## Executive Summary

Following the Appraisal Committee meeting on Tuesday 7 January 2014 a number of issues were relayed to Celgene in relation to the cost-effectiveness model for lenalidomide in MDS del(5q). Specifically these issues concerned the impact of assumptions regarding patient survival on the patient access scheme (and hence the ICER), the timing of the PAS rebate, and other general uncertainties with regard to the ICER. Celgene has now completed extensive additional analyses in response to the Committee's concerns. These additional analyses demonstrate that:

- there is sufficient evidence to support the projected proportion of patients remaining on treatment at 26 cycles
- the impact of treatment interruptions on the ICER is minimal

In addition, Celgene believes that remaining uncertainties regarding the expected cost-effectiveness of lenalidomide should be considered in the broader context of MDS del(5q) as an orphan disease, the strong clinical support for lenalidomide and the lack of alternative treatment options for patients. Celgene has responded to all of the issues raised by the Appraisal Committee and trusts that NICE will now be in a position to proceed with recommendations for lenalidomide without any further delays.

Please find below Celgene's response to three questions posed by NICE as part of the teleconference on the 16th January 2014.

**Question (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, it 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 52 weeks (12 cycles)**
- 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

## Response to question (a)

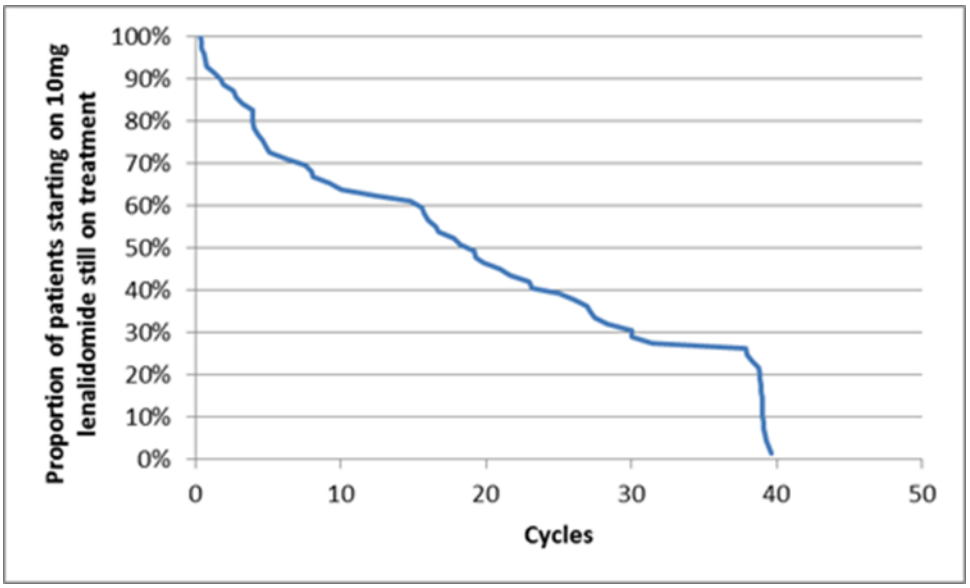
### Clarification of information in the Blood paper

The Appraisal Committee raised concerns regarding the estimate of 31.9% of patients remaining on treatment with lenalidomide to a point at which they become eligible for the PAS. The similarity of the two figures quoted is pure coincidence. 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. The licensed starting dose for lenalidomide in the UK is 10mg; in the Fenaux paper 42% of lenalidomide patients starting on 10mg remained on treatment at 52 weeks (double blind phase). 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, 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.

Figure 1 below shows the proportion of patients who started on lenalidomide 10mg (n=69) remaining on treatment by cycle using the June 2011 data cut.

**Figure 1:** Treatment duration for patients who started on lenalidomide 10mg




At exactly 26 cycles 38% of patients remained on treatment. At 26 cycles plus the average 16 days spent not receiving treatment due to dose interruption 36% of patients remained on treatment. The value used in the model (31.9% at 26 cycles) is slightly lower as a correction factor was included in the model to reduce survival on both arms to the levels seen in real life practice. This was based upon the analysis presented in the Kuendgen paper, as discussed at the initial committee meeting (Kuendgen et al. 2012).

**Real-world validation of the survival and response times included in the economic modelling**
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, we have collated the following information:

(i) Information on duration of treatment for MDS patients on lenalidomide from Celgene's in house database ( primarily used to administer the PAS for TA 171) supporting the model estimate of patients likely to remain on treatment at 26 cycles.

(ii) Published 'real-world' registry data from lenalidomide-treated, IPSS lower-risk del(5q) patients, which demonstrate that the real-world effectiveness, survival and duration of response to lenalidomide is at least equivalent to the economic model.

(iii) Recently published follow-up data from the Phase II MDS-003 trial which indicates high efficacy and prolonged RBC transfusion-independence with lenalidomide treatment in isolated del(5q) patients, consistent with the economic model.

(iv) Evidence from the MDS-003 and MDS-004 on tolerability for elderly del(5q) patients as this represents a subgroup which is likely to be over-represented in a real-world population compared to the trial.

(v) Evidence from the Phase III MDS-004 for the specific subgroup matching the licensed population (isolated del 5q) which shows comparable outcomes to the ITT population.

**UK real-world evidence on duration of treatment from the TCS Database**

The Treatment Continuation Scheme Database (TCS) was set up to monitor the Pregnancy Prevention Programme (PPP) in the UK which is a mandatory regulatory requirement given the teratogenic nature of lenalidomide. The database is also used to administer the PAS currently in place for TA 171. Lenalidomide cannot be prescribed without the physician signing the prescription authorisation form (PAF). All PAFs for lenalidomide are logged into the database regardless of the indication to monitor and assist with the PPP.

Data was extracted from the TCS to analyse the time spent on treatment of MDS patients who received lenalidomide between the 5th February 2009 and the 1st February 2014. Patient-level data detailed information on patients' age, the number of cycles (of 28 days) for which they were on treatment, and whether or not they were still on active treatment on the 1st February 2014. Patients were classed as inactive if their last PAF received by Celgene was more than 6 months before the 1st February 2014, as historically PAFs were usually received with a lag time between 3 and 6 months. Occasionally PAFs were received beyond 6 months, however, this is not standard practice.

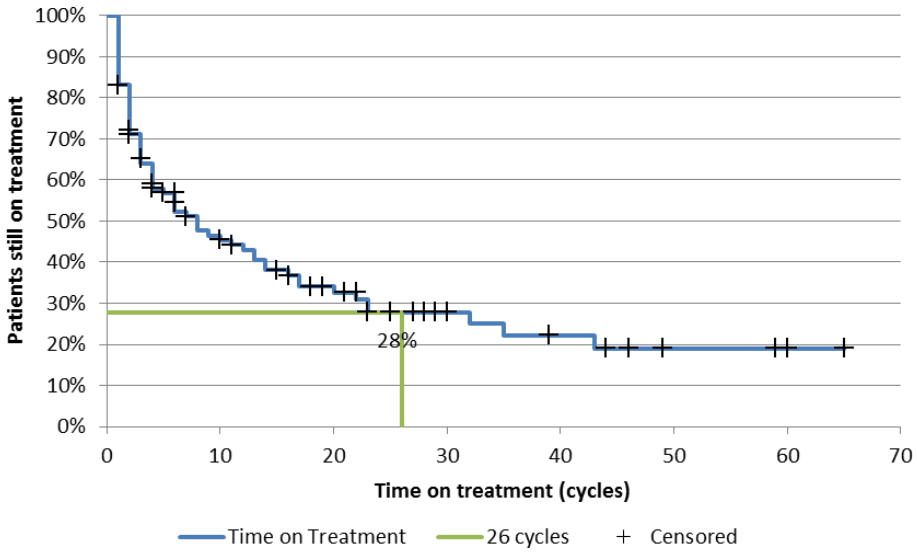
The following patient details were available:

- Total number of patients: 124
- Average age at start of treatment: 70.85
- Female: 68.5%
- Of these, 4.7% had child-bearing potential
- Number of patients still receiving treatment on 1st February 2014: 50

The time on treatment Kaplan-Meier curve derived from the patient level data is shown below in *Figure 2*. At the proposed 26 cycles (when the PAS is activated), 28% of patients are still on active treatment. Within the dataset, patients received treatment with lenalidomide for up to 65 cycles.

It is important to note that the analysis could in theory include del(5q) patients with a complex karyotype and also non del(5q) patients, who are known to have lower response rates and duration of RBC transfusion independence compared to del(5q) (Raza et al. 2008). Additionally there is a higher likelihood of patients being treated with more advanced disease due to the fact lenalidomide was not licensed at the time of starting treatment for many patients included in this dataset. Off label / compassionate use is often reserved for those patients most at need e.g. those patients whom a physician believes will progress more rapidly or have a higher transfusion burden, indicating a more aggressive disease. Therefore, the duration of treatment demonstrated in this analysis is likely an underestimation of what could be achieved within lenalidomide's isolated del(5q) licence.

**Figure 2:** Time on treatment of patients receiving lenalidomide for MDS within the UK




**Published survival and treatment duration data in lenalidomide treated 'real-world' IPSS lower-risk del(5q) registry patients and from the two lenalidomide trials:**

A literature search was conducted in order to identify real-world evidence for survival and treatment duration with lenalidomide in lower-risk MDS del(5q) patients. This search identified a number of lower-risk del(5q) registry studies and non-trial populations that examine outcomes in lenalidomide treated patients (data summarised in

Table **1**).

These survival and effectiveness results from the registry datasets reflect what can be expected in the 'real-world', elderly and frail lenalidomide-treated patients that are not subject to the specific exclusion criteria used in the pivotal trials (MDS-003 and MDS-004). The registry studies are also reflective of lenalidomide's licensed population of RBC transfusion-dependent, IPSS lower risk isolated del(5q) MDS, with the potential impact of prior ESA therapy also being addressed within the French compassionate use publications (Ades and Le Bras). The main difference to the licensed population is the inclusion of a minority of patients with del(5q) + additional cytogenetic abnormalities. It is known that a complex karyotype is an important, independent negative prognostic marker in MDS for reduced overall survival and increased transformation to AML (Schanz et al. 2012; Greenberg et al. 2012). The inclusion of these patients will therefore likely have a negative impact on survival and treatment effectiveness, making these an underestimation of the likely results that can be expected in a restricted isolated del(5q) population. A more detailed summary of these registry studies along with the follow-up data from the MDS-003 Phase II trial is provided in the Appendix.

**Table 1:** Summary of key survival and lenalidomide treatment duration data in lower-risk del(5q) MDS.

| **Citation** | **Le Bras 2011** | **Adès 2012** | **Sanchez-Garcia 2011** | **Mallo 2013** | **List 2006 and 2013 MDS-003** | **Fenaux 2011 MDS-004 trial** |
|---|---|---|---|---|---|---|
| **Study information** | Observational study based upon the French compassionate use programme | Observational study based upon the French compassionate use programme using a matched control group | Observational study using the Spanish MDS registry database | Observational study using data from the Spanish MDS Group and the Cleveland Clinic (USA). Prospective and retrospective recruitment | MDS-003 single arm trial + non-interventional extension study | MDS-004 RCT as described in the submission |
| **Number of LEN treated patients** | n=95 | n=71 | n=86 | n=52 | n=148 | ITT: n=69<br>Isolated del(5q): n=47 |
| **LEN dose and schedule** | 10mg, 1-21/28 | 10mg, 1-21/28 | 10mg or 5mg 1-21/28 (n=80 and 6) | NS | 10mg, 1-21/28 or daily (n=46 and 102) | 10mg, 1-21/28 used within the economic model (licensed dose) |
| **Median age (years)** | 70.4 | 69.8 | NS | 75.5 | 71 | 67.6 |
| **Cytogenetics**<br>**Isolated del(5q) + 1**<br>**del(5q) +≥2** | 79%<br>14%<br>6% | 79%<br>15%<br>6% | 83.7%<br>11.6%<br>4.7% | 73%<br>12%<br>8% | 74.3%<br>16.9%<br>8.1% | 68.1%<br>14.5%<br>10.1% |
| **IPSS low or int-1** | 100% | 100% | 100% | 98% | 79.7% confirmed lower-risk | 62.3% confirmed lower-risk, 31.9% missing |
| **RBC TD at baseline** | 100% | 100% | ~85% | NS | 100% | 100% |
| **Prior ESA use** | 67% | Allowed (67% in original series) | NS | NS | 73% | 58% |
| **RBC TI ≥8 weeks** | 65% | NS | Sustained and transient TI = 51% and 28% | 78% (29/37) | Isolated del(5q) 70.9% | Isolated del(5q) 63.8%<br>ITT population 60.9% |
| **Cytogenetic response** | NS | NS | NS | 30.8% complete | 45.5% complete, 26.1% partial (all patients) | Isolated del(5q)<br>29.5% complete<br>18.2% partial<br>ITT population<br>24.6% complete<br>19.7% partial |
| **Duration of response/ RBC TI** | One and two year TI = 92.5% and 77%, respectively | NS | 36 months | 30.4 months | 27.6 months<br>4yr rate of TI = ~40% | Isolated del(5q) = NE (95% CI: 19 months, NE)<br>ITT = NE (95% CI: 23 months, NE) |
| **Median OS** | NS | 150 months | 62 months | NS | Isolated del(5q) only = 47 months | Isolated del(5q) =44.4 months<br>ITT = 44.5 months |
| **Survival at:** | | | | | | Isolated del(5q) / ITT |
| **2 years** | NS | | 92% | NS | NS | 75% / 75% |
| **4 years** | NS | 67% | | NS | NS | 48% / 50% |
| **5 years** | NS | | 62% | NS | NS | 41% / 39% |

Key: NS: not stated; N/A: not applicable; NE: not evaluable; OS: overall survival; RBC-TD: red blood cell transfusion dependent; TI: transfusion independent; ESA: erythropoiesis stimulating agents; IPSS: International Prognostic Scoring System; LEN: lenalidomide

**Lenalidomide tolerability in the elderly**

The safety and tolerability of lenalidomide in patients ≥75 versus <75 years was evaluated in a pooled analysis of MDS-003 and MDS-004. Between both age groups, there were no significant differences in rates or duration of RBC transfusion-independence. In addition, rates of treatment discontinuation, requirement for dose reductions and overall treatment exposure were similar between both age groups (Fenaux et al. 2012).

**Evidence from the MDS-004 trial for the isolated del(5q) and ITT populations**

Whilst the committee previously reached the conclusion that evidence from the ITT population in MDS-004 could be used to provide a recommendation within the licensed indication for lenalidomide, Celgene would like to provide data for patients within the isolated del(5q) population compared to the ITT population in order to reduce the level of uncertainty felt by the Committee.

"The Committee noted that MDS-004 study included a broader range of patients than that specified in the marketing authorisation for lenalidomide, which includes people with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. However, the Committee was aware that a significant proportion of the people in the MDS-004 study were covered by the marketing authorisation, and that it would be able to make recommendations on lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality on the basis of the whole MDS-004 study population." Page 37 of appraisal consultation document.

As can be seen within the figures presented outcomes for the isolated del(5q) population are consistent with the ITT population. Available evidence from the MDS-003 trial and observational data suggests that outcomes in the isolated del(5q) population are either the same or better than in the overall population. In the MDS-003 trial, where TI duration is examined for up to 5 years, outcomes are similar for patients with and without additional abnormalities for just over 2 years, after which point transfusion independence is maintained for a longer time period in the isolated del(5q) population (Figure 1b , List 2013; log-rank test p=0.0198). The same trend of initially similar, followed by long-term improved, outcomes in the isolated del(5q) population is seen for OS in the same paper.

**Figure 3:** Isolated del(5q) vs ITT, response duration (transfusion independence)

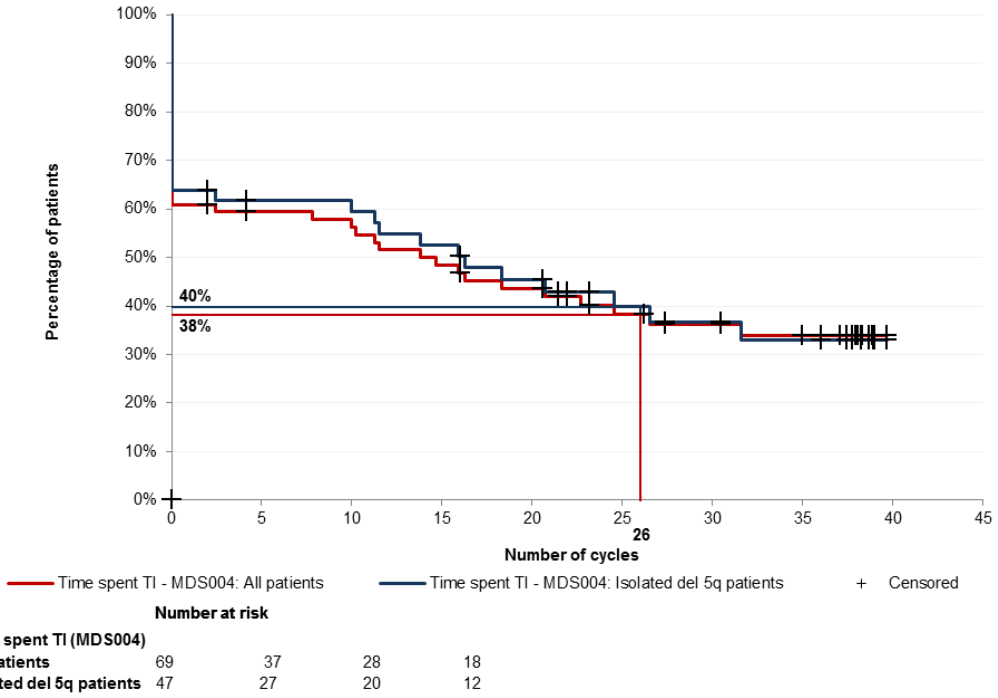



**Figure 4:** Isolated del(5q) vs ITT, overall survival

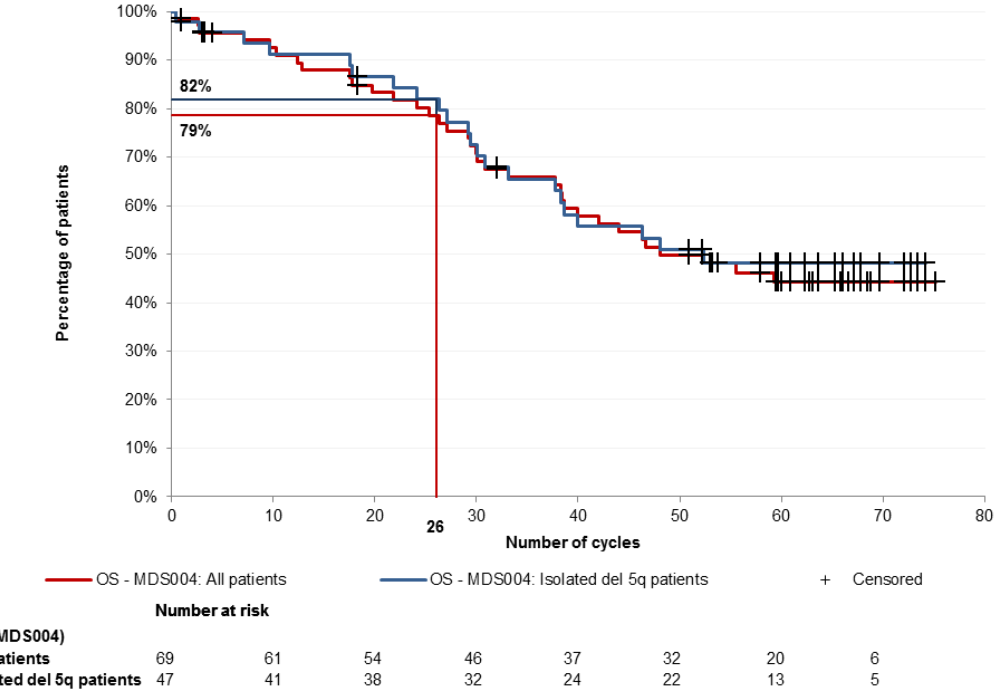
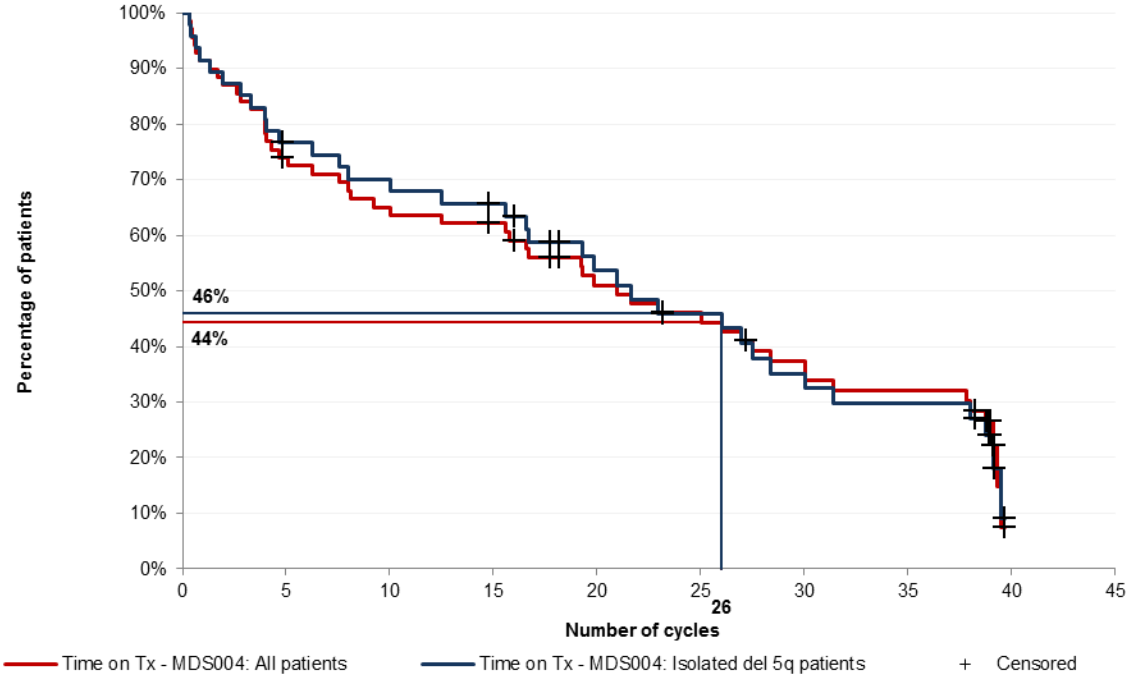


**Figure 5:** Isolated del(5q) vs ITT, time on treatment




| | Number at risk | | | |
|---|---|---|---|---|
| **Time on Tx (MDS004)** | | | | |
| **All patients** | 69 | 45 | 32 | 22 |
| **Isolated del 5q patients** | 47 | 33 | 22 | 14 |

## Conclusions

The published real-world evidence and in-house UK TCS data demonstrate, without exception, at least equivalent, if not superior, effectiveness (RBC TI and cytogenetic responses) and overall survival in lenalidomide-treated non-trial, elderly lower risk del(5q) MDS patient populations relative to MDS-004 and the economic model. For responding patients, the median duration of RBC transfusion-independence ranged from 26 to 36 months, demonstrating the prolonged duration of response with lenalidomide seen in clinical practice. The TCS data and other observational evidence demonstrate that along with the median being consistent with estimates within the submission, there are patients remaining on lenalidomide for considerable periods of time (over 60 cycles in the TCS data), which will be given lenalidomide free of charge with the patient access scheme. Long-term administration is also feasible given it is an oral therapy that is equally well tolerated in the elderly, with few long term complications to treatment after the initial myelosuppression.

Celgene have presented these analyses to five expert UK MDS consultants who have all agreed that 31% of patients reaching 26 cycles (as presented in the economic model) is valid in light of the real-world observational evidence and TCS data. This is consistent with the view from the haematologist who validated this figure at the first PAS expert panel meeting. Also Prof. Bowen at the first AC meeting validated the estimated survival in the model and agreed that the median survival estimates presented within the model were realistic. The panel can therefore be confident that the data and expert clinical opinion support the validity of the benefits which can be achieved through the PAS in this population.

**Question (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?

**Response to question (b)**

The Committee have highlighted that the cost-effectiveness analysis did not incorporate delayed lenalidomide costs beyond 27 cycles, whereby earlier treatment interruptions would put back the time point at which patients reach their 26$^{th}$ treatment cycle and activate the PAS. Celgene acknowledge that the Committee are correct. Treatment interruptions leading to a longer time before the PAS comes into effect have now been applied in all analyses presented below.

The mean duration of treatment interruptions across all lenalidomide patients who started on the 10mg dose is 16 days, which is shorter than the 5 weeks specified by the Committee. This has been calculated as follows:

- In the Revlimid patient flow sheet, the following formula has been used:
- =BU24*(1-T24)+BU25*(1-T25)+SUMPRODUCT(BU26:BU283,G26:G283)+BW24*(1-T24)+BW25*(1-T25)+SUMPRODUCT(BW26:BW283,G26:G283)
- As this is a new analysis, the formula has been provided for transparency
- Lenalidomide use in each 28-day model cycle is composed of time spent in receipt of each lenalidomide dose and experiencing an interruption, shown in the patient flow sheet in columns BT to BX
- The formula above calculates the average number of days spent experiencing a lenalidomide treatment interruption in each cycle, accounting for the proportion of patients that will have discontinued lenalidomide
- These are summed across all cycles to give a total, mean treatment interruption of 16.0 days

No correlation was found between the number of interruptions experienced and treatment duration (Pearson's product of moments correlation coefficient = 0.37). As such, Celgene have applied a delayed cost of 16 days of lenalidomide at the 27$^{th}$ model cycle in this updated analysis, and a revised set of model results are provided below. The first set of results are calculated for three different time horizons; in addition to the base case lifetime horizon, a 2 year horizon and a 3 year horizon are presented as requested by the Committee.

The Committee also note in their specification that comorbidities may lead to more dose interruptions in reality than are modelled. Results of a scenario analysis where various increased mean interruption durations are applied are provided below to investigate the potential impact of increased interruption durations.

The Committee requested clarification on how any cost saving achieved through the PAS is subject to discounting. Discounting is applied in the model as standard; future costs are discounted at a rate of 3.5% per year. When the PAS is activated, the saving accrued by lenalidomide costing £0 is implicitly discounted since best supportive care (BSC) costs at this stage will be subject to discounting. The lenalidomide acquisition cost remains fixed while cost of BSC is increasingly eroded by discounting.

**Results with delayed lenalidomide costs applied – Lifetime time horizon**

**Table 2:** Model outputs by clinical outcomes – Revlimid

| **Outcome** | **LY (undiscounted)** | **QALY (discounted)** | **Cost (£) (discounted)** |
|---|---|---|---|
| Transfusion independent | 1.72 | 1.35 | £48,096.02 |
| Transfusion dependent | 4.05 | 2.17 | £88,816.11 |
| AML | 0.29 | 0.15 | £4,558.26 |
| **Total** | **6.06** | **3.67** | **£141,470.38** |
| LY, life years; QALY, quality-adjusted life year | | | |

**Table 3:** Model outputs by clinical outcomes – Best supportive care

| **Outcome** | **LY (undiscounted)** | **QALY (discounted)** | **Cost (£) (discounted)** |
|---|---|---|---|
| Transfusion independent | 0.15 | 0.12 | £2,326.30 |
| Transfusion dependent | 4.78 | 2.70 | £117,044.59 |
| AML | 0.24 | 0.13 | £3,870.58 |
| **Total** | **5.17** | **2.95** | **£123,241.46** |
| LY, life years; QALY, quality-adjusted life year | | | |

**Table 4:** Revised base case results

| **Technology** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER (£) versus baseline (QALYs)** | **ICER (£) incremental (QALYs)** |
|---|---|---|---|---|---|---|---|---|
| BSC | £123,241 | 5.17 | 2.95 | - | - | - | £41,767 | - |
| Lenalidomide | £141,470 | 6.06 | 3.67 | £18,229 | 0.88 | 0.72 | £38,538 | **£25,310** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Scenario analysis results – 2 year, 3 year, 5 year and 10 year horizons**

**Table 5:** Two year time horizon

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £48,145 | 1.84 | 1.18 | - | - | - | £40,804 | - |
| Lenalidomide | £69,627 | 1.87 | 1.36 | £21,482 | 0.03 | 0.18 | £51,230 | **£119,876** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Table 6:** Three year time horizon

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £66,120 | 2.57 | 1.62 | - | - | - | £40,873 | - |
| Lenalidomide | £82,365 | 2.64 | 1.94 | £16,245 | 0.08 | 0.25 | £43,989 | **£63,780** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Table 7:** Five year time horizon

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £91,576 | 3.64 | 2.23 | - | - | - | £41,115 | - |
| Lenalidomide | £103,484 | 3.86 | 2.61 | £11,909 | 0.21 | 0.39 | £39,612 | **£30,923** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Table 8:** Ten year time horizon

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £117,295 | 4.84 | 2.82 | - | - | - | £41,562 | - |
| Lenalidomide | £131,445 | 5.42 | 3.43 | £14,150 | 0.59 | 0.60 | £38,363 | **£23,420** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Scenario analysis results – Cost effectiveness of lenalidomide whilst the PAS is in effect**

**Table 9:** Incremental cost effectiveness analysis from 3 years to lifetime

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| BSC | £57,121 | 2.60 | 1.33 | | | | - |
| Lenalidomide | £59,105 | 3.42 | 1.73 | £1,984 | 0.82 | 0.40 | **£4,960** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

**Scenario analysis results – Increased total lenalidomide interruption**

**Table 10:** Mean total lenalidomide interruption of 28 days

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £123,241 | 5.17 | 2.95 | - | - | - | £41,767 | - |
| Lenalidomide | £140,333 | 6.06 | 3.67 | £17,091 | 0.88 | 0.72 | £38,228 | **£23,731** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Table 11:** Mean total lenalidomide interruption of 35 days

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £123,241 | 5.17 | 2.95 | - | - | - | £41,767 | - |
| Lenalidomide | £139,777 | 6.06 | 3.67 | £16,536 | 0.88 | 0.72 | £38,077 | **£22,959** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Table 12:** Mean total lenalidomide interruption of 42 days

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| BSC | £123,241 | 5.17 | 2.95 | - | - | - | £41,767 | - |
| Lenalidomide | £139,237 | 6.06 | 3.67 | £15,995 | 0.88 | 0.72 | £37,930 | **£22,209** |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

**Conclusions**

As expected the ICERs are much higher, in line with the previous ICER presented without the PAS, at the 3 year time horizon. This is because at this point none of the benefits from the PAS are applied i.e. the costs of lenalidomide are at their highest compared to the benefits achieved. After this point additional benefits are accrued for patients, in line with the trial evidence, while lenalidomide is provided free of charge in line with the PAS making treatment highly cost-effective.

By approximately 5 years lenalidomide is cost-effective versus best supportive care. This is the time period which is based upon the least extrapolation of trial data as evidence is available for lenalidomide within MDS-004 for approximately 5 years.

Increasing the length of treatment interruptions makes little difference to the ICER, with the ICER decreasing with increased length of interruption.

**Question (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.**

**Response to question (c)**

The specification document noted the uncertainty around the PAS ICER. Please find below results of additional sensitivity analyses conducted in order to inform the Committee regarding areas of remaining uncertainty having incorporated the delayed lenalidomide costs described above.

Threshold analyses are presented below which explore the impact of assumptions around the duration of response and survival, investigating how low the proportion of patients still responding (i.e. on treatment) would have to fall for lenalidomide to no longer be cost-effective. As the response duration profile represented with a curve (rather than a point estimate) this analysis was carried out through alteration of the constant term i.e. we would expect a lower response in real-life due to patient prognostic characteristics being less favourable which would reduce response on both arms.

At 26 cycles lenalidomide remains cost-effective when 27% of patients are still on treatment, within the real-world data 28% of patients remained on treatment at this point.

As noted previously one-way sensitivity analysis shows that the model is most sensitive to the assumptions that are made around the absolute survival of patients receiving best supportive care and the duration of response to lenalidomide. As presented in the answer to question (a) the results within the model may represent an underestimate of the effectiveness of lenalidomide as equal or greater effectiveness has been shown throughout the available real-world evidence we would therefore suggest that the uncertainty surrounding the ICER is biased in that a lower ICER is more likely in reality.

**What is the minimum number of people who need to reach 26 cycles to still be cost-effective?**

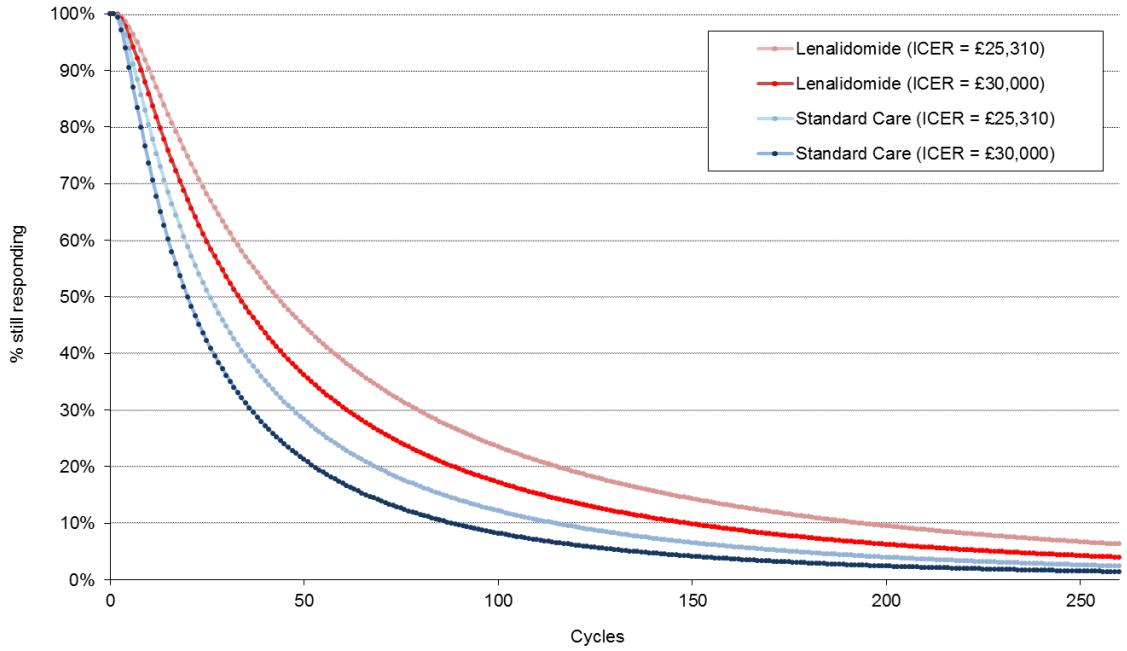
For lenalidomide to remain cost-effective, its ICER (incremental cost-effectiveness ratio) must remain less than, or equal to, £30,000. This was achieved by altering the response rate of lenalidomide by means of changing the log shape response duration curve parameter. This change is shown below in Table 13.

**Table 13:** Change in response parameter

| **Parameter** | **ICER = £ 25,310** | **ICER = £ 30,000** |
|---|---|---|
| Constant | **6.542** | **6.276** |
| Lenalidomide | -0.528 | -0.528 |
| Ln(p) | -0.172 | -0.172 |

This change in response rate is shown below in Figure 6.

**Figure 6:** Response rate




Originally, with an ICER of £25,310, 31% of patients reached 26 cycles of treatment. After the change in response rate, with an ICER of £30,000, 27% of patients reached 26 cycles of lenalidomide treatment.

**Profile of costs and QALYs over time**

The Committee have indicated some uncertainty regarding when the benefits of lenalidomide are accrued. The analysis below has been provided to remove some of this uncertainty. As demonstrated the majority of benefits are accrued within the first 5 years of the model with over 90% accrued within the first 10 years. This is the time period which is surrounded by the least uncertainty regarding outcomes as survival information from the trial is available for up to 5 years.

As Figure 7 demonstrates, with the PAS in place a substantial proportion of the costs on the lenalidomide arm are comprised by the costs of providing supportive care to patients. As patients are expected to survive for longer on the lenalidomide arm these supportive care costs (chelation, monitoring and transfusions) are much higher on the lenalidomide arm and the difference in these costs compared to BSC is in fact only 20% lower than the lifetime cost of treatment with lenalidomide itself by the end of the modelled time horizon.

In contrast the majority of the QALY gain for lenalidomide compared to BSC is achieved within the first 10 years of the modelled time horizon (91% of the incremental QALY gain is achieved by 10 years, 64% at 5 years).

The scenario analyses presented around time horizon previously support this analysis with lenalidomide being cost-effective when any time horizon is studied between 5 years and lifetime.

**Figure 7:** Cost profile over time

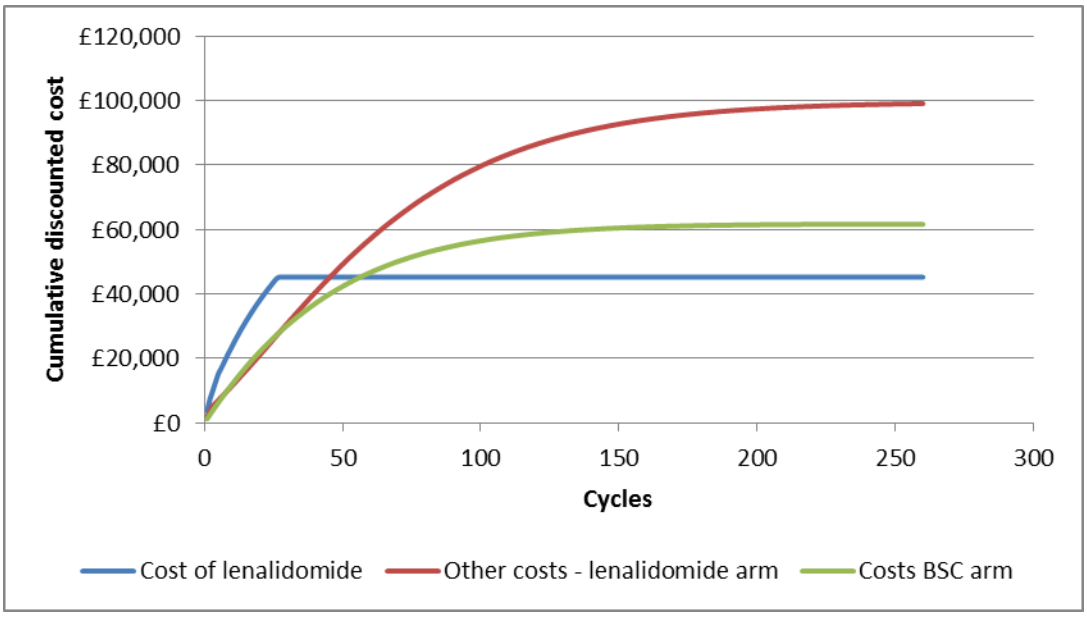
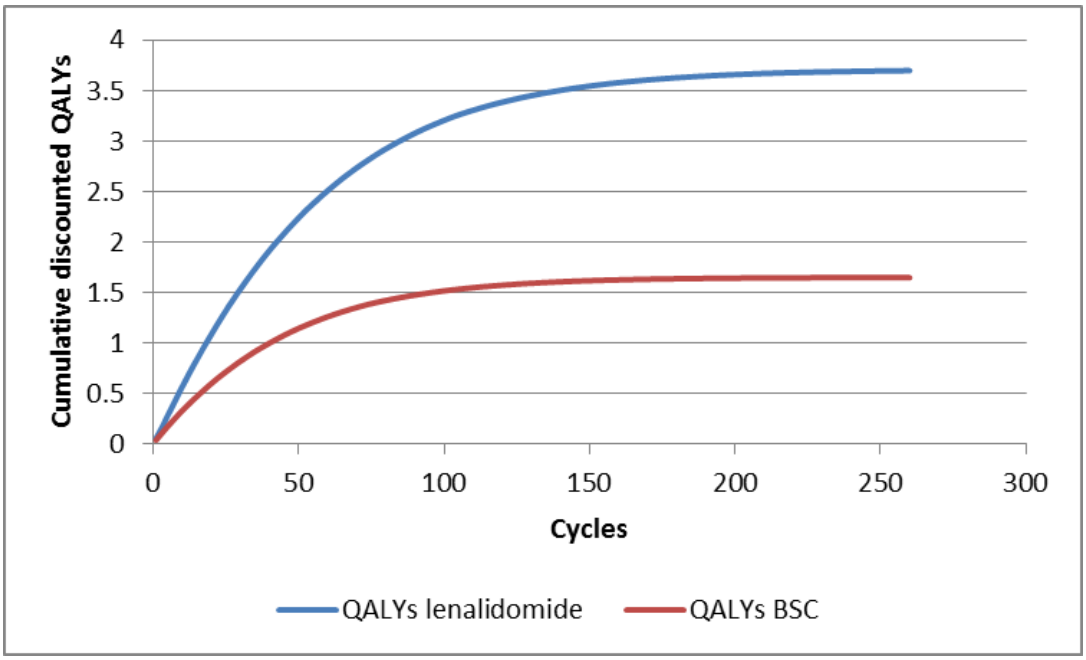



**Figure 8:** QALY profile over time



**Probabilistic and one-way sensitivity analysis using updated PAS results**

**Table 14:** Results from 1,000 PSA simulations

| Item | Model Result |
|---|---|
| Mean Incremental Costs | £17,784 |
| Mean Incremental QALYs | 0.692 |
| Mean ICER | **£25,708** |
| % of observations cost-effective at £20,000 threshold | 25.4% |
| % of observations cost-effective at £30,000 threshold | 64.5% |

**Figure 9:** Cost-effectiveness plane

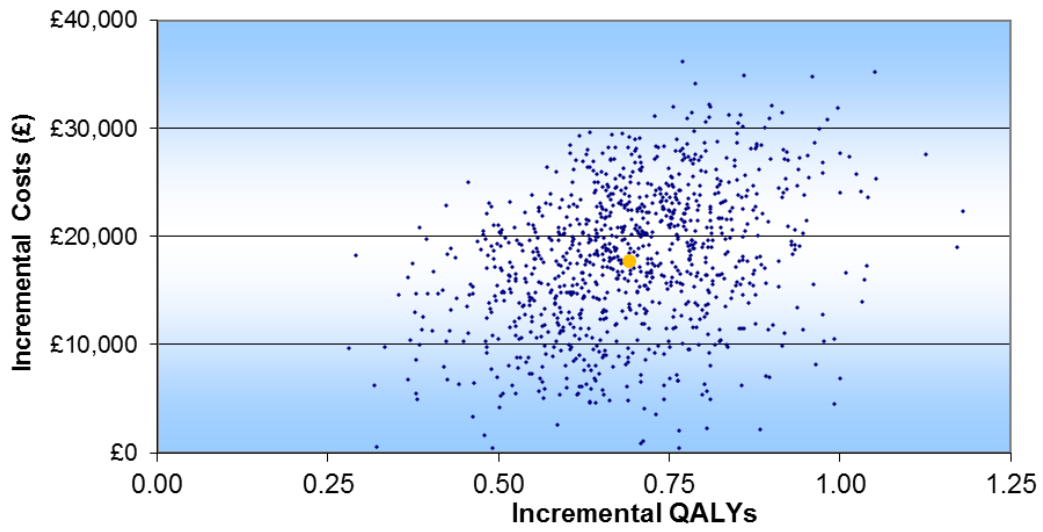



**Figure 10:** Cost-effectiveness acceptability curve

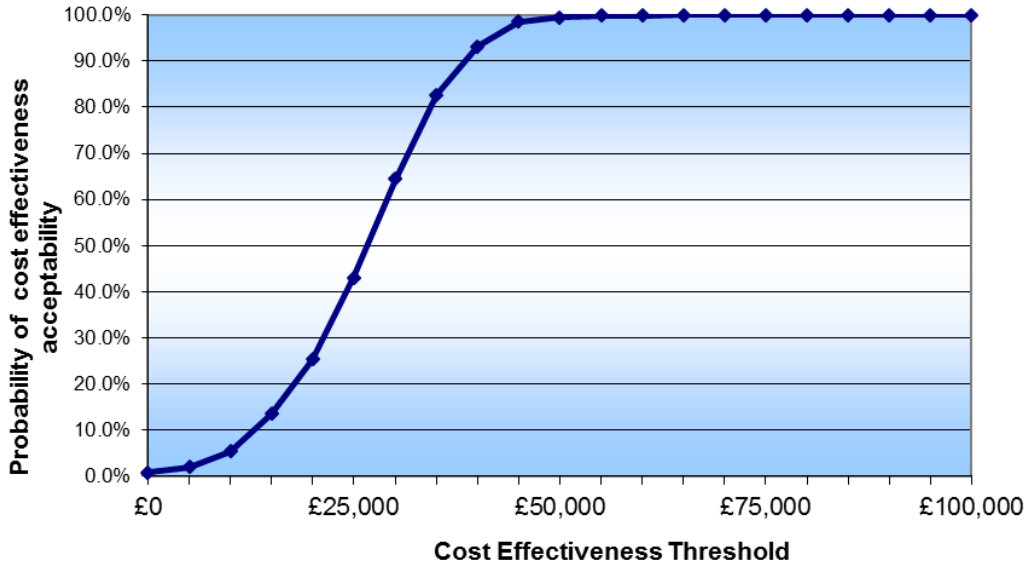
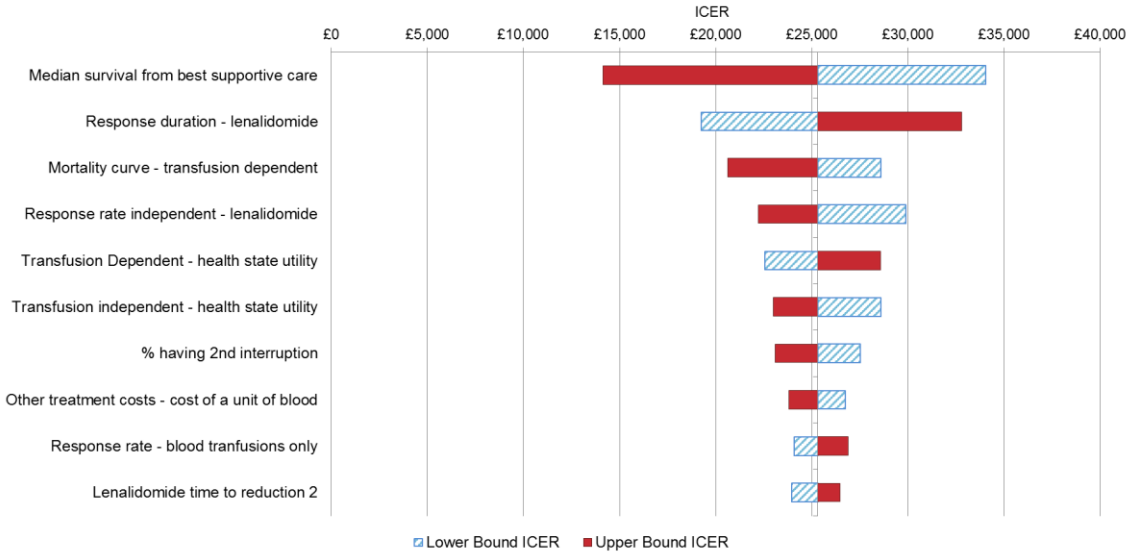


**Figure 11:** Deterministic sensitivity analysis output – tornado diagram




## Conclusions

The uncertainty surrounding the ICER should be viewed within the context of the available real-world evidence presented, the strong support voiced by UK clinicians as part of consultation with both NICE and the SMC, where lenalidomide has recently been approved within this indication, and the disease itself: MDS is an orphan disease and isolated del(5q) represents a very small sub-population within this orphan disease.

In this regard, Celgene would like to make the following points:

- MDS is an orphan disease and this particular condition (transfusion-dependent isolated del 5q) affects an even smaller population (less than in 1 in 100,000 people).
- The MDS-004 trial was the largest randomized trial so far in this orphan disease and contains efficacy data for treatment with lenalidomide at the licensed dose for up to 5 years.
- The treatment has already been approved in this indication (US 2005 and Europe 2013) and has been in use in the US since 2005 and the UK since 2009 which, as demonstrated, has allowed evidence to be built up demonstrating real-world effectiveness.
- Recent data presented at the ASH meeting confirm the clinical effectiveness of lenalidomide treatment in inducing cytogenetic response as well as transfusion independence and thereby increasing both OS and AML-free survival (evidence presented later within the answer to this question).
- There are no other alternative options for these patients barring regular blood transfusions which are associated with a high level of patient inconvenience, burden on NHS resources and poor clinical outcomes including quality of life.
- The recently published British Committee for Standards in Haematology (BCSH) guidelines recommend lenalidomide use within its licensed indication.
- There is strong clinical support for introduction of this treatment:
    - As noted by the Royal College of Physicians in response to the NICE appraisal for lenalidomide: "…the magnitude of haemoglobin increase, which is sustained by lenalidomide, is not normally achieved by alternative strategies to improve anaemia such as red cell transfusions or ESAs. Indeed red cell transfusion produces a cyclical

symptomatic benefit but peak haemoglobin concentrations are rarely >110 g/l which are achieved for perhaps only one week in the typical four week cycle. In contrast most responders to lenalidomide achieve sustained haemoglobin concentrations >110 g/l for a median response duration of around 2 years"

  - The Royal College of Pathologists stated – "Our experts believe that lenalidomide is a step change given the very high response rate and magnitude of haemoglobin increase in these patients"

- The UK haematologists consulted by Celgene were of the view that availability of lenalidomide would not only have a significant positive impact on patient convenience and clinical outcomes, but would also lower the resource utilization associated with blood transfusions and transfusion related side effects. Whilst these benefits may not all be explicitly visible in the health economic modelling, the actual benefit to UK patients could be significant.

## Appendix

## Ades et al. 2012 and Le Bras 2011

**Relevance to UK patient population:**
Elderly population (median age 70.4), compassionate patient named program with less stringent inclusion criteria than MDS-004. Patients were treated with the recommended schedule of 10mg lenalidomide daily, 21 days every 28 days for at least 16 weeks.

**Relevance to EU licence:**
Ninety five lenalidomide treated IPSS lower-risk del(5q) MDS patients. Majority (79%) had an isolated del(5q) abnormality and 62 (65%) patients previously received treatment for MDS, including ESAs (n=61) and/or thalidomide (n=3). Patients had baseline RBC transfusion-dependency with median baseline transfusion burden of 4 RBC units/ 2 months (range 2–12).

**Relevance to economic model and PAS:**
The overall response rate to lenalidomide was 65%, with 63% achieving transfusion independence. One and two-year freedom from RBC transfusions for patients achieving response was 92.5% (95%CI: 85.5–99.9) and 77% (95%CI: 64.9–91.5), respectively. In patients treated with lenalidomide, the median survival after diagnosis was 150 months and the 4-year survival after treatment onset was 67%.

**Conclusions:**
Supports applicability of PAS at 26+ cycles due to high rate of RBC transfusion-independence and prolonged duration of response within an elderly, real-world population.

## Sanchez-Garcia et al. 2011

**Relevance to UK patient population:**
Multi-centre registry study with less stringent inclusion criteria than MDS-004. 93% (80/86) received the recommended lenalidomide starting dose and schedule of 10mg 1-21/ 28 days.

**Relevance to EU licence:**
European patient population of IPSS lower risk del(5q) MDS patients. 84% of patients had isolated del(5q) and ~85% were RBC transfusion-dependent.

**Relevance to economic model and PAS:**
51% and 28% of patients achieved sustained or transient RBC transfusion-independence, respectively. In 49 assessed patients, 39% and 20% achieved a complete or partial cytogenetic response. In the lenalidomide treated patients, the median survival was 62 months, with 2 and 5 year overall survival of 92% and 62%. The median duration of RBC transfusion-independence was 36 months.

**Conclusions:**

Supports applicability of PAS at 26+ cycles due to high rate of RBC transfusion-independence and prolonged duration of transfusion independence within an elderly, real-world population.

## Mallo et al. 2013

**Relevance to UK patient population:**
Particularly elderly cohort with a median age of 75.5 years and with less stringent inclusion criteria than MDS-004.

**Relevance to EU licence:**
Predominantly European patient population. 73% of patients had isolated del(5q) and 98% were IPSS lower-risk del(5q) MDS.

**Relevance to economic model and PAS:**
78.4% (29/37) achieved RBC transfusion-independence with 30.8% complete cytogenetic response rate. Duration of response with lenalidomide was 30.4 months.

**Conclusions:**
Supports applicability of PAS at 26+ cycles due to high rate of RBC transfusion-independence and prolonged duration of response to treatment within an elderly, real-world population.

## List et al. 2006/2013

**Relevance to UK patient population:**
Median age was 71 years. Clinical trial patients with similar inclusion/ exclusion criteria to MDS-004. Patients treated with 10mg lenalidomide, 1-21/28 or continuous.

**Relevance to EU licence:**
148 IPSS lower risk RBC transfusion-dependent del(5q) MDS. 74.3% had isolated del(5q). Numerous efficacy analyses restricted to isolated del(5q) population.

**Relevance to economic model and PAS:**
When the analyses were restricted to isolated del(5q) patients, 70.9% achieved RBC transfusion-independence for ≥8 weeks and the median duration of transfusion independence was 2.3 years. In a Kaplan-Meier plot examining duration of transfusion independence over time in isolated del(5q) patients, ~40% of responders remained transfusion independent at 4 years (Figure 1b, List et al. 2013).

**Conclusions:**
Supports applicability of PAS at 26+ cycles due to high rate of RBC transfusion -ndependence and prolonged duration of response to treatment within a clinical trial setting.

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