in collaboration with:

Single Technology Appraisal:

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

Addendum to Evidence Review Group's Report following Celgene's response to the ACD

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

Authors
Rob Riemsma, Reviews Manager, KSR Ltd
Maiwenn Al, Health Economics Researcher, EUR
Hedwig Blommenstein, Health Economics Researcher, EUR
Sohan Deshpande, Systematic Reviewer, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Gill Worthy, Statistician, KSR Ltd
Caro Noake, Information Specialist, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Johan L Severens, Professor of Evaluation in Health Care, EUR
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Date completed 27th August 2013

Contents

1. Introduction 3
2. Transfusion independence as a prognostic factor of OS and AML progression 3
3. Implementing revisions to the economic model 7
4. Further information on utilities used in the submission 8
5. Trial crossover analysis 8
6. Additional safety information 9

1. Introduction

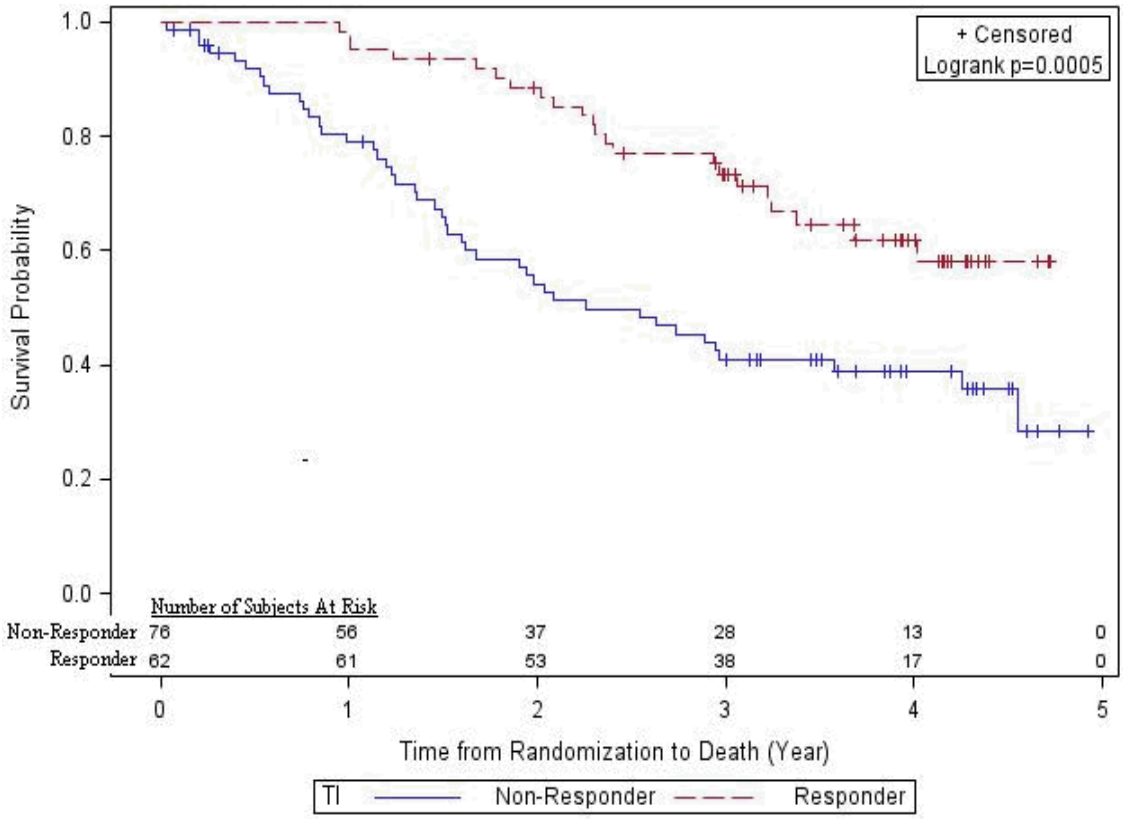
The Evidence Review Group (ERG) was requested by NICE to provide commentary on the manufacturer's response to the ACD and on a document send by the manufacturer to NHS healthcare professionals. The manufacturer's response to the ACD consists of four distinct subjects. Per subject, we will summarize briefly the information presented by the manufacturer. Where appropriate, we will then provide an ERG comment.

2. Transfusion independence as a prognostic factor of OS and AML progression

In the first AC meeting, the relationship between transfusion independence and overall survival was discussed. In their response to the ACD, the manufacturer has performed a systematic literature review (in July 2013) to better highlight the association between transfusion dependence /independence and survival.
Various observational studies confirm a relationship between developing or having developed transfusion dependence and decreased OS (e.g. Malcovati et al. 2005).
In addition, evidence also supports the argument that becoming transfusion independent following dependency at baseline leads to improved survival. This evidence is provided by the AZA-001 trial among intermediate-2 and high-risk MDS patients (Seymour et al. 2010). This trial showed that TD patients becoming TI had improved OS.

The manufacturer also explored the association between lenalidomide treatment and reduced rate of progression to AML. Evidence is presented which shows that 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 transfusion independence.

<u>ERG comment</u>
Regarding the association between transfusion independence and overall survival, the ERG considers it relevant to highlight the evidence contained in the MDS-004 trial. In the clinical study report, a Kaplan Meier analysis was performed assessing the OS of subjects who achieved the primary endpoint of > 26 weeks of transfusion independence (see Figure below).



In addition, they performed a Cox analysis on overall survival to assess the impact of baseline variables and the time dependent variable of transfusion independence and cytogenetic response on overall survival. The results are summarized in the table below.

Table 40: Analysis of Death Using the Cox Proportional Hazard Model for Subjects who Took at Least one Dose of Lenalidomide with 26-week RBC Transfusion Independence as a Time-dependent Covariate (Double-blind and Open-label Phases; Safety Population)

Variable	Univariate Model [a]			Final Model [b]		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Age (yrs)	1.03	(1.01, 1.06)	0.004	1.04	(1.02, 1.07)	0.001
Time since MDS diagnosis (yrs)	1.03	(0.97, 1.08)	0.340			
Baseline transfusion burden (units/8 weeks)	1.10	(1.04, 1.17)	0.002	1.10	(1.03, 1.17)	0.003
Baseline myeloblast (%)	1.04	(0.97, 1.12)				
Number of cytopenias at baseline (2 or 3 vs. 1)	1.12	(0.69, 1.84)	0.639			
Baseline Platelet count (10^9/L)	1.00	(1.00, 1.00)	0.005			
Baseline absolute neutrophil count (10^9/L)	1.02	(0.94, 1.10)	0.689			
Baseline hemoglobin (g/dL)	0.95	(0.74, 1.24)	0.727			
Del(5q) (complex vs. isolated)	1.22	(0.72, 2.08)	0.461			
Baseline EPO level (100mIU/mL)	0.99	(0.97, 1.01)	0.304			
Baseline ferritin level (mol/L)	1.01	(1.00, 1.02)	0.005	1.01	(1.00, 1.02)	0.006
WPSS group (High/Very High vs. Low/Intermediate)	1.36	(0.78, 2.36)	0.274			
26-Week transfusion independence (time-dependent)	0.42	(0.25, 0.71)	0.001	0.53	(0.31, 0.90)	0.019

[a] Model includes single risk factors.
[b] Model includes selected risk factors after using the backward elimination method to remove non significant risk factors.
Note: Only subjects in double-blind 5 mg or 10 mg lenalidomide groups are included in the analysis.
Source: Table 14.2.2.5A

Of the variables included in the Cox Proportional Hazard Model, age, baseline transfusion burden, baseline ferritin and the time-dependent variable of transfusion independence significantly affected overall survival. While age, baseline transfusion burden, and baseline ferritin adversely affected OS, achieving transfusion independence was associated with a significant reduction in the risk of death (HR=0.53; 95% CI 0.31, 0.90; p=0.019).

From this analysis, combined with the evidence from the AZA-001 trial and the observational studies, the ERG considers it plausible that responder-status at 26 weeks predicts survival.

It is also important to note that the statistical uncertainties related to this two-step approach of first determining response status and, based on that, predicting survival have been accounted for in the probabilistic sensitivity analysis. Some uncertainty does remain about the strength of the relationship for time horizons beyond 5 years.

Regarding the association between lenalidomide treatment and reduced rate of progression to AML the clinical study report of MDS-004 presents Kaplan-Meier curves for patients responding and not responding at 26 weeks. This shows a significant difference between the two curves. However, in the univariate Cox-regression analysis of time to AML, the response status is not significant (see tables below). The manufacturer also performed a Cox regression

on time to AML progression or death combined, and here response was a significant explanatory variable.

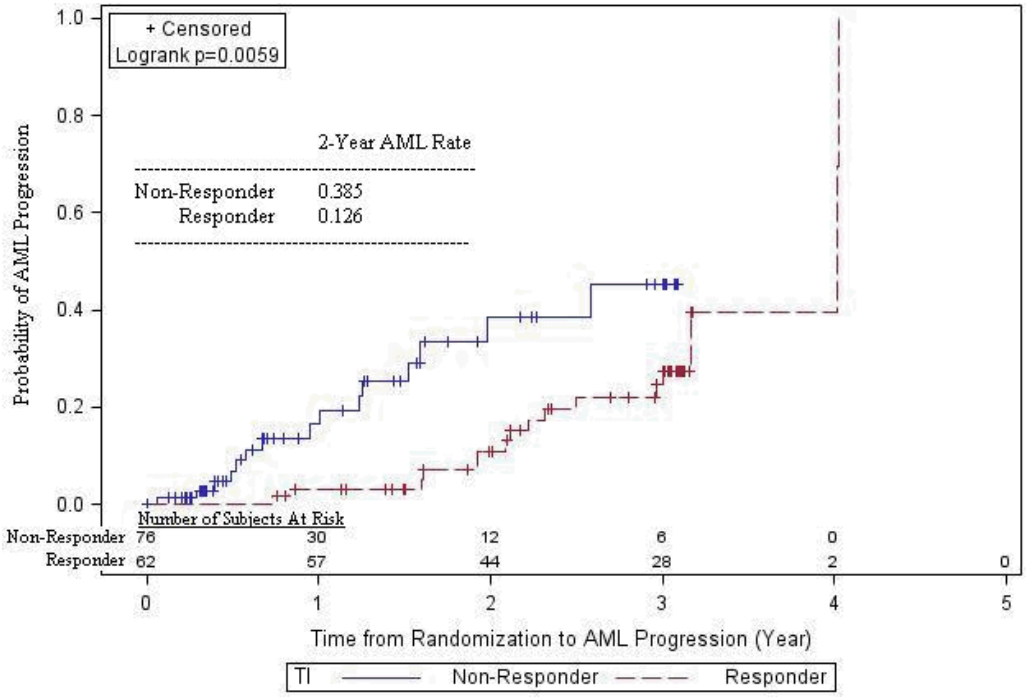


Table 36: Univariate Cox Proportional Hazard Model of AML Progression Throughout the Study for Subjects who Took at Least one Dose of Lenalidomide (Safety Population)

Variable	Univariate Model [a]		
	Hazard Ratio	95% CI	P-value
Age (years)	1.00	(0.97, 1.03)	0.896
Time since MDS diagnosis (years)	1.03	(0.96, 1.11)	0.377
Baseline transfusion burden (units/8 wks)	1.09	(0.98, 1.20)	0.110
Baseline myeloblast (%)	1.05	(0.94, 1.17)	0.352
Number of cytopenias at baseline (2 or 3 vs. 1)	1.03	(0.50, 2.10)	0.936
Baseline platelet count (10^9/L)	1.00	(1.00, 1.00)	0.693
Baseline absolute neutrophil count (10^9/L)	1.03	(0.93, 1.15)	0.576)
Baseline hemoglobin (g/dL)	0.90	(6.62, 1.32)	0.598
Del 5q (complex vs. isolated)	1.12	(0.51, 2.45)	0.783
Baseline EPO level (100 mIU/mL)	1.00	(0.97, 1.02)	0.762
Baseline ferritin level (mol/L)	1.01	(1.00, 1.02)	0.102
WPSS group (High/Very High vs. Low/Intermediate)	1.21	(0.52, 2.80)	0.655
26-week transfusion independence (time-dependent)	0.91	(0.45, 1.85)	0.795

[a] Model includes single risk factors. The final model is not included because there were no statistically significant risk factors after model selection.
Note: Only subjects in double-blind 5 mg or 10 mg lenalidomide groups were included in the analysis.
Source: Table 14.2.1.5A

3. Implementing revisions to the economic model

The manufacturer explores the sensitivity of base-case model results to three of the Committee's recommendations.

- 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) became £65,153 (versus the ERG base case ICER of £62,674.). The manufacturer also presents the deterministic and probabilistic sensitivity analyses with this cost change.
- Regarding the threshold at which iron chelation therapy begins, the manufacturer explains that a labelling error was made in the electronic model, causing the uncertainty expressed in the ERG report regarding the correct value. According to the manufacturer, the original value of 8 weeks was the correct value, thus no adjustment was required. However, if this threshold would be increased to 16 weeks, the ICER would further increase to £69,901.
- 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.
  However, considering the evidence presented in the previous section, the manufacturer considers this model revision 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.

<u>ERG comment</u>

The first analysis presented by the manufacturer was also reported in the ERG report (Table 6.3, page 108). In the ERG analysis an ICER of £64,079 was found. The difference between this ERG ICER and the one derived by the manufacturer is caused by the omission of the half cycle correction by the manufacturer. The reported sensitivity analyses show results almost equivalent to those presented in the ERG report (page 99 and 102).
The second ICER presented by the manufacturer also does not include a half cycle correction. However, this ICER is no longer relevant given the clarification provided by the manufacturer about the correct threshold for chelation therapy.
For the third ICER, it is not fully clear if this scenario also includes both changes or only the change in monitoring costs. It is however clear that the impact of assuming the same progression rate is limited.

4. Further information on utilities used in the submission

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, the manufacturer claims that 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).

ERG comment
Whilst the information about the mapping presented by the manufacturer is somewhat limited, the ERG agrees that this mapping would not have been a good alternative for the currently used approach. No EQ-5D data was collected after baseline, which means that no EQ-5D data is available in patients with transfusion independence. It is therefore very reasonable to assume that the predictive value of any mapping formula in patients with transfusion independence is of very limited value.

5. Trial crossover analysis

The manufacturer discusses various alternative methods that could be used for the analysis of the trial data in light of the crossovers that took place. Two well-known options are rank-preserving structural failure time models (RPSFTM) and the use of Inverse probability of censoring weights (IPCW).
Rank-preserving structural failure time models 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.
Instead, 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

ERG comment

The ERG agrees that the two-stage Weibull method is potentially a better method to adjust for treatment switching than methods such as the RPSFTM and IPCW. However, as far as the ERG can see this method was not used in the manufacturer submission. There is no mention in the manufacturer's submission of the Latimer report, nor of the two-stage Weibull method to analyse cross-over.
In the manufacturer's economic model, switching did not happen explicitly other than for cost purposes. The economic model used an ITT approach for efficacy, thus assuming that the dose changes observed in the trial will also be seen in practice where patients will switch upwards and downwards in their medication.

Latimer N, Abrams K, Lambert P, et al. Adjusting survival time estimates to account for treatment switching in randomised controlled trials - a simulation study: HEDs discussion paper. 2013. Ref Type: Unpublished Work
Available from: http://www.shef.ac.uk/polopoly_fs/1.259501!/file/HEDSDP1306.pdf

6. Additional safety information

The manufacturer provided NHS health care professionals with additional information on the safe use of lenalidomide. In agreement with the European Medicines Agency and Medicines and Healthcare products Regulatory Agency, Celgene Europe Ltd. produced a risk management plan for lenalidomide.

This was in response to risk minimisation measures requested by health authorities due to the teratogenic risk of lenalidomide and its safety profile (i.e. myelosuppression, thrombo-embolic events, and risk of progression to AML).

The safety data reported in that document are as follows (NOTE: →indicates an ERG addition to the manufacturer information):

- The estimated 2-year cumulative risk of progression to AML was 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

→The MS, reported that "A recent study showed that the cumulative rates for progression to AML in patients undergoing BSC measured at two and five years was 12.1% and 19.9%, respectively. " (MS, section 2.1, page 16-17)

- In a phase III clinical study in patients with MDS, lenalidomide was associated with a higher incidence of grade 3 or 4 neutropenia compared with placebo (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo).

→ The MS reported “neutropenia (14.9% in the placebo group, and 75.4% in each of the lenalidomide groups)” (MS, section 6.9.3, page 82). However, this was not reported as grade 3 or 4 AEs, but as “drug-related AEs that were reported with the highest incidence (≥20% of the patients in any group)”.

- Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% of patients on placebo. Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo).

→ Febrile neutropenia was not reported in the MS; while thrombocytopenia was reported as “thrombocytopenia (3.0% in the placebo group, 39.1% in the lenalidomide 5 mg group and 47.8% in the lenalidomide 10 mg group)” (MS, section 6.9.3, page 82). However, this was not reported as grade 3 or 4 AEs, but as “drug-related AEs that were reported with the highest incidence (≥20% of the patients in any group)”.

- In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma.

ERG comment

All in all, there is very little new evidence in this document compared to the MS.