NICE National Institute for Health and Care Excellence

PART 1
Slides for public observers
Redacted

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Chair's presentation

ERG: Aberdeen HTA Group

Technical team: Stephen O'Brien, Kirsty Pitt, Alex Filby, Ross Dent

Company: AbbVie

9 November 2021

Recap from ACM1

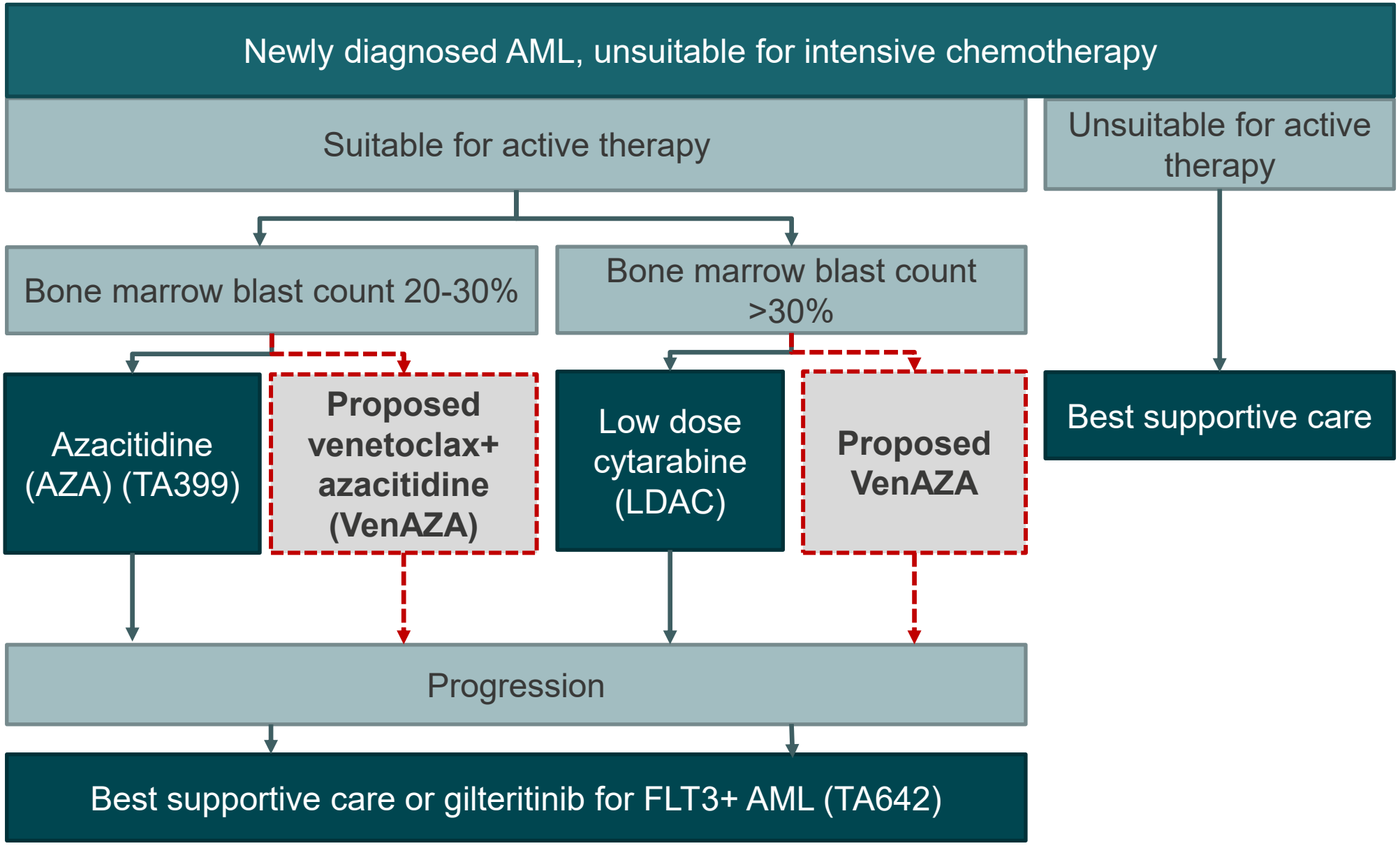
Venetoclax (Venclyxto, AbbVie)

Marketing authorisation (UK)	Venetoclax in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. **n.b. most common hypomethylating agent in NHS is azacitidine. Venetoclax + azacitidine = VenAZA**
Mechanism of action	Selective small molecule inhibitor of B-cell lymphoma 2. Overexpression of Bcl-2 can cause cells to resist apoptosis and therefore continue to survive.
Administration	Oral tablet
Price	At list price, a 28-day cycle (excluding first cycle*) of VenAZA (assuming 100% treatment compliance) is £7,869. A confidential PAS is in place for venetoclax.

NICE *Dose of venetoclax is stepped up over the first 3 days of the first course to reach target dose

Recap from ACM1

Treatment pathway



Recap from ACM1

Background

Comparators	VenAZA comparators: Blast cell count 20–30%: AZA Blast cell count >30%: LDAC	
Subgroups	Azacitidine is recommended by NICE for disease with blast cell count 20-30%, post-hoc subgroup analysis based on this.	
Clinical trial	VIALE-A, RCT comparing VenAZA with AZA (N=431)	VIALE-C, RCT comparing VenLDAC with LDAC (N=211)
Key results (post-hoc subgroups)	OS: VenAZA: [redacted] AZA: [redacted] HR: [redacted]	OS: VenLDAC: [redacted] LDAC: [redacted] HR: [redacted]
Comparing VenAZA to LDAC	Network meta-analysis and propensity score matching explored but results not used in model as similar to unadjusted comparison	
Model	Cohort Markov state transition model. 5 health states: remission, non-remission, progressive disease/relapse, cure, death	

Recap from ACM1

ACD: preliminary recommendation

- The committee recognised that venetoclax plus azacitidine is a promising new treatment, but was not persuaded that there is sufficient evidence of clinical and cost effectiveness to recommend it for routine commissioning for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.
- Given the uncertainties, the committee considered that venetoclax plus azacitidine may be suitable for use in the Cancer Drugs Fund. Therefore the company is invited to submit a proposal for including venetoclax plus azacitidine in the Cancer Drugs Fund for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.

ACD considerations

Recap from ACM1

Comparators	Splitting the trial population by blast cell count is necessary to compare venetoclax plus azacitidine with the relevant comparators but increases uncertainty
Clinical efficacy	Venetoclax plus azacitidine increases overall survival compared with azacitidine or low dose cytarabine alone
Cure health state in the model	The evidence is too uncertain to include a cure health state in the model
Subsequent treatment	The company's updated assumptions about the proportions of people having subsequent gilteritinib are acceptable
Dose intensity	The dose intensity of venetoclax used in clinical practice is likely to be between 12.5% and 25% of the full licensed dose
End of life criteria	Met (see next slide)
Cost-effectiveness	The upper end of the plausible ICER range is above £50,000 per QALY gained

Recap from ACM1

End of life considerations

Criterion	Data source	Overall survival	
		Median	Mean
Short life expectancy, normally < 24 months	VIALE: AZA (20-30% blasts)	[redacted]	-
	VIALE: LDAC (>30% blasts)	[redacted]	-
	Undiscounted life years from model: AZA (20-30% blasts)	-	1.83 years
	Undiscounted life years from model: LDAC (>30% blasts)	-	0.84 years
Extension to life, normally of a mean value of ≥ 3 months		Median increase (trial)	Mean increase (model)
	VenAZA versus AZA (20-30% blasts)	[redacted]	1.33 to 2.40 years across all scenarios
	VenAZA versus LDAC (>30% blasts)	[redacted]	1.33 to 2.71 years across all scenarios

Key issues for consideration

Issue	Impact	Question for committee
1. Cure assumption		• Is a 'cure' plausible? • Is applying a cure state only in the treatment arm plausible? • Does the company's mixture cure modelling provide validation for including a cure state? • How should any cure assumption be applied in the model ○ To what proportions and at what time point?
7. Dose of venetoclax		• Is the company's revised modelling appropriate?

Key:

 **Small impact**

 **Impact unknown**

 **Model driver**

ACD consultation responses

- Consultee comments from:
  - AbbVie (company)
    - CDF proposal not included
  - Royal College of Pathologists and British Society for Haematology
  - Leukaemia Care

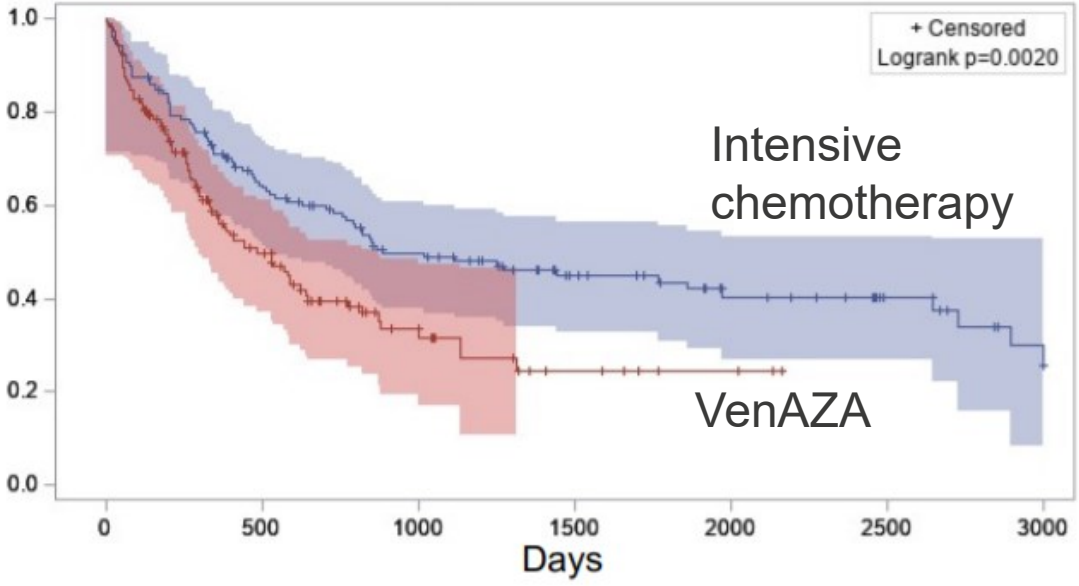
- Commentator comments from:
  - Jazz Pharmaceuticals

- Web comments

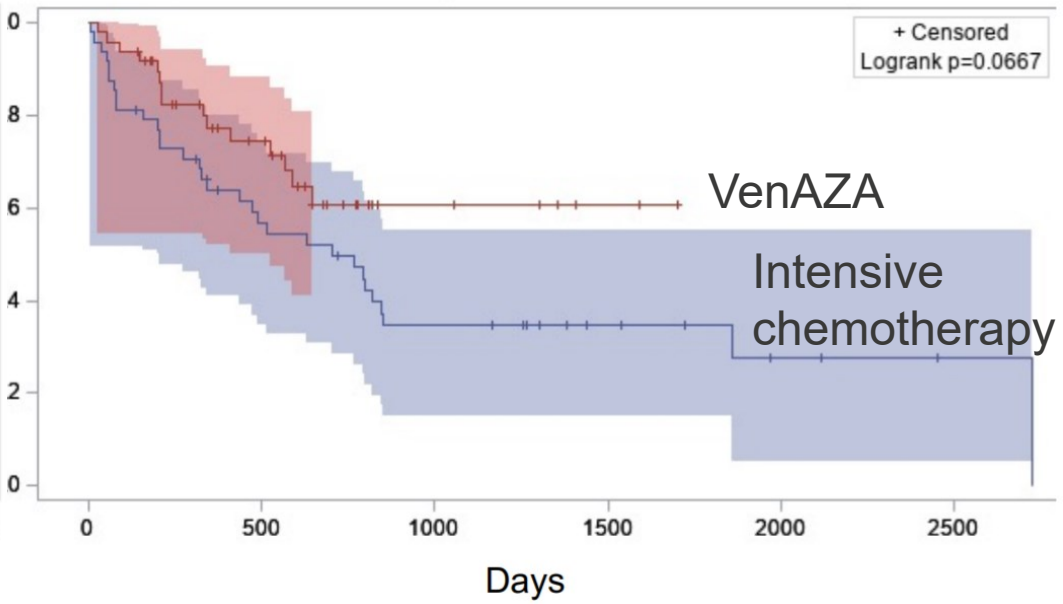
Patient and professional group comments

- **Patient group**
  - Prefer routine commissioning but would welcome CDF if needed to resolve uncertainties
- **Professional group**
  - Present evidence from recent study to support cure assumption (Cherry et al. 2021)
  - People with AML in a single US centre

Median overall survival – overall cohort (VenAZA: n=143, 23% had SCT Intensive chemotherapy: n=149, 75% had SCT)



Median overall survival – cohort propensity matched for age, European Leukemia Network risk group and transplant status (sample size 48 per matched group)



Web comments

NHS professionals

- Not appropriate to compare VenAZA to historical non-intensive treatments – biologically distinctive and novel therapeutic advance
- High rates of MRD negative remission close to levels seen with high dose chemotherapy
- Emerging data consistent with a cure in small proportion of patients
- Risk of relapse declines dramatically during 2-3 years after treatment for patients in remission
- Many patients will decide to stop treatment after 2 or 3 years, with emerging evidence that this doesn't affect risk of relapse

Chyn Chua study – authors' comments

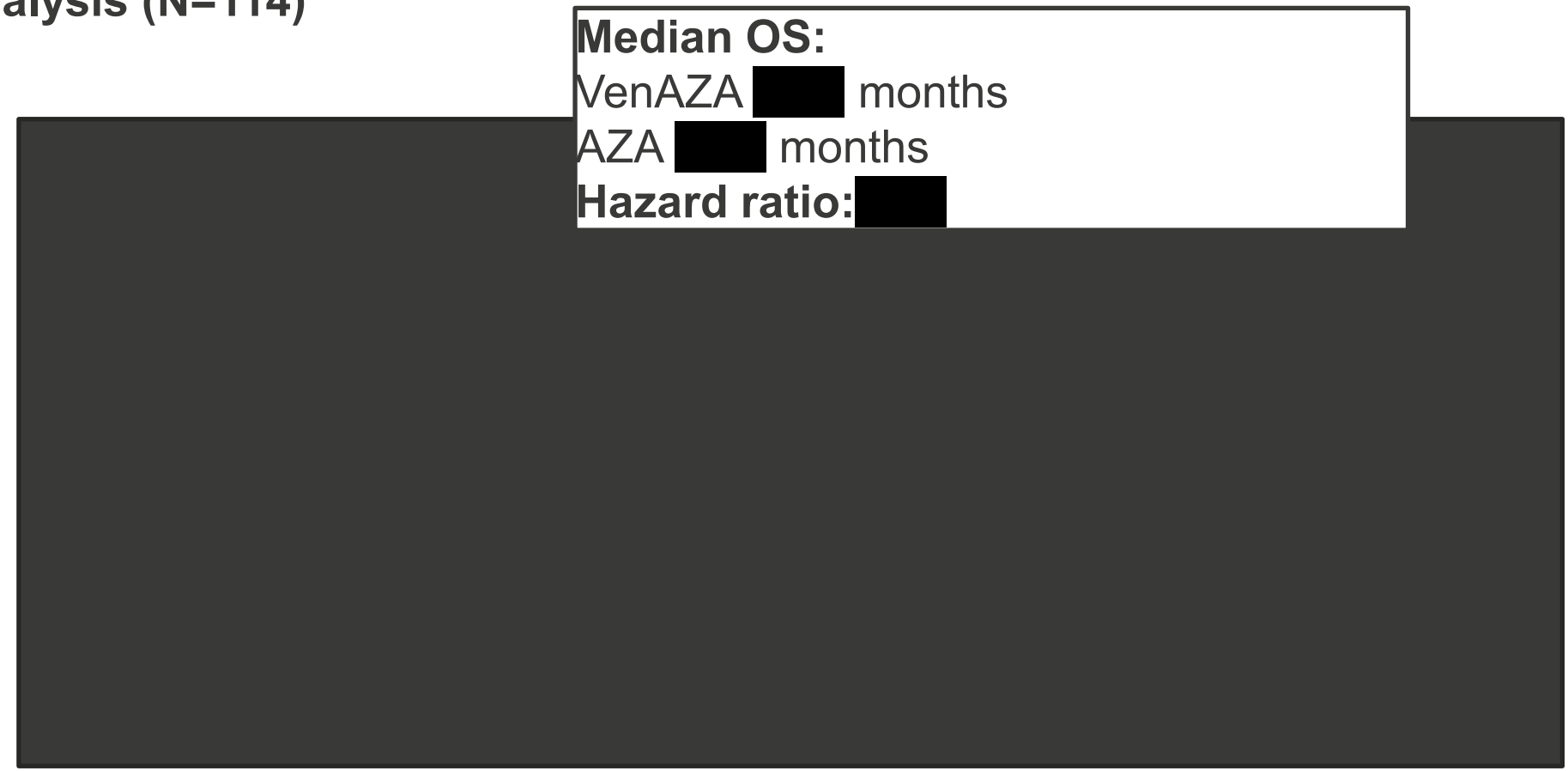
- Small numbers of patients who had late relapse had mostly acquired new cytogenetic or molecular abnormalities at time of relapse
- Suggests new or therapy-related AML, rather than relapse

Recap from ACM1

VIALE-A Overall survival results

Data cut-off January 2020, patients with 20-30% blasts

Kaplan–Meier plot of OS in the 20–30% blast subgroup in VIALE-A: Post-hoc analysis (N=114)

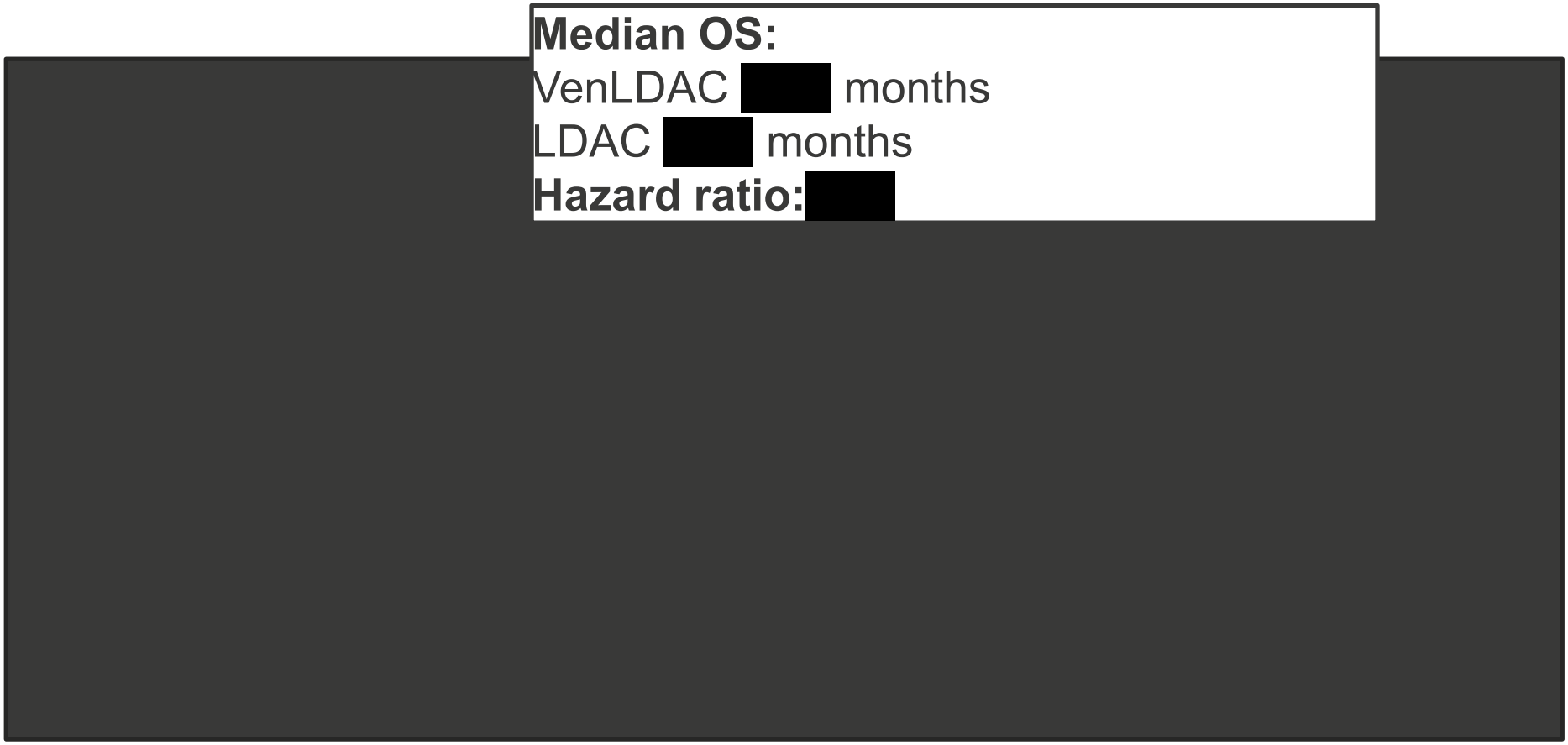


Recap from ACM1

VIALE-C Overall survival results

Data cut-off August 2019, patients with >30% blasts

Kaplan–Meier plot of OS in the >30% blast subgroup in VIALE-C: Post-hoc analysis (N=160)



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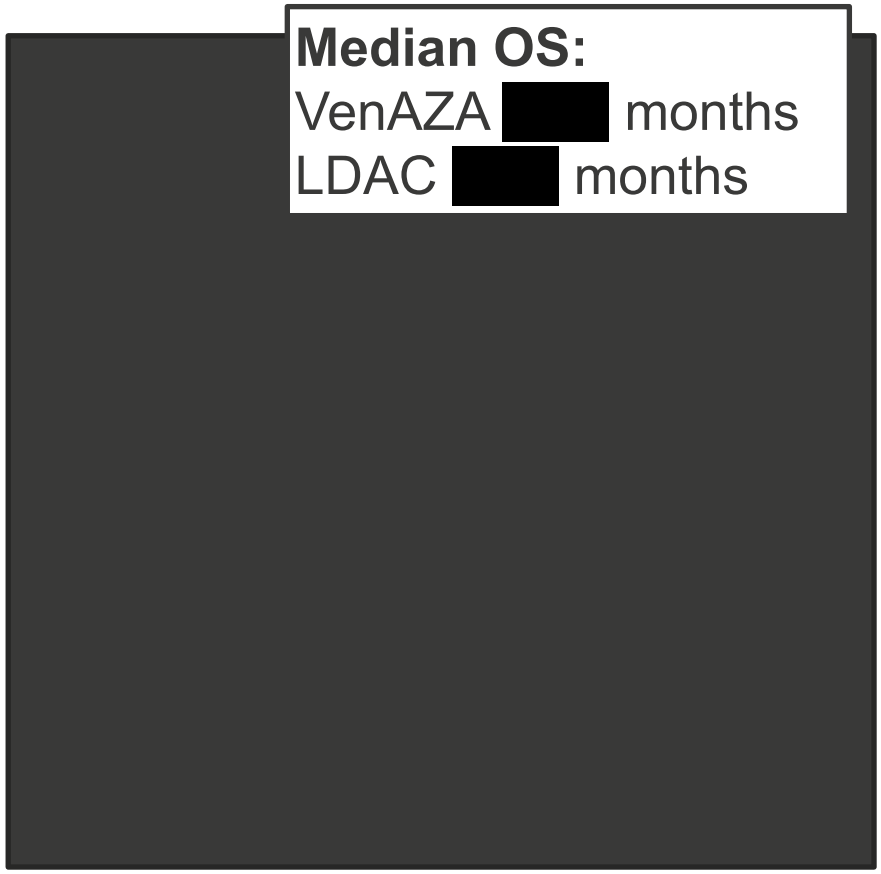
Comparing VenAZA with LDAC, >30% blasts

Kaplan–Meier plot of OS in the >30% blast subgroup: VenAZA data from VIALE-A (N=206), LDAC data from VIALE-C (N=36): Unadjusted post-hoc analysis



- Network meta-analysis (NMA) and propensity score matching (PSA) explored but results not used in model as similar to unadjusted comparison
- ERG acknowledges that the difference in OS, EFS and response are very small between the propensity score weighted and unadjusted data.

OS	Estimate (95% CI/CrI)
Unadjusted comparison	HR = [redacted]
PSA after weighting	HR = [redacted]
NMA	OR = [redacted]

Recap from ACM1

Time-to-relapse extrapolations (1)

VenAZA (20-30% blasts)

- Previous ERG scenarios assessed removing the cure assumption combined with alternative extrapolations for time from remission to relapse

[redacted]

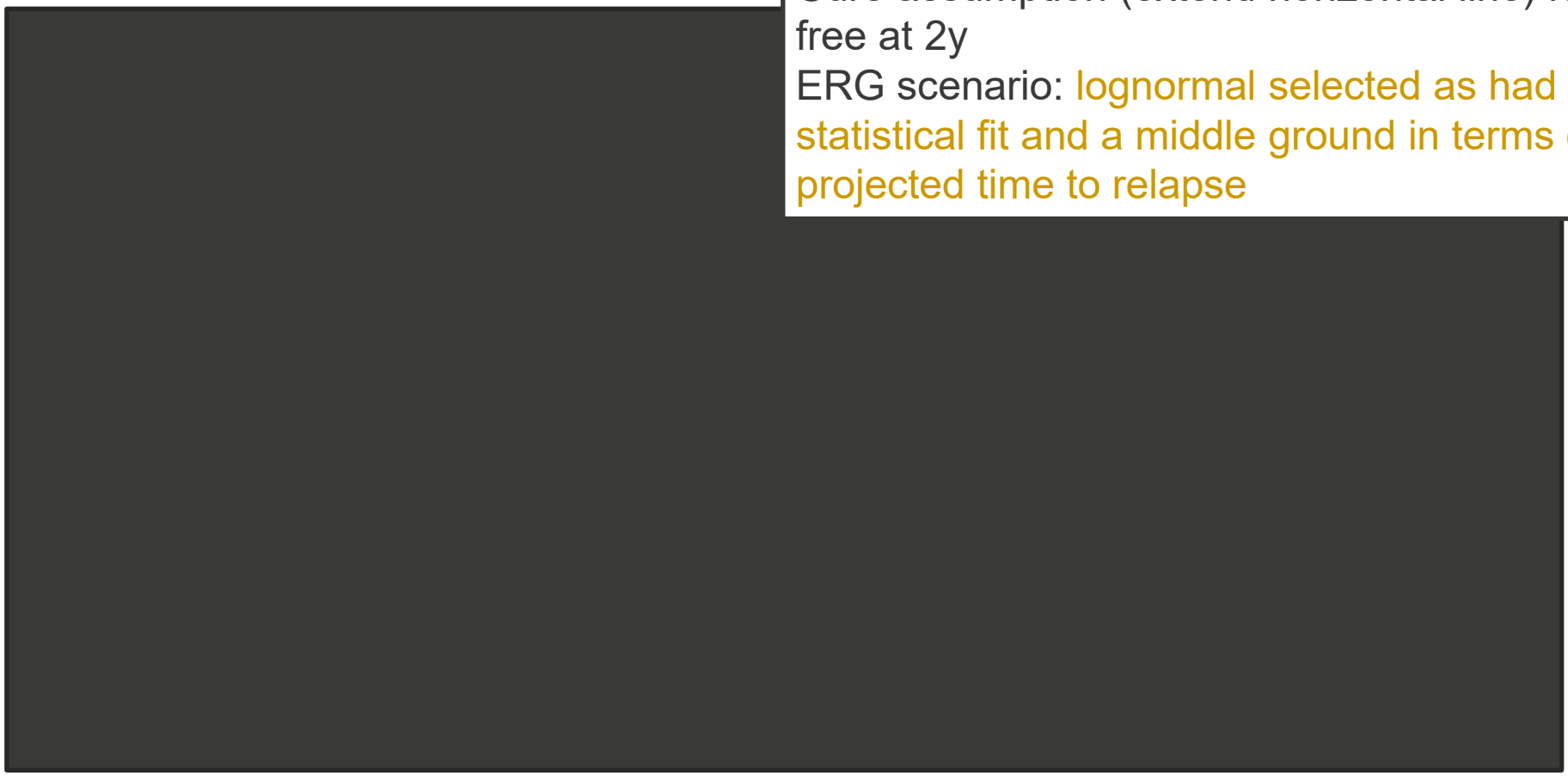
Company original extrapolation: lognormal - 2nd lowest AIC/BIC, supported by cumulative hazard plot, and captured shape of observed data
Cure assumption (extend horizontal line) for relapse free at 2y
ERG scenarios:
Generalised gamma selected based on visual fit
Log-logistic selected as preferred by clinical experts in company's submission

Recap from ACM1

Time-to-relapse extrapolations (2)

VenAZA (>30% blasts)

Company original extrapolation: generalised gamma - lowest AIC/BIC, good fit to cumulative hazard data and captured observed decreasing hazard.
Cure assumption (extend horizontal line) for relapse free at 2y
ERG scenario: lognormal selected as had 2nd best statistical fit and a middle ground in terms of mean projected time to relapse



Company's comments and new evidence

1. Cure assumption [1]

ACD consideration

- Committee concluded that the evidence was too uncertain to include a cure health state in the model and that it was unclear which time-to-relapse curve should be used

Company's comments

- VenAZA shows clinical outcomes similar to treatments with accepted capacity for cure
- VenAZA is currently being used (through interim COVID-19 guidance) for patients eligible for intensive chemotherapy who would normally receive treatment with curative intent
- Well-characterised relationship between complete remission and long-term survival
  - High proportions of durable complete remission with VenAZA
- Recent review by Short et al (2021) reports that VenAZA has longer median survival and improved 2 year survival compared with intensive chemotherapy regimens
- TA642 (gilteritinib) is relevant as population (relapsed/refractory AML) may have poorer prognosis than population in this appraisal (untreated AML)
  - Cure assumption included at 3 years in TA642

ERG comments

- Acknowledges that the cure assumption for gilteritinib appears less conservative than the one applied here – particularly for those who did not receive SCT in the gilteritinib model
- However it was applied to intervention and comparator arm, unlike in this appraisal

Company's comments and new evidence

1. Cure assumption [2]

Revised company base case

- Clinical experts at first committee meeting suggested a cure state at 3 years may be plausible
  - Company included cure state at 3 years in revised base case
  - Proportions of VenAZA patients predicted to enter cure state:

Subgroup	2-year timepoint	3-year timepoint
20-30% blasts	[redacted]	[redacted]
>30% blasts	[redacted]	[redacted]

  - Company's clinical advice suggested predictions for 3-year timepoint are lower than would be expected in clinical practice

ERG comments

- Some of the studies referenced to support decreasing rate of relapse focus on patients who had stem cell transplant
- Studies support a diminished rate of relapse beyond 2-3 years but do not support a zero risk

Company's comments and new evidence

1. Cure assumption [3]

Evidence for relapses after 2 years

- Chyn Chua study should not be used as not designed to investigate impact of time in complete remission on relapse, and is a retrospective study with a small sample size
- Company's base case does not permit any relapse after cure point
- Yanada 2007 reports on relapses after complete remission in 1,069 patients with AML on various treatments, but who have not had SCT

[redacted]

Company's scenario analyses

- Clinical opinion suggested that of patients in complete remission for 2 years, about 20% may experience late relapses, mostly between 2 and 3 years
- Conducted scenario analyses where only a proportion of patients in 'Remission' state transition to 'Cure' state after cure timepoint

Scenario	Proportion of patients in remission who transition into cure state
A	90% at 3 years
B	80% at 2 years
C	70% at 2 years

ERG: Reassuring that results not sensitive to the different proportions explored in scenarios.

Company's comments and new evidence
1. Cure assumption – mixture cure modelling [1]

ACD consideration

- Committee noted that cure fractions estimated from a mixture cure model may have been helpful to validate the proportion of patients remaining in the remission health state over time.

Methods

- Company conducted analyses removing the cure health state and exploring mixture cure models to extrapolate transitions from remission to relapse, and remission to death
- Explored scenario analyses where transitions from remission state informed by combinations of 3 best statistically fitting extrapolations
  - Gompertz model also explored for time-to-release in 20-30% blasts subgroup as considered only clinically plausible extrapolation.

Limitations

- Based on small numbers of patients and events from VIALE trials due to need to split into subgroups by blast cell count
  - Not used in base case as company state would increase uncertainty compared with using cure state
- Clinical experts stated they would not expect a significant difference in long-term survival between blast subgroups

Company's comments and new evidence

1. Cure assumption – mixture cure modelling [2]

Proportion of overall cohort in remission state between 2-5 years

Blast count subgroup	Remission to relapse extrapolation	Remission to death extrapolation	Proportion of overall cohort in remission (%)			
			2y	3y	4y	5y
20–30%	Previous base case (2-year cure)		[redacted]	[redacted]	[redacted]	[redacted]
	Revised base case (3-year cure)		[redacted]	[redacted]	[redacted]	[redacted]
	Weibull[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log Normal[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log Logistic[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]

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a – not considered plausible by clinical experts

Company's comments and new evidence

1. Cure assumption – mixture cure modelling [3]

Proportion of overall cohort in remission state between 2-5 years

Blast count subgroup	Remission to relapse extrapolation	Remission to death extrapolation	Proportion of overall cohort in remission (%)			
			2y	3y	4y	5y
>30%	Previous base case (2-year cure)		[redacted]	[redacted]	[redacted]	[redacted]
	Revised base case (3-year cure)		[redacted]	[redacted]	[redacted]	[redacted]
	Log Normal	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Log Logistic	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised Gamma	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments

- The mixture cure model analysis provides limited evidence to validate the cure fraction due to lack of data and small patient numbers.

Company's comments and new evidence

1. Cure assumption – utility in the cure state

ACD consideration

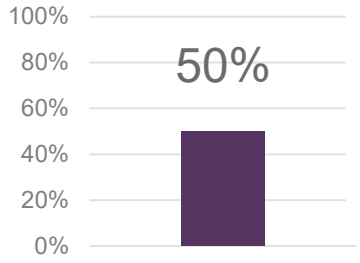
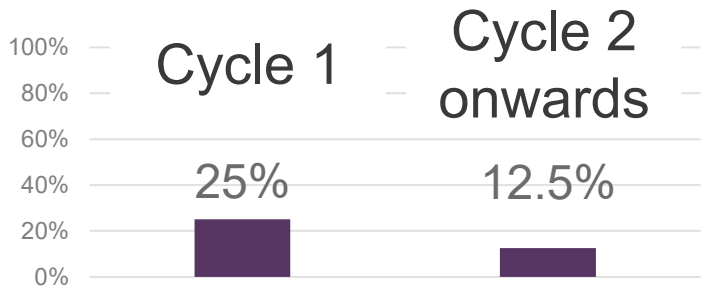
- Committee did not consider it plausible that patients in cure state would experience same quality of life as general population

- **Company** states there is only a small difference between utility values describing remission and cure health states
- As patients have a mean age of [redacted] years at original 2-year cure point, age-adjusted general population utility of 0.7465 is always less than remission health state utility of [redacted]
- Therefore, applying remission utility to patients in cure state makes little difference to inputs and does not impact cost-effectiveness results

- Is a 'cure' plausible?
- Is applying a cure state only in the treatment arm plausible?
- Does the company's mixture cure modelling provide validation for including a cure state?
- How should any cure assumption be applied in the model
  - To what proportions and at what time point?

Company's comments and new evidence

2. Dose intensity

Dose intensity of venetoclax component	Previous company base case	
	Committee preference in ACD - included in updated company base case	

Real world evidence from COVID interim treatment policy (N = 301)

(different population – includes people who would normally be eligible for intensive chemotherapy)

- 81% of patients received a 100 mg dose of venetoclax with concomitant use of strong CYP3A inhibitor
  - Complete remission reached in 70% of these
  - Median OS 12.8 months

Company's comments and new evidence
2. Dose intensity

Pharmacokinetic data

- One study showed 100 mg venetoclax administered with strong CYP3A inhibitor led to drug exposure between that of a 400 mg dose and established safe maximal administered dose of 1,200 mg per day
  - *Freise KJ, Shebley M, Salem AH. Quantitative Prediction of the Effect of CYP3A Inhibitors and Inducers on Venetoclax Pharmacokinetics Using a Physiologically Based Pharmacokinetic Model. J Clin Pharmacol 2017;57:796-804.*
  - Physiologically based pharmacokinetic model - independently verified against clinical studies of the strong CYP3A inhibitor ketoconazole, the strong CYP3A inducer, multiple-dose rifampin, and the steady-state venetoclax pharmacokinetics in people with chronic lymphocytic leukaemia
- Post-hoc analysis of VIALE-A data showed complete remission rates similar with use of moderate and strong CYP3A inhibitor with adjusted dose, compared with no use of CYP3A inhibitor

Is the company's revised modelling appropriate?

Cost-effectiveness results (1)

VenAZA v. AZA (20-30% blasts)

- Company's revised base case includes:
  - Corrected subsequent treatment costs (previously incorporated by ERG)
  - Alternative adverse event costs (previous ERG preference)
  - 3-year timepoint for cure state
  - Dose intensity for venetoclax of 25% in first cycle and 12.5% from cycle 2 onwards

The following results include PAS for venetoclax, but do not include PAS for gilteritinib – these will be shown in part 2

Cost-effectiveness results (2)

VenAZA v. AZA (20-30% blasts)

Scenario		ICER (£/QALY)
Company	**Previous company base case (2-year cure point), corrected and updated AE costs**	**£25,074**
	1. 3-year timepoint for cure state	£40,433
	1+2. Venetoclax dose intensity reduced **Revised company base case**	**£26,760**
	2+3a: 80% of patients in remission assumed cured at 2 years	£18,813
	2+3b: 70% of patients in remission assumed cured at 2 years	£21,437
	2+4a: 90% of patients in remission assumed cured at 3 years	£28,736
ERG	2+4b: 80% of patients in remission assumed cured at 3 years	£30,683
	2+4c: 70% of patients in remission assumed cured at 3 years	£32,718
	2+5a: Cure assumption applied to both arms at 2-years	£18,584
	2+5b: Cure assumption applied to both arms at 3-years	£27,650
Additional tech team	2+4d: 1% of patients in remission assumed cured at 3 years	£49,719

Cost-effectiveness results (2)

VenAZA v. LDAC (>30% blasts)

Scenario		ICER (£/QALY)
Company	**Previous company base case (2-year cure point), corrected and updated AE costs**	**£41,557**
	1. 3-year timepoint for cure state	£49,044
	1+2. Venetoclax dose intensity reduced **Revised company base case**	**£38,900**
	2+3a: 80% of patients in remission assumed cured at 2 years	£35,469
	2+3b: 70% of patients in remission assumed cured at 2 years	£36,908
	2+4a: 90% of patients in remission assumed cured at 3 years	£40,094
ERG	2+4b: 80% of patients in remission assumed cured at 3 years	£41,191
	2+4c: 70% of patients in remission assumed cured at 3 years	£42,329
	2+5a: Cure assumption applied to both arms at 2-years	£33,794
	2+5b: Cure assumption applied to both arms at 3-years	£39,271
Additional tech team	2+4d: 11% of patients in remission assumed cured at 3 years	£49,985

Proportions cured in scenario analyses
20-30% blasts subgroup

Scenario	Patients in remission at 2 years	Patients in remission at 3 years	Percentage of overall cohort entering cure state
2+3a: 80% of patients in remission assumed cured at 2y	[redacted]	-	[redacted]
2+3b: 70% of patients in remission assumed cured at 2y	[redacted]	-	[redacted]
2+4a: 90% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]
2+4b: 80% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]
2+4c: 70% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]

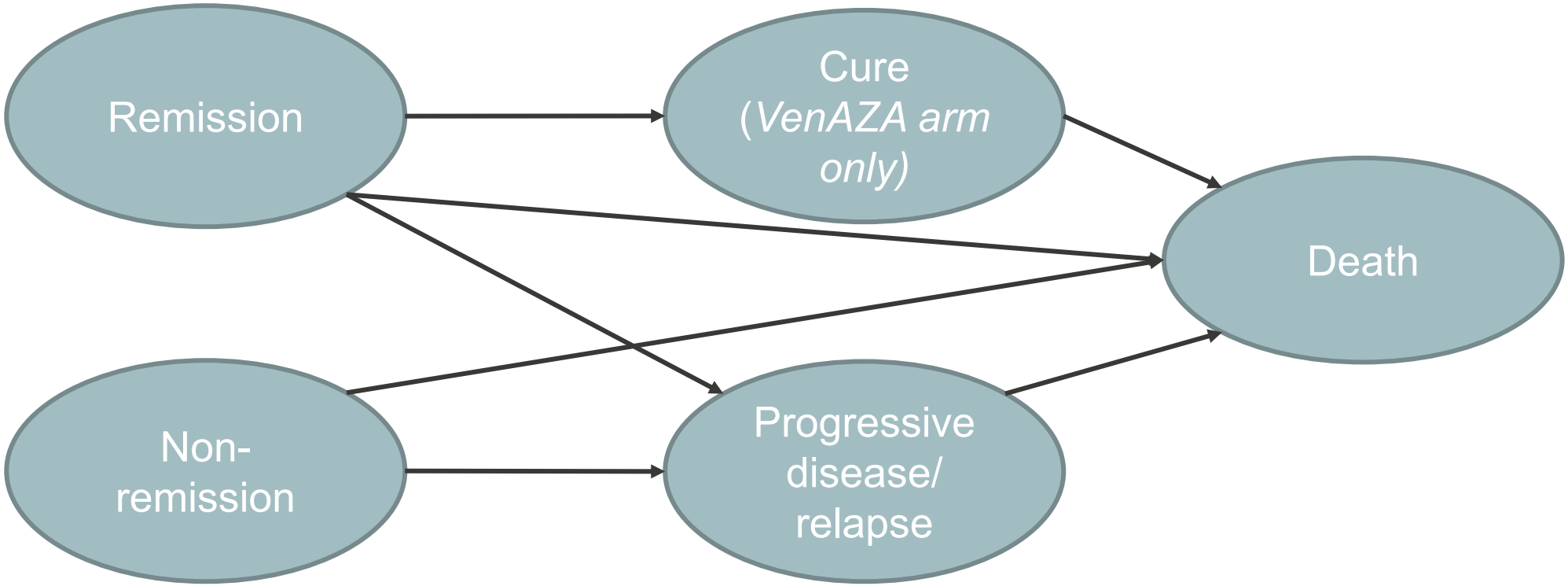
Proportions cured in scenario analyses
>30% blasts subgroup

Scenario	Patients in remission at 2 years	Patients in remission at 3 years	Percentage of overall cohort entering cure state
2+3a: 80% of patients in remission assumed cured at 2y	[redacted]	-	[redacted]
2+3b: 70% of patients in remission assumed cured at 2y	[redacted]	-	[redacted]
2+4a: 90% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]
2+4b: 80% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]
2+4c: 70% of patients in remission assumed cured at 3y	-	[redacted]	[redacted]

Additional slides

Recap from ACM1

Company model structure



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Proportions cured in the company's model

Intervention	Proportion of overall cohort receiving VenAZA	Year in model			
		2	3	4	5
20-30% blasts					
Previous company base case (2-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In complete remission (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case (3-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In complete remission (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
>30% blasts					
Previous company base case (2-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In complete remission (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case (3-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In complete remission (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Mixture cure modelling extrapolations

20-30% blasts, remission to relapse transition

– Gompertz model considered only clinically plausible extrapolation by clinical experts

Distribution	Cure rate
Exponential	[redacted]
Weibull	[redacted]
Log Normal	[redacted]
Log Logistic	[redacted]
Gompertz	[redacted]
Generalized Gamma	[redacted]

Mixture cure modelling extrapolations

20-30% blasts, remission to death transition

Distribution	Cure rate
Exponential	[redacted]
Weibull	[redacted]
Log Normal	[redacted]
Log Logistic	[redacted]
Gompertz	[redacted]
Generalized Gamma	[redacted]

Mixture cure modelling extrapolations

>30% blasts, remission to relapse transition

Distribution	Cure rate
Exponential	[redacted]
Weibull	[redacted]
Log Normal	[redacted]
Log Logistic	[redacted]
Gompertz	[redacted]
Generalized Gamma	[redacted]

Mixture cure modelling extrapolations

>30% blasts, remission to death transition

Distribution	Cure rate
Exponential	[redacted]
Weibull	[redacted]
Log Normal	[redacted]
Log Logistic	[redacted]
Gompertz	[redacted]
Generalized Gamma	[redacted]