

Session V. Lymphomas with good prognosis : do not harm

THE INDOLENT LYMPHOMAS

C. Thieblemont



ROMA
HEMATOLOGY
CONFERENCE
the lymphomas

Rome

October 15-16, 2026

Hotel nhow Roma

Disclosure: nome e cognome

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Travels
MSD			X			X	
Kyte/Gilead			X			X	
ROCHE			X			X	X
ABBVIE / GENMAB			X			X	
BeOne			X			X	X
BMS			X			X	X
Amgen			X			X	
Janssen			X			X	
Incyte			X			X	

THE INDOLENT B-CELL LYMPHOMAS

- **Long overall survival, but until now considered as incurable**
- **Chemo - antiCD20 immunotherapy is still the standard but cumulative toxicity, poor tolerability in unfit patients and emerging resistance**
- **Immunotherapies and targeted agents induce unprecedented high response rate , but is associated with a new profile of toxicity**

Follicular Lymphoma and Marginal Zone Lymphomas

Remarquable progresses in the understanding the biology

Genetic/molecular abnormalities

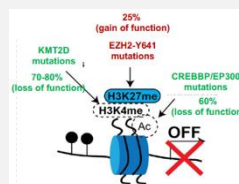
Early driver mutations

BCL2, not sufficient

FL

Epigenetic mutations

- CREBBP
- EZH2
- KMT2D

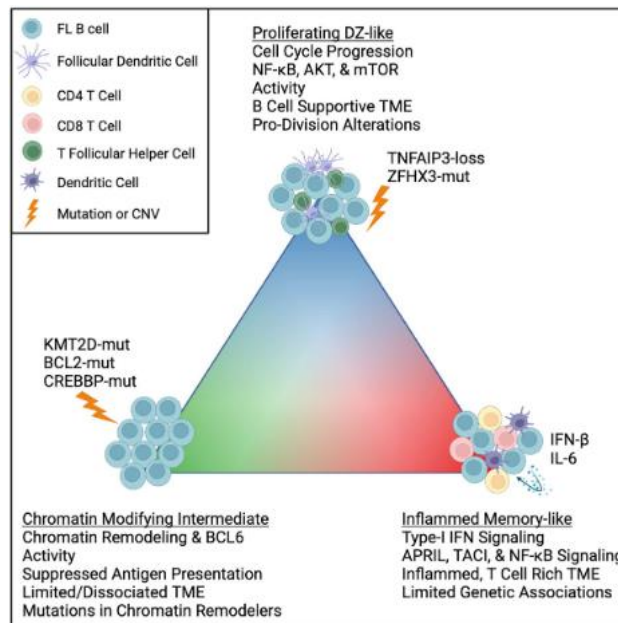


Genetic hallmarks

MZL

- NF-KB activation
- KLF2/NOTCH2
- KMT2D

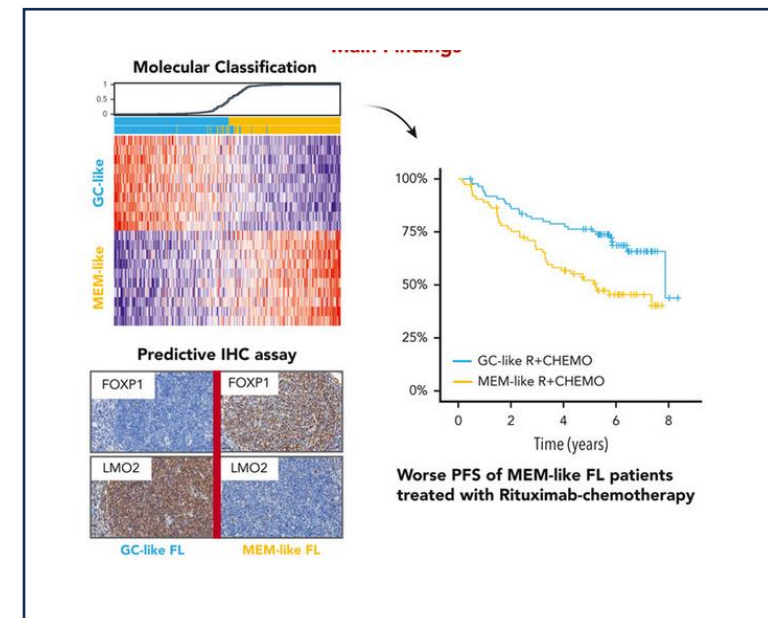
Heterogeneous Tumor microenvironment



FL Krull et al., Cell Reports Medicine, 2024

MZL Bonfiglio F, Blood. 2022

Multiple clones in the same patient



FL Laurent C et al. Blood 2024

FL Schroers-Martin et al Cancer Discov 2023

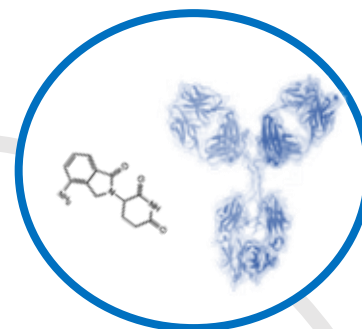
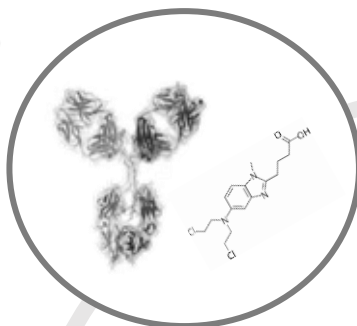
- Genetic/molecular abnormalities
- Microenvironment contribution
- Clonal heterogeneity

Precision medicine = significant challenge in these lymphomas

Variable options in the management of both newly diagnosed and relapsed indolent lymphomas

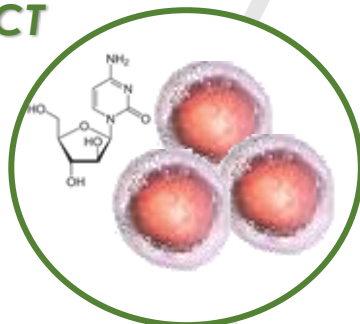
Fc ENGAGER THERAPIES

antiCD20-chemotherapy



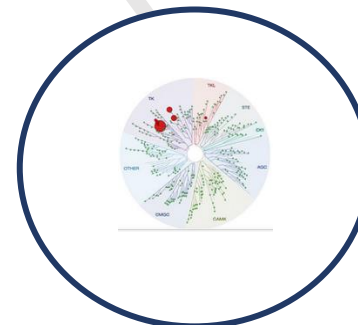
- R2- based regimen
- EZH2 inh=Tazemetostat

HDT/ASCT

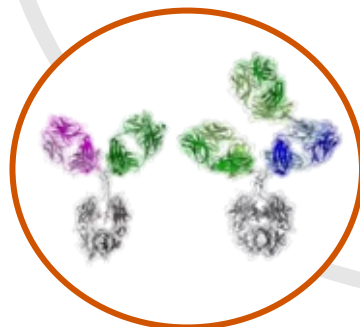


Options for indolent lymphomas

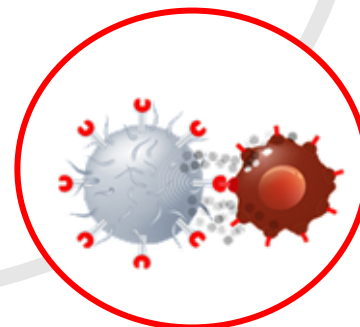
BTKi – based regimen



Bi-specific antibodies*



CAR T and Adoptive Cell Therapy



T-CELL ENGAGER THERAPIES

* Not approved in France for R/R iNHL.

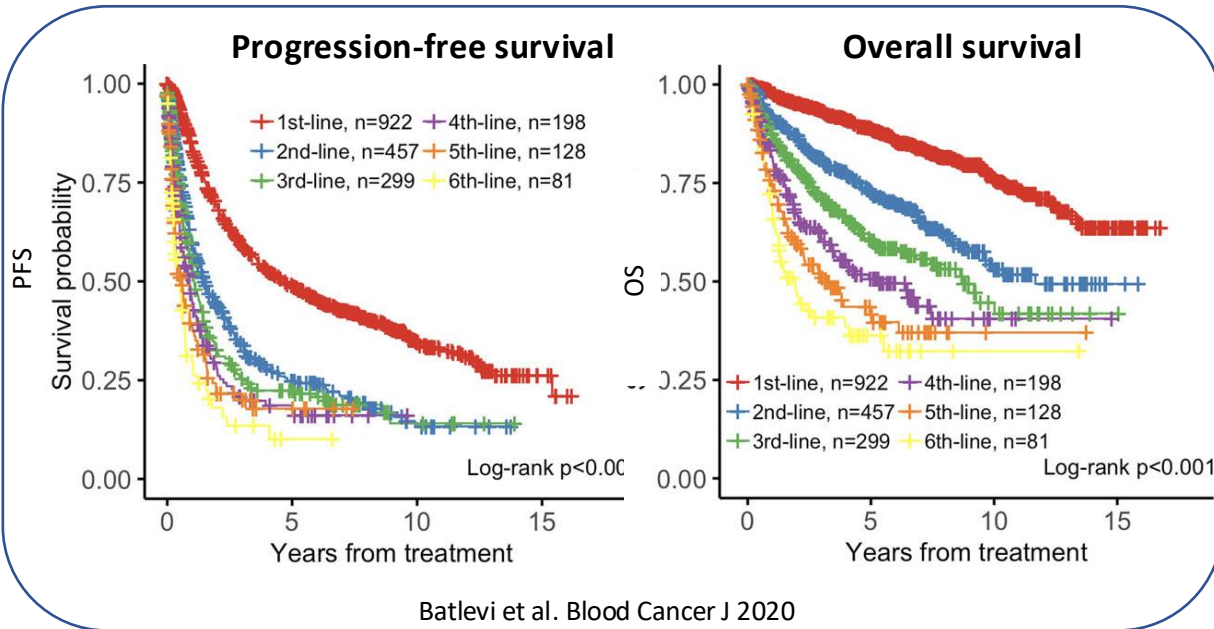
Courtesy of Guillaume Cartron

Old “dogma”

Vs.

New paradigms

FL outcomes by line of therapy



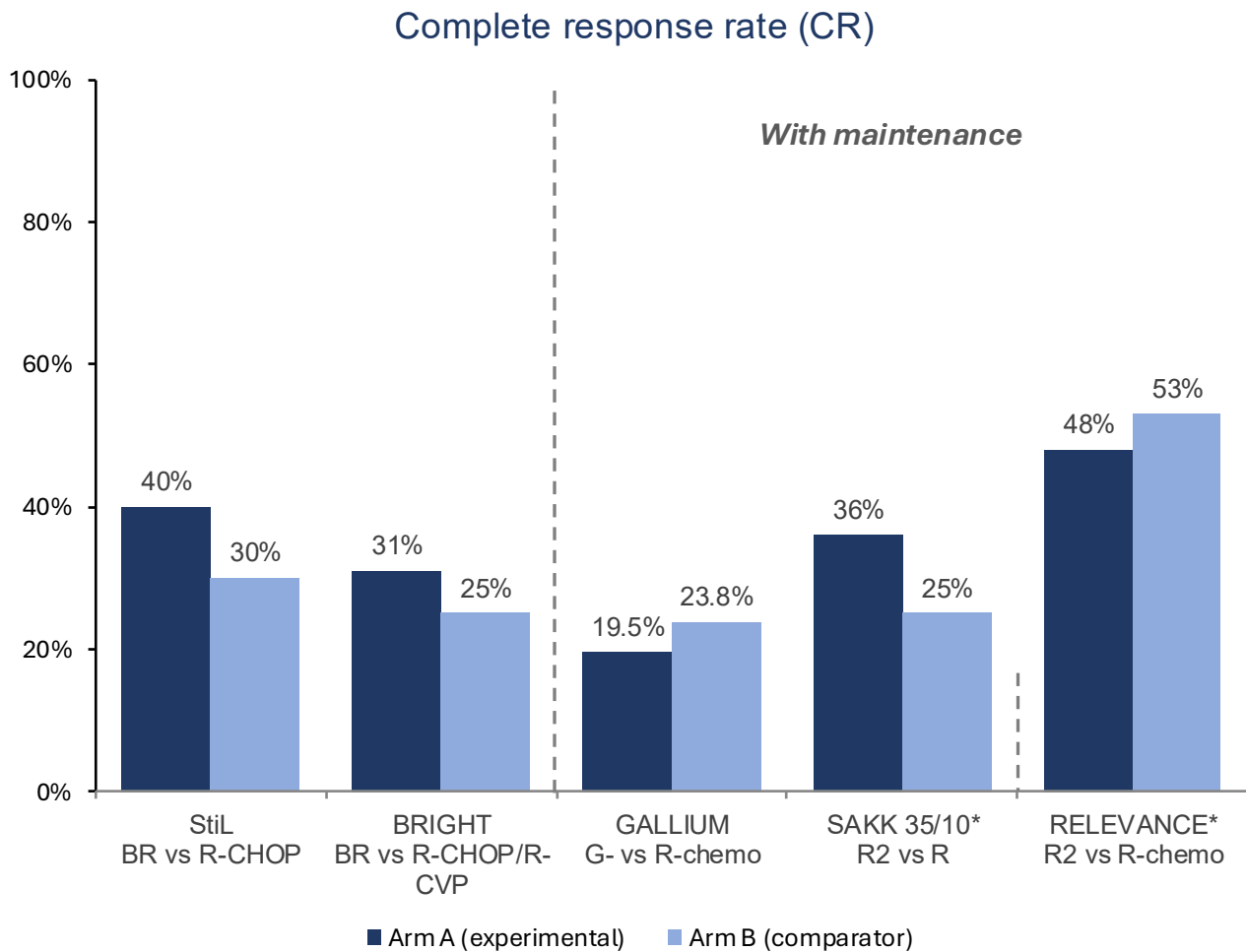
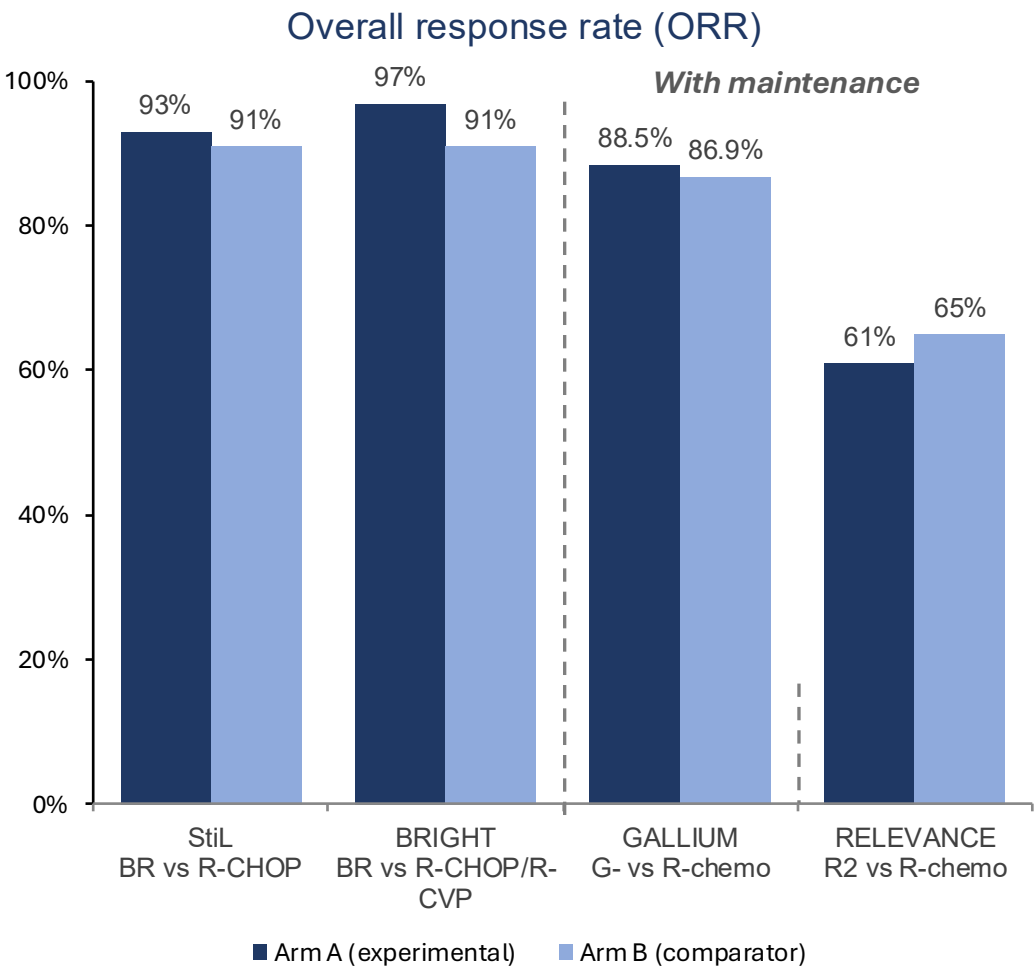
➤ No cure

- **Bispecific Antibodies**
- **CAR T-cells**
- **IMiDs, Lenalidomide**
- **EZH2i, Tazemetostat**
- **BTKi, G-Zanubrutinib**

- Better and long term control, Cure ?
- Increased quality of life
- New profile of toxicity

Response rates in first-line FL

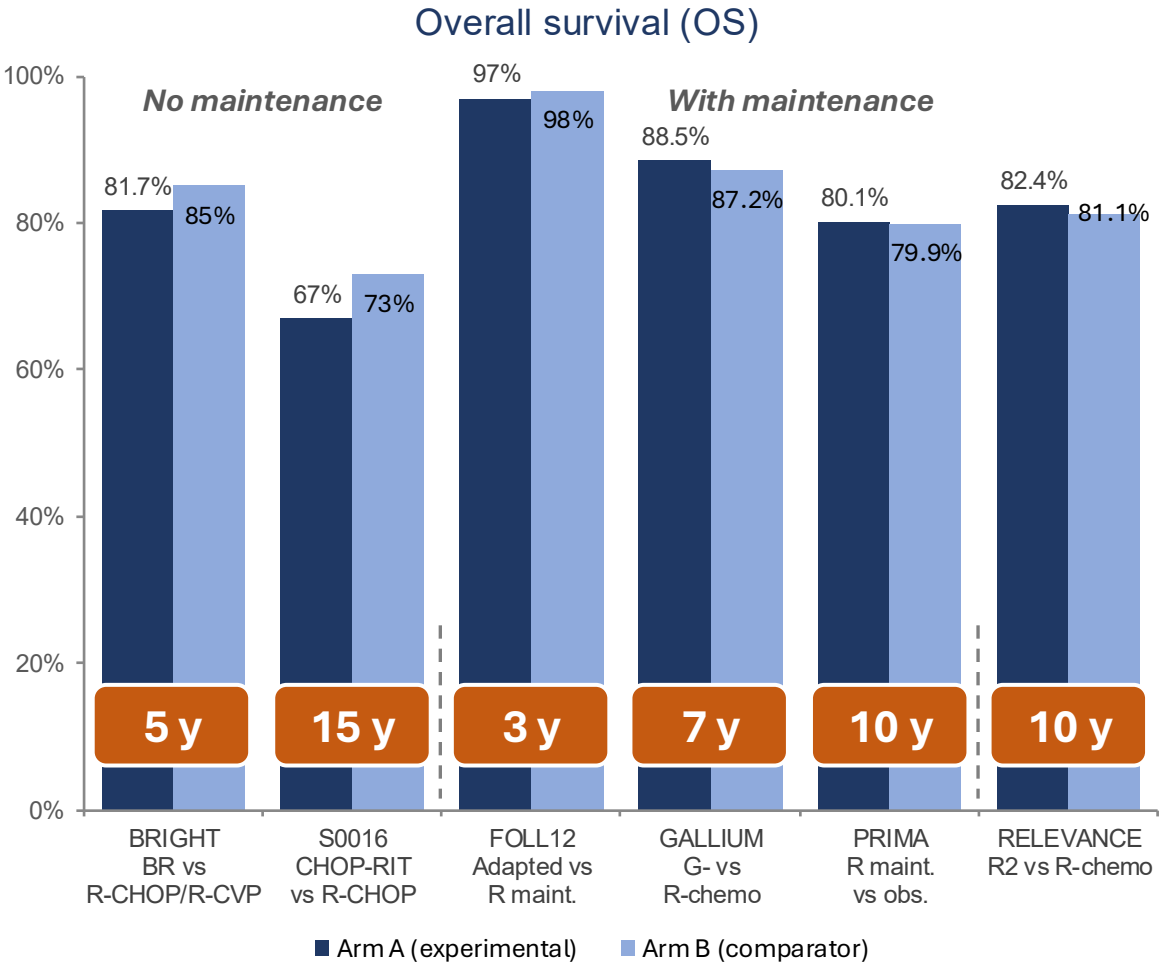
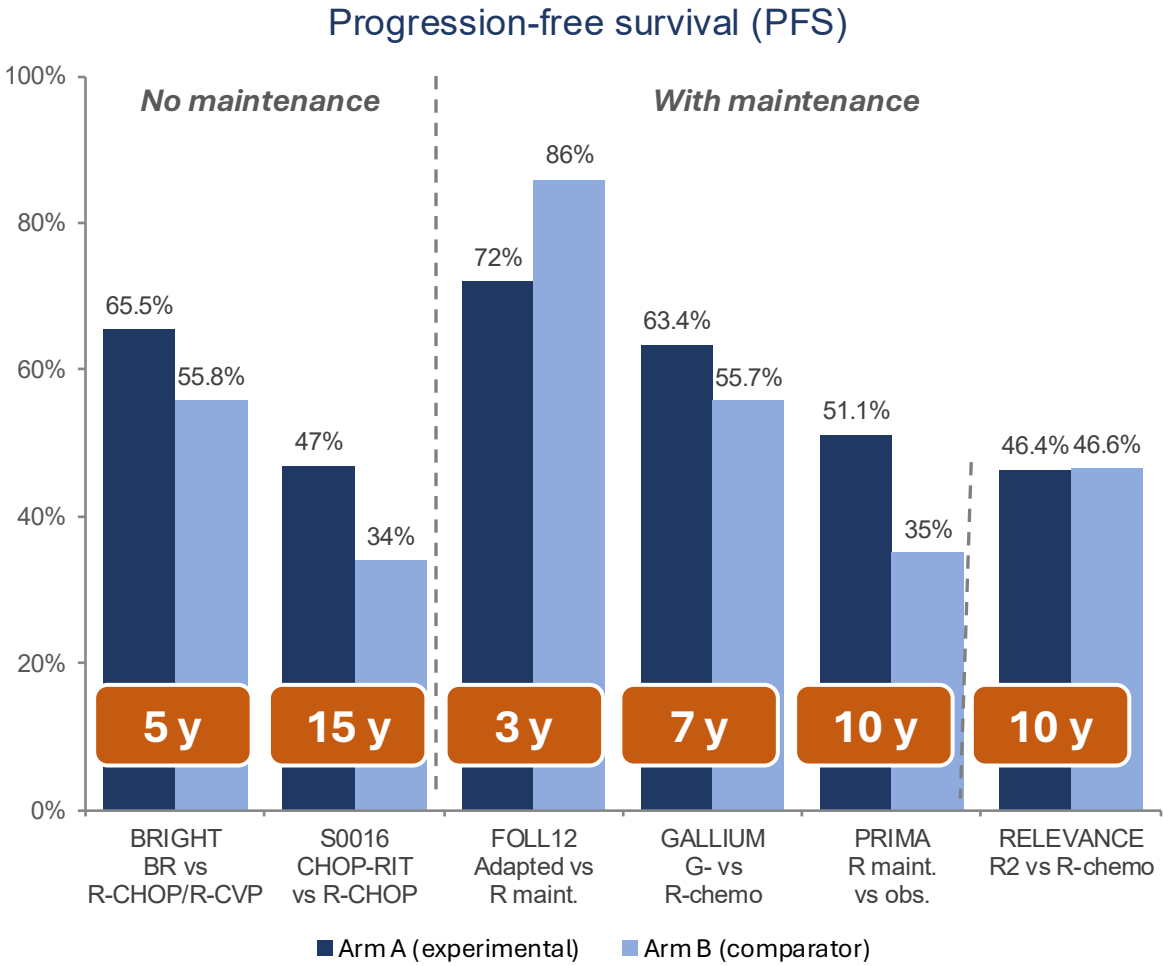
antiCD20-chemotherapy vs R2 strategy



References: StiL NHL1 – Rummel MJ et al. Lancet 2013;381(9873):1203-10 · RELEVANCE – Morschhauser F et al. N Engl J Med 2018;379:934-47 · BRIGHT – Flinn IW et al. J Clin Oncol 2019;37(12):984-91 · GALLIUM – Townsend W et al. HemaSphere 2023;7(7):e919 · SAKK 35/10 – Kimby E et al. Blood Adv 2025;9(7):1712-9.

Survival in first-line FL

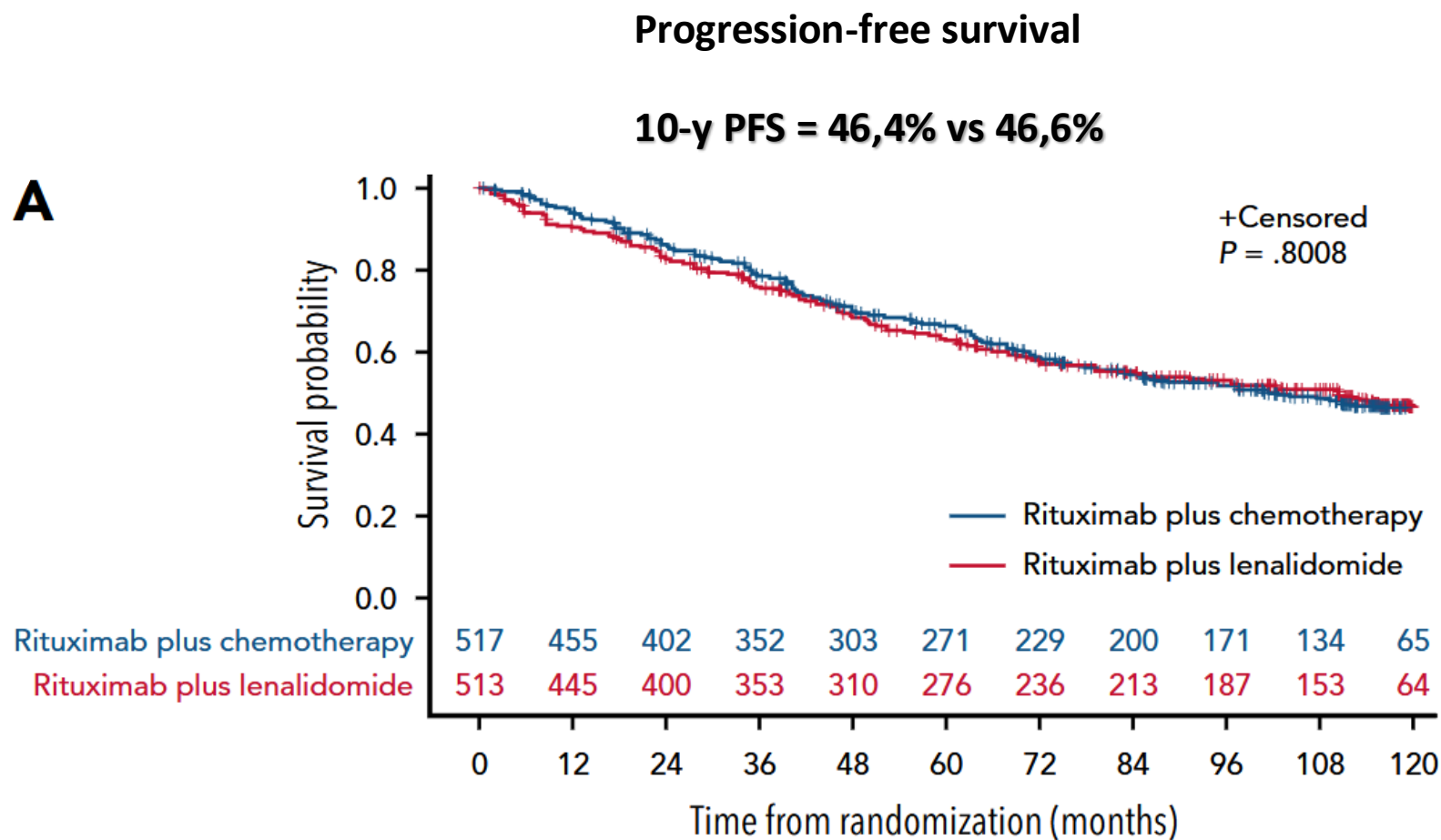
antiCD20-chemotherapy vs R2 strategy



Landmark rates at the time point shown for each trial. Not shown: StIL NHL1 (median PFS 69.5 vs 31.2 mo; OS no difference), SAKK 35/10 (10-y values to verify).

References: BRIGHT – Flinn IW et al. J Clin Oncol 2019;37(12):984-91 · SWOG S0016 – Shadman M et al. JAMA Oncol 2026;12(4):394-401 · FOLL12 – Luminari S et al. J Clin Oncol 2022;40(7):729-39 · GALLIUM – Townsend W et al. HemaSphere 2023;7(7):e919 · PRIMA – Bachy E et al. J Clin Oncol 2019;37(31):2815-24 · RELEVANCE 10-y – Gower N et al. Blood 2026;147(25):3061-8 · StIL NHL1 – Rummel MJ et al. Lancet 2013;381(9873):1203-10 · SAKK 35/10 – Kimby E et al. Blood Adv 2025;9(7):1712-9.

R2-based strategy : RELEVANCE: Final analysis in 2026 – 10 years -



	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	517	43.5% (225)	56.5% (292)	102.8 (82.8; not reached)
Rituximab plus lenalidomide	513	45.6% (234)	54.4% (279)	110.6 (84.4; not reached)

- R2 resulted in 10-year PFS, TTNLT, and OS rates comparable to immunochemotherapy in previously untreated FL

10-year overall survival exceeded 80% with either lenalidomide-rituximab (R2) or immunochemotherapy

10-y OS = 82,4% vs 81,1%

RELEVANCE: Neutropenia, the most common adverse event

Comparable long-term efficacy, transformation and safety signals

	Rituximab + lenalidomide (R ²)	Rituximab–immunochemotherapy
10-year PFS IRC assessment	46.4%	46.6%
10-year OS Median OS not reached	82.4%	81.1%
Histological transformation Events occurring after month 24	3	6
Neutropenia any grade	381 (75%)	386 (77%)
Neutropenia Gr 3-4	160 (32%)	252 (50%)
Cutaneous reactions	220 (43%)	120 (24%)
Tumor flare reaction	30 (6%)	1 (< 1)
Second primary malignancies Patients with ≥1 SPM	79 (15.6%)	85 (16.9%)
Nonmelanoma skin cancers Reported patients	22 (4.3%)	32 (6.4%)
At least 1 treatment-emergent adverse event Patients with ≥1 TEAE	100%	98.6%
Grade 5 TEAEs 15 patients overall (1.5%) • n=1,010	9 patients	6 patients

RELEVANCE: frequent cutaneous reactions

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RELEVANCE at 10 years : R2, chemofree regimen is not toxicity-free

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2,11 cases
per year

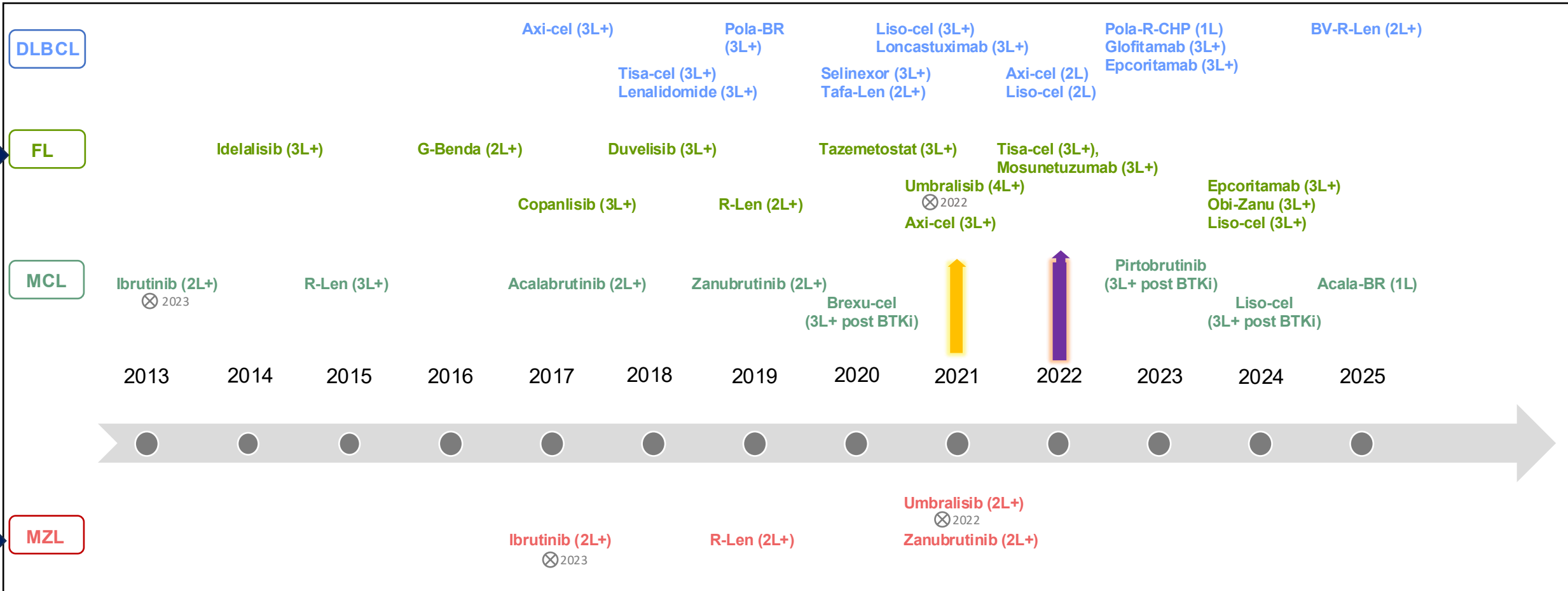
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1,5% Grade 5
No difference

Timeline of FDA approvals in B-cell non-Hodgkin lymphomas



⊗ 2022 : withdrawn in 2022



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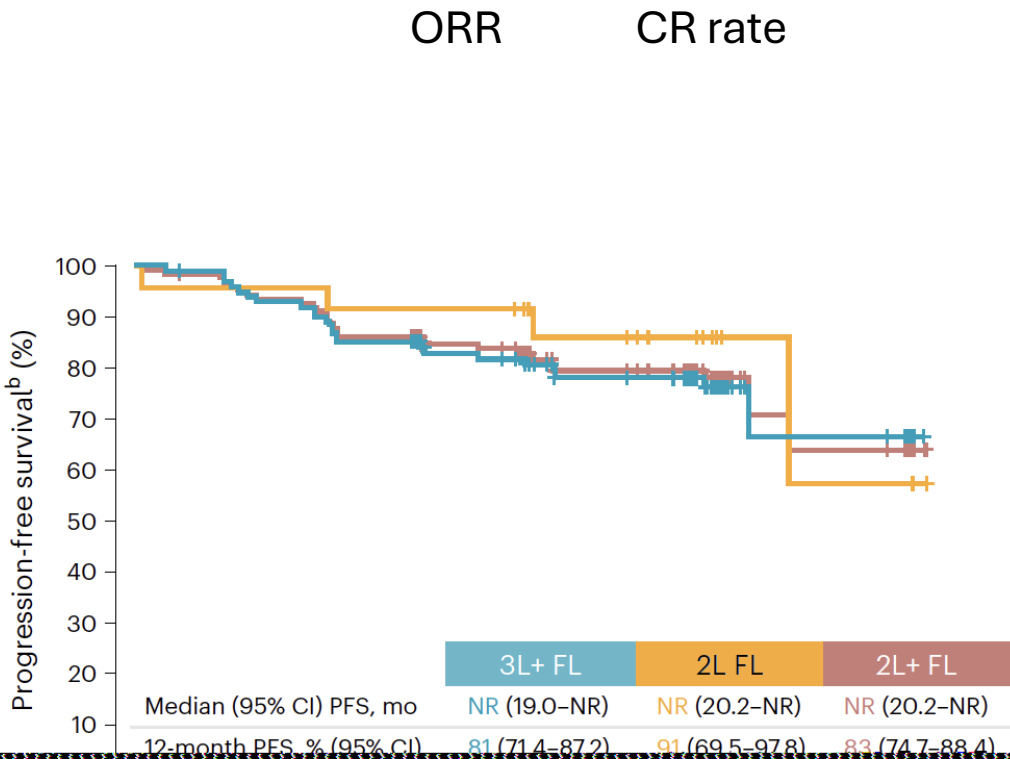
October 15-16, 2026

BsAb and CAR-T in R/R FL: moving into line 2

BsAbs : Epcoritamab monotherapy in line 2

	ORR	CR rate
2L FL (n=128)	82.0% (95% CI :74.3–88.3)	62.5% (95% CI 53.5–70.9)

CART : TRANSCEND Iso-cel in line 2



June 26, 2024

FDA accelerated approval to
Epcoritamab

Linton K, et al. Lancet 2024
Vitolo, et al. ASH 2025

Morschhauser et al. Nat Med 2024

BsAb vs CAR-T in FL: safety

CRS after bispecific is predictable

Mosunetuzumab

Cycle day	median time to CRS onset
C1 day 1	5 hours (range, 1-24)
C1 day 15	27 hours (range, 0-391)

The median CRS duration was 3 days (range, 1-29)

No relationship was observed between the occurrence of CRS and tumor response

Chemo-free regimens in R/R FL

Bispecific-combined strategies

- EPCORE FL-1 : Epcor R2 R/R FL line 2

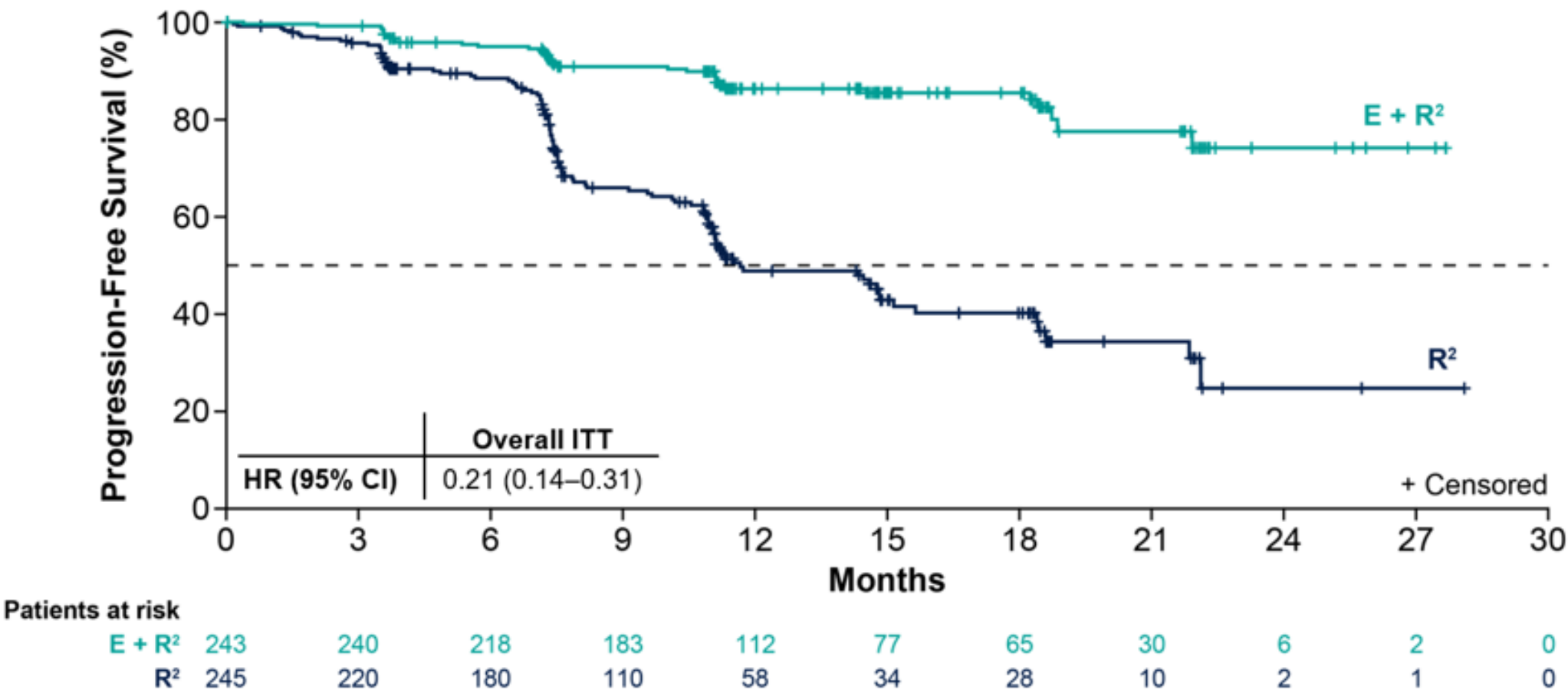
R2-based regimen

- AUGMENT : R2
- inMIND : Tafasitamab-R2
- SYMPHONY 1 : Tazemetostat-R2

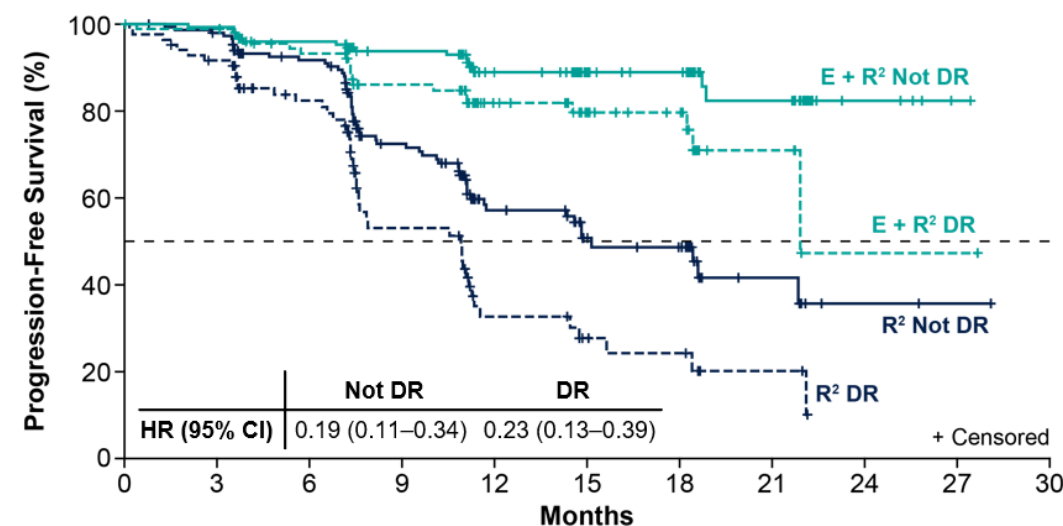
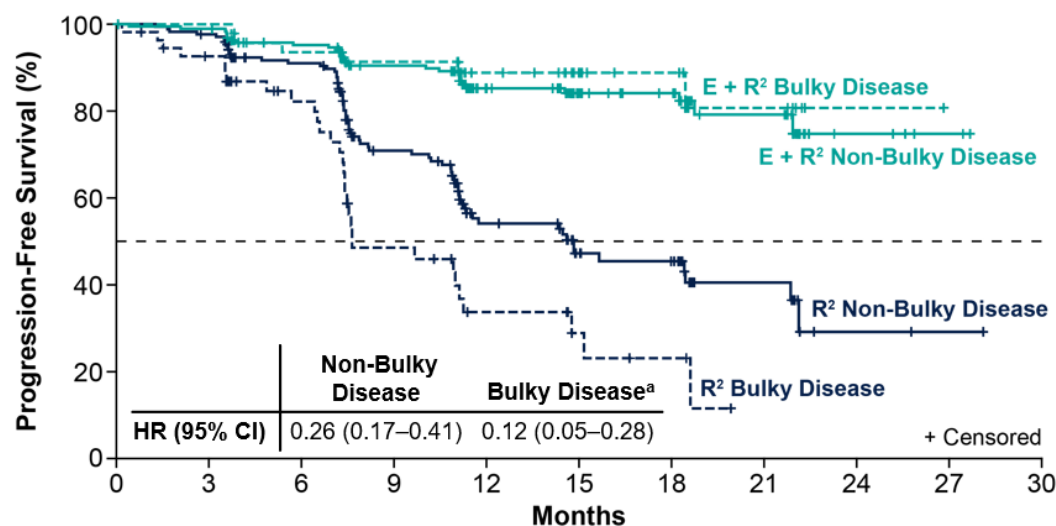
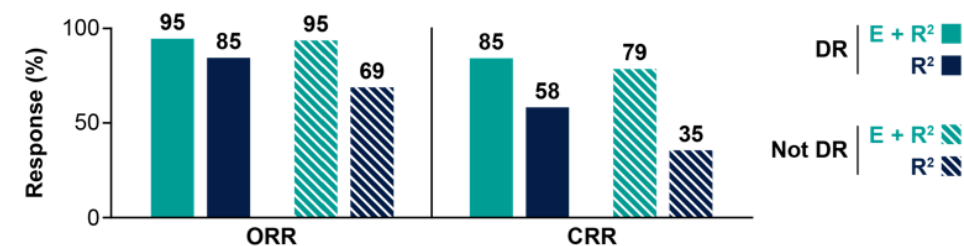
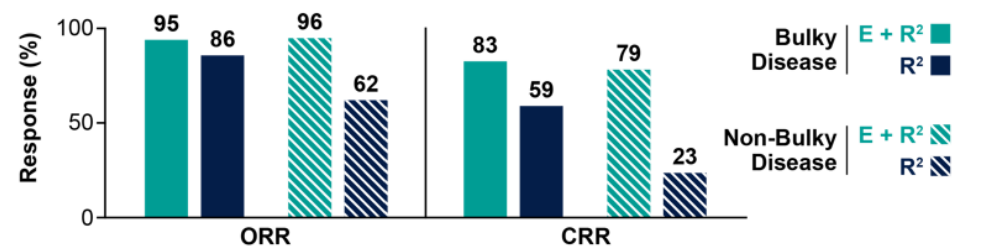
BTKi-based regimen

- SELENE : Ibrutinib+CIT vs placebo+CIT
- ROSEWOOD : Obi-Zanubrutinib vs Obi
- MAHOGANY (FL) : Obi-Zanubrutinib vs R2

EPCORE FL-1 : Epco R2 R/R FL line 2



Epcoritamab + R² Resulted in Higher Response Rates and Improved PFS Over R² Regardless of Bulky Disease or Double Refractory Status



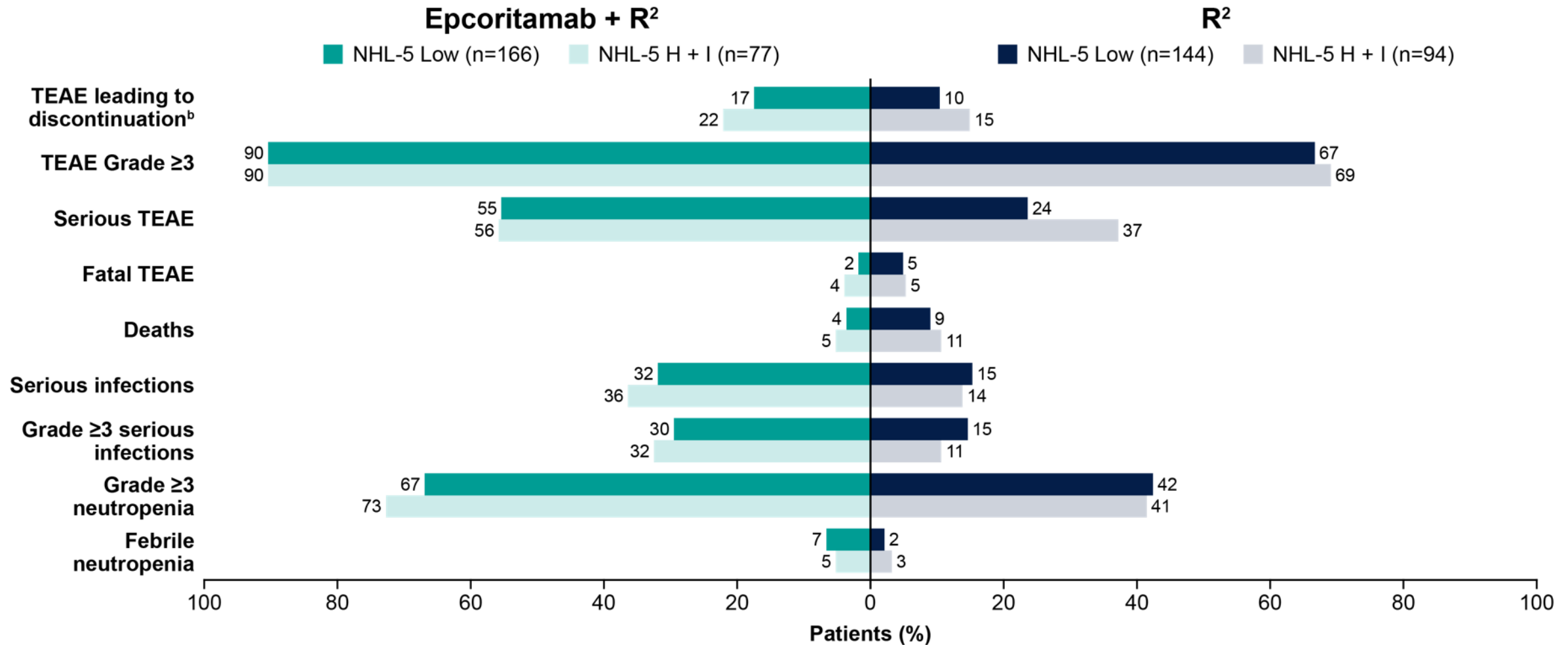
Patients at risk												
Non-Bulky Disease	E + R ²	191	188	170	140	83	57	50	24	5	2	0
	R ²	176	167	140	87	46	28	24	10	2	1	0
Bulky Disease	E + R ²	47	47	43	40	27	18	13	6	1	0	0
	R ²	61	48	35	19	10	5	3	0	0	0	0

Patients at risk												
Not DR	E + R ²	152	150	137	117	69	49	43	25	5	1	0
	R ²	154	145	123	81	44	25	21	7	2	1	0
DR	E + R ²	91	90	81	66	43	28	22	5	1	1	0
	R ²	91	75	57	29	14	9	7	3	0	0	0

^aBulky disease was defined by the presence of a lymph node ≥ 7 cm at baseline/screening.

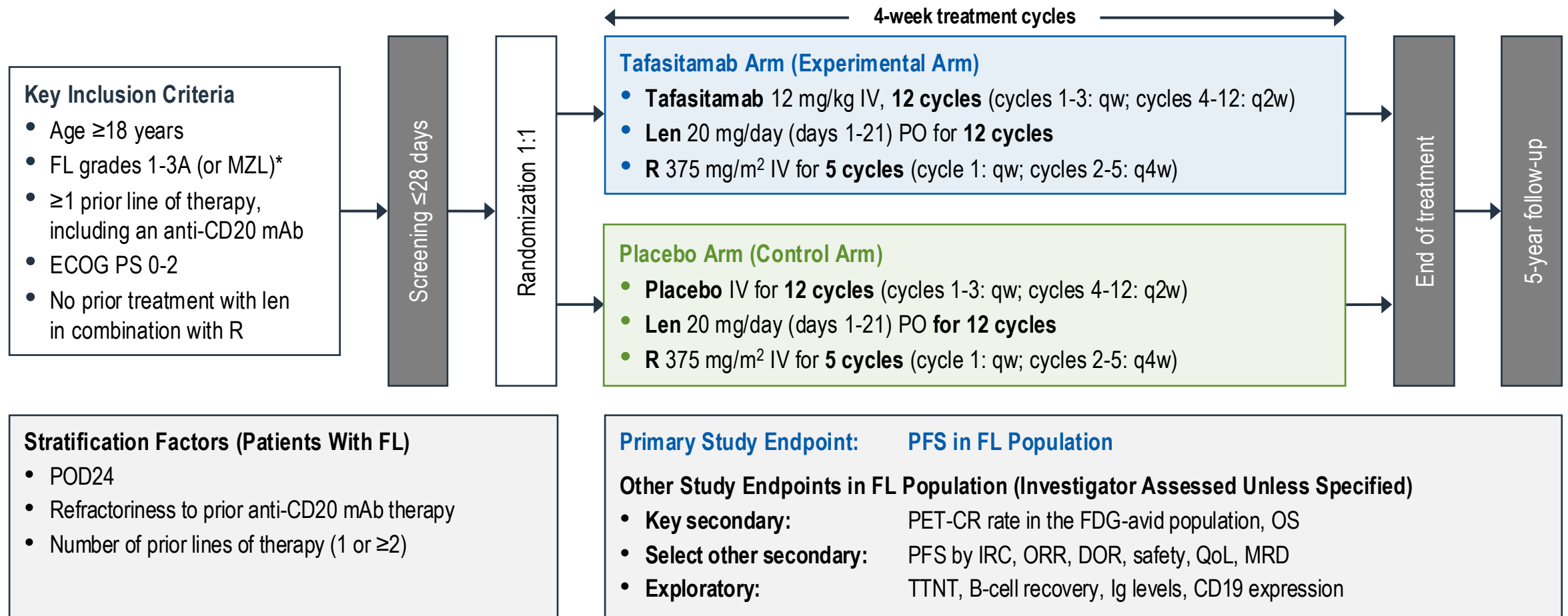
CRR, complete response rate; DR, double refractory; E, epcoritamab; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; R², lenalidomide and rituximab.

The Epcoritamab + R² Safety Profile Remained Generally Manageable Even in Patients With Increased Comorbidity Burden^a



^aComorbidity burden was based on the NHL-5 comorbidity score (Gordon MJ, et al. *JCO Clin Cancer Inform.* 2024;8:e2300223). ^bTEAE leading to discontinuation of any study drug. H + I, high and intermediate; NHL-5, non-Hodgkin lymphoma comorbidity score; R², lenalidomide and rituximab; TEAE, treatment-emergent adverse event.

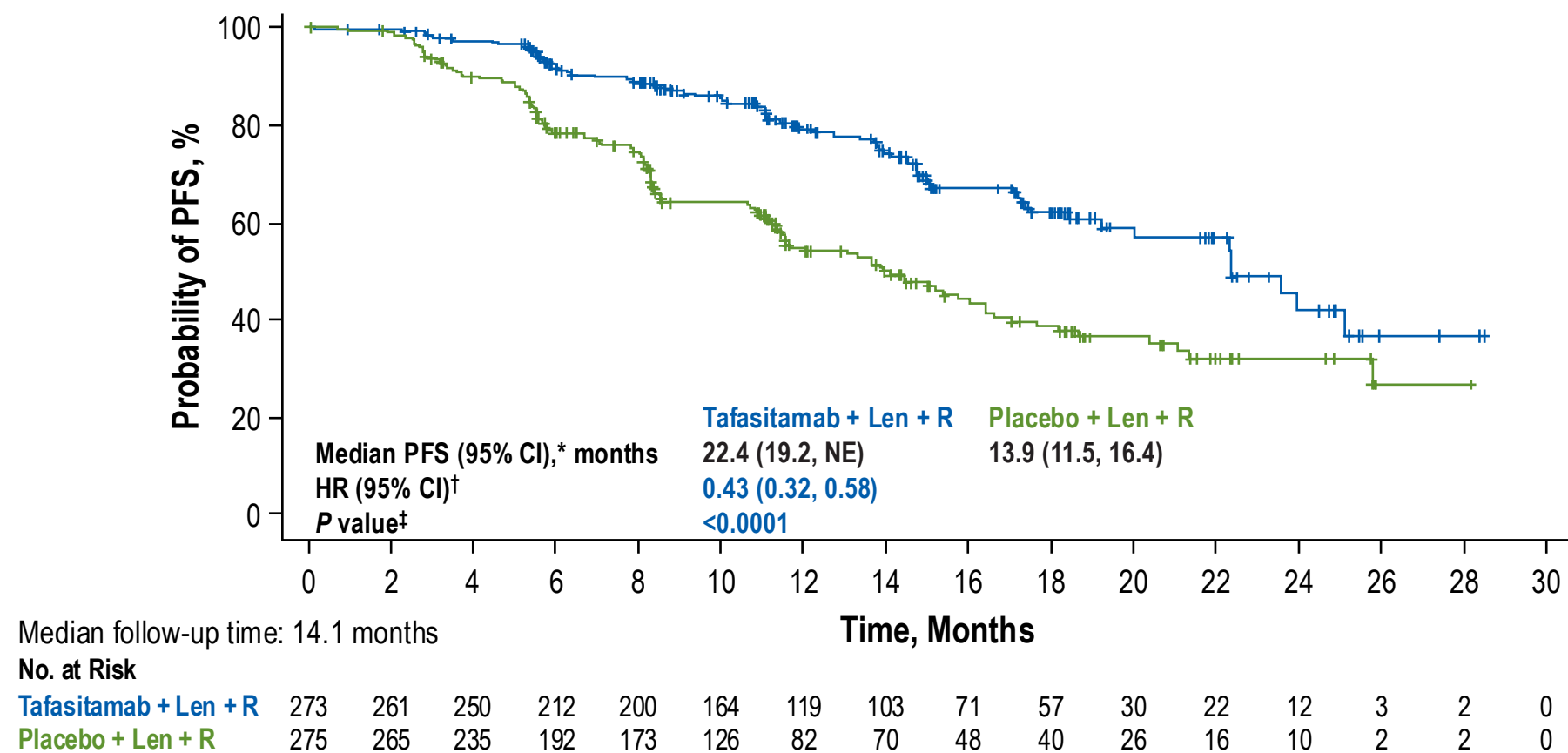
inMIND: Phase 3, Double-Blind, Placebo-Controlled, International, Multicenter, Randomized Study



- Powered to assess PFS in the FL population, triggered when 174 investigator-assessed events occurred
- OS analysis planned after 5 years of follow-up

*Limited number of patients with MZL were enrolled but the study was not powered for this population; data for patients with MZL will be presented separately. DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; FL, follicular lymphoma; Ig, immunoglobulin; IRC, independent review committee; IV, intravenous; len, lenalidomide; mAb, monoclonal antibody; MRD, minimal residual disease; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; PO, orally; POD24, disease progression within 24 months of initial diagnosis; QoL, quality of life; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; R, rituximab; TTNT, time to next treatment.

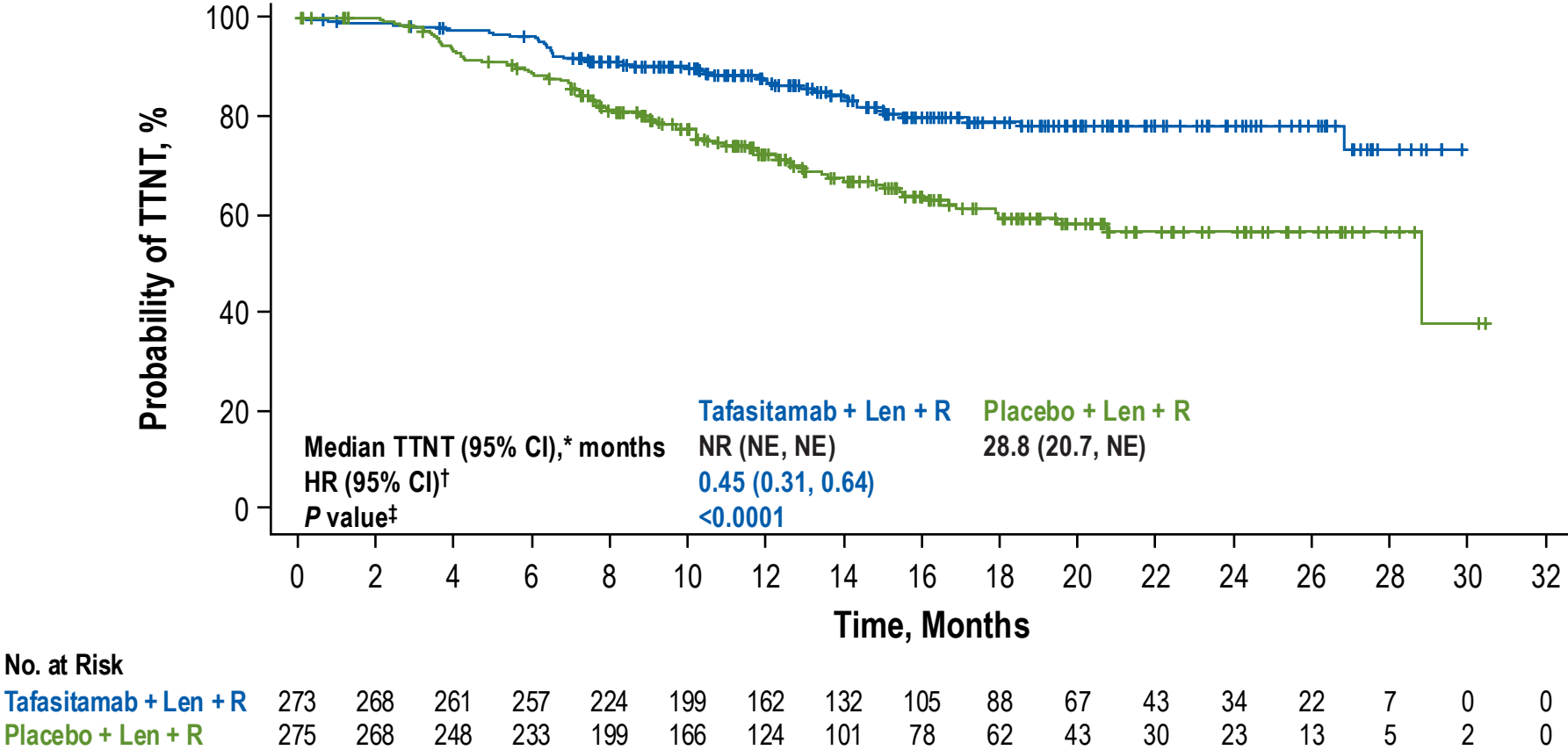
Primary Endpoint: PFS by Investigator Assessment



Significant improvement in PFS was observed with tafasitamab

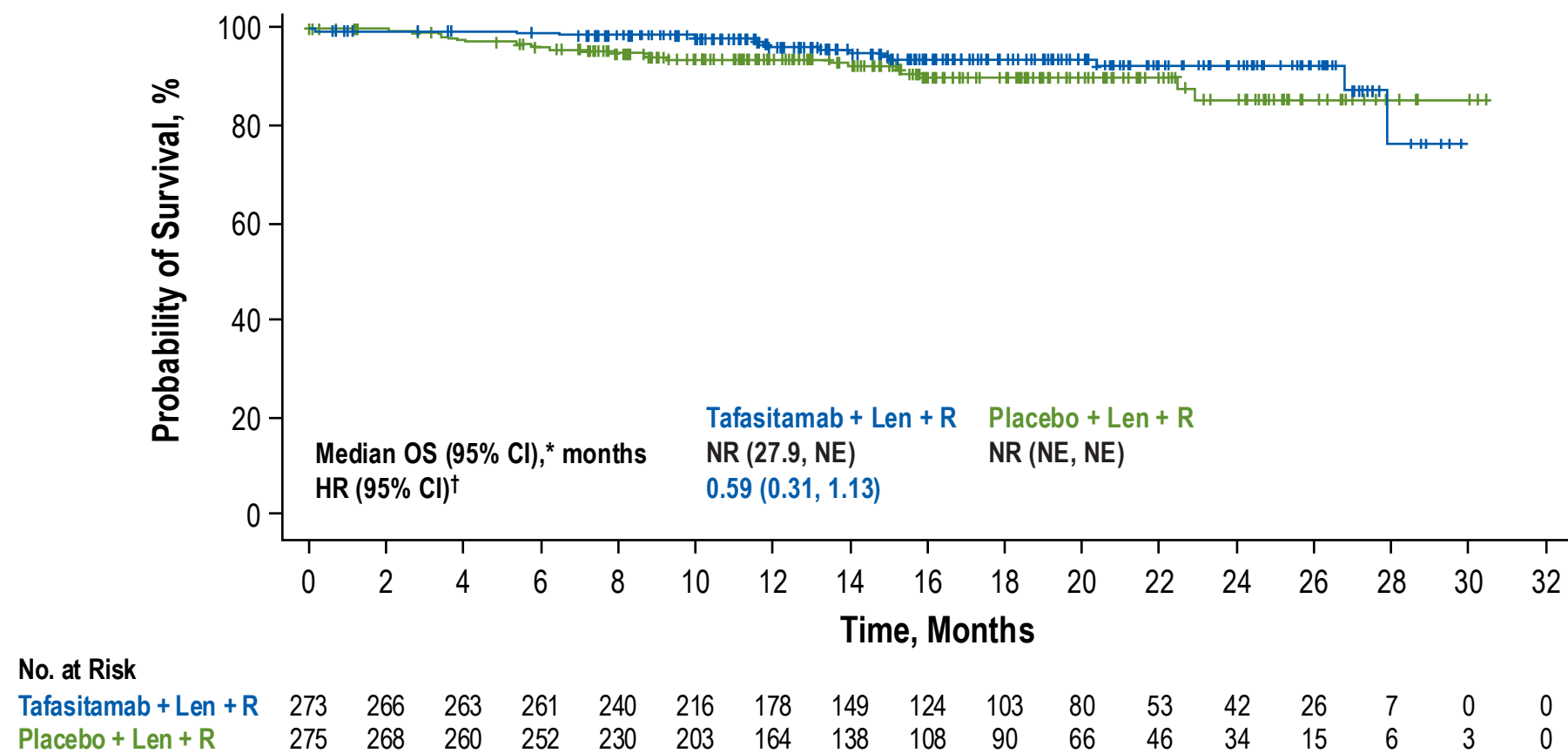
ITT population. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; R, rituximab.

Time to Next Treatment



ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. ‡Nominal P value; stratified log-rank test with a 2-sided significance level of 5%. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NR, not reached; R, rituximab; TTNT, time to next treatment.

Overall Survival



- OS was tested only for futility at the time of the primary analysis
- After a median follow-up of 15.3 months, the futility threshold was not crossed and a positive trend was observed

ITT population. Analysis by investigator assessment. *Estimated using Kaplan-Meier method. †Estimated using a stratified Cox proportional hazard model. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Len, lenalidomide; NE, not evaluable; NR, not reached; OS, overall survival; R, rituximab.

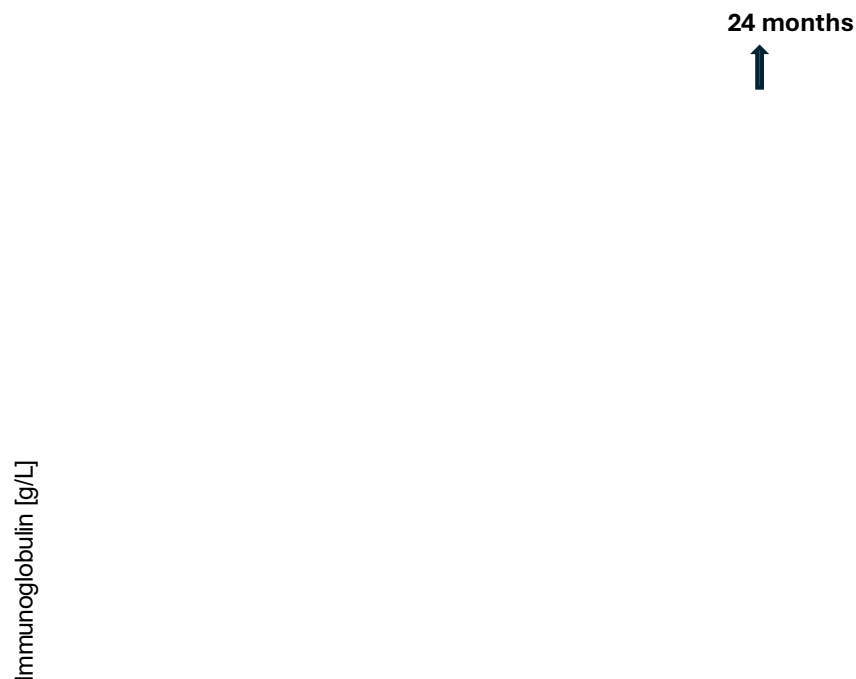
Safety profile: tafasitamab adds limited overall toxicity to R²

neutropenia and respiratory infections, while diarrhea was more frequent but rarely severe

Selected event	N=273	N=275
	Tafa-R ² For selected AEs: All grade Grade 3–4	Placebo-R ² For selected AEs: All grade Grade 3–4
Any TEAE	99%	99%
Grade 3–4 adverse events	71%	69.5%
Serious adverse events	36%	32%
Treatment discontinuation due to TEAE	11%	7%
Neutrophils decreased	75% 48%	71% 44%
Diarrhea	38% 0.7%	28% 1.8%
Pneumonia	18% 14%	11% 7%
COVID-19 infection	34% 10%	24% 2.9%
Rash	37% 3.6%	33% 1.5%
Fatigue / asthenia	34% 2.9%	25% 0.7%
Infusion-related reaction	16% 0.7%	16% 0.4%

Impact of B-cell recovery and Ig recovery

CAR-T: dynamics of B-cell, and Ig recovery



Luan et al. 2025

Mosunetuzumab: Dynamics of B-cell recovery

The median time to B-cell recovery = **18.4 mo** (95% CI, 12.8-25.0) from completion of C8

B-cell recovery is defined by ≥ 5 cells/ μL

Sehn et al. 2025

Immune Reconstitution after CAR-T

Early NK cell recovery emerging as a key predictor of survival

Beyond R/R FL: Comparative BsAb trials in 1L FL

NCT	Name	Phase	N.	Experimental arm	Control arm	Duration of therapy	Primary endpoint
NCT04663347	EPCORE FL-2	3	1095	Epcoritamab R ²	G/R-CHOP G/R-benda R ²	2.5 y	CR30, PFS
NCT06284122	MorningLyte	3	790	Mosunetuzumab- Lenalidomide	G/R-CHOP G/R-benda	1.5 y	PFS
NCT06091254	OLYMPIA-1	3	478	Odronextamab	R-CHOP R-CVP R-benda	2 y	CR30
NCT06097364	OLYMPIA-2	3	733	Odronextamab-CHOP/ CVP +/- O-maintenance	R-CHOP/CVP + R- maintenance	6 m vs 2.5 y	CR30
NCT06549595	SOUNDTRACK-F1	3	1015	AZD0486-rituximab +/- AZD0486 maintenance	R-CHOP/CVP + R- maintenance R-benda	6-12 m vs. up to 2.5 y	PFS

Indolent lymphoma: Aiming for Cure, Minimizing Harm

- **Novel immunotherapy strategies are much more effective than previous chemoimmunotherapy regimens**
 - * **How to sequence these new therapies**
 - * **How to adapt the duration**
 - * **Redefine the risk stratification**
- **Short-term and long-term immune dysfunctions are a major concern**
 - * **hypogammag, recurrent/severe infections, prolonged immunosuppression, impaired vaccine responses**
 - * **Shift of the toxicity profile: from cytotoxic damage to immune, infectious, and cardiovascular toxicities**
- **Quality of life must be considered alongside efficacy**
 - * **PRO : patient reported outcome ++**