Eppur si muove...

La terapia nel MONDO LINFOMI

Studi RE-MIND
e RE-MIND2
(+RE-MIND2 bis)

Carlo Visco

VERONA, 2 MAGGIO 2022

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma

Pier Luigi Zinzani[1], Thomas Rodgers[2], Dario Marino[3], Maurizio Frezzato[4], Anna Maria Barbui[5], Claudia Castellino[6], Erika Meli[7], Nathan H. Fowler[8], Gilles Salles[9], Bruce Feinberg[10], Nuwan C. Kurukulasuriya[11], Sascha Tillmanns[12], Stephan Parche[11], Debarshi Dey[11], Günter Fingerle-Rowson[11], Sumeet Ambarkhane[11], Mark Winderlich[11], and Grzegorz S. Nowakowski[12]

Aligned inclusion/exclusion criteria

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

L-MIND:
tafasitamab
+ LEN,
n=80

Find matching patients for:

- Age
- Tumour stage
- Response to prior therapies
- Number of prior therapies
- Blood laboratory parameters
- LEN treatment dose

RE-MIND:
LEN monotherapy,
n~500
(50%/50%
from US/EU)

Matched comparison cohort:
tafasitamab + LEN
vs
LEN monotherapy

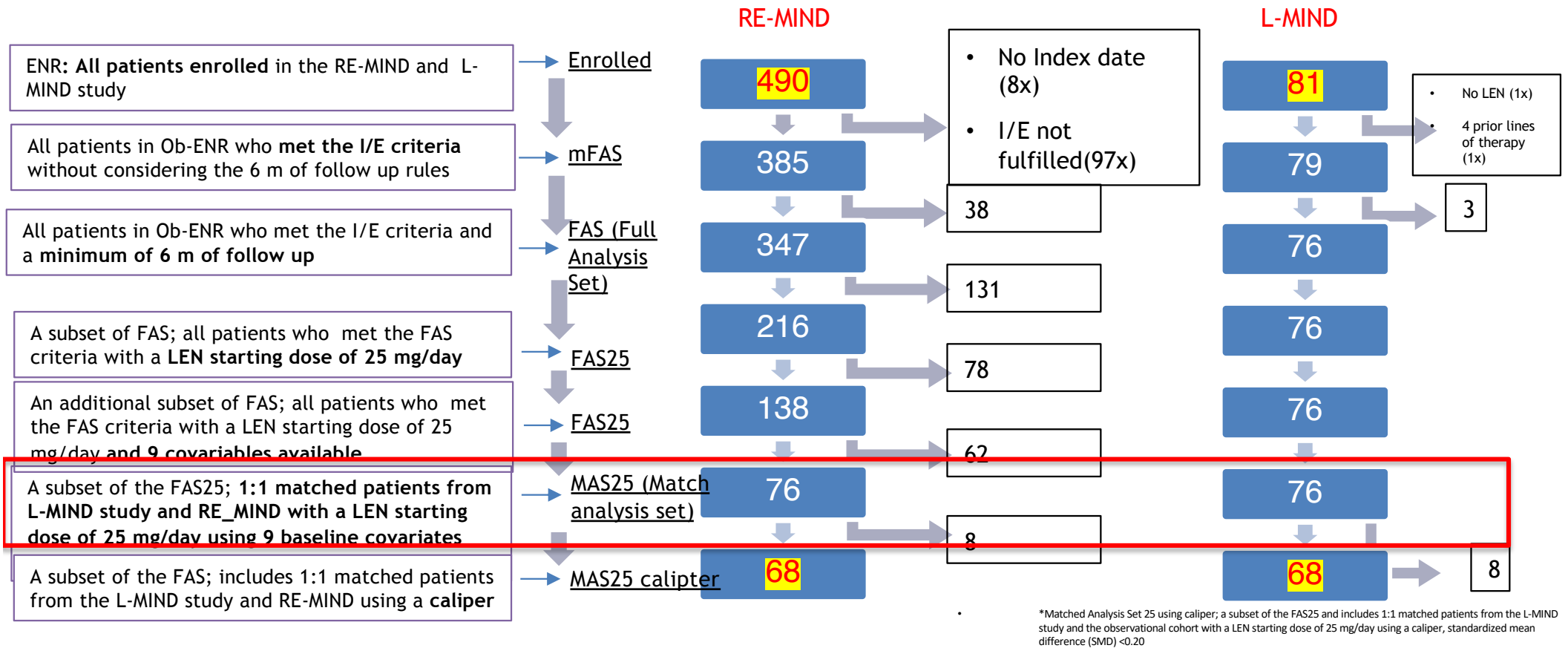
76 patients

Key endpoints

- Difference in:
  - Response rates (primary endpoint)
  - Complete response rates
  - DoR
  - Progression-free survival
  - Survival

ASCT, autologous stem cell transplantation; DoR, duration of response; EU, European Union; LEN, lenalidomide; US, United States.

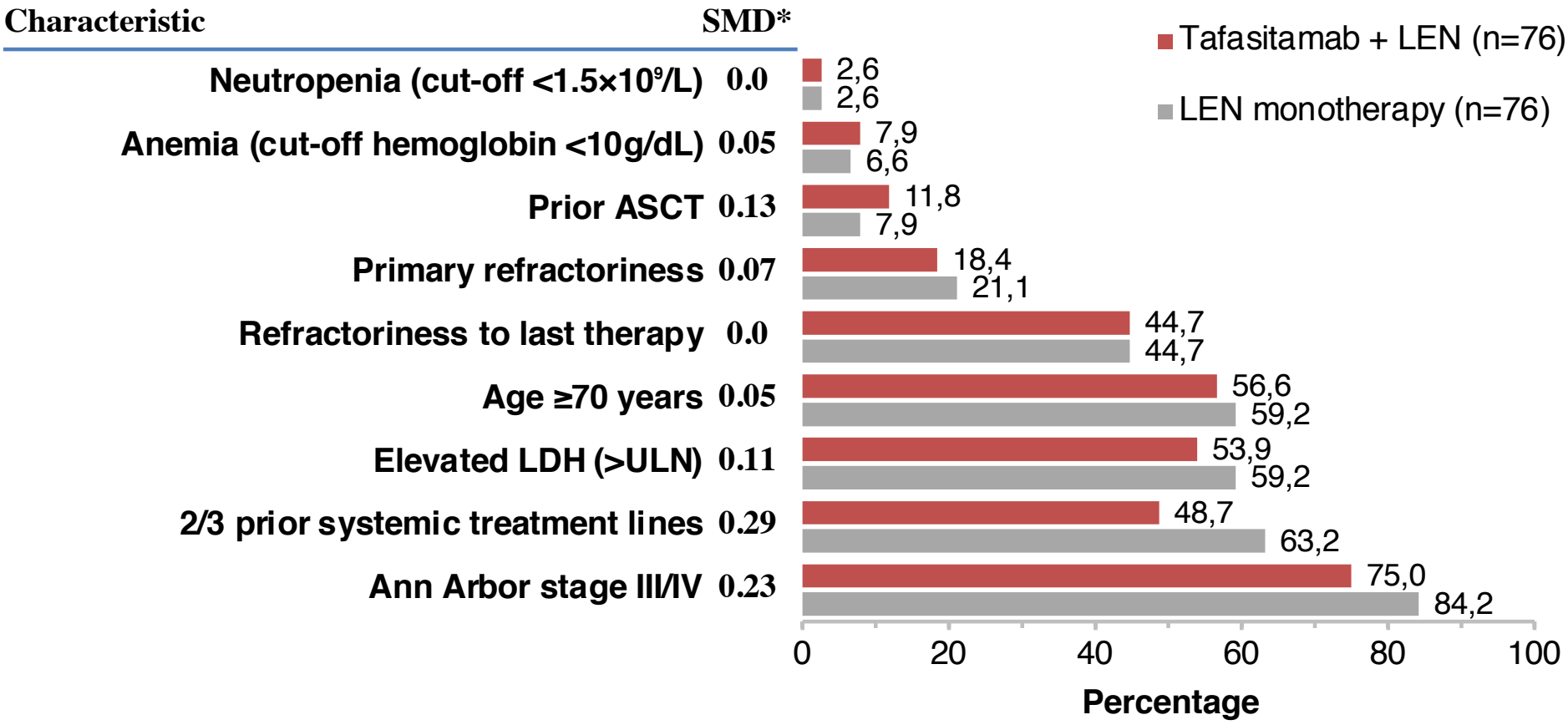
Analysis Populations I



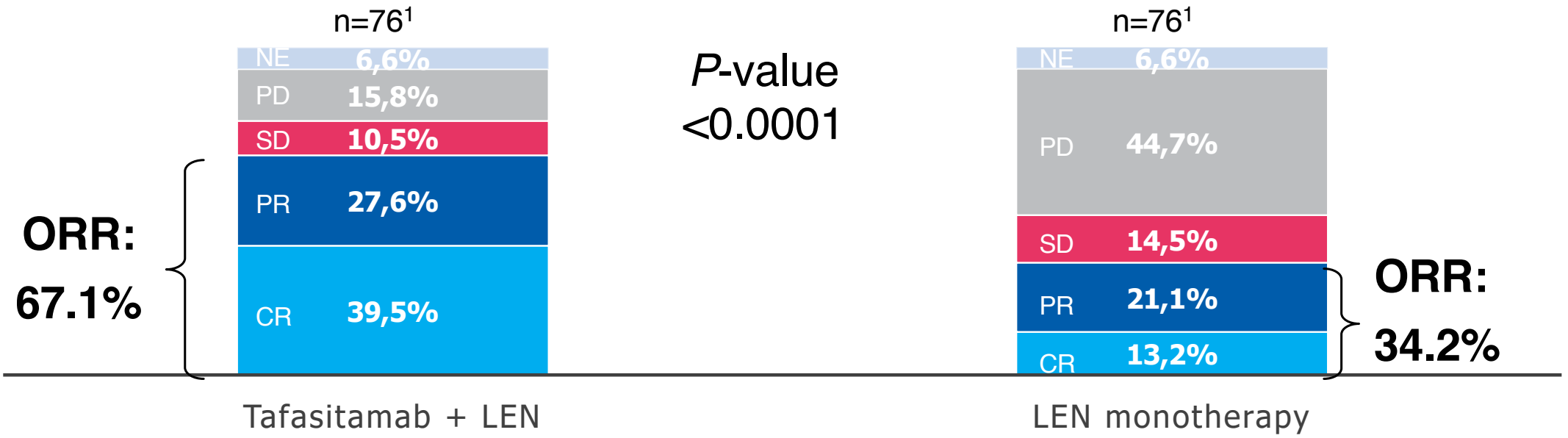
Fas, full analysis set; MAS, matched analysis set, Cal, caliper

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

Baseline characteristics

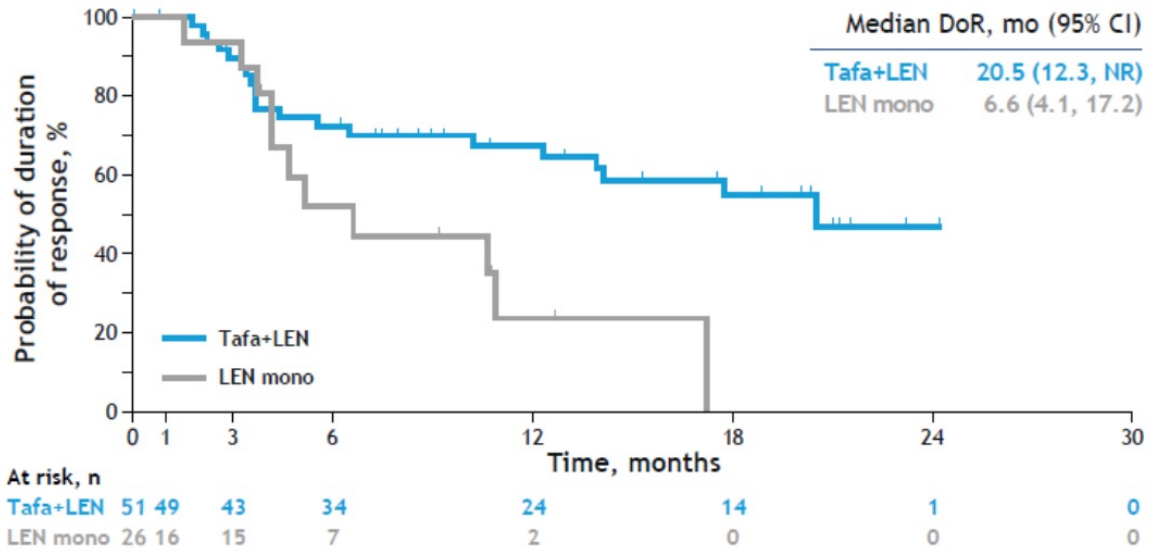


The primary endpoint was investigator-assessed ORR



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)

SECONDARY ENDPOINT: DURATION OF RESPONSE

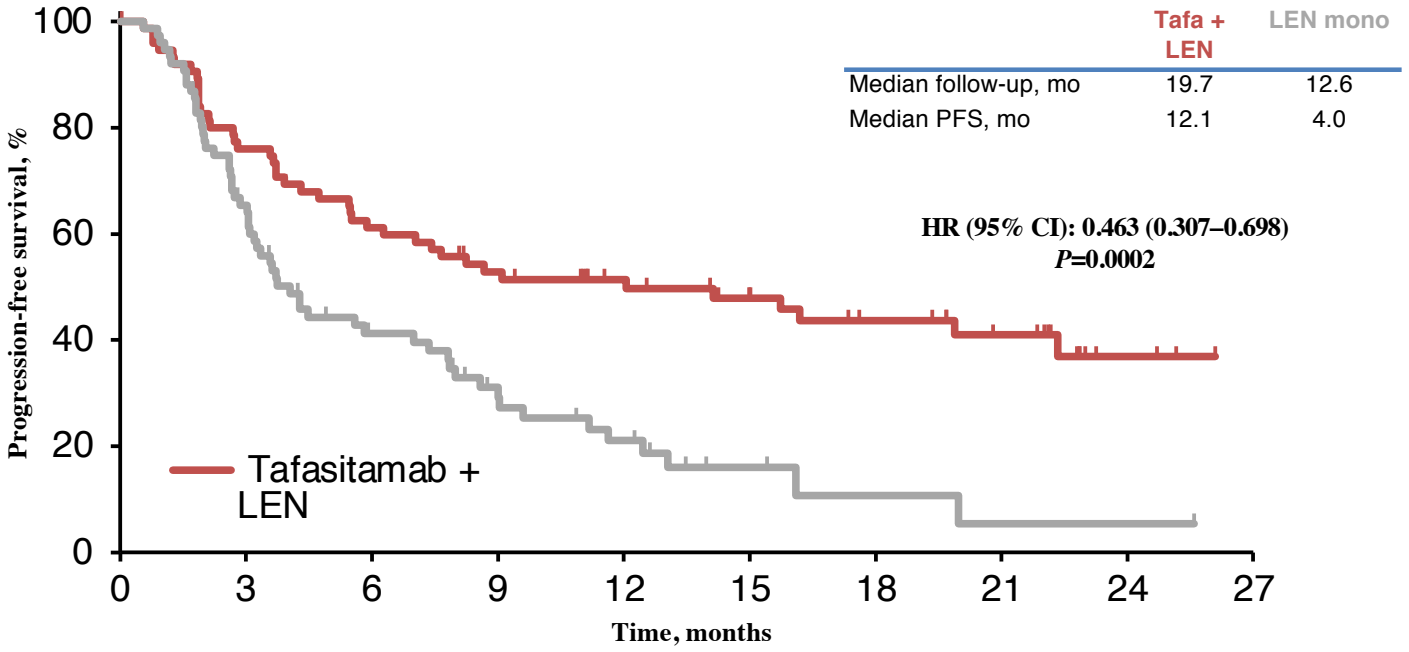


Median DoR was 20.5 (95% CI: 12.3, NE) months in the tafasitamab+LEN cohort and 6.6 (95% CI: 4.1, 17.2) months in the LEN-mono cohort.

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

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

SECONDARY ENDPOINTS: PFS



	Tafa + LEN	LEN mono
Median follow-up, mo	19.7	12.6
Median PFS, mo	12.1	4.0

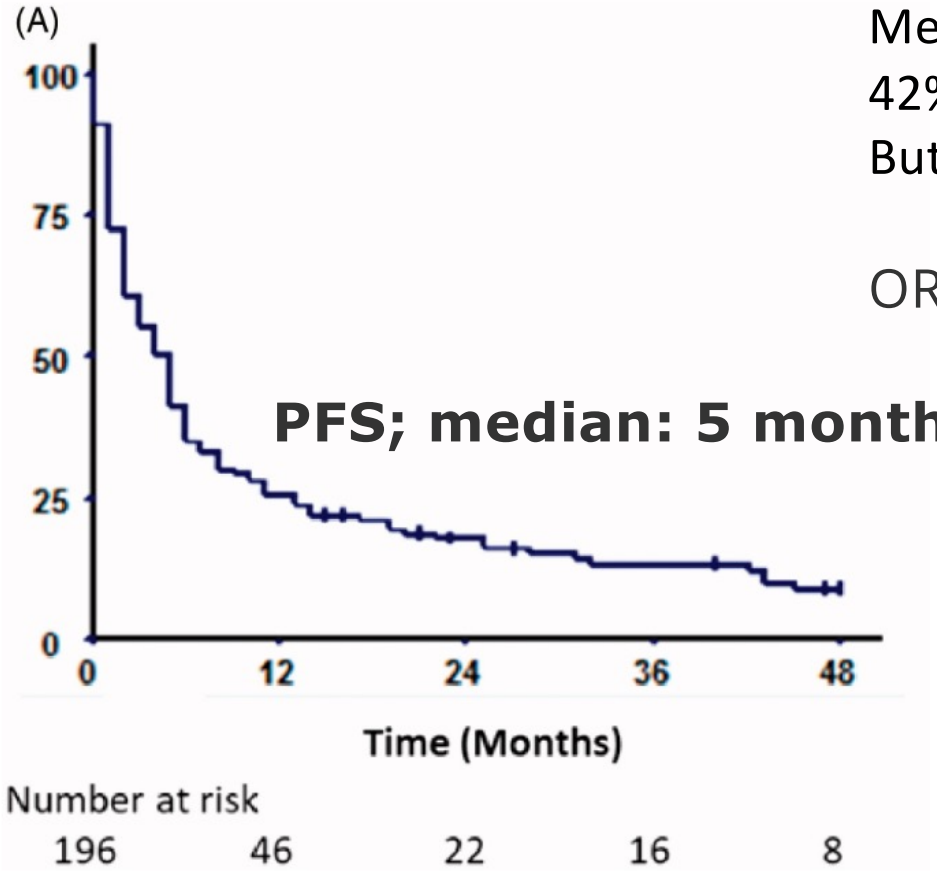
HR (95% CI): 0.463 (0.307–0.698)
P=0.0002

At risk, n										
Tafa + LEN	76	57	45	37	30	24	19	14	3	0
LEN mono	76	48	25	16	10	4	2	1	1	0

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.

R-GemOx in r/r DLBCL



PFS; median: 5 months

Median age 72,
42% 2 or more prior tx
But median prior Tx 1

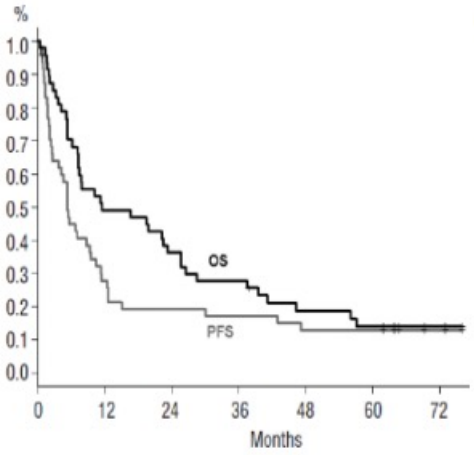
ORR and CRR were 38% and 33%

Cazelles et al, Leuk Lymph 2021

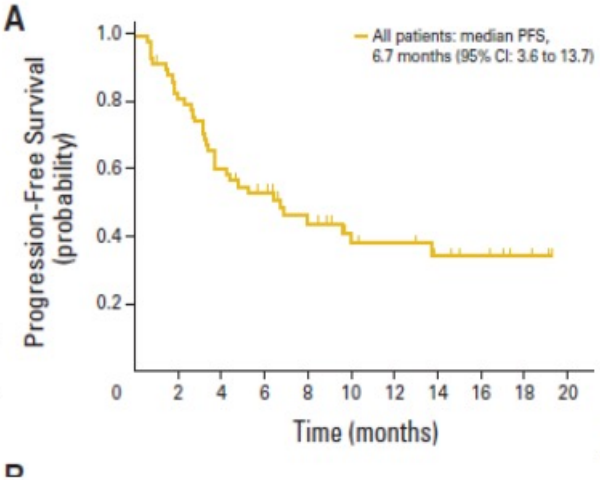
Chemotherapy

REGIMEN	N	Median age	ORR%	CR %	PFS	Reference
R-GEMOX	49	69	46	38	5-yrs 12.8%	Mounier N, Haematol 2013
R-Bendamustine	59	67	63	37	Median 6.7 mo	Ohmachi K, L Clin Oncol 2013
Pixantrone	70	60	37	20	Median 5.3 mo	Pettengel R, Lancet Oncol 2012

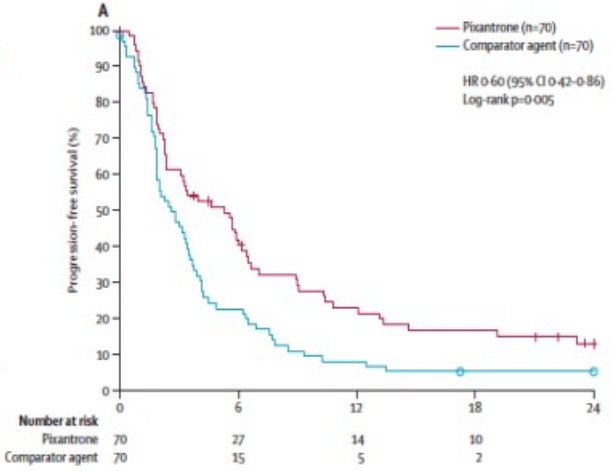
R-GEMOX



R-BENDAMUSTINE



PIXANTRONE



STUDIES WITH LENA MONOTHERAPY IN SIMILAR POPULATIONS

Historical patient's level cohort study

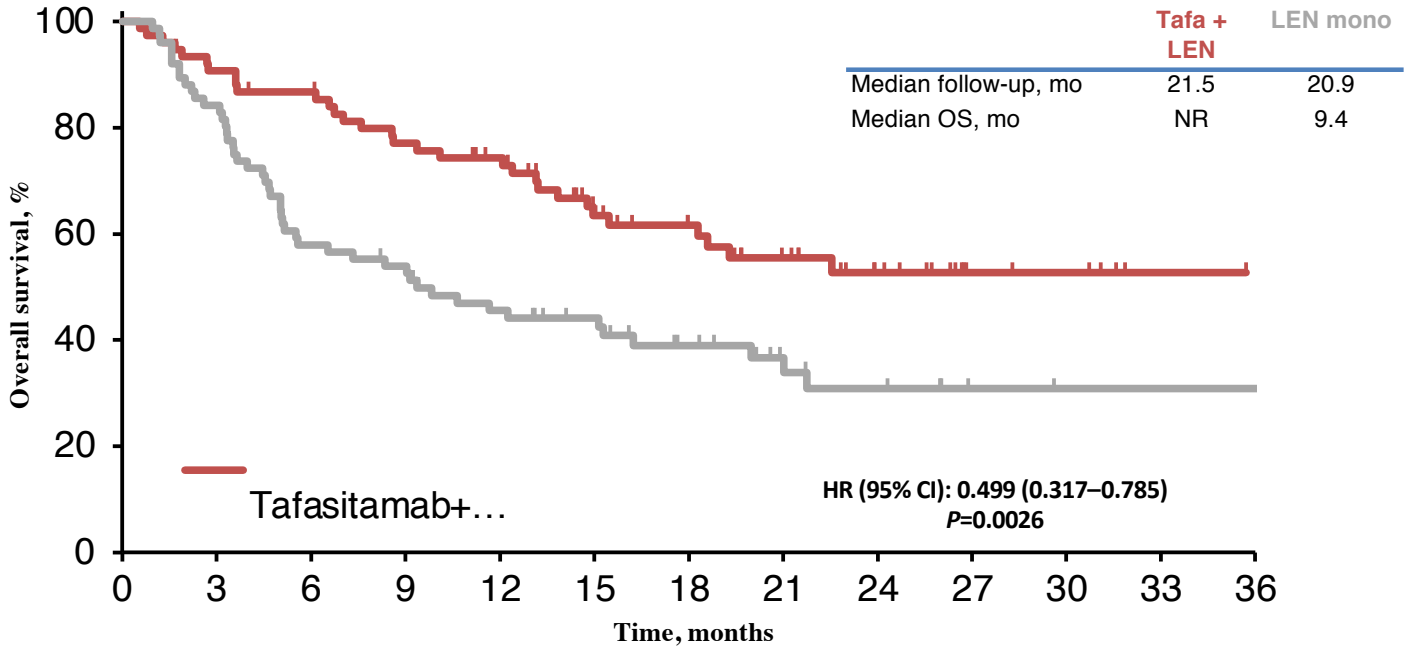
Observational national studies

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

SECONDARY ENDPOINTS: OVERALL SURVIVAL



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.

CONCLUSIONS (RE-MIND)

- 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
- The differences in the primary and secondary endpoints are clinically meaningful
- 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

CR, complete response; DLBCL, diffuse large B-cell lymphoma; ePS, estimated propensity score; LEN, lenalidomide; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory.
Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020.

RE-MIND2: STUDY DESIGN AND METHODS

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

Data collected between April and November 2020 in North America, Europe, and the Asia Pacific region

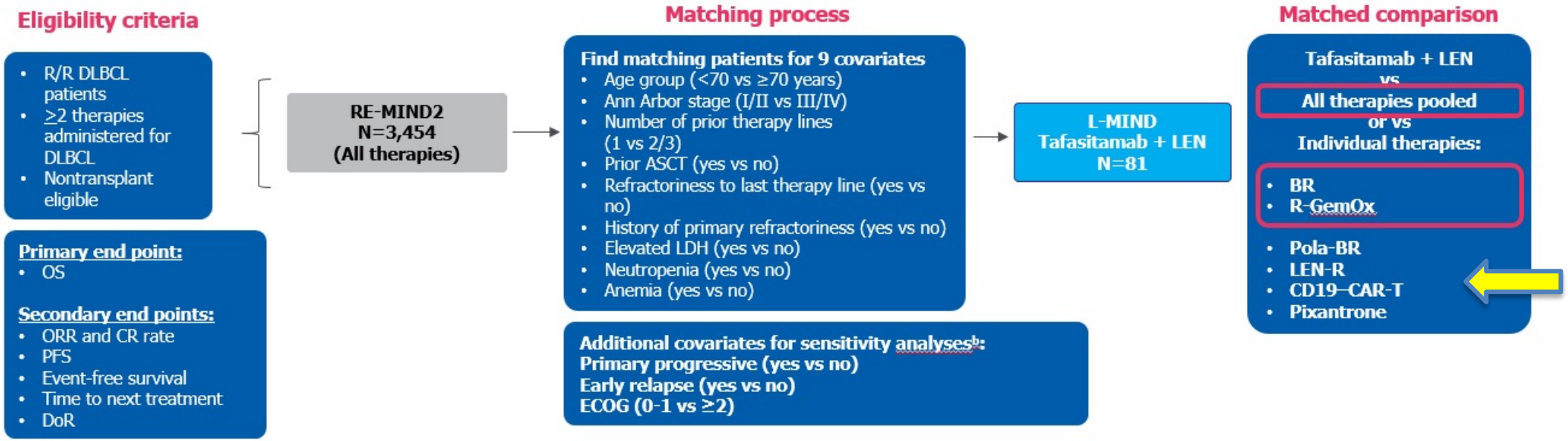
Eligibility criteria were based on the L-MIND study

The primary endpoint was OS and secondary endpoints included ORR, CR rate, progression-free urvival (PFS), and DoR

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

RE-MIND2: STUDY DESIGN AND METHODS

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



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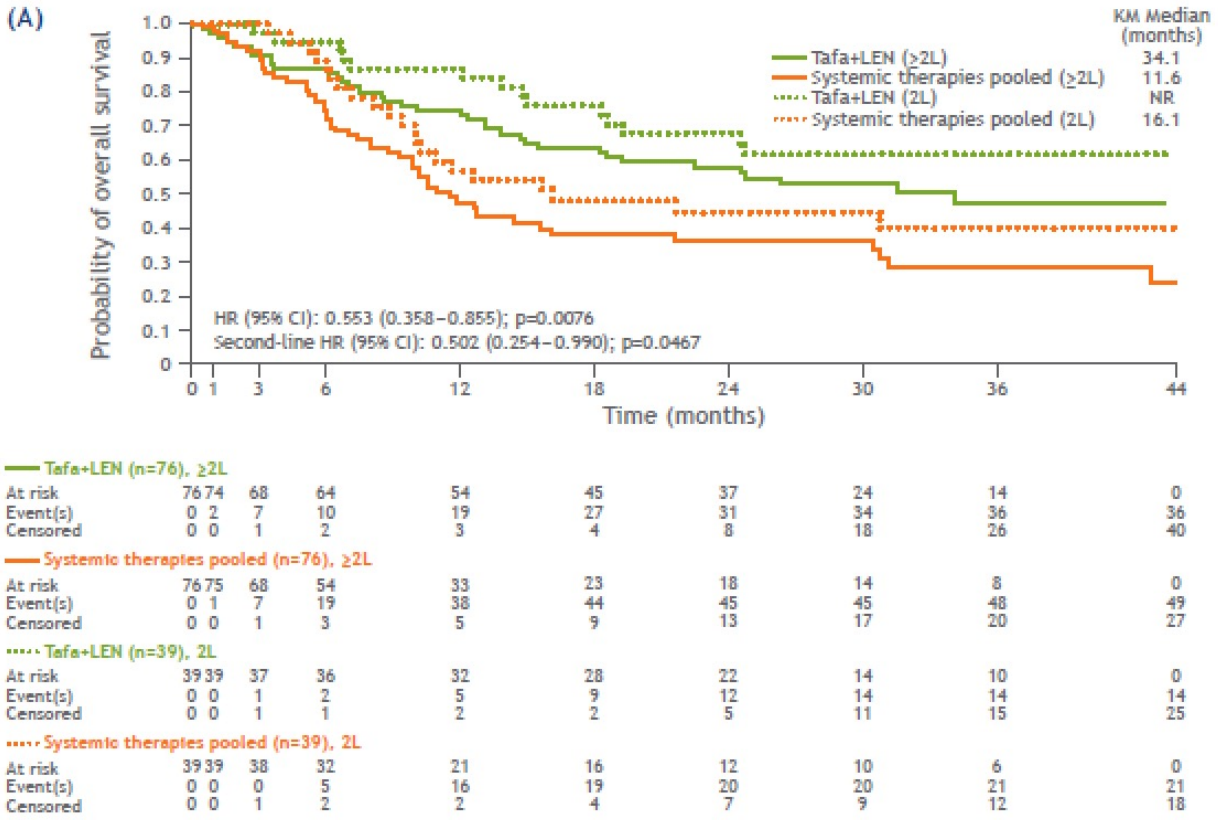
RE-MIND2: OVERALL SURVIVAL VS POOLED THERAPIES



Tafasitamab + LEN: longer OS vs systemic therapies pooled: 34.1m vs 16.1m

Second line median OS for Tafa+Lena: not reached, indicating >50% patients were alive by end of follow-up time.

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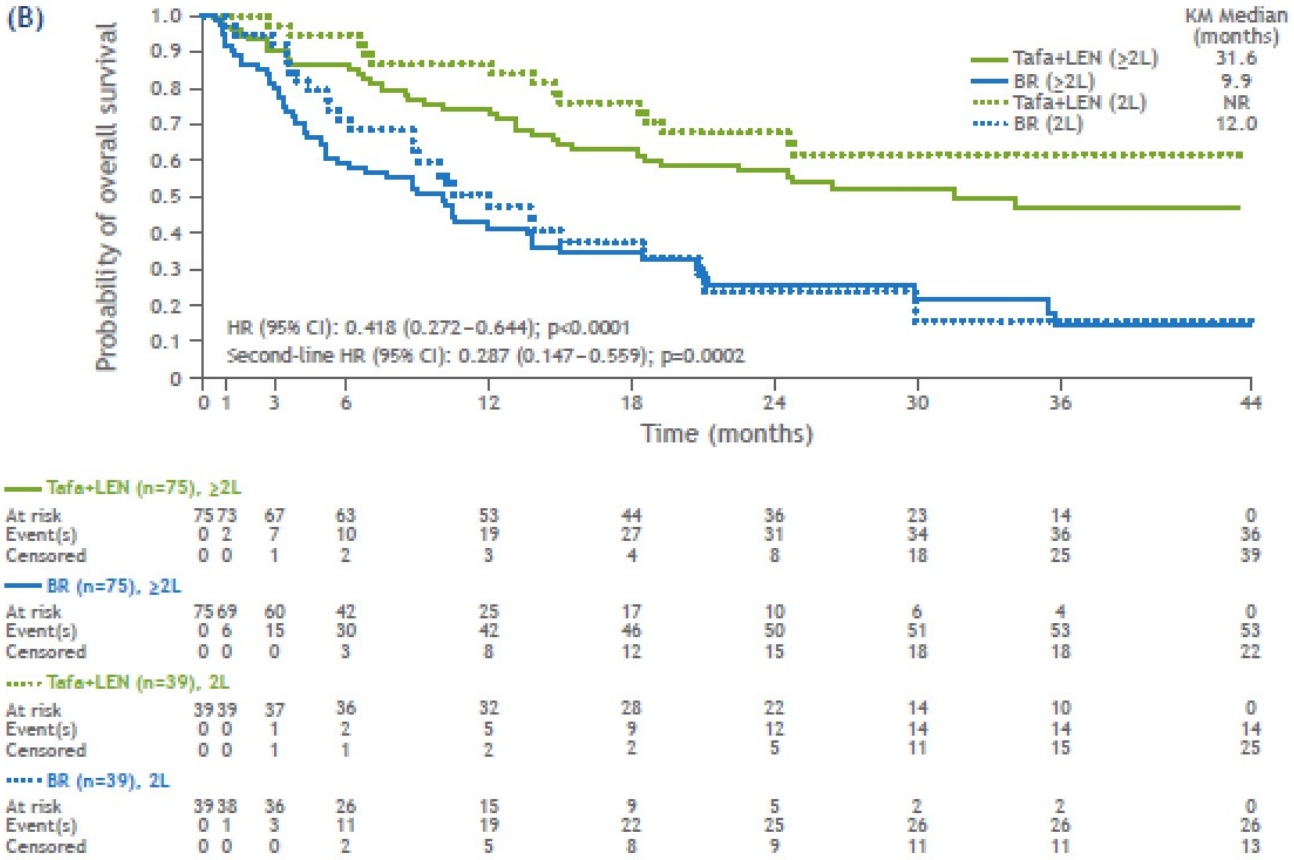
RE-MIND2: OVERALL SURVIVAL VS BR



Tafasitamab + LEN: longer OS vs BR: 31.6 vs 9.9

Second line median OS for Tafa+Lena: not reached, indicating >50% patients were alive by end of follow-up time.

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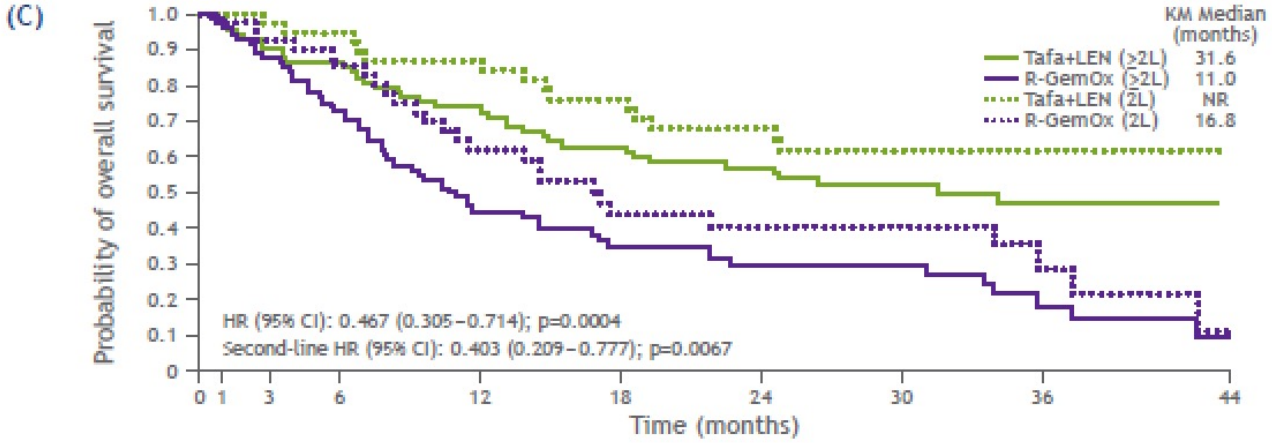
RE-MIND2: OVERALL SURVIVAL VS R-GEMOX



Tafa+LEN (n=74), ≥2L									
At risk	74	72	66	63	53	44	37	24	14	0
Event(s)	0	2	7	10	19	27	31	34	36	36
Censored	0	0	1	1	2	3	6	16	24	38
R-GemOx (n=74), ≥2L										
At risk	74	73	65	53	29	21	15	12	5	0
Event(s)	0	1	9	20	40	46	49	49	53	55
Censored	0	0	0	1	5	7	10	13	16	19
Tafa+LEN (n=39), 2L										
At risk	39	39	37	36	32	28	22	14	10	0
Event(s)	0	0	1	2	5	9	12	14	14	14
Censored	0	0	1	1	2	2	5	11	15	25
R-GemOx (n=41), 2L										
At risk	41	40	38	34	22	14	10	8	4	0
Event(s)	0	1	3	6	15	21	22	22	24	26
Censored	0	0	0	1	4	6	9	11	13	15

Tafasitamab + LEN: longer OS vs R-GEMOX: 31.6m vs 16.8m

Second line median OS for Tafa+Lena: not reached, indicating >50% patients were alive by end of follow-up time.

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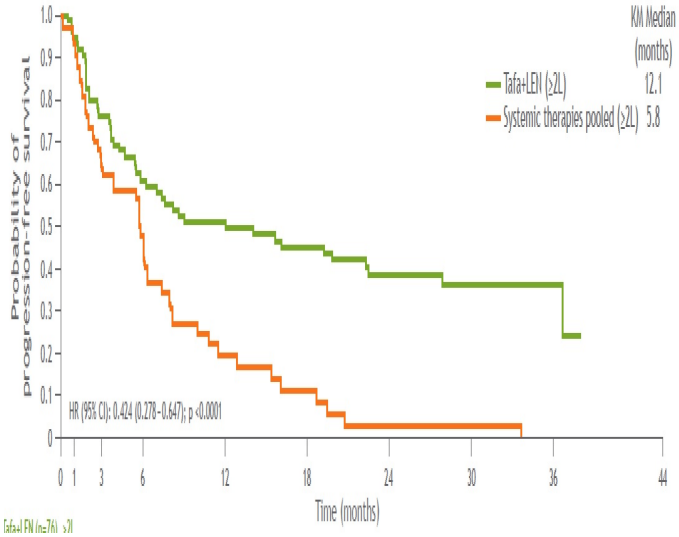
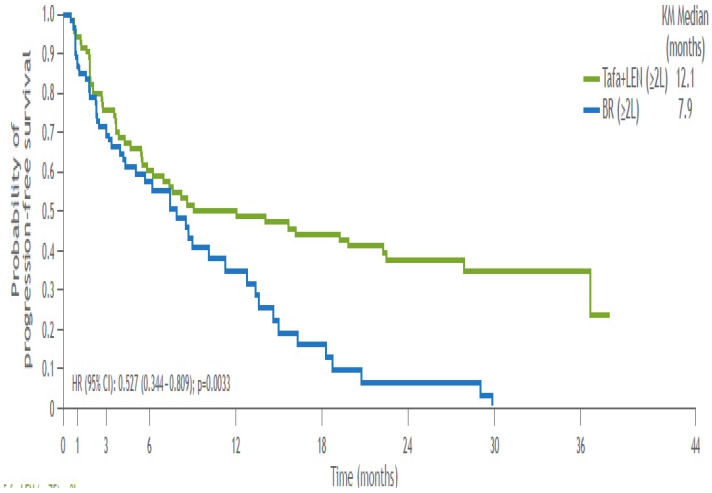
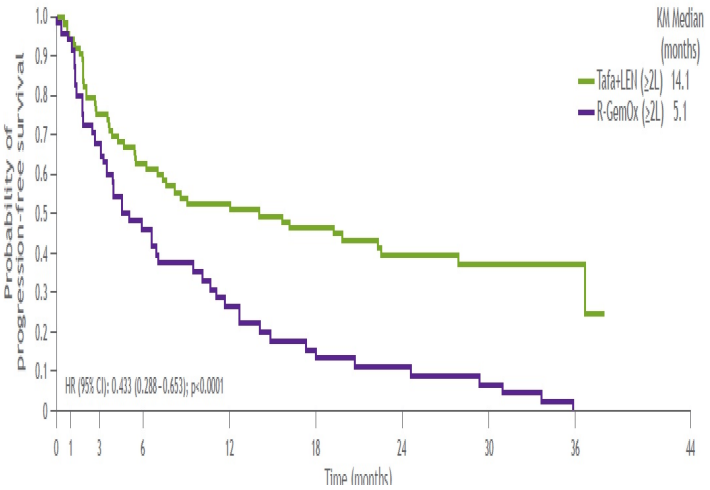
RE-MIND2: PROGRESSION FREE SURVIVAL

	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: 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

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)

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

Grzegorz S. Nowakowski,[1*] Dok Hyun Yoon,[2] Patrizia Mondello,[3] Erel Joffe,[3] Anthea Peters,[4] Isabelle Fleury,[5] Richard Greil,[6] Matthew Ku,[7] Reinhard Marks,[8] Kibum Kim,[9] Pier Luigi Zinzani,[10] Judith Trotman,[11] Lorenzo Sabatelli,[12] Dan Huang,[13] Eva E. Waltl,[13] Mark Winderlich,[13] Sumeet Ambarkhane,[13†] Nuwan C. Kurukulasuriya,[14] Raul Cordoba,[15] Georg Hess,[16] Gilles Salles[3]

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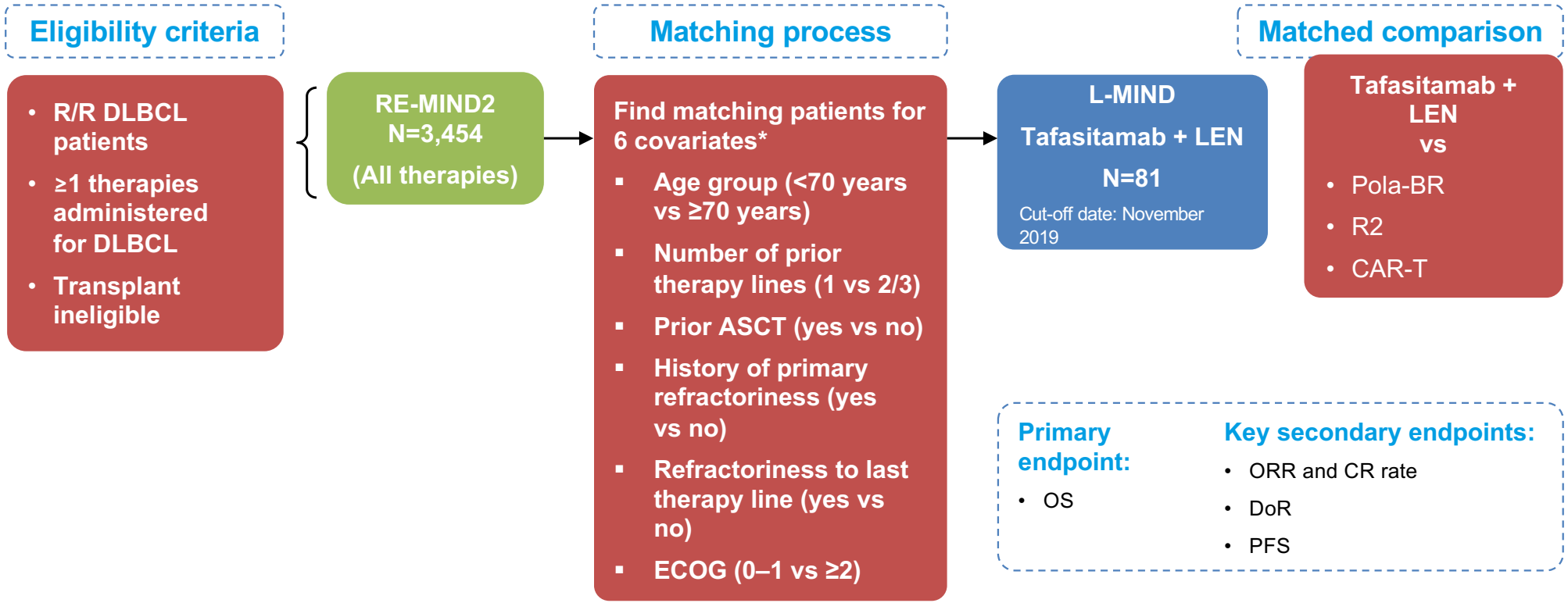
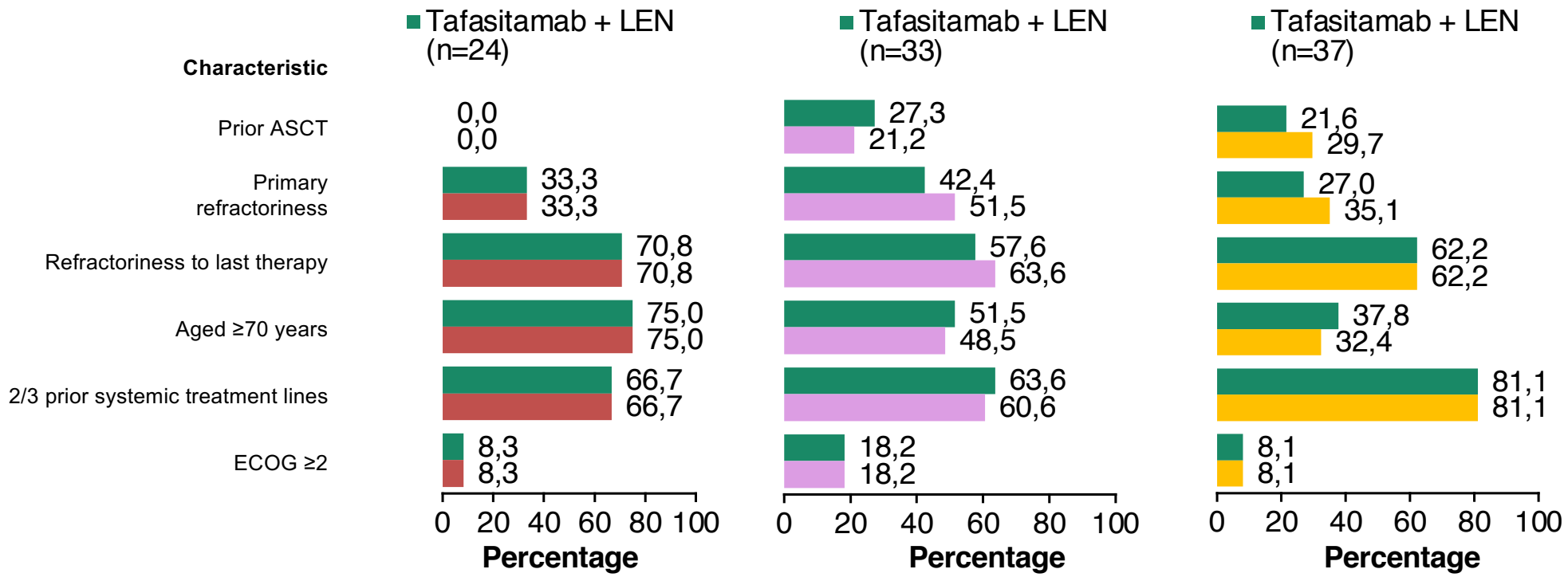
RE-MIND2 expanded analysis study design



* 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.

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

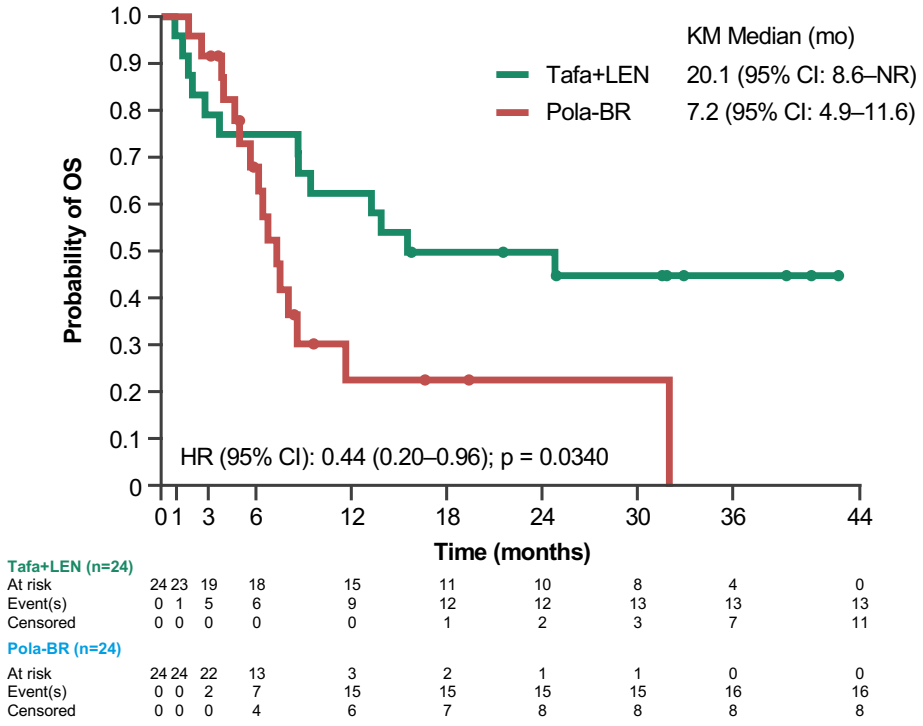
- A high degree of covariate balance was achieved between the tafasitamab plus LEN and comparator therapy cohorts



- 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.

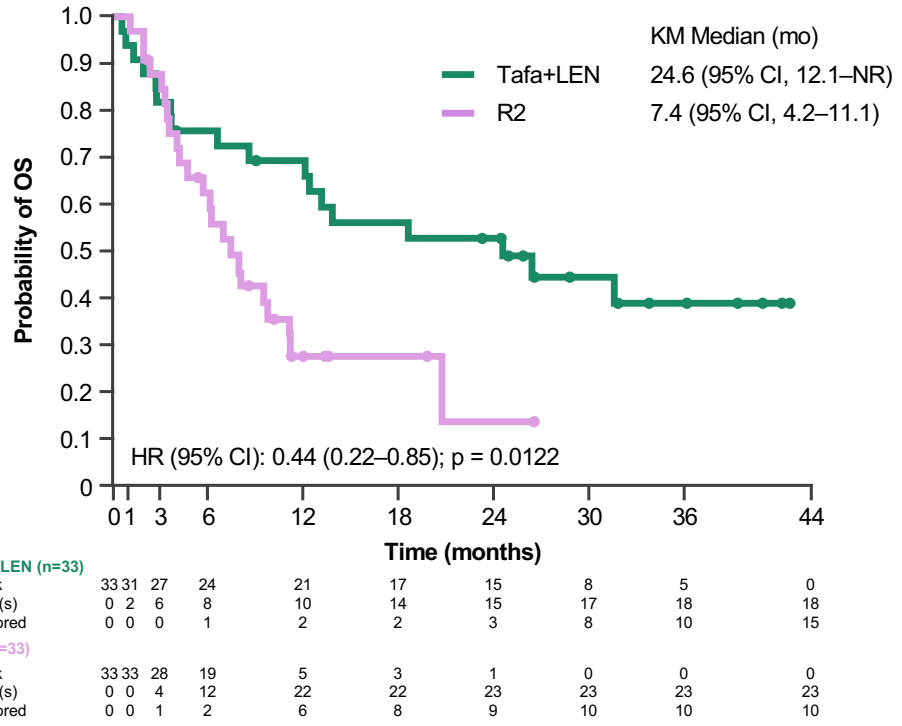
Primary endpoint: OS

- 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



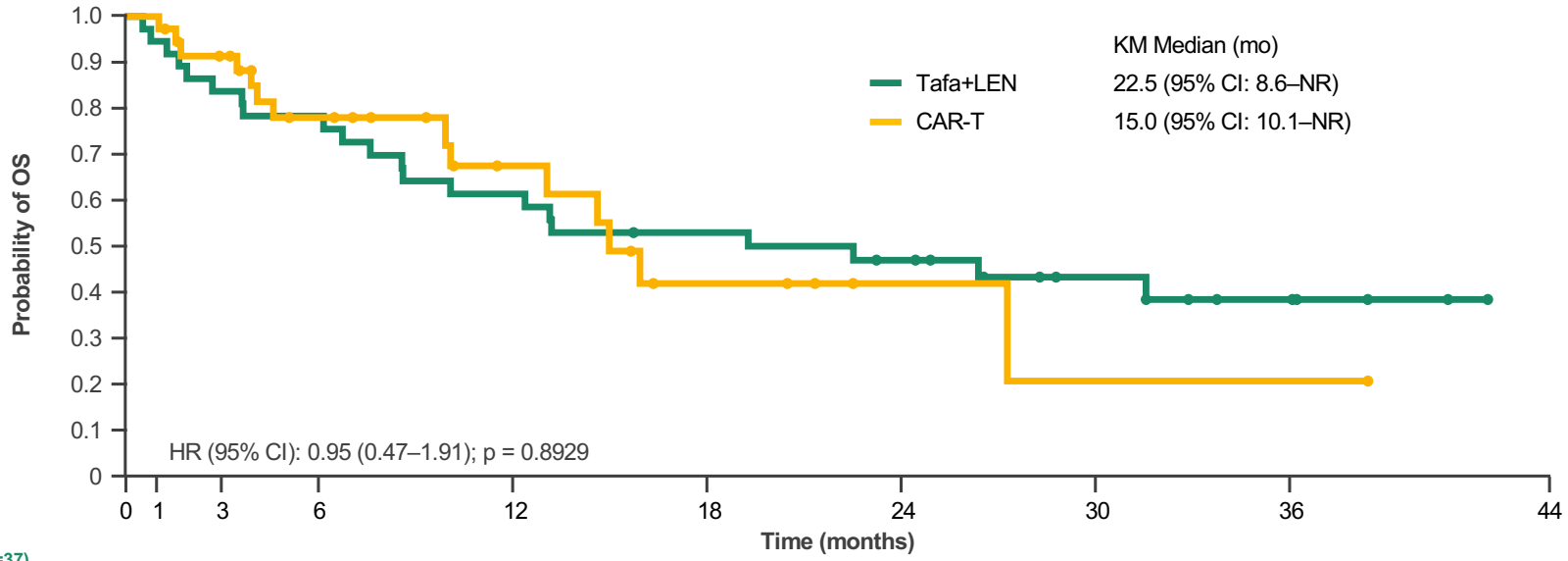
Tafa+LEN (n=33)										
At risk	33	31	27	24	21	17	15	8	5	0
Event(s)	0	2	6	8	10	14	15	17	18	18
Censored	0	0	0	1	2	2	3	8	10	15
R2 (n=33)										
At risk	33	33	28	19	5	3	1	0	0	0
Event(s)	0	0	4	12	22	22	23	23	23	23
Censored	0	0	1	2	6	8	9	10	10	10

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

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



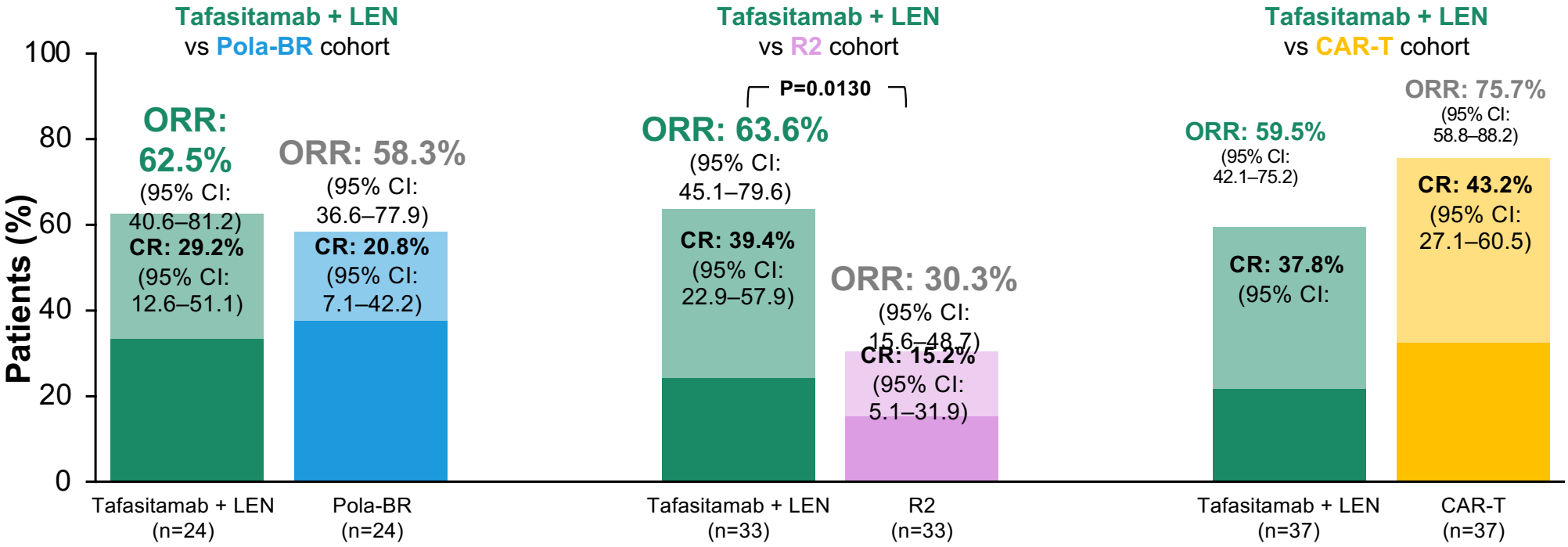
Tafa+LEN (n=37)										
At risk	37	35	31	28	22	18	15	9	5	0
Event(s)	0	2	6	8	14	17	19	20	21	21
Censored	0	0	0	1	1	2	3	8	11	16
CAR-T (n=37)										
At risk	37	37	30	22	11	5	2	1	1	0
Event(s)	0	0	3	7	9	13	13	14	14	14
Censored	0	0	4	8	17	19	22	22	22	23

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.

Secondary endpoint: ORR and 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.

Conclusions (RE-MIND2-bis)

- 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
- 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

CAR-T, CD19 chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma;
LEN, lenalidomide; OS, overall survival; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide; R/R relapsed/refractory; RWD, real-world data.

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