FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
26-27 gennaio 2026

I trattamenti chemo-free nella malattia recidivata, presente e futuro

Guido Gini

Clinica di Ematologia

AOU delle Marche - Ancona

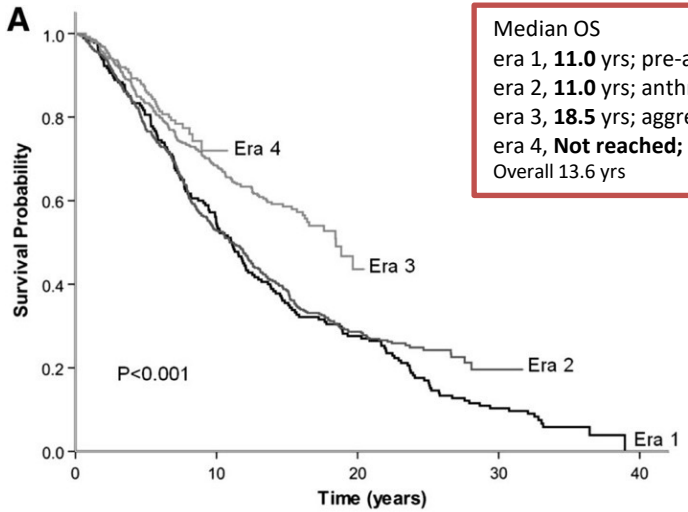
Disclosures (1) – Guido Gini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	Educational activity
Incyte					X	X	Educational activity
Kiowa Kirin						x	Educational activity
Janssen						X	Educational activity
Takeda					x	X	Educational activity
Astrazeneca						X	Educational activity
Gilead					X		Educational activity
Gentili					x	x	Educational Activity

Disclosures (2) – Guido Gini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sobi					X	X	Educational activity
Lilly					X	X	Educational activity
GSK						x	Educational activity
Abbvie						X	Educational activity

Improving Survival of Follicular NHL



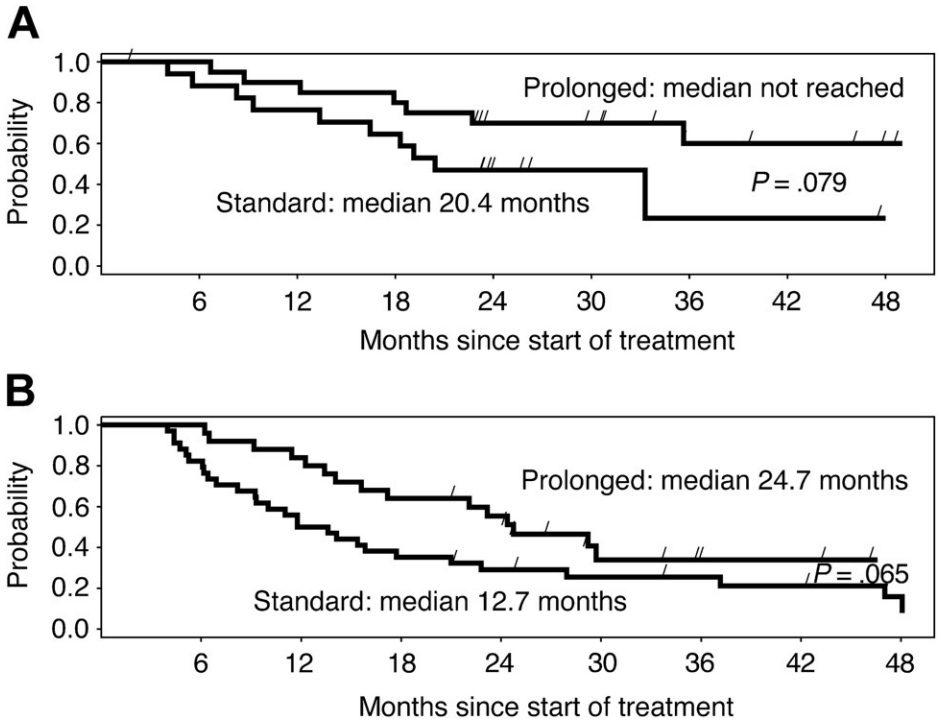
Median OS
era 1, **11.0** yrs; pre-anthracycline (1960-1975);
era 2, **11.0** yrs; anthracycline (1976-1986);
era 3, **18.5** yrs; aggressive cht/purine analogs (1987-1996);
era 4, **Not reached;** rituximab (1997-2003)
Overall 13.6 yrs

Daryl Tan et al. Blood 2013;122:981-987

blood

Rituximab alone in the treatment of pts with FL

Duration of response by study arm in chemotherapy-naive (A) and pretreated patients (B)



45% of chemo-naive responders in remission at 8 years
Martinelli et al. JCO 2010

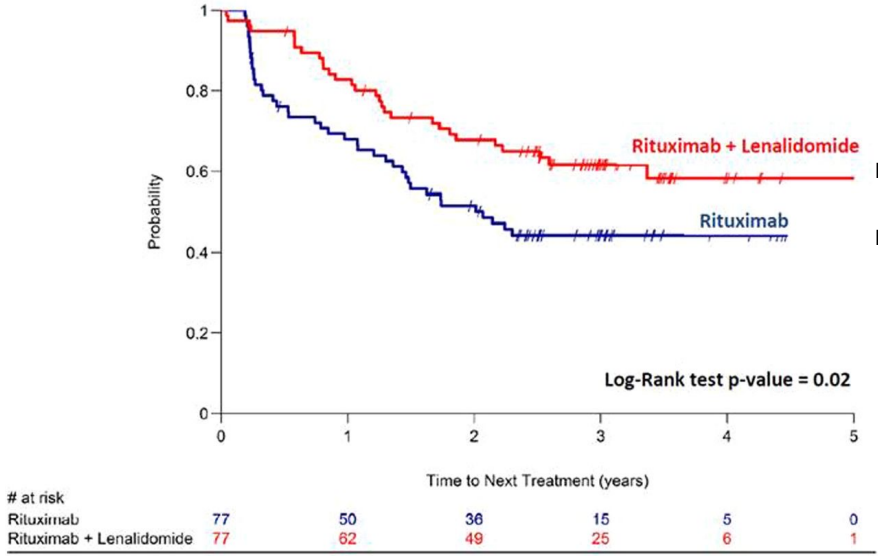
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Ghielmini M, et al. *Blood*. 2004;103(12):4416-4423.

Rituximab Plus Lenalidomide Versus Rituximab Monotherapy in Untreated Follicular Lymphoma Patients in Need of Therapy. First Analysis of Survival Endpoints of the Randomized Phase-2 Trial SAKK 35/10

	R	R2
ORR	61%	82%
CRR	25%	36%
CRR @ 30 m.	19%	42%

Grade 3/4 AEs	R (n = 76)	R2 (n = 77)
Fatigue	1 (1.3%)	2 (2.6%)
Allergic reaction		2 (2.6%)
Neutropenia	5 (6.6%)	18 (23.4%)
Thrombocytopenia		3 (3.9%)
Depression		1 (1.3%)
Psychosis		1 (1.3%)
Suicide attempt	1 (1.3%)	
Maculo-papular rash		4 (5.2%)
Hypertension	3 (3.9%)	7 (9.1%)
Discontinuation		12 (16%)



mPFS NR

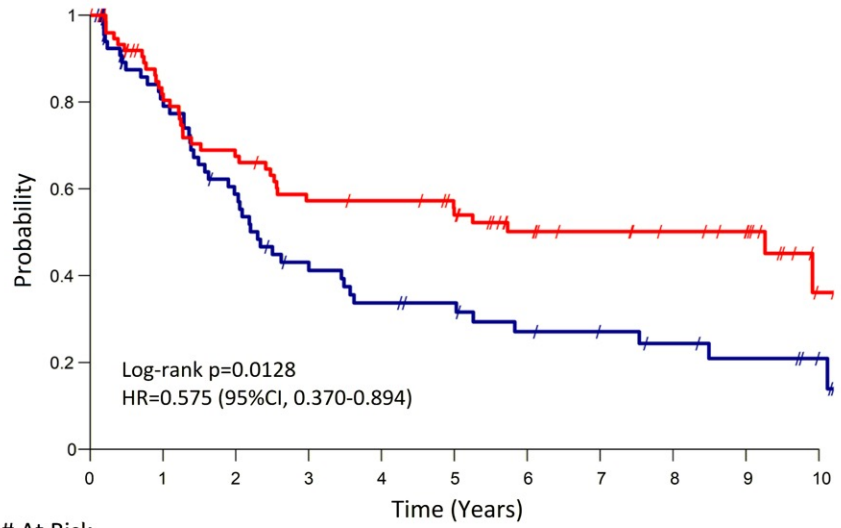
mPFS 2.3 yrs

Eva Kimby et al. Blood, 2016.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

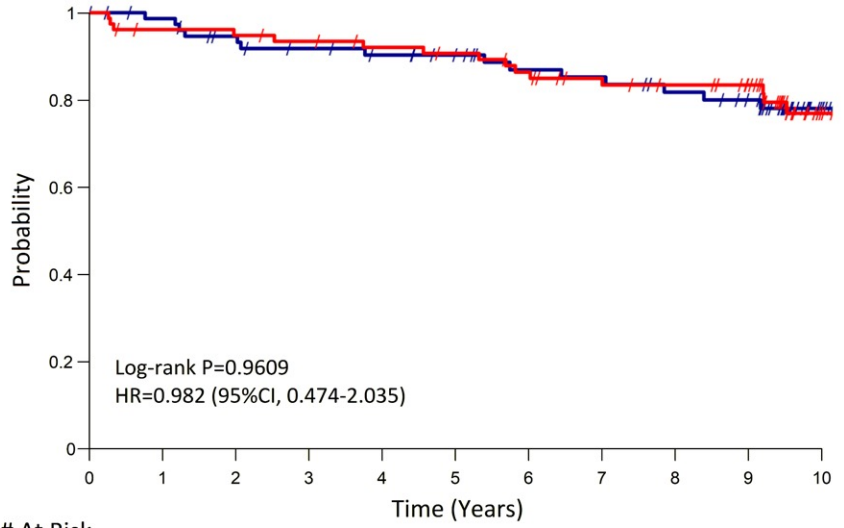
SAKK35/10 long term outcomes

Progression-free Survival



# At Risk											
R	77	48	34	23	18	16	12	10	8	6	3
R+L	77	57	47	39	38	33	24	20	17	15	3

Overall survival



# At Risk											
R	77	73	67	63	60	57	51	50	46	43	19
R+L	77	72	71	69	66	64	60	55	52	48	22

Long-Term Results of the SAKK 35/10 Randomized Trial of Rituximab Vs. Rituximab and Lenalidomide in Follicular Lymphoma in Need of First Therapy

E. Zucca et al. ASH 2023

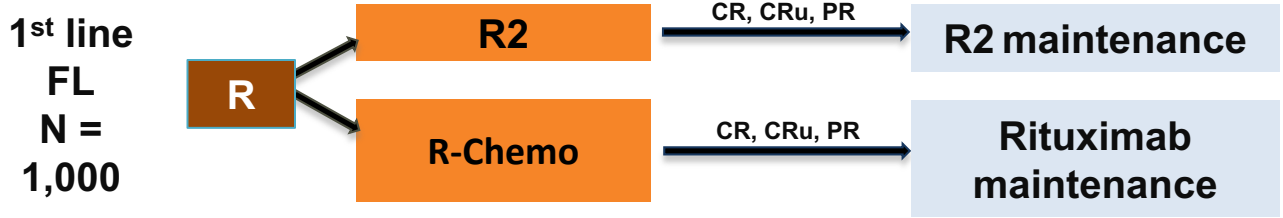
No unexpected toxicity

Adverse Events	R Any	R (G3-4)	R+L Any	R+L (G3-4)
Hematological toxicity				
Neutropenia	7%	(6%)	23%	(23%)
Anemia	3%	(0)	4%	(1%)
Thrombocytopenia	0	(0)	5%	(4%)
Non-hematological Aes				
Fatigue	34%	(1%)	52%	(3%)
Fever	4%	(0)	16%	(0)
Diarrhea	12%	(0)	25%	(0)
Skin rash	7%	(1%)	27%	(5%)
Cough	13%	(0)	25%	(0)
Infections	18%	(3%)	30%	(4%)

E. Zucca et al. ASH 2023

RELEVANCE: PHASE III STUDY DESIGN (RITUXIMAB AND LENALIDOMIDE VERSUS ANY CHEMOTHERAPY, FL-001)

International, multicentre, randomized study

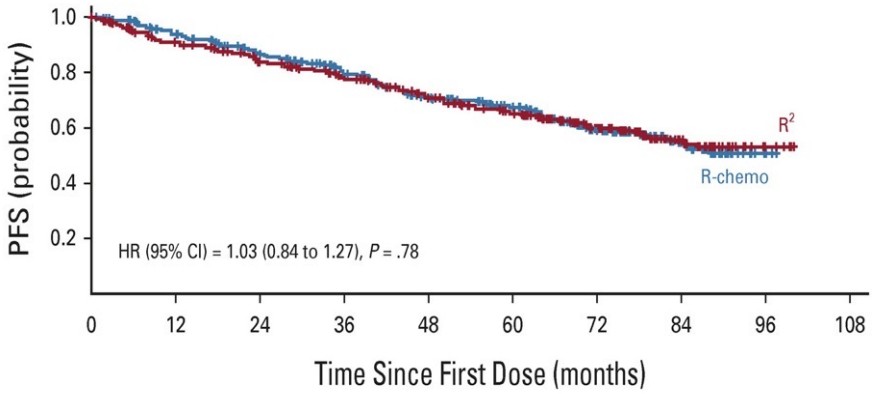


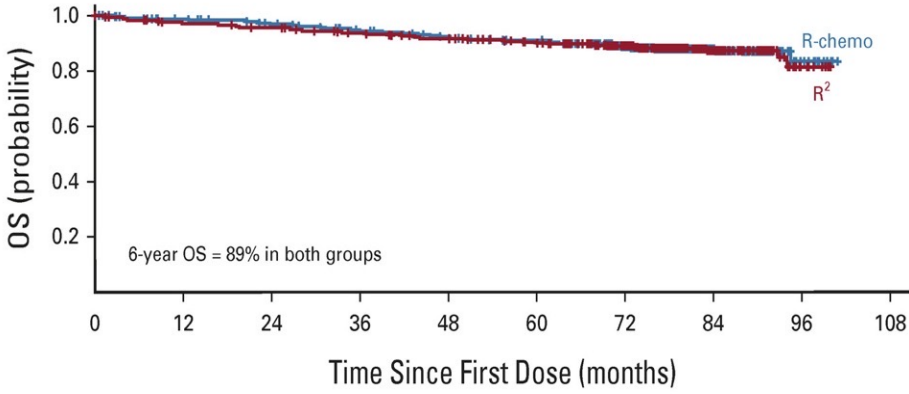
- R-Chemo
  - investigator choice of R-CHOP, R-CVP, R-B
- Lenalidomide
  - 20 mg × 6 cycles, if CR then 10 mg

- Co-primary endpoints
  - CR/CRu rate at 120 weeks
  - PFS

- CR, complete response; CRu, unconfirmed CR; FL, follicular lymphoma; PR, partial response; R2, lenalidomide and rituximab; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone; R-B, rituximab plus bendamustine; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone.

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma





No. at risk:										
R-chemo	517	446	390	333	277	243	146	56	3	0
R2	513	412	370	328	281	242	157	51	5	0

at risk:										
hemo	517	487	471	451	435	424	330	130	13	0
	513	490	479	461	447	425	343	137	13	0

- 6-yr PFS: 60% R^2 vs 59% R-chemo
- Transformation rates similar (2% range)
- Similar ORR and OS with subsequent therapy in both groups
- Similar rates of second primary malignancies
- 6-yr OS: 89% in both groups

Morschhauser. JCO 2022

RELEVANCE: Safety Comparisons

Safety Outcome	Lenalidomide/Rituximab (n = 513)	Rituximab/Chemo (n = 517)
Grade 3/4 neutropenia, %	32	50
Febrile neutropenia, %	2	7
Range of grade ≥3 TEAEs, %	~65	~70
Grade ≥3 rash, %	4	<1

- Rituximab/chemo associated with more febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, alopecia
- Lenalidomide/rituximab associated with more frequent cutaneous reactions, tumor flare, diarrhea

Morschhauser. NEJM. 2018;379:934.

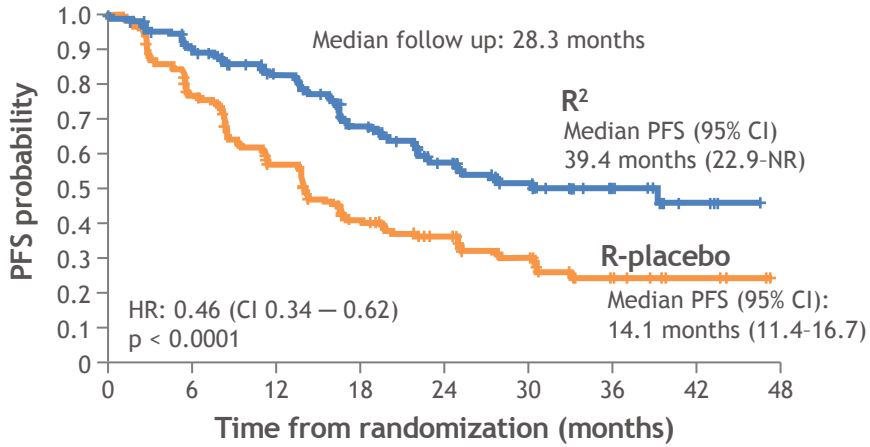
AUGMENT and MAGNIFY studies

Study	Patients, N	Inclusion criteria	Research question	Primary endpoint	Status
AUGMENT[1]	358	• Age ≥ 18 years • r/r MZL or FL (grade 1-3a) • ≥ 1 prior chemotherapy, immunotherapy, or chemoimmunotherapy • ≥ 2 prior doses of rituximab and not rituximab refractory • Not rituximab refractory • ECOG PS ≤ 2	To compare R^2 with SoC in r/r iNHL (R^2 vs placebo + rituximab in patients with r/r FL and MZL)	PFS per IRC	Active, not recruiting[a]
MAGNIFY[2]	394	• Age ≥ 18 years • r/r FL grade 1-3b, tFL, MZL, or MCL • ≥ 1 prior therapy of radiotherapy, chemotherapy, immunotherapy, or chemoimmunotherapy or novel agent (excluding lenalidomide) • Rituximab-refractory, double refractory • ECOG PS ≤ 2	To compare extended treatment with R^2 with rituximab following initial treatment with R^2 in patients with r/r FL, MZL, and MCL	PFS	Active, not recruiting[b]

ECOG, Eastern Cooperative Oncology Group; RT: radiotherapy; IRC, independent review committee; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PS, performance status; SoC, standard of care; tFL, transformed FL. 1. Leonard JP, et al. J Clin Oncol. 2019;37:1188-99. 2. Lansingan F, et al. Presented at ASH 2021; abstract 812.

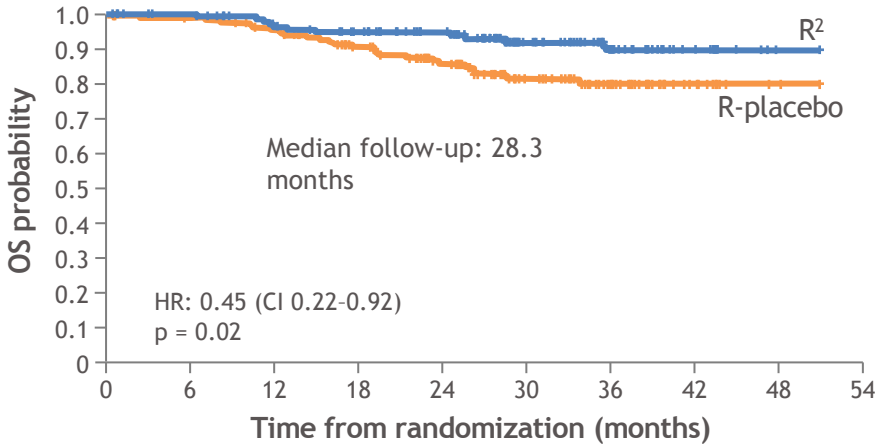
AUGMENT: PFS and OS advantage for R² in relapsed/refractory follicular lymphoma

PFS (ITT, IRC)



Number at risk									
R²	178	148	124	91	59	39	20	7	0
R-placebo	180	132	92	58	40	26	10	4	0

OS (patients with FL)



Number at risk										
R²	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

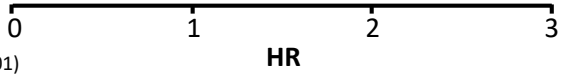
- 41 total deaths (15 with R²; 26 with R-placebo) in treated patients
- 2-year OS (95% CI) was 95% (90-98) for R² and 86% (79-91) for R-placebo

Data cutoff June 22, 2018. ITT, intention to treat; NR, not reached; R-placebo, R plus placebo.

Leonard JP, et al. J Clin Oncol. 2019;37:1188-99.

AUGMENT: IRC-Assessed PFS by Subgroup (ITT)

Subgroup	R², n/N	R-Placebo, n/N	HR (95% CI)
Number of prior systemic antilymphoma regimens			
1	35/102	58/97	0.46 (0.31-0.71)
> 1	33/76	57/83	0.47 (0.31-0.73)
Ann Arbor stage at enrollment			
1-2	12/41	26/56	0.60 (0.30-1.20)
3-4	56/137	89/124	0.40 (0.28-0.56)
Prior rituximab-containing chemotherapy regimen			
Yes	54/130	85/129	0.53 (0.37-0.74)
No	14/48	30/51	0.31 (0.16-0.59)
Refractory to last prior regimen			
Yes	13/30	22/26	0.20 (0.09-0.44)
No	55/148	93/154	0.50 (0.36-0.70)
High tumor burden (GELF)			
Yes	40/97	61/86	0.40 (0.27-0.61)
No	28/81	54/94	0.50 (0.32-0.79)
Chemoresistant			
Yes	9/25	21/26	0.18 (0.07-0.45)
No	59/153	94/154	0.51 (0.37-0.71)
Disease histology			
FL	56/147	99/148	0.40 (0.29-0.56)
MZL	12/31	16/32	1.00 (0.47-2.13)



Leonard. ASH 2018. Abstr 445.

Slide credit: clinic

Median IRC-assessed PFS (ITT): 39.4 vs 14.1 mo ($P < .0001$)

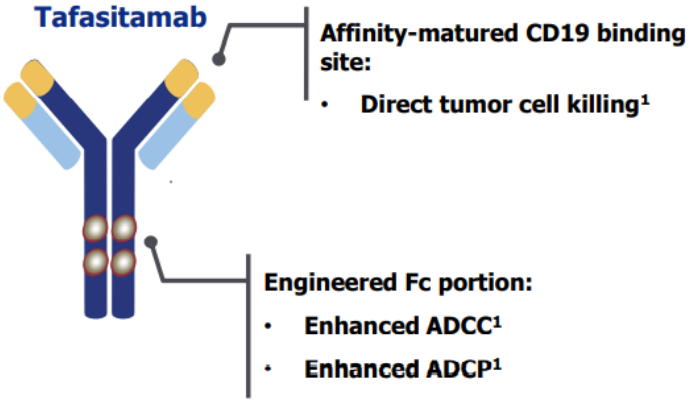
PFS benefit observed across subgroups, except for MZL

ORR median DoR improved with R²

OS improved with R² in FL

Tafasitamab

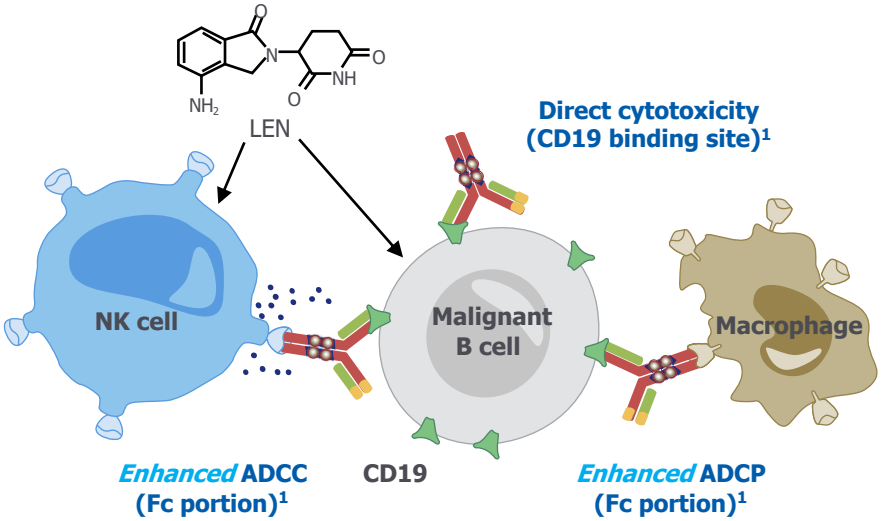
- Tafasitamab is novel Fc-engineered monoclonal antibody directed against human CD19 receptor
- The heavy chain constant region has been engineered with the introduction of two amino acid changes, S239D and I332E, in the CH2 domain, resulting in increased binding affinity for Fcγ receptors (FcγRs).



The Fc-modification of tafasitamab is **intended to lead to a significant potentiation of ADCC and ADCP activity, thus enhancing two key mechanisms of tumor cell killing.**

Zinzani PL, Minotti G. J Cancer Res Clin Oncol.

Tafasitamab & lenalidomide : rationale for a sinergistic activity



Tafasitamab (Fc-enhanced, anti-CD19 mAb)[1–3]

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

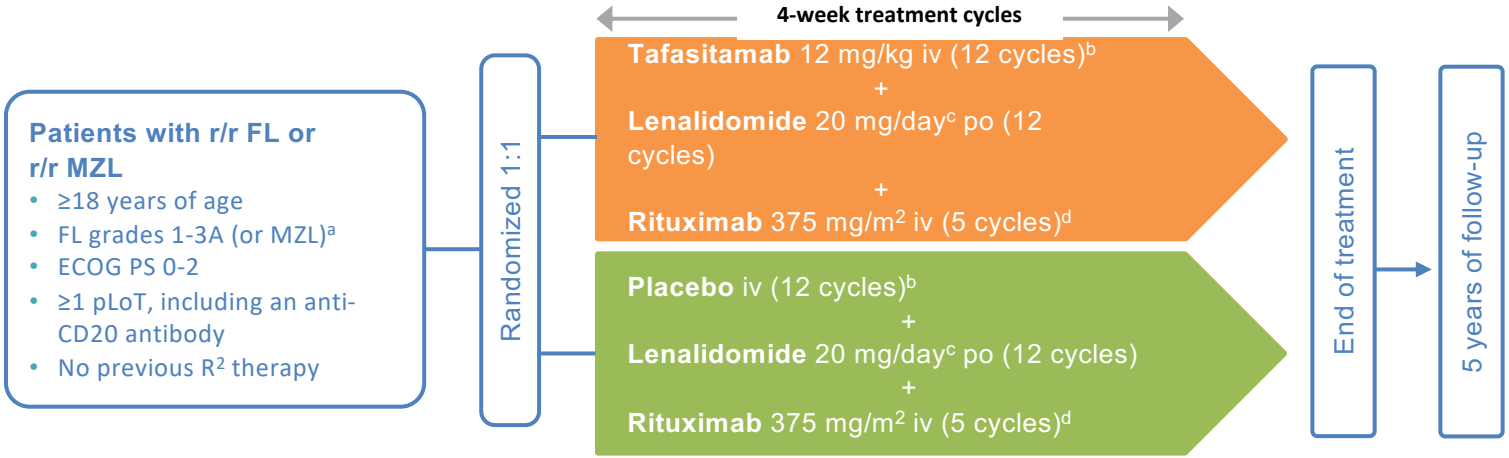
LEN[4,5]

- T-cell and NK-cell activation/expansion
- Direct cell death
- Well-studied as an antilymphoma agent, alone or in combination

The L-MIND trial provided clinical evidence supporting the efficacy and synergy of the combination of tafasitamab and lenalidomide in which **the affinity of tafasitamab for both effector and target cells is magnified by the immunomodulating effects of lenalidomide** (such as stimulation of NK cell proliferation, as well as activation and enhancement of NK-mediated ADCC)[6]

1. Horton HM, et al. Cancer Res. 2008;68:8049–57; 2. Woyach JA, et al. Blood. 2014;124:3553–60; 3. Jurczak W, et al. Ann Oncol. 2018;29:1266–72;
4. Witzig TE, et al. Ann Oncol. 2015;26:1667–77; 5. Czuczman MS, et al. Clin Cancer Res. 2017;23:4127–37; 6. Zinzani PL, Minotti G. J Cancer Res Clin Oncol. 2021;148:177–90.

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



Study endpoints in the FL population (investigator-assessed unless specified)

- **Primary:** **PFS**
- Key secondary: PET-CR rate in the FDG-avid population, OS
- Select other secondary: PFS by IRC, ORR, DoR, safety, QoL, MRD
- Exploratory: TTNT, B-cell recovery, Ig levels, CD19 expression

Stratification factors (patients with FL)

- POD24-ID (yes or no)
- Refractoriness to previous CD20-directed mAb (yes or no)
- Number of pLoTs (1 or ≥2)

Patient Disposition

FL Population

548 patients with r/r FL randomized to treatment

Tafa-R[2] (n=273), n (%)

Received treatment, 273 (100)
Ongoing study treatment, 51 (18.7)
Discontinued treatment, 222 (81.3)

- Completed treatment, 146 (53.5)
- Progression, 30 (11.0)
- Adverse event, 24 (8.8)
- Lack of efficacy, 7 (2.6)
- Withdrawal, 7 (2.6)
- Physician's decision, 4 (1.5)
- Death, 2 (0.7)
- Lost to follow-up, 1 (0.4)
- Other, 1 (0.4)

Ongoing in overall study, n=244 (89.4)
Withdrew from study, 29 (10.6)

- Death, 15 (5.5)
- Withdrawal, 11 (4.0)
- Lost to follow-up, 3 (1.1)
- Other: 0

Full analysis set (n=273)
Safety (n=274)[a]

Plc-R[2] (n=275), n (%)

Received treatment, 273 (99.3)
Ongoing study treatment, 42 (15.3)
Discontinued treatment, 231 (84.0)

- Completed treatment, 118 (42.9)
- Progression, 84 (30.5)
- Adverse event, 15 (5.5)
- Lack of efficacy, 5 (1.8)
- Withdrawal, 5 (1.8)
- Physician's decision, 0
- Death, 3 (1.1)
- Lost to follow-up, 0
- Other, 1 (0.4)

Ongoing in overall study, n=229 (83.3)
Withdrew from study, 46 (16.7)

- Death, 23 (8.4)[b]
- Withdrawal, 19 (6.9)
- Lost to follow-up, 2 (0.7)
- Other, 2 (0.7)

Full analysis set (n=275)
Safety (n=272)[c]

Data cutoff:
February 23, 2024

At primary analysis, the median number of cycles received was 12 with tafasitamab and 11 with placebo

Characteristics	Tafa-R² (n=273)	Plc-R² (n=275)	POD24-IT-positive			POD24-IT-negative			Total (N=548)
			Tafa-R² (n=121)	Plc-R² (n=128)	Total (n=249)	Tafa-R² (n=142)	Plc-R² (n=140)	Total (n=282)	
Median age, years (range)	64.0 (36-88)	64.0 (31-85)	64.0 (36-88)	62.0 (31-84)	63.0 (31-88)	65.0 (38-88)	67.0 (31-85)	66.0 (31-88)	64.0 (31-88)
≥75, n (%)	54 (19.8)	54 (19.6)	27 (22.3)	19 (14.8)	46 (18.5)	27 (19.0)	34 (24.3)	61 (21.6)	108 (19.7)
Male sex, n (%)	150 (54.9)	149 (54.2)	72 (59.5)	65 (50.8)	137 (55.0)	73 (51.4)	79 (56.4)	152 (53.9)	299 (54.6)
Median time since initial FL diagnosis, years (range)	5.2 (0-34)	5.5 (1-33)	3.4 (0-34)	2.7 (1-33)	3.1 (0-34)	6.7 (2-25)	8.5 (2-33)	7.7 (2-33)	5.3 (0-34)
ECOG PS at screening, n (%)									
0	181 (66.3)	192 (69.8)	77 (63.6)	86 (67.2)	163 (65.5)	97 (68.3)	102 (72.9)	199 (70.6)	373 (68.1)
1-2	92 (33.7)	83 (30.2)	44 (36.4)	42 (32.8)	86 (34.5)	45 (31.7)	38 (27.1)	83 (29.4)	175 (31.9)
Bone marrow involvement, n (%)									
Yes	88 (32.2)	91 (33.1)	NA	NA	NA	NA	NA	NA	179 (32.7)
No	169 (61.9)	162 (58.9)	NA	NA	NA	NA	NA	NA	331 (60.4)
Unknown/missing	16 (5.9)	22 (8.0)	NA	NA	NA	NA	NA	NA	38 (6.9)
									Ann Arbor stage, n (%)
I or II	52 (19.0)	50 (18.2)	23 (19.0)	16 (12.5)	39 (15.7)	29 (20.4)	32 (22.9)	61 (21.6)	102 (18.6)
III or IV	221 (81.0)	225 (81.8)	98 (81.0)	112 (87.5)	210 (84.3)	113 (79.6)	108 (77.1)	221 (78.4)	446 (81.4)
									FL grade, n (%)
1 or 2	203 (74.4)	203 (73.8)	88 (72.7)	89 (69.5)	177 (71.1)	109 (76.8)	108 (77.1)	217 (77.0)	406 (74.1)
3A	67 (24.5)	71 (25.8)	31 (25.6)	38 (29.7)	69 (27.7)	32 (22.5)	32 (22.9)	64 (22.7)	138 (25.2)

Patients' Baseline Characteristics (2/2)

FL Population[1,2]

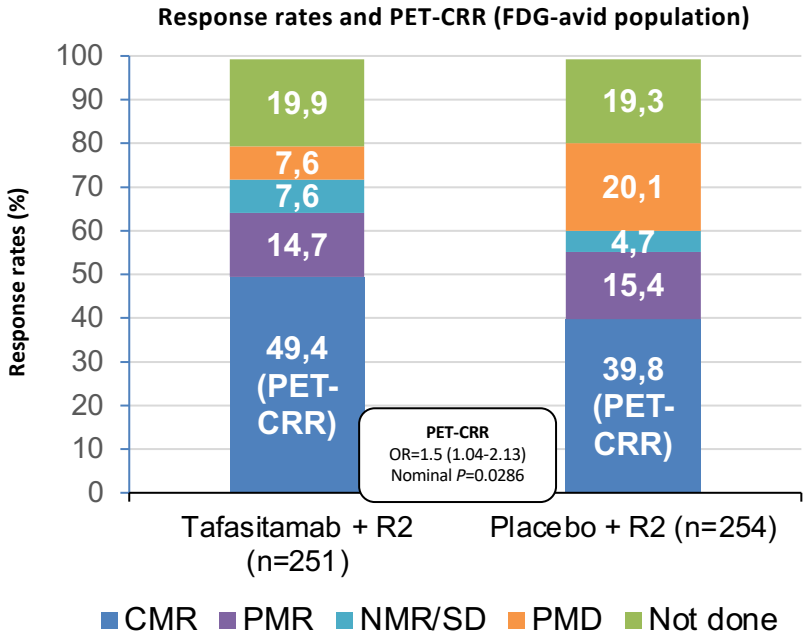
Characteristics	Tafa-R² (n=273)	Plc-R² (n=275)	POD24-IT-positive			POD24-IT-negative			Total (N=548)
			Tafa-R² (n=121)	Plc-R² (n=128)	Total (n=249)	Tafa-R² (n=142)	Plc-R² (n=140)	Total (n=282)	
B symptoms, n (%)	63 (23.1)	67 (24.4)	28 (23.1)	36 (28.1)	64 (25.7)	33 (23.2)	31 (22.1)	64 (22.7)	130 (23.7)
FLIPI score, n (%)									
0 or 1	57 (20.9)	57 (20.7)	22 (18.2)	21 (16.4)	43 (17.3)	35 (24.6)	36 (25.7)	71 (25.2)	114 (20.8)
2	79 (28.9)	67 (24.4)	33 (27.3)	30 (23.4)	63 (25.3)	42 (29.6)	36 (25.7)	78 (27.7)	146 (26.6)
3-5	137 (50.2)	150 (54.5)	66 (54.5)	77 (60.2)	143 (57.4)	65 (45.8)	67 (47.9)	132 (46.8)	287 (52.4)
GELF criteria, n (%)	222 (81.3)	232 (84.4)	97 (80.2)	109 (85.2)	206 (82.7)	117 (82.4)	117 (83.6)	234 (83.0)	454 (82.8)
Relapsed/refractory status to last therapy, n (%)									
Relapsed	148 (54.2)	164 (59.6)	49 (40.5)	59 (46.1)	108 (43.4)	97 (68.3)	101 (72.1)	198 (70.2)	312 (56.9)
Refractory	112 (41.0)	97 (35.2)	68 (56.2)	67 (52.3)	135 (54.2)	36 (25.4)	27 (19.3)	63 (22.3)	209 (38.1)
Undetermined	13 (4.8)	14 (5.1)	4 (3.3)	2 (1.6)	6 (2.4)	9 (6.3)	12 (8.6)	21 (7.4)	27 (4.9)
FL diagnosis confirmed by central pathology, n (%)	256 (93.8)	259 (90.5)	NA	NA	NA	NA	NA	NA	505 (92.2)
Refractory to prior CD20-directed therapy, n (%)	118 (43.2)	115 (41.8)	80 (66.1)	86 (67.2)	166 (66.7)	32 (22.5)	25 (17.9)	57 (20.3)	233 (42.5)

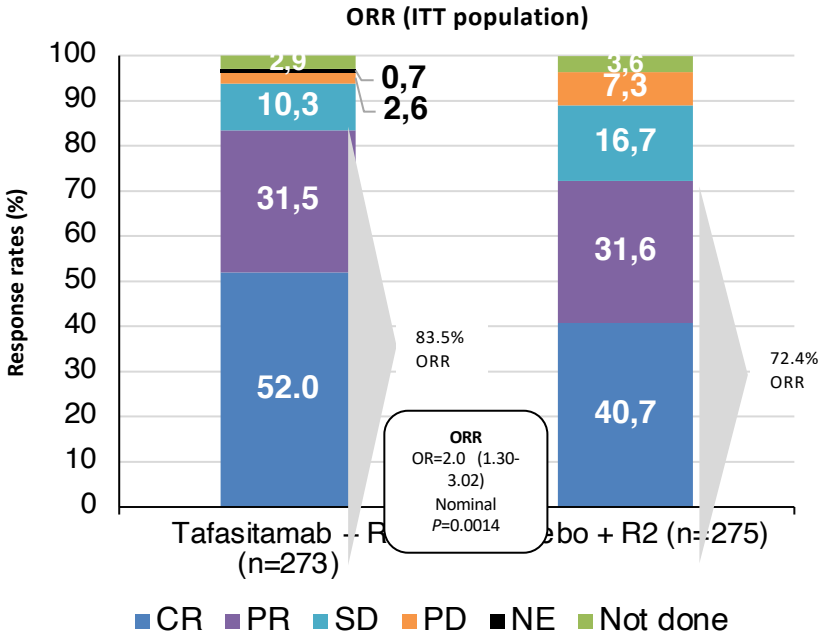
- Patient's characteristics generally similar across treatment groups, in the overall FL study population, between POD24-positive and POD24-negative groups, and within POD24-IT groups[1,2]
- High-risk FLIPI and refractoriness to previous CD20-directed therapy were more frequent in POD24-IT-positive patients than in POD24-IT-negative patients[1,2]

1. Sehn LH, et al. ASH 2024. Oral presentation LBA-1. 2. Trněný M, et al. EHA 2025. Poster PS1877.

PET CRR and ORR

FL Population



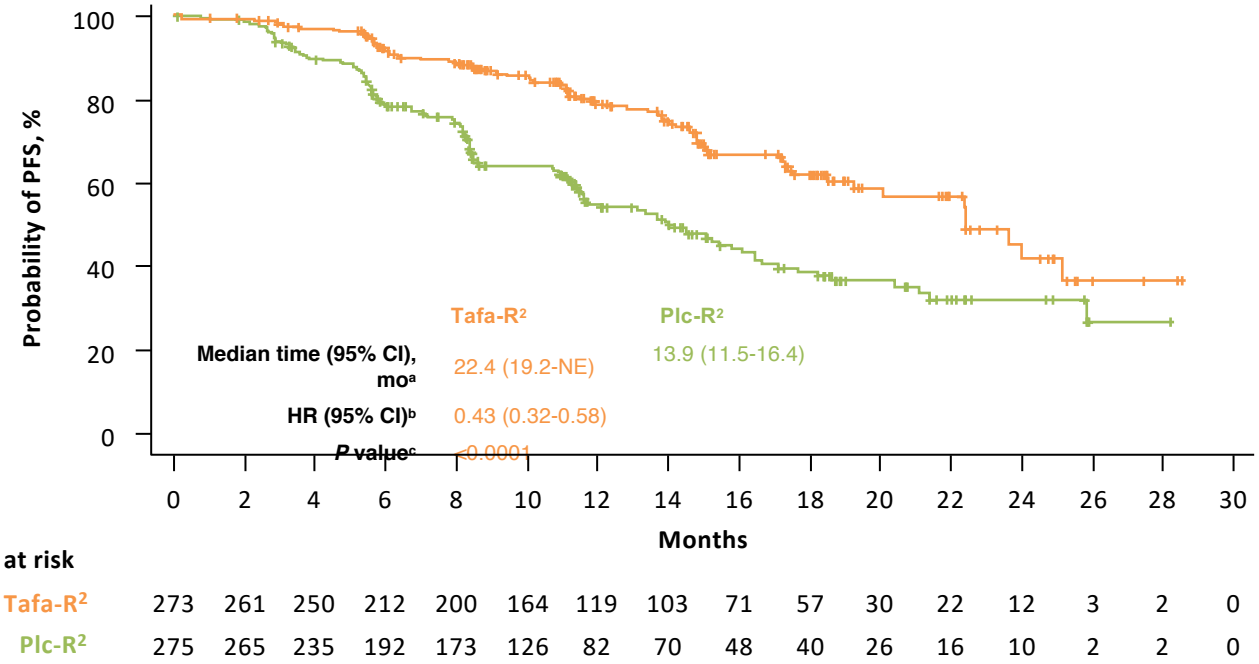


Significant improvement in PET-CRR and ORR was observed in the tafa-R^2 group

Efficacy endpoint by POD24-IT

PFS by Investigator Assessment

Primary Endpoint (FL Population)[1,2]



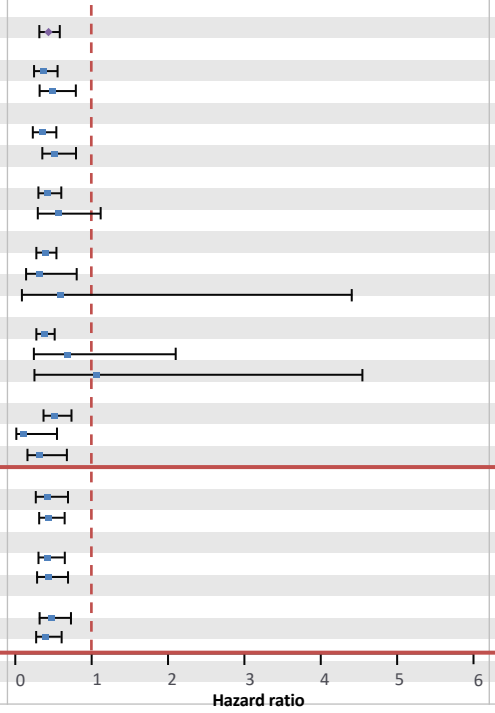
Significant improvement in PFS with tafa-R² vs plc-R², representing a 57% reduction in risk of progression, relapse or death[1,2]

PFS by independent review committee

PFS by Subgroups

FL Population[1,2]

Variable	Tafa+R² # Events/ # Patients censored	Plc-R² # Events/ # Patients censored	Hazard ratio (95% CI)
Subgroup			
All patients	75/198	131/144	0.43 (0.32-0.58)
Sex			
Male	40/110	78/71	0.38 (0.26-0.56)
Female	35/88	53/73	0.51 (0.33-0.80)
Age group 1			
<65	29/108	69/70	0.35 (0.23-0.55)
≥65	46/90	62/74	0.53 (0.35-0.80)
Age group 2			
<75	55/164	102/119	0.44 (0.31-0.61)
≥75	20/34	29/25	0.58 (0.30-1.12)
Race			
White	61/158	106/113	0.40 (0.29-0.55)
Asian	11/29	21/21	0.34 (0.14-0.81)
Other and missing	3/11	4/10	0.60 (0.08-4.41)
Ethnicity			
Not Hispanic or Latino	62/166	112/114	0.39 (0.28-0.53)
Hispanic or Latino	8/23	10/14	0.71 (0.24-2.10)
Other and missing	5/9	9/16	1.07 (0.25-4.56)
Geographic region			
Europe	52/124	88/105	0.53 (0.38-0.76)
North America	8/30	11/13	0.12 (0.02-0.55)
Rest of the world	15/44	32/26	0.33 (0.16-0.68)
POD24-ID			
Yes	29/56	52/36	0.43 (0.27-0.69)
No	46/142	79/108	0.45 (0.31-0.65)
Refractory to prior anti-CD20			
Yes	45/73	68/47	0.44 (0.30-0.65)
No	30/125	63/97	0.44 (0.28-0.68)
Number of pLoTs			
1 line	36/110	61/86	0.48 (0.32-0.74)
≥2 lines	39/88	70/58	0.41 (0.28-0.61)



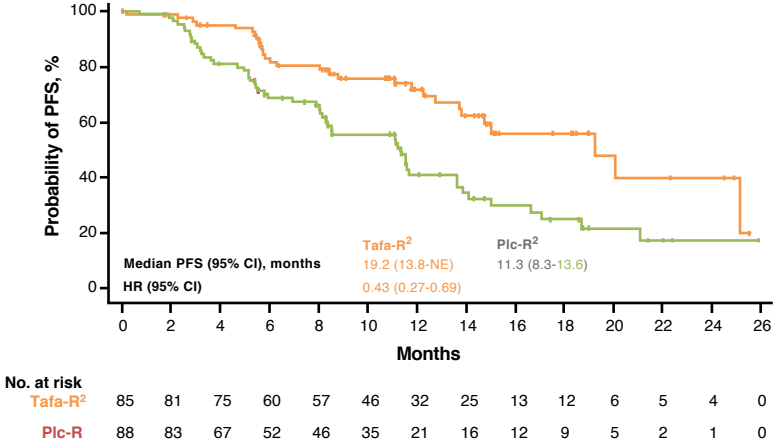
Improvement in PFS with tafa-R² vs plc-R² was reported in all subgroups analyzed, including:

- POD24-ID
- Refractory status
- 1 pLoT vs ≥2 pLoTs

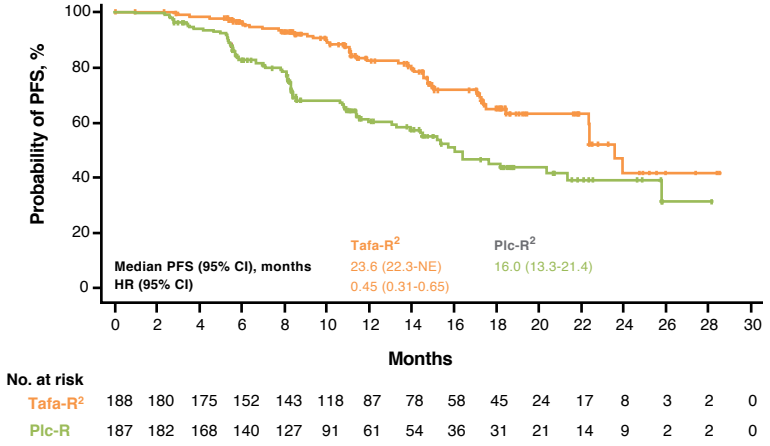
PFS by POD24-ID Status

FL Population

POD24-ID: Yes



POD24-ID: No



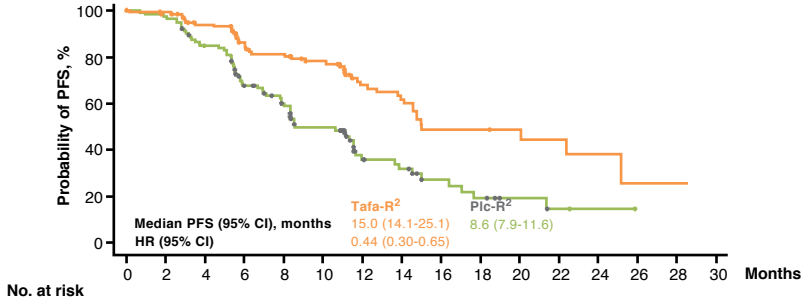
Treatment with tafa-R^2 prolonged PFS as compared with plc-R^2 irrespective of POD24-ID status

Trněný M, et al. EHA 2025. Oral presentation S230.

PFS by Refractoriness and Number of pLoTs

FL Population

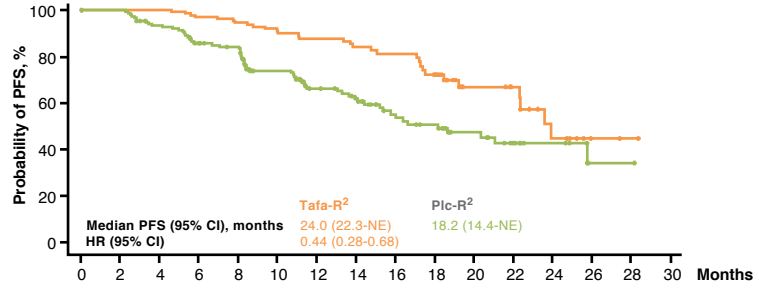
Anti-CD20 Refractory: Yes



No. at risk

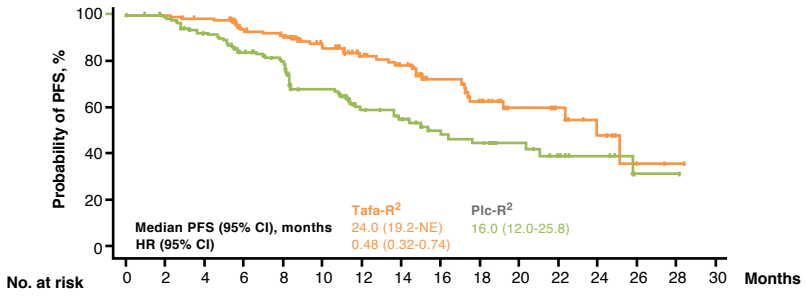
Tafa-R²	118	113	102	86	80	71	46	38	21	19	11	8	5	1	1	0
Plc-R²	115	108	91	66	54	41	20	16	10	7	4	2	1	0	0	0

Anti-CD20 Refractory: No



Tafa-R²	155	148	148	126	120	93	73	65	50	38	19	14	7	2	1	0
Plc-R²	160	157	144	126	119	85	62	54	38	33	22	14	9	2	1	0

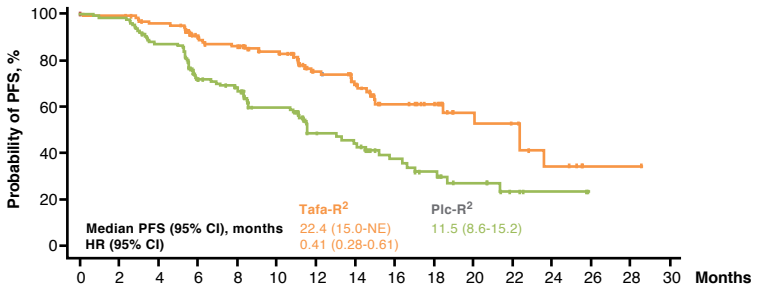
1 pLoT (2L Treatment)



No. at risk

Tafa-R²	146	140	136	115	110	88	65	57	40	31	18	12	7	2	1	0
Plc-R²	147	142	127	108	97	70	47	40	28	25	17	12	8	2	2	0

≥2 pLoTs (3L+ treatment)

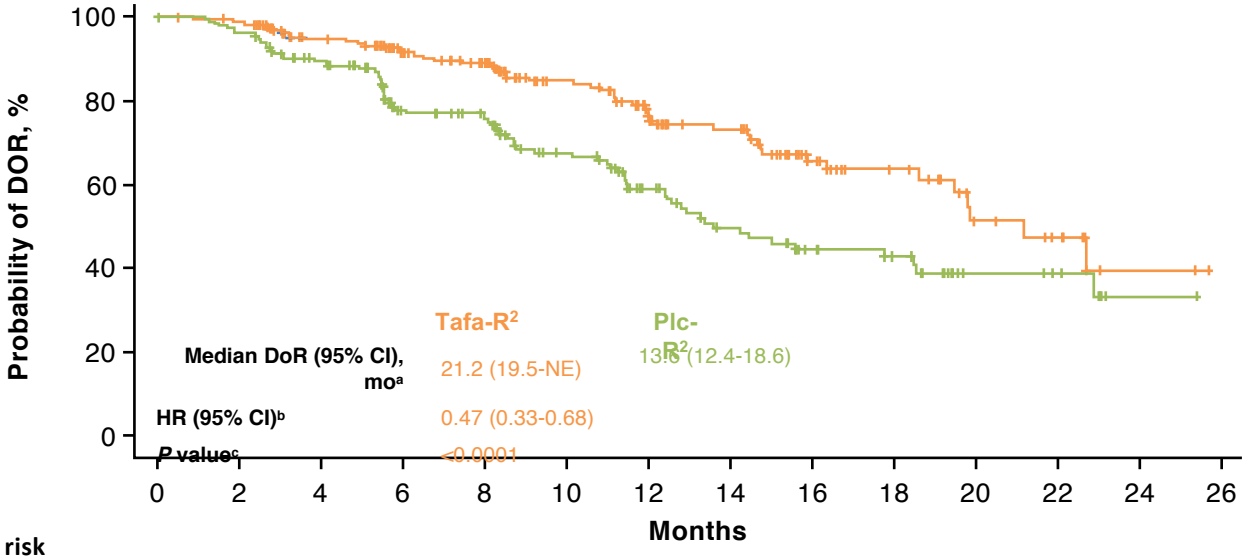


Tafa-R²	127	121	114	97	90	76	54	46	31	26	12	10	5	1	1	0
Plc-R	128	123	108	84	76	56	35	30	20	15	9	4	2	0	0	0

Trněný M, et al. EHA 2025. Oral presentation S230.

Duration of Response

FL Population



No. at risk

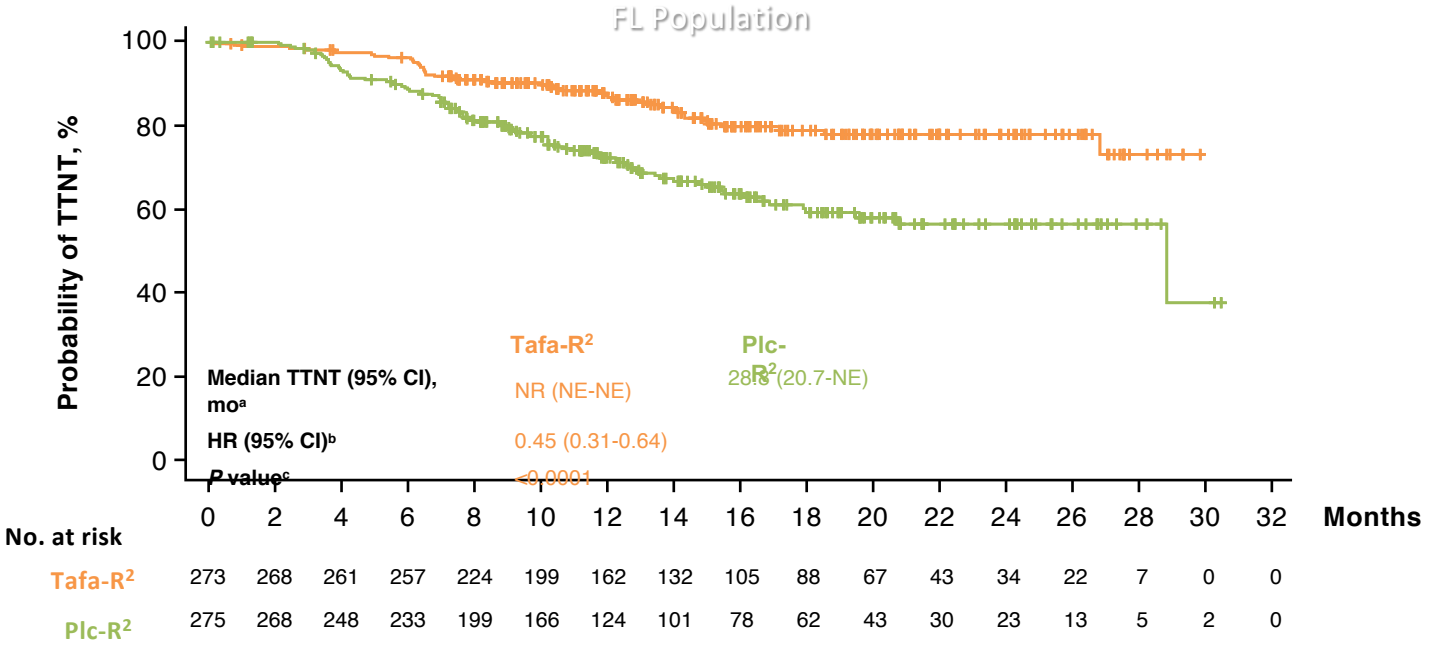
Tafa-R2	228	219	185	155	140	105	81	66	37	27	14	10	3	0
Plc-R2	199	188	163	115	106	75	54	40	29	22	10	8	2	0

Significant improvement in DoR was observed with tafa-R2 vs plc-R2

Duration of complete response

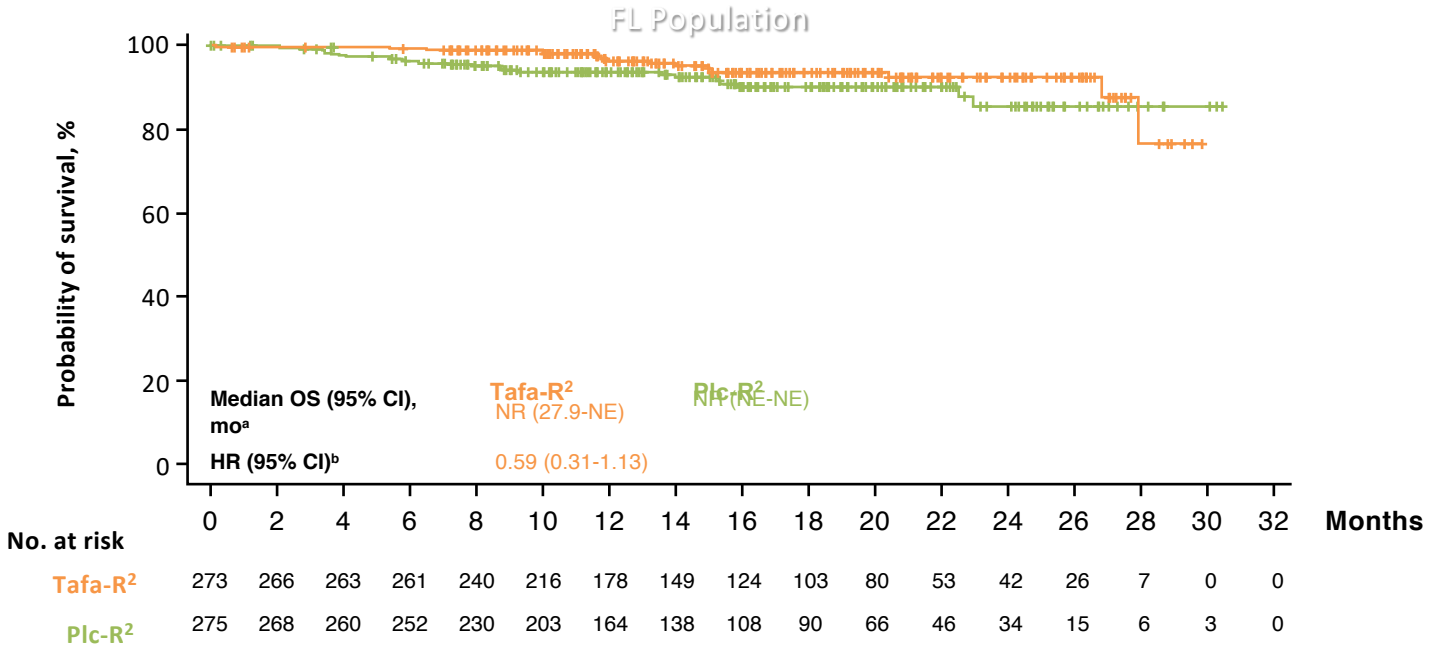
Trněný M, et al. EHA 2025. Oral presentation S230.

Time to Next Treatment



Median TTNT was not reached with tafa-R^2 and was 28.8 months with plc-R^2

Overall Survival



- OS was tested only for futility at time of the primary analysis
- After a median follow-up of 15.3 months, the futility threshold was not crossed and a positive trend in favor of tafa-R^2 was observed

Safety

Most Frequent Any-Grade TEAEs (≥15% in Any Group) in the FL Population

Preferred term, n (%)	Tafa-R² (n=274)[a]	Plc-R² (n=272)[b]	Total (N=546)
Any-grade TEAEs	272 (99.3)	270 (99.3)	542 (99.3)
Neutropenia	133 (48.5)	123 (45.2)	256 (46.9)
Diarrhea	103 (37.6)	77 (28.3)	180 (33.0)
COVID-19	86 (31.4)	64 (23.5)	150 (27.5)
Constipation	80 (29.2)	67 (24.6)	147 (26.9)
Rash	60 (21.9)	58 (21.3)	118 (21.6)
Fatigue	58 (21.2)	43 (15.8)	101 (18.5)
Cough	52 (19.0)	47 (17.3)	99 (18.1)
Pyrexia	52 (19.0)	44 (16.2)	96 (17.6)
Muscle spasms	49 (17.9)	49 (18.0)	98 (17.9)
Nausea	49 (17.9)	38 (14.0)	87 (15.9)
Infusion-related reaction	43 (15.7)	41 (15.1)	84 (15.4)
Thrombocytopenia	37 (13.5)	42 (15.4)	79 (14.5)
Pruritus	44 (16.1)	28 (10.3)	72 (13.2)

IgG, IgA and IgM at baseline and during the study

inMIND Summary (1/2)

- inMIND is a randomized, placebo controlled, double-blind, phase 3 study evaluating tafa-R^2 vs plc-R^2 in patients with r/r FL or r/r MZL[1,2]
- The study met its primary endpoint of prolonging PFS in patients with r/r FL[1,3]
  - Addition of tafasitamab to R^2 resulted in significant improvement in PFS, representing a 57% reduction in risk of progression, relapse, or death
- PFS benefit was observed in all prespecified subgroups including patients with POD24-ID, refractory to prior CD20-directed mAbs, and receiving multiple prior lines of therapy[3]
- Although the OS data were immature, a trend in favor of tafa-R^2 was observed[3]
- A post hoc analysis performed to explore outcomes according to POD24-IT showed:[4]
  - A higher proportion of POD24-IT-positive patients (45%) vs POD24-ID patients (32%) in the overall study population
  - Evidence that adding tafasitamab to R^2 reduced the risk of progression, and improves PET-CR, ORR and TTNT, regardless of POD24-IT status (positive or negative)
- Tafa-R^2 also prolonged PFS and improved other outcomes vs plc-R^2 regardless of the status of POD12-IT[3]

inMIND Summary (2/2)

- The safety profile was consistent with expected toxicities of these agents[1,2]
  - The most common, any-grade TEAEs seen in any group were neutropenia (47%), diarrhea (33%), COVID-19 (28%), constipation (27%), rash (22%), and fatigue (19%)
  - The most common grade 3 TEAEs were neutropenia (39%), pneumonia and thrombocytopenia (7% each), decreased neutrophil count (6%), anemia (5%), COVID-19 (4%), and COVID-19 pneumonia (3%)
  - 11% of patients (n=30) on tafa-R^2 treatment and 7% of patients (n=18) in the plc-R^2 group discontinued their treatment due to TEAEs
  - Fatal TEAEs occurred in 6 patients of each cohort, and were mostly due to infections
- Tafa-R^2 demonstrated a trend toward deeper MRD responses vs plc-R^2, no correlation of CD19 or CD20 alone or in combination with response to tafa-R^2, and retained CD19 expression at end of tafasitamab treatment[3]
- inMIND is the first study to validate the approach of combining a CD19- and a CD20-directed mAb in the treatment of FL.[1]

1. Sehn LH, et al. ASH 2024. Oral presentation LBA-1. 2. Trněný M, et al. EHA 2025. Oral presentation S230. 3. Reinke S, et al. EHA 2025. Poster PF1006.

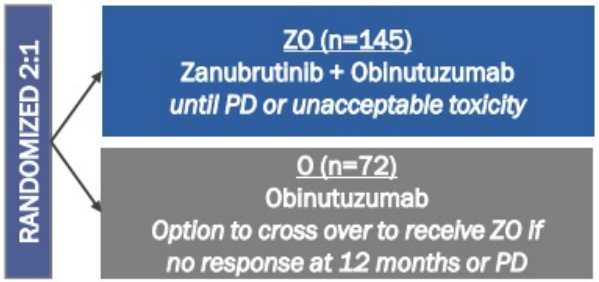
BTK inibitors in FL

BTKi	setting	N pts	ORR %	CRR%	mPFS (m)	Ref
Ibrutinib	PhI RR	16	38	18	NV	Advani et al. JCO 2013
Ibrutinib	PhII RR	110	21	10	4.6m	Gopal et al. JCO 2018
Ibrutinib	PhII RR	40	38	13	14m	Bartlett Blood 2018
Zanubrutinib	PhI/II RR	33	36	18	10.4m	Phiilips et al. Blood advances 2022
Rituximab+ ibrutinib	TN	60	85	40	41.9m	Fowler et al BJH 2020
Ibrutinib --> Ibrutinib+ rituximab	TN	20	75	50	NE	

Final Analysis of the ROSEWOOD Phase 2 Study of Zanubrutinib + Obinutuzumab vs Obinutuzumab in Patients With R/R FL: Study Design and Patients

Key Eligibility Criteria

- Histologically-confirmed grade 1-3a FL
- R/R, ≥2 prior treatments including an anti-CD20 mAb and an alkylating agent
- No prior BTKi
- ECOG PS ≤2



Primary endpoint: ORR (IRC; per Lugano 2014)
Key secondary endpoints: ORR (INV), DOR (IRC & INV), PFS (IRC & INV), OS, safety

Patient Characteristics	Z0 (n=145)	O (n=72)
Median age (range), years	63.0 (31-84)	65.5 (32-88)
ECOG PS ≥1, n (%)	59 (40.6)	41 (57.0)
FLIPI ≥3, n (%)	77 (53.1)	37 (51.4)
Ann Arbor stage III–IV, n (%)	119 (82.1)	60 (83.3)
Bulky disease ≥7 cm, n (%)	23 (15.9)	12 (16.7)
BM involvement, n (%)	39 (26.9)	26 (36.1)
High tumor burden (GELF), n (%)	83 (57.2)	40 (55.6)
LDH >ULN, n (%)	49 (33.8)	29 (40.3)
Median prior LOT, (range)	3 (2–11)	3 (2–9)
>3, n (%)	41 (28.3)	18 (25.0)
Rituximab refractory, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent LOT, n (%)	47 (32.4)	29 (40.3)
POD24, n (%)	51 (35.2)	30 (41.7)
Prior Benda, n (%)	79 (54.5)	40 (55.6)
Prior SCT, n (%)	32 (22.1)	13 (18.1)

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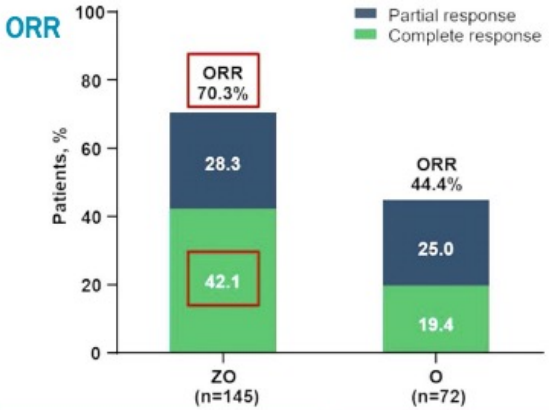
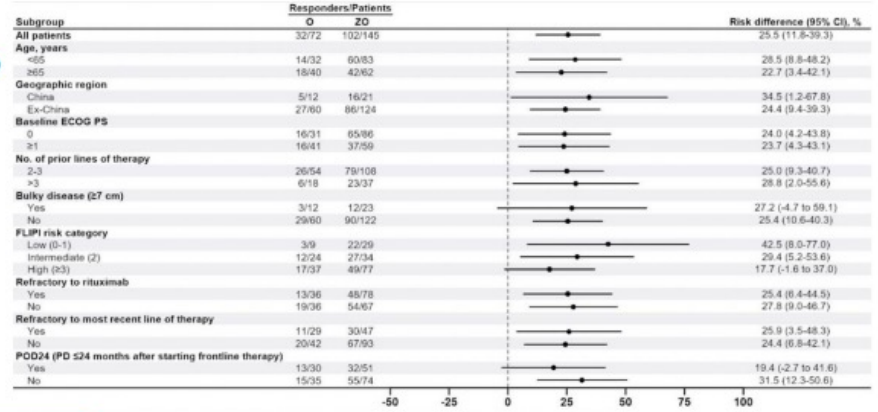
Final Analysis of the ROSEWOOD Phase 2 Study of Zanu + Obin vs Obin in Patients With R/R FL: Response





Response		ZO (n=145)	O (n=72)
ORR, n (%) [95% CI]		102 (70.3) [62.2-77.6]	32 (44.4) [32.7-56.6]
Risk difference (95% CI), %		25.5 (11.8-39.3); *P*=.0003	
CR rate, n (%) [95% CI]		61 (42.1) [33.9-50.5]	14 (19.4) [11.1-30.5]
		P=.0009	
Other responses, n (%)	SD	21 (14.5)	14 (19.4)
	Non-PD[a]/PD	6 (4.1)/13 (9.0)	9 (12.5)/16 (22.2)

[a] Defined as PET assessment missing or not evaluable.

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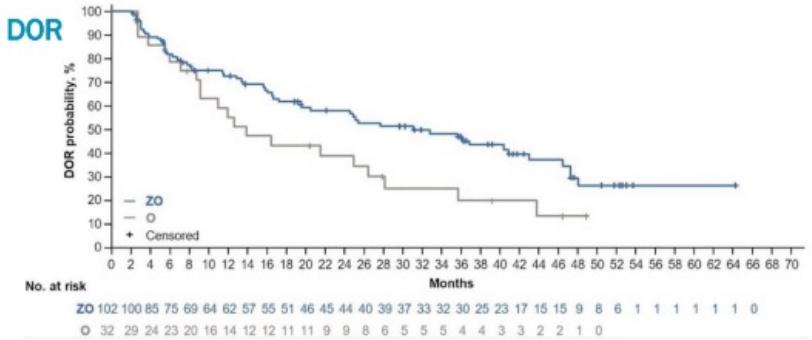
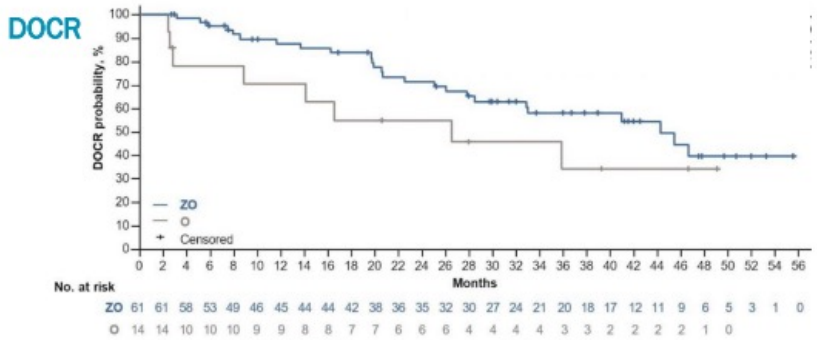
- ORR benefit with ZO vs O was consistent across subgroups (data not shown)
- Median follow-up: 34.6 months

Final Analysis of the ROSEWOOD Phase 2 Study of Zanu + Obin vs Obin in Patients With R/R FL: DOR





DOR per IRC	ZO	O
Median, months (95% CI)	32.9 (19.6-43.1)	14.0 (9.2-26.5)
36-month rate, % (95% CI)	47.2 (36.0-57.6)	20.3 (6.9-38.6)
Median follow-up (range), months	41.1 (0-64.4)	39.3 (0-49.0)

DOCR per IRC	ZO	O
Median, months (95% CI)	44.2 (28.4-NE)	26.5 (2.7-NE)
36-month rate, % (95% CI)	57.6 (42.4-70.2)	34.1 (9.7-60.9)
Median follow-up (range), months	38.9 (2.8-55.4)	39.3 (2.4-49.0)

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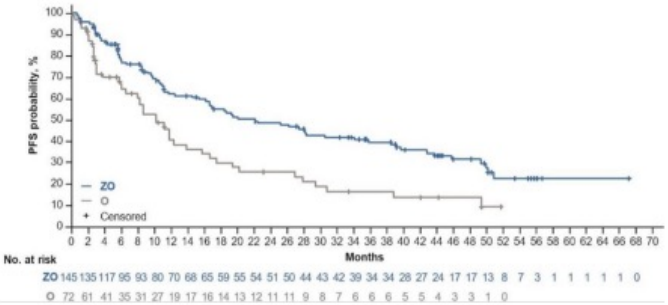
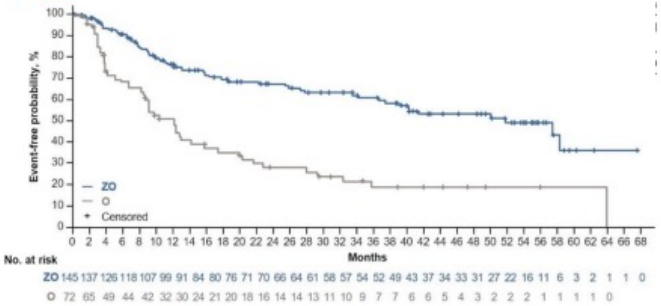
Final Analysis of the ROSEWOOD Phase 2 Study of Zanu + Obin vs Obin in Patients With R/R FL: PFS, TTNT, and OS

PFS



TTNT



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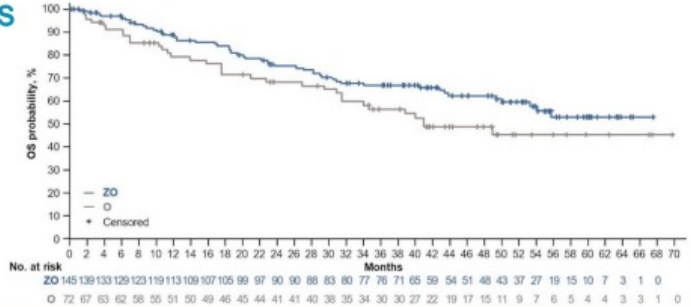
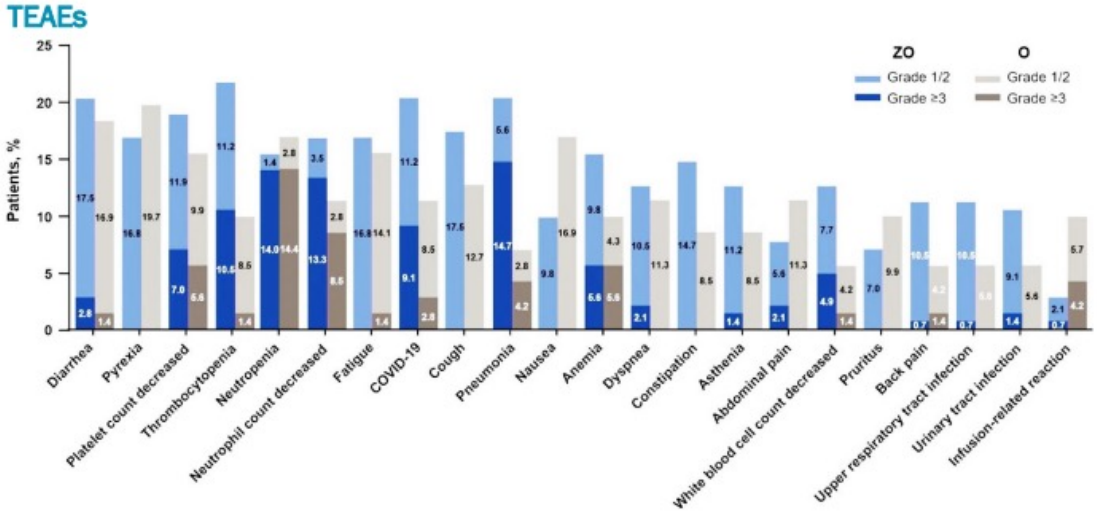
OS



PFS, TTNT, and OS		ZO	O
PFS per IRC	Median, months (95% CI)	22.1 (16.1-34.0)	10.3 (6.5-13.8)
	HR (95% CI); *P* value	0.54 (0.37-0.79); *P*=0.0012	
	Median follow-up (range), months	44.1 (0-67.2)	42.1 (0-51.8)
TTNT per IRC	Median, months (95% CI)	51.7 (36.6-NE)	12.1 (8.3-15.9)
	HR (95% CI); *P* value	0.37 (0.25-0.55); *P*<.0001	
	Median follow-up (range), months	40.6 (0.1-67.5)	38.8 (0.1-63.9)
OS	Median, months (95% CI)	NE (50.0-NE)	41.2 (31.5-NE)
	HR (95% CI); *P* value	0.66 (0.43-1.04); *P*=0.0698	
	Median follow-up (range), months	48.9 (42.5-52.8)	44.3 (41.5-49.6)

Final Analysis of the ROSEWOOD Phase 2 Study of Zanu + Obin vs Obin in Patients With R/R FL: Safety

Safety Summary, n (%)	ZO (n=145)	O (n=72)
Any TEAE	137 (95.8)	65 (91.5)
Treatment related	110 (76.9)	49 (69.0)
Grade ≥3	103 (72.0)	34 (47.9)
Treatment related	62 (43.4)	19 (26.8)
Serious	75 (52.4)	22 (31.0)
Treatment related	29 (20.3)	8 (11.3)
Leading to death	15 (10.5)	7 (9.9)
Treatment related	2 (1.4)	1 (1.4)
Leading to discontinuation	31 (21.7)	9 (12.7)
Treatment related	14 (9.8)	3 (4.2)



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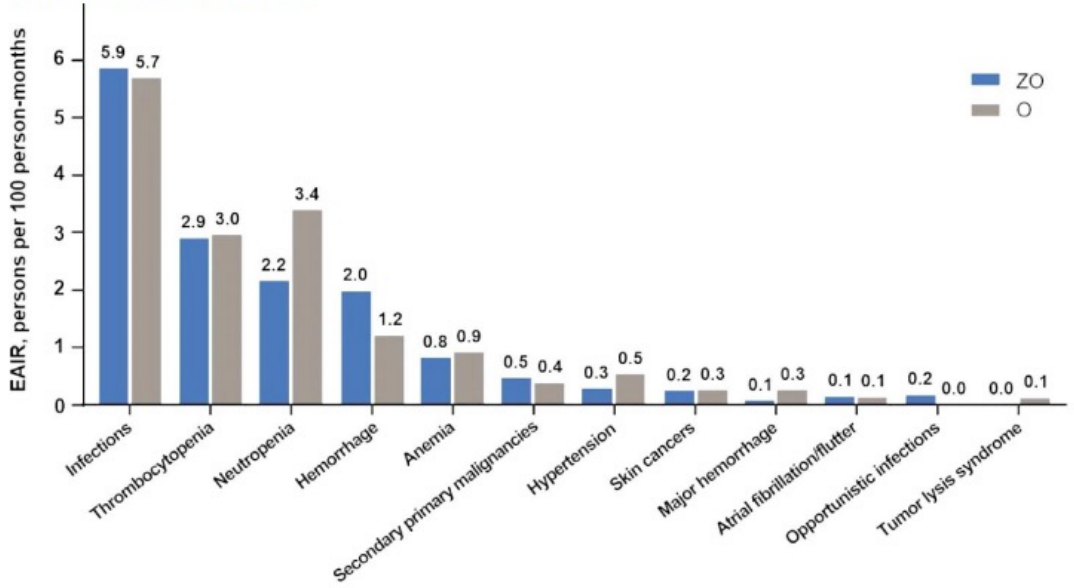
Final Analysis of the ROSEWOOD Phase 2 Study of Zanu + Obin vs Obin in Patients With R/R FL: Safety (cont'd) and Summary

TEAEs of Special Interest



Authors' Conclusions

- ZO demonstrated improved response rates, DOR, and PFS compared with O
- ZO had a manageable safety profile, with no new safety signals

Zinzani PL, et al. ASH 2025. Abstract 227.

GOLSEEK-4: A multicenter Phase 3 randomized open-label study comparing efficacy and safety of golcadomide + rituximab vs investigator's choice in patients with relapsed/refractory follicular lymphoma who have received ≥1 line of systemic therapy

Eliza Hawkes,[1] Clémentine Sarkozy,[2] Yuqin Song,[3] Muhit Ozcan,[4] Franck Morschhauser,[5] Alex Herrera,[6] Alev Akyol,[7] Parth Rao,[7] Antonia Di Micco,[8] Adrien Petel,[8] Serena Perna,[7] Charalambos Andreadis[9]

[1]Olivia Newton John Cancer Research Institute at Austin Health, Australia; [2]Institut Curie, Hôpital Saint-Cloud, Université de Versailles Saint-Quentin, France; [3]Director of Department of Lymphoma, Peking University Cancer Hospital & Institute, China; [4]Ankara University School of Medicine, Turkey; [5]University of Lille, Centre Hospitalier Universitaire de Lille, France; [6]City of Hope Comprehensive Cancer Center, California, USA; [7]BMS, USA; [8]BMS, Switzerland; [9]UCSF Health, USA

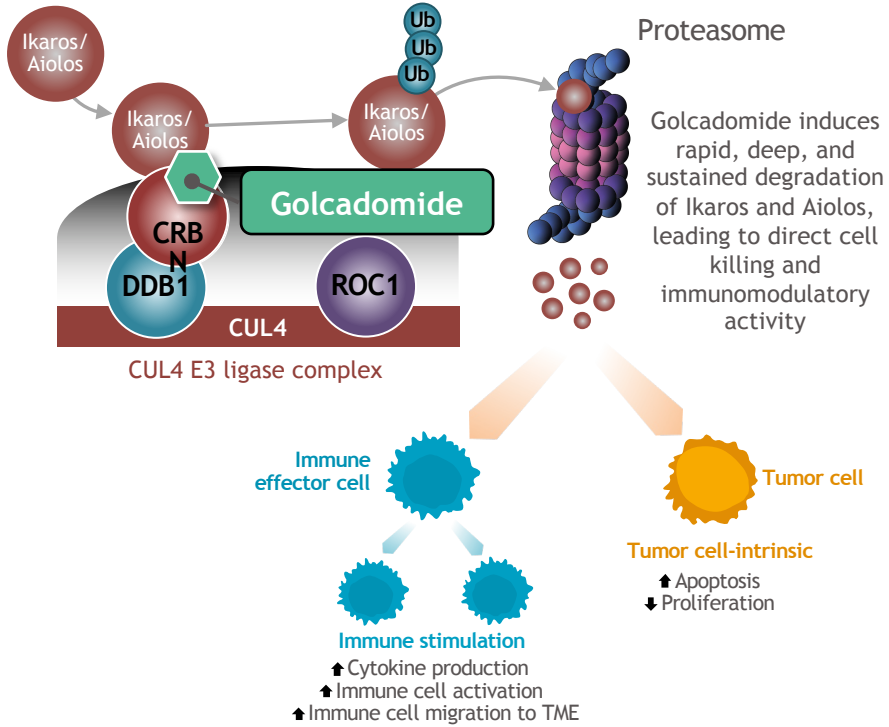
Background

- Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL), accounting for ~20% of all NHL cases[1]
- While a long remission with frontline treatment can be expected in many patients with FL, the disease remains incurable, and subsequent relapses are associated with significantly shorter remissions[2]
- Commonly used treatment regimens for relapsed/refractory (R/R) FL include rituximab (R), lenalidomide (len), or non–cross-resistant chemoimmunotherapy such as R + cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or R-bendamustine[3]
- More recently, T-cell–directed therapies such as chimeric antigen receptor T cells and bispecific antibodies in the third line or later have improved outcomes; however, they are associated with tolerability concerns and logistical challenges[4–7]
- An unmet need remains for highly efficacious, well tolerated, and more convenient chemotherapy-free regimens that improve outcomes in patients with R/R FL who have received 1 or more prior lines of systemic therapy

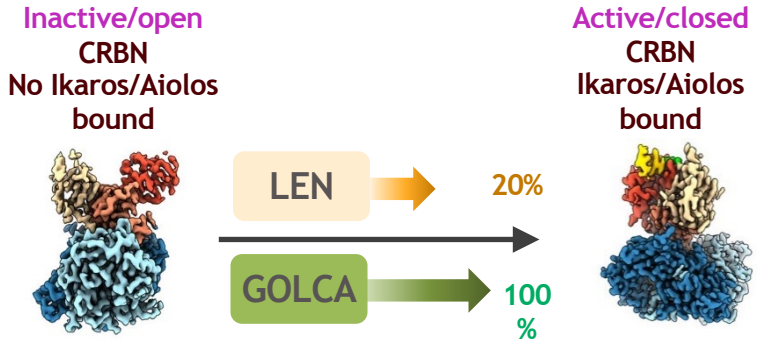
1. Cancer.gov. Accessed 17 July 2025. https://www.cancer.gov/types/lymphoma/hp/indolent-b-cell-lymphoma-treatment-pdq#_1723; 2. Batlevi CL, et al. Blood Cancer J 2020:10:1—12;
3. Casulo C et al. Lancet Haematol 2022;9:e289—e300; 4. Bartlett NL, et al. Blood 2022;140(suppl. 1):1467—1470; 5. Jacobson CA, et al. Lancet Oncol 2022;23:91—103; 6. Fowler NH, et al. Nat Med 2022;29:325—332; 7. Dreyling M, et al. Ann Oncol 2021;32:298—230.

Key Figure A. Golcadomide is a potential first-in-class, oral CELMoD™ agent for NHL

Mechanism of action[1,3,4]



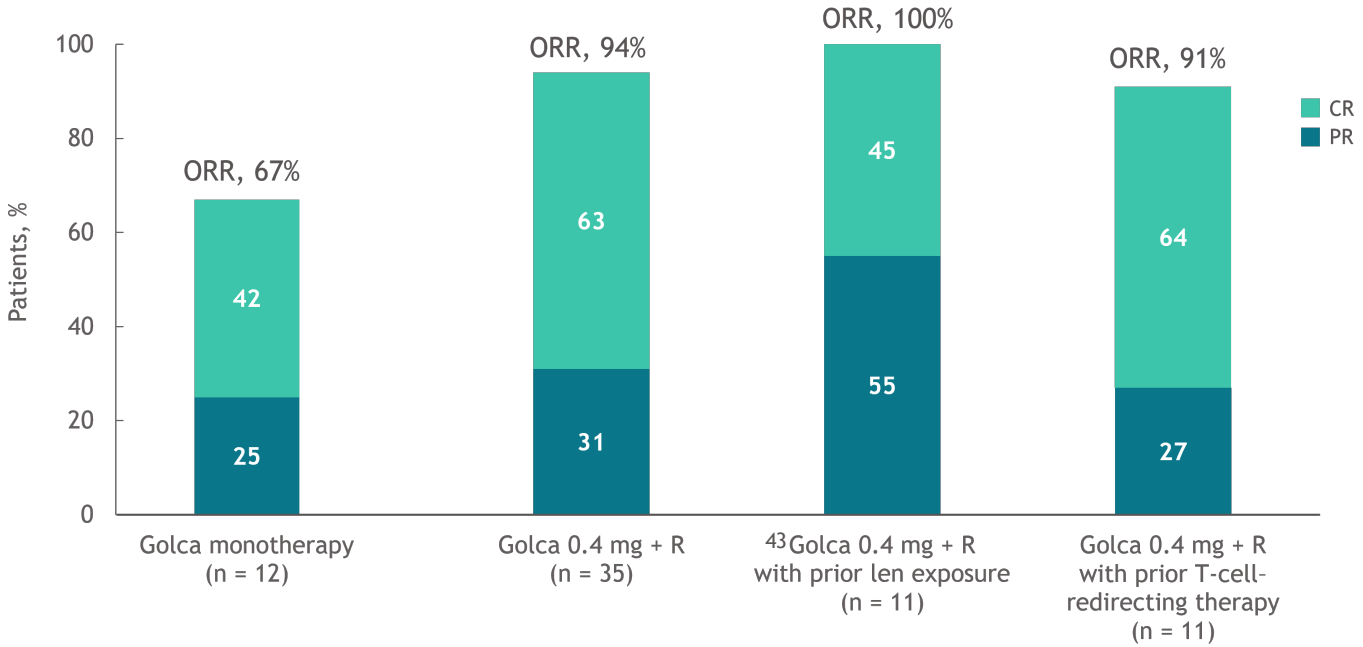
Allosteric regulation of CRBN[1]



- The distinct binding of golcadomide outside of the tri-TRP pocket induces the complete conversion to the active, 'closed' conformation of cereblon, vs LEN (100% vs 20%), leading to deeper and more rapid degradation of Ikaros/Aiolos compared with LEN
- Golcadomide deeply penetrates lymphoid tissue, an optimal feature for the treatment of lymphoma

CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; GOLCA, golcadomide; LBCL, large B-cell lymphoma; LEN, lenalidomide; ROC, regulator of cullins; TME, tumor microenvironment; TRP, tryptophan; Ub, ubiquitin. 1. Mo Z, et al. Blood Cancer Discov 2025; doi: 10.1158/2643-3230.BCD-25-0059. Online ahead of print. 2. Amzallag A, et al. ASH 2024. Oral presentation 579. 3. Carrancio S, et al. ASH 2024. Poster presentation 3104; 4. Nakayama Y et al. ASH 2024. Poster presentation 1617.

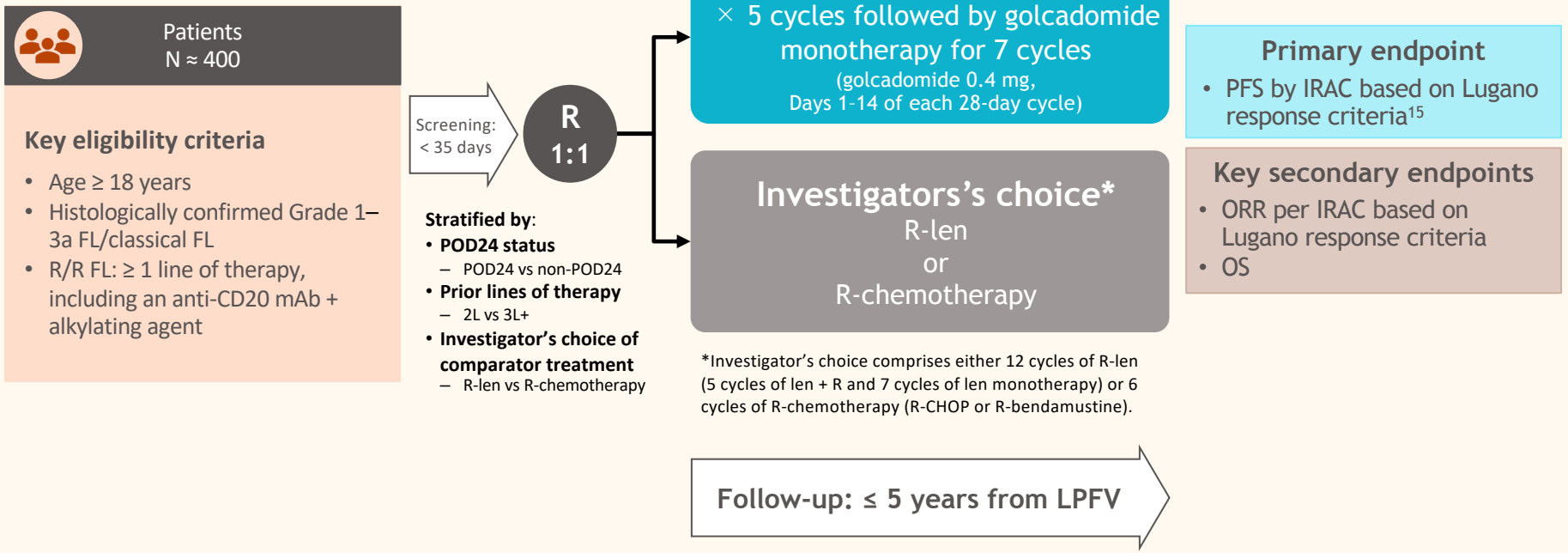
Figure 1. Phase 1/2 study (CC-99282-NHL-001): High response rates were observed with golcadomide 0.4 mg + R in heavily pre-treated R/R FL[1]



- The median number of prior treatments was 3 (range, 1–12); approximately one-third of the treated patients were exposed to prior T-cell–redirecting therapy, approximately one-third had prior lenalidomide (len) exposure, and approximately one-third were refractory to the last regimen received

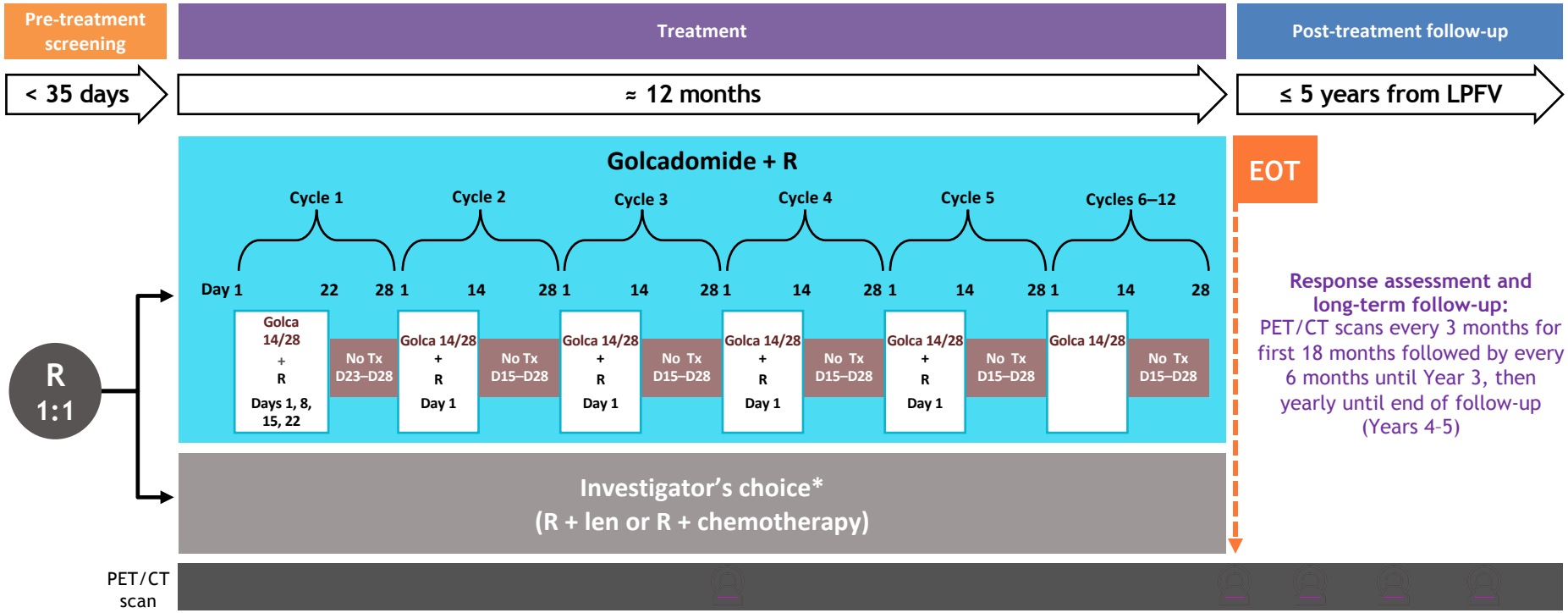
CR, complete response; FL, follicular lymphoma; Golca, golcadomide; len, lenalidomide; ORR, overall response rate; PR, partial response; R, rituximab; R/R, relapsed/refractory.
Data cut-off: 30 Dec 2024. 1. Cordoba, R, et al. EHA 2025. Poster 1879.

Key Figure B. Overview of the multicenter, open-label, Phase 3 GOLSEEK-4 study (NCT06911502)



2L, second line; 3L+, third line and beyond; CD, cluster of differentiation; CMRR, complete metabolic response rate; DOR, duration of response; FL, follicular lymphoma; HRQoL, health-related quality of life; IRAC, Independent Radiology Adjudication Committee; len, lenalidomide; LPFV, last patient first visit; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

Figure 2. Patient journey in GOLSEEK-4



* Investigator's choice comprises either (i) 12 cycles (28-day cycles) of R + lenalidomide that includes len (Days 1–21 of each cycle for 12 cycles) plus R (Days 1, 8, 15, 22 of cycle 1, followed by Day 1 of Cycles 2–5) *OR* (ii) 6 cycles of R (Day 1 of each cycle) + chemotherapy (CHOP in 21-day cycles or bendamustine in 28-day cycles)

CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CT, computed tomography; EOT, end of treatment; golca + R, golcadomide plus rituximab; len, lenalidomide; LPFV, last patient first visit; PET, positron emission tomography; R, rituximab; Tx, treatment.

Conclusions

- ✓ In less than 5 years the tretament landscape of r/r Indolent Lymphoma has dramatically changed with a significant improving in PFS
- ✓ We are progressively going towards a chemo –free approach
- ✓ Immunotherapy and BTKi are now the first choice in second line and maybe in first line of treatment in iNHL
- ✓ Tafa R2 is going to be the new standard in second line of therapy
- ✓ Zanubrutinib has a stronger safety profile in comparison with previous BTKi
- ✓ Golcadomide both as single agent and in combination has demonstred promising efficacy profile

GRAZIE PER L’ATTENZIONE