Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality [ID480]

Prepared by:

Celgene Limited

June 2014

CONFIDENTIAL VERSION

Response to the Appraisal Consultation Document: Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality [ID480]	
Confidential information is highlighted and underlined, e.g. XXXXXX (AiC) and XXXXXX (CiC)	
Approved Name of Medicinal Product:	Lenalidomide
Brand Name:	REVLIMID®
Company:	Celgene Ltd
Submitted by:	[redacted]
Position:	[redacted]
Date:	13th June 2014

Dear Frances,

Celgene is grateful for the opportunity to respond to the second Appraisal Consultation Document (ACD2) developed by the Appraisal Committee (the Committee) following its meeting on 1st April 2014. We are of course disappointed that the Committee was unable to recommend lenalidomide as a treatment option for the small cohort of patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality. However, we would like to take this opportunity to address the issues raised in ACD2, and remain hopeful that the Committee will review its preliminary recommendations and produce final guidance to the NHS that supports the use of lenalidomide as a clinically and cost-effective treatment for this group. I should say that we do feel that there has been a loss of focus on the patient throughout this lengthy appraisal process. This is particularly notable in Section 4.16 of ACD2:

"The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions offered a step change in treatment."

The Committee goes on to conclude that this convenience is incorporated in the QALY calculations, in a way that implies that the oral administration of lenalidomide is its only innovative feature. During the previous NICE consultation process patient groups and the Royal College of Physicians noted additional important aspects, over and above its oral administration. These included alleviation of depression and anxiety; improved ability to lead a normal life; high response rate and the magnitude of haemoglobin increase none of which are likely to be entirely captured by the QALY calculation.

These benefits are recognised by national Cancer Drugs Fund decision summary scores,[1] which show that since April 2013, lenalidomide for MDS with isolated deletion 5q cytogenetic abnormality was the only application to have scored maximum points for meeting an unmet need and for its health related quality of life (HRQL) benefit out of the 57 applications that have made to the CDF to date.

Ultimately, the Committee concluded that following updated analyses and with a lenalidomide patient access scheme (PAS) the 'final' incremental cost-effectiveness ratio (ICER) for consideration is £25,300, but that this figure was subject to uncertainty. As a result the Committee concluded that the actual figure may exceed £30,000. We think it is both unreasonable and unfair of the Committee to

cite uncertainty here given that the MDS-004 study is the largest trial conducted in patients with this small subset of MDS, which is in itself an orphan disease (only 6.3% of MDS patients having del(5q)).[2]

In order to address the specific concerns raised by the Committee regarding this uncertainty, we have structured our response to focus on the following 3 issues:

1. **Generalisability of the MDS-004 study population**
2. **Uncertainty in cost-effectiveness results with incorporation of the patient access scheme**
3. **Logistics of the patient access scheme**

1. Generalisability of the MDS-004 study population

In the Final Appraisal Document (FAD) issued in October 2013 the Committee concluded that the MDS-004 study population was generalisable for appraising lenalidomide for the relevant MDS del(5q) patient population.

The Committee however effectively reverses this conclusion in ACD2, stating that generalisability to the licensed population is limited. Given that no additional related evidence was provided to affect the conclusion reached in the FAD, this development in ACD2 lacks transparency and appears to us to be perverse.

Specifically, the proportion of patients who received prior erythropoiesis-stimulating agent (ESA) in MDS-004 was highlighted as the key factor reducing generalisability. The assumption underpinning this appears to be that prior ESA use is a condition of the lenalidomide license and that prior ESA use impacts prognosis. Both of these assumptions are, in fact, incorrect.

The lenalidomide license does not state any requirement for prior ESA use. The license states that lenalidomide is "indicated for the treatment of patients 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."

In the UK, as reflected in the trial, many patients are unlikely to receive prior ESA as it is widely recognised as an inadequate treatment for transfusion dependent MDS del(5q) patients.[2] ESA use in the UK is also limited by funding as no standard recommendation is available.[3] Additionally, prior ESA use has been shown not to be a statistically significant prognostic factor. Clinical feedback accepted as part of the Scottish Medicines Consortium (SMC) process indicated, that MDS-004 study patients were representative of the population that would be treated with lenalidomide in Scotland, both in terms of baseline characteristics (e.g. prior erythropoietin) and demographic characteristics. As such, we feel that there is sufficient evidence for the Committee to have confidence in the generalisability of the MDS-004 study and that any conclusion to the contrary would be hard to justify.

2. Uncertainty in cost-effectiveness results with incorporation of patient access scheme

In ACD2 the Committee took a view that uncertainty in the strength of the relationship between achieving transfusion independence (TI) and extended overall survival (OS) contrived to make the proportion of patients becoming eligible for free of charge lenalidomide through the PAS uncertain. Celgene have previously provided a body of evidence to support the association between TI and OS, including the results of a systematic literature review. This is now further supported by a recent systematic review and meta-analysis conducted by the School of Health and Related Research (ScHARR) at the University of Sheffield, which associated TI with a 57% decrease in the risk of death compared to transfusion dependent patients.[4]

Data collected as part of Celgene's lenalidomide Treatment Continuation Scheme (TCS), which includes patients with more severe characteristics (e.g. intermediate-2 and high risk) than permitted

by the lenalidomide marketing authorisation, show that 28% of UK patients continued to receive lenalidomide at 26 cycles: comparable to the predicted figure of 31.9%.

All of this represents conclusive evidence that supports the achievability of the outcomes projected for patients receiving lenalidomide. That the Committee have failed to recognise this evidence is surely both unfair and unreasonable.

Additionally, some patients within the TCS database have received up to 70 cycles of treatment: without the benefit of a PAS and at full cost to the NHS.

Recently published evidence from MDS-004 demonstrates a continued link between TI and OS for up to 7 years, and importantly lenalidomide becomes cost-effective at a model time horizon of between 5 and 6 years (over which time the relationship is shown to persist with considerably greater certainty).

3. Logistics of the patient access scheme

The lenalidomide PAS was approved by the Department of Health following review by the Patient Access Schemes Liaison Unit (PASLU), whose remit is to review and evaluate PAS proposals regarding a scheme's value for the NHS.[5] This was an involved process with expert panel review meetings with clinicians and pharmacists present, and requests for clarifications from the manufacturer. The scheme was recommended only after PASLU were satisfied that the lenalidomide PAS was achievable. More specifically it was clinically robust, plausible, appropriate, feasible to implement and monitorable.[6]

The PAS functions on the back of the pregnancy prevention programme (PPP) which is a mandatory requirement for prescribing lenalidomide. This approach has neutral burden on the NHS and dispensing pharmacists.

With regards to treatment interruptions increasing uncertainties, it is already noted in the FAD that treatment interruptions were accounted for in the cost-effectiveness analysis through previous clarifications provided, and have minimal impact on the lenalidomide ICER.

In summary, Celgene is disappointed that the Committee has decided to reverse its earlier conclusions around it's evidence consideration, which appears to us to have been undertaken unfairly and without the benefit of additional evidence; resulting in a negative ACD2.

Celgene would like to emphasize again that MDS del(5q) is an orphan condition affecting a very small patient population (≈350 patients per annum in England and Wales) for whom there are no other treatment options.

The robustness of the clinical and cost-effectiveness evidence that Celgene have provided is far more than would normally be possible for such a rare condition. We request that the emphasis of this process should therefore primarily be on the patient and enhancing access to innovative treatments, especially when they have already demonstrated cost-effectiveness.

Celgene is, of course, committed to ensuring that patients are ultimately able to gain access to this treatment on the NHS and we shall engage fully in those of the Institute's formal processes that remain open to us.

Thank you once again for the opportunity to respond to the recent ACD and we look forward to the ensuing discussions at the next Committee meeting.

Yours sincerely

[redacted]
[redacted]
Celgene Ltd

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Section 1: Generalisability of the MDS-004 study population

Summary:

- In the FAD issued in October 2013 the Committee concluded that the MDS-004 study population was generalisable for appraising lenalidomide for the relevant MDS del(5q) patient population (see FAD Section 4.3).
- In ACD2 issued in May 2014, however, the Committee reverses this conclusion by stating that the generalisability of the MDS-004 is limited (see ACD2 Section 4.4).
- The Committee cited the proportion of patients who received prior erythropoietin in MDS-004 to be the important factor reducing the study's generalisability. This is factually incorrect as:
  - The license for lenalidomide does not require prior use of an ESA
  - Many patients are unlikely to receive prior ESA in the UK as it is widely recognised as an inadequate treatment for transfusion dependent MDS del(5q) patients and receives only limited funding
  - In addition, as previously presented, prior erythropoietin use has no significant impact on lenalidomide outcomes (response, OS or acute myeloid leukaemia (AML)-free survival) meaning that this variable has no bearing on the generalisability of the trial
- During the assessment of lenalidomide by the SMC, based on independent clinical expert feedback provided, SMC concurred that MDS-004 study patients were representative of the population that would be treated with lenalidomide in Scotland, both in terms of baseline characteristics (e.g. prior erythropoietin) and demographic characteristics. The patient population in England and Wales is expected to be similar to that in Scotland, as shown by the TCS database which demonstrates similar patient characteristics and outcomes to those in the trial.
- Information from the TCS database, which is a registry of lenalidomide prescriptions in the UK, shows that the patient population in clinical practice in UK has a mean age of ~70 years, comparable to the 10mg MDS-004 trial arm (mean age of 68 years).
- In multivariate analysis of the MDS-004 trial, age has limited impact on both OS and AML-free survival, whereas the impact of TI is substantial. Even when MDS-004 data is age adjusted to reflect a UK MDS patient average age, (using OS and AML-related hazard ratios [HRs]) it has minimal impact on cost-effectiveness results.
- The license limits use of lenalidomide to patients with isolated del(5q). The trial contains patients with less favourable prognostic characteristics. However, as previously presented and agreed by the Committee, the majority of patients within the trial are isolated del(5q) patients and the results for response, OS and AML are similar to those in the ITT population.
  - In practice, given that isolated del(5q) patients are expected to have better prognosis and survival, a PAS applied to only this cohort is likely to further improve the cost-effectiveness of lenalidomide (as they are likely to receive more free cycles) and therefore current estimates are conservative.

Context

In ACD2 the Committee concluded that the generalisability of the MDS-004 study population to that covered by the marketing authorisation is limited (see ACD Section 4.3):

"The Committee heard from the manufacturer that around 59% of the study population had received previous treatment (see section 3.1), and therefore noted that the study population would have a better prognosis than those for whom the drug has a marketing authorisation, and that the generalisability of the study population was limited."

These points are repeated in ACD2 Section 4.9:

"It noted that, in clinical practice when other therapeutic options are insufficient or inadequate, the overall population with MDS associated with a deletion 5q cytogenetic abnormality was likely to have a poorer prognosis than the population included in the MDS-004 trial, and therefore in the model, because it heard from the manufacturer that around 40% of people in the trial had not had previous treatments that had failed. The Committee agreed that the model represented a group of patients with less severe disease than that of the marketing authorisation and was therefore likely to overestimate survival and effectiveness of treatment on both treatment arms."

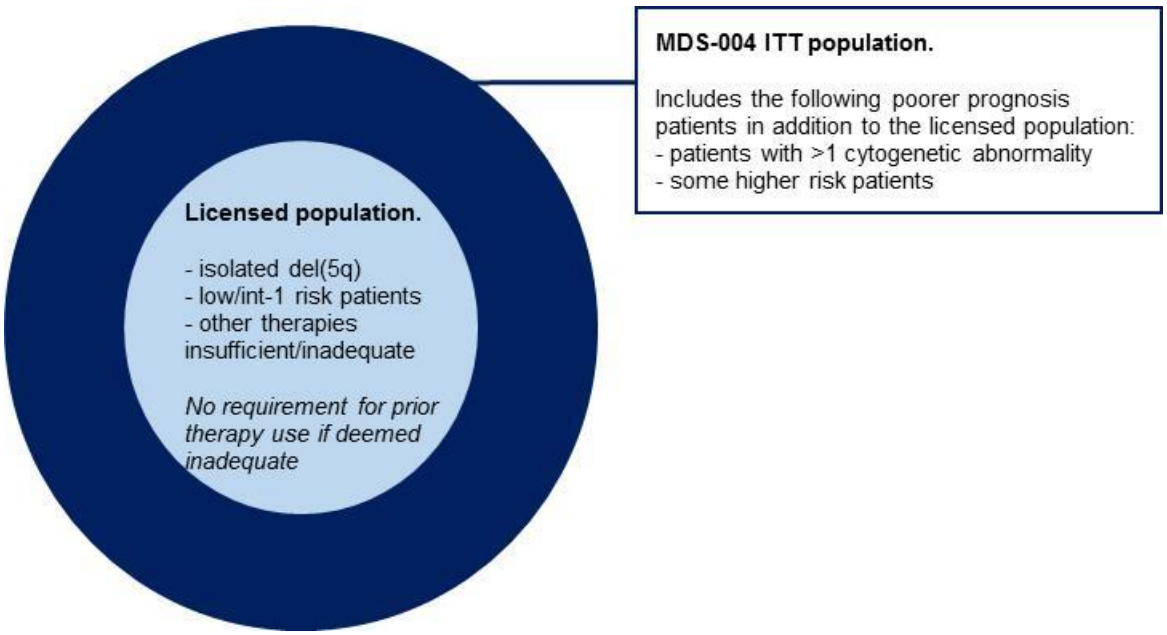
And ACD2 Section 4.10:

"The population in the MDS-004 study had a better prognosis than that specified in the marketing authorisation (see section 4.4), and therefore overall survival was likely to be overestimated."

The proportion of patients who receive prior erythropoietin was provided in the original submission document along with the evidence demonstrating that prior erythropoietin use had no impact on any of the relevant efficacy outcomes, including OS. In the FAD, the Committee concluded that the MDS-004 study population was suitably generalisable for appraising lenalidomide for the relevant (del-5q) patient population (see FAD Section 4.3).

In the sections below we address the key potential differences between the patients in the MDS-004 trial and the licensed population and the population to which lenalidomide would be given in UK clinical practice (Figure 1), and the impact of these differences on clinical outcomes.

Figure 1: Schematic of the MDS-004 trial, UK clinical practice and lenalidomide licensed populations



Prior erythropoietin use

In ACD2 the Committee cite prior ESA use as the basis for arguing that study MDS-004 exhibits poor generalisability to the licensed population. This inference appears to be based on no additional evidence since the release of the FAD, and is factually incorrect.

The marketing authorisation for lenalidomide covers patients for whom "other therapeutic options are insufficient or inadequate." This does not exclude patients who have not previously received an ESA, as not all patients are suitable for this treatment. The use of ESAs in the UK is likely to be similar to, or lower than, the proportion of patients who received such prior therapy in MDS-004 (58.5%).

As highlighted by Celgene in response to the Evidence Review Group (ERG) clarification request made on 1 February 2014, patients with a del(5q) chromosomal abnormality are less likely to respond to ESAs than MDS patients without del(5q).[3]

As presented in the original submission the majority of patients in the MDS-004 trial are unlikely to respond to ESA due to their high transfusion burden (Table 1). Patients in the trial can be categorised into one of three predictive groups using information from Hellström-Lindberg et al, dictating their likelihood of response to ESA + G-CSF (granulocyte colony-stimulating factor).[7] These groups are defined as follows:

- High probability of response: Serum erythropoietin (S-Epo) of ≤ 500 U/l, and a prior transfusion requirement of < 2 red blood cell (RBC) units per month on average.
- Intermediate probability of response: one of either S-Epo ≤ 500 U/l or a prior transfusion requirement of < 2 RBC units per month.
- Low probability of response: S-Epo of > 500 U/l, and a prior transfusion requirement of ≥ 2 RBC units per month on average

Table 1 Response rates to ESA + G-CSF and distribution of MDS-004 patients by predictive group

Predictive Group	Proportion of MDS-004 Patients
High probability of response	3.5%
Intermediate probability of response	36.4%
Low probability of response	60.1%

This clinically recognised lack of response in transfusion dependent del(5q) patients results in few patients receiving ESA in the UK, as it is deemed an insufficient therapeutic treatment for the majority of del(5q) patients. This is also supported by evidence from Germany, where analysis of the treatment of MDS del(5q) found low usage of other therapies', including ESA.[3] Furthermore access to ESA is limited in the UK as there is no standard recommendation or funding available.

During the assessment of lenalidomide by the SMC, based on independent clinical expert feedback provided, SMC concurred that MDS-004 study patients were representative of the population that would be treated with lenalidomide in Scotland, both in terms of baseline

characteristics (e.g. prior erythropoietin) and demographic characteristics.. The patient population in England and Wales is expected to be similar to that in Scotland, given that the TCS database shows similar patient characteristics and comparable outcomes to those shown in the lenalidomide trials (Appendix 3).

Fenaux *et al (*2011)[8] also evaluated prior ESA use and baseline erythropoietin level, and showed it to have no significant impact on:

- Response to lenalidomide (Figure 3; Fenaux 2011[8])
- Overall survival (p=0.390; Table 4; Fenaux 2011[8])
- AML-free survival (p= 0.539; Table 4; Fenaux 2011[8])

This means that even if prior ESA use was different to the trial in UK practice (either lower or higher) there would be no impact upon either clinical effectiveness or cost-effectiveness. Additionally, the MDS-004 study data were explored to evaluate the impact of prior ESA use on OS. This analysis, conducted for the present response, also showed no significant impact of prior ESA use on OS (log-rank test p=0.3270).

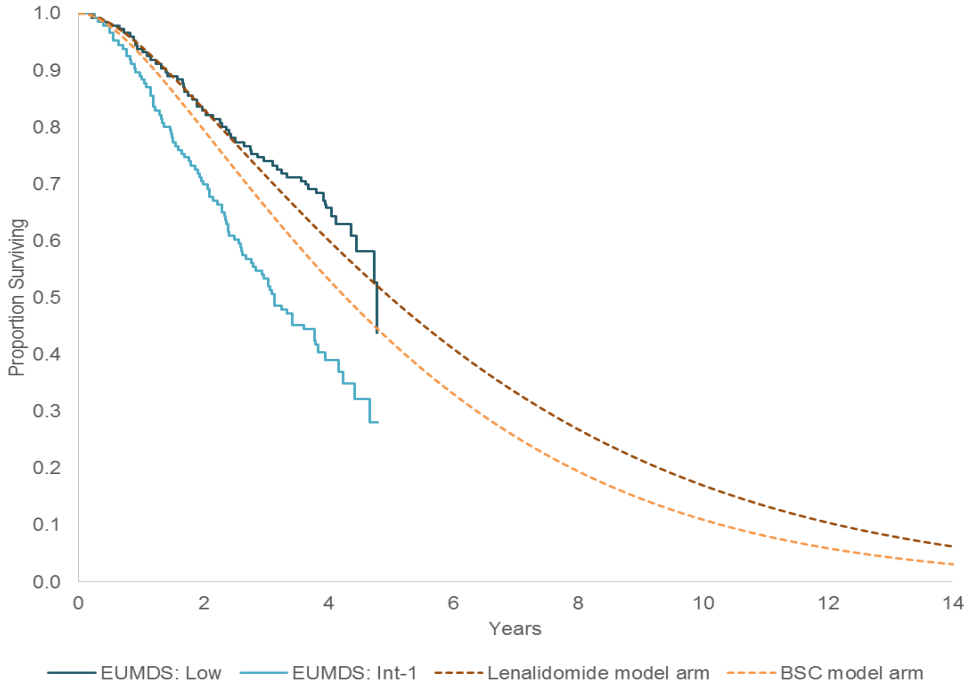
Age

The mean age of the MDS-004 study population is 68 years, comparable to around 70 years in Celgene's TCS data reflecting current UK use of lenalidomide. De Swart et al[9] provide detail and analysis of a multicentre European patient registry (European Leukemianet MDS [EUMDS]), where the median patient age for all MDS patients is 75 years. It is important to note that the registry includes all MDS patients and all risk categories therefore to compare the patient populations in the registry to the MDS-004 study, which only includes low and intermediate-1 risk MDS del(5q) patients, is not appropriate. In addition age is not a strong indicator of poor generalisability since the registry spans 16 countries and only 6% of patients had del(5q). It is therefore unlikely that the registry is itself reflective of UK practice.

A multivariate analysis of the MDS-004 trial also showed that age has only a limited effect on OS (HR 1.04; 95% confidence interval (CI) 1.01-1.07), whereas the impact of TI is considerably more substantial (HR 0.53; 95% CI 0.31-0.91).[8] Age was also shown to have only a limited impact upon AML-free survival (HR 1.04; 95% CI 1.01-1.06). To provide greater certainty around the impact of increased age on cost-effectiveness these OS and AML-related HRs were applied in the cost-effectiveness model. This analysis showed that raising the MDS-004 age profile to 70 years, in order to match the TCS data which is reflective of UK practice, has only a small impact on the ICER and lenalidomide remains cost-effective (see Appendix 1).

Additionally, Kaplan-Meier estimates of OS by risk status reported by de Swart et al[9] were digitised (Figure 2), showing that 2-year survival in all low and intermediate-1 risk EUMDS patients was around 84% and 70% respectively. These values are comparable to 83% and 80% on the lenalidomide and standard care arms of the cost-effectiveness model respectively. Survival projections from the model lie in between the plots for low risk and intermediate-1 risk patients from the EUMDS dataset, further supporting that the difference in age does not materially impact OS projections.

Figure 2: Survival of low and intermediate-1 risk MDS patients in EUMDS and cost-effectiveness model projected survival



Cytogenetic abnormalities

Contrary to what the Committee states in ACD2, the MDS-004 trial in fact contained patients with less favourable cytogenetic abnormalities than the licensed indication, which is for isolated del(5q) patients only. However, as presented in the response to the previous ACD document (ACD1), the majority of patients within the trial are isolated del(5q) patients and the results for response, OS and AML are similar to those in the ITT population on the basis of which the Committee agreed that it was appropriate to use the ITT population to evaluate the cost-effectiveness of lenalidomide (see FAD Section 4.4):

"The Committee was aware that a significant proportion of the people in the MDS-004 study were covered by the marketing authorisation. It concluded that it would be able to consider all of the evidence in the MDS-004 study when making recommendations on lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality."

It should be noted that, given isolated del(5q) patients are expected to have better prognosis and survival, a PAS applied to only this cohort is likely to further improve the cost-effectiveness of lenalidomide, as more of these patients are likely to remain on treatment for longer and receive more free cycles. As such, the current cost-effectiveness estimates are likely to be conservative to lenalidomide.

Conclusion

Given the above points of clarification, it is clear that the Committee's reversal with regard to the generalisability of MDS-004 to the licensed population is factually incorrect. The arguments for MDS-004 offering a robust evidence base on which to base a decision for patients in England and Wales are summarised below:

- The marketing authorisation for lenalidomide is for patients for whom 'other therapeutic options are insufficient or inadequate'; this can include patients who have not previously received ESA therapy, which is widely recognised as an inadequate

treatment option due to low response rates in transfusion-dependent MDS del(5q) patients.

- In fact prior ESA use in the trial is probably more than may be expected in UK clinical practice. Any differences in ESA use however do not impact either clinical or cost-effectiveness comparisons as trial subgroup analysis showed there to be no statistically significant impact of prior ESA or baseline erythropoietin level use on clinical outcomes.
- Available UK data indicates a similar mean age of patients currently receiving lenalidomide to that within the MDS-004 trial. Matching this age profile has minimal effect on the cost-effectiveness of lenalidomide.
- A registry of low/intermediate-1 risk MDS patients has a higher age profile, but the data spans 16 countries and only 6% of patients have del(5q). Despite this, the data shows similar survival to that estimated by the lenalidomide cost-effectiveness model, further supporting the generalisability of MDS-004 for a UK del(5q) patient population.
- The MDS-004 trial contains patients with a poorer prognosis than the licensed indication: more cytogenetic abnormalities and a small number of higher risk patients. Use of ITT data is therefore conservative to lenalidomide.

Section 2: Uncertainty in cost-effectiveness results with incorporation of the patient access scheme

Summary:

- In ACD2 the Committee concluded that the generalisability of study MDS-004 and uncertainty regarding the strength of the relationship between achieving TI and extended survival contrived to make the proportion of patients becoming eligible for free lenalidomide uncertain.
- A body of evidence was provided by Celgene in support of the link, including a systematic literature review in which 16 out of 22 studies identified showed a link between TI and OS and was accepted by the ERG.
- ScHARR, at the University of Sheffield, have recently conducted a systematic review and meta-analysis exploring the TI/OS link which found a significant positive survival effect of TI relative to transfusion dependence (TD). The headline result from this analysis shows that TI is associated with a 57% decrease in the risk of death compared to TD.[4]
- Further evidence available from MDS-004 also demonstrates a continued link between TI and OS for up to 7 years.
- Lenalidomide becomes cost-effective at a model time horizon of between 5 and 6 years, and MDS-004 shows that a significant TI and OS link persists at this time.
- As previously presented, ongoing data collection as part of the TCS demonstrates that 28% of UK MDS patients continued to receive lenalidomide at 26 cycles with some patients currently receiving up to 70 cycles and the NHS paying the full cost.
- Importantly, the PAS is a capping scheme which has no bearing on the evidence submitted and accepted by the Committee in the FAD.

Context

Celgene is disappointed that the Committee have decided to reverse their earlier conclusions, without the benefit of additional evidence; regarding the generalisability of the MDS-004 trial. Contrary to what the Committee concluded in the previous FAD, in ACD2 the Committee now questions the generalisability of study MDS-004, and is uncertain regarding the strength of the relationship between achieving TI and extended survival, and the proportion of patients who reach 26 treatment cycles and become eligible for free lenalidomide.

ACD Section 4.10:

"The Committee concluded that, although it was reasonable for the model to include some benefit in overall survival for people whose condition responds to lenalidomide compared with best supportive care, the amount of survival benefit was highly uncertain, and could be overestimated in the model."

ACD Section 4.12:

"*The Committee agreed that, because the proportion of people surviving beyond 26 cycles in clinical practice was uncertain (see above and section 4.5), so were the potential cost savings from the patient access scheme."*

A body of evidence was provided by Celgene in support of the link.

Strength of the association between TI and OS

The Committee state in ACD2 that while a relationship between achieving TI and extended OS is clinically plausible, the strength of this relationship is uncertain and therefore (by implication) the survival benefit achieved by treatment with lenalidomide is also uncertain (see ACD2 Section 4.5). The Committee concluded that this uncertainty means the survival benefit could potentially be overestimated.

"The population in the MDS-004 study had a better prognosis than that specified in the marketing authorisation (see section 4.4), and therefore overall survival was likely to be overestimated."

There was no specific reference to potential overestimation in the FAD, and it appears that the Committee's current uncertainty around this link fails to fully consider all of the available evidence. Furthermore, the direction of any uncertainty is not clear and therefore the assertion that the lenalidomide survival benefit could be overestimated is unsupported.

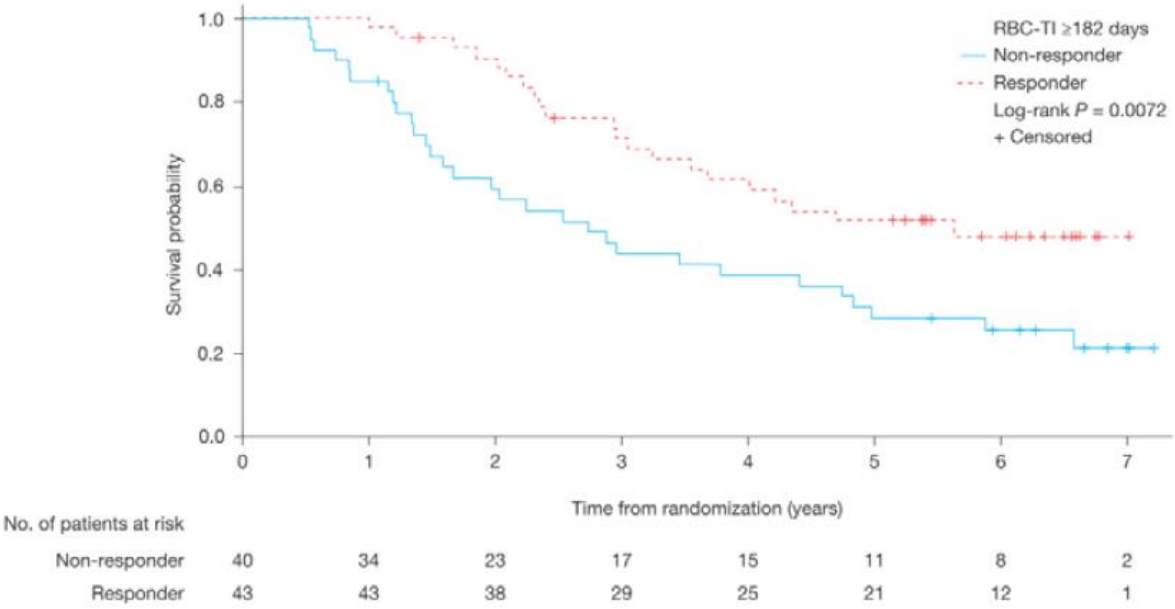
The ERG stated that the assumption of a "2-step" relationship between TI and OS was a reasonable one, supported by data (see ACD2 Section 4.5). In response to the ACD1, Celgene conducted a systematic literature review to evaluate the relationship, in which 16 out of 22 studies reported a statistically significant association.

Giagounidis *et al* (2014)

A recently published updated analysis of the MDS-004 study, using a more recent data cut, supports the existence of a significant link between TI and OS.[10] Figure 2 shows Figure 3B from the analysis, and shows clearly superior survival prospects in low/ intermediate-1 risk patients with isolated del(5q) who experienced a period of at least 182 days of TI. Median OS was 5.7 years (95% CI: 3.2-NR) in these responders compared to just 2.7 years (95% CI: 1.5-4.8; P=0.0072) in non-responders, a statistically significant difference despite relatively low patient numbers due to the orphan nature of this indication.

Furthermore, using this more recent data cut, median OS among patients who started on 10mg lenalidomide (4.0 years; 95% CI: 2.5-NR) was notably higher than the placebo group (2.9 years; 95% CI: 2.2-4.2). This relationship was not found to be statistically significant, but as noted by the authors this would have been affected by the extensive and early crossover from the placebo study group, and the absolute difference remains a good indication of improved survival with lenalidomide. As such, this study supports both the strength of the TI-OS relationship, with available evidence for this relationship now continuing for up to 7 years; and suggests support for a direct survival benefit from lenalidomide compared to placebo. Kuendgen *et al* (2013)[11] also report that treatment with lenalidomide was associated with a significant improvement in survival compared with untreated patients.

Figure 3: Overall survival in MDS-004 by transfusion dependence status



Data cut: 26 November 2012

Meta-analysis conducted by ScHARR (2014)

A recently conducted systematic literature review and meta-analysis by ScHARR provides additional significant evidence for the importance of TI as a prognostic factor. Based on 11 studies identified in which patients enrolled were either transfusion dependent or independent, a pooled effect of TI on OS was characterised by a HR of 0.43 (95% CI: 0.31, 0.56). This is strongly supportive of the TI/OS link, as in this instance a HR<1 indicates better survival among TI patients; it equates to a 57% decrease in the risk of death compared to TD patients.[4]

For low-risk MDS patients, the HR for TI relative to TD is estimated to be 0.53 (95% CI: 0.27, 1.05), a 47% decrease in the risk of death. Study overlap prevented a meta-analysis of studies where patients entered as TD and became TI during the course of the study, however, these studies did report HRs ranging from 0.53 to 0.36 (a mortality reduction ranging from 47% and 64% associated with the achievement of TI).

These estimates are consistent with the results reported within the MDS-004 trial (HR 0.53 95% CI: 0.31-0.91).[8]

Cost-effectiveness at the 5-year and 6-year time horizons

At a 5-year model time horizon lenalidomide is associated with an ICER of £30,923, at a 6-year model time horizon the ICER is £26,262 demonstrating that lenalidomide becomes cost-effective within a relatively short time-horizon. The ERG note in their evaluation that the first 5 years of the cost-effectiveness model time horizon is associated with the least uncertainty, because the evidence of a link between TI and OS is stronger within this time period. The updated MDS-004 analysis shows the relationship is robust over this duration, and in fact persists for up to 7 years.

Patients reaching 26 treatment cycles

The Appraisal Committee also expressed concern that low patient numbers in MDS-004 at 26 cycles limited their confidence around the proportion of patients expected to become eligible for the PAS (see ACD2 Section 4.12):

"The Committee was aware that the data supporting survival after 26 cycles were from small patient numbers in the MDS-004 trial (less than 38 patients), and were therefore very uncertain."

The Committee did note clinical support for the expected proportion of patients eligible for the PAS (see ACD2 Section 4.12):

"The Committee considered the manufacturer's evidence that supported the assumption of 31.9% of people reaching 26 cycles in practice (see section 3.48), and noted that this was supported by a clinical specialist."

However, in commenting on the number of patients, we feel that the Committee have disregarded the orphan disease status of low/ intermediate-1 risk MDS with isolated del(5q) and the very small number of patients expected to be treated in UK practice (≈350 patients). Additionally, the Committee have disregarded the supporting evidence provided in the previous AC response from the TCS database (n=124), and the supportive evidence presented from available observational and Phase II evidence (n=452), all of which indicate similar trends to the MDS-004 trial.

<u>Evidence from TCS</u>

To further validate the benefit to the NHS of the PAS, Celgene evaluated the longer term treatment continuation in the TCS database. This analysis was provided during the submission process and demonstrates that 28% of patients currently remain on treatment until the 26th treatment cycle, close to the modelled estimate of 31.9%, yet it may be an underestimate given that the TCS data include patients with more severe disease characteristics (includes patients with del(5q) + additional cytogenetic abnormalities and also non del(5q) patients) than the population covered by the licensed indication for lenalidomide. The mean treatment duration beyond cycle 26 within the TCS dataset is 15.9 cycles (sd: 12.7).

However, it appears that the Committee did not note the ERG's review of the TCS data analysis. The ERG agreed that it provides a reasonable estimate of the proportion of patients reaching eligibility for the PAS (see ACD Section 3.50):

"The ERG validated the changes to the manufacturer's model, confirming that the patient access scheme was incorporated appropriately. It agreed with the manufacturer that the real-world evidence suggested that about 30% of patients reach 26 cycles of treatment, and the ERG stated that this was a reasonable assumption."

Clinical experts were also consulted to elicit their view of the TCS data, both prior to and following ACD2, and advised that the analysis provides an accurate reflection of patients who will remain on lenalidomide to reach the PAS.

Additionally, we would like to remind the Committee that to reduce uncertainty in longer term survival estimates the median survival within the model for best supportive care was adjusted to match the reported median survival for untreated patients from the Kuendgen analysis.[11] This adjustment was applied to the scale parameter for the OS curve for transfusion dependent patients, keeping the HR for the difference in survival between transfusion independent and dependent patients fixed as per the MDS-004 trial. This means

that survival on both arms has already been adjusted downwards to account for any differences between real-life patients and those within the lenalidomide trials.

Conclusion

We hope that the points above will reduce any remaining uncertainty that the Committee have, regarding the proportion of patients likely to receive lenalidomide through the PAS:

- Patients are more likely to respond and achieve TI with lenalidomide, and a body of evidence supports a significant link between TI and OS. Published trial evidence demonstrates that this association continues for up to 7 years.
- Furthermore, analysis of Celgene's TCS database of existing lenalidomide use in MDS suggests that the proportion of patients expected to reach 26 cycles of lenalidomide is closely matched by existing lenalidomide uptake. This figure also received support from a clinical expert consulted by NICE.
- Finally, over shorter time horizons where the evidence base regarding the TI/OS link is strongest, and where MDS-004 trial outcomes require less extensive extrapolation, lenalidomide is cost-effective. Lenalidomide becomes cost-effective at a time horizon of between 5 and 6 years.

All of the evidence provided by Celgene represents conclusive evidence that supports the achievability of the outcomes projected for patients receiving lenalidomide. That the Committee have failed to recognise this evidence seems to us to be somewhat perverse.

Section 3: Logistics of the patient access scheme

Summary:

- In the ACD the Committee expressed concern that the practicalities of the lenalidomide PAS and the delaying impact of treatment interruptions might prevent the NHS receiving the expected level of discount (see ACD Section 4.13).
- The impact of lenalidomide treatment interruptions, which would delay eligibility for the PAS as patients must have received 26 cycles of treatment, was fully accounted for in the cost-effectiveness analysis and has been shown to have minimal impact on the lenalidomide ICER.
- The scheme has been accepted by the Department of Health, following a thorough assessment by PASLU involving two sets of clarifications and expert panel meetings. The remit of PASLU is to review, evaluate and advise on PAS proposals, and their expert panel would not have recommended the lenalidomide scheme if it did not offer value for the NHS.
- Pharmacies and hospitals have substantial experience of an identical scheme, currently being used for lenalidomide for multiple myeloma.
- Monitoring of lenalidomide cycles received is automated and undertaken by Celgene, therefore the administration burden placed on pharmacies is low and is not expected to impact the extent to which discounts are realised.
- Evidence from continued monitoring of lenalidomide use, suggests that uptake of the scheme for multiple myeloma is close to what was anticipated prior to NICE recommendation.

Context

The Committee were concerned that practical and logistical aspects of implementing the lenalidomide PAS would raise uncertainty around how much the NHS would benefit from the scheme (see ACD2 Section 4.13). Details of specific logistical issues that the Committee feel may affect whether all the savings are realised in practice are not provided. It is perceived that concerns stem from the scheme being a standard scheme rather than a direct price discount.

The Department of Health and the PASLU, whose remit is to review and evaluate PAS proposals, considered that the scheme does not provide an excessive administration burden on the NHS. Assessment is carried out via an involved process, requiring a full PASLU submission by Celgene which was reviewed with clarifications provided as requested, and discussed at expert panel meetings. In providing guidance to the Department of Health regarding a scheme's value for the NHS, the PASLU expert panel (which included clinicians and pharmacists) was satisfied that the lenalidomide scheme was *"clinically robust and plausible, appropriate, feasible to implement and monitorable"*.[6]

Further, the ACD reports that the Committee feels lenalidomide treatment interruptions are a complicating factor (see ACD2 Section 4.14):

"The Committee noted that the patient access scheme was based on the number of treatment cycles, and therefore any treatment interruptions would delay when the patient access scheme would take

effect and therefore the time to the NHS receiving the rebate or discount for those patients with dose interruptions."

Celgene explored the impact of treatment interruptions in their cost-effectiveness analysis, and this analysis was used to inform the 'final' ICER for consideration. The Appraisal Committee noted that the impact of treatment interruptions on the cost-effectiveness of lenalidomide is minimal (see ACD2 Section 4.14):

"The Committee acknowledged that accounting for treatment interruptions reduced the ICER minimally (from £25,300 with 16 days of interruptions to £25,700 with 42 days; see section 3.47)."

Despite this, the Committee went on to conclude that because of the nature of the lenalidomide PAS, treatment interruptions introduced uncertainty (see ACD2 Section 4.14):

"The Committee concluded that the nature of the patient access scheme meant that accounting for treatment interruptions introduces uncertainty about when people would reach 26 cycles of treatment, and therefore when the savings from the patient access scheme could be claimed by the NHS."

Treatment interruptions

The Committee concluded that the mechanism of the PAS means treatment interruptions will introduce uncertainty in the savings made by the NHS, noting that because free lenalidomide is provided after 26 treatment cycles, any period of interrupted treatment will delay the PAS (see ACD2 Section 4.14). Additionally, the Committee note that in the cost-effectiveness model, treatment interruptions reduce the cost of lenalidomide but do not affect its efficacy.

We would like to raise some important limitations of this argument to raise the confidence of the Committee in the lenalidomide PAS. Firstly, the scheme operates on the back of the mandatory pregnancy prevention programme (PPP). Each treatment cycle prescribed is recorded and once a patient becomes eligible for free of charge lenalidomide, this happens automatically.

Second, the Committee note that treatment interruptions do not explicitly reduce lenalidomide efficacy in the cost-effectiveness analysis, but do reduce its costs. However, the key clinical outcomes derived from study MDS-004 (OS, response and time to AML) implicitly incorporate any effect of interruptions, because patients experiencing treatment interruptions are included in the parametric survival curves used within the model. Additional analysis of the MDS-004 study data was conducted and showed no discernible difference in OS estimates between MDS-004 patients who started on lenalidomide 10mg and experienced zero, 1 or at least 2 treatment interruptions (log-rank test p=0.8508).

Finally, the delay in reaching 26 treatment cycles caused by treatment interruptions was incorporated into the cost-effectiveness analysis. The Committee note that extending this duration from the base case of 16 days, as derived from MDS-004 study data, to 42 days (6 weeks) increases the ICER by just £400. Treatment interruptions are therefore not a key determinant of the final ICER; any perceived uncertainty around delays in the NHS receiving this discount should not be considered crucial in evaluating the cost-effectiveness of lenalidomide.

Practicalities of the scheme

The Committee raised concerns that the lenalidomide PAS would provide an administrative burden that would reduce the cost savings realised by the NHS, although specific concerns were not provided. This view was not shared by PASLU, who advised the Department of

Health that the scheme does not provide an excessive burden on the NHS and is feasible, monitorable and clinically robust.[6]

Full details of how the scheme will be administered, as provided to the PASLU, are provided in Appendix 2. This describes the full process of entering and using the scheme which, in summary, places no additional administrative burden on the dispensing pharmacy. Due to the teratogenic nature of lenalidomide it is mandatory that pharmacies dispensing lenalidomide register with Celgene and return a completed Prescription Authorisation Form (PAF) for each lenalidomide treatment cycle prescribed as part of the PPP required by the EMA. This process automatically triggers patient enrolment in the PAS. Celgene monitor the number of treatment cycles a patient receives, and the pharmacy receives future cycles of lenalidomide at no cost. Pharmacies are given the choice of receiving the rebate in the form of either a credit note or free stock (typically opting for credit note in the identical multiple myeloma scheme). The introduction of electronic PAFs which is currently in its implementation phase in the NHS is only going to make this process more efficient.

Additionally, hospitals are likely to have experience with the PAS and this familiarity will help in the uptake of the scheme. The same scheme is already in place for lenalidomide for the treatment of multiple myeloma (discussed below). Over 200 hospitals currently take part in the multiple myeloma scheme.

Identical scheme in multiple myeloma

In ACD2 the Appraisal Committee noted that UK multiple myeloma patients are currently benefiting from an identical lenalidomide PAS (see ACD2 Section 4.13):

"The Committee considered the logistics of the patient access scheme, noting that the NHS has experience with this patient access scheme because it is available for multiple myeloma."

This existing, identical scheme for multiple myeloma provides further supportive evidence for the proportion of patients reaching eligibility. A publication presenting continued analysis of Celgene's TCS data for multiple myeloma lenalidomide prescriptions up to 2011 shows that 15–16%[12] of patients received 26 cycles of lenalidomide and therefore became eligible for free of charge treatment, close to the expected 17% of patients in TA171. Current information indicates that this percentage is on the increase. As shown within the TCS data for MDS discussed above, this suggests that the proportion of patients reaching 26 treatment cycles, and becoming eligible for the PAS, can be accurately projected.

Conclusion

We hope that the points above will reduce any remaining uncertainty that the Committee have, regarding the logistics of the PAS:

- The scheme has been assessed by PASLU via an extensive consultation process with expert guidance as clinically robust and plausible, appropriate, feasible to implement and monitorable
- Monitoring of lenalidomide cycles received is automated and undertaken by Celgene, therefore the administration burden placed on pharmacies is low
- Evidence from continued monitoring of lenalidomide use, suggests that uptake of the scheme for multiple myeloma is reflective of what was anticipated prior to NICE recommendation

Section 4: Other considerations

Summary:

- Regrettably, we feel that there has been a loss of focus on the patient throughout this lengthy appraisal process, with Committee conclusions highlighting the convenience associated with lenalidomide's oral administration but failing to consider the full benefit of lenalidomide.
- During previous consultation, patient groups and the Royal College of Physicians noted additional important features of treatment with lenalidomide, highlighting its innovative nature over and above its oral administration. Such features include:
  - Alleviation of severe fatigue
  - Alleviation of depression and anxiety
  - Improved ability to lead a normal way of life
  - The high response rate achieved with lenalidomide
  - The magnitude of haemoglobin increase caused by lenalidomide.
- A discrepancy raised by the ERG regarding the duration of treatment interruptions applied in Celgene's updated model is explained by clarification on datasets

Context

Celgene would like to this take this opportunity to highlight other considerations raised through the ACD2, particularly regarding an apparent general loss of a focus on the patient, and to address one specific data issue raised by the ERG.

Loss of focus on the patient

Regrettably, we feel that there has been a loss of focus on the patient throughout this lengthy appraisal process, with uncertainties disproportionately emphasised compared to the benefits of lenalidomide to the patient. While the Committee note that the oral administration of lenalidomide provides an innovative treatment option in the Section 4.16 of the ACD2, the lack of patient focus can be seen:

"The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions offered a step change in treatment."

The Committee go on to conclude that this convenience is incorporated in the QALY calculations and economic analyses. This focus on convenience implies that the oral administration of lenalidomide is its only innovative feature, and serves to detract from its wider benefits.

During consultation, ahead of ACD1, the joint statement from the patient carer organisations MDS UK Patient Support Group and Leukaemia CARE, highlighted the importance of lenalidomide in changing the nature of treating the disease, as opposed to mere supportive care offered by transfusions. The groups stated that independence from transfusions alleviates severe fatigue, and symptoms of depression and anxiety caused by inability to lead a normal way of life. All of which are unlikely to be adequately represented through the QALY calculations alone.

Further, during the consultation stage, the Royal College of Physicians (consultee comments on ACD1) confirmed the innovative nature of lenalidomide for reasons other than its oral administration with the following statements:

"Our experts believe that Lenalidomide is a step change given the very high response rate and magnitude of haemoglobin increase in these patients." – Royal College of Physicians

"…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" – Royal College of Physicians[13]

Given the above the consultation process statements from the patient and physician community do not appear to have been adequately reflected in the Committee's perspective of innovative nature of the treatment benefit for lenalidomide in this orphan indication.

These benefits are recognised by national Cancer Drugs Fund decision summary scores.[1] Since April 2013 an application for lenalidomide for MDS del(5q) was the only application to have scored maximum points for meeting an unmet need and for its HRQL benefit out of 57 applications to date.

Time points considered

Finally, we would like to take this opportunity to provide clarification to the ERG relating to the data used in the cost-effectiveness analysis. The ERG discussed the implementation of treatment interruptions in the updated cost-effectiveness analysis, noting discrepancies in how they were incorporated (see ACD2 Section 3.50). These concerns may have contributed to the Committee's uncertainty regarding the PAS, despite the minimal impact of interruptions on the lenalidomide ICER. This concern stems from confusion around which MDS-004 data cut was used. In the ERG critique dated 10 March 2014, the ERG made the following comment:

"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, 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 CSR versus 13.9 in the model."

Importantly, the data cut reported in the CSR had an earlier cut off point compared to the data used in the model (and therefore the additional analyses). The CSR data was assessed following cut off in October 2010, compared to the model data cut off point of June 2011. This explains the discrepancies in the numbers reported in the model and CSR.

Conclusion

Celgene feel that there has been a loss of focus on the patient during the progression of this lengthy appraisal process:

- Lenalidomide is only considered to be innovative in the context of convenience due to its method of administration.
- This fails to recognise the important input of patient carer organisations and the Royal College of Physicians, with lenalidomide described as shifting the nature of treatment away from mere supportive care.

Additionally, we would like to clarify that the ERG's concern regarding how treatment interruptions were incorporated in the cost-effectiveness analysis should not cause undue uncertainty. This stems from confusion around the use of a later data cut in the cost-effectiveness analysis.

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Appendix 1 – Impact of age-related hazard ratios on cost-effectiveness model outcomes

To evaluate the impact of changing the OS- and AML-related age profile of MDS-004 patients on the cost-effectiveness of lenalidomide, the age-related HRs from Fenaux *et al* (2011) were applied (see Section 1). These were used to increase the age profile of the MDS-004 ITT population from 68 years to 70 years, matching the mean age of patients initiating treatment in the TCS database.

The ICER for this scenario analysis is shown to increase from the base case value of £25,310 to £26,603/QALY gained. This is still well within the range typically considered to be cost-effective. The ICER only exceeds £30,000/QALY gained once the MDS-004 age profile is increased to represent 75 year old patients.

Table 2: Cost-effectiveness model results with age-related OS and AML hazard ratios used to increase patient age to 70 years

Treatment Arm	Total		Incremental			ICER
	Costs	QALYs	Costs	Life Years	QALYs	
Lenalidomide	£135,724	3.51	£18,525	0.84	0.70	£26,603
BSC	£117,199	2.81				

Appendix 2 – Description of each step of the lenalidomide patient access scheme's operation

The scheme will provide free drug to transfusion dependent low or intermediate-1 risk MDS del(5q) patients after a fixed time point on therapy with lenalidomide (26 cycles). There are no further criteria limiting the PAS.

The lenalidomide TCS operates alongside the existing PPP. Completion of a PAF is a prerequisite of the PPP. The PAF must be sent to Celgene for each lenalidomide treatment cycle. Once a pharmacy is enrolled, Celgene manages the treatment records and pharmacies have no additional paperwork. Pharmacies are notified when eligible patients have completed 26 cycles of lenalidomide treatment and, thereafter, automatically receive all future cycles of lenalidomide, for that patient, free-of-charge.

Dispensing Pharmacy Registration (Mandatory Requirement): It is a requirement of the PPP that pharmacies wishing to purchase and dispense lenalidomide are registered with Celgene. Registration involves receiving a Healthcare Professional's Information Pack (HPIP) and faxing (or posting) to Celgene a signed Pharmacy Registration Form to indicate agreement and compliance with the content. Once a pharmacy has been registered, Celgene will issue a unique Pharmacy Identification Number.

Enrolling on the TCS: Hospitals / Pharmacists wishing to enrol on the scheme need to complete and return the TCS Agreement which sets out the terms under which patients will be eligible for free treatment. Celgene will confirm in writing an acceptance onto the TCS, and the method of supply of free-of charge lenalidomide.

Enrolling patients: Sending in the first PAF for an unregistered, eligible patient to Celgene will automatically trigger patient enrolment. Celgene will confirm in writing that a new patient has been enrolled into the TCS and provide a unique Patient Identification Number. This will enable Celgene to track the number of PAFs received for each patient, and to supply free-of-charge lenalidomide for patients continuing treatment beyond cycle 26.

Cycle management: For Cycles 1 to 26, Celgene will use the PAFs to confirm which cycle of treatment a patient is on. When a pharmacist receives a PAF and prescription for lenalidomide from a physician, it needs to be checked for completion and a copy returned to Celgene. The original copy can be retained within the pharmacy.

Celgene will track the number of PAFs received for each patient; receipt of the 26th PAF for an eligible patient will trigger notification from Celgene that the patient will now receive lenalidomide free-of-charge.

Continuing treatment beyond cycle 26: Pharmacies must continue to send all completed PAFs to Celgene in order to receive free-of-charge lenalidomide for eligible patients. Celgene will provide quarterly and annual reports, using anonymised data of patients registered on the TCS and those who have become eligible to receive lenalidomide free-of-charge, patients' cycle status and doses used. The annual report will also summarise patients' PAF histories over the previous calendar year.