Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia ID6198

PART 1 slides for zoom

Technology appraisal committee C 6 February 2024

Chair: Richard Nicholas

Lead team: Arpit Srivastava, Ugochi Nwulu, Kate Ren

External assessment group: PenTAG

Technical team: Emilene Coventry, Victoria Kelly, Ian Watson

Company: Servier Laboratories

Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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IDH1-positive acute myeloid leukaemia

- Cancer of the blood and bone marrow
- Symptoms include anaemia, bleeding problems and serious infections
- Aim of treatment is cure; can include:
  - intensive induction chemotherapy to achieve remission
  - then consolidation chemotherapy, maintenance therapy, stem cell transplant
- **But** more than 50% ineligible for intensive chemotherapy and stem cell transplants (because of age, comorbidities)
- Around 3,100 new diagnoses of AML in the UK every year; incidence highest in age 85 to 89
- Poor survival: 5-year survival rate 15%
- 6% to 10% have isocitrate dehydrogenase-1 (IDH1) mutation

Patient perspectives

Unmet need in people with acute myeloid leukaemia (AML) who cannot tolerate chemotherapy

Submission from Leukaemia Care

- Unmet need for targeted treatment options for people with AML for whom chemotherapy is unsuitable
- Chemotherapy is an intensive treatment with severe side effects (for example rashes, high fevers, sepsis, erythema nodosum, lung fungal infections, vomiting, “excruciating” inflammation of the small intestine)
- Some people with AML cannot have tolerate such an intensive treatment; often but not always older people with AML who may be frailer
- Ivosidenib with azacitidine has better event-free and overall survival, and likelihood of complete remission than azacitidine alone
- Fewer side effects than azacitidine alone and some can be managed by healthcare professionals
- Oral treatment, which is convenient for people with AML

The illness and treatment alone had a significant effect on my physical health… However, I found the emotional impact of AML more significant and traumatic than the physical aspect

Existing treatments focus mainly on chemotherapy and stem cell transplant but there needs to be options if chemotherapy is not suitable

Clinical perspectives

Personalised medicine approach to treating acute myeloid leukaemia (AML)

Submission from Royal College of Pathologists

- Main aims of treatment: remission, prolong overall survival, reduce risk of relapse
- Clinically significant response is morphologic remission in bone marrow with normalisation or improvement of blood counts
- Unmet need: people with AML who cannot have intensive chemotherapy have a poor prognosis; will usually die from disease even with current standard treatment (venetoclax and azacitidine)
- Availability of targeted therapy may drive earlier testing for isocitrate dehydrogenase-1 (IDH1) mutations via new separate test
- Could mean less time in hospital because ivosidenib oral treatment
- Not clear that substantial benefit over current standard care
- One of few options for personalised medicine approach to treating AML
- Tolerable with good safety profile; can be given as outpatient so quality of life benefit

Ivosidenib (Tibsovo, Servier Laboratories)

Marketing authorisation	MHRA approval granted July 2023 in combination with azacitidine for 'the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy'
Mechanism of action	Inhibits mutated IDH1 enzyme, which blocks cellular differentiation and promotes tumour growth
Administration	Oral; 500mg once daily (2 x 250mg tablets)
Price	• List price per pack: £12,500 • List price for 12 months of treatment: £150,000 • Simple discount PAS applies

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme

Key issues

Key issues	ICER impact
Exclusion of comparators (key issue 1)	**Unknown**
The company's literature searches (key issue 8)	**Unknown**
Treatment effectiveness of IVO+AZA vs VEN+AZA (key issue 2)	**Varies depending on scenario**
OS and EFS extrapolation (key issue 3a)	**Large**
'Cured' health state (key issue 3b)	**Large**
3-year stopping rule (key issue 4)	**Large***
Severity weighting	**Moderate**
Key issues with a small effect on the ICER: • 100% Relative dose intensity (key issue 5) • Modelled proportion in complete remission on VEN+AZA (key issue 6) • Hospitalisation days for VEN+AZA during treatment initiation (key issue 7)	**Small**

*Removing stopping rule has no effect on ICER if cure assumption remains (cure assumption means treatment stops at 3 years); only relevant if cure assumption also removed (then big impact on ICER)

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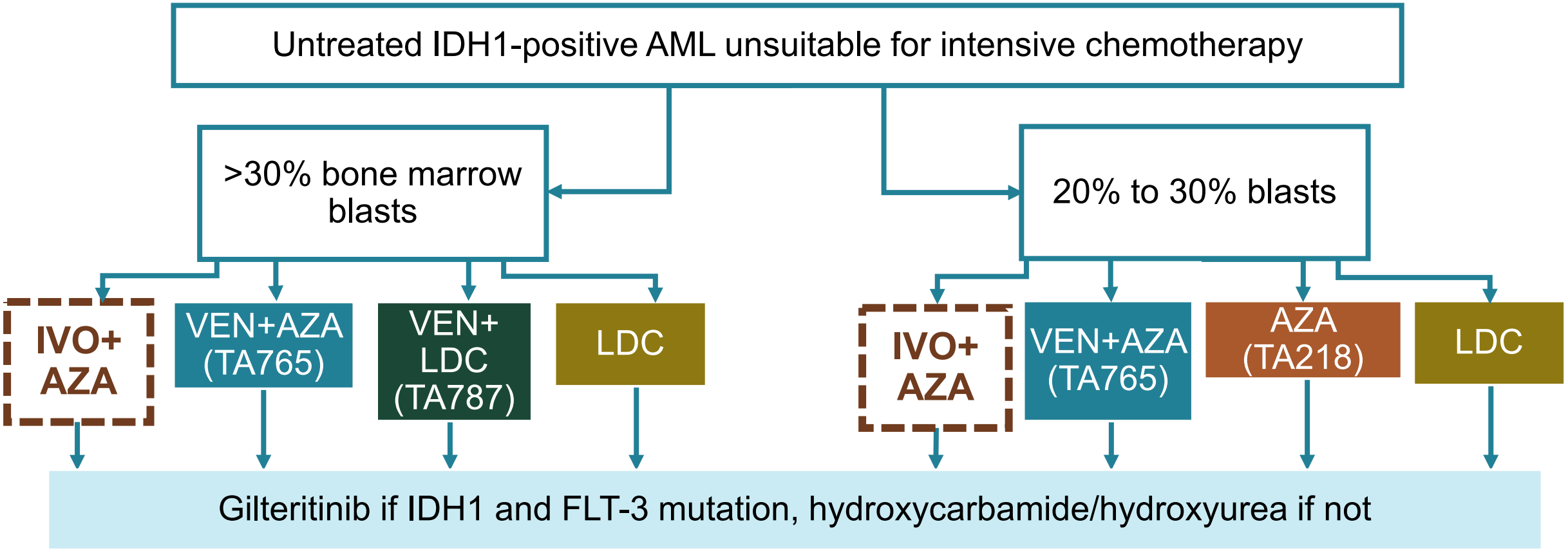
Abbreviations: AZA, azacitidine; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; OS, overall survival; VEN, venetoclax

Key issue: comparators (1/2)



What is current standard care in the NHS for people with untreated IDH1-positive AML who cannot have intensive chemotherapy?

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; FLT, FMS-like tyrosine kinase; IDH1, isocitrate dehydrogenase 1; IVO, ivosidenib; LDC, low-dose cytarabine; TA, technology appraisal; VEN, venetoclax

Key issue: comparators (2/2)

? impact on ICER

Company excluded 3 of 4 comparators in NICE scope

Background

Comparators in scope were:

- venetoclax with azacitidine
- venetoclax with low dose cytarabine (>30% bone marrow blasts)
- azacitidine (20% to 30% blasts)
- low-dose cytarabine

Company only included **venetoclax with azacitidine**

Decision on comparators affects which analysis is most appropriate:

- fully incremental analysis if multiple comparators appropriate for population
- pairwise comparison if relevant and justified (for example if only 1 comparator, or if specific displacement of individual comparator in a group/subgroup)

EAG comments

- Clinical experts say all scoped comparators can be used in UK
- Venetoclax with azacitidine only suitable for fitter people; other scoped comparators offered if cannot tolerate venetoclax
- NMA results for all the excluded comparators were available in company submission

Professional organisation submission

Current standard care is venetoclax with azacitidine

Company

- Since TA765 published, venetoclax with azacitidine supersedes azacitidine and low-dose cytarabine as standard care
- Population for venetoclax with low-dose cytarabine very small (only >30% blast levels and +NPM1 mutation)

What are the most appropriate comparators? Are there subgroups for whom 1 treatment is more suitable over another?

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Abbreviations: ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; NPM1, nucleophosmin; TA, technology appraisal

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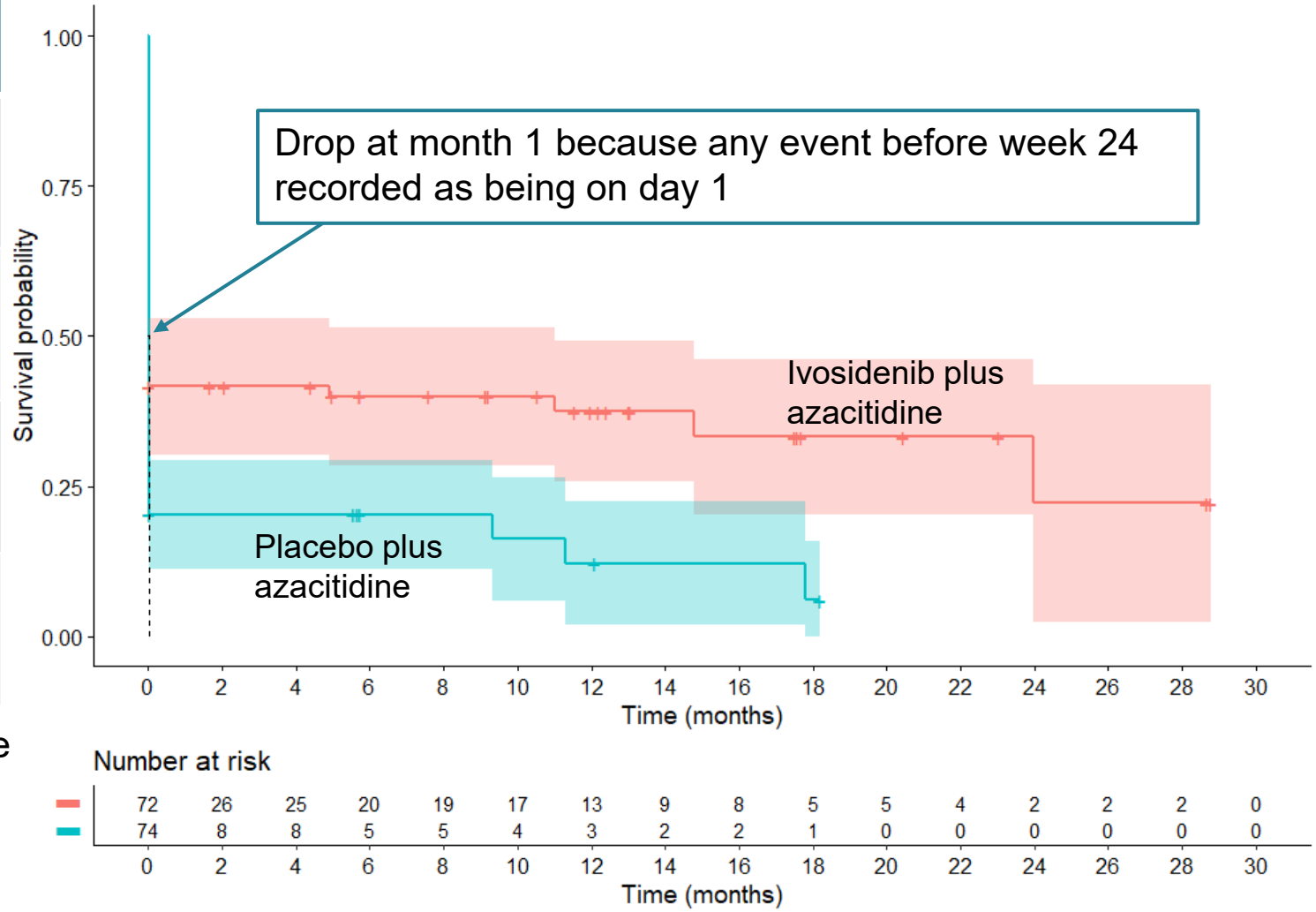
AGILE results: event-free survival

Significantly better EFS for ivosidenib plus azacitidine vs azacitidine alone (March 2021 data cut)

Outcome	IVO+AZA (n=72)	AZA+placebo (n=74)
HR (95% CI)	0.33 (0.16 to 0.69) p=0.0011	–
Median EFS (months [95% CI])*	0.03 (0.03 to 11.01)	0.03 (NE to NE)
EFS rate at 6 months (% [95% CI])	39.9 (28.6 to 51.0)	20.3 (12.0, 30.0)
EFS rate at 12 months (% [95% CI])	37.4 (25.9 to 48.9)	12.2 (4.3 to 24.4)

*Because > half patients in each group did not have complete remission by week 24 (because of EFS definition) median EFS same in 2 groups

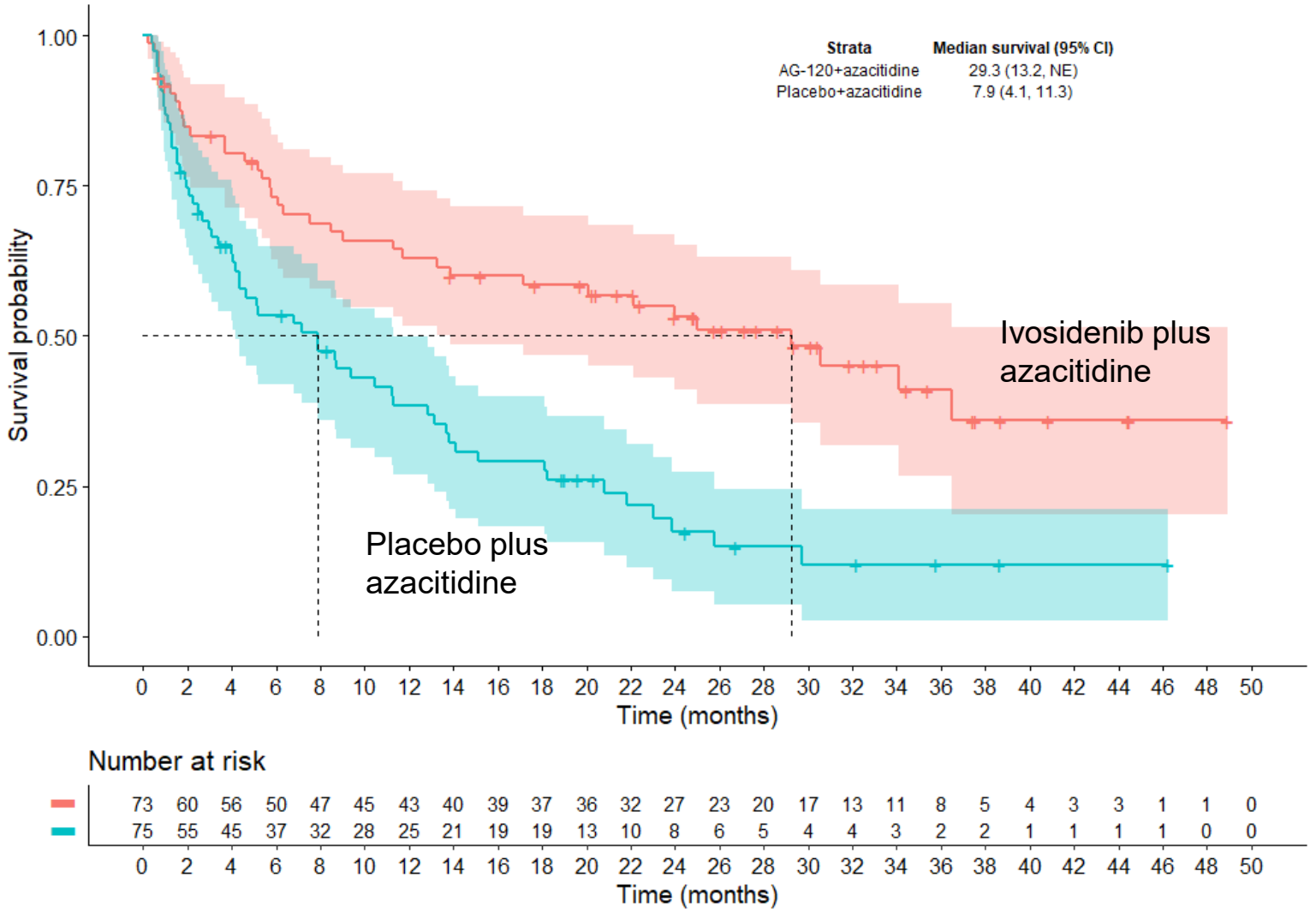


Abbreviations: AZA, azacitidine; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IVO, ivosidenib; NE, not estimable

AGILE results: overall survival

Significantly better overall survival for ivosidenib plus azacitidine than azacitidine (June 2022 data cut)

Outcome	IVO+AZA (n=72)	AZA+ placebo (n=74)
HR (95% CI)	0.42 (95% CI 0.27 to 0.65) p<0.0001	–
Median OS (months [95% CI])	29.3 (13.2 to NE)	7.9 (4.1 to 11.3)
KM survival rate at 6 months (% [95% CI])	73.1 (61.1 to 82.0)	53.5 (41.3 to 64.1)
KM survival rate at 12 months (% [95% CI])	62.9 (50.4 to 73.0)	38.3 (27.0 to 49.5)



Abbreviations: AZA, azacitidine; CI, confidence interval; OS, overall survival; HR, hazard ratio; IVO, ivosidenib; KM, Kaplan–Meier; NE, not estimable

Key issue: literature searches

? impact on ICER

EAG: searches narrowed in risky way

EAG comments

- Search strategies narrow population facet to include only articles that specifically mention: 'first line', 'treatment naive', 'untreated'
- Articles that do not include phrases in database record might have been missed and relevant evidence may not have been identified
- EAG search identified 1,336 additional documents that had not been screened that may be relevant

Company

- Population facet in line with target population
- Carefully constructed to exclude other/irrelevant indications (r/r AML, MDS)
- Balances sensitivity and specificity of the search
- Approach has been used in previous systematic literature reviews of clinical efficacy and safety submitted as part of NICE appraisals

Is the committee satisfied that the company's approach is likely to have identified all relevant evidence?

Abbreviations: AML, acute myeloid leukaemia; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MDS, myelodysplastic syndromes; r/r, relapsed/refractory

Network meta-analysis results

- No direct evidence for ivosidenib plus azacitidine compared with venetoclax plus azacitidine so company did an indirect treatment comparison
- All 3 outcomes: ivosidenib plus azacitidine favoured over venetoclax plus azacitidine but effect not statistically significant (fixed effects model)

Comparison	Low-dose cytarabine	Azacitidine	Venetoclax plus azacitidine	Venetoclax plus low-dose cytarabine
Ivosidenib plus azacitidine EFS (HR [95% CrI])	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib plus azacitidine OS (HR [95% CrI])	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib plus azacitidine CR/CRi (OR [95% CrI])	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CR, complete remission; CRi, CR with incomplete hematologic recovery; EFS, event-free survival; HR, hazard ratio; OS, overall survival

Key issue: treatment effect IVO+AZA vs VEN+AZA

Moderate impact on ICER

EAG considers company's NMA results uncertain

Company comments

- IVO+AZA improved OS and EFS compared with VEN+AZA
- NMA limited by lack of published data on IDH1+ AML; but IDH1 status not expected to be treatment effect modifier for venetoclax so considers NMA suitable to include in model

EAG comments

- Fixed effects (not random effects) models so CrIs do not properly express uncertainty
- Some violations of proportional hazards assumption
- Heterogeneity across studies in NMA; inconsistency could not be assessed – no closed loops
- NMAs reasonable standard but results uncertain, possibly more so than suggested by the CrIs
- IDH1 subgroup: no results in company submission; exploratory NMA effect estimate favoured VEN+AZA but not statistically significant
- IDH1 status potential effect modifier and source of bias; nearly 100% IDH1+ in AGILE but around 20% in other studies
- Scenario analyses to test uncertainty varying IVO+AZA.
  - OS HR by +/- 25%: EFS HR by +/- 25%
  - EFS and OS HRs using upper and lower bound CrIs – using lower bound OS HR ([redacted]) increased ICER by almost [redacted] per QALY gained

Does the committee agree with the company's assumption that ivosidenib plus azacitidine is more effective than venetoclax plus azacitidine?

Abbreviations: AZA, azacitidine; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; IDH1+, isocitrate dehydrogenase-1 positive; IVO, ivosidenib; NMA, network meta-analysis; OS, overall survival; VEN, venetoclax

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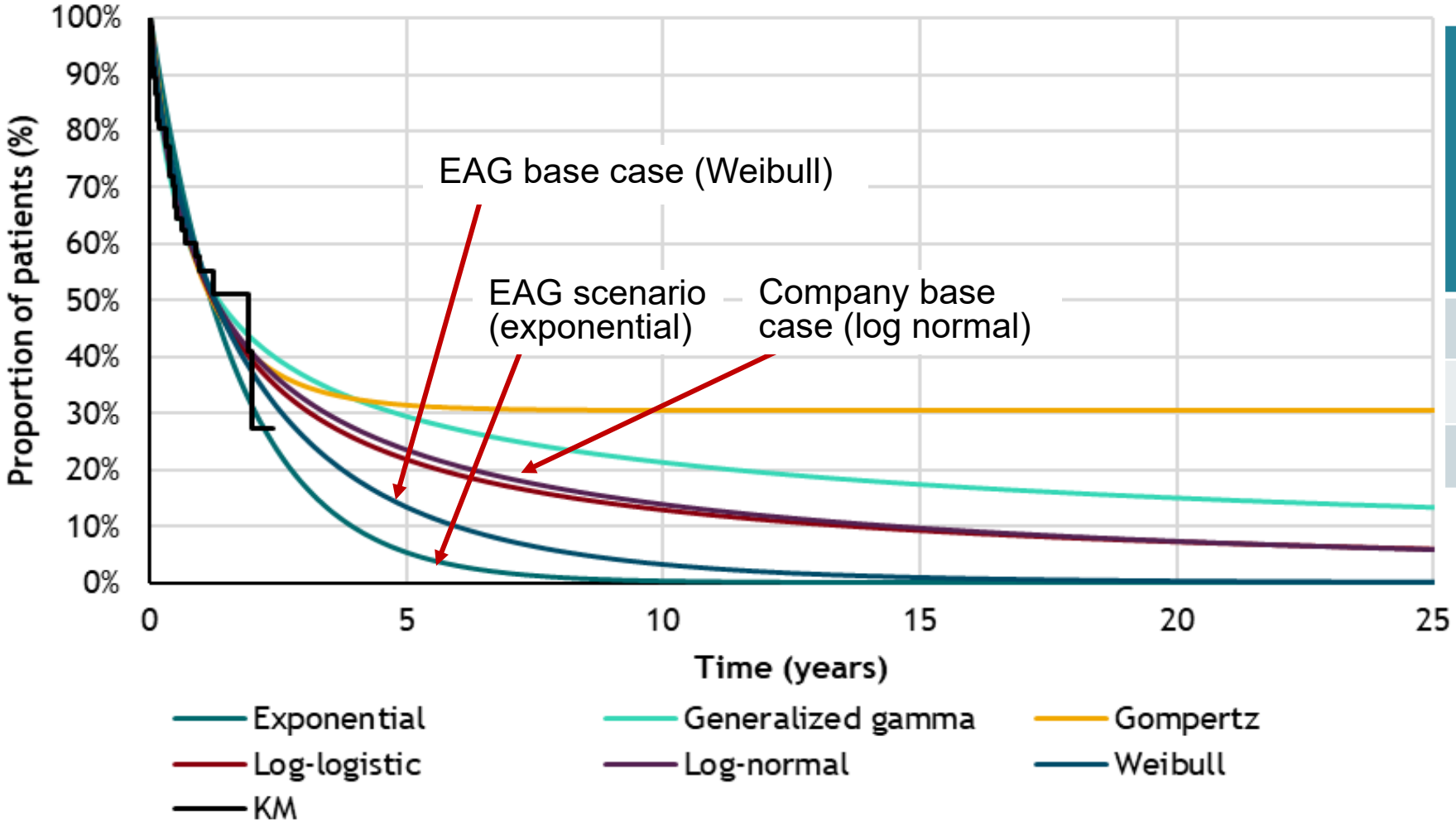
Key issue: OS and EFS extrapolation (1/3)

Big impact on ICER

Parametric models for EFS (ivosidenib plus azacitidine)



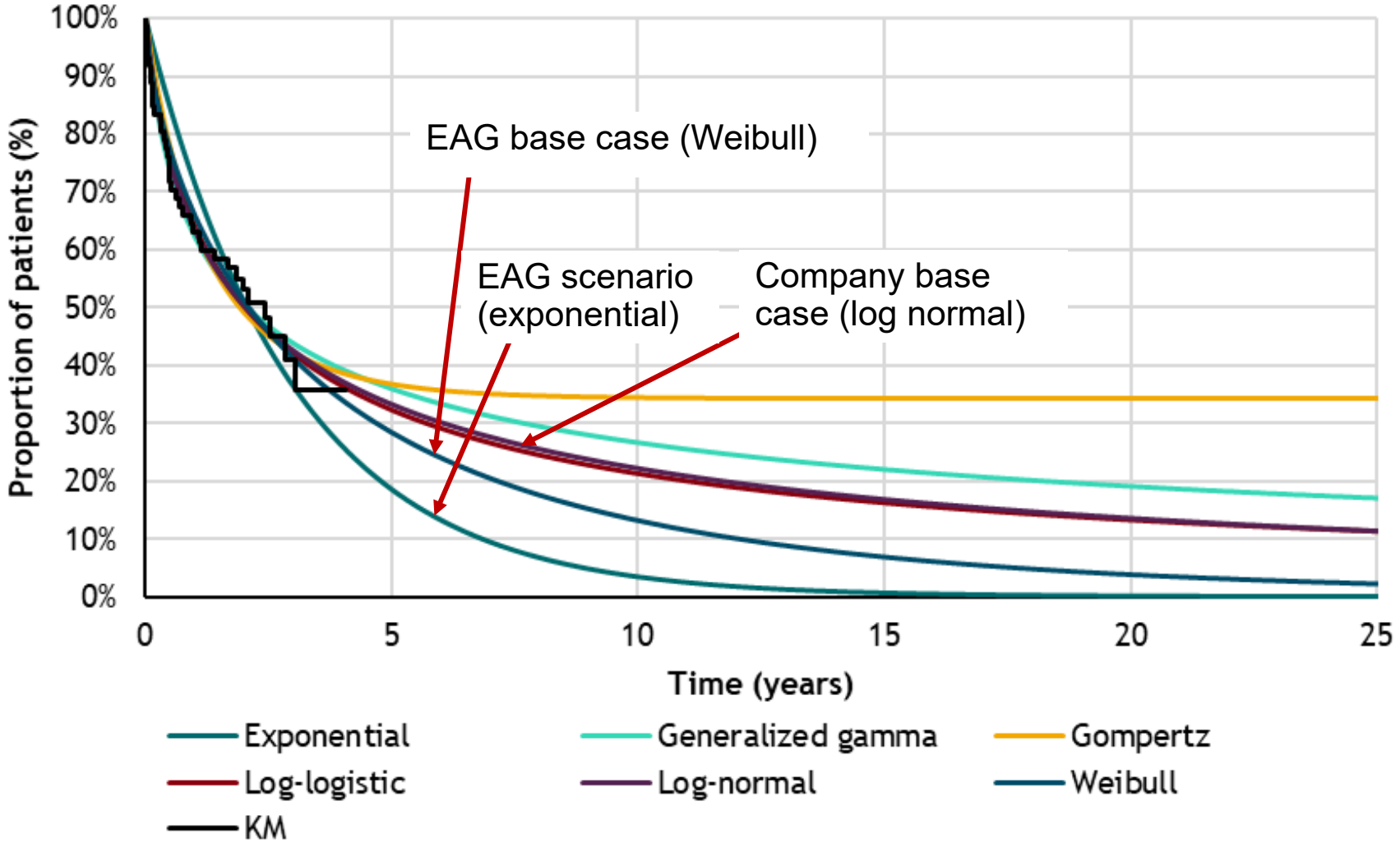
Years since start of treatment	People event free (%; company [log normal])	People event free (%; EAG [Weibull])
5	23.3	13.1
10	13.8	3.2
15	7.4	0.3

Abbreviations: EAG, external assessment group; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival

Key issue: OS and EFS extrapolation (2/3)

Big impact on ICER

Parametric models for overall survival (ivosidenib plus azacitidine)



Years since start of treatment	People alive (%; company [log normal])	People alive (%; EAG [Weibull]
5	33.2	28.1
10	22.3	13.1
20	13.7	3.8

OS estimates have not been adjusted to reflect the modelled cure assumption or background mortality see Key issue: cure assumption

Abbreviations: EAG, external assessment group; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival

Key issue: OS and EFS extrapolation (3/3)

Big impact on ICER

EAG considers long-term OS and EFS estimates implausibly high

Background

- Company estimated long-term OS and EFS using a log-normal survival curve

Company

- EFS and OS: log-normal model provided the best statistical fit; produces plausible extrapolations
- Log-normal used to inform majority of transitions to death in NICE TA765 for venetoclax plus azacitidine

EAG comments

- Clinical advice that 10-year OS estimate of 22.3% implausibly high; 2/3 clinician responses to company suggested Weibull (10-year survival 13.1%) or exponential (10-year survival 3.4%) more plausible
- EFS extrapolation also implausibly high; clinical advice to EAG that Weibull more plausible
- EAG preferred Weibull for OS and EFS in its base case
- Scenarios using exponential

Which is the most appropriate extrapolation to estimate long term OS and EFS for ivosidenib + azacitidine?

Abbreviations: EAG, external assessment group; EFS, event-free survival; OS, overall survival; TA, technology appraisal

Key issue: cure assumption (1/4)

Big impact on ICER

Company assume 100% of patients in EFS state are cured at 3 years

Background

- Company model assumes 'cure point' at 3 years for all patients in EFS state (for all treatment arms)
- All patients in 'EFS' health state transition to the 'LTS' (long-term survival) health state: OS from this timepoint onwards based on population-level life tables
- No drug acquisition, drug administration and concomitant medication costs for patients in cure state
- Cured patients similar health state utility and medical resource use cost to EFS patients with complete remission

Company: AGILE June 2022 data cut showed plateau in ivosidenib plus azacitidine overall survival; implies potential to 'cure' the target AML patients by providing sustained survival benefit

Previous NICE technology appraisal guidance

TA	Condition	Committee discussion
787	Venetoclax with low dose cytarabine for untreated AML when intensive chemotherapy unsuitable	"…evidence for including a cure state in the model was uncertain."
765	Venetoclax plus azacitidine for untreated AML when intensive chemotherapy unsuitable	Evidence for cure uncertain but "…plausible that some could be considered cured"
642	Gilteritinib for relapsed or refractory AML	"…cure point between 2 years and 3 years was plausible, and it was more likely to be closer to 2 years."
545	Gemtuzumab ozogamicin for untreated AML	5-year cure point appropriate

Abbreviations: AML, acute myeloid leukaemia; EAG, external assessment group; EFS, even-free survival; ICER, incremental cost-effectiveness ratio; TA, technology appraisal

Key issue: cure assumption (2/4)

Big impact on ICER

Company base-case OS extrapolations accounting for background mortality and cure point

[redacted]

EAG comments

- 10-year OS for ivosidenib plus azacitidine, which does not reflect the 3-year cure point, already implausibly high [see Key issue: OS and EFS extrapolation (2/3)]
- If adjusted for cure assumption, rises even higher – from 22.3% to [redacted]; and for venetoclax plus azacitidine rises from [redacted] to [redacted]
- Estimates lack clinical plausibility
- Higher proportion in ivosidenib plus azacitidine arm move into LTS state at 3 years than venetoclax plus azacitidine arm
- LTS health state produces majority of the incremental QALY gain associated with ivosidenib plus azacitidine
- LTS health state removed from EAG base case

Abbreviations: AZA, azacitidine; EAG, external assessment group; EFS, even-free survival; ICER, incremental cost-effectiveness ratio; LTS, long-term survival; OS, overall survival; QALY, quality-adjusted life year; VEN, venetoclax

Key issue: cure assumption (3/4)

Big impact on ICER

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LTS, long-term survival

Key issue: cure assumption (4/4)

Overall survival functions fitted to trial data

EAG comments:

- If remaining people on IVO+AZA cured, hazard of death expected to equal general population, that is, curves fitted to trial data would meet general population curve
- Point estimate hazard of death at end of trial remained above that of the general population
- 'Cure' cannot be ruled out because of uncertainty in hazard plots (CIs not shown but only [redacted] patients were at risk from month [redacted] [redacted] on figure], dropping to [redacted] from month [redacted] [redacted] on figure])
- No evidence to suggest a 'cure'; on average evidence suggests hazard of death remained higher than general population at trial end

Is it reasonable to assume that people with acute myeloid leukaemia surviving event-free at 3 years can be considered functionally 'cured'?

Abbreviations: AZA, azacitidine; EAG, external assessment group; IVO, ivosidenib

Key issue: stopping rule

? impact on ICER

Company assumes everyone stops treatment at 3 years

Background

- No stopping rule in ivosidenib SmPC or in TA765 (venetoclax plus azacitidine)
- Removing stopping rule has no effect on ICER if cure assumption remains (cure assumption means treatment stops at 3 years); only relevant if cure assumption also removed (then big impact on ICER)

Company

- Considered unlikely that treatment would continue beyond 3 years
- By this time most people's condition would have progressed or relapsed
- If still in EFS state considered long-term survivors who do not need further treatment

EAG comments

- Clinical advice that some could continue if response to treatment
- At 5 years estimated [redacted] still on treatment (using log-normal extrapolation from time on treatment curve)
- Removed stopping rule from base case
- Scenarios: 50% stop any treatment at 3 years, 100% stop at 5 years

Is treatment stopped at 3 years?

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Abbreviations: EFS, event-free survival; ICER, incremental cost-effectiveness ratio; SmPC, summary of product characteristics; TA, technology appraisal

Key issues with a minor impact on ICER

Minor impact on ICER

Relative dose intensity

- Company assumption [redacted]% (based on AGILE trial); EAG assumption 100% (people take tablets at home so full cost of pack incurred by NHS)

CR/CRi on venetoclax plus azacitidine

- Company used equation; EAG used NMA results

Days in hospital for venetoclax plus azacitidine

- Company: 32 days (Rausch et al. 2021); EAG 14 days (Othman et al. 2021)

Lead team preference: accept EAG assumptions

Does the committee agree with the lead team's preferences for these key issues?

Abbreviations: EAG, external assessment group; CR, complete remission; CRi, CR with incomplete hematologic recovery; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
OS and EFS extrapolation in the IVO+AZA arm (key issue 3a) – big impact on ICER	Company extrapolated OS and EFS using an independent lognormal curve	Preferred Weibull
Functionally 'cured' health state (key issue 3b) – big impact on ICER	• Cure assumption in model: long-term survival (LTS) state • At 3 years, 100% of patients in EFS state moved to LTS state	• Remove cure assumption • At 3 years patients in EFS state do not move into LTS state
Stopping rule (key issue 4) – big impact on ICER if cure assumption not applied	All patients stop treatment at 3 years (IVO+AZA and VEN+AZA)	No stopping rule
Minor impact on ICER • Proportion with complete remission in model for VEN+AZA (key issue 5) • Hospitalisation days for VEN+AZA during treatment initiation (key issue 6) • Relative dose intensity (RDI)	• CR/CRi % estimated using equation • 32 days for VEN+AZA based on Rausch et al[1]. • IVO: [redacted] (from AGILE); VEN+AZA assumed same	• CR/CRi % estimated using odds ratio from NMA • 14 days based on clinical opinion • 100% RDI for all treatments

Abbreviations: CR, complete remission; CRi, CR with incomplete haematological recovery; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; LTS, long-term survival; NMA, network meta-analysis; OS, overall survival

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

Decision on comparators affects which analysis is most appropriate:

- fully incremental analysis if multiple comparators appropriate for population
- pairwise comparison if relevant and justified (for example if only 1 comparator, or if specific displacement of individual comparator in a group/subgroup)

Effect on ICER of EAG preferred model assumptions

EAG base case over £30,000 for fully incremental and pairwise analyses

Base case	Total costs (£)	Total QALYs	Vs AZA and VEN+AZA (£/QALY) – fully incremental probabilistic cPAS ICER	Vs VEN+AZA alone (£/QALY) – pairwise deterministic cPAS ICER
Company (EAG corrected*)	See part 2	See part 2	Under £30,000	Dominant
EAG	Increase	Decrease	Substantially over £30,000	Substantially over £30,000

EAG preferred assumption (applied to company base case)	Total costs (£)	Total QALYs
Weibull used to extrapolate OS (IVO+AZA)	Decrease	Decrease
Weibull used to extrapolate EFS (IVO+AZA)	Increase	Decrease
No cure assumption + no stopping rule	Increase	Decrease
100% relative dose intensity	Increase	Same
% of patients with CR/CRi for VEN+AZA based on NMA	Increase	Same
14 day hospital stay for initiation with VEN+AZA	Increase	Increase

*Corrections: general population utility estimated using the Hernandez-Alva algorithm; life years discounted at 3.5%
Abbreviations: AZA, azacitidine; cPAS, comparator patient access scheme; CR, complete remission; CRi, CR with incomplete haematological recovery; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; NMA, network meta-analysis; OS, overall survival; QALY, quality-adjusted life year; ToT, time on treatment; VEN, venetoclax

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QALY weightings for severity

1.2 severity may apply if azacitidine is comparator

Treatment	Expected total QALYs without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Company base case [corrected by EAG]*					
AZA**	7.29	0.89	6.40	**0.89**	**1.2**
AZA+VEN	7.29	2.17	5.12	0.72	1
EAG base case					
AZA	7.29	0.79	6.50	0.89	1.2
AZA+VEN	7.29	1.84	5.45	0.74	1

- If venetoclax plus azacitidine only relevant comparator no severity weighting applies
- If azacitidine monotherapy is a comparator (either for the whole population or a defined subpopulation), proportional shortfall implies severity weighting of x1.2 may be considered

If azacitidine is a relevant comparator, does the x1.2 severity weighting apply in this population?

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*Corrections: general population utility estimated using the Hernandez-Alva algorithm; life years discounted at 3.5% **Company does not consider AZA a relevant comparator

Other considerations

No equality issues were raised by the company, external assessment group or stakeholders during the appraisal process

Managed access (including Cancer Drugs Fund) probably not appropriate

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Key issues

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The company's literature searches (key issue 8)	**Unknown**
Treatment effectiveness of IVO+AZA vs VEN+AZA (key issue 2)	**Varies depending on scenario**
OS and EFS extrapolation (key issue 3a)	**Large**
'Cured' health state (key issue 3b)	**Large**
3-year stopping rule (key issue 4)	**Large***
Severity weighting	**Moderate**
Key issues with a small effect on the ICER: • 100% Relative dose intensity (key issue 5) • Modelled proportion in complete remission on VEN+AZA (key issue 6) • Hospitalisation days for VEN+AZA during treatment initiation (key issue 7)	**Small**

*Removing stopping rule has no effect on ICER if cure assumption remains (cure assumption means treatment stops at 3 years); only relevant if cure assumption also removed (then big impact on ICER)

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Abbreviations: AZA, azacitidine; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; OS, overall survival; VEN, venetoclax