Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Prepared by:

Celgene Limited

31 July 2013

Response to the Appraisal Consultation Document: Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality

Approved Name of Medicinal Product:	Lenalidomide
Brand Name:	Revlimid
Company:	Celgene Ltd
Submitted by:	Sujith Dhanasiri
Position:	Senior Manager, Market Access
Date:	31/07/2013

31/07/ 2013

Lori Farar
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence

Dear Lori,

RE: Response to the Appraisal Consultation Document: Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality

Thank you for forwarding the Appraisal Consultation Document (ACD) on the single technology appraisal of lenalidomide on 3rd July 2013 and for the opportunity to comment on the Appraisal Committee's preliminary recommendation.

Celgene is pleased that the Committee recognises that on the basis of the evidence on transfusion independence and health-related quality of life, lenalidomide is a clinically effective treatment for people with MDS associated with a deletion 5q cytogenetic abnormality (MDS del(5q)). This was recently also recognised by the Cancer Drug Fund in evaluating lenalidomide in this patient population, endorsing the benefit for patients in England. Celgene would once again like to draw to the attention of the Committee, that MDS del(5q) continues to be an area of high unmet need. Currently there are no other treatment options available barring best supportive care consisting of regular blood transfusions, treatment of transfusion related side effects and management of disease associated morbidity.

Celgene is disappointed that the ACD presently doubts as to whether lenalidomide improves survival in these patients and concludes it is not cost-effective when based on Celgene's health economic analyses, or following the additional analyses performed by the ERG.

Following consideration of the content of the ACD and the Evidence Review Group Evaluation Report (ERGR), Celgene have structured an evidence-based response to the key issues which appear to have driven the Committee's recommendation:

- Transfusion dependency status as the primary prognostic factor, determining overall survival and the rate of progression to AML.
- Time to iron chelation initiation (as assumed to be at 8 weeks post treatment initiation in the economic model).
- Clinical monitoring of MDS (haematologist or GP).
- Assumptions on utility scores, based on either a mapping of EQ-5D values (from MDS-004 trial data) or published estimates (Szende et al.)
- Methodology used to produce estimates of survival and AML due to trial crossover.

Celgene have provided a set of supplementary information regarding the association between transfusion independence, survival and progression to AML, based on a systematic literature review, and has explained this further from the following evidence-based dimensions

- Baseline red blood cell transfusion dependence (RBC-TD) is associated with increased risk of non-leukaemic death and also more advanced disease, leading to increased risk of AML and hence leukaemic death.
- In addition, the reversal of RBC-TD to red blood cell transfusion independence (RBC-TI) leads to improved survival because by correcting severe anaemia and reducing the need to transfusions, non-leukaemic mortality is reduced through the avoidance of complications of anaemia.

In response to the critique from the ERGR, and the ACD, Celgene has made a number of amendments to the cost effectiveness analysis. We have provided a re-analysis of the base case and associated sensitivity analysis for consideration by the Committee.

Finally, Celgene has provided brief clarification on the appropriateness of utility score mapping and trial crossover adjustment, which were discussed during the appraisal committee meeting.

Celgene would urge the Committee in its reconsideration of the ACD to note the clarifications / changes to the economic modelling that have been made to address the key concerns raised in the ACD. We believe these clarifications now allow for an accurate and valid cost-effectiveness assessment.

Section 1: Transfusion independence as a prognostic factor

Summary of the issue

- The Committee was unclear on the model's use of transfusion dependency status as the primary prognostic factor, determining overall survival and the rate of progression to acute myeloid leukaemia (AML).
- Having taken into account clinical specialist opinion, the Committee was of the opinion that transfusion independence measured at 8 weeks would not lead to a survival gain in the long term, and that the effect of lenalidomide on reduced transfusion dependence would not attribute any benefit in terms of a reduced rate of progression to AML.

Summary of response

- In order to better highlight the association between transfusion dependence /independence and survival, a systematic literature review was performed in July 2013.
  - A substantial body of literature was reviewed and found to provide support for a relationship between transfusion dependence and shortened survival through multiple mechanisms.
  - Evidence also supports the argument that becoming transfusion independent following dependency at baseline leads to improved survival
- The association between lenalidomide treatment and reduced rate of progression to AML is supported from evidence which shows:
  - Baseline RBC-TD or severe anaemia is associated with more advanced disease and leads to increased risk of AML progression.
  - In many MDS del(5q) patients, lenalidomide treatment leads to clonal suppression resulting in reduced risk of AML. The clonal suppression often also results in TI.

Overall survival

A systematic literature review was conducted to explore the association between overall survival (OS) and red blood cell (RBC) transfusion status in patients with MDS (Celgene, data on file). Searches were carried out in the MEDLINE database using keywords relating to transfusion dependence, survival and myelodysplasia. The search included articles published in English over the last twenty years. Grey literature searches were conducted covering relevant clinical congress proceedings and snowballing was used to include additional relevant papers. Two reviewers screened titles, reviewed abstracts and identified full-text articles that met the following inclusion criteria: original studies reporting transfusion dependence and survival outcomes in patients with MDS. Initial searches revealed a total of 137 relevant results, once duplicates had been removed. Of these, 17 met the inclusion criteria. One further article was added through snowballing and 4 conference abstracts were also included.

The majority of studies reported retrospective analyses of case series or registry populations. One study reported the results of a randomised controlled trial (RCT) and a further study described the results of a post-hoc analysis of RCT data. A total of 16 studies involving some 5,000 patients report statistically significant associations between red blood cell transfusion

dependence (RBC-TD) or RBC transfusion independence (RBC-TI) and OS. Other studies have noted the importance of other factors in the relationship between RBC transfusion status and OS, namely transfusion burden (number of units of blood transfused per month) and serum ferritin levels. Overall, this systematic review points to a substantial and growing body of evidence in support of the relationship between transfusion dependence and shortened survival. The argument for this association is composed of three key points: Baseline anaemia and RBC-TD lead to shortened overall survival due to (i) increased non-leukaemic death and (ii) increased risk of AML and leukaemic death (iii) becoming RBC-TI following dependency at baseline leads to improved OS due to reduced complications from chronic anaemia. From a detailed review of the papers found in the systematic literature search and papers which have been referenced in Celgene's initial submission to NICE, the association between RBC transfusion status and OS is summarised below:

The association between anaemia and shortened OS due to increased non-leukaemic death is well established. This has been reported across a range of malignancies, including myeloma, lymphoma and various other cancers, with statistically significant increases in the relative risk of death for anaemic patients (Caro et al. 2001). A number of studies and review papers have also reported the association between RBC-TD and shortened OS in MDS (Malcovati et al. 2007, Platzbecker et al. 2012):

In a study investigating the relationship between RBC transfusion-dependency and cardiac morbidity and mortality, cardiac disease and death were significantly more frequent in RBC-TD patients compared to those who did not require regular RBC transfusions. A multivariable Cox regression model showed that RBC-TD patients had a significantly higher risk of cardiac death compared to those without regular transfusion need (HR 4.12, $P<0.001$) (Malcovati et al. 2011). A time-dependent prognostic scoring system for predicting OS and leukaemic evolution in MDS demonstrated in multivariable analyses stratified by WHO subgroups, that cytogenetic risk and RBC transfusion requirement significantly affected OS (HR = 1.48; 95% CI, 1.20 to 1.83; HR = 2.53; 95% CI, 1.71 to 3.75, respectively; $P<.001$) (Malcovati et al. 2007). In a study of health care utilization and mortality among elderly patients with MDS, anaemic patients had a 2.2-fold higher risk of death compared with patients without anaemia, after adjusting for baseline characteristics (Lindquist et al. 2011). Finally, in a retrospective analysis of 357 MDS patients, RBC-TD was independently associated with reduced OS (hazard ratio=1.48, P=0.017) (Alessandrino et al. 2010). These results indicate that baseline anaemia or RBC-TD is associated with a reduced OS due to increased risk of non-leukaemic death, particularly cardiac death. In addition, as described in the next section, baseline RBC-TD is associated with more advanced disease and lack of response to treatment, with concurrent achievement of RBC-TI, is also associated with an increased risk of AML progression. The importance of AML as a cause of mortality and morbidity is well established indicating that baseline RBC-TD can also result in reduced OS due to leukaemic death. Although baseline anaemia or RBC-TD confers a reduced OS, a number of publications, which examine a variety of therapies, indicate that an erythroid response or achievement of RBC-TI in MDS or AML patients results in increased OS. In an analysis of 52 consecutive patients with AML treated with 5-azacitidine, RBC-TI at baseline or achievement under therapy was associated with prolonged OS; the median OS was 11.1 months versus 5.0 months, with a 12-month OS of 40% (95% CI: 19-60%) versus 13% (95% CI: 2-32%) (P=0.0006) in RBC-TI and RBC-TD patients, respectively. In addition, patients who were RBC-TI at baseline or who achieved RBC-TI on treatment had similar OS: median 10.7 versus 11.9

months; 12-month OS 40% (95% CI: 17-63%) versus 45% (95% CI: 5-75%) respectively (Gavillet et al. 2012). Similarly, in a subanalysis of the AZA-001 trial, patients that achieved RBC-TI with 5-azacitidine had improved OS, regardless of baseline transfusion needs. Median OS was improved 3-fold for all RBC-TI patients compared with patients who remained RBC-TD (log-rank p<0.0001). OS at 2 years RBC-TI patients was 60-75% greater compared to patients who remained TD (Seymour et al. 2010).

Similar results are also observed in patients treated with erythropoiesis stimulating agents or lenalidomide. A study of MDS patients with moderate to severe anaemia treated with a combination of rEPO + 13-cisretinoic acid and dihydroxylated vitamin D3 compared the impact of erythroid response and other known prognostic factors on OS. OS was negatively affected by RAEB1 diagnosis, IPSS and WPSS intermediate scores and RBC-TD. Multivariate analysis indicated that erythroid response maintained an independent positive impact on OS, particularly in non-RAEB patients, in the first 3 years from diagnosis (90% survival compared to 50% of non-responders) (Crisa et al. 2012). In addition, in a Phase II GFM study of 99 lower-risk MDS patients treated with darbepoetin alfa with or without filgrastim, erythroid response was associated with an OS benefit (p=0.015). The 3- year mortality considered related to MDS (i.e. by haemorrhage, infection, AML transformation) was 9.9 % in responders and 27.9 % in non-responders (Kelaidi et al. 2013). Finally, the phase III MDS-004 study of lenalidomide versus placebo in RBC-TD patients with low or intermediate-1-risk del(5q) MDS found that achievement of RBC-TI for ≥ 8 weeks with lenalidomide was associated with statistically significant reductions of 47% and 42% in the relative risks of death and AML progression or death, respectively (*P* = .021 and .048) (Fenaux et al. 2011).

In conclusion, lenalidomide can correct severe anaemia and substantially reduce the need for transfusions. Given that complications of severe anaemia, such as cardiac death, are significantly higher in RBC-TD lower-risk MDS patients, prolonged correction of anaemia can reduce non-leukaemic mortality. This is consistent with the observation from lenalidomide pivotal trials but also from studies with azacitidine and erythropoiesis stimulating agents.

Acute Myeloid Leukaemia

A review of published literature has identified a number of articles that examine the association between transfusion status and risk of disease progression to AML. Baseline severe anaemia or RBC-TD are well established independent risk factors for AML progression. A retrospective multi-centre analysis of 381 untreated IPSS lower risk del(5q) MDS patients examined baseline prognostic factors for OS and AML progression. In a multivariate analysis, transfusion need was identified as an independent risk factor for AML progression (Germing et al. 2011). In the WHO classification–based prognostic scoring system (WPSS), RBC-TD (defined as having at least one RBC transfusion every 8 weeks over a period of 4 months) was shown to be an independent prognostic factor in MDS patients. In a multivariable analysis stratified by WHO subgroups, transfusion requirement significantly affected risk of AML (HR =2.4; 95% CI, 1.49 to 3.88; P<.001, respectively) (Malcovati et al. 2007). In addition, the degree of anaemia appears to be a good surrogate for RBC-TD with low haemoglobin levels recently replacing RBC-TD as a prognostic parameter of the WPSS (Malcovati et al. 2011). Finally, the revised-IPSS (IPSS-R) analysed 7012 primary MDS patients whose disease had not been treated with disease-altering therapy during their MDS phase and identified 5 major variables for evaluating clinical

outcomes: cytogenetic risk groups, marrow blast percentage, and depth of cytopenias (haemoglobin, platelet, and ANC levels, respectively). For haemoglobin values, cutpoints of <8, 8 to <10, and ≥ 10 g/dL were statistically and clinically important for OS and AML progression (Greenberg et al. 2012). Therefore, these data support that baseline severe anaemia or RBC-TD confers an increased risk of AML progression, possibly due to an intrinsic link of these factors with more advanced disease.

Studies indicate that in MDS patients with baseline anaemia, failure to achieve RBC-TI or an erythroid response results in increased risk of AML progression. In a long-term follow-up analysis of 42 RBC-TD patients with lower risk del(5q) MDS treated with lenalidomide in the MDS-003 trial, failure to achieve sustained erythroid remission after treatment with lenalidomide led to an increased risk for clonal evolution and AML progression. Patients with continuous or transient erythroid response (reached RBC-TI but lost it during follow-up) carried a significantly lower risk of progression to AML than patients without an erythroid response (p=0.001) (Göhring et al. 2010). Therefore, patients with del(5q) MDS without erythroid remission after treatment with lenalidomide have a high risk for clonal evolution and progression to AML. In addition, a phase II study examined the efficacy of darbepoetin (with G-CSF added at week 12 in non-responders) in lower-risk MDS patients with anaemia and endogenous erythropoietin (EPO) level <500 IU/L. 56% of patients achieved an erythroid response by 24 weeks with patients who did not achieved an erythroid response having a significantly increased risk of developing AML versus non-responders (p=0.02) (Kelaidi et al. 2013). These results may indicate that response to treatment selects patients with a better prognosis, whereas non-responders are deemed to have more MDS-related complications, especially AML transformation.

The pivotal trials with lenalidomide indicate that the drug has specific activity and can trigger apoptosis in the del(5q) clone. Lenalidomide has significantly greater efficacy (both RBC-TI rates and cytogenetic remissions) in del(5q) versus non del(5q) MDS. In the MDS-003 Phase II study of lenalidomide in RBC-TD, lower-risk del(5q) MDS, after 24 weeks of therapy, 67% achieved RBC-TI and 45% had a complete cytogenetic response. Multivariate analysis of prognostic variables indicated that progression of disease was associated only with a lower frequency of cytogenetic response (13% versus 45%, P=0.05) (List et al. 2006). In contrast, in the MDS-002 study of lenalidomide monotherapy in 215 RBC-TD MDS patients without a 5q deletion, only 26% achieved RBC-TI. In addition, in 47 patients with a clonal cytogenetic abnormality at baseline, only 9 (19%) were cytogenetic responders (4 complete, 5 partial responses) (Raza et al. 2008). The duration of RBC-TI was also shorter in non-del(5q) versus del(5q) patients within these trials (median 41.0 weeks versus not reached, respectively) (Raza et al. 2008; List et al. 2006). Consistent with these findings, in the Phase I/II MDS-001 trial, the response rate to lenalidomide was highest among patients with a del(5q) abnormality (83 percent, as compared with 57 percent among those with a normal karyotype and 12 percent among those with other karyotypic abnormalities; P=0.007) (List et al. 2005). In addition, in the MDS-003 subanalysis by Göhring et al., cytogenetic responders to lenalidomide had a significantly decreased risk of progression to AML (p=0.009) compared to non-responders. Three and 5 years after study entry, the cumulative incidence of AML for patients with a cytogenetic response was 10% and 21%, respectively, and for patients without cytogenetic response, it was 46% and 60% (Göhring et al. 2010). This evidence indicates that the efficacy of lenalidomide in MDS is closely associated with the 5q deletion and that suppression of the

del(5q) clone in lenalidomide responders can reduce the clone size, slowing down mutational events and help prevent progression to AML.

Finally, the pivotal trial data for lenalidomide in RBC-TD del(5q) MDS support that the response of the underlying disease to treatment, with associated achievement of RBC-TI leads to reduced risk of AML progression. In the Phase III MDS-004 trial, the achievement of RBC-TI was associated with a significantly reduced risk of AML progression. Lenalidomide responders (RBC-TI for ≥ 8 weeks) had longer AML-free survival than non-responders (6-month landmark analysis; $P = .0085$). Cox proportional hazards model showed that in the combined lenalidomide groups, RBC-TI for ≥ 8 weeks was associated with a 42% reduction in the relative risk of AML progression or death ($P = .048$) (Fenaux et al. 2011). In addition, a combined subanalysis of 274 lenalidomide-treated patients from MDS-003 and MDS-004, RBC-TI for ≥26 weeks was the only significant covariate associated with reduced AML risk (hazard ratio [HR] 0.587; P =0.040) (Giagounidis et al. 2011). These results indicate that the reversal of RBC-TD translates into a reduced risk of developing AML.

Section 2: Implementing revisions to the economic model

Summary of the issues

- The Committee indicated that the monitoring of patients with MDS would be performed by a haematologist, rather than by a general practitioner, as assumed in the submitted base-case model.
- The Committee accepted comments from the ERG regarding the modelling of iron chelation; that the time to iron chelation initiation is more likely to be at 16 weeks rather than the modelled 8 weeks. The ERG applied this change due to uncertainty regarding a calculation in the electronic model for the threshold at which iron chelation therapy is required for transfusion dependent patients.
- The Committee were not convinced of the appropriateness of transfusion dependency as a factor in determining the rate of progression to AML.

Summary of response

- The sensitivity of base-case model results to the Committee's recommendations was investigated. The impact on the model results of routine MDS monitoring being performed by a haematologist rather than a GP was assessed. The base case incremental cost-effectiveness ratio (ICER) becomes £65,153 (versus a submitted ICER of £62,674.).
- Secondly, the threshold at which iron chelation therapy begins was extended from 8 weeks to 16 weeks. This change was made in addition to the assumption of monitoring by a haematologist, , increasing the ICER further to £69,901.
    - The assumption of an iron chelation threshold of 16 weeks rather than 8 comes from a labelling error in the model. The original value for RBC units was for the preceding 4 weeks, incorrectly labelled as the preceding 8 weeks. This value was multiplied by 2, assuming a constant transfusion rate over the preceding 8-week period in full.
- To test the impact of the removal of any benefit of lenalidomide on the rate of progression to AML, the modelled rate was set equal to that of transfusion independent patients for all patients. This was applied in addition to the above 2 assumptions of monitoring by a haematologist. Resulting incremental quality-adjusted life years (QALYs) are 0.72 and the ICER becomes £68,125.
    - This model revision is also likely to be inappropriate. Literature suggests that the Committee's view of there being no link between transfusion independence and reduced AML progression ignores a key area in which transfusion dependency is an important prognostic factor.

Methods

The ERG and Appraisal Committee raised concerns regarding some areas of the cost-effectiveness model. In particular, these are the time until iron chelation is initiated, the link between rate of progression to AML and transfusion dependency, and the assumption of a GP visit being sufficient for the monitoring of MDS patients. These issues were added to the model as additional scenarios, to present sensitivity analyses of their impact on the cost-effectiveness of lenalidomide.

Firstly, the model was also updated with a scenario analysis in which all MDS monitoring visits are undertaken by a haematologist rather than a GP. This replaces the GP cost of a monitoring appointment with the NHS reference cost (2011/12) for a clinical haematology outpatient visit. Haematologists performing routine MDS monitoring is accepted as a revised base case model assumption.

Secondly an option was implemented to change the number of weeks at which transfusion dependent patients require iron chelation therapy from the base case model setting of 8 weeks to 16 weeks, as was discussed in the ERG report. This issue was raised this due to a calculation in which the number of RBC units delivered over the preceding 8 weeks was doubled. The ERG commented that the reason for this multiplication was unclear. The number of RBC units delivered presented in the model was in fact the value over the preceding 4 weeks, not the preceding 8 weeks as stated in the label. This figure was multiplied by 2 to obtain the number of RBC units delivered over 8 weeks, and applied assuming a constant transfusion rate over this period.

Thirdly a model scenario was implemented that removes any reduction in the rate of progression to AML due to transfusion independence. This was performed by applying the parametric model of AML progression for transfusion independent patients to all patients regardless of their transfusion dependency status. When selected, this setting leads to no benefit through reduced AML progression associated with lenalidomide.

Results of the model scenarios

Attributing the cost of visiting a haematologist in clinical practice to MDS monitoring appointments increases discounted incremental costs by £2,013. This generates an ICER of £65,153 relative to a previous base case ICER of £62,674.

Extending the threshold at which iron chelation therapy is initiated from 8 weeks to 16 weeks, in addition to assuming a haematologist undertakes monitoring, leads to an ICER of £69,901. There is a marginal increase in incremental QALYs associated with lenalidomide of 0.002, and an increase in discounted incremental costs of £3,996. The ERG had stated that the number of RBC units that people in the transfusion-dependent state had already received had been incorrectly multiplied by 2 in the model and therefore it was assumed that they started iron chelation therapy earlier in the model, after 8 weeks instead of 16 weeks. This misunderstanding was due to a labelling issue within the model. As explained above, the calculation was actually obtaining the RBC units over 8 weeks but this was mislabelled. Applying an iron chelation threshold of 16 weeks is an extension that will overestimate the time to chelation for transfusion dependent patients.

Setting the rate of progression to AML equal to the rate associated with transfusion independency for all patients increases the difference between treatment arms in time spent in the AML health state. A lenalidomide patient is predicted to spend 0.29 years with AML compared to 0.32 years in the base-case model (with AML progression linked to transfusion dependency status). A best supportive care patient experiences AML for 0.24 years compared to 0.30 in the original base-case model. The resulting model outcome is an ICER of £68,125, with a reduction in incremental QALYs from 0.81 to 0.72. However, disassociating transfusion dependency status and progression to AML is likely to understate the benefits of transfusion independence as an important prognostic factor which is highlighted in the above Section 1 of

Celgene's response. A retrospective multicentre analysis of patients with MDS and del(5q) belonging to the IPSS low and intermediate-I risk groups (Germing et al, 2012) identified transfusion need and increased medullary blast count as independent risk factors for AML progression. A patient's RBC transfusion requirement at diagnosis is highlighted as a very important parameter, exhibiting a positive relationship with risk of AML progression.

TABLE 1: RESULTS OF THE AMENDED MODEL

Technology	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Revised Base Case – Routine monitoring performed by a haematologist (Previous base case: GP)							
Lenalidomide	£161,904	5.65	3.45	£52,911	1.07	0.81	£65,153
BSC	£108,993	4.58	2.64				
Scenario – Chelation initiates after 16 weeks of transfusion dependency (on revised base case) (Base case: 8 weeks)							
Lenalidomide	£164,416	5.65	3.45	£56,906	1.07	0.81	£69,901
BSC	£116,183	4.58	2.64				
Scenario – Rate of progression to AML set equal for all patients (on revised base case) (Base case: varies by transfusion dependency status)							
Lenalidomide	£172,307	6.09	3.67	£49,065	0.88	0.72	£68,125
BSC	£123,241	5.21	2.95				

AML, acute myeloid leukaemia; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Deterministic sensitivity analysis

Figure 1~~Figure 1~~ shows the results of the deterministic sensitivity analysis for the ten variables to which the ICER was most sensitive. This analysis was performed after applying the cost of a haematologist visit for routine MDS monitoring appointments. The model results are the most sensitive to health state utilities and the lenalidomide response rate inputs.

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FIGURE 1: TORNADO DIAGRAM SHOWING THE TEN MOST INFLUENTIAL MODEL PARAMETERS

AML, acute myeloid leukaemia; ICER, incremental cost-effectiveness ratio.

Probabilistic sensitivity analysis (PSA)

The scatter plot shown in Figure 2~~Figure 2~~ presents the results of 1,000 PSA simulations having implemented routine MDS monitoring by a haematologist. All simulations had an ICER exceeding a willingness to pay threshold of £30,000 per QALY. The deterministic ICER lies centrally within the elliptical scatter of results, which is clustered between 0.5 and 1.0 incremental QALYs, and incremental costs of around £40,000 to £65,000. The mean ICER produced by PSA was £66,807 (SD: £10,953).

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The cost-effectiveness acceptability curve shows that at the £80,000 per QALY willingness to pay (WTP) threshold, there is a 91% chance lenalidomide is cost-effective (see Figure 3~~Figure 3~~). At the £70,000 threshold there is a 69% chance lenalidomide is cost-effective.

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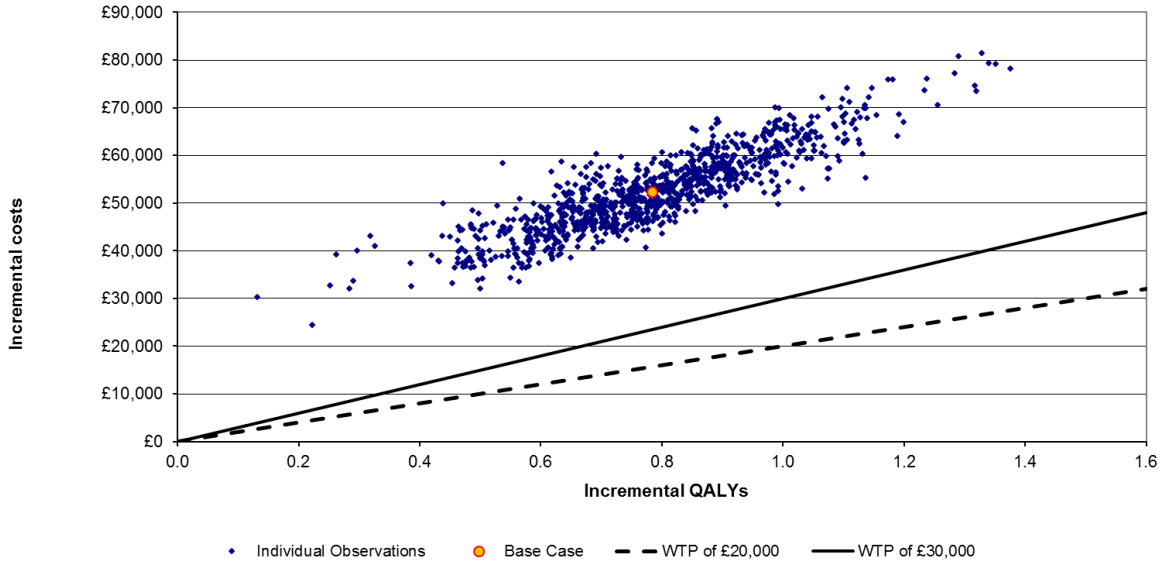
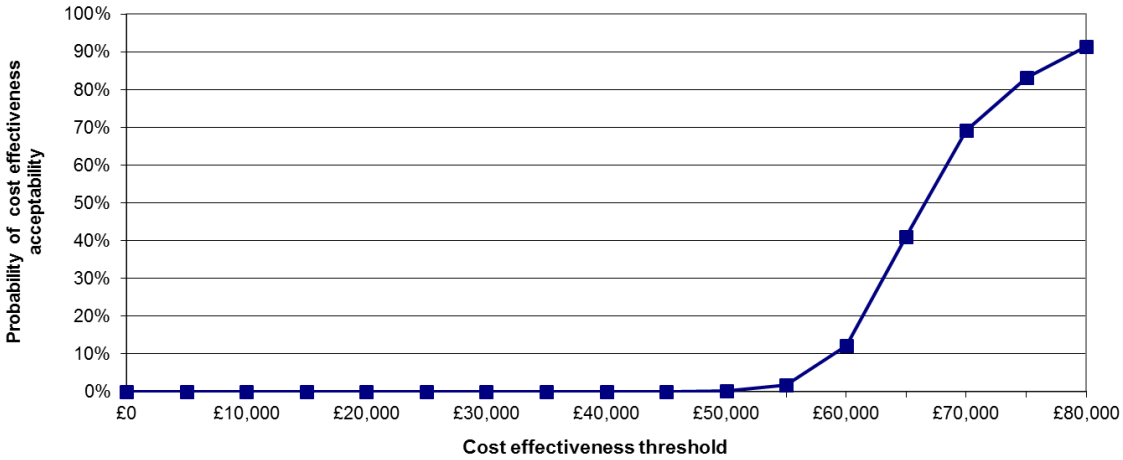
FIGURE 2: SCATTER PLOT FROM 1,000 PROBABILISTIC SENSITIVITY ANALYSIS SIMULATIONS



WTP, willingness to pay; QALYs; quality-adjusted life years.

FIGURE 3: COST-EFFECTIVENESS ACCEPTABILITY CURVE FROM PROBABILISTIC SENSITIVITY ANALYSIS



Conclusion

The model base case has been revised in line with the comment that routine monitoring would be performed by a haematologist rather than a GP. With this revision the base case incremental cost-effectiveness ratio (ICER) becomes £65,153 (versus a submitted ICER of £62,674.).

An explanation of the misunderstanding regarding the time to initial chelation has been provided along with scenarios testing the impact of using the ERG assumption for time to initial chelation (ICER £69,901) and assumption of equal time to AML progression (ICER £68,125). As can be seen these changes have little impact upon the ICER.

Section 3: Further information on utilities used in the submission

Summary of the issue

- During the appraisal meeting the Committee requested additional information on the mapping from FACT-An scores to EQ-5D.

Summary of response

- Regression models were generated using both FACT-An summary scales and FACT-An individual items to predict EQ-5D utility.
- All models produced had a high mean absolute error indicating that they were not accurate predictors of EQ-5D utility.
- Additionally the items used within the best fitting mapping did not include the items which showed large variation based upon transfusion dependency status. The relative reduction in TD scores compared to TI scores using the total FACT-An score was substantially greater than for all items included in the best mapping model evaluated
- As such, a strong argument is presented for not using the mapped EQ-5D values in modelling the MDS-004 trial data; and using instead more sensitive utility scores from a source such as Szende et al (2009).

Background

Functional Assessment of Cancer Therapy – Anaemia (FACT-An) is a disease-specific instrument used for the assessment of quality of life outcomes in patients with cancer, anaemia and fatigue. FACT-An was measured throughout the MDS-004 trial, whereas EQ-5D was measured only at baseline.

NICE guidelines recommend that economic evaluations should utilise the generic quality of life measures such as EQ-5D. Therefore, mapping was attempted by the School of Health and Related Research (ScHARR) in Sheffield in order to establish a relationship between FACT-An and EQ-5D making use of regression models to map the observed FACT-An scores reported in MDS-004 into corresponding EQ-5D scores.

Methods used to map FACT-An

Several regression models including either FACT-General (FACT-G) items or subscale scores alongside squared terms and interaction terms were estimated using ordinary least squares.. The preferred regression models were then used to obtain estimated EQ-5D scores using observed FACT-An responses.

The preferred model was chosen using mean absolute error (MAE) generated at the EQ-5D state level, root MSE generated at the observational level and R-squared. Although R-squared is of primary interest to determine explanatory power, this is of limited use for mapping regressions as it focuses on how well the model performs on the data on which it was based; whereas how well it will perform on the dataset to which it is applied is more important. R-squared also does

not indicate whether the mapping function is appropriate for the entire dataset, or for example whether it performs well for mild states and poorly for severe states. Therefore a useful indicator for how well the mapping function may perform on another dataset is the difference between observed and predicted EQ-5D scores, the error. This can be reported at the observational level or the EQ-5D state level.

The preferred regression models were then used to obtain estimated EQ-5D scores using observed FACT responses.

Results

Table 2~~Table 2~~ presents the regression models generated to estimate EQ-5D utility scores using FACT-An items. R-squared was highest and root MSE (calculated at the observational level) was lowest for model (3), indicating that this performed better than the other models. However all models have a large number of significant coefficients (11) and similar R-squared (ranging from 0.54 to 0.56), root MSE (ranging from 0.159 to 0.163) and high MAE (ranging from 0.161 to 0.165) and there is little to choose between them.

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TABLE 2: PREDICTION MODELS FROM FACT-AN ITEMS ONTO EQ-5D

	(1)	(2)	(3)
Limit social activity because am tired (AN16)			
Level 3	-0.009		
Level 2	-0.066***		
Level 1	-0.137*		
Level 0	-0.159*		
Feel listless (“washed out”) (AN1)			
Level 3		0.000	
Level 2		-0.058	
Level 1		-0.087**	
Level 0		-0.143*	
Need help doing usual activities (AN14)			
Level 3			-0.040
Level 2			-0.089**
Level 1			-0.198*
Level 0			-0.157*
Have pain (GP4)			
Level 3	-0.126*	-0.129*	-0.135*
Level 2	-0.162*	-0.159*	-0.131*
Level 1	-0.247*	-0.252*	-0.232*
Level 0	-0.299*	-0.310*	-0.269*
Feel sad (GE1)			
Level 3	-0.034	-0.017	-0.029
Level 2	-0.038	-0.040	-0.053
Level 1	-0.203*	-0.190*	-0.204*
Level 0	-0.161*	-0.163*	-0.184*
Content with QoL right now (GF7)			
Level 3	-0.023	-0.014	-0.022
Level 2	-0.014	-0.037	-0.022
Level 1	-0.071	-0.102***	-0.089
Level 0	-0.129**	-0.143*	-0.118**
Constant	0.954*	0.947*	0.955*
Observations	181	181	181

R-squared	0.552	0.540	0.561
Root MSE (observation level)	0.161	0.163	0.159
MAE (state level)	0.161	0.162	0.165

Notes: *** significant at 10%; ** significant at 5%; * significant at 1%.
The reference level 4 category is 'not at all', level 3 is 'a little bit', level 2 'somewhat', level 1 'quite a bit', level 0 'very much', with the exception of GF7 where the response categories are reversed.

Table 3~~Table 3~~ presents regression models generated to estimate EQ-5D utility scores using FACT-An subscale scores, squared subscale scores and interaction terms. Model (8) regressed TOI-An, a FACT summary score onto EQ-5D. Out of models (4) to (8) estimated using subscale scores and a summary score, models (6) and (7) performed best with highest R-squared (0.483 to 0.480) joint lowest root MSE (0.167) and lowest MAE (0.172 to 0.173). Yet overall model (3) arguably performs best out of all models, using R-squared (0.561), root MSE (0.159) and MAE (0.165).

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TABLE 3: PREDICTION MODELS FROM FACT-AN SUBSCALE SCORES AND SUMMARY SCORES ONTO EQ-5D

	(4)	(5)	(6)	(7)	(8)
Physical well-being score	-0.013*	-0.012*	0.003		
Emotional well-being score	-0.007**	-0.008**	-0.008**	-0.007**	
Functional well-being score	-0.004	-0.004	0.004		
Additional concerns (anaemia) subscale score	-0.005*	-0.013*	-0.004*	-0.004*	
Additional concerns subscale score squared		0.000**			
Physical well-being x functional wellbeing			-0.001*	-0.001*	
Trial Outcome Index-Anaemia score (TOI-An)					-0.007*
Constant	1.085*	1.206*	0.973*	1.004*	1.095*
Observations	181	181	181	181	181
R-squared	0.446	0.459	0.483	0.480	0.418
Root MSE	0.172	0.171	0.167	0.167	0.175
MAE	0.186	0.187	0.172	0.173	0.190

Notes: *** significant at 10%; ** significant at 5%; * significant at 1%

Conclusions

In aiming to map FACT-An data from MDS-004 patients onto the EQ-5D scale, it was deemed that 'model (3)' performed best out of all models evaluated. FACT-An items included in this model were:

- the requirement of help in doing usual activities (AN14),
- experiencing pain (GP4),
- feeling sad (GE1),
- being content with current quality of life (GF7).

There was some variability between the mean scores in these items from patients who were RBC-TD and those who were transfusion independent. The mean score in AN14 from TI patients is 3.10, compared to 2.75 from TD patients – an 11.5% reduction. Similarly, the mean scores for

GE1 and GF7 are 13.5% and 14.6% lower for TD patients than TI. There was only a minor differential in the GP4 scores.

However within the overall FACT-An questionnaire there were several items which had scores very different depending on transfusion status. In particular, these focus on the impact of fatigue on patient quality of life – an area which has no explicit place in the EQ-5D questionnaire. Such items and their mean scores are summarised in Table 4~~Table 4~~ and Figure 4~~Figure 4~~.

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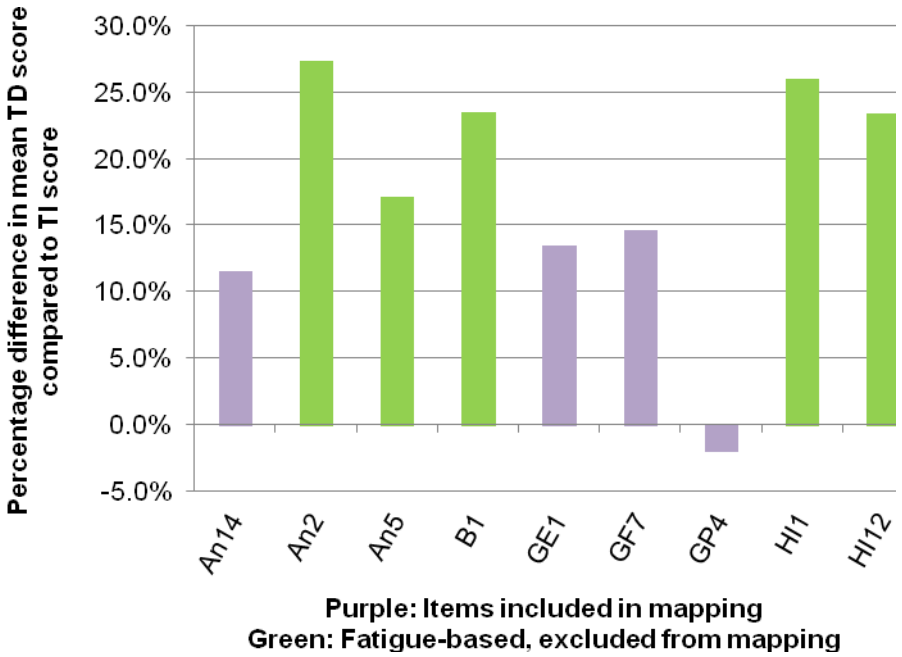
TABLE 4: FACT-AN QUESTIONNAIRE ITEMS RELATED TO FATIGUE AND HIGHLY VARIABLE BY TRANSFUSION STATUS

Code	Definition	Mean Score TI	Mean Score TD	Difference as % TI
An 2	Feel tired	2.82	2.05	27.4%
An 5	Have energy	2.01	1.67	17.1%
B1	Breathlessness	3.38	2.59	23.5%
HI1	Fatigued	2.84	2.10	26.0%
HI12	Feel weak all over	3.06	2.35	23.3%

TD, transfusion dependent; TI, transfusion independent.

FIGURE 4: DIFFERENCE IN MEAN TD SCORE AS A PERCENTAGE OF THE MEAN TI SCORE.



TD, transfusion dependent; TI, transfusion independent.

Clearly there was large variation in these items between the two groups, which was likely to be reflective of a high degree of sensitivity to transfusion status and their importance to MDS patients. The relative reduction in TD scores compared to TI scores for these items and the FACT-An as a whole was substantially greater than for all items included in the best mapping

model evaluated. As such, a strong argument is presented for not using the mapped EQ-5D as the base case in modelling the MDS-004 trial data; and using instead more sensitive utility scores from a source such as the utilities from Szende et al used in the model base case.

Section 4: Trial crossover analysis

Summary of the issue

- Uncertainty was raised by the Committee around the methodology used to produce estimates of survival and AML due to trial crossover.

Summary of response

- The two-stage Weibull method used to analyse crossover was selected based upon a paper by Latimer et al. (2013) analysing various methods of adjusting for crossover
- Rank-preserving structural failure time models (RPSFTM) were not used as the method relies on an underlying assumption of exchangeability which may not uphold in oncology due to potential changes in the underlying characteristics of subjects at the point of crossover relative to randomisation
- Inverse probability of censoring weights (IPCW) was not used as this method assumes there are no unmeasured confounders predictive of switching or death. This approach has been found to produce biased estimates even if all common predictors are taken into account if the study sample size is small or there is strong selection bias. As the MDS-004 trial contained only a small sample size the method was not considered appropriate.

Summary of crossover in MDS-004

MDS-004 was a three arm study in which subjects were treated with placebo (n=67), lenalidomide 5mg (n=69) or lenalidomide 10mg (n=69). Patients were given the opportunity to crossover at 16 weeks if they had failed to respond to their initial treatment. In this study 63% (24/67) subjects switched from placebo to lenalidomide (10mg), whilst 6% (4/69) subjects switched from lenalidomide 5mg to lenalidomide 10mg.

Appropriateness of techniques to adjust for crossover

There are a number of approaches that may be used to adjust for crossover trials. These include simple methods such as removing subjects who crossover, censoring subjects who crossover at the point of crossover or introducing a time dependent treatment effect. However, these approaches have been shown to be biased (Latimer et al. 2013, Robins et al. 1991, White et al. 1999, Weinstein et al. 1989). Alternative approaches commonly used in oncology trials include randomisation-based methods (Rank Preserving Structural Failure Time Models (RPSFTM)) or observational-based methods (Inverse Probability of Censoring Weights (IPCW)). These methods are designed to estimate counterfactual survival times and treatment effect (i.e. survival estimates that would have been observed in absence of crossover).

The RPSFTM is a randomisation-based approach that estimates the survival times and treatment effect using an accelerated failure time framework and relates counterfactual survival time with observed survival time using an acceleration factor (time ratio) Phi (ψ) (Robins et al. 1991, White et al. 1999, White et al. 2002).

The IPCW approach artificially censors subjects at the point of crossover and uses common predictors of switching and survival to predict what the survival estimates would have been in the absence of crossover (Latimer et al. 2013, Howe et al. 2011).

Latimer et al. (2013) undertook a simulation study in which a range of techniques were compared under different conditions (Latimer et al. 2013). This study concluded that the RPSFTM approach worked well providing that the underlying assumptions, in particular the assumption of exchangeability were met. However, this assumption may not uphold in oncology due to potential changes in the underlying characteristics of subjects at the point of crossover relative to randomisation (e.g. more advanced stage). The simulation study indicated that if the underlying treatment effect differed by more than 25% the RPSFTM method appeared biased.

The IPCW approach assumes there are no unmeasured confounders predictive of switching or death. However, this approach has been found to produce biased estimates even if all common predictors are taken into account, the study sample size is small or there is strong selection bias. The IPCW was also found to produce biased estimates in simulation studies if there was a very high percentage of switchers (>90%) (Latimer et al. 2013, Howe et al. 2011).

Latimer et al proposed a novel approach, the two stage Weibull. This model uses a disease-related crossover trigger (e.g. progression) acting as a second baseline. This method allows separate estimation of the treatment effects for switchers compared to patients originally randomised to treatment and has been designed to address some of the issues encountered with existing methods. In the simulation study the two stage approach was found to perform well providing that a defined crossover point was available (Latimer et al. 2013).

Conclusion

In view of this evidence and given the limited study sample size and potential time varying treatment effect, the two stage approach was applied in this study. It is recognised that other approaches may have been viable, however, there are limitations to the other available methodologies which indicated that they would be unlikely to provide as robust an estimate:

- RPSFTM – the underlying assumption of exchangeability may not uphold due to potential changes in the underlying characteristics of subjects at the point of crossover relative to randomisation.
- IPCW- the assumption of no unmeasured confounders predictive of switching or death is unlikely to be true, additionally this approach has been found to produce biased estimates even if all common predictors are taken into account if the study sample size is small as is the case for the MDS-004 trial.

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