Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

For screen – confidential information is redacted

Technology appraisal committee C [5 May 2026]

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Company: Incyte Pharmaceuticals

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

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

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Background on follicular lymphoma (FL)

Common, slow growing lymphoma with high risk of relapse or refractory disease

Causes

- FL is caused by abnormal B lymphocytes build-up; this disrupts regular lymphatic system function

Epidemiology

- Second most diagnosed lymphoma: 2,411 diagnoses of FL in England in 2023, mainly affects adults aged 60+
- FL has a high risk of relapse or refractory disease (cancer returns or stops responding to treatment)

Diagnosis and classification

- FLs staged from 1 (best prognosis) to 4 (worse prognosis) based on size, number and location of nodes affected
- FLs graded from slow growing low grade (1 to 3a, ~90% of cases) to high grade (3b) that grow more quickly

Stage	Diagnoses	%
1	364	20%
2	269	15%
3	617	34%
4	552	31%

NHS digital cancer registration stats 2023 (England)

Symptoms and prognosis

- FL presents as painless lumps in the neck, armpit or groin, night sweats, recurrent fevers or weight loss
- Some people do not have symptoms so the disease may have advanced by the time it is diagnosed
- FL is incurable and has a 5-year net survival rate of about 85%

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Abbreviations: FL, follicular lymphoma.

Patient perspectives

People living with incurable FL want more non-chemotherapy treatment options, fewer side effects and more durable remissions

Submissions from Lymphoma Action and patient expert

- From being symptomatic to diagnosed with an incurable cancer to awaiting treatment, FL incurs a great burden on the emotional and mental wellbeing of people with the condition
- Current treatments like chemoimmunotherapy are intensive, come with short- or long-term side effects, and need many hospital visits
    - Side effects like fatigue and recurrent infections (due to suppressed immune system) are life limiting – some need to stop work or driving
- Unmet need for another effective option that is less toxic and has fewer side effects
- Tafasitamab with lenalidomide and rituximab offers another non-chemotherapy-based treatment option which may improve outcomes and quality of life

"All [patients] have to live with the prospect of relapse after each treatment"

"Anything less toxic and with fewer side effects [than chemoimmunotherapy] would make life so much more bearable…"

"For me, the most important criterion is which drug is safest, and is likely to give me a good remission?"

Abbreviations: FL, follicular lymphoma.

Clinical perspectives

Tafasitamab + R^2 is innovative, well tolerated and delays disease progression compared to R^2

Submissions from clinical experts

- FL is incurable and the aim of treatment is to achieve maximal durable disease control whilst mitigating treatment-related side effects and toxicity
- NHS practice varies and outcomes vary across treatment options, so shared decision making is key to managing FL long-term
- Tafa+R^2 needs 30 extra infusions at 22 extra hospital visits, and 1.5-2 hours extra chair time per infusion compared with oral lenalidomide in R^2
    - Addition of a third agent would increase treatment burden compared with R^2, impacting day case capacity and patient convenience
- Tafa+R^2 is well tolerated and has durable response (delaying TTNT)
- Tafasitamab + R^2 delays progression which is important for people with FL, it may benefit older people more and may replace R^2 SoC at second-line

"There is… a continued need for therapies with improved toxicity profiles, given the cumulative burden of treatment over a patient's lifetime."

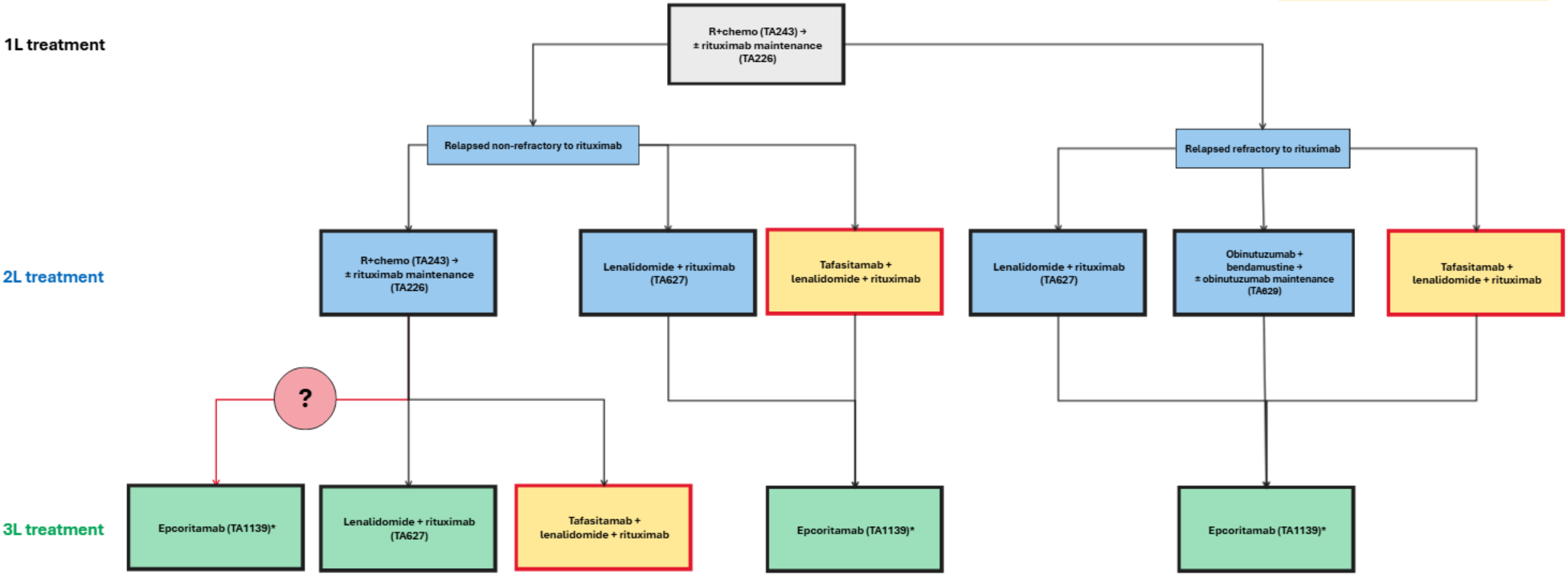
"First validated approach combining two unconjugated monoclonal antibodies targeting different B-cell antigens, establishing a new clinical paradigm."

"[Tafa+R^2] would have the most evidence in the 2L setting and would be used preferentially."

Abbreviations: FL, follicular lymphoma; R^2, lenalidomide with rituximab; SoC, standard of care; Tafa+R^2, tafasitamab with lenalidomide and rituximab; TTNT, time to next treatment.

Relapsed or refractory FL treatment pathway

Note: not all treatments shown



Is the treatment pathway illustrated here accurate?
Which patient characteristics influence treatment decisions?
How might tafasitamab + R^2 displace current treatments in 2L and 3L?

* Recently recommended in March 2026

See appendix for R+chemo combinations

Abbreviations: 1L/2L/3L, first-, second- or third-line; FL, follicular lymphoma; R+chemo, rituximab with chemotherapy combination; R^2, lenalidomide with rituximab.

Tafasitamab (MINJUVI, Incyte Pharmaceuticals)

Marketing authorisation	• MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy. • Marketing authorisation granted in February 2026, MHRA via IRP pathway from EMA

Mechanism of action	• Tafasitamab is a CD19-targeting monoclonal antibody which mediates B-cell lysis by:
	  • engaging immune effector cells to fight tumour cells
	  • direct induction of tumour cell death
	• R^2 adjunct results in dual targeting of CD19 and CD20, improving patient outcomes

Administration	Tafasitamab administered as intravenous infusion of 12mg/kg body weight on days 1, 8, 15 and 22 of cycles* 1-3, then days 1 and 15 of cycles 4-12
Price	• List price per 200 mg vial: £705.00 • List price for average course (48 weeks) of tafasitamab treatment: £108,195 • List price for average course of R^2 treatment: £9,520 • A simple patient access scheme is applicable

R^2 component	Lenalidomide is taken orally alongside tafasitamab infusions for up to 12 cycles* Rituximab is given via infusion for 5 cycles*

NICE * 1 cycle = 28 days

Abbreviations: EMA, European Medicines Agency; FL, follicular lymphoma; IRP, international recognition procedure; MHRA, Medicines and Healthcare Products Regulatory Agency; R^2, lenalidomide with rituximab.

Key issues

Issue	ICER impact
Relevance of treatments as comparators	Unknown
Uncertain overall survival benefit of tafasitamab + R^2	Large
Uncertain relative effectiveness of tafasitamab + R^2 against all comparators	Unknown
Suitability of model structure, surrogacy assumptions and tafasitamab + R^2 post-progression survival benefit	Large
Extrapolation of progression-free survival	Moderate
Treatment effect waning approach	Large
Modelling of 2L and 3L populations together	Large
Other issues: generalisability of inMIND to NHS	Small
Other issues: PFS events that are death and RDI approach	Small

Abbreviations: 2L/3L, second- or third-line; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; R^2, lenalidomide with rituximab; RDI, relative dose intensity.

Epcoritamab recommendation timeline

The recent epcoritamab recommendation impacts 3L+ considerations for tafa+R^2

- **October 2025**, epcoritamab monotherapy considered at 4L+ only (optimised from 3L+ as requested by AbbVie) and it received negative draft guidance recommendation
- **February 2026**, due to limited OB use in the NHS and negative draft guidance for epcoritamab, both the company submission and the EAG report considered OB and epcoritamab were not relevant comparators
- **March 2026**, further evidence for epcoritamab at 3L+ (its entire marketing authorisation) was presented at the second ACM and epcoritamab monotherapy was recommended (TA1139) for treating R/R FL in 3L+
- **April 2026**, Incyte Pharmaceuticals submitted addendum with fuller comparison of tafa+R^2 with epcoritamab in 3L+ incl. MAIC, cost effectiveness modelling and comparison of appraisals/assumptions
- **April 2026**, EAG did a high-level summary of addendum (see slide 16), it notes that time limitations did not allow for a full technical critique of modelling and that results should be interpreted with caution

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Abbreviations: 3L/4L, third- or fourth-line; ACM, appraisal committee meeting; CS, company submission; EAG, external assessment group; FL, follicular lymphoma; MAIC, matching-adjusted indirect comparison; OB, obinutuzumab with bendamustine; R/R, relapsed or refractory; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Relevance of treatments as comparators (1/2)

Unknown ICER impact

R^2

- R^2 is a 2L+ treatment which may be offered after relapse whether or not rituximab-refractory
- inMIND trial compared tafa+R^2 vs R^2

Is tafasitamab considered an add-on to R^2? Would tafa+R^2 be used throughout the pathway where R^2 is currently available?

R+chemo

- R+chemo is a 1L+ treatment that can be followed up with rituximab maintenance
- R+chemo regimens include R-CHOP, R-CVP and more (see appendix)

Would tafa+R^2 displace use of R+chemo at 2L or 3L?

Obinutuzumab + Bendamustine

- OB is a 2L+ treatment that can be taken following rituximab-refractory relapse
- Company and EAG agree OB is rarely used

Is OB used routinely in clinical practice? If so, would tafa+R^2 displace OB use?

Abbreviations: 1L/2L/3L, first-, second- or third-line; ICER, incremental cost effectiveness ratio; OB, obinutuzumab with bendamustine; R^2, lenalidomide with rituximab; R+chemo, rituximab with chemotherapy combination; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone;R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Additional issue: Relevance of treatments as comparators (2/2)

Unknown ICER impact

Background

- Epcoritamab monotherapy (TA1139) was recommended in March 2026 for R/R FL at 3L or later

Company

- Tafa+R^2 use overlaps with epcoritamab in the treatment pathway
- Clinical community would welcome introduction of 2 new treatments where no single patient journey exists
- Tafa+R^2 time-limited treatment better suited to some, and it lacks epcoritamab's CRS and ICANS risk

EAG comments

- At the time of writing EAG report, NICE draft guidance was that epcoritamab should not be used in 3L+
- Time constraints have limited critique of company addendum ahead of ACM1

Clinical experts stated:

- Tafa+R^2 will be offered 2L and epcoritamab at 3L+
- Tafa+R^2 would not generally displace epcoritamab
- Tafa+R^2 may displace epco if:

1. Refractory to CD20 therapies
2. Risk of CRS
3. ICANS concerns
4. Administration setting concerns (e.g CRS monitoring, tocilizumab access)
5. preference for fixed-duration therapy

Is epcoritamamb a relevant comparator at 3L+? How do CRS/ICANs risk influence treatment decisions? Should epcoritamab be modelled as a subsequent treatment for the 2L+ population?

Abbreviations: 2L/3L/4L, second-, third- or fourth-line; ACM1, appraisal committee meeting 1; CRS, cytokine release syndrome; EAG, external assessment group; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost effectiveness ratio; R/R, relapsed or refractory; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

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Key clinical evidence

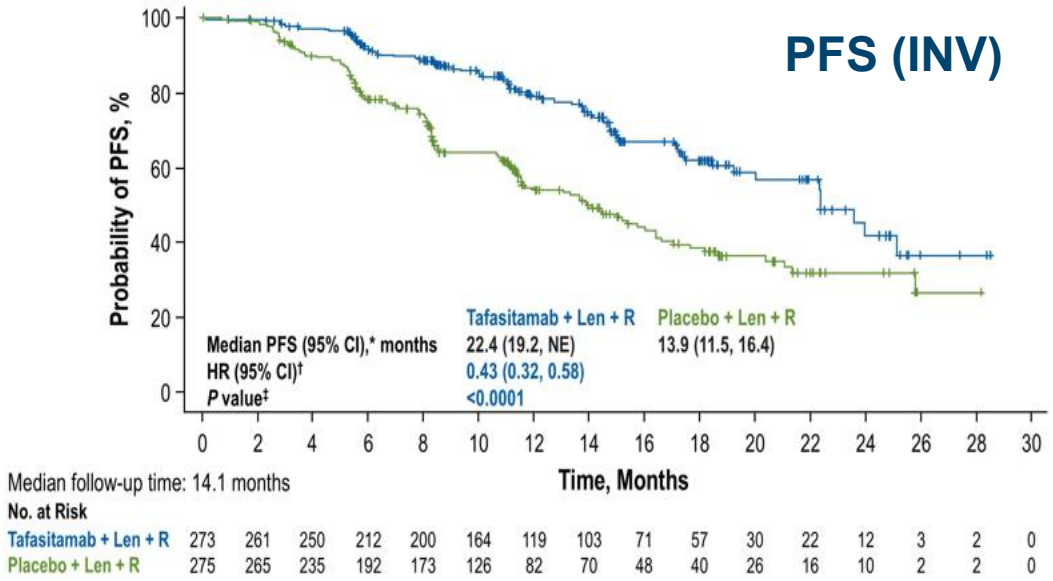
	inMIND (NCT04680052)
Design	Phase III double-blind, placebo-controlled, randomised trial
Population	Adults with R/R FL grade 1-3a with 1+ prior systemic therapy (n=548) 2L n=293 3L n=255
Intervention	Tafasitamab + R^2 (n=273)
Comparator(s)	Placebo + R^2 (n=275)
Primary outcome	PFS by investigator
Key secondary outcomes	PET-CR, OS, PFS by IRC, ORR, DoR, AEs, HRQoL
Locations	210 locations incl. [redacted] in the UK
Used in model?	Yes – main evidence for tafasitamab + R^2 and R^2 alone

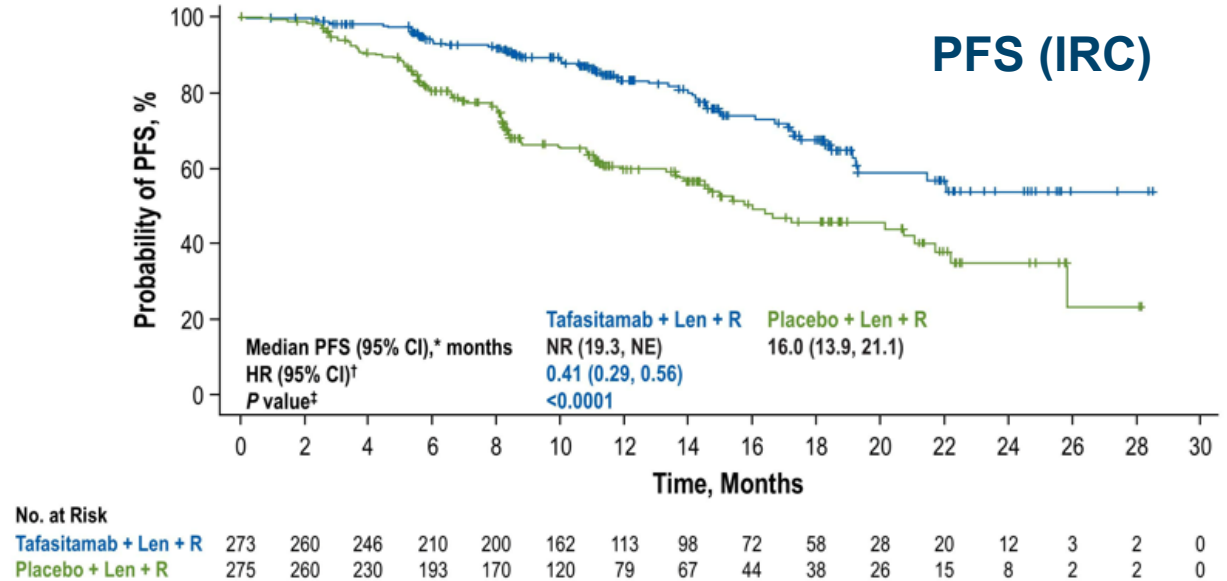
Abbreviations: 2L/3L, second- or third-line; AE, adverse event; DoR, duration of response; FL, follicular lymphoma; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; R^2, lenalidomide with rituximab; R/R, relapsed or refractory.

Key clinical trial results – inMIND

Tafasitamab + R^2 improves PFS compared to placebo + R^2

- Median follow-up of 14.1 months for PFS
- PFS INV drives model in company and EAG base cases





Outcome	Tafasitamab + R^2	Placebo + R^2	Hazard ratio
Median PFS [INV], months (95% CI)	22.4 (19.2 to NE)	13.9 (11.5 to 16.4)	0.43 (0.32 to 0.58)
Median PFS [IRC] months (95% CI)	NR (19.3 to NE)	16.0 (13.9 to 21.1)	0.41 (0.29 to 0.56)

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; NE, not evaluable; NR, not reached; PFS, progression-free survival; R^2, lenalidomide with rituximab

Key issues: Uncertain overall survival benefit of tafasitamab + R²

Large ICER impact

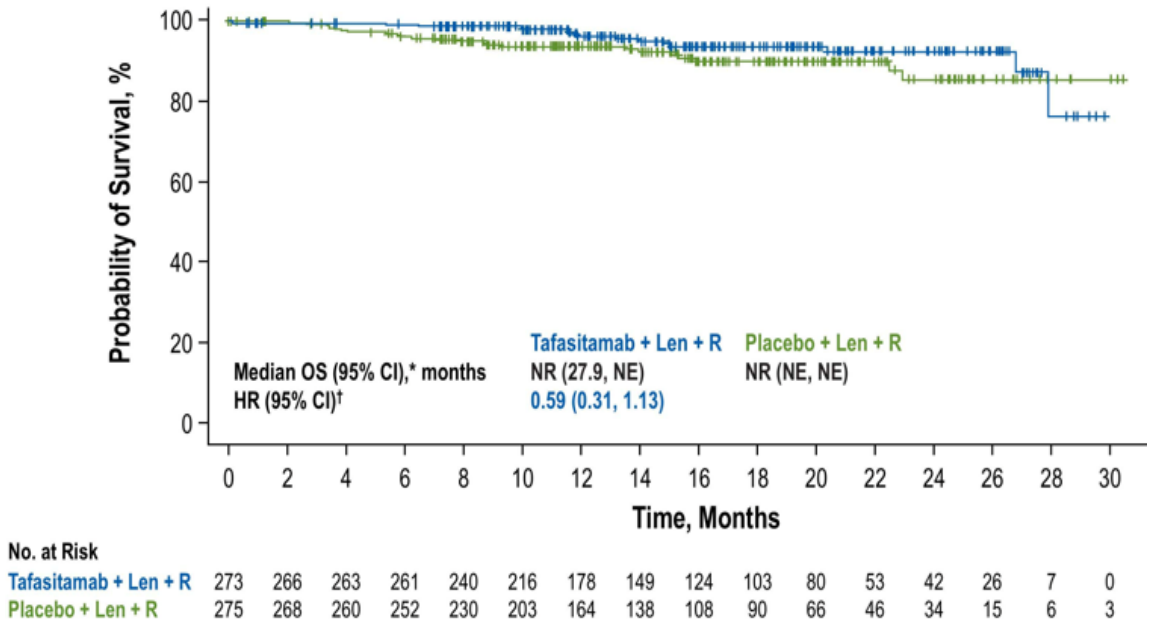
Background

- Company and EAG agree inMIND OS data is immature
- 15.3 months median follow-up in tafa+R² arm
- Neither arm reached median OS
- OS HR = 0.59 (95% CI: 0.31 to 1.13; p=[redacted])
- Company and EAG agree crossing of OS curves may be statistical artefact – not indicative of long-term OS

Company

- Immature OS data and few death events (38) at short follow-up are characteristic of indolent FL
- Trial not powered to test OS at time of primary PFS analysis

inMIND OS KM curves, tafa+R² and R²



EAG comments

- Much more mature OS data needed to establish whether tafasitamab + R² improves OS vs R²
- Observational data (i.e. CDF) may provide long-term reliable OS data that has external validity to the NHS

Would an alternative data source, CDF entry, or longer follow-up of inMIND overcome uncertainties in OS between arms?

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Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; EAG, external assessment group; FL, follicular lymphoma; HR, hazard ratio; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; R², lenalidomide with rituximab; Tafa+R², tafasitamab with lenalidomide and rituximab

Key issues: Uncertain relative effectiveness of tafasitamab + R² against all comparators

Unknown ICER impact

Lack of direct comparison for most comparators led company to do MAICs which have limitations

Background

- Company considered its MAICs not suitable, used inMIND R² as proxy for R+chemo (see appendix)
- Company said TA627 (R² for 2L+ FL) showed R² was more effective than R+chemo, so conservative
- EAG noted lack of evidence comparing tafa+R² with R+chemo, considered company approach reasonable

Company

- Addendum expanded on tafa+R² vs epcoritamab MAIC in CS appendix, SLR identified EPCORE NHL-1
- EPCORE NHL-1 had poorer prognosis (more high risk/high ECOG PS/refractory patients) than inMIND 3L+
- MAIC HR results favoured tafa+R²: PFS = [redacted] (95% CI: [redacted] to [redacted]), OS = [redacted] (95% CI: [redacted] to [redacted])

EAG comments

- Notes that company addendum received after EAG report and there has been limited time to fully scrutinise
- Agrees EPCORE NHL-1 population has poorer prognosis, epcoritamab MAIC uncertain like for R+chemo
- Unadjusted Cox models (based on digitised KM curves) estimated more favourable PFS and OS HRs for tafa+R² vs epcoritamab; PFS HR = [redacted] (95% CI: [redacted] to [redacted]), OS HR = [redacted] (95% CI: [redacted] to [redacted])
- MAICs and Cox models are indirect and uncertain, prefers company's more conservative HRs

Is R² a suitable proxy for R+chemo? Are indirect comparison estimates between tafa+R² and epcoritamab suitable for decision-making?

See appendix for MAIC matching variables

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Abbreviations: 2L/3L, second- or third-line; CI, confidence interval; CS, company submission; EAG, external assessment group; ECOG PS, Easter Cooperative Oncology Group performance status; ESS, effective sample size; FL, follicular lymphoma; HR, hazard ratio; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; R², lenalidomide with rituximab; R+chemo, rituximab with chemotherapy combination; SLR, systematic literature review; Tafa+R², tafasitamab with lenalidomide and rituximab.

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

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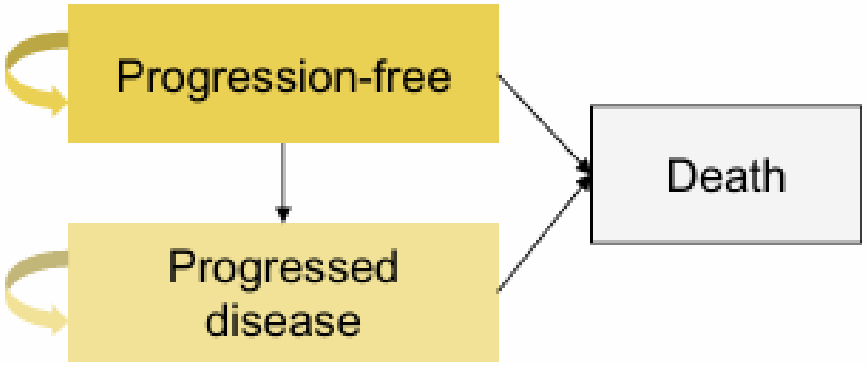
Company's model overview (1/2)

PSM used in company base case, but STM developed to explore limitations of OS data



- Partitioned survival model (PSM) used for base case
- NHS and PSS perspective, 3.5% discount rate for costs & QALYs
- Time horizon of 36 years with 1-week cycle length
- Compares tafasitamab + R^2 against R^2 and R+chemo
- After company addendum, also compares against epcoritamab
- R+chemo comparison relies on efficacy from placebo + R^2 arm of inMIND & costs for R-B, R-CHOP & R-CVP per SmPC dosing
- HSUVs mapped to EQ-5D-3L from inMIND EQ-5D-5L data

Technology affects costs by:

- Higher drug acquisition / administration costs

Technology affects QALYs by:

- Increasing PFS and OS

Assumptions with greatest impact on ICER:

- (extrapolated) OS benefit for tafa+R^2
- PSM vs STM approach
- Treatment waning
- How RDI is applied in the model

State transition modelling also provided with 3 STM scenarios

Abbreviations: EQ-5D-5L, EuroQol 5 dimension 5 level (questionnaire); OS, overall survival; PSM, partitioned survival model; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab; R+chemo, rituximab with chemotherapy combination; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity; SmPC, Summary of Product Characteristics; STM, state transition model; Tafa+R2, tafasitamab with lenalidomide and rituximab.

Company's model overview (2/2)

STM estimates OS using PFS and external PPS instead of immature inMIND OS

- Company built STM to explore uncertain OS benefit for tafa+R^2 in the inMIND trial, used in scenario
- STM uses PSM health states, but uses transition probabilities to estimate PPS and therefore OS instead of inMIND OS curves

Outcome	Approach used in PSM	Approach used in STM
PFS	inMIND PFS KM curves	inMIND PFS KM curves
PPS	Not directly modelled (PPS = OS – PFS)	PPS rate taken from external data
OS	inMIND OS KM curves	Not directly modelled (OS = PFS + PPS)

Three state transition probabilities dictate OS in the STM:

- **Probability of progression:** from extrapolated inMIND PFS curves and dictates movements between PF and PD health states
- **Probability of death in PF health state:** fixed proportion of PFS events represent deaths in each cycle (derived from inMIND)
- **Probability of death in PD health state:** derived from external sources – 3 scenarios explore different PPS approaches

The STM structural relationship means that differences in OS between tafa+R^2 and R^2 are driven by differences in PFS (HR = 0.41 [95% CI 0.29 to 0.56]) and any differences in PPS.

See appendix for STM approaches.

Abbreviations: CI, confidence interval; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; R^2, lenalidomide with rituximab; STM, state transition model; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Suitability of model structure, surrogacy assumptions and tafasitamab + R^2 post-progression survival benefit (1/2)

Large ICER impact

Background

- Company base case uses a partitioned survival model (PSM), EAG prefers state transition model (STM1)
- EAG says STM1 overcomes reliance on immature OS data but relies on there being a weak surrogate relationship between PFS and OS

Company

Model structure and surrogacy assumptions

- Prefers PSM which is widely used in oncology/FL and doesn't rely on PFS/OS surrogacy which is considered weak – Milrod et al. (2024) found PFS/OS correlation coefficient of 0.383 ($p<0.001$)
- Clinical advice suggests PFS/OS relationship weaker in slow progressing FL but stronger in advanced

Post progression survival benefit

- Concerns with immaturity of inMIND OS data also apply to analysis of PPS
- Clinical advice suggests refractory status may impact PPS, i.e.:
  - If FL is rituximab-refractory with poorer prognosis then PFS/OS surrogacy may be stronger
  - While for non-refractory FL with better prognosis (and longer life expectancy) surrogacy link is weaker
- STM1 relies on PFS only for OS benefit, using HMRN data to model common PPS across arms
- In STM2, GADOLIN outcomes inform treatment-specific PPS which, with PFS, determines OS
- STM3 is most plausible STM and takes a weighted approach based on % refractory to rituximab in inMIND

Abbreviations: EAG, external assessment group; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; R^2, lenalidomide with rituximab; STM, state transition model; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Suitability of model structure, surrogacy assumptions and tafasitamab + R^2 post-progression survival benefit (2/2)

Large ICER impact

EAG comments

Model structure and surrogacy

- inMIND OS data too immature and uncertain to underpin OS benefit of tafasitamab + R^2, particularly when extrapolated over lifetime horizon and potentially confounded by subsequent treatments not in NHS
- Evidence from FL trials suggest PFS may be weak surrogate predictor of OS but evidence has limitations
- STM more structured for estimating OS benefits, & makes PSM's implied surrogacy of PFS to OS explicit
- STM allows (more mature) PFS to be primary driver of benefits in the model
- If PSM is used, proposes scenario with no OS benefit for tafa+R^2 to reflect uncertainty around OS
- Longer-term OS evidence needed to establish magnitude of tafa+R^2 OS benefit
- Scenario assuming no relative OS benefit for tafa+R^2 increased ICER significantly

Post-progression survival benefit

- Company's PSM extrapolations imply minimal PPS benefit
- Unclear biological rationale for a tafa+R^2 PPS benefit when (unlike solid tumours) there is no tumour shrinkage to suggest a differential benefit after disease progression
- GADOLIN compared non-rituximab-based regimens so unclear if PPS benefit would apply to tafa+R^2
- Use STM1 (no post-progression benefit) in EAG base case, this increases the ICER

Is there a biological rationale for a PPS benefit for tafa+R^2 compared with R^2?
Which model structure is appropriate for decision making?
If STM used, which version of the STM should be used?

See appendix for STM approaches

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Abbreviations: EAG, external assessment group; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; R^2, lenalidomide with rituximab; STM, state transition model; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Extrapolation of progression-free survival (1/2)

Moderate ICER impact

Background

- Company extrapolated PFS across treatment arms jointly, EAG prefers individually-fitted extrapolations
- Choice of PFS extrapolation has small impact in PSM, but impact is larger if STM model chosen

Company

- Base case PSM: jointly-fitted generalised gamma chosen based on Q-Q plot supporting AFT joint fitting (see appendix), AIC/BIC ±5 of best fitting model, consistent with OS extrapolations and close fit to KOL landmark estimates
- Jointly-fitted log-logistic explored in scenario, small ICER increase

EAG comments

- Appears joint-fitting of PFS curves influenced more by OS extrapolations concerns than the PFS data
- Company's preferred extrapolations overestimate PFS vs observed data – especially for tafasitamab + R^2
- Individually-fitted log-logistic curves gave good statistical fit and visual fit to KM curves in both arms
- Changing PFS extrapolations from jointly- to individually-fitted curves modestly increased the ICER

Which approach and distributions should be used to extrapolate PFS in both arms?

See appendix for distribution model statistics

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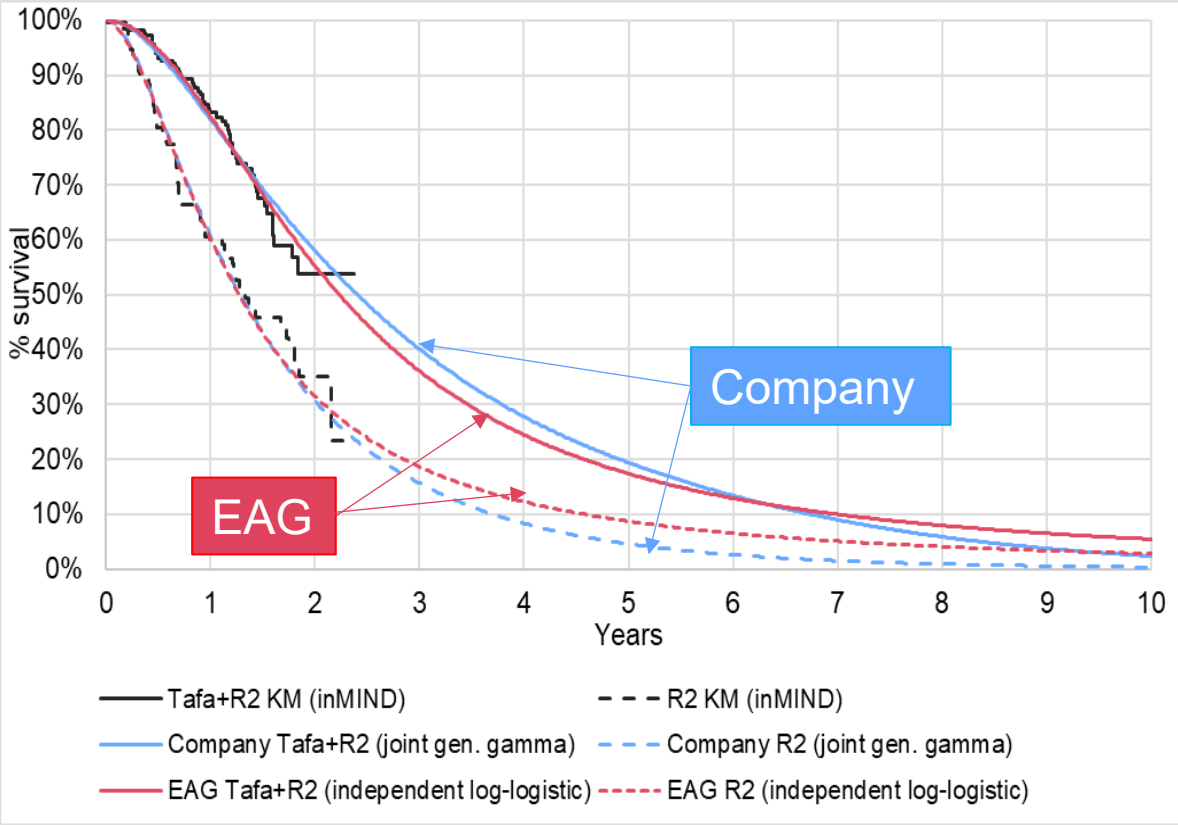
Abbreviations: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EAG, external assessment group; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; KOL, key opinion leader; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; Q-Q, quantile-quantile; R^2, lenalidomide with rituximab.

Extrapolation of progression-free survival (2/2)

Moderate ICER impact

Company and EAG select different long-term extrapolations, ICER impact is small in PSM

inMIND PFS KM curves and chosen extrapolations, tafasitamab + R^2 and R^2



Chosen PFS approach	Tafa+R^2 PFS		R^2 PFS	
	5-year	10-year	5-year	10-year
Company Joint gen. gamma	19.5%	3.7%	4.6%	0.3%
EAG Independent log-logistic	17.5%	5.2%	8.7%	2.8%
Company KOL estimate	20-30%	5%	5-10%	1-4%

Which approach and distributions should be used to extrapolate PFS in both arms?

Abbreviations: EAG, external assessment group; gen. gamma, generalised gamma; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; KOL, key opinion leader; PFS, progression-free survival; R^2, lenalidomide with rituximab; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Treatment effect waning approach

Large ICER impact

Background

- Tafa+R^2 treatment maximum duration is 48 weeks, does not fundamentally alter disease biology
- Company and EAG agree permanent treatment effect not plausible and explicit waning should be applied

Company

- Waning would be gradual, proposes 5 years of full treatment effect followed by gradual 5-year waning
  - Informed by clinical expert opinion on hazard convergence and conclusions from TA627 (R^2 for 2L FL)
- No treatment effect waning was considered or applied to epcoritamab in TA1139, applying waning to tafasitamab penalises it in any third-line plus comparison with epcoritamab (see key issue)

EAG comments

- Assumptions from TA627 appear arbitrary and aren't linked to mechanism of action or disease biology
- Log-cumulative hazard and Schoenfeld residual plots (see appendix) question longer period of full effect
- EAG agrees that a gradual waning is probably most plausible
- EAG base case: full treatment effect for 2 years followed by 3-year waning (hazards equalise)
- Also explore a 5-year full treatment effect followed by instant hazard equalisation

Should treatment effect waning be explicitly modelled?
If so, what start point and duration of treatment effect waning should be used?

Abbreviations: 2L, second-line; EAG, external assessment group; FL, follicular lymphoma; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; R^2, lenalidomide with rituximab; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Key issues: Modelling of 2L and 3L populations together

Large ICER impact

Background

- Company base case reflects full MA population, involves modelling treatments in 2L and 3L in one analysis
- EAG thinks modelling treatment lines together masks differences in cost effectiveness at different lines

Company

- Base case uses 2L+ which reflects the full indication of the UK marketing authorisation
- Trial not powered for 2L-only subgroup analysis, so analysis considered exploratory & not decision-relevant
- 2L-only subgroup has fewer people and outcome events, so more uncertain effects and ICERs

EAG comments

- Baseline characteristics, comparators and treatment effects vary by line
- Clinical expert advises that line of treatment is itself a key prognostic factor
- inMIND subgroup analysis suggests greater relative effect for tafa+R^2 in 3L vs 2L – notes that HRs overlap
- Treatment line subgroup analysis suggests tafa+R^2 is less cost effective when limited to 2L only compared to 3L+

Treatment line	PFS HR (95% CI)
2L	0.48 (0.32 to 0.74)
3L	0.41 (0.28 to 0.61)

Which population(s) should be used for decision making?

Abbreviations: 2L/3L, second- or third-line; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; MA, marketing authorisation; PFS, progression-free survival; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Other issues: Generalisability of inMIND to NHS

Small ICER impact

Background

- Uncertainty around generalisability of inMIND to NHS practice (e.g starting age, POD24 %, refractory %)

Company

- Full 2L+ inMIND population reflects expected NHS use. Where inMIND differs from NHS is subsequent treatments (CAR-T therapy not in NHS) which are accounted for
- HMRN data lacks variables to compare generalisability (see MAIC limitations)

EAG comments

- Considers inMIND modelled population broadly applicable to patients with grade 1-3a FL in NHS practice
- Trial patients may be: younger, longer times to diagnosis and remission, higher rates of rituximab-refractory disease and more favourable POD24 status
- While not a major issue, how closely inMIND participants reflect the NHS practice population is uncertain

How generalisable is inMIND to NHS practice?
If needed, how is this issue accounted for in decision making?

Abbreviations: 2L, second-line; CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; POD24, progression of disease within 24 hours.

Other issues: Generalisability of inMIND to NHS

Small ICER impact

Parameter	inMIND	NHS practice	Source
Age at diagnosis (median)	64.0 years	[redacted] years	HMRN (n=[redacted])
POD24 of diagnosis	32%	[redacted]	HMRN (n=[redacted])
Anti-CD20 (e.g. rituximab) refractory	42.5%	[redacted]	
ECOG performance status 0	68%	[redacted]	HMRN (n=[redacted])
ECOG performance status 1	29%	[redacted]	
ECOG performance status 2	3%	[redacted]	
ECOG performance status 3/4	?	[redacted]	
Ann Arbor stage 1/2	19%	[redacted]	HMRN (n=[redacted])
Ann Arbor stage 3/4	81%	[redacted]	
FL grade 1 or 2	74%	?	N/A
FL grade 3A	25%	?	
FLIPI low (0 or 1)	21%	[redacted]	HMRN (n=[redacted])
FLIPI intermediate (2)	27%	[redacted]	
FLIPI high (3 to 5)	52%	[redacted]	

Note: HMRN data collected 2005 to 2022

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HMRN, Haematological Malignancy Research Network; POD24, progression of disease within 24 months.

Other issues: PFS events that are death and RDI approach

Small ICER impact

Issue	1. Different approaches for calculating proportion of PFS events that are deaths	2. Different approaches to modelling RDI
Company base case	• Common [redacted] proportion across tafa+R^2 and R^2 from pooled inMIND data • Tafa+R^2 not expected to have more death events than R^2 pre-progression	• Per-cycle RDI informed by inMIND • Applies same per-cycle RDI over treated duration
EAG base case	• Pooling masks differences between arms • Higher pre-progression risk of death with tafa+R^2 triple regimen is plausible • Uses [redacted] for tafa+R^2 and [redacted] for R^2	• inMIND RDI suggests there are fewer full doses of tafa+R^2 over time • Per-cycle RDI for tafa+R^2 reduces over time
Impact	PSM = Small ICER decrease STM1 = Large ICER increase	Small decrease
Key question	How should PFS death events be modelled?	Constant or reducing per-cycle RDI?

Abbreviations: EAG, external assessment group; HMRN, Haematological Malignancy Research Network; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; R^2, lenalidomide with rituximab; RDI, relative dose intensity; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Model structure	PSM	STM1 (no PPS benefit)
OS distribution used	Jointly fitted generalised gamma	N/A
PFS distribution used	Jointly fitted generalised gamma	Separately fitted log-logistic
Treatment effect waning (PFS & OS)	5-year gradual waning starting at 5 years	3-year gradual waning starting at 2 years
Proportion of PFS events that are deaths	Treatment-independent (pooled from inMIND)	Treatment-specific from each arm of inMIND
Per-cycle RDI application	Average RDI (constant over time)	Per-cycle RDI (reduces over time)

Abbreviations: EAG, external assessment group; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; RDI, relative dose intensity; STM, state transition model.

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

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

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Other considerations

Equalities

No equalities issues were identified

Uncaptured benefits

- Possible effect on histological transformation to more aggressive lymphomas not captured in modelling
- EAG notes inMIND transformation results are promising but exploratory and immature so this remains uncertain

Managed access criteria

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**.

Managed access perspectives

Company

- Would support recommendation with managed access via CDF to collect more data and reduce uncertainty
- inMIND trial completes in [redacted] so further analysis of OS/TTNT, exploration of waning will be done
- Early access through CDF allows SACT (outcomes) and Blueteq (patient demographics and clinical characteristics) data collection in real-world NHS population
- CDF used successfully for R/R FL in the past (obinutuzumab with bendamustine, TA629)

EAG comments

- Tafa+R^2 needs 7 more infusions than R^2 – may be an implementation concern due to limited chair capacity
- Clinical advice to company and EAG suggest additional infusions may adversely impact tafa+R^2 uptake

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- Immature OS uncertainties could be resolved with further SACT and inMIND data collection
- Tafa+R^2 would be suitable for CDF entry to collect data to resolve uncertainties (if criteria met)

How mature would the inMIND trial PFS and OS be expected to be at the final data cut-off?
Are there any registries or other trials that could give a reasonable estimate?

Abbreviations: CDF, Cancer Drugs Fund; EAG, external assessment group; FL, follicular lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; R^2, lenalidomide with rituximab; SACT, Systematic Anti-Cancer Therapy; Tafa+R^2, tafasitamab with lenalidomide and rituximab; TTNT, time to next treatment

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

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

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Cost-effectiveness results

All ICERs are reported in **PART 2** slides because they have confidential PAS discounts

ICER ranges presented below

Summary

2L+

- Company base case deterministic ICERs were below £35,000 per QALY gained
- Company base case probabilistic ICERs were above £35,000 per QALY gained
- EAG base case deterministic and probabilistic ICERs were above £35,000 per QALY gained

3L+

- Company base case deterministic and probabilistic ICERs were below £35,000 per QALY
- EAG was uncertain about 3L+ comparison and could not support a base case analysis

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Abbreviations: ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab.

Key issues

Key issue	ICER impact	Slide
Relevance of treatments as comparators	Unknown	10
Uncertain overall survival benefit of tafasitamab + R^2	Large	15
Uncertain relative effectiveness of tafasitamab + R^2 against all comparators	Unknown	16
Suitability of model structure, surrogacy assumptions and tafasitamab + R^2 post-progression survival benefit	Large	20
Extrapolation of progression-free survival	Moderate	22
Treatment effect waning approach	Large	24
Modelling of 2L and 3L populations together	Large	25
Other issues: generalisability of inMIND to NHS	Small	26
Other issues: PFS events that are death and RDI approach	Small	28

Some key issues (like the uncertainty around OS due to data immaturity) may be potentially resolved through entry into the CDF

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Abbreviations: 2L/3L, second- or third-line; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; R^2, lenalidomide with rituximab; RDI, relative dose intensity.

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments

Supplementary appendix

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R+chemo treatments

R+chemo is an umbrella term for multiple rituximab-based treatment combinations

Rituximab-based combination treatments (per TA243)

Constituent drug	Combination treatment				
	R-CHOP*	R-CHVPi	R-CVP*	R-MCP	Rituximab with chlorambucil
Rituximab	✓	✓	✓	✓	✓
Chlorambucil				✓	✓
Cyclophosphamide	✓	✓	✓		
Doxorubicin	✓	✓			
Etoposide		✓			
Interferon-alpha		✓			
Mitoxantrone				✓	
Prednisolone	✓	✓	✓	✓	
Vincristine	✓		✓		

* R-CHOP and R-CVP are the most used R+chemo options

Abbreviations: R+chemo, rituximab with chemotherapy combination.

Additional clinical evidence

	HMRN data	GADOLIN (NCT01059630)	EPCORE-NHL-1
Design	Retrospective, observational dataset	Phase III open-label, active-controlled, randomised trial	Phase II, open-label, single arm trial
Population	Adults with R/R FL initiating treatment 2L/3L • N=[redacted]	Adults with R/R FL in 2L+ (n=335)	Adults with R/R FL in 3L+ (N=128)
Intervention	N/A	Obinutuzumab + bendamustine (n=164)	Epcoritamab monotherapy
Comparator(s)	R-CHOP (n=[redacted]), R-CVP (n=[redacted])	Bendamustine monotherapy (n=171)	N/A
Primary outcome	OS, PFS, TTD, ORR, CR, PR	Number of people with PD, PFS	ORR, rate of grade ≥2 CRS, rate of any CRS
Key secondary outcomes	N/A	OS, ORR, DoR, TTNT, AEs, HRQoL	PFS, OS, DoR, TTNT, AEs and more
Locations	Yorkshire and Humber & Yorkshire Coast	83 locations	88 sites across 15 countries
Used in model?	Yes – main evidence for R + chemotherapy	Yes – alternative evidence for PPS benefit in STM approach scenarios	Yes – MAIC estimate used to model tafa+R^2 vs epcoritamab

Abbreviations: 2L/3L, second- or third-line; AE, adverse event; CR, complete response; DoR, duration of response; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PD, progressed disease; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; PPS, post-progression survival; PR, partial response; R^2, lenalidomide with rituximab; R/R, relapsed or refractory; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; TTD, time to treatment discontinuation; TTNT, time to next treatment.

inMIND adverse events (1/2)

Treatment-emergent and treatment-related AEs in R/R FL safety population (N=546)

Participants (n [%]) who had at least 1	Tafasitamab + R^2 (n = 274)	Placebo + R^2 (n = 272)	Total (N = 546)
TEAE	272 (993)	270 (993)	542 (993)
Serious TEAE	99 (36)	86 (32)	185 (34)
Grade 3 or 4 TEAE	195 (71)	189 (70)	384 (70)
Fatal TEAE	6 (2)	6 (2)	12 (2)
Tafasitamab/placebo-related TEAE	202 (74)	179 (66)	381 (70)
Serious tafasitamab/placebo-related TEAE	29 (11)	32 (12)	61 (11)
Grade 3 or 4 tafasitamab/placebo-related TEAE	112 (41)	100 (37)	212 (39)
Fatal tafasitamab/placebo-related TEAE	0 (0.	2 (1)	2 (<1)
Lenalidomide-related TEAE	245 (89)	237 (87)	482 (88)
Serious lenalidomide-related TEAE	35 (13)	38 (14)	73 (13)
Grade 3 or 4 lenalidomide-related TEAE	154 (56)	136 (50)	290 (53)
Fatal lenalidomide-related TEAE	0 (0)	2 (1)	2 (<1)
Rituximab-related TEAE	173 (63)	162 (60)	335 (61)
Serious rituximab-related TEAE	17 (6)	24 (9)	41 (8)
Grade 3 or 4 rituximab-related TEAE	72 (26)	69 (25)	141 (26)
Fatal rituximab-related TEAE	0 (0)	1 (<1)	1 (<1)

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Abbreviations: AE, adverse event; FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; R2, lenalidomide and rituximab; R/R, relapsed or refractory

inMIND adverse events (1/2)

Treatment-emergent and treatment-related AEs in R/R FL safety population (N=546)

Participants (n [%]) who had at least 1	Tafasitamab + R^2 (n = 274)	Placebo + R^2 (n = 272)	Total (N = 546)
TEAE leading to permanent discontinuation of tafasitamab/placebo	30 (11)	18 (7)	48 (9)
TEAE leading to permanent discontinuation of lenalidomide	39 (14)	31 (11)	70 (13)
TEAE leading to permanent discontinuation of rituximab	8 (3)	8 (3)	16 (3)
TEAE leading to dose delay or dose interruption of tafasitamab/placebo	203 (74)	190 (70)	393 (72)
TEAE leading to dose reduction, dose missed, or dose interruption of lenalidomide	210 (77)	197 (72)	407 (75)
TEAE leading to dose delay or dose interruption of rituximab	124 (45)	125 (46)	249 (46)

Abbreviations: AE, adverse event; FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; R2, lenalidomide and rituximab; R/R, relapsed or refractory

Indirect treatment comparisons for R+chemo

Company conducted MAICs to compare tafasitamab + R^2 with R+chemo but considered outcomes uncertain and some lacked face validity

- SLR identified BRB single-arm trial for R-B and Van Oers et al. (2006)* RCT for R-CHOP versus CHOP, FA found many sources of heterogeneity including study design, patient characteristics and prior therapies
- Company sought RWE to mitigate evidence gap: HMRN dataset provided retrospective, observational data for [redacted] people in the UK with R/R FL taking either R-CHOP (n=[redacted]) or R-CVP (n=[redacted]) at 2L/3L
- The company conducted unanchored MAICs to indirectly compare tafasitamab + R^2 from inMIND to R+chemo treatments using BRB, Van Oers (2006) or HMRN.

Limitations (noted by company and EAG)

- The company could not adjust for most prognostic factors or identified key treatment effect modifiers
- Adjustments gave ESS which were [redacted]% of original sample size, and wide CIs around MAIC estimates
- Some results for PFS and TTNT contradicted results from inMIND – findings lacked face validity

Company opted to use inMIND R^2 efficacy to model R+chemo which it considered a conservative approach as TA627 showed R^2 was more effective than R+chemo – company used MAIC estimates in scenarios

EAG said limited MAIC evidence makes it difficult to conclude on relative benefits of tafa+R^2 over R+chemo. MAIC in TA627 also limited (unanchored, couldn't match for all TEMs) so uncertain R^2 benefit over R+chemo

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Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; PFS, progression-free suvrvival; R^2, lenalidomide with rituximab; R-B, bendamustine with rituximab; R+chemo, rituximab with chemotherapy combination; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; RCT, randomised controlled trial; RWE, real-world evidence; SLR, systematic literature review; TEM, treatment effect modier; TTNT, time to next treatment.

Indirect treatment comparison for epcoritamab

Patient characteristics before and after weighting, 3L+ FL

(only characteristics used in matching shown)

Characteristic	Tafasitamab + R^2		Epcoritamab (N = 128)
	Before (N=126)	After (ESS=[redacted])	
Age ≥ 65 years	[redacted]	[redacted]	[redacted]
ECOG PS 0	[redacted]	[redacted]	[redacted]
ECOG PS 1–2	[redacted]	[redacted]	[redacted]
Ann Arbor stage 1/2	[redacted]	[redacted]	[redacted]
Ann Arbor stage 3/4	[redacted]	[redacted]	[redacted]
FLIPI low (0–1)	[redacted]	[redacted]	[redacted]
FLIPI intermediate (2)	[redacted]	[redacted]	[redacted]
FLIPI high (≥ 3)	[redacted]	[redacted]	[redacted]
Refractory to last prior therapy	[redacted]	[redacted]	[redacted]

Time constraints have limited full critique of tafa+R^2 vs epcoritamab MAIC, but EAG considers…

- Epcoritamab MAIC limited like R+chemo MAICs (i.e. heterogenous study design/population characteristics)
- Populations have some overlap (ESS=[redacted] of inMIND sample size), but EPCORE NHL-1 has poorer prognosis

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Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; MAIC, matching-adjusted indirect comparison; R+chemo, rituximab with chemotherapy combination; R^2, lenalidomide with rituximab; tafa+R^2, tafasitamab with lenalidomide and rituximab.

R+chemo MAIC results

Both company and EAG thought MAIC results were uncertain and some violated face validity

Results of MAICs for R+chemo

Source	Comparator	Pop.	N	Tafasitamab + R^2 ESS, n (%*)	OS HR (95% CI)	PFS HR (95% CI)	TTNT HR (95% CI)
BRB	R-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Van Oers	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R+chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* % of original sample size

Abbreviations: 2L/3L, second- or third-line; CI, confidence interval; EAG, external assessment group; ESS, effective sample size; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NR, not reached; PFS, progression-free survival; OS, overall survival; R^2, lenalidomide with rituximab; R-B, bendamustine with rituximab; R+chemo, rituximab with chemotherapy combination; R-CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; TTNT, time to next treatment.

STMs post-progression survival approaches

PSM supplemented with STMs with 3 different methods to model PPS (and therefore OS)

STM1	
Sources	HMRN data (R+chemo)
PPS benefit modelled?	None
Median PPS, months	64.7
Per cycle PPS rate	0.25% for both

STM2		
Sources	GADOLIN trial	
PPS benefit modelled?	Yes	
Median PPS, months	Tafa+R^2=67.9	R^2=46.6
Per cycle PPS rate	Tafa+R^2=0.23%	R^2=0.34%

STM3 takes a weighted average of both approaches based on the % rituximab-refractory from inMIND

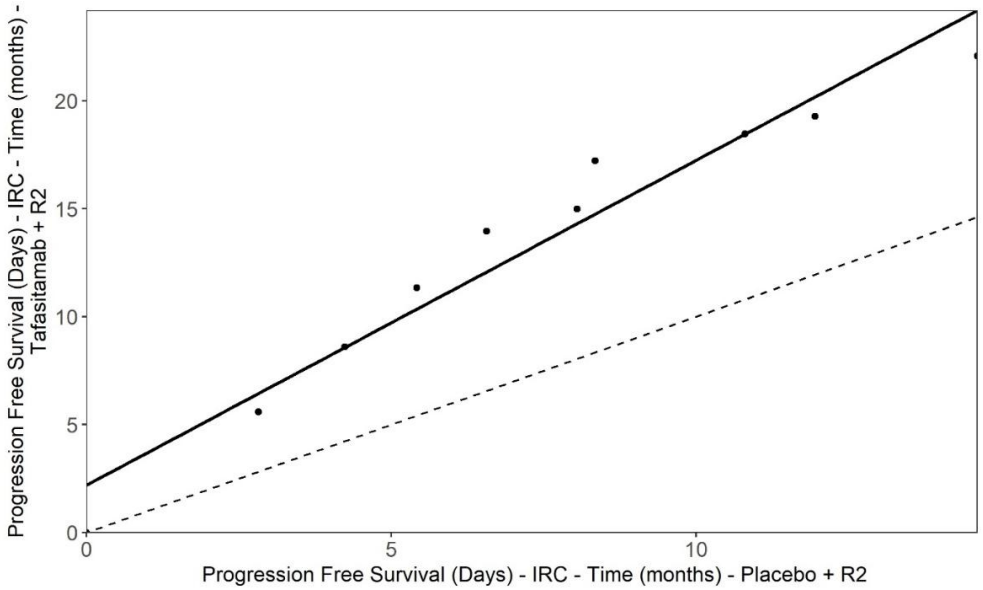
- **HMRN data** is for R-CHOP, R-CVP or both in non-refractory FL
- **GADOLIN trial** compares OB vs bendamustine in refractory FL

STM3		
Sources	HMRN data, GADOLIN and inMIND trials	
PPS benefit modelled?	Weighted approach (inMIND %): • PPS benefit for refractory (41%) • None for non-refractory (59%)	
Median PFS, months	Tafa+R^2=66.7	R^2=55.9
Per cycle PPS rate	Tafa+R^2=0.24%	R^2=0.29%

Abbreviations: HMRN, Haematological Malignancy Research Network; OB, obinutuzumab with bendamustine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; R^2, lenalidomide with rituximab; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone;STM, state transition model; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

Company assessment for PFS extrapolation

Quantile-quantile plot for joint fitting of AFT model, PFS



- Separately fitted models disregarded due to estimating higher R^2 OS than observed in tafasitamab+R^2 arm
- Generalised gamma aligned best with clinical expert expectations over time
- Log-logistic considered next best fit (across criteria) and explored in scenario

Model fit statistics, jointly fitted PFS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	1529.2	7	1537.8	7
Gamma	1492.1	3	1505.0	2
Generalised gamma	1491.6	2	1508.9	4
Gompertz	1511.7	6	1524.6	6
Log-logistic	1488.5	1	1501.5	1
Log-normal	1494.2	4	1507.2	3
Weibull	1496.3	5	1509.2	5

Return to PFS extrapolation slide

Abbreviations: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival; PFS, progression-free survival; R^2, lenalidomide with rituximab.

PFS model fit statistics and rank

Model fit statistics (rank), PFS

Distribution	Jointly fitted		Independently-fitted Tafa+R^2		Independently-fitted R^2	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1,529.2 (7)	1,537.8 (7)	592.2 (7)	595.8 (7)	936.9 (7)	940.6 (6)
Gamma	1,492.1 (3)	1,505.0 (2)	573.9 (3)	581.1 (3)	919.3 (4)	926.6 (4)
Generalised gamma	**1,491.6 (2)**	**1,508.9 (4)**	575.1 (4)	585.9 (5)	914.5 (2)	925.3 (3)
Gompertz	1,511.7 (6)	1,524.6 (6)	576.5 (5)	583.7 (4)	933.5 (6)	940.8 (7)
Log-logistic	1,488.5 (1)	1,501.5 (1)	**573.4 (2)**	**580.6 (2)**	**916.4 (3)**	**923.608 (2)**
Log-normal	1,494.2 (4)	1,507.2 (3)	583.1 (6)	590.3 (6)	912.7 (1)	919.9 (1)
Weibull	1,496.3 (5)	1,509.2 (5)	573.1 (1)	580.3 (1)	922.7 (5)	929.9 (5)

Blue = company selected for base case
Orange = EAG selected for base case

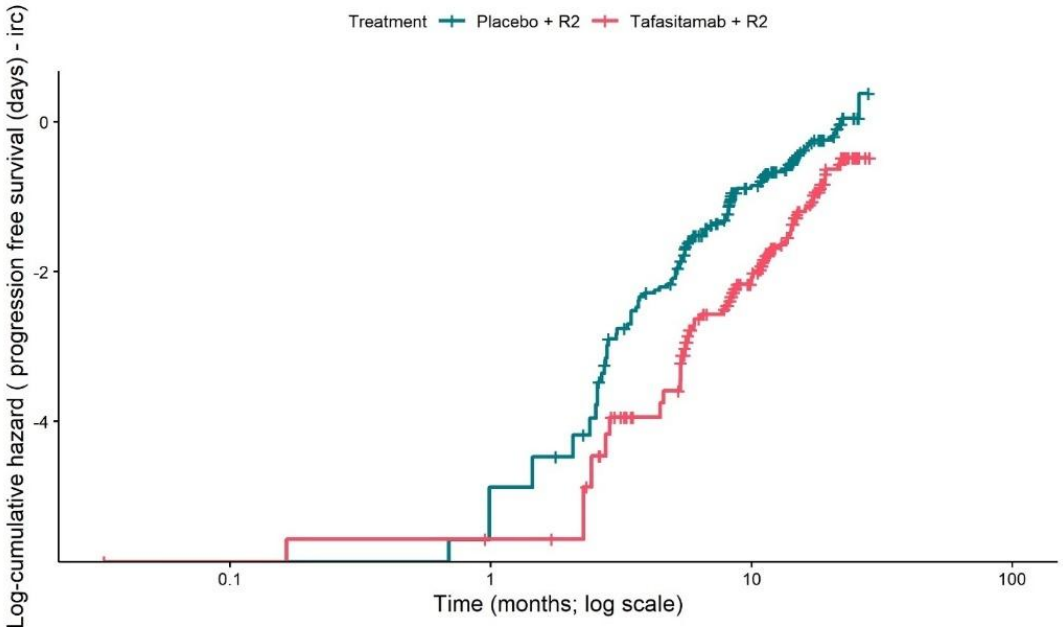
Return to PFS extrapolation slide

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EAG, external assessment group; PFS, progression-free survival; R^2, lenalidomide with rituximab; Tafa+R^2, tafasitamab with lenalidomide and rituximab.

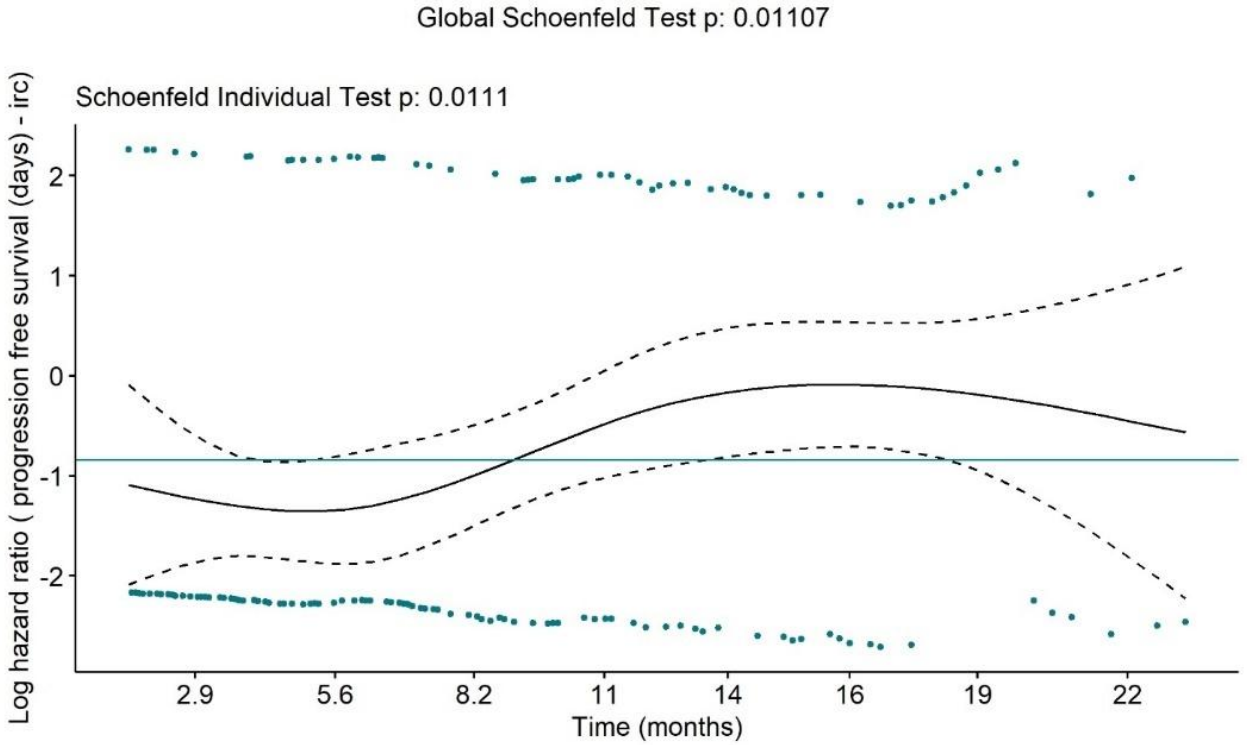
PFS proportional hazards assessment

Testing inMIND KM curves indicates that, although seeming parallel, PH assumption violated and relative effect varies over time

Log-cumulative hazard plot (PFS by IRC), tafa+R^2 vs R^2



Schoenfeld residual plot (PFS by IRC), tafa+R^2 vs R^2



[Return to treatment effect waning slide]

Abbreviations: IRC, independent review committee; KM, Kaplan-Meier; PH, proportional hazards; PFS, progression-free survival; R^2, lenalidomide with rituximab; tafa+R^2, tafasitamab with lenalidomide and rituximab.

Implied PFS hazard ratios

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

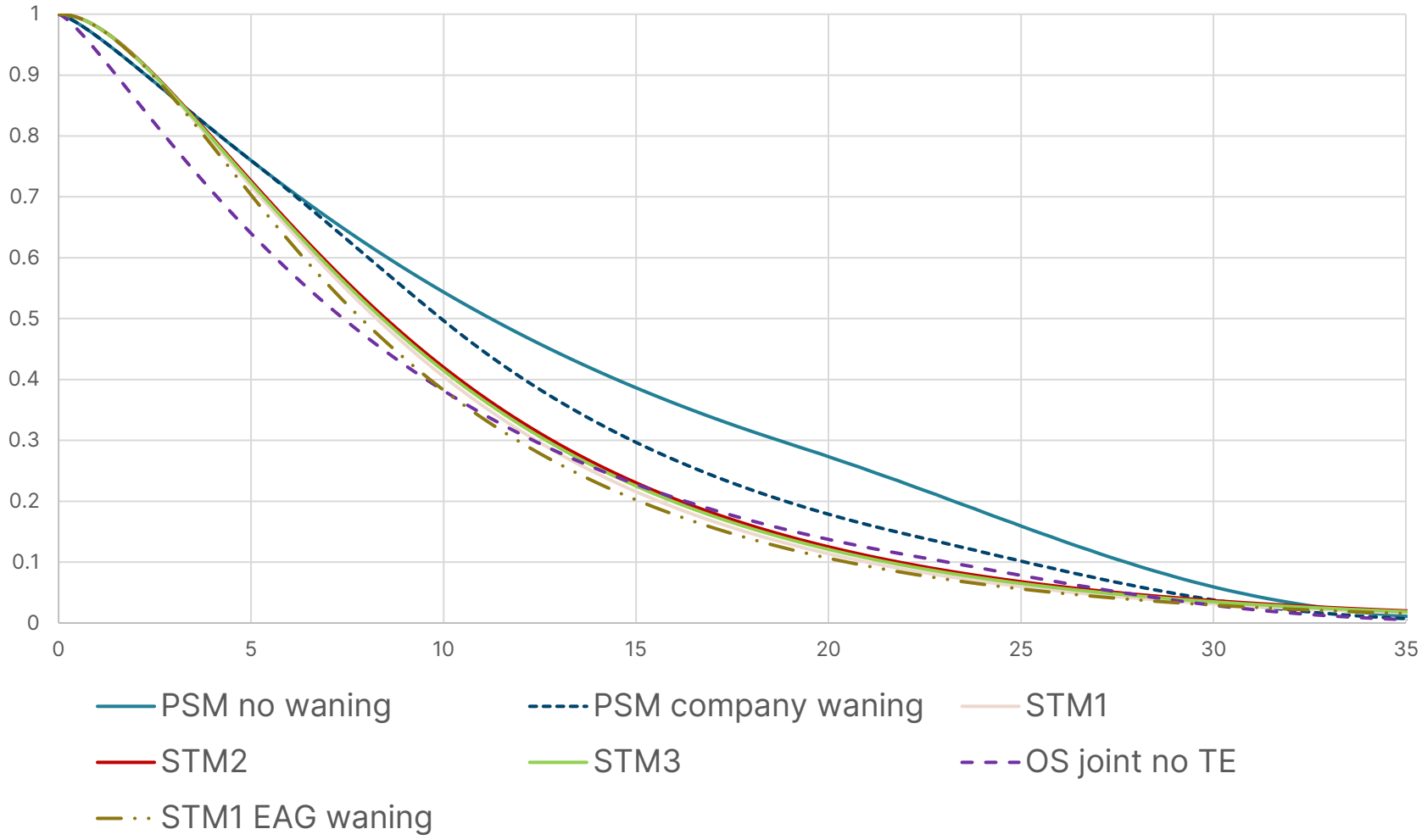
Implied OS hazard ratios

EAG base case assumptions which affect OS HR

- STM1 (no PPS benefit)
- PFS separately fitted log-logistic
- Treatment effect waning on PFS and OS (3 years starting at 2 years)

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

Modelled OS under different assumptions – Tafasitamab +R2

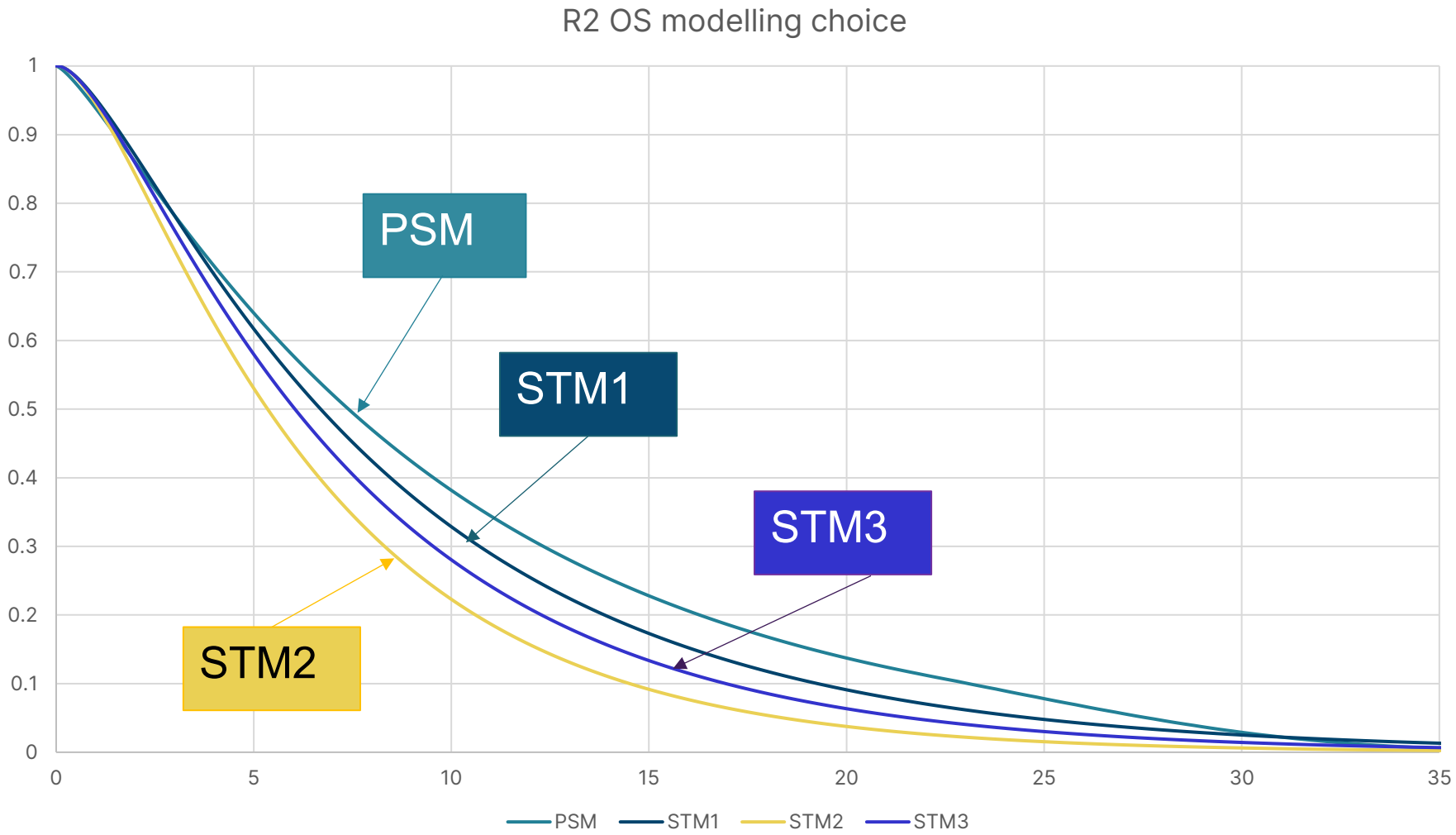


- Choice of STM does not have large effect on tafa+r2 extrapolations as PPS rate does not change much
- It has a large effect on ICERs due to changes in R2 OS (see next slide)

Model	PPS rate tafa+R2
PSM	n/a
STM1	0.25%
STM2	0.23%
STM3	0.24%

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

Modelled OS under different assumptions – R^2



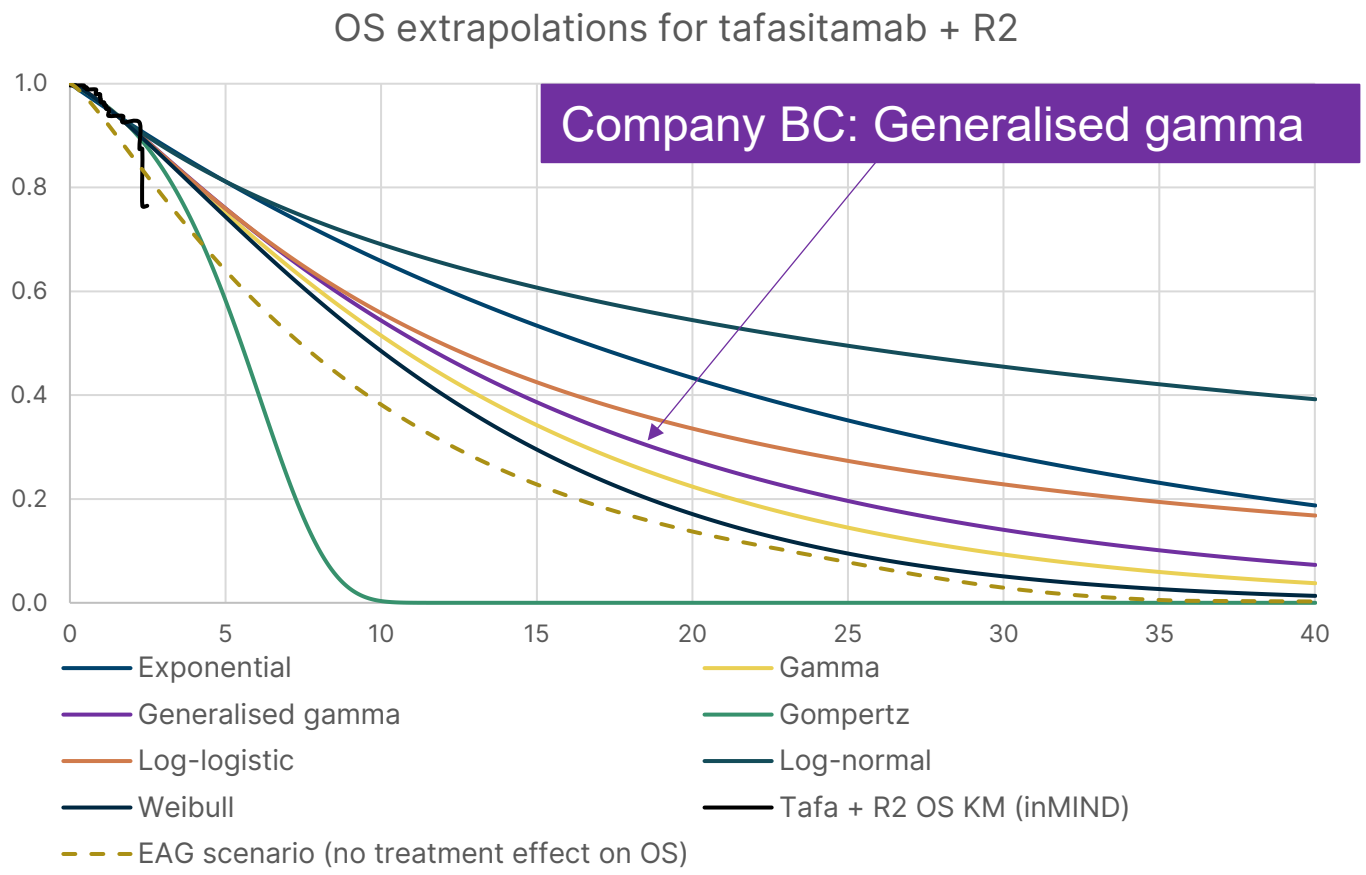
- Choice of STM has large effect on ICERs by changing R2 OS extrapolations
- PPS rate changes much more for R2 between STM models

Model	PPS rate R2
PSM	n/a
STM1	0.25%
STM2	0.34%
STM3	0.29%

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

Visual fit of OS extrapolations: tafasitamab + R2

To be used if PSM selected



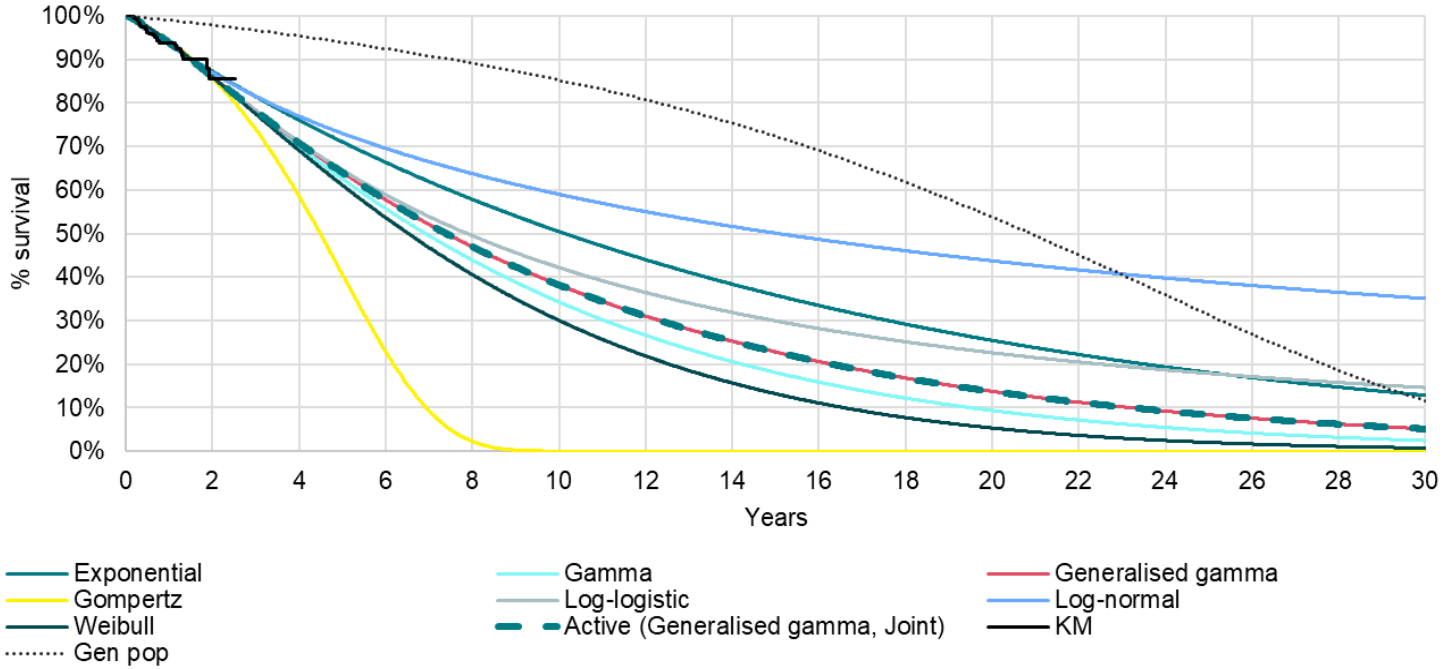
	5yr	10yr	20yr
Exponential	81.2%	65.8%	43.3%
Gamma	75.2%	51.5%	22.4%
Generalised gamma	76.1%	54.4%	27.5%
Gompertz	58.5%	0.3%	0.0%
Log-logistic	76.0%	55.8%	33.6%
Log-normal	81.2%	69.1%	54.5%
Weibull	74.4%	48.6%	17.1%

EAG preferred scenario if PSM used is with no OS treatment effect (dashed brown line)

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

Visual fit of OS extrapolations: R2

To be used if PSM selected



	5yr	10yr	20yr
Exponential	71.1%	50.5%	25.5%
Gamma	62.7%	34.3%	9.3%
Generalised gamma	64.1%	38.2%	13.7%
Gompertz	40.9%	0.0%	0.0%
Log-logistic	64.7%	42.2%	22.6%
Log-normal	73.1%	59.0%	43.7%
Weibull	61.2%	30.1%	5.3%

Abbreviations: EAG, external assessment group; HR, hazard ratio; OS, overall survival; PSM, partitioned survival model; R2, lenalidomide with rituximab; STM, state transition model.

US example of R/R FL treatments

Note: this is US data, not NHS
Source