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

2nd Appraisal Committee meeting: 11 May 2016

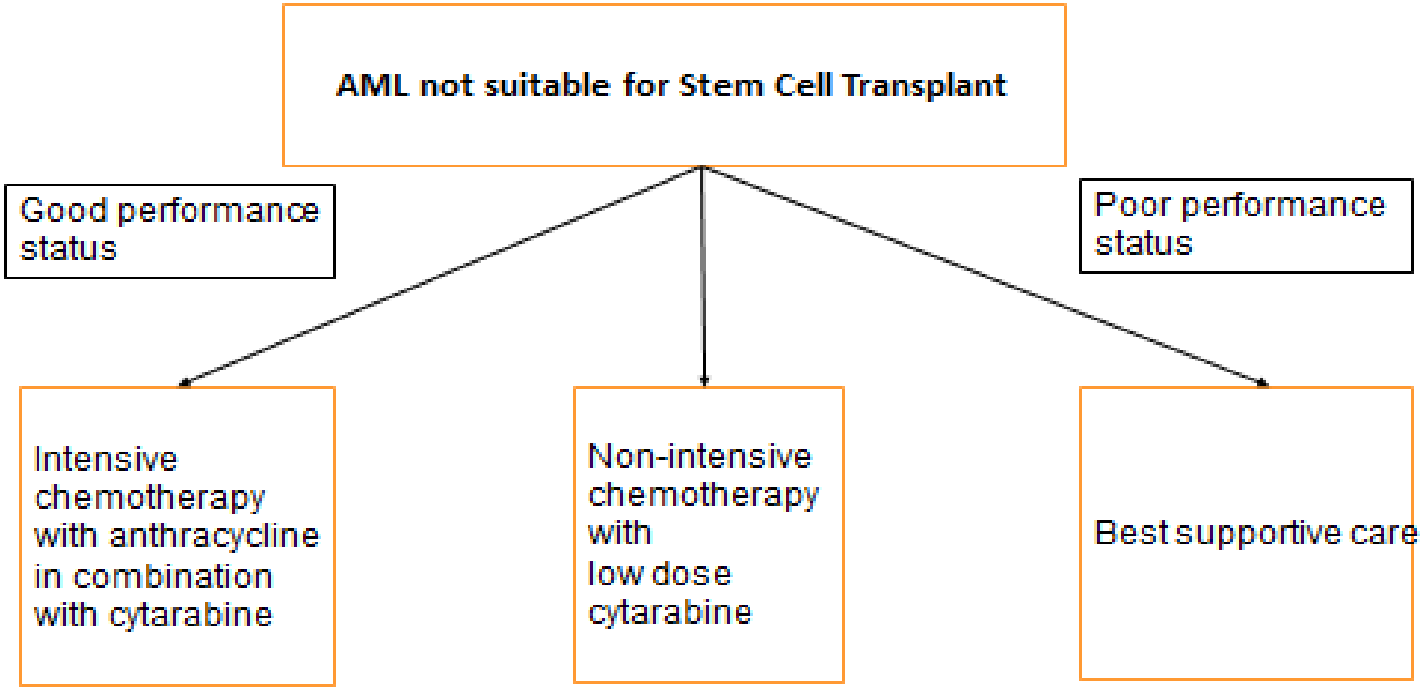
Azacitidine

- Mechanism of action
  - an analogue of cytidine, a component of RNA. It inhibits DNA methytransferase
- Marketing authorisation granted
  - Adult patients ≥ 65 years who are not eligible for haematopoietic stem cell transplant with acute myeloid leukaemia with > 30% bone marrow blasts
- Dosage from AZA-AML-001 trial
  - 75 mg/m2 per day for 7 days followed by rest period of 21 days. Minimum 6 cycles recommended
- The company has agreed a confidential patient access scheme with the Department of Health

Comparison of NICE scope and company decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with acute myeloid leukaemia with bone marrow blasts more than 30%	Adults ≥65 years not eligible for haematopoietic stem cell transplant with AML with >30% bone marrow blasts.
Intervention	Azacitidine	
Comparators	• Intensive chemotherapy with an anthracycline in combination with cytarabine • Non-intensive chemotherapy with low dose cytarabine • Best supportive care (blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide	Conventional care regimen (CCR) consisting of: • intensive chemotherapy (IC) • non-intensive chemotherapy with low dose cytarabine (LDAC) • best supportive care (BSC).

NICE Pathway



ACD preliminary recommendation

- Azacitidine is not recommended, within its marketing authorisation, 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

Committees key considerations in the ACD

- In AZA-AML-001 median overall survival was 5.8 months in the azacitidine group compared with 3.7 months in the best supportive care group. The clinical trial showed overall survival gains favouring azacitidine versus combined conventional care regimen but failed to reach statistical significance
- The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain
- There were limitations in the approaches used by both the company and the ERG to extrapolate overall survival and adjust for treatment switching
- The most plausible incremental cost effectiveness ratio (ICER) for azacitidine compared with a conventional care regimen is £240,000 per quality-adjusted life year (QALY) gained

Clinical effectiveness results – AZA-AML-001

Outcome	Azacitidine (n= 241)	CCR (n= 247)
Death n (%)	193 (80.1)	201 (81.4)
Censored n (%)	48 (19.9)	46 (18.6)
Median OS (95% CI), months	10.4 (8.0, 12.7)	6.5 (5.0-8.6)
Difference (95% CI, months)	3.8 (1.0, 6.5)	
HR [AZA:CRR] (95% CI)	0.85 (0.69, 1.03)	
1-year survival (95% CI) %	46.5 (40.1, 52.7)	34.3 (28.3, 40.3)
Difference (95%) CI	12.3 (3.5, 21.0)	

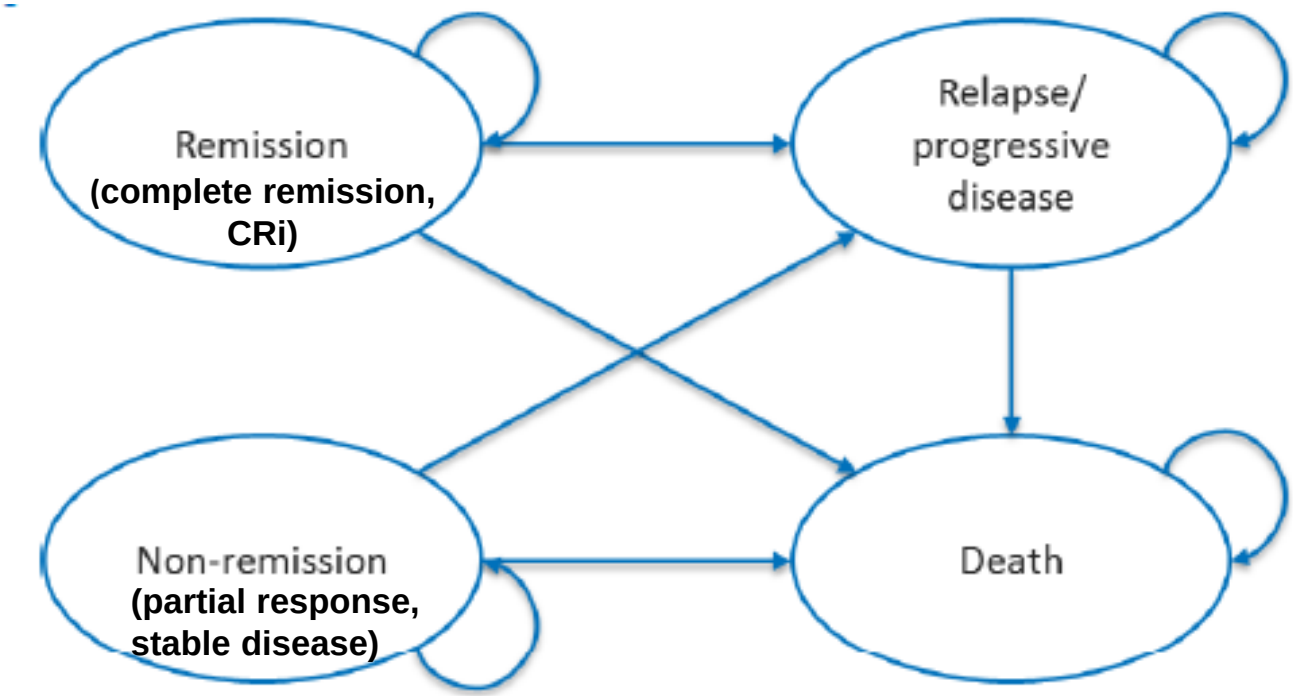
Company azacitidine vs individual CCR results

	BSC		LDAC		IC	
	Azacitidine (N=44)	**BSC (N=45)**	**Azacitidine (N=154)**	**LDAC (N=158)**	**Azacitidine (N=43)**	**IC (N=44)**
Events, n (%)	38 (86.4)	42 (93.3)	124 (80.5)	126 (79.7)	31 (72.1)	33 (75.0)
Median OS months (95% CI)	5.8 (3.6, 9.7)	3.7 (2.8, 5.7)	11.2 (8.8, 13.4)	6.4 (4.8, 9.1)	13.3 (7.2, 19.9)	12.2 (7.5, 15.1)
HR (95% CI)	0.60 (0.38, 0.95)		0.90 (0.70, 1.16)		0.85 (0.52, 1.38)	
Unstratified log-rank test: p-value	0.0288		0.4270		0.5032	
1-year survival, % (95% CI)	30.3 (17.5, 44.2)	18.6 (8.7, 31.4)	48.5 (40.3, 56.2)	34.0 (26.6, 41.6)	55.8 (39.8, 69.1)	50.9 (35.2, 64.6)
Difference, % (95% CI)	11.7 (-6.3, 29.8)		14.5 (3.5, 25.5)		4.9 (-16.2, 26.0)	

Company ITT Post hoc analyses (2)

Estimation method	HR (AZA vs CCR)	95% CI for HR	p-value
Primary ITT analysis (stratified log rank test)	*0.85*	*0.69,1.03*	*0.1009*
Sensitivity analyses censoring patients on date of first subsequent therapy			
Stratified log-rank test	0.76	0.60, 0.96	0.0190
Unstratified log-rank test	0.75	0.59, 0.95	0.0147
Cox-Proportional Hazards			
Adjusted for subsequent therapy but not baseline characteristics (time dependent) – Model 1	0.75	0.59, 0.94	0.0130
Adjusted for baseline characteristics but not subsequent therapy – Model 2	0.80	0.66, 0.99	0.0355
Adjusted for subsequent therapy and baseline characteristics (time dependent) – Model 3	0.69	0.54, 0.88	0.0027
IPCW Cox-PH Models – adjusted for subsequent azacitidine therapy in the CCR arm only			
Unadjusted for baseline characteristics	xxxx	xxxxxxxxxx	xxxx
Adjusted for baseline characteristics	xxxx	Xxxxxxxxxx	xxxx

Model structure



- Cycle length – 4 weeks
- Time in remission state = RFS curve from AZA-AML-001
- Time in non-remission state = PFS curve from AZA-AML-001
- Time in death state = 1 - OS curve from AZA-AML-001
- Time in relapse/progressive disease state = OS – RFS - PFS

Company's base case results

Deterministic analysis:

	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Azacitidine	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	£20,648
CCR	£40,608	0.6365	-	-	-

Probabilistic analysis:

	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Azacitidine	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	£17,423
CCR	£41,429	0.6386	-	-	-

ERG preferred base case analyses i

Analysis	Outcome	AZA	CCR	Difference
Corrected base case (A)	Costs QALYs **ICER**	xxxxxxx xxxxx	£45,954 0.637	xxxxxxx xxxxx **£62,518**
B: Calibration to no. of treatment cycles in trial	Costs QALYs **ICER**	xxxxxxx xxxxx	£50,064 0.637	xxxxxxx xxxxx **£131,698**
C: Using the same costs of relapse/PD across treatments	Costs QALYs **ICER**	xxxxxxx xxxxx	£68,688 0.637	xxxxxxx xxxxx **£159,352**
D: OS adjusted for treatment switching in both arms	Costs QALYs **ICER**	xxxxxxx xxxxx	£52,225 0.728	xxxxxxx xxxxx **£47,482**
E: K-M curves for RFS for each trial arm	Costs QALYs **ICER**	xxxxxxx xxxxx	£46,221 0.636	xxxxxxx xxxxx **£63,569**
F: K-M curves for PFS for each trial arm	Costs QALYs **ICER**	xxxxxxx xxxxx	£45,753 0.635	xxxxxxx xxxxx **£75,471**
G: OS adjusted for switching and baseline covariates	Costs QALYs **ICER**	xxxxxxx xxxxx	£44,818 0.622	xxxxxxx xxxxx **£65,188**

ERG preferred base case analyses ii

Analysis	Outcome	AZA	CCR	Difference
Corrected base case (A)	Costs QALYs **ICER**	xxxxxxx xxxxx	£45,954 0.637	xxxxxxx xxxxx **£62,518**
A + B	Costs QALYs **ICER**	xxxxxxx xxxxx	£50,064 0.637	xxxxxxx xxxxx **£131,698**
A + B + C	Costs QALYs **ICER**	xxxxxxx xxxxx	£72,798 0.637	xxxxxxx xxxxx **£238,674**
A + B + C + D	Costs QALYs **ICER**	xxxxxxx xxxxx	£91,847 0.728	xxxxxxx xxxxx **£171,511**
A + B + C + D + E	Costs QALYs **ICER**	xxxxxxx xxxxx	£92,676 0.727	xxxxxxx xxxxx **£174,205**
A + B + C + D + E + F	Costs QALYs **ICER**	xxxxxxx xxxxx	£98,046 0.724	xxxxxxx xxxxx **£246,488**
A + B + C + D + E + F + G = **ERG preferred base case**	Costs QALYs **ICER**	xxxxxxx xxxxx	£71,138 0.621	xxxxxxx xxxxx **£273,308**

ACD consultation responses

- There were two comments from consultees and commentators
  - Leukaemia CARE
  - NCRI-RCP

ACD consultation responses

- Leukaemia CARE were disappointed with the preliminary decision and noted:
  - AML is an aggressive, rapidly growing disease with limited effective, tolerable treatments currently available
  - 74.7% of people with AML are over 60 and might be unable to withstand toxicity and side effects of current treatment. Azacitidine could be a more tolerable option for these people
  - As azacitidine is currently recommended for people with 20-30% bone marrow blasts not recommending for patients with a higher blast count would produce an inequitable situation

- NCRI-RCP noted that:
  - azacitidine is increasingly being perceived internationally as the standard of care for this patient group

Issues for consideration

- Clinical need: AML is an aggressive, rapidly growing disease with limited effective, tolerable treatments
- Azacitidine is currently recommended for people with 20-30% bone marrow blasts
- Azacitidine is increasingly being perceived internationally as the standard of care for this patient group
- Does the committee have any comments about EOL / Innovation / PPRS?
- Does the committee have any comments about any potential equality issues?
- Is there a case for inclusion in the CDF?