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# Single Technology Appraisal:

# Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

ERG critique of Celgene's additional analyses


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# 1. Introduction

Celgene has produced additional analyses in response to specific questions from the appraisal committee following the Appraisal Committee meeting on Tuesday 7 January 2014.

Specifically NICE requested a cost-effectiveness analysis at 2-3 years (i.e. when the PAS comes into effect beyond 26 cycles of treatment). The cost effectiveness analysis should address the following issues/concerns raised by Committee:

a. At 26 cycles, the PAS submission assumes that 31.9% of people survive and will be eligible for the PAS. The Committee was concerned that the UK patient population likely to receive lenalidomide after 26 cycles would be much less than 31 %, and that the proportion of post 26- cycle cycles of lenalidomide would be even fewer. This has implications for the estimated ICER reduction with the PAS versus the ICER estimate pre-PAS.

   Therefore, the Committee questions what the real world UK population attrition rate would be for these survivors > 26 cycles? Given that:
   - Duration of exposure from the Blood paper on the MDS 004 trial shows 31.9% **at <u>52 weeks (12 cycles)</u>**
   - The Celgene model for percentage of patients still on drug, and therefore eligible for PAS, had a figure of **31.9% at 104 weeks (26 cycles)**.
   - These are identical figures: have Celgene modelled that all those still on drug after 12 cycles will still be on after 26 cycles because there is no actual follow up?.
   - If you use the Blood data using a simple linear and exponential regression, the linear model would have no patients left on drug by about 72 weeks (18 cycles). The probably better fitting, exponential regression would project **of the order of 10% patients on drug at 104 weeks (26 cycles)**. This would push the ICER up

b. The timing of the PAS rebate to the NHS needs to be modelled in line with implementation at 26 cycles.
   - The model incorporated 2 dose interruptions which added about 5 weeks or so to the 26 cycles so this would mean an additional time before the NHS could expect reimbursement for the drug. In the real world population with comorbid illness there could well be more dose interruptions than the model indicates. The inclusion/exclusion criteria did not really mention comorbidity other than exclusion of patients with renal dysfunction.
   - A delayed saving of the kind proposed might also to be subject to discounting? How/ does the model account for this?

c. The ‘cloud’ of uncertainty which surrounded the FAD most plausible without PAS ICER of at least £70,000, now surrounds the with PAS manufacturer base-case ICER of £25,468 and also needs to be explored.

## 2. Response to question A

According to Celgene, "the duration of exposure quoted from the Fenaux paper (Fenaux et al. 2011) for the MDS-004 trial (31.9% at 52 weeks) combines data from the 5mg and 10mg lenalidomide arms of the trial, is taken from Table 41 in the CSR and relates only to the double blind phase of the trial." Celgene explained that "it is essential that treatment exposure is determined with a 10mg starting dose as the higher dose is associated with significantly increased cytogenetic responses, rates of RBC transfusion-independence and subsequent AML-free survival (Sekeres et al. 2013)". Additionally, Celgene explained that "the data used in the Fenaux paper is from an older data cut to that used in the model (14 June 2010 vs 15 June 2011). When the additional year of data is included the number of patients reaching 52 weeks (and 26 cycles) is greater."

**ERG Comment**

The ERG agrees that all data for lenalidomide in the economic model were taken from the 10mg lenalidomide arm, while data for placebo were taken from the placebo-arm and the 5mg arm in the MDS-004 trial. Although this may seem a conservative approach, it should be taken into account that for some outcomes the placebo arm had better results than the 5mg arm (e.g. median survival was 35.9 months (95% CI: 2.1 to 56.5) in the placebo arm and 35.5 months (95% CI: 1.9 to 59.4) in the 5mg arm).

In order to address the concerns regarding real-world UK patient survival and lenalidomide treatment duration (i.e. maintenance of RBC transfusion-independence) extending beyond 26 cycles to enable implementation and benefit from the PAS, Celgene produced several sources of information, including a literature search. However, the methods of the systematic review were not described, nor were search strategies and inclusion criteria reported. Therefore, it was not possible for the ERG to critique this information. For the remaining information, no references or full papers were provided or were received on or after 10 March (the date this critique was submitted). Therefore, this information has to be taken at face value.

Data from the Treatment Continuation Scheme Database (TCS), which was set up to monitor the Pregnancy Prevention Programme (PPP) in the UK, was used to analyse the time spent on treatment of MDS patients who received lenalidomide between the 5th February 2009 and the 1st February 2014. However, this was a wider group of patients than the population under consideration in this assessment (adults with MDS associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent). In this dataset, 28% of patients were still on active treatment after 26 cycles.

Overall, the real-world evidence presented by Celgene seems to suggest that 31% of patients reaching 26 cycles could be a reasonable assumption.

## 3. Response to question B

The committee raised some concerns on the impact of treatment interruptions. Treatment interruptions delay treatment with lenalidomide and therefore delay the timing of the PAS taking effect in patients experiencing these treatment interruptions. In addition, the committee felt that more dose interruptions might be expected in the real world population with comorbid illness.

As suggested by the committee, the manufacturer incorporated delayed lenalidomide costs beyond 26 cycles due to earlier treatment interruptions. The length of the 1st interruption was reported as 17.5 days while the length of the 2nd interruption was reported as 13.9 days. These interruptions put back the time point at which patients reach their 26th cycle of lenalidomide and from whereon the drug is provided free-of-charge. A 1st interruption is experienced by 68.7% of the patients, 73.8% of these patients experience a 2nd interruption. According to the manufacturer, the mean duration of the first treatment interruption was 12.0225 days (0.687* 17.05 days) and 7.047 days (0.687*0.738*13.9 days) for the second interruption. However, the average number of days spent experiencing a lenalidomide treatment interruption in each cycle was adjusted for the proportion of patients that will have discontinued lenalidomide (i.e. patients who died or stopped responding). The overall average was therefore 16.03 days.

**ERG Comment**

Since the effectiveness (in the model) is not influenced by treatment interruptions, the proportion of patients experiencing treatment interruptions as well as the average duration only influences the costs (in the model). This impacts the ICER in two ways; first, the treatment costs are postponed and due to discounting, the drug costs are reduced. Second, there is a small proportion of patients that goes off treatment during the 27th cycle and thus these patients no longer benefit from the PAS where before a benefit of the PAS was assigned to these patients.

The average duration of treatment interruptions according to the manufacturer (16.03 days) seems to be weighted twice by accounting for the proportion of patients that will have discontinued lenalidomide (i.e. patients who died or stopped responding). According to the ERG the mean duration of lenalidomide should be similar to the mean length of the 1st and 2nd interruption, weighted for the proportion of patients experiencing one or two interruptions, 68.7% and 50.7% respectively. This would result in a mean duration of 19.07 days (0.687*17.5 + 0.507* 13.9) instead of 16.03 days. Nevertheless, the impact on the ICER of this double weighting is negligible, £25,455 vs. £25,310.

In addition, there appears to be a discrepancy between the length of treatment interruptions reported in the model and those reported in the clinical study report for MDS004. In table *14.3.1.3* of the CSR (appendix 1), a mean length of the first interruption of 26.8 days is reported instead of the 17.5 days in the model. Likewise, for the second interruption a length of 23.9 days is reported in the CRS versus 13.9 in the model.

A possible way to reconcile these numbers is that the 17.5 in the model is the average over all patients instead of the average per patient with interruption. If that is indeed the case, again data is adjusted twice. If this is corrected, the ICER becomes £24,263.

**Comorbidities and more interruptions**

The committee noted that comorbidities in the real world population may lead to more dose interruptions in daily practice. The manufacturer conducted scenario analysis that increased the mean duration of interruptions. According to the ERG, these scenario analysis do not provide an answer to the question of the impact of comorbidities on the ICER and PAS scheme since these scenarios assume that the number of days without treatment increases, hence the cost of treatment are reduced while the effectiveness is not altered. According to the ERG these scenarios do not reflect reality and therefore do not provide additional information.

Nevertheless, as noted by the committee, the exclusion criteria did not contain comorbidities other than exclusion of patients with abnormal laboratory values, so it is well possible that the MDS004 population resembles the UK population that will be treated with regards to comorbidities. Besides, while treatment interruptions postpone costs and delay the activation of the PAS, the impact of treatment interruptions on the total costs is not substantial. But again, the model assumes that the effectiveness is unaffected by longer treatment interruptions. While the manufacturer mentioned that no correlation was found between the number of interruptions experienced and treatment duration the ERG considers it reasonable to assume that treatment duration and the number of interruptions are associated with response duration.

The ERG was able to replicate all additional analyses done by the manufacturer, except for the scenario in which the duration of treatment interruption was varied. This was due to the fact that no information was provided how this time would be divided between 1st and 2nd interruption.

## 4. Response to question C

The committee requested the manufacturer to explore the cloud of uncertainty surrounding the ICER with PAS.

The manufacturer presented threshold analyses to investigate how low the proportion of patients still responding would have to fall for lenalidomide to be no longer cost-effective by altering the response curve. At 26 cycles, lenalidomide treatment remained cost-effective (ICER £30,000) when 27% of the patients reach the 26$^{th}$ cycles.

In addition, to reduce the uncertainty of the committee regarding when the benefits of lenalidomide are accrued, the manufacturer demonstrated that 90% of the benefits accrued

within the first 10 years while the majority of benefits are obtained during the first 5 years. This time frame is surrounded by the least uncertainty regarding survival and progression to AML since information from the trial was available for up to 5 years.

**ERG Comment**

As can be seen from Figure 7 and 8 in the additional evidence submitted by the manufacturer, the ERG agrees with the manufacturer that 90% of the QALY gain happens during the first 10 years and 64% at 5 years. This is important since the first 5 years is surrounded by the least uncertainty.

The output from the PSA with PAS including treatment interruptions is almost similar to the results from the PSA with PAS without treatment interruptions. The same 10 parameters affecting the ICER were identified.

# Appendix 1

Celgene Corporation
Protocol: CC-5013-MDS-004



Table 14.3.1.3
Study Drug Dose Reduction for All Subjects by Initial Treatment Group (Double-blind - Safety Population)

| Dose Reduction | PLACEBO (N=67) | 5 MG QD (N=69) | 10 MG QD (N=69) |
|---|---|---|---|
| Had at least one dose reduction/interruption due to AE | n (%) | n (%) | n (%) |
| Yes | 2 ( 3.0) | 41 ( 59.4) | 43 ( 62.3) |
| No | 65 ( 97.0) | 28 ( 40.6) | 26 ( 37.7) |
| Time to first dose reduction/interruption(days) due to AE[1] | | | |
| N | 2 | 41 | 43 |
| Mean | 79.0 | 59.2 | 50.1 |
| SD | 9.90 | 48.75 | 56.66 |
| Median | 79.0 | 43.0 | 27.0 |
| Min, Max | 72.0, 86.0 | 7.0, 215.0 | 10.0, 269.0 |
| Duration of first dose interruption(days)[2] | | | |
| N | 2 | 41 | 43 |
| Mean | 7.0 | 16.2 | 26.8 |
| SD | 8.49 | 15.50 | 34.37 |
| Median | 7.0 | 11.0 | 14.0 |
| Min, Max | 1.0, 13.0 | 1.0, 64.0 | 1.0, 161.0 |
| Had second dose reduction/interruption due to AE | n (%) | n (%) | n (%) |
| Yes | 0 ( 0.0) | 8 ( 11.6) | 24 ( 34.8) |
| No | 67 (100.0) | 61 ( 88.4) | 45 ( 65.2) |
| Interval between first and second reduction/interruption(days)[3] due to AE | | | |
| N | 0 | 8 | 24 |
| Mean | NA | 40.4 | 86.0 |
| SD | NA | 30.45 | 84.80 |
| Median | NA | 36.0 | 61.0 |
| Min, Max | NA, NA | 6.0, 105.0 | 3.0, 350.0 |
| Duration of second dose interruption(days)[2] | | | |
| N | 0 | 8 | 24 |
| Mean | NA | 16.1 | 23.9 |
| SD | NA | 15.85 | 49.80 |
| Median | NA | 11.5 | 13.5 |
| Min, Max | NA, NA | 1.0, 49.0 | 1.0, 252.0 |

[1] Time to dose reduction/interruption is the time from first dose of study medication to the start of first reduction/interruption.
[2] Duration of dose interruption is the time from last dose of one dosing regimen to first dose of the next dosing regimen. A dosing change is considered an interruption if the start of the new dosing record is greater than 1 day after the end of the previous dosing record.
[3] Time from the start of the first dose reduction/interruption to the start of the second dose reduction/interruption.

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