Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma

For public observers – ACIC information redacted [redacted]

Technology appraisal committee C [01 June 2022]

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NICE

Background on diffuse large B-cell lymphoma

Causes

- Diffuse large B-cell lymphoma (DLBCL) is a type of non-Hodgkin lymphoma (NHL), a cancer of the lymphatic system
- It develops when the body makes abnormal B lymphocytes (a type of white blood cell that normally help to fight infections) which build up in lymph nodes or other body organs

Epidemiology

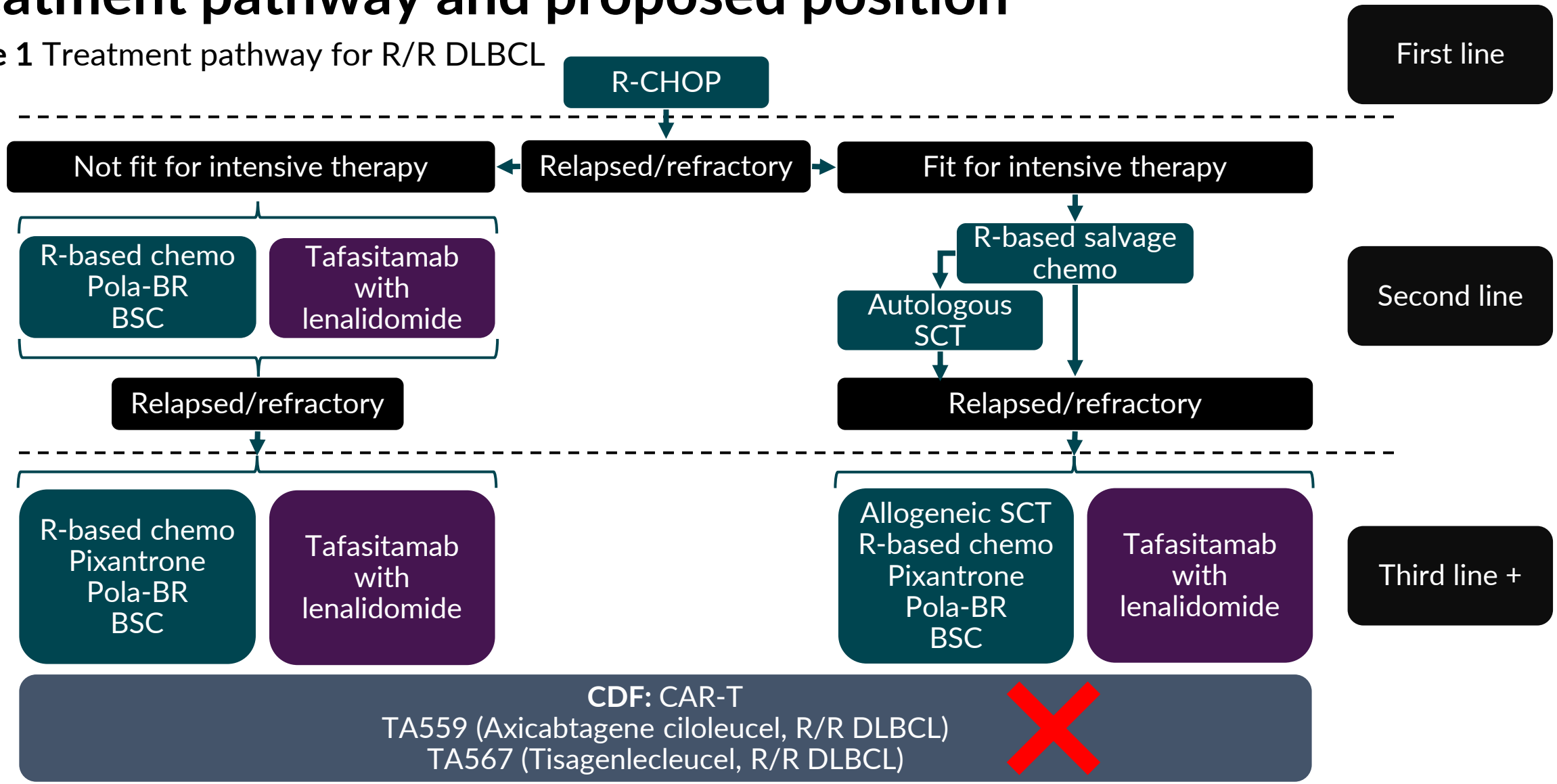
- Each year about 5,500 people are diagnosed with DLBCL in the UK, around 40% of NHL in adults
- Most people diagnosed are over 65 and male

Symptoms and prognosis

- NHL often presents as painless lumps in the neck, armpit or groin
- Most people diagnosed with DLBCL are cured with first-line chemotherapy
- However, about 10-15% have primary refractory disease and a further 20-30% relapse

Treatment pathway and proposed position

Figure 1 Treatment pathway for R/R DLBCL



Abbreviations: BSC, best supportive care; CAR-T, Chimeric Antigen Receptor Cell Therapy; CDF, Cancer Drugs Fund; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R-based, rituximab-based; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed or refractory; SCT, stem cell transplant

Patient perspectives

Patients seek a more tolerable treatment that improves outcomes

Submission from Lymphoma Action

- Relapsed or refractory DLBCL has a significant impact on the quality of life of patients and their families and carers. The psychological, social and economic impact of the disease is considerable
- Current treatments are very intensive, requiring long stays in hospital away from family and friends and incurring serious side effects even after treatment has ended
- The potential of outpatient treatment is viewed very positively, allowing people to maintain a more normal life, see family and friends, and improve physical and mental health by being outdoors
- Many people are unable to tolerate the intensive regimens currently available, and these people have very limited treatment options
- Tafasitamab with lenalidomide has the potential to improve outcomes in this challenging population

"I think it would provide huge advantage to those unable or unwilling to have stem cell transplant"

"any home-based* treatment would have a significant, positive effect on the quality of life, for patients and their families"

*Home-based refers to treatments given in outpatient day case settings rather than inpatient settings

Clinical perspectives

Tafasitamab with lenalidomide could be an alternative to palliative care

Submissions from NCRI, ACP, RCP, RCR, and a clinical oncologist

- The main aim of treatment in this indication is to delay progression
- Particularly effective treatments would provide a durable response, allow for bridging to consolidation therapies, or be curative
- There is no standard of care for this population: people fit for intensive therapy are offered treatments with curative intent, those unfit for intensive therapy have treatment with a limited chance of success
- Tafasitamab with lenalidomide is a new mechanism of action, with limited toxicity compared to current treatments; the combination would be easy to implement as lenalidomide is already widely used
- Tafasitamab with lenalidomide could dramatically change patient care as it would offer another therapeutic option for a cohort of patients where the options are poor and limited and durable remissions are uncommon
- Tafasitamab with lenalidomide is innovative in its potential in a population with a poor outcome and limited effective treatment options. Response rates are clinically meaningful in cohort of patients with poor prognosis

"A treatment approach for which there is no accepted standard of care"

"unmet need of patients who are older and / or have co-morbidities…where other options are palliative"

Abbreviations: ACP, Association of Cancer Physicians; NCRI, National Cancer Research Institute; RCP, Royal College of Physicians; RCR, Royal College of Radiologists

Key issues
Comparators, clinical data, and end-of-life criteria

Table 1 Key issues

Issue	Resolved?	ICER impact
1. Should all comparators in the NICE final scope be considered?	Partially – for discussion	Unknown
2. Which indirect treatment comparison approach is most robust for decision making?	No	Unknown
3. Which OS and PFS extrapolations for pola-BR are most appropriate for decision making?	No	Large
4. Which PFS extrapolation for tafasitamab with lenalidomide is most appropriate for decision making?	No	Large
5. Does tafasitamab with lenalidomide meet the end-of-life criteria?	No	N/A

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

Tafasitamab (Minjuvi, Incyte)

Table 2 Technology details

Marketing authorisation	• Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy for treating adult patients with relapsed or refractory DLBCL who are not eligible for ASCT • MHRA licence granted in October 2021, accepting EMA orphan designation
Mechanism of action	• Tafasitamab is an monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes • Tafasitamab has potential synergy with lenalidomide, an immunomodulatory agent that enhances the activity and recruitment of natural killer (NK) cells. NK cells are engaged by tafasitamab
Administration	• The recommended dose of tafasitamab is 12 mg per kg body weight administered as an intravenous infusion. It is taken until disease progression or unacceptable toxicity • Lenalidomide is self-administered by the patient as oral capsules for up to 12 cycles of 28 days (25mg taken daily for the first 21 days in each cycle)
Price	• List price of £705 per vial of tafasitamab containing 200 mg powder for concentrate for solution for infusion; lenalidomide list price of £4,368 for 25mg tablets (21 pack) • Year 1 list price of [redacted] for 12 months treatment (£120,639 for tafasitamab) • Year 2 onwards list price of £95,049 for 12 months treatment (tafasitamab monotherapy) • A patient access scheme is available for tafasitamab

Abbreviations: ASCT, autologous stem cell transplant; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency

Decision problem
Comparators deviate in company submission from final scope

Table 3 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	Adults with relapsed or refractory DLBCL and who are not eligible for ASCT	Same as final scope	-
Intervention	Tafasitamab with lenalidomide followed by tafasitamab monotherapy	Same as final scope	-
Comparators	• R-based chemo • Pixantrone • Pola-BR • Best supportive care	Only Pola-BR, R-GemOx, BR included in submission on the basis of expert opinion	Unclear whether the comparators match clinical practice in England and Wales [See next slide]
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse events • Health-related QoL	Same as final scope plus time to discontinuation and duration of response	-

Abbreviations: ASCT, autologous stem cell transplant; QoL, quality of life

Key issue 1: Comparators

Comparators in the submission are narrower than final scope

Final scope comparators
- R-Gem
- R-GemOx
- BR
- Pola-BR
- R-P-MitCEBO
- (R-)DECC
- Pixantrone
- BSC

Submission comparators
- R-GemOx
- BR
- Pola-BR

ERG comments
- Unclear whether the comparators match clinical practice in England and Wales

Company
- UK clinical experts suggested following regimens are not widely used: R-Gem, R-DECC or R-P-Mit-CEBO, pixantrone, and BSC/palliative care

Other considerations
- **NHSEI:** "In practice pola-BR will be the main competitor…pixantrone…is not used in practice due to high toxicity and poor efficacy…the various rituximab+ chemotherapy options in the NICE scope have been largely replaced by pola-BR"
- **Clinical experts:** Indicate pola+BR as main comparator, R-GemOx less commonly used; all other treatments infrequently used
- **Other points:**
- Limited evidence available for comparators not included in company submission
- BR considered reasonable proxy for standard of care in TA649 (Pola-BR, R/R DLBCL)

Which comparators are relevant for tafasitamab with lenalidomide in R/R DLBCL?

Abbreviations: BR, bendamustine and rituximab; NHSEI, NHS England and NHS Improvement; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R-GemOx, rituximab plus gemcitabine and oxaliplatin

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials
Trials for tafasitamab combination and monotherapy

Table 4 Clinical trial designs and outcomes

	L-MIND (N=81)	MOR208C201 (N=35, DLBCL cohort)
Design	Phase II, Single-Arm, Open-Label	Phase IIa, Single-Arm, Open-Label
Population	Adults with R/R DLBCL ineligible for ASCT (50% had 1 previous line of systemic therapy; 11% had prior ASCT)	Adults with R/R B-cell NHL who have had ≥1 prior therapy containing rituximab
Intervention	Tafasitamab with lenalidomide	Tafasitamab monotherapy
Comparator(s)	-	-
Follow-up	PFS: 33.9 months; OS: 42.7 months	Not reported in submission
Primary outcome	ORR	ORR
Key secondary outcomes	OS, PFS, DoR, DCR	SD, DoR, TTP, PFS
Locations	Europe, USA (4 UK sites, 5 UK patients)	Europe, USA (0 UK sites)
Used in model?	OS and PFS outcomes	N/A (provided as supportive evidence)

Key trial: provides evidence for tafasitamab with lenalidomide

Abbreviations: DoR, duration of response; ORR, objective response rate; SD, stable disease; TTP, time to progression

ERG comments on the L-MIND trial
Questions around generalisability to UK practice

Table 5 Differences in some baseline characteristics across L-MIND and UK retrospective data

L-MIND vs UK study to assess generalisability to UK population	L-MIND (N=81)	Northend et al. 2022 (UK study) (N=78)
Proportion of males	54%	69%
Presence of bulky disease	19%	28%
International Prognostic Index score	0 to 2: 49% 3 to 5: 51%	0 to 2: 27% ≥3: 72%
Median (range) lines of prior therapy	1 (1 to 4)	1 (1 to 6)
1 line of prior therapy	50%	55%
2 lines of prior therapy	43%	17%
3+ lines of prior therapy	3 or 4: 7%	≥3: 26%
Refractory to last line of treatment	44%	58%

Northend et al. 2022 is a retrospective analysis of real-world data from the UK. Company notes a higher proportion of patients using pola-BR as bridging therapy to SCT or CAR-T than as standalone therapy

ERG is still uncertain about the generalisability of L-MIND to the UK population with R/R DLBCL who are not eligible for SCT due to the differences above

Abbreviations: AE, adverse event; SCT, stem cell transplant

Results from L-MIND trial (1)
The disease completely responded in 40% of patients

Table 6 Best ORR (October 20 data cut)

	Tafasitamab with lenalidomide (N=80)*
ORR (CR + PR), n (%)	46 (58) [46, 69]
CR, n (%)	32 (40) [29, 52]
PR, n (%)	14 (18) [10, 28]
SD, n (%)	13 (16)
PD, n (%)	13 (16)
Not evaluable, n (%)	8 (10)

Figure 2 Kaplan-Meier plot of overall survival (October 20 data cut)

Median overall survival: 33.5 months [18.3, NR]

*80 patients used for efficacy results as 1 patient had tafasitamab monotherapy

Abbreviations: CR, complete response; NR, not reached; PD, progressed disease; PR, partial response; SD, stable disease

Results from L-MIND trial (2)

Median progression-free survival was 11.6 months

Figure 3 Kaplan-Meier plot of PFS (October 20 data cut)

Median progression-free survival:
11.6 months [6.3, 45.7]

Figure 4 Kaplan-Meier plot of DoR (October 20 data cut)

Median duration of response:
43.9 months [26.1, NR]

 Abbreviations: NR, not reached; DoR, duration of response; PFS, progression-free survival

Indirect treatment comparisons (ITCs)
2 different ITC approaches were taken by the company

- No comparative efficacy data available from L-MIND single-arm trial
- Company instead used 2 main indirect treatment comparison approaches

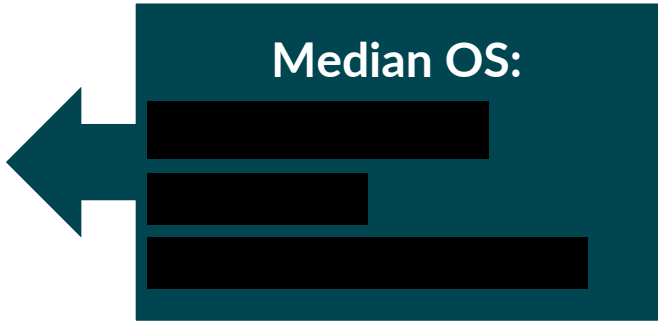
Table 7 Overview of indirect treatment comparison approaches

	RE-MIND2 (N=3,454)	Matching-adjusted indirect comparison (MAIC)
Overview of approach	• Observational, retrospective cohort study of adults with R/R DLBCL ineligible for ASCT • 1:1 NN-matched population treated with BR, R-GemOx, pola-BR (plus other interventions not included as comparators) • IPTW also used as another approach to match cohorts, but not used in company base case • Cohorts balanced with L-MIND population on 9 baseline covariates	• Population from L-MIND matched with published comparator populations • 4 prospective comparator studies were identified by SLR and expert input • 3 studies included for BR, 1 for pola-BR, 1 for R-GemOx
Treatments where ITC used in base case	R-GemOx	Pola-BR BR

Abbreviations: IPTW, inverse probability of treatment weighting; SLR, systematic literature review

Pola-BR survival outcomes vs. TAFA + LEN for RE-MIND2

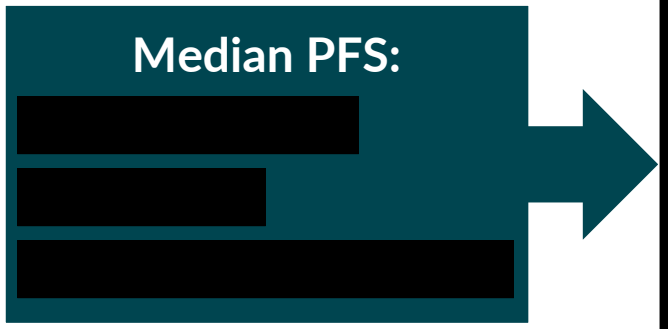
Figure 5 RE-MIND2 OS for TAFA + LEN vs pola-BR



Pola-BR NN-matching using 9 covariates and multiple imputation to address missing data

Figure 6 RE-MIND2 PFS for TAFA + LEN vs pola-BR

Note: RE-MIND2 not used in company or ERG base case for pola-BR due to underestimation of OS/PFS



Abbreviations: NN, nearest neighbour

MAIC methodology
4 prospective comparator studies were included in the MAIC

The L-MIND population was adjusted via propensity score weighting in order to be comparable to the respective comparator population

35 studies identified via SLR

4 key studies for R-based comparator regimens identified following interviews with clinical experts

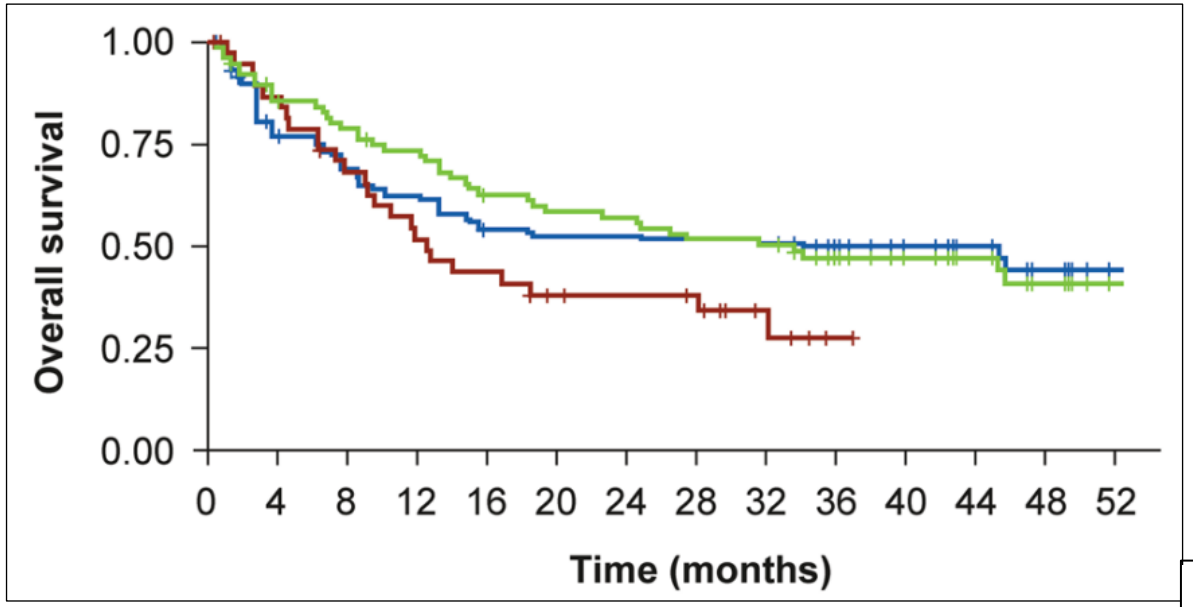
Table 8 Features of studies included in the MAIC

Trial (comparator)	Sample size	Covariates included in weighting
GO29365 (pola-BR) [Used in TA649 for pola-BR]	40	Age, ECOG score, IPI, prior treatment/ASCT, refractoriness to prior treatment, histology
GO29365 (BR) [Base case MAIC for BR, used in TA649 for BR]	40	
Ohmachi et al., 2013 (BR)	59	
Vacirca et al., 2014 (BR)	59 for efficacy results	Age, sex, ECOG score, Ann Arbor stage, IPI, prior treatment/ASCT
Mounier et al., 2013 (R-GemOx)	48 for efficacy results	Age, ECOG score, IPI, prior ASCT, refractoriness to prior treatment, cell origin of disease

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

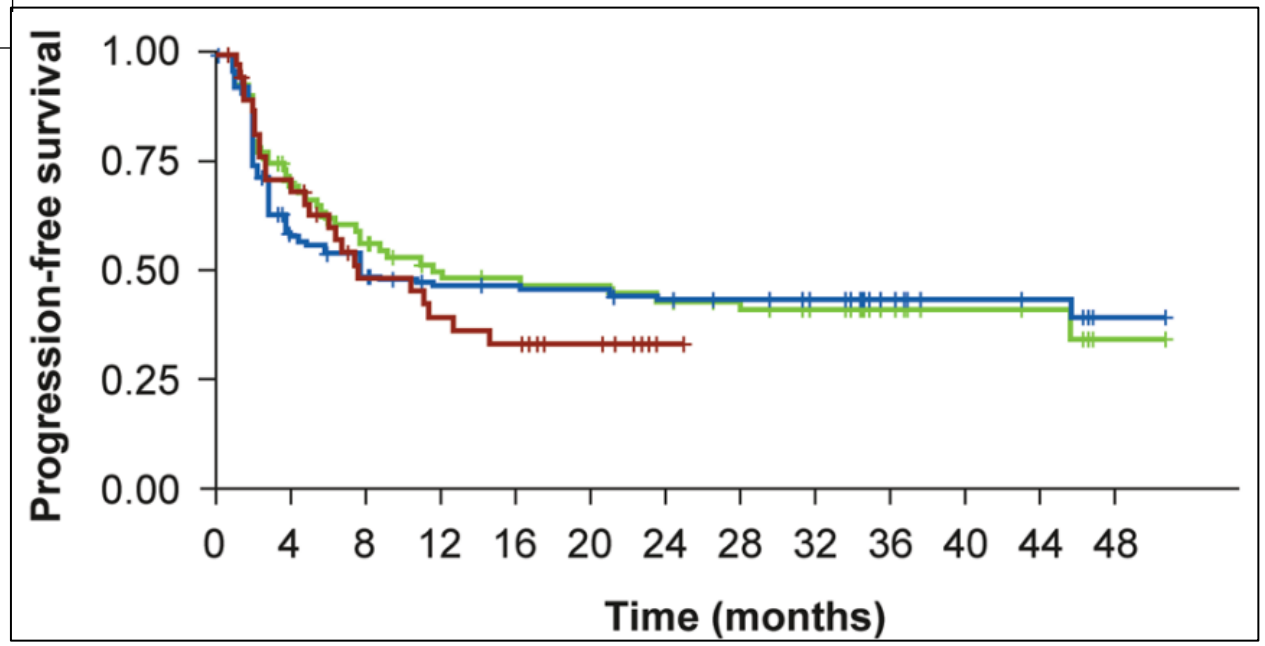
Pola-BR survival outcomes vs. TAFA + LEN from MAIC

Figure 7 MAIC OS for TAFA + LEN vs pola-BR



- TAFA + LEN unadjusted
- TAFA + LEN adjusted
- Pola-BR

Figure 8 MAIC PFS for TAFA + LEN vs pola-BR



Summary of indirect treatment comparison results
OS/PFS outcomes vary by adjustment method adopted

- RE-MIND2 base case population adjustment used NN-matching on 9 covariates (multiple imputation to address missing data)
- Company also did regression adjustment at technical engagement using Cox regression models with 9 covariates

Table 9 OS/PFS hazard ratios for tafasitamab with lenalidomide versus comparators for different ITCs

Tafasitamab with lenalidomide vs …	Pola-BR	R-GemOx	BR
RE-MIND2: NN-matching on 9 covariates	**OS:** [redacted] **PFS:** [redacted]	**OS:** [redacted] **PFS:** [redacted]	**OS:** [redacted] **PFS:** [redacted]
RE-MIND2: IPTW on 9 covariates	**OS:** [redacted] **PFS:** [redacted]	OS: - PFS: -	OS: - PFS: -
RE-MIND2: RA on 9 covariates	**OS:** [redacted] **PFS:** [redacted]	**OS:** [redacted] **PFS:** [redacted]	**OS:** [redacted] **PFS:** [redacted]
MAIC	**OS:** [redacted] **PFS:** [redacted]	**OS:** 0.55 [0.28, 1.06] **PFS:** 0.59 [0.30, 1.17]	**OS:** 0.39 [0.18, 0.82] **PFS:** 0.35 [0.18, 0.71]

[redacted]

[redacted]

Abbreviations: NN, nearest neighbour; RA, regression adjustment

Key issue 2: Validity of indirect treatment comparisons (1)

ERG prefers RE-MIND2 in principle, but unclear on nature of treatment effect

Background (NICE TSD17)

- **Average treatment effect (ATE):** treatment effect averaged across the population. Typically of greatest interest in technology appraisals as is the effect measured in an RCT, but difficult to identify
- **Average treatment effect on the treated (ATT):** average treatment effect for the subgroup of individuals who have had the intervention treatment (i.e., tafasitamab with lenalidomide)
- Pooled individual patient data preferable to population adjustment (e.g., a MAIC)

ERG comments

- To estimate treatment effect vs each comparator using the MAICs, the intervention data must be adjusted differently for each comparator. Likely to lead to bias. ERG in principle therefore prefers RE-MIND2 to the MAICs, given the need to compare tafasitamab with lenalidomide with several comparators
  - However, the MAIC results have better clinical validity for pola-BR
- Company claims that RE-MIND2 estimated the ATT
- However, the baseline characteristics of the tafasitamab with lenalidomide cohort varied depending on the comparator. Suggests that RE-MIND2 did not estimate the ATT, but ERG unclear on what type of treatment effect it estimated
- In general, there was a lack of clarity on the methods used for the indirect treatment comparisons

Abbreviations: RCT, randomised controlled trial; TSD, technical support document

Key issue 2: Validity of indirect treatment comparisons (2)

ITCs lack clarity and are potentially biased

Company

- Asserts that matching in RE-MIND2 was used to estimate ATT
- Provided analyses to support validity of RE-MIND2 and MAICs and similarity in comparator/intervention populations
  - Results consistent between sensitivity analyses for each comparator
  - Provided regression analyses with RE-MIND2 using 9 covariates included in RE-MIND2 base case – results aligned with other approaches. However, results should be treated with caution
  - Comparison of baseline characteristics and standardised mean differences for different approaches

ERG comments

- Although no assessment of overlap was performed, the SMDs largely indicate reasonable overlap
- However, within RE-MIND2, intervention population has been adjusted meaning the ATT is not estimated
- ERG consider the validity of ITCs remains unresolved

Which ITC approach is most robust for decision making?

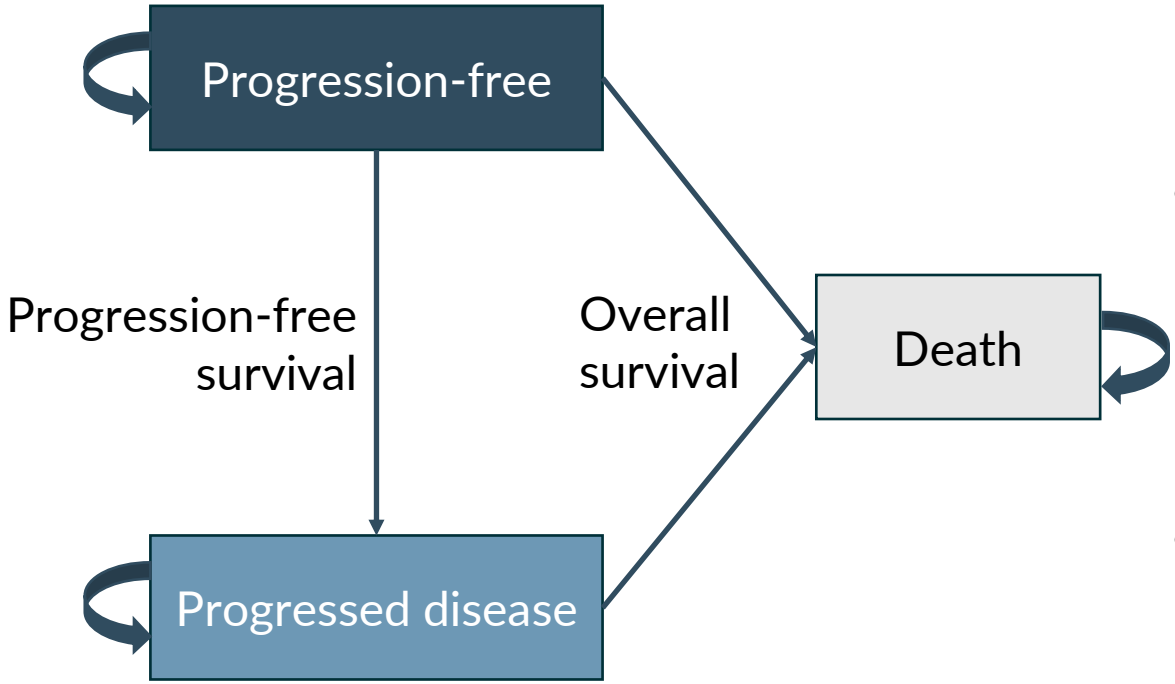
Abbreviations: ATT, average treatment effect on the treated; SMD, standard mean difference

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview
A three-state partitioned survival model was used

Figure 9 Model structure



- **Tafasitamab with lenalidomide affects costs by:**
  - Its higher unit price compared to current treatments
  - Increasing administration and monitoring costs
  - Decreasing costs associated with disease management and subsequent treatments
- **Tafasitamab with lenalidomide affects QALYs by:**
  - Increasing the progression-free and reducing the post-progression health state occupancy
  - The decrease in utility due to adverse events associated to the new technology is minor
- **Assumptions with greatest ICER effect:**
  - Alternative OS and PFS assumptions
  - Alternative TTD assumptions
  - Alternative utility values
  - Equal disease management costs for all treatments

 Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTD, time to discontinuation

How company incorporated evidence into model

Evidence from L-MIND, ITCs, and previous NICE appraisals was used

Table 10 Input and evidence sources in the company base case model

Input	Assumption and evidence source
Baseline characteristics	L-MIND population characteristics
Intervention efficacy	Various distributions based on L-MIND trial data
Comparator efficacy (see next slide)	**Pola-BR and BR:** hazard ratios applied to L-MIND trial data based on MAIC **R-GemOx:** lognormal distributions based on RE-MIND2
Utilities	Previous NICE appraisal TA559
Costs and resource use	NHS reference costs, PSSRU Unit Costs of Health and Social Care, previous NICE appraisals, clinical trial and observational data, disease treatment guidelines
Adverse event incidence	**TAFA + LEN:** L-MIND **Pola-BR and BR:** GO29365 trial **R-GemOx:** Mounier et al., 2013

Abbreviations: PSSRU, Personal Social Services Research Unit

Company base case model survival extrapolations

Figure 10 Company base case OS extrapolations

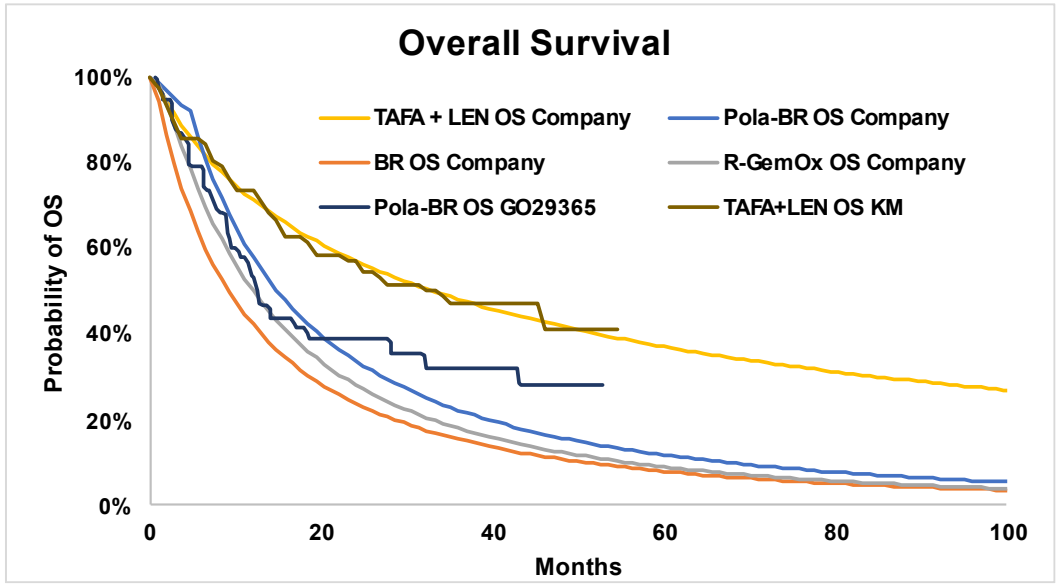
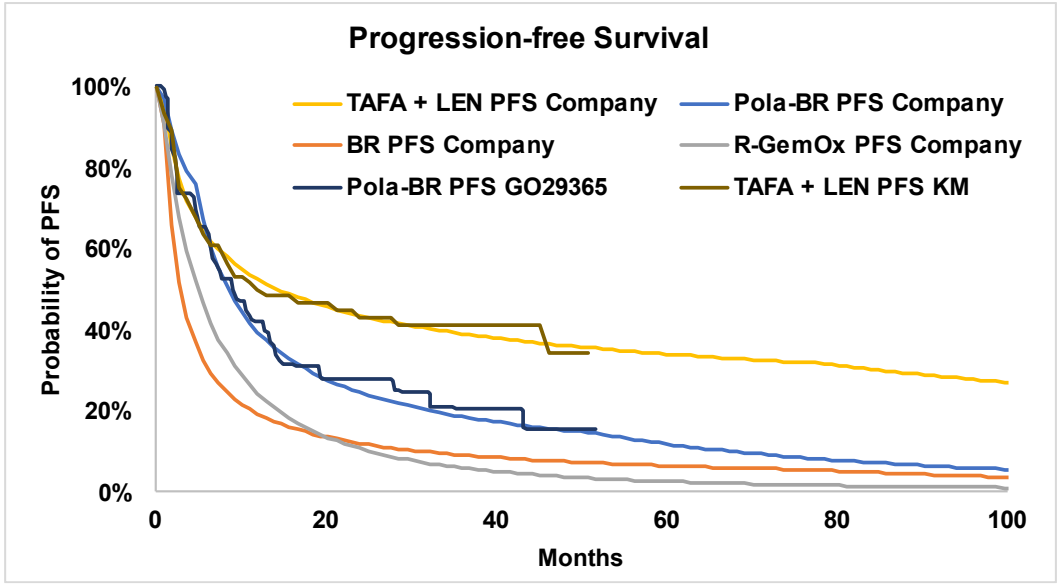


Figure 11 Company base case PFS extrapolations



GO29365 data above was digitised from the latest available Kaplan-Meier curves from Sehn 2022

Table 11 Data source and extrapolations used for OS/PFS outcomes in the company base case model

Treatment	OS extrapolation	PFS extrapolation
TAFA + LEN	Lognormal (L-MIND)	Generalised gamma (L-MIND)
Pola-BR	Time-varying HRs, 4-month split (MAIC) Up to 4 months: 1.82; After 4 months: 0.41	Time-varying HRs, 4-month split (MAIC) Up to 4 months: 1.42; After 4 months: 0.39
BR	Constant HR of 0.39 (MAIC)	Constant HR of 0.35 (MAIC)
R-GemOx	Lognormal (RE-MIND2)	

Abbreviations: HR, hazard ratio *HR<1 indicates greater efficacy for TAFA + LEN; inverse HRs used to generate curves

Key issue 3: Validity of pola-BR survival extrapolations (1)

Clinical validity of OS/PFS parametric extrapolations for pola-BR

Background

- ERG largely aligned with company on the OS/PFS extrapolations for BR and R-GemOx, focus on pola-BR
- Clinical opinion also suggests that pola-BR is the main comparator for tafasitamab with lenalidomide

Company

- RE-MIND2 data does not align with GO29365 data (used in TA649), not appropriate to use for pola-BR
- Time-varying HRs (MAIC) is most appropriate to use as PH assumption is violated for constant HR (MAIC)
  - 4-month split reflects change in hazards and other clinical factors, 11-month split provided as scenario
- Comparison with UK RWE (Northend) and Japanese trial (Terui) suggests company's estimates more plausible

ERG comments

- RE-MIND2 not aligned with TA649 results, treatment effect estimated unclear
- Time-varying HRs (MAIC) implies effect of pola-BR wanes vs BR, underestimates outcomes for pola-BR compared with TA649, 4-month change in hazards unclear
- Constant HR (MAIC) overestimates outcomes (conservative for TAFA + LEN), but results are closest to TA649; Northend/Terui comparisons interpreted with caution
- **TA649; pola-BR:** 3.1 LYs, 2.1 QALYs (some uncertainty due to redaction)
- **Time-varying HRs (MAIC); pola-BR:** 2.2 LYs, 1.5 QALYs
- **Constant HR (MAIC); pola-BR:** 3.4 LYs, 2.2 QALYs

Clinical experts

- RE-MIND2 underestimates pola-BR outcomes
- Time-varying HRs (MAIC) appropriate, estimated outcomes are closer to the literature

Abbreviations: HR, hazard ratio; LY, life year; PH, proportional hazards; RWE, real-world evidence

Key issue 3: Validity of pola-BR survival extrapolations (2)

Figure 12 Company/ERG pola-BR OS extrapolations

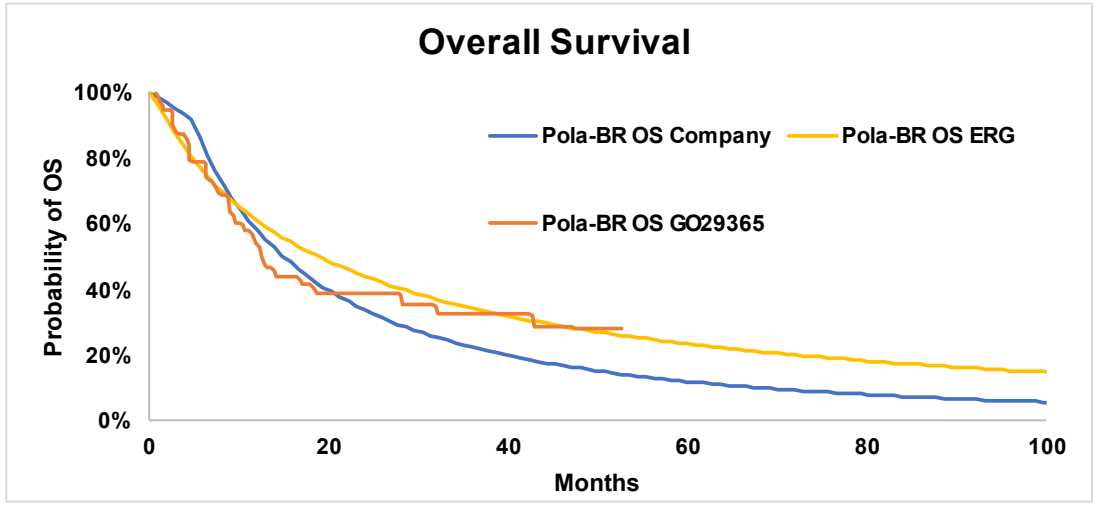
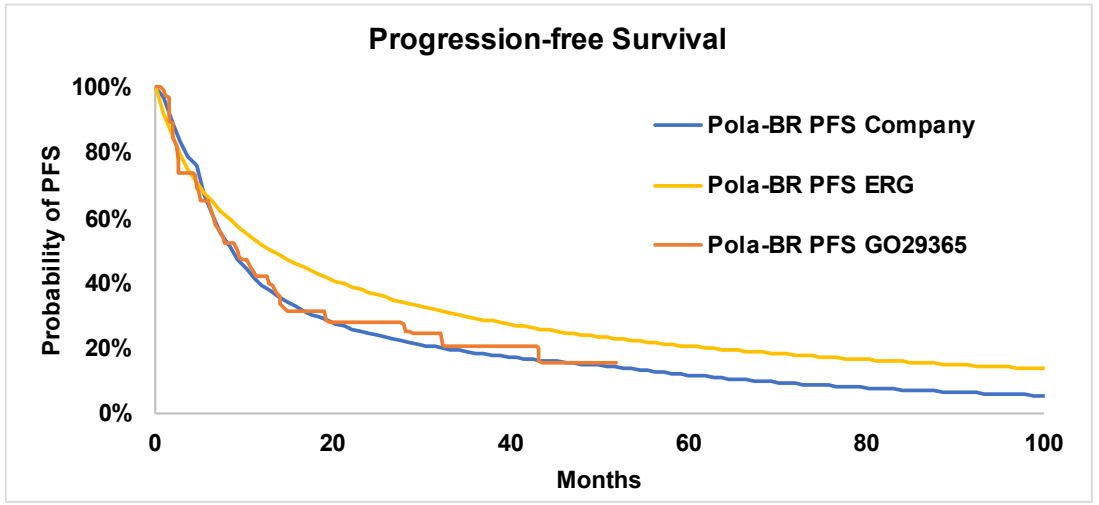


Figure 13 Company/ERG pola-BR PFS extrapolations



GO29365 data above was digitised from the latest available KM curves from Sehn 2022

Table 12 Comparison of MAIC-based extrapolations against recently published data for pola-BR

Outcome	Company base-case	ERG base-case	GO29365 (Sehn 2022) (N=40)	Northend 2022 - stand-alone* (N=78)	Northend 2022 - all patients (N=131)	Terui 2022 (N=35)
Median OS, months	14.8	18.7	12.4 (9.0-32.0)	10.2 (5.2-14.3)	8.2 (5.9-14.3)	NR (8.4-NE)
OS at 1 year	58%	61%	~54%	NA	~43%	~59%
Median PFS, months	10.8	15.3	9.2 (6.0-13.9)	5.4 (3.0-10.8)	4.8 (3.7-9.3)	5.2
PFS at 1 year	39%	52%	42%	NA	~28%	~38%

Which OS/PFS extrapolations for pola-BR are more robust for decision making?

*No planned bridge to CAR-T/SCT

Key issue 4: Validity of TAFA + LEN PFS extrapolation

Clinical validity of PFS parametric extrapolations for TAFA + LEN

Background

- ERG is aligned with company on the OS extrapolation for tafasitamab with lenalidomide

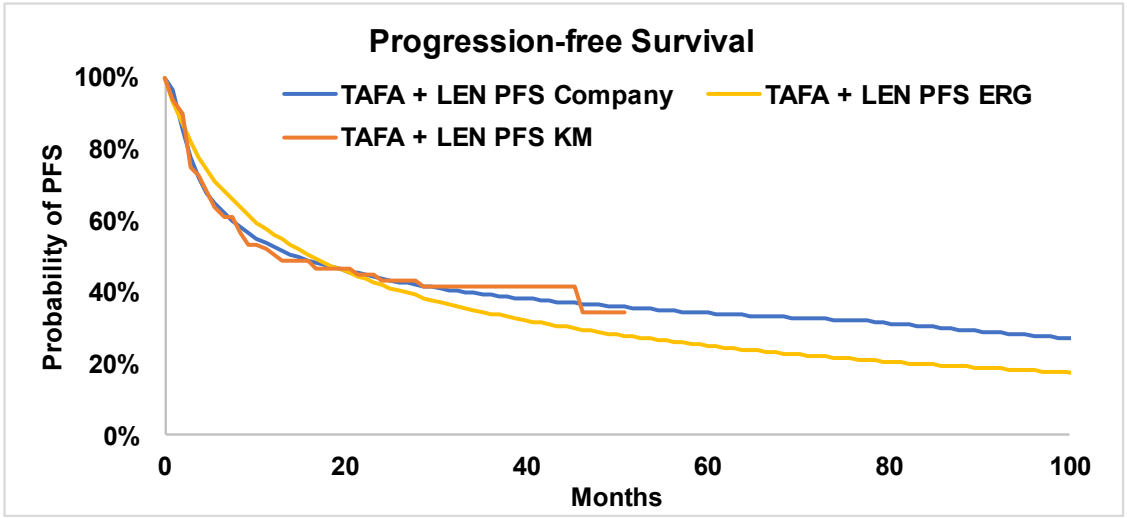
Company

- Company chose generalised gamma distribution for PFS based on statistical and visual fit to observed data
- Lognormal distribution resulted in poor statistical and visual fit to the data, but explored in scenario analysis as most aligned with clinical expert expectations for long-term PFS and hazard profiles for TAFA+LEN

ERG comments

- Recognises uncertainty but disagrees with generalised gamma
- Generalised gamma overpredicts long-term PFS, hazard profile inconsistent with company expert predictions
- Lognormal overestimates PFS for 20 months, but provides the smallest overestimation, better than long-term overestimation

Figure 14 Company/ERG TAFA + LEN PFS extrapolations



Which PFS extrapolation for TAFA + LEN is more appropriate for decision making?

Key issue 5: End-of-life criteria (1)

Unclear if life expectancy with pola-BR would be less than 24 months

End-of-life criteria

1. Patients face a short life expectancy, normally less than 24 months
2. Treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatment

Company

- People with R/R DLBCL have a life expectancy of 3 to 9 months, are limited to palliative care
- SLR by Thuresson et al. 2020 found median OS across different treatments ranged from 5.0 to 22.2 months
- RE-MIND2 median OS (pooled cohort) was 11.6 months [8.8, 16.1]
- GO29365 study for pola-BR reported an updated median OS of 12.4 months [9.0, 32.0]

Clinical experts

- Shared studies which indicated median OS for pola-BR for R/R DLBCL as between 8.2 and 12.5 months
- Consider that end of life criteria are met

ERG comments

- Some references shared to support criterion 1 were of limited relevance and/or poor quality
- **Criterion 1 not met with pola-BR as comparator:** TA649 estimated 3.08 LYs (discounted), company base case estimates 2.43 LYs and ERG base case estimates 4.03 LYs (undiscounted), all exceeding 24 months
- **Criterion 2 met:** company base case undiscounted TAFA + LEN mean LY gains 3.97 vs. pola-BR; 4.66 vs. BR; 4.41 vs. R-GemOx

Key issue 5: End-of-life criteria (2)

Summary of data for end-of-life criterion 1

Figure 15 Modelled and published OS for pola-BR

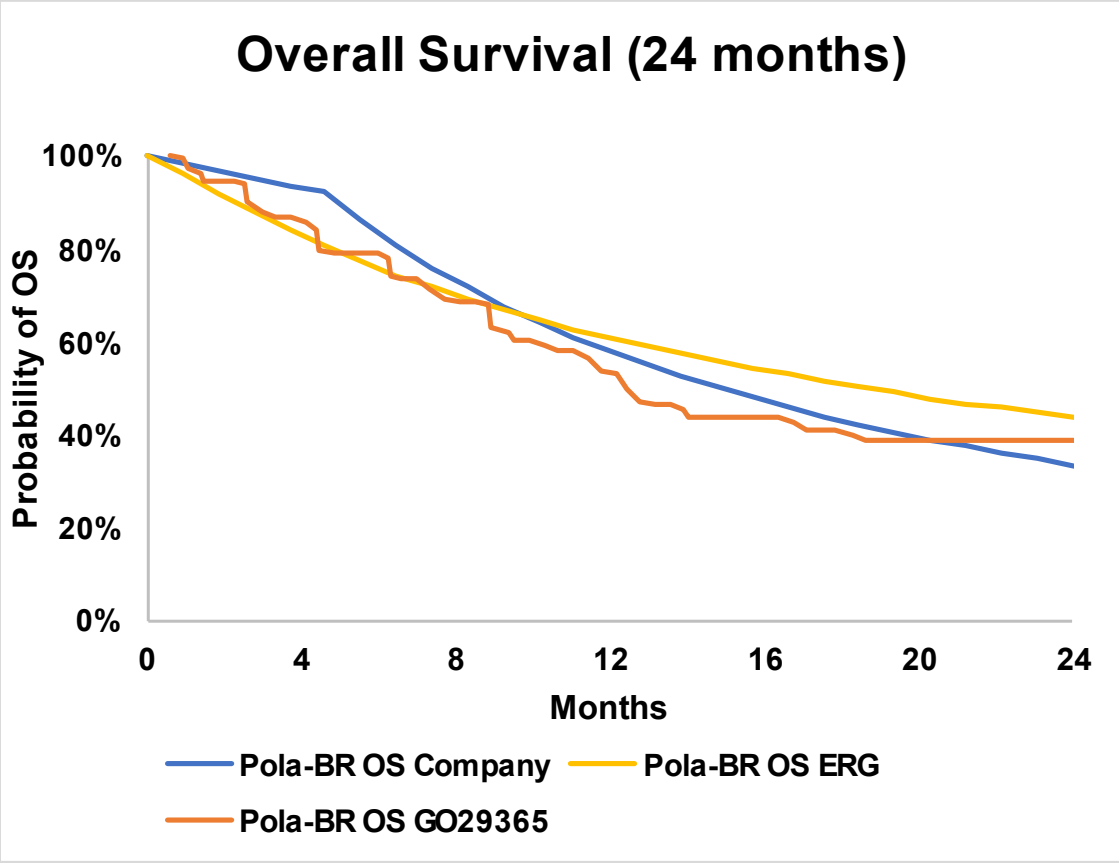


Table 13 Evidence on end-of-life criterion 1

Data source	Average OS	% alive at 24 months
Literature	**Median OS:** 8.2 to 12.5 months	-
GO29365 (Sehn 2022)	**Median OS:** 12.4 months	38%
TA649	**Mean OS:** 37 months (discounted)	-
Company model	**Mean OS:** 29 months (undiscounted)	34%
ERG model	**Mean OS:** 48 months (undiscounted)	44%

GO29365 data from Sehn 2022

Is expected survival with pola-BR less than 24 months?
Does TAFA + LEN extend survival by at least 3 months vs. pola-BR?
Does tafasitamab with lenalidomide meet the end-of-life criteria?

Other clinical and cost effectiveness issues
SLR best practices and adverse event data

Table 15 Other issues

Issue	Resolved?	ICER impact
The SLR of clinical effectiveness evidence adopted a limited date range and data extraction methods did not follow best recommended practices • Clinical effectiveness searches adopted a 2010+ date limit, the ERG believes that a longer date range might have been beneficial • The ERG considers that data extraction was not performed in line with best recommended practice and as such, the outcome data and resulting estimates may be subject to error	No	Unknown
ERG noted the paucity of adverse event data in L-MIND and MOR208C201, adding that it is unclear if results are for FAS or safety population	No	Small

Abbreviations: FAS, full analysis set; SLR, systematic literature review

Summary of company and ERG base case assumptions

Key ERG assumptions involve updated survival extrapolations

Table 16 Assumptions in company and ERG base cases

Assumption	Company base case	ERG base case
Pola-BR OS	MAIC with time-varying hazard ratio	MAIC with constant hazard ratio
Pola-BR PFS	MAIC with time-varying hazard ratio	MAIC with constant hazard ratio
Tafasitamab with lenalidomide PFS	Generalised gamma distribution (L-MIND)	Lognormal distribution (L-MIND)

Figure 16 Modelled survival curves for company base case

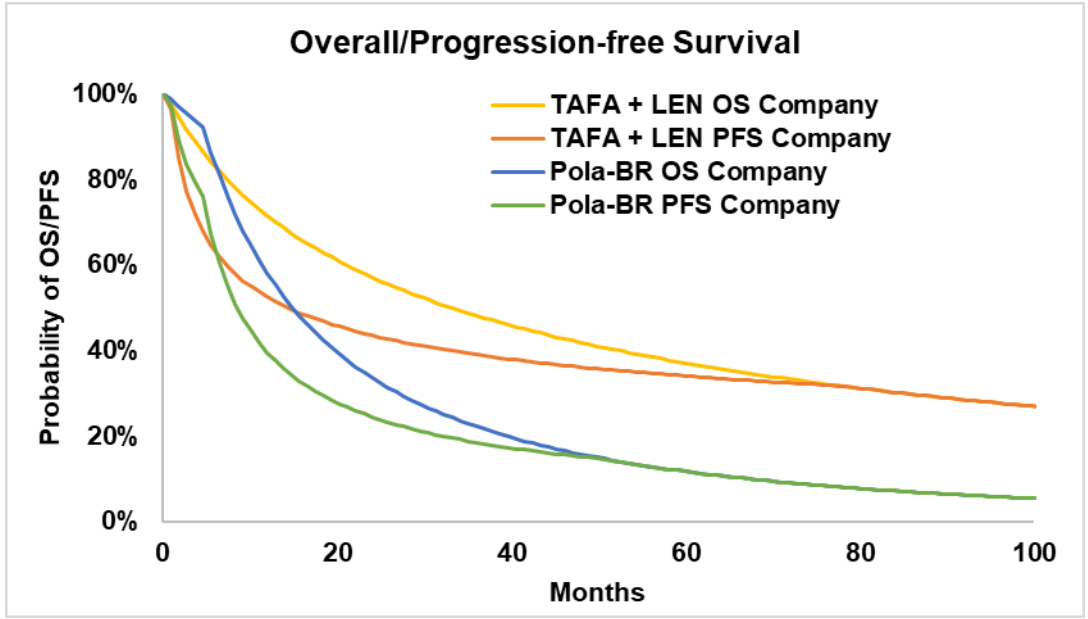
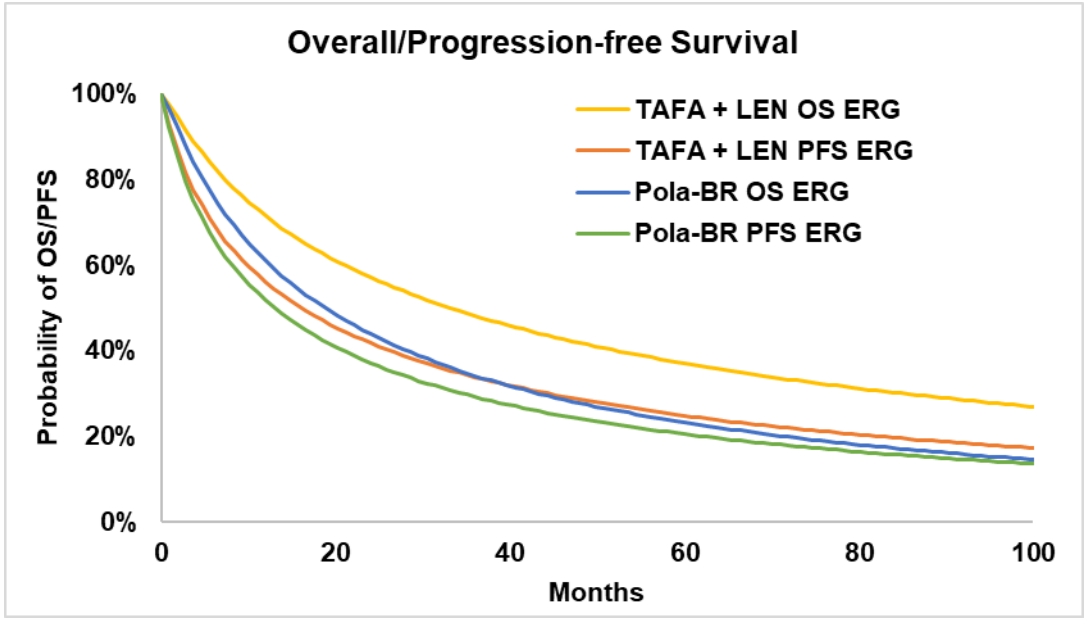


Figure 17 Modelled survival curves for ERG base case



Company and ERG base case results

Table 17 Deterministic incremental company base case results (tafasitamab PAS, list price for all other treatments)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Pairwise ICER (£/QALY)
R-GemOx	[redacted]	1.82	1.16				[redacted]
BR	[redacted]	1.60	1.04	[redacted]			[redacted]
Pola-BR	[redacted]	2.20	1.45	[redacted]			[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	[redacted]	[redacted]	

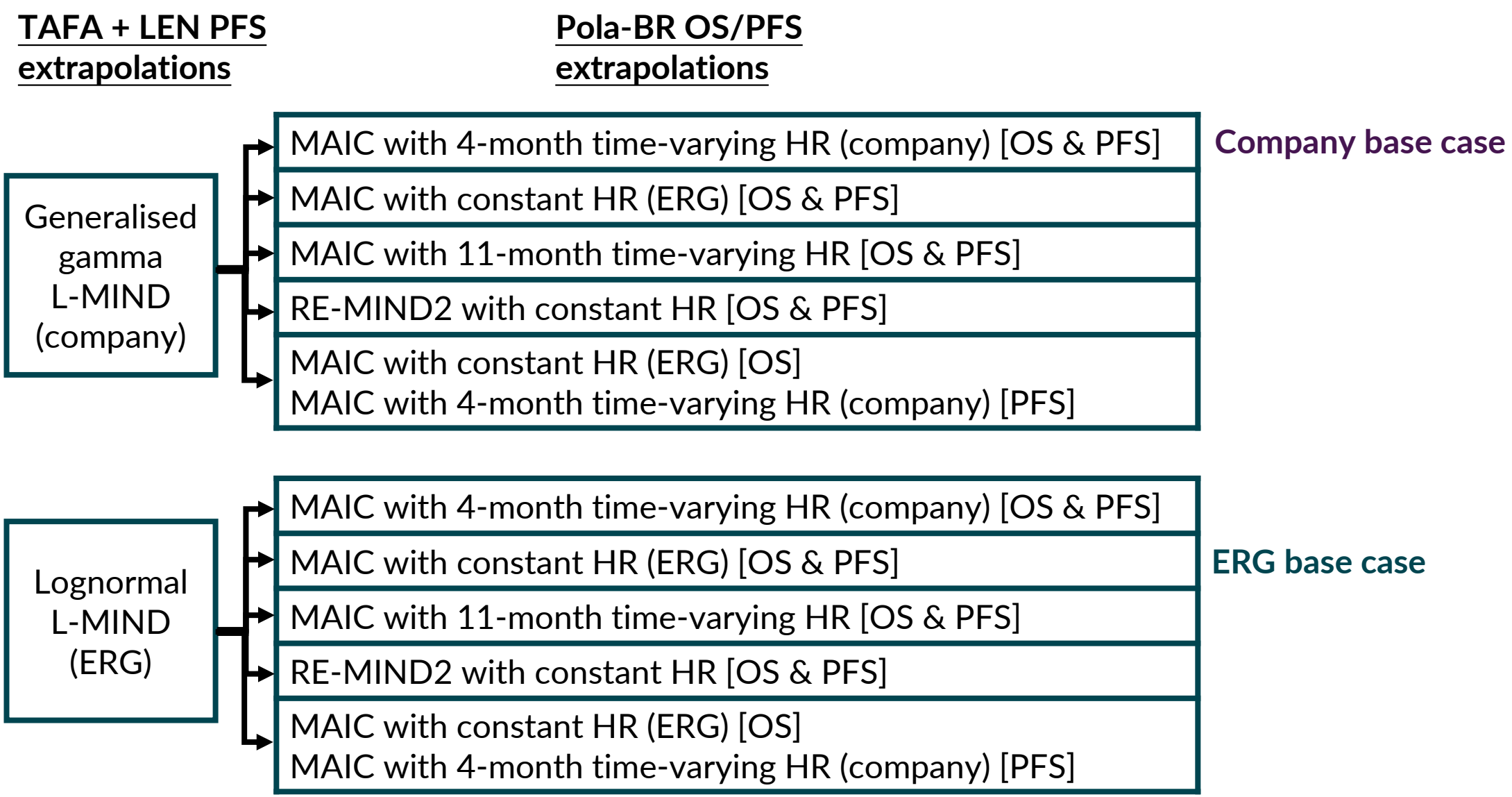
Table 18 Deterministic incremental ERG base case results (tafasitamab PAS, list price for all other treatments)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Pairwise ICER (£/QALY)
R-GemOx	[redacted]	1.82	1.16				[redacted]
BR	[redacted]	1.60	1.02	[redacted]			[redacted]
Pola-BR	[redacted]	3.36	2.20	[redacted]	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	[redacted]	[redacted]	

Results do not include confidential commercial discounts for lenalidomide, comparators, co-medications and subsequent treatments

Abbreviations: PAS, patient access scheme

Key cost-effectiveness scenarios



All ICERs are reported in PART 2 slides because they include confidential commercial discounts

Other considerations

Tafasitamab with lenalidomide was designated as innovative by the MHRA

Equality considerations

- There are no known equality issues relating to the use of tafasitamab in patients with relapsed/refractory DLBCL who are not eligible for ASCT

Innovation

- Tafasitamab awarded Promising Innovative Medicines designation by the MHRA
- MHRA upheld the EMA orphan designation after EMA and MHRA assessed that DoR could be clinically relevant and supportive of a significant benefit over Pola+BR (based on MAIC analysis)
- Clinical experts consider tafasitamab with lenalidomide to be innovative, though not necessarily a step change

Abbreviations: EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency

NICE National Institute for Health and Care Excellence

Thank you.