NICE National Institute for Health and Care Excellence

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

Lead team presentation

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Company: AbbVie

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Acute myeloid leukaemia

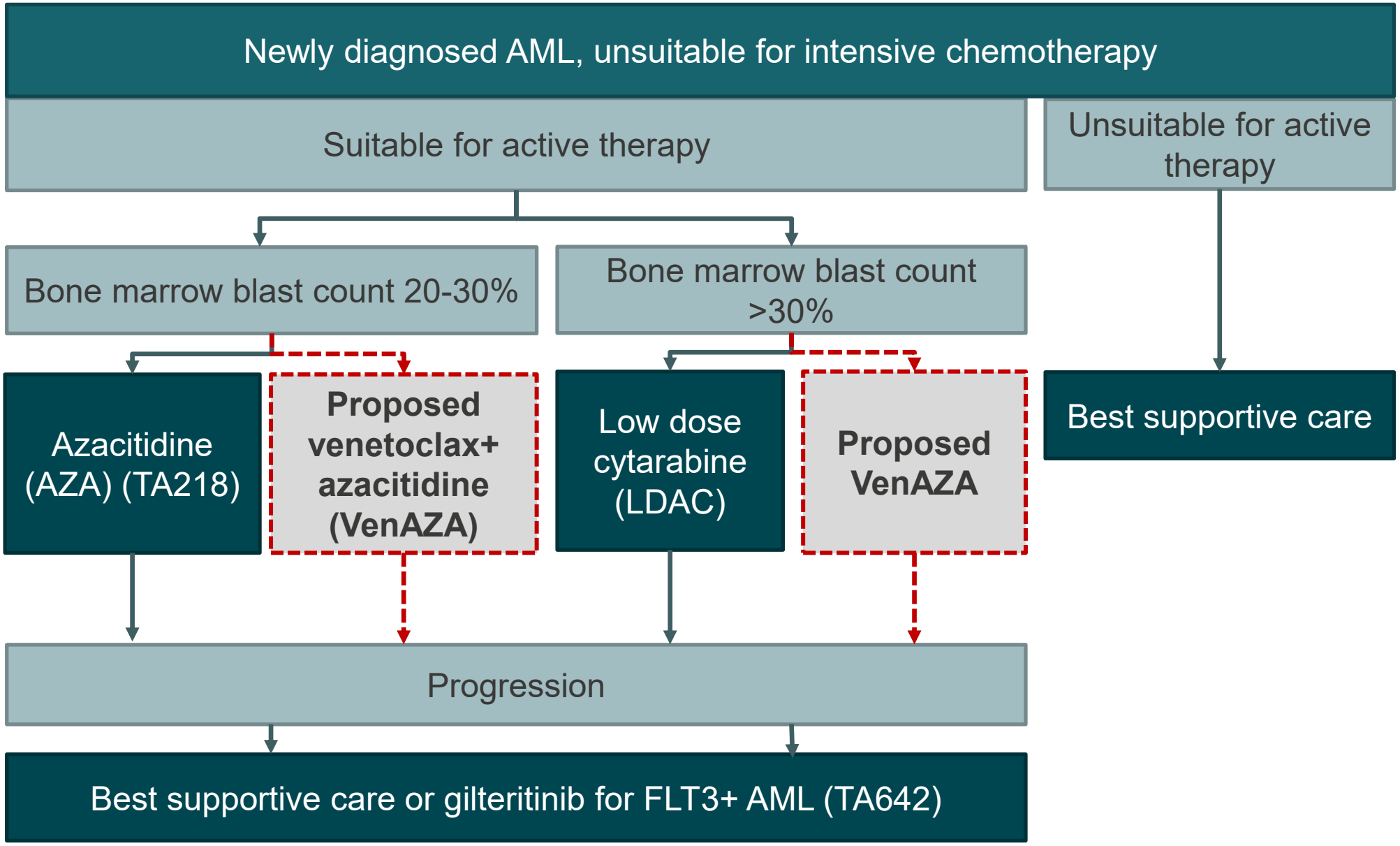
- Aggressive, rapidly progressing blood cancer characterised by abnormal myeloblasts multiplying and disrupting growth and function of healthy cells
- Symptoms include fatigue, feeling weak or breathless, memory loss or loss of concentration, bleeding and bruising, itchy skin, nausea or vomiting, sleeping problems, infections, bone or joint pain, weight loss and muscle pain
  - 54% of people are diagnosed after emergency presentation
- Acute myeloid leukaemia (AML) has a poor survival outcome
  - overall five-year relative survival rate of 15% in England, and 6% in patients aged 65 and older
- 2,895 new cases in England and Wales in 2017
- Treatment goals:
  - eligibility for intensive chemotherapy reflects guidelines, fitness status, age and presence of comorbidities
  - unmet need for treatment to extend life or improve quality of life for the 40% of people who have AML and for whom intensive chemotherapy is unsuitable

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

Treatment pathway



Acknowledgements

We're grateful to everybody who has participated in this process from the scoping events onwards.

We thank the experts and organisations for their time, experience, expertise and resources in preparing for this meeting, their submissions and testimonies and those who are participating today.

- Patient organisation – Leukaemia Care
- Professional organisations – Royal College of Pathologists, Royal College of Physicians-Association of Cancer Physicians-National Cancer Research Institute
- Clinical experts
- Patient expert

Perspectives on living with AML

AML has a significant impact on the quality of life of patients, their families and informal carers

- symptoms and activities of everyday life
- psychological, social and economic impact is considerable

Advantages and disadvantages of proposed treatment options

- balance of gains and toxicity
- self-management of side-effects
- possibility of remission
- quality of life

"impact of [this] disease…ripples through your immediate family and…your network of friends…"

"The [distance] made it complicated…to visit [me]"

"daily panic attacks…"

"If you have responsibilities such as looking after…children or grandchildren then it is possible whilst on venetoclax. This is priceless [for] any parent or grandparent…"

"alleviates the burden on your loved ones"

Professional perspectives

Unmet need for improved options

- current guidance predates publication of relevant studies

VenAZA non-intensive treatment

- may facilitate or restore good performance status contributing to:
  - additional options
  - gains relative to toxicity
  - improved quality of life

Cure assumption

- immature data

"AML is predominantly a disease of older patients…Current therapies are inadequate and patients are poorly served by them…[Patients who do not] achieve CR/CRi…have high demand of in-patient care…"

"the overall time…functioning independently and away from hospital is also crucial"

"licensed dose is excessive"

"the cure assumption is plausible, however this needs to be assessed in a prospective study."

Clinical evidence

	VIALE-A (N=431)	VIALE-C (N=211)
Population	Newly diagnosed, untreated adults with AML, not eligible for intensive chemotherapy due to age or comorbidities	
Intervention	VEN (400 mg once daily) + AZA (75 mg/m2 on days 1–7 of each 28-day cycle)	VEN (600 mg once daily) + LDAC (20 mg/m^2 on days 1–10 of each 28-day cycle)
Comparator	Placebo + AZA	Placebo + LDAC
Primary outcomes	OS, CR + CR with incomplete haematological recovery (CRi), EFS, adverse effects, health-related quality of life	
Secondary outcomes	Blood transfusion dependence Duration of response	

Abbreviations: VEN venetoclax, AZA azacitidine, LDAC low dose cytarabine, CR complete remission, OS overall survival, EFS, event-free survival

- Results used in the model are based on post-hoc subgroups of these trials, split by blast count, to provide results for relevant comparators in UK clinical practice.
- Data from LDAC arm in VIALE-C used in indirect comparisons.

Baseline characteristics

Overall population

Characteristic	VIALE-A		VIALE-C	
	VenAZA (n=286)	AZA (n=145)	VenLDAC (n=143)	LDAC (n=68)
Age, mean (range) SD, years	75.6 (49.0–91.0) 6.1	75.1 (60.0–90.0) 5.7	75.1 (36.0–93.0) 8.1	74.3 (41.0–88.0) 8.6
Sex, n (%) (Male/Female)	172 (60.1) / 114 (39.9)	87 (60.0) / 58 (40.0)	78 (54.5) / 65 (45.5)	39 (57.4) / 29 (42.6)
ECOG performance status score, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow blast count, n (%)				
<30%	85 (29.7)	41 (28.3)	[redacted]	[redacted]
≥30 to <50%	61 (21.3)	33 (22.8)	[redacted]	[redacted]
≥50%	140 (49.0)	71 (49.0)	[redacted]	[redacted]

- ERG considered baseline characteristics were balanced between treatment groups in both trials, and across the 2 trials.
- ERG's clinical expert was not concerned with any of the differences between arms.

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Clinical trial results
Overall population

- VIALE-C: No statistically significant OS difference at planned primary analysis date (Feb 19)
  - company states this was due to greater censoring in VenLDAC arm than LDAC arm as more patients in VenLDAC arm had not yet reached median OS (enrolment was still ongoing 3.4 months before planned analysis).
- Table below shows updated (unplanned) analysis with 6 months more follow up.
  - In the original analysis of VIALE-C, OS HR was 0.75 (p=0.11)

	VIALE-A (Jan 2020 datacut)		VIALE-C (later datacut, Aug 2019)	
	VenAZA	AZA	VenLDAC	LDAC
n	286	145	143	68
Median OS	14.7 months	9.6 months	8.4 months	4.1 months
OS HR	0.66 (p<0.001)		0.70 (p=0.041)	
Median event-free survival	9.8 months	7.0 months	[redacted]	[redacted]
EFS HR	0.63 (p<0.001)		[redacted]	

Clinical trial results

Subgroup populations

Trial population split into subgroups (20-30% blasts and >30% blasts) to compare against the relevant comparators

- VIALE trials not powered to identify clinical benefit in these subgroups
- Further splitting of data to inform transition probabilities in the economic model results in some further uncertainty.

	VIALE-A (Jan 2020 datacut) 20 – 30% blasts		VIALE-C (later datacut, August 2019) > 30% blasts	
	VenAZA	AZA	VenLDAC	LDAC
n	78	36	108	52
Median OS	[redacted]	[redacted]	[redacted]	[redacted]
OS HR	[redacted]		[redacted]	
Event-free survival	[redacted]	[redacted]	[redacted]	[redacted]
EFS HR	[redacted]		[redacted]	

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)

Median OS:
VenAZA [redacted] months
AZA [redacted] months
Hazard ratio: [redacted]

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)

Median OS:
VenLDAC [redacted] months
LDAC [redacted] months
Hazard ratio: [redacted]

Comparing VenAZA with LDAC, >30% blasts

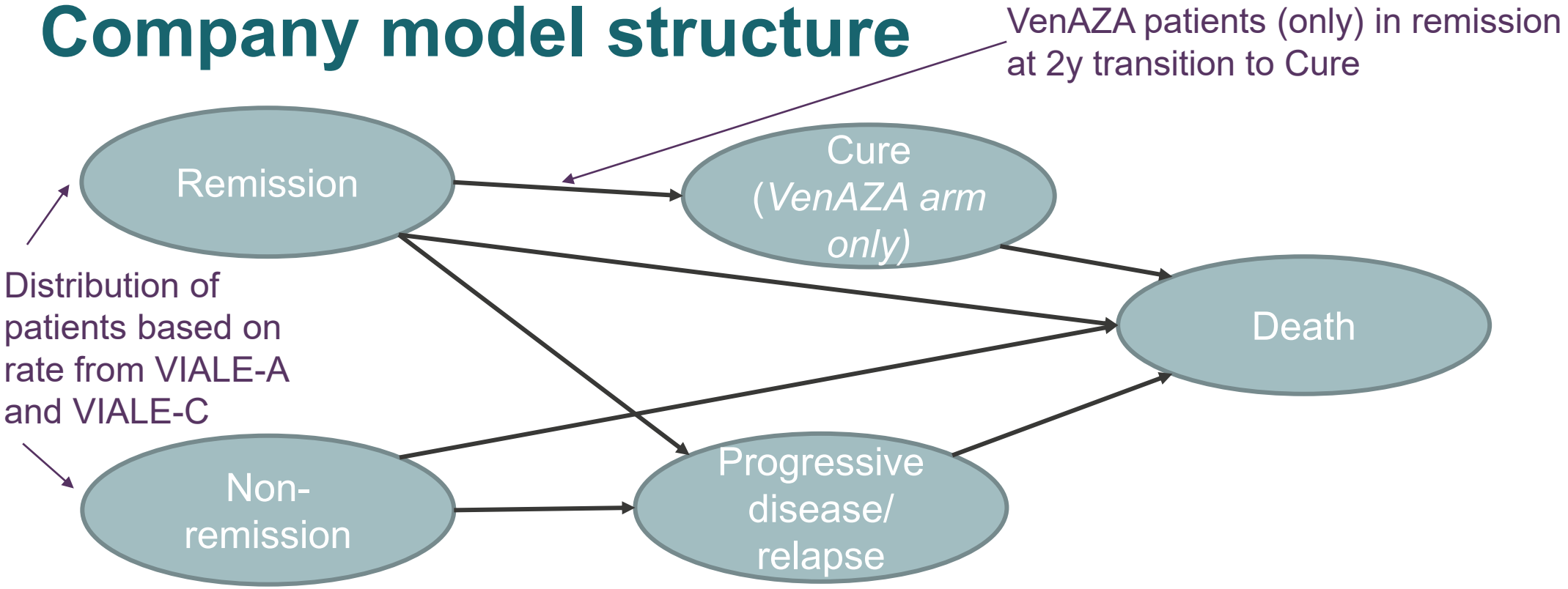
Kaplan–Meier plot of OS in the >30% blast subgroup: VenAZA data from VIALE-A (N=206), LDAC data from VIALE-C (N=36): Unadjusted post-hoc analysis

Median OS:
VenAZA [redacted] months
LDAC [redacted] months

- 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]

Company model structure



- Cohort Markov state transition model
- 28-day cycle length
- Lifetime horizon of 40 years (starting age 75.2y), 3.5%pa discounting
- All (five) transitions derived from parametric survival functions independently fitted to data from VIALE-A/C (censored for competing events), except remission to cure
- Time to treatment discontinuation modelled (using parametric survival functions) independently of health state transitions
- Mortality adjustment included for transitions (removed after technical engagement)
- Cure state mortality: same general population (after TE, SMR of 1.2 applied)

Company's extrapolation of time-to-event data

	Relapse	Survival	Treatment discontinuation
20-30% blasts			
VenAZA	Lognormal	Gen gamma	Lognormal
AZA	Weibull	Lognormal	Lognormal
>30% blasts			
VenAZA	Gen gamma	Log-logistic	Lognormal
LDAC	Exponential	Exponential	Lognormal

ERG

- Difficult to validate individual time-to-event curves as small amount of observed data to base on, and censoring for competing events (e.g. death) reduces numbers
- Overall model output provides good fit to observed trial data but extrapolations remain uncertain
- ERG presented scenario analyses using alternative time to relapse from remission extrapolations (see later slides) but other extrapolations unchanged

Company model inputs

Health-related quality of life
Pooled EQ-5D data from both VIALE trials
Adjusted to account for impact of adverse events
Treatment-independent utility values estimated for remission, non-remission and progressive disease/relapse health states
Utility decrements for AEs taken from separate study
Cure state: assumed same utility value as general population

Health State	Utility value
Remission	[redacted]
Non-remission	[redacted]
PD/relapse	[redacted]
Cure	[redacted]

Resource use/cost	Source
Treatment costs	NHS National Tariff
Health states: remission, non-remission and progressed/relapse	Adapted from TA642
Health state: cure	Same as remission
End of life	Georghio & Bardsley 2014
Adverse events	NHS costs/TA451

ERG considers it is appropriate to use the health state costs from TA642 in the model as clinical advice indicates they will provide a reasonable proxy for the resource use of patients having venetoclax in clinical practice.

Issues resolved after technical engagement (1)

	Summary	Impact	Stakeholder responses	In updated base case?
2	Company applied a general population mortality adjustment to all parametric survival curves informing transition probabilities in the model, including transitions to progression/relapse state.		Company removed this adjustment from transition to progression/relapse state.	Company ✓ ERG ✓
3	Modelling of time-to-treatment discontinuation led to implausible effects in the model regarding treatment with venetoclax after 2 years.		Company updated model to address these concerns. ERG considers updated model acceptable. Supported by experts at engagement.	Company ✓ ERG ✓
6	No drug wastage applied to venetoclax prescribed but not used due to treatment discontinuation or death during a cycle.		Experts and professional groups suggested 7 days' wastage would be reasonable to include. Company updated base case to include 7 days' wastage - consistent with the adjustment applied in TA642 (gilteritinib).	Company ✓ ERG ✓

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Key: Small impact | Impact unknown | Model driver

Issues resolved after technical engagement (2)

	Summary	Impact	Stakeholder responses	In updated base case?
4a	Adverse event data sourced from separate study to VIALE trials.	Likely small	ERG preferred to see observed data from trials used in model. However, impact of AEs unlikely to be model driver so ERG accepts company approach.	Company ✓ ERG ✓
4b	Treatment-independent utility values from pooled VIALE A/C in model. ERG concerned that the pooled values (used in model) were not from trial data split by blast count.		Company analysis showed no sig. differences in health state utility values by treatment arm. ERG agrees this analysis seems to support treatment-independent health state utility values. Pooling likely conservative.	Company ✓ ERG ✓

Company analysis after TE of utility values (EQ-5D) by health state in each trial

VIALE-A	VenAZA	AZA	p-value
Remission	[redacted]	[redacted]	0.857
Non-remission	[redacted]	[redacted]	0.741
PD/relapse	[redacted]	[redacted]	0.198
VIALE-C	VenLDAC	LDAC	p-value
Remission	[redacted]	[redacted]	0.954
Non-remission	[redacted]	[redacted]	0.324
PD/relapse	[redacted]	[redacted]	0.067

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Unresolved issues post-engagement

Issue	Impact	Question for committee
1. Cure assumption		• Is including a cure point plausible? If so, at how many years after remission? • If cure state removed, what extrapolation should be used for time-to-relapse curve?
6. Subsequent treatment distribution		• Is the company's updated proportion of people having subsequent gilteritinib appropriate? • Should stem cell transplant be included in model?
7. Dose of venetoclax		• What dose of venetoclax should be considered for the cost-effectiveness results?
Other considerations		• Are the end-of-life criteria met? • Is venetoclax innovative? • Are there any equality considerations?

Issue 1: Cure assumption (1)

Company model

- Patients on venetoclax and alive at 2 years in 'remission' state are assumed cured
- In cure state, patients have same mortality risk and quality of life as general pop.
- Company argue VenAZA has an innovative mechanism of action which is able to drive sustained deep remission
- Company cite clinical advice that rate of relapse after 2 years is low and plateau in KM curve at 24 months for VenAZA

ERG comments

- Lack of long-term data to validate cure assumption – max. follow up:
  - VIALE-A 2.56 years
  - VIALE-C [redacted] years
- Historically, non-intensive treatments have not been curative in this population
- Apparent plateauing of Kaplan-Meier curves for OS and EFS based on small numbers

Responses at technical engagement

- Some evidence for prolonged remission off therapy
- Rates and depths of responses seen with venetoclax comparable to conventional intensive chemotherapy, where cure is seen in a proportion of patients
- Cure seems plausible from clinical experience, perhaps at 2 or 3 years
- Patients may not initially be eligible for stem cell transplant, but after treatment become fitter and therefore eligible. Around 25% may become eligible (as in gilteritinib trial). Not currently modelled.

Issue 1: Cure assumption (2)

Company engagement response

- Complete remission rates for VenAZA similar to those seen in patients over 60 receiving treatment with intensive chemotherapy (40-60%)
- Minimal residual disease negativity is a strong prognostic indicator for overall survival and risk of relapse
- Evidence from VIALE-A suggests sustained deep remission leading to longer duration of response, event-free survival and overall survival

VIALE-A Results	VenAZA	AZA	P value
Complete remission (CR + CRi)	66.4%	28.3%	<0.001
Sustained deep remission (minimal residual disease <0.001 and CR + CRi)	23.4%	7.6%	[redacted]

Mortality rate for patients in long-term remission

- Company's updated base case includes standardised mortality ratio of 1.2 for patients in cure health state, based on clinical expert opinion

Company's original submission included scenario analyses exploring cure points at 2.5 and 3 years. This increased the ICERs by £9k and £20k for VenAZA vs AZA and by £8k and £16k for VenAZA vs LDAC.

Issue 1: Cure assumption (3)

ERG comments

- Cure may be plausible but remains uncertain as trial data not mature enough
- Very few patients in VIALE-A had a stem cell transplant, and none in VIALE-C, so excluding transplant costs unlikely to affect cost-effectiveness results
- Small study (Chyn Chua et al., N=25) suggests treatment with venetoclax can be stopped for patients in remission at 2 years without negative impact on outcomes
  - However, in this study a number of relapses occurred after 2 years

Chyn Chua et al.	Stopped venetoclax treatment in first remission	Continued treatment until disease progression
Median treatment-free remission	45.8 months	-
Relapsed	5/13	8/12
Relapse timing	2/5 occurred after 36 mths of treatment-free remission	5/8 occurred after >24 months of therapy

- ERG scenarios remove cure state and explore alternative time-to-relapse curves
  - Using these extrapolated curves, a proportion will never relapse

Is including a cure point plausible? If so, at how many years after remission?

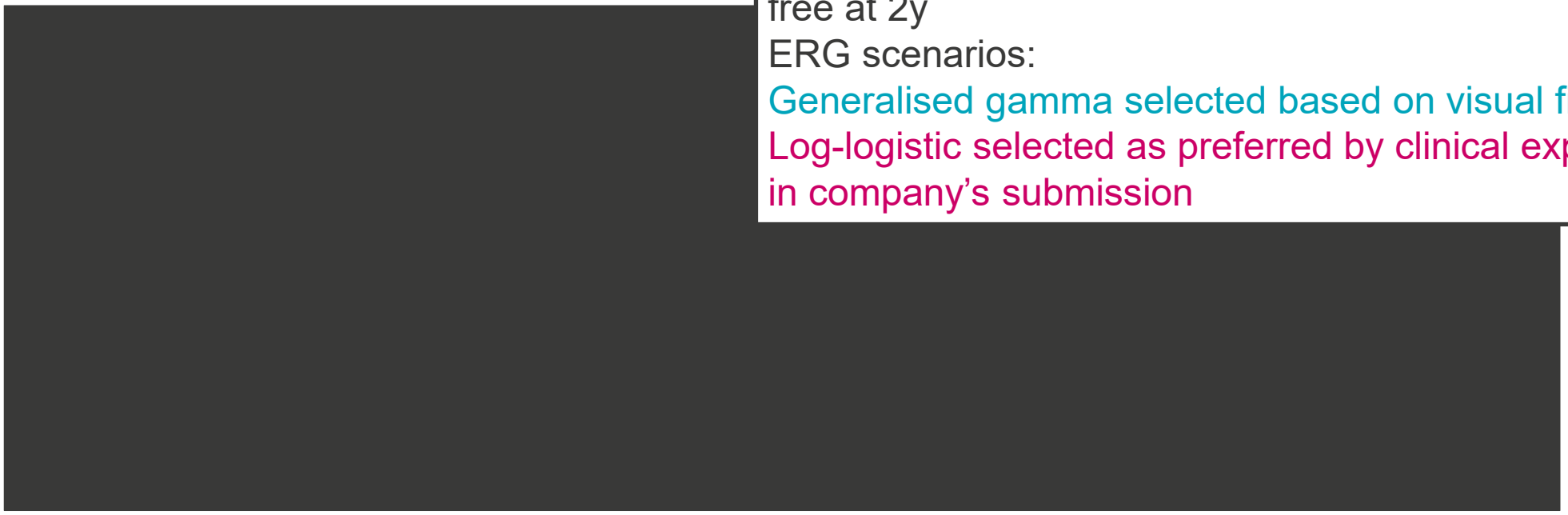
If cure state removed, what extrapolation should be used for time-to-relapse curve?

Time-to-relapse extrapolations (1)

VenAZA (20-30% blasts)

- ERG's scenarios assess removing the cure assumption combined with alternative extrapolations for time from remission to relapse

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



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

Comparison with TA642

	Gilteritinib TA642*	Venetoclax ID1564
Population	People with relapsed/ refractory FLT3-positive AML	People with AML that is unsuitable for intensive chemotherapy
Proportion having stem cell transplant in trial	Gilteritinib arm: 25.5% Salvage chemo arm: 15.3%	VIALE-A: VenAZA arm: [redacted] AZA arm: [redacted] VIALE-C: [redacted]
**In TA642, cure assumptions reflected all patients alive at two years, regardless of transplant status and whether in remission or not*		

Issue 6: Subsequent treatment distribution

Company model
- 3% have gilteritinib after VenAZA
- All others have hydroxycarbamide

ERG comments
- Clinical advice was that a similar proportion would be expected to have subsequent gilteritinib in all arms, and this would be higher than 3%
- Scenario where 15% in all arms receive gilteritinib

Technical engagement responses – experts and professional groups
- Estimate 10% in all treatment arms have FLT3 disease and eligible for gilteritinib
- Patients may be fitter after venetoclax so eligibility for treatment changes
- A small subset of patients may be eligible for stem cell transplant ([redacted] and [redacted] in each arm of VIALE-A and VIALE-C respectively had stem cell transplant)

Company:
- Clinical advice suggests ERG's estimate of 15% of people eligible for treatment with gilteritinib in this population is to high, and that more would be eligible after venetoclax than after AZA or LDAC

Company's updated base case
- Includes 5% in VenAZA arm and 3% in AZA or LDAC arms having subsequent gilteritinib. 15%/10% tested in sensitivity analysis: small impact on ICER
  - ERG's clinical advice suggests company's update is appropriate

Are company's updated proportions having subsequent gilteritinib appropriate? Should stem cell transplant be included in model?

Issue 7: Dose of venetoclax

Company model

- Daily dose of venetoclax after treatment initiation is 400 mg
- Dosing regimen and dose intensity based on VIALE-A except relative dose intensity of 50% applied to VenAZA (expert opinion that [redacted] in trial was higher than expected)

Technical engagement responses

- In clinical practice, all patients have concomitant azoles (CYP3A inhibitors), which increases venetoclax exposure
- Unpublished data suggests dose and duration reductions reduce toxicity and do not impact on response rates and duration
- Therefore doses of venetoclax are reduced to 100mg and duration reduced to 21, 14 or even 7 days per 28 day cycle to limit toxicity

SmPC: venetoclax dose modifications for use with CYP3A inhibitors

Strong inhibitor	Initiation and dose-titration	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less
	Steady daily dose	100 mg or less (or reduce by at least 75% if already modified for other reasons)
Moderate inhibitor	Reduce dose by at least 50%	

ERG comments

- ERG has provided scenarios based on clinical opinions:
  - 50% dose intensity (company base case)
  - 25% dose intensity
  - 12.5% dose intensity

What dose of venetoclax should be considered for the cost-effectiveness results?

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

Are the end-of-life criteria met?

Cost-effectiveness results (1)

VenAZA v. AZA (20-30% blasts)

ERG scenarios 1-2c. all include alternative costs accounting for long-stay admissions for adverse events. **Results do not include confidential PAS for gilteritinib – these will be shown in part 2.**

Scenario	ICER (£/QALY)		
	Licensed dose of venetoclax, 50% dose intensity	Licensed dose of venetoclax, 25% dose intensity	Licensed dose of venetoclax, 12.5% dose intensity
Company base case	**£24,824**	**-**	**-**
Company base case - ERG corrected subsequent treatment costs	**£24,596 Probabilistic: £24,378**	**£16,747**	**£13,017**
1. ERG: AE costs updated	£25,074	£17,225	£13,496
1+2a. Removing VenAZA cure assumption (lognormal time-to-relapse)	£67,404	£54,911	£48,976
1+2b. Removing VenAZA cure assumption + log-logistic time-to-relapse	£68,011	£55,424	£49,444
1+2c. Removing VenAZA cure assumption + generalised gamma time-to-relapse	£78,626	£64,586	£57,923

Cost-effectiveness results (2)

VenAZA v. LDAC (>30% blasts)

Scenario	ICER (£/QALY)		
	Licensed dose of venetoclax, 50% dose intensity	Licensed dose of venetoclax, 25% dose intensity	Licensed dose of venetoclax, 12.5% dose intensity
Company base case	**£41,481**	**-**	**-**
Company base case - ERG corrected subsequent treatment cost	**£41,361** **Probabilistic: £40,872**	**£34,975**	**£31,946**
1. ERG: AE costs updated	£41,557	£35,171	£32,142
1+2a. Removing VenAZA cure assumption (generalised gamma time-to-relapse)	£63,919	£55,069	£50,871
1+2b. Removing VenAZA cure assumption + lognormal time-to-relapse	£88,588	£77,032	£71,556

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Issue 6: Subsequent treatment distribution

Company scenario analyses

- Company explored following scenarios for proportion of patients having subsequent gilteritinib:

	VenAZA	AZA/LDAC
Original company base case	3%	0%
Scenario 1	5%	3%
Scenario 2	15%	10%

- Results below based on **original pre-TE company base case**, with error corrections (not post-TE base case presented in previous slides, which includes other adjustments, including scenario 1)

Cost-effectiveness results	20-30% blasts	>30% blasts
	VenAZA vs. AZA	VenAZA vs. LDAC
Original company base case	£16,638	£33,858
Scenario 1	£16,234	£33,023
Scenario 2	£21,905	£32,920

Innovation

- Company and professional groups believe venetoclax is innovative:
  - Targeted therapy, different to currently available therapies
  - Increased overall survival
  - Increased rates of complete remission
  - Less need for blood transfusions

- Additionally, VenAZA combination offers:
  - Increased rates of deep remissions
  - Longer time to deterioration of quality of life

Is venetoclax innovative?
Are there any benefits not captured in the QALY calculations?

Equality considerations

Age

- venetoclax could provide effective treatment options for older people who have not benefitted from other recent advances in treatment

Access to treatment options

- anyone who lives a long way from a major hospital who can't make it into a hospital easily may particularly benefit from venetoclax

Are there any equality considerations?

Unresolved issues post-engagement

Issue	Impact	Question for committee
1. Cure assumption		• Is including a cure point plausible? If so, at how many years after remission? • If cure state removed, what extrapolation should be used for time-to-relapse curve?
6. Subsequent treatment distribution		• Is the company's updated proportion of people having subsequent gilteritinib appropriate? • Should stem cell transplant be included in model?
7. Dose of venetoclax		• What dose of venetoclax should be considered for the cost-effectiveness results?
Other considerations		• Are the end-of-life criteria met? • Is venetoclax innovative? • Are there any equality considerations?