HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]

The following documents are made available to the consultees and commentators:

1. **Response to the consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:

    - **Leukaemia CARE**
    - **Association of Cancer Physicians, Royal College of Physicians and National Cancer Research Institute joint response**

‘No comment’ response received from the Department of Health

No Comments on the Appraisal Consultation Document received through the NICE website

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Leukaemia CARE	We are writing on behalf of acute myeloid leukaemia (AML) patients in response to the recently published appraisal consultation document concerning azacitidine (Vidaza) for treating acute myeloid leukaemia with more than 30% bone marrow blasts, in people of 65 years or older who are not eligible for haematopoietic stem cell transplant (ID829).	Comment noted. No action required.
	As a national blood cancer patient organisation, we are disappointed to see that the appraisal committee has released and initial decision to not recommend azacitidine, within its marketing authorisation, in this setting. Whilst we understand the complexity and the economic restrictions present in the process of appraisal and recommendation of cancer drugs in England and Wales, we would like to draw your attention to the concerns that we have with this preliminary decision.	Comment noted. No action required.
	1. Acute myeloid leukaemia (AML) is an aggressive, rapidly progressing disease and over half (53%) of patients are diagnosed following emergency presentation (compared to a cancer average of 22%). Existing remission-inducing therapies outside of a stem cell transplant used in this setting are limited, can be unsuitable for older or less fit patients and are not always considered active treatment. As such, increased access in effective, tolerable treatment options in this hard to treat patient group would be strongly welcomed.	Comment noted. The committee heard that this is a difficult-to-treat group with few treatment options currently available. The committee understood that patients with acute myeloid leukaemia with more than 30% bone marrow blasts tend to be older are often diagnosed late and their prognosis is poor. The committee understood the severity of acute myeloid leukaemia and its effect on patients and their families. The committee concluded that there is an important unmet need for people with acute myeloid leukaemia. See FAD section 4.1. No action required. .

Consultee	Comment [sic]	Response
Leukaemia CARE	2. Nearly three quarters (74.7%) of all AML patients are over sixty years old and, as they are more likely to have co-morbidities, may be unable to withstand the toxicity and side effects of traditional treatment. Azacitidine could therefore provide a tolerable, life extending treatment option for a group of patients who, on average, live just two months post diagnosis if they do not receive active treatment.	Comment noted. The committee was aware that the clinical trial demonstrated gains favouring azacitidine in overall survival, but noted that it failed to reach statistical significance when comparing azacitidine with the combined conventional care regimen. The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain. See FAD sections 4.5 and 4.6. No action required. The committee considered the comment received during consultation which highlighted that around 75% of people with acute myeloid leukaemia are over the age of 60 years, and that these people may be less able to tolerate the toxicity and side effects associated with current treatments. The committee was aware that age is a protected characteristic as defined by the Equalities Act. The committee was also aware that azacitidine has a marketing authorisation for people of 65 years or older, and that it was this subgroup who were enrolled in the AZA AML 001 trial that both underpinned the marketing authorisation for azacitidine and was the main focus of the company's submission. However, the committee was aware that it could only make recommendations in accordance with the marketing authorisation for azacitidine. See FAD section 4.20. It agreed that its recommendations were not made because of the age of the patients, but rather because azacitidine within its marketing authorisation was not cost effective, and that it had not identified any special factors which would require or justify making a positive recommendation despite the very high ICERs.

Consultee	Comment [sic]	Response
	3. Azacitidine is currently recommended for AML patients with a 20-30% bone marrow blast. Whilst the availability of azacitidine for these patients is extremely welcome, we would argue that in not recommending it for patients with a higher blast count (and therefore patients with a poorer prognosis associated with significantly shorter survival outcomes), an inequitable situation is created.	Comment noted. NICE technology appraisal guidance on azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia recommends azacitidine as an option for acute myeloid leukaemia with 20% to 30% bone marrow. The committee noted the comment received during consultation which highlighted that an inequitable situation would therefore be created by not recommending azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. The committee was aware that severity of disease is not a protected characteristic as defined by the Equalities Act, and that it did not fall within NICE's obligations to avoid discrimination in the performance of its functions. The committee noted, however, that azacitidine being considered by NICE separately for acute myeloid leukaemia with 20% to 30% and more than 30% bone marrow blasts was a result of the timing of the regulatory marketing authorisation approval process and as such was outside NICE's control, but agreed that it would have been preferable to develop a single piece of guidance for azacitidine in this indication. See FAD section 4.21.

Consultee	Comment [sic]	Response
Leukaemia CARE	The key benefits of azacitidine (demonstrated during clinical trials) were improved over survival, whilst demonstrating fewer adverse effects for older patients or patients with certain genetic mutations. It is therefore important that patients with the most limited available treatment options are able to benefit from a therapy that can help extend their time with family and loved ones, whilst not compromising their quality of life.	Comment noted. The committee was aware that the clinical trial demonstrated gains favouring azacitidine in overall survival, but noted that it failed to reach statistical significance when comparing azacitidine with the combined conventional care regimen. The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain. The committee also noted that the most plausible incremental cost effectiveness ratio (ICER) for azacitidine compared with a conventional care regimen was £240,000 per quality-adjusted life year (QALY) gained and agreed that azacitidine should not be considered a step change, and that azacitidine did not meet the criteria to be considered a life-extending, end-of-life treatment See FAD sections 4.4, 4.6, 4.13 4.14, 4.16 and 4.17. No action required.

Consultee	Comment [sic]	Response
	Whilst these comments were raised in our original submission, we felt it necessary to highlight further the limited options available to patients in this setting. The availability of effective, tolerable treatment has an impact on both their overall survival and their quality of life, whilst having a wider impact on their carers' and family. Azacitidine, already routinely available to some AML patients, has the potential to improve the treatment pathway of patients who have fewer options available to them (due to comorbidities or genetic mutations) that make them difficult to treat.	Comment noted. Please see responses to previous comments. No action required
	As such, we hope you bear these comments in mind when considering your final recommendation and encourage you to reconsider this preliminary decision in order to make azacitidine available to all of those who could benefit from it.	The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain. The committee also noted that the most plausible incremental cost effectiveness ratio (ICER) for azacitidine compared with a conventional care regimen was £240,000 per quality-adjusted life year (QALY) gained and agreed that azacitidine should not be considered a step change, and that azacitidine did not meet the criteria to be considered a life-extending, end-of-life treatment The committee concluded that it could not recommend azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant as a cost-effective use of NHS resources. See FAD sections 1.1, 1.2, 4.4, 4.6, 4.13 4.14, 4.16 and 4.17. No action required.

Consultee	Comment [sic]	Response
Association of Cancer Physicians, Royal College of Physicians and National Cancer Research Institute joint response	The NCRI-RCP-RCP are grateful for the opportunity to respond to the above consultation. We would like to note that internationally this is increasingly being perceived as the standard of care in this patient group, based upon the evidence submitted and evaluated within the technology appraisal.	Comment noted. The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain. The committee also noted that the most plausible incremental cost effectiveness ratio (ICER) for azacitidine compared with a conventional care regimen was £240,000 per quality-adjusted life year (QALY) gained and agreed that azacitidine should not be considered a step change, and that azacitidine did not meet the criteria to be considered a life-extending, end-of-life treatment The committee concluded that it could not recommend azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant as a cost-effective use of NHS resources. See FAD sections 1.1, 1.2, 4.4, 4.6, 4.13 4.14, 4.16. No action required.

Blood and Lymphatic cancers
Leukaemia CARE
supporting a quality of life

Leukaemia CARE
One Birch Court
Blackpole East
Worcester
Worcestershire
WR3 8SG
01905 755977

Dear NICE Technology Appraisal Committee C,

We are writing on behalf of acute myeloid leukaemia (AML) patients in response to the recently published appraisal consultation document concerning azacitidine (Vidaza®) for treating acute myeloid leukaemia with more than 30% bone marrow blasts, in people of 65 years or older who are not eligible for haematopoietic stem cell transplant [ID 829].

As a national blood cancer patient organisation, we are disappointed to see that the appraisal committee has released an initial decision to not recommend azacitidine, within its marketing authorisation, in this setting. Whilst we understand the complexity and the economic restrictions present in the process of appraisal and recommendation of cancer drugs in England and Wales, we would like to draw your attention to the concerns that we have with this preliminary decision.

1. Acute myeloid leukaemia (AML) is an aggressive, rapidly progressing disease and over half (53%) of patients are diagnosed following emergency presentation (compared to a cancer average of 22%). Existing remission-inducing therapies outside of a stem cell transplant used in this setting are limited, can be unsuitable for older or less fit patients and are not always considered active treatment. As such, increased access in effective, tolerable treatment options in this hard to treat patient group would be strongly welcomed.

2. Nearly three quarters (74.7%) of all AML patients are over sixty years old and, as they are more likely to have co-morbidities, may be unable to withstand the toxicity and side effects of traditional treatment. Azacitidine could therefore provide a tolerable, life-extending treatment option for a group of patients who, on average, live just two months post diagnosis if they do not receive active treatment.

3. Azacitidine is currently recommended for AML patients with a 20-30% bone marrow blast. Whilst the availability of azacitidine for these patients is extremely welcome, we would argue that in not recommending it for patients with a higher blast count

Blood and Lymphatic cancers
Leukaemia CARE
supporting a quality of life

(and therefore patients with a poorer prognosis associated with significantly shorter survival outcomes), an inequitable situation is created. The key benefits of azacitidine (demonstrated during clinical trials) were improved overall survival, whilst demonstrating fewer adverse effects for older patients or patients with certain genetic mutations. It is therefore important that patients with the most limited available treatment options are able to benefit from a therapy that can help extend their time with family and loved ones, whilst not compromising their quality of life.

Whilst these comments were raised in our original submission, we felt it necessary to highlight further the limited options available to patients in this setting. The availability of effective, tolerable treatment has an impact on both their overall survival and their quality of life, whilst having a wider impact on their carers' and family. Azacitidine, already routinely available to some AML patients, has the potential to improve the treatment pathway of patients who have fewer options available to them (due to comorbidities or genetic mutations) that make them difficult to treat.

As such, we hope you bear these comments in mind when considering your final recommendation and encourage you to reconsider this preliminary decision in order to make azacitidine available to all of those who could benefit from it.

Kind Regards,

[redacted]

[redacted]

Leukaemia CARE

Blood and Lymphatic cancers
Leukaemia CARE
supporting a quality of life
Registered charity 259463 and SC039207

Received by email:

Dear Stephanie

The NCRI-ACP-RCP are grateful for the opportunity to respond to the above consultation.

We would like to note that internationally this is increasingly being perceived as the standard of care in this patient group, based upon the evidence submitted and evaluated within the technology appraisal.

I would be grateful if you could confirm receipt.

Best wishes

[redacted] | [redacted]
Membership Support and Global Engagement Department| Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE