The young side of
LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
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Nuove terapie nei linfomi indolenti

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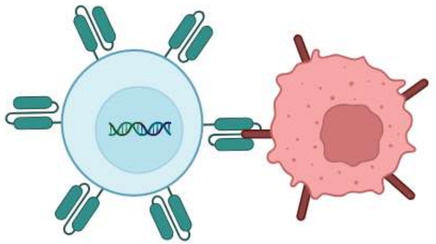
Disclosures of Candida Vitale

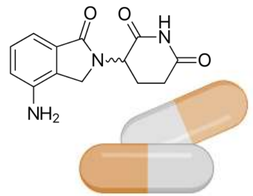
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Johnson & Johnson			X			X	
Abbvie			X			X	
AstraZeneca			X				
Lilly					X		
BeOne						X	

Novel therapies for indolent lymphomas

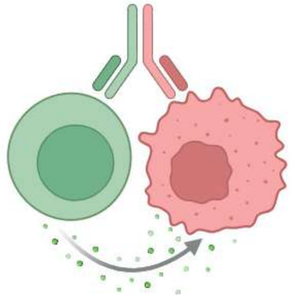
Cellular therapies



Immunomodulatory drugs

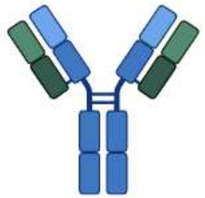


Bispecific antibodies

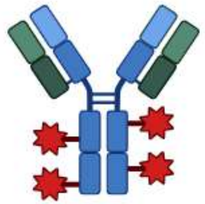


Targeted agents

Monoclonal antibodies



Conjugated monoclonal antibodies



... and combinations

Clinical case

A.C. ♂ 1949

Relevant comorbidities: myocardial infarction (angioplasty and stent placement in 2010), mild hypertension, emphysematous COPD (previous smoker)

April 2013 (64 yo)

Admitted for abdominal pain. Bulky retroperitoneal mass (R 16x8x8 cm, L 5.4x5x5 cm) + mediastinal adenopathies 2 cm

BM: negative

Descrizione Macroscopica:
Frustolo cilindriforme biancastro della lunghezza di cm 2.

Descrizione Microscopica:
Si esamina un frustolo di tessuto linforeticolare in campi diffusi nei quali di apprezzano noduli vagamente definiti. Tutti gli ambiti sono popolati da cellule medio-piccole dotate di citoplasma chiaro o debolmente basofilo, nuclei ovalari o con profilo inciso, cromatina omogenea e nucleoli piccoli o inapparenti. Sono frammiste alcune grandi cellule (circa 2/hpf) con ampio citoplasma basofilo e nuclei vescicolosi con uno o più voluminosi nucleoli. In alcuni noduli sono anche riconoscibili minimi aggregati di cellule centrofollicolari.
Le immunocolorazioni documentano la distribuzione fitta e diffusa di cellule B intensamente CD20 positive coesprimenti estesamente BCL2 tranne piccoli gruppi di elementi centrofollicolari BCL6 positivi CD10 negativi situati in corrispondenza di impalcature rarefatte e frammentate di cellule reticolari dendritiche CD21/CD35 positive. La modesta quota di linfociti T (CD3) è concentrata in ambito follicolare o perifollicolare. L'indice proliferativo valutato con anticorpi anti-Ki67, clone MIB1, è circa 8%.

DIAGNOSI ISTOPATOLOGICA

LINFOMA DELLA ZONA MARGINALE NODALE.

Treated with R-COMP x6 + 2R → CR (CT and PET)

Clinical case

July 2023 (74 yo)
Inguinal lymphadenopathy
CT: solid tissue surrounding both carotid artheries, mediastinal adenopathies (8x6 cm), inguinal confluent and colliquative adenopathies (6x3 cm)
PET: SUVmax 10

Descrizione Macroscopica :
Un frammento grigiastro dal profilo cerebroide delle dimensioni di cm 1.5X1X0,8.

Descrizione Microscopica :
Frammento di linfonodo con architettura completamente cancellata le cui sezioni sono occupate da una fitta e densa popolazione di cellule linfoidi per lo più di piccola taglia disposte in modo diffuso o a costituire sfumati noduli nel contesto dei quali si osservano sparsi ed isolati elementi di taglia maggiore e di aspetto centroblastico. Le cellule linfoidi hanno scarso citoplasma chiaro e nuclei dai contorni lievemente irregolari alcuni di media taglia cromatina dispersa e piccoli nucleoli. Tali elementi sono di linea B CD20, coesprimono diffusamente MNDA, BCL2 e sono negativi per CD10, BCL6, CD5, CD23, CD43, LEF1 e Ciclina D1. Nei noduli si osservano cellule di aspetto centroblastico positive per BCL6 e parzialmente CD10, negative per BCL2 e qui la colorazione per CD23 rivela la presenza di reti dendritiche frammentate. Le colorazioni per le catene leggere kappa e lambda e per le IgD sono positive in rare cellule sparse. Piccoli linfociti T CD3 e CD5 positivi si dispongono in scarso numero e in modo sparso nel contesto dei noduli sfumati. L'indice di proliferazione è molto basso nelle cellule linfoidi monomorfe, del 2% circa e moderatamente elevato nei noduli dove sono presenti elementi centroblastici (30% circa).

Diagnosi:
LINFOMA DELLA ZONA MARGINALE NODALE sec. WHO 2017.

Started second line treatment with zanubrutinib

Clinical case

December 2023: start treatment with zanubrutinib

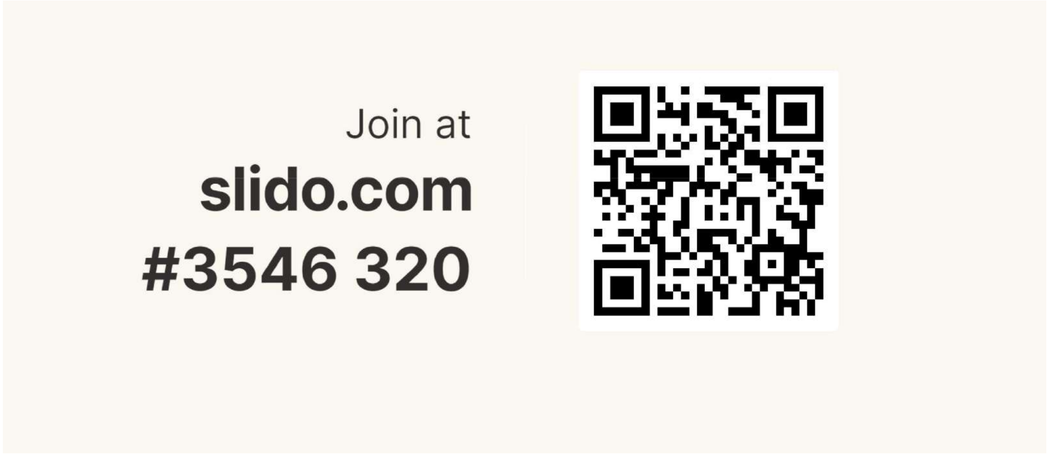
February 2024: slight decrease in disease burden (SD @CT scan)

July 2024: slight decrease in disease burden (SD @CT scan)

January 2025: new abdominal adenopathies

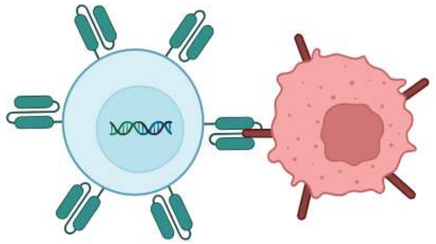
Without considering the current regulatory and prescriptive limitations, how would you treat A.C.?

1) Chemo-immunotherapy
2) Immunomodulatory agent
3) Targeted agent
4) Bispecific antibody
5) Cellular therapy



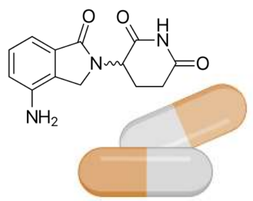
Novel therapies for indolent lymphomas: MZL vs FL

Cellular therapies



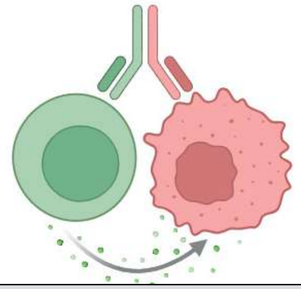
Lisocel (CD19 CAR T)
Tisacel (CD19 CAR T)
Axicel (CD19 CAR T)

Immunomodulatory drugs



Lenalidomide

Bispecific antibodies

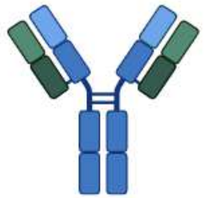


Mosunetuzumab (bsAb CD3xCD20)
Epcoritamab (bsAb CD3xCD20)
Odronextamab (bsAb CD3xCD20)

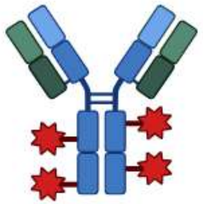
Targeted agents

Tazemetostat (*EZH2* inhibitor)
Zanubrutinib (*BTK* inhibitor)

Monoclonal antibodies



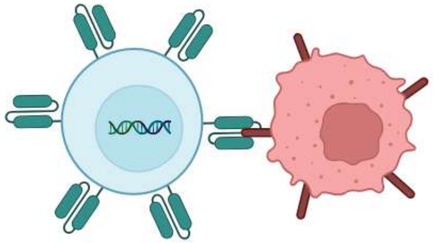
Conjugated monoclonal antibodies

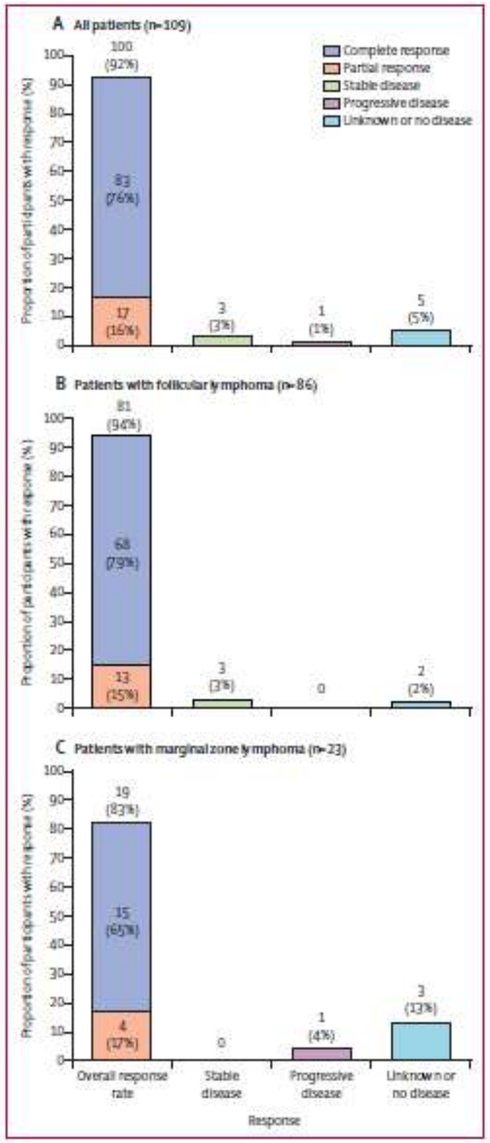


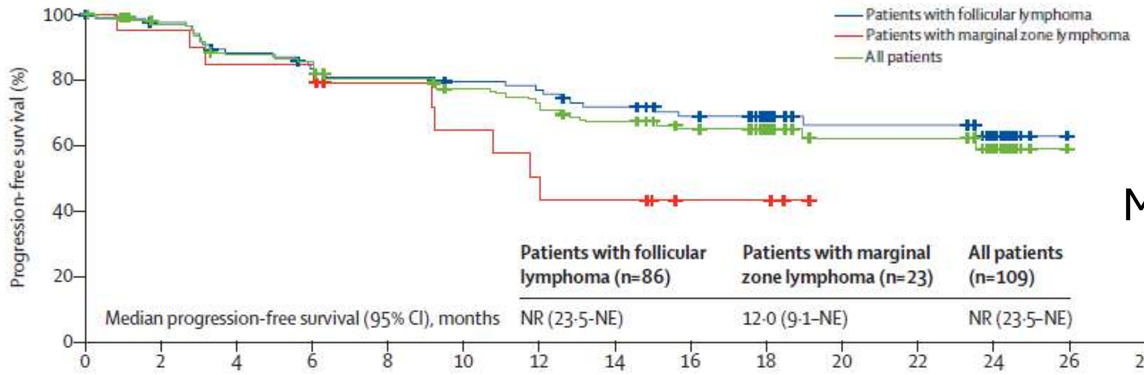
... and combinations

Axicabtagene ciloleucel in RR FL and MZL

ZUMA-5 phase II trial



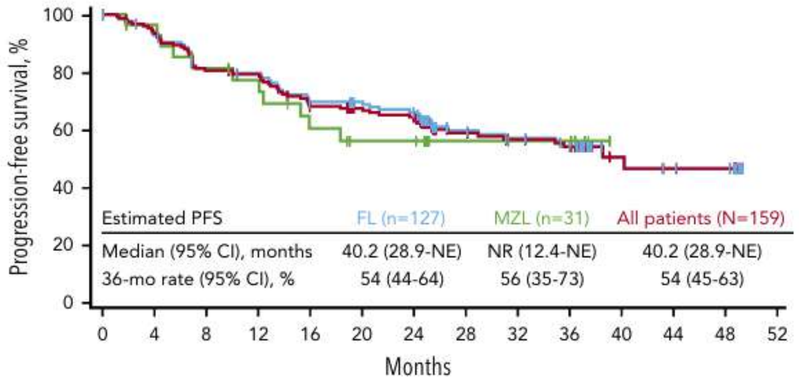




	Patients with follicular lymphoma (n=86)	Patients with marginal zone lymphoma (n=23)	All patients (n=109)
Median progression-free survival (95% CI), months	NR (23·5-NE)	12·0 (9·1–NE)	NR (23·5–NE)

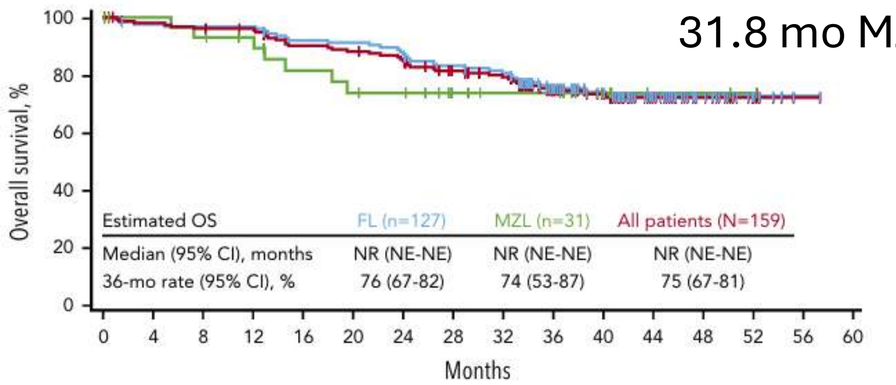
Number at risk (number censored)																		
Patients with follicular lymphoma	86 (0)	82 (2)	73 (3)	68 (4)	64 (6)	61 (8)	59 (8)	54 (9)	49 (12)	40 (21)	24 (36)	24 (36)	12 (47)	0 (59)	..	..	..	..
Patients with marginal zone lymphoma	23 (0)	19 (3)	16 (4)	15 (5)	11 (8)	9 (8)	7 (8)	6 (8)	3 (11)	3 (11)	0 (14)	..	..	..	..	..	..	..
All patients	109 (0)	101 (5)	89 (7)	83 (9)	75 (14)	70 (16)	66 (16)	60 (17)	52 (23)	43 (32)	24 (50)	24 (50)	12 (61)	0 (73)	..	..	..	..

Median FU: 17.5 mo



Estimated PFS	FL (n=127)	MZL (n=31)	All patients (N=159)
Median (95% CI), months	40.2 (28.9-NE)	NR (12.4-NE)	40.2 (28.9-NE)
36-mo rate (95% CI), %	54 (44-64)	56 (35-73)	54 (45-63)

No. at risk														
FL	127	115	98	96	83	79	74	46	42	38	13	11	10	0
MZL	31	26	21	19	14	11	11	6	5	5	0			
All patients	159	141	119	115	97	90	85	52	47	43	13	11	10	0



Estimated OS	FL (n=127)	MZL (n=31)	All patients (N=159)
Median (95% CI), months	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
36-mo rate (95% CI), %	76 (67-82)	74 (53-87)	75 (67-81)

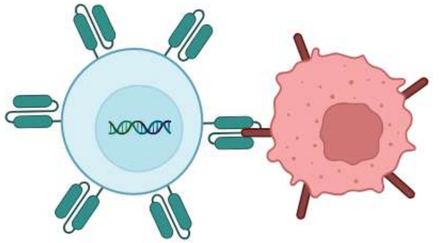
No. at risk																
FL	127	123	122	122	115	114	110	103	99	73	54	34	19	9	1	0
MZL	31	29	27	25	21	19	18	12	10	10	5	2	2	1	0	
All patients	159	152	149	147	136	133	128	115	109	83	59	36	21	10	1	0

Median FU:
41.7 mo FL
31.8 mo MZL

Jacobson CA et al., Lancet Oncol 2022; Neelapu SS et al., Blood 2024

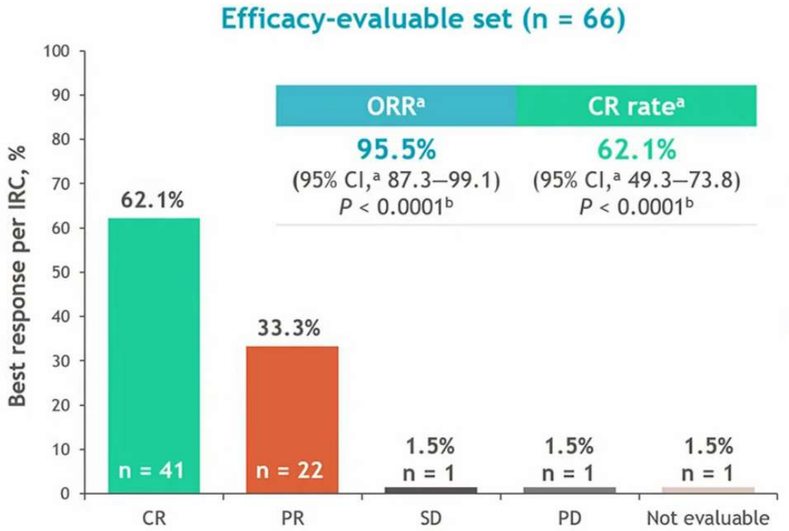
Lisocabtagene maraleucel in RR MZL

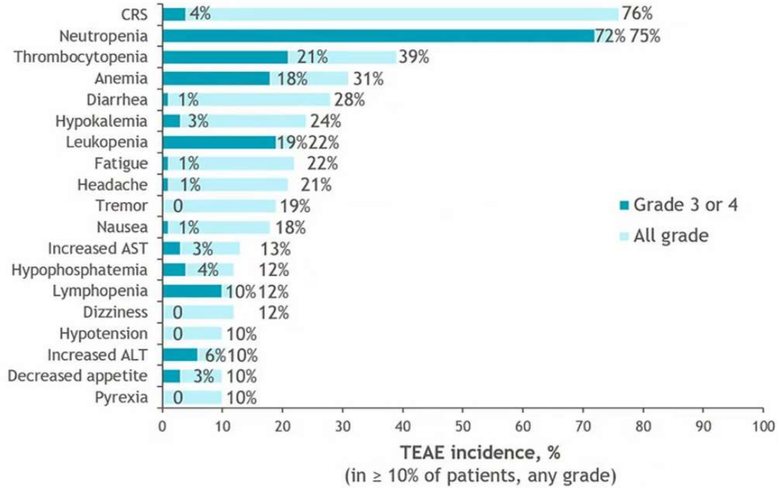
TRANSCEND FL phase II trial

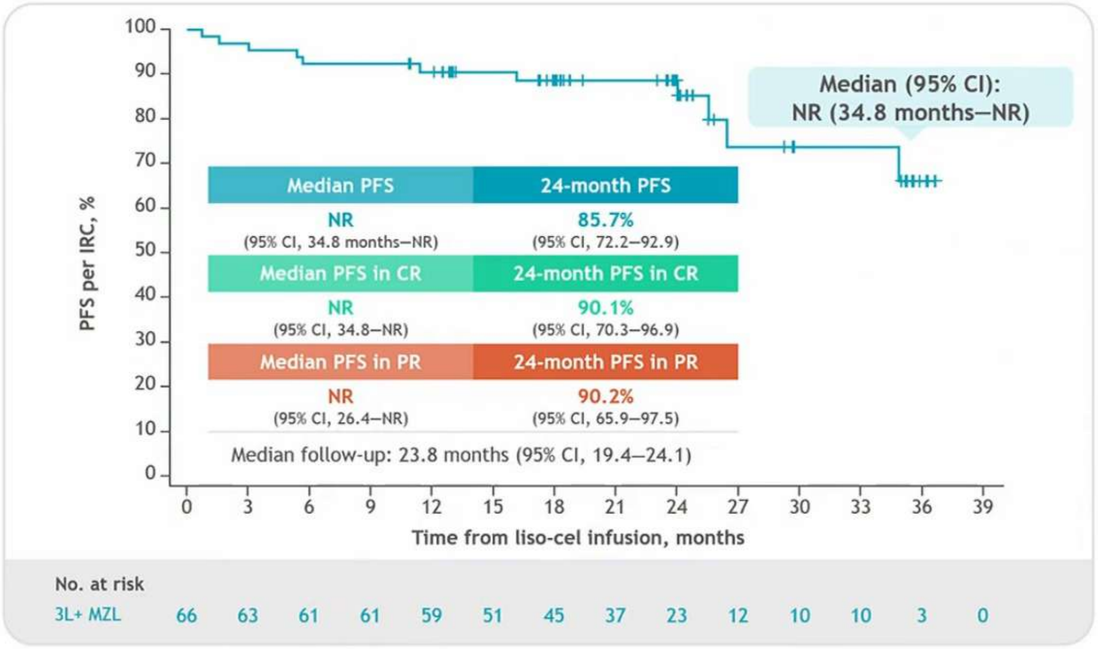


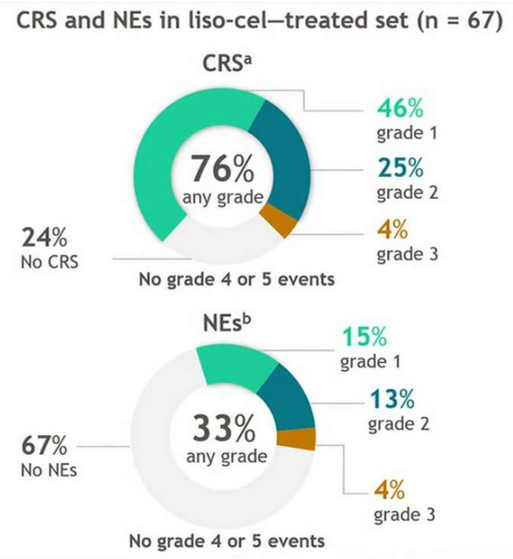
Nodal MZL 48%
Splenic MZL 27%
Extranodal MZL 25%

Previous systemic treatments: 3 (2-12)
Prior BTKi 39%









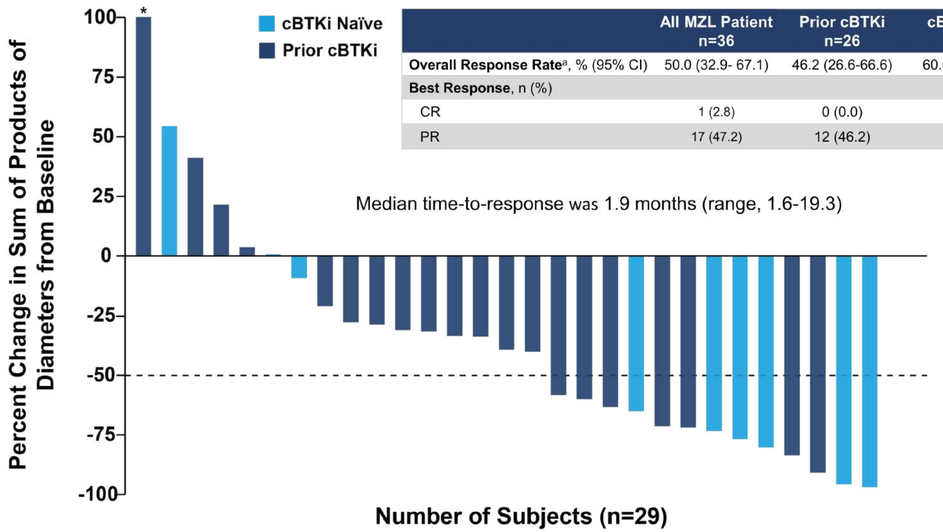
Palomba ML et al., ICML 2025

Pirtobrutinib in RR MZL

BRUIN phase I/II trial

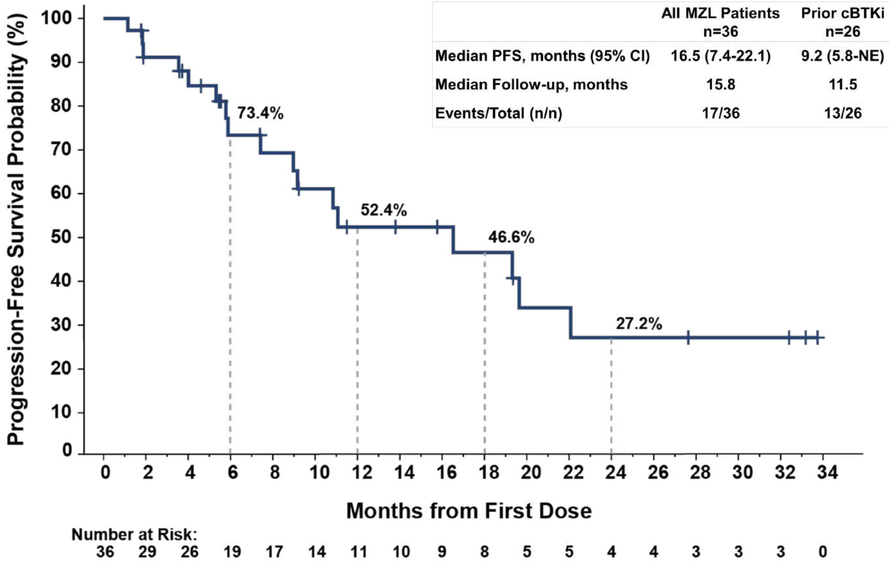
n=36

Median Number of Prior Lines of Systemic Therapy (range)	3 (2-10)
Prior Therapy, n (%)	
cBTK inhibitor	26 (72)
Anti-CD20 antibody	36 (100)
Chemotherapy + Anti-CD20 antibody	31 (86)
PI3K inhibitor	6 (17)
Lenalidomide	8 (22)
BCL2 inhibitor	1 (3)
Autologous stem cell transplant	1 (3)
Other Systemic Therapy[a]	4 (11)



	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Overall Response Rate[a], % (95% CI)	50.0 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)

Median time-to-response was 1.9 months (range, 1.6-19.3)



	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median PFS, months (95% CI)	16.5 (7.4-22.1)	9.2 (5.8-NE)	NE (1.9-NE)
Median Follow-up, months	15.8	11.5	32.4
Events/Total (n/n)	17/36	13/26	4/10

	Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**
Diarrhea	16.7	2.8
Fatigue	11.1	0
Neutropenia[a]	13.9	13.9
Anemia	8.3	5.6
Dyspnea	2.8	0
Nausea	2.8	0
Platelet Count Decrease	11.1	2.8
Arthralgia	2.8	0
Abdominal Pain	0	0
AEs of Interest[b]	**Any Grade**	**Grade ≥3**
Infection[c]	5.6	0
Bruising[d]	25.0	0
Rash[e]	19.4	0
Hemorrhage[f]	2.8	0
Hypertension	2.8	2.8
Atrial Fibrillation/Flutter[g]	0	0

Discontinuations due to treatment-related AEs: 5.6% (n=2)

Dose reductions due to treatment-related AEs: 11.1% (n=4)

Patel K et al., ASH 2023

Loncastuximab tesirine in RR MZL

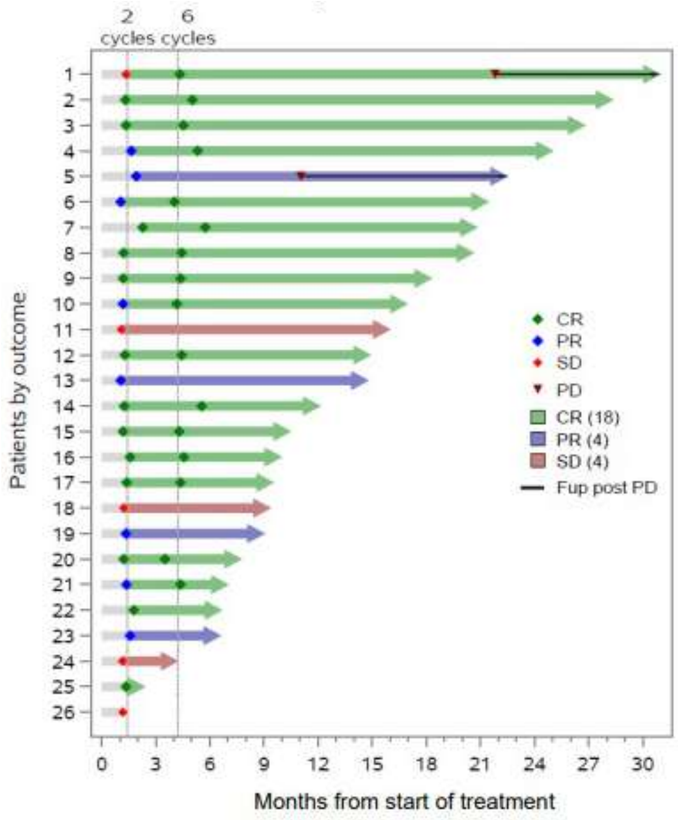
Phase II LOTIS-7 trial

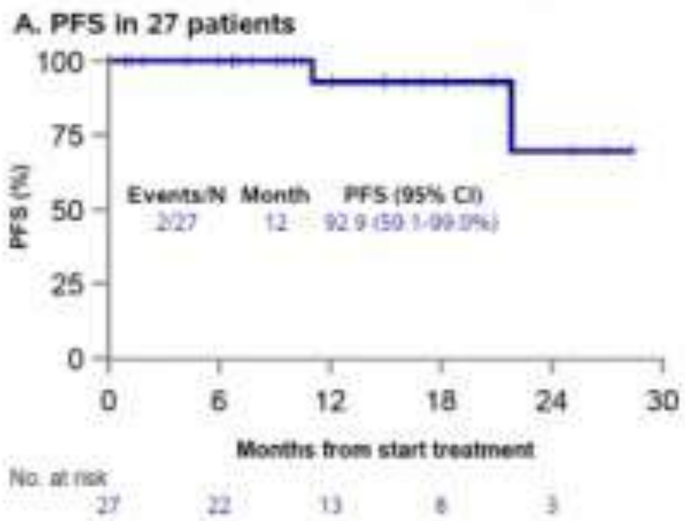
Loncastuximab IV every 3 weeks
0.15 mg/kg for 2 cycles
0.075 mg/kg for 4 cycles

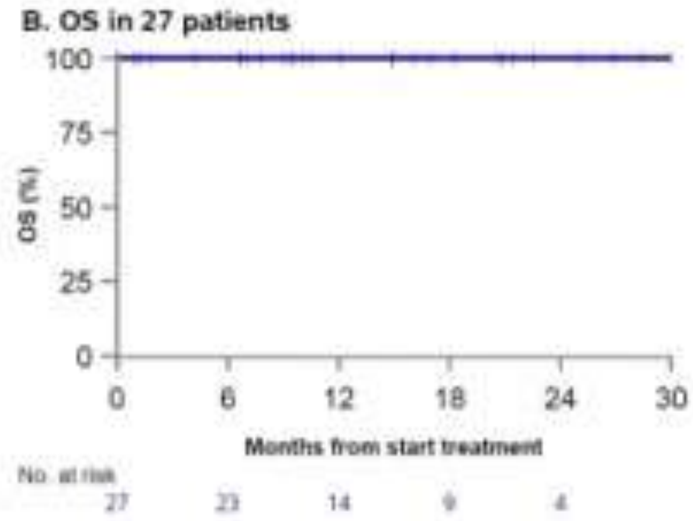
n=27

Previous systemic treatments: 2 (1-4)

ORR: 84.6%
CR rate: 69.2%





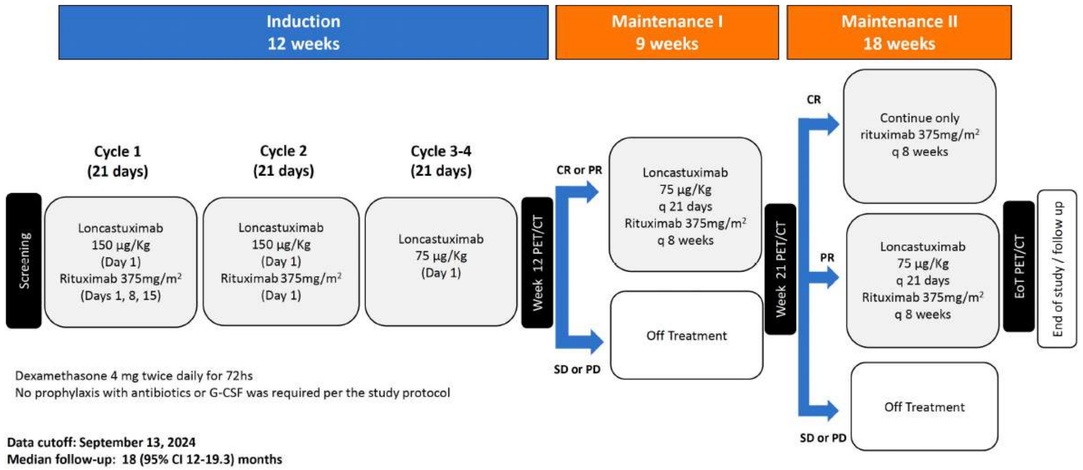


TEAE, n (%)	Patients (N=27)		
	Any grade	Grade 3	Grade 4
Maculopapular rash	16 (59.3)	1 (3.7)	0
Increased AST	16 (59.3)	0	0
Increased ALT	15 (55.6)	2 (7.4)	0
Increased alkaline phosphatase	13 (48.1)	3 (11.1)	0
Neutropenia	13 (48.1)	4 (14.8)	1 (3.7)
Local edema	11 (40.7)	0	0
Photosensitivity	8 (29.6)	0	0
Anemia	8 (29.6)	2 (7.4)	0
Lung infection	4 (14.8)	1 (3.7)	1 (3.7)
Urinary infection	3 (11.1)	1 (3.7)	0
Pleural effusion	3 (11.1)	0	0
Anorexia	1 (3.7)	1 (3.7)	0
COVID-19	1 (3.7)	0	0
Weight loss	1 (3.7)	1 (3.7)	0
Hyponatremia	1 (3.7)	0	1 (3.7)

Lossos IS et al., ICML 2025

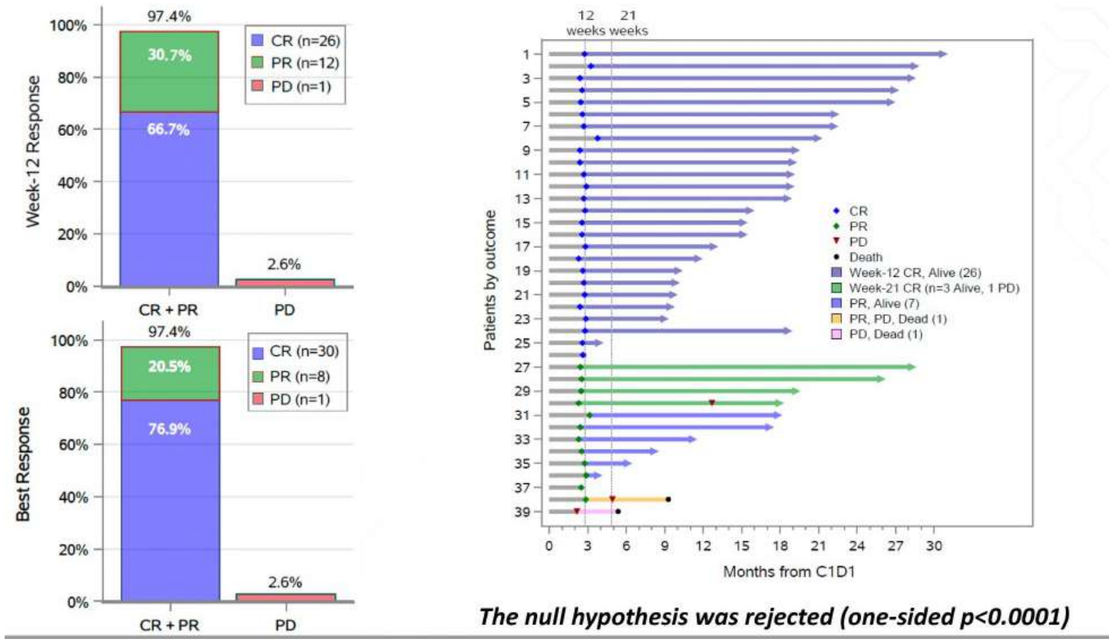
Loncastuximab + Rituximab in RR FL

Phase II trial



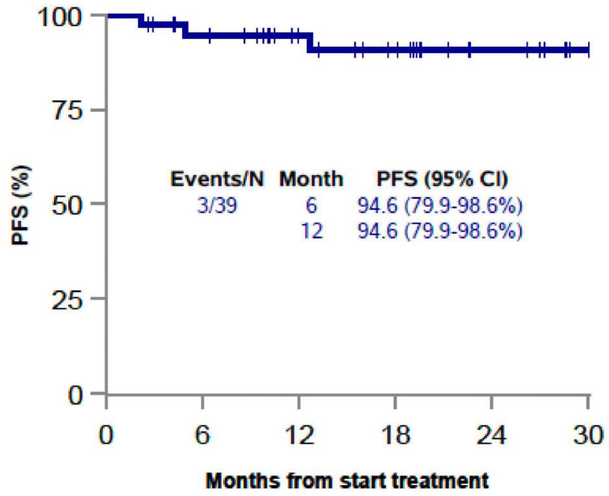
Previous systemic treatments: 1 (1-6)

n=39



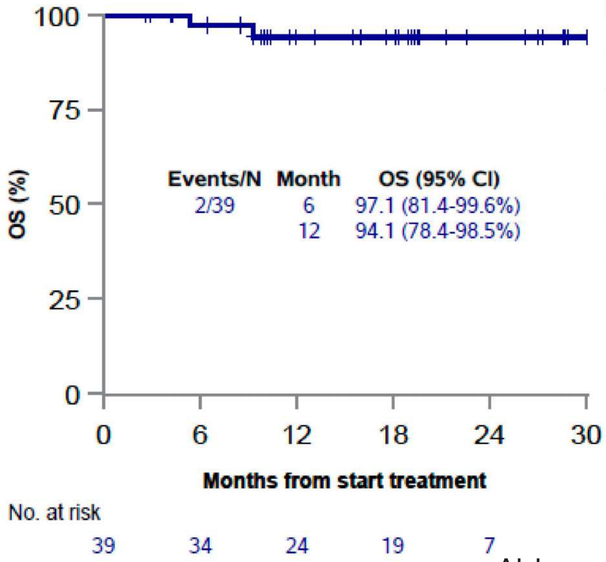
The null hypothesis was rejected (one-sided p<0.0001)

Median FU: 15.6 mo



No. at risk

39 33 24 18 7



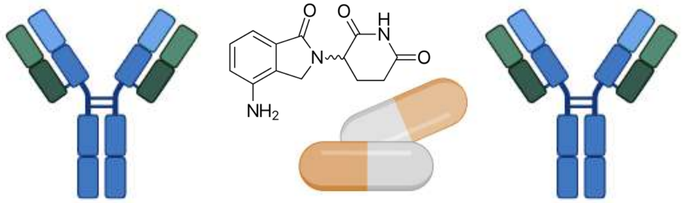
No. at risk

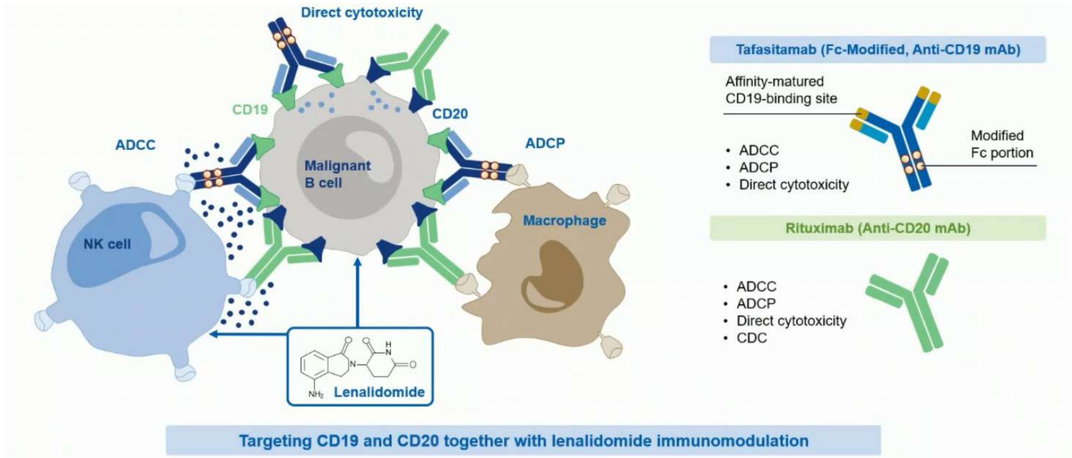
39 34 24 19 7

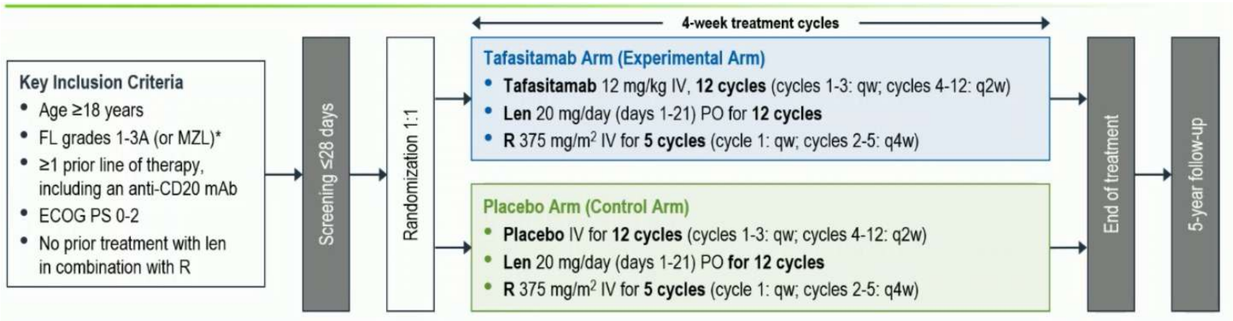
Alderuccio JP et al., ASH 2024

Tafasitamab + R2 in RR FL

inMIND phase III trial





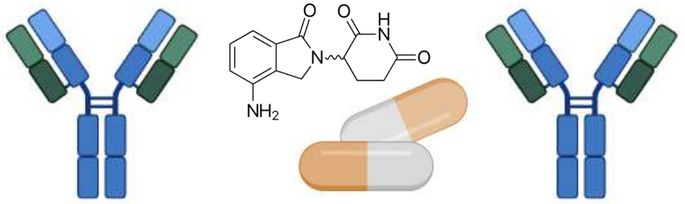


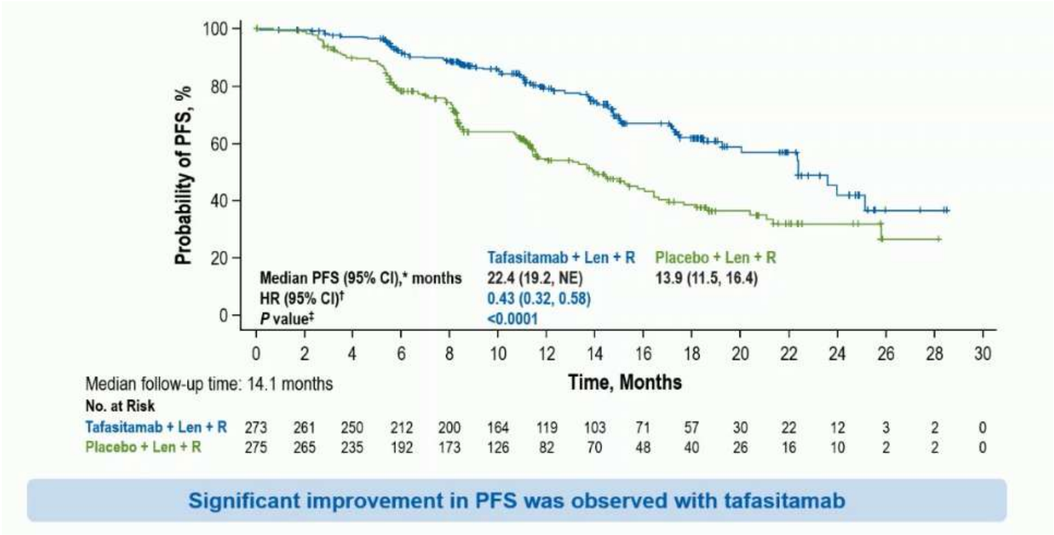
Variable	Tafasitamab + Len + R (n=273)	Placebo + Len + R (n=275)	Total (N=548)
Median age, years (range)	64.0 (36, 88)	64.0 (31, 85)	64.0 (31, 88)
≥75, n (%)	54 (19.8)	54 (19.6)	108 (19.7)
Male sex, n (%)	150 (54.9)	149 (54.2)	299 (54.6)
Median time since initial diagnosis of FL, years (range)	5.2 (0, 34)	5.5 (1, 33)	5.3 (0, 34)
ECOG PS at screening, n (%)			
0	181 (66.3)	192 (69.8)	373 (68.1)
1-2	92 (33.7)	83 (30.2)	175 (31.9)
Ann Arbor stage, n (%)			
I or II	52 (19.0)	50 (18.2)	102 (18.6)
III or IV	221 (81.0)	225 (81.8)	446 (81.4)
FL grade, n (%)			
1 or 2	203 (74.4)	203 (73.8)	406 (74.1)
3A	67 (24.5)	71 (25.8)	138 (25.2)
B symptoms, n (%)	63 (23.1)	67 (24.4)	130 (23.7)
FLIPI score, n (%)			
0-1	57 (20.9)	57 (20.7)	114 (20.8)
2	79 (28.9)	67 (24.4)	146 (26.6)
3-5	137 (50.2)	150 (54.5)	287 (52.4)
Met at least 1 GELF criteria, n (%)	222 (81.3)	232 (84.4)	454 (82.8)
FL diagnosis confirmed by central pathology, n (%)	256 (93.8)	259 (90.5)	505 (92.2)
Median number of prior lines of therapy (range)	1.0 (1, 7)	1.0 (1, 10)	1.0 (1, 10)
Number of prior lines of therapy, n (%)			
1	147 (53.8)	153 (55.6)	300 (54.7)
2	66 (24.2)	71 (25.8)	137 (25.0)
3	39 (14.3)	30 (10.9)	69 (12.6)
≥4	21 (7.7)	21 (7.6)	42 (7.7)
Time since last anti-lymphoma therapy, n (%)			
≤2 years	147 (53.8)	157 (57.1)	304 (55.5)
>2 years	126 (46.2)	118 (42.9)	244 (44.5)
POD24, n (%)	85 (31.1)	88 (32.0)	173 (31.6)
Relapsed/refractory status to last therapy, n (%)			
Relapsed	148 (54.2)	164 (59.6)	312 (56.9)
Refractory	112 (41.0)	97 (35.2)	209 (38.1)
Undetermined	13 (4.8)	14 (5.1)	27 (4.9)
Refractory to prior anti-CD20 therapy, n (%)	118 (43.2)	115 (41.8)	233 (42.5)

Trneny M et al., EHA 2025

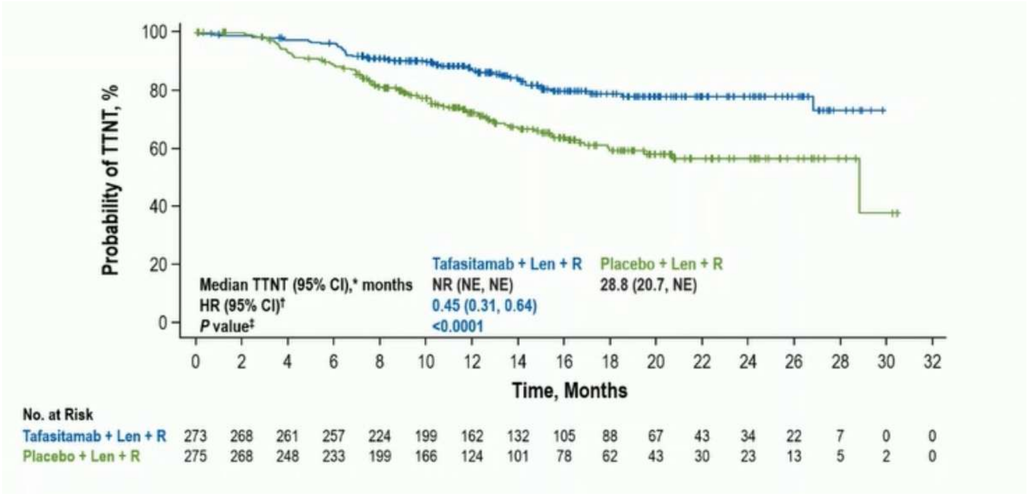
Tafasitamab + R2 in RR FL

inMIND phase III trial





Significant improvement in PFS was observed with tafasitamab



Most Common Grade 3 or 4 TEAEs (≥5% in Any Group)

Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†	Total (n=546)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
Anemia	12 (4.4)	16 (5.9)	28 (5.1)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)

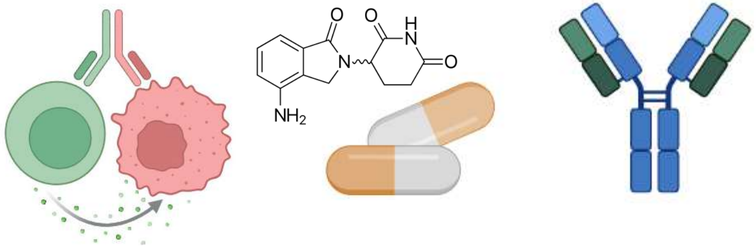
- 15 patients (6%) in tafasitamab arm and 23 (9%) in placebo arm died during the study
  - Disease progression: 5 patients (2%) tafasitamab; 17 patients (6%) placebo
  - **Fatal adverse events:** 6 patients (2%) in each treatment arm (most commonly due to infection)

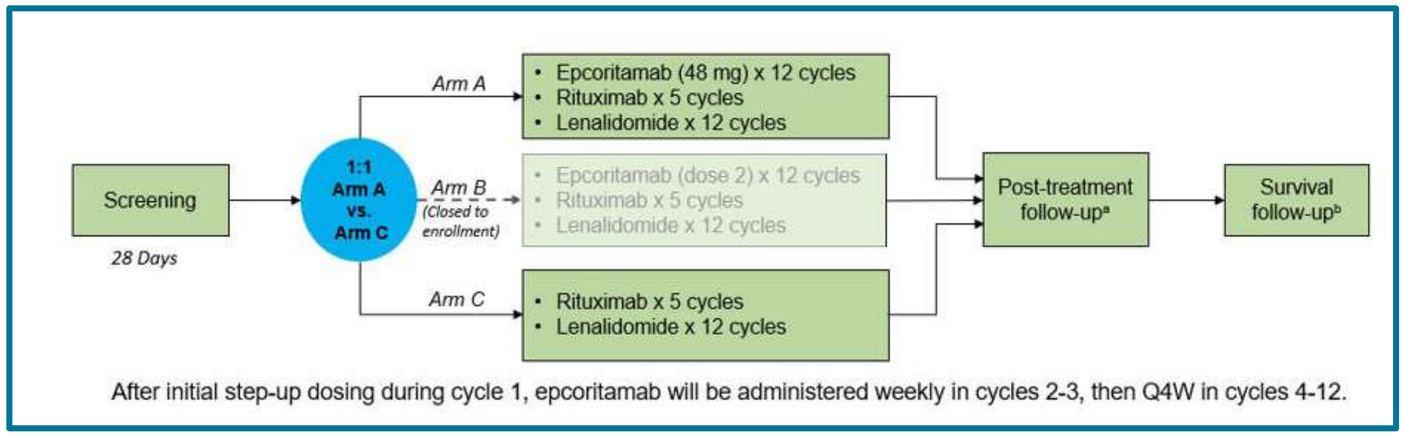
- Tafasitamab and placebo dose interruptions or discontinuations due to TEAEs were similar between treatment arms, n (%):
  - Dose delay or interruption due to TEAEs: 203 (74%) vs 190 (70%)
  - Discontinued study treatment due to TEAEs: 30 (11%) vs 18 (7%)
- Len discontinuations due to TEAEs were similar between tafasitamab and placebo arms, n (%):
  - 39 (14%) vs 31 (11%)
- Len dose reductions were similar between tafasitamab and placebo arms
  - Median relative dose intensity: 86% vs 87%

Trneny M et al., EHA 2025

Epcoritamab + R2 in RR FL

EPCORE FL-1 phase III trial





Press release

Phase 3 EPCORE® FL-1 Clinical Trial Met Dual Primary Endpoints in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

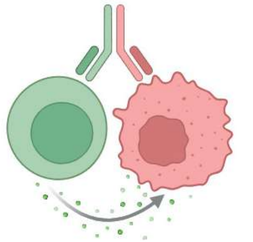
Company Announcement

COPENHAGEN, Denmark; August 7, 2025

- **Epcoritamab in combination with rituximab and lenalidomide (R^2) demonstrated statistically significant improvement in Overall Response Rate (ORR; 95.7%, $p < 0.0001$) and Progression-Free Survival (HR 0.21, p-value <0.0001) versus R^2 alone in patients with relapsed/refractory (R/R) Follicular Lymphoma (FL)**
- **Results from EPCORE FL-1 form the basis of global regulatory submissions**
- **U.S. FDA has accepted for priority review new supplemental Biologics License Application (sBLA) for epcoritamab plus R^2, with action date of November 30, 2025**
- **If approved, epcoritamab plus R^2 would be the first bispecific antibody combination regimen available as a second-line treatment option for patients with R/R FL**

Odronextamab in RR MZL

ELM-2 phase II trial

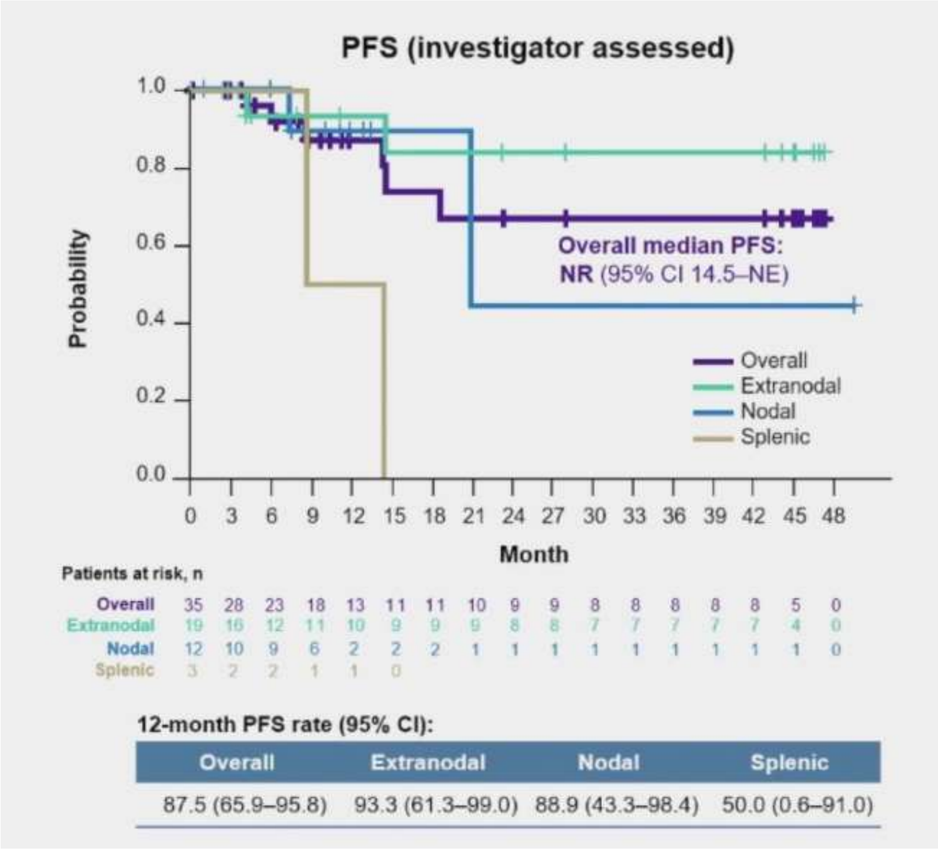


Nodal MZL n=12
Splenic MZL n=2
Extranodal MZL n=19
Unknown n=1

Previous systemic treatments: 2 (1-8)

ORR 79.3%
CR rate 79.3%

Median FU: 11.7 months



12-month PFS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
87.5 (65.9–95.8)	93.3 (61.3–99.0)	88.9 (43.3–98.4)	50.0 (0.6–91.0)

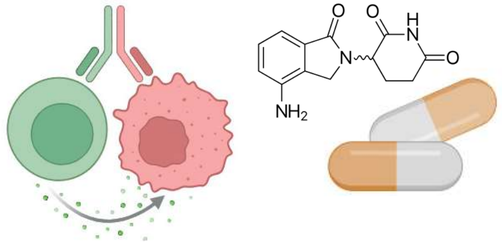
Most common AE:
- CRS 52.9%
- neutropenia 44.1%
- pyrexia 35.3%

CRS in the optimized 0.7/4/20 mg step-up regimen 53.3% (G1 33.3%, G2 20%)
No ICANS
G3 infections 23.5%

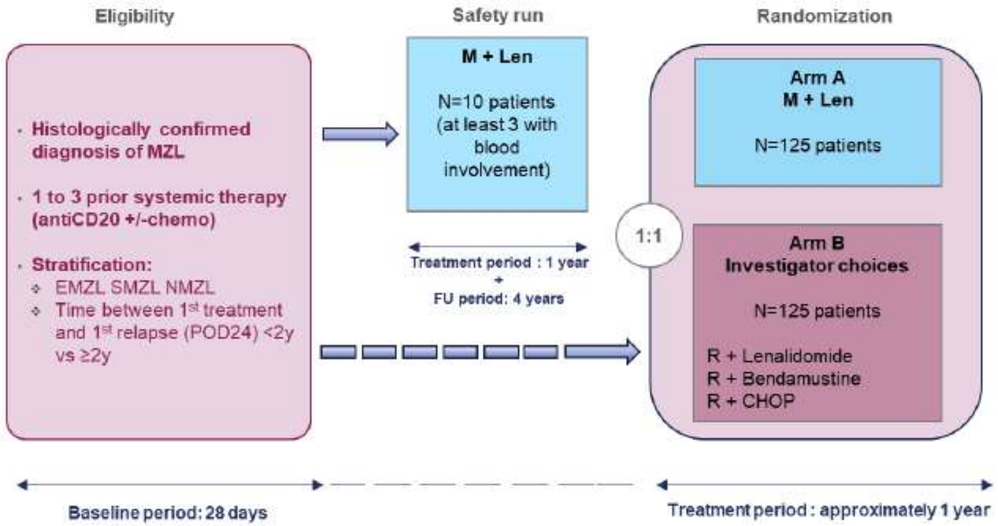
Treatment discontinuation due to AE 14.7%

Kim TM et al., ASH 2024

Mosunetuzumab + lenalidomide in RR MZL



MARSUN phase III trial



FONDAZIONE ITALIANA LINFOMI

Arm A: Mosunetuzumab + Lenalidomide

Mosunetuzumab SC 5 mg on Day 1 of Cycle 1

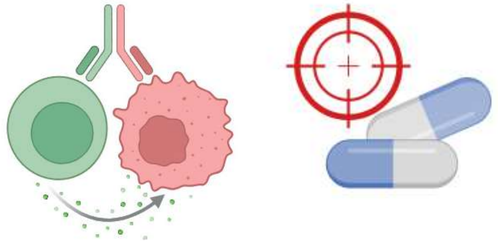
Mosunetuzumab SC 45 mg on Day 8 and 15 of Cycle 1 and then on D1 of each cycles for up to 12 total cycles

Lenalidomide PO 20 mg/d on D1-21 of C2-C6

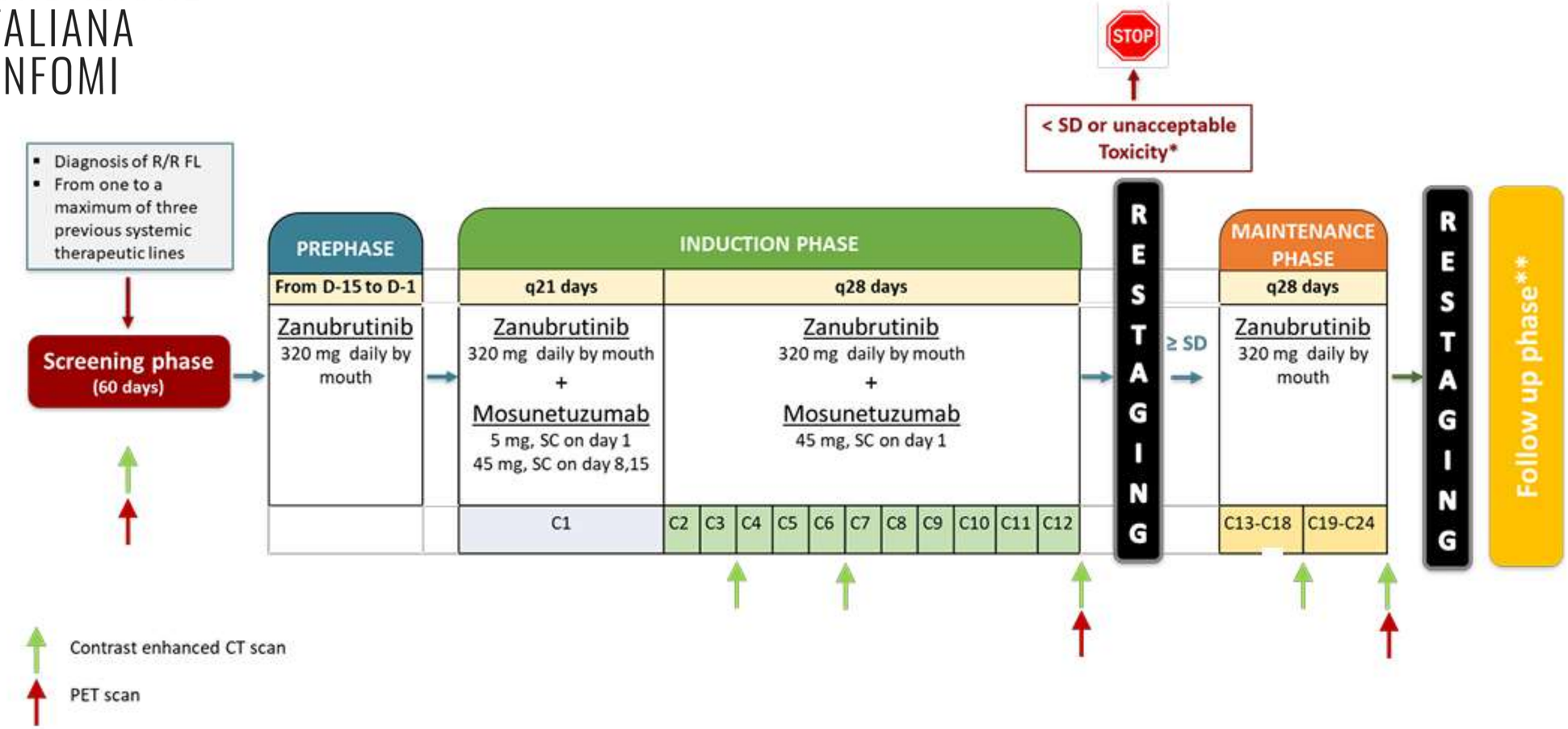
FU visit

Mosunetuzumab + zanubrutinib in RR FL

MOZART phase II trial



FONDAZIONE ITALIANA LINFOMI




BRIGHT
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AHEAD

Which is the most relevant parameter to select treatment for relapsed/refractory indolent lymphomas?

1) **Efficacy**
2) **Safety**
3) **Treatment duration/route of administration**
4) **Quality of life**

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Clinical case (conclusion)

March 2025: start treatment with IKS03 (CD19-targeting Antibody Drug Conjugate) [phase I clinical trial] Completed C1 without toxicity but treatment suspended as per Sponsor’s decision (areas of pulmonary fibrosis on baseline CT scan)

June 2025: start treatment with R-bendamustine. Good initial efficacy but recurrent infections.

Acknowledgments

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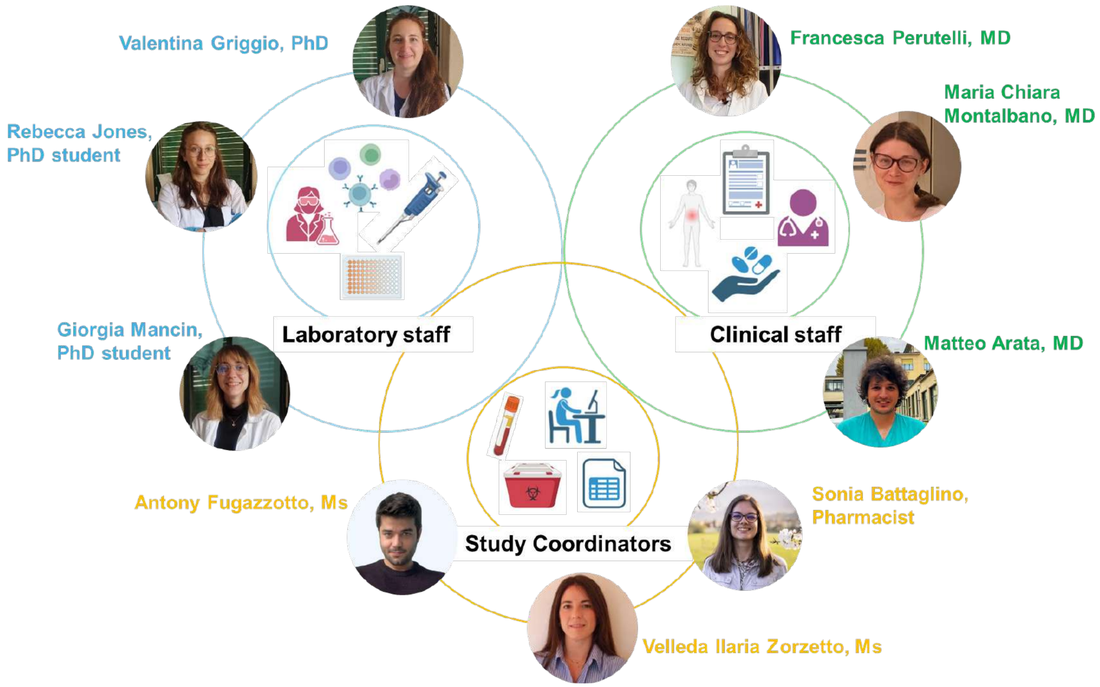
University of Torino

Ematologia U
A.O.U. Città della Salute e della Scienza di Torino

Laboratory of Translational Hematology



Gruppo malattie linfoproliferative