24th August 2009

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Dear Mr Powell,

Azacitidine for the treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML)

Thank you for forwarding the Appraisal Consultation Document (ACD) on the single technology appraisal of azacitidine on 24th July 2009 and for the opportunity to comment on the Appraisal Committee's preliminary recommendation.

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

A summary of the key points that have been addressed by Celgene

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

Celgene have provided supplementary information regarding overall survival from an MDS disease registry showing the potential long-term survival to support the curve fit chosen. Treatment patterns in the UK have also been provided demonstrating that best supportive care (BSC) should not be the sole treatment comparator for consideration by the Committee in this appraisal given the wide variation in treatment.

Finally, Celgene would like to provide plans for a 7% discount to the basic NHS list price and provide further details regarding the development plans and commercial launch of an alternative vial strength of azacitidine and the resultant impact on the cost-effectiveness.

Celgene agree with the summarisation of the clinical evidence and are pleased that the Committee recognises the clinical value of azacitidine. However, the ACD presently concludes that azacitidine is not cost-effective when based on Celgene's health economic analyses or on the additional analyses performed by the ERG due to concerns related to the economic modelling.

Furthermore, Celgene also agree with the Committee in their determination that azacitidine within this appraisal fulfils the criteria for consideration as a life-extending, end-of-life treatment, but as detailed above, we are disappointed with the conclusion that the cost-effectiveness estimates were not sufficiently robust due to the nature of the uncertainties outlined in the ERGR and the cost-effectiveness section of the ACD.

We regret that the evidence provided in our submission related to the health economic modelling has resulted in this outcome. Celgene have therefore taken the following actions:

- Provided a revised economic model incorporating the ERG comments where appropriate
- Provided a revised base case and associated sensitivity analyses

These changes are detailed with a summary of comments related to the ERGR in the Appendix of this response.

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

The aims of this response document are to address the concerns detailed in the ACD by the Committee and the ERG and to provide our comments regarding the ACD and revised economic analyses.

Executive Summary

Part A: Cost-effectiveness

- Face validity of log-logistic fits for modelled overall survival
- Survival in the AML state
- Administration cost associated with azacitidine
- Calculation of mortality rate
- Utilities
- Age-dependant mortality
- Costs
- Economic model functionality

Part B: Comments

- Treatment patterns in the UK
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- Patient access scheme
- Factual inaccuracies

Part C: Results

- Revised base-case analyses
- Sensitivity analyses

Appendix

- Comments on the ERGR and addendum to health economic model

Executive Summary

Celgene agree with the summarisation of the clinical evidence and are pleased that the Committee recognises the clinical value of azacitidine. However, the ACD presently concludes that azacitidine is not a cost-effective use of NHS resources when based on Celgene's health economic analyses or on the additional analyses performed by the ERG due to concerns related to the cost-effectiveness modelling.

In response to the concerns in the ACD regarding the cost-effectiveness, we have made the following changes to the economic evaluation:

- Inclusion of all-cause age-dependant mortality to the extrapolation of survival benefits
- Updating costs to reflect the HRG 4.0 tariff for 2009/10
- Inclusion of weekend administration costs for azacitidine

Furthermore, several functional amendments have been made to the economic model in accordance to comments raised by the ERG. Comments in the ACD to which no amendments have been made by Celgene due to ERG misinterpretation are also fully described, such as the calculation of mortality rates.

In addition, we present real-life data obtained from the Düsseldorf MDS registry for patients treated with best-supportive care alone to demonstrate the appropriate curve selection for long-term survival.

With respect to the Committee's recommendation that best-supportive care should be the sole comparator in the economic analysis, we present data on treatment patterns collected from UK haematologists. These data show significant variation in the use of active treatments such as low-dose and standard-dose chemotherapy, and as a result, demonstrate that best-supportive care should not be considered as the only treatment comparator for high-risk MDS in the UK.

Celgene also present research on haematology clinical practice indicating that the pooling of patients on common treatment days is likely given the currently available vial size and dosing regimen of azacitidine. The pooling of patients and subsequent splitting of vials reduces the cost of azacitidine to the NHS. The resulting improvement in cost-effectiveness is described below.

[redacted]n its re-evaluation of the ACD, we urge the Committee to consider the effect of actual patient pooling in clinical practice, as well as the effect of future additional vial strengths.

Lastly, to address the time required for commercialisation of an additional vial size, Celgene propose a patient access scheme involving a temporary 7% discount on the basic NHS list price until such a time as an alternative vial strength is available.

A summary of the revised base-case cost-effectiveness results are presented in the Table 1.

Table 1. Summary of base-case cost-effectiveness results

Treatment option	**Cost per QALY gained**			
	Base-case results		*Base-case results with patient access scheme*	
	No Vial sharing	**Vial sharing**	*No Vial sharing*	*Vial sharing*
Pre-selected for best-supportive care				
Azacitidine BSC	£46,632	£43,744	*£44,803*	*£42,641*
Pre-selected for low-dose chemotherapy				
Azacitidine LDC	£39,714	£37,173	*£38,105*	*£36,203*
Pre-selected for standard-dose chemotherapy				
Azacitidine SDC	£36,591	£34,012	*£34,959*	*£33,028*

Part A: Cost-effectiveness

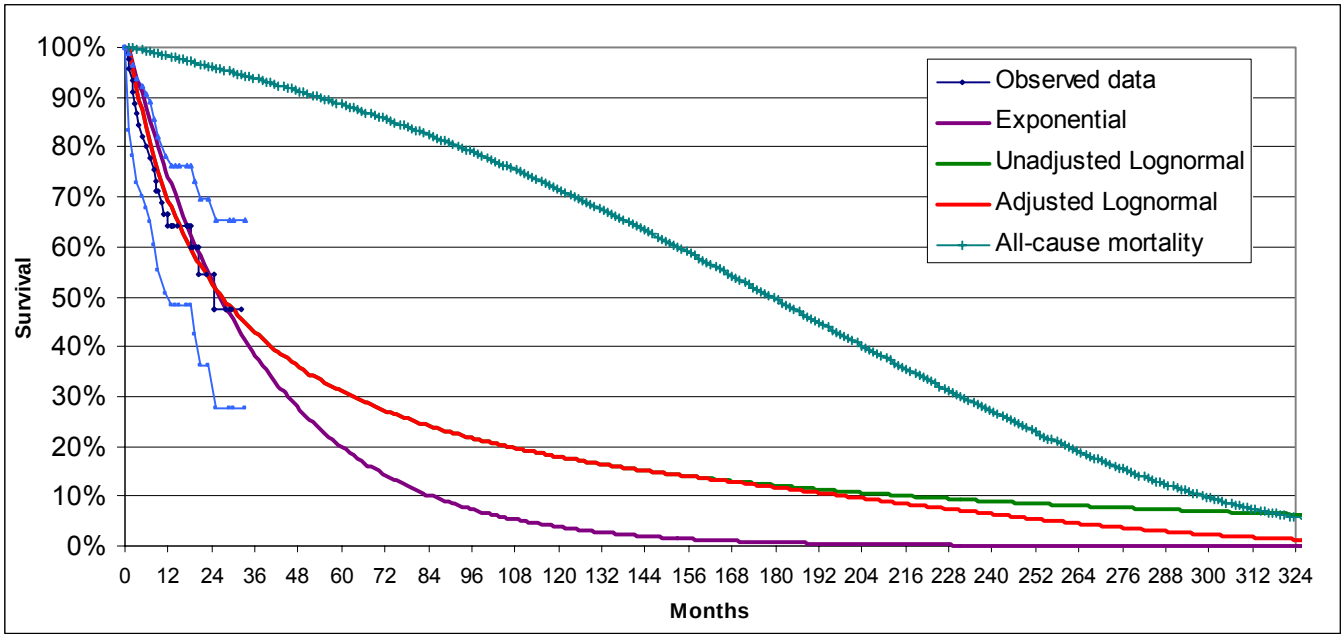
A1. Overall survival gain

The ERG and the Committee have raised concerns regarding the face validity of the results of the economic model relative to the results of the main source of the clinical effectiveness (section 3.10 of the ACD).

Celgene have duly noted these concerns and have therefore adjusted the extrapolation of survival to include all-cause age-dependant mortality for all extrapolations. As a consequence, patients in the model no longer survive to an unrealistic age (see Appendix 1 for full details) as recommended by the ERG and the Committee.

Figure A1 shows an example of the impact of the inclusion of age-dependant mortality on the tail end of the lognormal survival curve.

Figure A1: Kaplan–Meier (and 95% CI) and modelled survival curves for azacitidine-treated patients (pre-selected for LDC alone) from Study AZA-001



Furthermore, the ERG expressed the view that the use of the log-logistic function in the base case is inappropriate (section 3.10 of the ACD). The curve was selected based on the Akaike Information Criterion (AIC). After adjusting the economic modelling, the AIC has been recalculated using Study AZA-001 data along with the AZA-001 extension data presented in Celgene's original submission. Based on these new estimates, the exponential is the best fit to the azacitidine (BSC), azacitidine (SDC) and LDC data, and the lognormal is the best fit for the azacitidine (LDC), BSC and SDC data. Further information is provided in the Appendix to this document.

Moreover, given the ERG's concerns regarding the uncertainty associated with estimates of long-term survival, Celgene have also sought an external data source to further assess and present to the Committee the potential long-term survival for patients with high-risk MDS.

The Düsseldorf MDS registry contains data on more than 3,000 MDS patients and was established in 1982. Celgene sought data from the registry on the recorded long-term survival of high-risk MDS patients who have not received any active treatment. These patients have only been treated with BSC throughout the course of their disease, with BSC specifically consisting of transfusion of red blood cells and/or platelets, antibiotics, and antifungal and antiviral agents.

Prof Ulrich Germing and his team at the University of Düsseldorf conducted an analysis of patients aged over 18 years and who were diagnosed with International Prognostic Scoring System (IPSS) intermediate-2 and high-risk MDS (WHO classification RAEB-I, RAEB-II and CMML-II, and/or French-American-British [FAB] classification RAEB-T or CMML) within the registry. The survival follow-up of 655

patients (mean age 70, range 18–96) demonstrates that survival at the tail-end of the extrapolation curve was observed. Use of the lognormal curve fit results in a survival curve that is very similar to what has been observed in this analysis of BSC-only patients from the Düsseldorf registry.[1]

Table A1: Patient characteristics from the Düsseldorf MDS registry treated with BSC alone

	BSC alone (n=655)
Age (years)	
Mean [range]	69.9 [18-96]
Median	71.7
≤64 years	27%
≥65 years	73%
Sex	
Men	371 (57%)
Women	288 (43%)
FAB classification	
RAEB	366 (56%)
RAEB-T	209 (32%)
CMML	80 (12%)
WHO classification	
RAEB-I	44 (7%)
RAEB-II	322 (49%)
CMML-I	15 (2%)
CMML-II	65 (10%)
RAEB-T	209 (32%)
ECOG performance status (available for 367 patients)	
0-1	176 (48%)
2	164 (45%)
≥3	27 (7%)

Figure A2: Kaplan–Meier survival curve for patients with high-risk MDS treated with BSC alone from the Düsseldorf MDS registry

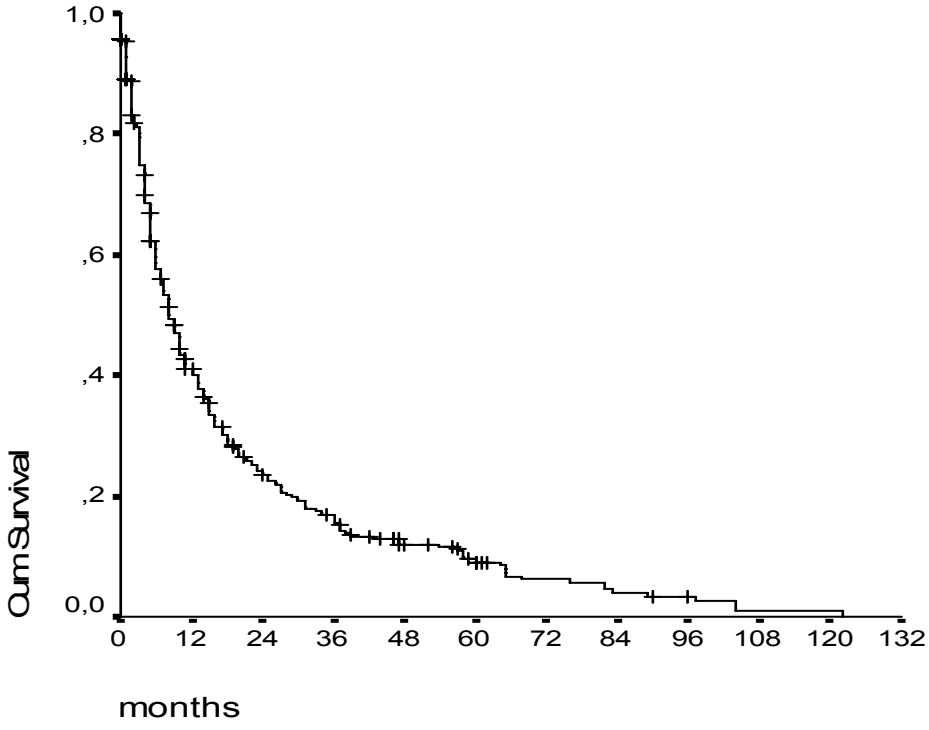
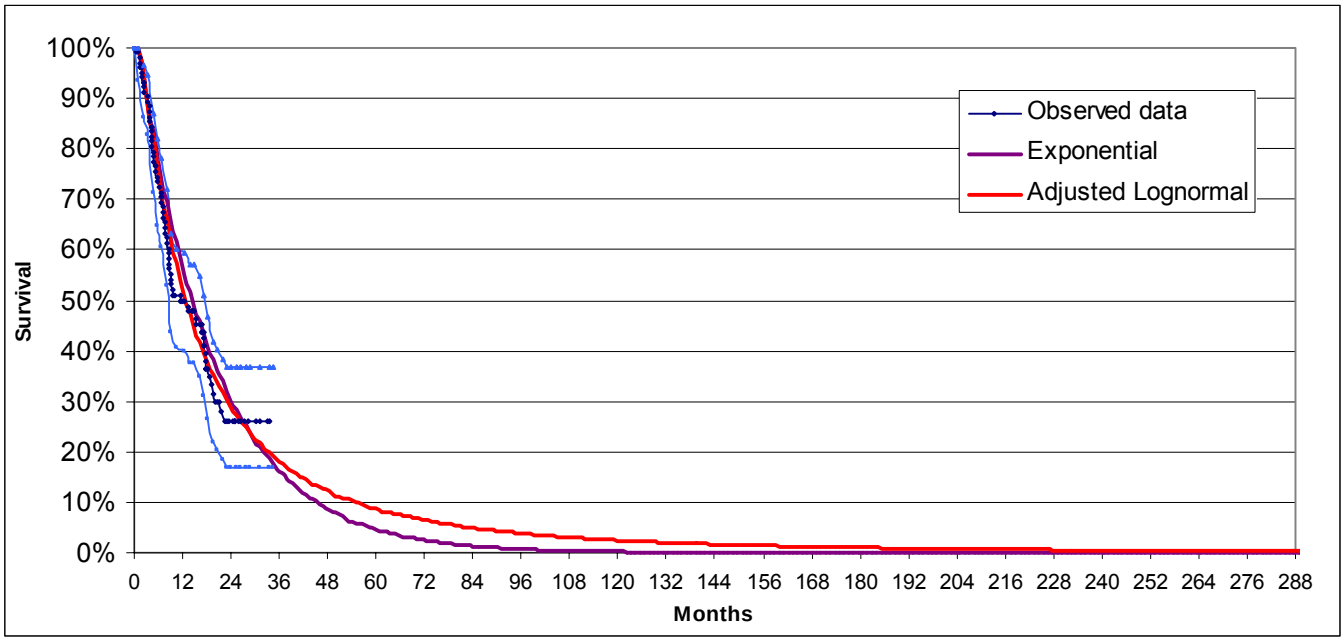


Figure A3: Kaplan–Meier (and 95% CI) and modelled survival curves for BSC alone from Study AZA-001



In contrast to the similarity between the lognormal curve and the actual registry data, the use of the exponential curve would underestimate (<5% survival at five years and <0.4% survival at 9 years, compared to 9% and 2% respectively with the registry data) the long-term survival data recorded in the registry which demonstrate survival beyond ten years.

Therefore, whilst the exponential curve has shown to provide the best estimate of goodness of fit based on the AIC for some of the cohorts described above, real-life data for similar higher-risk MDS patients treated with BSC alone show long-term survival up to 10 years which is underestimated using an exponential curve. Furthermore, it may be reasonable to assume that active treatment with azacitidine may result in benefits beyond the overall survival gain due to the epigenetic mechanism of action and hypothesised disease modification. Use of the exponential curve would similarly underestimate survival for patients under active treatment. Based on these results from real-life data, Celgene have selected the lognormal curve as the base-case curve selection for all the treatment arms. Celgene believe this is most likely to represent the long-term overall survival benefit of active treatment with azacitidine whilst incorporating all-cause age-dependant mortality to remove any unrealistic long-term survival.

Celgene were unable to acquire data on the long-term survival of other treatment options such as low-dose chemotherapy (LDC) and standard-dose chemotherapy (SDC) from the Düsseldorf MDS registry.

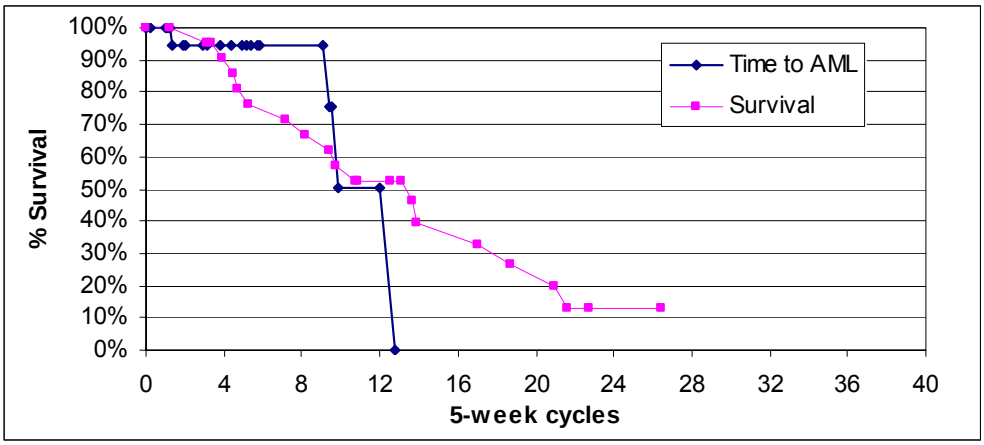
Additionally, the ACD (section 3.10) states the overall survival gains attributable to azacitidine observed in the trial were 9.6 months, 9.2 months and 9.4 months for BSC, LDC and SDC groups respectively, and modelled estimates overall survival gains of 33.9 months, 32.3 months and 32.2 months for the same respective groups. Celgene would like to remind the Committee that this is a comparison of trial median and modelled mean results and does not allow representation of the tail-end distribution that has been observed with the real-life data from the Düsseldorf registry. Following the inclusion of all-cause age-dependant mortality, and the fitting of the lognormal curve, the mean overall survival gain for the three treatment groups is now 24.3 months, 29.2 months and 29.9 months for BSC, LDC and SDC, respectively.

Celgene would urge the Committee to further evaluate this aspect of the appraisal based on the inclusion of all-cause age-dependant mortality in the economic model to account for the ERG's face-validity concerns, as well as the selection of the lognormal curve fit and long-term survival from the Düsseldorf MDS registry.

A2. Survival in the AML state

There is some uncertainty from the ERG (section 3.11 and 4.10 of the ACD) as to the effect of the chosen method to model time to progression to AML. As stated in our evidence submission, the relationship between time to AML and time to mortality is difficult to estimate due to the number of censored patients. This is demonstrated by Figure A4, which shows the Kaplan–Meier curves for progression to AML and survival, as well as the difficulty in fitting a suitable curve through the data.

Figure A4: Kaplan–Meier curves for time to AML and overall survival on SDC



This aspect was discussed in depth with clinicians during advisory meetings. The clinician consensus was that there would be no expectation of any difference between treatment arms with respect to the time spent in AML. There would, however, be differences in the time to AML, as overall survival is extended for patients treated with azacitidine.

Clinicians also described the treatment requirements of patients that progressed to AML as being very similar to those of patients receiving BSC alone. By the time most patients progress to AML in all treatment arms, they are often being treated with BSC only, and as a consequence the impact of AML progression is minimal. It was even recommended by clinicians that the AML state be removed and that AML progression be considered part of MDS. Progression would then be accounted for by decreasing patients' utility in the cycle before death. However, Celgene preferred a more conservative approach that closely reflected the trial data as far as possible to avoid having data deficiencies heavily influence the economic results.

Therefore, the modelling approach taken by Celgene attempts to ensure close alignment with the actual trial data while reflecting clinician expectations with regard to the course of the disease, and more specifically, with regard to time spent in AML.

A3. Administration cost of azacitidine

The Committee have noted that despite the seven-day continuous treatment cycle with azacitidine and the need for treatment over a weekend, no additional costs above normal administration have been included in the evidence submission.

Celgene have duly noted this and increased the cost associated with treatment with azacitidine over the weekend period. The costs of preparation and administration are assumed to be twofold greater for the two days of weekend administration per cycle. This assumption is now included in the revised economic model and base-case analyses.

A4. Calculation of mortality rate

Section 3.12 of the ACD notes the Committee's concerns about the assumption in the model regarding the proportion of patients that suffer mortality in the MDS health state and the AML health state. The ERG stated that this occurs in the majority of cycles and would lead to overestimation of overall survival.

This conclusion from ERG is incorrect, as this assumption does not affect overall survival in the model in any way. It is used because it is the most appropriate way to distinguish which patients have suffered

mortality (MDS or AML); however, survival in the model is always based on the overall survival extrapolation. The number of patients that are predicted by the overall survival curves to die in each cycle is equal to the number of patients that die in the model.

A consequence of this assumption is that in the tail of the model, most, if not all patients die in the AML state rather than the MDS state. Therefore, the number of cycles without MDS deaths is higher than the number of cycles with MDS deaths. However, by the time this situation is reached, the majority of patients have already died. In the BSC, LDC and SDC arms, 75%, 75% and 86% of patients respectively had died by the time the MDS mortality was reduced to zero. Therefore, although the assumption does affect the majority of cycles of the model, it does not affect the majority of patients in the model.

Furthermore, the model demonstrates face validity compared to the trial data with respect to this aspect. In Study AZA-001, 104 (29%) patients died in MDS. In the model, 28% of patients, averaged across the six treatment arms, die in MDS.

A5. Utilities

The ACD notes in section 3.13 that the ERG stated that the results of the mapping algorithm used to calculate utilities should be treated with caution due to differences in the underlying conditions between the oesophageal cancer patients used to generate the algorithm and the MDS patients to which the mapping was applied.

Celgene acknowledge that there are some deficiencies in the algorithm, but reiterate that this mapping instrument is the only tool available to enable conversion of the EORTC scores from the CALGB 9221 study data into the utility scores required by the economic model.

The analysis attempts to treat the mapping as conservatively as possible, by downgrading the utility scores to reflect the differences in the underlying patient characteristics in the CALGB 9221 and Study AZA-001 patient cohorts, and includes an examination of the uncertainty around the estimate in the probabilistic sensitivity analysis (PSA).

It is also plausible that the utility mapping underestimates the benefits of treatment with azacitidine. The committee noted that clinicians expected the benefits of improved transfusion independence and reduction of symptoms such as fatigue to result in greater gains in quality of life. However, given the available data, this underestimation is unquantifiable.

In summary, Celgene agree with the Committee with respect to the likely underestimation of the gains in health-related quality of life based on the mapping methodology, and whilst there are uncertainties with the utility mapping, it was the only available option to access utility scores given the available data at the time of the evidence submission. Furthermore, due to this reason, the mapping methodology has been applied as conservatively as possible by Celgene. We welcome the Committee's recommendation for further research to direct eliciting health-related quality of life values from patients with myelodysplastic sysndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia.

A6. Age-dependant mortality

The ACD states in section 3.14 that the ERG reported that the model included no estimate of age-dependant mortality, resulting in an overestimation of survival in the economic model.

Celgene have duly noted these concerns and incorporated age-dependant mortality into the economic model. This is described in section A1 and also in Appendix 1.

A7. Costs

The Committee note that the use of the NHS 2009/10 tariff would be potentially more appropriate than the NHS reference costs (2006/07) as it could provide a more precise estimate of hospital costs by breaking down those costs attributable to adverse events (AEs) (section 4.10 of ACD).

Celgene have duly noted these comments and revised the base-case estimate to include the NHS 2009/10 tariff costs where available. Celgene would like to add that the NHS reference costs 2006/07

(inflated to 2008 prices) were used in the original submission as they provided a more realistic estimate for the cost of an inpatient stay associated with SDC of 28 days per treatment cycle.

A8. Economic model functionality

The ERG identified a series of functional problems related to the economic model; these are stated in section 3.15 of the ACD and concern the inclusion of per-cycle discount rates, the incorporation of parameter covariance, health-state-specific mortality, the extrapolation of overall mortality, exploration of alternative assumptions about AEs and the modelled time horizon.

Celgene have duly noted these concerns and have incorporated the amendments raised by the ERG in the revised economic model. These amendments are detailed in Appendix 1 and Celgene have provided a revised version of the model for review by the Institute.

Part B: Comments

B1. Treatment patterns in the UK

At the Appraisal Committee meeting, the Committee heard from the clinical specialists that current treatment for this group of patients most often consists of BSC, with only approximately 10% of patients able to tolerate chemotherapy (section 4.2 of ACD). Furthermore, the Committee considered that chemotherapy was not an appropriate comparator, since there was limited statistically significant clinical evidence (section 4.7 of ACD). Hence, BSC was used as the sole comparator within the assessment.

Celgene are very concerned at the Committee's assessment that BSC represents the only suitable comparator in this appraisal. This assessment prejudices a proportion of both patients and their physicians who actively choose to use either LDC or SDC (intensive chemotherapy) for the management of higher-risk MDS, in addition to providing BSC (symptom management). It is important to recognise that treatment choices depend on a number of factors including disease status, patient age and performance status. In Study AZA-001 the three conventional care groups were not identical with patients selected to receive standard-dose (intensive) chemotherapy being younger with better ECOG performance status and with higher risk disease. As the best supportive care, low-dose chemotherapy and standard-dose chemotherapy are not mutually exclusive therapeutic options, with patients potentially receiving more than one treatment as their disease progresses, it is important that all three be considered fully.

Celgene wish to provide data to demonstrate that current UK treatment practice does indeed include both low-dose cytarabine and SDC.

Treatment practice – healthcare resource utilisation questionnaires

Treatment practice was elicited in February 2009 from 13 haematologists who treat MDS as part of the structured questionnaire that was used for gathering healthcare resource utilisation for the management of MDS. Following the ACD recommendation, Celgene re-approached all 13 physicians and re-asked the question, *"In your current practice, what proportion of intermediate-2 and high-risk MDS patients (according to IPSS) are currently treated with each treatment option in those who are not eligible for stem cell transplant?"* The haematologists were asked the refined question to ensure it was valid to the indication and scope of the decision problem. The results are summarised in Table B1.

Table B1: Haematologist treatment patterns of higher-risk MDS (February 2009)

Physician name	Location	Treatment Strategy (%)		
		BSC alone	LDC (and BSC)	SDC (and BSC)
Professor David Bowen	Professor of Haematology and Consultant Haematologist, St. James's Institute of Oncology, Leeds	80	0	20
Professor Richard Clark	Professor of Haematology and Consultant Haematologist, Royal Liverpool University Hospital, Liverpool	20	30	50
Dr Christopher Dalley	Consultant Haematologist, The Royal Hallamshire Hospital, Sheffield	20	30	50
Dr Ranjit Dasgupta	Consultant Haematologist, Arrowe Park Hospital, Merseyside	70	20	10
Dr Mike Dennis	Consultant Haematologist, The Christie Hospital, Manchester	25	25	50
Dr Aloysius Ho	Consultant Haematologist, King's College Hospital, London	5	65	30
Dr Jonathan Kell	Consultant Haematologist, University Hospital of Wales, Cardiff	50	25	25
Dr Alan MacWhannell	Consultant Haematologist, New Cross Hospital, Wolverhampton	15	40	45
Dr Kavita Raj	Consultant Haematologist, Guy's and St. Thomas's Hospital, London	40	50	10
Anonymous*	Anonymous	80	0	20
Anonymous*	Anonymous	0	50	50
Average [range]		**43.3% [0–80%]**	**27.1% [0–65%]**	**29.6% [10–50%]**

Note: *Anonymised treatment pattern responses at the request of the haematologist interviewed. One (of the 13) haematologist was unable to estimate their MDS treatment practice patterns.

These data illustrate that approximately 43% of patients are treated with BSC alone, while 27% are treated with LDC (and BSC) and 30% are treated with SDC (and BSC). Furthermore, this illustrates the degree of variation in BSC and active treatment of high-risk MDS.

Celgene would like to bring these data to the Committee's attention as they demonstrate the variation in use in the UK; we regret not illustrating this in the primary submission. Additionally, section 4.7 states that "the Committee considered that chemotherapy was not an appropriate comparator since there was limited evidence of statistically significant clinical evidence". We feel that this does not constitute an appropriate reason to exclude chemotherapy, since there are other therapies that have historically been used within the NHS and form part of routine treatment despite also lacking such evidence.

Celgene would also wish to remind the Committee of section 2.2.4 of the Guide to Methods of Technology Appraisal (June 2008), where it states that "There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice." We hope the individual haematologist data presented above illustrate the current variation in the management of high-risk MDS in the UK.

In summary, while there is no recognised standard of care in this patient population we acknowledge that current treatment for this group of patients primarily consists of BSC, since this is indeed a minimum provision of symptom management for such patients. However, additional therapies (LDC and SDC) have been cited by UK physicians and identified as being used to varying degrees regionally within the NHS, demonstrating the variation in routine practice based on both physician and patient choice, and also on patient characteristics and their ability to tolerate such therapy. Therefore, any final recommendation based solely on BSC as the comparator will not provide the NHS with a suitable basis for implementation of such guidance, as this will not include all the main treatment options currently used in the UK by all physicians. This variation in routine NHS practice exemplifies the unmet treatment need in this disease, as well as the potential for the first licensed treatment, if adopted, to provide consistent care throughout the UK.

B2. xxxxxxxxxxxxxxxxxxxxxx

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Table B2: xxxxxxxxxxxxxxx xxxxxxx xxxxxxxxxxx xxxxxxxxxxxx xxxxxxxx xxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

xxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxx		Average daily cost per dose (£)	Average total cost per cycle (£)
	xx xxxxxxxxx	xx xxxxxxxx		
xxxxxxxxxx	xxx	xxxxxxx	xxx	xxx
xxxxxxxxx xxx	xxx	xxx	xxxxxx	xxx

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[redacted]

Celgene would urge the Committee to consider Celgene's commitment to the EMEA, the ongoing development and planned commercial release of a new vial size and the subsequent improvement in cost-effectiveness as presented in the results section of this document.

B3. Patient access scheme

Celgene are pleased to provide details of a proposed discounting scheme for azacitidine. This is a proposed discount of 7% on the basic NHS list price of azacitidine, which is currently £321 per 100 mg/4 ml vial of powder for suspension for injection. (This discount equates to a £22.47 saving on each 100 mg/4 ml vial.)

The discount will be temporary, applicable until Celgene launches a new azacitidine vial strength in the UK.

The aim of this patient access scheme is to minimise any logistical or administrative burden on the NHS; therefore, all administrative processes will be managed by Celgene. This will ensure that the current procedure for ordering azacitidine is not altered and, as a result, no administrative burden will be placed on the NHS.

The impact of the proposed discount is included in the cost-effectiveness results section.

B4. Vial sharing

Celgene has undertaken market research with physicians who treat MDS. This research has indicated that pooling of patients on treatment days would occur given the available vial sizes and dosing regimen of azacitidine. All twenty physicians interviewed indicated that they would pool patients and estimated that this would likely result in 49% of patients sharing azacitidine vials on common treatment days to reduce the amount of unused medication.[2]

In the revised version of the model we have included an option to allow a proportion of patients to be pooled and vials shared. [redacted]

Celgene have provided the results of vial sharing and the reduction in the amount of unused medication in the cost-effectiveness results section.

B5. Factual inaccuracies

Section 2.3 of the ACD incorrectly states that "based on a body surface of 1.7 m^2 and a dose of 75 mg/m^2, 9 vials would be required for one cycle". This statement should be amended to *14 vials would be required for one cycle*, since two vials are required per dose per day based on shelf life after reconstitution.

Part C: Results

Base case analysis

Deterministic cost-effectiveness results are shown for the base-case parameters in Table C1. Two scenarios are presented in table C1. The first assumes that, as present, the 100mg vial is available and there is no patient pooling on common treatment days to allow vial sharing. The second scenario assumes that 49% of treated patients are pooled to reduce the amount of unused medication and only trhe 100mg vial is available. Results are presented in table C2 examining the effect of implementing the patient access scheme and applying a 7% discount to the acquisition cost of azacitidine. A detailed breakdown of the base case results are shown in Table C3a, C3b and C3c.

These results show that the marginal cost increase ranges from £80,644 in the comparison with BSC to £71,316 in the comparison with standard-dose chemotherapy. Azacitidine use results QALY gains of 1.73 compared with BSC and 1.95 compared with standard-dose chemotherapy. These results lead to an ICER of £46,632 compared with BSC, £39,714 compared with low-dose chemotherapy and £36,951 compared with standard-dose chemotherapy.

Additionally, Tables C3a-c demonstrate that patients with high-risk MDS, due to the nature of their disease have high levels of symptom or disease management and monitoring requirements. For example patients pre-selected for BSC alone and treated with azacitidine; of the total cost (£114,232), approximately 60% is attributable to disease and symptom management alone. Thus, any incremental benefit in overall survival provided by azacitidine includes the additional high-cost associated with disease management.

Table C1. Summary of base-case cost-effectiveness results

Treatment option	Costs incurred	QALYs gained	Marginal costs [inc. vial sharing]	Marginal QALYs gained	Cost per QALY gained	
					No vial sharing	Vial Sharing
Preselected for BSC						
Azacitidine	£114,232	2.99	£80,644 [£75,649]	1.73	£46,632	£43,744
BSC	£33,587	1.26				
Preselected for low-dose chemotherapy						
Azacitidine	£122,023	3.28	£80,419 [£75,273]	2.02	£39,714	£37,173
LDC	£41,604	1.25				
Preselected for standard-dose chemotherapy						
Azacitidine	£115,725	2.94	£71,316 [£66,290]	1.95	£36,591	£34,012
SDC	£44,410	0.99				

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Table C2. Summary of base-case cost-effectiveness results including the proposed patient access scheme and applying a 7% discount to the acquisition cost of azacitidine

Treatment option	Costs incurred	QALYs gained	Marginal costs [inc. vial sharing]	Marginal QALYs gained	Cost per QALY gained	
					No vial sharing	Vial Sharing
Preselected for BSC						
Azacitidine	£111,069	2.99	£77,482	1.73	£44,803	£42,641
BSC	£33,587	1.26	[£73,742]			
Preselected for low-dose chemotherapy						
Azacitidine	£118,765	3.28	£77,161	2.02	£38,105	£36,203
LDC	£41,604	1.25	[£73,309]			
Preselected for standard-dose chemotherapy						
Azacitidine	£112,543	2.94	£68,134	1.95	£34,959	£33,028
SDC	£44,410	0.99	[£64,371]			

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Table C3. A detailed breakdown of the cost-effectiveness results

a) Azacitidine and BSC versus BSC alone

Item	Azacitidine (pre-selected for BSC)				BSC		
	MDS state (on active treatment)	MDS state (off active treatment)	AML state	Total	In MDS (BSC alone)	AML state	Total
Total Cost	**£64,807**	**£40,692**	**£8,733**	**£114,232**	**£25,018**	**£8,569**	**£33,587**
Premedication	£520			£520			£0
Treatment administration	£2,707	£1,391		£4,099	£781		£781
Pharmacology (active treatment)	£48,946			£48,946			£0
Follow-up appointments	£2,695	£6,061		£8,756	£3,400		£3,400
Blood/platelet transfusion	£7,816	£17,578		£25,393	£12,052		£12,052
Concurrent medication on treatment	£1,446			£1,446	£1,334		£1,334
Concurrent medication off treatment		£2,377		£2,377			£0
Routine tests on treatment	£678			£678	£598		£598
Routine tests off treatment		£1,067		£1,067			£0
AML health state treatment							
Follow-up appointments			£1,498	£1,498		£1,470	£1,470
Adverse events			£2,303	£2,303		£2,259	£2,259
Concurrent medication			£682	£682		£669	£669
Blood/platelet transfusion			£4,049	£4,049		£3,973	£3,973
Routine tests			£201	£201		£197	£197
Adverse event management	£4,988	£12,218		£17,205	£6,854		£6,854

Key: AE: adverse event; AML: acute myeloid leukaemia; BSC: best supportive care; MDS: myelodysplastic syndrome

b) Azacitidine (and BSC) versus LDC (and BSC)

Item	Azacitidine (pre-selected for LDC)				LDC			
	MDS state (on active treatment)	MDS state (off active treatment)	AML state	Total	MDS state (on active treatment)	MDS state (off active treatment)	AML state	Total
Total Cost	**£66,970**	**£46,473**	**£8,580**	**£122,023**	**£14,893**	**£18,142**	**£8,569**	**£41,604**
Premedication	£537			£537	£53	£448		£501
Treatment administration	£2,798	£1,589		£4,387	£1,380			£1,380
Pharmacology (active treatment)	£50,579			£50,579	£141			£141
Follow-up appointments	£2,785	£6,922		£9,707	£1,830	£1,952		£3,782
Blood/platelet transfusion	£8,076	£20,075		£28,152	£10,034	£10,699		£20,734
Concurrent medication on treatment	£1,494			£1,494	£1,033			£1,033
Concurrent medication off treatment		£2,715		£2,715		£765		£765
Routine tests on treatment	£700			£700	£422			£422
Routine tests off treatment		£1,218		£1,218		£343		£343
AML health state treatment								
Follow-up appointments			£1,472	£1,472			£1,470	£1,470
Adverse events			£2,262	£2,262			£2,259	£2,259
Concurrent medication			£670	£670			£669	£669
Blood/platelet transfusion			£3,978	£3,978			£3,973	£3,973
Routine tests			£198	£198			£197	£197
Adverse event management	£5,349	£13,954		£19,302	£3,126	£3,934		£7,060

Key: AE: adverse event; AML: acute myeloid leukaemia; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome

c) Azacitidine (and BSC) versus SDC (and BSC)

Item	Azacitidine (pre-selected for SDC)				SDC			
	MDS state (on active treatment)	**MDS state (off active treatment)**	**AML state**	**Total**	**MDS state (on active treatment)**	**MDS state (off active treatment)**	**AML state**	**Total**
Total Cost	**£66,112**	**£41,184**	**£8,430**	**£115,725**	**£15,592**	**£18,634**	**£10,184**	**£44,410**
Premedication	£530			£530				
Treatment administration	£2,762	£1,408		£4,170	£9,933	£372		£10,305
Pharmacology (active treatment)	£49,931			£49,931	£1,220			£1,220
Follow-up appointments	£2,749	£6,134		£8,883		£1,622		£1,622
Blood/platelet transfusion	£7,973	£17,790		£25,763	£4,110	£12,446		£16,556
Concurrent medication on treatment	£1,475			£1,475	£476			£476
Concurrent medication off treatment		£2,406		£2,406		£636		£636
Routine tests on treatment	£691			£691				
Routine tests off treatment		£1,080		£1,080		£286		£286
AML health state treatment								
Follow-up appointments			£1,446	£1,446			£1,747	£1,747
Adverse events			£2,223	£2,223			£2,685	£2,685
Concurrent medication			£658	£658			£796	£796
Blood/platelet transfusion			£3,908	£3,908			£4,722	£4,722
Routine tests			£194	£194			£234	£234
Adverse event management	£5,925	£12,365		£18,290		£3,270		£3,270

Key: AE: adverse event; AML: acute myeloid leukaemia; SDC: standard-dose chemotherapy; MDS: myelodysplastic syndrome

Sensitivity analysis

Probabilistic sensitivity analysis

A PSA was performed utilising the updated assumptions for the characterisation of survival and utility uncertainty to examine the combined effect of the uncertainty in all the variable parameters. Values were sampled from the distributions associated with each parameter. Where there were no estimates of parameter uncertainty, ±30% intervals were assumed.

In the PSA, 10,000 sets of parameters were estimated and the marginal costs and QALYs calculated. The results of these analyses are presented as scatter plots in Figures C4a to C4c and cost-effectiveness acceptability curves (CEACs) in Figures C5a to C5c.

Figure C4a. Scatter plot PSA results for patients pre-selected for BSC alone

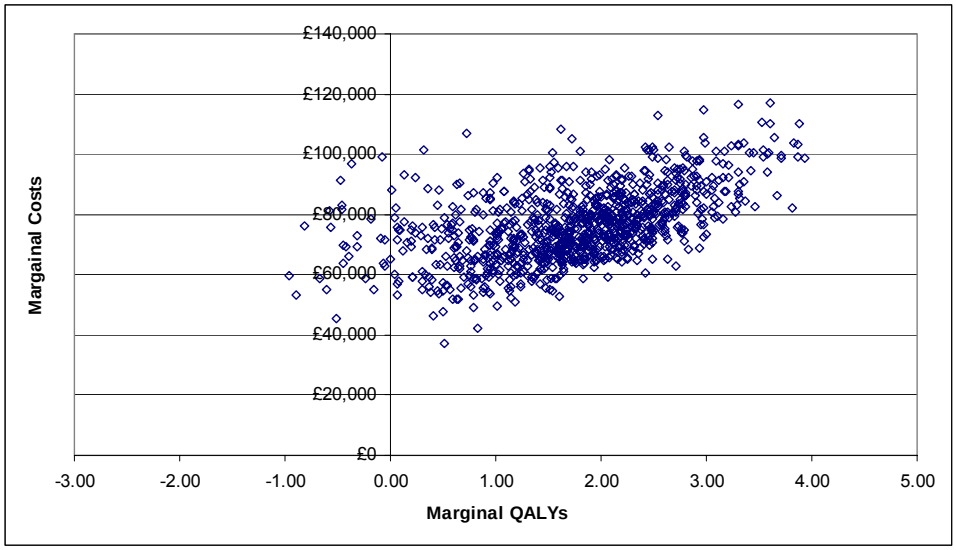

Figure C4b. Scatter plot PSA results for patients pre-selected for LDC

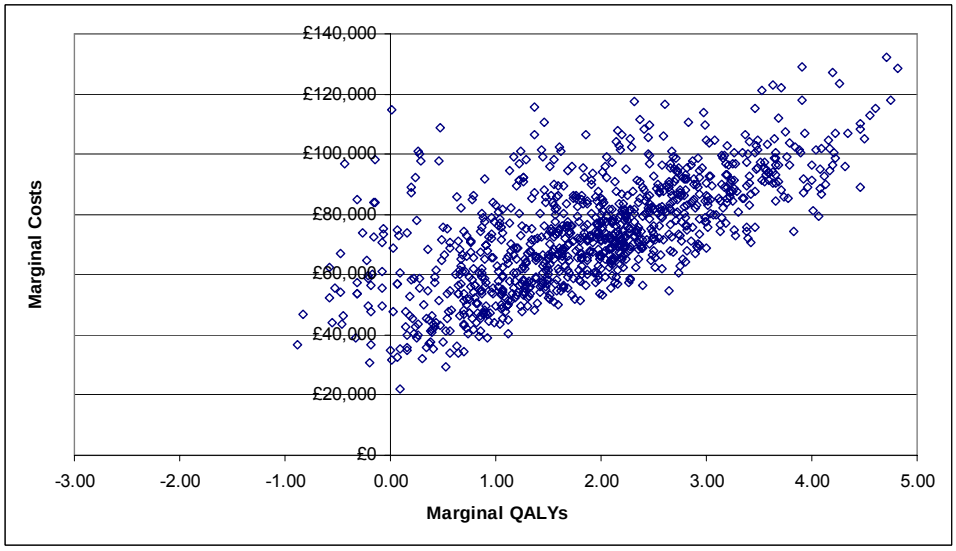

Figure C4c. Scatter plot PSA results for patients pre-selected for SDC

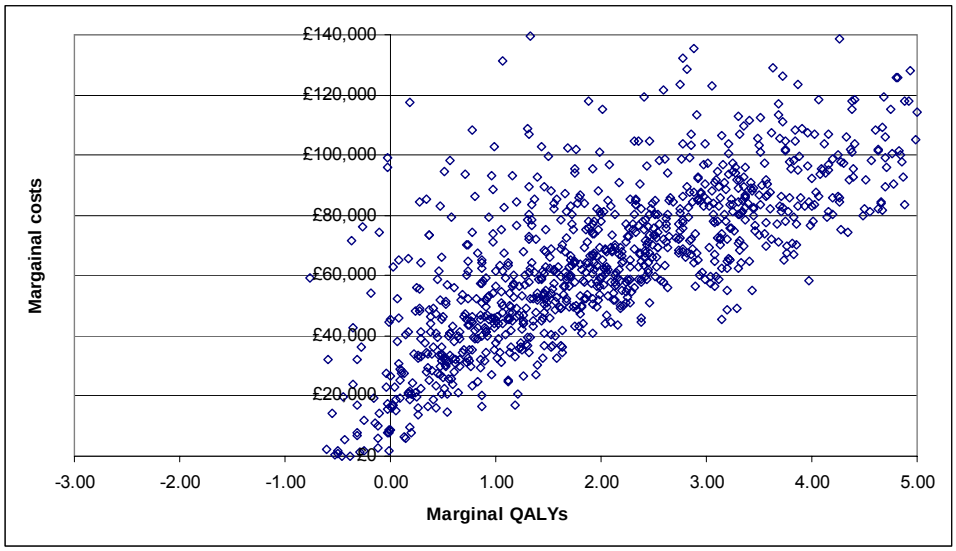

Figure C5a. CEAC for patients pre-selected for BSC alone

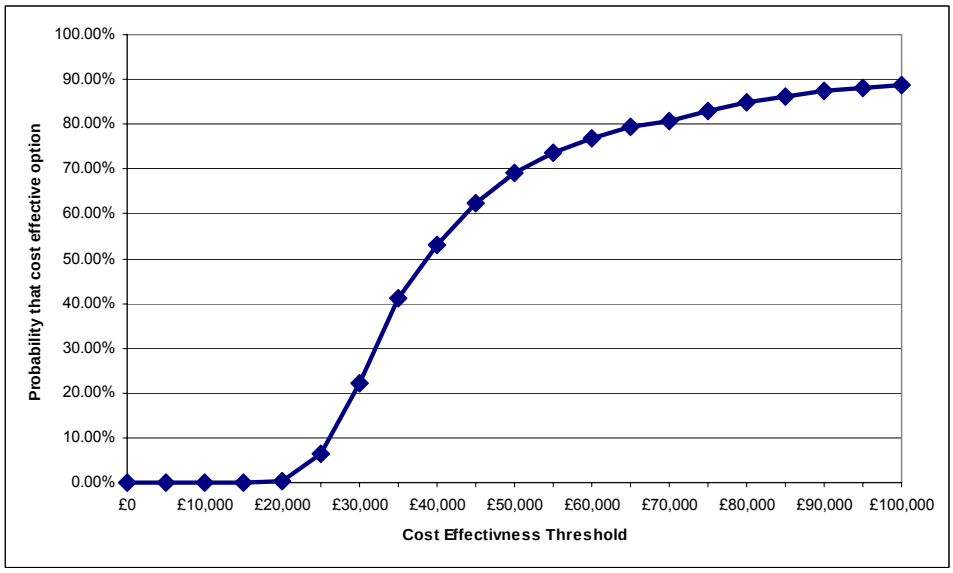

Figure C5b. CEAC for patients pre-selected for LDC

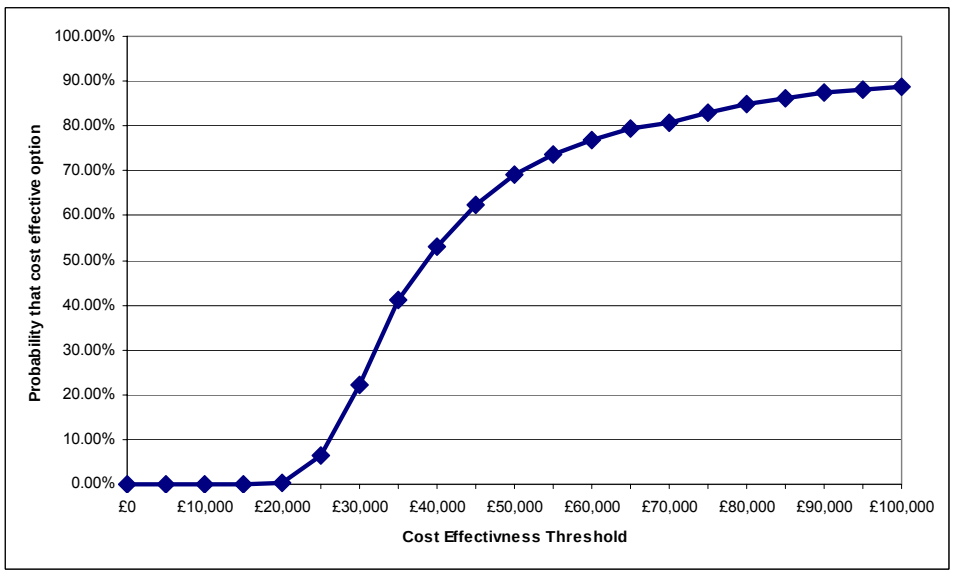

Figure C5c. CEAC for patients pre-selected for SDC

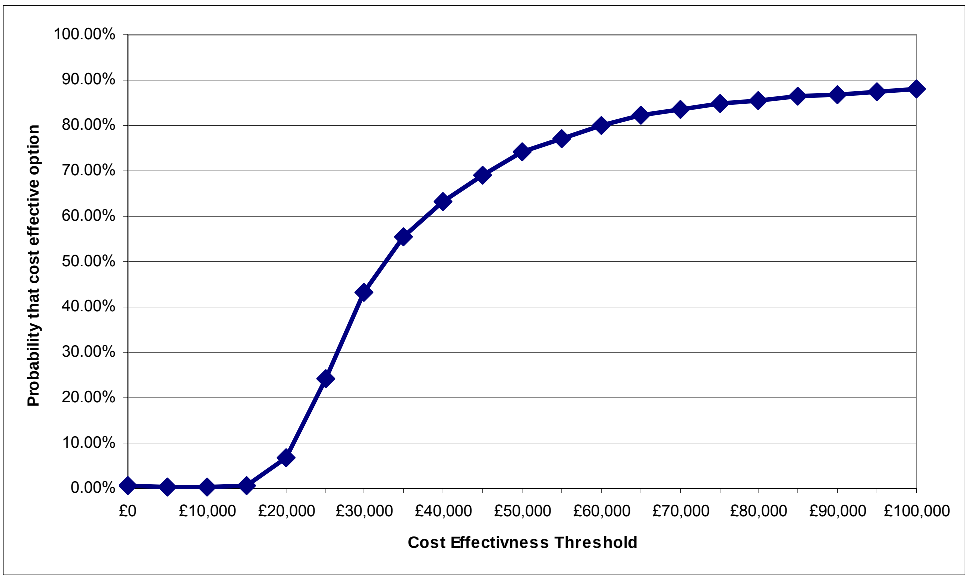

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Table C6. Results of sensitivity analysis of the effect of introducing a xx xxxxxl of azacitidine

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£xx	xx	£xxxx	xxx	£xxx
BSC	xx	xx			
Preselected for low-dose chemotherapy					
Azacitidine	xx	xx	£xxxx	xxx	£xxx
LDC	xx	xx			
Preselected for standard-dose chemotherapy					
Azacitidine	xx	xx	£xxxx	xxx	£xxx
SDC	£xx	xx			

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Application of adverse events

In the base case, AEs are modelled from the patient-level data from the trial, calculating the AE rate by five-week cycle. In the model, these time-dependent rates are applied while patients are on treatment. Once patients are off treatment, they assume the annualised AE rate for BSC. Two alternative scenarios are considered.

1. The annualised AE rates for azacitidine, BSC, LDC and SDC are applied in each cycle in which the patient is on treatment. Once they move off treatment, the annualised AE rate for BSC is used.

2. The annualised AE rates for azacitidine, BSC, LDC and SDC are applied to patients throughout their time in the MDS health state.

The results of these analyses are shown in Table C7. The results show that there is little difference between the base case and Scenario 1, where the annualised AE rates are used during the treatment period. When the annualised AE rates are assumed to have effect throughout patients' time in the MDS health state, the ICER increases compared with BSC and LDC due to the increased cost in the azacitidine extended survival period. However, compared with SDC, the ICER decreases due to the high annualised AE rate in this treatment arm.

Table C7. Sensitivity analysis of the methodology of applying AE rates

Comparator treatment arm	AE methodology					
	Base case		Annualised rate on treatment (1)		Annualised rate in MDS (2)	
	No vial sharing	Vial Sharing	No vial sharing	Vial Sharing	No vial sharing	Vial Sharing
BSC	£46,632	£43,744	£49,819	£46,931	£54,398	£51,510
LDC	£39,714	£37,173	£39,848	£37,307	£43,685	£41,144
SDC	£36,591	£34,012	£35,537	£32,959	£27,857	£25,278

Key: AE: adverse event; BSC: best supportive care; MDS: myelodysplastic syndrome

Modelled time horizon

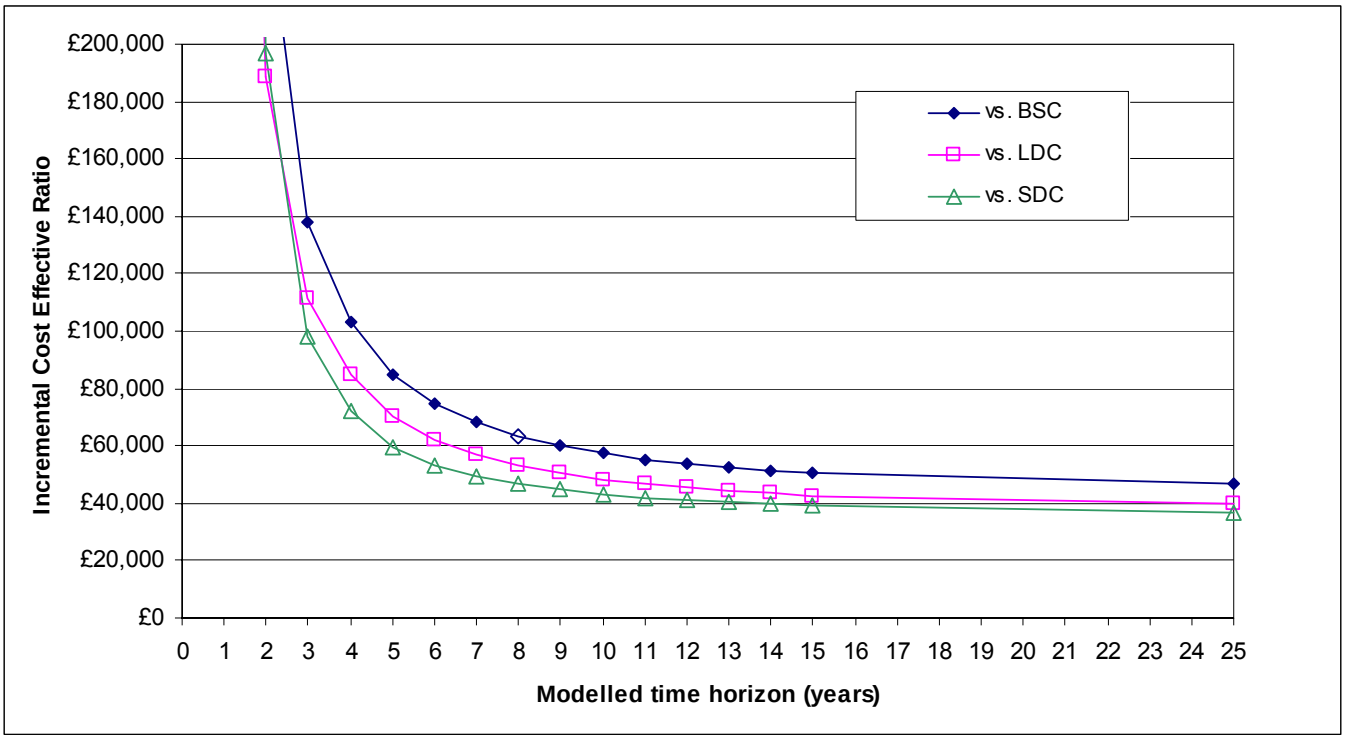
Two sensitivity analyses are performed examining the modelled time horizon. The first examines the effect of only modelling for the three-year period of Study AZA-001. The results of this analysis are shown in Table C8. The second analysis examines the effect on the ICER for each treatment arm of changing the model time horizon from one year through to lifetime. The results of this analysis are presented in Figure C6.

Table C8. Results of a sensitivity analysis using a three-year time horizon, reflecting Study AZA-001 trial period.

Treatment option	Costs incurred	QALYs gained	Marginal costs [inc. vial sharing]	Marginal QALYs gained	Cost per QALY gained	
					No Vial sharing	Vial sharing
Preselected for BSC						
Azacitidine	£78,543	1.28	£54,046 [£49,094]	0.39	£138,238	£125,572
BSC	£24,497	0.89				
Preselected for low-dose chemotherapy						
Azacitidine	£80,741	1.37	£50,027 [£44,928]	0.45	£111,436	£100,077
LDC	£30,714	0.92				
Preselected for standard-dose chemotherapy						
Azacitidine	£79,084	1.29	£37,292 [£32,290]	0.38	£98,199	£85,028
SDC	£41,792	0.91				

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Figure C6. Results of sensitivity analysis varying the modelled time horizon

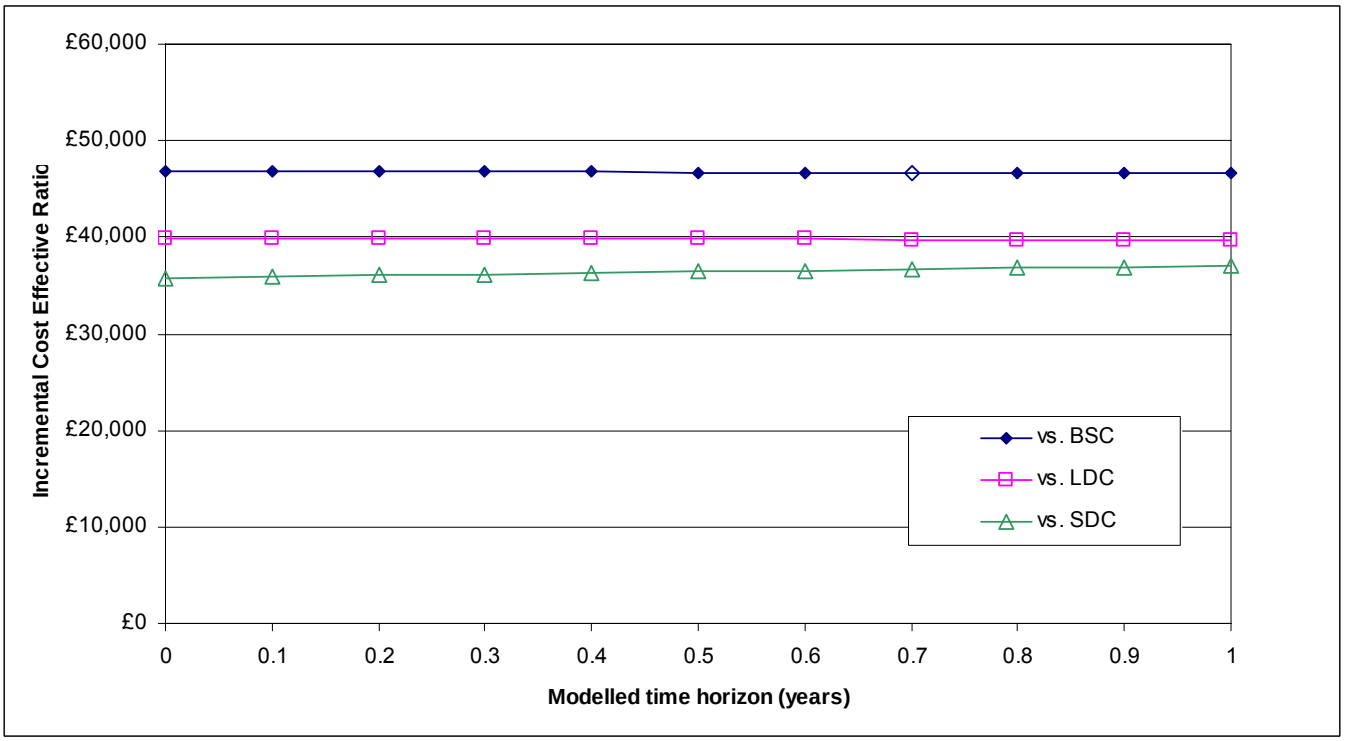


The utility value assigned to AML

There are no utility values available in the literature for patients that are in the AML (blasts >30%) health state. In the base case, this value is assumed to equal the baseline MDS utility score of 0.67.

The effect on the ICER of varying this figure is examined in a sensitivity analysis, the results of which are shown in Figure C7. The analysis shows that varying the utility score of the AML (blasts >30%) health state has minimal effect on the ICER.

Figure C7. Results of sensitivity analysis varying the AML utility value



Longitudinal utility scores

The utility scores used in the base case are based on longitudinal data from two independent studies. The model assumes that the last recorded utility value is used as the constant MDS utility value beyond the end of the utility data. However, the values recorded at later time points are in some cases based on small numbers of patients. A sensitivity analysis is performed which fixes the utility scores at earlier time points to remove the potential effect of small patient numbers. When the utility score is fixed, the fixed value is applied for the remainder of the patient's time in the MDS health state. The results of this analysis are shown in Table C9 and demonstrate that this assumption has little effect on the ICER.

Table C9. Results of sensitivity analysis fixing the utility scores at different longitudinal time points

Comparator treatment arm	Time point from which utility scores are fixed			
	Baseline	50 days	106 days	182 days
Best supportive care	£58,661	£55,140	£50,741	£46,632
Low-dose chemotherapy	£49,649	£47,520	£43,879	£42,589
Standard-dose chemotherapy	£44,364	£41,309	£39,609	£36,153

Adjusted azacitidine and BSC utility values

The utility values for patients in the azacitidine and BSC arms are mapped from EORTC scores from Study CALGB 9221. The patients in the CALGB 9221 data set were slightly younger and healthier at baseline than those in Study AZA-001. A regression analysis was performed to adjust the mapped utility values to account for the differences in these baseline characteristics. The results of using these values are shown in Table C10.

Table C10. Results of sensitivity analysis of adjusted azacitidine and BSC utility values

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained	
					No Vial sharing	Vial sharing
Preselected for BSC						
Azacitidine	£114,232	2.91	£80,644	1.69	£47,766	£44,807
BSC	£33,587	1.22				
Preselected for low-dose chemotherapy						
Azacitidine	£122,023	3.19	£80,419	1.95	£41,249	£38,610
LDC	£41,604	1.24				
Preselected for standard-dose chemotherapy						
Azacitidine	£115,725	2.87	£71,316	1.88	£37,851	£35,184
SDC	£44,410	0.98				

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Reference costs

Recently released HRG-4 reference costs are used in the base-case analysis where appropriate. The validity of using these, however, is unclear and a more appropriate source may be the 2006/07 NHS reference costs. These costs have been inflated to 2008 values. This assumption affects the AE costings, SDC treatment costs and outpatient visits. The results of this analysis are presented in Table C11.

Table C11. Results of sensitivity analysis using 2006/07 NHS reference costs

Treatment option	Costs incurred	QALYs gained	Marginal costs [inc. vial sharing]	Marginal QALYs gained	Cost per QALY gained	
					No Vial sharing	Vial sharing
Preselected for BSC						
Azacitidine	£114,703	2.99	£80,852 [£75,857]	1.73	£46,752	£43,864
BSC	£33,851	1.26				
Preselected for low-dose chemotherapy						
Azacitidine	£122,507	3.28	£80,658 [£75,512]	2.02	£39,832	£37,291
LDC	£41,849	1.25				
Preselected for standard-dose chemotherapy						
Azacitidine	£116,112	2.94	£60,072 [£55,046]	1.95	£30,822	£28,243
SDC	£56,040	0.99				

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

Yours faithfully,

References:

1. Professor Ulrich Germing, Department of Haematology, Oncology and Clinical Immunology, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany. Düsseldorf MDS registry.
2. Celgene – Data on file – August 2008

Appendix : Comments on the ERG Evaluation Report and technical addendum to the updated Azacitidine Health Economic Model

Introduction

This addendum details comments in response to the Evidence Review Group Evaluation Report (ERGR) and changes that have been made to the Azacitidine Health Economic Model in response to the Appraisal Consultation Document (ACD) and the ERGR.

There are four main areas that have been addressed in the addendum. They are:

- Survival curve selection
- Extrapolation of survival gain with azacitidine compared to comparators analysed and calculation of mortality rates
- Calculation of period in acute myeloid leukaemia
- Probabilistic sensitivity analysis (PSA) assumptions
- Amended and additional economic model functionality

1. Survival curve selection

The ERG performed a survival analysis of overall survival based on the data provided in the model and concluded that the log-logistic was on no occasions the best fit curve based on the Akaike Information Criterion (AIC). This analysis did not include the Study AZA-001 extension data which was only supplied is graphical format in the primary evidence submission. The analysis performed by the ERG has been repeated for a dataset which includes the extension data. The results of this analysis are shown in Table A1 below. The best fit curve based on the lowest AIC are highlighted.

Table A1: AIC values for curve fits to overall survival data including the AZA-001 extension data

Fitted distribution	AIC for pre-selected subgroup					
	Azacitidine (BSC)	Azacitidine (LDC)	Azacitidine (SDC)	BSC	LDC	SDC
Exponential	301.2125	121.4813	48.85525	276.5794	130.7675	55.11062
Weibull	303.1845	122.7963	50.79613	277.3018	131.8855	51.44694
Gompertz	302.8256	122.0447	50.8036	278.464	132.1136	53.44262
Lognormal	303.6514	120.9462	51.00725	270.196	131.3413	50.24947
Log-logistic	302.7885	121.9108	50.88705	271.382	132.7571	51.19378

The analysis of the overall survival data shows that the exponential and the lognormal provide the best fit to the observed Study AZA-001 data, however, it should be noted that all the AIC values are very close for the different curve selctions, showing that they demonstrate similarly good fits to the observed data. Therefore as highlighted by the ERG, the long-term survival element of the data becomes most important to ensure that it reflects long-term survival expectations.

2. Extrapolation of survival gain with azacitidine compared to comparators analysed and calculation of mortality rates

All-cause mortality adjustment

The ERG and the Appraisal Committee have raised concerns regarding the face validity of the results of the economic model relative to the results of the main source of the clinical effectiveness.

Celgene accept the ERG's criticism that the tail of the curve should be adjusted for age-dependant all-cause mortality so that patients are not seen to survive to an unrealistic age. We have therefore adjusted the survival curves to include all-cause mortality. Using annual mortality rates extracted from UK life tables,[1] we calculate a cycle risk of all-cause mortality. There are different all-cause mortality risks associated with male and female patients, so we weight the risk based on the male:female split in Study AZA-001 (74% males, 26% females). The annual rate of all-cause mortality is divided into a 35-week cycle mortality using the equation:

[1] Government Actuary's Department. *UK interim life tables: 2006-based projection.* Available at http://www.gad.gov.uk/Demography%20Data/Life%20Tables/Interim_life_tables.html

$$\text{Cycle mortality} = 1-(1-\text{annual risk})^{1/(365/35)}$$

The analysis and results are shown in Table A2.

In each cycle of the model, both the mortality risk based on the extrapolation of the trial overall survival data and the all-cause mortality risk are calculated. The greater of the two risks is used as the mortality rate in that cycle. The graphs below show the survival curves for the unadjusted log-logistic fit to the data used in the primary submission, the age-adjusted lognormal fit to the data used in the updated version of the model, the exponential fit to the data, and the all-cause mortality survival curve for a non-MDS patient cohort. These survival curves are shown for the six treatment arms in Figures A1a to A1f.

Table A2: All-cause mortality data and adjustment analysis

Age	Annual all-cause mortality rate*		Sex-weighted annual mortality risk	Cycle mortality risk
	Male	Female		
64	0.0141	0.0087	0.0127	0.0012
65	0.0153	0.0094	0.0138	0.0013
66	0.0166	0.0105	0.0150	0.0015
67	0.0182	0.0115	0.0165	0.0016
68	0.0201	0.0126	0.0182	0.0018
69	0.0217	0.0138	0.0197	0.0019
70	0.0238	0.0153	0.0216	0.0021
71	0.0269	0.0169	0.0243	0.0024
72	0.0297	0.0190	0.0269	0.0026
73	0.0326	0.0211	0.0296	0.0029
74	0.0367	0.0240	0.0334	0.0033
75	0.0404	0.0268	0.0369	0.0036
76	0.0455	0.0301	0.0415	0.0041
77	0.0507	0.0338	0.0463	0.0045
78	0.0556	0.0380	0.0510	0.0050
79	0.0622	0.0429	0.0572	0.0056
80	0.0686	0.0478	0.0632	0.0062
81	0.0766	0.0537	0.0706	0.0070
82	0.0852	0.0598	0.0786	0.0078
83	0.0937	0.0675	0.0869	0.0087
84	0.1030	0.0755	0.0958	0.0096
85	0.1118	0.0842	0.1046	0.0105
86	0.1203	0.0915	0.1128	0.0114
87	0.1306	0.1025	0.1233	0.0125
88	0.1412	0.1138	0.1341	0.0137
89	0.1691	0.1331	0.1598	0.0166
90	0.1778	0.1443	0.1691	0.0176
91	0.1896	0.1610	0.1822	0.0191
92	0.2074	0.1784	0.1999	0.0212
93	0.2258	0.1986	0.2187	0.0234
94	0.2371	0.2144	0.2312	0.0249
95	0.2650	0.2347	0.2571	0.0281
96	0.2824	0.2545	0.2752	0.0304
97	0.3090	0.2721	0.2994	0.0335
98	0.3383	0.2967	0.3275	0.0373
99	0.3372	0.3125	0.3308	0.0378
100†	0.3795	0.3342	0.3677	0.0430

* Government Actuary's Department. *UK interim life tables: 2006-based projection.* Available at http://www.gad.gov.uk/Demography%20Data/Life%20Tables/Interim_life_tables.html

† No data are presented in the life tables for ages >100. We therefore assume that the rates for patients aged >100 are equal to those for patients aged 100

Figure A1a: Survival curves for azacitidine (pre-selected for BSC alone)

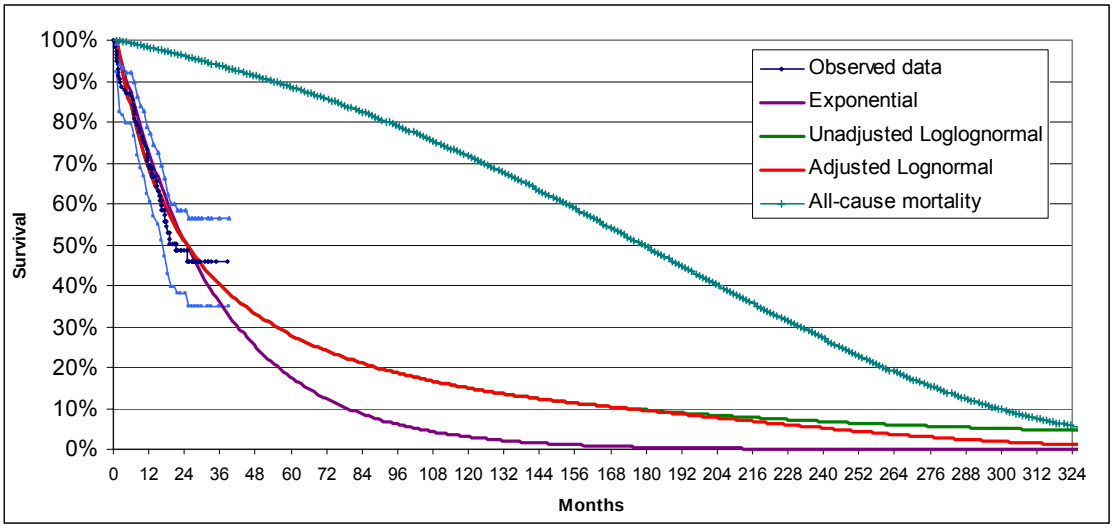


Figure A1b: Survival curves for azacitidine (pre-selected for LDC)

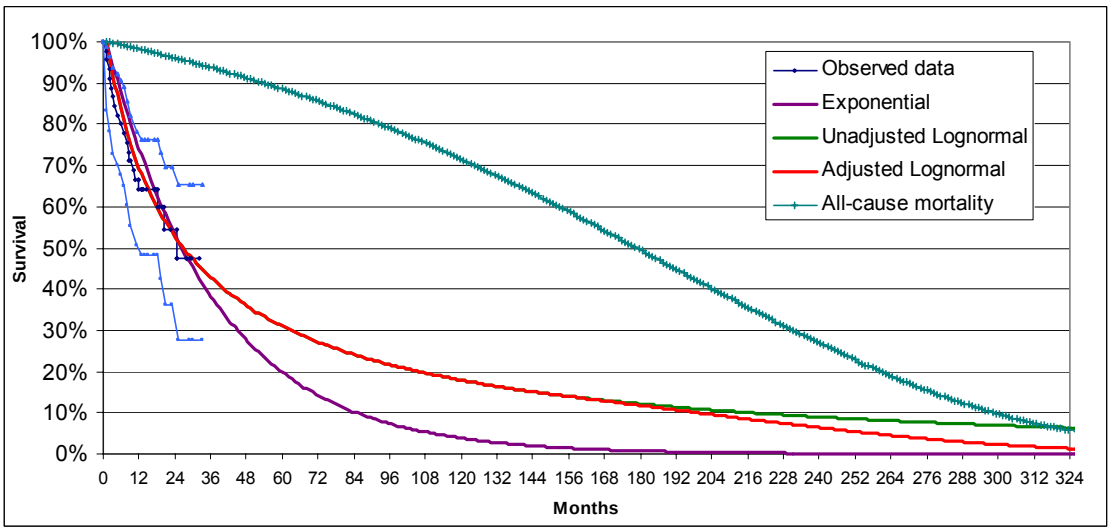


Figure A1c: Survival curves for azacitidine (pre-selected for SDC)

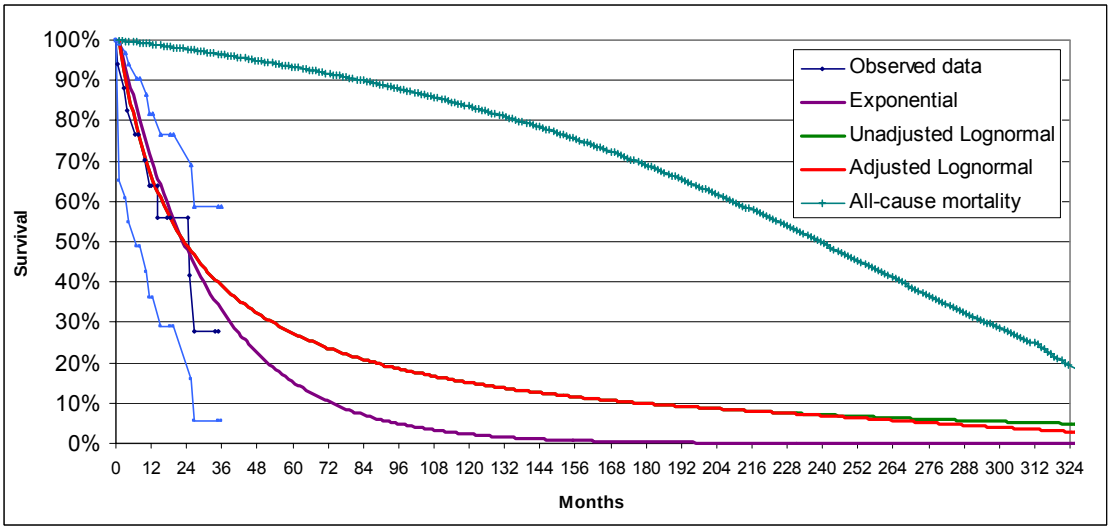


Figure A1d: Survival curves for BSC alone

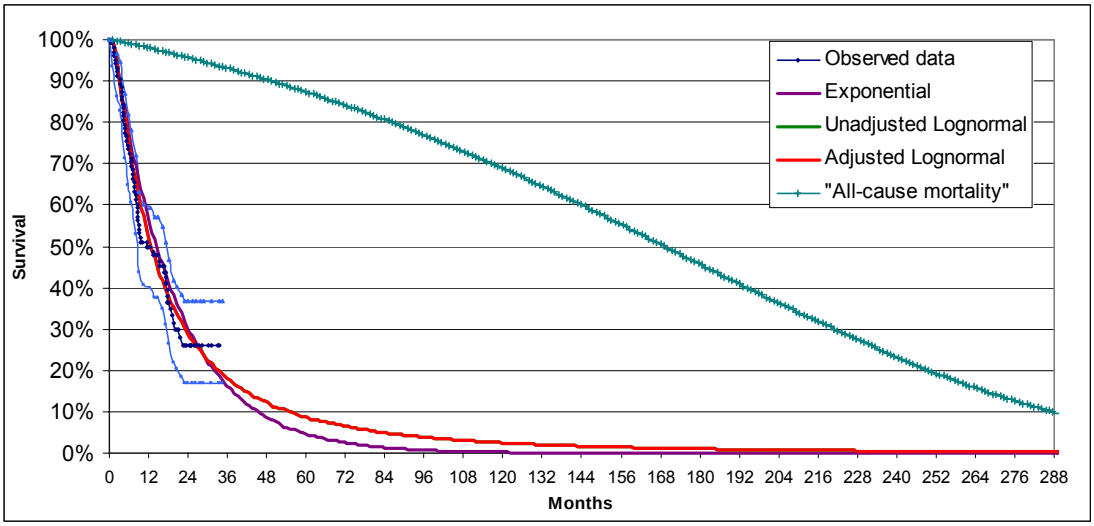


Figure A1e: Survival curves for LDC

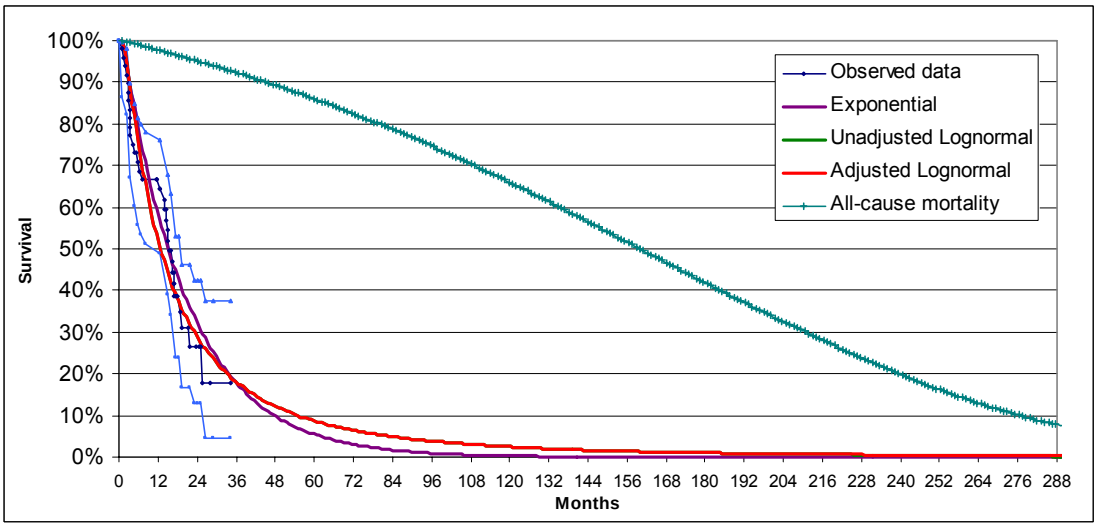
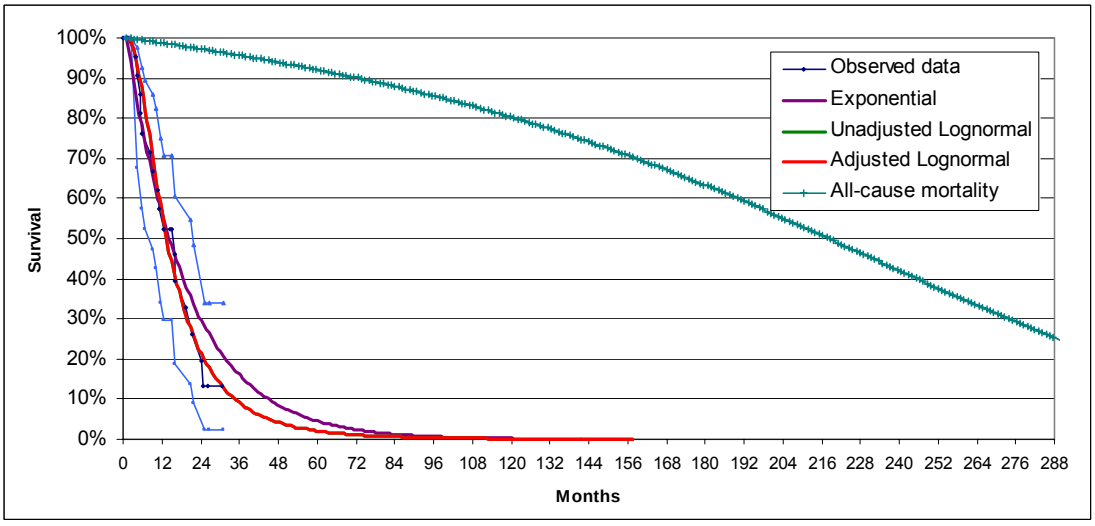


Figure A1f: Survival curves for SDC

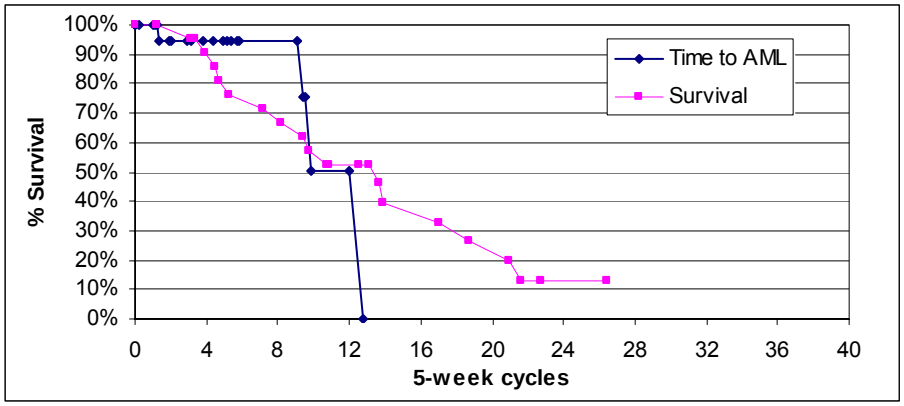


3. *Calculation of period in acute myeloid leukaemia*

a. Overview

There is some uncertainty from the ERG (section 3.11 and 4.10 of the ACD) as to the effect of the chosen method to model time to progression to AML. As stated in our evidence submission, the relationship between time to AML and time to mortality is difficult to estimate due to the number of censored patients. This is demonstrated by Figure A2, which shows the Kaplan–Meier curves for progression to AML and survival, as well as the difficulty in fitting a suitable curve through the data.

Figure A2: SDC Time to AML and Overall Survival Kaplan-Meier Curves



b. Clinician input into progression to AML assumption

This issue of progression to AML and time in AML was discussed in depth with clinicians in advisory meetings and it was agreed that there was no expectation that there would be any difference between treatment arms on the time spent in AML. There would be however differences in time to AML as overall survival is extended on treatment with azacitidine.

Clinicians also described the treatment requirements of patients that progressed to AML as being very similar to patients receiving BSC. By the time most patients progress to AML in all treatment arms they are often being treated only with BSC and therefore there is minimal impact of progression. In was recommended by the clinicians that we even remove the AML state and consider AML progression to be part of MDS and assume 1 cycle of decreased mortality in the cycle before death. We decided that we should try to reflect the trial data as much as possible, without letting the deficiencies in the data drive the economics.

c. Mortality rate of patients in AML

In Study AZA-001, for patients that progressed to AML in all the treatment arms, the mean pooled mortality rate was 0.135 per 5-week cycle; equivalent to a mean survival of 7.4 five-week cycles. This rate is used in the AML arm of the model. Mortality is calculated by firstly determining the overall survival and then applying the 0.135 rate to all patients in AML. If the number of patients that suffer mortality based on the overall survival is greater than those that die in AML then the remainder are taken from the MDS population. This assumption partitions which health state patients die in, but does not alter overall mortality. A consequence of this assumption is that as the number of patients remaining in the model drops and the overall mortality rate decreases, the rate of mortality in AML drops so that the overall mortality rate is maintained. For example, in the BSC arm at 8 years there are 1.7% patients in the AML health state. The mortality rate at this time is 1.1% which results in 0.0021 of the cohort dying. 0.135 of the AML population however is 0.0023, and so the AML mortality rate is lowered to 0.120 so that the overall survival rate is maintained. The 0.135 rate however is maintained throughout the modelled trial period in all the trial arms and the lower rate is only used in the tail of the data. Overall survival is not affected by this assumption.

d. Progression to AML

It is discussed in above that estimation of time to AML is difficult to measure due to issues of censoring and measuring AML. Previous estimates of time in AML have been confused by inclusion of patients of patients who did not progress to AML. The mean time spent in AML for those patients who progress to AML is 7.4, five-week cycles (1/0.135). Previously a median of 3.65 months (4.56 5-week cycles) was

reported but this contained data on patients who had not progressed to AML and so was underestimated.

To ensure that the time to AML is related to overall survival, we estimate the time to progression by offsetting the survival curves by a number of cycles so that patients progress to AML 8 cycles before mortality (time in AML is 7.4 cycles and so this slightly overestimates the time in AML). Based on an assumption of a lognormal fit to the overall survival data, the time to AML and the time spent in AML based on these assumptions are summarised in the table below. These have been calculated by dividing the time spent in AML by the number of patients that progress to AML.

Table A3: Results on time in AML for patients that progress to AML health state

Treatment arm	Time in AML for patients that progress (5 week cycles)
Azacitadine (BSC)	7.68
BSC	7.67
Azacitadine (LDC)	7.74
LDC	7.67
Azacitadine (SDC)	7.61
SDC	7.50

4. Probabilistic sensitivity analysis assumptions

Survival curve fits

The ERG identified that the linear correlation assumptions utilised in the PSA analysis in the primary submission were potentially causing a mischaracterisation of the uncertainty around the survival curve fits sampled in the analysis (ERGR addendum section 3.6.2). It was recommended that a Cholesky decomposition be used with the curve parameters. This approach has been included in the updated version of the model.

In each survival calculation sheet in the *Survival* section of the input sheet, the analysis has been updated to include the Stata output for each curve, the matrix of variance and covariance for each fit and the method of sampling of the curve for the PSA using a new function, MULTINORMINV, added to Excel. This function performs the Cholesky decomposition A=L*L^t of matrix, and uses this along with a sample from a uniform distribution (random number [0,1]) and parameter vector to generate samples from a multivariate normal with mean and covariance given by the parameter and covariance matrixes. This can be found in the VBA module *Cholesky.*

Utility scores

The ERG (ERGR addendum section 3.6.2) also criticised an assumption of linear covariance between utility scores in the PSA. The ERG recommended that all utility scores at all time points be considered independent and, therefore, a separate random number be used for each sample utility score. This amendment has been made to the model.

5. Amended and additional economic model functionality

Amended economic model functionality

The ERG reported concerns related to the economic model (ERGR section 3). In summary, these referred to critical flaws, coding errors, discounting errors and broken links within the model. Celgene thank the ERG for identifying these errors and we can confirm that they have been corrected or removed from the revised economic model that has been sent to the Institute as part of this consultation.

Discounting of costs and QALYs

In a previous response to the ERG the issue of cost not being correctly discounted in the economic model had been addressed. The model now correctly applies an annual discount rate to all costs and QALYs gained.

In section 3.5.1 of the ERGR, the ERG state that the discount rate was not applied correctly and that a cycle discount rate of 0.46% (3.5% * 35/365) should be applied. The company do not understand the requirements of the ERG here nor understand their calculation as 3.5%*35/365 = 0.34. We have therefore retained the discounting previously used in the economic model as we feel this is most appropriate.

Labelling of censored or dead patients in the survival analysis

In section 3.3 of the ERGR, the ERG noted that the labelling on the censored/dead survival analysis was inconsistent, however was happy that the analysis was performed correctly. The survival analysis has been updated to include the extension data, a full range of curve fits and all columns are correctly labelled so that no confusion can incur.

Unclear labelling of survival graphs

In section 3.3 of the ERGR, the ERG also reported that they were unclear as to whether the survival graphs were plotted in months or in 5-week cycles. The survival graphs and the model have been updated so that labelling is consistent and is clear as to which approach has been used.

Double counting of adverse events

Additionally, following independent validation of the economic model, an error was discovered in which some adverse events (AEs) were double-counted. The error occurred in the formulas used to calculate the cost of 'MDS off Active treatment'; for example, cell R8 in the 'Vidaza (BSC) Flow' sheet.

This calculation adds AE costs to the 'range_MDSOffTreatmentCostVidaza', based on different methods chosen for the AE rates to be used for the cost calculation (see cell AS 12 in the input sheet).

However, the calculation of 'range_MDSOffTreatmentCostVidaza' (cell CL15 in the input sheet) already included annualised AE costs associated with BSC (range_CostAEBSC). Therefore, the AE costs after active treatment cessation have been counted twice. This double-counting has been corrected in the revised model.

Additional economic model functionality

The ACD details a series of assumptions and scenarios (for example, cost source or weekend administration) that have been incorporated into the model to allow scenario analyses.

Costs

The Committee stated that the HRG 4.0 2009/10 tariff costs should be used as the base-case costing source for the model. Celgene have included an option to switch between costing sources in the *Unit Cost* section of the input sheet. NHS 2009/10 tariff costs are used for the revised base-case analysis.

Administration costs of azacitidine

Functionality has been added to the model to examine the effect of including weekend administration of azacitidine. This option is displayed in the *Unit Cost* section of the input sheet. We assume that if weekend administration is required, then the cost of administration is doubled over the weekend period. This assumption of higher administration costs has been built into the revised base-case analysis.

Alternative AE assumptions

The ACD (section 3.15) describes the ability to explore alternative assumptions regarding AEs as described in the primary evidence submission (pages 115–116). Exploration of this is possible through the functionality in the *AE Rates* section of the input sheet.

Unused medication and waste

The base case assumed that only a 100 mg vial was available to patients; therefore, the cost of unused medication incurred per dose was included in the analysis. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxXxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Table A2: Number of xxxxxxxxxxxxxx xxx required in each xxxxxxxxx

xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	
	xxxx	xxxx
xxx	xxx	xxx
xxx	xxx	xxx
1xxxxx	xxx	xxx

A further scenario has also been included in which it is assumed that no medication is left unused.

Vial sharing

Celgene have been advised by clinicians that vial sharing between patients is envisaged, based on pooling of patients on common treatment days. There is evidence that this occurs in 49% of patients. Where vial sharing occurs, we assume that the amount of unused medication is equal to that expected xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Removal of redundant sheets

A number of sheets that were no longer used in the economic model have been removed.