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18 March 2010

### **Final Appraisal Determination**

#### **Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia**

#### **Appeal against Final Appraisal Determination**

On 4<sup>th</sup> of March 2010, the Institute issued its Final Appraisal Determination (FAD) on azacitidine for the treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML). In section 1.1 of the FAD, azacitidine is not recommended as a treatment option for intermediate-2 and high risk MDS, CMML with 10-29% marrow blasts without myeloproliferative disorder or AML with 20-30% blasts and multilineage dysplasia.

Celgene is appealing against this guidance. This letter should be treated as our appeal in accordance with the Institute's guidance for appellants.

A summary of our key points is as follows:

- The Appraisal has failed to take into account all relevant comparators. Despite the requirements of the Final Scope for the appraisal and evidence that a range of treatments are currently given to patients with MDS, including chemotherapy, the Institute has opted to consider health economic evidence relating to the comparison with best supportive care (BSC) only. The way in which information about comparators was handled is procedurally unfair and outside the scope of NICE's remit. Further, the conclusions drawn from the available evidence are perverse.
- The Institute has failed to recognise that the NICE criteria for end-of-life, life-extending treatments ("Life Extending Guidance") apply equally to any comparison with chemotherapy comparators as they do to a comparison with standard care. By ignoring the magnitude of the life extension which azacitidine patients experience and focussing on small patient numbers in one sub group of the pivotal azacitidine trial, the Institute has made a perverse recommendation.
- The Institute has failed to take account of the ultra-orphan indication for azacitidine and that it is bound under its Social Value Judgements to consider

appraisals of such drugs differently than orphan or non-orphan drugs. When considering azacitidine in the context of the Life Extending Guidance, the Appraisal Committee should have taken into account the very small patient population (approximately 700 patients in the UK, less than the 1,000 specified by the ultra-orphan definition) and placed even greater weight on the benefits of azacitidine, whether based on the chemotherapy ICERs or the BSC alone ICER. Had it done so when making its recommendations, we consider that the only appropriate outcome would be to recommend the reimbursement of azacitidine.

- NICE has exceeded its powers by making recommendations that are incompatible with certain fundamental freedoms under the European Convention of Human Rights (ECHR), as transposed into national law under the Human Rights Act 1998. In particular, the guidance breaches Articles 2 (right to life), 3 (freedom from inhuman and degrading treatment), 8 (right to family and private life) and 14 (discrimination) as the recommendations may result in patients with high risk MDS – the vast majority of whom are over 70 years of age – dying sooner than would be the case if the drug were to be recommended.

We note also that the draft guidance runs counter to other areas of Government activity designed to encourage and reward innovation, for example, work around the Office of Life Science, such as the innovation pass and so-called patent box, and the ongoing NICE consultation about the Kennedy Review. These initiatives are all designed to encourage companies to produce genuine innovation in areas where there has been little recent scientific progress. This is exactly the type of development that azacitidine represents and yet NICE has chosen to judge this drug making little allowance for the fact that it is highly innovative, treats a very small population and in a disease area where there are few treatment options. We cannot believe that this is consistent with what Government wishes to achieve in this area.

Celgene's detailed grounds for appeal comprise four key arguments. These four arguments are addressed separately and, for each argument, the grounds for appeal have been set out to reflect those in the Institute's guidance for appellants.

## GROUND OF APPEAL

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The permitted grounds of this appeal are: (1) that the Institute has failed to act fairly and in accordance with its Directions from the Secretary of State and its published procedures as set out in the Institute's Guide to the Technology Appraisal Process and Guide to the Methods of Technology Appraisal, (2) that the Institute has prepared a FAD that is perverse in the light of the evidence submitted, and (3) that the Institute has exceeded its powers.

The following sections summarise the company's appeal points giving information about which grounds apply in each case.

### 1 COMPARATORS

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The Appraisal Committee ignored chemotherapy as a valid comparator treatment and instead considered that best supportive care (BSC) alone was the most appropriate comparator for the economic modelling. Relying solely on BSC is procedurally unfair

characteristics and needs. Indeed, as discussed above, the current guidelines in the UK on MDS support exactly this type of approach.

What is important in the consideration of this survey evidence is whether chemotherapy is used in sufficiently large proportions of MDS patients to make chemotherapy a valid and important comparator in the cost-effectiveness assessment. The Institute's summation of the Celgene survey data omits the fact that chemotherapy was in fact quite commonly used by many haematologists. The survey data do not provide robust support for the view that BSC alone is the only comparator worth considering in this appraisal, and the Institute's handling and logic around this information is clearly perverse.

### 1.2.2 Opinion of clinical specialists

In addition to the information provided by Celgene, the Institute received evidence about the use of chemotherapy in the treatment of MDS from a wide range of sources, including professional bodies and individual experts throughout the appraisal. Extracts from these submissions and also extracts from clinical guidelines on MDS are attached in a table at Annex 1.

Again, we find it difficult to understand how the Appraisal Committee can ignore chemotherapy as a comparator when submissions in this appraisal from key experts in MDS state that chemotherapy is the "commonest default" treatment for high risk MDS. For example, the Royal College of Pathologists ("RCPath") states in its evidence submission to NICE:

*"Management options range from observation only, supportive care, 'active treatment' (low dose chemotherapy, intensive chemotherapy, stem cell transplantation), to symptom relief only for patients whose general health is so poor that an improvement in their haematological status would confer no corresponding improvement in quality of life."* (Emphasis added).

Further, [redacted] representing the RCPath and the British Committee for Standards in Haematology ("BCSH"), sent a personal statement to NICE that states:

*"High risk patients are frequently treated with low dose cytosine arabinoside. This is the commonest 'default treatment' for high risk MDS but produces remissions in only 10-20% and a median survival of only 4-6 months. Low dose cytosine arabinoside remains the standard comparator arm in NCRI AML 16."* (Emphasis added).

Moreover, [redacted] representing the Royal College of Physicians, National Cancer Research Institute, Royal College of Radiologists, Joint Collegiate Council for Oncology and the Association of Cancer Physicians, said in a personal statement to NICE that he agrees with comments made by the foregoing institutions as follows:

*"The proportion of patients treated with each of the three conventional care regimens in the 001 study approximately reflects everyday practice with the majority of patients treated with best supportive care, fewer with low dose chemotherapy such as low dose cytarabine and fewer still with intensive*

and is inconsistent with NICE's remit given the explicit reference to chemotherapy, particularly low-dose chemotherapy, in the Final Scope and the Institute's guidance on use of comparators. The decision is also perverse in the face of evidence provided by expert clinicians and patients, a Celgene research study and the azacitidine clinical trial. The evidence suggests that around 60 per cent of stem-cell transplant (SCT) ineligible patients with higher risk MDS receive some form of chemotherapy, and that doctors are able routinely to identify such patients. The evidence suggests that there is some variation in UK clinical practice around the use of chemotherapy. But to conclude from this evidence that chemotherapy regimens are rarely used, only used prior to SCT, or that there are no nationally recognised standards for this patient population is factually inaccurate or, at best, a gross misinterpretation of the evidence that directly impacts on the final decision for azacitidine.

## **1.1 The Institute has failed to act fairly and in accordance with its remit and its published appraisal procedures**

### **1.1.1 Final Scope**

NICE is required to appraise products in accordance with the Final Scope as agreed between NICE, the Department of Health and Consultees and the NICE Guide to the Methods of Technology Appraisals 2008. The Final Scope for this appraisal states that:

*“the **mainstay** of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients.”* (Emphasis added.)

The Final Scope actually lists “chemotherapy (such as cytarabine and anthracyclines) low and high dose” in the table of comparators. The distinction between high and low dose chemotherapy was included in the Final Scope following a consultation on the draft scope that included comments on the chemotherapy regimens that are “routinely” used in clinical practice.

On this point, the NICE Guide to the Methods of Technology Appraisals 2008 states:

*“Relevant comparators are identified, with consideration given specifically to **routine and best practice** in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment. **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.** For example, this may occur when new technologies are used inconsistently across the NHS.”* (Emphasis added.)

According to the NICE Guide to Methods of HTA, regional variation in routine clinical practice should be a reason for inclusion of additional comparators, not for their exclusion.

In addition, the Final Scope cites other related NICE guidance that should be taken into account when appraising azacitidine, including the Cancer Service Guidance, October 2003, *Improving outcomes in haemato-oncology cancer* (“NICE Cancer Clinical Guideline”). The NICE Cancer Clinical Guideline states:

*“The choice of agents and the way they are used depends both on the type of cancer and on the individual features of the case. For some patients, no treatment is necessary at the time of diagnosis; for the majority, conventional dose therapy is appropriate, but some of these may be offered high dose therapy if the disease does not respond or if they relapse. Patients whose disease progresses despite continued or intensified treatment may reach a point at which anti-cancer therapy does more harm than good, and palliative therapy becomes more appropriate. **Systems for decision making and delivery of treatment must therefore be flexible and responsive to changing patient needs.**” (Emphasis added).*

The failure by the Appraisal Committee to consider the ICER figures using chemotherapy as a comparator is therefore unfair given that the Committee is obliged to do so under the terms of the Final Scope and in accordance with the methods guidance above. Further, any decision-making by NICE in this regard must, according to the NICE Cancer Guideline, be flexible and responsive to changing patient needs.

#### 1.1.2 Existing guidelines

In establishing its position on comparators, the Institute has failed to take into account currently published guidelines and standards from across the UK, relating to the treatment of MDS, that demonstrate that chemotherapy is a routine treatment in appropriate patients. It has acted unfairly in ignoring guidance published by national bodies, including NICE itself (see above), for the management of MDS. The key guidelines relevant to this appraisal all stress the need for either chemotherapy, or a flexible approach:

#### **British Committee for Standards in Haematology – Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes 2003<sup>1</sup>**

*“Both patients > 65 years and those < 65 years who are ineligible for stem cell transplantation **should be considered for intensive chemotherapy alone.**” (Emphasis added).*

#### **National Horizon Scanning Centre report 2008 – Decitabine**

*“There are no specifically licensed products for MDS. The current treatment and supportive options include:*

- *Supportive care which may include:*
  - *Regular red cell and/or platelet transfusions*
  - *Erythropoietin and granulocyte-colony stimulating factor*
  - *Antibiotics to treat infections*
- ***Low-intensity chemotherapy e.g. cytarabine.***
- ***High-intensity chemotherapy given to people with high-risk MDS.***
- *Allogenic bone marrow transplantation may be considered for younger patients with high-risk MDS or reduced intensity allograft for older patients (<65 years).” (Emphasis added).*

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<sup>1</sup> Bowen D et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003;120:187-200.

## **NICE Cancer Clinical Guideline**

*“Systems for decision making and delivery of treatment must therefore be **flexible and responsive to changing patient needs**”* (Emphasis added).

Myelodysplastic syndrome is a heterogeneous condition demanding individualised treatment. However, the clinical guidelines listed all illustrate that chemotherapy ought to be among the treatments routinely considered for the SCT-ineligible, high-risk MDS population.

### **1.1.3 Failure to assess fully the information from the Celgene survey**

Celgene conducted a survey among 11 leading British haematologists to assess their current treatment of SCT-ineligible, high-risk MDS patients. The company considered the results of the survey to be clear evidence that a significant proportion of relevant patients receive chemotherapy.

However, the Appraisal Committee failed to give due consideration to these data, apparently on the basis that they reflected *“pronounced variation”* (FAD Section 4.2). Yet it seems from the FAD that there was no detailed consideration of the distribution of responses in this survey; not even the standard deviation for percentages treated with BSC or BSC plus chemotherapy is reported.

The Institute’s failure to give due consideration to these data or to provide Celgene with any understanding of how the Appraisal Committee analysed the survey data is inconsistent with the published procedures for health technology assessment and unfairly prejudices the company and its product.

## **1.2 The Institute has prepared guidance which is perverse in the light of the evidence submitted**

The FAD contains a number of mistakes of fact and interpretation of the clinical and cost-effectiveness evidence for azacitidine. These mistakes have led to the perverse decision to rely solely on BSC as a comparator. The FAD states at paragraph 4.2 that “best supportive care alone was the most appropriate comparator as it was received by the majority of patients in the UK”. According to the FAD, this conclusion was reached by the Committee following a review of survey data supplied by Celgene and on hearing evidence from clinical specialists about their own standard practice, as well as their views on the AZA-001 clinical trial.

We are nonplussed by the Appraisal Committee’s interpretation of the above evidence and our arguments under section 1.1 that the Institute has ignored key guidelines and evidence applies equally here.

### **1.2.1 Celgene survey data**

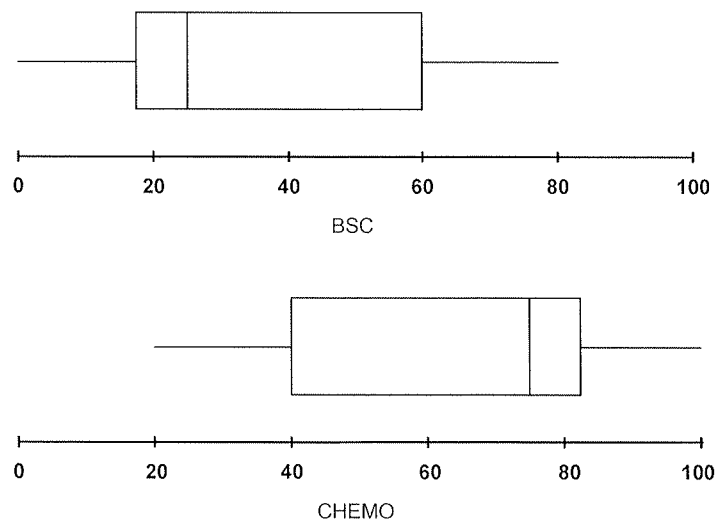
It is claimed in FAD Section 4.2 that the Celgene survey data demonstrates *“pronounced variation in treatment patterns”* as well as *“no nationally recognised standard of care for this patient population, particularly regarding patients’ eligibility for chemotherapy”*.

These comments make it clear that the Appraisal Committee has inappropriately and incompletely considered the survey evidence submitted by Celgene, which in part has contributed to the perverse decision in Section 4.2 of the FAD to exclude chemotherapy comparators.

Celgene's survey of 11 UK haematologists showed that a sizable proportion of clinicians often use some kind of chemotherapy regimen in those of their MDS patients who are ineligible for stem-cell transplantation (SCT) – the survey data only applies to SCT-ineligible patients.

A simple consideration of the distribution of responses, as shown in the box plots below, reveals that more than half of the respondents were currently treating 75 per cent or more of their SCT-ineligible MDS patients with some form of chemotherapy plus BSC. More than half of the respondents said that fewer than 25 per cent of their SCT-ineligible MDS patients were receiving BSC alone.

**Figure 1. Distribution of responses in Celgene survey of haematologists**



BSC: Best supportive care; CHEMO: combined responses for “low dose chemotherapy” and “standard dose chemotherapy”. Central boxes denote the interquartile range for responses and the central line in boxes indicate the median. Whiskers on either side of boxes indicate the minimum and maximum values observed.

The Committee appears to have disregarded the available evidence on the basis of what it considered to be “*pronounced*” variation in treatment patterns and lack of a “*nationally recognised standard of care for the patient population*”. These conclusions cannot be reasonably inferred from the survey data considered in Section 4.2 of the FAD or, for that matter, from the clinical and patient evidence submitted (see below). There will always be some variability in the treatment of patients with MDS, but that does not mean that there is no nationally recognised standard of care. A national standard may exist under which flexible treatment is promoted in which case a variation in current practice would be expected, given the wide range of patient

*chemotherapy... The proportion of patients treated with the different CCR regimens broadly reflects UK practice.*” (Emphasis added).

Given the weight of evidence from the seven leading organisations above and the personal testimony of two clinical experts that chemotherapy is used in everyday practice for these patients, it is extremely disconcerting to find that the Appraisal Committee has ignored this treatment as a comparator. We can only assume, therefore, that the Appraisal Committee has taken the clinician’s evidence out of context, particularly the oral evidence submitted by [redacted] at the appraisal committee meeting on 1 July 2009. This is demonstrated by their submissions above and a joint statement signed by both of them and other leading clinicians that chemotherapy is used in more than 50 per cent of patients with high risk MDS. This statement was sent to the Secretary of State for Health and [redacted] in response to the guidance in the FAD.

We are also concerned to learn that at the Appraisal Committee meeting on 7 January 2010, the Appraisal Committee Chair relied on second-hand hearsay about treatments for MDS patients. Such deliberations are, of course, unfair given that neither Celgene nor other consultees are able to challenge the basis for those assumptions.

We therefore can see no basis for the Institute’s conclusion that “*chemotherapy is rarely used*” in MDS treatment. Likewise, the statement that “*the AZA-001 trial data suggest that considerably fewer patients receive chemotherapy*” is also incorrect. Of the 179 patients AZA-001 patients who received conventional care regimens, 105 received BSC, 49 received low dose chemotherapy and 25 received standard dose chemotherapy. In total, 41 per cent of conventional care regimen patients in AZA-001 received chemotherapy. Any recommendation based on these errors of fact is clearly perverse.

### 1.2.3 Standards for identifying chemotherapy-eligible patients

The Institute has also wrongly concluded that “*there are no clear standards for identifying patients who are eligible for chemotherapy*”. There is no evidence to support this statement and it is clearly factually incorrect.

Clinicians rely on various criteria based on cytogenetic and broader patient characteristics to determine eligibility for, and likely response to, active treatments including chemotherapy regimens. The Institute would have been well aware of this had it duly referenced the guidelines in place before the advent of azacitidine, which set out very clear haematological standards by which chemotherapy-eligible patients can be identified. For example:

- British Committee for Standards in Haematology – Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes 2003 (see above) state:
  - Both patients > 65 years and those < 65 years who are ineligible for stem cell transplantation should be considered for intensive chemotherapy alone. (page 196).



- Cohort studies suggest that all of high-risk MDS patients ( $\geq$ INT-2), those with RAEB in transformation and lacking an independent adverse risk factor respond best to intensive ‘AML-type’ chemotherapy (evidence grade B, level IIb, Wattel et al, 1997. Thus, intensive chemotherapy alone is recommended for consideration in these patients.
- No chemotherapy combination is clearly superior, but most commonly used regimens contain cytosine arabinoside with any of an anthracycline, etoposide and / or fludarabine. The median number of chemotherapy courses in most studies is two (one induction and one consolidation) and patients rarely tolerate more than this. In all other high-risk MDS patients (namely those for whom intensive chemotherapy alone is not recommended), intensive remission-induction chemotherapy (two courses) should be offered only if stem cell transplantation is proposed as consolidation. (page 196-197).
- Guidelines for the diagnosis and treatment of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia, Nordic MDS Group, Issue 5, 4<sup>th</sup> update, January 2010 state:
  - Treatment of high-risk MDS and MDS/AML in patients not eligible for allogeneic stem cell transplantation [includes]: Azacitidine, AML like chemotherapy, Low dose chemotherapy
  - AML like chemotherapy: A number of studies have been published where a total of more than 1100 patients with HR-MDS or MDS-AML have been treated with different combinations of induction chemotherapy, (page 26).
  - In elderly patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML (less than 30% blasts):
    - Azacitidine is recommended as first choice.
    - In elderly, where azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR. (page 27).
  - Low dose chemotherapy: “...in individual patients routine use of low-dose chemotherapy may be used to reduce high white blood cell counts as well as bone-marrow blast counts, and to improve pancytopenia in MDS” (page 27).
- Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines<sup>2</sup>. These guidelines state:

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<sup>2</sup> Leuk Res (2010), doi: 10.1016/j.leukres.2010.018

- According to the existing evidence, use of AML-like therapy is appropriate in patients with a bone marrow blast percentage >10% and aged less than 65 years (grade C), (page 5).

Moreover, in the AZA-001 trial, patients were assigned to pre-selection groups according to criteria which were agreed by all participating centres, including UK centres, prior to commencement of recruitment. The European Public Assessment Report for azacitidine states that patients were assigned to these groups by the investigator “based on local practice and on evaluation of the patient’s underlying disease condition at the time of screening”.<sup>3</sup>

Therefore, NICE’s view that there are no clear standards for identifying chemotherapy-eligible patients, is clearly perverse given the clear standards and criteria above.

#### 1.2.4 Interpretation of clinical evidence

The Appraisal Committee also suggests at paragraphs 3.4 and 3.11 of the FAD that the data for chemotherapy “were less robust” because of the low numbers of patients in the relevant arms of the AZA-001 trial. However, this is an unreasonable and perverse interpretation of the data, given that a relatively high number of patients (n=74) in AZA-001 received chemotherapy and the overall survival rate for patients receiving low-dose chemotherapy was clinically and statistically significant. In any event, an average nine month extension to survival was observed across all three sub-groups, an observation that NICE itself considers to be “robust” at paragraph 4.3 of the FAD. Moreover, the distribution of overall survival times seen in the standard-dose chemotherapy group does not indicate a radical departure from those seen in other sub-groups. To recap for the Appeal Panel’s consideration, the efficacy data from our primary submission are presented in the following table.

**Table 1. Efficacy Data from AZA-001**

<b>BSC only comparison group (n=222)</b>				
	Azacitidine (n=117)	BSC (n=105)	HR	p-value
Overall survival (months)	21.1 (10.5–NR)	11.5 (5.7–NR)	0.58 (0.40–0.85)	0.0045
<b>Low-dose chemotherapy comparison group (n=94)</b>				
	Azacitidine (n=45)	LDC (n=49)	HR	p-value
Overall survival (months)	24.5 (8.4–34.7)	15.3 (4.9–25.8)	0.36 (0.20–0.65)	0.0006
<b>Standard-dose chemotherapy comparison group (n=42)</b>				
	Azacitidine (n=17)	SDC (n=25)	HR	p-value
Overall survival (months)	25.1 (10.0–NR)	15.7 (8.2–24.1)	0.76 (0.33–1.74)	0.51

Survival data are median (interquartile range). Hazard Ratios (with 95% confidence interval) calculated with stratified Cox proportional hazards model adjusted for treatment, subgroup, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, haemoglobin, n. of previous red blood cell transfusions, and presence or absence of cytogenetic -7/del(7q) abnormality. No subgroup-by-treatment interactions were significant (p>0.20)

We believe that the Committee may have misinterpreted the data in this regard as the FAD goes on to state at paragraph 3.11 that “to consider the arms of the trial in

<sup>3</sup> See page 23 of the EPAR available at <http://www.cma.europa.eu/humandocs/PDFs/EPAR/vidaza/H-978-en6.pdf>

isolation effectively breaks randomisation”. The AZA-001 trial randomised patients after pre-selection into the BSC, LDC and SDC groups. A sub-analysis within pre-selection group does not introduce any selection bias in respect of azacitidine’s treatment effect; the randomisation eliminates such bias as can be seen from the pre-planned analysis in the AZA-001 clinical study report where many results are separated by BSC, LDC, SDC treatment groups.

#### 1.2.5 Summary

The evidence from the appraisal which we have highlighted in this section demonstrates that a substantial proportion of SCT-ineligible, high-risk MDS patients receive chemotherapy. In the face of this evidence the only reasonable interpretation is to include the chemotherapy ICERs in the appraisal. The Committee’s decision to base its recommendation on BSC alone as a comparator is therefore perverse.

### 1.3 The Institute has exceeded its powers

Celgene submits similar arguments to that advanced under section 1.1, in that we believe NICE has exceeded its powers by departing from the Final Scope of this appraisal. The Final Scope states clearly that the Appraisal Committee must appraise the azacitidine using the comparators best supportive care **and** chemotherapy.

## 2 APPRAISING LIFE-EXTENDING, END-OF-LIFE TREATMENTS

The Appraisal Committee considers that azacitidine meets the criteria in section 2.1 of NICE’s guidance on life-extending, end-of-life treatments (“Life-Extending Guidance”). However, the Appraisal Committee has unfairly and perversely applied the Life-Extending Guidance by failing to take account of the significant extension of life offered by azacitidine compared with previous life-extending/end-of-life technologies appraised by the Committee. In addition, the Appraisal Committee has fettered its discretion by overly restricting the application of the Life-Extending Guidance to areas where the data are “robust”.

### 2.1 The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute’s Guide to the Technology Appraisal Process

#### 2.1.1 Chemotherapy comparator

Following on from our arguments in section 1, Celgene believes that the only fair and reasonable interpretation of the evidence is for the Appraisal Committee to incorporate the ICERs for chemotherapy into its appraisal. The relevant ICERs for chemotherapy are stated in section 3.10 of the FAD, that is £49,030 per QALY for the low-dose chemotherapy group and £51,252 per QALY gained for the standard-dose chemotherapy group. These ICERs incorporate the patient access scheme and are based on the Weibull survival function, which was accepted by the Appraisal Committee as the most appropriate model.

If the Appraisal Committee had included the chemotherapy ICERs, then the base case ICER would be within the range previously accepted by NICE when considering end-of-life treatments as being cost-effective (see TA169, Sunitinib for the first-line

treatment of advanced and/or metastatic renal cell carcinoma, March 2009). In the Sunitinib appraisal, NICE accepted an ICER of between £49,300 to £54,400 on the basis that (i) the evidence suggested that sunitinib increased survival by more than 3 months in comparison with the current treatment alone; and (ii) sunitinib provided a step-change in the first-line treatment of advanced and/or metastatic renal cell carcinoma and more than 20 per cent of the public and patients that responded in consultation highlighted this “impressive” benefit from sunitinib.

Celgene therefore has a legitimate expectation that an ICER similar to the one approved in the sunitinib appraisal would also be approved in this case, particularly as the nine month average overall survival rate was observed across all three treatment arms (BSC, low-dose chemotherapy and standard-dose chemotherapy) of the AZA-001 trial compared with 4.6 months for sunitinib. We believe strongly that the significant extension of life justifies a positive recommendation for azacitidine, particularly when taking account of the chemotherapy ICERs.

We note that NICE appears to consider that the data for the clinical effectiveness of azacitidine compared with chemotherapy are less than robust. However, we must point out that applying this standard is an overly restrictive and unfair interpretation of the Life-Extending Guidance. This states that “*the estimates of the extension to life are robust and can be shown or **reasonably inferred** from either progression free survival or overall survival*”. The available data clearly allow a significant life extension to be inferred and attempting to generate additional data is extremely difficult for these types of drug for ethical reasons.

#### 2.1.2 BSC alone comparator

Regardless of the chemotherapy ICERs, Celgene considers that an ICER of £63,000 based on BSC alone is justifiable given the robust and statistically significant evidence that azacitidine extends life by an average of 9.5 months in the BSC alone group. As stated above, this life extending period is well above the durations normally accepted as meeting end-of-life criteria and fairly deserves a greater degree of weight when considering whether or not to make a positive recommendation. This is particularly important when considering ultra-orphan populations (see separate arguments below).

We note in that connection the decision by the Appeal Panel in TA 178 Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009), where the Panel said that the multiplier for temsirolimus was “well above that applied normally to other products appraised”, citing the 1.6 multiplier used in TA169 discussed above.

In TA178, the ICER for Wyeth’s temsirolimus was £102,000 per QALY indicating a multiplier of 3.4. In this case, however, the extra value multiplier needed to bridge the gap between the ICER of £63,000 per QALY and the normal upper end of the threshold (£30,000) is 2.1. Given the significance and robustness of the 9.5 months extension to life and the very small patient population, the only fair interpretation of the Life-Extending Guidance and previous Appeal Panel rulings is to recommend azacitidine.

## **2.2 The Institute has prepared guidance which is perverse in the light of the evidence submitted**

Celgene considers that its arguments in section 2.1 apply equally here on the basis that the only reasonable approach is to recommend azacitidine for use on the NHS given the significant extension to life provided to patients. However, we argue that the NICE's decision not to recommend azacitidine meets the higher judicial standard: that of irrationality, when bearing in mind the chemotherapy ICERs.

## **3 ULTRA-ORPHAN INDICATION**

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There are approximately 700 patients with higher risk MDS in England and Wales, as stated in section 4.12 of the FAD. Of these patients, only a portion is eligible for active treatment with azacitidine. This very small number of patients meets NICE's definition of an ultra-orphan drug according to NICE's binding guidance on Social Value Judgements: Principles for the Development of NICE Guidance ("SVJ").<sup>4</sup> The SVJ defines an ultra-orphan drug as "*interventions for very rare conditions or diseases that occur in fewer than 1 in 50,000 of the population*". The SVJ guidance states that orphan drugs are evaluated in the same way as any other treatment but then makes a distinction between orphan drugs and ultra-orphan drugs, which the Institute does not expect to review. NICE therefore must apply a different approach to assessing such ultra-orphan drugs, bearing in mind existing guidance (final, draft or otherwise) available for the Appraisal Committee on appraising ultra-orphan indications.

### **3.1 The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process**

Azacitidine satisfies NICE's definition of an ultra-orphan drug as it is used to treat less than 1,000 people in the UK. NICE is bound to follow not only its Guide to the Technology Appraisal Process but also the SVJ. The SVJ states at page 3:

*"All NICE guidance, and the procedures NICE uses to develop its guidance, should be in line with the Institute's legal obligations and the social value principles set out in this document. If any parts of NICE's guidance do not conform to these principles, NICE and its advisory bodies should identify them and explain the reasons why."*

On the issue of drugs for rare conditions, the SVJ makes a distinction between its appraisal techniques for appraising "orphan drugs" (drugs for rare conditions) and "ultra-orphan drugs" (drugs for "very rare" conditions). Page 20 of the SVJ states:

*"NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary).*

*NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS."*

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<sup>4</sup> See <http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf>

An ultra-orphan drug is defined in the SVJ on page 36 as:

*“Ultra-orphan drug A term used by NICE to describe interventions for very rare conditions or diseases that occur in fewer than 1 in 50,000 of the population; it also covers interventions for which there are no other known or possible uses.”*

The SVJ makes clear, therefore, that although orphan drugs are appraised using normal appraisal techniques, the position is different for ultra-orphan drugs. Any appraisal of ultra-orphan drugs must, therefore, be in accordance with applicable guidance on ultra-orphan drugs and must be fair, *i.e.*, taking into account the very small patient population. NICE was issued with guidance on ultra-orphan drugs by NICE’s Citizens Council in 2004.<sup>5</sup> The Citizens Council was established to ensure that the views of those who fund the NHS – the public – are incorporated into the decision-making process. That guidance states that the NHS should reimburse ultra-orphan drugs at “premium prices” by adopting a different approach to appraising such products than normal.

Although there is no final guidance on the level of “premium” that should be paid, NICE has issued draft guidance<sup>6</sup> on appraising orphan drugs stating that indicative ICERs for ultra-orphan products are in the range of “£200,000 to £300,000 per QALY (*ie a ten-fold increase on the decision rules currently applied in conventional appraisals.*)” The draft guidance explains the problems in appraising ultra-orphan, as opposed to orphan drugs, as follows:

*“There would, however, be problems in the appraisal of drugs for very rare diseases – “ultra-orphan drugs” – largely because of their high costs. The Institute recommends that this group be defined as conditions with a UK prevalence of less than 1 in 50,000. NICE’s advises the adoption of this definition for two reasons: first, it matches the prevalence criteria (less than 1000 persons in the UK) used by the National Specialist Commissioning Advisory Group in determining those conditions that should fall within its programmes; and, second, it encompasses all products that appear, both now and in the foreseeable future, to be particularly problematic.”*

Although the above NICE orphan guidance is in draft form, the content of this guidance is well known to the Appraisal Committee and should have been taken into account when considering the appraisal of the product in general and particularly when applying the Life Extending Guidance. We note that the Appeal Panel in the Lapatinib appeal<sup>7</sup> expected both NICE and the appellant in that case to be aware of the terms of the draft guidance on life-extending drugs. In this case, therefore, Celgene has a legitimate expectation that the Appraisal Committee would be aware of and apply NICE draft guidance on ultra-orphan indications where appropriate.

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<sup>5</sup> Citizens Council Report: Ultra Orphan Drugs (November 2004) See [http://www.nice.org.uk/niceMedia/pdf/Citizens\\_Council\\_Ultraorphan.pdf](http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf).

<sup>6</sup> National Institute for Health and Clinical Excellence Appraising Orphan Drugs, Draft v3 (2006). See <http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf>.

<sup>7</sup> See <http://www.nice.org.uk/nicemedia/pdf/AppealDecision230609.pdf>

When considering azacitidine in the context of the Life-Extending Guidance, therefore, the Appraisal Committee should have taken into account the very small patient population (less than 1,000 people in the UK) and placed even greater weight on the benefits of azacitidine, whether based on the chemotherapy ICERs or the BSC alone ICER, in making its recommendations. Had it done so, we consider that the only reasonable recommendation would be to recommend azacitidine.

### **3.2 The Institute has exceeded its powers**

Celgene has supported the Institute's undertaking to appraise azacitidine within its usual health technology assessment framework and offered a patient access scheme to ensure that the Institute's cost-effectiveness requirements are satisfied. Notwithstanding this scheme and the application of the Life Extending Guidance, the results of the appraisal have demonstrated that the usual methodology is probably incompatible with ultra-orphan drugs in general, and definitely not compatible in this instance.

Despite our position that the ultra-orphan nature of azacitidine requires the Institute to give even greater weight to azacitidine's extension of life benefits, if the Institute maintains its negative recommendation then we can only conclude that the Institute's appraisal methodology is flawed and that the Institute would be exceeding its powers in continuing to review azacitidine for high risk MDS. We urge NICE, therefore, to work with the Department of Health to arrange appropriate review and funding for this technology, as was the case in NICE's appraisal of drugs for the treatment of pulmonary arterial hypertension.

## **4 HUMAN RIGHTS**

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NICE has exceeded its powers by making recommendations that are incompatible with certain fundamental freedoms under the European Convention of Human Rights (ECHR), as transposed into national law under the Human Rights Act 1998. In particular, the guidance breaches Articles 2, 3, 8 and 14 of the ECHR for the following reasons:

- the recommendations rob patients of the right to an average of 9.5 months of extra life (Art. 2),
- refusing azacitidine to high risk MDS patients with just months to live amounts to inhumane and degrading treatment (Art. 3),
- patients with MDS will die 9.5 months earlier than they otherwise would if they are treated with azacitidine and this denies such patients the right of a family life and privacy (Art. 8), and
- patients with high risk MDS are on average more than 70 years old and denying such patients treatment with azacitidine therefore discriminates against older people (Art 14).

We consider that NICE should have taken the implications of the ECHR into account not only in its final recommendations but also in its appraisal methodology when considering comparators. As such, refusing to acknowledge that chemotherapy is an appropriate comparator is tantamount to a clinician refusing an active treatment to a

high-risk MDS patient, which amounts to inhumane and degrading treatment (Art. 3), as well as being a clear breach of doctor's ethical obligations to act in the patient's best interests.

#### **Concluding Remarks**

In light of the above, Celgene believes that the current recommendation is fundamentally flawed and asks the Appeal Panel to instruct the Institute to reconsider its appraisal of azacitidine and revise its recommendation accordingly.

Celgene reserves the right to add to and/or elaborate upon these appeal arguments in any oral presentation scheduled with the Appeal Panel. It also reserves the right to put further evidence or arguments before the Appeal Panel, within the guidelines set out in the Institute's Guidance to Appelants.

We look forward to the Appeal Panel's response in due course.

Yours Sincerely



ANNEX 1

Evidence supporting the use of chemotherapy

Source	Quote
<p>Guidelines for the Diagnosis and Therapy of Adult Myelodysplastic Syndromes, British Journal of Haematology, 2003, 120, 187-200</p>	<p><i>Both patients &gt; 65 and those &lt; 65 years who are ineligible for stem cell transplantation should be considered for intensive chemotherapy alone (page 196)... Cohort studies suggest that all of high-risk MDS patients (<math>\geq</math>INT-2), those with RAEB in transformation and lacking an independent adverse risk factor respond best to intensive 'AML-type' chemotherapy (evidence grade B, level IIb, Wattel et al, 1997. Thus, intensive chemotherapy alone is recommended for consideration in these patients.</i></p> <p><i>No chemotherapy combination is clearly superior, but most commonly used regimens contain cytosine arabinoside with any of an anthracycline, etoposide and / or fludarabine. The median number of chemotherapy courses in most studies is two (one induction and one consolidation) and patients rarely tolerate more than this. In all other high-risk MDS patients (namely those for whom intensive chemotherapy alone is not recommended), intensive remission-induction chemotherapy (two courses) should be offered only if stem cell transplantation is proposed as consolidation. (Page 196-197).</i></p>
<p>Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines", Leuk Res (2010), doi: 10.1016/j.leukres.2010.018</p>	<p><i>According to the existing evidence, use of AML-like therapy is appropriate in patients with a bone marrow blast percentage &gt;10% and aged less than 65 years (grade C), (page 5).</i></p>
<p>Guidelines for the diagnosis and treatment of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia", Nordic MDS Group, Issue 5, 4<sup>th</sup> update, January 2010</p>	<p><i>Treatment of high-risk MDS and MDS/AML in patients not eligible for allogeneic stem cell transplantation [includes]:</i></p> <ul style="list-style-type: none"> <li>• Azacitidine</li> <li>• AML like chemotherapy</li> <li>• Low dose chemotherapy</li> </ul> <p><b>AML like chemotherapy</b></p> <p><i>A number of studies have been published where a total of more than 1100 patients with HR-MDS or MDS-AML have been treated with different combinations of induction chemotherapy, (page 26).</i></p> <p><i>In elderly patients with high-risk MDS (IPSS INT-2 or HR) and MDS-AML (less than 30% blasts):</i></p> <ul style="list-style-type: none"> <li>• Azacitidine is recommended as first choice.</li> </ul>

	<ul style="list-style-type: none"> <li>• <i>In elderly, where azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR. (page 27).</i></li> </ul> <p><b>Low dose chemotherapy</b>  <i>"...in individual patients routine use of low-dose chemotherapy may be used to reduce high white blood cell counts as well as bone-marrow blast counts, and to improve pancytopenia in MDS"</i> (page 27).</p>
<p>Royal College of Physicians, NICE Professional organisation statement template</p>	<p><b>What is the expected place of the technology in current practice?</b>  <i>Finally the 001 trial was carefully designed to reflect real clinical practice, hence the choice of CCR [current care regimes] as the comparator after much debate. The proportion of patients treated with the different CCR regimens broadly reflects UK practice. The trial analysed the most important outcomes and the primary endpoint of overall survival advantage was comfortably achieved (page 3).</i></p> <p><b>Any additional sources of evidence</b>  <i>The final draft of European LeukemiaNet guideline has the following draft guidance for the use of hypomethylating agents including azacitidine:  The Expert Panel agreed on the following recommendations:</i></p> <ul style="list-style-type: none"> <li>• <i>Patients with intermediate -2 or high risk IPSS risk disease who are not eligible for AML-like chemotherapy should be treated with azacitidine (Recommendation level B) (page 4).</i></li> </ul>
<p>Royal College of Pathologists, NICE Professional organisation statement template</p>	<p><b>What is the expected place of the technology in current practice?</b>  <i>Management options range from observation only, supportive care, 'active treatment' (low dose chemotherapy, intensive chemotherapy, stem cell transplantation), to symptom relief only for patients whose general health is so poor that an improvement in their haematological status would confer no corresponding improvement in quality of life. Identification of risk factors for disease progression and use of the IPSS score to predict outcome may help guide the clinician in deciding patient management (page 2).</i></p> <p><b>Low-intensity therapy</b>  <i>Low-intensity therapy includes the use of low</i></p>

	<p>does chemotherapy or biologic response modifiers. The UK national AML 14 trial showed that in elderly AML patients, low dose Cytarabine had superior overall survival rates than oral chemotherapy (hydroxycarbamide).</p> <p><b>High-intensity</b> High-intensity therapy includes intensive induction chemotherapy and haematopoietic stem cell transplantation.</p>
Rare Cancers Forum, NICE Patient/carer organisation statement	<p><b>Please list any current standard practice (alternatives if any) used in the UK.</b></p> <ul style="list-style-type: none"> <li>• Best supportive care</li> <li>• Chemotherapy</li> </ul>