Ruxolitinib for treating acute graft versus host disease that responds inadequately to corticosteroids in people 12 years and over

2nd Technology appraisal committee D [12 February 2025]

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Company: Novartis

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Ruxolitinib for treating acute graft versus host disease that responds inadequately to corticosteroids in people 12 years and over

- ✓ Background and recap of committee conclusions from ACM1
- ❑ Consultation comments and updated cost-effectiveness estimates

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Background: condition + technology (ruxolitinib; Jakavi®, Novartis)

- Acute GvHD occurs when donor T-cells attack recipient's cells, usually after allogeneic haematopoietic stem cell transplant (HSCT); corticosteroids main treatment
- Differs from chronic GvHD
- In 2022 in UK, 1,535 HSCTs, 1/3 to 1/2 develop acute GvHD; 1/2 of these corticosteroid refractory (eligible population: ~250 to ~400 people)
- Corticosteroid-refractory acute GvHD – ~25% survival at 2 years; ~10% at 4 years

UK marketing authorisation	• 'Patients aged ≥12 years with acute graft versus host disease who have inadequate response to corticosteroids'
Mechanism	• Inhibits ATP-binding catalytic site on JAK1/2 enzymes + cytokines
Other indications	• Chronic GvHD (TA840; terminated appraisal) • Myelofibrosis (TA386; recommended) • Polycythaemia vera (TA921; recommended)
Administration	• Oral tablet, self-administered, recommended starting dose 10 mg taken twice daily
Duration	• Consider tapering in patients with a response after discontinued corticosteroids • Mean treatment duration in REACH2 trial = ■■■
Price	• Commercial arrangement available; unchanged since 1st meeting

NICE   GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant.

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Ruxolitinib 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

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

ACM1 – Draft recommendation and uncertainties

> Ruxolitinib is not recommended, within its marketing authorisation, for treating acute graft versus host disease that has an inadequate response to corticosteroids in people 12 years and over.

Uncertainties:

Explored in model?

- Open-label design of REACH2 affected failure-free survival – informs model structure ✗

- Distribution of 3rd line treatments would differ between ruxolitinib and standard care ✓

- REACH3 trial used for **chronic** GvHD health states, but may not generalise to people who have previously had acute GvHD ✗

- Utility value of 'chronic GvHD – new systemic treatment' health state was implausible ✓

- Company excludes wastage for ruxolitinib ✓

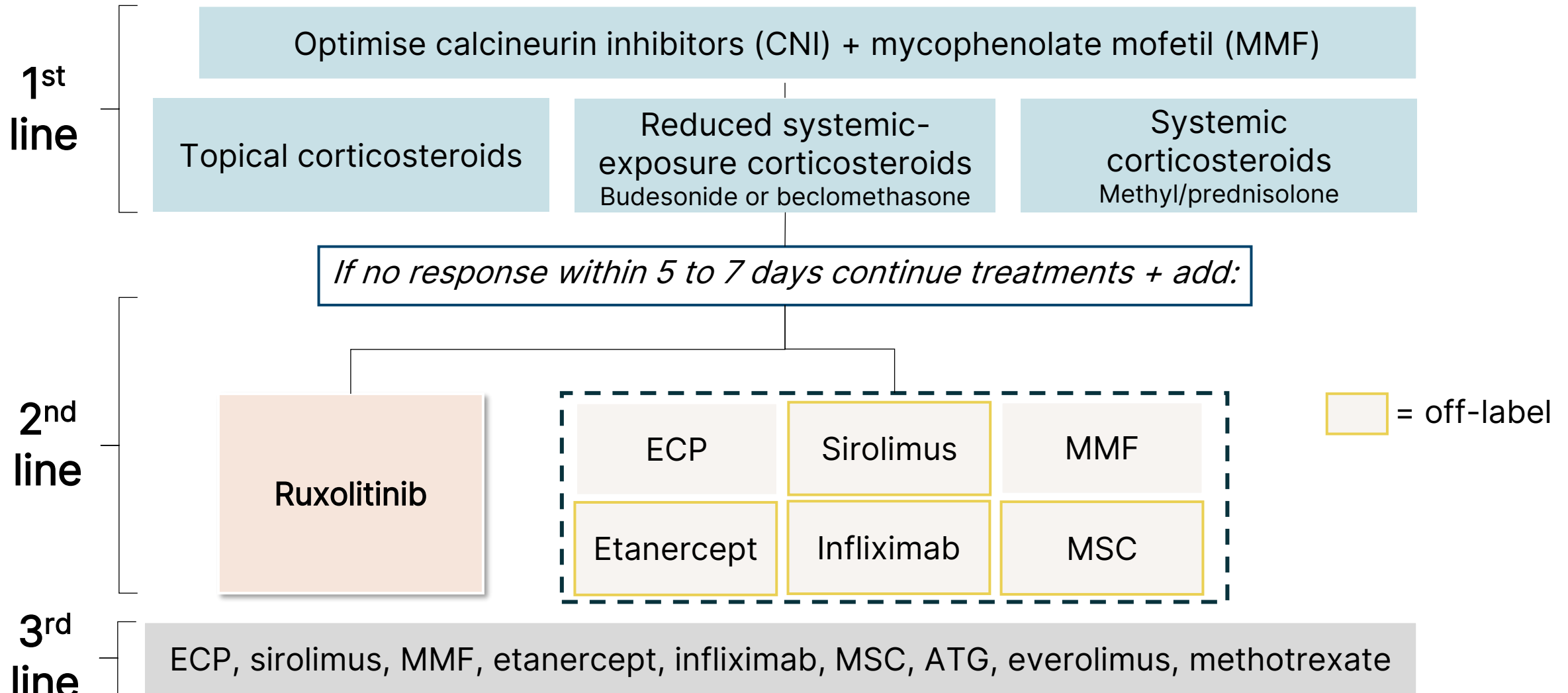# Treatment pathway for acute GvHD
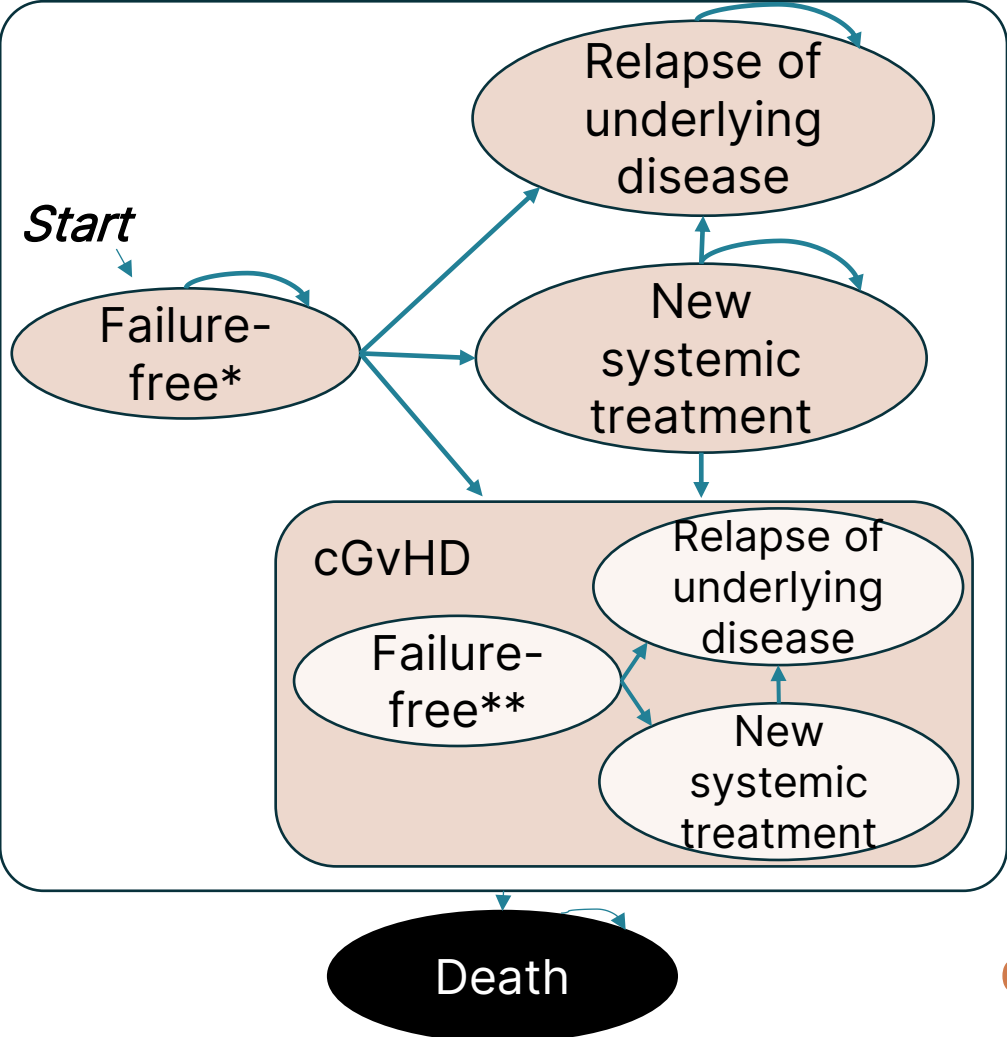
1st line

Optimise calcineurin inhibitors (CNI) + mycophenolate mofetil (MMF)

| Topical corticosteroids | Reduced systemic-exposure corticosteroids
Budesonide or beclomethasone | Systemic corticosteroids
Methyl/prednisolone |

If no response within 5 to 7 days continue treatments + add:

2nd line

Ruxolitinib

| ECP | Sirolimus | MMF |
| Etanercept | Infliximab | MSC |

= off-label

3rd line

ECP, sirolimus, MMF, etanercept, infliximab, MSC, ATG, everolimus, methotrexate

Model overview and committee preferred assumptions

ACM1: committee accepted model but acknowledged high uncertainty

Assumption	Committee preference
Transition probabilities	• Only benefit of ruxolitinib is delaying time from acute GvHD failure free to new systemic treatment • For all other acute GvHD transitions, probabilities from pooled ruxolitinib and standard care arms • For chronic GvHD transitions, probabilities from REACH3 standard care arm
Utility values	• Model fit to pooled REACH2 + 3 data, utility for chronic GvHD ≤4 cycles equal to failure-free ≤4 cycles • Adverse event disutilities changed from additive to multiplicative

Committee preferences aligned with EAG base case at ACM1

*aGvHD failure-free: remain until treatment failure: new systemic 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)
ACM1, appraisal committee meeting 1; cGVHD, chronic graft versus host disease, EAG, external assessment group.

Analysis requested of company by committee

In addition to implementing the committee's preferred assumptions

1. Different distribution of 3rd line treatments depending on if 2nd line treatment was ruxolitinib or not

2. Lower utility values for 'chronic GvHD – new systemic treatment' health state which was implausibly high

3. Cost of wastage of ruxolitinib
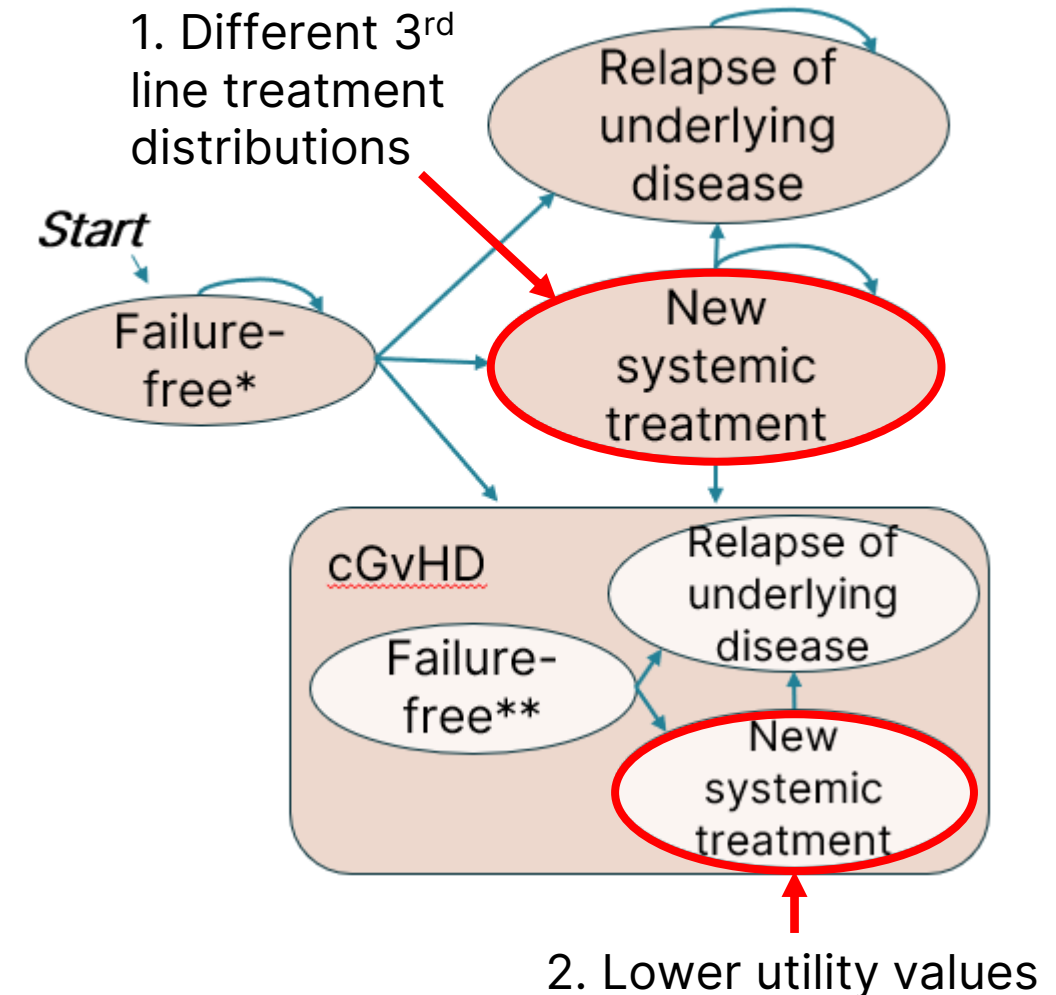
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Consultation responses

Novartis (company) • Accepted committee's preferred assumptions from 1st meeting • Provided requested analyses with scenarios and updated base case
Anthony Nolan (Patient organisation) • Highlighted potential equality issues from negative draft recommendation • Noted people with chronic GvHD can have high health-related quality of life
NHS England Specialised Commissioning • Highlighted potential equality issues from negative draft recommendation • Noted people with chronic GvHD can have high health-related quality of life
Clinical expert • Noted benefits of ruxolitinib • Recent guidelines recommend ruxolitinib for acute GvHD • Disagreed with committee assessment that failure free survival in REACH2 was confounded by open-label design
Therakos (comparator company) • Extracorporeal photopheresis available at 29 NHS sites • Long hospital stays are usually the result of disease severity/complications and not the administration of extracorporeal photopheresis

Equality concerns and unmet need

NHS England Specialised Commissioning and Anthony Nolan consultation responses

- Draft recommendation will exacerbate existing inequalities:
  - Some people struggle to have extracorporeal photopheresis* because of work or caring commitments; or do not have means to get to hospital; or cannot make journey because they lack physical ability
- Ruxolitinib is an option for all patients as an oral tablet

Clinical expert consultation response

- Ruxolitinib offers substantial benefits over standard care
- UK significantly disadvantaged because of no routine access
- Ruxolitinib recommended in many guidelines to manage steroid-refractory acute GvHD
  - ↪ most recent European Society for Blood and Marrow Transplantation guidelines

*Note, extracorporeal photopheresis is not the only comparator in this appraisal
GvHD, graft versus host disease

Key issue: 3rd line treatments

Company addresses committee's preference

ACM1: Committee – people who had ruxolitinib at 2nd line would have different 3rd line treatment than people who had standard care at 2nd line

Company consultation response: Adjusted 3rd line treatment distribution for ruxolitinib patients to match standard care 2nd line distribution

3rd line treatment	% after ruxolitinib	% after standard care
Anti-thymocyte globulin	0%	10%
Extracorporeal photopheresis	45%	16%
Etanercept	15%	19%
Everolimus	0%	1%
Infliximab	15%	7%
Low-dose methotrexate	0%	1%
Mycophenolate mofetil	17%	21%
Mesenchymal stromal cells	5%	11%
Sirolimus	1%	2%
No treatment	3%	0%
Source	REACH2 2nd line standard care distribution, adjusted by clinical advice	REACH2, pooled ruxolitinib + standard care 3rd line distribution
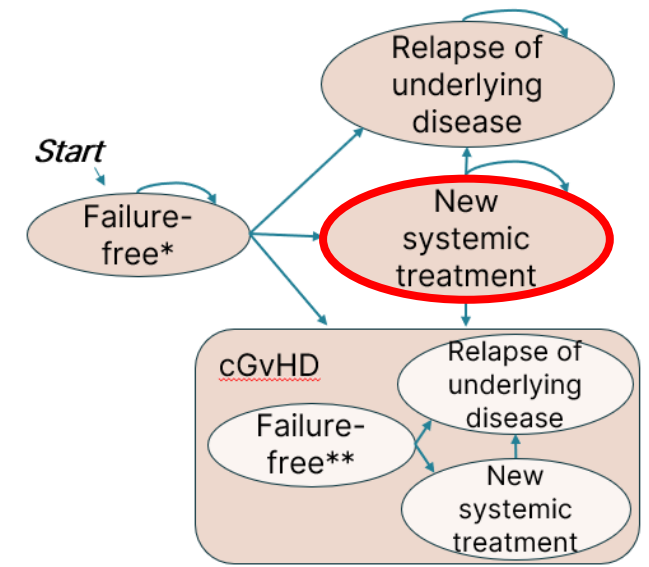
EAG: Reasonable approach
- Alternative – could have used REACH2 ruxolitinib and standard care arms separately

Is the revised modelling of 3rd line treatment appropriate?

ACM1, appraisal committee meeting 1; EAG, external assessment group; ICER, incremental cost-effectiveness ratio.

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Key issue: Chronic GvHD utility values

ACM1: Committee – utility value for 'chronic GvHD – new systemic treatment' health state implausibly high and likely to worsen over time
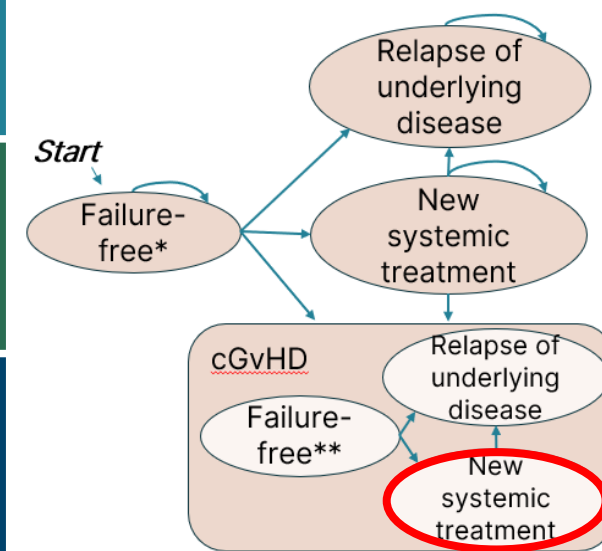
NHS England Specialised Commissioning and Anthony Nolan responses
- Most people with chronic GvHD are outpatients – manage symptoms well – can have high utility

Company consultation response
- Utilities in REACH3 (ruxolitinib chronic GvHD) did not substantially change over time (see appendix)
- Include 3 additional scenarios

EAG: New utility plausible

Abbreviations in notes

Health state	Utility value
'Chronic GvHD – failure-free'	0.689
'Chronic GvHD – new systemic treatment'	
Original submission – from regression model	0.673
Non-crossover REACH3 standard care patients – **new base case**	0.628
REACH3 data including crossover patients	0.656
EAG preference from TA949 – belumosudil for treating chronic GvHD	0.608

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Which utility value is most plausible for 'chronic GvHD – new systemic treatment'?

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Key issue: Wastage of ruxolitinib

Small ICER effect

ACM1: Committee – likely some wastage of ruxolitinib, especially for outpatients

Company consultation response
- Clinical advice –   ruxolitinib dispensed monthly to minimise wastage
  - about 35% of ruxolitinib patients would be outpatients
  - half a pack wastage per outpatient over entire treatment period is reasonable*
- Applied half a pack wastage to 35% in revised base case
- Included scenario analysis where 100% of patients incur half a pack wastage

EAG
- Half a pack wastage per patient reasonable
- 35% outpatients assumption – could validate by looking at REACH2 data
- Company suggests scenario analysis shows model insensitive to wastage

🗩 Has the company appropriately modelled wastage of ruxolitinib?

*Average treatment duration ▮▮▮▮; approximately ▮▮▮▮ 56-tablet packs of 10 mg ruxolitinib BID
ACM1, appraisal committee meeting 1; BID, twice daily; EAG, external assessment group; GvHD, graft versus host disease; ICER, incremental cost-effectiveness ratio.

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Results – cost-effectiveness ranges

Confidential discounts for comparators – ICERs in Part 2 slides
ICER ranges presented below

Summary – ruxolitinib versus standard care

Company base case probabilistic ICER:

o between £20,000 and £30,000 per QALY gained

EAG base case aligns with company base case

Company scenario analyses:

o Lowest ICER: between £20,000 and £30,000 per QALY gained
o Highest ICER: between £20,000 and £30,000 per QALY gained

Scenarios include:

- Different 'chronic GvHD – NST' health state utility values
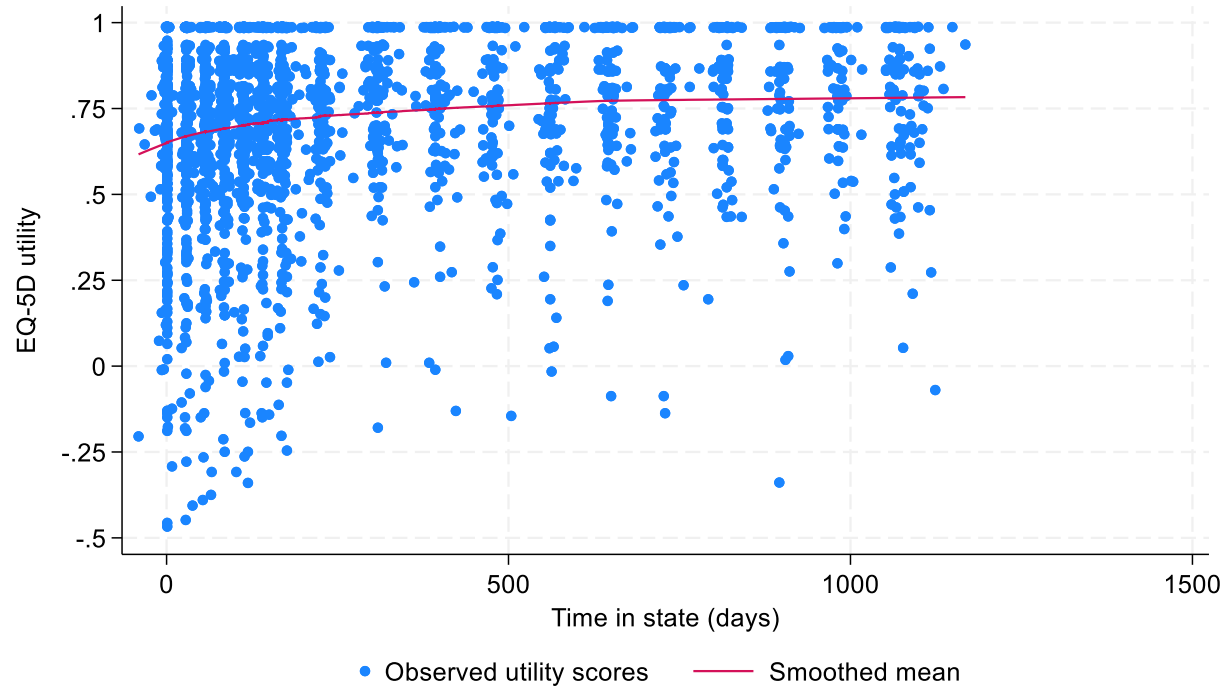- Different wastage assumptions

NICE *1.2 severity weighting accepted at ACM1 and weighting is unchanged by new analyses
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issues recap

Issue and committee position in draft guidance	ICER impact	Company analyses
3rd line treatment distribution • Would differ between people who have ruxolitinib at 2nd line and people who have standard care at 2nd line • More people on ruxolitinib would have ECP at 3rd line	Small	New base case uses same treatment distribution for standard care 2nd line and ruxolitinib 3rd line
'Chronic GvHD – new systemic treatment' utility value • Seems implausibly high	Small	• New base case lower value • Scenarios varying value
Ruxolitinib wastage • Would occur, but not modelled	Small	• New base case assumes 1/2 pack wastage for 35% patients • Scenario assumes 1/2 pack wastage for 100% patients

NICE ECP, extracorporeal photopheresis; GvHD, graft versus host disease; ICER, incremental cost-effectiveness ratio.

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Supplementary appendix

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Observed utility values in REACH3

REACH3 failure free survival, chronic GvHD

REACH3 new systemic treatment, chronic GvHD

GvHD, graft versus host disease.