Eppur si muove...

La terapia nel MONDO LINFOMI

Studi RE-MIND e RE-MIND2

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ROMA, 26 MAGGIO 2022

Real-world data in drug development strategies for orphan drugs: Tafasitamab in B-cell lymphoma, a case study for an approval based on a single-arm combination trial

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Tafasitamab (TAF) plus lenalidomide (LEN) is a novel treatment option for patients with relapsed/refractory diffuse large B-cell lymphoma (rrDLBCL) who are not eligible for autologous stem cell transplantation. The initial US/EU approvals for TAF represent precedents because this is the first time that approval of a novel combination therapy was granted based on a pivotal single-arm trial (SAT). Matching real-world data (RWD) helped to disentangle the contribution of individual agents. In this review, we present the TAF development strategy, the prospective incorporation of RWD within the clinical development plan, the corresponding regulatory hurdles of this strategy, and the prior regulatory actions for other cancer drugs that previously incorporated RWD and propensity score matching in EU and US regulatory submissions. We also outline how RWD could further advance and impact orphan drug development.

https://doi.org/10.1016/j.drudis.2022.02.017

Please cite this article in press as: P. Serrano et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.02.017

TAFA-LENA: This is the first time that approval of a novel combination therapy was granted based on a pivotal single-arm trial (SAT)

- **RE-MIND:** to establish the effectiveness of LEN and the contribution of the two combination partners not previously approved in r/r DLBCL to the overall effect

- **RE-MIND2:** to characterize the effectiveness of tafasitamab + LEN in a real-world setting

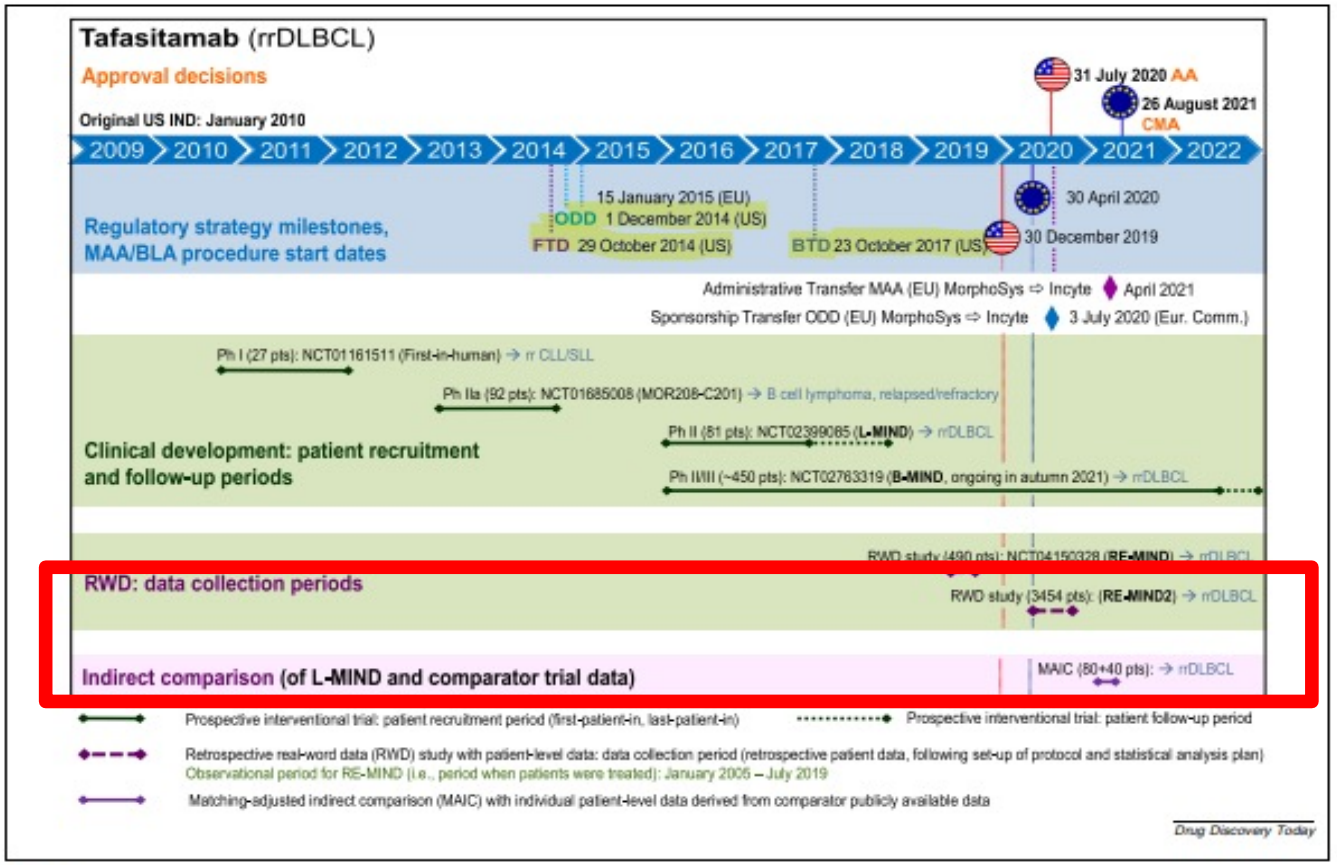


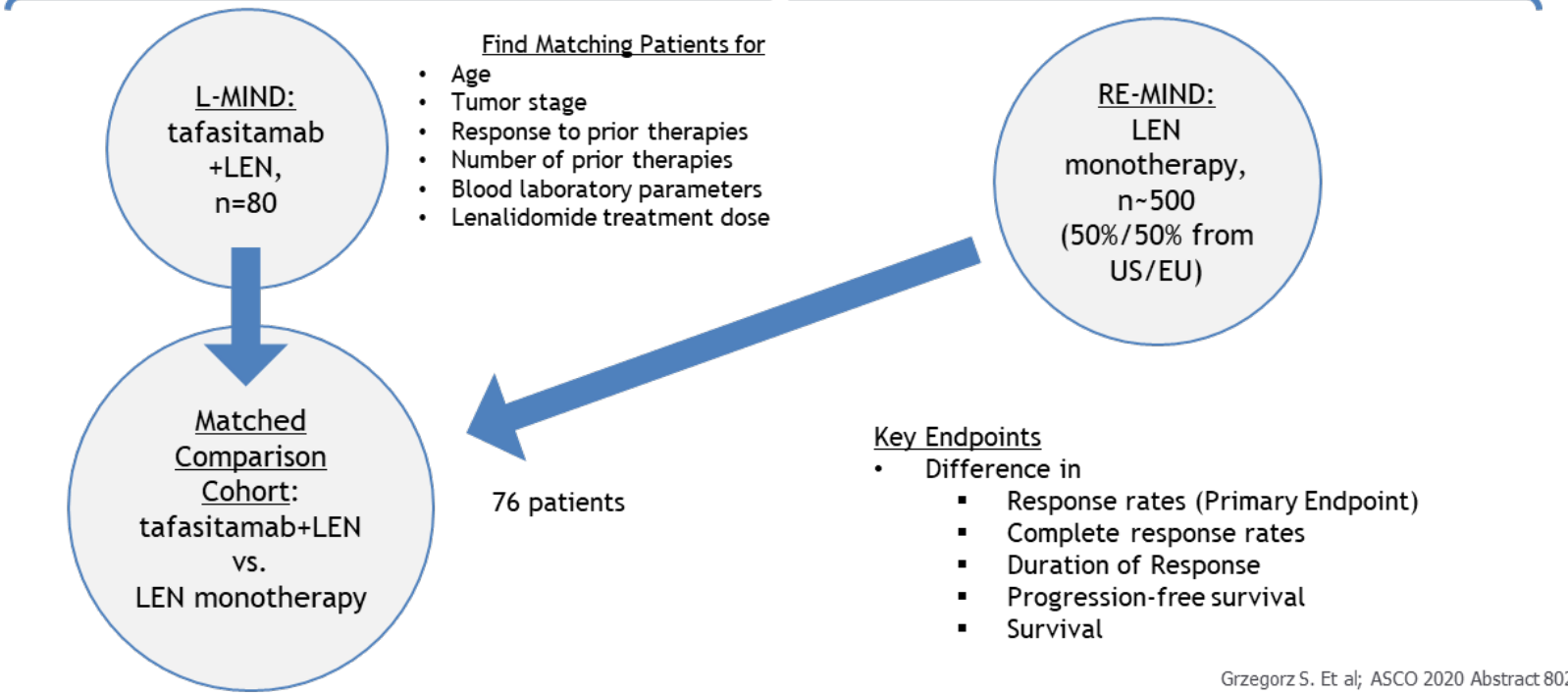
FIGURE 1
Regulatory strategy milestones, clinical trial recruitment periods and supporting real-world data (RWD) studies of tafasitamab. *Abbreviations*: AA, accelerated approval (US); BLA, biological license application (US); BTD, breakthrough therapy designation (US); CMA; conditional marketing authorization (EU); Eur Comm, European Commission; FTD, fast-track designation (US); IND, investigational new drug (designation); MAA, marketing authorization application (EU); MAIC, matching-adjusted indirect comparison; ODD, orphan drug designation; pts, patients; rrCLL/SLL, relapsed/refractory chronic lymphatic leukemia/small lymphocytic lymphoma; rrDLBCL, relapsed/refractory diffuse large B cell lymphoma.

RE-MIND: COMPARING TAFASITAMAB + LENALIDOMIDE (L-MIND) WITH A REAL-WORLD LENALIDOMIDE MONOTHERAPY COHORT IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

RE-MIND: PROSPECTIVE-RETROSPECTIVE OBSERVATIONAL STUDY OF LEN MONOTHERAPY AS COMPARATOR TO L-MIND

Aligned Inclusion/Exclusion Criteria

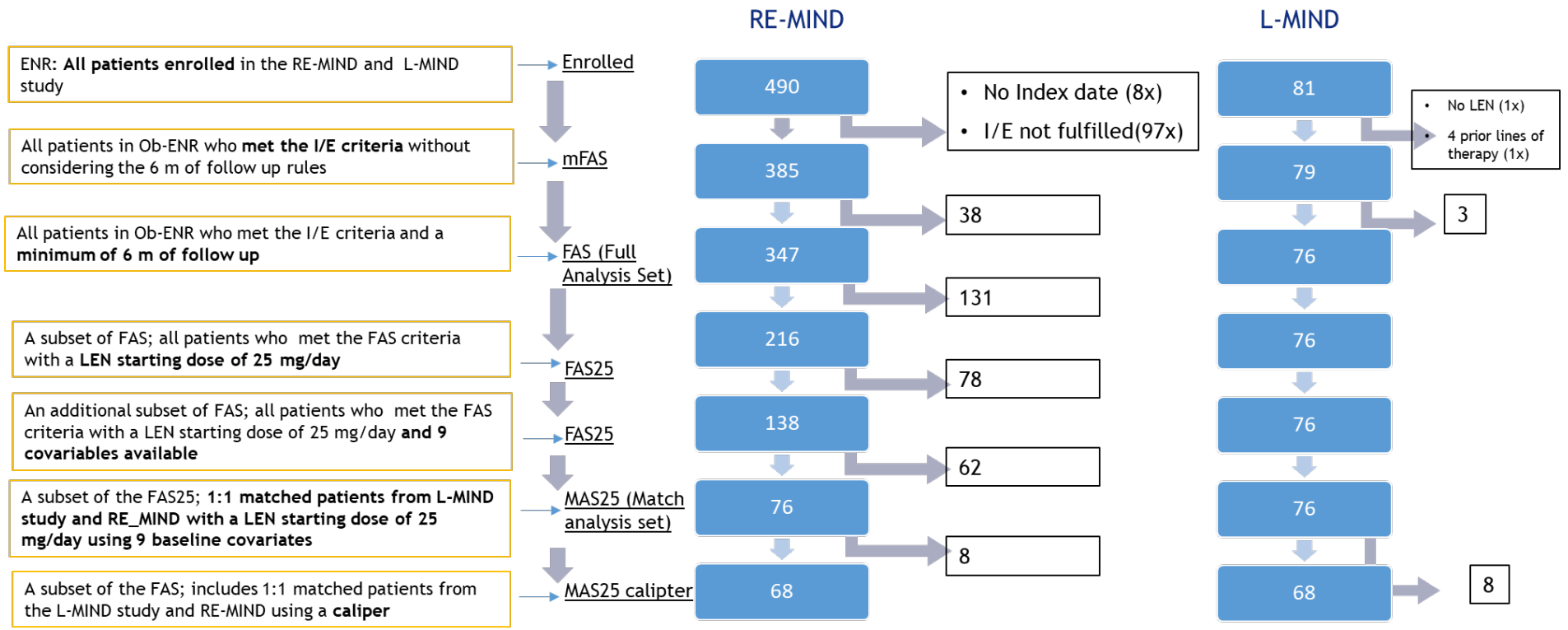
Same histologies, 1-3 prior systemic therapies, not eligible for ASCT



Grzegorz S. Et al; ASCO 2020 Abstract 8020

Zinzani PL. et al. Clin Cancer Res. 2021;27(22):6124-6134. doi:10.1158/1078-0432.CCR-21-1471

ANALYSIS POPULATIONS I



Fas, full analysis set; MAS, matched analysis set, Cal, caliper

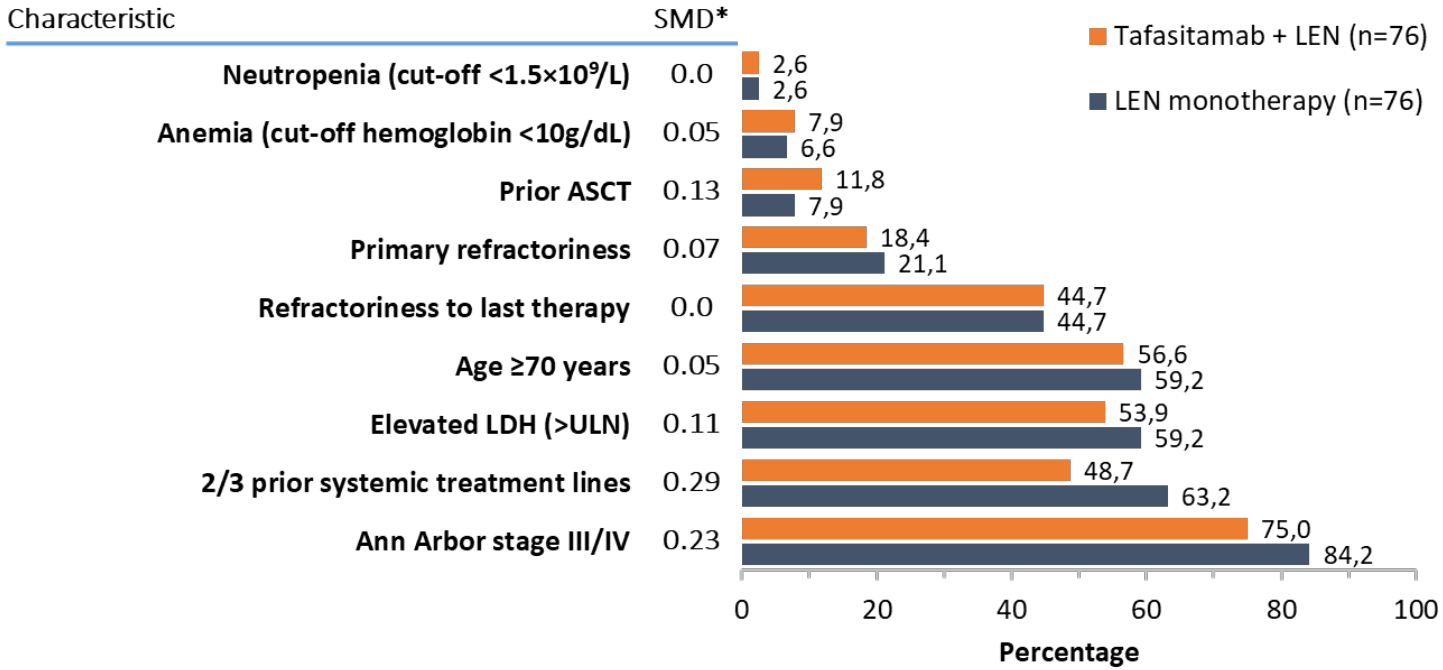
*Matched Analysis Set 25 using caliper; a subset of the FAS25 and includes 1:1 matched patients from the L-MIND study and the observational cohort with a LEN starting dose of 25 mg/day using a caliper, standardized mean difference (SMD) <0.20

Zinzani et al, Journal of Cancer Research and Clinical Oncology 2020

FULL ANALYSIS SET (FAS)
MATCHING ANALYIS SET (MAS)

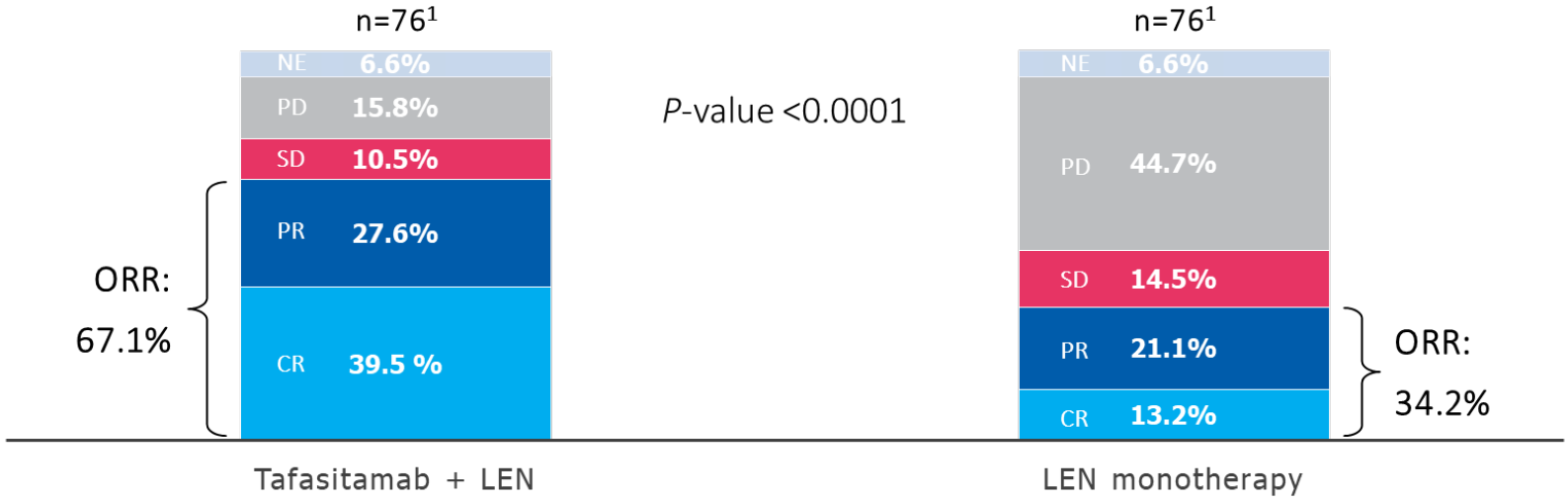
BASELINE CHARACTERISTICS USED FOR COHORT BALANCING

- Baseline characteristics were well balanced across the two cohorts after the matching procedure



*SMD is defined as the ratio of the difference of proportions of a baseline characteristic to the standard deviation of the pooled difference. This standardisation allows for comparison of the relative balance achieved across different baseline characteristics occurring in a low or high proportion.
ASCT, autologous stem cell transplantation; LDH, lactate dehydrogenase; LEN, lenalidomide; SMD, standardised mean difference; ULN, upper limit of normal.
Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020.

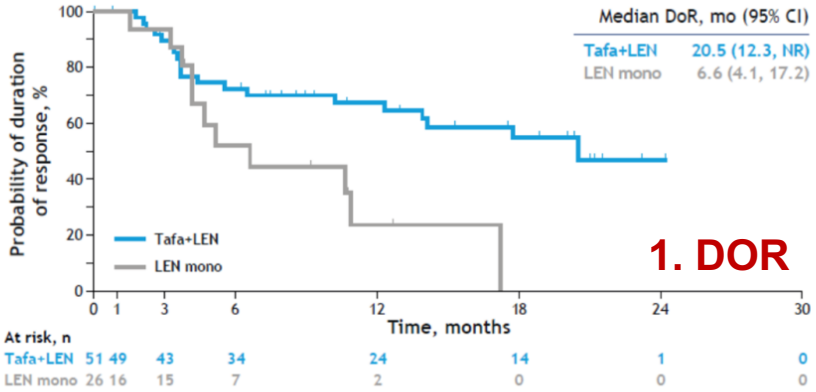
ORR AND CR RATE



Endpoint/cohort	Tafasitamab + LEN (L-MIND cohort) (n=76[1])	LEN monotherapy (observational cohort) (n=76[1])
ORR (%, 95% CI)	67.1 (55.4–77.5)	34.2 (23.7–46.0)
Odds ratio (95% CI)	3.9 (1.9–8.1); *P*<0.0001	
CR (%, 95% CI)	39.5 (28.4–51.4)	13.2 (6.5–22.9)

Investigator assessed (IRC-assessed ORR for tafasitamab + LEN in L-MIND was 57.5%[2]).
CI, confidence interval; CR, complete response; IRC, independent review committee; LEN, lenalidomide; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
1. Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020; 2. Duell J, et al. Oral presentation at Virtual ICML 2021; Abstract 28.

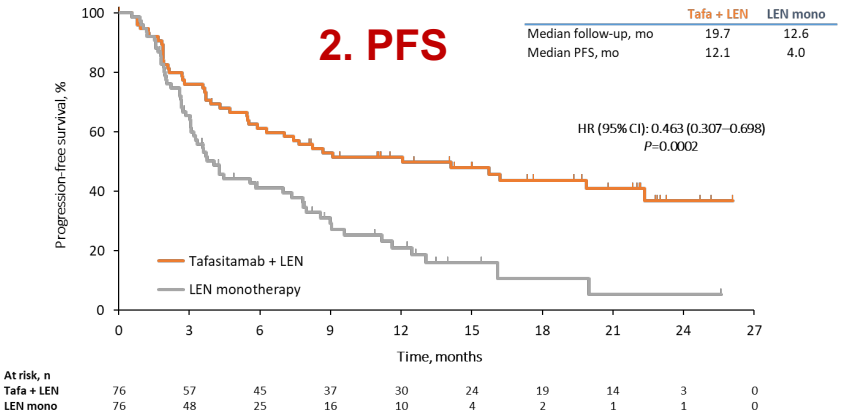
2nd.ry endpoints



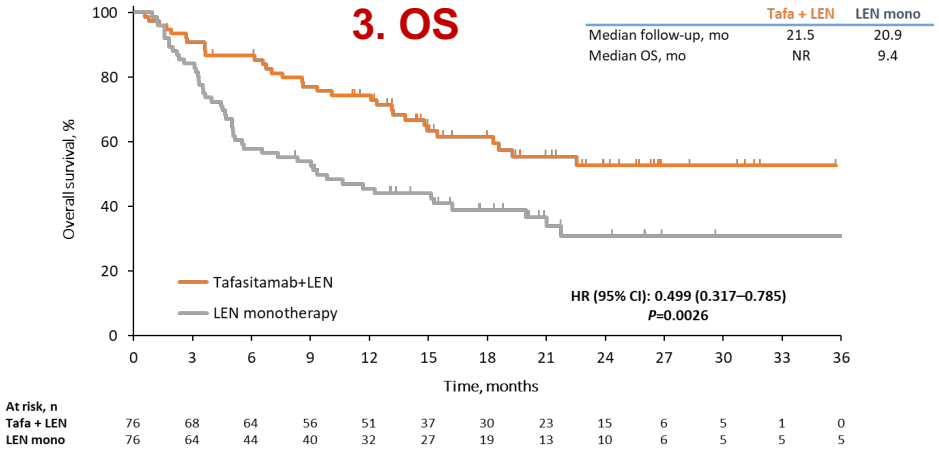
1. DOR

CI, confidence interval; DoR, duration of response; LEN, lenalidomide; MAS25, matched analysis set 25; mo, month; NR, not reached

Median DoR was 20.5 (95% CI: 12.3, NE) months in the tafasitamab+LEN cohort and 6.6 (95% CI: 4.1, 17.2) months in the LEN-mono cohort.



CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; mo, month(s); mono, monotherapy; NR, not reached; PFS, progression-free survival.
Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020.



CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; mo, month(s); mono, monotherapy; NR, not reached; OS, overall survival.
Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020.

SUMMARY

Historical patient's level cohort study

Observational national studies

Historical pooled analysis from 2 Phase III CT and 3 observational studies

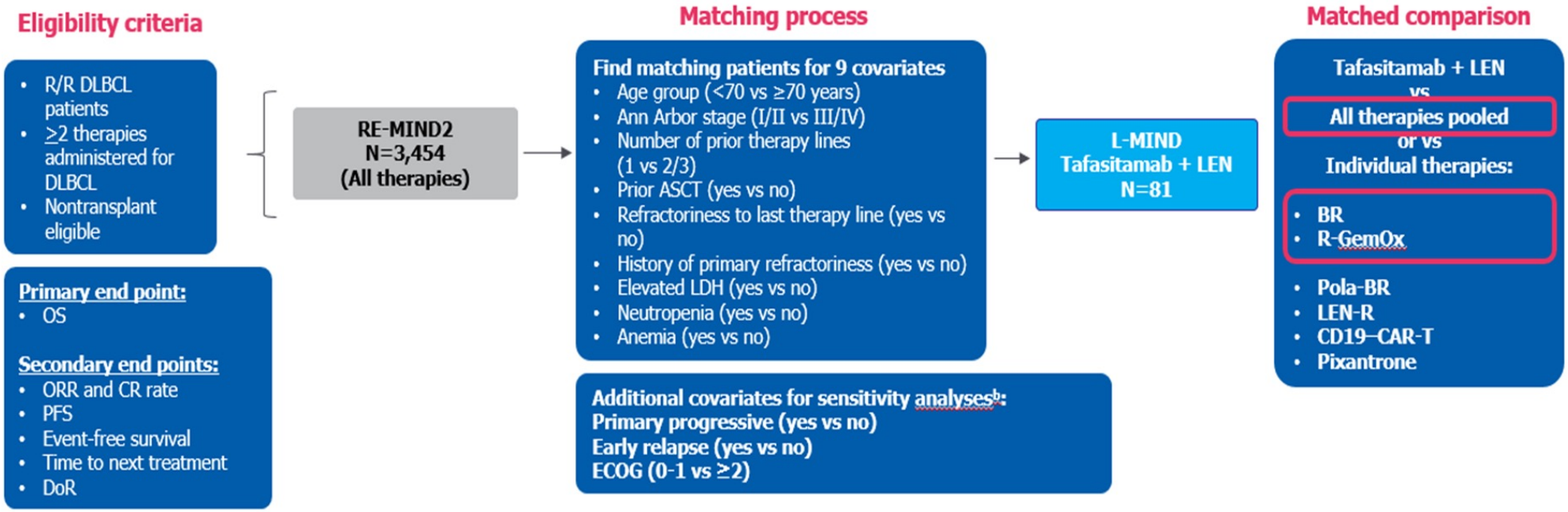
	L-MIND (n 81)	RE-MIND (n 76)	Broccoli et al (n 153)	Mondello et al (n 123)	SCHOLAR trial (n 636)
	Tafa + Lena	Tafa+lena vs Lena	Lena	Lena	r/r therapies
ORR	**59%**	**67% vs 34%**	**29%**	**37%**	**26%**
CR	41%	39% vs 12%	23%	21%	7%
PR	17%	27% vs 22%	6%	16%	18%
mOS	31.6m	NR vs 9.4m	12m	Not reported	6.3m

Salles et al, Lancet Onc 2020
Salles G et al. EHA. 2020; Abstract EP1201
Crump et al, Blood 2017
Broccoli et al, The Oncologist 2019
Mondello et al, The Honcologist 2016

CONCLUSIONS

- Significantly better ORR, CR and OS outcomes indicate substantial additional activity for the novel combination of tafasitamab + LEN versus LEN monotherapy in transplant-ineligible R/R DLBCL patients
- All time-to-event endpoints supported the primary analysis results and were in line with the overall result
- The differences in the primary and secondary endpoints are clinically meaningful
- All sensitivity analyses demonstrate that the results obtained in the primary analysis are robust
- Within the limitations of non-randomised trials, ePS-based 1:1 matching allows for a robust estimation of the additional treatment effect attributable to tafasitamab when added to LEN as in the L-MIND trial
- RE-MIND outcomes are comparable to those published for LEN monotherapy in clinical trials

RE-MIND2 is a retrospective, observational cohort study designed to generate a real-world control for outcomes from the L-MIND study, to characterize the effectiveness of tafasitamab + LEN, in a real-world setting, relative to commonly administered systemic therapies for ASCT ineligible patients with R/R DLBCL



MATCHING ANALYIS SET (MAS). Matching criteria and estimated propensity score (ePS)-based method were applied and efficacy outcomes from the L-MIND cohort were compared with those treated with the observational cohort of patients enrolled in RE-MIND2 database

RE-MIND2: POPULATION

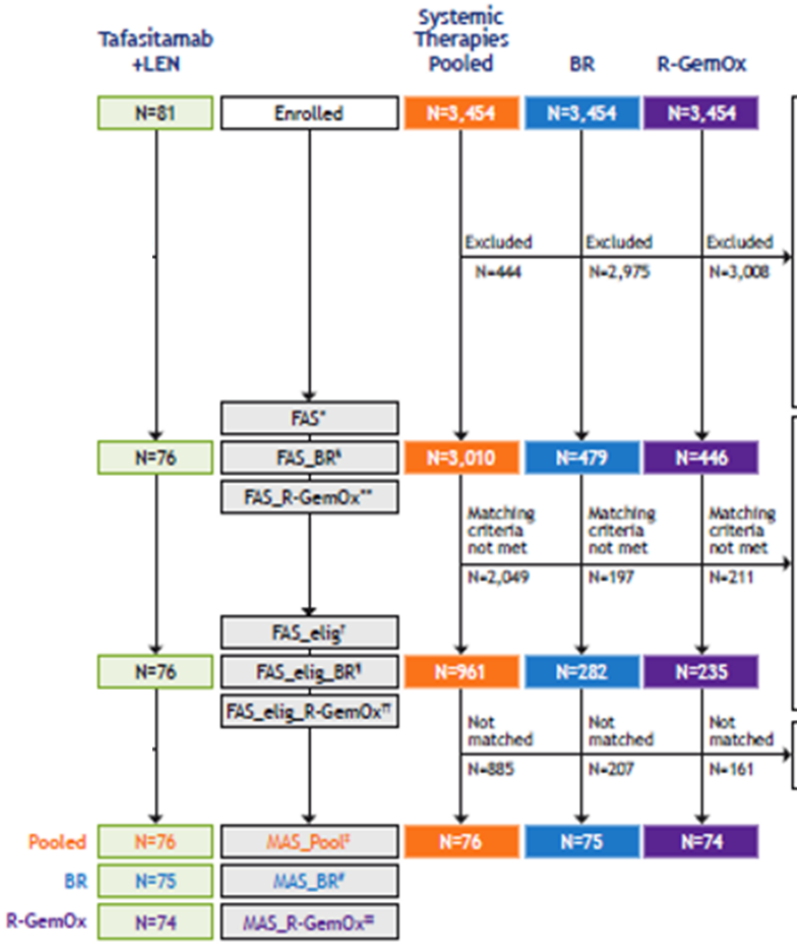
FAS population: patients who met the eligible/non-eligible criteria of RE-MIND2 and L-MIND study with a minimum of 6 months follow-up

FAS_elig population: patients who were eligible for matching

MAS_Pool population: 1:1 matched patients from the L-MIND study and the observational cohort using baseline covariates.

	T-L vs pooled therapies	T-L vs BR	T-L vs R-GEMOX
m follow up in matched cohorts	31.84m vs 33.25m	32.92 vs 25.00	32.92 vs 33.18

Figure 2. Number of patients analyzed per MAS

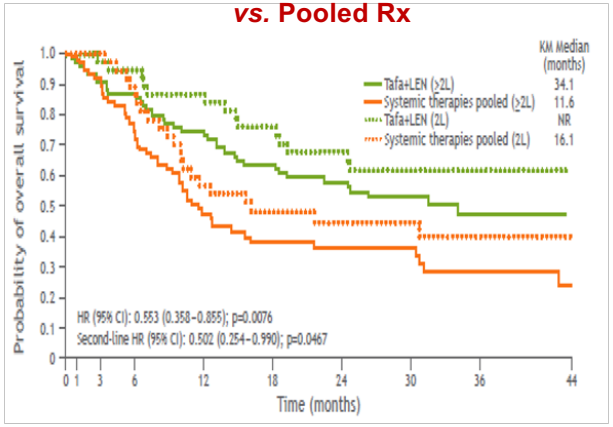


Grzegorz S. Nowakowski et al, SOHO September 8-11, 2021: Poster number ABCL-346

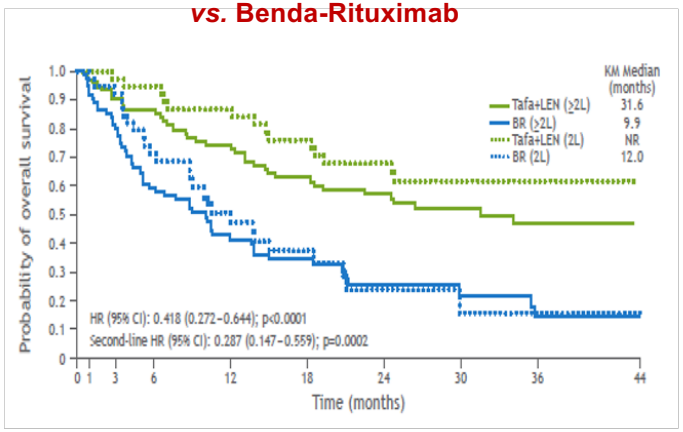
RE-MIND2: OVERALL SURVIVAL

	Pooled therapies ≥2L (m)	Tafa-Lena ≥2L (m)	BR ≥2L (m)	Tafa-Lena ≥2L (m)	R-GEMOX ≥2L (m)	Tafa-Lena ≥2L (m)	Pooled therapies 2L (m)	Tafa-Lena 2L (m)	BR 2L (m)	Tafa-Lena 2L (m)	R-GEMOX 2L (m)	Tafa-Lena 2L (m)
mOS	11.6	34.1	9.9	31.6	11.0	31.6	16.1	NR	12.0	NR	16.8	NR
HR (95% CI)	0.553 (0.358-0.855)		0.418 (0.272-0.644)		0.467 (0.305-0.714)		0.502 (0.254-0.990)		0.287 (0.147-0.559)		0.403 (0.209-0.777)	
p value	0.0076		<0.0001		0.0004		0.0467		0.0002		0.0067	

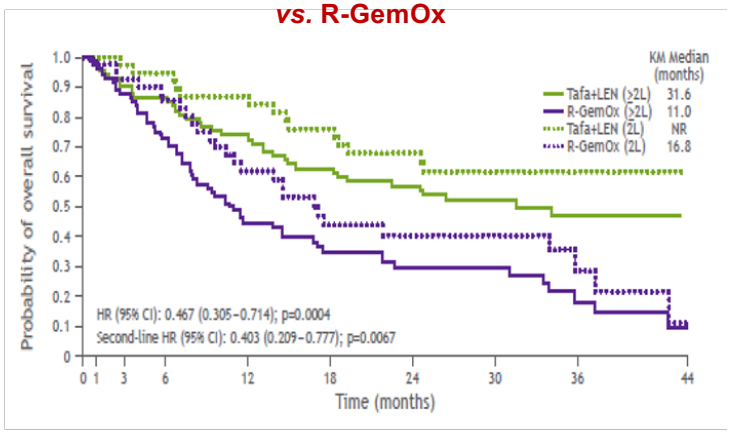
***vs.* Pooled Rx**



***vs.* Benda-Rituximab**



***vs.* R-GemOx**



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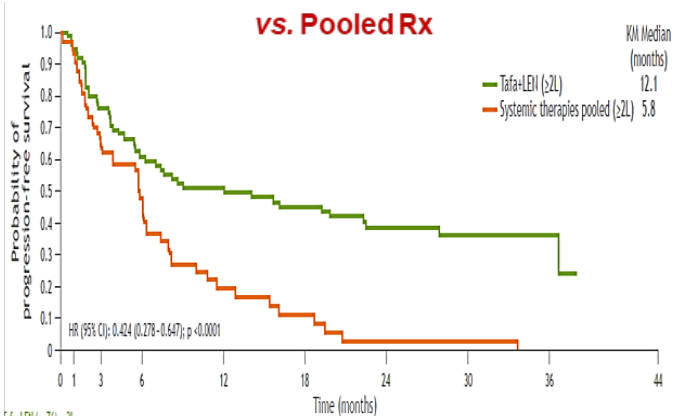
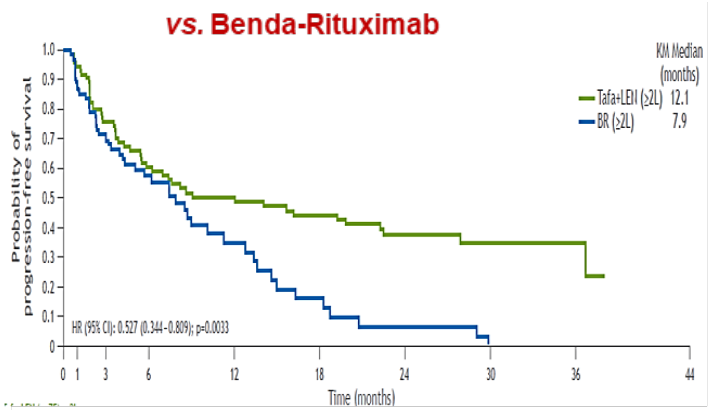
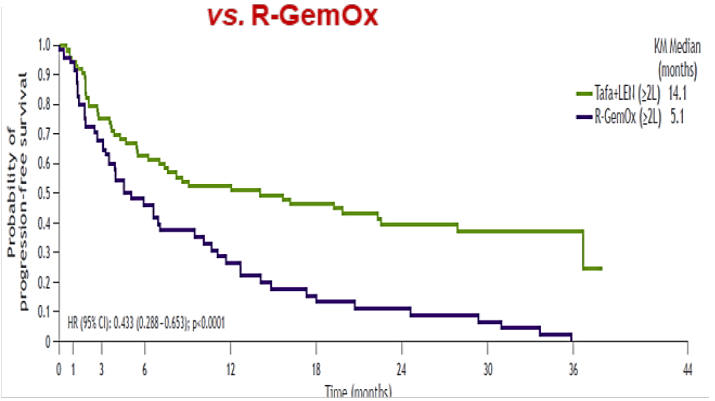
RE-MIND2: PROGRESSION FREE SURVIVAL

	Pooled therapies ≥2L (m)	Tafa-Lena ≥2L (m)	BR ≥2L (m)	Tafa-Lena ≥2L (m)	R-GEMOX ≥2L (m)	Tafa-Lena ≥2L (m)	Pooled therapies 2L (m)	Tafa-Lena 2L (m)	BR 2L (m)	Tafa-Lena 2L (m)	R-GEMOX 2L (m)	Tafa-Lena 2L (m)
mPFS	5.8	12.1	7.9	12.1	5.1	14.1	8.0	16.2	8.8	16.2	7.1	16.2
HR (95% CI)	0.424 (0.278-0.647)		0.527 (0.344-0.809)		0.433 (0.288-0.653)		0.452 (Not reported)		0.475 (Not reported)		0.466 (Not reported)	
p value	<0.0001		0.0033		0.0001		0.0081		0.0155		0.0096	







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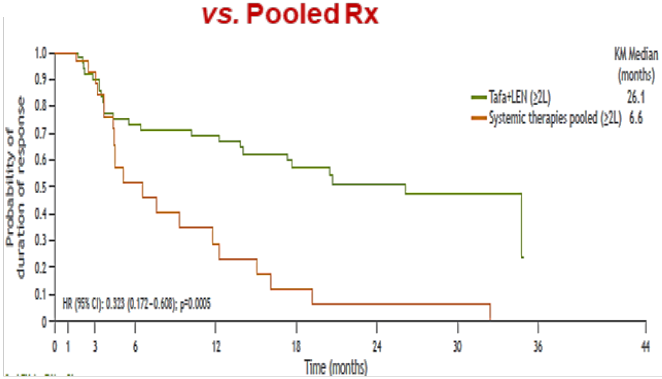
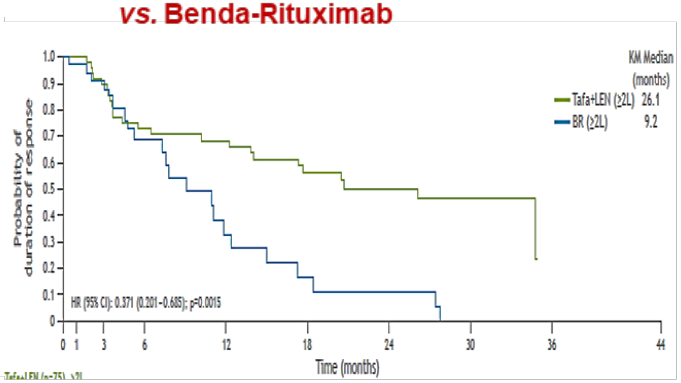
RE-MIND2: DURATION OF RESPONSE

	Pooled therapies ≥2L (m)	Tafa-Lena ≥2L (m)	BR ≥2L (m)	Tafa-Lena ≥2L (m)	R-GEMOX ≥2L (m)	Tafa-Lena ≥2L (m)
mDoR	6.6	26.1	9.2	26.1	9.5	26.1
HR	0.323		0.371		0.372	
p value	0.005		0.0015		0.0009	

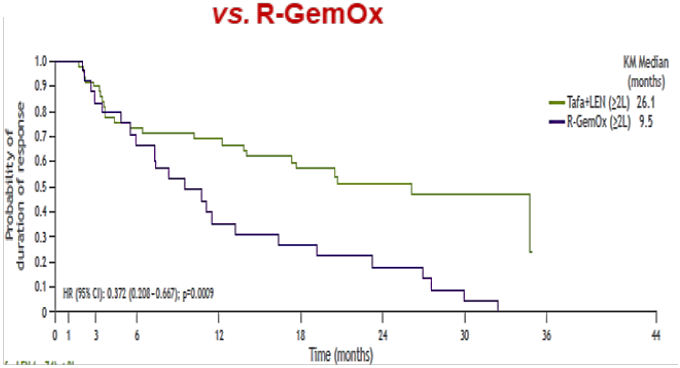
vs. Pooled Rx



vs. Benda-Rituximab



vs. R-GemOx



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RE-MIND2: conclusion (1/2)

Results from the present study align with data reported from previous studies on BR and R-GemOx

Table 3. Overview of BR and R-GemOx results reported in literature vs RE-MIND2 study

	Key studies with BR				Key studies with R-GemOx				
	Literature-reported outcomes			RE-MIND2 outcomes	Literature-reported outcomes				RE-MIND2 outcomes
Reference:	12	13	8		14	9	15	16	
N	59	59	40	75	49	196	32	46	74
ORR, %	62.7	45.8	25	54.7	61	38	78	83	45.9
CR, %	37.3	15.3	22.5	28.0	44	33	50	50	23.0
mPFS, months	6.7	3.6	3.7	7.9	5	5	NA	NA	5.1
mOS, months	NA	NA	4.7	9.9	11	10	NA	NA	11.0

18.5

8. Sehn LH, et al. J Clin Oncol 2019;38(2):155-65; 9. Cazelles C, et al. Leuk Lymphoma 2021;25; 12. Ohmachi K, et al. J Clin Oncol 2013;312103-9; 13. Vacirca JL, et al. Ann Hematol 2014;93(3):403-9; 14. Mounier N, et al. Haematologica 2013;98(11):1726-31; 15. Corazzelli G, et al. Cancer Chemother Pharmacol 2009;64(5):907-16;: 16. El Gnaoui T, et al. Ann Oncol 2007;18(8):1363-8

RE-MIND2: CONCLUSION (2/2)

RE-MIND2 was designed to generate a real-world control for outcomes from the L-MIND study to characterize the effectiveness of tafasitamab + LEN relative to other systemic therapies, currently recommended for the treatment of ASCT ineligible patients with R/R DLBCL, using a 1:1 NN ePS-based matching method

Tafasitamab + LEN was associated with **longer OS vs systemic therapies pooled, BR, and R-GemOx with an HR of 0.553, 0.418, and 0.467, respectively**

Overall, results of this study show that this **immunomodulatory regimen may improve outcomes compared with NCCN/ESMO-recommended therapies** used in routine clinical care for the treatment of R/R DLBCL

As large randomized trials in R/R DLBCL are limited, real-world data can be used to compare efficacy in well-designed studies with matching for multiple covariates

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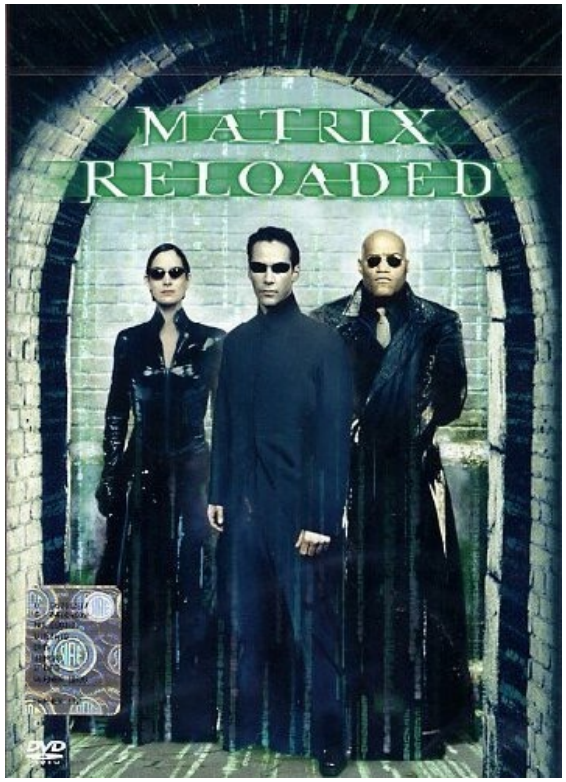

Tafasitamab plus lenalidomide versus Pola-BR, R2, and CAR-T: comparing outcomes from RE-MIND2, an observational, retrospective cohort study in relapsed/refractory diffuse large B-cell lymphoma

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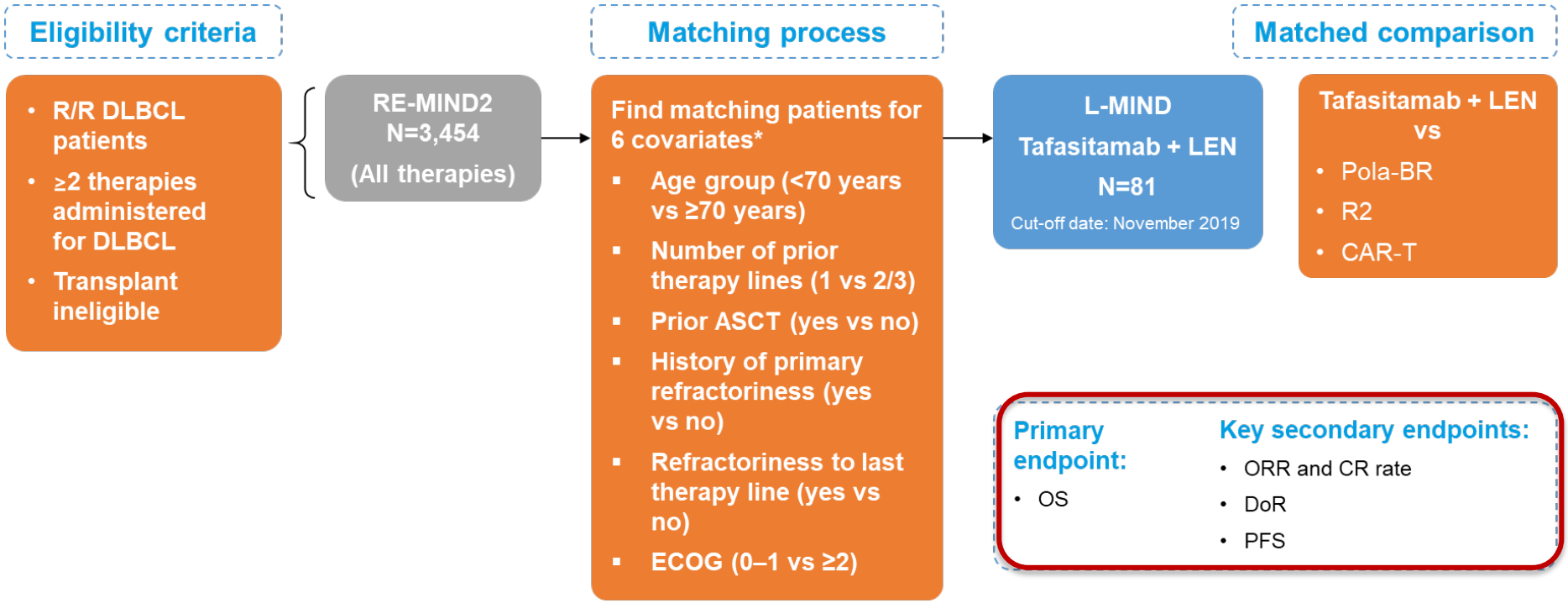
ASH 2021

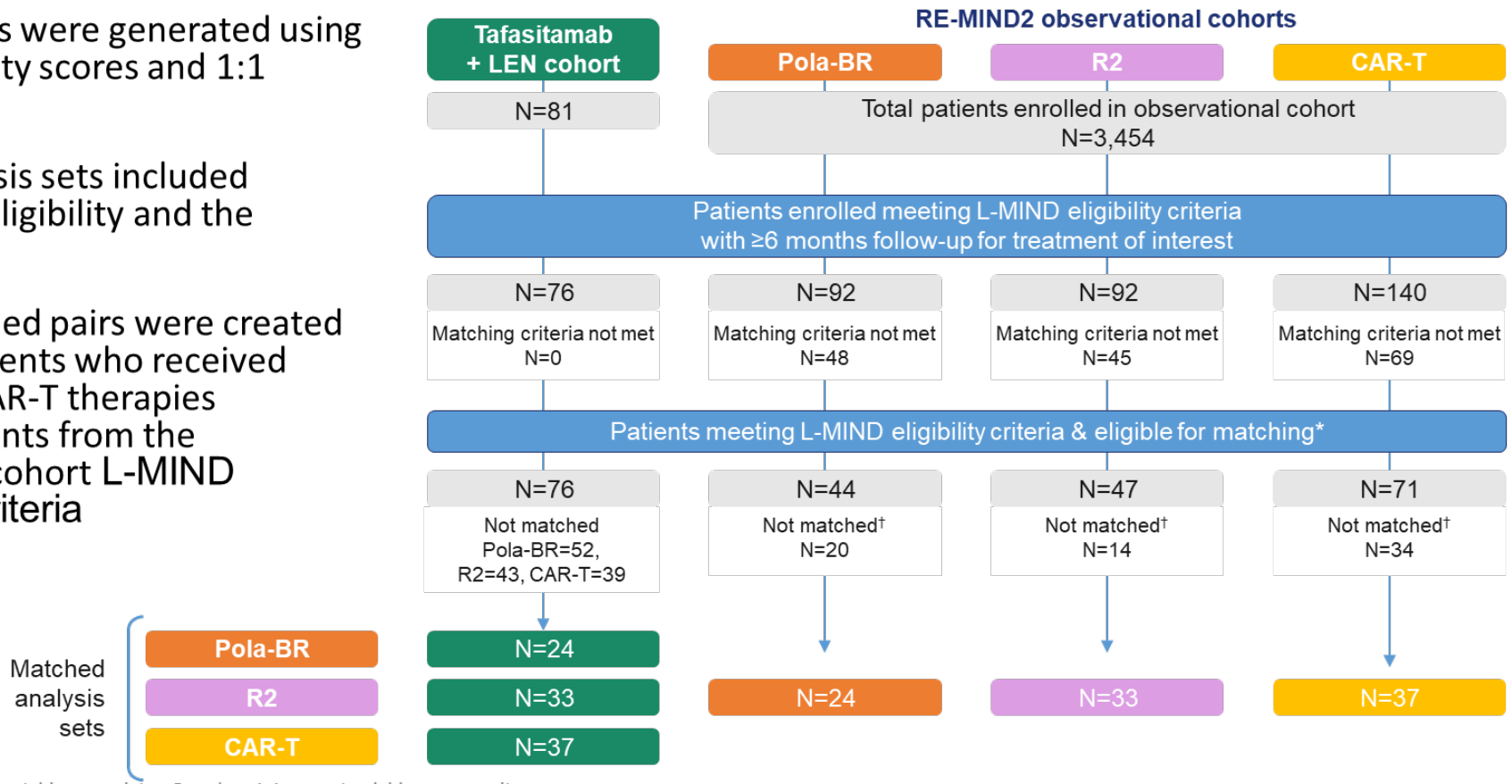
RE-MIND2 expanded analysis study

RE-MIND2 expanded analysis study design



* 9 covariates were used for the primary analysis; ASCT, autologous stem cell transplant; CAR-T, CD19 chimeric antigen receptor T-cell therapies; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; LEN, lenalidomide; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R2, rituximab plus lenalidomide; R/R, relapsed/refractory.

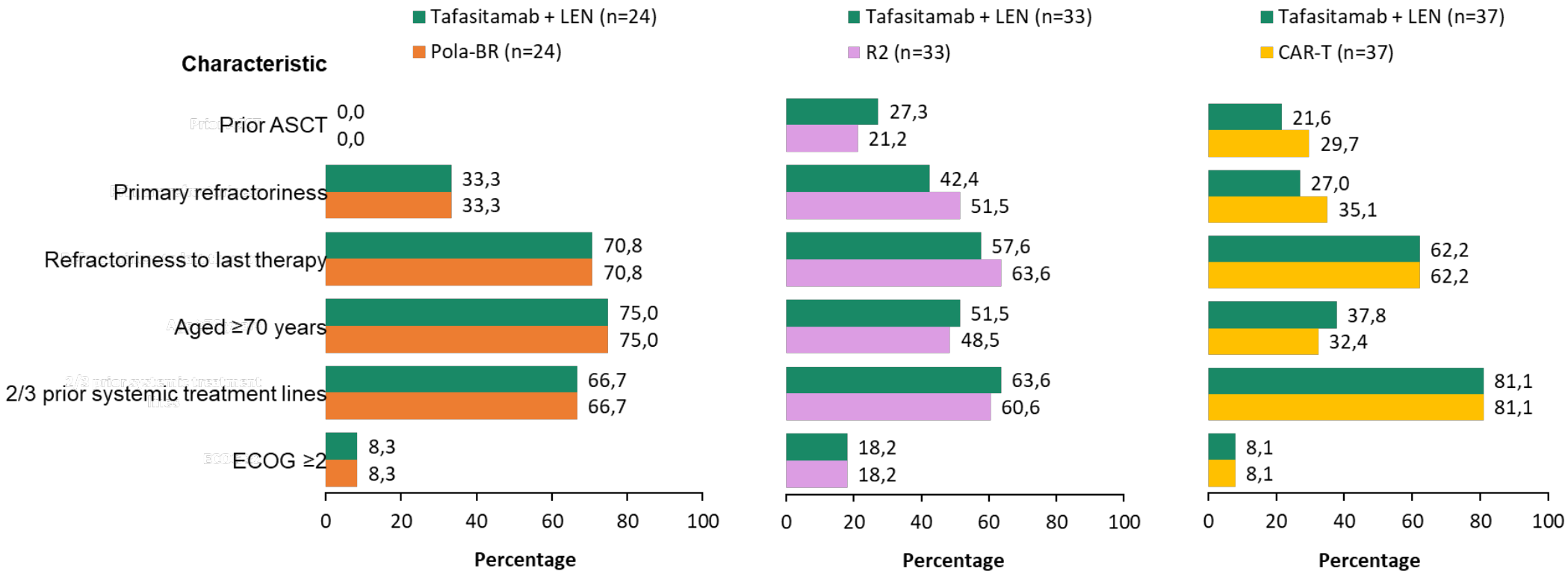
- Comparator cohorts were generated using estimated propensity scores and 1:1 matching
- The resulting analysis sets included patients who met eligibility and the matching criteria
- Patient-level matched pairs were created and comprised patients who received Pola-BR, R2, and CAR-T therapies matched with patients from the tafasitamab + LEN cohort L-MIND criteria L-MIND criteria



- *With complete data for six matching covariates, Based on 1:1 nearest neighbor propensity score.
- CAR-T, CD19 chimeric antigen receptor T-cell therapies; LEN, lenalidomide; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R2, rituximab plus lenalidomide; R/R, relapsed/refractory.

Results: Baseline characteristics for tafasitamab + LEN versus Pola-BR, R2, and CAR-T

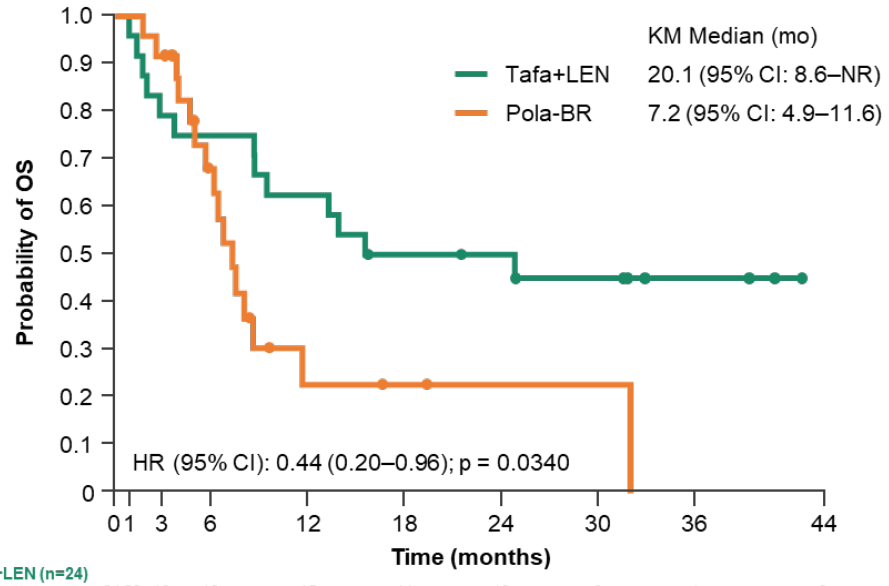
- A high degree of covariate balance was achieved between the tafasitamab plus LEN and comparator therapy cohorts



- ASCT, autologous stem-cell transplant; CAR-T, CD19 chimeric antigen receptor T-cell therapies; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide.

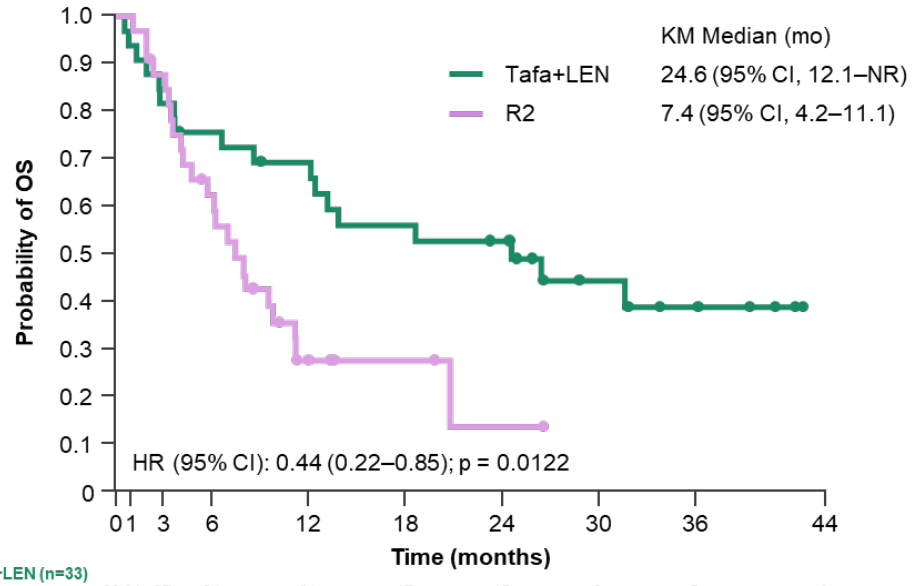
Primary endpoint: OS (*vs.* Pola-BR & R2)

- Tafasitamab + LEN was associated with statistically significant improvements in OS versus Pola-BR and versus R2



Tafa+LEN (n=24)										
At risk	24	23	19	18	15	11	10	8	4	0
Event(s)	0	1	5	6	9	12	12	13	13	13
Censored	0	0	0	0	0	1	2	3	7	11
Pola-BR (n=24)										
At risk	24	24	22	13	3	2	1	1	0	0
Event(s)	0	0	2	7	15	15	15	15	16	16
Censored	0	0	0	4	6	7	8	8	8	8

Median duration of follow-up: tafasitamab plus + LEN: 32 mo; Pola-BR: 16.6 mo



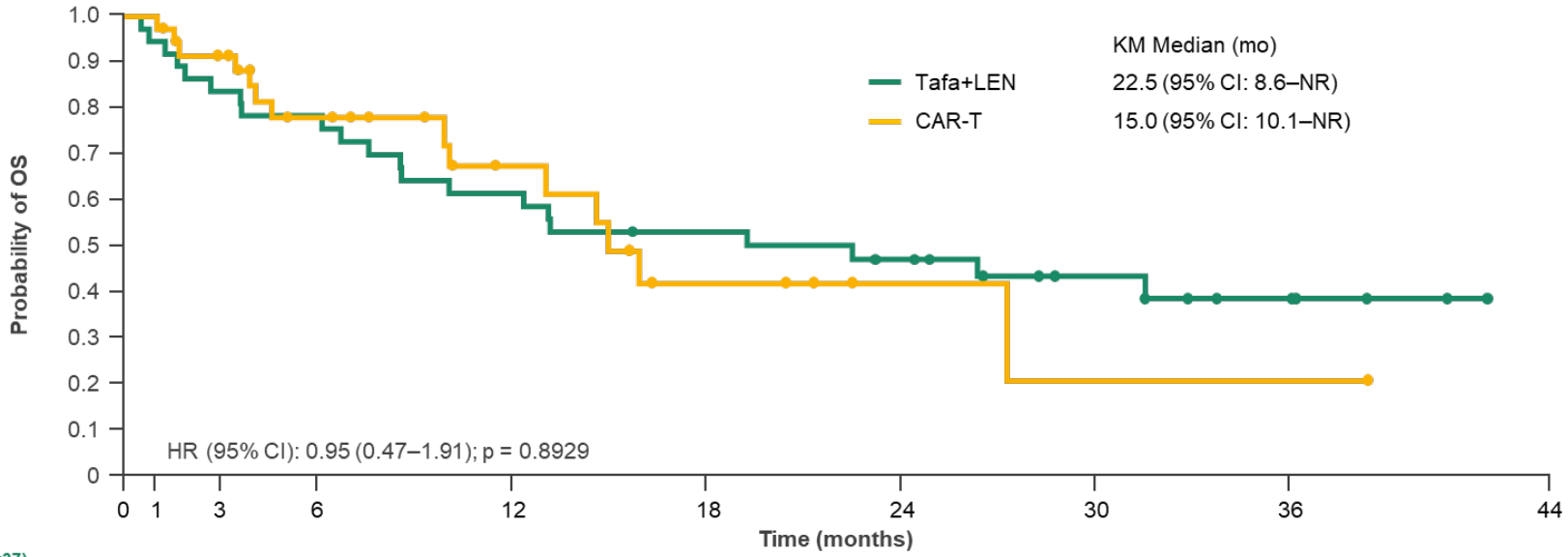
Tafa+LEN (n=33)										
At risk	33	31	27	24	21	17	15	8	5	0
Event(s)	0	2	6	8	10	14	15	17	18	18
Censored	0	0	0	1	2	2	3	8	10	15
R2 (n=33)										
At risk	33	33	28	19	5	3	1	0	0	0
Event(s)	0	0	4	12	22	22	23	23	23	23
Censored	0	0	1	2	6	8	9	10	10	10

Median duration of follow-up: tafasitamab plus + LEN: 32; mo; R2: 13.4 mo

- CI, confidence interval; KM, Kaplan-Meier; LEN, lenalidomide; mo, month; NR, not reached; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; OS, overall survival; R2, rituximab plus lenalidomide; Tafa, tafasitamab. P values were calculated using Log-rank test.

Primary endpoint: OS (*vs.* CAR-T)

- A comparable OS benefit with tafasitamab + LEN versus CAR-T (22 versus 15 months), without statistical significance, was observed



Tafa+LEN (n=37)										
At risk	37	35	31	28	22	18	15	9	5	0
Event(s)	0	2	6	8	14	17	19	20	21	21
Censored	0	0	0	1	1	2	3	8	11	16
CAR-T (n=37)										
At risk	37	37	30	22	11	5	2	1	1	0
Event(s)	0	0	3	7	9	13	13	14	14	14
Censored	0	0	4	8	17	19	22	22	22	23

Median duration of follow-up: tafasitamab plus + LEN: 32 mo; CAR-T: 10.2 mo

- CAR-T, CD19 chimeric antigen receptor T-cell; CI, confidence interval; KM, Kaplan-Meier; LEN, lenalidomide; mo, month; NR, not reached; OS, overall survival; Tafa, tafasitamab.

2nd.ry endpoints: PFS, DoR

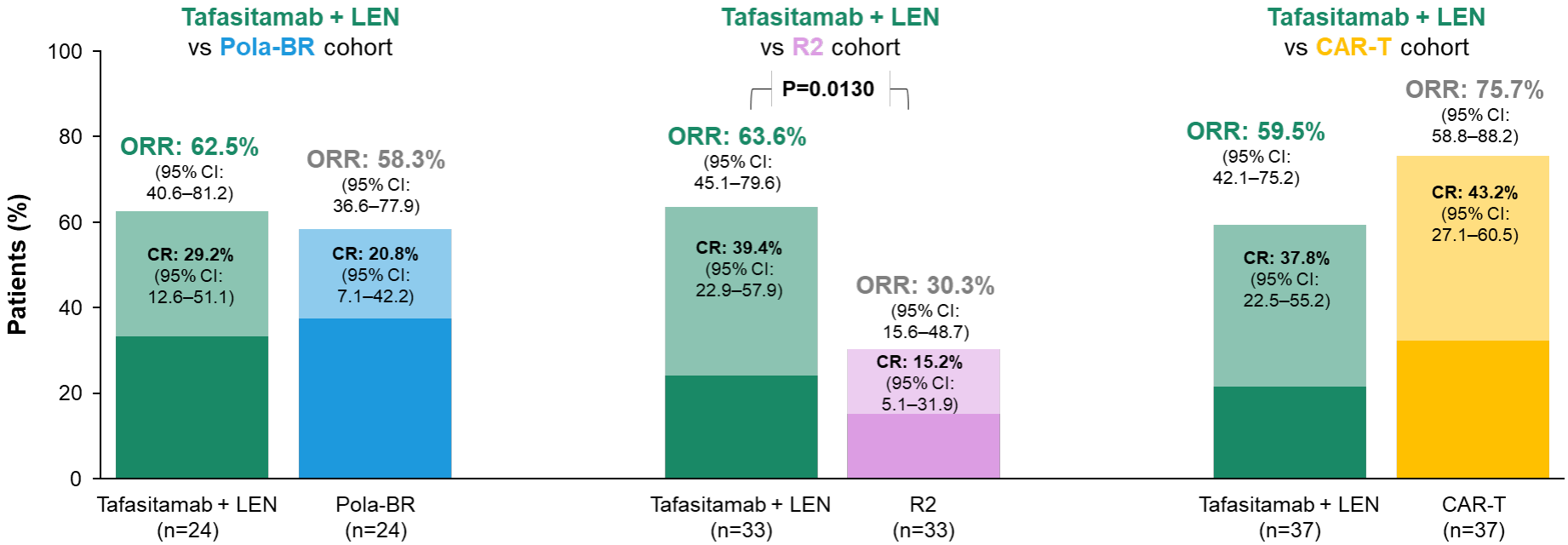
- Tafasitamab + LEN was associated with statistical and clinically meaningful improvements in PFS versus R2
  - Improvements in PFS were observed versus Pola-BR and versus CAR-T
- A low number of patients with tumor assessment data precluded comparative analysis of DoR

	Tafa + LEN (n=24)	Pola-BR (n=24)	Tafa + LEN (n=33)	R2 (n=33)	Tafa + LEN (n=37)	CAR-T (n=37)
Median **PFS**, mo (95% CI)	8.0 (1.9–19.9)	5.0 (2.5–5.6)	5.9 (3.6–36.7)	2.8 (2.0–5.8)	6.3 (3.6–22.5)	4.0 (3.1–12.8)
HR (95% CI) p* value	0.482 (0.217–1.073) 0.0689		0.511 (0.281–0.927) **0.0252**		0.612 (0.302–1.240) 0.1696	
Median **DoR**, mo (95% CI)	17.7 (3.6–34.8)	2.3 (0.3–6.1)	34.8 (3.6–34.8)	12.4 (2.7–19.3)	26.1 (4.4–NR)	5.9 (2.0–10.0)

- CAR-T, CD19 chimeric antigen receptor T-cell; CI, confidence interval; DoR, duration of response; KM, Kaplan-Meier; LEN, lenalidomide; mo, months; PFS, progression-free survival; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide; tafa, tafasitamab.
  *Calculated using Log-rank test.

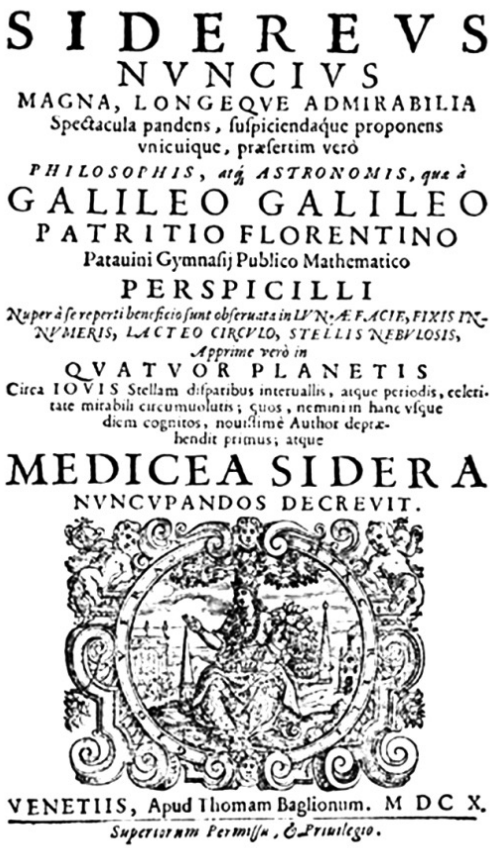
2nd.ry endpoints: ORR, CR rate

- ORR and CR rate were statistically significantly higher with tafasitamab + LEN versus R2
- Statistical differences versus Pola-BR and CAR-T were not detected with the sample sizes in the matched cohorts



- CAR-T, CD19 chimeric antigen receptor T-cell; CI, confidence interval; CR, complete response; LEN, lenalidomide; ORR, overall response rate; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide.

- **The primary endpoint was met for comparisons with tafasitamab + LEN compared with Pola-BR and R2**
  - Statistically significant improvements in median OS were observed
  - Median OS was comparable with tafasitamab + LEN relative to CAR-T therapies
- Numerical differences, favoring tafasitamab + LEN, were observed for the secondary endpoints
- Sensitivity analyses which confirmed the main analysis were performed
- The RE-MIND2 study design used strict patient-level matching to compare real-world and clinical trial populations
  - This allows a contextualization of outcomes with different treatments in the absence of head-to-head trials
- Due to the recent approval of the comparator treatments, these data may inform treatment decisions in the context of emerging therapies for R/R DLBCL


SIDEREVS
NVNCIVS
MAGNA, LONGEQVE ADMIRABILIA
Spectacula pandens, suspiciendaque proponens
vnicuique, præsertim verò
PHILOSOPHIS, atq; ASTRONOMIS, quæ à
GALILEO GALILEO
PATRITIO FLORENTINO
Patauini Gymnasij Publico Mathematico
PERSPICILLI
Nuper à se reperti beneficio sunt obseruata in LVNÆ FACIE, FIXIS IN-
NVMERIS, LACTEO CIRCVLO, STELLIS NEBVLOSIS,
Apprime verò in
QVATVOR PLANETIS
Circa IOVIS Stellam disparibus interuallis, atque periodis, celeri-
tate mirabili circumuolutis; quos, neminem in hanc vsque
diem cognitos, nouissimè Author depræ-
hendit primus; atque
MEDICEA SIDERA
NVNCVPANDOS DECREVIT.
VENETIIS, Apud Thomam Baglionum. M DC X.
Superiorum Permissu, & Priuilegio.

TAFA-LENA: This is the first time that approval of a novel combination therapy was granted based on a pivotal single-arm trial (SAT)

- **RE-MIND:** to establish the effectiveness of LEN and the contribution of the two combination partners not previously approved in r/r DLBCL to the overall effect

- **RE-MIND2:** to characterize the effectiveness of tafasitamab + LEN in a real-world setting

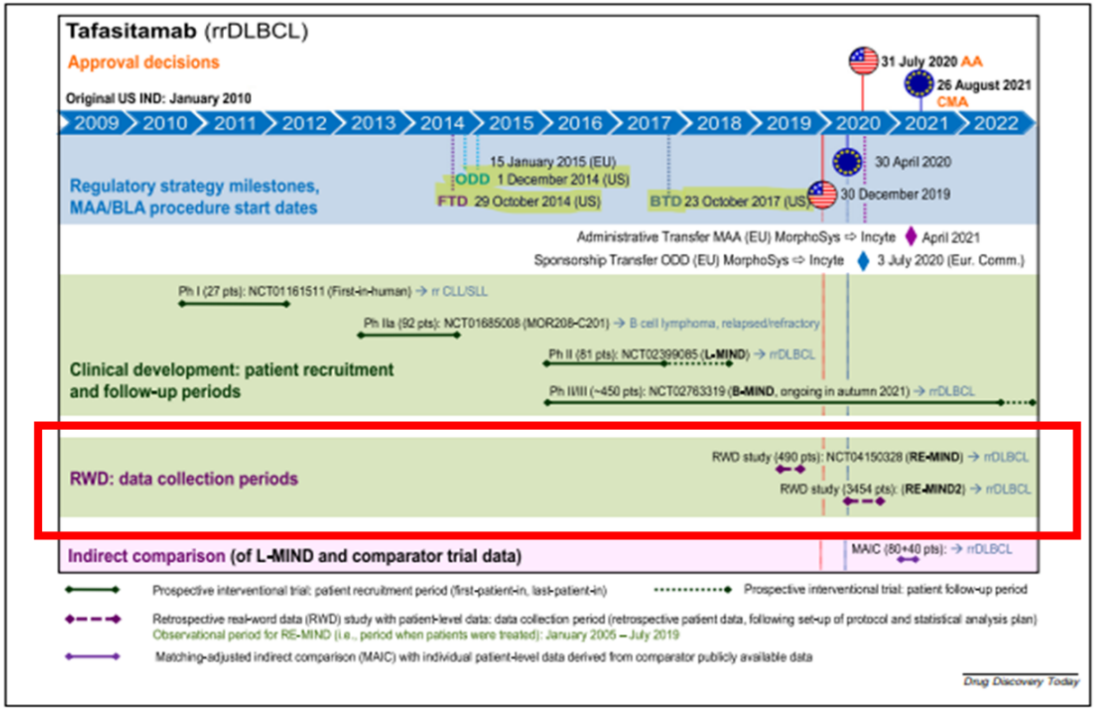


FIGURE 1
Regulatory strategy milestones, clinical trial recruitment periods and supporting real-world data (RWD) studies of tafasitamab. *Abbreviations*: AA, accelerated approval (US); BLA, biological license application (US); BTD, breakthrough therapy designation (US); CMA; conditional marketing authorization (EU); Eur Comm, European Commission; FTD, fast-track designation (US); IND, investigational new drug (designation); MAA, marketing authorization application (EU); MAIC, matching-adjusted indirect comparison; ODD, orphan drug designation; pts, patients; rrCLL/SLL, relapsed/refractory chronic lymphatic leukemia/small lymphocytic lymphoma; rrDLBCL, relapsed/refractory diffuse large B cell lymphoma.