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

Technology appraisal committee D - 13 September 2023

Chair: Dr Stephen Smith

Lead team: Carole Pitkeathley, Giles Monnickendam, Andrew Hitchings

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Company: Sanofi

NICE

Background on chronic graft versus host disease (GvHD)

Causes

- Usually occurs after an allogeneic haematopoietic stem cell transplant (HSCT) when donated white T-cells attack the body's own cells
- Chronic GVHD (cGVHD) results in fibrotic skin disease, bronchiolitis, salivary & lacrimal gland disease & eosinophilic fasciitis, typically occurs later after a HSCT (acute GVHD usually occurs much sooner)
- Signs appear within 1st year after HSCT, when immunosuppressive medications are reduced

Classification

- Staged as limited or extensive; graded as mild, moderate or severe

Complications

- Infections cause severe morbidity & mortality

Epidemiology

5 -11% allograft recipients may develop extensive cGVHD (and 2nd or subsequent lines of therapy)

713 people diagnosed with extensive cGVHD in England (2016 - 2020)

Allogeneic transplants in England (2019)

1,506

% developed cGVHD

Malignant indications

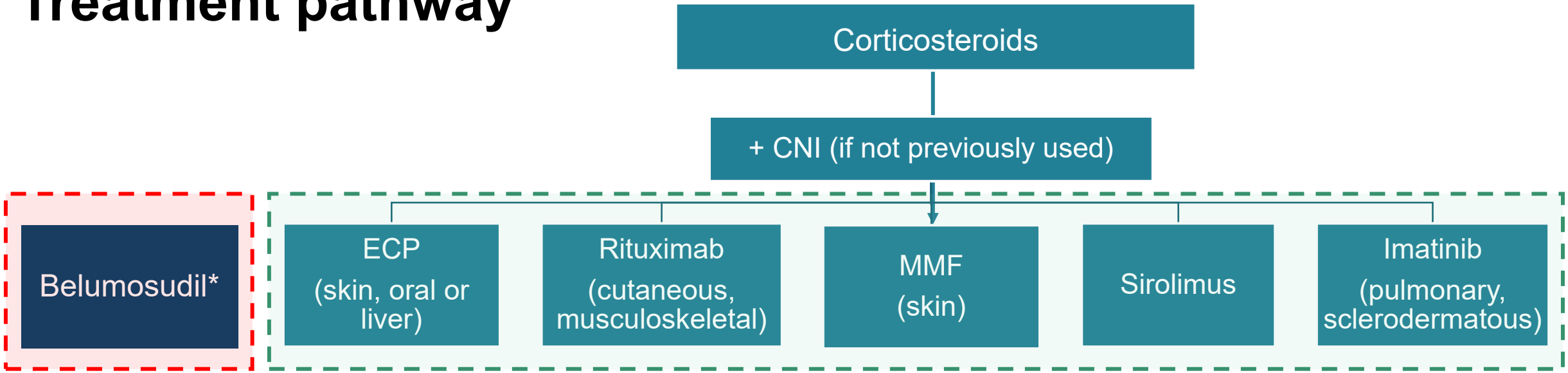
33% adult
16% paediatric

Non-malignant indications

23% adult
12% paediatric

Source: Company submission, NICE final scope for ID4021

Treatment pathway



What are the most appropriate comparators for belumosudil? What is the treatment pathway in UK clinical practice?

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

Patient perspectives

Submission from Anthony Nolan

- cGvHD onset varies widely between people, in terms of timing and severity, with multiple treatments being given
- Impact of QoL can be significant, affecting people's eyesight, lung capacity, dietary needs, relationships, work and social life
- Common to have 4th, 5th, 6th line therapies; finding an effective 3rd line therapy beneficial to the person and cost-effective in long term
- Irreversible lung damage and resolving eye management therapies has left some people with a worsening prognosis. Improved screening of potential cGvHD symptoms is needed, and must be monitored when introducing new treatments
- People favour an oral treatment; potential for QoL and cost-saving benefits of belumosudil over other treatments

cGvHD can be a *"massive step backwards"* for people's recoveries. They saw the stem cell transplant as a potentially lifesaving treatment, which was hindered by cGvHD

Managing inflammatory symptoms can take months or years, with long-term side effects potentially leading to life-long disabilities

Abbreviations: cGVHD, chronic graft-versus-host disease; QoL, quality of life

Clinical perspectives (1)

Submissions from clinical expert, Christie NHS Foundation Trust

- Belumosudil is an oral therapy with favourable toxicity profile - Generally well tolerated unlikely to adversely affect patients' quality of life
- No investment in infrastructure and could lead to reduced infrastructure costs if better than other treatments (e.g. due to less IV therapy or use of ECP)

"Approximately 30% develop cGVHD of which around 45% is extensive"

"Extensive cGvHD is however a major cause of morbidity"

Abbreviations: cGVHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; IV, intravenous

Clinical perspectives (2)

BCSH/BSBMT 2012 report and NHS England 2017 Clinical Commissioning Policy

- (1L) treatment: corticosteroids with or without CNI
- (2L) treatment: ECP, pentostatin, rituximab, and/or imatinib
- (3L) treatment: MMF, methotrexate, or pulsed corticosteroids

Submissions from clinical expert, Christie NHS Foundation Trust

- Company's positioning for belumosudil not consistent with UK clinical practice:
  - CNI unlikely used as 2L therapy but alongside steroids in 1L therapy
  - For 3L, belumosudil should be positioned for people who have failed recognised 2L (ECP, rituximab, imatinib, pentostatin); or 2 lines of 2L therapy
  - ECP most widely used in UK, reasonable to assume majority of people reaching 3L therapy would have failed prior ECP; therefore, ECP not plausible comparator in 3L setting in NHS

Abbreviations: 1L/2L/3L, first/second/third line; BCSH/BSBMT, British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation; CNI, calcineurin inhibitors; CS, corticosteroids; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil

Equality considerations

Company:

- People more at risk of developing cGvHD if:
    - they have a mismatched unrelated donor transplant
    - from an ethnic minority family background (less likely to find a related donor match)
- Potential for errors or delays in diagnosis of skin manifestations (major complication of cGvHD)
    - current physician & patient-reported outcome measures may not adequately capture subtle changes for people with non-white skin
- Geographical access to ECP services and specialist blood and marrow transplant clinics
    - barrier to people in lower socioeconomic groups who may be unable to take time off work or afford to travel to appointments
- **No potential equality issues have been raised by stakeholders**

Source: Company submission, NICE final scope for ID4021

Abbreviations: cGVHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis

Key issues

Issue (identified by the EAG)	Resolved?	ICER impact
Evidence for adolescents not available from ROCKstar and KD025-208	No – for discussion	Unknown
Naïve comparison of belumosudil versus BAT	No – for discussion	Unknown
Removal of OS benefit for belumosudil+BAT	Partially – for discussion	Large
Removal of response outcomes from the economic model	Partially – for discussion	Small
Inclusion of concomitant medication costs for belumosudil, such that the intervention for the cost-effectiveness analysis is belumosudil in addition to BAT (belumosudil+BAT)	Yes – EAG consider company's scenario analysis resolves issue	Small
Issue (identified by Lead Team)	**Resolved?**	**ICER impact**
Extrapolation of REACH-3 FFS for the BAT arm	No – for discussion	Unknown
Utility value for failure – new cGvHD systemic therapy	No – for discussion	Large
Disease management costs for failure – new cGvHD systemic therapy	No – for discussion	Large

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

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

Decision problem

	Final scope	As per final scope	EAG comments
Population	People 12 ≥ years with cGVHD after 2 or more lines of systemic therapy	As per final scope	• KD025-208 eligibility criteria: patients at minimum of 1 LOT & excluded adolescents • Patients in REACH-3 BAT arm appropriate but at earlier stage, patients with 3 previous LOTS excluded
Intervention	Belumosudil with established clinical management	As per final scope	• People in belumosudil trials on PPIs didn't exclusively receive belumosudil 200 mg twice daily • Established clinical management in trials appropriate for USA; in UK, more receive ECP, fewer receive sirolimus
Comparators	Established clinical management without belumosudil (ECP, Imatinib, rituximab, sirolimus, MMF, tacrolimus, cyclosporine)	As per final scope	• EAG's clinical experts: number having ECP higher in UK. Ibrutinib, methotrexate, everolimus & infliximab rare, 38% had ruxolitinib after week 24 in REACH-3 BAT arm & no NICE guidance on ruxolitinib for cGvHD
Outcomes	Response to treatment, immunosuppressant sparing, mortality, treatment AEs, FFS, HRQoL	As per final scope	• ROCKstar, KD025-208, REACH-3 report steroid sparing • Inconsistencies in outcome definitions and time points between belumosudil trials & REACH-3

NICE Abbreviations: cGVHD, LOT, line of therapy; BAT, best available therapy; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil, AEs, adverse events; FFS, Failure-free survival; HRQoL, health-related quality of life; PPI, proton pump inhibitor

Unknown impact on ICER

Key issue: Evidence for adolescents not available from ROCKstar and KD025-208

Company consider it reasonable to align eligible trial population with MA licence

Background

- Belumosudil MA & population in NICE final scope: people aged 12 years and older with cGvHD after 2 or more lines of systemic therapy
- No adolescents recruited to ROCKstar & KD025-208 at time of latest data cut (September 2022)
- EAG noted lack of efficacy & safety data for belumosudil in adolescents

Company

- Unmet need for cGVHD across all age groups & biological plausibility of using belumosudil in patients aged 12-18 years
- Reasonable & appropriate to align eligible trial population with MA licence

EAG comments

- Cannot confirm if adult clinical outcomes would be seen in adolescents as no efficacy & safety data for belumosudil in adolescents
- EAG's clinical experts agreed from a biological perspective, no reason why belumosudil wouldn't work as effectively as in adults

Abbreviations: cGVHD, chronic graft-versus-host disease; MA, marketing authorisation

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

	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

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 (%)	114 (73.1%)
CR	6 (3.4%)
PR	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

ITC methodology (1)

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]

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;

Unknown impact on ICER

Key issue: Naïve comparison of belumosudil versus BAT (1)

EAG note uncertainty associated with naïve comparisons of clinical outcomes from different trials

Background

- Company chose BAT arm from REACH-3 in naïve direct comparison with belumosudil + BAT
- EAG's clinical experts agreed REACH-3 was reasonable comparator arm in absence of head-to-head data
- EAG's clinical experts assessed eligibility criteria & baseline characteristics of people in belumosudil+BAT & REACH-3 → impossible to predict direction of any bias (due to differences in people recruited in arms)

Company

- Acknowledge limitations of using BAT arm in REACH-3 & explored approaches to address uncertainty
- Agree with EAG and clinical experts; naïve comparison is currently only feasible option comparing clinical outcomes for belumosudil + BAT with BAT
- Low ICERs in company base case, EAG preferred scenario, & extensive scenario analyses provide confidence belumosudil + BAT is cost-effective vs BAT and low decision risk

EAG comments

- Acknowledge only feasible option to compare clinical outcomes is via a naïve comparison
- Emphasises uncertainty associated with naïve comparisons of clinical outcomes from different trials

Is the committee satisfied with the decision-making approach that led to the naïve comparison? Is it the best approach available?

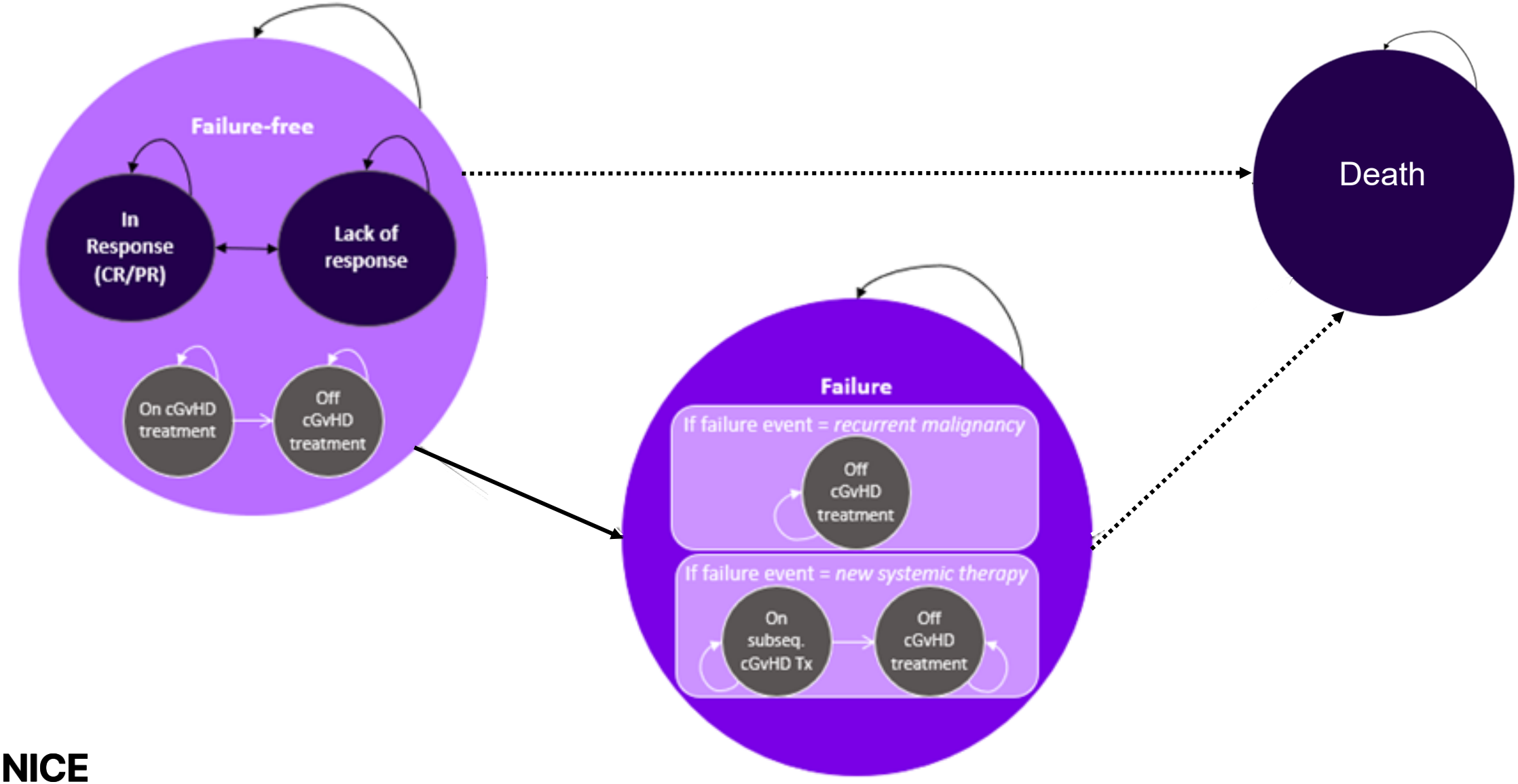
Abbreviations: cGVHD, chronic graft-versus-host disease; BAT, best available therapy

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview (1)

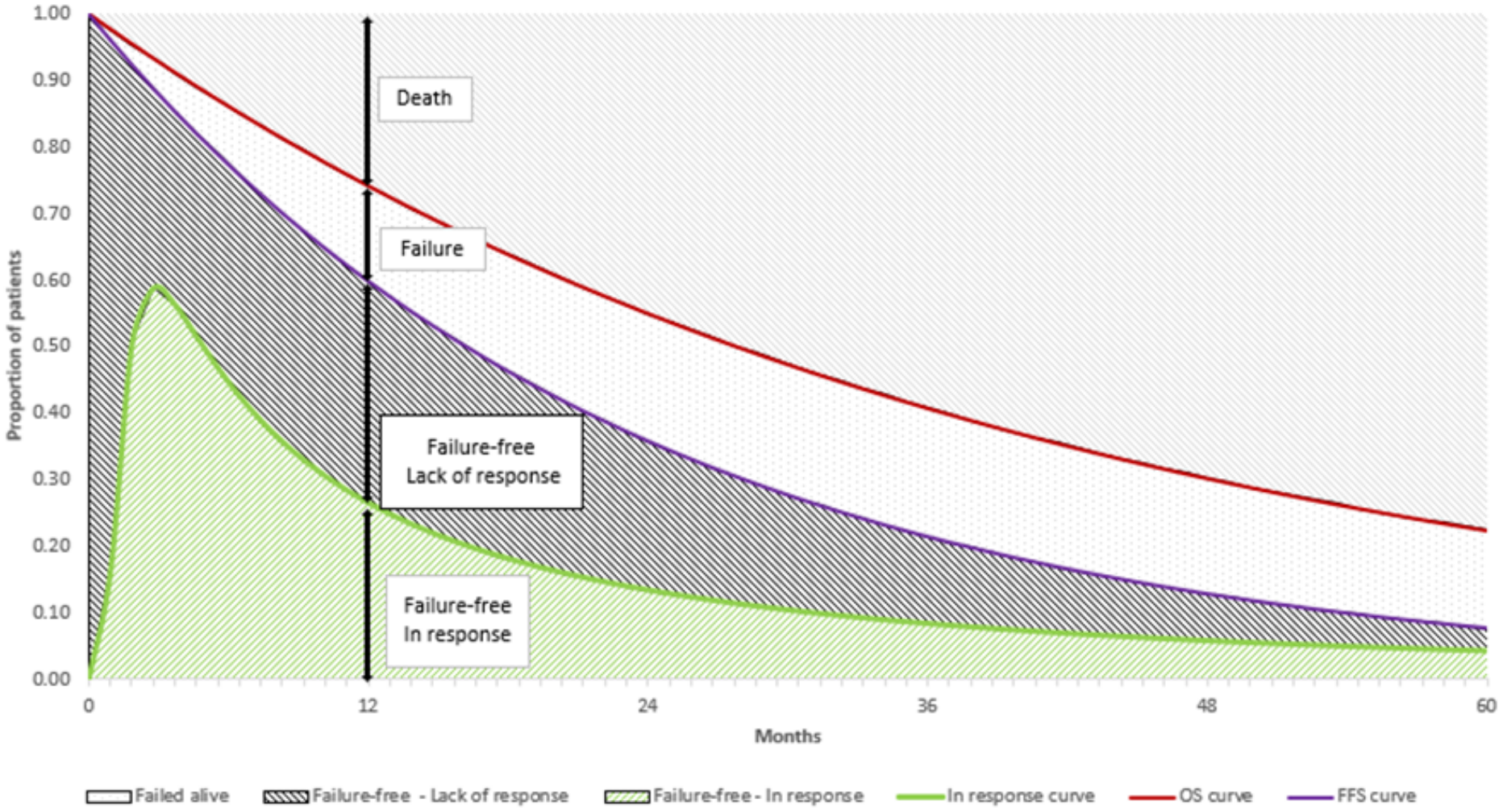
Model based on partitioned survival approach



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)

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

How company incorporated evidence into model

Key inputs reflect company revised base-case analysis post clarification

Input	Assumption and evidence source
Baseline characteristics	Pooled ROCKstar and KD025-208 (combined dose data) for ≥2 LOTs subgroup
Belumosudil efficacy	FFS, OS, DOR, TTD, TTR from pooled analysis
BAT efficacy	FFS, OS, DOR from REACH-3
Survival curves	OS: exponential distribution for BAT, belumosudil 200 mg once daily & belumosudil 200 mg twice daily; FFS: generalised gamma distribution independent for BAT, joint-fit belumosudil 200 mg once daily & belumosudil 200 mg twice daily
Utilities	FF health state: ROCKstar (PROMIS-GH data mapped to EQ-5D-3L [Thompson et al. algorithm]; Failure health state, AEs: published EQ-5D data
Costs and resource use	NHS reference costs, PSSRU, BNF, eMIT, NHS Drug tariff
Max. treatment duration	TTD capped by FFS, assumed 5-year max. treatment duration (all arms)
Proportion of belumosudil	Based on feedback from advisory board with expert clinicians in England (95% once daily and 5% twice daily)
Adverse Events	Disutility estimates: TAs in indications related to underlying disease of patients in ROCKstar; costs based on probability of AE multiplied by unit cost of AE

NICE

Abbreviations: LOT, lines of therapy; FFS, failure-free survival; OS, overall survival; DOR, duration of response; TTD, time to treatment discontinuation; TTR, time to response; BAT, best available therapy; FF, failure free; AEs, adverse events; BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQoL-5 Dimensions measure; PSSRU: Personal Social Services Research Unit; PROMIS-GH, Patient-Reported Outcomes Measurement Information System Global Health

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

Background

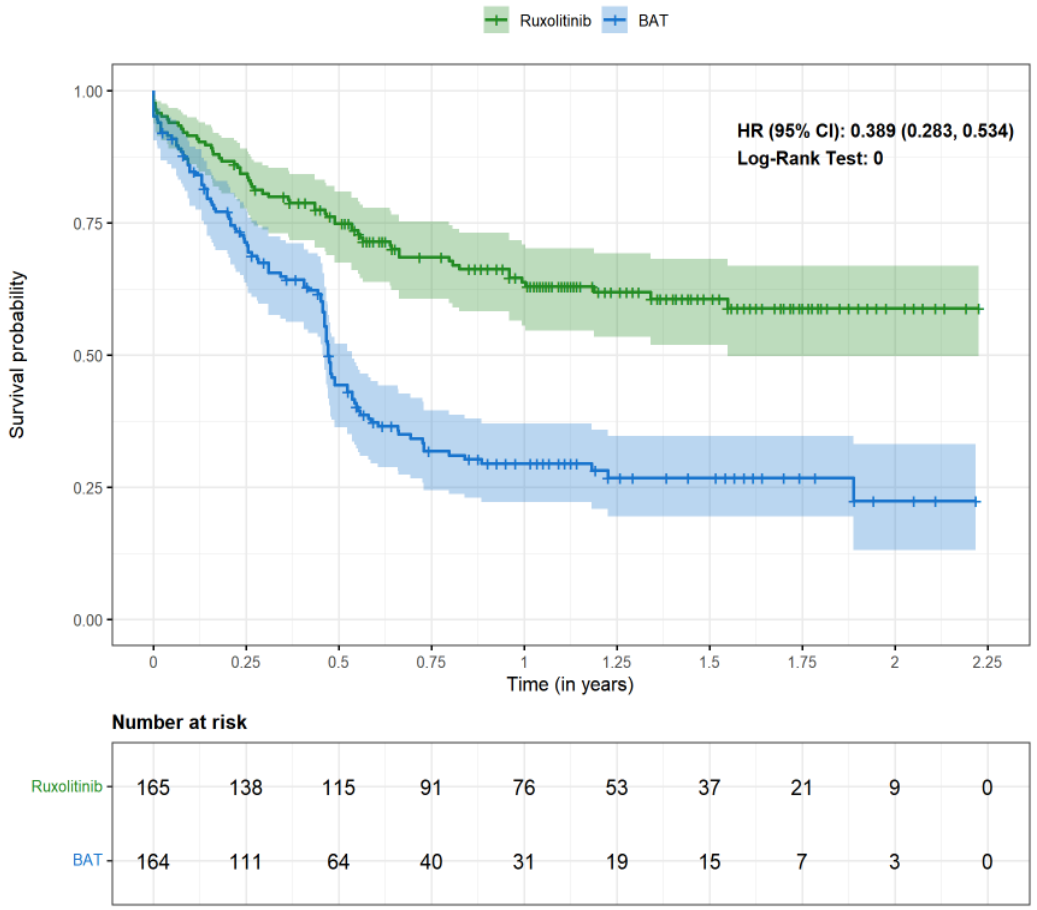
- REACH-3: crossover from control therapy to ruxolitinib allowed on/after week 24
- People in control group who had CR/PR at week 24 couldn't cross over to ruxolitinib (unless/until disease progression, mixed response, lack of response, toxicity to BAT or cGVHD flare
- 38% of BAT patients crossed over to ruxolitinib at week 24

Lead team comments

- Concerned BAT KM curve not interpretable after 24 weeks due to impact crossover
- Requested EAG scenario: FFS KM data for BAT (REACH-3) truncated at week 24 & extrapolated

EAG comments

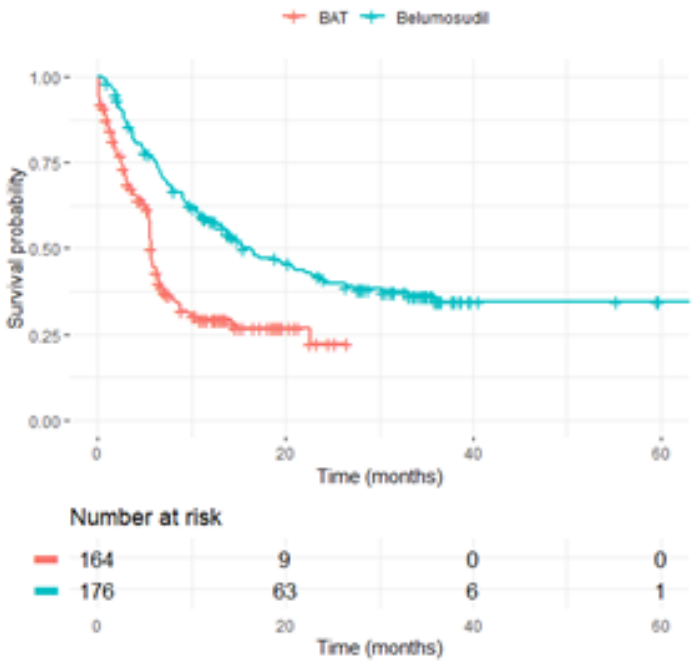
- Truncating KM curve at 24 weeks likely to give clinically implausible overestimation of treatment effect for BAT
- Base case estimation of FFS may not reflect "unbiased" FFS curve; likely less biased than suggested scenario
- Considers scenario needs careful consideration by committee to interpret resulting ICER

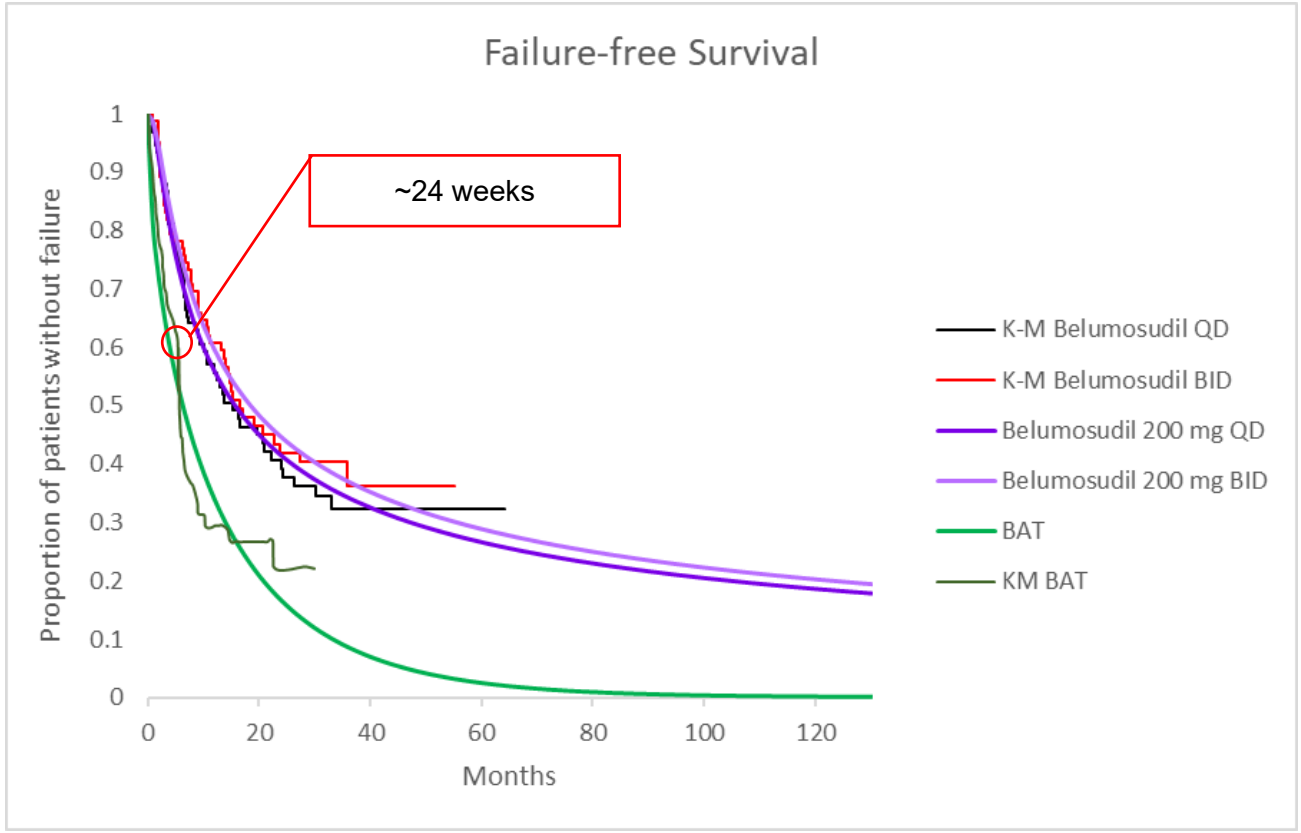


Abbreviations: CR, complete response; PR, partial response; LR, lack of response; BAT, best available therapy; FFS, failure free survival; KM, Kaplan–Meier; ICER, incremental cost-effectiveness ratio

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

Comparison of belumosudil and BAT KM curves and modelled extrapolation



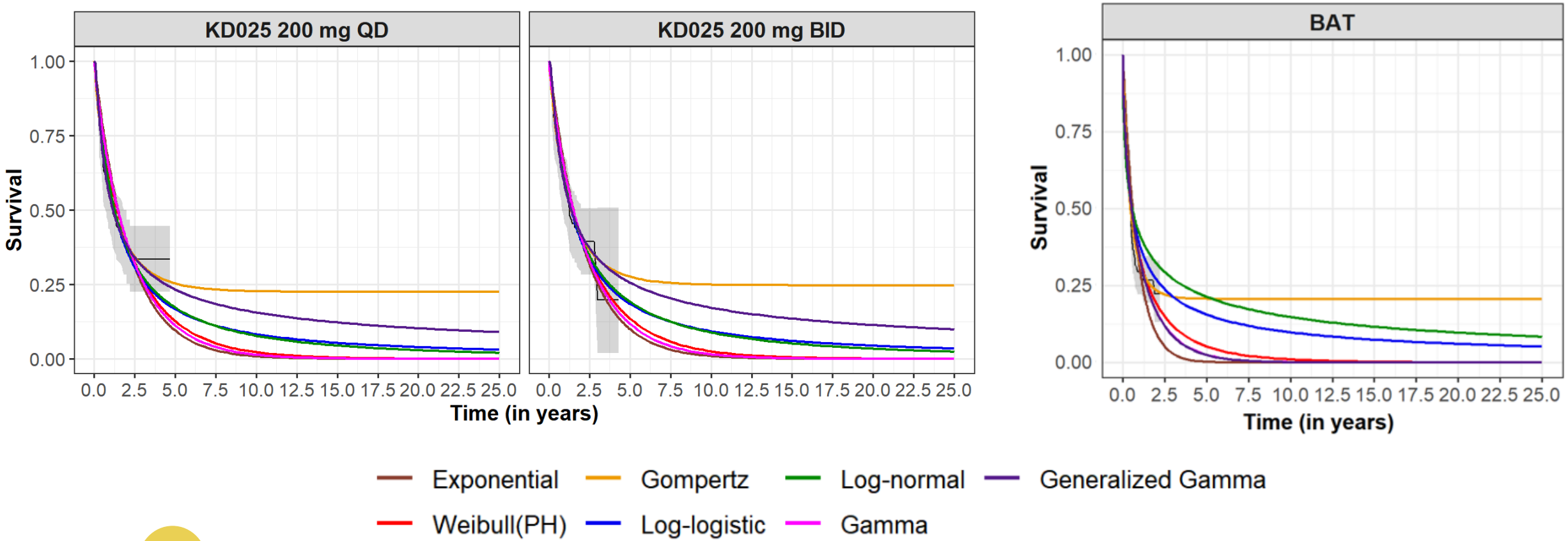


How credible are the extrapolations?/ are the company's extrapolations appropriate for decision making?

Abbreviations: BAT, best available therapy; KM, Kaplan–Meier

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

Comparison of belumosudil and BAT alternative extrapolation models (from company submission)



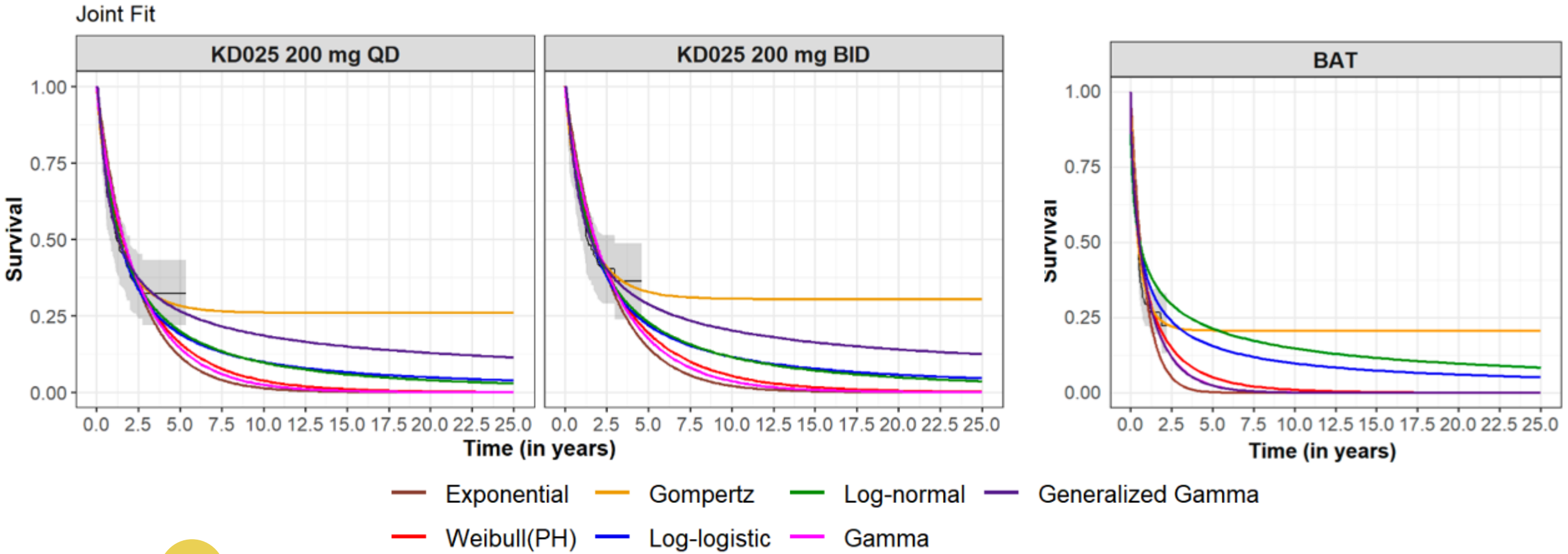
How credible are the extrapolations?/ are the company's extrapolations appropriate for decision making?

*Source: company submission

Abbreviations: BAT, best available therapy; KM, Kaplan–Meier

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

Comparison of belumosudil and BAT alternative extrapolation models*



How credible are the extrapolations?/ are the company's extrapolations appropriate for decision making?

*Figures extracted and compiled from the company's post-clarification model (September 2022 data cut). Figures not submitted in committee papers and were provided at short notice to respond to a factual inaccuracy.

Abbreviations: BAT, best available therapy; KM, Kaplan–Meier

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

Lead team comments

- Company analysis of ROCKStar utility values → no statistically significant impact of treatment failure on utility
- Requested EAG scenario: assume utility value for failure – new cGvHD systemic therapy = utility value for FF – lack of response ([redacted]) → minimal impact on ICER

Utility value for failure – new cGvHD systemic therapy	Source
Company base case: (0.479); assumed equal to utility value for failure – recurrent malignancy	Recurrent malignancy calculated as weighted average of published utility values for AML, ALL, CML, CLL
EAG preferred utility value: 0.608	Midpoint value (Crespo et al [2012], and Adelphi DSP study)
ROCKStar: [redacted]; company noted value lacked face validity	ROCKStar study; based on 69 observations from 22 patients

EAG comments

- High degree of uncertainty for failure – new cGvHD systemic utility value due to few observations
- Disagrees company's assumption (QoL for all failure patients is same), disagrees with lead team (QoL for people who changed treatment same as people who are FF but have lack of response to treatment [[redacted]])
- Considers its base case assumption (0.608) between company's base case and lead team

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

Abbreviations: FF, failure free; ALL, acute lymphoblastic leukaemia; AML, acute myelogenous leukaemia; QoL, quality of life CLL, chronic lymphocytic leukaemia, CML, chronic myelogenous leukaemia; cGVHD, chronic graft-versus-host disease

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

Lead team comments

- Assumption of constant disease management cost for failure – new cGvHD systemic therapy pessimistic

Health states	Mean cost per cycle per year					Source
	1st year	2nd year	3rd year	4th year	≥5th year	
Failure-free						
Complete response (CR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean cost incurred by HSCT patients without GVHD in (HES study)
Partial and lack of response (PR/LR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed mean cost incurred by all HSCT patients with cGVHD (HES study)
Failure						
New cGvHD systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to incur mean cost of HSCT patients with ≥2 records of high-cost therapy (HES study)
Recurrent malignancy	£2,719.46	£2,719.46	£2,719.46	£2,719.46	£2,719.46	TA642 (unavailable from HES study)
Requested scenario - New cGvHD systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1st year cost same as company base case with linear decline down to ≥5th year cost for failure-free (CR/PR/LR)**

NICE

Abbreviations: cGVHD, chronic graft-versus-host disease; HES, hospital episode statistics

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

Summary of yearly disease management costs by health states

Health states	Mean cost per year					Source
	1st year	2nd year	3rd year	4th year	≥5th year	
Failure-free						
Complete response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	HES study
Partial response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	HES study
Lack of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	HES study
Failure						
New chronic GVHD systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	HES study
Recurrent malignancy	£35,474.42	£35,474.42	£35,474.42	£35,474.42	£35,474.42	TA642

What are the most appropriate estimates for year 1 costs and most appropriate assumptions for the profile over time?

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

Annual disease management costs by health states

Original category in HES	All non-GVHD patients	Chronic GVHD patients with no high-cost therapy	Chronic GVHD patients with first high-cost therapy	Chronic GVHD patients with at least two high-cost therapies
Mean cost of inpatient attendance per person-year	[redacted]	[redacted]	[redacted]	[redacted]
Mean cost of outpatient attendance per person-year	[redacted]	[redacted]	[redacted]	[redacted]
Mean cost of A&E attendances per person-year	[redacted]	[redacted]	[redacted]	[redacted]
Mean cost of ICU attendance per person-year	[redacted]	[redacted]	[redacted]	[redacted]
Mean total cost per person-year	[redacted]	[redacted]	[redacted]	[redacted]

Source: Sanofi 2022

Abbreviations: A&E, accident and emergency; GVHD, Graft-Versus-Host Disease; HES, Hospital Episode Statistics; ICU, intensive care unit

Company's model overview

Technology affects **QALYs** by:

- Increasing FFS and OS
- Increasing time patients spend in response to treatment
- Reducing impact of AEs, including impact of IV infusions
- Reducing impact on caregiver HRQoL

Technology affects **costs** by:

- Its higher unit price than current treatments
- Being given as a tablet, rather than intravenously at hospital as with ECP and rituximab
- Increasing FFS; reducing proportion of people and length of time spent occupying failure health state
- Reducing the impact of AEs on patients.

Assumptions with greatest ICER effect:

- Inclusion of concomitant medications for belumosudil, such that the intervention in the model is belumosudil+BAT

Abbreviations: FFS, failure-free survival; OS, overall survival; BAT, best available therapy; FF, failure free; AEs, adverse events; IV, intravenous; ECP, extracorporeal photopheresis; HRQoL, health-related quality of life; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Large impact on ICER

Key issue: Removal of OS benefit for belumosudil+BAT

Background

- Observed OS for belumosudil and BAT immature & crossover in BAT adds uncertainty to OS estimates
- Company notes no direct data demonstrating relative OS benefit for belumosudil vs standard care
- 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
- EAG note scenario removing OS benefit for belumosudil+BAT (post clarification) → belumosudil dominant; impact of including OS benefit in EAG base case → large impact on ICER

Company

- Not unreasonable for EAG to remove OS benefit originally included in company submission model
- Note ICER remains under £30,000/QALY in EAG's scenario including OS benefit in EAG base case
- ICERs indicate inclusion/exclusion of OS benefit → belumosudil cost-effective, no risk of decision error

EAG comments

- Company & EAG aligned on issue, but company hasn't revised base case excluding OS benefit

Other considerations (clinical expert comments)

- OS advantage not entirely implausible however based on published data less likely & cannot be assumed

Is it reasonable not to include OS benefit for belumosudil+BAT in the model?

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

Small impact on ICER

Key issue: Removal of response outcomes from model

Company's scenario removing response has limited impact on ICER

Background

- Company model considers response outcomes as people in FF state are distributed into different response states according to level of response achieved
- Company noted uncertainty regarding comparability of response outcomes across trials:
  - Primary endpoint of ROCKstar was best response at any post-baseline assessment, while response in REACH-3 assessed at week 24
- 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's clinical experts advised in clinical practice FFS is a more clinically relevant outcome for people
- EAG considers company's scenario more appropriate approach to cost-effectiveness analysis and removes a source of unresolvable uncertainty in the analysis, thus limiting decision risk

Company

- Agree with EAG that FFS most clinically relevant outcome for people & consider it to be the most suitable endpoint for modelling (consistent with company clinical expert)
- Agree with EAG that excluding response from model removes source of unresolvable uncertainty whilst having a minimal impact on resulting ICERs

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Abbreviations: FFS, failure-free survival; FF, failure free; ICER, incremental cost-effectiveness ratio

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Concomitant medication costs	Excluded	Included (belumosudil only)
Cost of background therapies	Included	Excluded
TTD data for belumosudil	Lognormal distribution	KM TTD data
Distribution for BAT TTD	TTD curve estimated by applying HR to TTD curve of belumosudil once daily. HR derived based on reported median TTD from REACH-3	Exponential distribution
Accommodation costs for patients in ECP	Included	Excluded
Subsequent treatment duration	Duration of subsequent treatments assumed a lifetime	Maximum subsequent treatment duration of five years (except for rituximab)
Failure – New cGvHD Systemic Therapy utility value	Assumed equal to utility value for failure – recurrent malignancy (0.479)	Midpoint utility value of (0.608) for failure
Caregiver disutility failure – new cGvHD systemic therapy	Sourced from sourced from Acaster et al. 2013 study on caregivers of patients with MS = (-0.142)	New cGvHD systemic therapy equal to failure-free (partial response/lack of response) = (-0.045)
Disutility & duration for central line-related infections	Assumption of no disutility for central line-related infections	Based on disutility for infections and infestations from TA689
IV disutility for BAT	Included	Excluded

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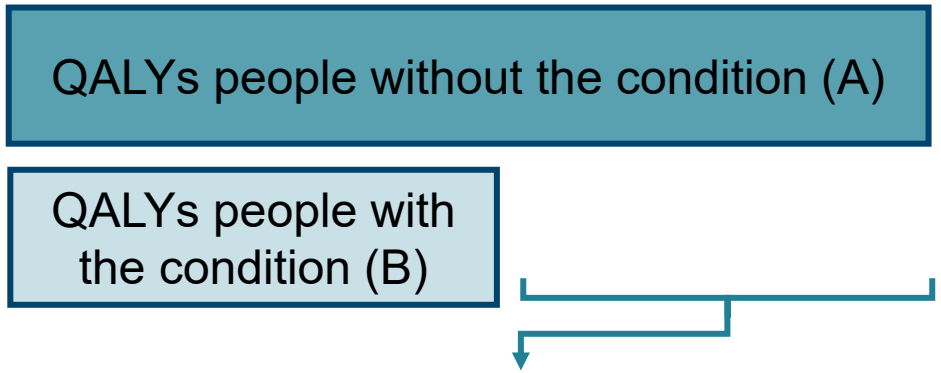
Abbreviations: TTD, time to treatment discontinuation; HR, hazard ratio; BAT, best available therapy; KM, Kaplan-Meier; cGVHD, chronic graft-versus-host disease; IV, intravenous; ECP, extracorporeal photopheresis; TA, technical appraisal; MS, multiple sclerosis

QALY weighting for severity

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition having current standard care

Health: length and quality of life (QALYs)



Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

NICE QALY weighting for severity used to decide whether to apply additional weight, and how much

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- QALY weightings for severity can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

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Abbreviations: QALYs, quality-adjusted life years

Company QALY shortfall analysis

- Company used the base case total QALYs estimated for the BAT arm
- Company data inputs for QALY shortfall calculations:
  - mean age (53.9 years) and sex distribution (58% male) (post clarification economic model – pooled data for the ≥2 LOT subgroup of ROCKstar and KD025-208 [September 2022 data cut])

Deterministic calculations	Mean QALYs	Absolute shortfall (has to be ≥12)	Proportional shortfall: • 0.85 to 0.95 for x1.2 • at least 0.95 for x1.7
General population	14.61	N/A	N/A
People with the condition under standard care (BAT)	[redacted]	[redacted]	[redacted]

- **Company estimated severity modifier of 1.2 should be considered based on QALY shortfall analysis**
- **Severity modifier of 1.2 does not apply to EAG's preferred cost effectiveness results (QALY weighting for severity = 1)**

Abbreviations: QALY, quality-adjusted life year; BAT, best available therapy

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 no severity weighting: below £20,000/QALY gained
  - with 1.2 severity weighting: below £20,000/QALY gained

EAG's preferred base case estimated a severity modifier of 1, however the company's and EAG's base case ICERs are below the lower bound of the cost-effectiveness range typically used by NICE, £20,000 per QALY/ or belumosudil is dominant

EAG results of lead team requested scenarios also presented in Part 2 slides

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

Managed access

Criteria for a managed access recommendation

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**.

Key issues

Issue (identified by the EAG)	Resolved?	ICER impact
Evidence for adolescents not available from ROCKstar and KD025-208	No – for discussion	Unknown
Naïve comparison of belumosudil versus BAT	No – for discussion	Unknown
Removal of OS benefit for belumosudil+BAT	Partially – for discussion	Large
Removal of response outcomes from the economic model	Partially – for discussion	Small
Inclusion of concomitant medication costs for belumosudil, such that the intervention for the cost-effectiveness analysis is belumosudil in addition to BAT (belumosudil+BAT)	Yes – EAG consider company's scenario analysis resolves issue	Small
Issue (identified by Lead Team)	**Resolved?**	**ICER impact**
Extrapolation of REACH-3 FFS for the BAT arm	No – for discussion	Unknown
Utility value for failure – new cGvHD systemic therapy	No – for discussion	Large
Disease management costs for failure – new cGvHD systemic therapy	No – for discussion	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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Back-up slides

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