Eppur si muove...

La terapia nel MONDO LINFOMI

Nuove Strategie terapeutiche anti CD19 nel paziente ricaduto/refrattario: STUDI RE-MIND E RE-MIND2

Enrico Derenzini

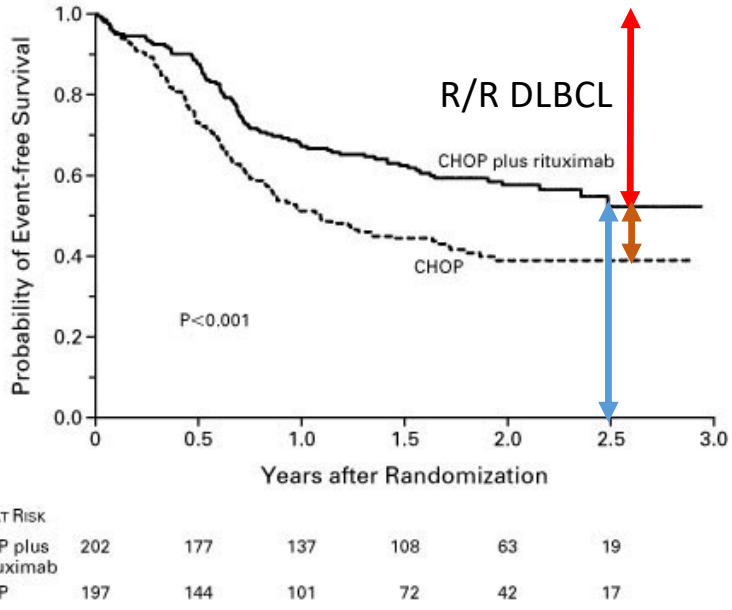
MILANO, 4 APRILE 2022

DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ADC-Therapeutics	Y	N	N	N	N	N	N
Roche	N	N	N	N	N	Y	N
BeiGene	N	N	N	N	N	Y	N
Astra-Zeneca	N	N	Y	N	N	Y	N
Takeda	Y	N	N	N	N	Y	N
Abbvie	N	N	N	N	N	Y	N
Y= Yes							
N= No							

BACKGROUND

(IMMUNO)CHEMORESISTANT PHENOTYPE IN DLBCL



Coiffier et al. NEJM 2002

60-70%

30-40%

R-CHOP

CURED

R/R

IMMUNE ESCAPE MECHANISMS

INTACT IMMUNE FUNCTION

DISRUPTED IMMUNE FUNCTION

GENOMICS

INTACT G1/S CHECKPOINT
-LOW INCIDENCE OF TP53/CDKN2A ALTERATIONS

FUNCTIONAL STATUS

LOW APOPTOTIC THRESHOLD
LOW LEVELS OF INHERENT OXIDATIVE STRESS
NO DDR ACTIVATION

<u>GENOMIC REWIRING</u>

ENRICHMENT IN G1-S CHECKPOINT GENOMIC ALTERATIONS (TP53, CDKN2A)

<u>FUNCTIONAL REWIRING</u>

METABOLIC REWIRING (MYC)

CONSTITUTIVE ACTIVATION OF THE DDR (MYC) AND TOLERANCE TO DNA DAMAGE

RESISTANCE TO APOPTOSIS AND OXIDATIVE STRESS (BCL-2)

BACKGROUND

NOVEL THERAPEUTIC STRATEGIES FOR R/R DLBCL

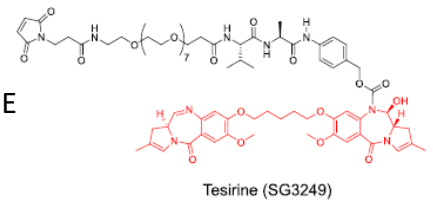
IMMUNOTOXINS

ANTIBODY DRUG CONJUGATES:

TP53 AND CELL CYCLE-INDEPENDENT ACTIVITY

PBD- DIFFICULT TO REPAIR INTERSTRAND CROSSLINKS
CELL-CYCLE INDEPENDENT ACTIVITY

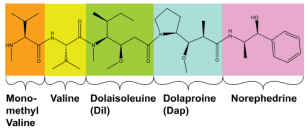
TESIRINE



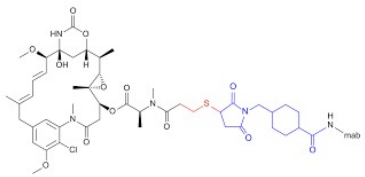
G2/M CHECKPOINT BLOCKADE

ANTI-TUBULIN AGENTS

MMAE

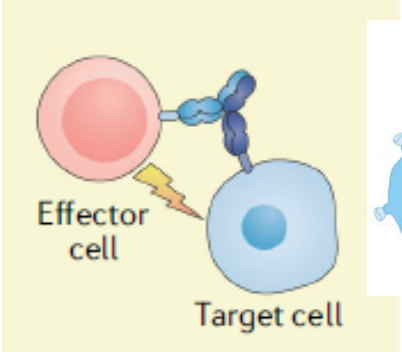


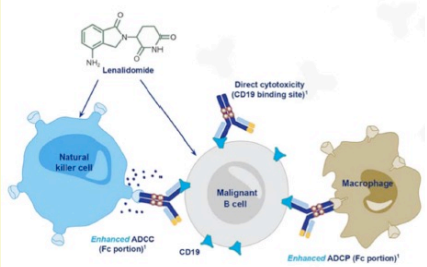
EMTANSINE



«ENHANCED» IMMUNOTHERAPY

IMMUNO COMBOs (TAFA-LENA)
BISPECIFIC ANTIBODIES, BITES, TRIKES





MOSUNETUZUMAB
EPCORITAMAB
ODRONEXTAMAB
GLOFITAMAB

TAFASITAMAB-LENALIDOMIDE

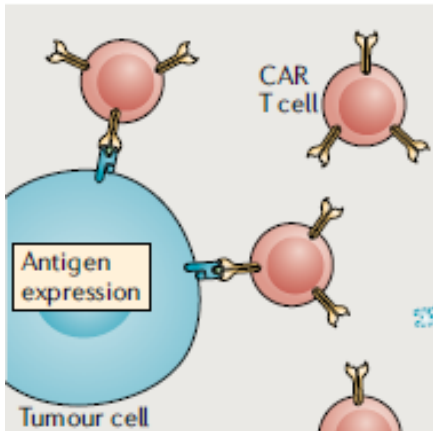
Labrijn et al.
Nat Rev Drug Disc 2019

Salles et al. Lancet Oncol 2020
Cheson et al. BCJ 2021

CELL THERAPY

CAR-T CELLS

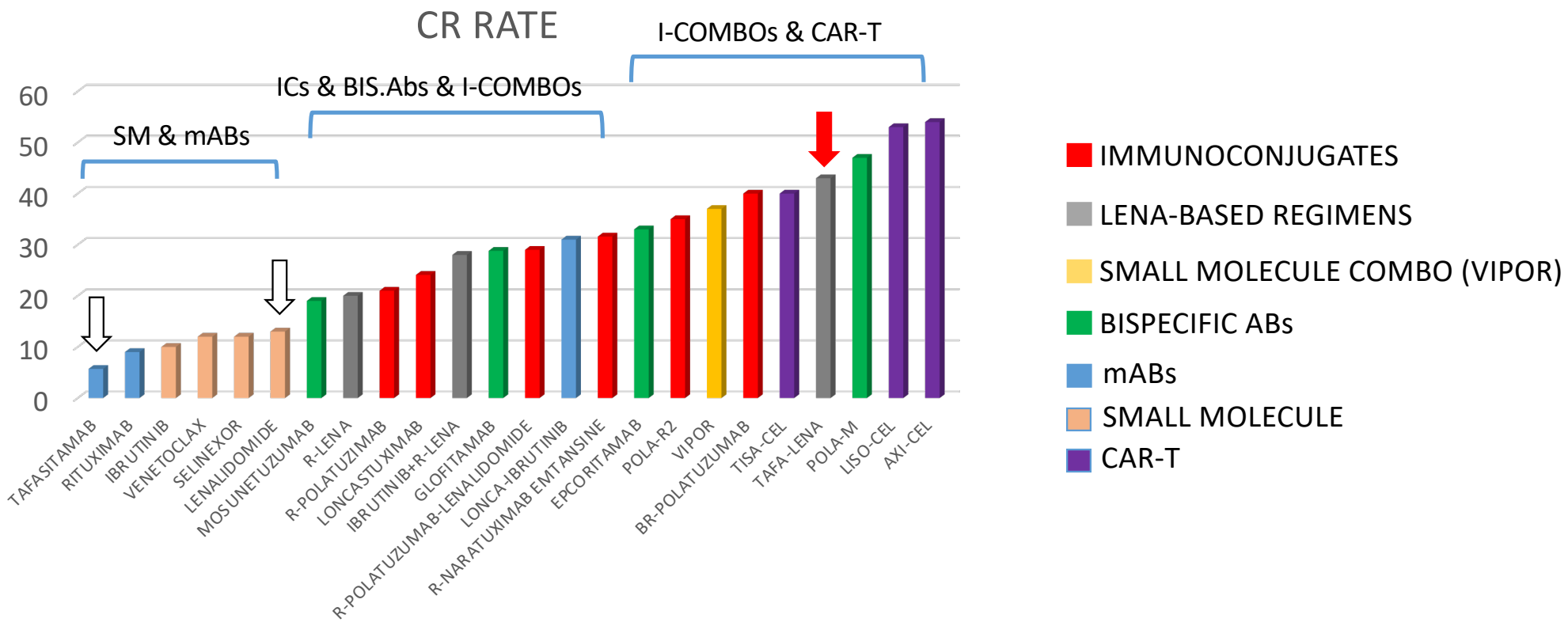
CAR-NK CELLS



Brown and Mackall
Nat Rev Immunology 2019

BACKGROUND

NOVEL THERAPEUTIC STRATEGIES FOR R/R DLBCL SUMMARY



L-MIND STUDY

L-MIND

Tafasitamab-Lenalidomide
CD19

Phase II

80 DLBCL PTS receiving at least 1 dose

43% CR RATE

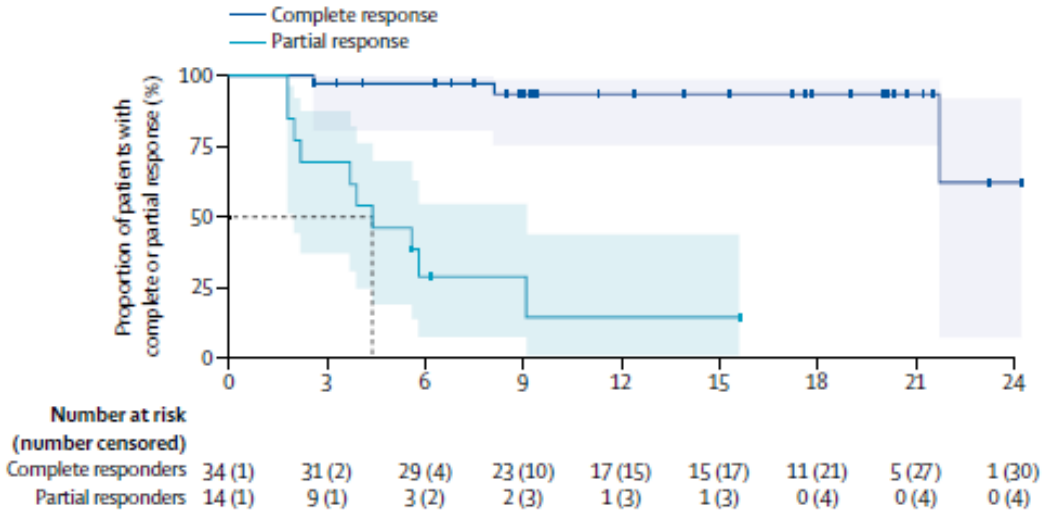
Primary refractory 19%

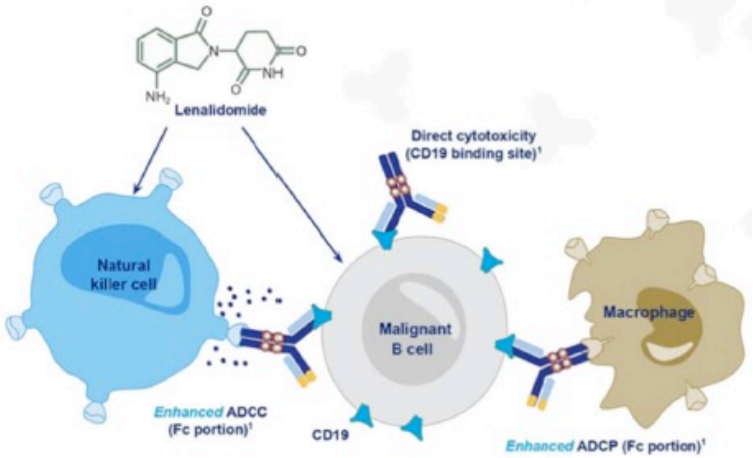
DHL 2%

	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

Data are n (%; 95% CI) or n/N (%). *One patient received tafasitamab only. †Patients had no valid postbaseline response assessments. ‡Complete response plus partial response. §Complete response plus partial response plus stable disease.

Table 2: **Best objective response according to independent radiology**





Salles et al. Lancet Oncol 2020
Cheson et al. BCJ 2021

RE-MIND AND RE-MIND2 STUDIES

L-MIND STUDY OPEN QUESTIONS:

WHAT IS THE RELATIVE CONTRIBUTION OF TAFASITAMAB TO THE EFFICACY OF THE COMBINATION

RE-MIND

WHAT IS THE RELATIVE EFFICACY OF TAFA-LEN COMPARED TO CURRENT SALVAGE TREATMENTS

RE-MIND 2

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]

Study Objective:

- to characterize the effectiveness of lenalidomide monotherapy
- to compare a matched cohort with the efficacy of tafasitamab plus lenalidomide combination therapy in L-MIND (primary endpoint ORR).

Estimated propensity score (ePS)-based Nearest Neighbor 1:1 **Matching methodology** used to balance the two cohorts for nine prespecified baseline covariates of prognostic importance

Zinzani et al. CCR 2021

METHODS

……A matched real-world comparative lenalidomide-monotherapy cohort with similar prognostic baseline characteristics to the L-MIND cohort…….

TAFA-LEN **VS** **LEN mono Real World**

1-age (<70 vs. ≥70 years),
2-Ann Arbor
3-stage (I/II vs. III/IV),
4-refractoriness to last therapy line
5-number of prior lines of therapy
6-history of primary refractoriness
7-prior ASCT
8-neutropenia
9-anemia

10-ECOG (prespecified sensitivity analysis)

METHODS

INCLUSION/EXCLUSION CRITERIA

Eligibility criteria (L-MIND study):

Age ≥18 years

Histologically confirmed DLBCL
(including transformed lymphoma)

R/R after 1 to 3 prior systemic therapies (including ≥1 CD20-targeting regimens)

Not candidates for HDC and subsequent ASCT.

Exclusion criteria:

Central nervous system lymphoma involvement

Lenalidomide in combination with another anti-lymphoma therapy, including radiation

Prior treatment with anti-CD19 therapy or immunomodulatory drugs, such as thalidomide/lenalidomide

Known ‘double/triple-hit’ DLBCL

Prior history of malignancies other than DLBCL (unless disease-free for ≥5 years)

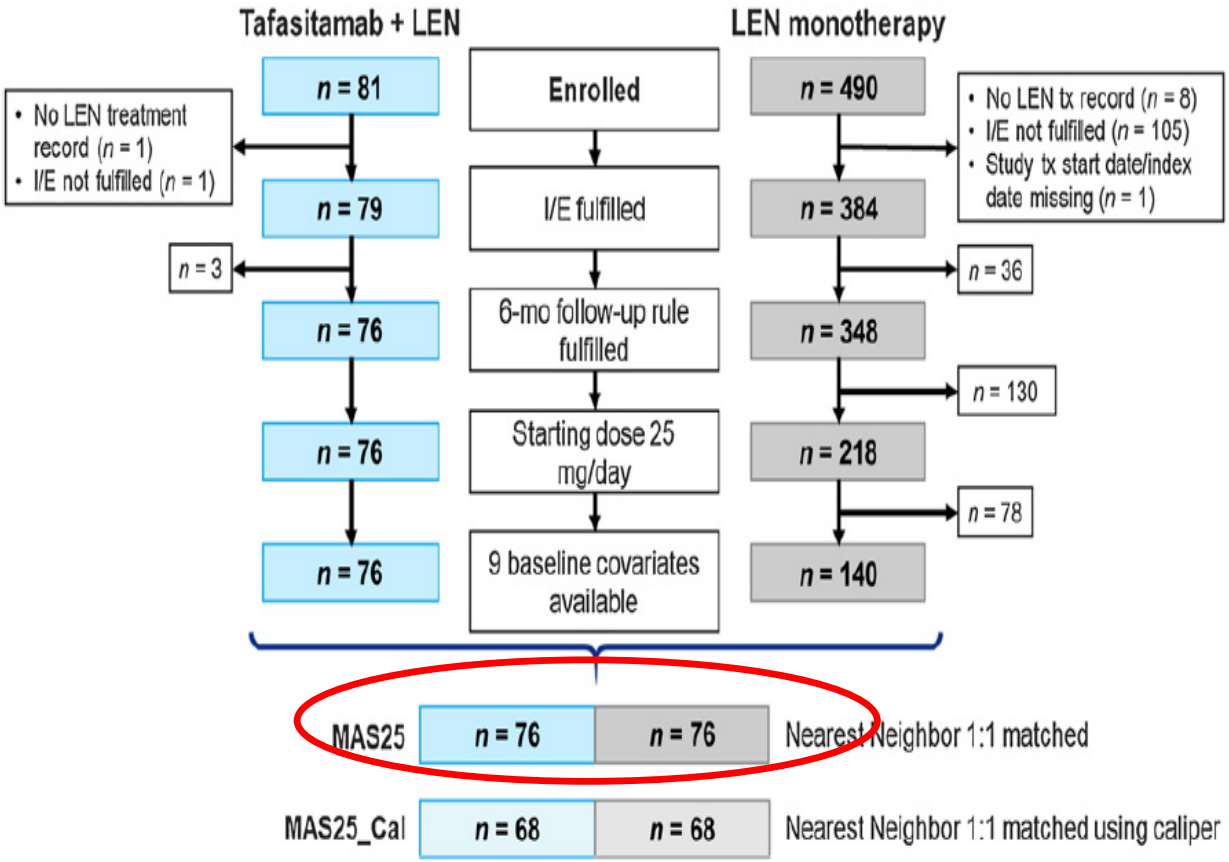
METHODS

Observational period: January 2005 to July 2019.

Statistical Power:

With an assumed difference of 23% in ORR for lenalidomide monotherapy (35%) versus the tafasitamab–lenalidomide combination (58%), the achieved power was 80% and the minimal detectable statistical difference in ORR was 17% using Fisher's exact test for unpaired data.

A sample size of 500 patients was projected for the lenalidomide monotherapy cohort.

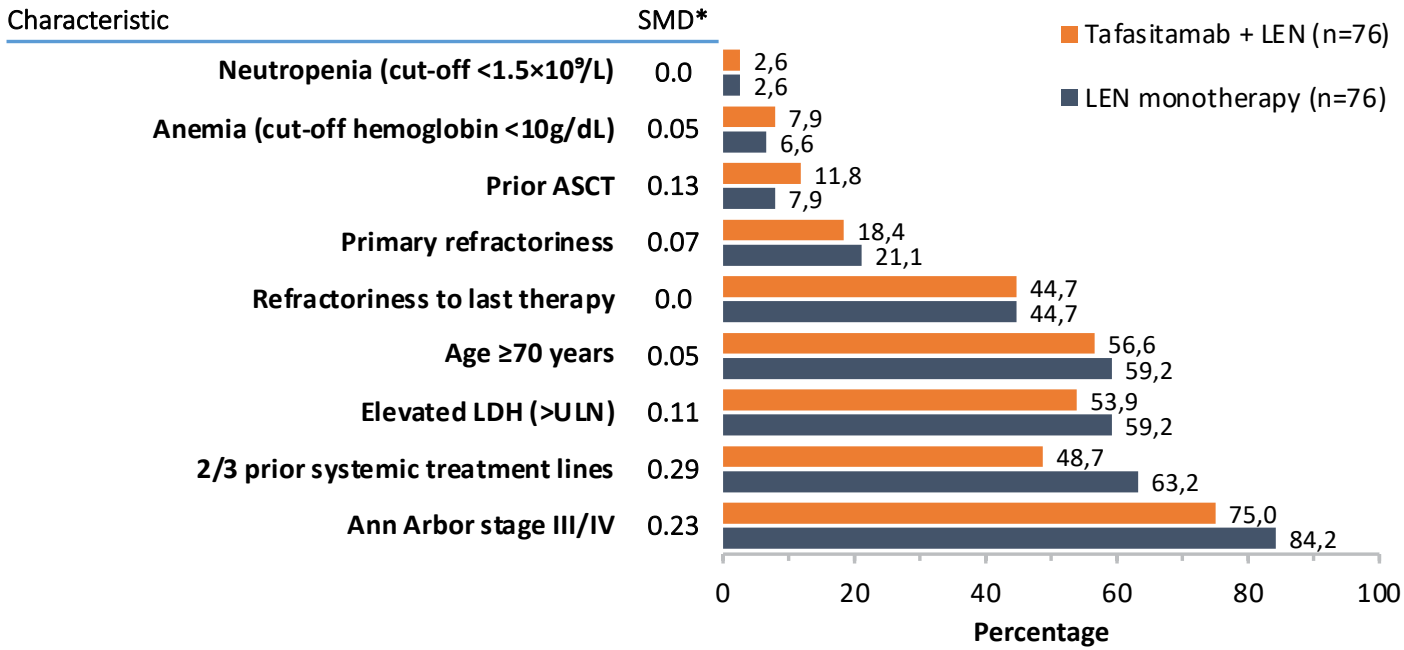


Zinzani et al. CCR 2021

RESULTS

BASELINE CHARACTERISTICS USED FOR COHORT BALANCING

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

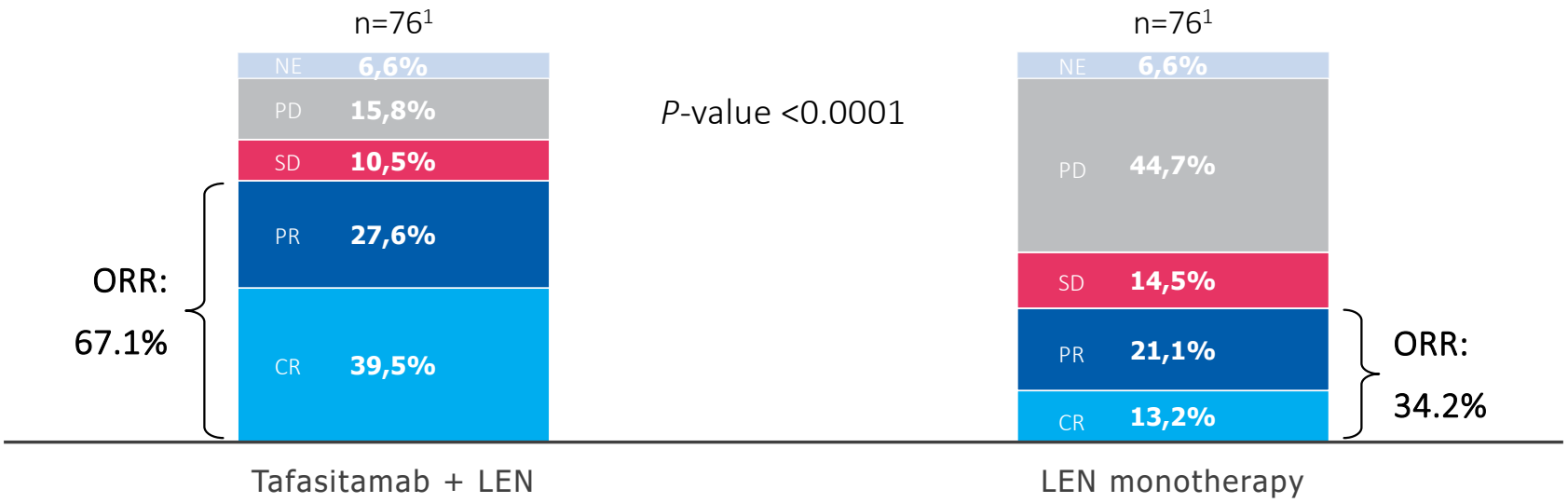


*SMD is defined as the ratio of the difference of proportions of a baseline characteristic to the standard deviation of the pooled difference. This standardisation allows for comparison of the relative balance achieved across different baseline characteristics occurring in a low or high proportion.
ASCT, 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.

Zinzani et al. CCR 2021

RESULTS

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)

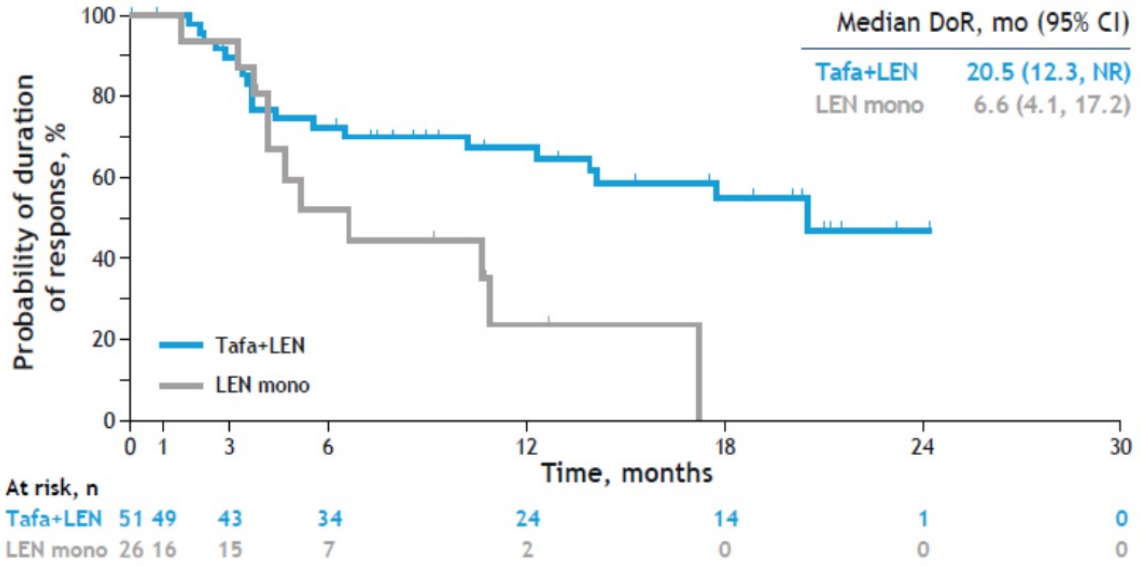
Investigator assessed (IRC-assessed ORR for tafasitamab + LEN in L-MIND was 57.5%[2]).
CI, confidence interval; CR, complete response; IRC, independent review committee; LEN, lenalidomide; NE, not evaluated;
ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
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.

Zinzani et al. CCR 2021

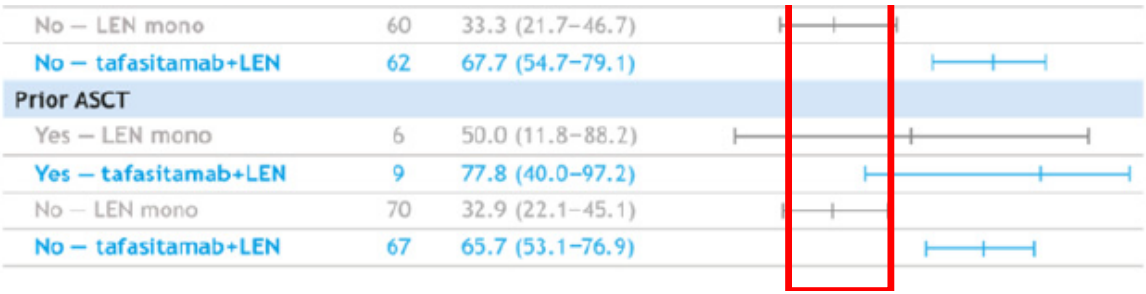
ORR
DoR

RESULTS

DURATION OF RESPONSE



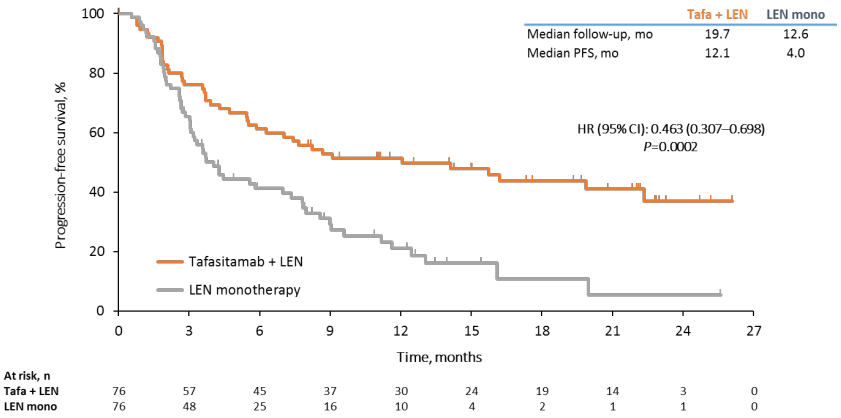
CI, confidence interval; DoR, duration of response; LEN, lenalidomide; MAS25, matched analysis set 25; mo, month; NR, not reached



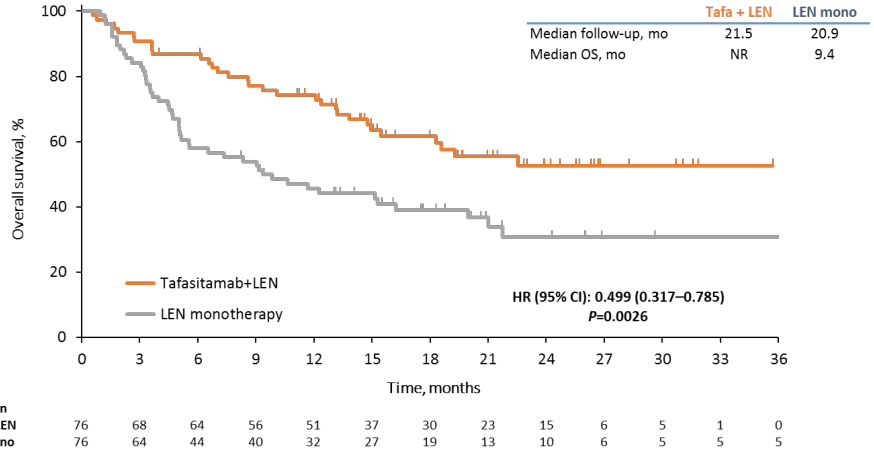
Zinzani et al. CCR 2021

RESULTS

PFS



OS



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

Zinzani et al. CCR 2021

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

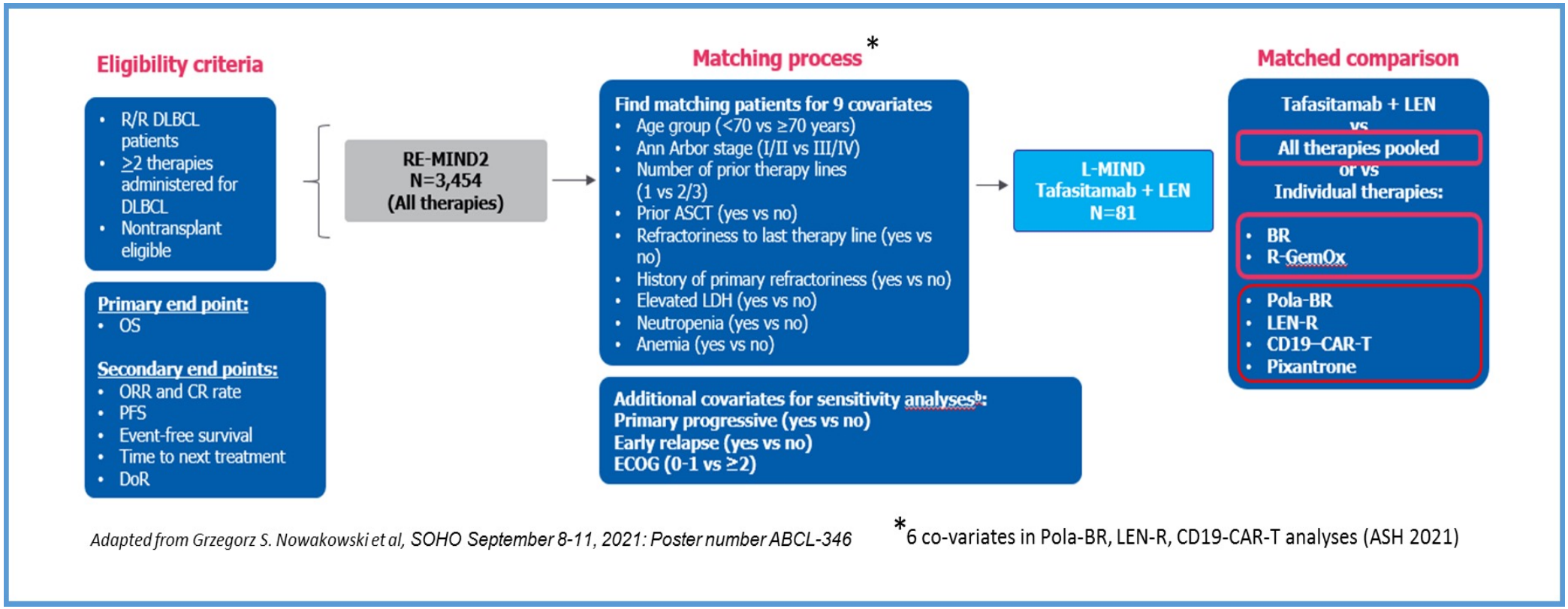
CONCLUSIONS: RE-MIND

- Substantial additional activity for the novel combination of tafasitamab + LEN versus LEN monotherapy in transplant-ineligible R/R DLBCL patients
- 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

Adapted from Nowakowski G, et al. Poster presentation at ASCO 2020; Abstract 8020.

SOHO & ASH 2021

RE-MIND2: STUDY DESIGN AND METHODS



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

*6 co-variates in Pola-BR, LEN-R, CD19-CAR-T analyses (ASH 2021)

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

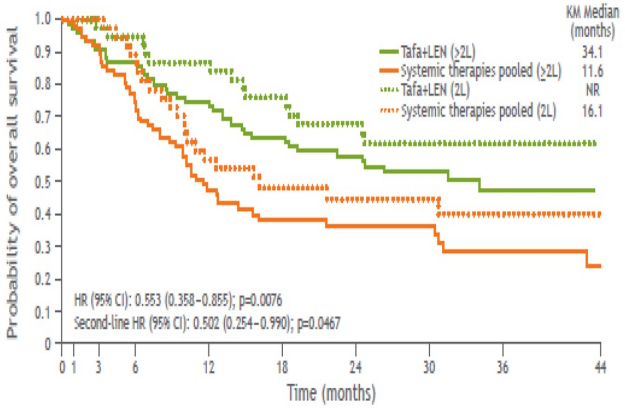
Adapted from Grzegorz S. Nowakowski et al, SOHO September 8-11, 2021: Poster number ABCL-346

SOHO 2021
BR, GEMOX

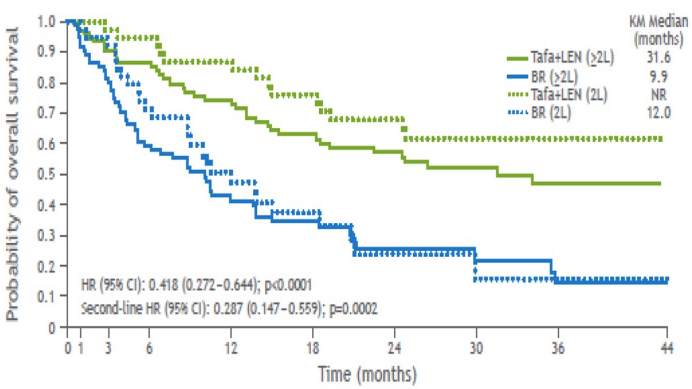
RE-MIND2: OVERALL SURVIVAL

	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	

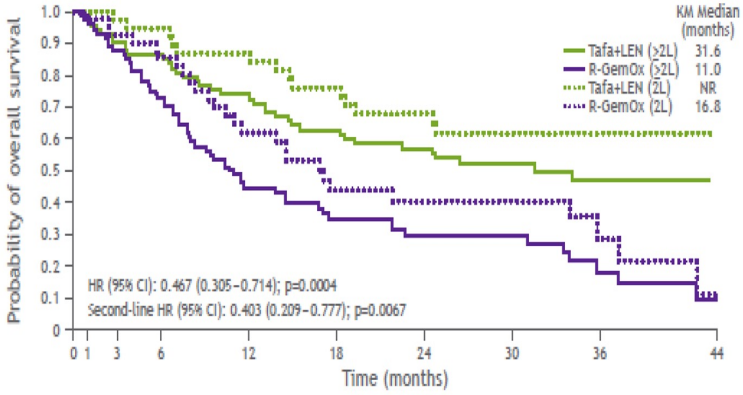
N=76



N=75



N=74



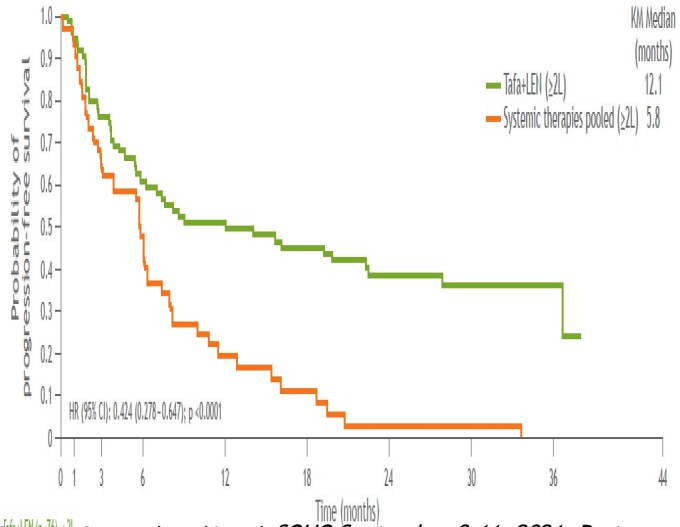
Grzegorz S. Nowakowski et al, SOHO September 8-11, 2021: Poster number ABCL-346

SOHO 2021
BR, GEMOX

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	

N=76



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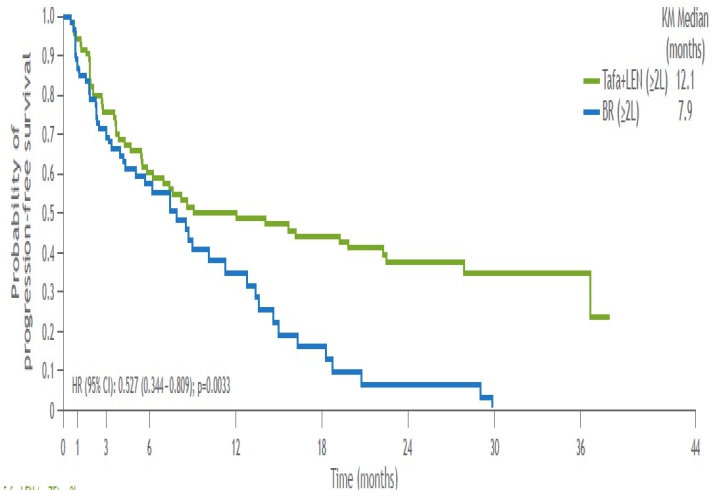
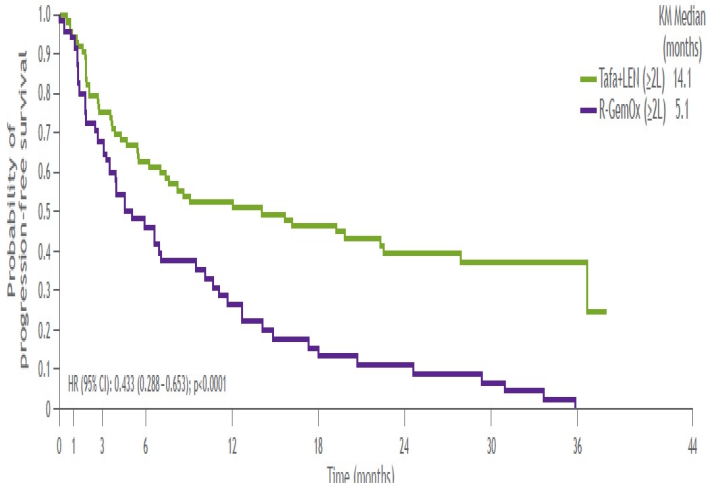


N=74

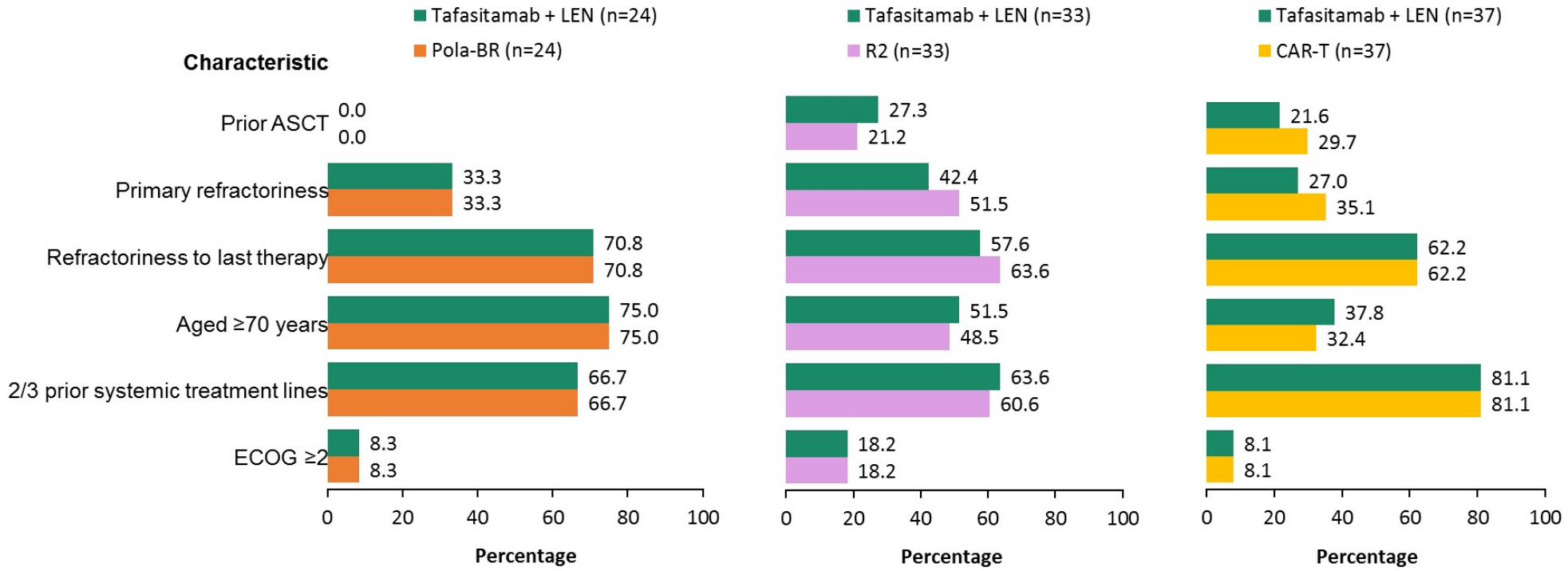


Grzegorz S. Nowakowski et al, SOHO September 8-11, 2021: Poster number ABCL-346

Analysis populations: Pola-BR, R2, CAR-T

ASH 2021

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



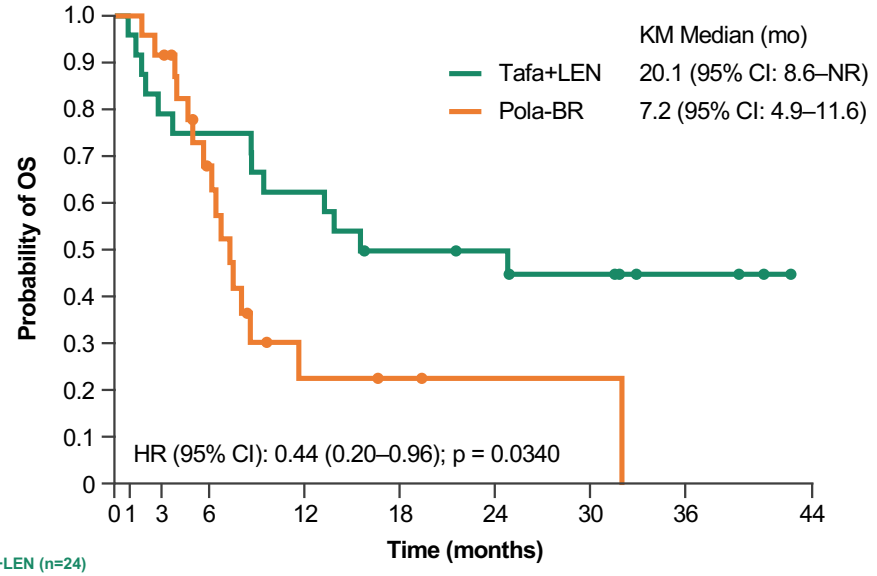
- ASCT, autologous stem-cell transplant; CAR-T, CD19 chimeric antigen receptor T-cell therapies; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide.

Grzegorz S. Nowakowski et al, ASH 2021

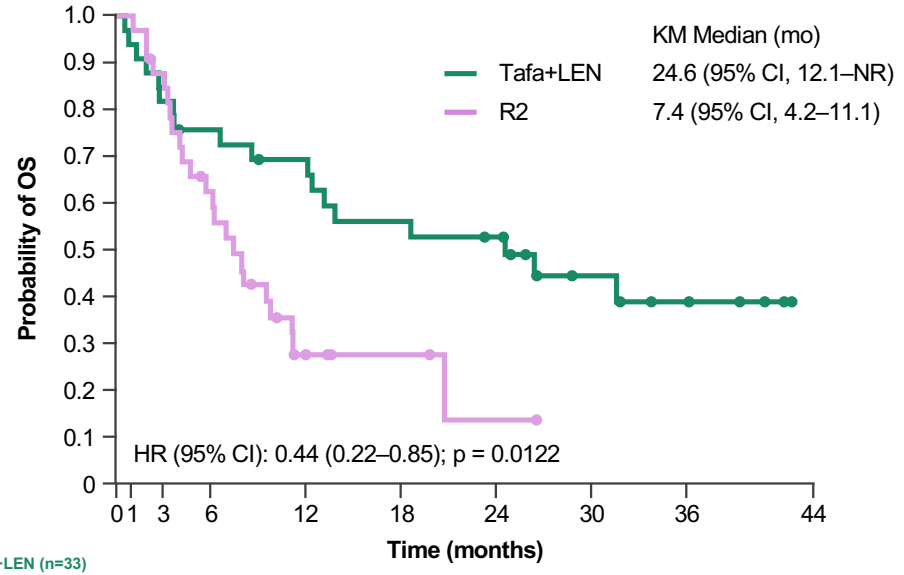
Primary endpoint: OS (Pola-BR, R2)

ASH 2021

- 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



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; Pola-BR: 16.6 mo

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.

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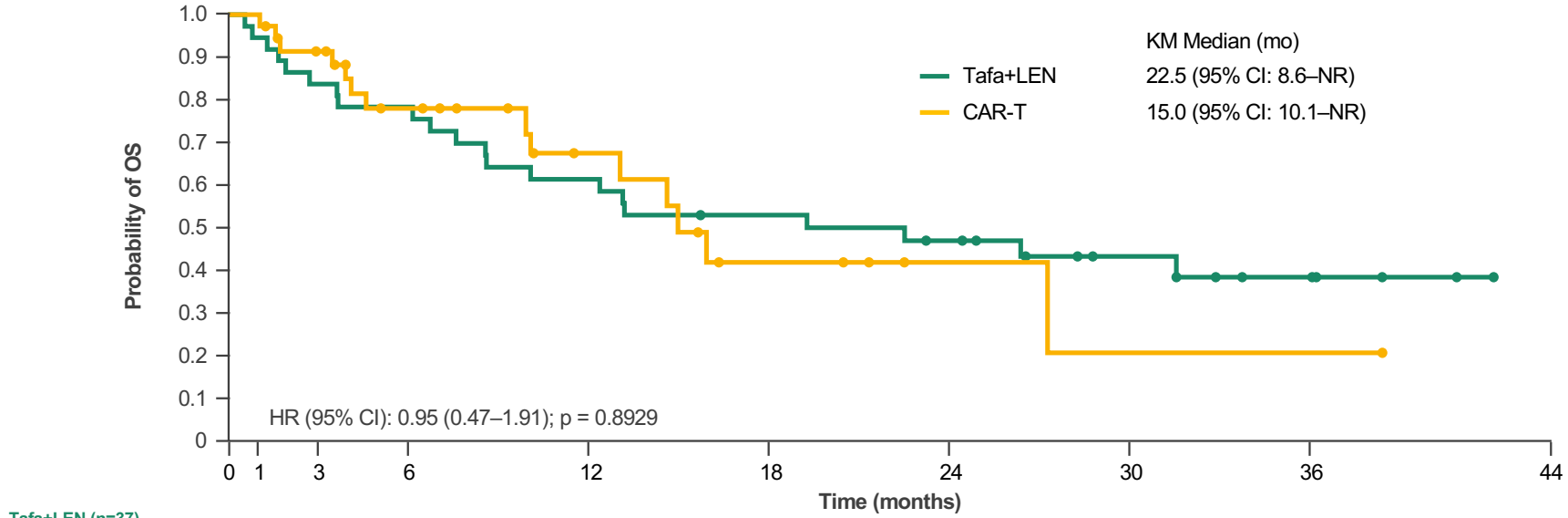
Primary endpoint: OS (CAR-T)

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



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.

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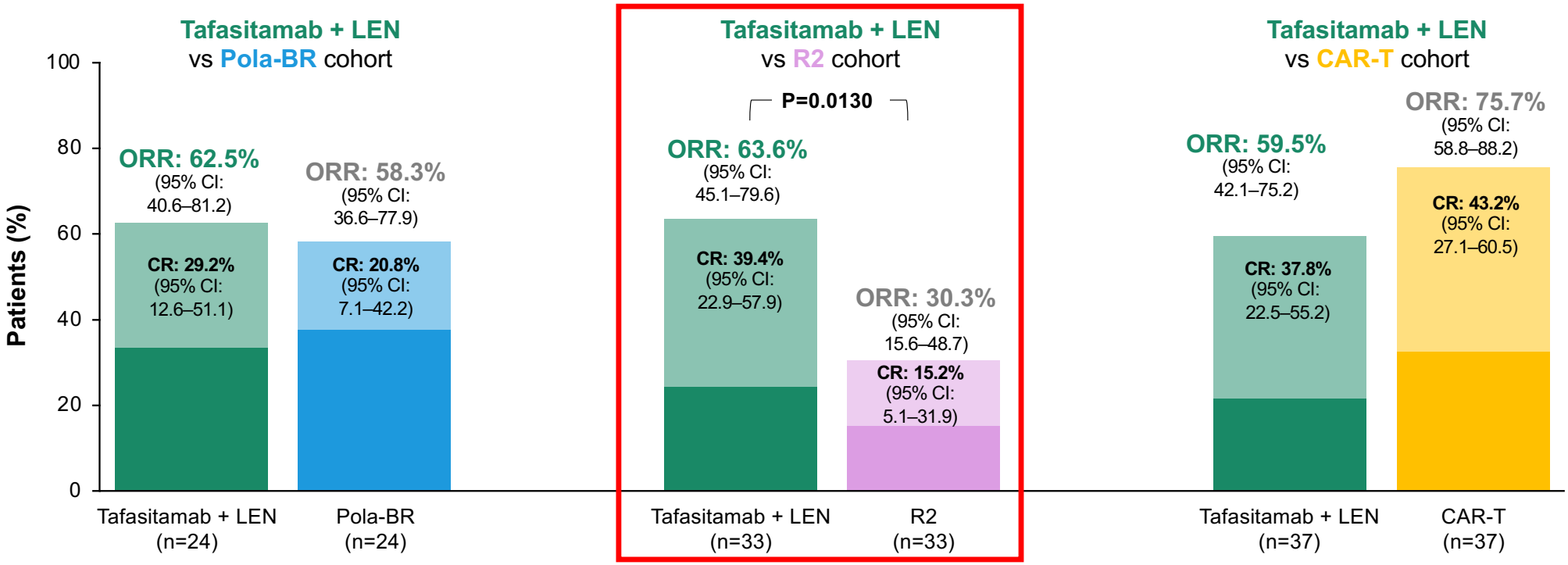
Secondary endpoint: ORR and CR rate

ASH 2021

- 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.

Grzegorz S. Nowakowski et al, ASH 2021

RE-MIND2: CONCLUSIONS

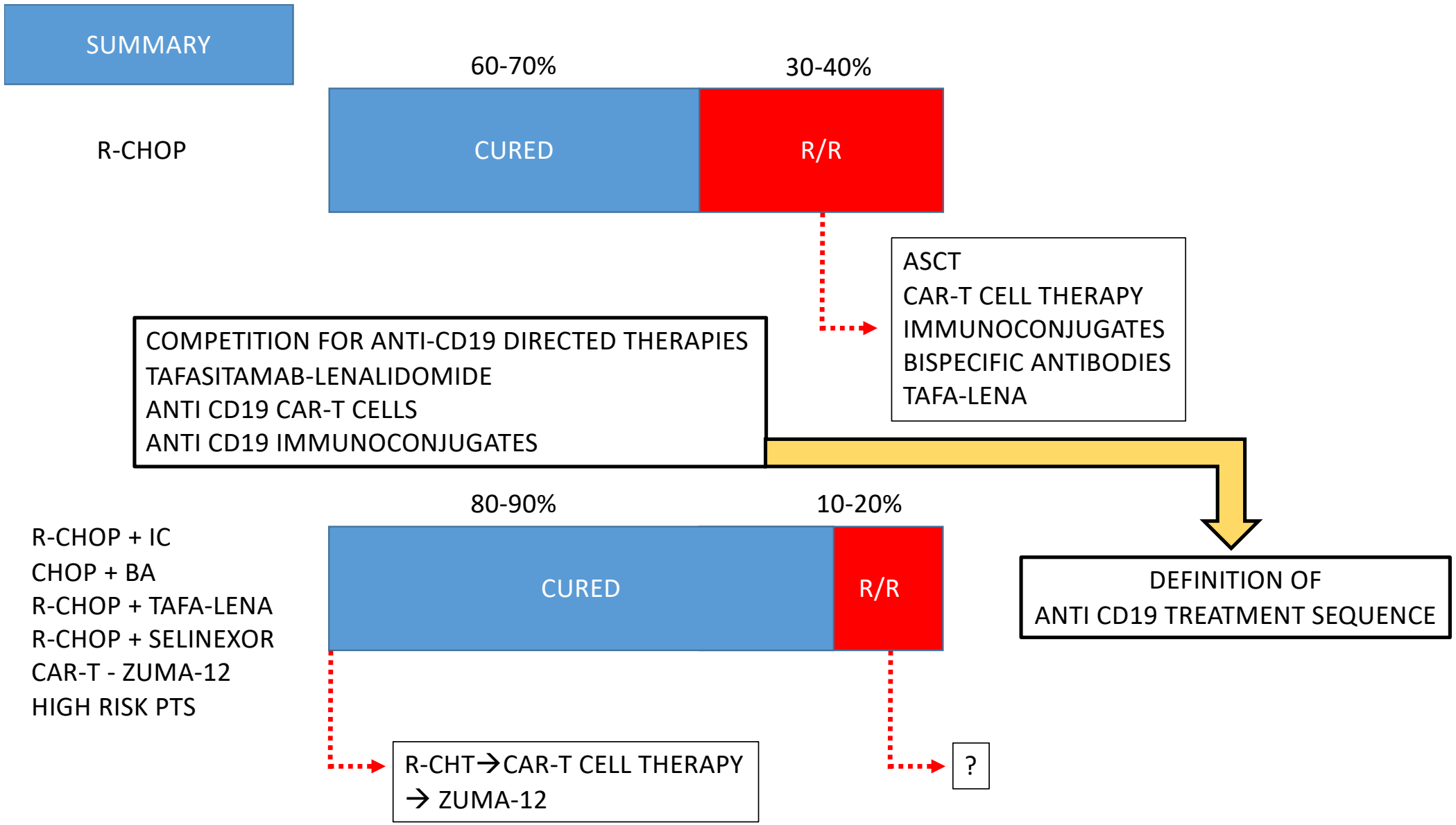
Tafasitamab + LEN was associated with longer OS
vs systemic therapies pooled, BR, and R-GemOx
vs Pola-BR and R2

Median OS was comparable with tafasitamab + LEN relative to CAR-T therapies

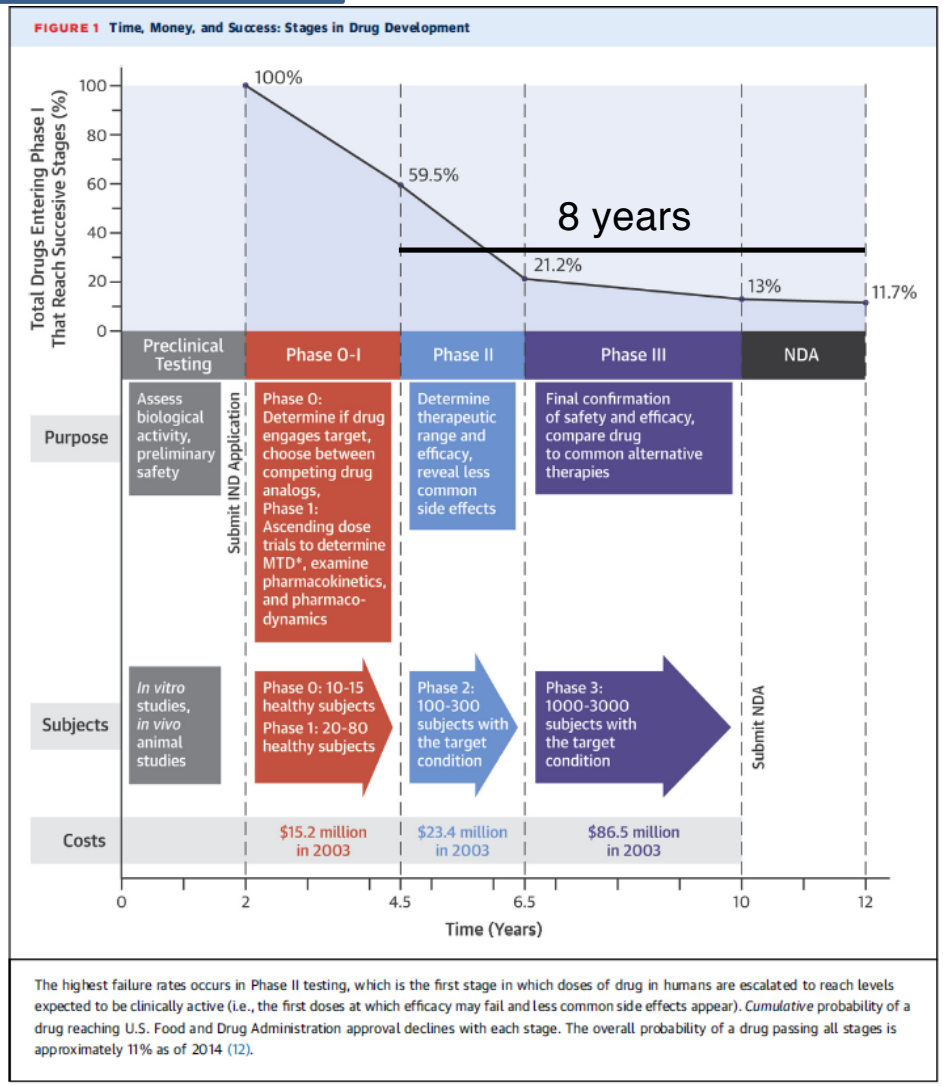
The RE-MIND2 study design allows a contextualization of outcomes with different treatments in the absence of head-to-head trials: possible accelerated drug development.
Head to head trials have biases as well (e.g. ROBUST, PHOENIX)

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

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


SUMMARY
R-CHOP
60-70%
30-40%
CURED
R/R
ASCT
CAR-T CELL THERAPY
IMMUNOCONJUGATES
BISPECIFIC ANTIBODIES
TAFA-LENA
COMPETITION FOR ANTI-CD19 DIRECTED THERAPIES
TAFASITAMAB-LENALIDOMIDE
ANTI CD19 CAR-T CELLS
ANTI CD19 IMMUNOCONJUGATES
DEFINITION OF
ANTI CD19 TREATMENT SEQUENCE
R-CHOP + IC
CHOP + BA
R-CHOP + TAFA-LENA
R-CHOP + SELINEXOR
CAR-T - ZUMA-12
HIGH RISK PTS
80-90%
10-20%
CURED
R/R
R-CHT→CAR-T CELL THERAPY
→ ZUMA-12
?

GRAZIE



The highest failure rates occurs in Phase II testing, which is the first stage in which doses of drug in humans are escalated to reach levels expected to be clinically active (i.e., the first doses at which efficacy may fail and less common side effects appear). *Cumulative* probability of a drug reaching U.S. Food and Drug Administration approval declines with each stage. The overall probability of a drug passing all stages is approximately 11% as of 2014 (12).

PROPENSITY SCORE MATCHING
ALLOWS contextualization of outcomes with different treatments in the absence of head-to-head trials.

Possible implication for accelerated drug-development platforms

PS MATCHING SHOULD NOT SUBSTITUTE RANDOM PHASE III TRIALS

BUT RANDOM PHASE III TRIALS ARE NOT EXEMPT FROM BIASES

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