National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Wording	Celgene	The remit could need updating as the expected wording of the license is: Azacitidine is indicated for the Treatment of newly diagnosed AML with > 30% bone marrow blasts in patients ≥ 65 years of age.	Comment noted. The wording of the remit was updated to remove reference to ineligibility for haematopoietic stem cell transplantation. However, attendees were concerned that adding 'newly diagnosed' may be misinterpreted to exclude people who have AML that had

Section	Consultee/ Commentator	Comments	Action
			developed on pre-existing myelodysplastic syndrome. NICE guidance is issued within the marketing authorisation, however noting the NICE obligations towards people protected by the equality legislation; it was decided that age restriction should not be specified in the remit or the scope at this stage. Attendees at the scoping workshop considered that the remit should remain broad by not specifying age restriction and 'newly diagnosed'.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Timing Issues	Celgene	No Comments.	Response noted

Section	Consultee/ Commentator	Comments	Action
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Additional comments on the draft remit	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	We have three comments to make with regards to the background information. Our first comment is with regards to the listed incidence of acute myeloid leukaemia (2500); which we believe to be inaccurate. A more accurate figure would be around 2900 (CRUK 2011- 2921; as referenced by NICE in the recent scope for 'Haematological Cancers: Improving Outcomes'. Secondly, there needs to be reference to the fact that untreated AML is a rapidly fatal disease in many cases. Thirdly, with regards to the fatality of AML, reference ought to be made to the emotional impact this has on patients, as well as their carers, families and	Comments noted. The figure in the scope refers to the incidence of AML in England and is correct. Please see reference in the updated scope. The background section

Section	Consultee/ Commentator	Comments	Action
		friends. In particular this includes feelings of shock/disbelief, denial, anger, fear/uncertainty, resentment, blame/guilt, isolation and depression. As such there may be a profound impact on their physical and psychological wellbeing.	has been updated to reflect the fatality of AML. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS. Evidence on emotional impact of condition on patients, their carers, families and friends will be included in the consultees' submissions for the Committee's consideration.
The technology/ intervention	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia	No response	Response noted

Section	Consultee/ Commentator	Comments	Action
	CARE		
Population	Celgene	The expected license is for the Treatment of newly diagnosed AML with > 30% bone marrow blasts in patients ≥ 65 years of age. As such Celgene believe that the population for this appraisal may need to specify this age limitation.	Comment noted. Population has been updated to remove reference to ineligibility for haematopoietic stem cell transplantation. However, attendees at the scoping workshop considered that the population should remain broad in line with the proposed remit and not specify age restriction or newly diagnosed (see above for the response to the comments on the wording of the proposed remit).
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Comparators	Celgene	Decitabine is not a relevant comparator. This technology is not used in the UK and has not been appraised by NICE (TA270 terminated) or included for funding via the cancer drugs fund (CDF).	Comments noted. Decitabine has been removed from the comparators and the

Section	Consultee/ Commentator	Comments	Action
		Best supportive care should not include low dose chemotherapy. This forms part of the non-intensive chemotherapy group. The best-supportive care arm of AZA-AML-001 did not include low dose chemotherapy. Intensive chemotherapy is appropriate. At a recent advisory board (2014) the clinical experts estimated that 20% intensive chemotherapy, 60% LDAC and 20% BSC reflected routine practice. CCR (conventional care regimen) should be added as a further comparator. IN TA218 (for higher risk MDS and AML up to 30% blasts) the committee made a decision comparing to a weighted average of the conventional care regimens as the populations eligible for each regimen cannot be clearly identified. Advice from clinical experts on the current appraisal has been that the older AML population is highly heterogenous and there is still no clinical consensus on treatment differentiation, and treatment decisions are made on the judgement of the clinician and patient.	description of 'best supportive care' has been updated. Attendees understood that 3 conventional care regimens are used in slightly different patient population according to their performance status, presence of comorbidities etc. and did not agree that all 3 treatment options could be considered as a single comparator. Therefore, conventional care regimen was not specified as a single comparator in the scope.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Outcomes	Celgene	PFS was not captured in the AZA-AML-001 trial and is not a relevant outcome for this appraisal. Event Free Survival (EFS) should be included	Attendees noted that the way event free

Section	Consultee/ Commentator	Comments	Action
		instead. Health care resource should be included as this will feature in the economic modelling.	survival was defined in the trial may confound the true effectiveness of azacitidine. Attendees heard from clinical specialists that in their opinion, disease progression is a relevant outcome measure. Attendees understood time to disease progression was collected in the trial because it was part of composite outcome 'events' and could be worked out. It was agreed that it would be appropriate to include both 'progression free survival' and 'time to disease progression' in the outcomes.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Economic	Celgene	A lifetime time horizon is appropriate to model AML treatment.	Comment noted. NICE

Section	Consultee/ Commentator	Comments	Action
analysis			recommends using a lifetime time horizon when the technology leads to differences in survival or benefits that persist for the remainder of a person's life. Please see Guide to the methods of technology appraisal (2013) for further details.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Equality and Diversity	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Innovation	Celgene	For older AML patients (≥65 years), treatment options remain limited and outcomes dismal. In particular, for patients not eligible for an intensive approach due to factors such as medical comorbidities and fitness, outcomes have remained very poor over the last 40 years . The clinically meaningful improvement in AML survival seen with azacitidine in AML-001 therefore represents an important advance in an area of significant unmet clinical need.	Comment noted. The innovative nature of azacitidine will be considered by the Committee during the

Section	Consultee/ Commentator	Comments	Action
			appraisal.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Other considerations	Celgene	As stated above, in the comparators section, CCR should be included as a comparator.	Comment noted. Attendees understood that 3 conventional care regimens are used in slightly different patient population according to their performance status, presence of comorbidities etc. and did not agree that all 3 treatment options could be considered as a single comparator. Therefore, conventional care regimen was not specified as a single comparator in the scope.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted

Section	Consultee/ Commentator	Comments	Action
NICE Pathways	Celgene	Azacitidine already features in the pathway as follows: Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have: acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification. After this appraisal, > 30% blasts should be included.	Comment noted. The NICE pathway will be reviewed following publication of the guidance.
	NCRI/RCP/RCR /ACP	No response	Response noted
	Leukaemia CARE	No response	Response noted
Questions for consultation	Celgene	Is the trial population, that is, people of age 65 years or more with acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplant, expected to be the subject of the marketing authorisation? Yes. Have all relevant comparators for azacitidine been included in the scope? Which treatments are considered to be established clinical practice in the NHS for acute myeloid leukaemia with more than 30% bone marrow blasts? • Is decitabine an appropriate comparator for this appraisal? Is it used in routine clinical practice for treating acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplantation in England?	Comments noted. Decitabine has been removed from the comparators.

Section	Consultee/ Commentator	Comments	Action
		As stated in the comparators section above, decitabine is not a valid comparator. • Do patients who are not eligible for haematopoietic stem cell transplantation receive intensive chemotherapy in routine clinical practice in England? Yes. Intensive chemotherapy is an established treatment for this patient group. • Is best supportive care an appropriate comparator? How should it be defined? Best supportive care is a comparator in the UK. It should be defined as per the best supportive care arm in AZA-AML-001. Are there any subgroups of people in whom azacitidine is expected to be more clinically effective and cost effective or other groups that should be examined separately?	

Section	Consultee/ Commentator	Comments	Action
		Potential subgroups are currently being investigated by the clinical team in Celgene looking at the data from AZA-AML-001.Currently there are no specific subgroups which have identified from a clinical or cost-effectiveness viewpoint. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. The STA process is appropriate.	
	NCRI/RCP/RCR /ACP	Is the trial population, that is, people of age 65 years or more with acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplant, expected to be the subject of the marketing authorisation? Patients >65 up to 70 years in first remission of AML after intensive therapy are also eligible for intensive therapy and BMT if they have minimal co-morbidities QHave all relevant comparators for azacitidine been included in the scope? Which treatments are considered to be established clinical practice in the NHS for acute myeloid leukaemia with more than 30% bone marrow blasts? • Is decitabine an appropriate comparator for this appraisal? Is it used in routine clinical practice for treating acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplantation in England?	Comments noted. Decitabine has been removed from the comparators.

Section	Consultee/ Commentator	Comments	Action
		Decitabine is rarely used in the UK; primarily because the trial data showed limited efficacy and it is not reimburse • Do patients who are not eligible for haematopoietic stem cell transplantation receive intensive chemotherapy in routine clinical practice in England? Yes, many do as it is possible to obtain complete remissions in a significant proportion of patients (65%-70%). The AML18 trial of intensive therapy is currently recruiting patients aged 60 – 75 + years • Is best supportive care an appropriate comparator? How should it be defined? Only for very frail and elderly patients Are there any subgroups of people in whom azacitidine is expected to be more clinically effective? Our experts are unsure if this has been established.	
	Leukaemia CARE	No response	Response noted
Additional comments on the draft scope	Celgene	No Comments.	Response noted
	NCRI/RCP/RCR /ACP	No response	Response noted

Section	Consultee/ Commentator	Comments	Action
	Leukaemia CARE	No response	Response noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Royal College of Nursing
Royal College of Pathologists

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed:					
Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:

1.	African Caribbean Leukaemia Trust (ACLT)	NICE Secretariat	1.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the African Caribbean Leukaemia Trust (ACLT) have been added to the matrix under 'patient/carer' groups.
2.	Anthony Nolan	NICE Secretariat	2.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the Anthony Nolan have been added to the matrix under 'patient/carer' groups.

3.	Chronic Myeloid Leukaemia Support Group	NICE Secretariat	3.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the Chronic Myeloid Leukaemia Support Group have been added to the matrix under 'patient/carer' groups.
4.	Delete Blood Cancer	PIP	4.	Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore Delete Blood Cancer has been added to the matrix under 'patient/carer' groups.