Ruxolitinib for treating acute graft-versus-host disease refractory to corticosteroids in people aged 12 and over

PART 1
For screen – confidential information redacted

Technology appraisal committee D [6 November 2024]

Chair: Amanda Adler

Lead team: David Meads, Bernard Khoo, Paul Caulfield

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Tom Palmer, Michelle Green, Ian Watson

Company: Novartis

Ruxolitinib for treating acute graft-versus-host disease refractory to corticosteroids in people aged 12 and over

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

NICE National Institute for Health and Care Excellence

Background acute graft versus host disease (aGvHD)

Causes

- Occurs when donor T-cells attack recipient's cells
- Primarily from allogeneic (when donor and recipient differ genetically) haematopoietic stem cell transplant (HSCT)

Manifestations + classification

- Differs from chronic GvHD by manifestations, diagnostic criteria + pathology (see appendix)
- aGvHD damages skin, liver, GI tract; chronic GvHD manifestations – any organ
- Graded 1 (least severe) skin only to 4 (most severe) skin, liver, GI tract (see appendix)

Epidemiology

- In 2022 in UK, 1,535 allogeneic HSCTs
- 1/3 to 1/2 develop aGvHD; 1/2 of these refractory to steroids

Prognosis

- People with steroid-refractory aGvHD have ~25% survival at 2 years and ~10% at 4 years

NICE aGvHD, acute graft versus host disease; GI, gastrointestinal; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant.

Patient and clinical perspectives

See appendix – patient and clinical perspectives

Anthony Nolan and Leukaemia Care joint submission + 2 PE

aGvHD:

- causes physical symptoms that are distressing and difficult to manage
- can lead to frequent hospitalisations due to infection

Minimising infection risk involves prolonged isolation → harm mental health

Steroids associated with significant debilitating adverse effects

Substantial unmet need → oral administration of ruxolitinib is appealing

"Ruxolitinib… had an almost immediate impact on all his GvHD symptoms. It was life changing and life saving for him"

British Society of Bone Marrow Transplantation and Cellular Therapy + 1 CE

- Treat to improve disease, decrease steroid use + infections, improve QoL
- Treatments largely un-licenced with limited evidence → extracorporeal photopheresis, infliximab, alemtuzumab, MMF, sirolimus, ciclosporin

Updated British guidelines will recommend ruxolitinib 2nd line

When assessing response to ruxolitinib, stopping criteria should include complete response, progression of GvHD, intolerance

"Real world data [suggest] improved survival, reduction in hospitalisation and health care use. Also, would be reduction of costs with swifter recovery and reduced attendances for treatment and review."

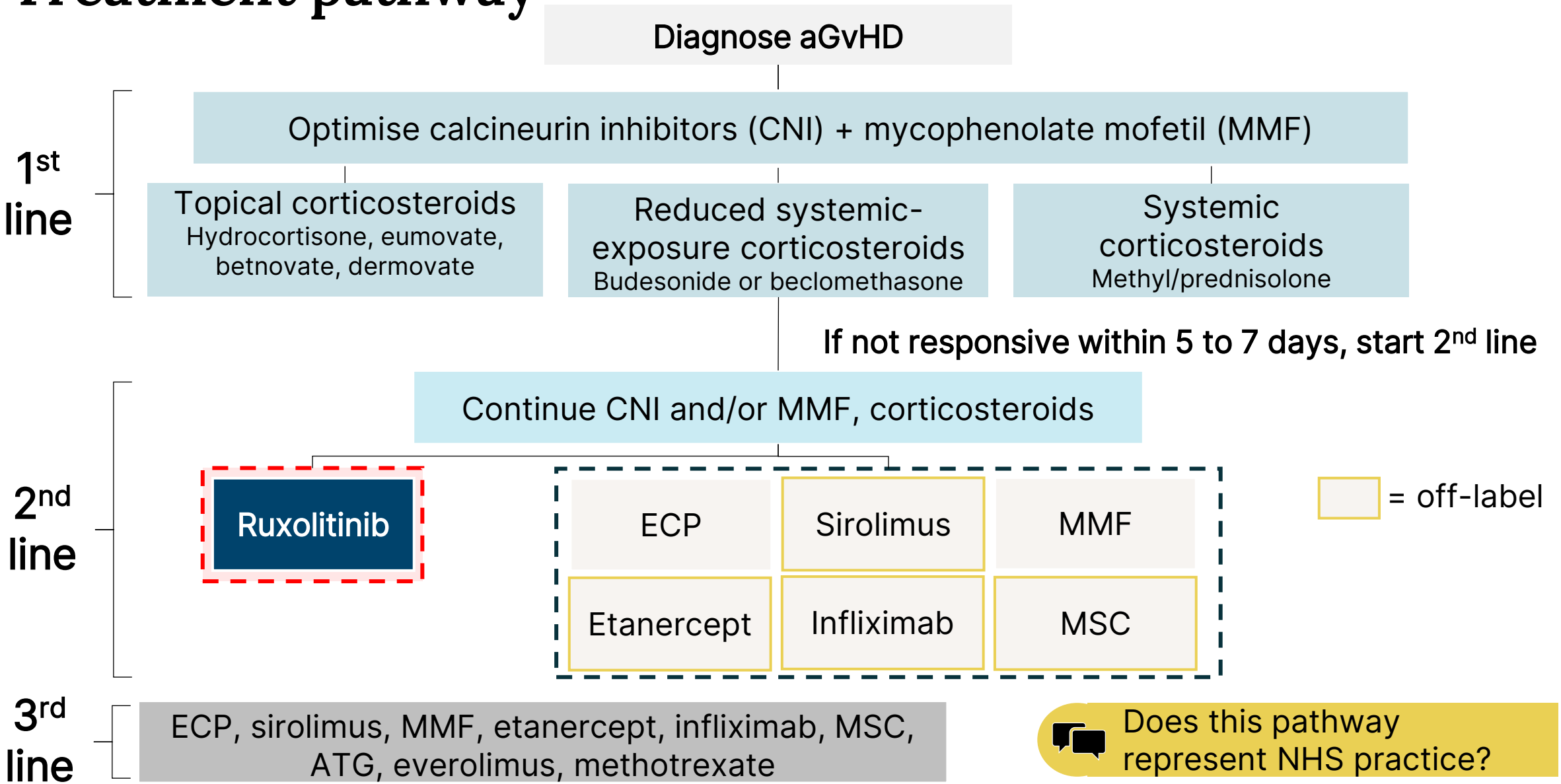
aGvHD, acute graft versus host disease; CE, clinical expert; GvHD, graft versus host disease; MMF, mycophenolate mofetil; PE, patient expert; QoL, quality of life.

Equality considerations

- Human leukocyte antigen (HLA) matched transplants reduce the risk of GvHD
- Chance of finding a perfect match especially low for some ethnic groups
  - ↳ Some ethnic groups therefore may be more likely to develop GvHD
- NHSE Rapid Commissioning Policy made ruxolitinib available during COVID-19 pandemic
  - ↳ Some people in England can still access ruxolitinib through individual funding requests or local approval by individual trusts
  - ↳ This creates inequality of access across England
- Limited access to a few specialist centres of current preferred treatment, extracorporeal photopheresis, may require travel

COVID-19, coronavirus disease 2019; GvHD, graft versus host disease; HLA, human leukocyte antigen; NHSE, NHS England.

Treatment pathway



NICE aGvHD, acute graft versus host disease; CNI, calcineurin inhibitors; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells

Ruxolitinib (Jakavi, Novartis Pharmaceuticals)

Other indications for myelofibrosis and polycythaemia vera

UK Marketing authorisation	• 'Patients aged 12 years and older with acute graft versus host disease who have inadequate response to corticosteroids' • Granted March 2022
Mechanism of action	• Selectively inhibits JAK enzymes, competitively inhibits ATP-binding catalytic site on JAK1/2 • Inhibits signalling of proinflammatory cytokines involved in pathogenesis of aGvHD associated with inflammation, tissue damage, fibrosis
Administration	• Oral tablet, self-administered • Recommended starting dose 10mg taken twice daily

Price	• List price:
	  ○ £1,428 per 56 pack of 5 mg tablets
	  ○ £2,856 per 56 pack of 10 mg tablets
	• A commercial arrangement is available

- NICE previously issued terminated guidance for ruxolitinib for acute GvHD (TA839) as company did not provide a submission
- See appendix for timeline of ruxolitinib approval and appraisal history

aGvHD, acute graft versus host disease; ATP, adenosine triphosphate; GvHD, acute graft versus host disease; JAK, janus kinase.

Key issues identified by the EAG

Issues	Resolved?	
Decision problem issues		
Clinical evidence not generalisable to adolescents and Grade I disease	No	
A blended comparator reflecting standard care might overlook subgroups or overestimate treatment effect	No	
Clinical effectiveness issues		
REACH1 study has worse outcomes for ruxolitinib than REACH2, the key trial	Partially	
Potential underestimate of the treatment effect on chronic GvHD incidence	Yes	
Cost-effectiveness issues		
Model does not capture likely mixture of patients in failure-free health states	No	
Company's modelled chronic GvHD population and REACH3 do not align	No	
EAG does not agree with company's time-to-event extrapolations	No	Known ICER impact
Uncertainty about implementation health state utilities – some values of health states, and some modelling assumptions	No	

NICE EAG, external assessment group; GvHD, graft versus host disease; ICER, incremental cost-effectiveness ratio.

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Clinical evidence summary

	REACH1	REACH2	REACH3
Phase	2	3	3
Design	Single-arm, open label	Randomised, controlled, open label	Randomised, controlled, open label
Population	Acute GvHD	Acute GvHD	Chronic GvHD
Intervention	Ruxolitinib 5 mg BID* (n=71)	Ruxolitinib 10 mg BID (n=154)	Ruxolitinib 10 mg BID (n=165)
Comparator	None	Standard care (n=155)	Standard care (n=164)
Use in model	Not used	• Acute GvHD transition probabilities • Utility values	• Chronic GvHD transition probabilities (from standard care arm only) • Utility values

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*Could increase to 10 mg after 3 days.
BID, twice daily; GvHD, graft versus host disease.

Clinical evidence – trial summary

	REACH2
Design	Randomised, controlled, open-label, **phase 3**
Population	• 12 years or older • Allogenic stem cell transplant • Suspected grade 2 to 4 aGvHD
Intervention(s)	Ruxolitinib **10 mg** twice daily (n=154)
Comparator	**Standard care** based on investigator judgement (n=155)
Pre-planned subgroups	Several including age, gender, race, aGvHD grade, graft source, donor characteristics
Key outcomes	1°: ORR at day 28 2°: ORR (day 14, 56), DOR, BOR, OS, EFS, FFS, NRM, cGvHD, HRQoL, malignancy relapse/progression, steroid use, safety
Locations	**22 countries**, including UK (3 centres)

- **Company:** REACH1 also completed → single-arm study (US only), lower starting dose (5 mg BID)
- **EAG:** REACH1 showed worse outcomes than REACH2, not fully explained why (see appendix)

- Does REACH2 reflect UK practice (comparators) and outcomes?
- Are data from REACH1 relevant to this appraisal?

REACH2 results – primary outcome

Ruxolitinib better than standard care in overall response rate (ORR) at day 28

ORR = proportion who had a:

- Complete response (score of 0 for grading in all evaluable organs), or
- Partial response (improvement of 1 stage in 1 or more organs)

	Ruxolitinib N=154	Standard care N=155
Complete response (CR), n (%)	53 (34.4)	30 (19.4)
Partial response (PR), n (%)	43 (27.9)	31 (20.0)
Overall response: CR + PR, n (%)	96 (62.3)	61 (39.4)
95% CI	54.2, 70.0	31.6, 47.5
Odds ratio (95% CI)	2.64 (1.65, 4.22)	
p-value	<0.0001	

NICE CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response.

REACH2 results – failure-free survival

Ruxolitinib better than standard care in failure-free survival (FFS)

FFS = time from the date of randomisation to date of haematological disease relapse/progression, non-relapse mortality, or addition of new systemic aGvHD treatment

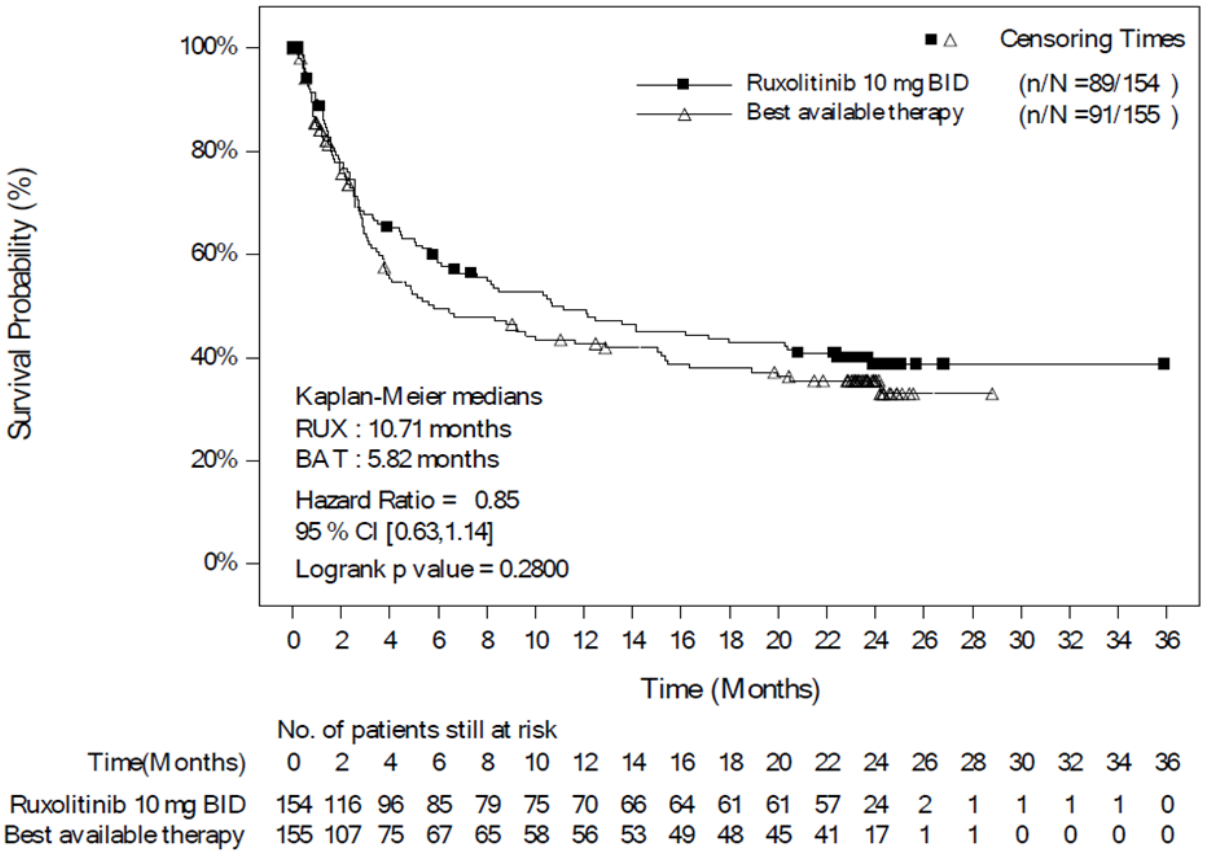
- Median FFS ruxolitinib longer than standard care (4.86 vs. 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001)

NICE aGvHD, acute graft versus host disease; CI, confidence interval; FFS, failure-free survival; HR, hazard ratio.

REACH2 results – overall survival

Non-significant difference in overall survival between ruxolitinib and standard care

Unadjusted overall survival



No. of patients still at risk

Time(Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Ruxolitinib 10 mg BID	154	116	96	85	79	75	70	66	64	61	61	57	24	2	1	1	1	1	0
Best available therapy	155	107	75	67	65	58	56	53	49	48	45	41	17	1	1	0	0	0	0

Overall survival curves adjusted for crossover

- 49 patients (32%) switched from standard care to ruxolitinib
- Company → 2-stage method to adjust for switchers
- Standard care median OS adjusted for crossover was [redacted] months (vs. 5.82 months unadjusted)
- Adjusted HR = [redacted] (95% CI: [redacted]

NICE CI, confidence interval; HR, hazard ratio; OS, overall survival.

Key issue: Clinical effectiveness evidence not generalisable to adolescents and Grade I disease

Background

- Licence and decision problem (see appendix) do not exclude adolescents or grade 1 aGvHD
- But,
  - ↳ Only 3% in REACH2 <18 years (none in REACH1; see appendix)
  - ↳ Eligibility criteria for trials excluded grade 1 disease

Company

Adolescents

- Few adolescents because low incidence of aGvHD in <18 years
- Clinical advice → no differences between adults and adolescents in manifestation of aGvHD, pathophysiology, or treatment

Grade 1 disease

- Clinical advice → need ruxolitinib for grade 1 disease as likely progression to grade 2+

EAG

- Question whether to include adolescents and grade 1 disease

- Would ruxolitinib be used in adolescents and people with grade 1 disease?
- Is the evidence sufficient to justify this, and to support a recommendation in those groups?

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aGvHD, acute graft versus host disease; EAG, external assessment group.

Key issue: A blended comparator reflecting standard care might overlook subgroups or overestimate treatment effect

Background: Blended comparator used in the model as per REACH2 and adjusted by expert input

EAG:

- Company adjust proportions from REACH2 to reflect expert input, but only affects costs and not efficacy
- Standard care efficacy from REACH2 blended comparator
- ECP is NHS preferred treatment – why low use in REACH2?
- Should standard care efficacy improve if higher proportion of ECP?

Company: Do not have data available to conduct analyses for each treatment, would break randomisation

- Evidence of similar efficacy for each treatment (see appendix 1, 2, 3, 4)

Standard care in REACH2 + model

	REACH2	Expert input	Model
ATG	13%	0%	0%
ECP	27%	46%	45%
Etanercept	15%	15%	15%
Everolimus	1%	0%	0%
Infliximab	11%	15%	15%
Low-dose methotrexate	3%	0%	0%
MMF	17%	18%	17%
MSC	10%	5%	5%
Sirolimus	2%	1%	1%
No treatment	3%	–	3%

ATG; anti-thymocyte globulin; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells.

- Are the results of REACH2 generalisable to the NHS given the standard care mix?
- Are some comparators more effective than others? Why ECP preferred?
- Should the comparators be modelled individually, instead of blended?
- Does the model underestimate NHS standard care efficacy?

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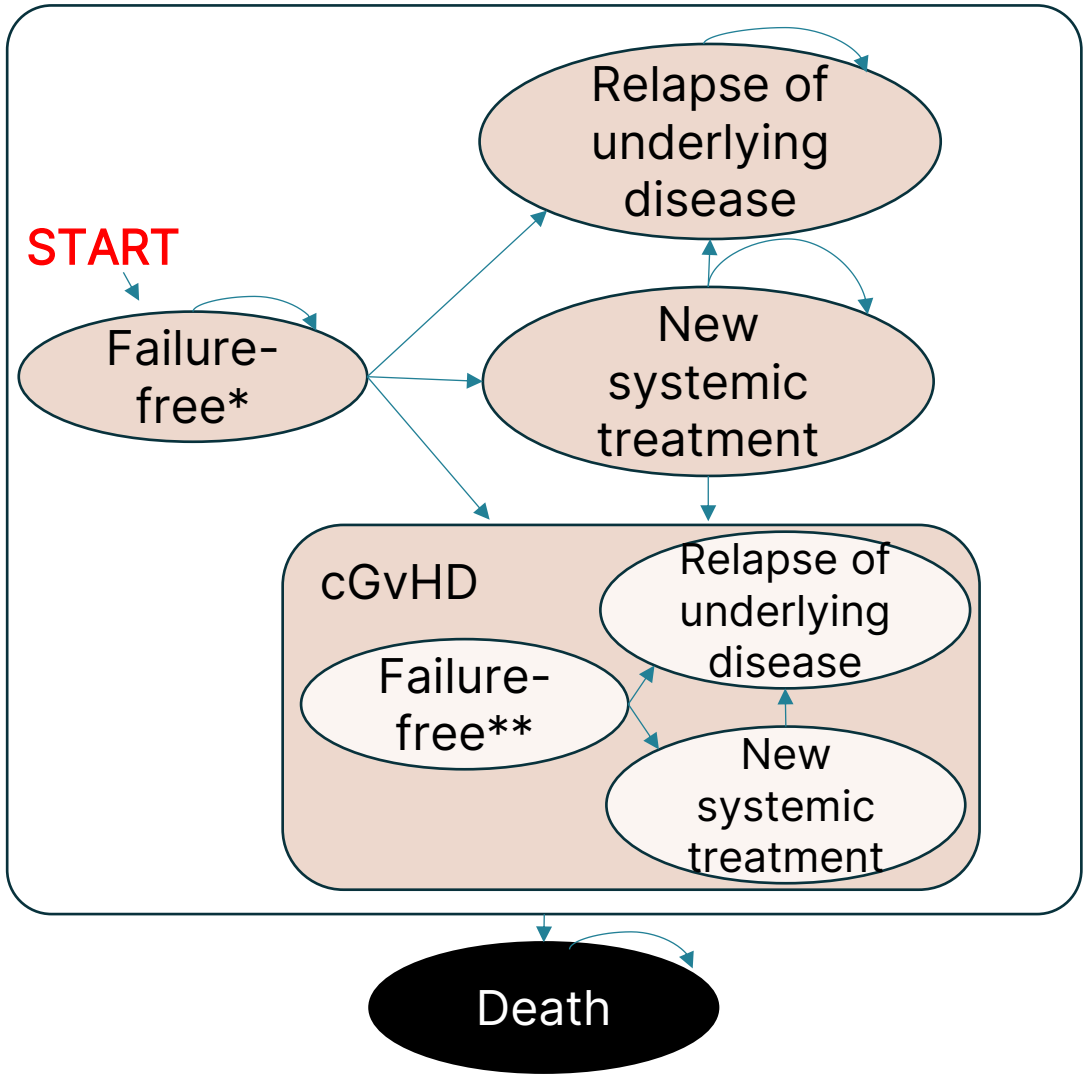
Company's model structure



Multi-state model of 7 health states

- Transitions from failure-free derived separately for ruxolitinib and standard care from REACH2
- Transitions between cGVHD states derived from standard care arm of REACH3 (phase 3 study of ruxolitinib in cGVHD – see appendix)

Ruxolitinib affects **QALYs** by:

- Increasing overall survival
- Increasing QALYs in failure-free (aGvHD) and cGvHD
- Decreasing QALYs in NST (aGvHD)

Ruxolitinib affects **costs** by:

- Lower acquisition and subsequent treatment costs
- Increasing management and cGvHD treatment costs
- Minor increase in adverse event costs

*aGvHD failure-free: remain until treatment failure: new systemic aGvHD treatment, relapse of underlying disease, non-relapse mortality; or develop cGvHD

**cGvHD failure-free: develop cGvHD, remain until treatment failure (new systemic therapy, relapse of underlying disease)

aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease; QALY, quality-adjusted life year.

Key issue: Model does not capture likely mixture of patients in failure-free health states

Background

- Patients remain in the failure-free health state until:
  - ↳ Treatment failure per REACH2: new systemic therapy for aGvHD, relapse of underlying disease, or die from cause other than relapse
  - ↳ Develop chronic GvHD

EAG

- Company does not capture treatment response – failure-free state will contain people who respond and are symptomless, and people who do not respond, have symptoms, but have not yet had treatment failure
- These subgroups would likely have different outcomes and utilities
- Mixture of patients in each subgroup changes over time as patients move to different health states
  - ↳ Increase in utility of failure-free patients in REACH2 after 4 cycles may indicate people with symptoms leaving this health state and moving to another treatment

- Is the model structure suitable for decision-making?
- Does the failure-free health state require subhealth states to capture response?

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aGvHD, acute graft versus host disease; EAG, external assessment group; GvHD, graft versus host disease.

Treatment duration and stopping

REACH2

Duration:

- Mean: [redacted] (max. 678 days)

Stopping/tapering criteria:

- Within 28 days, people with acute GvHD progression, or mixed or no response, could have new systemic treatment
- After 56 days, people with response could taper off ruxolitinib

Licence

Duration:

- Not specified

Stopping/tapering criteria:

- Tapering may be considered in people with response and after discontinued steroids. 50% dose reduction of ruxolitinib every 2 months recommended. Re-escalate if GvHD reoccurs

Model

Duration:

- Mean: [redacted] (from REACH2)

- Duration does not appear to be linked to health state – unclear whether some patients who develop chronic GvHD continue to incur ruxolitinib costs
- Cost of ruxolitinib calculated using average dose in each week of REACH2

Clinical expert statement
When assessing response at day 28 to ruxolitinib, stopping criteria should include complete response, progression of GvHD, intolerance

Does the modelled treatment duration reflect how ruxolitinib will be used in clinical practice?

GvHD, graft versus host disease.

Key issue: Company's modelled chronic GvHD population and REACH3 do not align

Background: Company uses REACH3 standard care arm to model chronic GvHD

Company

- Clinical advice: REACH3 data are reasonable proxy
- REACH3 FFS outcome seem comparable between those who did and did not have prior aGvHD

EAG

- In REACH3, only 10.4% of patients had steroid-refractory aGvHD prior to cGvHD
- Unclear if clinical profile and outcomes of people who have cGvHD after aGvHD would differ to people who have cGvHD without aGvHD
- Important as most QALYs generated in cGvHD

FFS in REACH3 by prior aGvHD status

Would similar outcomes be expected for people who have cGvHD after steroid-refractory aGvHD and people who have cGvHD without previous aGvHD?

 aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease; EAG, external assessment group; FFS, failure-free survival; QALY, quality-adjusted life year.

Key issue: EAG does not agree with company's time-to-event extrapolations (1/3)

Company

- Used survival analysis to extrapolate time-to-event outcomes
- Assessed proportionality of hazards to determine joint or independent model fitting – see appendix
- Chose survival curves using goodness-of-fit, clinical plausibility, and visual inspection
- Chose joint models for failure-free to new systemic treatment, relapse + death, independent models used for cGvHD
- Standard care landmark survival estimates validated with clinicians

Landmark survival estimates
(% of patients remaining in FF health state)

	FF-NST		FF-Relapse		FF-cGvHD		FF-Death	
	BAT	RUX	BAT	RUX	BAT	RUX	BAT	RUX
0	100	100	100	100	100	100	100	100
8 w	52	84	93	96	96	99	81	85
16 w	40	78	87	91	86	91	73	77
24 w	35	76	82	88	78	80	69	73
1 y	33	74	73	79	61	52	62	65
2 y	33	74	64	70	46	30	56	59
5 y	33	74	53	58	31	13	49	51
10 y	33	74	46	50	22	7	44	46
15 y	33	74	42	46	18	5	42	44
20 y	33	74	39	43	16	3	40	42

BAT, best available therapy; cGvHD, chronic graft versus host disease; FF, failure-free; NST, new systemic therapy; RUX, ruxolitinib.

Key issue: EAG does not agree with company's time-to-event extrapolations (2/3)

Company

- Not plausible that risk of death or relapse higher with ruxolitinib than standard care because of censoring for competing events
- At clarification – assumed same rate of cGvHD for both arms

[redacted]

Key issue: EAG does not agree with company's time-to-event extrapolations (3/3)

Company approach inconsistent; EAG propose assuming benefit only failure-free to NST

EAG

- Few patients at risk after 3 months → uncertainty
- Question validity of survival curves:
  - ↳ Inappropriate selection of proportional hazards models, and poor fit of extrapolations to Kaplan-Meier data
- Based on the log-log plots (see appendix), proportional hazards only appropriate for failure-free to NST

EAG proposes pragmatic approach assuming treatment benefit only for delaying time to NST

- ↳ Incremental costs + QALYs both decrease, but costs decrease more → decreases ICER

- What is the committee's view on the appropriate approach to extrapolation of time to NST, relapse, cGvHD and death?
- Is it appropriate to assume a treatment benefit in NST, relapse + death (company) or NST only (EAG)?

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EAG, external assessment group; ICER, incremental cost-effectiveness ratio; NST, new systemic treatment; QALY, quality-adjusted life year.

Key issue: Utility values (1/2)

Company derived utility values from pooled EQ-5D from trials, clinical advice + past TA

Company

- Single model fit to pooled REACH2 and 3 data to estimate utility values for each health state
- FF utility in REACH 2 lower than expected, but it increases and stabilises after cycle 4, so added a covariate
- Acknowledge few observations for relapse (n=[redacted]) and cGvHD relapse (n=[redacted]) health states
  ↳ Instead, took utility estimate for relapse from TA949 (belumosudil for cGvHD)
- Developed 4 models (see appendix) +/- subject level random-effects, +/- estimating a relapse utility (utility instead from TA949)
- Clinical advice preferred model 4 – without subject level random-effects, without relapse utility

State	Utility value	Justification
Failure-free, first 4 cycles	[redacted]	REACH2 + 3, clinical opinion
Failure-free, >4 cycles	[redacted]	
New systemic treatment	[redacted]	
Relapse	0.479	TA949
cGvHD, relapse	0.479	
cGvHD, failure-free	[redacted]	REACH2 + 3, clinical opinion
cGvHD, new systemic treatment	[redacted]	

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cGvHD, chronic graft versus host disease.

Key issue: Utility values (2/2)

EAG: pooling REACH2 + 3 inappropriate; utilities do not align with previous appraisals

EAG

- May not be appropriate to pool REACH 2 + 3 data, given different populations and disease characteristics – company then provided separate models (see appendix)
- Patients who transition to cGvHD from FF (first 4 cycles) have a utility increase
  - ↳ Unlikely in real life as some patients who develop cGvHD will still have aGvHD symptoms
  - ↳ Prefer to use a lower utility value for cGvHD in first 4 cycles
- Previous company submissions to CADTH (Canada) and PBAC (Australia) used different utility values from REACH2 + 3 data, although data cut and models were different (see appendix)
  - ↳ Concerned utility for FF after 4 cycles much higher than for responders in CADTH and PBAC appraisals

For the base case, EAG reduced the 'cGvHD, first 4 cycles' utility (= to "failure-free, first 4 cycles")

- EAG conducted scenarios using the separate aGvHD/cGvHD models → small increase/decrease to ICER depending on model

- Does the committee prefer to use separate or pooled REACH2 + 3 data to derive utility values?
- Is the increase in utility when transitioning to cGvHD within the first 4 cycles of aGvHD plausible?

aGvHD, acute graft versus host disease; CADTH, Canadian Agency for Drugs and Technologies in Health; cGvHD, chronic graft versus host disease; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; PBAC, Pharmaceutical Benefits Advisory Committee.

Key differences in base cases

Assumption	Company	EAG
Transition probabilities	For failure-free: • Survival analyses for all transitions, separate ruxolitinib and standard care data, joint or individual models For all other transitions: • Survival analyses for all transitions from pooled ruxolitinib and standard care	For failure-free: • Only benefit of ruxolitinib is delaying time to new systemic treatment For all other transitions: • As company base case
Utility values	Derived from model fit to pooled REACH2 + 3 data	As company base case, but utility for cGvHD ≤4 cycles is equal to failure-free ≤4 cycles Adverse event disutilities changed to multiplicative (minimal ICER effect)
Other differences	-	Corrected errors in survival data and costs

NICE cGvHD, chronic graft versus host disease; EAG, external assessment group; ICER, incremental cost-effectiveness ratio.

QALY weightings for severity

Background

- Expected QALYs for the general population generated using England and Wales lifetables and general population utility values for the UK derived from Hernández Alava et al, 2022
- Assumes patient population baseline age of 49.5 years, 41% female
- QALYs for people on current treatment estimated from the standard care arm of the model

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)	Weighting
Company base case	15.86	1.43	14.43	0.91	1.2
EAG base case	15.86	1.39	14.47	0.91	1.2

Does the committee agree with applying a 1.2 QALY weighting for severity?

EAG, external assessment group; QALY, quality-adjusted life year

See appendix for weighting methods

Cost-effectiveness results

Confidential discounts available for comparators, so ICERs in Part 2 slides ICER ranges presented below

Summary – ruxolitinib versus standard care

Company base case probabilistic ICER:

- with 1.2 severity weighting: between £20,000 and £30,000 per QALY gained

EAG base case probabilistic ICER:

- with 1.2 severity weighting: less than £20,000 per QALY gained

Scenario analyses with 1.2 severity weighting:

- Lowest ICER: less than £20,000 per QALY gained
- Highest ICER: between £20,000 and £30,000 per QALY gained

Scenarios include:

- Adjusting proportions of standard care treatments (costs only)
- Different time-to-event extrapolations
- Utility models
- Different utility values

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

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EAG does not agree with company's time-to-event extrapolations	No	Known ICER impact
Uncertainty about implementation health state utilities – some values of health states, and some modelling assumptions	No	

NICE EAG, external assessment group; GvHD, graft versus host disease; ICER, incremental cost-effectiveness ratio.

Supplementary appendix

NICE National Institute for Health and Care Excellence

Ruxolitinib timeline

2019
REACH2 trial primary completion

2020
NHS England commissions ruxolitinib for acute GvHD as part of COVID-19 rapid policy

2022
Ruxolitinib receives UK licence for acute + chronic GvHD

2022
NICE issues terminated guidance (TA839) as company did not provide a submission*

2022
NHS England commissioning ends (local funding available at some trusts)

2024
This appraisal (ID6377) begins

Clinical expert statement:
"England is an outlier – ruxolitinib is standard care in Scotland and Wales, and in Europe and the US"

Other NICE approvals for ruxolitinib
- TA386 – disease-related splenomegaly or symptoms in adults with myelofibrosis
- TA921 – polycythaemia vera

*NICE also issued terminated guidance for chronic GvHD (TA840), as the company did not provide an evidence submission
GvHD, graft versus host disease.

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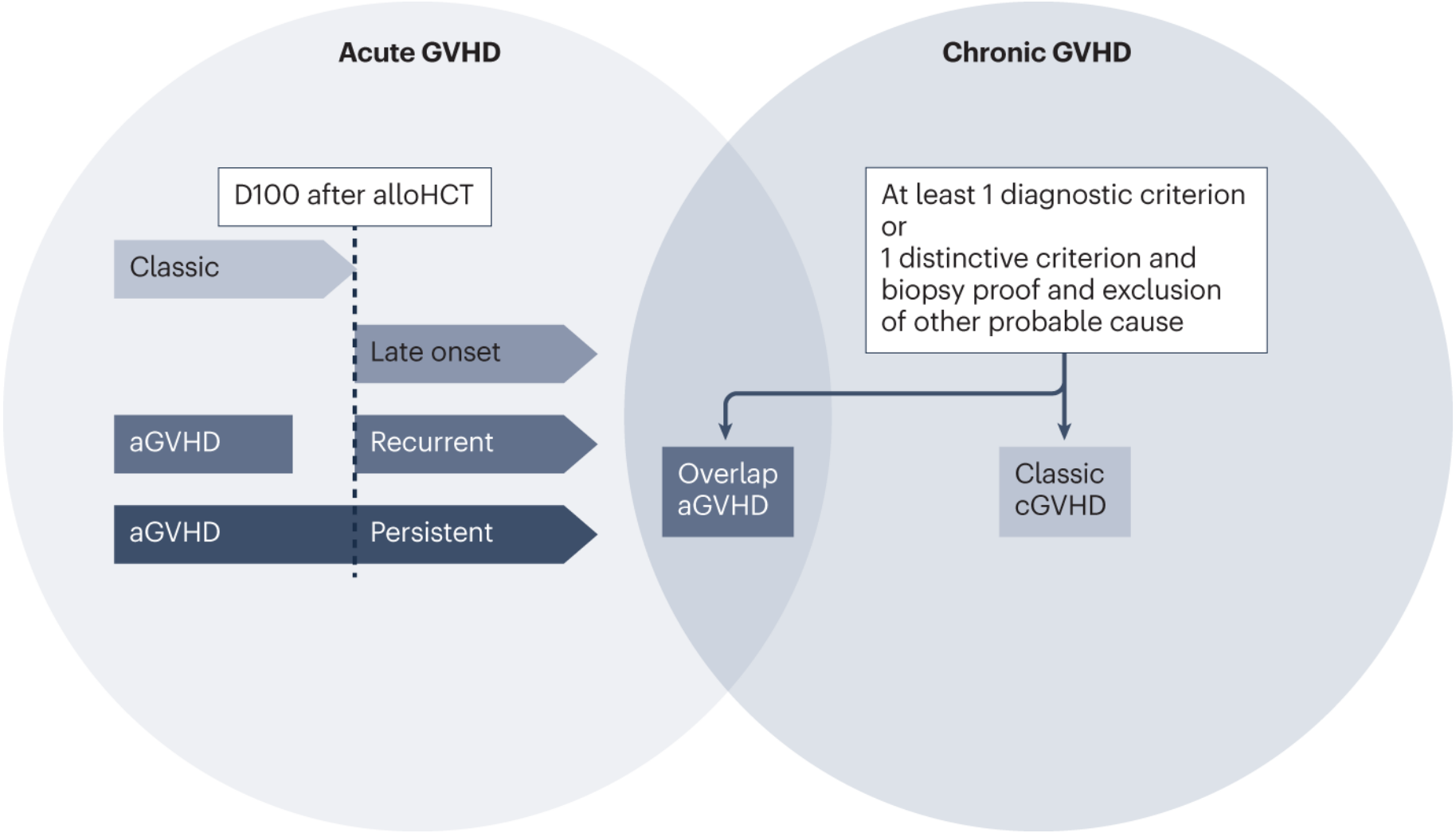
aGvHD versus cGvHD



Back to main deck

NICE aGvHD, acute graft versus host disease; alloHCT, allogenic haemopoietic cell transplant; cGvHD, chronic graft versus host disease.

aGvHD staging and grading

Stage	Skin based on maculopapular rash	Liver based on bilirubin	GI based on quantity of diarrhoea
+	<25% of surface	34–50 µmol/L	500–1000 mL
++	25–50% of surface	51–102 µmol/L	1001–1500 mL
+++	Generalised erythroderma	103–255 µmol/L	>1500 mL
++++	Generalised erythroderma with bullae and desquamation	>255 µmol/L	Severe abdominal pain with and without ileus
Grade			
I	Skin + to ++		
II	Skin + to +++, GI, and/or liver + Mild decrease in clinical performance		
III	Skin ++ to +++, GI, and/or liver ++ to +++ Marked decrease in clinical performance		
IV	Skin ++ to ++++, GI, and/or liver ++ to ++++ Extreme decrease in clinical performance		

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NICE aGvHD, acute graft versus host disease; GI, gastrointestinal

Patient perspectives

Joint submission from Anthony Nolan and Leukaemia Care

aGvHD causes physical symptoms that are distressing and difficult to manage:

↳ skin symptoms can cover large portions of the body and make contact against clothes, sheets and furniture painful

↳ struggling to swallow due to mouth ulcers, can cause extreme weight loss, in severe cases a feeding tube might be needed

People with aGvHD can experience frequent hospital admissions due to infection, which can be life-threatening if sepsis develops

Steroids associated with significant debilitating side effects

For people with steroid-refractory aGvHD, ECP requires travel to and from the ECP centre, this can be costly and causes an added burden

Substantial unmet need for new treatments for steroid-refractory aGvHD

Oral administration of ruxolitinib is very appealing

"Ruxolitinib … had an almost immediate impact on all his GvHD symptoms. It was life changing and life saving for him."

"Ruxolitinib greatly improved my quality of life in a very short time. The ability to take tablets at home, reducing the number of hours spent in hospital appointments every week."

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aGvHD, acute graft versus host disease; ECP, extracorporeal photopheresis.

Clinical perspectives

Submission from the British Society of Bone Marrow Transplantation and Cellular Therapy (BSBMTCT)

Steroid-refractory aGvHD has very poor prognosis and transplant related mortality of more than 60% within 6 to 12 months if unresponsive

Main aim of treatment is to reduce organ grading and staging, decrease steroid use, reduce infections, improve QoL

Treatment for aGvHD includes a basket of non-licensed treatments with limited evidence → ECP, infliximab, alemtuzumab, MMF, sirolimus, ciclosporin

British guidelines are being updated, will recommend ruxolitinib for 2nd line

England is outlier → ruxolitinib considered standard care in Scotland and Wales, and in Europe and US

Ruxolitinib response should be assessed at day 28, stopping criteria to include:

↳ Complete response (following stopping of other immunosuppressive treatments)

↳ Progression of GvHD

↳ Intolerance of ruxolitinib

aGvHD, acute graft versus host disease; BSBMTCT, British Society of Bone Marrow Transplantation and Cellular Therapy; ECP, extracorporeal photopheresis; GvHD, graft versus host disease; MMF, mycophenolate mofetil; QoL, quality of life.

Key issue: REACH1 has worse outcomes for ruxolitinib than REACH2, which is the key trial

EAG
- No clear explanation for better survival outcomes observed in REACH2 versus REACH1

- REACH1 starting dose was 5 mg twice daily, could escalate to 10 mg after 3 days
- REACH2 dose was 10 mg

	REACH2		REACH1
	Ruxolitinib N=154	Standard care N=155	Ruxolitinib N=71
Overall response			
CR, n (%)	53 (34.4)	30 (19.4)	19 (26.8)
PR, n (%)	43 (27.9)	31 (20.0)	6 (8.5)
ORR: CR + PR, n (%)	96 (62.3)	61 (39.4)	40 (56.3)
OS, months	10.71	5.82*	7.63
FFS, months	4.86	1.02	2.80

REACH1 subgroup analysis

Are data from REACH1 relevant to this appraisal?

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*Not adjusted for crossover

NICE CR, complete response; EAG, external assessment group; FFS, failure-free survival; ORR, overall response rate; OS, overall survival; PR, partial response.

Decision problem

	Final scope	EAG comments
Population	People aged 12 years and older with aGvHD who have inadequate response to corticosteroids	• Lack of evidence for adolescents and Grade I disease • Two subgroups identified with a different comparator: ECP, where patients must be haematologically stable and have good venous access ↳ Implies a subgroup who are not haematologically stable and/or do not have good venous access
Comparators	ECM without ruxolitinib, including but not limited to: • ECP • Combination therapy with mTORs and/or MMF	• According to the potential subgroups, it appears that ECP is applicable for one and off-label therapies such as etanercept, infliximab, MSC, and sirolimus, are applicable for those not suitable for ECP
Outcomes	The outcome measures to be considered include: • Response to treatment • Mortality • FF survival • Adverse effects • HRQoL	• Potential issue with the definition of FF survival

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REACH1 and 2 baseline characteristics

	REACH2		REACH1
	Ruxolitinib n=154	BAT n=155	Ruxolitinib N=71
Age (years)			
n	154	155	71
Mean (SD)	48.1 (16.30)	50.9 (14.97)	52.9 (14.18)
Median	52.5	54.0	58.0
Q1-Q3	32.0–61.0	41.0–63.0	–
Min-max	12.0–73.0	13.0–71.0	18.0–73.0
Age category – n (%)			
Adolescents, 12 – <18 years	5 (3.2)	4 (2.6)	0
18–65 years	128 (83.1)	126 (81.3)	58 (81.7)
≥65 years	21 (13.6)	25 (16.1)	13 (18.3)
Overall severity of aGvHD at randomisation			
Grade 0	4 (2.6)	1 (0.6)	0
Grade I	2 (1.3)	0	0
Grade II	47 (30.5)	54 (34.8)	22 (31.0)
Grade III	70 (45.5)	67 (43.2)	33 (46.5)
Grade IV	31 (20.1)	33 (21.3)	16 (22.5)

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NICE aGvHD, acute graft versus host disease; SD, standard deviation.

REACH2 failure-free survival by standard care

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ATG; anti-thymocyte globulin; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; MTX, methotrexate.

REACH2 failure-free survival – ECP versus other

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NICE ECP, extracorporeal photopheresis; HR, hazard ratio.

REACH2 overall survival by standard care

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ATG; anti-thymocyte globulin; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; MTX, methotrexate.

REACH2 overall survival – ECP versus other

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NICE ECP, extracorporeal photopheresis; HR, hazard ratio.

RESOLVED key issue: Potential underestimation of the treatment effect on cGvHD incidence

EAG: relative cGvHD incidence underestimated due to crossover to ruxolitinib

Secondary outcome: cGvHD incidence

- By study end, 33.8% on ruxolitinib and 21.9% on standard care had developed cGvHD

[redacted]

Company

- Longer survival increases risk of cGvHD, so as people on ruxolitinib survive longer, incidence of cGvHD is higher

EAG

- Crossover from standard care to ruxolitinib is expected to improve survival and therefore inflate cGvHD incidence
- So, relative difference in cGvHD incidence may be underestimated
- Confirmed that crossover adjustment was applied, no longer key issue

NICE cGvHD, chronic graft versus host disease; EAG, external assessment group.

REACH3 summary

	REACH3
Design	Randomised, open-label, phase 3
Population	• 12 years or older • AlloSCT • Moderate to severe chronic GvHD • Evident myeloid and platelet engraftment
Intervention(s)	Ruxolitinib 10 mg twice daily (n=165)
Comparator	Standard care based on investigator judgement (n=164)
Key outcomes	1°: ORR at cycle 7 day 1 visit (each cycle was 4 weeks) 2°: Modified Lee cGvHD Symptom Scale Score, ORR at end of cycle 3, DOR, BOR, OS, FFS, NRM, HRQoL, malignancy relapse/progression, steroid use, safety
Locations	29 countries, including UK

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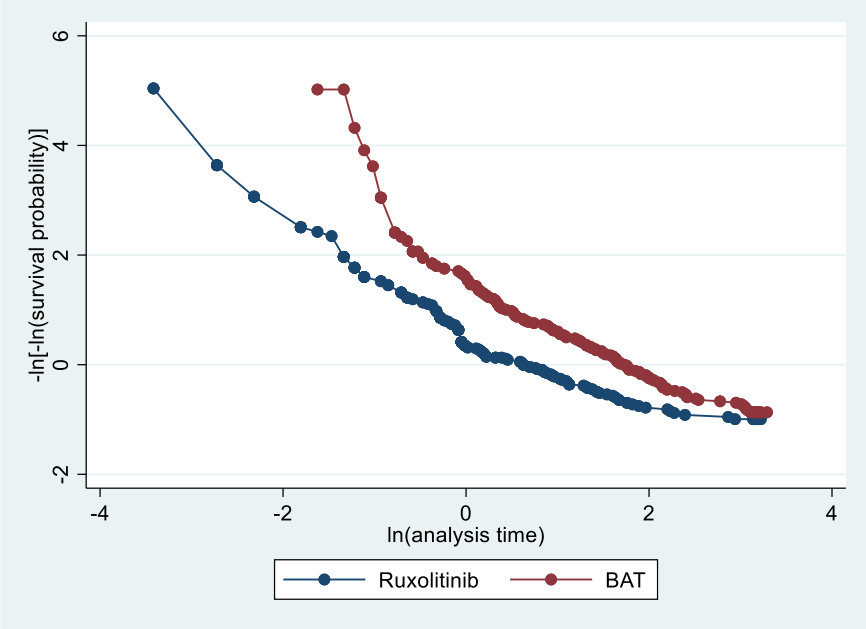
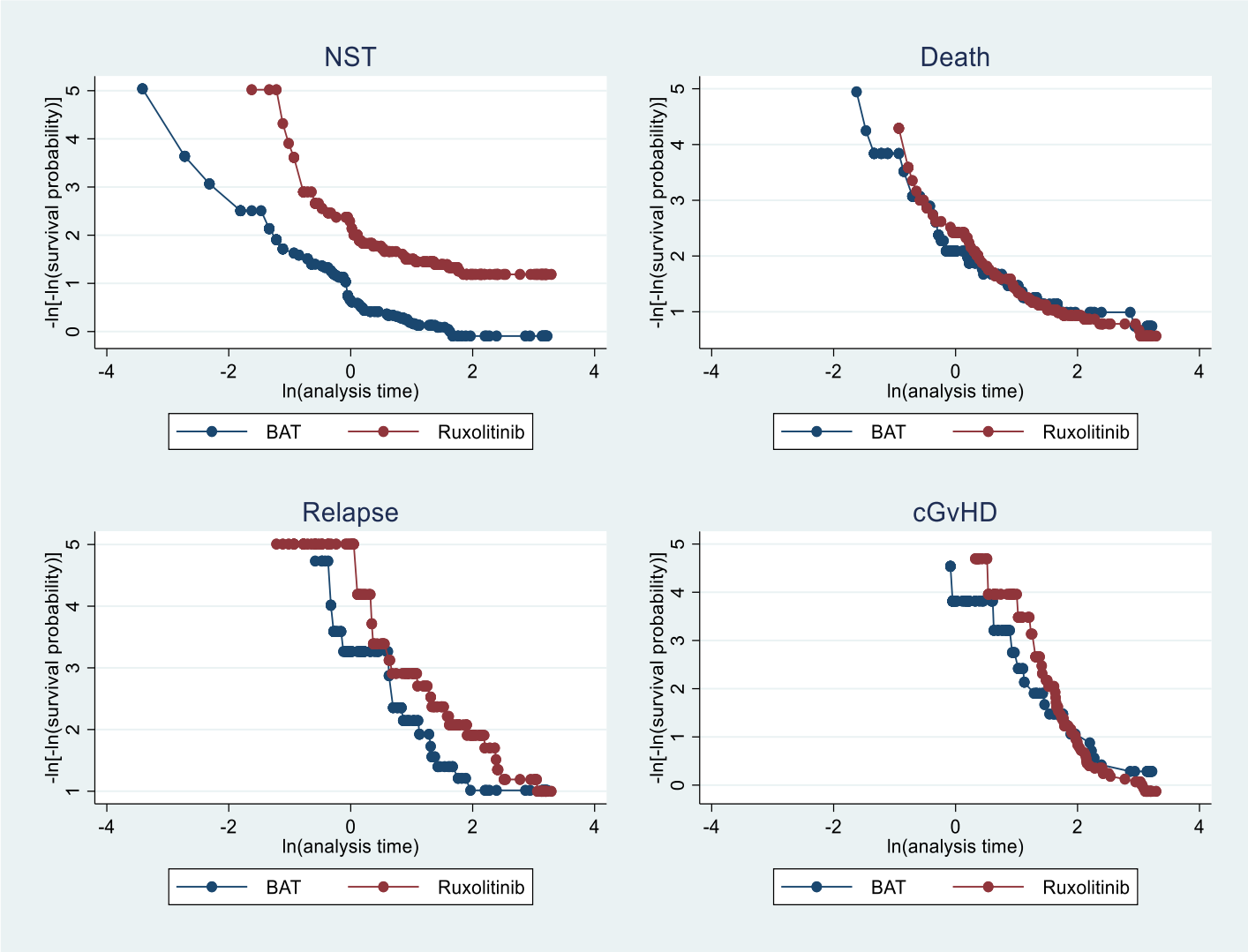
AlloSCT; allogenic stem cell transplant; BOR, best overall response; cGvHD, chronic graft versus host disease; DOR, duration of response; FFS, failure-free survival; HRQoL, health-related quality of life; NRM, non-relapse mortality; ORR, overall response rate; OS, overall survival.

Log-log survival plots

FFS





Company: Global test upheld PH for individual transitions but not overall FFS

- NST is proportional, relapse only crosses briefly, death curves are identical

EAG: Crossing death, relapse, cGvHD curves indicate PH violated

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NICE BAT, best available therapy; cGvHD, chronic graft versus host disease; FFS, failure-free survival; NST, new systemic therapy; PH, proportional hazards.

Utility models – pooled data

Health state	Average health state values	Model 1: With subject level REs	Model 2: With subject level REs without relapse	Model 3: No subject level REs	Model 4: No subject level REs, without relapse
Utility values					
Failure-free, ≤4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure-free, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, failure-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Goodness-of-fit statistics					
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; cGvHD, chronic graft versus host disease; NST, new systemic therapy; RE, random effects.

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Utility models – separate data

aGvHD

	Model 1	Model 2	Model 3	Model 4
Utility values				
Failure-free, ≤4 cycles	[redacted]	[redacted]	[redacted]	[redacted]
Failure-free, >4 cycles	[redacted]	[redacted]	[redacted]	[redacted]
NST	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]
Goodness-of-fit statistics				
AIC	–579.0	–579.3	430.9	430.9
BIC	–538.9	–545.0	465.3	459.5

cGvHD

	Model 1	Model 2	Model 3	Model 4
Utility values				
cGvHD, failure-free	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, NST	[redacted]	[redacted]	[redacted]	[redacted]
cGvHD, relapse	[redacted]	[redacted]	[redacted]	[redacted]
Goodness-of-fit statistics				
AIC	–3025.7	–3029.8	–1635.9	–1643.1
BIC	–2988.9	–2999.2	–1605.3	–1618.6

NICE AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; cGvHD, chronic graft versus host disease; NST, new systemic therapy.

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Utility values – comparison of appraisals

This appraisal, company submission (ID6377)

State	Utility value	95% CI		Justification
FF, first 4 cycles	[redacted]		[redacted]	REACH2 and 3, clinical opinion
Relapse	[redacted]		[redacted]	TA949
cGvHD, relapse	[redacted]		[redacted]	
Difference in utility compared to FF, first 4 cycles				
FF, >4 cycles	[redacted]		[redacted]	REACH2 and 3, clinical opinion
NST	[redacted]		[redacted]	
cGvHD, FF	[redacted]		[redacted]	
cGvHD, NST	[redacted]		[redacted]	

CADTH appraisal

Health state	aGvHD	cGvHD
Disease baseline	0.47	0.66
Week 4, overall responder	0.51	0.72
Week 4, non-responder	0.42	0.66
Week ≥12, overall responder	0.59	0.75
Week ≥12, non-responder	0.5	0.69

PBAC appraisal

Health state	aGvHD	cGvHD
Ruxolitinib responders	0.553	0.746
Ruxolitinib non-responders	0.441	0.687
BAT responders	0.553	0.695
BAT non-responders	0.441	0.636

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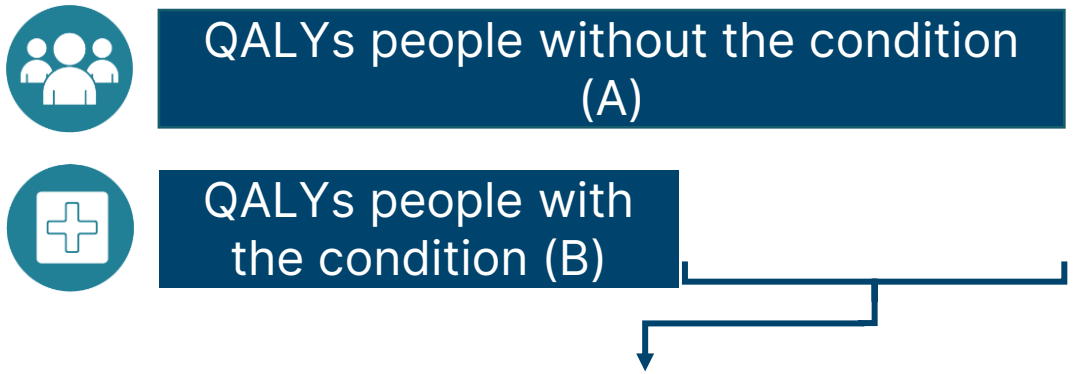
aGvHD, acute graft versus host disease; BAT, best available therapy; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; cGvHD, chronic graft versus host disease; FF, failure-free; NST, new systemic therapy; PBAC, Pharmaceutical Benefits Advisory Committee.

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

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

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