Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

PART 1

Slides for public, contains **no ACIC** information

Technology appraisal committee C – 02 August 2022

Chair: Stephen O'Brien

Evidence review group: Kleijnen Systematic Reviews (KSR)

Technical team: Anna Willis, Anita Sangha, Christian Griffiths, Ross Dent

Company: Celgene, a Bristol Myers Squibb company

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Key issues for consideration

Key issues	
End of life criteria	Does oral azacitidine meet the short life expectancy criterion?
Equality	How should the equality issues raised by stakeholders be taken into account?

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy

- ✓ **Recap of technology, pathway and clinical evidence**
- ❑ Consultation comments
- ❑ End of life
- ❑ Other issues (company's model and modelling assumptions)
- ❑ Other considerations (equality, innovation)
- ❑ Preferred assumptions and ICERs

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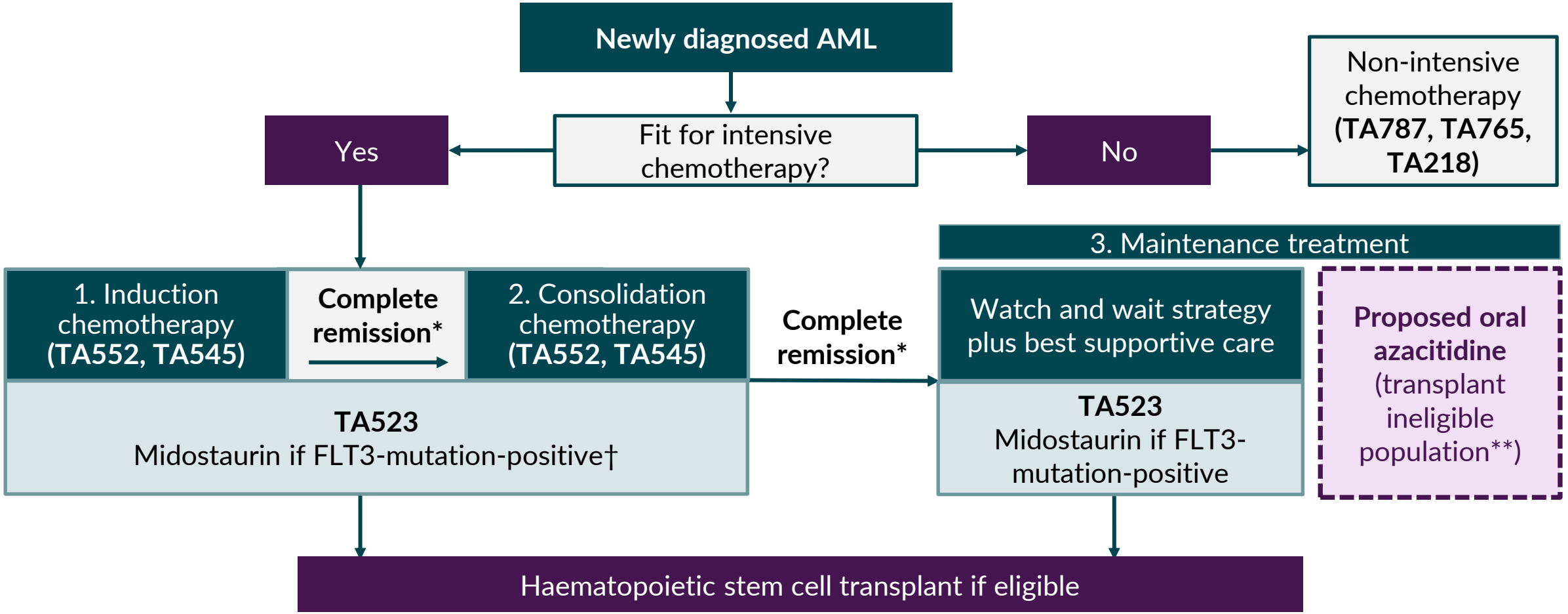
Oral azacitidine (Onureg, Celgene)

Marketing authorisation (UK)	• Oral azacitidine is indicated as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT
Mechanism of action	• Hypomethylating agent which is incorporated into DNA and RNA of AML cells
Administration	• Oral therapy taken 14 days per 28 day cycle (treatment can be extended to 21 days per cycle if relapse occurs)
Price	• The list price is [redacted] for a 200 mg and 300 mg pack of 14 tablets. • The cost per cycle for 21 tablets is [redacted] • The total annual cost per patient is [redacted]/14 tablets per cycle and [redacted]/21 tablets per cycle • The company has a confidential commercial arrangement (simple discount patient access scheme – remains unchanged from ACM1)

Abbreviations: ACM, appraisal committee meeting; AML, acute myeloid leukaemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; HSCT, haematopoietic stem cell transplant.

Treatment pathway for AML in adults



Company is positioning oral azacitidine for people who have achieved complete remission* after induction chemotherapy with or without consolidation chemotherapy and who are not candidates for HSCT**

Notes: *Complete remission or complete remission with incomplete blood count recovery; ** Includes people eligible for HSCT but who choose not to undergo the procedure; † Midostaurin given with standard daunorubicin plus cytarabine during induction therapy and high-dose cytarabine during consolidation therapy.

Clinical evidence – QUAZAR- AML-001

Overall survival, EU subgroup - September 2020 cut off

Committee concluded that EU-subgroup from QUAZAR should be used for decision-making

[redacted]

Median OS (95% CI), months		HR oral azacitidine vs placebo	ITT population (n=472)
Oral azacidine	Placebo		
[redacted]	[redacted]	[redacted]	EU-subgroup (n=[redacted])

Abbreviations: BSC, best supportive care; CI confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival.

ACD preliminary recommendation

Oral azacitidine is not recommended, within its marketing authorisation, as maintenance therapy for acute myeloid leukaemia in adults who:

- are in complete remission, or complete remission with incomplete blood count recovery after induction therapy, with or without consolidation treatment, and
- cannot have or do not want a haematopoietic stem cell transplant

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ACD consultation responses

Comments received from:

- Celgene (company)
- Leukaemia Care
- 1 clinical expert
- 1 public response (from a person with AML)

Consultation comments summary

Public comments:

Patient perspective:

"I am an AML in remission patient on oral azacitidine since October 2015 as part of the Quazar trial, as extended. It has kept me alive for almost seven years but as the trial ends in three months I will no longer receive the drug. I believe that your assessment does not give sufficient weight to age related problems accessing other therapies (I am 74 now) and your recommendation…does not take account of people in my situation where the funding was external to the NHS although the drug given within the NHS"

Patient group and clinical expert comments:

End of life:

- NICE guidelines do not specify whether mean or median life expectancy should be used when considering end of life
- There is precedent for using median survival, for example NICE TA541 (inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia)
- There is abundant evidence that life expectancy is under 24 months for the great majority (~80%) of the patient population
- A small group of people who are cured skew the mean → end of life not met even though drug considered life-extending for majority of people

Equality:

- People from ethnic minority backgrounds are less likely to find a stem cell donor and are therefore unable to receive stem cell transplantation
- Oral azacitidine would provide an alternative treatment to address this inequality

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Key issue: End of life (1)

Background

Estimates for EU-subgroup, months					
Median OS from QUAZAR		Median OS from model (company base case)		Mean OS from model, (company base case - discounted)	
Oral azacidine	Placebo	Oral azacitidine	Watch and wait + BSC	Oral azacidine	Watch and wait + BSC
[redacted]	[redacted]	[redacted]	[redacted]	47.7	31.5

- Committee agreed that oral azacitidine extends life by at least 3 months
- Committee concluded that short life expectancy criterion not met:
  - mean estimates from the model are significantly higher than 24 months (undiscounted results are higher – 36.5 months for BSC arm)
  - short-term prognosis for most people would be poor but those cured after intensive chemotherapy (around 20% based on clinical expert opinion in ACM1) would likely live beyond 2 years

Company's ACD response (1)

- In NICE TA788* (May 2022), the appeal panel concluded it would be unreasonable to state that life expectancy was not normally less than 24 months if 65% of modelled cohort had died before 24 months
  - a similar proportion of people in the EU subgroup ([redacted]) did not survive beyond 24 months

*Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy

Abbreviations: ACD, appraisal consultation document.

Key issue: End of life (2)

Company's ACD response (2)

- Extrapolated mean survival is not reflective of the life expectancy for most people with AML in practice
- Clinical opinion in ACM1 suggested that around 80% of people who are not eligible for a transplant, relapse within the first 12 months. For these people, the expected survival is less than 24 months
- Only [redacted] of people contribute to the survival data beyond 24 months, by 60 months this decreases further to [redacted], highlighting the long tail of the survival curve.

ERG comments on short life expectancy criterion (remain unchanged from ACM1)

- There is a discrepancy between the results from the trial and the model

Patient group and clinical expert comments

- *"…Great majority of patients clearly fulfil 'end of life' criteria and it would seem perverse that simply because a small number of patients survive long term the great majority of patients for whom there is a clear unmet need might be denied effective therapy."*
- *"…We submit that a decision to base the life expectancy on the mean average is unreasonable considering the uncertainties around calculating the mean and the clinical expert evidence submitted to NICE."*

Does oral azacitidine meet the short life expectancy criterion?

Abbreviations: ERG, evidence review group.

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New evidence

Other issues: Extrapolation of overall and relapse-free survival (1)

Small impact on ICER

Background

- Company used joint accelerated failure time (AFT) models to estimate OS (generalised gamma) and RFS (log-logistic) for the ITT population and EU-subgroup (company base)
- Committee considered that joint modelled curves underestimate survival for the comparator arm, compared to trial Kaplan-Meier curves (based on the ITT population)
- Committee requested scenarios to explore the impact of using individually fitted parametric models

Company's ACD response

- Joint survival curves selected in company's base case are most appropriate → quantile-quantile plots show no violation of AFT assumption for OS or RFS
- Joint models do not overestimate the expected treatment benefit with oral azacitidine for the EU-subgroup
- Company explored scenario using individual models selecting the generalised gamma for OS and log-logistic for RFS (for both arms)→ minimal impact on the ICER (~£1K increase)

ERG comments

- The company's joint and individual modelling results are comparable
- ERG agrees that the impact of choosing between these two approaches is likely minor

Abbreviations: AFT, accelerated failure time; ICER, incremental cost-effectiveness ratio; RFS, relapse-free survival.

New evidence

Other issues: Extrapolation of overall and relapse-free survival (2)

Figures show Kaplan-Meier curves and jointly or individually fitted parametric models (generalised gamma) to OS outcomes in QUAZAR (EU-subgroup)

Jointly fitted parametric models (company base case)

Individually fitted parametric models

Are joint or individual models more appropriate for modelling OS and RFS?

Abbreviations: KM, Kaplan-Meier.

New evidence

Other issues: Duration of treatment benefit

Small impact on ICER

Background

- Committee considered that it is highly optimistic to assume a constant treatment benefit with oral azacitidine (company base case) based on the observed trial data

Company's ACD response

- End of trial follow up (90 months =7.5 years) no patients remained on treatment (oral azacitidine). Impact of treatment waning during the trial is already captured in the survival estimates and any potential waning of treatment effect after trial follow-up will be minor
  - smoothed hazard plots show similar mortality risk from ~[redacted] months onwards
- Company presented scenarios for joint and individual curves assuming equivalence of hazards between oral azacitidine and no active therapy from month 90 → minimal impact (<1%) on the ICER

ERG comments

- ERG assessed the relative treatment effect on OS and RFS over time between oral azacitidine and no active treatment for EU-subgroup (same individual models selected by company and ERG):
  - risk of death or relapse are similar for oral azacitidine and no active treatment from ~[redacted] years onwards, so treatment waning may be implicitly incorporated when using an individual modelling approach
- ERG scenarios including treatment waning from 3 and 5 years after randomisation → small ICER impact

Is it appropriate to include a treatment waning effect?
If so, which approach to modelling this effect is most appropriate?

No comments received, no new evidence

Other issues: Model structure and relapse utility

HSCT not appropriately reflected in the modelling

Unknown impact on ICER

- HSCT was not included as a separate health state in the model, but was implicitly included in the modelling through the survival analysis of the QUAZAR ITT population
- In QUAZAR, 6.3% in oral azacitidine arm and 13.7% in placebo arm had a transplant after stopping treatment
- ERG and committee would have preferred company to have included HSCT as a health state in the model:
  - uncertain whether company's current model captures the long-term benefit after a HSCT
  - temporary disutility associated with HSCT should be removed as no benefit in HRQoL after having a transplant has been included in the model → small impact on the ICER
- ERG scenario analysis adding a utility increment after HSCT slightly increases the ICER

Utility for relapse-free survival (RFS) health state

Small impact on ICER

- ERG noted that RFS utility ([redacted]) was higher than the age-adjusted population norm in the UK (0.785)
- Committee considered that the RFS utility value used in the model is not plausible as it would imply that people with AML have a better quality of life than people without the disease
- Committee conclusion → RFS utility should be capped at age and sex matched general population levels
- ERG scenario analysis capping RFS utility has a small impact on the ICER

Company's model and base case assumptions remain unchanged from ACM1

Abbreviations: HRQoL, health-related quality of life.

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Other considerations (1)

Equality issues considered in ACM1 (1)

Background

- Many people with AML who are in complete remission are unable to have a transplant because of a lack of donor availability. This disproportionately affects people from ethnic minority groups
- Some people may struggle financially to have current treatment because of the cost of regular travel to hospital and having to take time off work. Having a transplant may be especially difficult for people with caring responsibilities because of the significant time commitment needed
- Committee conclusion → oral azacitidine could reduce these potential equality issues but uncertainties in the cost-effectiveness results need to be addressed before oral azacitidine can be recommended

ACD responses (company and other stakeholders)

- People from ethnic minority backgrounds are less likely to find a stem cell donor resulting in inequitable access to a potentially curative treatment option:
  - estimates range from 20-61% for Black Asian and Minority Ethnic groups versus 69-96% for White Northern European groups*
- Oral azacitidine gives people who are unable to find a stem cell donor an alternative treatment option:
  - *"I do not believe the importance of [oral azacitidine] as a strategy to increase equity of access to effective treatment options for patients from particular ethnic backgrounds has been appropriately recognised."*

*References: NBTA (2018); Anthony Nolan (2016); Anthony Nolan (2021)

Other considerations (2)

Equality issues considered in ACM1 (2)

ACD responses (company and other stakeholders)

- There are also geographical barriers to accessing a stem-cell transplant:
  - 35 allograft centres across the UK → people may not be seen at their local hospital
  - longer distances, and increased travel impact access to transplant, post-transplant care and follow up

NICE Guide to the methods of technology appraisal 2013

- Section 6.2.21: The committee will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related (see back up slide 35)

Innovation

- Company and stakeholders consider technology to be innovative
- Committee concluded that the benefits or oral azacitidine are captured in the cost-effectiveness analysis

How should the equality issues raised by stakeholders be taken into account?

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Summary of company and ERG preferred assumptions

Assumption	Company base case (remains unchanged from ACM1)	ERG base case (updated to align with committee preferred assumptions from ACM1)
Overall population from QUAZAR	EU-subgroup	EU-subgroup*
Temporary disutility with HSCT	Include	Remove
Source for relapse utility	Joshi (2019)	Tremblay (2018)
Utility for RFS health state	Not capped at age-adjusted population norm in UK	Capped at age-adjusted population norm in the UK*

*These assumptions have been updated post ACM1 to align with committee's preferences

Additional committee considerations in ACD:

- Scenario analyses exploring the use of individual parametric models for extrapolating survival and treatment effect waning would reduce the uncertainty that the expected treatment benefit with oral azacitidine has been overestimated in the model
- These analyses would form part of the committee's preferred assumptions if they could be done robustly

Cost effectiveness results - company base case

Company base case results remain unchanged from ACM1

Deterministic base case results – include oral azacitidine PAS

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	32,718
Watch and wait + BSC	[redacted]	[redacted]	-	-	-

Probabilistic base case results – include oral azacitidine PAS

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	32,480
Watch and wait + BSC	[redacted]	[redacted]	-	-	-

Note: ICERs including confidential comparator discounts are slightly higher for all scenarios and will be presented in part 2 of the meeting

Abbreviations: PAS, patient access scheme; QALY, quality-adjusted life year.

Company deterministic scenario analyses

ICERs include oral azacitidine PAS

No.	Scenario (applied to company base case)	ICER (£/QALY)
1	**Company base case**	**32,718**
2	Company base case + treatment effect waning at 7.5 years	32,764
3	Best fitting individual models for both OS and RFS*	33,728
4	Best fitting individual models for both OS and RFS* + treatment effect waning at 7.5 years	33,714

*For OS: individual generalised gamma for both arms. For RFS: individual log-logistic for both arms.

Cost effectiveness results - ERG base case and scenarios

ICERs include oral azacitidine PAS (deterministic unless otherwise stated)

Scenario	ICER (£/QALY)
Company base case (EU-subgroup)	**32,718**
ERG change 1 – relapse utility based on Tremblay 2018	31,857
ERG change 2 – no temporary disutility for HSCT	32,749
ERG change 3 – RFS utility cap	33,958
Updated ERG base case (1 to 3 combined) – committee's preferred ICER from ACM1	**33,991**
ERG probabilistic base case	33,830
Scenario 1: adding a post-HSCT utility increment	36,887
Scenario 2: individual modelling of OS and RFS*	35,073
Scenario 3: individual modelling of OS and RFS* + treatment effect waning at 3 years	35,571
Scenario 4: individual modelling of OS and RFS* + treatment effect waning at 5 years	35,205
Scenario 5: individual modelling of OS and RFS* + treatment effect waning at 7.5 years	35,107

*For OS: individual generalised gamma for both arms. For RFS: individual log-logistic for both arms.

FLT3 subgroup – company and ERG base case results

ICERs include oral azacitidine PAS – company base case results remain unchanged from ACM1

	Pairwise ICER versus oral azacitidine (£/QALY)	
Scenario	**Midostaurin**	**Watch and wait + BSC**
Deterministic results		
Company base case	**Oral azacitidine is dominant**	**19,063**
ERG change 1 - relapse utility based on Tremblay 2018	Oral azacitidine is dominant	19,048
ERG change 2 – no temporary disutility for HSCT	Oral azacitidine is dominant	19,076
ERG change 3 – RFS utility cap*	Oral azacitidine is dominant	20,212
Updated ERG base case (1 to 3 combined)	**Oral azacitidine is dominant**	**20,229**
Probabilistic results		
Company probabilistic base case	Oral azacitidine is dominant	19,878
Updated ERG probabilistic base case	Oral azacitidine is dominant	21,340

*Assumption added post ACM1

Note: ICERs including confidential comparator discounts are slightly higher for most scenarios and will be presented in part 2 of the meeting