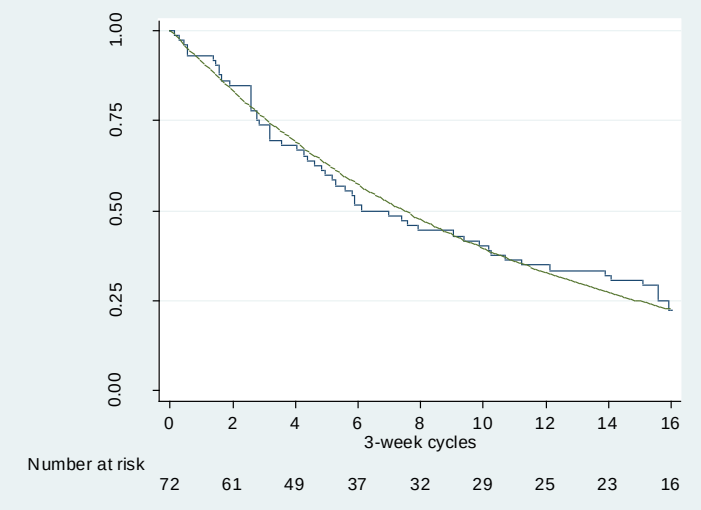
[4] Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

PANO/BTZ/DEX (four sets of results for an equal number of different indirect comparison methods applied to the full trial sample and three to the subpopulation with two or three prior lines of treatment). It was assumed that these HRs were applicable to the subgroup under investigation (the subpopulation with at least two prior lines of treatment including IMiD and BTZ). It was not clear to the ERG why the submission had considered the set of results for the full trial sample in the PANO/BTZ/DEX arm of PANORAMA-1, in addition to the results for the subpopulation in their subgroup analysis rather than the three sets of results for the subpopulation of 2-3 prior regimens alone, nor how population with at least one prior line of treatment results should be interpreted in the context of the full trial sample results presented in the full trial sample analysis.

The transition probabilities for risk of treatment discontinuation were derived in the same way as for the risk of progression or pre-progression death. The same five parametric survival models were fitted to treatment discontinuation data from the PANORAMA-1 trial using the safety analysis set of patients (72 patients). Subsequently, AIC and BIC values are provided to justify the use of the exponential distribution to be the best fitting model amongst the five tested for discontinuation while on PANO/BTZ/DEX. The exponential model was considered the best model for BTZ/DEX responders. The Kaplan-Meier plots and fitted models are reported in Figure 31 below.

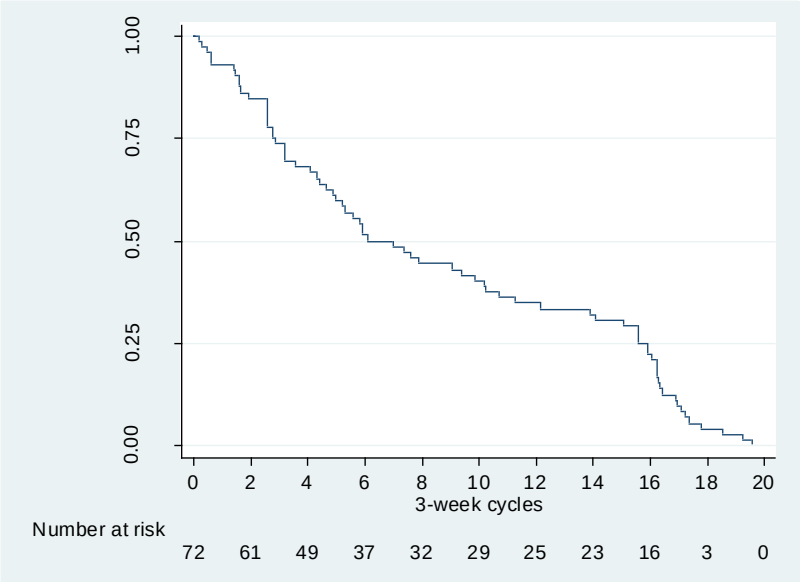
Figure 31: Proportion of patients without treatment discontinuation: subpopulation with prior IMiD and BTZ and ≥ 2 prior lines of treatment; a) Kaplan–Meier curve and fitted parametric models (PANO/BTZ/DEX – exponential model) for 48 weeks b) Kaplan–Meier curve presenting full follow-up data

a) PANO/BTZ/DEX – exponential model (48 weeks)



Source: Appendix Figure 4a)

b) PANO/BTZ/DEX – full follow up data



BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.
Source: Appendix Figure 4 a) and 4 b)

For the LEN/DEX group, unlike PFS and OS, treatment discontinuation cannot be compared between the two treatment regimens using indirect treatment comparisons because LEN/DEX is a continuous treatment. Comparing the median PFS and median treatment duration for the PANORAMA-1 full trial population (11.1 and 10.1 months) and the PANORAMA-1 subpopulation with two or three prior lines of treatment (9.5 and 9.2 months), it was assumed that the risk of treatment discontinuation for the full trial sample is 9.9% higher (11.1/10.1) than the risk of PFS in each model cycle and 3.3% higher (9.5/9.2) in the subpopulation.

Table 62 below summarises the approaches used to derived transition probabilities and their use in the model.

Table 62: Approaches used to derived transition probabilities and their use in the economic model

Parameter	*Data source*	*Model used for base case*	*Use of transition probabilities*
PANO/BTZ/DEX			
Risk of progression or death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level PFS data*	*Weibull*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of treatment discontinuation	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level treatment duration data*	*Exponential*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level OS data*	*Gompertz*	*Post-progression (derived as OS-PFS) PANO/BTZ/DEX*
Risk of experiencing adverse events	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level AE data*	*Occurrence probability*	*Pre-progression, Tx1, PANO/BTZ/DEX*
LEN/DEX[a]			
Risk of progression or pre-progression death (relative to PANO/BTZ/DEX)	*Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS*	*Hazard ratio*	*Pre-progression, Tx1, LEN/DEX*

Parameter	Data source	Model used for base case	Use of transition probabilities
Risk of treatment discontinuation	*Median PFS and median treatment duration published for MM-009/010*	*Hazard ratio*	*Pre-progression, Tx1 PANO/BTZ/DEX*
Risk of death (relative to PANO/BTZ/DEX)	*Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS*	*Hazard ratio*	*Post-progression, Tx1 (derived as OS-PFS) LEN/DEX*

[a] For LEN/DEX, to keep the model parsimonious, exponential distribution was applied.

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; Tx, treatment.

San Miguel et al. 2013[5], Dimopoulos et al 2009[6], Stadtmauer et al 2009[7]

Source: Novartis submission, Appendix 17 Table

For OS, the Kaplan-Meier curves and the fitted Gompertz distribution for PANO/BTZ/DEX patients in the subgroup of ≥2 prior therapies did not display the divergence between the actual and predicted outcomes observed for the full PANORAMA-1 trial sample, as shown in Figure 32 (compare this with Figure 26). In the subgroup analysis, the model underestimates PFS compared with the clinical trial results for patients people who have received at least 2 previous treatments including an IMiD and BTZ receiving PANO/BTZ/DEX (12 months vs. 12.5 months). Modelled OS is also underestimated compared with the clinical trial (26.2 months vs. [redacted] months). Median OS derived from the model of 26.2 months or 2.18 years **corresponds in the model with a mean survival of 2.43 years (undiscounted) or 27.46 months. Although, the ERG have validated the median OS, it should be noted that the company do not give an explanation on how the median OS was derived.** The median survival figures are presented in Table 72 of this report. As PFS and OS for LEN/DEX were derived from the indirect treatment comparison, it was not possible to compare the Kaplan-Meier curves with the modelled data. Median survival was not reported for patients receiving LEN/DEX, while mean survival was 2.22 years derived from the full trial population data using MAIC approach. The mean survival based on Unadjusted Cox method using the subpopulation data was 2.19 years. Details of the MAIC and Unadjusted Cox approaches for indirect treatment comparisons are given in Section 4.3 of this report.

[5] San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet oncology 2013;14:1055–66.

[6] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52.

[7] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Table 68: Clinical data for subgroup populations

Outcome	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)*	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT including THAL only and BORT)*
Median PFS (PANO/BTZ/DEX)	*12.5 months*	*12.5 months*
Median OS (PANO/BTZ/DEX)	[redacted] *months*	[redacted] *months*
Median treatment duration (PANO/BTZ/DEX)	*4.2 months*	***4.8** months*

Source: Adapted from Appendix 17 Table 28

Other limitations are described by Novartis:

- Post-progression treatments have not been reported for LEN/DEX therefore the impact of difference in the post-progression treatments (between PANO/BTZ/DEX vs. LEN/DEX) on survival could not be assessed;
- there was a mismatch between the efficacy data from Dimopoulos et al. 2009[8], Stadtmauer et al. 2009[9] for the combined MM-009/010 trial data, used for the indirect treatment comparisons, and the data used for the treatment costs of LEN/DEX (TA171 NICE Guidance based on the European MM-010 trial only);
- four-weekly cost of LEN/DEX were rescaled to 3-weekly cost, which may also introduce some bias;
- there may be some double counting of terminal care costs as it is not clear from the study of Gooding et al whether end of life care costs were included in their study or not. Novartis claim that because the difference between the OS profiles of the PANO/BTZ/DEX and LEN/DEX is minor, the inclusion or exclusion of terminal care costs has a negligible impact on the results.

6.1 Critique of approach used

6.2.1. Critique of the modelling approach and structure

The structure of the model constructed by Novartis for the subgroup analysis appeared to be logical and had greater clarity than the full trial sample model in terms of the treatment of death and the correspondence between the two arms of the model (PANO/BTZ/DEX and LEN/DEX). The model followed the structure set out in Figure 29. The model structure and health states are justified with respect to previous models, including those developed for NICE submissions. The health states included in the model are the same as in the model presented by Novartis for the analysis of full PANORAMA-1 trial sample with the exception that there is no transition to the state LEN+DEX. Transition probabilities have been estimated using standard methods and the probabilities for the transitions in each time period sum to one.

Key features of the analysis are justified with reference to previous cost-effectiveness models and NICE's guide to the methods of technology appraisals. One aspect of the model design which is not justified is the choice of comparators. While the relevance of LEN/DEX as a comparator for

[8] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM–009 and MM–010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23 2147–52.

[9] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Table 87: Base-case ICER if HRs estimated using the Naïve comparison method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Naïve comparison' deriving HRs from full trial populations	*PANO/BTZ/ DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.009*	*-0.0066*	*£[redacted]*	*[redacted]*
	LEN/DEX	*£155,466*	*2.279*	*1.527*					
''Naïve comparison' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/ DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Table 88 Base-case ICER if HRs estimated using the Naïve comparison method – subcutaneous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Naïve comparison' *deriving HRs from full trial populations*	*PANO/BTZ/ DEX*	***£[redacted]***	*2.288*	*1.521*	***£[redacted]***	***0.009***	***-0.007***	[redacted]	***£[redacted]***
	LEN/DEX	***£155,466***	***2.279***	***1.527***					
'Naïve comparison' *deriving HRs from subpopulation (2 to 3 prior lines)*	*PANO/BTZ/ DEX*	***£[redacted]***	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Hazard ratios estimated using the Unadjusted Cox method

The ERG re-run the model using the Unadjusted Cox method to estimate the HRs for PFS and OS for the full trial population only since this method was used for the subgroup of patients with 2 to 3 prior lines of therapy in the base case.

Table 89: Base-case ICER if HRs estimated using the Unadjusted Cox method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Unadjusted Cox' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.004*	*-0.0230*	*[redacted]*	*[redacted]*
	LEN/DEX	*£152,456*	*2.292*	*1.544*					

Source: Produced by the ERG

Table 90: Base-case ICER if HRs estimated using the Unadjusted Cox method – subcutaneous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
***'Unadjusted Cox'** deriving HRs from full trial populations*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	***£**[redacted]*	*-0.004*	*-0.023*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£152,456*	*2.292*	*1.544*					

Source: Produced by the ERG

Hazard ratios estimated using the MAIC method

The ERG re-run the model using the MAIC method to estimate the HRs for PFS and OS for the group of patients with 2 to 3 prior lines of therapy only since this method was used for the full trial population in the base case.

We found that this amendment would decrease the ICER of 18% from £[redacted] to £[redacted] for intravenous BTZ administration and increase the ICER of 38% from £[redacted] to £[redacted] for subcutaneous BTZ administration.

Table 91: Base-case ICER if HRs estimated using the MAIC method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.461*	*0.2839*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£120,148*	*1.827*	*1.237*					

Source: Produced by the ERG

Table 92: Base-case ICER if HRs estimated using the MAIC method – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,148	1.827	1.237					

Source: Produced by the ERG

The ERG believe that this indirect comparison may be the preferred option to estimate the relative effectiveness between LEN/DEX and PANO/BTZ/DEX. The generated ICER for the subcutaneous administration of BTZ is £[redacted]. However, as explained in more details in Section 6.2.2.2 the MAIC estimates are likely to be unreliable and biased by unobserved confounding.

In addition the ERG re-run the model using the MAIC method with the cost of Lymphopenia set at a zero instead of £167; and the specialist visit frequency at every 2nd cycle instead of every cycle, the

Table 93: Base-case ICER if HRs estimated using the MAIC method with updated specialist visit frequency and zero cost of Lymphopenia – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,108	1.827	1.237					

Source: Produced by the ERG

The ERG believe that the generated ICER for the subcutaneous administration of BTZ of £[redacted] is the most plausible ICER for patients with 2 to 3 prior lines of therapy.

The ERG ran a PSA with these new parameters. The probabilistic ICER £[redacted]. The 95% CIs around key model outcomes are presented in Table 94 below:

Table 94: Values and 95% confidence intervals for the ERG's preferred assumptions

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£[redacted] (£[redacted] to £[redacted])	£[redacted] (£[redacted] to £[redacted])	1.521 (1.051 to 2.142)	0.257 (–0.451 to 0.820)	£[redacted]
LEN/DEX	£120,108 (£52,266 to £241,099)		1.237 (0.678 to 2.180)		

Source: Produced by the ERG