Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (part-review of TA171). Celgene's response to Technology Appraisal Committee's Critique of the Economic Case

A Critique of the Response Submitted by Celgene

Erratum

June 2014

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None.

Rider of responsibility for report

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Contribution of authors

Mariana Bacelar: Contributed to project management, the critique of the manufacturer's submission, report writing and editing.

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This document contains errata in respect of the ERG report in response to the manufacturer'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
58, 59, 64 – 74, 76	The ERG agreed that there were no issues with the method originally employed by Celgene to calculate the Bort PAS. Therefore the ERG updated all their ICER calculations to reflect the Bort PAS originally presented by the manufacturer.

Celgene mention that clinical opinion supports that the effectiveness of Bort is directly related to the number of cycles administered. The manufacturer say that this idea is reinforced by the Petrucci (2012) study, *which reports a TTP for only the 40% of patients who responded. This is still lower than that of the overall population (including non-responding patients) in the Taverna et al data (8.4 months vs 10.5 months).*

The manufacturer also state that data from MM-010 and MM-009 show that patients who respond to Len/Dex experience considerably longer TTP than those who don't. They go on to the conclude that as both OS and TTP/PFS are only available from the Taverna and the Hrusovsky studies, *the most reasonable comparison with bortezomib retreatment is one which assumes that treatment continues for longer than 8 cycles, provided the patient is continuing to receive benefit.*

Celgene therefore decide to model the use of Bort until disease progression. The manufacturer mention that scenario analysis explored the use of Bort for fewer cycles, but that the impact on the treatment effectiveness could not be assessed due to lack of evidence. Therefore only costs were reduced as a result of less treatment cycles, which Celgene deem to bias the results in favour of Bort retreatment.

Critique of the method applied in the revised analysis

Inclusion of the cost of corticosteroids in the comparator arm of the model

Celgene included the cost of Dex for 64% of the Bort patients, which is in agreement with the Taverna (2012) study.

From analysing the cost calculations in the excel model it seems that Celgene assumed the following dose regimen: 38mg per day, for 12 days every cycle, in the initial 4 cycles of treatment and then 4 days ever cycle after the fifth cycle. However, this was left to the ERG interpretation, by observing the calculations in the excel model, when it should have been clearly stated in the revised submission.

Len and Bort PASs

- Third-line Len PAS

The manufacturer explained that in the revised analysis the PAS within the model was changed in order to simplify the analysis and improve consistency between the methodology used in the intervention and comparator arms of the model. Overall the ERG are confused with the cost calculations associated with Len/Dex at third line in the comparator arm of the model.

- Bort PAS

Celgene have applied a 15% discount for 55% of Bort patients in the base case analysis. Clinical opinion sought by the ERG confirmed that the Bort PAS is hardly ever used in clinical practice.

Duration of Bort retreatment

Celgene claim that published evidence indicates that Bort retreatment is given for longer durations than 8 cycles. This statement should be interpreted with caution.

The manufacturer claim that both in the Taverna (2012) and Sood (2009) studies, patients receive up to 19 cycles of Bort. This should be clarified, as only a very small number of patients actually receive more than 8 cycles.

In Taverna (2012), the median duration of Bort retreatment is 3 cycles, with **90.4% of patients receiving 1 – 6 cycles** and only 2% of patients receiving more than 10 cycles (max 19 cycles). In the analysis undertaken by Sood (2009), 50% of patients received 5 cycles of Bort retreatment, with the range being 1 to 12 cycles.

Celgene also claim that patients receiving bortezomib for the first time in the APEX study were allowed to continue on bortezomib as maintenance after receiving an initial 8 cycles. The ERG have looked into the APEX study and 56% of patients completed 5 cycles of Bort while 29% completed 8 cycles of Bort.

Celgene also mention that the Bort SPC *does not specify a maximum number of cycles in patients who receive monotherapy*. Even though the wording in the SPC (Table 26) is reported by the manufacturer to back up this statement, it seems that the SPC clearly defines a maximum of 8 cycles of treatment with Bort.

Furthermore the manufacturer claim that only the Petrucci (2013a) study reported a maximum of 8 cycles but that this study did not present OS, PFS or TTP for all patients. The ERG believe this argument backs up our view on the matter and that the duration of Bort treatment is approximately 8 cycles. Furthermore Petrucci (2013b) which reports a maximum of 9 cycles of Bort presents OS and PFS (even though Bort is administrated along with chemotherapy).

The manufacturer state that data from MM-010 and MM-009 show that patients who respond experience considerably longer TTP than those who don't. They go on to the conclude that as both OS and TTP/PFS are only available from the Taverna and the Hrusovsky studies, *the most reasonable comparison with bortezomib retreatment is one which assumes that treatment continues for longer than 8 cycles, provided the patient is continuing to receive benefit.* Celgene therefore decide to model the use of Bort until disease progression.

6.0 Economic modelling results

In this section the ERG present the base case ICERs as well as the outputs of different scenario analyses.

To note is that a wide range of results could have been presented, resulting from all the possible combinations of alternative methodologies and assumptions used in the economic model. Each scenario considered could be presented for all the following alternatives:

- Duration of Bort retreatment (until disease progression, 19 cycles and 8 cycles)
- Inclusion of subsequent treatment lines vs considering second-line treatment only
- MOC method vs the CGP method

Since the number of potential scenarios is vast, we have presented the ones deemed more relevant. As a result, we do not present some of the scenarios ran by Celgene and we report some additional ones ran by the ERG.

For consideration of all the scenarios presented by the manufacturer, the reader should consult Section 5 in Celgene's revised submission.

Furthermore, the ERG emphasise that all ICERs presented in this section should be interpreted with extreme caution. As we have explained throughout the report, there are several flaws to the analysis undertaken by Celgene and the impact of these on the final ICERs is not easily predictable.

All values presented are discounted.

Base case

Celgene's revised cost-effectiveness analysis produced a dominant ICER over 25 years (Table 29).

The ERG corrected the errors related to the HR calculations and present the results in Table 30. It can be noted how the originally dominant ICER remained dominant after the ERG corrections and that there was a change only in the comparator arm of the model (the costs and QALYs for Len/Dex remained the same after the ERG corrections).

Both Table 29 and Table 30 present the base case ICERs including third and fourth-treatment lines and assuming that Bort is given until disease progression. In Table 31 we present the base case ICER with the ERG corrections but using the CGP method.

However the ERG have several concerns with the inclusion of subsequent treatment lines in the economic model and with the use of Bort until disease progression. Therefore in the next sections we present the ICERs for second-line patients only and consider different treatment durations for Bort.

Table 1. Len/Dex vs bortezomib retreatment – Celgene base case

Treatment	Costs	QALYs	LYs	ICER
Len/Dex	£104,864	3.05	4.69	Lenalidomide dominates
Bort retreatment	£118,498	2.24	3.28	
Incremental	-£13,634	0.81	1.41	

Table 2. Len/Dex vs bortezomib retreatment with ERG corrections (HRs)

Treatment	CPASosts	QALYs	LYs	ICER
Len/Dex	£104,864	3.05	4.69	Lenalidomide dominates
Bort retreatment	£110,274	2.11	3.08	
Incremental	-£5,410	0.94	1.62	

Table 3. Len/Dex vs bortezomib retreatment with CGP method and ERG corrections (HRs)

Treatment	Costs	QALYs	LYs	ICER
Len/Dex	£102,361	2.90	4.47	Lenalidomide dominates
Bort retreatment	£117,659	2.10	3.05	
Incremental	-£15,298	0.80	1.42	

In Table 32 we present the base case ICER for Len/Dex compared with chemotherapy (MP) reported by Celgene. The reported ICER is **£54,898** including all treatment lines. To note is that after 22 cycles, the cost of MP is <£1. Comparing Table 32 with Table 29, the ERG find the ICERs reported for chemotherapy quite surprising given the size of the HRs reported for Len/Dex vs chemotherapy (section 2.2). The following issues should be considered:

- The HRs reported for Len/Dex vs chemotherapy are four to five times fold the HRs reported for Len/Dex vs Bort. This suggests that Bort is significantly superior to chemotherapy with regards to OS and PFS. It is therefore surprising that the difference in QALYs between Bort and chemotherapy is only 0.18 QALYs.

- The total costs of chemotherapy are lower than the costs associated with Bort by around £68,000.

- The fact that the total treatment cost with chemotherapy is half of the total treatment cost with Len/Dex (when Bort is more expensive than Len/Dex) but that the QALY gain associated with chemotherapy compared to Len/Dex is similar to the QALY gain associated with Bort compared to Len/Dex produced very dissimilar ICERs.

It is therefore counterintuitive that chemotherapy, which supposedly performs much worse than Bort (according to the difference in HRs) in relation to Len/Dex, would produce ICERs above **£50,000** (potentially indicating that Len/Dex was not cost-effective) while the ICERs comparing Len/Dex with Bort suggest that Len/Dex dominates Bort.

In Table 33 and Table 34 we present the ICERs with the ERG corrections (related to the HRs calculations) and with the CGP method. As above, these ICERs include all treatment lines.

Table 4: Summary results vs MP – Celgene base case

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£104,864	3.05	4.69	**£54,898**
Melphalan + prednisolone	£50,450	2.06	3.35	
Incremental	£54,414	0.99	1.34	

Table 5. Len/Dex vs MP - ERG corrections (HRs)

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£104,864	3.05	4.69	**£34,076**
Melphalan + prednisolone	£36,796	1.05	1.57	
Incremental	£54,414	2.00	3.12	

Table 6. Len/Dex vs MP - CGP method and ERG corrections (HRs)

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£102,361	2.90	4.47	**£35,222**
Melphalan + prednisolone	£34,578	0.97	1.44	
Incremental	£67,782	1.92	3.03	

ICERs for second-line treatment

Here we present the ICERs for second-line treatment. Third and fourth-treatment lines have therefore been excluded from the analysis.

Celgene's revised cost-effectiveness analysis produced a **£4,126** ICER over 25 years (Table 35) for second-line patients.

The ERG corrected the errors related to the HR calculations and present the results in Table 36. This produced a final ICER of **£11,325** per QALY gained. Again, this increase was due to changes in the comparator arm of the model (the costs and QALYs for Len/Dex remained the same after the ERG corrections).

Both Table 36 and Table 37 present the second-line ICERs assuming that Bort is given until disease progression. In Table 37 we present the second-line ICER with the ERG corrections but using the CGP method.

To note is that when only second-line treatment is included in the analysis, the resulting ICERs are significantly higher than when all treatment lines are included, with the ERG corrected ICER being **££11,325.**

Table 7. Len/Dex vs bortezomib retreatment – second-line

Treatment	Costs	QALYs	ICER
Len/Dex	£98,231	3.05	**£4,126**
Bort retreatment	£94,893	2.24	
Incremental	£3,338	0.81	

Table 8. Len/Dex vs bortezomib retreatment with ERG corrections (HRs) -second-line

Treatment	Costs	QALYs	ICER
Len/Dex	£98,231	3.05	**£11,325**
Bort retreatment	£87,547	2.11	
Incremental	£10,684	0.94	

Table 9. Len/Dex vs bortezomib retreatment with CGP method and ERG corrections (HRs) - second-line

Treatment	Costs	QALYs	ICER
Len/Dex	£96,117	2.90	Lenalidomide dominates
Bort retreatment	£97,665	2.10	
Incremental	-£1,548	0.80	

In Table 38 we present the ICER derived with the MOC method for Len/Dex compared with chemotherapy (MP) for second-line patients with the ERG corrections. The reported ICER is **£43,708**. To note is that after 22 cycles, the cost of MP is <£1. In relation to the ICER presented in Table 36, the chemotherapy ICER is still considerably higher than the Bort ICER, even though the difference is less drastic than the one observed when all treatment lines are included.

Table 10. Len/Dex vs MP with ERG corrections (HRs) – second-line

Treatment	Costs	QALYs	ICER
LEN/DEX	£98,231	3.05	**£43,708**
Melphalan + prednisolone	£10,922	1.05	
Incremental	£87,309	2.00	

Duration of Bort treatment

In Table 39 we present Celgene's reported ICERs resulting from reducing the duration of Bort to 19 cycles. The ERG are confused with the calculations in the model as it seems that costs are still incurring after 19 cycles. We present the results for all treatment lines and for the second-line treatment alone. No note is that the ICERs reported in Table 39 do not include the ERG corrections.

In Table 40 we present the ICERs with the ERG corrections for 19 and 8 cycles for the second-line treatment only. We have not presented the corresponding ICERs for all treatment lines as we have focused our additional analysis on the second-line population and producing the ICERs for all treatment lines would have required further manipulation of Celgene's model.

Table 41 presents the ICERs with the ERG corrections for 19 and 8 cycles of Bort respectively, for the second-line treatment only and using the CGP method. To note is that when the duration of Bort is fixed (instead of administering the drug until disease progression) the CGP method produces higher ICERs than the MOC method, whilst when Bort is given until disease progression the CGP ICERs were lower than the ones produced with the MOC method.

In the analysis presented in Table 40 and Table 41 we have considered that the total costs for 8 and 19 cycles in the model were simply the sum of costs from cycle 0 to cycle and 8 and 19 respectively.

As we can observe, diminishing the treatment duration for Bort has a massive impact on the final ICERs. Even if Bort is given for 19 cycles (note that only 2% of patients received Bort for 19 cycles in the Taverna, 2012 study) the ICERs for the second-line treatment option are above **£30,000** per QALY gained.

When we consider the 8-cycle treatment regimen (to note is that more than 50% of patients in most comparator studies received Bort for less than 6 cycles) the final ICERs are generally above **£50,000** per QALY gained.

Table 11. Len/Dex vs bortezomib retreatment – 19 cycles

All treatment lines	**Costs**	**QALYs**	**ICER all treatment lines**
Len/Dex	£104,864	3.05	**£15,409**
Bort retreatment	£92,335	2.24	
Incremental	£12,528	0.81	
Second-line treatment only	**Costs**	**QALYs**	**2nd line ICER**
Len/Dex	£98,231	3.05	**£36,465**
Bort retreatment	£68,731	2.24	
Incremental	£29,500	0.81	

Table 12. Len/Dex vs bortezomib retreatment with ERG corrections (HRs) -19 and 8 cycles

Second-line treatment only	**Costs**	**QALYs**	**2nd line ICER**
Len/Dex	£98,231	3.05	**£38,871**
Bort retreatment 19 cycles	£61,558	2.11	
Incremental	£36,673	0.94	
Bort retreatment 8 cycles	£41,759	2.11	**£59,856**
Incremental	£56,472	0.94	

Table 13. Len/Dex vs bortezomib retreatment with CGP method and ERG corrections (HRs) - 19 and 8 cycles

Second-line treatment only	**Costs**	**QALYs**	**2nd line ICER**
Len/Dex	£96,117	2.90	**£42,808**
Bort retreatment 19 cycles	£62,057	2.10	
Incremental	£34,060	0.80	
Bort retreatment 8 cycles	£41,302	2.10	**£68,893**
Incremental	£54,815	0.80	

To note is that the effectiveness of Bort has not been changed in this exploratory analyses. As only costs were changed, we are potentially skewing the final ICERs upwards (as the incremental effectiveness of Len/Dex compared with Bort would theoretically increase).

Scenario analysis

Corrections applied to the CGP method

As mentioned in Section 2.1, the ERG have some concerns regarding the calculation of the weights used in the CGP method. We have corrected this accordingly. However, we could only apply this correction to the intervention arm of model, in that we could only change the survival curves used for OS, PFS and TTF for Len/Dex. We could not update the HR calculation, as this was not flexible in the excel model hence we could not update the survival curves in the comparator arm of the model.

Additionally, we cannot predict the impact on the final ICER resulting from not adjusting the curves in the comparator model. We also identified other problems with the CGP method which we could not address. For these reasons, this analysis is presented as scenario analysis, and was not incorporated in the base case values under the ERG corrected ICERs.

Table 42 and Table 43 present the ICERs for Len/Dex vs Bort with all ERG corrections (HRs and the CGP weights corrections). Table 42 presents the ICER for all treatment lines while Table 43 shows the ICER for second-line treatment only. Both ICERs assume that Bort is given until progression.

To note is that when the treatment duration with Bort was reduced to 19 cycles, the ICER for second-line patients was above £40,000 per QALY gained.

Table 14. Len/Dex vs bortezomib retreatment with CGP method and ERG corrections (HRs and CGP)

Treatment	Costs	QALYs	ICER
LEN/DEX	£108,722	3.11	Lenalidomide dominates
Bort retreatment	£127,241	2.31	
Incremental	-£18,520	0.79	

Table 15. Len/Dex vs bortezomib retreatment with CGP method and ERG corrections (HRs and CGP) – second-line

Treatment	Costs	QALYs	ICER
LEN/DEX	£102,296	3.11	Lenalidomide dominates
Bort retreatment	£104,384	2.31	
Incremental	-£2,088	0.79	

Alternative chemotherapy regimens

Celgene present the ICERs for Len/Dex compared with alternative chemotherapy regimens (CY-DEX). Even though this alternative analysis was not functioning in the excel model, once the ERG corrected this, the resulting ICERs were the same ones reported by Celgene in their revised submission (Table 44). The ICERs presented are for all treatment lines. The ERG have not corrected these ICERs as the resulting values would only be higher than the ones reported in Table 44.

Table 16. Len/Dex vs CY-DEX

Parameter	Base case assumption	Scenario analysis	Incremental		ICER
			Costs	QALYs	
Comparator	Defined by user	LD cyclophosphamide + MD-Dex	£56,548	1.00	**£56,738**
		HD cyclophosphamide + LD-Dex	£58,197	1.00	**£58,393**

Alternative distributions and comparator sources

As previously mentioned, the ERG are not very clear why some distributions were considered the best fit while others were deemed inappropriate. Visual inspection of the curves and assessment of the AIC and BIC statistics do not reveal clear preferences within a certain range of distributions. Therefore we have presented the final ICERs when different distributions are used. Table 45 reports the ICERs with the ERG corrections (HR calculations), include all treatment lines and assume that Bort is given until disease progression.

Again, it should be noted that the ICER estimates presented are based on what the ERG consider to be a flawed analysis. Therefore the alternative values here presented should also be interpreted with caution. The ICERs reported serve the main purpose of illustrating the variation in the base case ICER when different distributions are used.

As before, we also present the ICERs relating to second-line treatment and assuming Bort is given for 19 cycles (Table 46). The base case equivalent ICER is £38,871. When different distributions are considered separately, these estimate can go up to **£46,710**. Additionally, all these changes have been considered in isolation (i.e. changing one distribution at a time). If these were changed simultaneously, the impact on the final ICER would also be different.

The ERG also present the final ICER using the alternative sources suggested by Celgene and implemented in the model as scenario analysis (Table 47). We present the estimates for all treatment lines and assuming Bort is given until disease progression. After the ERG corrections were applied to the model, the final ICER increase up to **£600.**

Table 17. Use of alternative distributions in the economic model – all treatment lines included and Bort given until progression

Parameter	Base case assumption	Scenario analysis	ICER
Curve fit for OS	Gompertz with MOC method	Piecewise exponential MOC	Lenalidomide dominates
		Gamma MOC	
		Piecewise exponential CGP	
		Gamma CGP	
Curve fit for PFS	Gamma with MOC method	Lognormal MOC	
		Log-logistic MOC	
		Lognormal CGP	
		Log-logistic CGP	
Curve fit for TTF	Gamma with MOC method	Lognormal MOC	
		Log-logistic MOC	
		Lognormal CGP	
		Log-logistic CGP	

Table 18. Use of alternative distributions in the economic model – second-line treatment and Bort given for 19 cycles

Parameter	Base case assumption	Scenario analysis	Incremental		ICER
			Costs	QALYs	
Curve fit for OS	Gompertz with MOC method	Piecewise exponential MOC	£39,153	1.32	**£29,752**
		Gamma MOC	£38,017	1.11	**£34,116**
		Piecewise exponential CGP	£36,491	1.20	**£30,393**
		Gamma CGP	£35,461	0.95	**£37,415**
Curve fit for PFS	Gamma with MOC method	Lognormal MOC	£37,711	0.95	**£39,777**
		Log-logistic MOC	£37,199	0.94	**£39,367**
		Lognormal CGP	£34,070	0.79	**£43,041**
		Log-logistic CGP	£34,065	0.79	**£42,905**
Curve fit for TTF	Gamma with MOC method	Lognormal MOC	£39,179	0.94	**£41,531**
		Log-logistic MOC	£38,952	0.94	**£41,299**
		Lognormal CGP	£36,533	0.80	**£45,913**
		Log-logistic CGP	£37,162	0.80	**£46,710**

Table 19. Use of alternative sources for Bort effectiveness– all treatment lines included and Bort given until progression

Parameter	Base case assumption	Scenario analysis	Incremental		ICER
			Costs	QALYs	
Source of Bort retreatment evidence	OS & PFS: Taverna 2012	OS & PFS: Celgene MTC	£362	0.60	**£600**
		OS & PFS: Hrusovsky 2010	£153	1.09	**£141**

Bort PAS

As mentioned before, one of the key drivers of the final ICER is the total cost of Bort in the analysis (whether through the length of treatment administration or the cost of the drug).

When the Bort PAS is removed from the economic analysis, we can observe that for all treatment lines considered, Len/Dex dominates Bort. When only second-line treatment is considered, the ICER using the MOC method is £5,428 and dominant with the CGP method.

When 19 cycles of Bort are considered, the MOC method produces an ICER of £34,883 and when 8 cycles of Bort are considered the equivalent ICER is £57,322.

It is noticeable how the cost of Bort (changed through the PAS) and the length of the treatment have a major impact on the final ICER. Therefore these two issues should be carefully considered by the Committee.

Table 20. Len/Dex vs bortezomib retreatment with ERG corrections (HRs) with no Bort PAS

Treatment	Costs	QALYs	ICER
Len/Dex MOC	£104,864	3.05	**Lenalidomide dominates**
Bort MOC	£115,837	2.11	
Incremental MOC	-£10,973	0.94	
Len/Dex CGP	£108,722	3.11	**Lenalidomide dominates**
Bort CGP	£133,935	2.31	
Incremental CGP	-£25,213	0.79	

Table 21. Len/Dex vs bortezomib retreatment with ERG corrections (HRs) with no Bort PAS – second-line treatment

Treatment	Costs	QALYs	ICER
Len/Dex MOC	£98,231	3.05	**£5,428**
Bort MOC	£93,109	2.11	
Incremental MOC	£5,121	0.94	
Len/Dex CGP	£102,296	3.11	**Lenalidomide dominates**
Bort CGP	£111,078	2.31	
Incremental CGP	-£8,781	0.79	

Alternative utilities

As previously mentioned, the ERG are not very confident that the scenario analysis undertaken by Celgene addresses the Committee issues in full. However we present the final ICERs when different sources are used. Table 50 reports the ICERs with the ERG corrections (HRs), include all treatment lines and assume that Bort is given until disease progression.

Table 22. Len/Dex vs bortezomib retreatment with ERG corrections (HRs) using different utilities sources

Treatment	Costs	QALYs	ICER
Len/Dex McKenzie & van der Pol	£104,864	2.89	**Lenalidomide dominates**
Len/Dex Kontodimopoulos		2.95	
Len/Dex Palumbo		2.96	
Bort retreatment McKenzie & van der Pol	£110,274	1.95	
Bort retreatment Kontodimopoulos		1.99	
Bort retreatment Palumbo		2.11	
Incremental McKenzie & van der Pol	-£5,410	0.93	
Incremental Kontodimopoulos		0.96	
Incremental Palumbo		0.85	

HRs used in the analysis

Since the effectiveness of Len/Dex compared with Bort raised several concerns during the previous Committee meeting the Committee suggested that Celgene presented a model that assumed Len/Dex and Bort to have equal effectiveness (that is, assuming a HR of 1 throughout the analysis). However, Celgene did not present such analysis.

The ERG have replaced the HRs used in the economic model by HR = 1, to understand the impact of assuming the same effectiveness for Len/Dex and Bort. As expected, the incremental QALY gain was close to 0, and so the final ICER depends entirely on the difference between the total costs of the two treatment regimens. The total costs, in their turn, will depend on the duration of Bort treatment. So the final ICERs obtained with HR=1 vary:

- When Bort is given until disease progression: Len/Dex dominates.
- When Bort is given for 19 or less cycles: the final ICER is >£1,000,000.

Unadjusted analysis

One of the ERG main concerns with Celgene's analysis is the series of adjustment processes applied to the survival models. Therefore it would have been extremely helpful if Celgene had run an unadjusted analysis, removing all potential bias from the different models. More specifically, Celgene could have run a model where intervention and comparator curves were unadjusted as well as with unadjusted HRs.

To note is that Celgene claim to use unadjusted HRs as scenario analysis. However, as the ERG have pointed in their report, these HRs are not truly unadjusted as they are still adjusted for the MM studies population characteristics.

Len vs placebo

The Committee also recommended that Celgene run a model that compared lenalidomide with placebo because it would be based on high-quality data from MM-009 and MM-010. Unfortunately, Celgene did not run such analysis.

Sequence of treatments

The Committee recommended including sequences of Len/Dex followed by Bort compared with Bort followed by Len/Dex (without asymmetry between the Len/Dex and comparator arms).

After the ERG corrections (HRs) were applied to the model, comparing Len/Dex followed by Bort compared with Bort followed by Len/Dex produced an ICER of £8,758.

To note is that running this scenario was one of the options provided in the excel model. However, due to time constraints, the ERG could not verify how this scenario was run in the model.

Sensitivity analysis

Celgene ran deterministic and probabilistic sensitivity analysis. The respective outputs can be found in Section 5 of their revised submission.

Due to time constraints, the ERG did not have the time to analyse how sensitivity analysis was undertaken in the excel model. However, and similarly to the previous submission, the revised sensitivity analysis consistently reports dominant ICERs, which is somewhat questionable.

state also the ERG question the value of including third and fourth-treatment lines, especially in the intervention arm of the model, as only cost data is available and the basket of drugs considered might not accurately reflect current clinical practice.

- There are still several issues related with the **data extrapolation process**. The adjustment processes undertaken to estimate survival models are fundamentally flawed and are potentially introducing a high level of noise to the analysis. OS seems to be modelled in a more plausible fashion however PFS and TTF survival curves seem to flatten off too soon in the model. OS curves cross and PFS and TTF curves after 10 years in the intervention arm of the model.

- Finally, the ERG are still concerned with the assumption of keeping patients on Bort until disease progression in the economic model. Literature and clinical opinion consistently report that Bort is given for a fixed period of time to MM patients. Furthermore, the duration of treatment is one of the key drivers of the final ICER. With regards to the utility values used in the analysis, even though Celgene tried to address some of the issues raised by the Committee, the values are still based on some uncertainty.

Overall there is a high level of uncertainty embedded in several steps of the analysis and it is extremely difficult to assess to which extent the issues raised impact the final ICER.

For all the reasons provided, the ERG lack confidence in the final ICERs presented, therefore all estimates presented in the previous section should be interpreted with extreme caution.

When the ERG changed the duration of treatment with Bort, the final second-line ICER increased to £38,871. Whilst we do not suggest that this is a reliable alternative ICER it shows the sensitivity of the model outcomes to these parameters. The key determinants of the final ICERs seem to be the **duration of Bort treatment** and the **inclusion (or exclusion) of subsequent treatment lines.**