Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

Technology appraisal committee D [9 April 2026]

Confidential information redacted

Chair: Megan John

Lead team: Paul Caulfield, Ben Searle, Giles Monnickendam

External assessment group: Sheffield Centre for Health and Related Research

Technical team: Kirsty Pitt, Vicky Kelly, Ross Dent

Company: Brancaster

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

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

NICE National Institute for Health and Care Excellence

Background on acute myeloid leukaemia

Uncommon cancer, more common in older people

Causes

- *De novo* AML: series of recurrent genetic alterations accumulated with age in haematopoietic stem cells
- Secondary AML: usually induced by cytotoxic therapies used when treating solid tumours or other haematologic malignancies (5-20% of all AML cases)

Epidemiology

- Accounted for less than 1% of all new cancer cases in the UK in 2017-2019
- Most common in those over 60 years old and more frequent in men than women

Diagnosis and classification

- Categorised based on genetic risk at diagnosis: favourable, intermediate or unfavourable/adverse risk

Symptoms and prognosis

- Symptoms include fatigue, fever, infections, bruising, memory loss, pain, nausea and vomiting
- Younger patients, with good functional status generally have more favourable prognosis, whilst typical survival prognosis for older people, with impaired functional status, concomitant diseases, secondary AML and certain genetic alterations is generally poor

Abbreviations: AML, acute myeloid leukaemia

Histamine dihydrochloride (Brancaster)

Marketing auth-orisation	UK MA granted 1st August 2025 • Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy has not been fully demonstrated in patients older than age 60.

Mechanism of action	• Immunotherapy
	  • histamine protects lymphocytes, in particular NK cells and T cells, responsible for immune-mediated destruction of residual leukaemic cells
	  • IL-2 activates anti-leukaemic properties of NK cells and T cells and expands these cell populations

Admin-istration	Subcutaneous injection self-administered for up to 18 months (histamine dihydrochloride 0.5mg (1 vial) twice daily, plus IL-2 at 16,400 IU/kg twice daily)
Price	• Histamine dihydrochloride (HDC): £1,200 for 14 vials of histamine dihydrochloride (1 week), IL-2: £636 per 18 million IU vial • 3-week treatment cycle of HDC is £3,600 and of IL-2 is £1,908 No patient access scheme in place

Patient perspectives

Patient expert statements

- All patients are individuals and may respond to treatments differently depending on condition, genetics, health, strength etc.
    - Many treatment options available
    - Every patient's journey is different, making it hard to compare
- Focusing on wellbeing whilst undergoing treatment has helped develop a positive attitude

I … experienced the effects that AML has on the quality of life, being able to work, self care and care for others. It has a massive impact on all aspects of life

For me not being able to work and run my business has a huge financial strain

Abbreviations: AML, acute myeloid leukaemia

Clinical perspectives

HDC/IL-2 may be beneficial for some groups of patients

Clinical expert statements

- Long term survival with AML remains <25-30% and, even in those able to receive intensive therapy, long term survival still remains around (or slightly below) 50%.
- Difficult to determine who would benefit from this treatment because trial evidence before many gene mutations discovered, and new treatments approved
    - likely to benefit patients in 1st remission, aged<60yrs who have normal karyotype AML – perhaps those with FLT3-negative, NPM1-mutated disease (around 15% of those suitable for intensive treatment)
    - would be used in place of best supportive care or oral azacitidine
        - oral azacitidine is given indefinitely until progression
- 840 (mostly) self-administered injections over 18-months, each taking 5-15 minutes
- Would require more monitoring than BSC – for efficacy and side effects

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; AML, acute myeloid leukaemia; FLT3, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3; BSC, best supportive care

Equality considerations

Considerations around age and disability, potential benefits for people from ethnic minorities

- Acute myeloid leukaemia is more common in men and older adults.
- Marketing authorisation states: ‘the efficacy of histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.’
    - NICE will appraise within the marketing authorisation and cannot make a recommendation outside the marketing authorisation, but will consider all evidence
- People from ethnic minorities are under-represented on donor registries so are less likely to receive an allogeneic stem cell transplant. Maintenance treatments which decrease the risk of leukaemia relapse are particularly important for these patients.
- The treatment may be more difficult for patients with disabilities to self-administer
- Geographical issues may impact access – smaller rural hospitals will require support to be able to prescribe, deliver and monitor this treatment

Are there any equality issues?

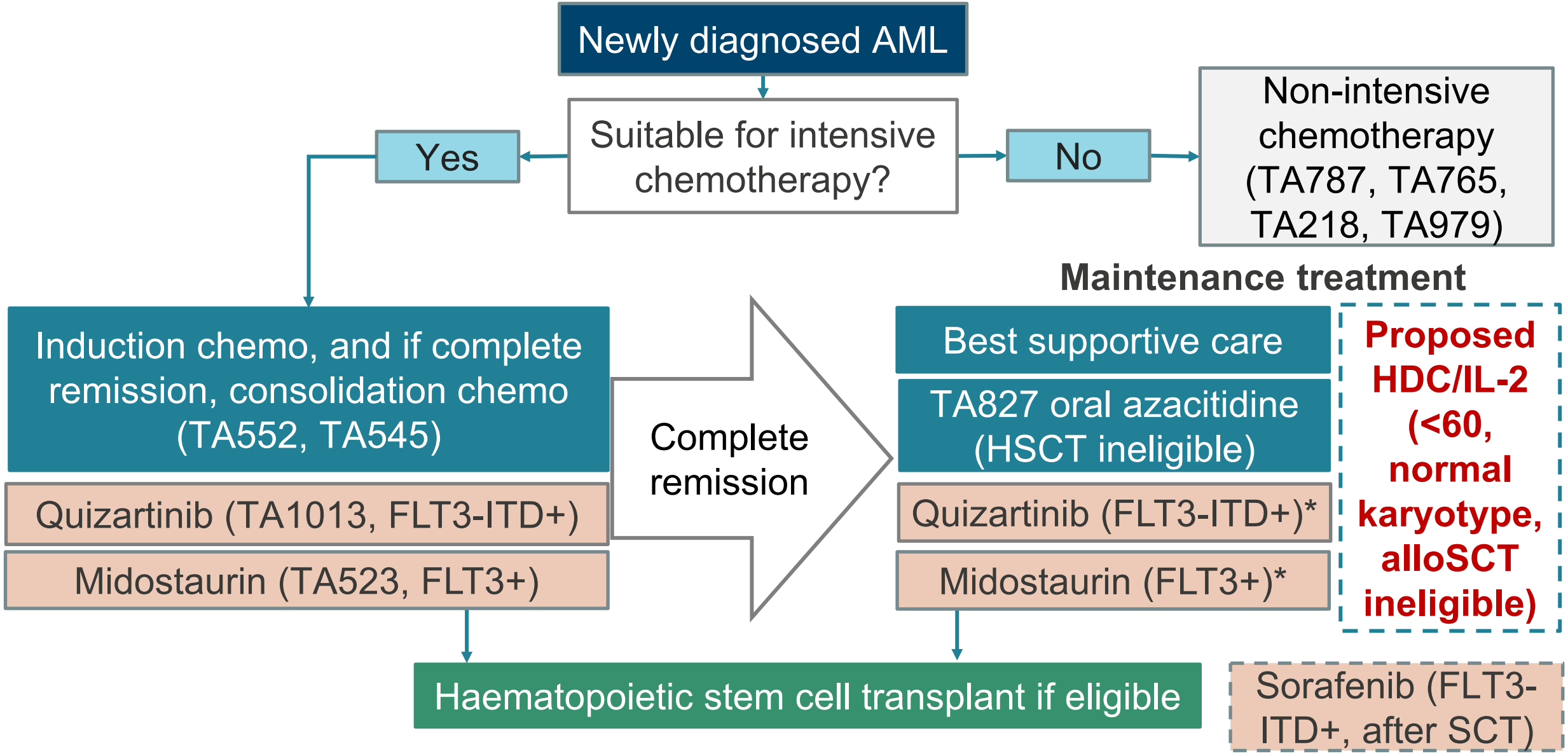
Uncaptured benefits

Company considers there are some uncaptured benefits

- Company states that caregivers of people with acute myeloid leukaemia experience substantial burden and psychological morbidity over the course of treatment
    - There may be quality of life impact on carers, although no carer quality of life included in the economic model

Are there any uncaptured benefits?

Treatment pathway for acute myeloid leukaemia in adults



*Company: people with FLT3 +ve AML would have mido/quiz at induction and unlikely to switch for maintenance treatment

Abbreviations: AML, acute myeloid leukaemia; HDC/IL-2, histamine dihydrochloride with interleukin-2; FLT3, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3; ITD, internal tandem duplication; SCT, stem cell transplant

Key issues

Issue	Key question	ICER impact
Comparators	What are the most appropriate comparators for HDC/IL-2?	**Large decision-altering impact**
Generalisability	Are the trial outcomes generalisable to the relevant population? Is the post-hoc analysis robust for decision-making?	**Large decision-altering impact**
Indirect treatment comparison	What are the most plausible hazard ratios to use in the model?	**Small**
Survival extrapolations	Which survival extrapolations are the most plausible for LFS and for OS?	**Large (vs SoC)**
Utility values	What is the best source for utility values? Is it appropriate to include a utility decrement?	**Small (bigger for SoC)**
Treatment discontinuation	Which approach is more appropriate for modelling AE-related discontinuation: company or EAG's?	**Small**
Severity	Is it appropriate to apply a QALY weighting for severity for the comparison with standard care only?	**Small**

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; LFS, leukaemia-free survival; OS, overall survival; SoC, standard of care, QALY, quality-adjusted life year

Key issues: Comparators

Large impact

Company

- Target population in this evaluation:
  - patients in first complete remission, ≤60 years-old, normal karyotype, allogeneic stem cell transplant unsuitable → these patients would mostly have SoC
- Considers oral azacitidine is not a relevant comparator as target population is almost completely distinct (pts in QUAZAR AML-001 trial of azacitidine were >55 years)
  - done comparison with azacitidine requested by EAG but maintains that this is not clinically appropriate, and analysis is weak due to differences in patient populations
- Company base case vs SoC is £20k/QALY gained, HDC/IL-2 is dominated by oral aza when confidential comparator prices included
- Patients with FLT3+/FLT3-ITD+ AML would have midostaurin/quizartinib in induction and consolidation and would be unlikely to switch to non-targeted therapies for maintenance

EAG comments

- No restriction on age in marketing authorisation or NICE TA for oral azacitidine

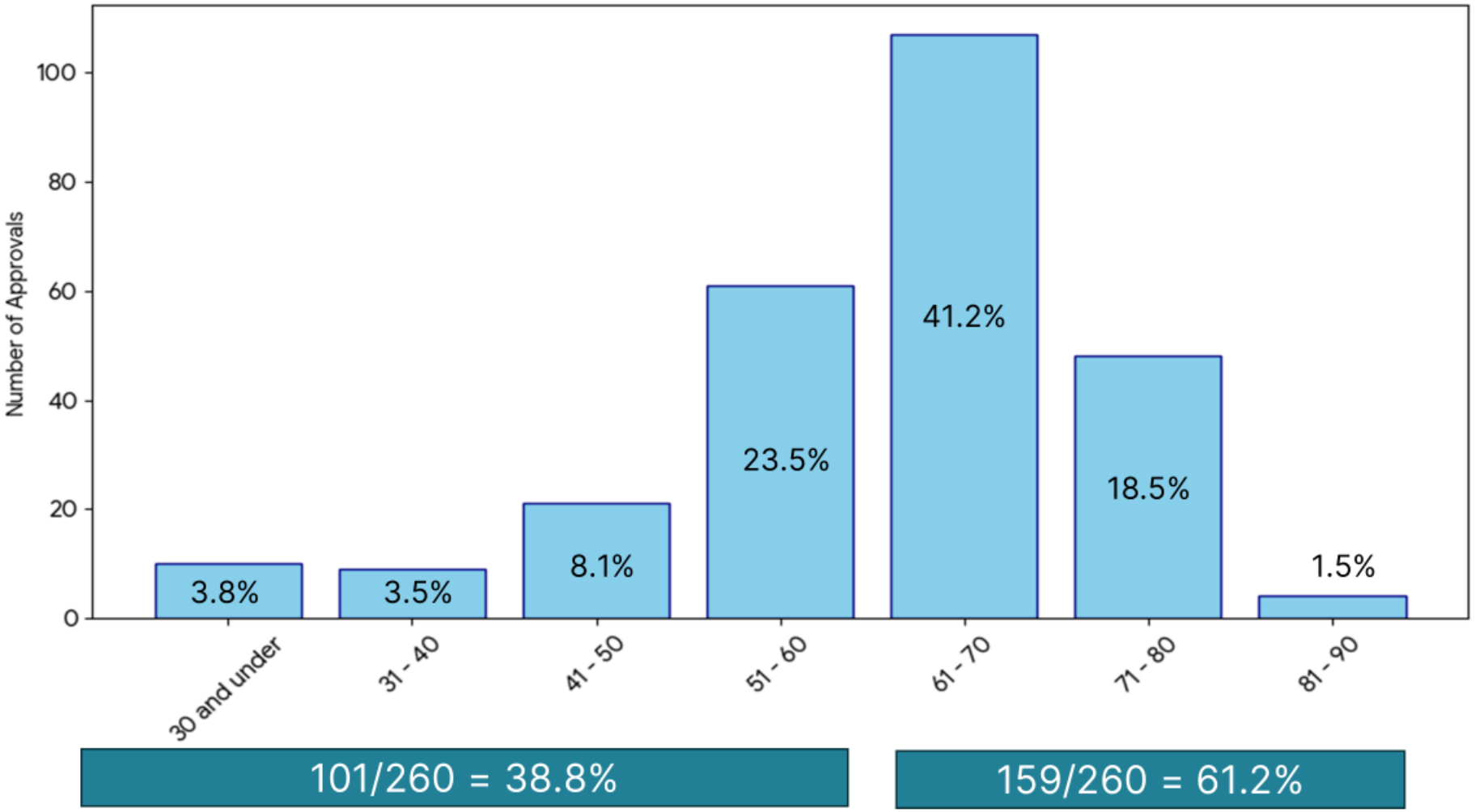
Clinical expert submissions: HDC/IL-2 would be used in place of BSC or azacitidine

What are the most appropriate comparators for HDC/IL-2?

Abbreviations: HSC/IL-2, histamine dihydrochloride/interleukin 2; FLT3, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3; ITD, internal tandem duplication; BSC, best supportive care

NHS England submission: Blueteq data

Age distribution of requests for oral azacitidine since 2022 (TA827, Oct 22)



Blueteq data

All requests since 2022

101/260 (38.8%) requests were for patients age 60 or less

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

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

NICE National Institute for Health and Care Excellence

History of evaluation

Histamine dihydrochloride historically marketed by several different companies

RCT recruitment

Results published: Brune et al

EMA licence*

Subgroup results published: Nilsson et al.

Brancaster licensed UK rights

UK MA granted

HDC/IL-2 vs standard care (n=320 incl 3 UK)

- Population: AML
  - Allo-HSCT unsuitable
  - In CR after induction and consolidation
  - ECOG 0 or 1

HDC/IL-2 (as Celpene) considered by NICE topic selection but not prioritised for appraisal

SMC / AWMSG assessments

n=72

Population (target in this evaluation):

- CR1, normal karyotype, ≤60y

NICE appraisal planned but previous company stopped engaging

Q for clinical experts: What is the experience with this drug in clinical practice in UK and elsewhere?

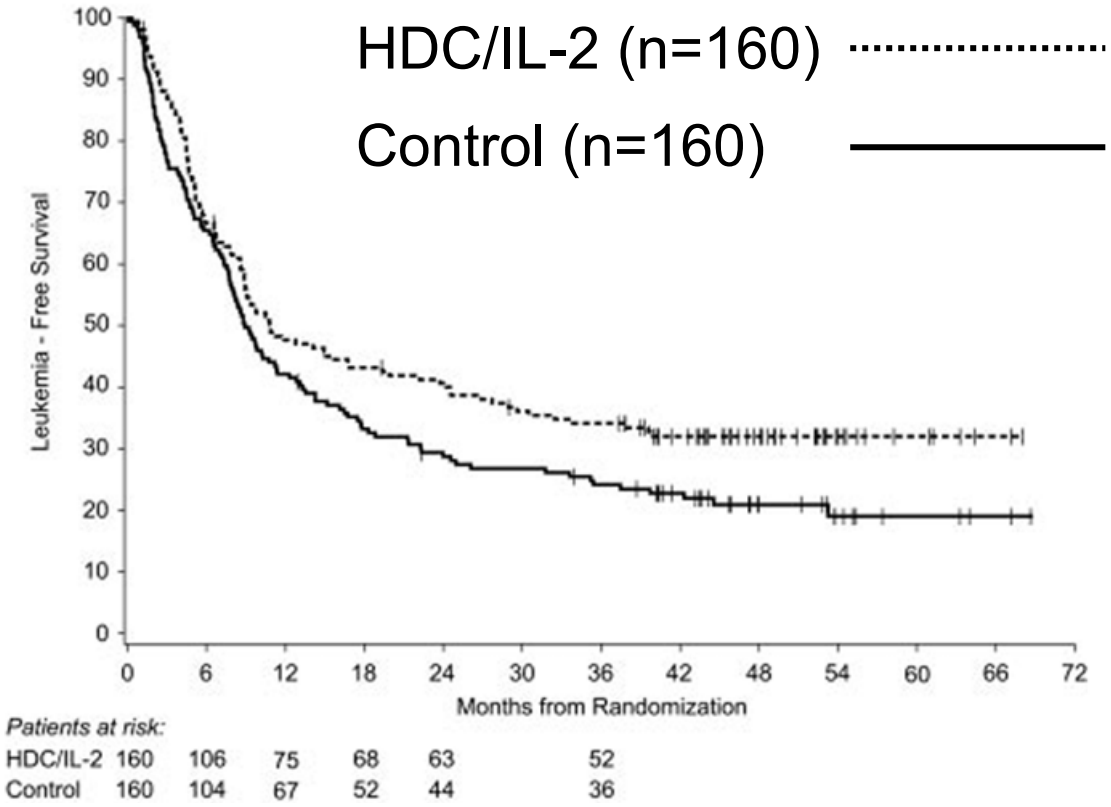
**>60yr restriction included in 2008 MA*

Timeline not to scale

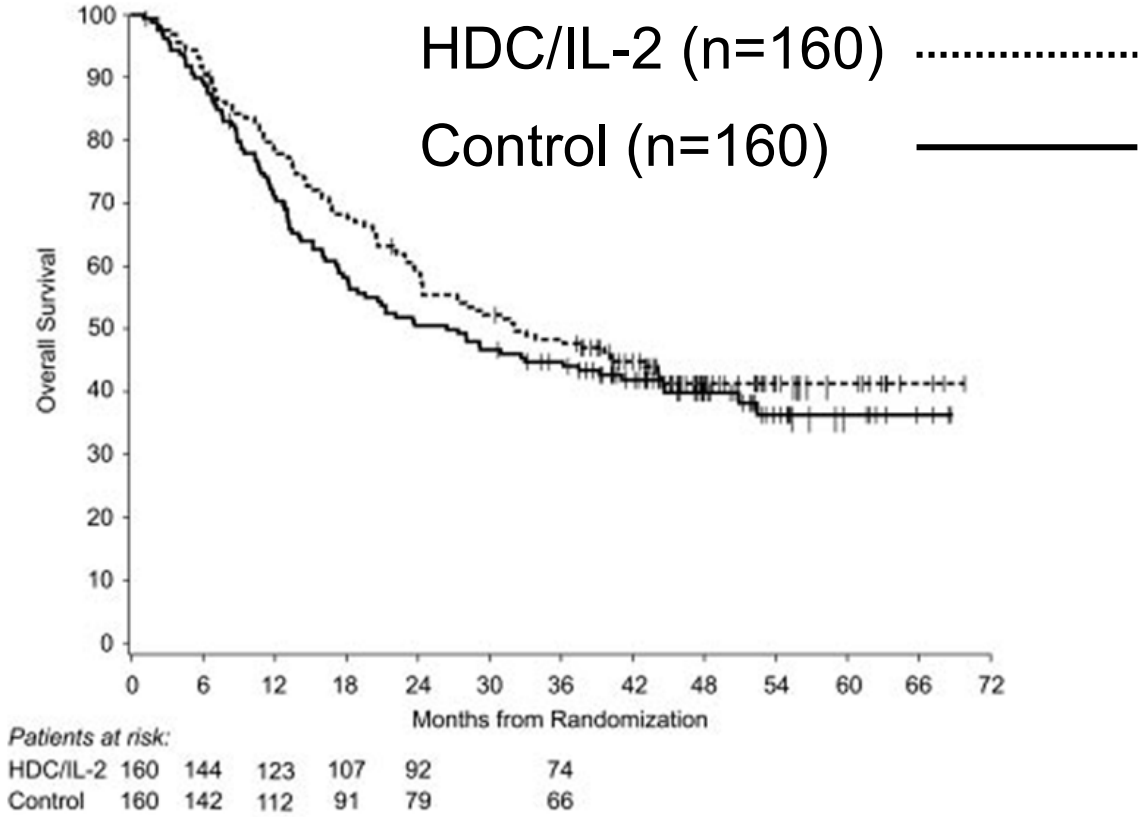
Abbreviations: AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplant; CR, complete remission; CR1, first complete remission; ECOG, European Cooperative Oncology Group; EMA, European Medicines Agency; HDC/IL-2, histamine dihydrochloride with interleukin-2; SMC, Scottish Medicines Consortium; AWMSG, All Wales Medicines Strategy Group; MA, marketing authorisation

Brune study results: ITT population

Kaplan-Meier curve of leukaemia-free survival



Kaplan-Meier curve of overall survival



Outcome	HDC/IL-2: Median	Control: Median	HR (95% CI)	P-value
LFS, n=320	324 days	264 days	0.71 (0.54 to 0.92)	<0.01
OS, n=360	NR	NR	0.82 (0.61 to 1.11)	0.21

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; ITT, intention-to-treat; HR, hazard ratio; LFS, leukaemia-free survival; OS, overall survival; CI, confidence intervals

Key Issue: Brune et al. 2006 study

Large impact

Substantial changes in practice since trial was conducted

Company

- Target population for evaluation is post-hoc subgroup of Brune: Nilsson et al. 2020 (n=72)
  - people in first complete remission (CR1), normal karyotype, ≤60 years
- Presented naive comparisons of 3-year overall survival with other recent studies, suggesting similar outcomes between patients in population of interest:
  - 58.7% in control arm of Nilsson subgroup of Brune
  - 58% / 69% in Potter 2025 (UK AML 17&19, NPM1 and FLT3-ITD positive subgroup, non-monitored / monitored group)
  - 59.4% in Juliusson 2020 (Swedish RWE, NPM1 mutation subgroup)

EAG comments

- New personalised and targeted therapies, molecular risk stratification now used and supportive care improved: FLT3 status not known in Brune: unclear how many FLT3-positive patients have contributed to the efficacy data
- Subgroup results selected by company above may not be comparable populations
- No information on subsequent treatment in Brune
- Uncertain whether results from Nilsson are generalisable to currently eligible population

Are the trial outcomes generalisable to the relevant population?

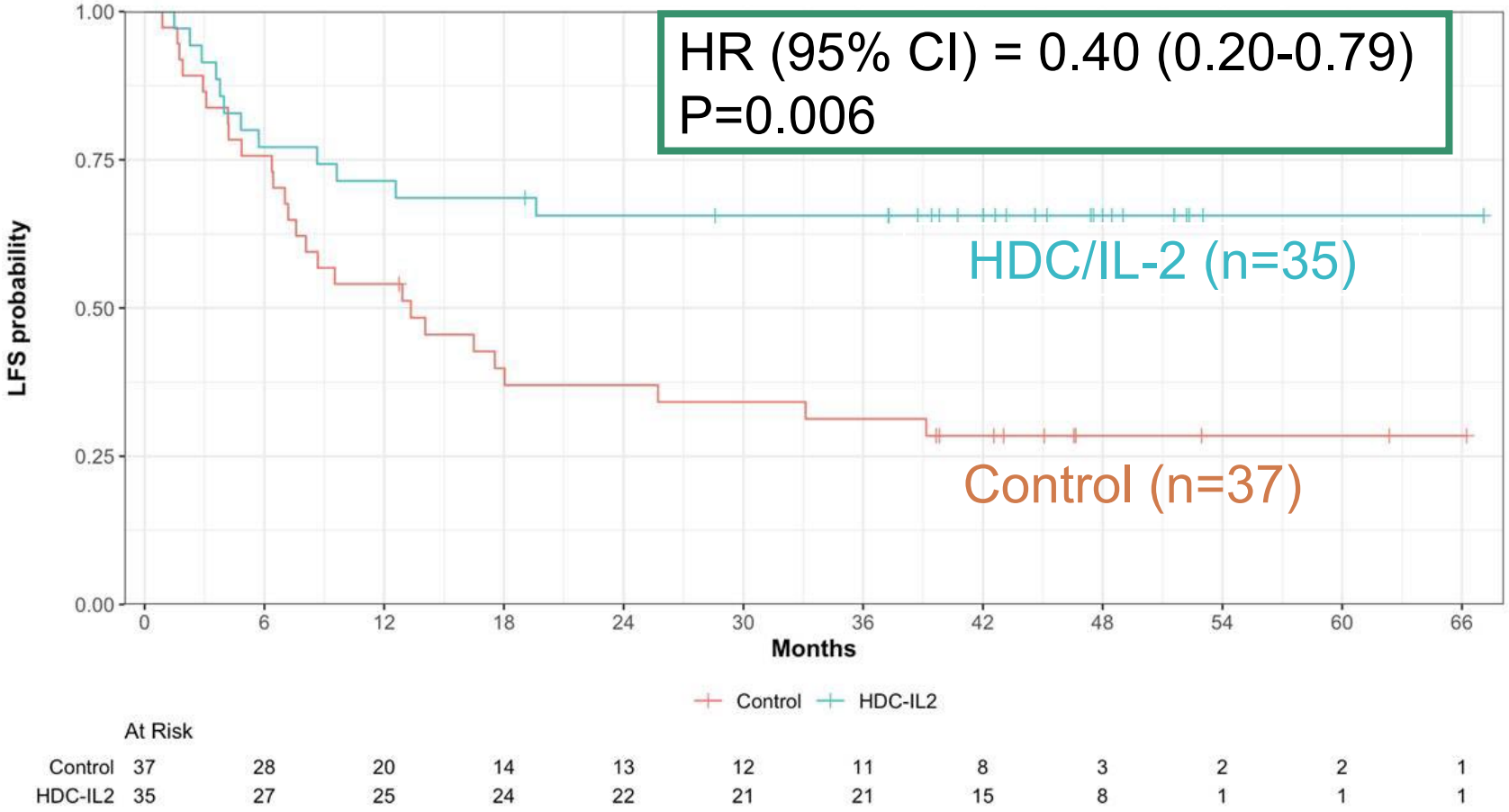
*See also baseline characteristics

Abbreviations: AML, acute myeloid leukaemia; CR1, first complete remission; ECOG, Eastern Cooperative Oncology Group; HSCT, haematopoetic stem cell transplant; Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3; RWE, real world evidence

Key Issue: Nilsson et al. - Post-hoc subgroup analysis results

Primary outcome: Leukaemia-free survival

Kaplan-Meier curve of leukaemia-free survival in people in CR1, with normal karyotype, 60 years or below (n=72)



Percentage alive and leukaemia-free at different time points

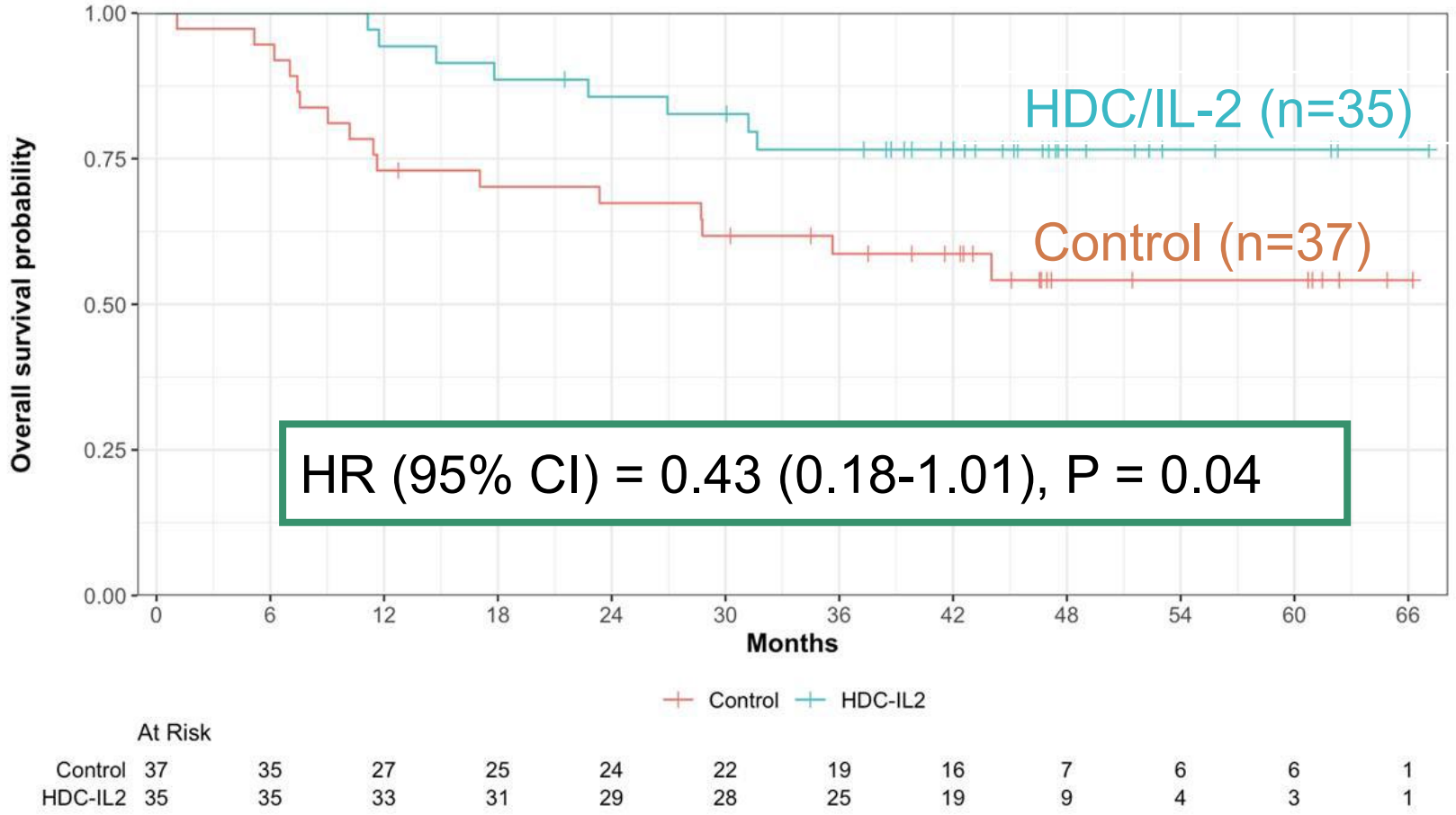
Percentage alive and leukaemia-free	HDC/ IL-2 N=35	BSC N=37
At 12 months	71.4	54.1
At 24 months	65.6	37.0
At 36 months	65.6	31.3
At 48 months	65.6	28.4
At 60 months	65.6	28.4

Abbreviations: BSC, best supportive care; CR1, first complete remission; HR, hazard ratio; CI, confidence intervals; HDC/IL-2, histamine dihydrochloride with interleukin-2

Key Issue: Nilsson et al. - Post-hoc subgroup analysis results

Secondary outcome: Overall survival

Kaplan-Meier curve of overall survival in people in CR1, with normal karyotype, 60 years or below (n=72)



Percentage patients alive at different times

Percent alive	HDC/ IL-2 N=35	BSC N=37
At 12m	94.3	73.0
At 24m	85.6	67.4
At 36m	76.5	58.7
At 48m	76.5	54.1
At 60m	76.5	54.1

EAG cautions against interpretation of the results from these subgroups: not pre-specified - exploratory. High risk of bias.

Is the post-hoc analysis sufficiently robust for decision-making?

Abbreviations: BSC, best supportive care; CR1, first complete remission; HR, hazard ratio; HDC/IL-2, histamine dihydrochloride with interleukin-2

Indirect treatment comparison vs azacitidine*

Estimated treatment effect difference is highly uncertain

Background

- Company claims oral azacitidine would be used mainly for older people (trial was limited to over 55), and HDC/IL-2 would be used for under 60s
- In response to clarification, company did ITC using QUAZAR AML-001 for oral azacitidine
- Results based on the ITT populations are used in company's economic model

ITC results for OS and LFS with oral azacitidine versus HDC/IL-2 (HR<1 favours aza)

	HR	Lower 95% CI	Upper 95% CI	p
OS (ITT populations)	[redacted]	[redacted]	[redacted]	[redacted]
OS (QUAZAR AML-001 ITT and Brune et al. normal karyotype, CR1 and <60 years populations)	[redacted]	[redacted]	[redacted]	[redacted]
LFS (ITT population)	[redacted]	[redacted]	[redacted]	[redacted]
LFS (QUAZAR AML-001 ITT and Brune et al. normal karyotype, CR1 and <60 years populations)	[redacted]	[redacted]	[redacted]	[redacted]

*See also baseline characteristics comparison

Abbreviations: ITT, intention-to-treat; ITC, indirect treatment comparison; CR1, first complete remission; HR, hazard ratio; CI, confidence intervals; HDC/IL-2, histamine dihydrochloride with interleukin-2; OS, overall survival; LFS, leukaemia-free survival

Key issue: Reliability of ITC

Small impact

EAG concerns about differences between trials and data used in economic model

EAG comments

- Population in Brune et al. younger and healthier than in QUAZAR
  - Age may be a treatment effect modifier for HDC/IL-2 and oral azacitidine
- Brune et al. conducted much earlier than QUAZAR – change in treatment landscape
  - Concerns with using standard of care arms as common comparator
- No results for the relevant subgroup in QUAZAR so **ITT population** ITC used in model
- HRs used in model derived from a mixture of stratified and unstratified HRs
  - Unstratified HR for OS from QUAZAR used (less favourable to oral azacitidine than the stratified HR)

→ EAG presents alternative scenarios to explore uncertainty:

Scenario	HR for oral azacitidine versus HDC/IL-2	
	LFS	OS
Company's updated base case	[redacted]	[redacted]
EAG's preferred - stratified OS HR from QUAZAR	[redacted]	[redacted]
Lower bound of LFS and OS 95%CIs	[redacted]	[redacted]
No treatment difference	1.00	1.00

What are the most plausible HRs to use in the model?

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; ITT, intention-to-treat; ITC, indirect treatment comparison; HR, hazard ratio; OS, overall survival; LFS, leukaemia-free survival

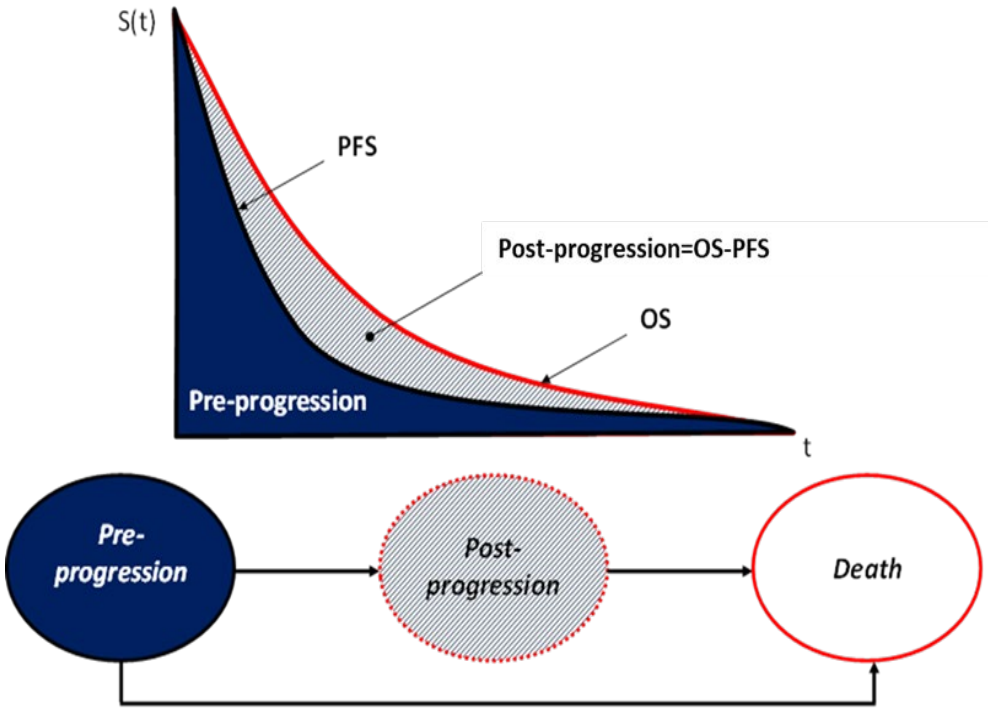
Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

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

NICE National Institute for Health and Care Excellence

Company's model overview

Partitioned survival model



*Nested sub-states for HDC/IL-2 and oral azacitidine groups with different HRQoL outcomes and costs

Company's model

- Population: Patients with AML, in CR1, ≤ 60 years, normal karyotype, alloSCT unsuitable
- 60-year time horizon
- 1 month cycle length
- All patients self-administer HDC/IL-2, no accessories costed
- Subsequent treatment only alloSCT: one-off cost, no impact on health outcomes

HDC/IL-2 affects QALYs by:

- Extending LFS and OS vs SoC, reducing vs azacitidine
- Increasing AE-related QALY losses vs SoC

HDC/IL-2 affects costs by:

- Increasing drug and health state costs
- Increasing AE-related costs vs SoC
- Reducing costs for allo-SCT as a subsequent treatment vs SoC

NICE

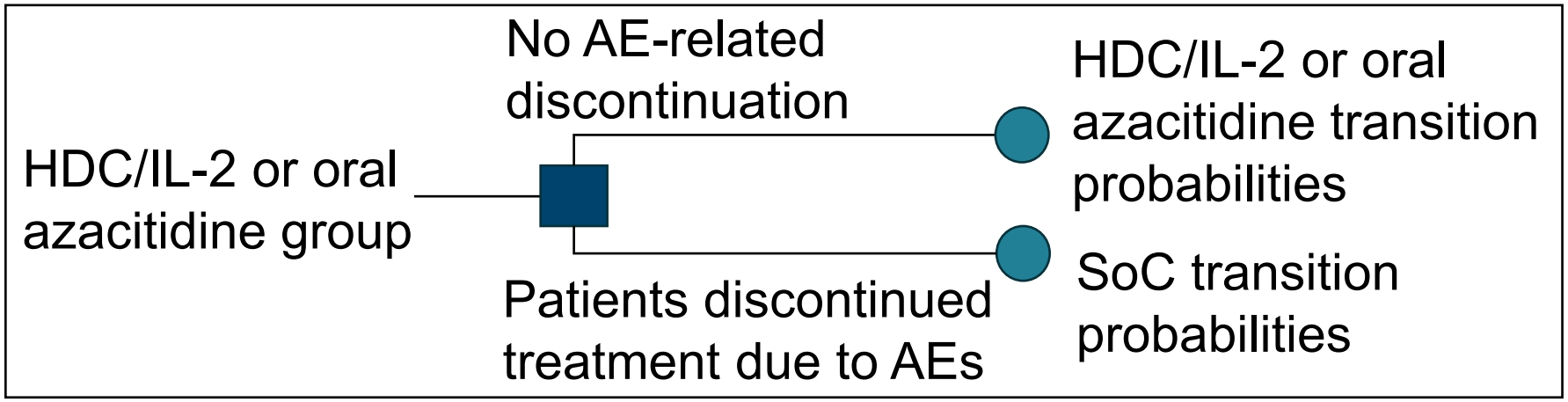
Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; HRQoL, health-related quality of life; AML, acute myeloid leukaemia; CR1, first complete remission; allo-SCT, allogeneic stem cell transplant; LFS, leukaemia-free survival; OS, overall survival; AE, adverse events; QALY quality-adjusted life year; SoC, standard of care

Small impact

Key issue: Discontinuation/blended survival model

EAG considers discontinuation is double-counted

EAG notes there is an implicit decision tree for active treatment in 1st cycle of model:



Company's blended model: Overall LFS/OS cumulative probabilities based on weighted mean estimates for discontinuers and non-discontinuers

EAG comments

- Individual patient data used to produce standard parametric models for LFS and OS of HDC/IL-2 already included 8.3% of patients who discontinued treatment due to adverse events unrelated to relapse - treatment discontinuation is double counted
  - EAG approach (non-blended): treatment discontinuation only applies to partitioning between on-treatment and off-treatment groups within leukaemia-free state
  - LFS and OS modelled using a non-blended approach, based directly on standard parametric survival estimates

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; AE, adverse events; SoC, standard of care; LFS, leukaemia-free survival; OS, overall survival

Key Issue: Long-term survival extrapolations

Large impact

Company jointly fitted parametric survival models, EAG prefers to fit independently

Summary of company and EAG preferred parametric survival models

	Treatment	Company model	EAG's preferred model	Company model 10y survival	EAG model 10y survival
LFS	HDC/IL-2	Joint fit Exponential	Independent Exponential	Over 25%	Just above 25%
	SoC	Joint fit Exponential	Independent Log-normal	Less than 10%	Approx 10%
OS	HDC/IL-2	Joint fit Exponential	Independent Weibull	Nearly 50%	Around 40-45%
	SoC	Joint fit Exponential	Independent Weibull	20%	>25%

Extrapolations for oral azacitidine obtained by applying HR from ITC (from ITT population) to selected parametric models for HDC/IL-2 group:

- LFS: HR = [redacted]
- OS: Company HR = [redacted], EAG HR = [redacted]

NICE

Abbreviations: LFS, leukaemia-free survival; HDC/IL-2, histamine dihydrochloride with interleukin-2; SoC, standard of care

Large impact

Key Issue: Long-term survival extrapolations

EAG highlights concerns about survival extrapolations

EAG comments

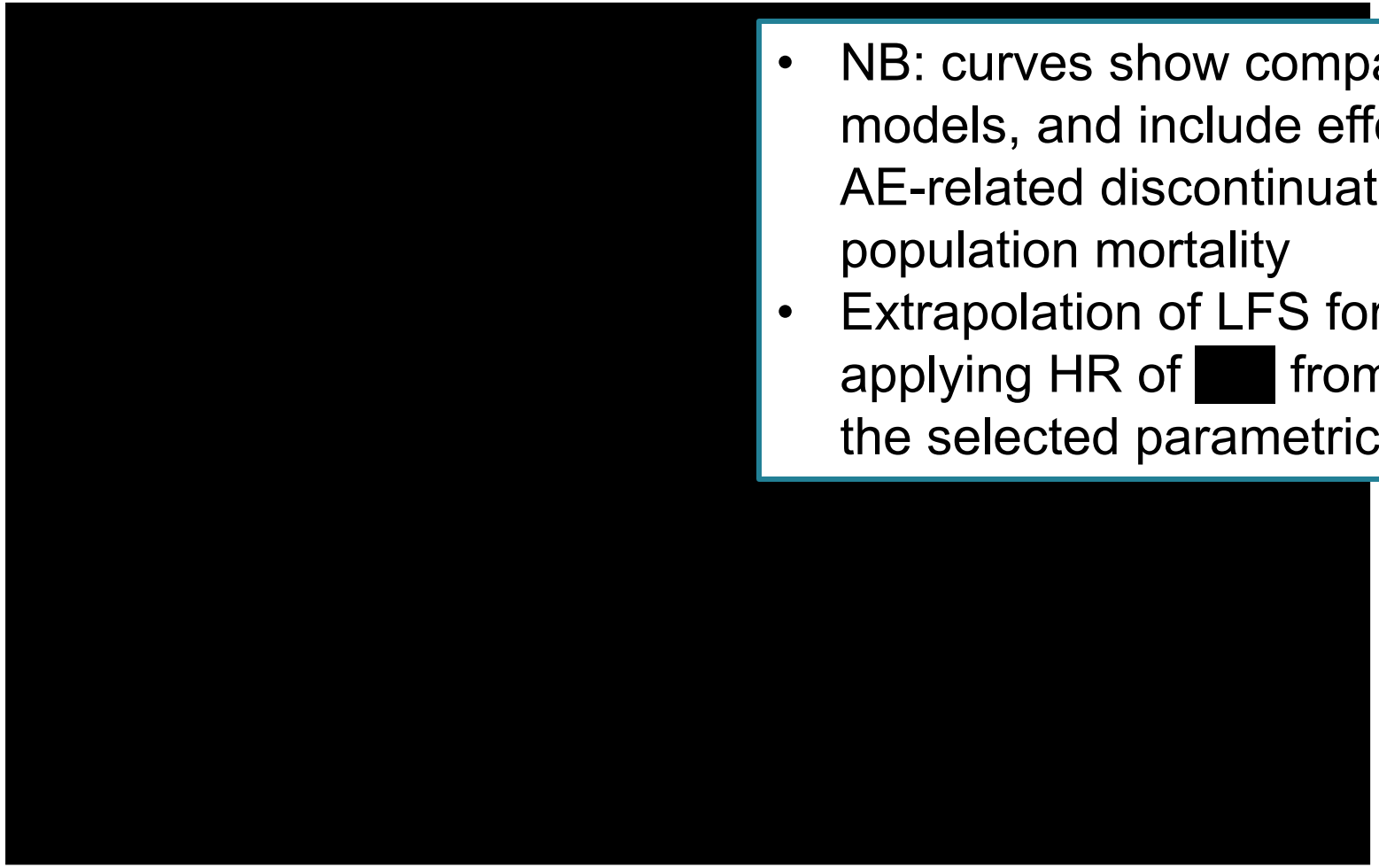
- Proportional hazards assumption may not hold and no clinical evidence to suggest that the treatment effect remains constant over time
  - EAG prefers to fit independent models
- Small sample size (<40 per treatment arm), high censoring and limited follow-up
- Company's preferred models did not converge to zero within plausible time frame
- Clinicians' expected survival estimates may reflect current standard of care and subsequent treatment options not available at time of trial
- All-cause mortality may increase at older ages – may not be fully reflected in models

Abbreviations: OS, overall survival; HDC/IL-2, histamine dihydrochloride and interleukin 2; SoC, standard of care

Large impact

Key Issue: Long-term survival extrapolations – LFS*

EAG preferred independently fitted parametric survival models



- NB: curves show company and EAG preferred models, and include effect of different approaches to AE-related discontinuation, and cap for general population mortality
- Extrapolation of LFS for oral azacitidine obtained by applying HR of [redacted] from ITC using ITT population to the selected parametric models for HDC/IL-2 group.

*see also jointly and independently fitted models

Abbreviations: LFS, leukaemia-free survival; ITC, indirect treatment comparison; ITT, intention-to-treat; AE, adverse events; HR, hazard ratio

Large impact

Key Issue: Long-term survival extrapolations - OS

EAG preferred independently fitted parametric survival models

[redacted]

- NB: curves include effect of different approaches to AE-related discontinuation, and cap for general population mortality
- Extrapolation of OS for oral azacitidine obtained by applying HR from ITC using ITT population to the selected parametric models for the HDC/IL-2 group.
  - Company HR = [redacted], EAG HR = [redacted]

Which survival extrapolations are the most plausible for LFS and for OS?

Which approach is more appropriate for modelling AE-related discontinuation: company or EAG's?

Abbreviations: OS, overall survival; LFS, leukaemia-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2

Key Issue: Utility values

Small impact

Various literature sources identified but unclear which is most plausible

Background

- HRQoL data collected in Brune et al. were unavailable to the company
- Health state utility values in company's model informed by external data: Tremblay et al.
- Scenarios with alternative sources in original submission but not in updated model
- EAG unclear which is the best source of utilities

Company's utility source	EAG comments
Base case: Tremblay et al.	Economic evaluation study – utility estimates based on different literature sources - some using EQ-5D-5L or in patients with myelodysplastic syndromes in US
Joshi et al.	Composite time trade off method
Stein et al.	Discrete choice experiment method (US)
Russell-Smith et al.	From TA399: trial-based disease specific EORTC QLQ-C30 data mapped to EQ-5D

EAG also highlights number of self-administered injections for people having HDC/IL-2 (controlled manual subcut injection by syringe with timer) - no evidence from company about HRQoL impact or patient preferences.

- EAG scenario: 0.124 utility decrement added (based on study in type 2 diabetes)

Abbreviations: HRQoL, health-related quality of life; HDC/IL-2, histamine dihydrochloride with interleukin-2

Small impact

Key Issue: Utility values

Health state utility values identified by the company in literature

Mean utility value applied in each health state of the model

Analysis	Pre-progression utility, on treatment (not SoC)	Pre-progression utility, off treatment + SoC	Post-progression utility, all groups
Base case: Tremblay	0.81	0.83	0.53
Scenario 1: Joshi	0.89	0.89	0.51
Scenario 2: Stein	0.87	0.87	0.62
Scenario 3: Russell-Smith	0.74	0.74	0.57

Company assumed patients having treatment with oral azacitidine would incur same utility value as patients receiving HDC/IL-2.
EAG notes that the reasons behind this approach are unclear.

What is the best source for utility values?
Is it appropriate to include a utility decrement of 0.124 for self-administration?

NICE

Abbreviations: SoC, standard of care; HDC/IL-2, histamine dihydrochloride with interleukin-2

Small impact (vs SoC)

Key issue: QALY weightings for severity

Background

- EAG calculated general population QALYs (based on baseline characteristics from company's model), absolute and proportional shortfalls
- Results suggest 1.2x severity modifier should be applied to comparison with SoC only

	QALYs of people without condition	QALYs with the condition on current treatment	Absolute QALY shortfall (must be >12)	Proportional QALY shortfall (must be >0.85)
Company base case: SoC	17.62	3.54	14.08	79.91%
Company base case: Oral aza	[redacted]	[redacted]	[redacted]	[redacted]
EAG: SoC	17.62	4.13	13.49	76.56%
EAG: Oral aza	[redacted]	[redacted]	[redacted]	[redacted]

Does the committee agree it is appropriate to apply a QALY weighting for severity for the comparison with standard care only?

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care; QALY, quality-adjusted life year

Summary of company and EAG-preferred analysis assumptions

Assumptions in company and EAG base case

Issue	Company's base case assumption	EAG view / scenario	Key
Comparator	Oral azacitidine not relevant comparator	Considers there is an overlap in populations	-
Trial generalisability	Brune population is relatable to currently eligible population	Significant uncertainty about applicability of Brune to NHS practice	-
Treatment effect from ITC	Unstratified HR for OS from QUAZAR AML-001 (oral azacitidine)	Stratified HR for OS from QUAZAR AML-001	EA2
Survival extrapolations	Jointly fitted exponential models for extrapolating LFS and OS	• LFS: Independently fitted exponential model for HDC/IL-2 and log-normal model for SoC • OS: Independently fitted Weibull models for both HDC/IL-2 and SoC	EA3

Abbreviations: HR, hazard ratio; LFS, leukaemia-free survival; HDC/IL-2, histamine dihydrochloride with interleukin-2; OS, overall survival; SoC, standard of care

Summary of company and EAG-preferred analysis assumptions

Assumptions in company and EAG base case

Issue	Company's base case assumption	EAG scenario	Key
Costs	• No RDI, premedication and admin costs for oral azacitidine • No wastage for IL-2 • Admin costs include 1 dispensing of HDC/IL-2 per treatment cycle • Proportion of patients receiving each SoC regimen from TA827	• Includes RDI, premedication and admin costs for oral azacitidine • Includes wastage for IL-2 • HDC/IL-2 is dispensed twice per treatment cycle in model • Proportions slightly revised (exclusion of fluconazole – clinical opinion)	EA4 EA5 EA6 EA7
Treatment discon-tinuation	Blended approach for LFS and OS, based on rate of discontinuation	Blended approach removed, LFS and OS informed by data from Nilsson	EA8
Utilities	No disutility included related to the frequency of injections for HDC/IL-2	Inclusion of disutility of 0.124 in cycles where HDC/IL-2 treatment given.	EA9

Abbreviations: RDI, relative dose intensity; LFS, leukaemia-free survival; HDC/IL-2, histamine dihydrochloride with interleukin-2; OS, overall survival; SoC, standard of care

Cost-effectiveness results

- EAG states that company's PSA provides a weak characterisation of parameter uncertainty, and considers deterministic results to be more reliable than probabilistic
- Full results compared with oral azacitidine are confidential because of confidential comparator prices and presented in part 2 for committee only

Company base case with EAG deterministic scenario analyses (1/2)

Results comparing HDC/IL-2 with SoC and with oral azacitidine (confidential PAS included)

No.	Scenario (applied to company base case)	Inc QALYs vs SoC	Inc costs vs SoC	ICER (£/QALY) vs SoC*	ICER (£/QALY) vs oral aza
	Company base case	**3.20**	**£77,317**	**£20,153**	**HDC/IL-2 dominated**
EA1	Error corrections	3.06	£76,809	£20,915	HDC/IL-2 dominated
EA2	Oral aza: stratified HR for OS from QUAZAR	-	-	-	HDC/IL-2 dominated
EA3	Alternative LFS and OS models for HSC/IL-2 and SoC	1.74	£57,046	£27,357	HDC/IL-2 dominated
EA4	Include additional elements for oral aza costs	-	-	-	HDC/IL-2 dominated
EA5	Include wastage for IL-2	3.06	£79,494	£21,646	HDC/IL-2 dominated

*ICER includes 1.2x severity modifier for SoC comparison

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; LFS, leukaemia-free survival; HDC/IL-2, histamine dihydrochloride with interleukin-2; OS, overall survival; SoC, standard of care; Inc., incremental

Company base case with EAG scenario deterministic analyses (2/2)

Results comparing HDC/IL-2 with SoC and with oral azacitidine (confidential PAS included)

No.	Scenario (applied to company base case)	Inc QALYs vs SoC	Inc costs vs SoC	ICER (£/QALY) vs SoC*	ICER (£/QALY) vs oral aza
	Company base case	**3.20**	**£77,317**	**£20,153**	**HDC/IL-2 dominated**
EA6	Alternative admin costs for HDC/IL-2	3.06	£79,244	£21,578	HDC/IL-2 dominated
EA7	Alternative SoC drugs	3.06	£76,835	£20,922	HDC/IL-2 dominated
EA8	Remove discontinuation approach to health outcomes	3.34	£79,370	£19,806	HDC/IL-2 dominated
EA9	Include disutility for HDC/IL-2 injections	2.97	£76,809	£21,520	HDC/IL-2 dominated
EA10	**EAG-preferred (1-9 combined)**	**1.81**	**£62,851**	**£28,918**	**HDC/IL-2 dominated**

NICE

*ICER includes 1.2x severity modifier for SoC comparison

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HR, hazard ratio; LFS, leukaemia-free survival; HDC/IL-2, histamine dihydrochloride with interleukin-2; OS, overall survival; SoC, standard of care; Inc., incremental

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

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

NICE National Institute for Health and Care Excellence

Managed access

Criteria for a managed access recommendation

No managed access proposal submitted

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia

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

NICE National Institute for Health and Care Excellence

Key issues

Issue	Key question	ICER impact
Comparators	What are the most appropriate comparators for HDC/IL-2?	**Large decision-altering impact**
Generalisability	Are the trial outcomes generalisable to the relevant population? Is the post-hoc analysis robust for decision-making?	**Large decision-altering impact**
Indirect treatment comparison	What are the most plausible hazard ratios to use in the model?	**Small**
Survival extrapolations	Which survival extrapolations are the most plausible for LFS and for OS?	**Large (vs SoC)**
Utility values	What is the best source for utility values? Is it appropriate to include a utility decrement?	**Small (bigger for SoC)**
Treatment discontinuation	Which approach is more appropriate for modelling AE-related discontinuation: company or EAG's?	**Small**
Severity	Is it appropriate to apply a QALY weighting for severity for the comparison with standard care only?	**Small**

Abbreviations: HDC/IL-2, histamine dihydrochloride with interleukin-2; LFS, leukaemia-free survival; OS, overall survival; SoC, standard of care, QALY, quality-adjusted life year

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with AML who are in first remission.	Adult AML patients who have undergone intensive therapy with induction and consolidation treatment, who are not considered suitable for allogeneic stem cell transplant, who are in CR1 and 60 years old or younger	Narrower than population eligible for HDC/IL-2 in the marketing authorisation. Company also excluded patients with FLT3 mutations.
Intervention	Histamine dihydrochloride with interleukin-2 as maintenance therapy.	No change.	N/A

Abbreviations: AML, acute myeloid leukaemia; CR1, first complete remission; HDC/IL-2, histamine dihydrochloride with interleukin-2; FLT3, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3

Decision problem

	Final scope	Company	EAG
Comparators	Established clinical management including: • oral azacitidine for people who cannot have or do not want a HSCT • midostaurin for people with an FLT3-mutation • sorafenib, after a stem cell transplant, for people with an FLT3-ITD mutation • quizartinib for people with an FLT3-ITD mutation • cytarabine alone or in combination with other antineoplastic agents • best supportive care	Best supportive care Oral azacitidine included at clarification. Patients with FLT3 mutations would have already received targeted treatment in induction and consolidation and would not switch to HDC/IL-2. Target population is people not eligible for stem cell transplant. Cytarabine not being used in UK clinical practice.	Agree that patients with FLT3 mutations would remain with FLT3 targeted therapies during maintenance treatment. Also agree with excluding cytarabine.

Abbreviations: FLT3, Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3; HSCT, haematopoeitic stem cell transplant; HDC/IL-2, histamine dihydrochloride with interleukin-2;

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Minimal residual disease • Remission rate • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	• Leukaemia-free survival (LFS) • OS • Remission rate • AEs of treatment • HRQoL	No results for minimal residual disease, remission rate or HRQoL. LFS used as equivalent to PFS.

Brune 2006 baseline characteristics

For the target population of the submission

Adults with AML in CR1, under 60 years, normal karyotype, not eligible for allo-SCT

Baseline characteristic	HDC/IL-2 (n=35)	Control (n=37)
Age (mean, median)	45.4, 46.0	43.0, 44.5
Female/male (%)	19/16 (54%/46%)	17/20 (46%/54%)
ECOG performance status (0/1)	30/5 (86%/14%)	31/6 (84%/16%)
Prior auto-SCT (yes/no)	8/27 (23%/77%)	5/32 (14%/86%)
Prior high-dose cytarabine (yes/no)	32/3 (91%/9%)	33/4 (89%/11%)

EAG

- 18% had prior auto-SCT: not commonly used in current UK practice
- May not be comparable with overall population of trial
- Risk profile of target population may differ, as outcomes in younger patients have substantially improved since the time of trial, due to advances in AML management

Link back to Key Issue : Clinical trial: Brune et al. 2006

Abbreviations: AML, acute myeloid leukamia; CR1, first complete remission; allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; HDC/IL-2, histamine dihydrochloride with interleukin-2

Comparison of QUAZAR AML-001 and Brune

Baseline characteristics of populations in QUAZAR AML-001 and Brune

	QUAZAR AML-001 (N=472)	Brune et al. ITT (N=320)	Company target population
Mean age	67.9	[redacted]	44.2
Median age	68	55 intervention, 54 control	46.0 intervention, 44.5 control
Proportion male, %	52%	53.13%	50%
ECOG 0	227 (48%)	239 (74.7%)	61 (84.7%)
ECOG 1	207 (44%)	81 (25.3%)	11 (15.3%)
ECOG 2 or 3	38 (8%)	0	0
Favourable cytogenetics	0	27 (8.4%)	0
Intermediate cytogenetics	406 (86%)	190 (59.4%)	72 (100%)
Poor cytogenetics	66 (14%)	17 (5.3%)	0
Unknown cytogenetics	0	86 (26.9%)	0

Link back to Key issue: Reliability of ITC

Abbreviations: ITT, intention-to-treat; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison

How company incorporated evidence into model

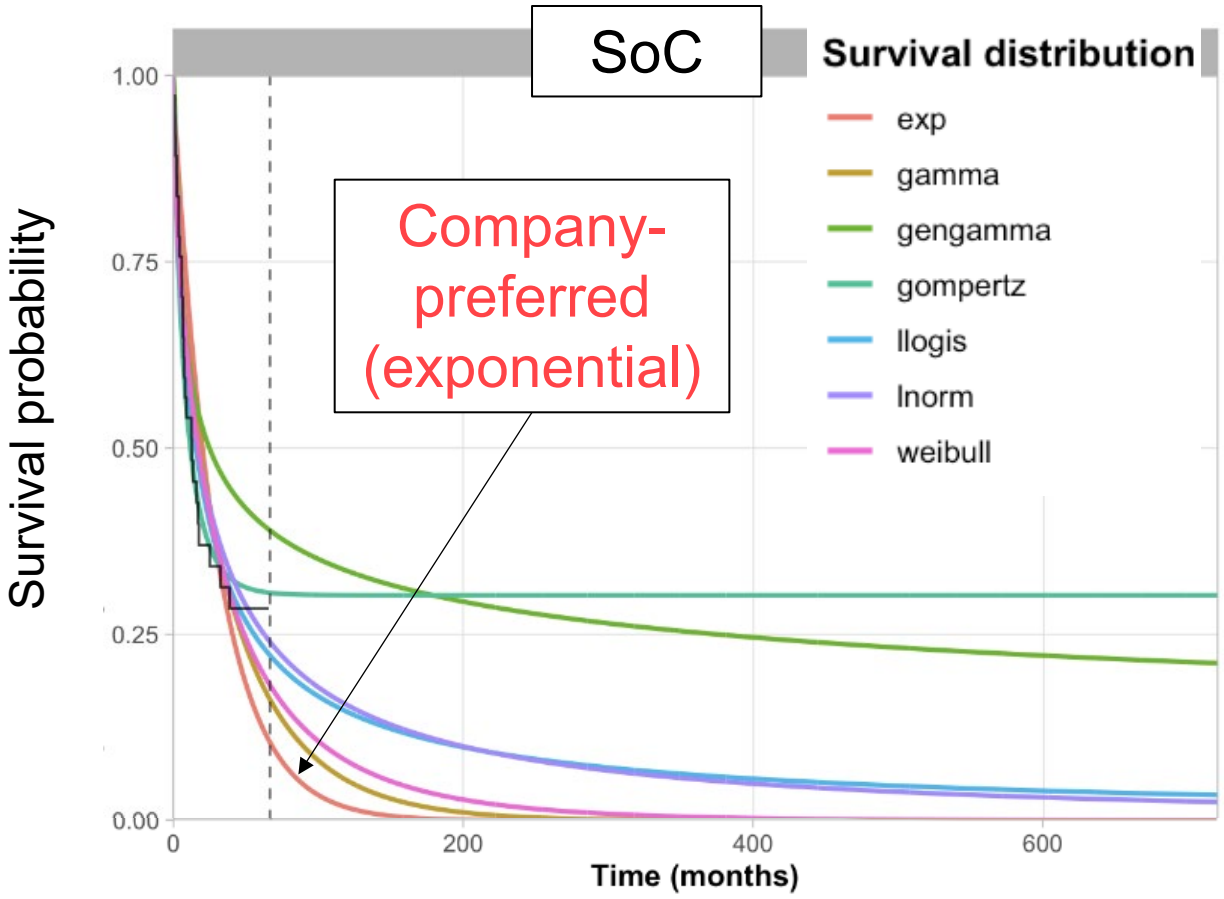
Input and evidence sources

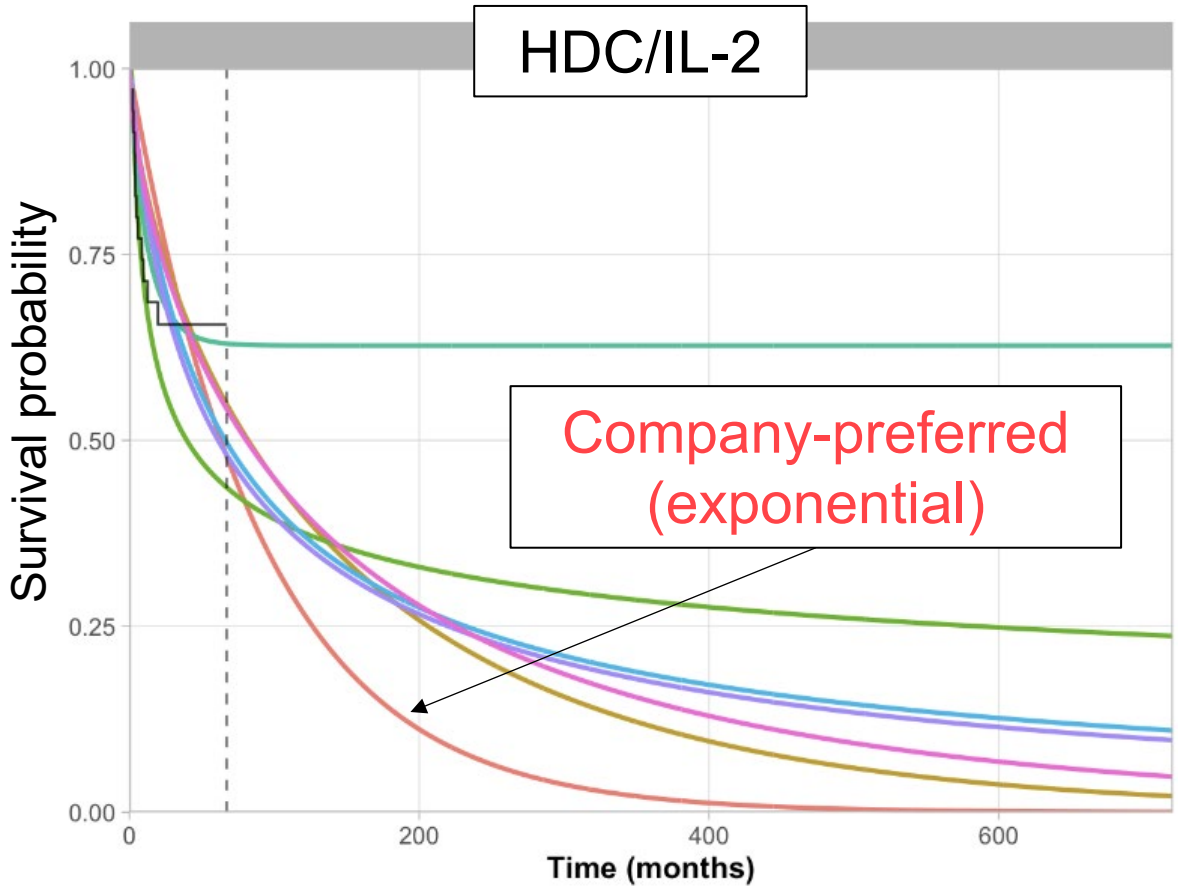
Input	Assumption and evidence source
Baseline characteristics	Subgroup (Nilsson et al.) of the Brune study. Mean weight from NHS HSE – EAG corrects to Brune data
Intervention efficacy	Exponential models fitted to data from subgroup in Nilsson.
Comparator efficacy	Same for SoC, oral azacitidine based on HR from ITC
Discontinuation (first cycle only)	Incidence of discontinuation due to AEs not related to relapse from Brune ITT population for HDC/IL-2 and TA827 for oral azacitidine
Utilities	Tremblay et al. For leukaemia-free state, oral azacitidine utilities assumed same as HDC/IL-2.
Costs and resource use	Drug acquisition: BNF, RDI not included Drug administration: NHS Cost Collection 2023/24 SoC post-progression drug costs: TA827 and eMIT Allo-SCT: Wei et al., NHS Cost Collection 23/24 Health state costs: TA827 and NHS Cost Collection 23/24 AE management: NHS Cost Collection 23/24 End of life: Round et al.

Abbreviations: HSE, Health Survey for England; SoC, standard of care; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2; BNF, British National Formulary; ITC, indirect treatment comparison; RDI, relative dose intensity; SCT, stem cell transplant; AE, adverse events

Jointly-fitted leukaemia-free survival extrapolation

Company preferred jointly-fitted models



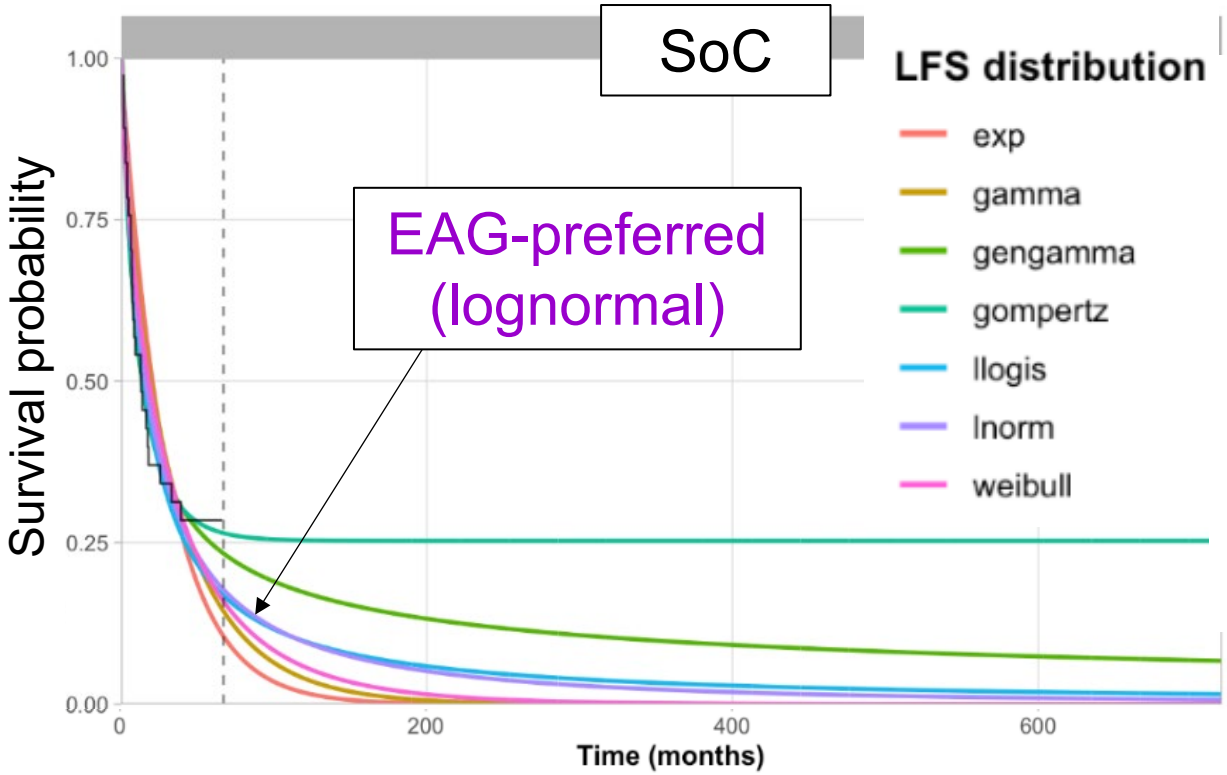


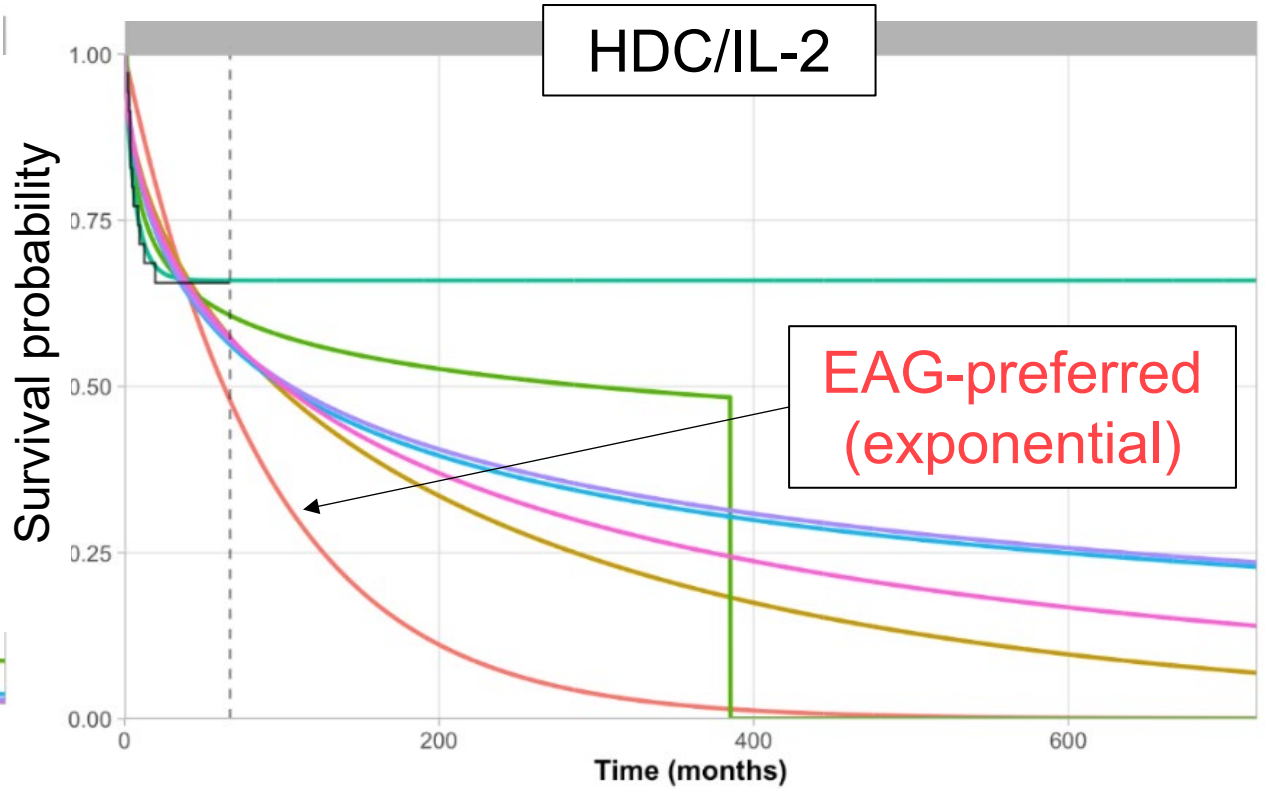
Abbreviations: OS, overall survival; LFS, leukaemia-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2

Independently-fitted leukaemia-free survival extrapolations

EAG preferred independently fitted parametric survival models

Observed vs predicted LFS from **independent** models



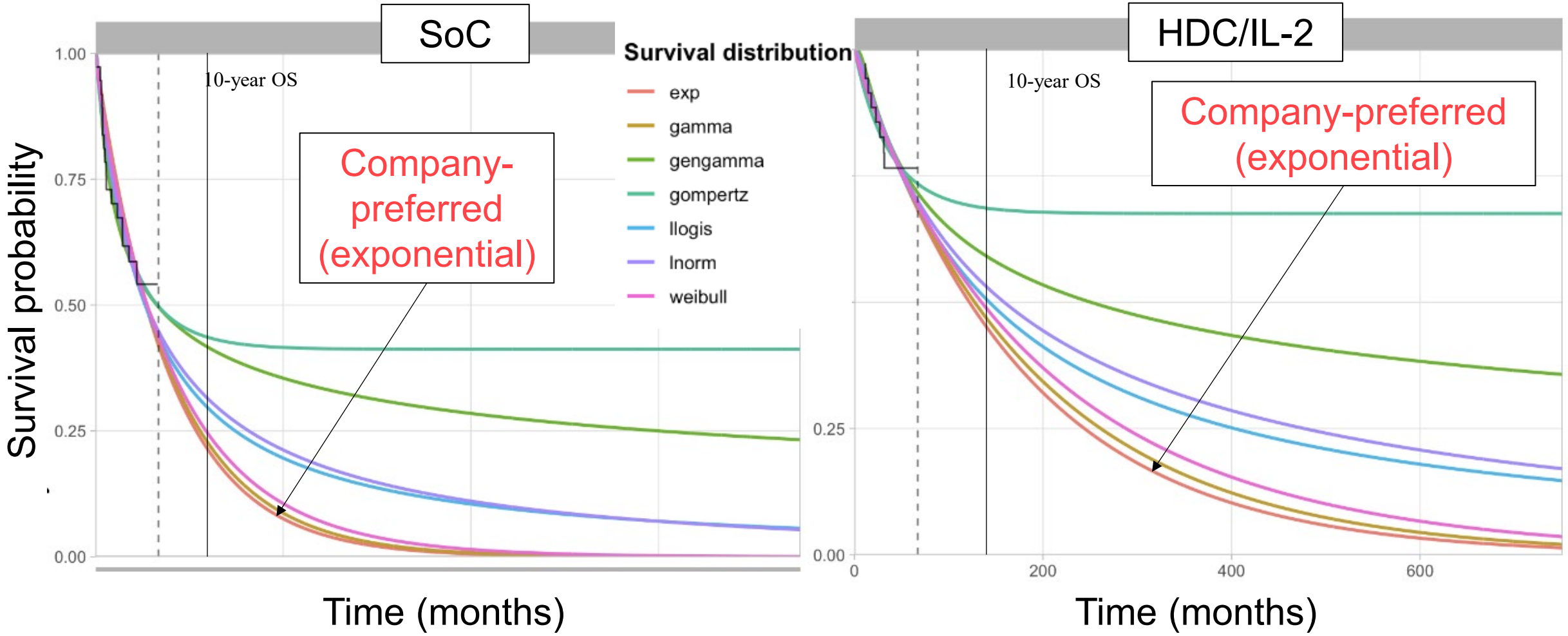


Link back to Key Issue: Long-term survival extrapolations – LFS*

Abbreviations: OS, overall survival; LFS, leukaemia-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2

Jointly-fitted overall survival extrapolations

Company preferred jointly fitted models

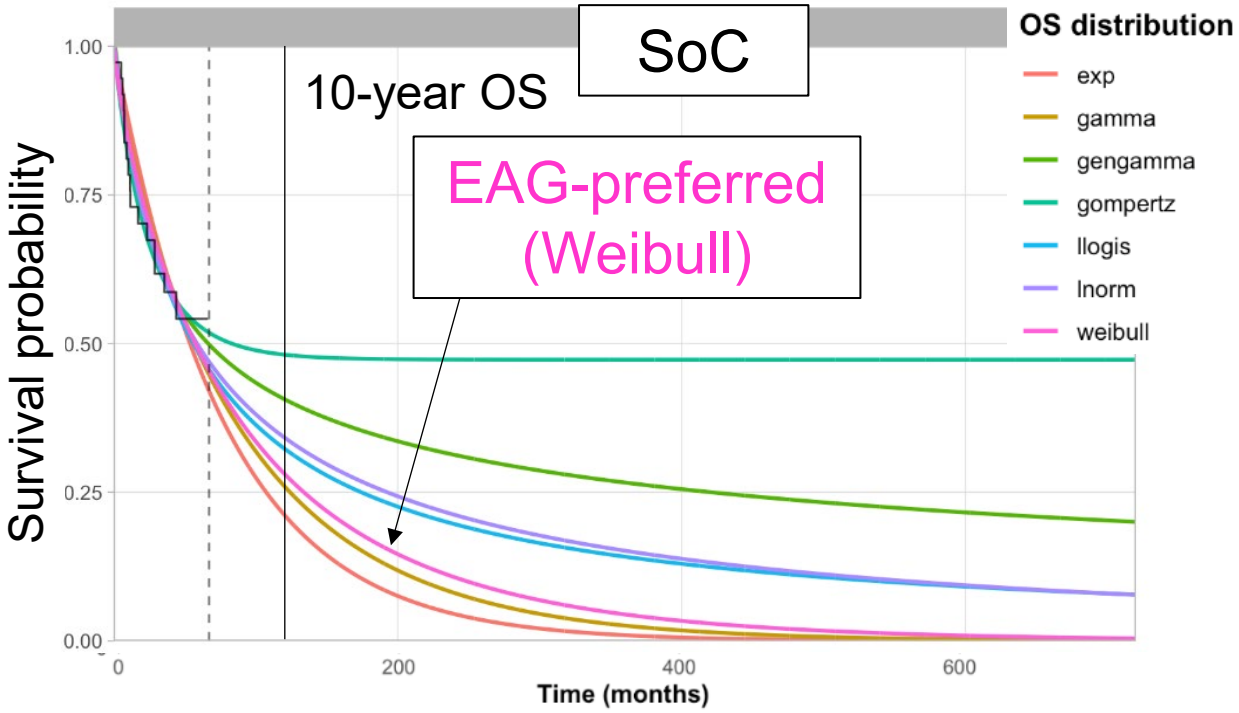


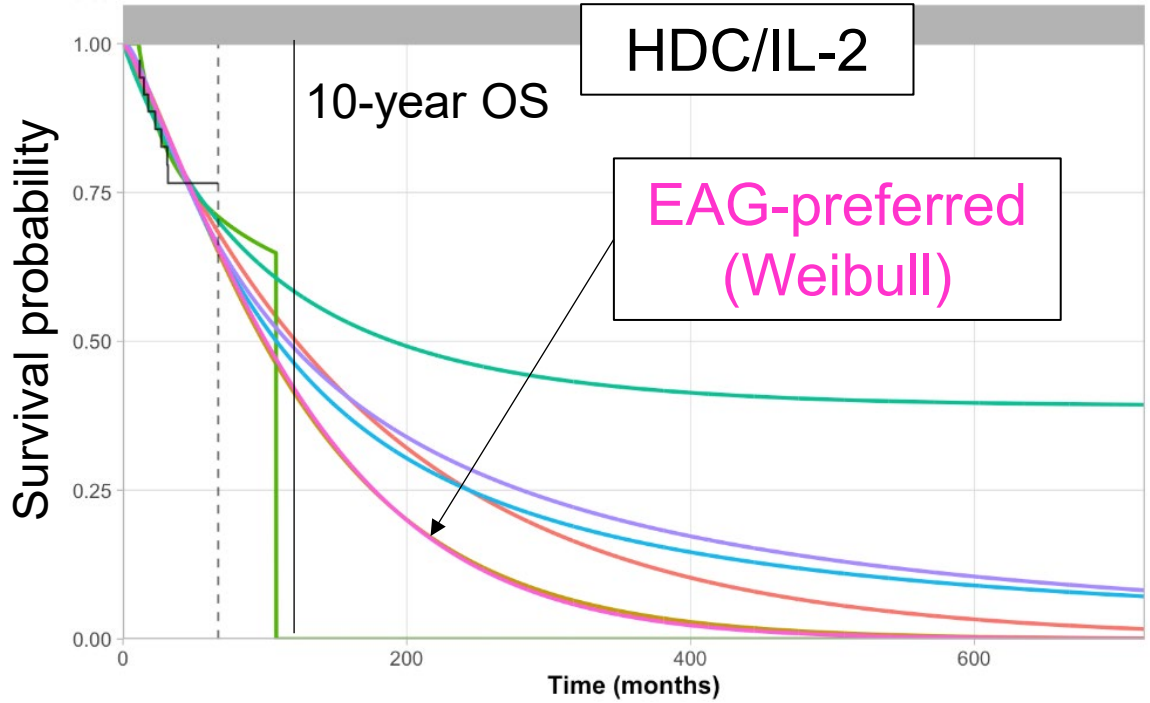
Abbreviations: OS, overall survival; LFS, leukaemia-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2

Independently-fitted overall survival extrapolations

EAG preferred independently fitted parametric survival models

Observed vs predicted OS from **independent** models





Link back to Key Issue: Long-term survival extrapolations - OS

Abbreviations: OS, overall survival; LFS, leukaemia-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HDC/IL-2, histamine dihydrochloride with interleukin-2