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Dear [REDACTED]

Final Appraisal Determination

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

Appeal against Final Appraisal Determination

On 4th 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. In effect, the Appraisal Committee changed the scope of the appraisal without any formal consultation with stakeholders as required by the Institute's procedures. Further, the decision not to consider chemotherapy as a comparator was perverse given the evidence available.
- By ignoring the magnitude of the life extension which azacitidine patients experience, the Institute has made a perverse recommendation in light of the NICE criteria for end-of-life, life-extending treatments ("Life Extending Guidance").
- 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. NICE's position on ultra-orphan drugs, available on its website and marked as a draft,

makes clear that NICE considers that appraising such drugs under its normal procedures would render the products “cost ineffective” by default. Any appraisals of such drugs, such as azacitidine, are therefore predetermined by NICE as cost ineffective. This is unfair and is evidence of institutional bias in this appraisal.

- 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 FAD 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 the four key arguments outlined above. These four arguments are addressed separately under the grounds for appeal set out in the Institute’s guidance for appellants.

GROUND OF APPEAL

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.

1 THE INSTITUTE HAS FAILED TO ACT FAIRLY AND IN ACCORDANCE WITH ITS REMIT AND ITS PUBLISHED APPRAISAL PROCEDURES

1.1 Comparators

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. The relevant ICERs relative to 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, which are in line with ICERs NICE has previously accepted for life-extending

drugs. Relying solely on BSC is inconsistent with NICE's remit and procedures given the explicit reference to chemotherapy, particularly low-dose chemotherapy, in the Final Scope and unfairly prejudices azacitidine.

The Final Scope sets out the terms of the appraisal. The importance of complying with this document cannot be overstated, which is why it is consulted on with national groups representing patients and carers, organisations representing healthcare professionals, manufacturer(s) or sponsor(s) of the technology, the Department of Health, the Welsh Assembly Government, specialised commissioning groups, primary care trusts and local health boards. The resulting Final Scope document also forms the basis for the Secretary of State for Health's formal referral of the technology to NICE for appraisal.

The NICE Guide to the Methods for Technology Appraisal ("Methods Guide") reinforces the importance of the scope, indicating that it is "fundamental" to the assessment process:

"During the scoping process, the Institute determines the appropriateness of the remit and the specific questions that are to be addressed for each technology appraisal. The scope defines the issues of interest (for example, population, comparators and potential subgroups) as clearly as possible and the questions that should be addressed by the Appraisal Committee when considering the clinical and cost effectiveness of the technology. The questions to be addressed by the appraisal are fundamental to the assessment process and require an understanding of the context within which a technology is to be investigated, including currently available care and any alternative technologies for the specific indication. Consultees and commentators are consulted during the scoping process. The Institute revises the scope in response to comments received and develops a final scope that describes the boundaries of the appraisal and the issues that will be investigated." (Paragraph 1.3.1.)

The document also reflects the consensus view of all consultees on which evidence¹ and comparators² the Appraisal Committee should consider.

We accept that that Institute is not bound to base its final recommendations on all aspects of the final scope. However, the Appraisal Committee must give due consideration to the issues highlighted in the Final Scope and it did not do so in this appraisal. Rather, it discarded the consensus view of numerous consultees during the scoping process in favour of the views of two individual clinicians who use best supportive care alone rather than chemotherapy in their clinical practice and, it seems from statements by the Chair of the Appraisal Committee during its meeting on 7 January 2010, second-hand hearsay evidence from an unnamed acquaintance of the Chair.

¹ The 'scoping' process examines the appropriateness of the proposed remit and defines in detail what the appraisal will and will not examine. Scoping is an important step because it determines the nature and content of the evidence included in the assessment phase of the appraisal. (Methods Guide, para 2.1.1)

² See Methods Guide, para. 2.1.2, which states that "The purpose of a scope is to provide a framework for the appraisal. The scope defines the issues of interest (for example, population and comparators) as clearly as possible and sets the boundaries for the work undertaken by those producing reports for the Appraisal Committee, including the independent assessment groups and the manufacturer(s) or sponsor(s) of the technology." and para. 2.2.4, which states that "The scoping process aims to specify the comparator technologies as precisely as the technology under appraisal."

This amounted to an informal re-scoping of the appraisal, a process that is not envisaged by the Institute's procedures and one that has unfairly prejudiced Celgene and other stakeholders, since they were all unable to challenge the basis for those assumptions.

As we will demonstrate in our appeal points under perversity ground 2, the Appraisal Committee's decision not to consider chemotherapy was also perverse based on the evidence before it.

1.2 Ultra-orphan indications

1.2.1 Social Value Judgements

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").³ 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*", i.e. less than 1,000 people in the UK. 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.

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."

While the Institute would not normally expect to receive referrals for ultra-orphan drugs, it has done in this case. Under these circumstances, it seems that the Institute is obliged to either:

- (i) suspend the appraisal of azacitidine, while the Department of Health conducts an appropriate review and considers specialist funding for this technology. We note that the Institute has previously ceased to appraise ultra-orphan drugs when the NHS has made alternative commissioning arrangements for them

³ See <http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf>. 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."

(see, for example, its removal of the multi-technology appraisal of drugs for the treatment of pulmonary arterial hypertension (PAH) from its programme.⁴

- (ii) continue with its appraisal of azacitidine, but to do so fairly and in accordance with available guidance on ultra-orphan drugs, *i.e.*, taking into account the very small patient population and its implications for product cost. This is the option that NICE took in this case.

Given that NICE opted to continue with the appraisal under option (ii) above, it should have appraised azacitidine in accordance with available guidance. NICE was issued with guidance on ultra-orphan drugs by NICE's Citizens Council in 2004.⁵ 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.

We note that NICE has not adopted final guidance on the level of “premium” that should be paid, but it has issued draft guidance on appraising orphan drugs stating that indicative ICERs for ultra-orphan products are in the range of “£200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals).”⁶ The guidance states:

“If the Institute is to appraise ultra-orphan drugs, and be prepared to accept substantially higher ICERs than those hitherto considered to be cost effective, then separate decision rules (i.e. the range of ICERs considered “cost effective”) will need to be developed and adopted for these products. The Institute proposes that these ultra-orphan drug decision rules are based on the ICERs of those ultra-orphan drugs currently on the UK market ... it appears that at current prices indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals).”

Although the above NICE orphan guidance is marked as “Draft v3,” the website states that the document was submitted to the Department of Health as a “formal response”. The content of this guidance is current and therefore 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. The Institute took current draft guidance into account in its appraisal of lapatinib⁷ and Celgene has a legitimate expectation that the Appraisal Committee would be aware of and apply NICE draft guidance on ultra-orphan indications in this appraisal.

⁴ See <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11708>.

⁵ Citizens Council Report: Ultra Orphan Drugs (November 2004) See http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf.

⁶ National Institute for Health and Clinical Excellence Appraising Orphan Drugs, Draft v3 (2006). See <http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf>, last accessed 13 April 2010.

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

Its failure to apply such guidance and/or the Committee's failure to appraise this ultra-orphan drug differently to normal drugs is procedurally unfair as the SVJ implicitly makes clear that ultra-orphan drugs should be treated differently to orphan drugs. Otherwise, the SVJ would have stated that orphan drugs "and ultra-orphan drugs" will be appraised in the same way as any other treatment.

1.2.2 The Outcome was Predetermined by NICE as Cost Ineffective

In its draft guidance on appraising ultra-orphan drugs, the Institute concedes that its appraisals of such products "*will invariably give rise to values that would be considered cost ineffective under NICE's conventional criteria*" and which "*therefore, the Institute would be most unlikely to ever recommend their use in the NHS.*"⁸ (Emphasis added.)

Having accepted the referral for an ultra-orphan drug, the Institute is bound to take account of the specific features of such products and the challenges they present. By failing to do so, it has carried out a process that, by its own admission "*will invariably give rise to values that would be considered cost ineffective.*"

To appraise azacitidine on that basis is procedurally unfair and amounts to institutional bias against ultra-orphan drugs such as azacitidine as NICE had predetermined its views on ultra-orphan drugs and conducted the appraisal with a closed mind.⁹ Further, it is a concept of natural justice that the decision-maker, *i.e.*, NICE, should not have preconceived views as this can amount to an unlawful fettering of its discretion.

2 THE INSTITUTE HAS PREPARED GUIDANCE WHICH IS PERVERSE IN THE LIGHT OF THE EVIDENCE SUBMITTED

2.1 Reliance on BSC alone is perverse

As indicated in our first ground for appeal, the Institute effectively changed the scope of the appraisal following consultations with two clinical experts and an unnamed acquaintance of its Chair and without any formal consultation with stakeholders as required by the Institute's procedures.

The FAD also contains a number of mistakes of fact and interpretation of the available evidence that render perverse its decision to rely solely on BSC as a comparator. In particular, 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 section 4.2 of the FAD, this conclusion was reached by the Committee based on limited evidence from a small number of clinical specialists about their own standard practice, as well as their views on the AZA-001 clinical trial and, it seems from statements by the Chair of the Appraisal Committee during its meeting on 7 January 2010, second-hand hearsay evidence from an unnamed acquaintance of the Chair.

⁸ National Institute for Health and Clinical Excellence Appraising Orphan Drugs, Draft v3 (2006). See <http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf>, last accessed 13 April 2010.

⁹ See *R (on the application of Fraser and another) v National Institute for Health and another* [2009] EWHC Admin (452), at paragraph 50. In deciding whether there has been bias, Simon J said that claimants "have to show (at least) predetermination: a closed mind at an early stage."

Having decided to disregard the use of chemotherapy as a comparator, the Appraisal Committee has sought to justify its decision based on a number of arguments, all of which are either factually inaccurate or, at best, based on a misinterpretation of the available evidence. We discuss these issues further below.

(a) Final Scope

The Appraisal Committee's decision to disregard chemotherapy is perverse in light of the Final Scope itself and the evidence submitted during the scoping phase of this appraisal.

The Draft Scope included three standard comparators for azacitidine: (i) best supportive care ("BSC"); (ii) chemotherapy; and (iii) stem cell transplantation. During the consultation process, a number of parties commented that stem cell transplantation is not an appropriate comparator as these transplantations are only a viable option for a small number of patients. Despite consulting widely with a significant number of consultees, only the Cardiff and Vale NHS Trust suggested that "few patients are suitable for chemotherapy." The Institute responded that the mainstay treatment is BSC and low dose or standard chemotherapy, and that stem cell transplantation has been removed from the list of comparators. This conclusion is reflected in the Final Scope itself:

*"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 also 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.

Given the Institute's clearly stated position at the scoping phase, the fact that all but one consultee considered chemotherapy to be an appropriate comparator, and the wording of Final Scope itself, it is clearly perverse for the Appraisal Committee to reject it as a comparator on the basis of clinical evidence from two clinicians and hearsay from an unnamed third. This is particularly true when all available evidence discussed further below points the other way.

(b) Existing guidelines

In establishing its position on comparators, the Appraisal Committee acted perversely by failing 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 perversely by ignoring guidance published by national bodies, including NICE itself (see below), 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 2003¹⁰

*“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).

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.

(c) Celgene survey data

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.

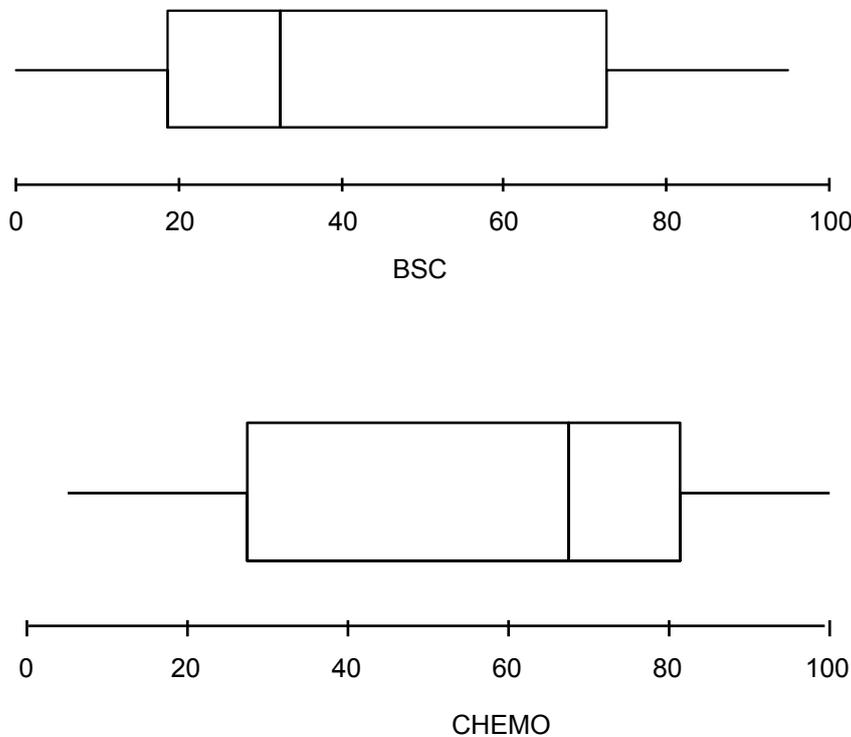
However, the Appraisal Committee perversely failed to give due consideration to these data, apparently on the basis that they reflected *“pronounced variation in treatment patterns”* as well as *“no nationally recognised standard of care for this patient population, particularly regarding patients’ eligibility for chemotherapy”*. (FAD, Section 4.2)

¹⁰ Bowen D et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003;120:187-200.

These comments make it clear that the Appraisal Committee has inappropriately and incompletely considered the survey evidence submitted by Celgene without any detailed analysis of the distribution of responses in this survey; not even the standard deviation for percentages treated with BSC or BSC plus chemotherapy was reported. This has contributed to the perverse decision in Section 4.2 of the FAD to exclude chemotherapy comparators.

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 65 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 35 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. Graphics revised to reflect complete dataset.

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 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.

(d) 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

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] and [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 in AZA-001 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.

(e) 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, 4th 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 guidelines¹¹. These guidelines state:
 - 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

¹¹ Leuk Res (2010), doi: 10.1016/j.leukres.2010.018

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”.¹²

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.

(f) 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 analysis for patients in the low-dose chemotherapy group 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

BSC only comparison group (n=222)				
	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
Low-dose chemotherapy comparison group (n=94)				
	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
Standard-dose chemotherapy comparison group (n=42)				
	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 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

¹² See page 23 of the EPAR available at <http://www.ema.europa.eu/humandocs/PDFs/EPAR/vidaza/H-978-en6.pdf>

AZA-001 clinical study report where many results are separated by BSC, LDC, SDC treatment groups.

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.

2.2 The Institute has acted perversely in its appraisal of this life-extending, end-of-life treatment

2.2.1 The Institute has not taken into account the significant life extension attributable to azacitidine and has therefore prepared guidance which is perverse in the light of the evidence submitted

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 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.

The 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. This life extending period is well above the durations normally accepted as meeting end-of-life criteria and it is perverse for the Institute to fail to take this into account.

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 using BSC alone as a comparator. If chemotherapy is used as a comparator then the multiplier is 1.6 (low-dose chemotherapy based on an ICER of £49,030) or 1.7 (standard chemotherapy based on an ICER of £51,252).

Moreover, in the Sunitinib appraisal (TA169, Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma, March 2009), 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.

A 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. Given the significance of the extension to life achieved using, it is perverse of the Committee not to recommend azacitidine.

2.2.2 The Appraisal Committee has acted perversely by overly restricting the application of the Life-Extending Guidance to areas where the data are “robust”, when NICE’s own policies make clear that estimates of the extension need only be “*reasonably inferred from either progression free survival or overall survival*”.

In addition to the above, the Appraisal Committee has acted perversely by overly restricting the application of the Life-Extending Guidance to areas where the data are “robust”, when NICE’s own policies make clear that *estimates of the extension need only be “reasonably inferred from either progression free survival or overall survival.”*

To this end, we note that NICE appears to suggest that the data for the clinical effectiveness of azacitidine compared with chemotherapy are less than robust. Applying the criteria above, however, 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. In any event, the FAD states at paragraph 4.3 that “*estimates of total overall survival appeared robust.*”

2.3 Ultra-orphan indications

Our arguments under paragraph 1.2 above apply equally here, *i.e.*, given the special properties of ultra-orphan drugs and NICE’s published views of such drugs, it is perverse to apply the same methods that the Institute uses in appraising orphan or non-orphan drugs as the only outcome will be that azacitidine would be cost-ineffective.

3 THE INSTITUTE HAS EXCEEDED ITS POWERS

3.1 By changing the scope of the appraisal without any formal consultation 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.

3.2 Ultra-orphan

The arguments under paragraph 1.2.1 apply equally here, *i.e.*, that NICE’s preconceived views on ultra-orphan drugs amounts to an unlawful fettering of its discretion as azacitidine would never have been deemed cost-effective under NICE’s own procedures and its own admission.

3.3 Human Rights

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 Appellants.

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

Yours Sincerely



General Manager UK

ANNEX 1

Evidence supporting the use of chemotherapy

Source	Quote
Guidelines for the Diagnosis and Therapy of Adult Myelodysplastic Syndromes, British Journal of Haematology, 2003, 120, 187-200	<p><i>Both patients > 65 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 (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.</i></p> <p><i>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>
Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines", Leuk Res (2010), doi: 10.1016/j.leukres.2010.018	<p><i>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).</i></p>
Guidelines for the diagnosis and treatment of Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia", Nordic MDS Group, Issue 5, 4 th update, January 2010	<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"> • Azacitidine • AML like chemotherapy • Low dose chemotherapy <p>AML like chemotherapy</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"> • 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). <p>Low dose chemotherapy</p> <p><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" (page 27).</i></p>

<p>Royal College of Physicians, NICE Professional organisation statement template</p>	<p><i>What is the expected place of the technology in current practice?</i> <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><i>Any additional sources of evidence</i> <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"> • <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>
<p>Royal College of Pathologists, NICE Professional organisation statement template</p>	<p><i>What is the expected place of the technology in current practice?</i> <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><i>Low-intensity therapy</i> <i>Low-intensity therapy includes the use of low doses 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).</i></p> <p><i>High-intensity</i> <i>High-intensity therapy includes intensive induction chemotherapy and haematopoietic stem cell transplantation.</i></p>
<p>Rare Cancers Forum, NICE Patient/carer organisation statement</p>	<p><i>Please list any current standard practice (alternatives if any) used in the UK.</i></p> <ul style="list-style-type: none"> • <i>Best supportive care</i> • <i>Chemotherapy</i>