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

PART 1 for Zoom

Technology appraisal committee C 3 April 2024

Chair: Richard Nicholas

External assessment group: PenTAG

Technical team: Emilene Coventry, Michelle Green, Ian Watson

Company: Servier Laboratories

Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia

- ✓ **Recap**
- ❑ Response to consultation

NICE National Institute for Health and Care Excellence

Committee's key conclusions from first committee meeting

Ivosidenib plus azacitidine is not recommended, within its MA, for treating newly diagnosed AML with an IDH1 R132 mutation in adults who cannot have standard intensive induction chemotherapy

Clinical evidence: not seen clear evidence that ivosidenib plus azacitidine improved overall and event-free survival compared with venetoclax plus azacitidine

Cure assumption: some evidence to support but uncertain

Economic analysis: ICERs based on improved overall and event free survival for ivosidenib plus azacitidine compared with venetoclax plus azacitidine not reliable

Long-term treatment effects: uncertainty about appropriate extrapolations, potentially overestimating survival; exponential curve may produce more clinically plausible estimates

Cost savings: not seen evidence ivosidenib results in healthcare expenditure savings

Abbreviations: AML, acute myeloid leukaemia; ICER, incremental cost-effectiveness ratio; IDH1, isocitrate dehydrogenase 1; MA, marketing authorisation

Committee preferred assumptions and requested analyses

Preferred assumptions	Company base case	EAG base case
14-day hospital stay for venetoclax plus azacitidine	23 days	14 days
100% RDI for both interventions	100%	100%
NMA results used to inform CR and CRi for venetoclax plus azacitidine	Yes	Yes
Including the cost of rapid testing for IDH1 mutation	No – provided as scenario	Yes

Further analyses	Submitted by company
Scenario analysis exploring effect on ICER of setting HR at 1 for overall and event-free survival between ivosidenib plus azacitidine and venetoclax plus azacitidine (that is, no difference in treatment effect)	No (but provided by EAG)
Cure assumption scenarios with alternative cure points at 2, 3 and 5 years and SMRs of 1.0, 1.1, 1.2 and 2	Yes Revised company base case: SMR changed to 1.2
Scenario using exponential curve to extrapolate overall and event-free survival	Yes

See section 3.19 in the draft guidance

Abbreviations: CR, complete response; CRi, CR with incomplete haematological recovery; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IDH1, isocitrate dehydrogenase 1; RDI, relative dose intensity; SMR, standardised mortality ratio

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

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NICE National Institute for Health and Care Excellence

Outstanding key issues

Key issues from 1st committee meeting	ICER impact	Company and EAG analyses
Treatment effectiveness of IVO+AZA vs VEN+AZA (key issue 2)	Large	Additional analyses presented by company to support NMA point estimates showing IVO+AZA better OS and EFS than VEN+AZA EAG and company base case uses NMA point estimates
'Cured' health state (key issue 3b)	Large	Company revised base case: cure assumption at 3 years, SMR 1.2 Only people with CR/CRi moved to cure state Scenarios with cure points at 2, 3 and 5 years and SMRs 1.0, 1.1, 1.2 and 2.0 EAG base case: cure assumption included
OS and EFS extrapolation (key issue 3a)	Large	OS: company and EAG use Weibull EFS: company uses log-normal, EAG uses Weibull Presented scenarios using exponential
Hospitalisation days for VEN+AZA during treatment initiation (key issue 7)	Small	Company uses 23 days – average of EAG-preferred 14 days (based on Othman et al.) and original company base case of 32 days (based on Rausch et al.) EAG uses 14 days

Abbreviations: AZA, azacitidine; CR, complete response; CRi, CR with incomplete haematological recovery; EAG, external assessment group; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; NMA, network meta-analysis; OS, overall survival; SMR, standardised mortality ratio; VEN, venetoclax

Consultation responses (1/2)

Consultation comments received from:

- AbbVie UK (comparator – manufacturer of venetoclax)
- Jazz Pharmaceuticals (comparator – manufacturer of cytarabine)
- Leukaemia Care (patient group)
- One web comment from the clinical expert nominated by Servier (company) – see slide 11 Clinical evidence: treatment effectiveness of IVO+AZA vs VEN+AZA

Abbvie UK

- Agrees 14 days appropriate hospital stay for venetoclax plus azacitidine because source data (Othman et al.) from NHS hospitals
- Highlights that although venetoclax not designed to specifically target IDH1, "…many therapies can show increased efficacy in mutational subgroups despite not being designed to specifically target that mutation."

Jazz Pharmaceuticals

- Concerned that statement that 'ivosidenib is an oral treatment that can be taken at home' could be misleading; ivosidenib is given with subcutaneous azacitidine – not a homebased treatment in most cancer centres; suggest amending to clarify how it is administered, or add 'where home treatment is provided'

Abbreviations: AZA, azacitidine; IDH1, isocitrate dehydrogenase 1; IVO, ivosidenib; VEN, venetoclax

Consultation responses (2/2)

Leukaemia Care

- Urgent need for further treatments when chemotherapy not an option
- Could Cancer Drugs Fund address remaining uncertainties
- Welcomes acknowledgement that some people with acute myeloid leukaemia can be cured
- Urges committee to accept uncertainties: direct comparison with venetoclax not available at time
- Scaling up IDH1 testing should be relatively easy; can NHS England provide further detail on costs
- Clinical advice suggests multiple frequent hospital stays with venetoclax because of side effects; would like to see further clinical input on this

Abbreviations: IDH1, isocitrate dehydrogenase 1

Equality considerations

Severity modifier

Leukaemia Care

Disappointed severity modifier not considered relevant; thinks modifier disadvantages older people at the end of life; terminal illness inherently severe and life threatening

Draft guidance

When taking into account the committee's preferred comparator of venetoclax plus azacitidine, both the absolute and proportional QALY shortfall were not within the range that indicates a severity modifier may be considered. The committee concluded that the severity weighting did not apply.

How severity is assessed

- Absolute and proportional QALY shortfall calculated based on estimate of the total QALYs for the general population with the **same age and sex distribution as those with the condition**
- QALY weightings for severity applied based on absolute and proportional shortfall, whichever implies the greater severity level
- For this appraisal shortfall only large enough for severity to be taken into account if azacitidine was comparator (QALYs on azacitidine alone lower than on venetoclax plus azacitidine)
- Committee accepted that venetoclax plus azacitidine was relevant comparator, so shortfall not in range to apply severity modifier - company agrees

No other equality issues raised during consultation

NICE health technology evaluations: the manual section 6.2.12 to 6.2.22

Abbreviations: QALY, quality adjusted life year

Clinical evidence: treatment effectiveness of IVO+AZA vs VEN+AZA (key issue 2)

Committee conclusions at first committee meeting

- Uncertainty in NMA
- Lack of significance in difference in treatment effect
- Potential for IDH1 status to affect results
- No clear evidence that ivosidenib plus azacitidine improved OS and EFS vs venetoclax plus azacitidine

Company response to draft guidance

- CrIs indicate uncertainty, not significance; do not indicate IVO+AZA = VEN+AZA
- Uncertainty from small sample size: trial stopped early because number of deaths favoured IVO+AZA
- Further analyses of NMA outputs show high probability of added benefit IVO+AZA vs VEN+AZA
- Supplementary analyses using MAIC support NMA (base case adjusted HRs):
  - anchored MAIC of OS: HR [redacted] 95% CI [redacted] (NMA HR [redacted] 95% CrI [redacted])
  - anchored MAIC of EFS: HR [redacted] 95% CI [redacted] (NMA HR [redacted] 95% CrI [redacted])
  - unanchored MAIC of OS (IDH1 subgroup): HR [redacted] 95% CI [redacted]
- Previous TAs have accepted evidence of clinical benefit when CrIs included 1 (TA741, TA666, TA587)
- No conclusive evidence that IDH1 mutation is a treatment effect modifier for venetoclax plus azacitidine

Clinical expert response to draft guidance

Analysed data and no survival difference based on IDH1 status for people having venetoclax plus azacitidine

EAG comments

- On balance likely to be a treatment effect; NMA point estimates are all below 1 but chance cannot be ruled out
- Has provided HR=1 as a worst-case scenario
- Agrees no conclusive evidence IDH1 mutation treatment effect modifier

Network meta-analysis results

Abbreviations: AZA, azacitidine; CI, confidence interval; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; IVO, ivosidenib; hazard ratio; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; TA technology appraisal; VEN, venetoclax

Cure assumption: ‘cured’ health state (key issue 3b)

Committee conclusions at first committee meeting

- Some evidence to support cure assumption in this population but uncertain
- Point estimate hazard of death at trial end above general population, so preferred to see scenarios that increased SMR

Company response to draft guidance

- Scottish Medicines Consortium accepted 2-year cure assumption when recommending ivosidenib plus azacitidine in Scotland; scenario analyses included 3-year cure point with SMR 1.2
- Revised base case uses 3-year cure point (as original) but SMR changed to 1.2 (in line with TA765 venetoclax plus azacitidine)
- Provided scenarios with cure points at 2, 3 and 5 years and SMRs of 1.0, 1.1, 1.2 and 2.0
- Only people with CR/CRi moved to cure state

EAG comments

- Agrees with only CR/CRi moving to cure state (if cure assumption valid)
- Reiterates that hazard of mortality at trial end higher than for general population (but uncertain); flattening of the curve does not necessarily indicate a cure because of small numbers at risk
- SMR provides compromise allowing for increased mortality despite the ‘cure’ definition.

Cure assumption slides from ACM1

Abbreviations: CR, complete response; CRi, CR with incomplete haematological recovery; EAG, external assessment group; SMR, standardised mortality ratio; TA, technology appraisal

Stopping rule

Long-term treatment effects: OS and EFS extrapolation (key issue 3a) 1/5

Committee conclusions at first committee meeting

- Uncertainty about appropriate extrapolations
- Potentially overestimating survival
- Exponential curve may produce more clinically plausible estimates

Company response to draft guidance

- Agrees with EAG-preferred Weibull for OS; exponential model poor fit to data but provided as scenario
- Maintains log-normal most appropriate for EFS:
  - Exponential and Weibull do not fit pattern of hazard of composite EFS
  - If exponential used for EFS and Weibull for time on treatment, curves cross at around [redacted] years: not clinically plausible

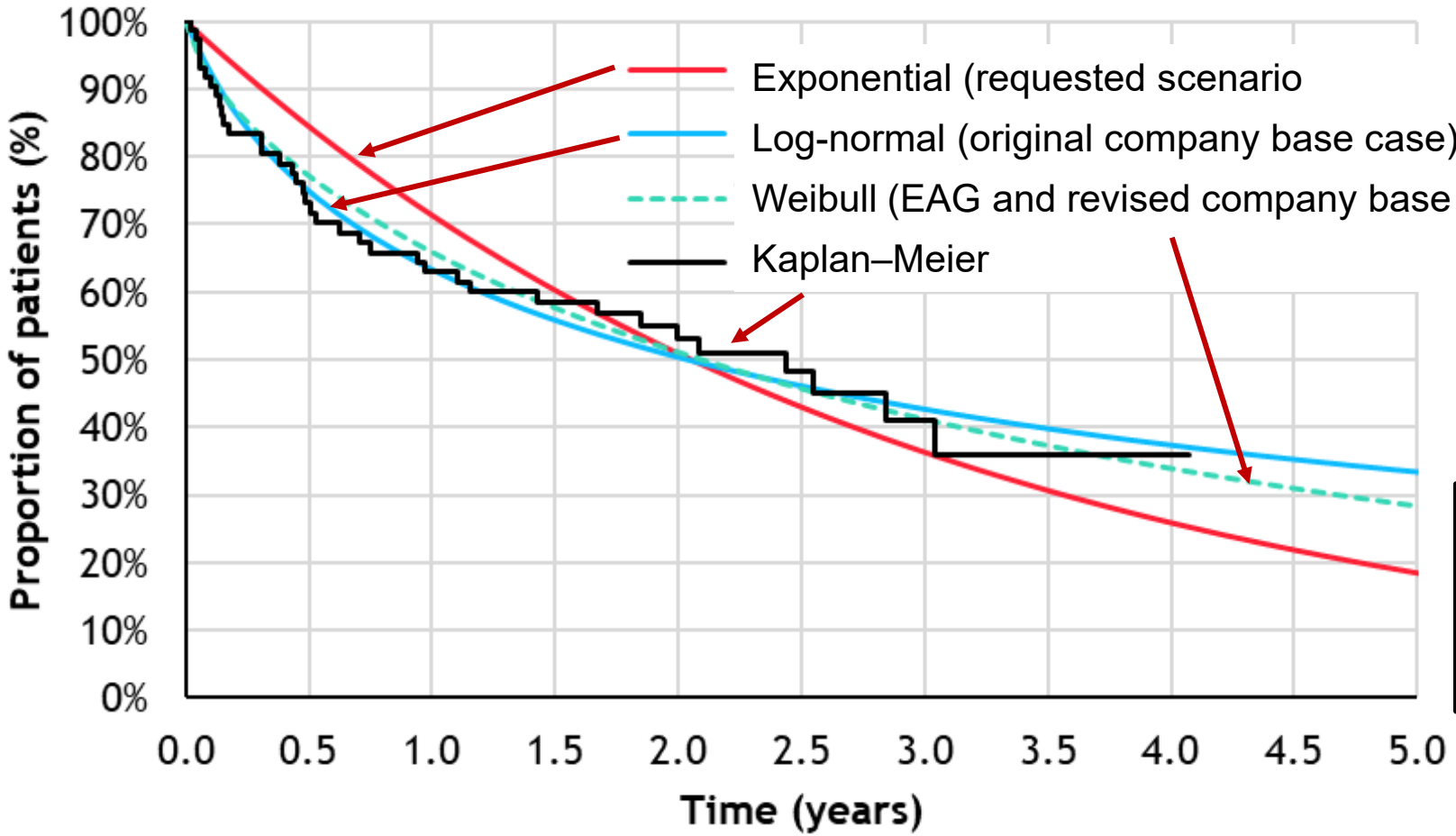
EAG comments

- Agrees exponential poor fit to observed data for EFS and OS but key issue is plausibility of long-term extrapolations beyond observed data
- 2 of 3 clinicians felt Weibull or exponential more plausible long term for OS
- Good fit to observed data can generate implausible longer-term predictions and vice versa
- Maintains Weibull or exponential more appropriate for EFS and OS long-term extrapolations

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

Long-term treatment effects: OS and EFS extrapolation (key issue 3a) 2/5

Overall survival with ivosidenib plus azacitidine – company and EAG preferences, plus committee-requested scenario (exponential) up to 5 years

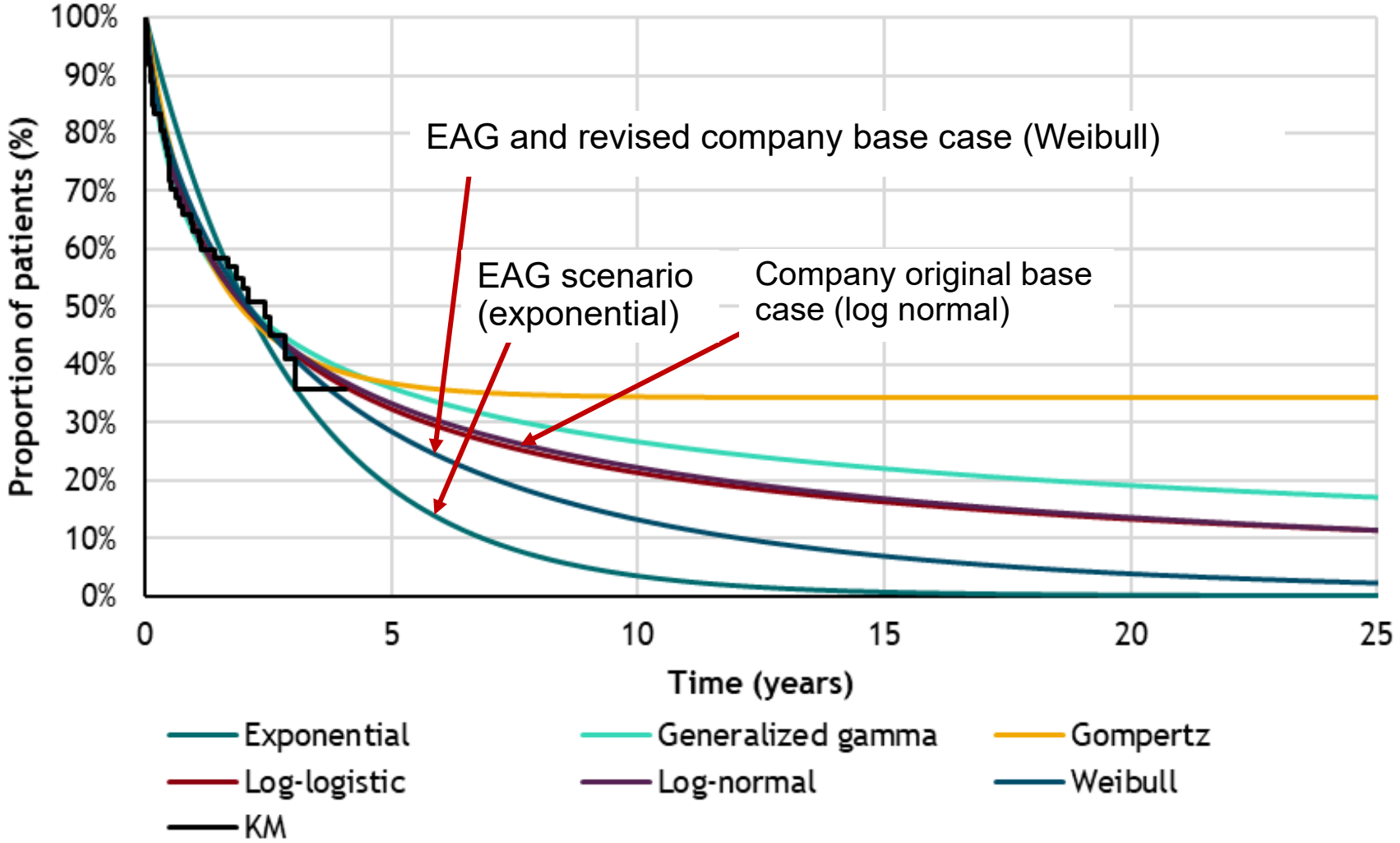


Estimates not adjusted to reflect the modelled cure assumption or background mortality

Abbreviations: EAG, external assessment group; EFS, event-free survival; KM, Kaplan-Meier; OS, overall survival

Long-term treatment effects: OS and EFS extrapolation (key issue 3a) 3/5

Overall survival with ivosidenib plus azacitidine up to 25 years (all extrapolations)



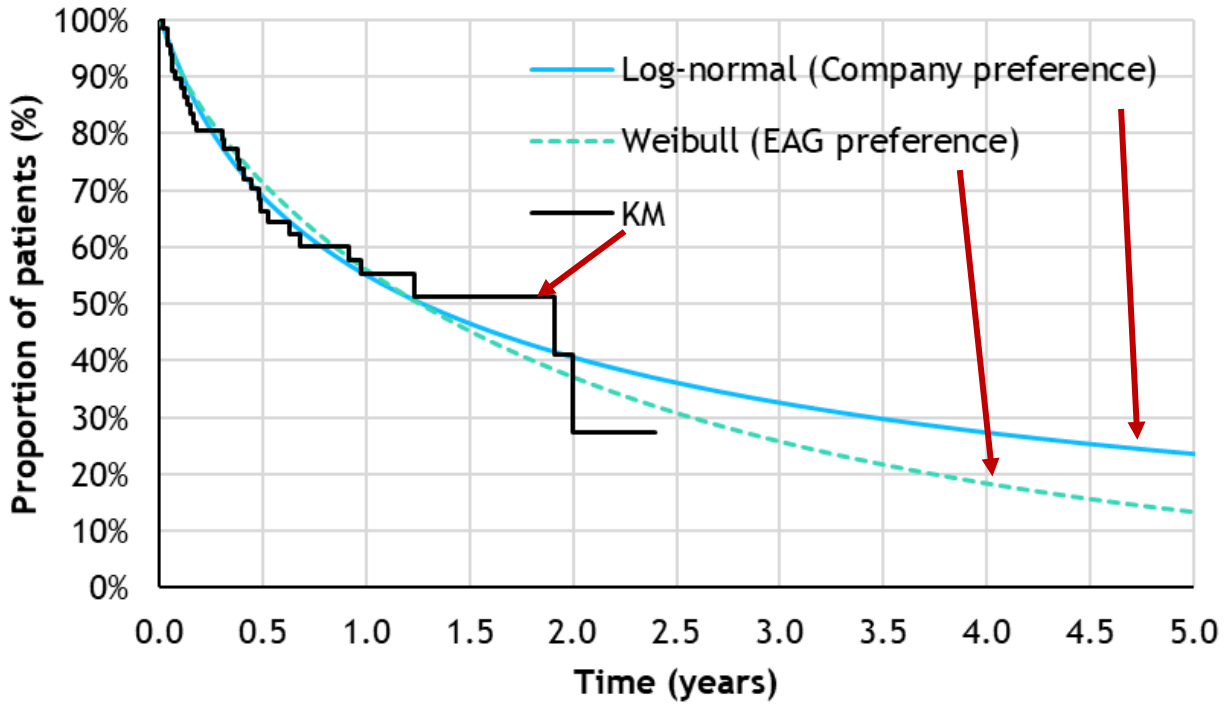
Years since start of treatment	People alive (%; company [log normal])	People alive (%; EAG [Weibull]
5	33.2	28.1
10	22.3	13.1
20	13.7	3.8

Estimates not adjusted to reflect the modelled cure assumption or background mortality

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

Long-term treatment effects: OS and EFS extrapolation (key issue 3a) 4/5

EFS with ivosidenib plus azacitidine – company and EAG preferences, plus committee-requested scenario (exponential) up to 5 years



Log-normal and Weibull EFS

[redacted]

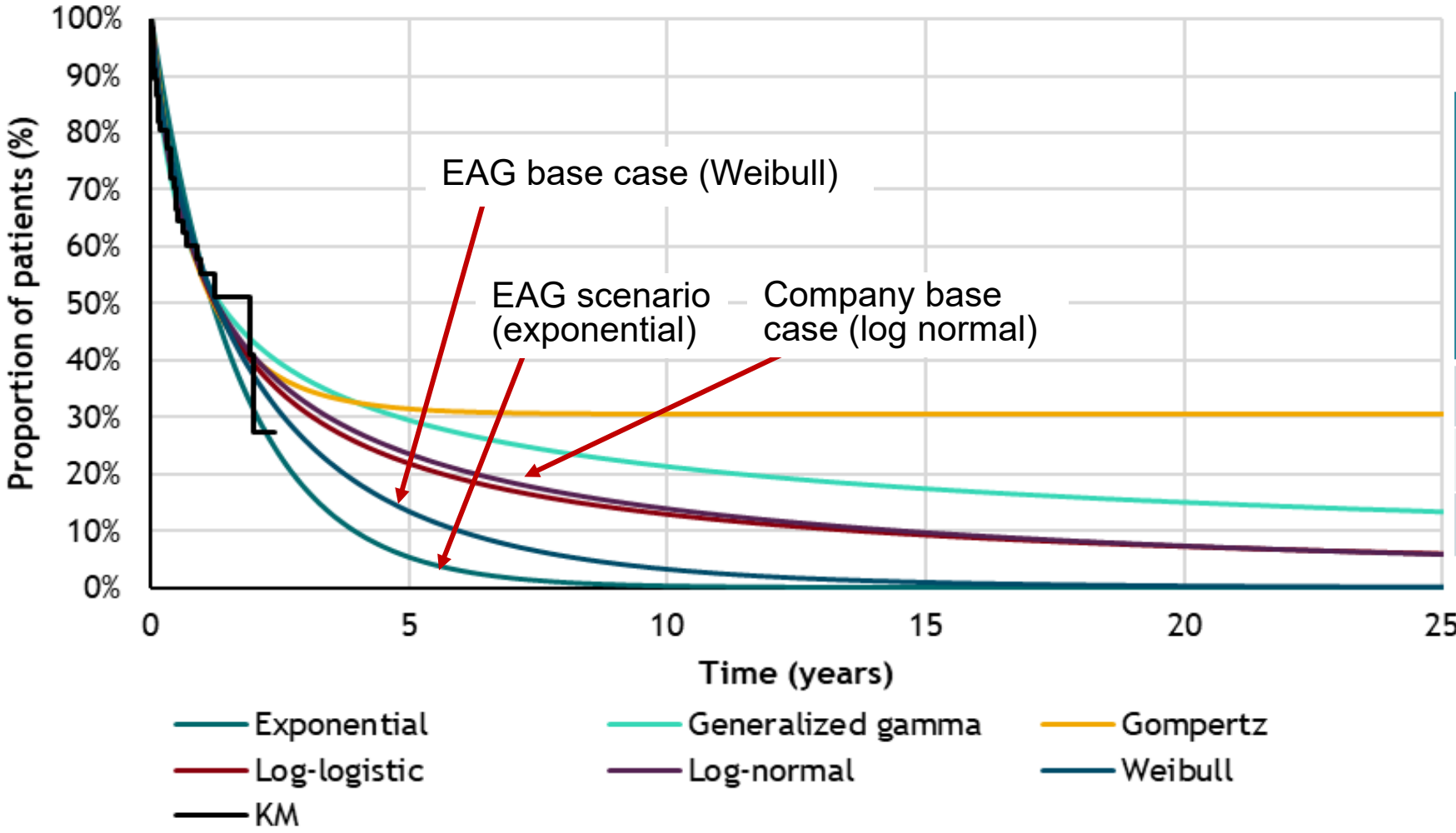
Exponential EFS with ToT (Weibull)

Estimates not adjusted to reflect the modelled cure assumption or background mortality

Abbreviations: EAG, external assessment group; EFS, event-free survival; KM, Kaplan-Meier; OS, overall survival; ToT, time on treatment

Long-term treatment effects: OS and EFS extrapolation (key issue 3a) 5/5

EFS with ivosidenib plus azacitidine up to 25 years (all extrapolations)



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

Estimates not adjusted to reflect the modelled cure assumption or background mortality

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Costs (1/2)

Draft guidance

- Company claim: using ivosidenib plus azacitidine would lead to cost savings related to healthcare expenditure
- Committee concluded no evidence for this

EAG comments

- Company's post-consultation base case no longer makes claim to cost saving
- Main difference in costs between IVO+AZA and VEN+AZA is in medical resource use
- Difference mostly disappears in EAG base case; almost entirely driven by the assumed survival function for EFS
- Using Weibull means more people in progressed state than log-normal, which has higher costs than EFS

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Costs (2/2)

Transfusions

- **Committee:** in trial blood counts for IVO+AZA similar to VEN+AZA so company claim of cost savings uncertain
- **Company:** transfusion costs are health state dependent; people on IVO+AZA have lower transfusion costs because of more time in remission; at 24 weeks or longer more people on IVO+AZA in AGILE had transfusion independence than people on VEN+AZA in VIALE trial

Rapid testing for IDH1 mutation

- **Committee:** rapid IDH1 testing needed so cost should be included in model
- **Company:** not appropriate to include in base case – service redesign rather than new test; IDH1 testing already recommended by British Society for Haematology (within 14 days as part of NGS panel), European Society For Medical Oncology and European LeukemiaNet (3 to 5 days); option to include test cost in model (based on TA948 ivosidenib for cholangiocarcinoma – £34 per test, with assumed IDH1 mutation incidence of 8% – extra £425 in IVO+AZA arm)

Hospital days for VEN+AZA during treatment initiation

- **Committee:** preferred EAG's assumption of 14 days
- **Company:** EAG assumption based on study done during COVID-19 pandemic – not representative; company-preferred duration based on US pre-pandemic study; used average of 23 days in revised base case

Hospitalisation days for VEN+AZA slides from ACM1

NICE

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

Acceptable ICER below £30,000 per QALY gained (see section 3.18 of draft guidance)