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

For public observers – ACIC information redacted [redacted]

Second appraisal committee meeting

Technology appraisal committee C [02 August 2022]

Chair: Stephen O'Brien

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Owen Swales, Louise Crathorne, Ross Dent

Company: Incyte

NICE

TAFA + LEN for R/R DLBCL

→ **About**

- Clinical evidence
- Points to consider:
  - Consultation responses
  - ITCs and pola-BR survival extrapolations
  - End-of-life criteria
- ICERs
- Other considerations: equality; innovation; uncaptured benefits
- Summary

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Abbreviations: ICERs, incremental cost-effectiveness ratios; ITCs, indirect treatment comparisons; R/R DLBCL, relapsed or refractory diffuse large B-cell lymphoma

Tafasitamab (Minjuvi, Incyte)

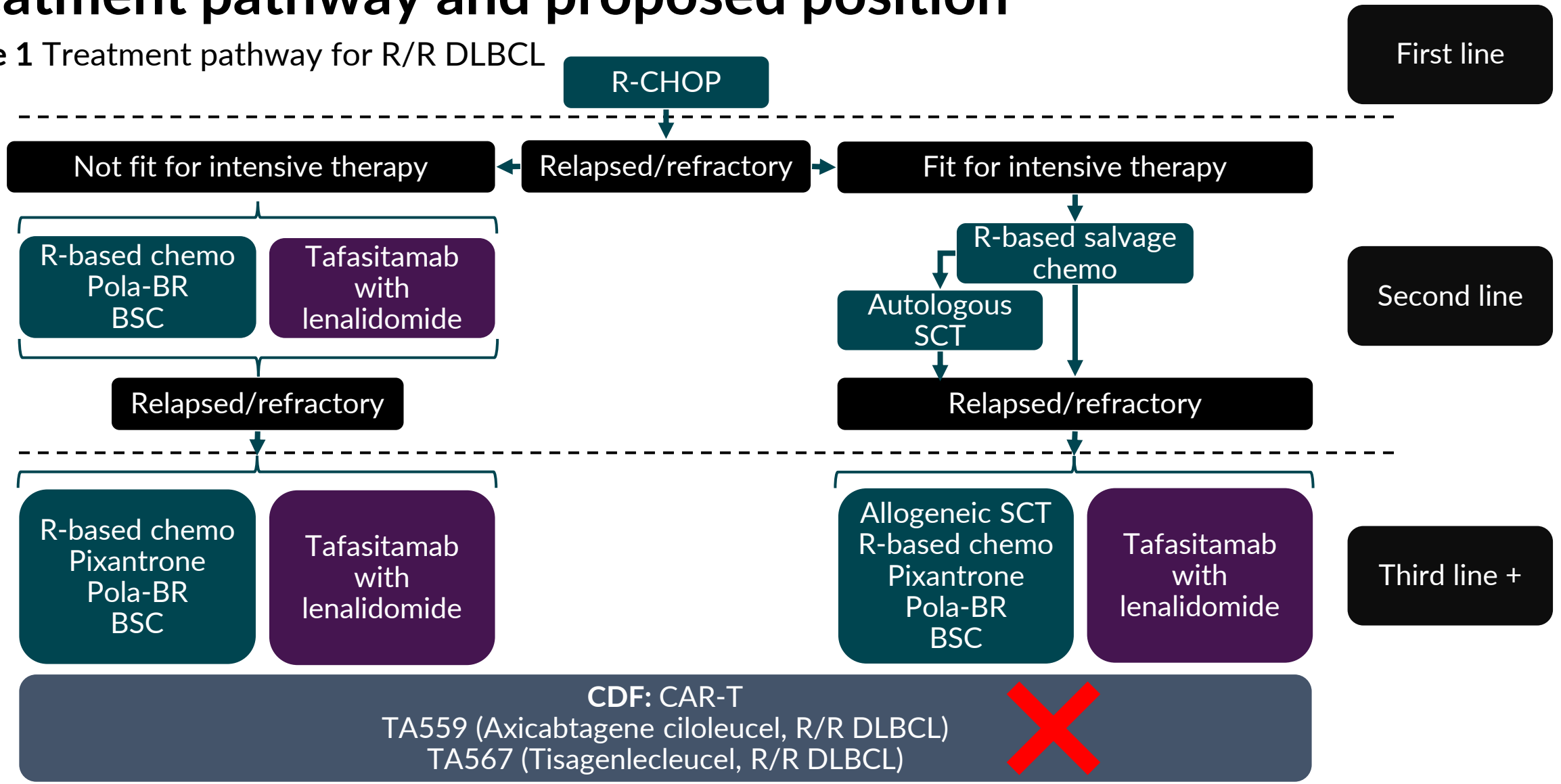
Table 1 Technology details

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 and was increased at consultation

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

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

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

Table 2 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

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

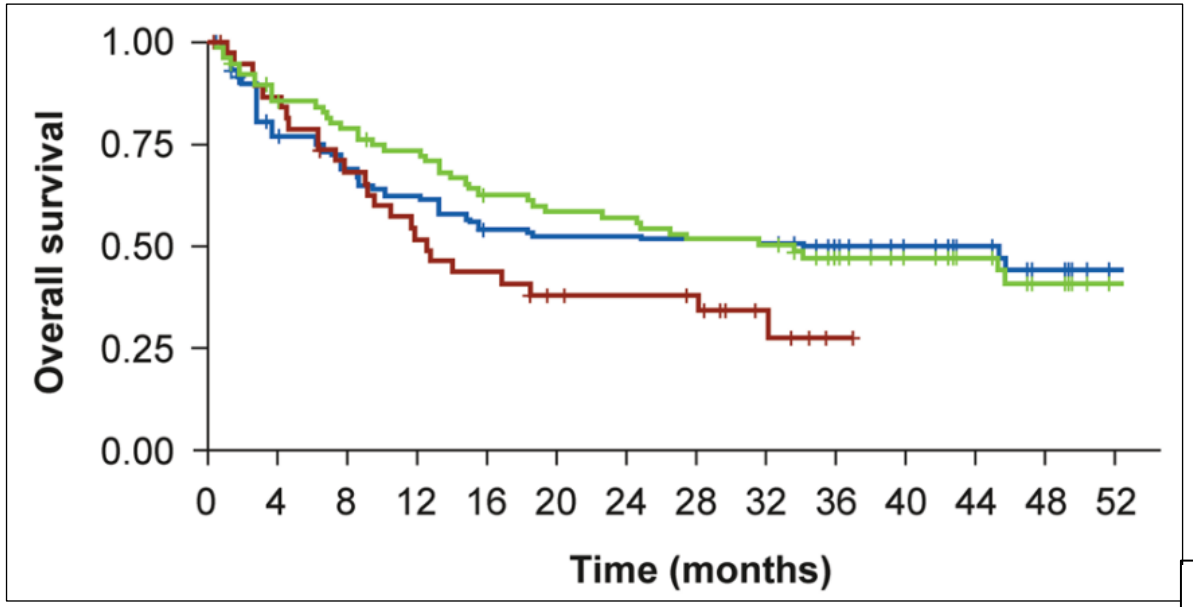
Table 3 Overview of indirect treatment comparison approaches

	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

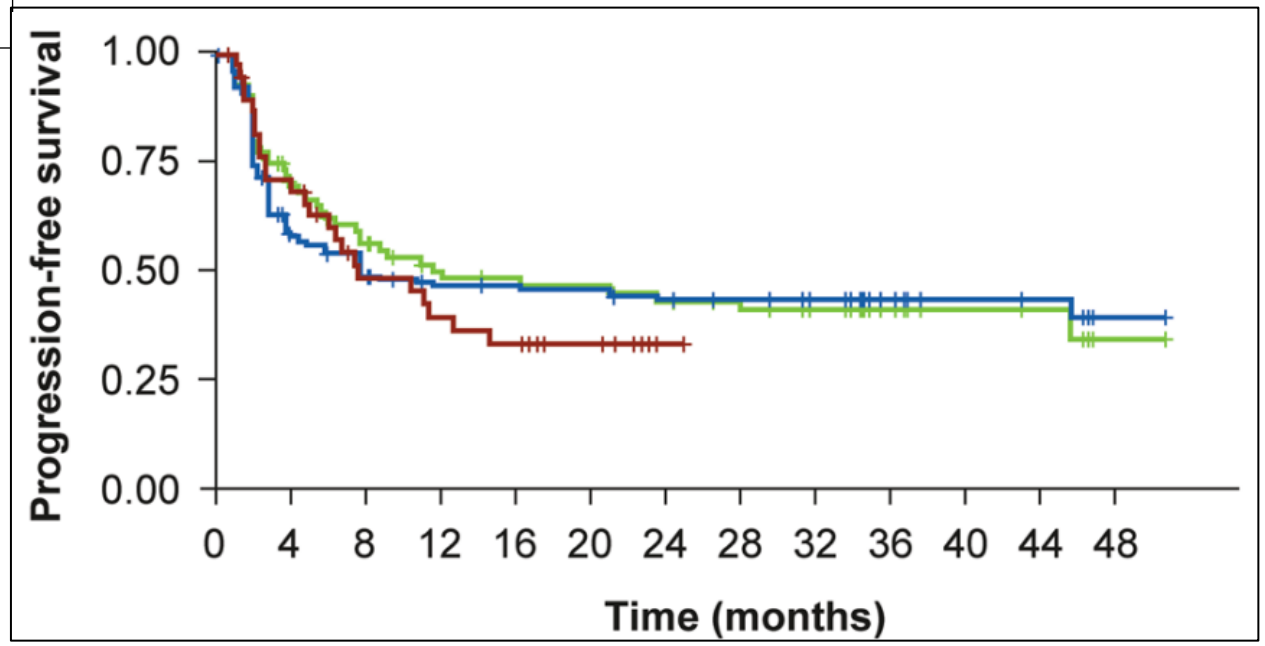
Pola-BR survival outcomes vs. TAFA + LEN from MAIC

Figure 3 MAIC OS for TAFA + LEN vs pola-BR



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

Figure 4 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 4 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 (constant hazard ratio)	**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

Company base case model survival extrapolations

Figure 5 Company base case OS extrapolations

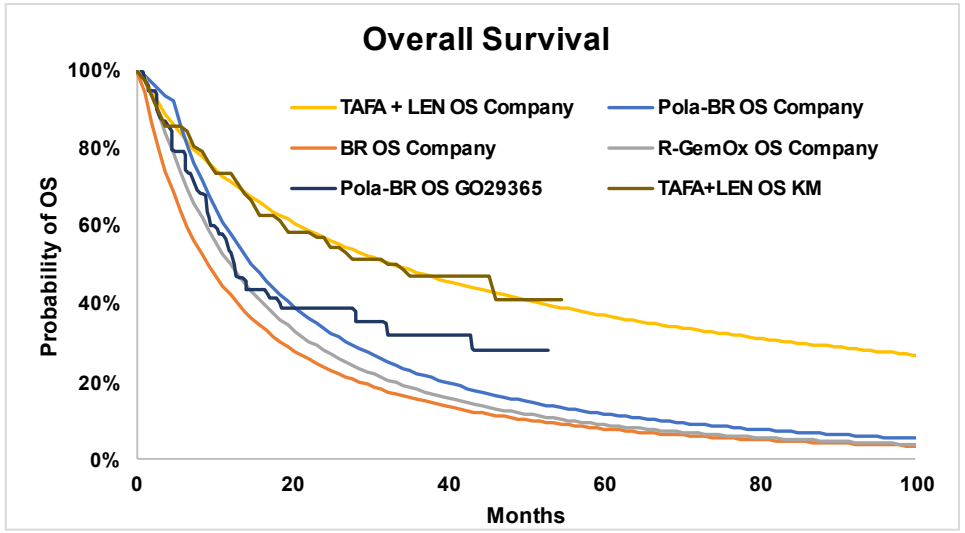
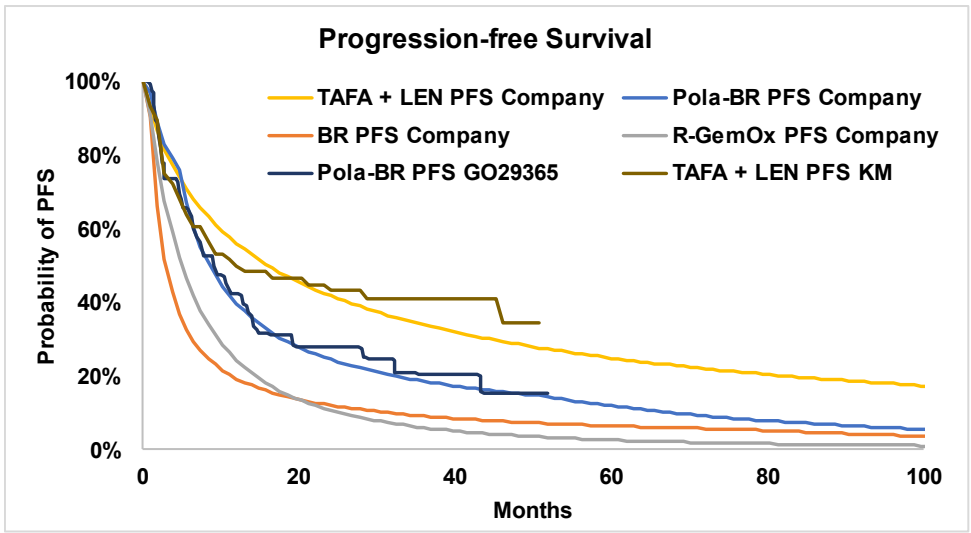


Figure 6 Company base case PFS extrapolations



GO29365 data digitised from Sehn 2022 Kaplan-Meier curves; company extrapolations based on Sehn 2020 (latest available at submission)

Table 5 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)	
Pola-BR	Time-varying HRs, 4-month split (MAIC) Up to 4 months: 1.82 [0.58, 5.65] After 4 months: 0.41 [0.19, 0.90]	Time-varying HRs, 4-month split (MAIC) Up to 4 months: 1.42 [0.65, 3.09] After 4 months: 0.39 [0.14, 1.06]
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

TAFA + LEN for R/R DLBCL

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Consultation responses

Comments received from:

- Incyte (company)
- NCRI, ACP, RCP, RCR (professional organisations)
- Members of the public

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

Patient and professional organisation consultation comments
Summary of responses

Interpretation of the evidence on end-of-life criteria is not reasonable:

- Survival with pola-BR is less than 12-18 months
- The 24 months overall survival probability for pola-BR was only 38% (Sehn 2022)
- The trial data, subsequent data from extended cohort analysis, and Northend 2022 does not suggest average OS of 24 months with pola-BR
- The survival times for people who have pola-BR used in the modelling does not reflect the estimated survival in NICE's guidance on pola-BR (TA649)
- Outcomes for pola-BR seen in the GO29365 trial cannot be replicated in the real world, the Northend 2022 data is more appropriate
- Committee seems to have given excessive weighting to survival assumptions made during TA649 for pola-BR

Cancer Drugs Fund:

- Could tafasitamab with lenalidomide be entered into the Cancer Drugs Fund so longer follow up data and real world data can be gathered?

Abbreviations: OS, overall survival

Key issues
Clinical data and end-of-life criteria

Table 6 Key issues

Issue	Resolved?	ICER impact
1. Which indirect treatment comparison approach is most robust for decision making?	No	Unknown
2. Which OS and PFS extrapolations for pola-BR are most appropriate for decision making?	No	Large
3. Does tafasitamab with lenalidomide meet the end-of-life criteria?	No	N/A

Note: the company accepted the committee's preferred PFS extrapolation for tafasitamab with lenalidomide and is reflected in the presented company base case, representing a resolved key issue

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

Key issue 1: Validity of indirect treatment comparisons

Unclear what type of treatment effect is being estimated

Issue background

- Uncertainty about the methods used for RE-MIND2 because the baseline characteristics of the tafasitamab with lenalidomide cohort varied depending on the comparator, potentially causing bias
- Unclear what type of treatment effect is estimated in RE-MIND2, ITC results are very uncertain

Company ACD response

- The indirect treatment comparisons rigorously followed NICE TSD 17 and 18 guidelines
- The same modelling approach was used for all comparators, EMA/MHRA accepted MAIC results (for DoR)
- Despite limitations, relative efficacy estimates derived using indirect evidence provided consistent results
- Baseline characteristics of matched TAFA + LEN cohort varied where patients could not be matched

ERG comments

- As no additional evidence has been submitted, previous ERG comments still stand that the "average treatment effect on the treated" (ATT) was not estimated (as recommended by NICE TSD 17)
- Instead it appears that what was estimated was the "average treatment effect on the treated patients for whom a comparator patients could be found", questioning the validity of the results
- In addition to MAIC, additional analyses using IPD from RE-MIND2 were conducted for pola-BR

Which ITC approach is most robust for decision making?

Abbreviations: EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; TSD, technical support document

Key issues
Clinical data and end-of-life criteria

Table 7 Key issues

Issue	Resolved?	ICER impact
1. Which indirect treatment comparison approach is most robust for decision making?	No	Unknown
2. Which OS and PFS extrapolations for pola-BR are most appropriate for decision making?	No	Large
3. Does tafasitamab with lenalidomide meet the end-of-life criteria?	No	N/A

Note: the company accepted the committee's preferred PFS extrapolation for tafasitamab with lenalidomide and is reflected in the presented company base case, representing a resolved key issue

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

Key issue 2: Validity of pola-BR survival extrapolations

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

Issue background

- Survival benefit for pola-BR underestimated compared to TA649 and expert opinion (vs BR alone)
- Committee wanted to see different approaches that fitted underlying hazards and were aligned with TA649

Company ACD response

- During ACM1, experts indicated that the company's pola-BR OS and PFS extrapolations were more plausible
- Northend 2022 data is preferred to GO29365 (Sehn 2022) due to larger sample size and some pola-BR patients receiving CAR-T treatment in Sehn 2022 (9 patients at follow-up, not clear for randomised cohort)
- Aligning OS to GO29365 (Sehn 2022) may bias results in favour of pola-BR due to CAR-T use
- Company's PFS extrapolation for pola-BR is closer to PFS for the randomised cohort in the Sehn 2022

ERG comments

- Company extrapolations imply a treatment waning for pola-BR vs BR (OS curves get closer over time), no clear rationale, leads to underestimation of pola-BR versus BR, and possibly versus TAFA + LEN
- Agree Sehn 2022 OS results may be biased in favour of pola-BR, but effect not expected to be large
- TA649 survival estimates for pola-BR seem to be invalid, unclear what the long-term benefit of pola-BR is vs BR alone and R-GemOx, highly uncertain to estimate cost effectiveness of tafasitamab with lenalidomide
- Including more recently available studies (e.g. Northend 2022 and Sehn 2022) could help reduce uncertainty

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

Abbreviations: ACM1, first appraisal committee meeting; CAR-T, Chimeric Antigen Receptor Cell Therapy

Key issues
Clinical data and end-of-life criteria

Table 8 Key issues

Issue	Resolved?	ICER impact
1. Which indirect treatment comparison approach is most robust for decision making?	No	Unknown
2. Which OS and PFS extrapolations for pola-BR are most appropriate for decision making?	No	Large
3. Does tafasitamab with lenalidomide meet the end-of-life criteria?	No	N/A

Note: the company accepted the committee's preferred PFS extrapolation for tafasitamab with lenalidomide and is reflected in the presented company base case, representing a resolved key issue

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

Key issue 3: 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

Issue background

- Committee concluded criterion 2 is met
- Committee concluded criterion 1 is not met as pola-BR survival estimated at around 4 years in TA649

Company ACD response

- Clinical experts agree that normal survival expectations are below 24 months with pola-BR in the UK
- 4 year survival is a substantial overestimate for patients with R/R DLBCL not eligible for transplant
- GO29365 data (Sehn 2022) and UK real world data (Northend 2022) not available when TA649 published
- Additional evidence shows pola-BR survival lower than that observed in GO29365 for TA649, median survival estimated between 10.2 months (Northend 2022) and 12.4 months (Sehn 2022)
- Criterion 1 includes “normally” with no further information, therefore this could mean:
  - 24 months life expectancy for the majority of the patient population
  - Flexibility in the 24 month threshold
- Latest evidence and clinical expert opinion shows that criterion 1 is met with pola-BR

Key issue 3: End-of-life criteria (2)

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

NICE technical team

- Mindful of the appeal panel conclusions for short life expectancy criterion as part of TA788:
- *"The appeal panel, therefore, do not accept the argument advanced by the appraisal committee that the mean survival of 24 months must be used as the threshold for application of end of life criteria"*
- *"Key stakeholders of NICE would consider it unreasonable to state that life-expectancy was not 'normally less than 24 months', even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months."*
- *"The appeal panel agreed that a totality of the data and analysis have to be looked at when considering if life expectancy is 'normally less than 24 months'."*

ERG comments

- As no additional evidence has been submitted, previous ERG comments still stand: "depending on the comparator being considered, TAFA + LEN may not meet criterion 1 of the NICE EOL criteria"
- Interpretation of evidence and the term "normally" by the committee are outside the remit of the ERG
- **Relevant responses for key issue 2:**
- TA649 survival estimates for pola-BR seem to be invalid, unclear what the long-term benefit of pola-BR is
- Including more recently available studies (e.g. Northend 2022 and Sehn 2022) could help reduce uncertainty
- GO29365 data (Sehn 2022) OS results may be biased in favour of pola-BR due to patients receiving subsequent treatment with CAR-T, but effect not expected to be large

Key issue 3: End-of-life criteria (2)

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

Figure 7 Modelled and published OS for pola-BR

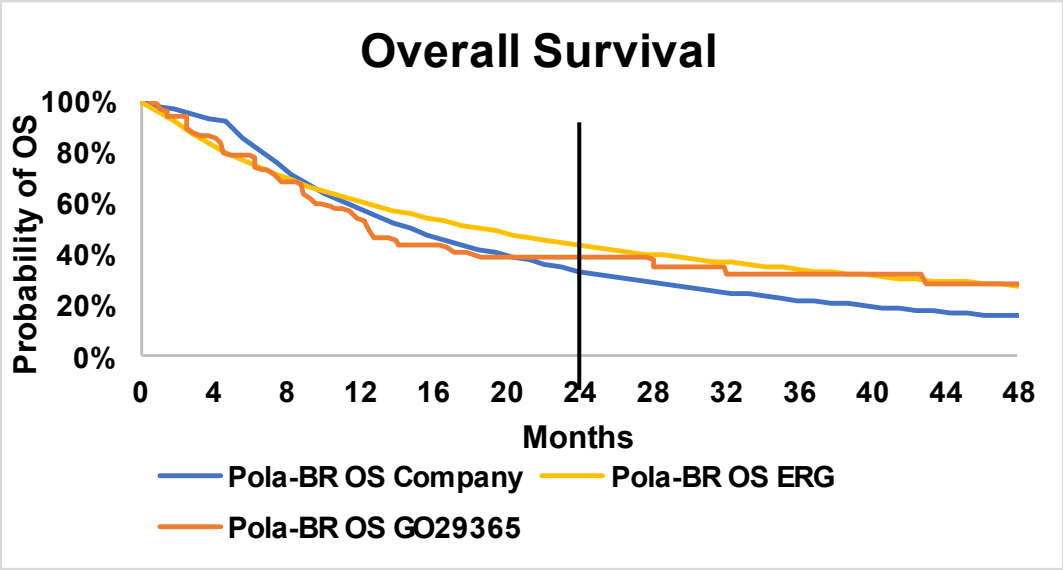


Table 9 Evidence on end-of-life criterion 1

Data source	Average OS	% alive at 24 months
Literature	**Median OS:** 8.2 to 12.5 months	-
Sehn 2022	**Median OS:** 12.4 months	38%
Northend 2022	**Median OS:** 10.2 months (stand-alone)	-
TA649	**Mean OS:** 37 months (discounted)	-
Company model	**Mean OS:** 29 months (undiscounted)	34%
ERG model	**Mean OS:** 48 months (undiscounted)	44%

GO29365 data digitised from Sehn 2022 Kaplan-Meier curves; company extrapolations based on Sehn 2020 (latest available at submission)

Pola-BR patients receiving CAR-T therapy in Sehn 2022 (GO29365)

- 9 patients received CAR T-cell therapy after pola-BR
- For patients treated with CAR T-cell therapy after pola + BR, OS after treatment with pola-BR ranged from 11.5 to 28.0 months; 4 patients were still alive at publication
- For context, 40 patients in the entire cohort; not clear how many received CAR-T therapy and were in the randomised cohort, but may have biased survival among some patients in the pola-BR cohort

Does tafasitamab with lenalidomide meet the end-of-life criteria?

Summary of company and ERG base case assumptions

Key ERG assumptions involve updated pola-BR survival extrapolations

Table 10 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

Figure 8 Modelled survival curves for company base case

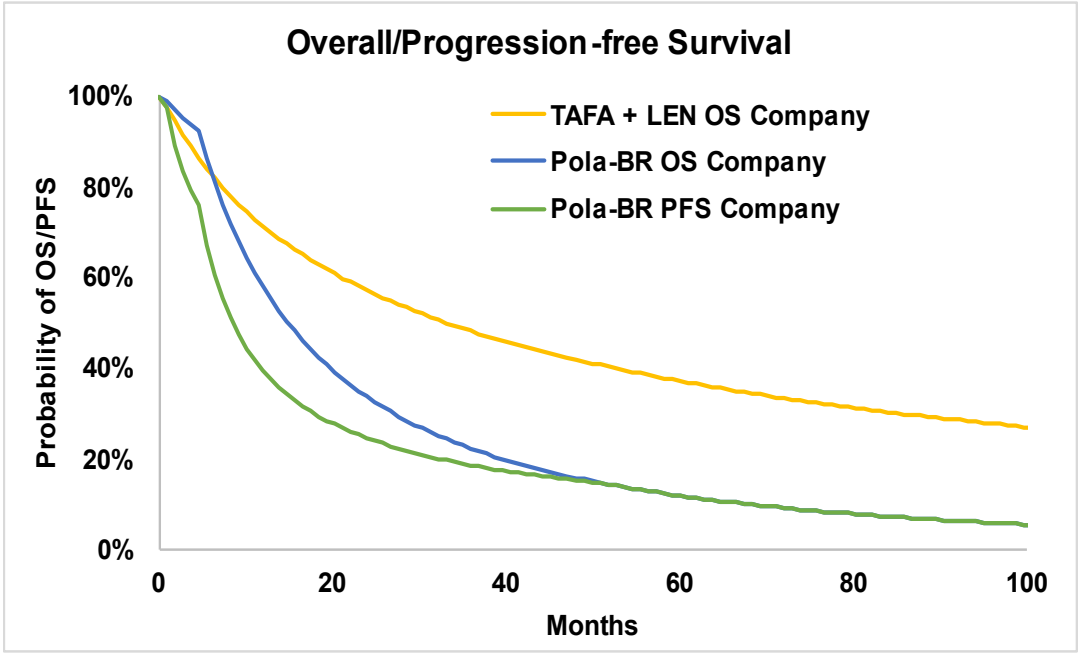
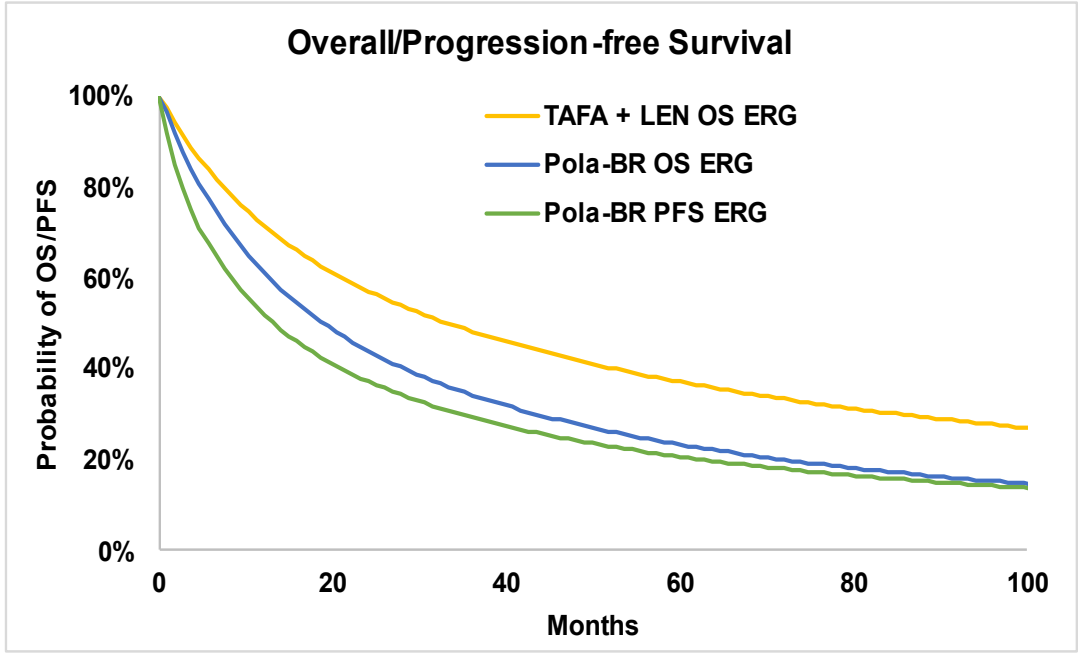


Figure 9 Modelled survival curves for ERG base case



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→ **ICERs**

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Company and ERG base case results

Table 10 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 11 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

Probabilistic cost-effectiveness results – company base case

Figure 10 PSA cost-effectiveness plane (tafasitamab PAS price, lenalidomide and polatuzumab list price)

Figure 11 PSA cost-effectiveness acceptability curve (tafasitamab PAS price, lenalidomide and polatuzumab list price)

At the common thresholds of £20,000, £30,000 and £50,000 per QALY gained, the estimated probability that TAFA + LEN is a cost effective alternative was: [redacted] for all comparators, [redacted] respectively for pola-BR only.

Deterministic cost-effectiveness scenarios (vs pola-BR)

	Pola-BR OS extrapolation	Pola-BR PFS extrapolation	ICER vs pola-BR (£/QALY)	Pola-BR total life years (discounted)	TAFA + LEN total life years (discounted)
1	MAIC with 4-month time-varying HR (company base case)		[redacted]	2.20	5.08
2	MAIC with constant HR (ERG base case)		[redacted]	3.36	5.08
3	MAIC with 11-month time-varying HR		[redacted]	2.04	5.08
4	RE-MIND2 with constant HR		[redacted]	1.77	5.08
5	MAIC with constant HR (ERG)	MAIC with 4-month time-varying HR (company)	[redacted]	3.36	5.08
6	MAIC with 4-month time-varying HR (company)	MAIC with constant HR (ERG)	[redacted]	2.20	5.08

ICERs reported in PART 2 slides include confidential commercial discounts

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→ **Other considerations: equality; innovation; uncaptured benefits**

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Other considerations (1)

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

Other considerations (2)
Benefits not captured in QALYs

Additional benefit of tafasitamab with lenalidomide not captured in the QALYs

Company ACD response
- In submissions to NICE, clinical experts considered that tafasitamab with lenalidomide may result in health-related benefits not captured in the QALY calculation
- MHRA Promising Innovative Medicines and orphan designation for tafasitamab could be supportive of a significant health benefit over pola-BR
- Tafasitamab has a different mechanism of action to other treatments, representing a shift in the treatment paradigm for R/R DLBCL, with the potential for longer treatment durations
- Lymphoma Action notes that effective treatments can reduce the impact of R/R DLBCL on patient anxiety and carer time and wellbeing
- Tafasitamab can be administered in an outpatient setting with minimal training required for its introduction

ERG comments
- Possible that tafasitamab with lenalidomide is associated with additional benefit that is not captured
- However, without a proper estimate of this assumed benefit, the ERG cannot assess the impact on the cost-effectiveness results

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; QALY, quality-adjusted life year

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Key issues
Clinical data and end-of-life criteria

Table 13 Key issues

Issue	Resolved?	ICER impact
1. Which indirect treatment comparison approach is most robust for decision making?	No	Unknown
2. Which OS and PFS extrapolations for pola-BR are most appropriate for decision making?	No	Large
3. Does tafasitamab with lenalidomide meet the end-of-life criteria?	No	N/A

Note: the company accepted the committee's preferred PFS extrapolation for tafasitamab with lenalidomide and is reflected in the presented company base case, representing a resolved key issue

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

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Thank you.