Belumosudil for treating chronic graft versus host disease after two or more lines of systemic therapy [ID4021]

Slides for the public – contains no ACIC or CPAS information

PART 1

Technology appraisal committee D – [16 November 2023, 2nd evaluation meeting]

Chair: Dr Stephen Smith

Lead team: Carole Pitkeathley, Andrew Hitchings, Giles Monnickendam

External assessment group: BMJ Technology Assessment Group (BMJ TAG)

Technical team: Janet Boadu, Christian Griffiths, Linda Landells

Company: Sanofi

Belumosudil mesilate (Rezurock, Sanofi)

Marketing authorisation (MHRA, July 2022)	• Belumosudil is indicated for the treatment of patients aged 12 years and older with chronic graft-versus-host disease who have received at least two prior lines of systemic therapy

Key issues

Issue (identified by Lead Team)	Resolved?	ICER impact
Extrapolation of REACH-3 FFS for the BAT arm	No	Unknown
Utility value for failure – new cGvHD systemic therapy	No	Large
Disease management costs for failure – new cGvHD systemic therapy	No	Large

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Abbreviations: BAT, Best available therapy; ICER, Incremental cost-effectiveness ratio; FFS, failure free survival; cGVHD, chronic graft-versus-host disease

DG summary on modelling, cost-effectiveness & other considerations

RECAP

Issue	Committee's considerations	Company's DG response
Company's model	Acceptable, provided issues below addressed	• **Presented scenario analyses responding to committee requests:** -Extrapolation of REACH-3 FFS for BAT -Utility value and disease management costs for 'failure – new cGvHD systemic therapy' health state
Extrapolation of REACH-3 FFS for BAT arm	• BAT KM curve not interpretable to belumosudil trials after 24 weeks • Requested scenario: FFS BAT arm of REACH-3 truncated at week 24 and extrapolated	
Utility value: 'failure – new cGvHD systemic therapy' health state	• Uncertainty in 'failure – new cGvHD systemic therapy' utility value • Requested scenario analyses using EAG midpoint and Crespo et al. utility value	
Disease management costs: 'failure – new cGvHD systemic therapy' health state	• Concerns about disease management cost estimates • (1) More information on HES data and (2) process deriving costs for 'failure – new cGVHD systemic therapy' health state • Requested scenario analyses: % of people in 'failure – new cGVHD systemic therapy' health state linearly reduced to baseline	

Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier; cGvHD, chronic graft versus host disease; HES, Hospital Episode Statistics

DG summary on modelling, cost-effectiveness & other considerations

RECAP

Issue	Committee's considerations	Company's DG response
OS benefit	• EAG's preference removing OS acceptable in absence of more evidence	• **Base case updated removing OS and response outcomes**
Response outcomes	• EAG's preference removing response outcomes appropriate	
Cost-effectiveness results	• Company's base-case ICERs less than £20,000 per QALY for belumosudil (all doses) vs BAT ○ **Uncertainties in model and clinical evidence, cost-effectiveness results not sufficiently robust → further analyses needed to address uncertainty**	
Other considerations	• Noted equality concerns → not sufficient to affect its recommendations • Innovation → all additional benefits captured in model	

Summary of preliminary recommendation

Belumosudil is not recommended, within its marketing authorisation, for treating chronic graft-versus-host disease in people 12 years and over after 2 or more systemic treatments

Abbreviations: OS, overall survival; BAT, best available therapy; ICER, incremental cost-effectiveness ratio

Clinical effectiveness recap: Key clinical trials*

RECAP

- **Phase 2a (KD025-208),** open-label, single arm
  - People ≥18 years, allogeneic bone marrow transplant/ alloHSCT & cGVHD after 1-3 prior LOT
  - ≥2 LOT subgroup used in model

- **ROCKstar (KD025-213) – phase II trial,** open-label, single arm
  - People ≥12 years, alloHSCT & cGVHD after 2-5 prior LOT
  - Sep. 2022 data cut used in model

- **REACH-3 ruxolitinib versus BAT,** randomised, open-label
  - People ≥12 years, alloHSCT & moderate/ severe glucocorticoid-refractory or cGVHD (≥2 cGvHD therapies excluded)
  - Used in model to inform comparator arm

*See more trial details in appendix

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; cGvHD, chronic graft versus host disease; LOT, lines of therapy;

Consultation comments

Comments received from:

- Sanofi (company)
- Therakos
- Anthony Nolan
- NHS England Blood and Marrow Transplantation Clinical Reference Group
- Web comments (n=8)

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Summary of comments from non-company stakeholders

Unmet clinical need

- Current options for accessible cGvHD treatment limited
  - people struggle to access current main treatment (ECP) due to cGvHD-induced immobility
  - challenging to travel for ECP → time consuming

Lasting effects on quality of life

- cGvHD is chronic and therefore unlikely to be in a position where it resolves itself
- Frequently results in new comorbidities because of GvHD treatment or specific organ involvement with GvHD

Severity modifier

- Severity modifier should be applied. Those that have been rendered immobile → psychological and life impacts are life-altering

Abbreviations: cGvHD, chronic graft versus host disease; ECP, Extracorporeal photopheresis

Key Issue: Extrapolation of REACH-3 FFS for the BAT arm (1)

Recap of committee's considerations in draft guidance

- BAT KM curve not interpretable to belumosudil trials after 24 weeks, due to impact of crossover
- Requested scenario: FFS KM data for BAT arm of REACH-3 is truncated at week 24 and extrapolated to exclude possible impact from crossover

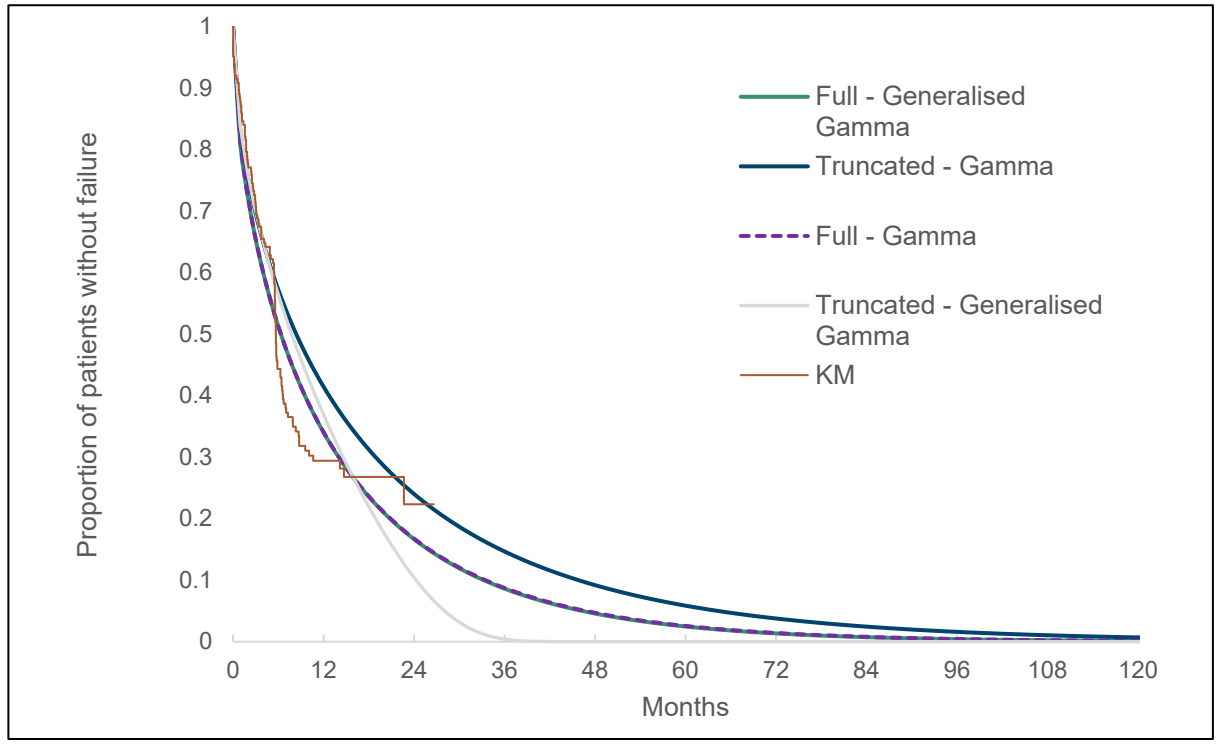
Company's draft guidance response

- Truncated KM curve for BAT, fitted generalised gamma curve gave lower mean predicted FFS ([redacted] years)
- Gamma distribution gave best goodness-of-fit statistics and chosen for base case (mean FFS higher than expected in clinical practice ([redacted] years) → company consider conservative choice)
- Dominance maintained with gamma distribution
- Do not consider scenario most suitable → adds uncertainty and potential bias to BAT arm, less clinical plausibility

Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier

Key Issue: Extrapolation of REACH-3 FFS for the BAT arm (2)*

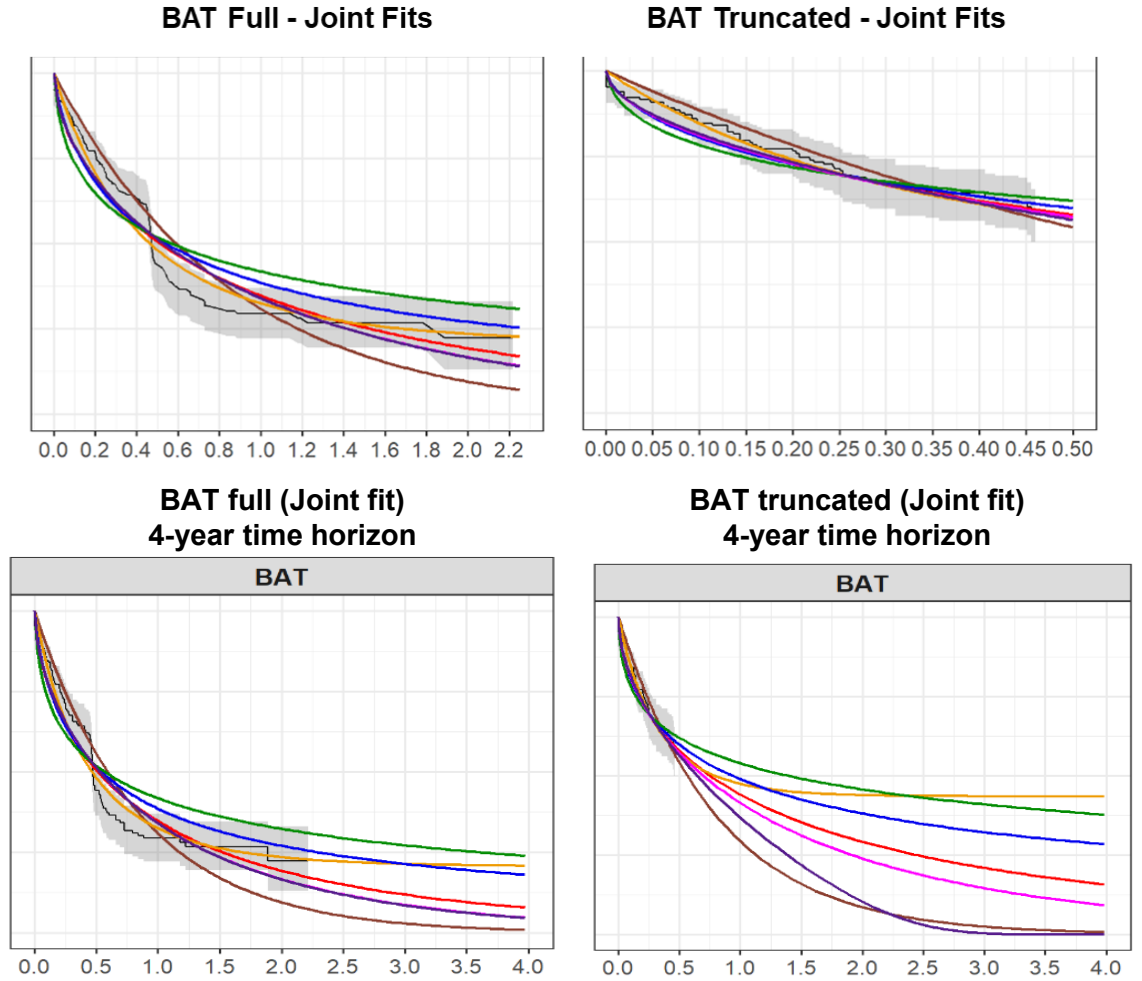
BAT FFS: Generalised Gamma and Gamma fitted curves based on full KM data vs Generalised Gamma and Gamma fitted curves based on KM data truncated at 24 Weeks



Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier

FFS BAT parametric curve comparison (x-axis in years)

Short term



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Key Issue: Extrapolation of REACH-3 FFS for the BAT arm (3)

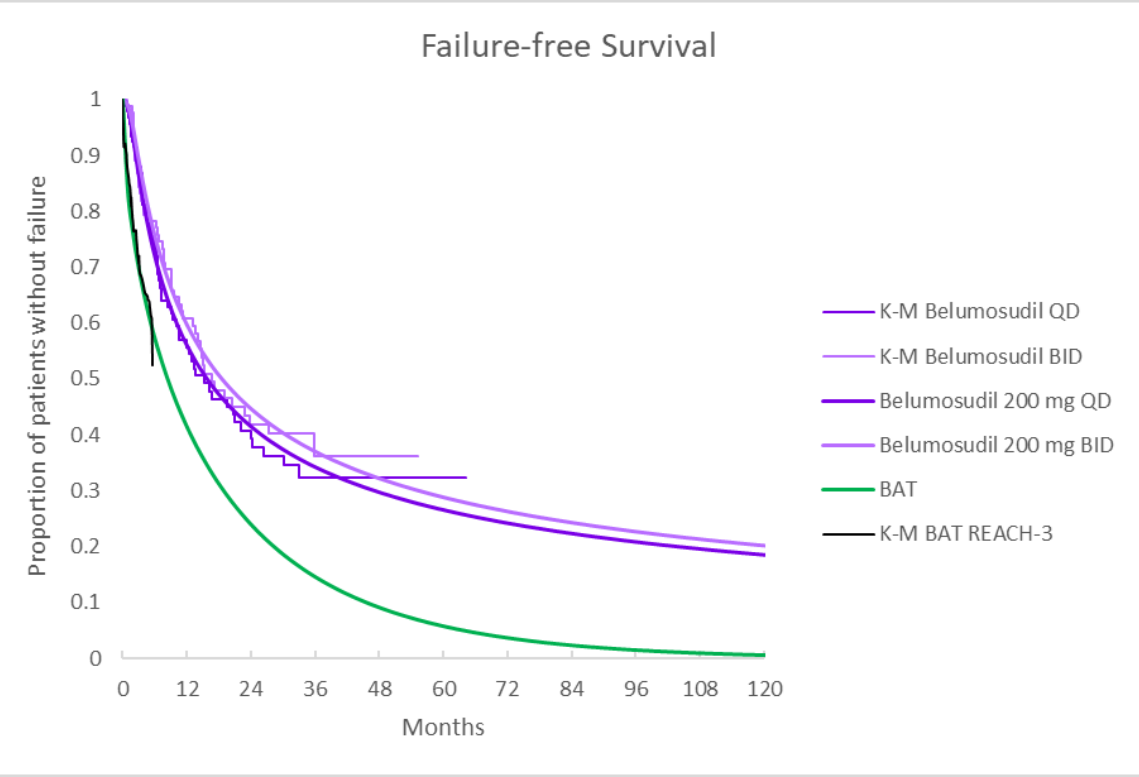
EAG comments

- Gamma distribution provided poor fit to observed belumosudil pooled data; generalised gamma curve for BAT results in more pessimistic mean FFS compared to EAG's base case → may not be clinically plausible
- Generalised gamma for belumosudil+BAT arm could be considered reasonable
- Weibull curve also reasonable → similar statistical & visual fit to company preference (gamma curve) for BAT arm, (mean FFS using Weibull curve BAT = [redacted] years)

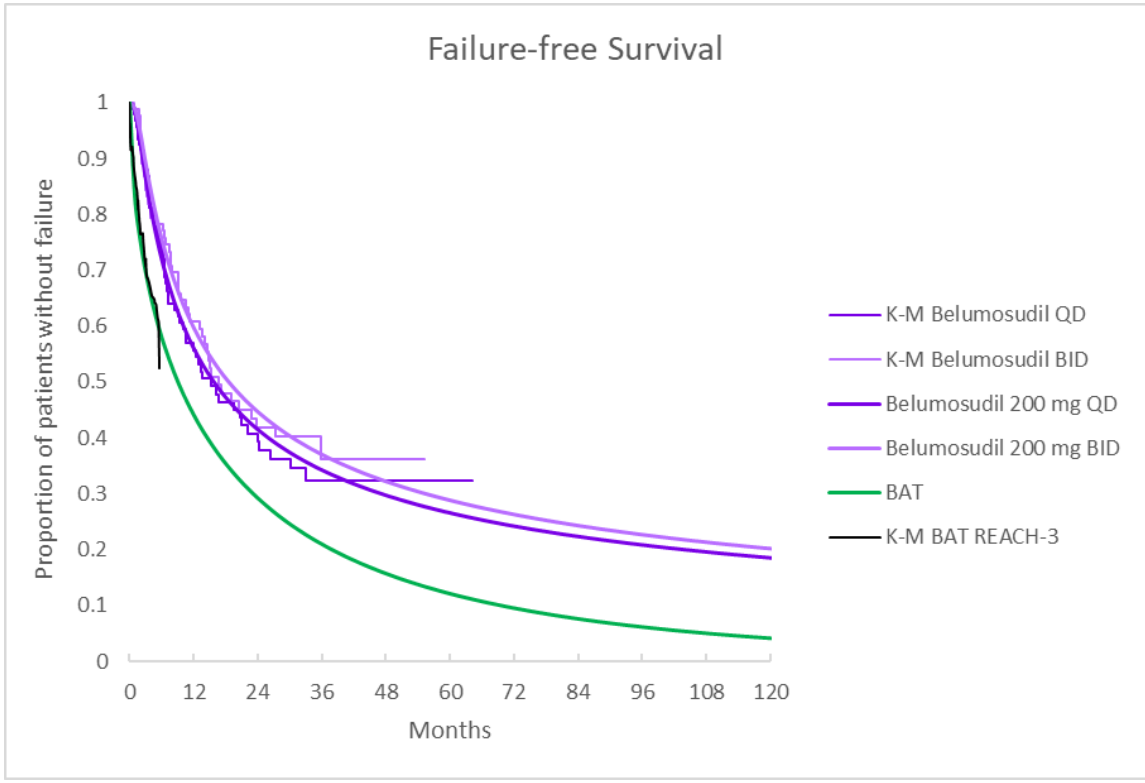
Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier

Key Issue: Extrapolation of REACH-3 FFS for the BAT arm (4)

Modelled FFS– generalised gamma distribution for belumosudil, gamma distribution for BAT (based on truncated REACH-3 data): mean FFS for BAT [redacted] years



EAG modelled scenario: FFS– generalised gamma distribution for belumosudil, Weibull distribution for BAT (based on truncated REACH-3 data): mean FFS for BAT [redacted] years



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Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier

Key Issue: Utility value for failure – new cGvHD systemic therapy (1)

Recap of committee's considerations in draft guidance

- Requested scenario analyses using midpoint value preferred by EAG, and Crespo et al. (2012) utility value

Company's draft guidance response

- Did interviews with 15 clinicians → all described 'failure – new systemic therapy' health state involving ongoing substantial decline of QoL
- Conducted QoL study*: adults with cGvHD who had 2+ prior lines of systemic therapy, and ongoing symptoms
- EQ-5D-5L survey with 17 patients and 8 carers, EQ-5D-5L domain scores mapped onto EQ-5D-3L
- Mean patient QoL → [redacted] (rated [redacted] by patients and [redacted] by carers)
- New utility values more appropriate for use model than EAG-preferred [redacted]
- [redacted] utility value (QoL study) implemented in revised base case, when lower value applied → ICER remains dominant

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*under the conditions of market research in collaboration with Anthony Nolan (study is unpublished). Abbreviations: QoL, quality of life; QALYs, quality-adjusted life year; EQ-5D, EuroQoL-5 Dimensions measure; cGvHD, chronic graft-versus-host disease; ICER, incremental cost-effectiveness ratio

Key Issue: Utility value for failure – new cGvHD systemic therapy (2)

EAG comments

- Company didn't explore committee preferences as part of their revised base case
- Noted number of responses informing utility estimate from QoL study larger (n=25) compared to Adelphi DSP study (n=10)
- Calculating midpoint utility value using data from Crespo et al. still valid. Company QoL study limited
- EAG calculated new midpoint value ([redacted]) based on Crespo *et al.,* (0.696) and company's QoL study ([redacted])
- Scenario analysis results using revised mid-point value, and company's base case utility value of [redacted] and [redacted] → ICER remains dominant

Comments from web

- Not clinically plausible to presume utility maintained moving from FF to failure state
- QoL for this cohort significantly overestimates the QoL for this group of patients

What is the most appropriate estimate of utility value for the Failure - new cGVHD systemic therapy health state?

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Abbreviations: QoL, quality of life; DSP; Disease Specific Programme; ICER, incremental cost-effectiveness ratio; FF, failure-free

Key Issue: Disease management costs for failure – new cGvHD systemic therapy (1)

Recap of committee's considerations in draft guidance

- Acknowledge challenges of estimating costs using HES data
  - Justification for category choices in HES data, and description of process deriving costs for 'failure – new systemic therapy' health state
  - Company's assumption of constant disease management cost for 'failure – new systemic therapy' health state pessimistic
    - requested scenario analyses: disease management costs for % of people in 'failure – new systemic therapy' health state linearly reduce to baseline
    - estimate of year 1 costs for 'FF– partial and lack of response' health state used mean costs of all patients with cGVHD
    - 'Failure – new systemic therapy' health state used ≥2 high-cost therapies → uncertainty regarding treatments patients would have had as third-line therapy
  - Unclear if health state costs (all other health states but recurrent malignancy) excluded possible costs from recurrent malignancy → potential bias if costs not excluded

Abbreviations: cGvHD, chronic graft-versus-host disease; BAT, best available therapy; FF, failure-free; KM, Kaplan–Meier; ICER, incremental cost-effectiveness ratio

Key Issue: Disease management costs for failure – new cGvHD systemic therapy (2)

Impact of reducing disease management costs in the failure-new systemic therapy health state

Company's draft guidance response

- Lack of real-world data to estimate long-term costs for people whose failure related to cGvHD treatment change
- Conducted survey (15 clinical experts) → all clinical experts considered it clinically implausible disease management costs reduce over time; likely costs would increase
- If no data, more appropriate to model constant cost of disease management
- Updated model (adjusted to allow incorporation of time dependency in application of failure-new systemic therapy state costs) and presented committee requested scenarios
- Revised base case → ICER below £20k threshold (all scenarios). Using preferred EAG assumptions → ICER remains below threshold
- Note results from these scenarios should be treated with extreme caution

EAG comments

- Company's scenarios appropriately explores impact of this assumption on cost-effectiveness results

 Abbreviations: cGvHD, chronic graft-versus-host disease; ICER, incremental cost-effectiveness ratio

Key Issue: Disease management costs for failure – new cGvHD systemic therapy (3)

Justification for source of disease management costs (application of HES study costs in model)

Company's draft guidance response

- Treatments considered high-cost therapy in HES analysis included ECP, rituximab and protein TKIs (i.e., ruxolitinib and imatinib) - only identifiable therapies in database
- Disease management costs for 'failure – new cGvHD therapy', (restricted to ≥ 2 high-cost therapies) → population likely had 1 of these treatments as 3L therapy
- Not possible to identify other low-cost therapies in HES database

EAG comments

- Company didn't comment on assumption disease management costs for FF partial and lack of response health state: based on mean 1st year costs for all patients with cGvHD
- Company's restriction to mean 1st year costs likely capture a patient's 1st year treatment pathway which may consist of mostly low-cost treatments and ECP
- Likely for many patients, high-cost 3L treatments will be their first high-cost treatment
- Assuming ≥2 high-cost treatments for 'failure – new systemic cGvHD therapy' could be considered reasonable

NICE Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier; ICER, incremental cost-effectiveness ratio; TKIs, tyrosine kinase inhibitors

Key Issue: Disease management costs for failure – new cGvHD systemic therapy (4)

Impact of recurrent malignancy on costs in the failure-new systemic therapy health state

Company's draft guidance response

- Not possible to identify relapses of malignancy in HES data due to recording in patient records
- Criteria for identifying people in 'failure-new systemic therapy' health state required ≥2 high-cost drugs (people with recurrent malignancy unlikely prescribed immunosuppressive cGvHD medication → would not meet criteria for subgroup of interest)
- Provided scenario removing proportion of recurrent malignancy disease management costs from disease management costs of 'failure – new systemic cGvHD therapy' health state
- Likely overestimation of relapse events, but impact on remains ICER small

EAG comments

- Company's scenario may be reasonable approach to explore impact of reduction in disease management costs for failure-new systemic therapy health state

Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier; ICER, incremental cost-effectiveness ratio

Key Issue: Disease management costs for failure – new cGvHD systemic therapy (5)

Comments from web

- People who have had 3 or more GvHD therapies will almost invariably have increasing healthcare costs; these are people admitted for long periods due to either debilitation secondary to their GvHD symptoms and treatment
- The economic burden to the NHS of cGvHD treatment for patients that fail 3 or more treatment lines is hugely underestimated here
- People in failure state will require significantly more healthcare resource than patients in FF state
- Do not consider 'burned out' patients (who can only achieve PR), to remain in failure state
- Company's assumption is entirely in keeping with my experience as a cGvhD expert looking after patients in the failed state

Abbreviations: GvHD, chronic graft-versus-host disease; FF, failure-free; PR, partial response

Equality considerations

Considerations in draft guidance

- Committee took these issues into account in its decision making, but concluded that they had no material effect on its recommendations

Stakeholder draft guidance response

- Not recommending belumosudil will have an adverse impact on a group of patients who will all share at least one 'protected characteristic' under the Equality Act 2010 - namely having a disability
- Ruxolitinib not available in England, not recommending belumosudil means access to the 2 GvHD treatments with high quality trial evidence behind them will be denied
- While additional research is needed there is thought to be health inequality related to both socioeconomic status and ethnicity in terms of ability to access therapies

Abbreviations: GvHD, graft-versus-host disease

RECAP

QALY shortfall analysis and weighting for severity

- Company used base case total QALYs estimated for BAT arm
- Baseline characteristics in QALY shortfall calculations → (post clarification economic model – pooled data for ≥2 LOT subgroup of ROCKstar and KD025-208 [September 2022 data cut])
- Company estimated severity modifier of 1.2 based on QALY shortfall analysis
- Severity modifier does not apply to EAG's preferred cost effectiveness results

Committee's considerations in DG	Company's DG response
• Acknowledged condition has a significant impact on QoL • Agreed with EAG that no severity modifier should apply in absence of further exploration of most appropriate source to inform utility value for 'failure – new cGvHD systemic therapy' health state	**Presented updated QALY shortfall calculations:** • Using updated utility value for failure-new systemic therapy state to update estimate for QALYs with BAT • Maintains cGvHD at 3L or later should qualify for severity modifier of 1.2

Abbreviations: QALY, quality-adjusted life year; QoL, quality of life; BAT, best available therapy; LOT, line of therapy; cGvHD, chronic graft-versus-host disease; 3L, third line; Qol, quality of life

Cost-effectiveness results

As confidential discounts are available for comparators in the pathway, ICERs will be presented in Part 2 slides

ICER ranges have been presented below for transparency

Summary – belumosudil versus BAT

- Company base case probabilistic ICER:
  - With 1.2 severity weighting: belumosudil dominant
  - with no severity weighting: belumosudil dominant
- EAG base case: belumosudil dominant

Additional scenarios (some scenarios ranged from dominant to above £50,000/ QALY)

- Company's deterministic scenario analyses – no severity modifier applied
- Company scenarios applied to EAG base case
- EAG's deterministic scenario analyses
- Combined committee requested deterministic scenarios

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issues

Issue (identified by Lead Team)	Resolved?	ICER impact
Extrapolation of REACH-3 FFS for the BAT arm	No	Unknown
Utility value for failure – new cGvHD systemic therapy	No	Large
Disease management costs for failure – new cGvHD systemic therapy	No	Large

Abbreviations: BAT, Best available therapy; ICER, Incremental cost-effectiveness ratio; FFS, failure free survival; cGVHD, chronic graft-versus-host disease

Thank you.

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Belumosudil for treating chronic graft versus host disease after two or more lines of systemic therapy [ID4021]

Supplementary appendix

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Resolved: Removal of OS benefit for belumosudil+BAT

The company updated its base case aligned with committee and EAG preference of no survival benefit for belumosudil vs BAT

Recap of committee's considerations in DG

- EAG considers substantial uncertainty in estimated OS benefit associated with belumosudil → removal of OS benefit for belumosudil+BAT excludes another source of unresolvable uncertainty in model
- Removing OS benefit reduced time spent in failure states in belumosudil arm, reducing costs but minimally reducing QALYs
- EAG's preference for removing overall survival was acceptable in absence of more evidence

Company's DG response

- Aligned with committee and EAG preference of no survival benefit for belumosudil vs BAT, and reflect this in their revised base case

Abbreviations: OS, overall survival; BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Resolved: Removal of response outcomes from model

The company updated its base case aligned with committee and EAG preference to remove response outcomes from the model

Background

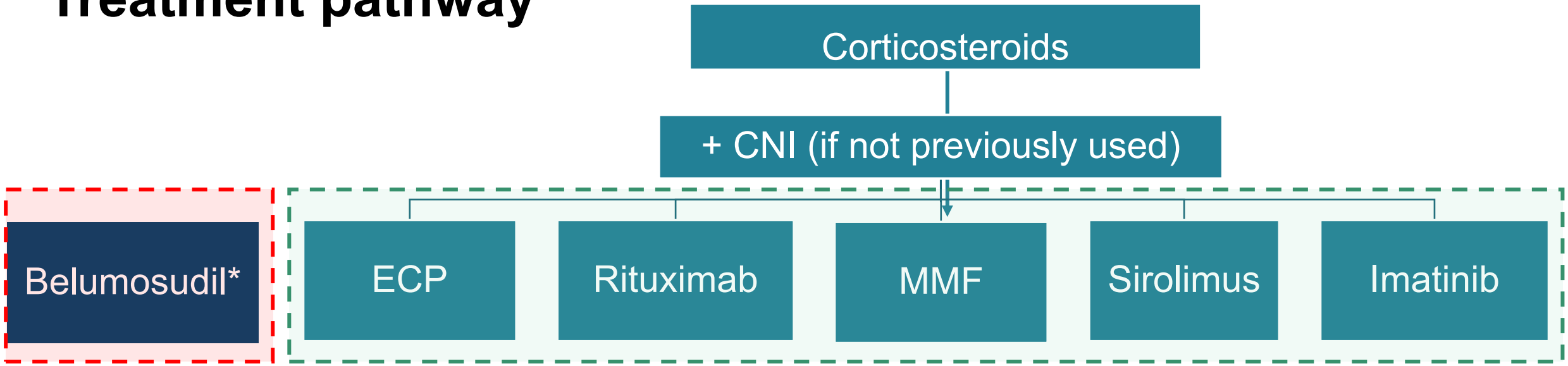
- Company noted uncertainty regarding comparability of response outcomes across trials
- EAG considers inclusion of response in model potentially adding unnecessary complexity to analysis
- Company provided scenario removing response from model → limited impact on ICER
- EAG felt company's scenario was more appropriate
- Committee concluded EAG's preference for removing response outcomes was appropriate

Company's DG response

- Aligned with committee and EAG preference to remove response outcomes in model and reflect this in their revised base case

Abbreviations: ICER, incremental cost-effectiveness ratio

Treatment pathway



Treatment pathway recommended by EAG's clinical experts:

- 1L: corticosteroids +/- CNIs
- 2L: ECP
- 3L: belumosudil, imatinib, MMF, pentostatin, pulsed corticosteroids, rituximab, sirolimus

*Only after two systemic treatments

Abbreviations: CNI, calcineurin inhibitors; CS, corticosteroids; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil

Belumosudil mesilate (Rezurock, Sanofi)

Technology details

Marketing authorisation (MHRA, July 2022)	• Belumosudil is indicated for the treatment of patients aged 12 years and older with chronic graft-versus-host disease who have received at least two prior lines of systemic therapy • Granted an innovation passport by MHRA (April 2021)
Mechanism of action	• Potent and selective ROCK2 inhibitor that mediates signalling in immune cellular function and fibrotic pathways
Administration	• Belumosudil 200 mg administered orally once daily until disease progression or unacceptable toxicity • Dose increased to 200 mg twice daily when given with strong CYP3A inducers or proton pump inhibitors
Price	• The list price per pack is £6,708.00 per box of 30 x 200 mg tablets • Average cost of treatment course*: £67,326.62 (based on list price) • The company has simple discount patient access scheme

*Based on median treatment duration of 9.2 months for belumosudil once daily and 11.2 months for belumosudil twice daily
Abbreviations: MHRA, medicines and healthcare products regulatory agency; ROCK2, rho-associated, coiled-coil containing protein kinase-2; CYP3A, human cytochrome P450 3A

Draft guidance summary on clinical evidence

Committee's considerations

REACH-3 comparator trial

- Recruitment criteria for Bat arm in REACH-3 trial generally appropriate, but people in BAT arm were at an earlier stage in treatment pathway than people in belumosudil trials

Cross over of the REACH-3 trial

- 38% best available therapy arm crossed over to ruxolitinib. Crossover would have large impact on clinical outcomes in trial for BAT arm

Company naïve comparison of belumosudil and BAT

- In absence of more robust comparisons, committee had to consider naive indirect comparison in its decision making

Patient population

- Efficacy of belumosudil likely similar in adolescents and adults although lack of data for belumosudil in adolescents

Abbreviations: BAT, best available therapy

Key clinical trials

RECAP

	Phase 2a (KD025-208)	ROCKstar (KD025-213) – phase II trial	REACH-3 (comparator)
Design	Open-label, dose-escalation, multicentre	Randomised, open-label, multicentre	Phase 3 randomised, open-label, multicentre
Population	People ≥18 years, allogeneic bone marrow transplant/ alloHSCT & cGVHD after 1-3 prior LOT	People ≥12 years, alloHSCT & cGVHD after 2-5 prior LOT	People ≥12 years, alloHSCT & moderate/ severe glucocorticoid-refractory or cGVHD (≥2 cGvHD therapies excluded)
Intervention	Belumosudil 200 mg daily/twice daily/400 mg daily	Belumosudil 200 mg daily/ twice daily	Ruxolitinib 10 mg twice daily
Comparator(s)	None		BAT (investigator's choice)
Duration	64.2, 45.9, 49.2 (max.) months respectively for each dose	6 months	24 weeks
Primary outcome	Best ORR at any time		ORR at week 24
Key secondary outcomes	DOR, FFS, OS, LSS		
Locations	United States		International, incl. United States
Used in model?	≥2 LOT subgroup	Sep. 2022 data cut	Yes

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; DOR, duration of response; FFS, failure-free survival; cGvHD, chronic graft versus host disease; LOT, lines of therapy; LSS Lee Symptom Score; ORR, overall response rate; OS, overall survival

Back to trial summary slide

ROCKstar study design

- Age ≥12 years
- Had alloHSCT
- Active chronic GVHD
- 2-5 prior lines of systemic therapy for chronic GVHD
- Systemic therapy for chronic GVHD is indicated

Stratification
- Prior ibrutinib (Y/N)
- Severe chronic GVHD (Y/N)

R

Arm A: Belumodusil 200mg once daily (n=66)

Arm B: Belumodusil 200mg twice daily (n=66)

Treat to clinically significant progression

Primary Endpoint
ORR

Statistical Considerations
- IA at 2 months (1-sided α = 0.25%); PA at 6 months
- At PA, in each arm, target ORR = 55%; 1-sided α = 2.25%; 90% power; 10% drop out rate
- Multiplicity adjustment – Hochberg procedure
- N=66 per arm
  - Target at least 10% per arm previously treated with ibrutinib

Secondary Endpoints
- DOR
- Change in LSS score
- Response rate by organ system
- Time to response
- Time to next treatment
- Change in CS and CNI dose
- FFS
- OS

Source: Company submission

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; CNI, calcineurin inhibitor; CS, corticosteroid; cGVHD, chronic graft-versus-host disease; DOR, duration of response; GVHD, graft-versus-host disease; FFS, failure-free survival; IA, interim analysis; LSS, Lee Symptom Scale; ORR, overall response rate; OS, overall survival; PA, primary analysis; R, randomisation; Y/N, yes/no

Clinical trial results

Results of pooled efficacy analysis (ROCKstar and [KD025-208 ≥ 2 prior lines of therapy subgroup]), September 2022 data cut

Outcome	Combined 200 mg* (N=176)
Median time to response, weeks (range)	7.71 (3.7 to 80.1)
Best ORR,[a] n (%) CR PR	114 (73.1%) 6 (3.4%) 123 (69.9%)
Median DOR in responders (primary/secondary)[b] weeks (95% CI)	25.7 (17.29 to 36.14)
Median DOR in responders (quaternary), weeks (95% CI)	69.9 (40.43 to 95.43)

*There were two different dosing regimens to account for drug interactions (once daily and twice daily doses; which showed similar efficacy results)

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; DOR, duration of response; CI confidence interval

Clinical trial results

RECAP

Outcome	200 mg once daily (n=92)	200 mg twice daily (n=84)	Combined 200 mg (N=176)
Median FFS, months (95% CI)	15.2 (9.26 to 24.02)	16.6 (11.27 to 35.88)	15.4 (12.42 to 22.74)
FFS, % (95% CI)			
FFS at 6 months	74% (0.64 to 0.82)	78% (0.68 to 0.86)	76% (0.69 to 0.82)
FFS within 12 months	56% (0.45 to 0.65)	61% (0.49 to 0.70)	58% (0.50 to 0.65)
FFS within 24 months	41% (0.30 to 0.51)	42% (0.31 to 0.53)	41% (0.33 to 0.49)
OS, % (95% CI)			
OS within 12 months	91% (83 to 95)	91% (83 to 96)	91% (86 to 95)
OS within 24 months	86% (76 to 92)	84% (74 to 91)	85% (78 to 90)
Median TTD, months (range)	9.18 (0.5 to 64.2)	11.78 (0.4 to 39.6)	10.38 (0.4 to 64.2)
Median TTR in responders, weeks (range)	n=59 7.86 (3.7 to 80.1)[c]	n=55 5.29 (3.7 to 40.1)[c]	n=114 7.86 (3.7 to 80.1)[c]

[c] August 2021 data cut (ROCKstar) and ≥2 LOT subgroup (KD025-208)

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Source: Company clarification response (additional questions); EAG report

Abbreviations: FFS, failure-free survival; OS, overall survival; TTD, time to treatment discontinuation; TTR, time to response

ITC methodology (1)

RECAP

An adjusted ITC for belumosudil was not feasible

- ROCKstar study of belumosudil is a phase II study with no active control arm
- Company conducted SLR (January 2023) to identify studies reporting on:
  - clinical efficacy and safety of treatment options for adults with cGVHD after alloHSCT in people where at least 1 prior LOT has failed
  - criteria for which each trial was assessed and selected for inclusion in a potential ITC
- Robust statistical & methodological analysis not possible (differences in population characteristics, outcome definitions & prior LOT between ROCKstar & comparator trials) → not feasible to conduct ITC for belumosudil

Reason for not considering further if conducting an ITC for belumosudil	Number of studies excluded (N)
LOT (not limited to >2 LOT, population and outcomes not reported by line of therapy)	14
Study took place in Asian countries; company state inclusion of studies could create heterogeneity in patient populations and/or health systems	6
Population not comparable	4

Abbreviations: ITC, indirect treatment comparison; SLR, systematic literature review; cGVHD, chronic graft-versus-host disease; alloHSCT, allogenic haematopoietic stem cell transplant; LOT, line of therapy

ITC methodology (2)

- [redacted]
  - [redacted]

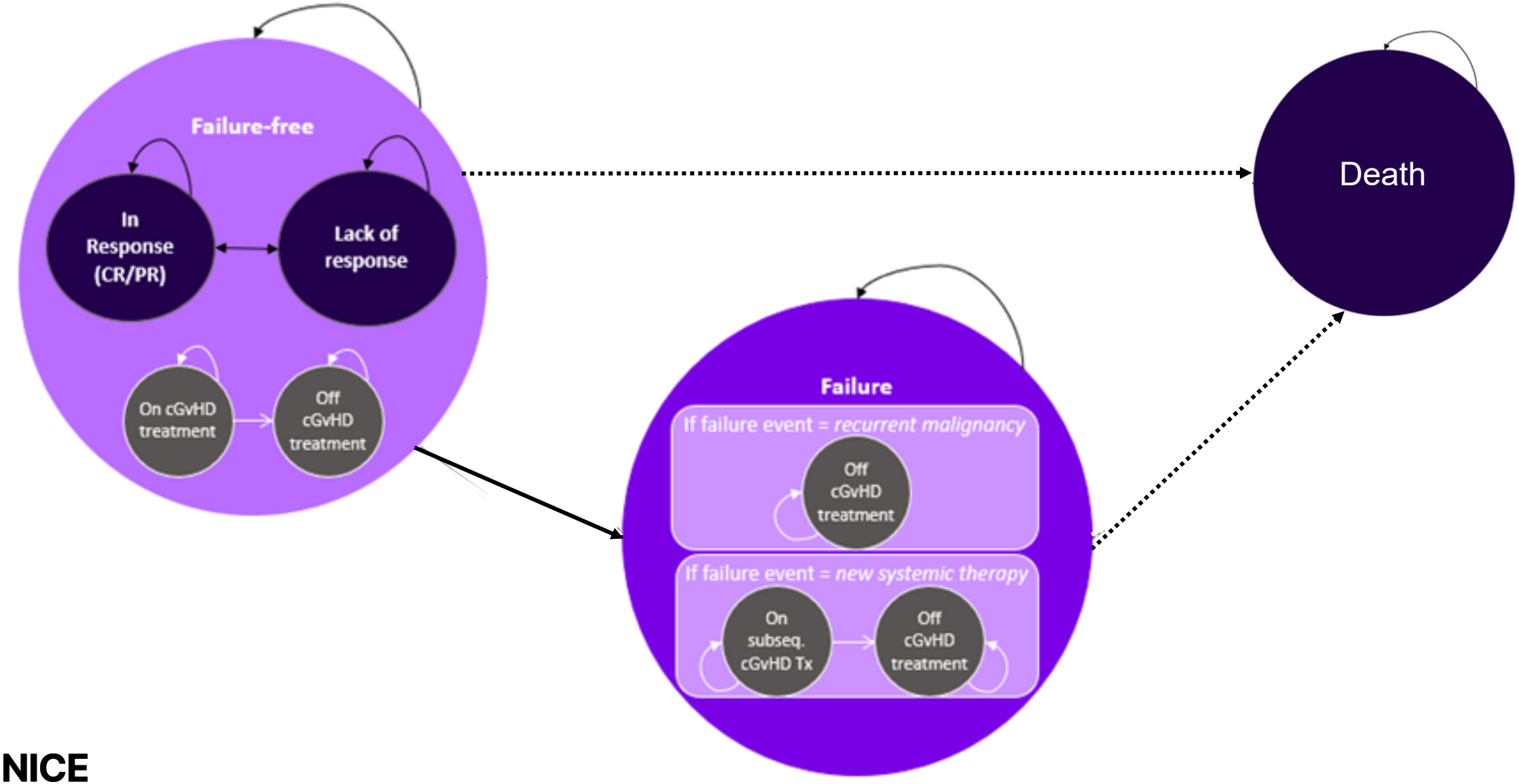
Company use data from the Phase 3 REACH-3 trial of ruxolitinib vs. investigator's choice after one prior line of therapy to allow comparison to currently available treatments in economic model through a naïve direct comparison

- REACH-3 did not include TTR and TTD as endpoints
- Given, eligibility criteria of REACH-3 and belumosudil+BAT trials, company concluded this was a conservative approach, but EAG uncertain if this was the case

 Abbreviations: BAT, best available therapy; TTR, time to response; TTD, time to treatment discontinuation;

Company's model overview (1)

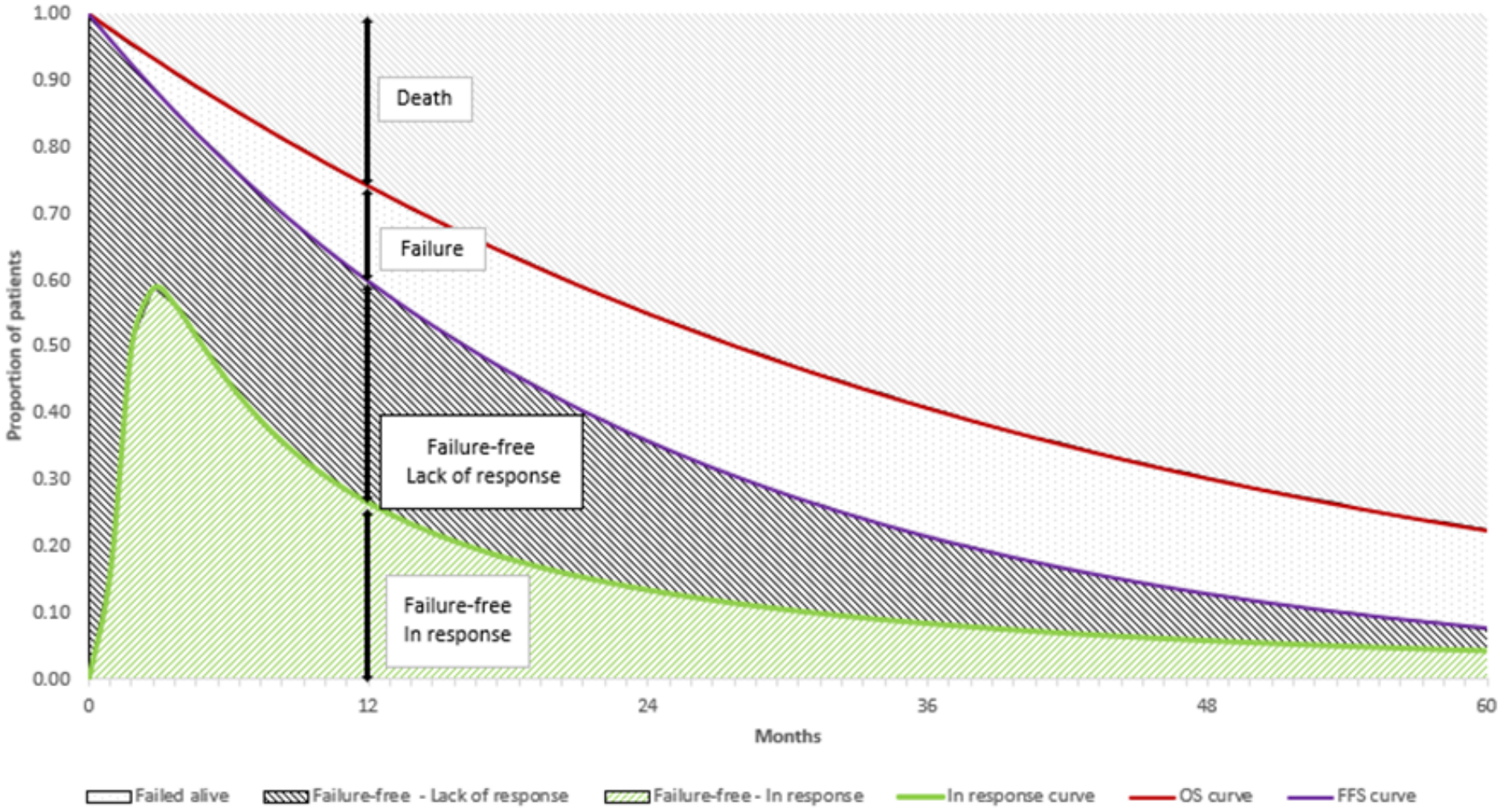
Model based on partitioned survival approach



Abbreviations: cGVHD, chronic graft-versus-host disease; CR, complete response; PR, partial response; LR, lack of response

Company's model overview (2)

Model based on partitioned survival approach



Abbreviations: FFS, failure-free survival; OS, overall survival

Company's model overview (3)

RECAP

Model structure: partitioned survival model approach with 3 main health states:

- Failure free
  - People can have CR, PR, LR
  - People can be on or off cGvHD treatment
- Failure
  - Recurrent malignancy or initiation of a new systemic cGvHD therapy
  - For people whose failure event is a new systemic cGvHD therapy, they can be on or off treatment
- Death

Population: people aged 12 years and older with chronic GVHD who have received at least two prior lines of systemic therapy

Intervention: belumosudil

Comparator: BAT

Cycle length: 4 weeks (with half cycle correction)

Time horizon: 40 years (lifetime)

NICE

Abbreviations: cGVHD, chronic graft-versus-host disease; BAT, best available treatment; CR, complete response; PR, partial response; LR, lack of response

Company's response to draft guidance consultation

Provided additional analyses and justification for approaches

Summary of company response to draft guidance – company provided:

Failure-free survival for comparator (BAT) arm

- Scenario extrapolating FFS data from REACH-3 BAT arm after truncating KM curve at 24 weeks

Disease management costs

- Justification for source & application of HES study costs in model
- Scenario removing proportion of recurrent malignancy disease management costs
- Scenarios reducing disease management costs in failure-new systemic therapy health state

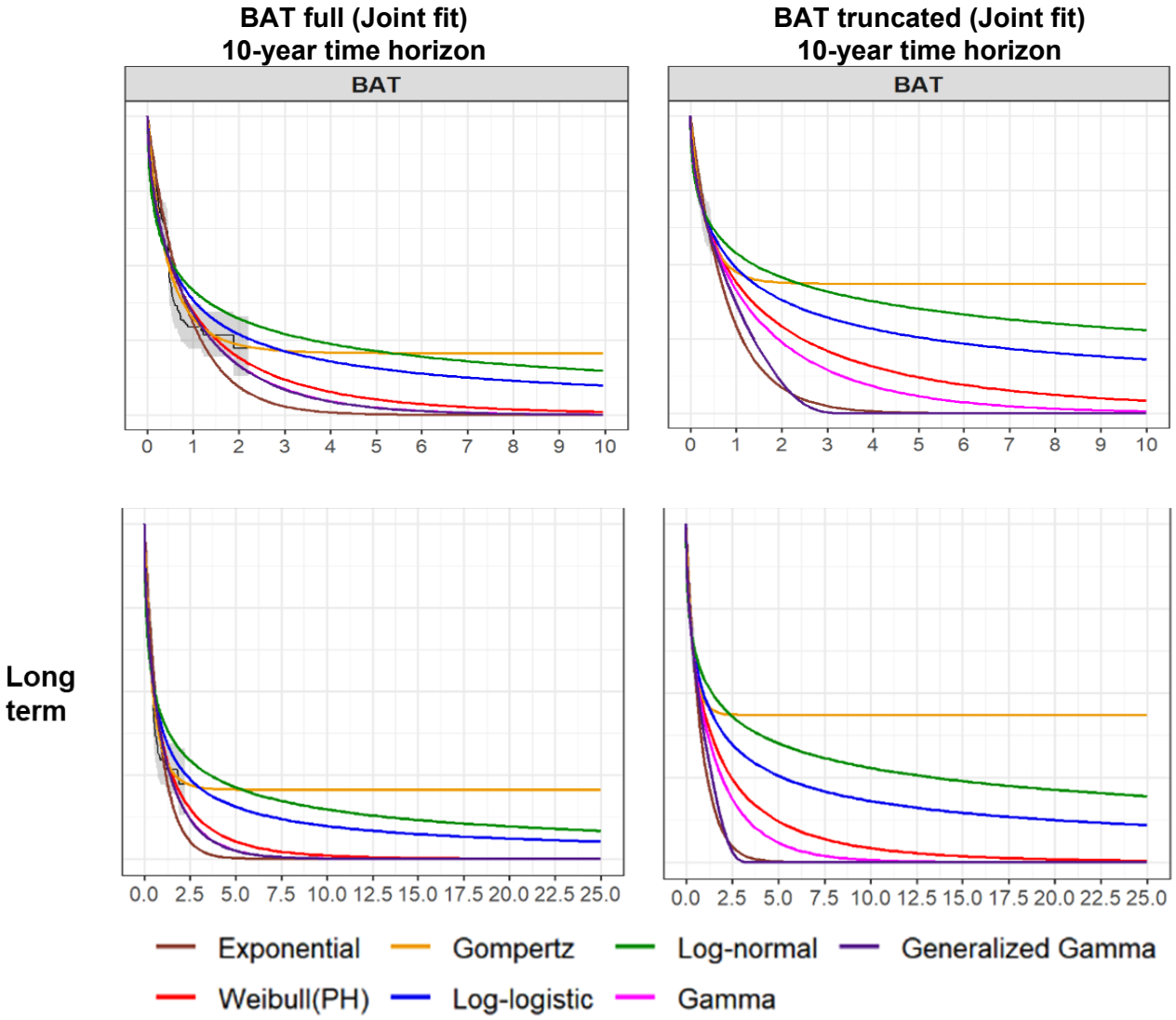
Utility values in failure-new systemic therapy health state

- Conducted QoL study and updated utility value for failure-new systemic therapy state
- Scenario analyses based on results from QoL study for failure-new systemic therapy health-state
- Updated QALY shortfall analysis using updated utility for failure-new systemic therapy state to calculate severity weighting

Abbreviations: BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier; HES, hospital episode statistics; QoL, quality of life; QALYs, quality-adjusted life year; EQ-5D, EuroQoL-5 Dimensions measure

Key Issue: Extrapolation of REACH-3 FFS for the BAT arm

FFS BAT parametric curve comparison
(x-axis in years)



Abbreviations: BAT, best available therapy; FFS, failure free survival

Back extrapolation key issue (2) slide