FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Linfomi indolenti non follicolari: un futuro chemo-free?

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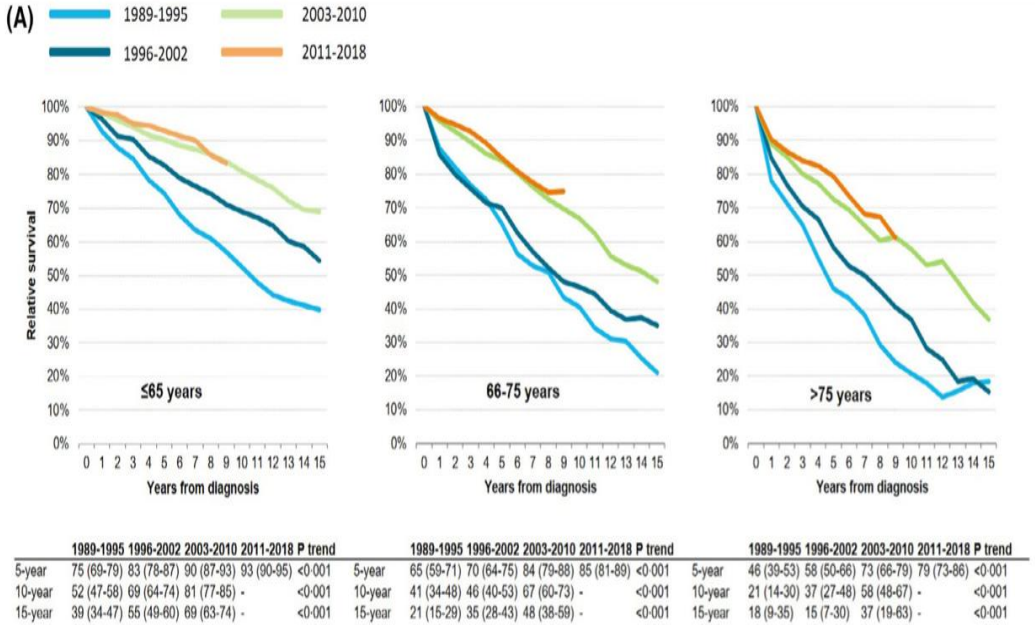
Disclosures of Marzia Varettoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						x	x
AstraZeneca						x	x
Beigene						x	x
Janssen						x	
Lilly					x		

Rituximab-based therapies have improved survival of WM pts in the last 20 years

Combination	Pts	ORR%	CR%	Median PFS (months)	Reference
DRC	72	83	7	35	Dimopoulos JCO 2007
R-Fludarabine	43	96	4	51	Treon, Blood 2009
FCR	43	79	12	50	Tedeschi, Cancer 2012
R-Cladribine	29	90	24	Not reached	Laszlo, JCO 2010
R-Bendamustine	69	97	19	87% at 2 years	Laribi et al, Br J Haematol 2019



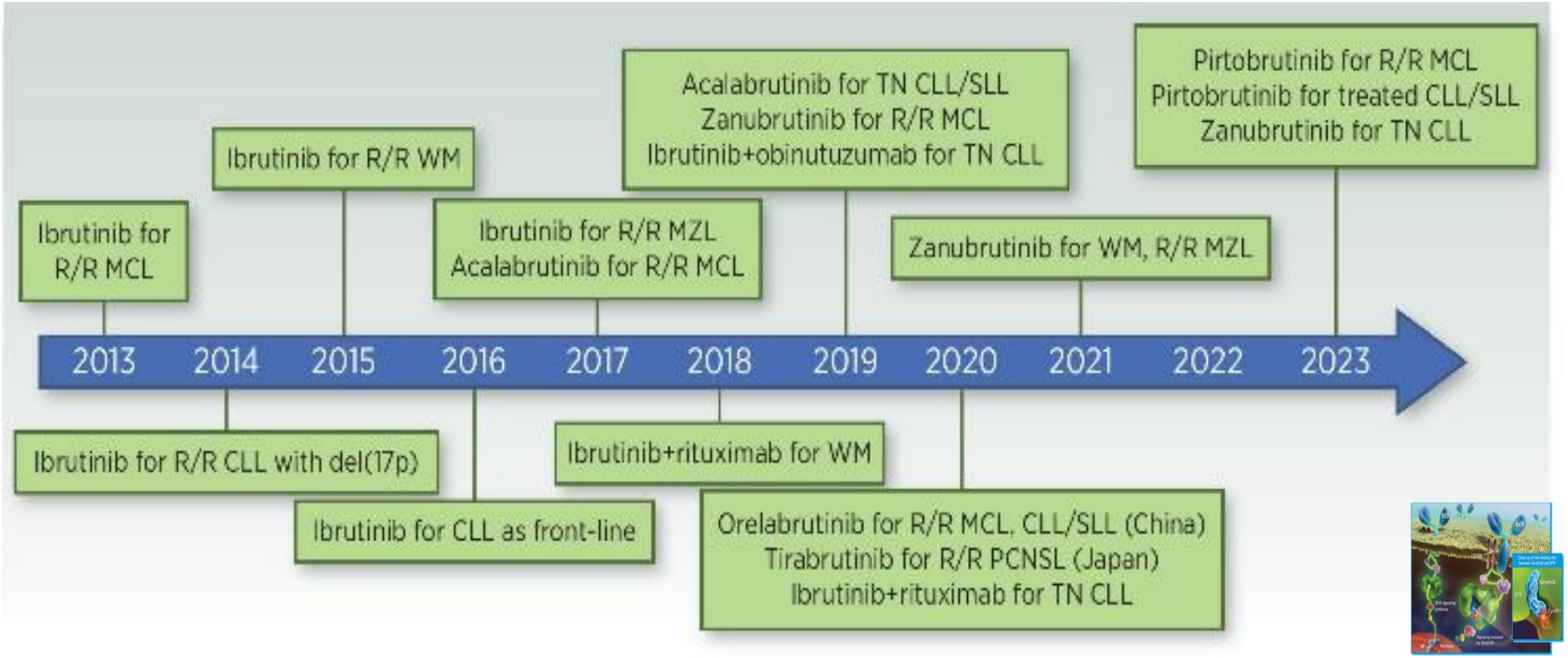
	1989-1995	1996-2002	2003-2010	2011-2018	P trend
5-year	75 (69-79)	83 (78-87)	90 (87-93)	93 (90-95)	<0·001
10-year	52 (47-58)	69 (64-74)	81 (77-85)	-	<0·001
15-year	39 (34-47)	55 (49-60)	69 (63-74)	-	<0·001

	1989-1995	1996-2002	2003-2010	2011-2018	P trend
5-year	65 (59-71)	70 (64-75)	84 (79-88)	85 (81-89)	<0·001
10-year	41 (34-48)	46 (40-53)	67 (60-73)	-	<0·001
15-year	21 (15-29)	35 (28-43)	48 (38-59)	-	<0·001

	1989-1995	1996-2002	2003-2010	2011-2018	P trend
5-year	46 (39-53)	58 (50-66)	73 (66-79)	79 (73-86)	<0·001
10-year	21 (14-30)	37 (27-48)	58 (48-67)	-	<0·001
15-year	18 (9-35)	15 (7-30)	37 (19-63)	-	<0·001

Amadoor K et al, Br J Haematol 2021

BTKi have changed treatment paradigm in lymphoproliferative disorders



Clin Cancer Res 2024;30(11):2333-2341

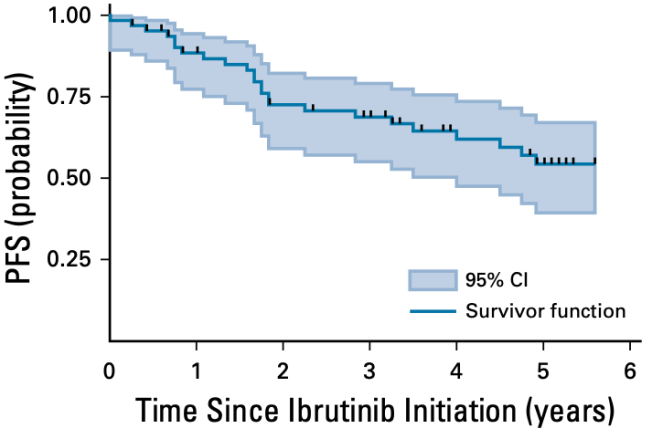
Ibrutinib in R/R WM: long-term follow-up

63 symptomatic WM patients who received at least one prior therapy
Median number of prior therapies: 2 (1-9), 40% of patients were refractory to their previous therapy

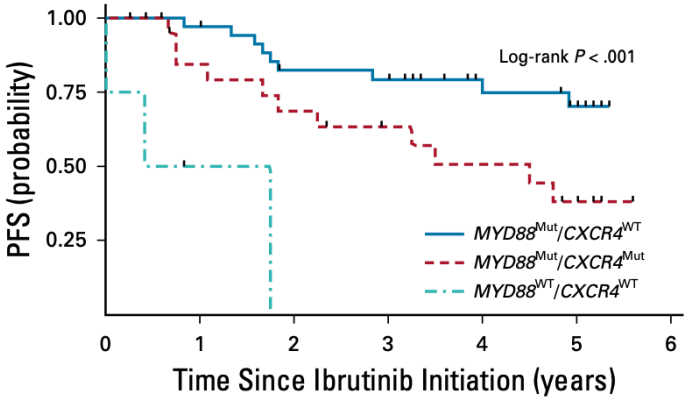
Rates of response

Overall Responses %	90.4%
Major Responses %	77.7%
VGPR	27%
Median Time to Minor Response or better	1 month
Median Time to Major Response or better	2 months

5 year PFS: 54%



PFS & genotype



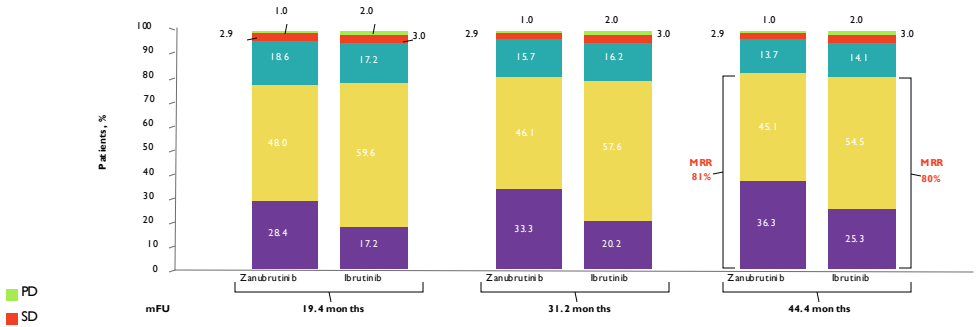
CXCR4 mutations associated with lower VGPR rate and slower response
No major responses in MYD88 WT patients

Treon et al, NEJM 2015; Treon et al, JCO 2021

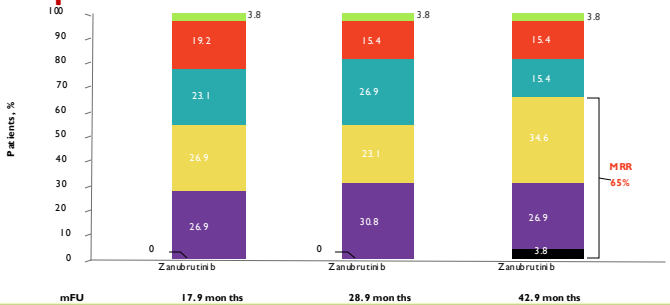
ASPEN study: zanubrutinib versus ibrutinib in WM

- Randomized, open-label, multicenter phase III study

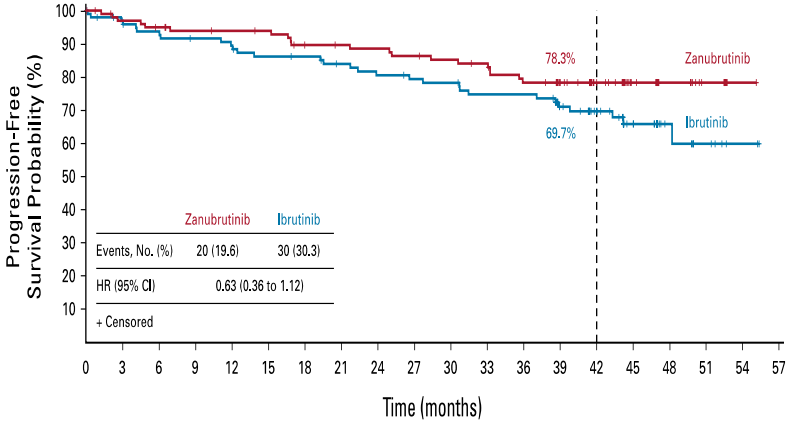
Responses Over Time in Patients With MYD88^{MUT}



Responses Over Time in Patients With MYD88^{WT}



PFS in Patients with MYD88^{MUT}

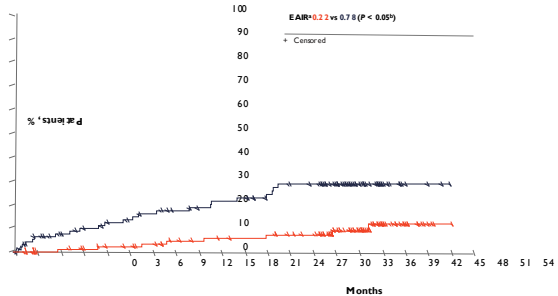


- In MYD88 WT patients, 42-month PFS was lower than cohort 1 (53.8% vs 78.3%); OS was comparable between cohorts (87.5% vs 83.9%)

Dimopoulos M et al, JCO 2023

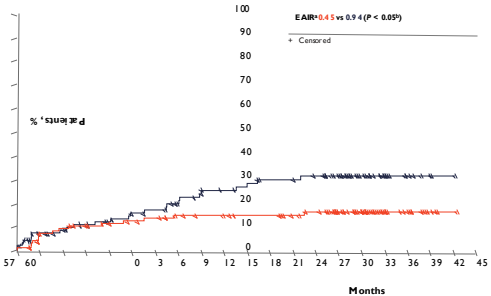
Time to Event Analysis for AEs of interest – Cohort 1

Atrial Fibrillation/Flutter



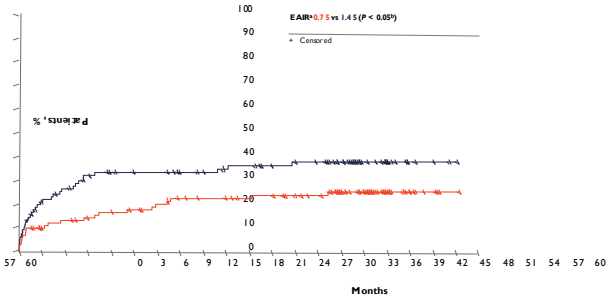
No. of Patients at Risk:																									
Zanubrutinib	101	95	94	92	89	87	84	79	77	75	74	74	70	68	52	41	Zanubrutinib	4	101	0					
Ibrutinib	98	87	83	78	74	71	68	64	62	59	58	54	49	48	40	25	Ibrutinib	4	2	98					

Hypertension



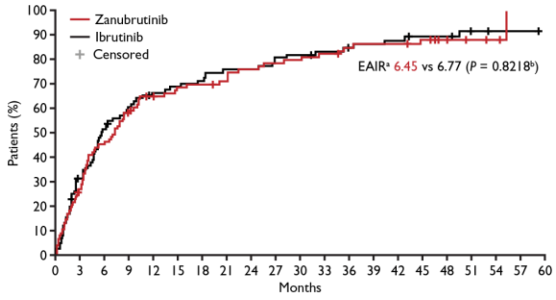
No. of Patients at Risk:																									
Zanubrutinib	89	87	83	80	77	75	70	68	67	65	65	61	58	46	34	Zanubrutinib	14	1	0						
Ibrutinib	84	80	75	71	66	64	58	52	50	47	44	43	41	34	22	Ibrutinib	6	1	0						

Diarrhea



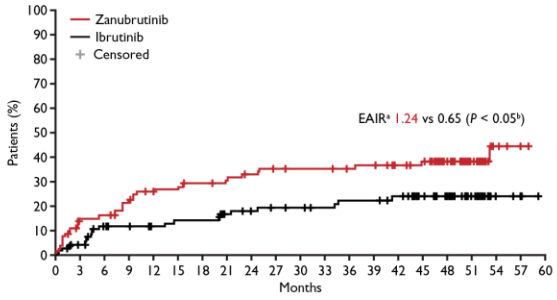
No. of Patients at Risk:																									
Zanubrutinib	101	85	82	78	76	73	69	65	63	62	60	59	55	53	41	33	16	7	4	1	0				
Ibrutinib	98	73	67	60	56	54	54	50	49	46	45	41	39	38	32	18	9	4	2	0					

Infections



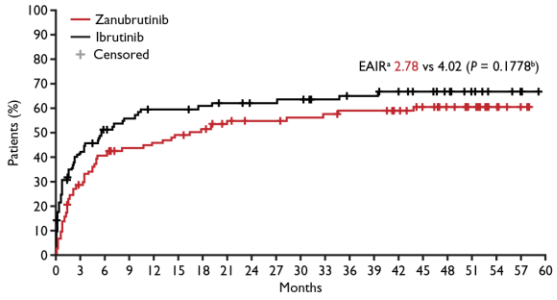
No. of patients at risk:																									
Zanubrutinib	101	68	51	38	30	26	25	23	19	17	16	14	11	10	10	8	5	3	2	0					
Ibrutinib	98	83	43	34	28	28	24	20	20	16	15	12	10	9	8	8	6	4	1	1	0				

Neutropenia



No. of patients at risk:																									
Zanubrutinib	101	81	79	72	66	64	60	57	54	51	50	50	48	47	43	40	31	19	7	4	0				
Ibrutinib	98	87	77	75	72	70	70	64	61	58	57	54	52	52	47	39	33	19	5	3	0				

Hemorrhage



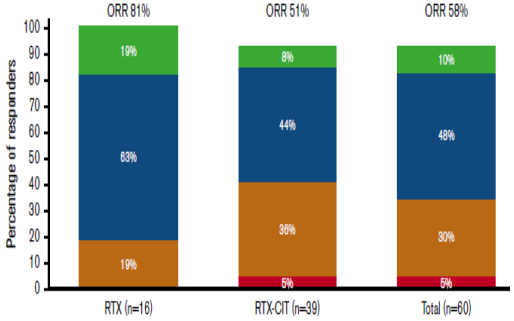
No. of patients at risk:																									
Zanubrutinib	101	67	56	51	49	46	43	38	35	35	33	32	30	30	27	23	19	14	8	4	0				
Ibrutinib	98	55	44	37	33	33	31	29	27	27	26	23	21	21	19	16	13	10	4	3	0				

Dimopoulos M et al, JCO 2023

Covalent BTKi in RR MZL

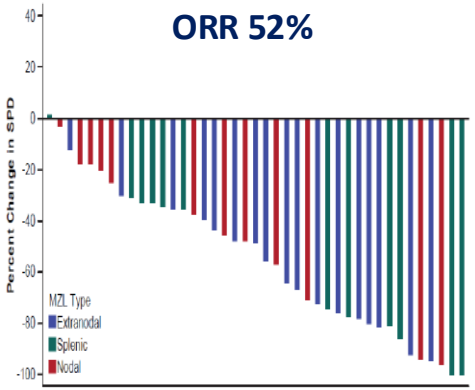
Ibrutinib

ORR 58% (INV-based)



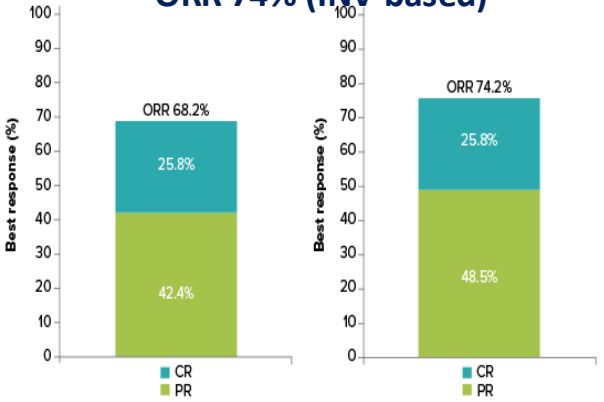
Acalabrutinib

ORR 52%

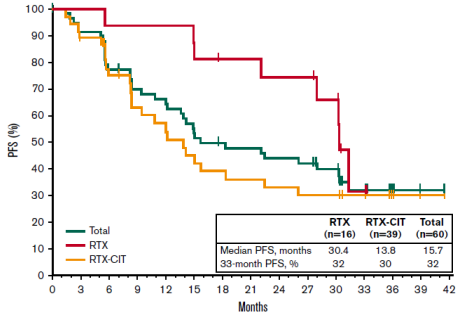


Zanubrutinib

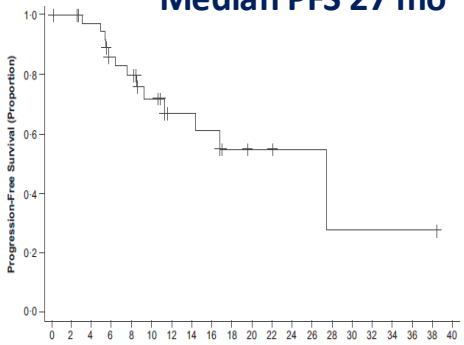
ORR 74% (INV-based)



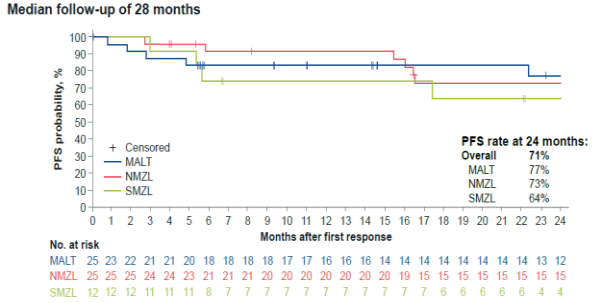
Median PFS 15.7 mo



Median PFS 27 mo



PFS 71% at 24 mo



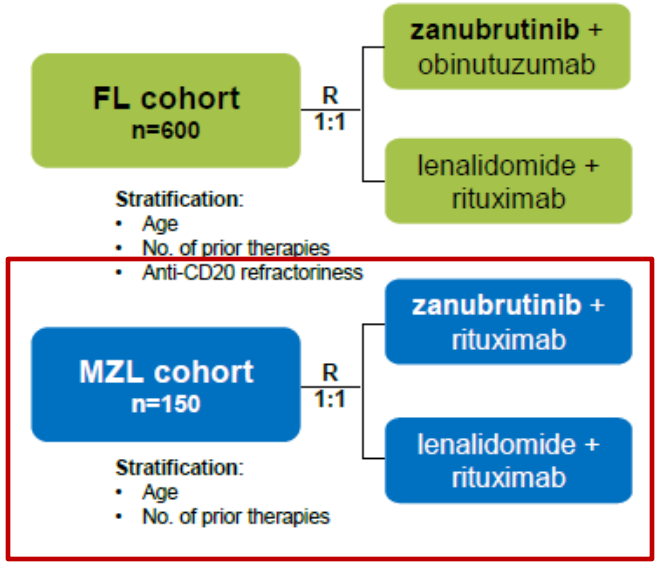
Noy et al. Blood Adv 2020, Strati et al BJH 2022, Opat et al. Blood Adv 2023

MAHOGANY: A phase III trial with Zanu+Rituximab vs Lena-Rituximab in RR MZL

- MAHOGANY (BGB-3111-308; NCT05100862) is a randomized, open-label, multicenter phase 3 trial of **zanubrutinib + anti-CD20 antibody** in R/R FL and with R/R MZL

Key eligibility criteria

- Age ≥18 years
- Histologically confirmed R/R FL (grade 1-3A) or MZL (extranodal, nodal, or splenic)
- Previous treatment with ≥1 prior line of systemic therapy, including an anti-CD20–based regimen
- In need of treatment according to modified GELF criteria[1]
- Adequate bone marrow and organ functions
- No prior treatment with BTK inhibitor
- Prior lenalidomide treatment allowed unless no response or short remission (DOR <24 months)
- No clinically significant cardiovascular disease, severe or debilitating pulmonary disease, or history of a severe bleeding disorder



Primary endpoint
PFS

Secondary endpoints
ORR
OS
TTNT
HR-QoL
Safety

Accrual completed

IELSG-48 study: first randomized study in TN SMZL

- Age of ≥ 18 years
- Patients with diagnosis of SMZL
- Patients not previously treated
- In need for treatment according to guidelines
- No prior splenectomy
- No active hepatitis C infection
- No organ dysfunction

Arm A (N = 60)
Zanubrutinib
160 mg BID for 12 cycles
plus rituximab
(8 infusions)

- **If CR after 12 cycles: stop treatment**
- **If PR after 12 cycles:**
  Zanubrutinib
  160 mg BID for 12 cycles
  plus rituximab
  (4 infusions)

Arm B (N = 60)
Rituximab
(8 infusions)

- **If CR after 12 cycles: stop treatment**
- **If PR after 12 cycles:**
  Rituximab
  (4 infusions)

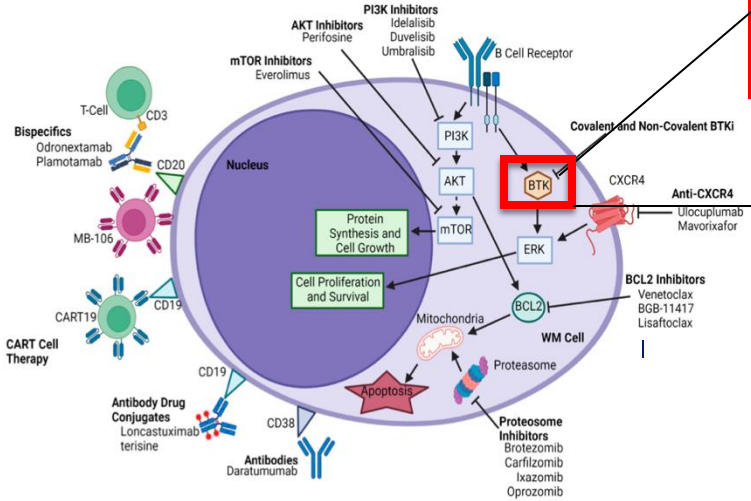
Primary Endpoint

- **PFS at 3 years** according to Cheson 2007

Secondary Endpoints

- CR at 6, 12, 18 and 24 mos
- Best ORR
- DoR, TTNT
- OS
- Safety
- QoL
- Correlatives: mutational profiling on circulating tumor DNA (ctDNA)

Emerging treatment options in WM



Non covalent BTKi
Phase I/II study BRUIN
Palomba ASH 2023

BTK-degraders
Phase I/II study CADANCE-101 (BGB-16673-101).
Frustaci AM, EHA 2025

PROTACs
KIN-8194 (dual HCK/BTK PROTAC)
(Yang G et al, Blood 2021)
DFCI-002-06 (dual HCK/BTK PROTAC)
(Liu S et al. ASH 2024

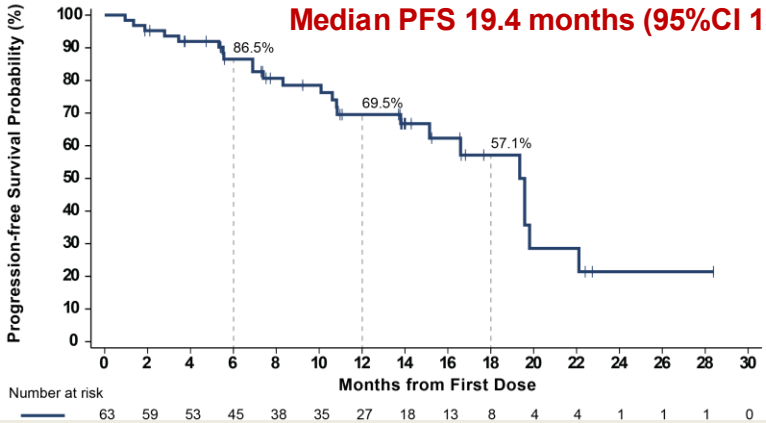
Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

Pirtobrutinib in WM and MZL: phase 1/2 BRUIN Study

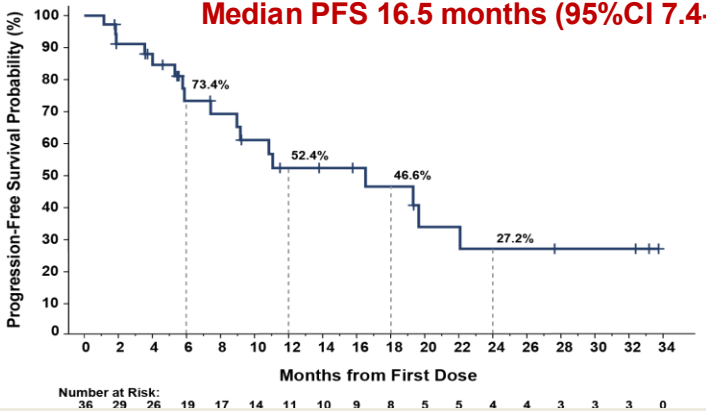
Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
ORR, % (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 PFS 19.4 months (95%CI 15.1-22.1)



Median PFS 16.5 months (95%CI 7.4-22.1)



Discontinuation due to treatment-related AEs 2.6%/Dose reductions due to treatment related AEs 4.5%
Grade ≥3 neutropenia (11.5%)/grade ≥3 hemorrhage <1%/ any grade AF <1%

Palomba L, ASH 2022; Patel ASH 2023

Phase I/II study CADANCE-101 with BGB-16673

BGB-16673, a chimeric degradation activating compound, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination

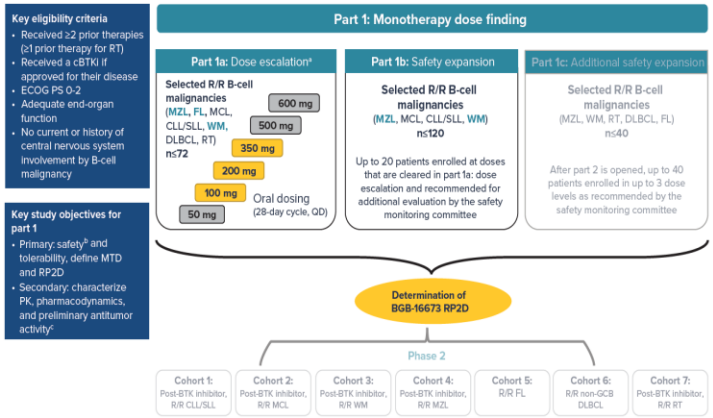


Table 4. Responses by Histology in Evaluable Patients

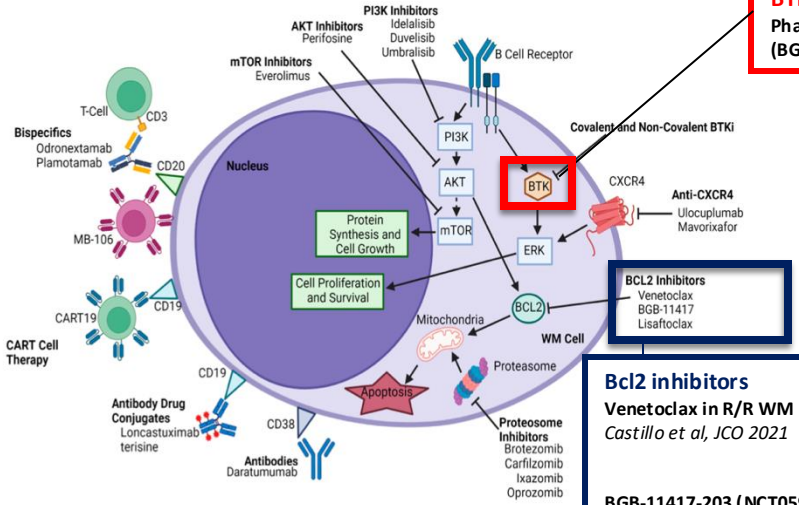
	WM (n=12)	FL (n=7)	MZL (n=5)
Best overall response, n (%)			
CR	0	1 (14)	0
VGPR	2 (17)	0	0
PR	9 (75)	3 (43)	3 (60)
SD	1 (8)	2 (29)	1 (20)
PD	0	1 (14)	1 (20)
Disease control rate, n (%)[a]	12 (100)	6 (86)	4 (80)
ORR, n (%)[b]	11 (92)	4 (57)	3 (60)
Time to first response, median (range), months[c]	0.95 (0.9-3.7)	2.71 (2.6-3.3)	2.83 (2.8-2.9)

[a] Proportion of patients with a best overall response of SD or higher . [b] Proportion of patients who achieved a best overall response better than SD .
[c] Time to first qualifying response in patients with a best overall response better than SD .
VGPR, very good PR

Most common grade ≥3 TEAEs: neutropenia (n=5, 20%), anemia (n=2, 8%), infections (n=5, 20%)

Tam CS, et al. ASH 2024; #1649

Emerging treatment options in WM



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(Yang G et al, Blood 2021)
DFCI-002-06 (dual HCK/BTK PROTAC)
(Liu S et al. ASH 2024

Bcl2 inhibitors
Venetoclax in R/R WM
Castillo et al, JCO 2021

BGB-11417-203 (NCT05952037) – Cohort 1-2-3
Multicenter, phase 2, open label therapy with Sonrotoclax (BGB-11417) in RR WM pts
Lee et al. Blood 2024 (Suppl)

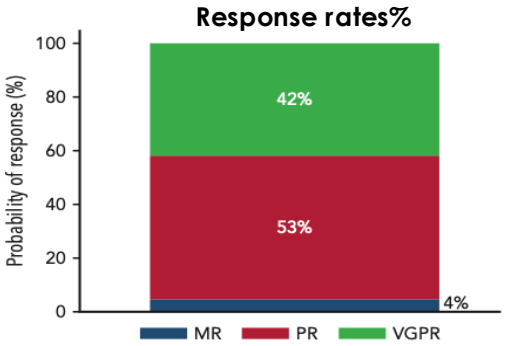
Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

Ibrutinib and venetoclax as primary therapy of WM

Cycle 1
Ibrutinib 420 mg PO QD

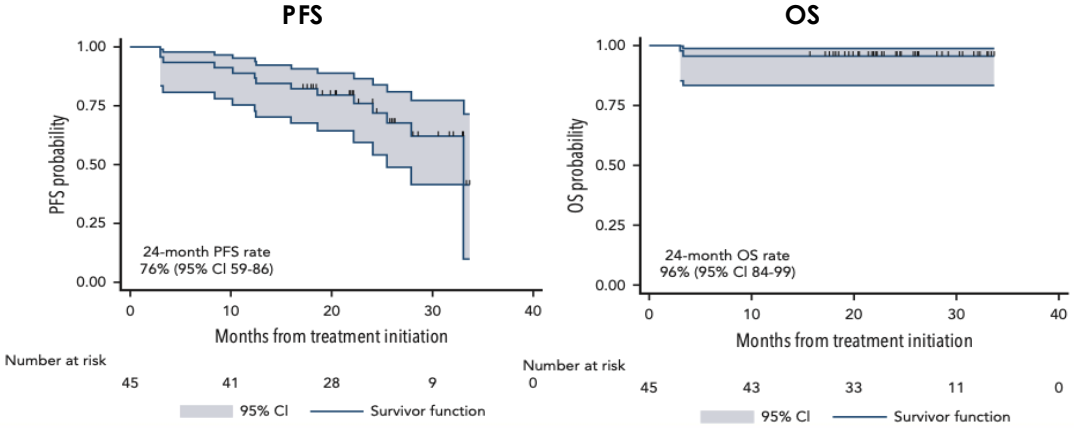
Cycle 2
Ibrutinib 420 mg PO QD
Venetoclax weekly ramp up
100-200-400 mg PO QD

Cycle 3-24
Ibrutinib 420 mg PO QD
Venetoclax 400 mg PO QD



Rationale for Combining Ibrutinib With Venetoclax

- nonoverlapping mechanism of action
- nonoverlapping toxicity profile
- synergy in preclinical studies
- reduced TLS risk by ibrutinib lead-in prior to venetoclax



AEs observed in ≥3 pts and AEs of clinical interest

Safety

Adverse events	*Grade 2*	*Grade 3*	*Grade 4*	*Grade 5*	*Total*
Anemia	1	2			3
Atrial fibrillation	1	2	1		4
Diarrhea	8	1			9
Reflux	10				10
Mucositis	7	2			9
Nausea	5				5
Neutropenia	1	10	3		14
Hyperphosphatemia	8				8
Muscle/joint pain	14	2			16
Skin rash	6				6
Ventricular arrhythmia	1		1	2	4
Laboratory TLS		2			2

Planned study therapy was stopped early due to a higher-than- expected occurrence of ventricular arrhythmia in 4/45 pts

Castillo J et al, Blood 2024

Ibrutinib and venetoclax as primary therapy of WM

Cycle 1
Ibrutinib 420 mg PO

Cycle 2
Ibrutinib 420 mg PO
Venetoclax weekly ra
100-200-400 mg PO

Cycle 3-24
Ibrutinib 420 mg PO
Venetoclax 400 mg P

Response rates%

Rationale for Combining Ibrutinib With Venetoclax

ion

n prior to venetoclax

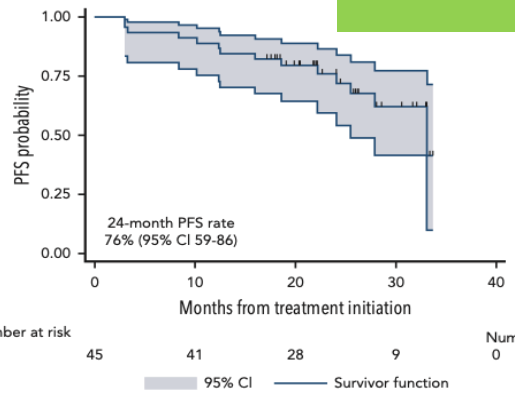
Ongoing studies with BTKi+BCL2i:

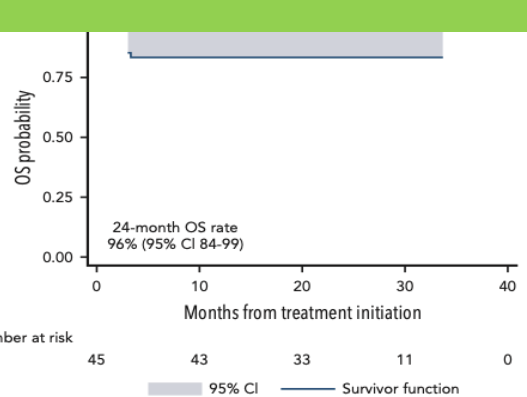
- Pirtobrutinib+Venetoclax in RR WM
- Zanubrutinib+Sonrotoclax in TN WM

s and AEs of clinical interest

		Grade 3	Grade 4	Grade 5	Total
Safety					
		2			3
		2	1		4
		1			9
					10
		2			9
					5
Neutropenia	1	10	3		14
Hyperphosphatemia	8				8
Muscle/joint pain	14	2			16
Skin rash	6				6
Ventricular arrhythmia	1		1	2	4
Laboratory TLS		2			2

PFS

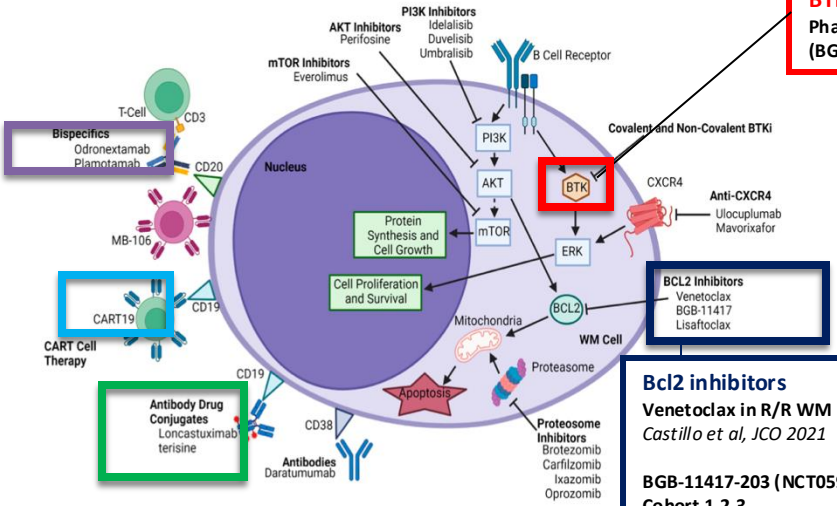




Planned study therapy was stopped early due to a higher-than- expected occurrence of ventricular arrhythmia in 4/45 pts

Castillo J et al, Blood 2024

Emerging treatment options in WM



Non covalent BTKi
Phase I/II study BRUIN
Palomba ASH 2023

BTK-degraders
Phase I/II study CADANCE-101 (BGB-16673-101). Frustaci AM, EHA 2025

PROTACs
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Single-arm, multicenter, phase 2 study to evaluate the efficacy and safety of Loncastuximab in patients with (R/R) WM/LPL
(Castillo et al. ASH 2024)

Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

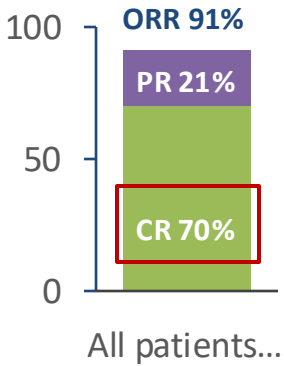
Loncastuximab tesirine monotherapy in R/R MZL

Open-label multi-institutional investigator-initiated study evaluating safety and efficacy of Lonca (6 cycles*) in R/R marginal zone lymphoma (NCT05296070)

23 patients enrolled

- Median age 65 years (45–82)
- 83% were stage III/IV
- 48% had POD24
- 39% were refractory
- Median n of prior tx 2 (1–4)

Response rates



Additional efficacy findings

93% of CRs currently maintained

64% of POD24 patients achieved CR

1 patient received prior CAR-T and achieved CR

67% 18-mo DoCR

92% 12-mo PFS

Lonca was generally well tolerated

%	Any Grade	Grade 3–4
Maculopapular rash	65	4
Increased AST	65	0
Increased ALT	61	9
Increased ALP	48	13
Neutropenia	43	17
Local oedema	43	0
Photosensitivity	30	4
Anaemia	30	4

- 1 patient discontinued treatment†
- 3 patients required Lonca dose reductions
- No treatment-related deaths occurred

Loncastuximab demonstrates clinically meaningful activity in R/R MZL patients with a robust CR rate and the safety profile is consistent with known adverse events

Lossos et al. ASH 2024; Poster #3032

Emerging treatment options in WM

Bispecific Antibodies
Epcoritamab (NCT06510491) – WM-NET2
Single-arm, multicenter, phase 2 study to evaluate the efficacy and safety of epcoritamab in patients with relapsed or refractory (R/R) WM/LPL
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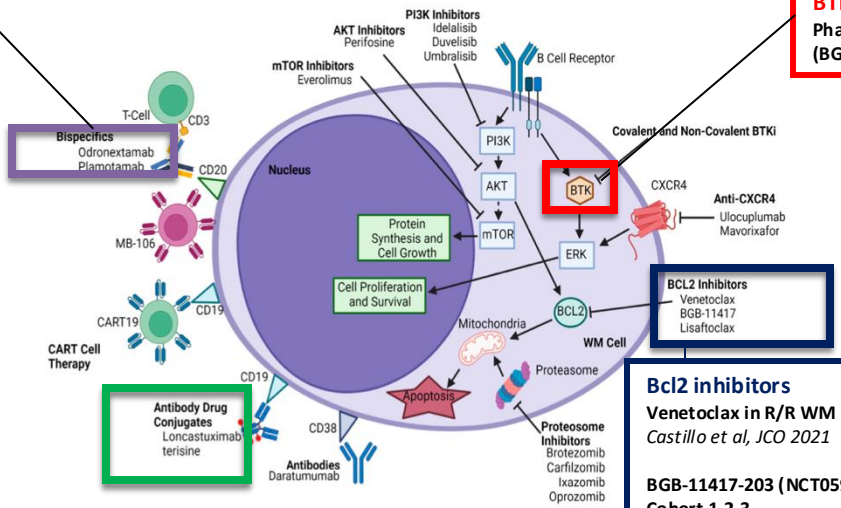

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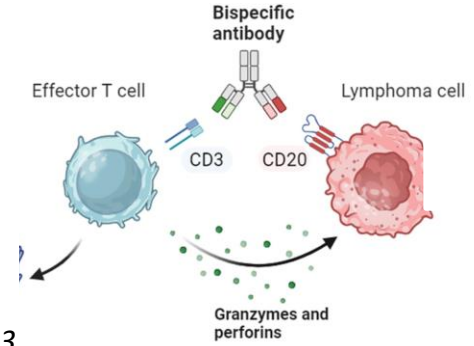
Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

Bispecific antibodies under advanced development in iNHL

- Harness the **power of a patient's own T cells**
- **Off-the-shelf** products
- T-cell–engaging BsAbs **simultaneously bind to:**
  - **CD20** expressed **on tumor cells**
  - **CD3 on T cells**, resulting in T-cell activation and triggering target-dependent tumor-cell killing



Falchi L et al, Blood 2023

Product Name	Schematic Depiction	Format	Technology	CD20:CD3 Ratio	CD3 Clone	CD20 Clone	Fc Silencing Mutations
Mosunetuzumab	CD20 CD3	IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Epcoritamab	CD20 CD3	IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34- der) (CD3ε)	7D8 (type 1 epitope, shared by ofatumumab)	L234F, L235E, D265A (no FcγR, C1q binding)
Odronextamab	CD20 CD3	IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumumab)	Modified IgG4 (no FcγRIII binding)

Odronextamab in +3L R/R MZL: ELM-2 study

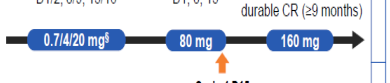
- Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105)

Key eligibility criteria
- ≥18 years old
- MZL (extranodal, splenic, or nodal subtype)*
- ECOG PS 0 or 1
- Refractory to, or relapsed after, ≥2 prior lines of systemic therapy

Primary endpoint
- ORR† by ICR

Secondary endpoints
- ORR† by local investigator
- DOR,† PFS,† and OS
- Safety and tolerability
- Patient-reported outcomes

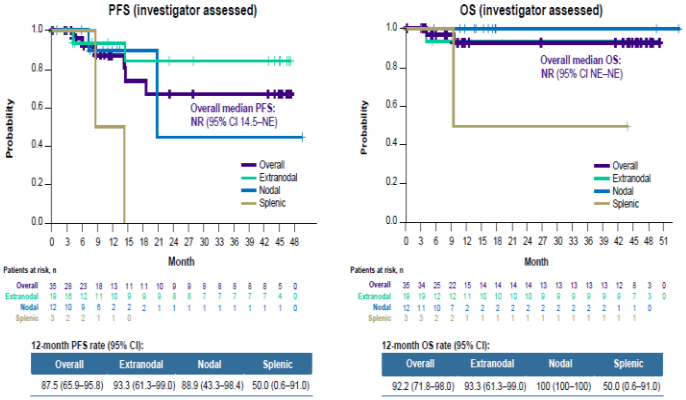
Odronextamab IV administration

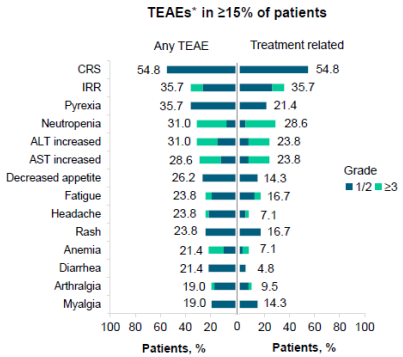


Measures taken to facilitate diverse, inclusive enrollment:
- Diverse trial sites
- Translated consents
- Extended screening windows
- Broad eligibility criteria
- Investigator training

Anti-infection prophylaxis including IVIg supplementation and antivirals was recommended, and PJP prophylaxis was mandated

Best overall response, %*	Overall (n=35)	Extranodal (n=19)	Nodal (n=12)	Splenic (n=3)
Objective response rate (ORR)	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Complete response	77.1 (95% CI 59.9–89.6)	78.9 (95% CI 54.4–93.9)	75.0 (95% CI 42.8–94.5)	100 (95% CI 29.2–100)
Partial response	0	0	0	0
Stable disease	8.6	10.5	8.3	0
Progressive disease	0	0	0	0
Not evaluable	14.3	10.5	16.7	0



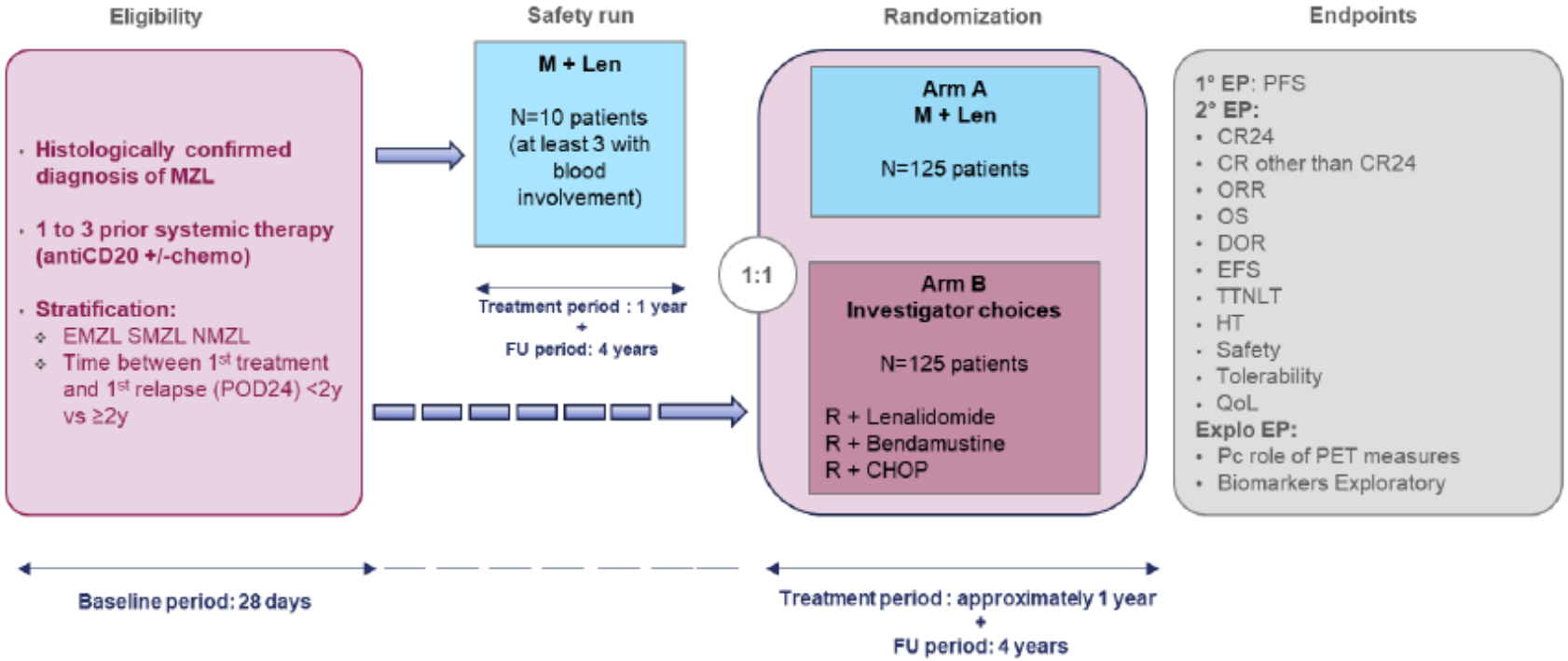


- CRS events all Grade 1/2 generally confined to C1
- No ICANS events reported
- Infections: any grade 69%, grade ≥3 24% (n grade 5)

Efficacy observed across high-risk subgroups (POD24, prior BTKi, double refractory)

Kim T et al. ASH 2020

Marsun trial: study design/overview



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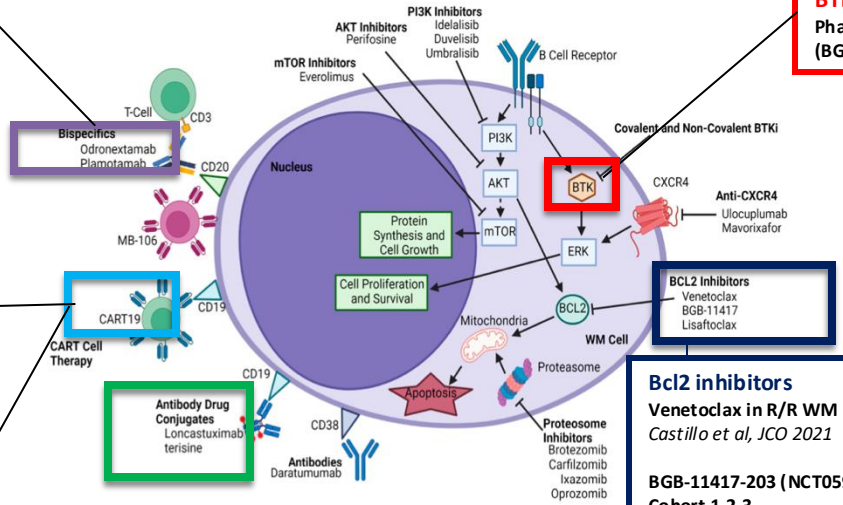

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(Yang G et al, Blood 2021)
DFCI-002-06 (dual HCK/BTK PROTAC)
(Liu S et al. ASH 2024

CAR-T cells

MB-106 (third gen CD20-directed CAR-T therapy) Phase 1/2 clinical trial with MB-106 at Fred Hutchinson Cancer Center *(Till B et al, Hemasphere. 2024; Shadman et al. 2023 ASH meeting)*

CAR-T cells

ZUMA-25 (NCT05537766)
Efficacy of Brexu-cel in rare B-cell malignancies including WM

Bcl2 inhibitors

Venetoclax in R/R WM
Castillo et al, JCO 2021

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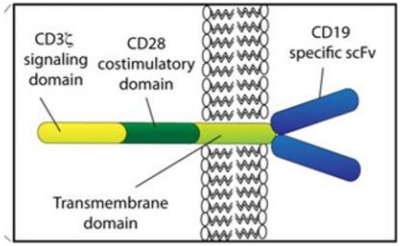
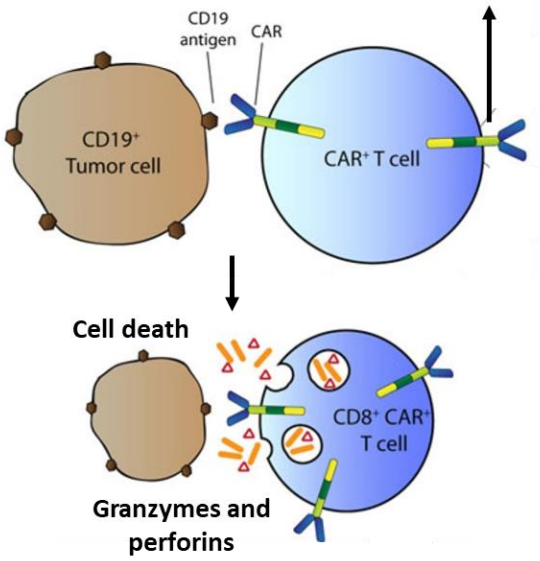
Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

CAR T-Cells *(ZUMA-5)*

CD19 CAR-T



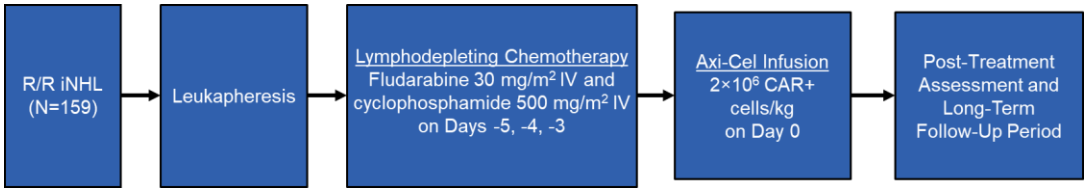


Adapted from **Davila M *et al***, *Int J Hematol 2013*

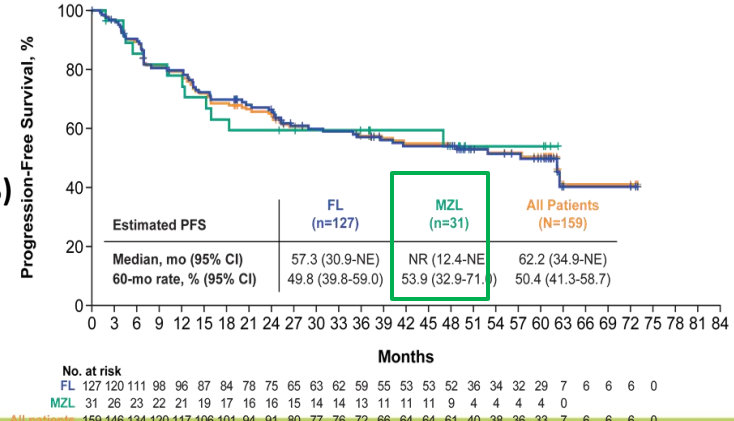
Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1-3a) or MZL (nodal or extranodal)
- ≥2 prior lines of therapy (anti-CD20 mAb combined with an alkylating agent)

Primary Endpoint: ORR (Lugano criteria)

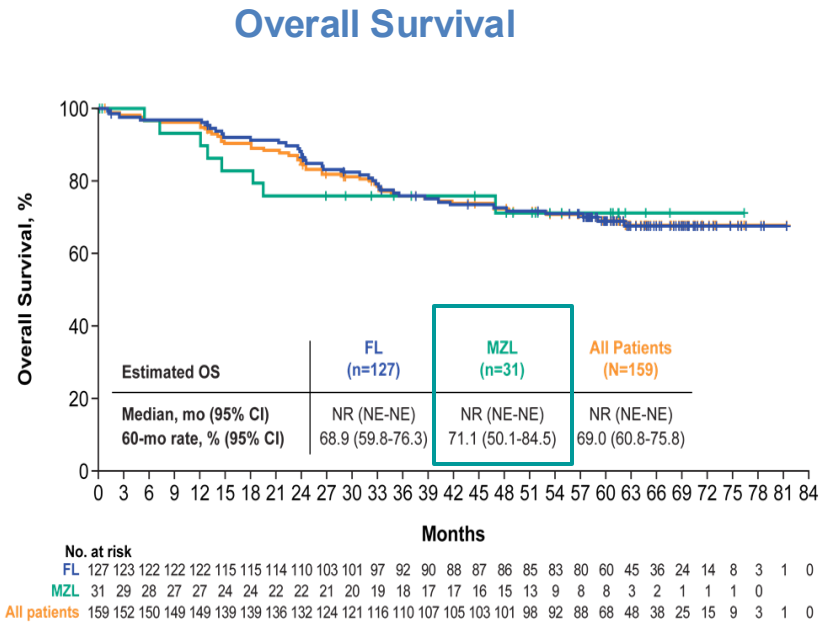


- 124 FL, **31 MZL** (POD24 50%)
- Median 3 prior lines (2-8)
- ORR rate in MZL: 75% **(CR rate 65%)**
- Grade ≥3 CRS in MZL: 9%
- **Grade ≥3 ICANS in MZL: 36%**
- No Grade 5 ICANS



Jacobson et al. Lancet Oncology 2022

CAR T-Cells: Axi-cel *(ZUMA-5, 5 year follow-up)*



n, (%)	All Patients N=152	Years Post–Axi-Cel Infusion 0-1	1-2	2-3	3-4	4-5	>5
Patients who died	46 (30)	10 (7)	15 (10)	11 (7)	6 (4)	3 (2)	1 (1)
Relapse mortalities							
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)	0
Non-PD after PD	9 (6)	1 (1)	3 (2)	4 (3)	1 (1)	0	0
Non-relapse mortalities							
Secondary malignancy[a]	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0	0
Cardiac-related	3 (2)	0	1 (1)	0	1 (1)	0	1 (1)
Infection-related[b]	11 (7)	2 (1)	2 (1)	4 (3)	1 (1)	2 (1)	0
Other[c]	3 (2)	1 (1)	2 (1)	0	0	0	0

- **Median OS** was **NR** in **MZL**; the 60-month OS rate in MZL was 71.1%

Neelapu et al. ASH 2024 Abstract #864

Conclusions and perspectives

Chemo-free treatment options are available in WM and MZL and further chemo-free therapies are under investigation with promising results

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Open issues/objectives with expanding treatment options:

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- should chemo-free regimens be used frontline instead of CIT in WM?

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- predictive tools for selection of the best treatment for each patient

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Open issues/objectives with expanding treatment options:

- optimal sequencing of therapies
- should chemo-free regimens be used frontline instead of CIT in WM?
- predictive tools for selection of the best treatment for each patient
- risk-adapted approach (higher risk in iNHL acceptable only for higher risk patients)


The End