Linfomi della zona marginale
Terapie target

Candida Vitale

Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università di Torino
Ematologia U, A.O.U. Città della Salute e della Scienza di Torino

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	

blood® Editorial

MARGINAL ZONE LYMPHOMA

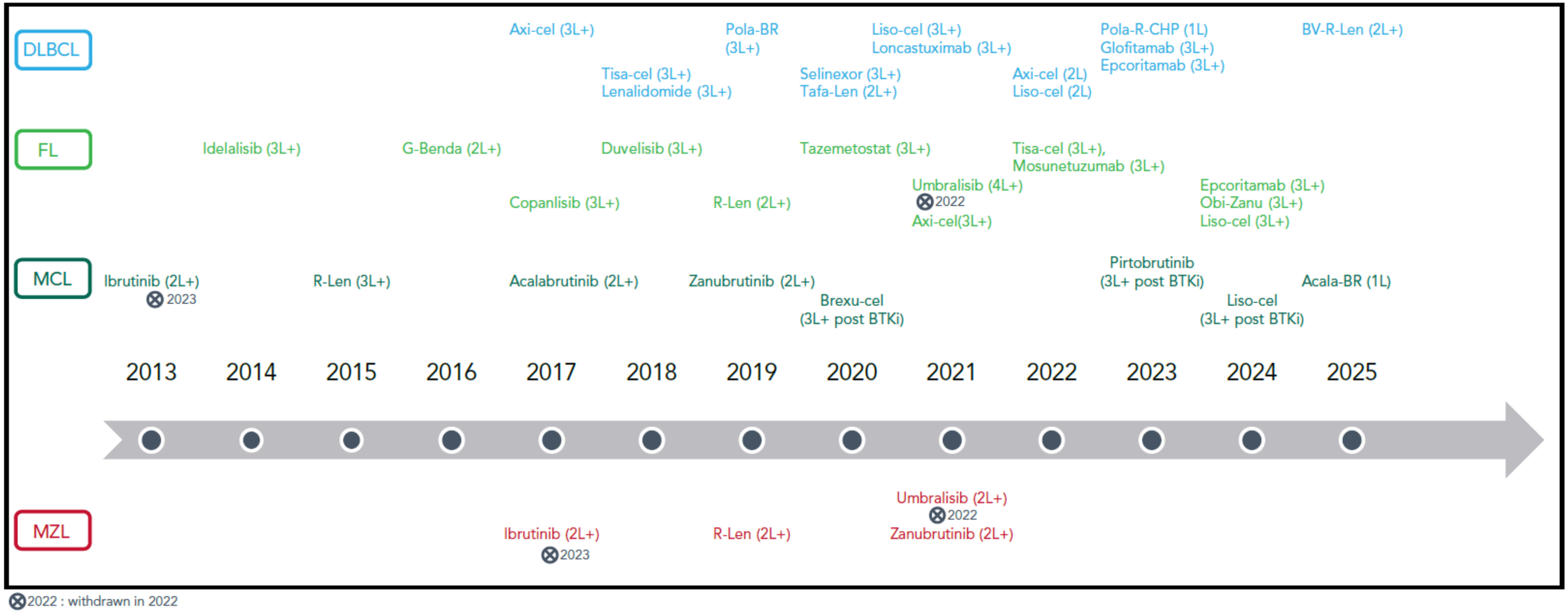
Introduction to a review series on marginal zone lymphoma: reclaiming the afterthought

“To date, no therapy for MZL has truly been developed on the basis of our biologic understanding of the disease.”

Philippe Armand
Associate Editor, *Blood*

blood® 8 JANUARY 2026 | VOLUME 147, NUMBER 2

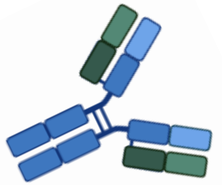
Therapeutic innovation in B-cell lymphomas over the last decade



2022 : withdrawn in 2022

Thieblemont C et al., Blood 2026

Rituximab monotherapy

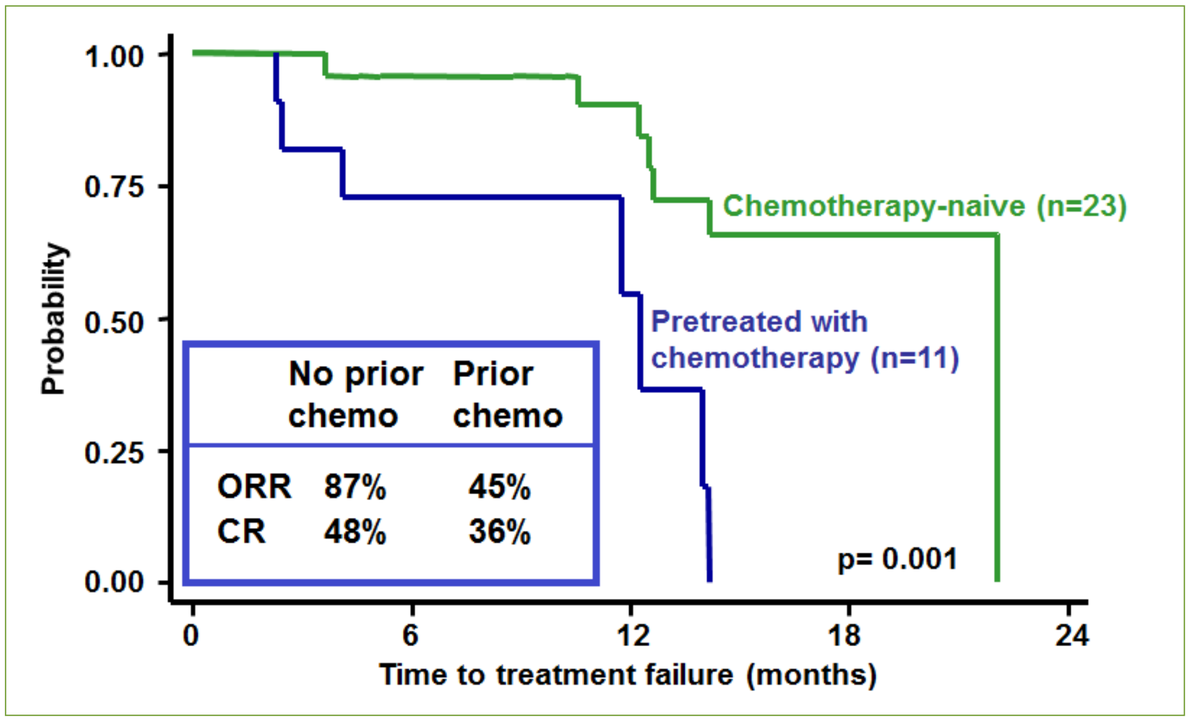


EMZL

n=34, 11 with prior chemotherapy,
15 gastric, 20 stage IV

4 weekly doses (375 mg/m^2)

ORR 25/34 (73%)



Conconi A et al., Blood 2003

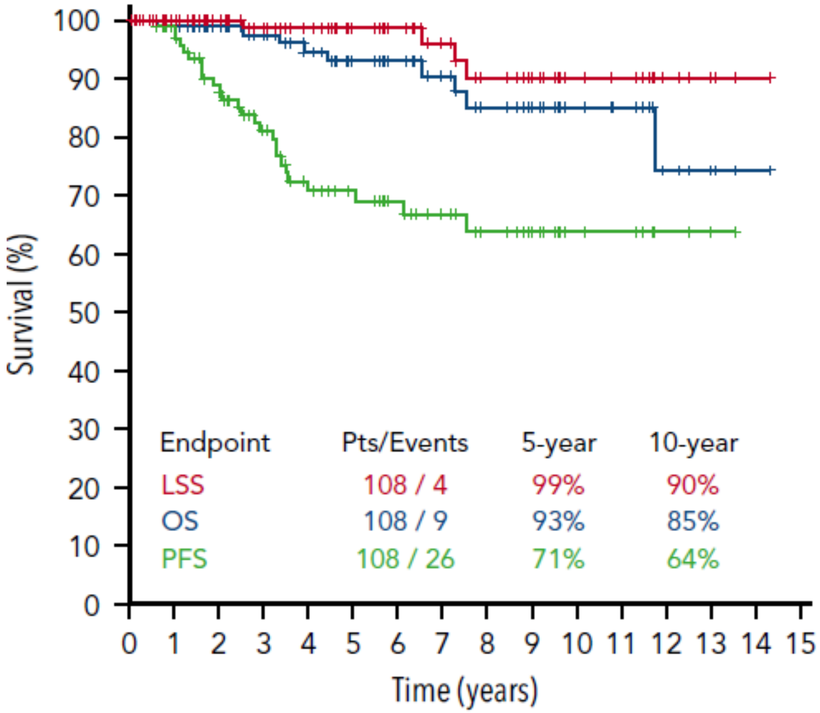
SMZL

n=106

6 weekly doses (375 mg/m^2)
Possible maintenance q2m for 1-2 years

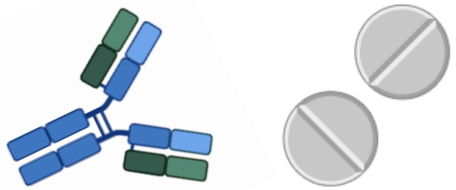
ORR 97/106 (92%)

44% CR
21% CRu
27% PR



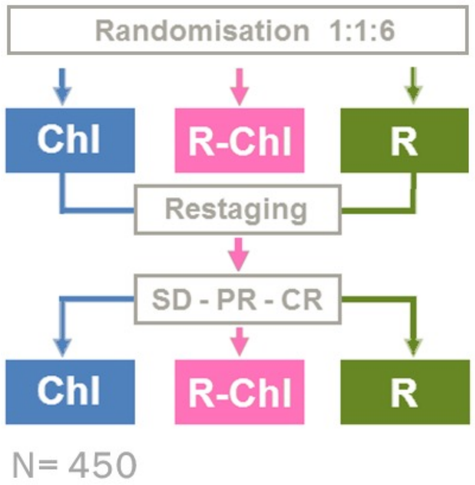
Kalpadakis C et al., Blood 2018

Rituximab + chlorambucil



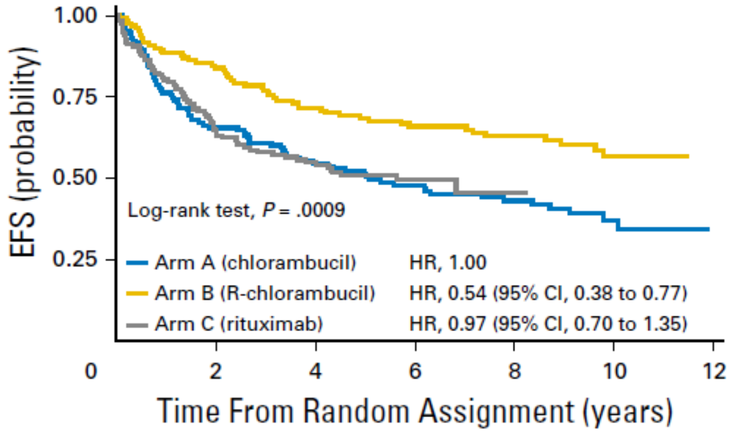
IELSG19 phase III randomized study

EMZL



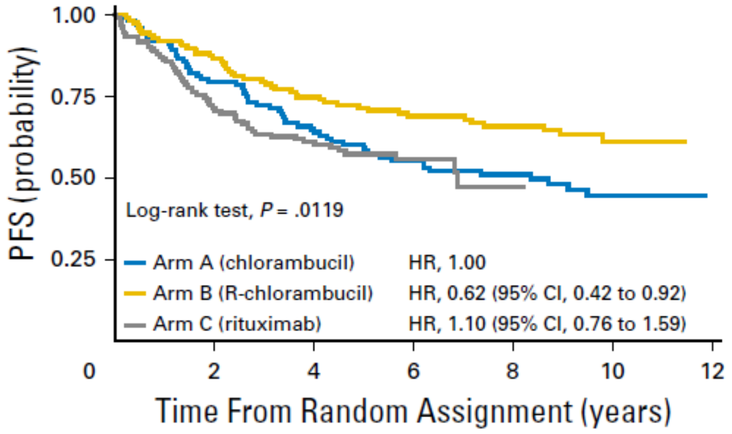
Response	All Patients (N = 401) No.	% (95% CI)	Arm A Chlorambucil (n = 131) No.	% (95% CI)	Arm B Chlorambucil Plus Rituximab (n = 132) No.	% (95% CI)	Arm C Rituximab (n = 138) No.	% (95% CI)
Complete remission*	264	65.8 (61.0 to 70.5)	83	63.4 (54.5 to 71.6)	104	78.8 (70.1 to 85.4)	77	55.8 (47.0 to 64.2)
Partial remission	81	20.2 (16.4 to 24.5)	29	22.1 (15.3 to 30.2)	21	15.9 (10.1 to 23.3)	31	22.5 (15.8 to 30.3)
Stable disease	28	7.0 (4.7 to 9.9)	11	8.4 (4.3 to 14.5)	1	0.8 (0.02 to 4.1)	16	11.6 (6.8 to 18.1)
Progressive disease	23	5.7 (3.7 to 8.5)	7	5.3 (2.2 to 10.7)	4	3.0 (0.8 to 7.6)	12	8.7 (3.0 to 12.0)
Not assessed	5	1.3 (0.4 to 2.9)	1	0.8 (0.02 to 4.2)	2	1.5 (0.2 to 5.4)	2	1.5 (0.2 to 5.1)
Overall response rate *	345	86.0 (82.2 to 89.3)	112	85.5 (78.3 to 91.0)	125	94.7 (89.4 to 97.8)	108	78.3 (70.4 to 84.8)

*$P < .001$.



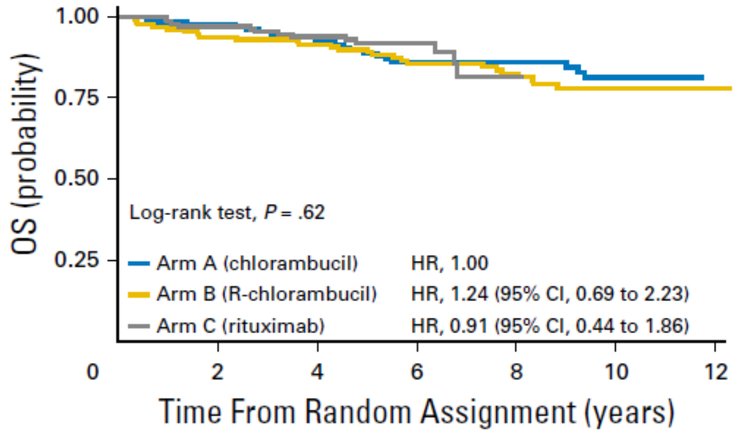
No. at risk:

Arm A	131	85	68	53	41	16	0
Arm B	132	109	93	76	58	23	0
Arm C	138	87	69	30	2	0	0



No. at risk:

Arm A	131	89	70	53	42	16	0
Arm B	132	110	94	77	59	23	0
Arm C	138	90	71	31	2	0	0

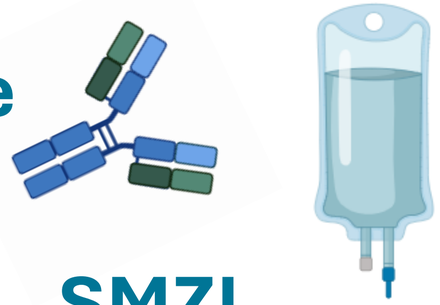


No. at risk:

Arm A	131	126	116	92	79	37	0
Arm B	132	121	118	95	77	35	1
Arm C	138	130	118	50	3	0	0

Zucca E et al., JCO 2017

Rituximab + bendamustine



EMZL

MALT2008-01 phase II trial

n=57

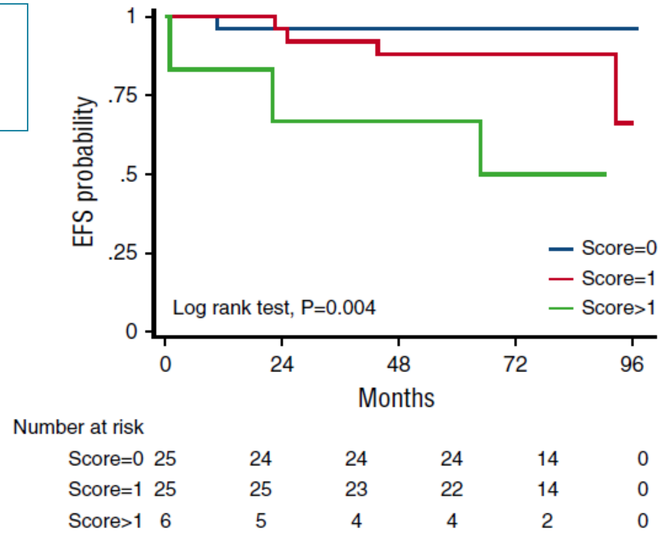
4-6 cycles based on response after cycle 3

Only 25% of patients needed >4 cycles (no survival difference)

Table 1. Outcome according to MALT-IPI (n = 57)

Number of risk factors	N (%)	EFS at 7 years, % (95% CI, %)	PFS at 7 years, % (95% CI, %)	OS at 7 years, % (95% CI, %)
0	25 (44.6)	96.0 (74.8-99.4)	100	96.0 (74.8-99.4)
1	25 (44.6)	88.0 (67.3-96.0)	91.8 (71.1-97.9)	96.0 (74.8-99.4)
>1	6 (10.7)	50.0 (11.1-80.4)	66.7 (19.5-90.4)	100
P (log rank)		.004	.049	.662

7-year EFS 88%



Salar A et al., Lancet Haematol 2014; Salar A et al., Blood 2017

SMZL

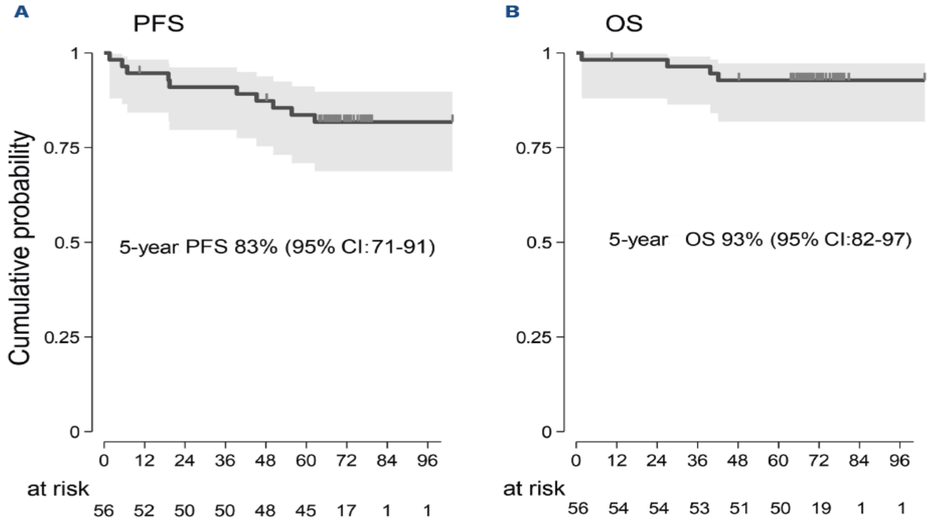
BRISMA/IELSG36 phase II trial

n=56

6 cycles

Table II. Treatment response.

Response	Restaging after 3 cycles	% (95% CI)	Final	% (95% CI)
CR	7	13 (5–24)	41	73 (60–84)
PR	39	70 (56–81)	10	18 (9–30)
ORR	46	82 (70–91)	51	91 (80–97)
SD	3	5 (1–15)	4	7 (2–17)
NA	6	11 (4–22)	1*	2 (0–10)
Early withdrawal	1†	2 (0–10)	–	–



Iannitto E et al., Br J Haematol 2018; Iannitto E et al., Haematologica 2024

Rituximab + lenalidomide

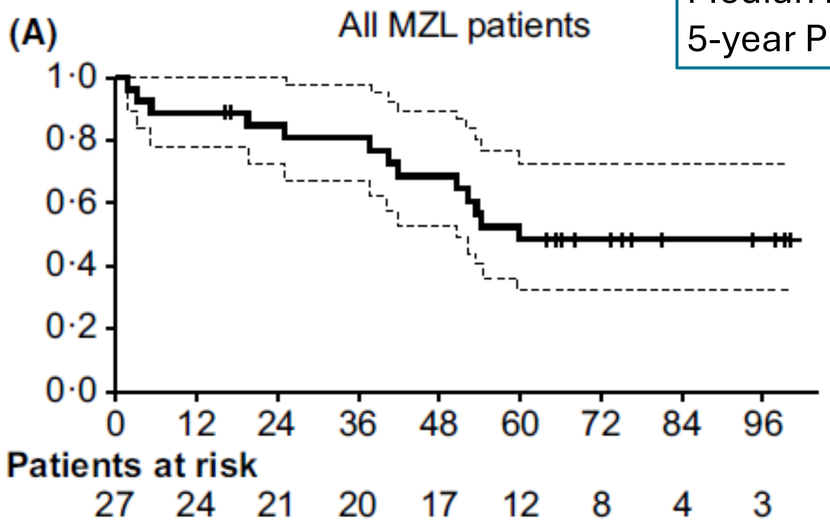
TN MZL

n=27

Lenalidomide 20 mg/day D1–21, Rituximab 375 mg/m2 D1
Response after six cycles → could continue for max 12 cycles

		ORR		CR/CRu		PR	
Subtype	*n*	*n*	%	*n*	%	*n*	%
Nodal MZL*	16	16	88	10	56	4	22
Extranodal MZL/MALT lymphoma	10	10	80	8	73	0	0
Splenic MZL	1	1	100	1	100	0	0
All patients	27	25	93	19	70	6	22

Median PFS 59.8 mo
5-year PFS 49%



Becnel MR et al., Br J Haematol 2019

EMZL

n=46

Lenalidomide 20 mg/day D1–21, Rituximab 375 mg/m2 D1

30% primary gastric MALT lymphoma
70% extragastric MALT lymphoma

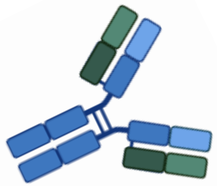
24% previously treated

ORR 80%
CR 54%
PR 26%

Median time to best response 3.6 months

Kiesewetter B et al., Blood 2017

Obinutuzumab



TN MZL

GALLIUM phase III trial

n=195

Obinutuzumab vs rituximab immunochemotherapy and maintenance

MZL patients

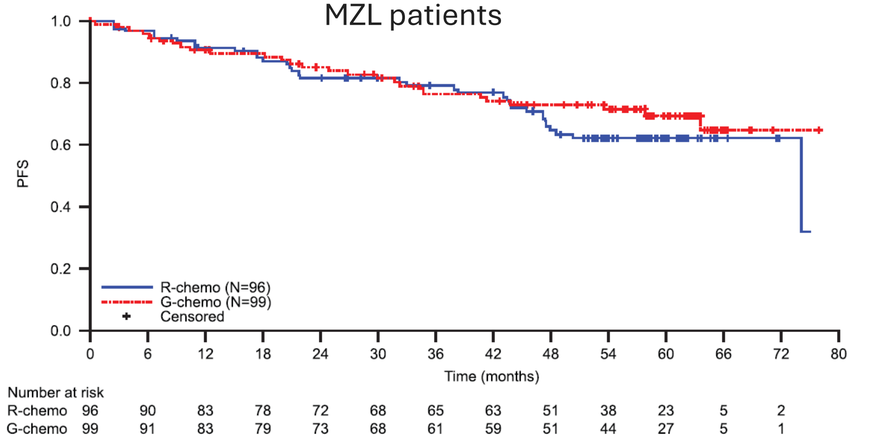


Figure 1. Kaplan-Meier plot of investigator-assessed progression-free survival in patients with MZL. Chemo = chemotherapy; G = obinutuzumab; MZL = marginal zone lymphoma; PFS = progression-free survival; R = rituximab.

n (%) of Patients Reporting ≥1 Event	G-Benda (n = 74)	G-CHOP (n = 14)	G-CVP (n = 12)	G-Chemo (Total) (N = 101)[b]	R-Benda (n = 63)	R-CHOP (n = 18)	R-CVP (n = 11)	R-Chemo (Total) (N = 93)[b]
Any AE	74 (100.00)	14 (100.0)	12 (100.0)	101 (100.0)	63 (100.0)	18 (100.0)	11 (100.0)	93 (100.0)
Grade 3–5 AE	64 (86.5)	13 (92.9)	10 (83.3)	87 (86.1)	48 (76.2)	15 (83.3)	8 (72.7)	72 (77.4)
Grade 5 AE	13 (17.6)	2 (14.3)	0	15 (14.9)	6 (9.5)	2 (11.1)	1 (9.1)	9 (9.7)
Infections	6 (8.1)	1 (7.1)	0	7 (6.9)	2 (3.2)	0	0	2 (2.2)
SAE	52 (70.3)	8 (57.1)	7 (58.3)	67 (66.3)	35 (55.6)	6 (33.3)	6 (54.5)	48 (51.6)
Any AESI								
Infections[c]	62 (83.8)	12 (85.7)	12 (100.0)	86 (85.1)	47 (74.6)	13 (72.2)	9 (81.8)	69 (74.2)
Second neoplasms[d]	12 (16.2)	0	1 (8.3)	13 (12.9)	7 (11.1)	3 (16.7)	1 (9.1)	11 (11.8)
AE leading to treatment discontinuation	21 (28.4)	1 (7.1)	3 (25.0)	26 (25.7)	15 (23.8)	2 (11.1)	1 (9.1)	19 (20.4)

Herold M et al., Hemasphere 2022

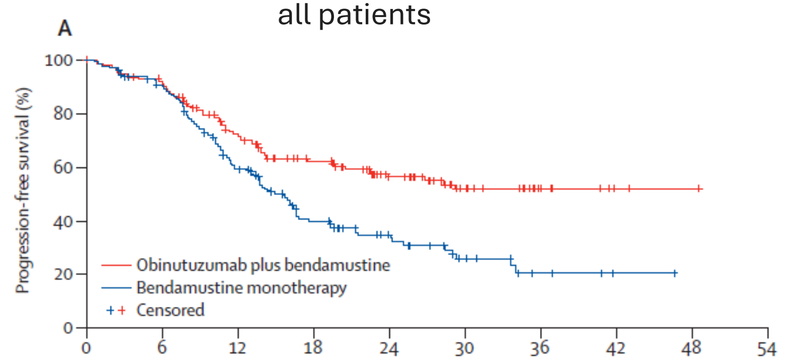
RR MZL

GADOLIN phase III trial

n=46

Obinutuzumab + bendamustine vs bendamustine

all patients

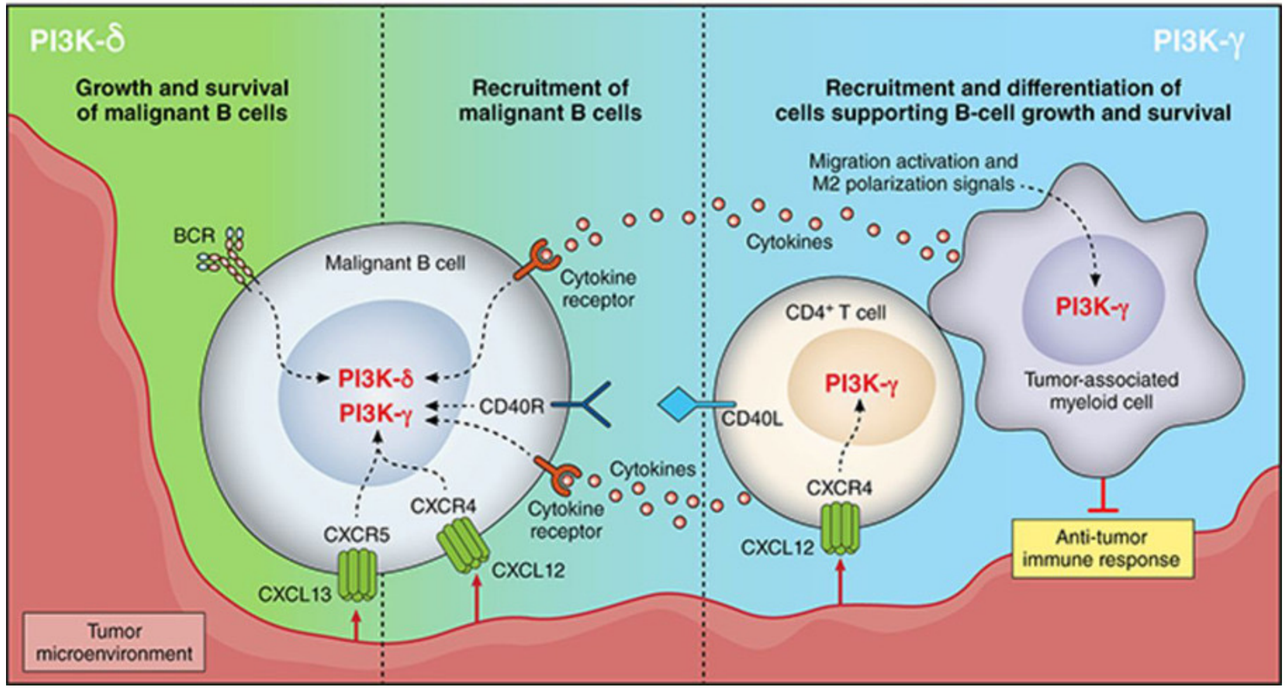


Number at risk										
Obinutuzumab plus bendamustine	194	157	106	75	47	27	7	2	1	0
Bendamustine monotherapy	202	149	86	42	26	13	4	1	0	0
Number censored										
Obinutuzumab plus bendamustine	6	22	40	57	79	96	116	121	122	0
Bendamustine monotherapy	16	36	49	69	80	87	94	97	0	0

No PFS benefit observed in patients with non-FL histology, with the experimental arm presenting more common grade ≥3 hematological and infusion reaction toxicity

Sehn LH et al., Lancet Oncol 2016

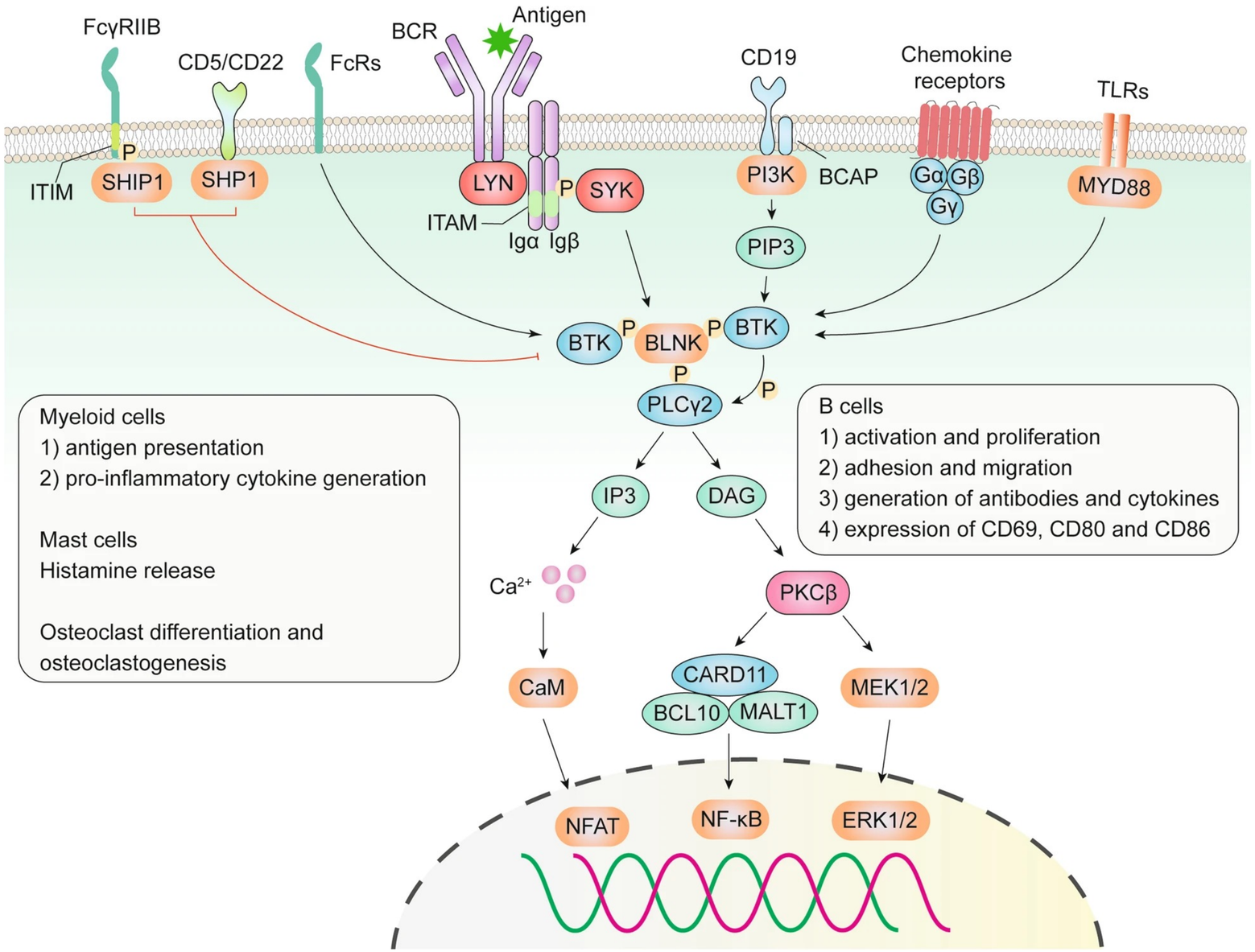
PI3K inhibitors for the treatment of MZL



Flinn IW et al., Blood 2018

Target	Drug	MZL, n	ORR	CR	PFS	Reference
PI3Kδ	**Idelalisib**	15	47%	7%	Median: 7 mo	Gopal, NEJM 2014
	Umbralisib	69	52%	19%	66%@12 mo	Zinzani, ICML 2019
	Parsaclisib	99	54%	6%	Median: 13.8 months	Phillips, ASH 2020
PI3Kγδ	**Duvelisib**	18	39%	5%	Median: 15.5 mo	Jacobsen, SOHO 2019
PI3Kαβ	**Copanlisib**	23	78%	13%	Median: 24 mo	Panyiotidis, Blood Adv 2021

BTK inhibitors for the treatment of MZL

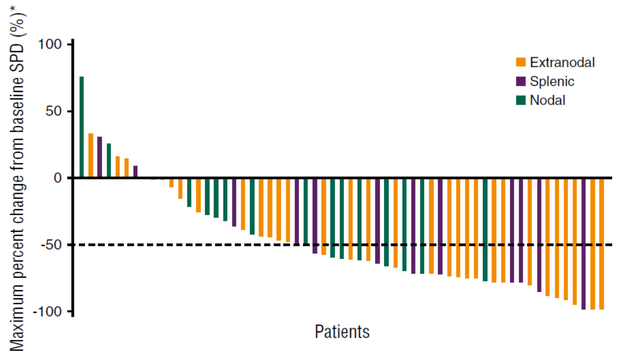


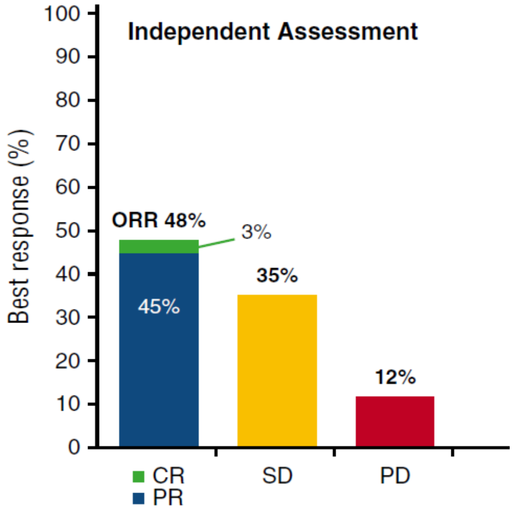
Alu A et al., Journal of Hematology & Oncology 2022

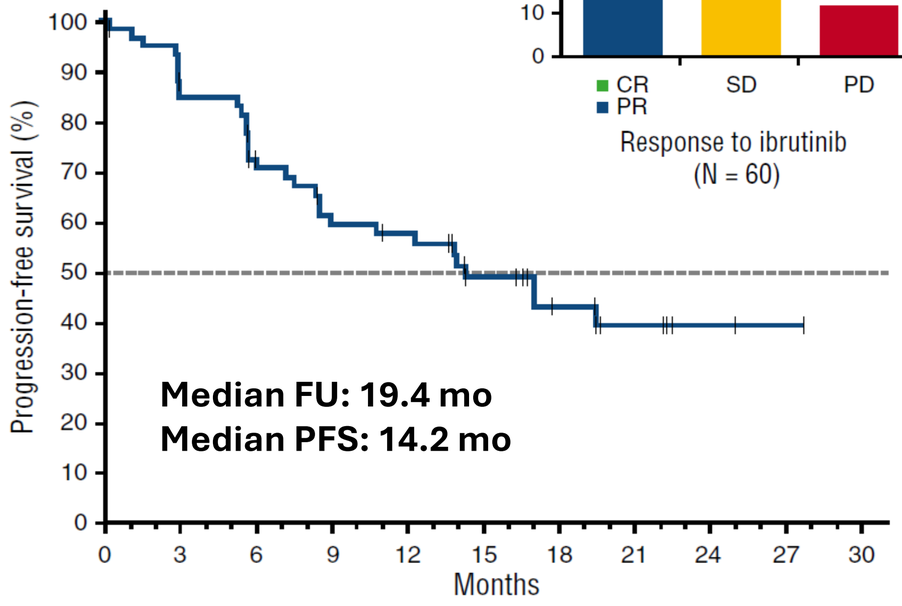
1st generation BTK inhibition: ibrutinib

Ibrutinib 560 mg ibrutinib orally once daily until progression/unacceptable toxicity
≥1 prior therapy with an anti-CD20 antibody–containing regimen

Characteristic	Total (N = 63)
Median age (range), y	66 (30-92)
Age ≥65 y	36 (57)
Male sex	26 (41)
ECOG performance status	
0	33 (52)
1	25 (40)
2	5 (8)
MZL subtype	
Extranodal	32 (51)
Splenic	14 (22)
Nodal	17 (27)
Bulky disease ≥6 cm	14 (22)
B symptoms	15 (24)
Bone marrow involvement	21 (33)
Baseline cytopenias	
Any cytopenia	27 (43)
Hemoglobin ≤11 g/dL	27 (43)
Platelet count ≤100 × 10^9/L	6 (10)
Absolute neutrophil count ≤1.5 × 10^9/L	1 (2)
Lactate dehydrogenase	
Median lactate dehydrogenase (range), U/L	227 (117-1198)
≥350 U/L	12 (19)
Creatinine clearance <60 mL/min	9 (14)
Median time from initial diagnosis (range), months	45 (8-271)
Median time from first treatment (range), months	38 (1-271)
Median time from last prior therapy (range), months	12 (0.8-113)
No. of prior systemic therapies	
Median no. of prior therapies (range)	2 (1-9)
1 prior therapy	23 (37)
2 prior therapies	18 (29)
≥3 prior therapies	22 (35)
Types of prior therapies	
Rituximab monotherapy only	17 (27)
Rituximab-based chemoimmunotherapy	40 (63)
Radiation	9 (14)
Splenectomy	4 (6)
Autologous hematopoietic stem cell transplantation	2 (3)
Median no. of prior rituximab treatments (range)	1 (1-7)
Refractory to last prior systemic therapy	14 (22)





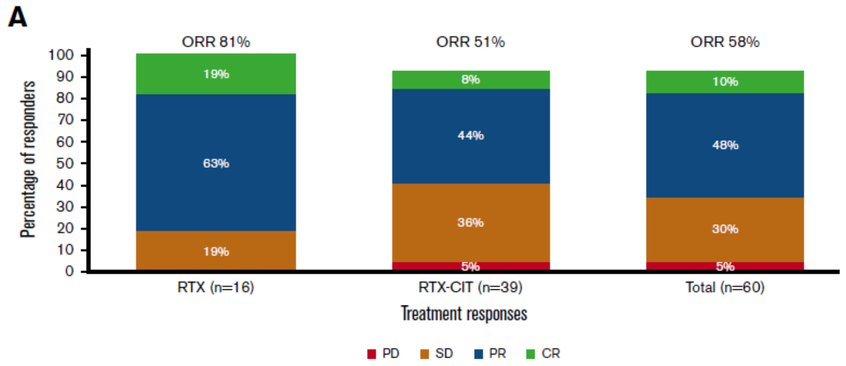


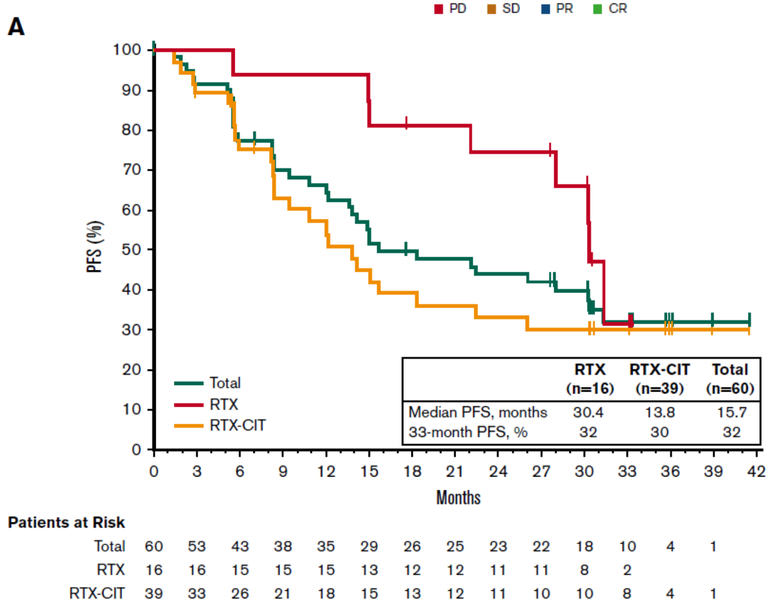
Event	Total (N = 63)
Most common adverse events of any grade*	
Fatigue	28 (44)
Diarrhea	27 (43)
Anemia	21 (33)
Nausea	16 (25)
Arthralgia	15 (24)
Peripheral edema	15 (24)
Thrombocytopenia	15 (24)
Cough	14 (22)
Dyspnea	13 (21)
Upper respiratory tract infection	13 (21)
AEs grade ≥3†	
Anemia	9 (14)
Pneumonia	5 (8)
Fatigue	4 (6)
Cellulitis	3 (5)
Diarrhea	3 (5)
Hypertension	3 (5)
Lymphocyte count decreased	3 (5)
Neutropenia	3 (5)
Asthenia	2 (3)
Autoimmune hemolytic anemia	2 (3)
Blood bilirubin increased	2 (3)
Muscle spasms	2 (3)
Multiple organ dysfunction	2 (3)
Neutrophil count decreased	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)
Serious AEs‡	
Pneumonia	5 (8)
Cellulitis	2 (3)
Autoimmune hemolytic anemia	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)

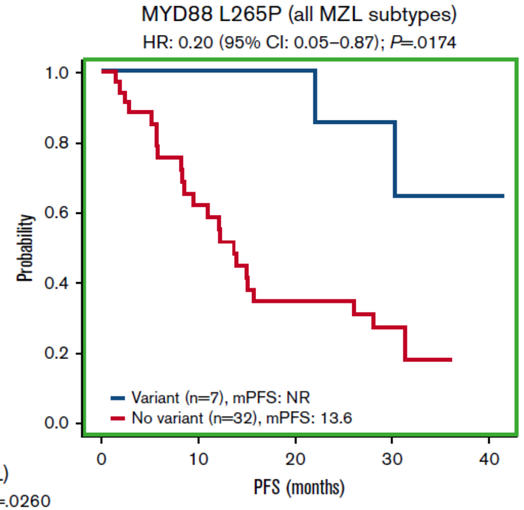
Noy A et al., Blood 2017

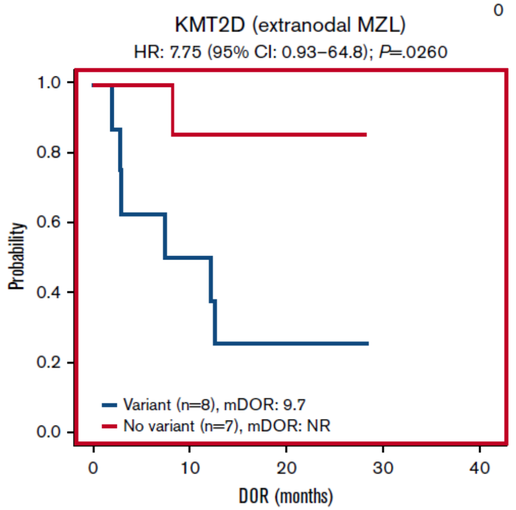
1st generation BTK inhibition: ibrutinib

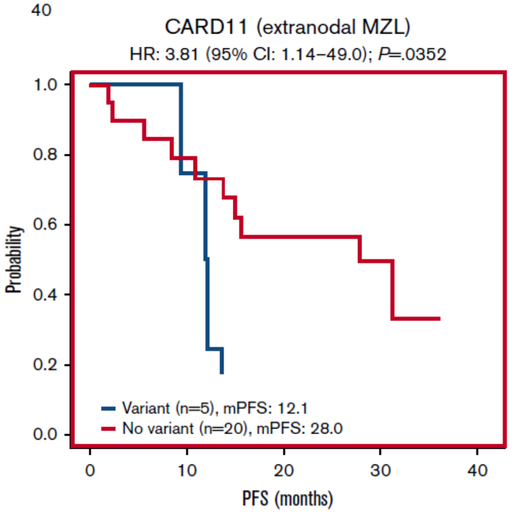
- With extended follow-up (median 33 months), ibrutinib demonstrated durable clinical benefit in patients with RR MZL
- Biomarker data correlated with clinical outcomes and suggest that ibrutinib's efficacy may be related to its disruption of NF-kB signaling











Noy A et al., Blood Adv 2020

1st generation BTK inhibition: ibrutinib

Real-word findings

Retrospective multicenter study, 21 Italian centers

Ibrutinib available in Italy for the treatment of R/R MZL, based on 648/96 Italian national law (November 2020-January 2024)

Parameter	N (%)
Age at ibrutinib start, median (range)	74 (30-89)
Gender, M/F (%)	54/40 (57/43)
MZL subtype	
SMZL	55 (59)
NMZL	17 (18)
EMZL	16 (17)
dissMZL	6 (6)
ECOG ≥2 pre-ibrutinib (n=72)	10 (11)
LDH > ULN pre-ibrutinib	48 (51)
Hb <12 g/dl pre-ibrutinib	57 (61)
Plt <100 x 10^9/l	33 (35)
Absolute lymphocyte count < 1 x 10^9/l	24 (25)
MZL-IPI pre-ibrutinib	
Low risk (0 factors)	8 (9)
Intermediate risk (1-2 factors)	61 (65)
High risk (3-5 factors)	27 (26)
Leukemic disease	41 (44)
TP53 mutation and/or del17p (n=24 SMZL)	10 (42)
Number of prior lines, median (range)	1 (1-5)
Prior rituximab monotherapy only	8 (9)
At least prior one immunochemotherapy	86 (91)
BR	*69 (73)*
R-CHOP/R-COP	*38 (40)*
Primary refractory	16 (20)
POD24	44 (47)
Refractory to last therapy	24 (26)

	All pts (n=94)	SMZL (n=55)	NMZL/diss (n=23)	EMZL (n=16)	p
ORR, N (%) (95% CI)	71 (74) (65.6-83.8)	44 (80) (67.0-89.6)	13 (57) (34.5-76.8)	14 (88) (61.7-98.4)	0.010
CR	12 (13)	6 (11)	2 (9)	4 (25)	0.266
PR	59 (63)	38 (69)	11 (48)	10 (63)	
SD	16 (17)	8 (15)	7 (30)	1 (6)	
PD	7 (7)	3 (5)	3 (13)	1 (6)	
2y DOR % (95% CI)	67.9 (53.7-78.6)	70.4 (52.7-82.6)	66.6 (33.1-86.1)	58.4 (17.5-84.8)	0.701
2y PFS % (95% CI)	48.5 (37.3-58.8)	51.6 (36.3-64.9)	29.0 (12.0-48.5)	66.7 (36.9-84.8)	0.011
2y OS % (95% CI)	74.5 (63.4-82.6)	77.9 (62.5-87-6)	61.6 (37.2-78.9)	81.2 (52.5-93.5)	0.629

Median follow-up: 23.8 months

Median PFS: 22.5 months

Pre-ibrutinib MZL-IPI significantly predicted distinct PFS

82 pts (87%) discontinued ibrutinib

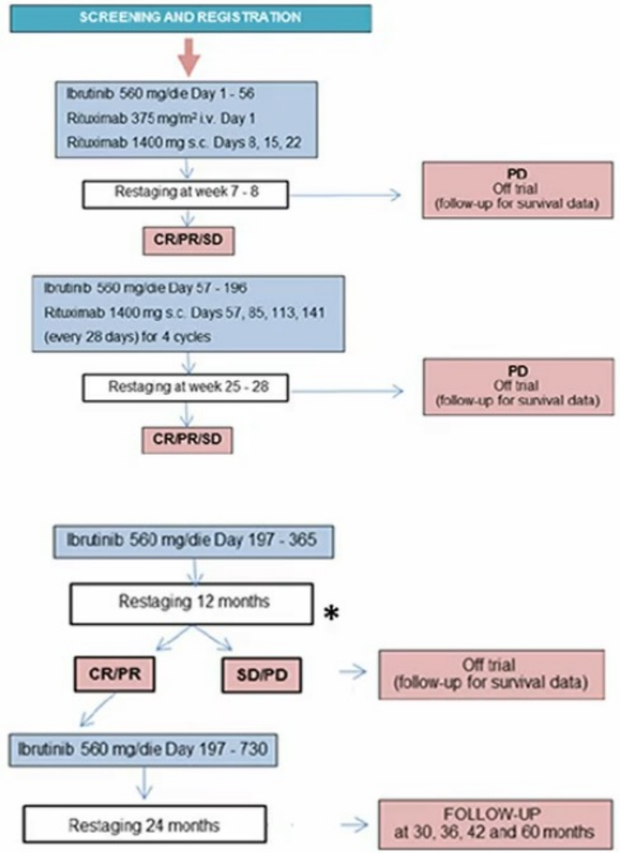
- 16 for AE
- 32 for PD
- 34 for switch to zanubrutinib

	Any grade	Grade 1-2	Grade 3-5
Hematologic AEs, N pts (%)	23 (25)	8 (9)	15 (16)
Anemia	*10 (10)*	*5 (5)*	*5 (5)*
Thrombocytopenia	*8 (9)*	*5 (5)*	*3 (3)*
Neutropenia	*9 (10)*		*9 (10)*
Extra-hematologic AEs, N pts (%)	48 (51)	30 (32)	18 (19)
Infections	*12 (15)*	*5 (6)*	*7 (9)*
Atrial fibrillation	*8 (10)*	*3 (4)*	*5 (6)*
Bleeding	*7 (9)*	*5 (7)*	*2 (2)*
Diarrhea	*6 (8)*	*5 (7)*	*1 (1)*
Rash	*5 (6)*	*4 (5)*	*1 (1)*
Hypertension	*1 (1)*	*1 (1)*	*0*
AEs leading to drug interruption	16 (17)		
Fatal AEs (Gr 5)	8 (5)		

Merli M et al., SIE 2025

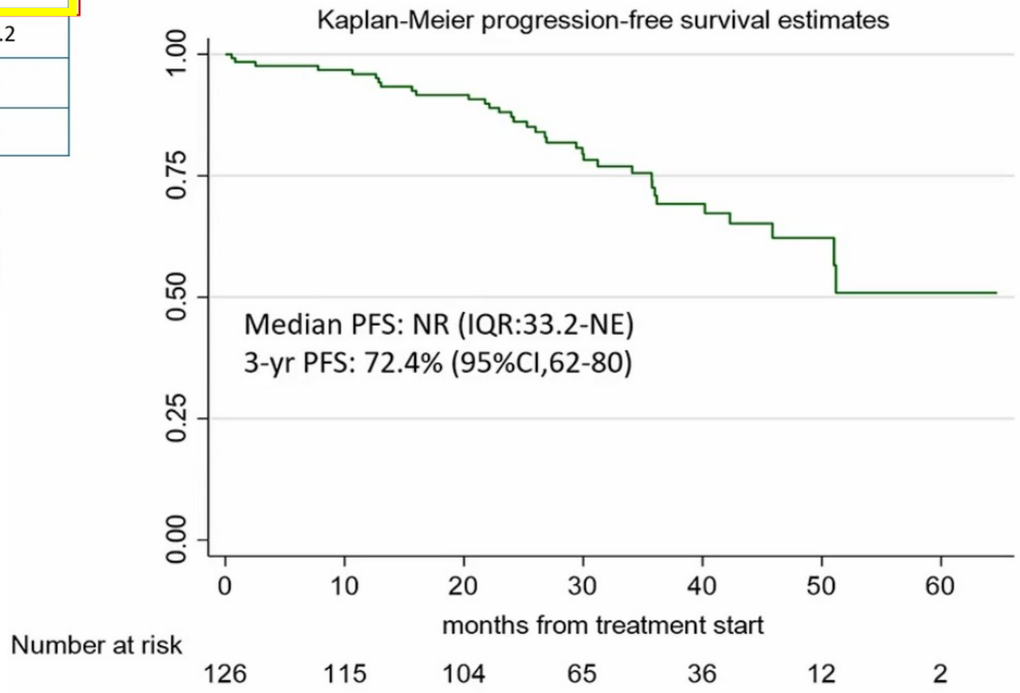
Ibrutinib + rituximab in TN MZL

IELSG47/MALIBU phase II trial



	Response at 12 months		Best objective response	
	n=97/126	%	N=107/126	%
Overall response rate	91	93.8	107	92.3
Complete response	49	50.5	72	62.1
Partial response	42	43.3	35	30.2
Stable disease	4	4.1	-	-
Progressive disease	2	2.1	-	-

Median time to first response (IQR)	1.64 months	1.5- 2.3
Median time to best response (IQR)	6.16 months	1.7-11.9



	Any grade			Grade ≥ 3		
AESI class of event	**AE (n)**	**Patients (n)**	**Patients (%)**	**AE (n)**	**Patients (n)**	**Patient (%)**
Diarrhea	29	22	17.5	2	2	1.25
Skin rash	25	20	15.9	1	1	0.8
Neutropenia	26	18	14.3	24	17	13.5
Hemorrhage	37	18	14.3	1	1	0.8
Infection*	10	9	7.1	3	3	2.4
Cardiac	36	25	19.8	26	19	15.1
• Atrial fibrillation/flutter	18	13	10.3	14	10	7.9
• Hypertension	11	9	7.1	6	6	4.8
• Ventricular extrasystoles	4	2	1.6	3	1	0.8
• Ventricular tachycardia	3	2	1.6	3	2	1.6
2° primary malignancy	0.0	0.0	0.0	0.0	0.0	0.0

Conconi A et al., ICML 2025

2nd generation BTK inhibition: zanubrutinib

Zanubrutinib 320 mg orally
Until progression/unacceptable toxicity

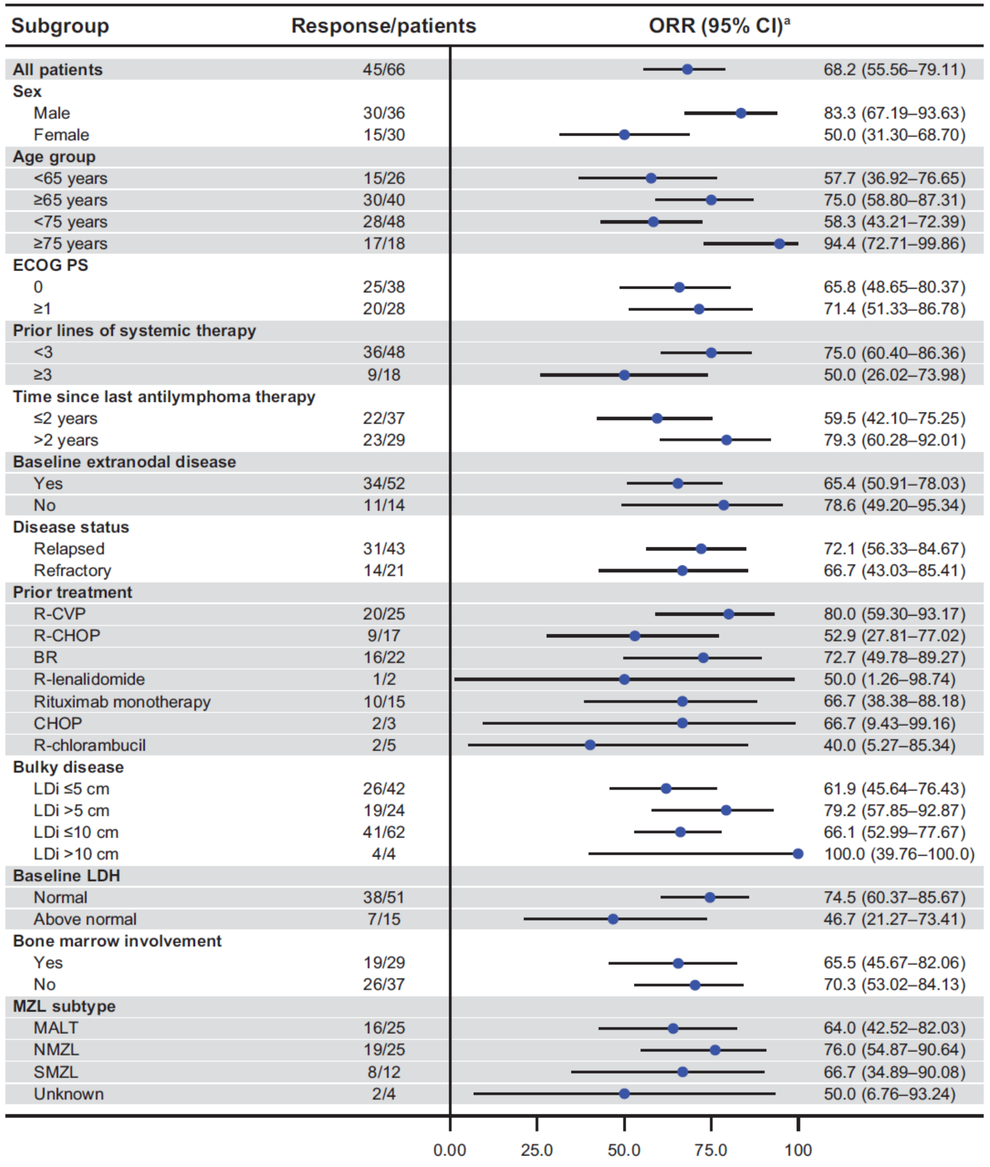
MAGNOLIA phase II trial

Characteristics	BGB-3111-214 (MAGNOLIA study) R/R MZL (*N* = 68)
Age, years	
Median (range)	70 (37–95)
Age category, *n* (%)	
≥65 years and <75 years	22 (32.4)
≥75 years	19 (27.9)
Sex, *n* (%)	
Male	36 (52.9)
Female	32 (47.1)
Baseline ECOG PS score, *n* (%)	
0	39 (57.4)
1	24 (35.3)
2	5 (7.4)
Bulky disease, *n* (%)	
LDi >5 cm	25 (36.8)
Bone marrow involvement, *n* (%)[a]	29 (42.6)
Extranodal disease, *n* (%)[b]	53 (77.9)
Refractory disease[c]	22 (32.4)
Evidence of FDG-avid disease by IRC, *n* (%)	
FDG-avid	61 (89.7)
Non–FDG-avid	7 (10.3)
MZL subtype, *n* (%)	
Extranodal (MALT)	26 (38.2)
Nodal	26 (38.2)
Splenic	12 (17.6)
Unknown[d]	4 (5.9)
Site of disease for MALT subtype, *n* (%)	
Gastric	2 (7.7)
Cutaneous	4 (15.4)
Nongastric/noncutaneous	19 (73.1)
Unknown	1 (3.8)
Baseline cytopenia[e]	20 (29.4)
LDH (U/L)	
Median (range)	204 (128.5–1,405)
LDH, *n* (%)	
Above normal	16 (23.5)
Number of previous therapies	
Median (range)	2 (1–6)
Time from end of last therapy to study entry (months)	
Median (range)	20.6 (1–176.6)
Previous therapy[f], *n* (%)	
Rituximab-based chemotherapy	60 (88.2)
R-CVP	25 (36.8)
BR	22 (32.4)
R-CHOP	17 (25.0)
Rituximab monotherapy	15 (22.1)[g]
Rituximab + lenalidomide	2 (2.9)
Radiation therapy	15 (22.1)
Splenectomy	7 (10.3)
Autologous hematopoietic stem cell transplant	4 (5.9)

Response Rates	Total (N=66)
ORR, n (%)	45 (68.2)
CR, n (%)	17 (25.8)
PR, n (%)	28 (42.4)

Median and event-free rate	Total (N=66)
12-month DOR, %	93.0
12-month PFS, %	82.5
12-month OS, %	95.3

AE, *n* (%)	BGB-3111-214 (MAGNOLIA study) (*N* = 68) Any-grade AE	Grade ≥3 AE
Patients with ≥1 AE	65 (95.6)	27 (39.7)
Diarrhea	15 (22.1)	2 (2.9)
Contusion	14 (20.6)	0
Constipation	10 (14.7)	0
Pyrexia	9 (13.2)	2 (2.9)
Abdominal pain	8 (11.8)	
Upper respiratory tract infection	8 (11.8)	1 (1.5)
Back pain	7 (10.3)	0
Nausea	7 (10.3)	0
COVID-19 pneumonia	4 (5.9)	3 (4.4)
Pneumonia	2 (2.9)	2 (2.9)
AE of interest		
Bleeding	25 (36.8)	0
Major hemorrhage[a]	0	0
Atrial fibrillation/flutter	2 (2.9)	1 (1.5)
Hypertension[b]	2 (2.9)	1 (1.5)
Second primary malignancies[c]	5 (7.4)	3 (4.4)
Skin cancers	2 (2.9)	0
Infections	31 (45.6)	11 (16.2)[f]
Opportunistic infections	2 (2.9)	1 (1.5)
Tumor lysis syndrome	0	0
Anemia	4 (5.9)	2 (2.9)
Neutropenia[d]	9 (13.2)	7 (10.3)
Thrombocytopenia[e]	10 (14.7)	3 (4.4)



Opat S et al., Clin Cancer Res 2021

2nd generation BTK inhibition: zanubrutinib

MAGNOLIA phase II trial

Table 1. Summary of IRC-assessed disease responses by MZL subtypes (efficacy analysis set)

	Extranodal (MALT) (n = 25)	Nodal (n = 25)	Splenic (n = 12)	Unknown* (n = 4)	Total† (N = 66)
ORR, % (95% CI)‡	64.0 (42.5-82.0)	76.0 (54.9-90.6)	66.7 (34.9-90.1)	50.0 (6.8-93.2)	68.2 (55.6-79.1)
Best overall response, n (%)					
CR	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
PR	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	28 (42.4)
Stable disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	13 (19.7)
Progressive disease	3 (12.0)	1 (4.0)	1 (8.3)	1 (25.0)	6 (9.1)
Nonprogressive disease§	1 (4.0)	0	0	0	1 (1.5)
Discontinued study before first assessment	1 (4.0)	0	0	0	1 (1.5)
Median time to response, mo (IQR)	2.8 (2.7-2.9)	2.8 (2.7-3.8)	3.6 (2.7-6.0)	2.7 (2.6-2.8)	2.8 (2.7-3.7)

The zanubrutinib safety profile was consistent with the primary analysis

Atrial fibrillation/flutter: 2.9%

Hypertension: 4.4%

Neutropenia G≥3: 11.8%

Older patients subgroup analysis ≥65 yo: 40/68 (59%)

ORR 75%, CR 25%

Atrial fibrillation/flutter: 5%

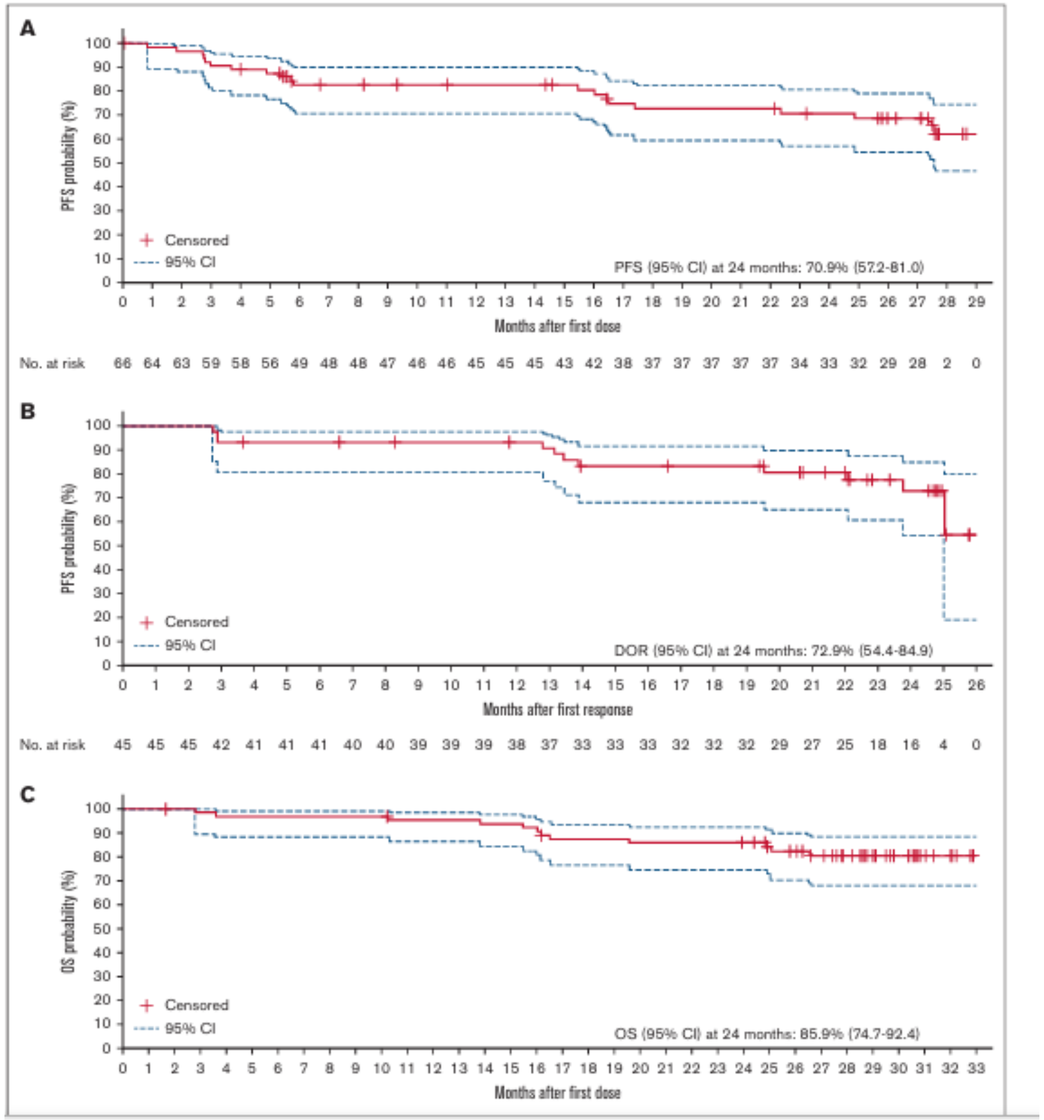
Hypertension: 5%

Neutropenia G≥3: 7.5%

Treatment discontinuation due to unrelated fatal adverse events in 2 patients (myocardial infarction and COVID-19 pneumonia)

Opat S et al., EHA 2022

Median FU: 27.4 months

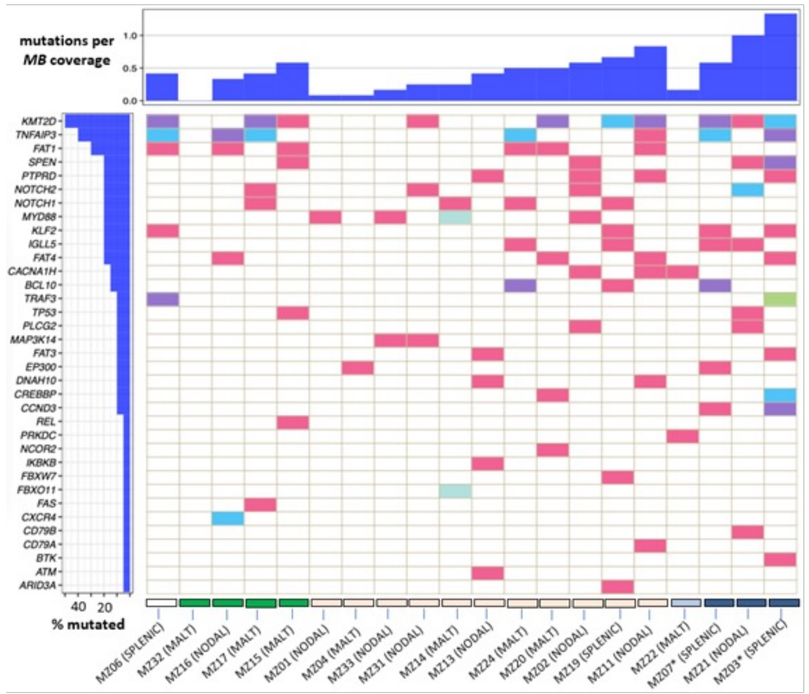


Opat S et al., Blood Adv 2023

2nd generation BTK inhibition: zanubrutinib

MAGNOLIA phase II trial- molecular correlate substudy

- Baseline WES performed on 17 patients focusing on 48 genes known to be currently mutated in MZL
- More than 1 mutations found in 16/17 (94%) patients
- *MYD88* or *TNFAIP3* mutations associate with improved PFS

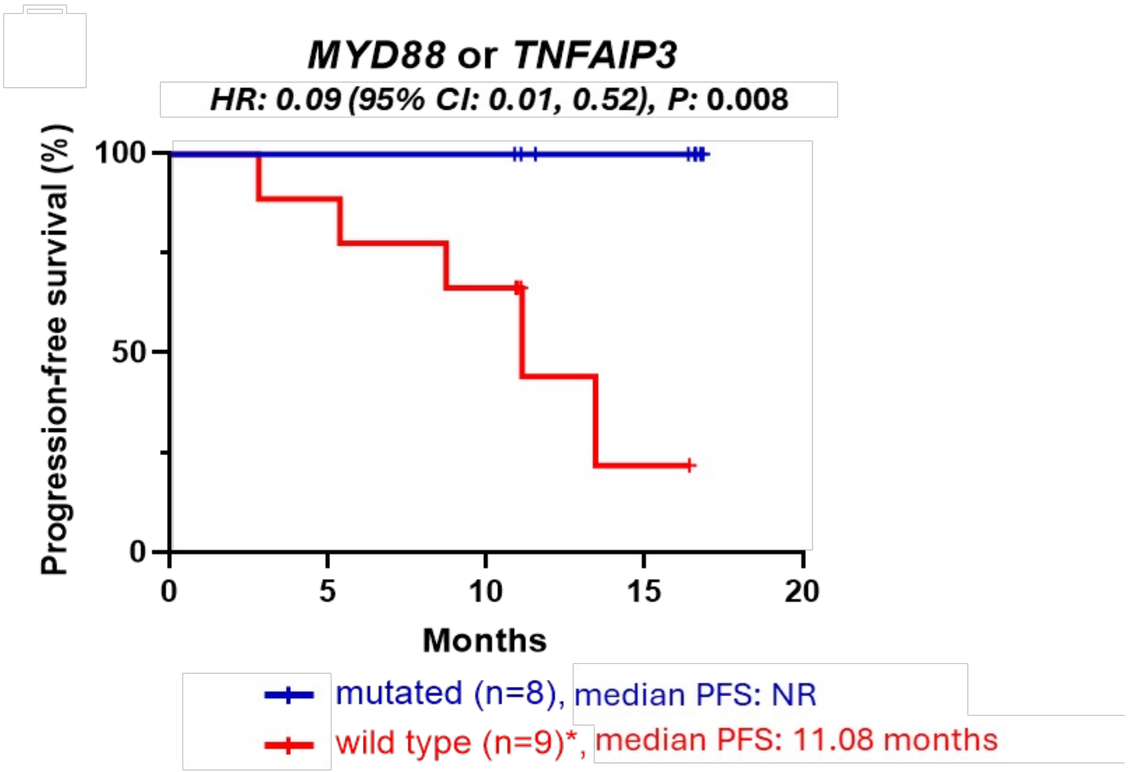


Mutation Type

- Missense
- Stop gain/loss
- Frameshift ins/del
- Inframe ins/del
- Splice site

Clinical Response

- PD
- SD
- PR
- CR
- Failed at screen



Tatarczuch et al., HemaSphere 2022

2nd generation BTK inhibition: zanubrutinib

Real-word findings

Multicenter retrospective cohort study - 10 U.S. centers
n=78
33% splenic, 32% extranodal, 28% nodal, 6% unspecified MZL
1L: 14%, 2L: 36%, 3L: 30%, ≥4L 20%
ORR 75%
CR rate 44%
Response not affected by MZL subtype or treatment line
Ki-67 >20% and shorter duration of response to 1L were associated with primary progression on zanubrutinib
MYD88 mutation (n=38) significantly associated with CR rate (but not with PFS).

Median follow up: 18 months
Median PFS: 45 months, **2-year PFS was 71.7%**
Median OS: not reached, **2-year OS: 96.1%**
Ki-67 >20% was prognostic of inferior PFS

Zanubrutinib dose reduction: 12%
Zanubrutinib discontinuation due to AE: 13% (3 related to cardiac AE and 2 related to bleeding).

Epperla N et al., ASH 2025

Multicenter retrospective cohort study - 39 Spanish centers
n=118
55% splenic, 19% extranodal, 20% nodal, 6% unspecified MZL
1L: none, 2L 50%, 3L 25%, ≥4L 25%
ORR 76%
CR rate 22%
Response not affected by MZL subtype, stage, MYD88 status, POD24, MAGNOLIA eligibility, age or refractoriness to prior line
Number of prior LoT influenced outcomes

Median follow-up: 14 months
Median PFS: not reached, **1-year PFS 79.4%**
Median OS: not reached, **1-year OS: 86.8%**
Response to zanubrutinib impacted PFS and OS, number of prior LoT impacted PFS only

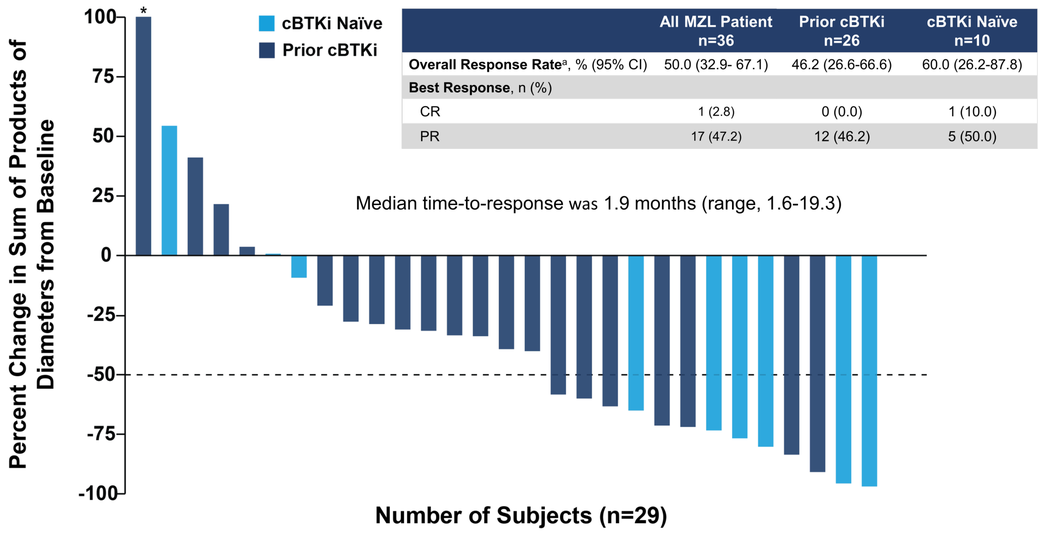
Zanubrutinib discontinuation due to AE: 8%

Prat AM et al., ASH 2025

Non-covalent BTK inhibition: pirtobrutinib

BRUIN phase I/II trial

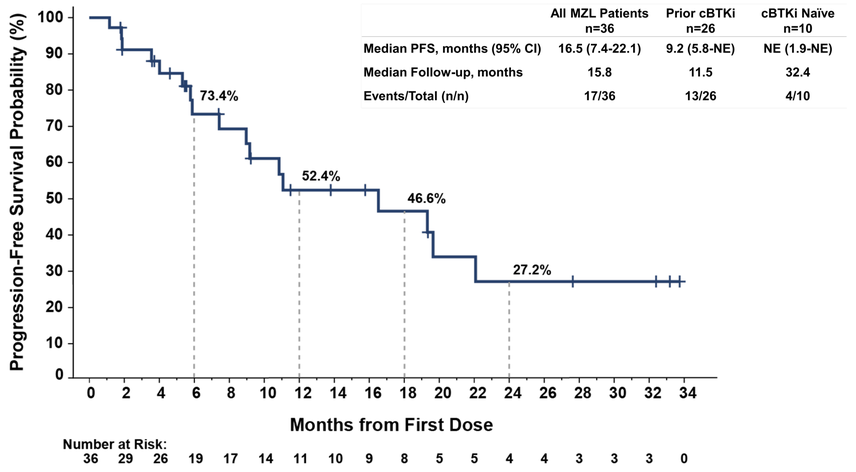
Characteristics	n=36
Median age, years (range)	68 (22-83)
Male, n (%)	16 (44)
Female, n (%)	20 (56)
ECOG PS, n (%)	
0	18 (50)
1	17 (47)
2	1 (3)
MZL Subtype, n (%)	
Nodal	17 (47)
Splenic	13 (36)
Extranodal*	6 (17)
Tumor Bulk (cm), n (%)	
≥5	4 (11)
<5	23 (64)
No measurable lymph node	9 (25)
Elevated LDH, n (%)	
Yes	15 (42)
No	21 (58)
Baseline Hemoglobin >12g/dL	
Yes	29 (81)
No	7 (19)
Involved Nodal Sites, n (%)	
≤4	20 (56)
>4	16 (44)
Ann Arbor Staging, n (%)	
Stage I/II	1 (3)
Stage III/IV	29 (81)
Missing	6 (17)
MALT-IPI Risk Group, n (%)	
Low Risk (0)	1 (3)
Intermediate Risk (1)	10 (28)
High Risk (≥2)	19 (53)
Missing	6 (17)
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)
Reason for Discontinuation of any Prior cBTKi[b], n (%)	
Progressive disease	20 (77)
Toxicity/Other	6 (23)



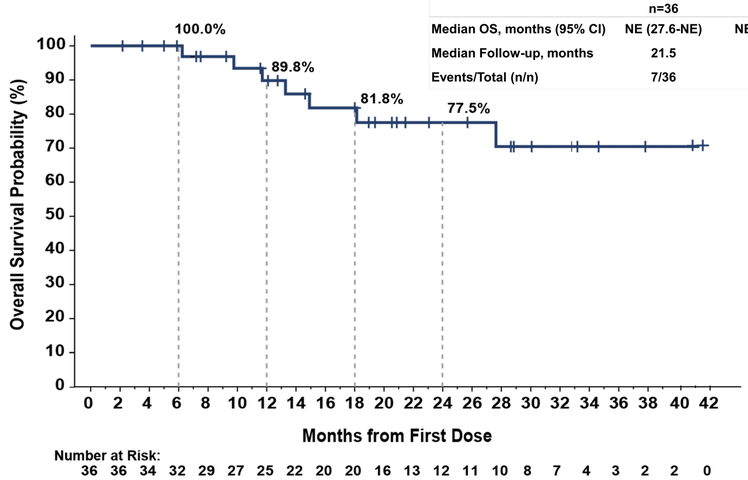
	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Overall Response Rate[a], % (95% CI)	50.0 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)

	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)



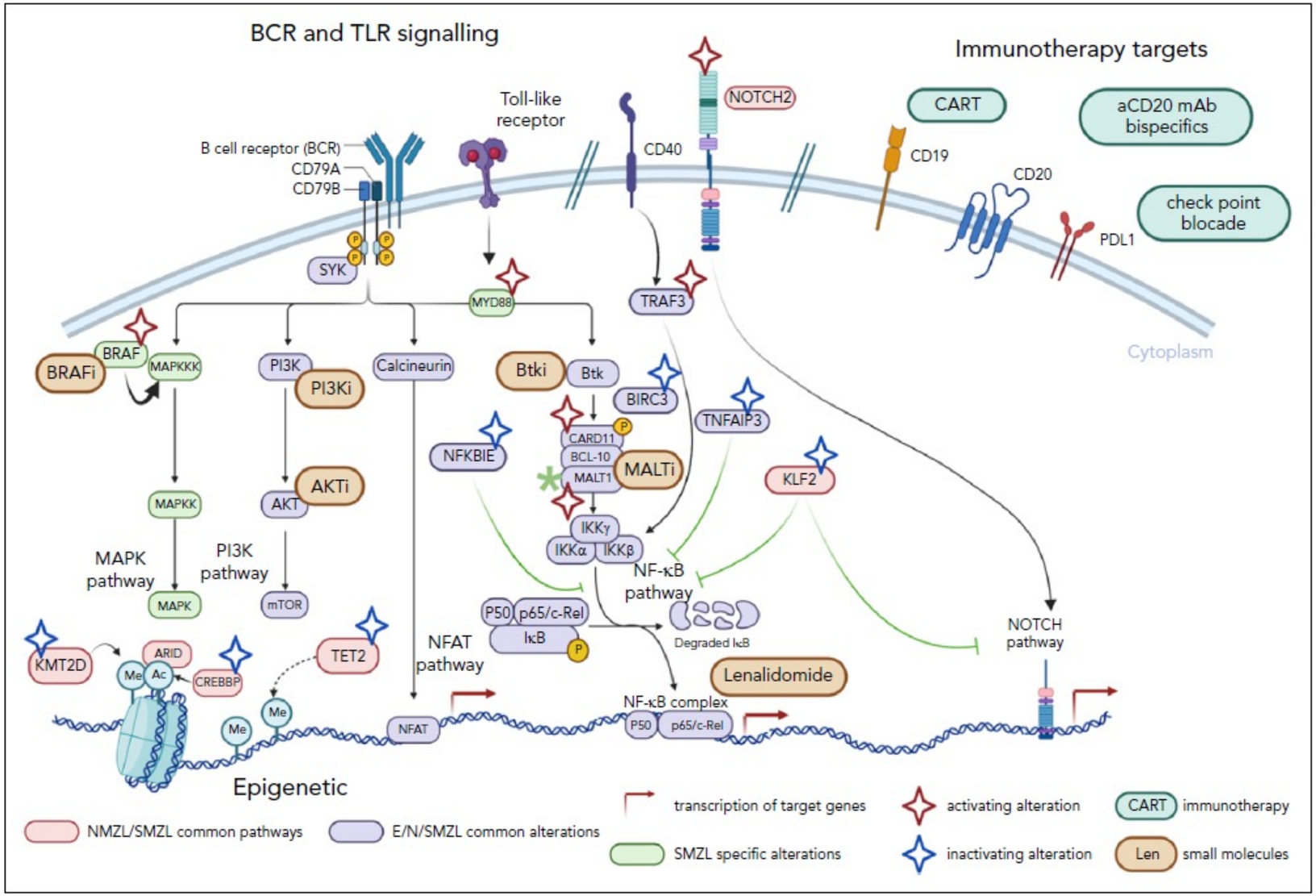
	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median PFS, months (95% CI)	16.5 (7.4-22.1)	9.2 (5.8-NE)	NE (1.9-NE)
Median Follow-up, months	15.8	11.5	32.4
Events/Total (n/n)	17/36	13/26	4/10



	All MZL Patients n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Median OS, months (95% CI)	NE (27.6-NE)	NE (NE-NE)	NE (11.7-NE)
Median Follow-up, months	21.5	19.0	33.2
Events/Total (n/n)	7/36	3/26	4/10

Patel K et al., ASH 2023

Targeted therapies for MZL: need for new targets?



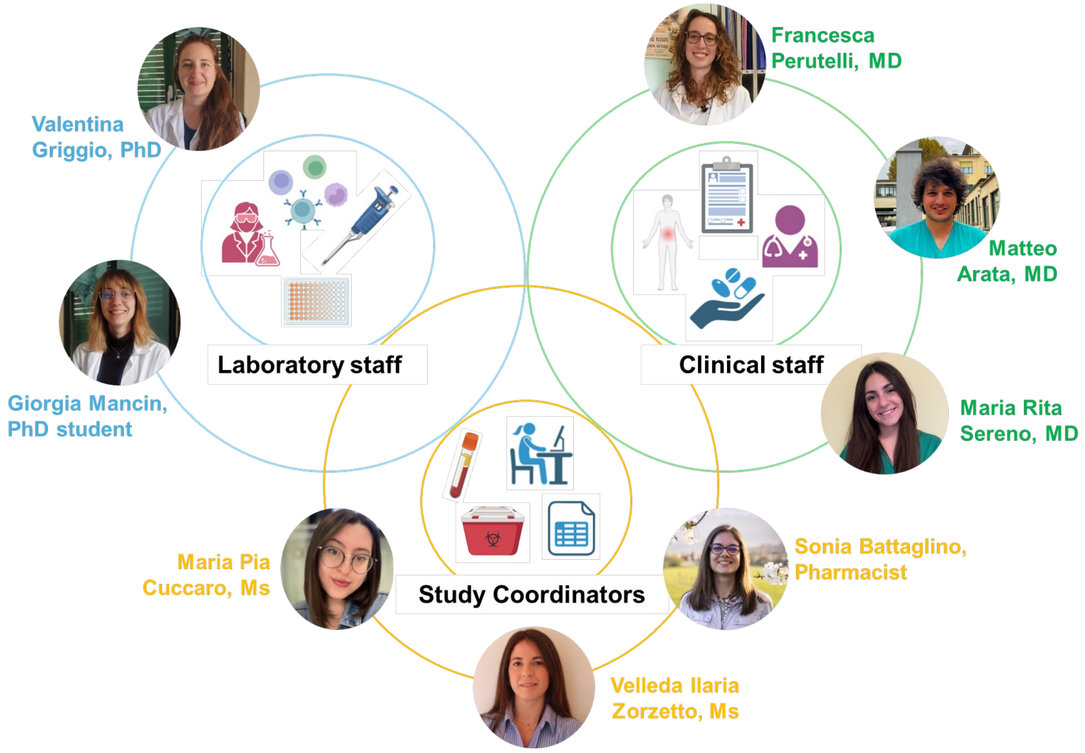
Thieblemont C et al., Blood 2026

Acknowledgments

Department of Molecular Biotechnology and Health Sciences
University of Torino

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

Laboratory of Translational Hematology



Gruppo malattie linfoproliferative