Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

¿Cómo tratamos a los pacientes con Macroglobulinemia de Waldenstrom?

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Ramón García-Sanz

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HEMATOLOGÍA

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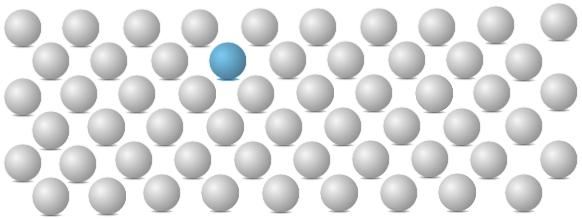
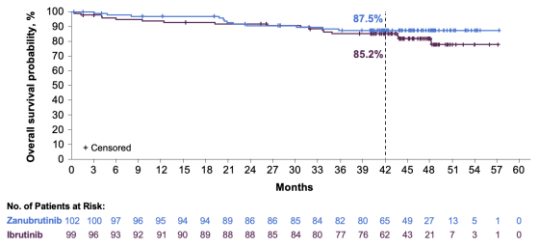
Waldenström's Macroglobulinemia

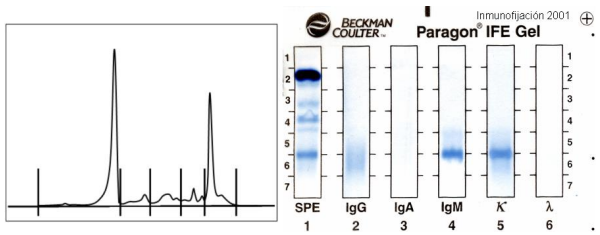


Low frequency: 6% of all M-gammopathies:
2-5 cases/mill. inh/yr (GEM, 3'1) 2500 cases/yr in Europe

Advanced age
Median: 71. Male/Female: 2:1

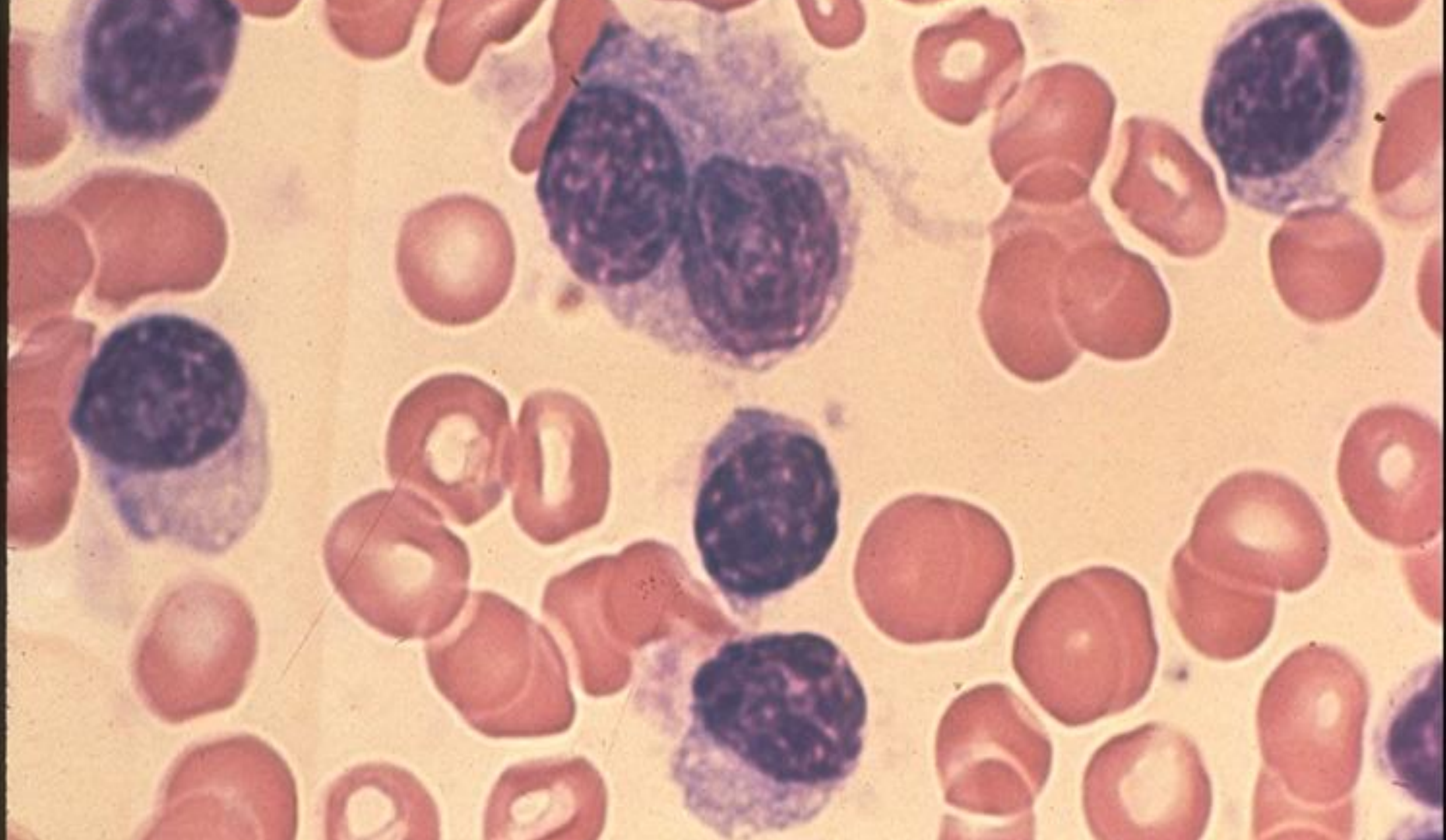


Natural history
Indolent disease, Median survival: 11 years
1/3 die for other causes; 2/3 die of WM

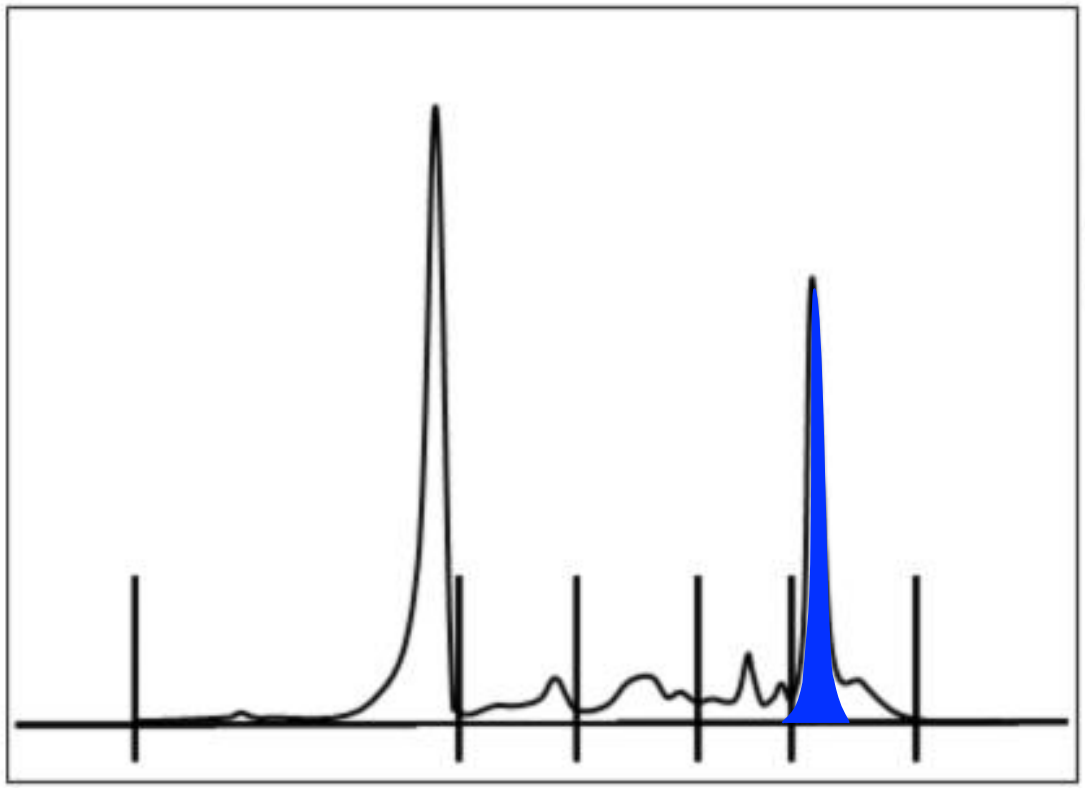


High therapeutic efficacy

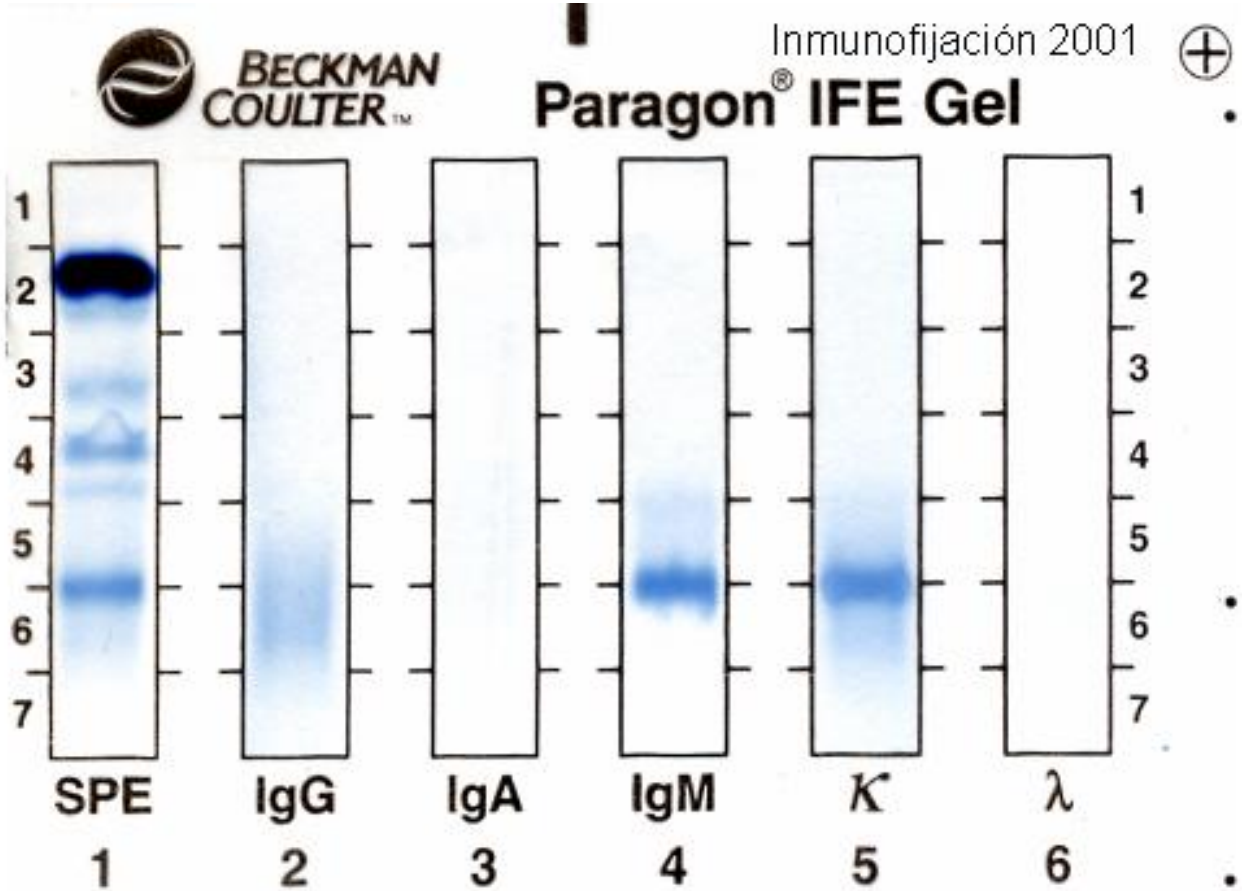
Biological interest



Protein Electrophoresis

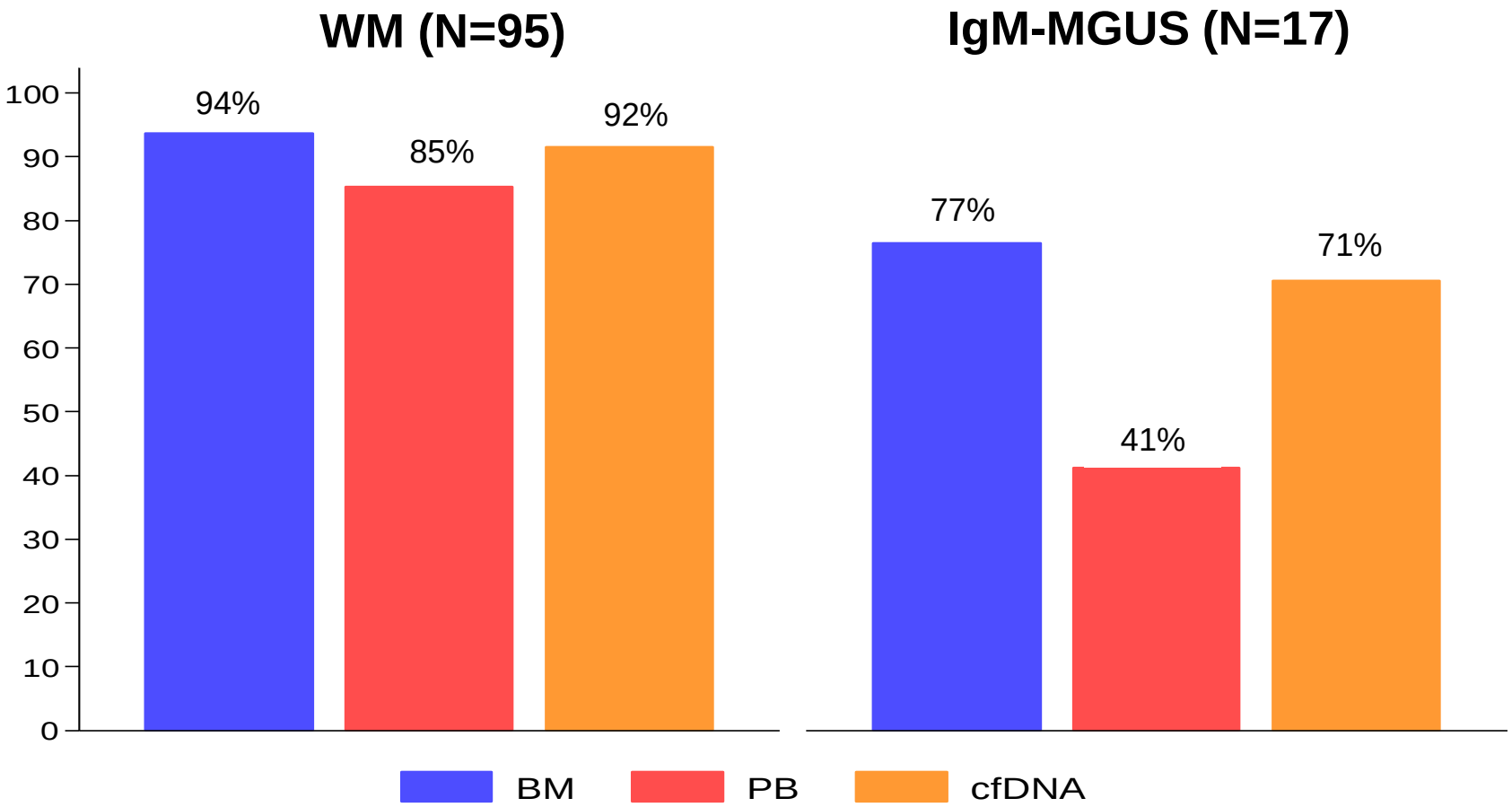


Immunofixation



MYD88^{L265P} rate in WM vs IgM-MGUS

MGUS showed significantly lower rates than WM in all tissues, but…



MYD88^{L265P} is present in most cases of IgM-MGUS

Ferrante et al, Blood (2023) 142 (Supplement 1): 1621

WM Treatment: So many possibilities

So many possibilities…

Chemo-Immunotherapy

BTK inhibitors

Other drugs

Chemo-Immunotherapy

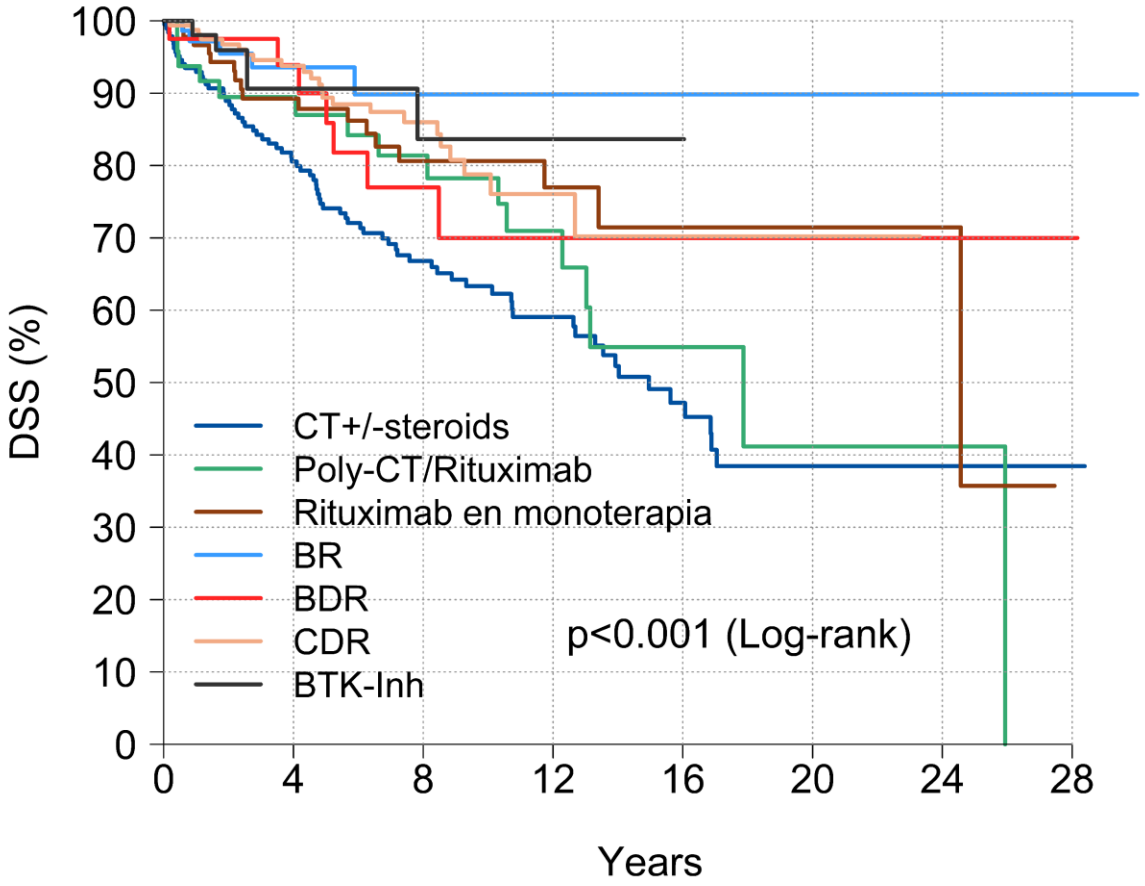
- **Rituximab combinations:**
  - Cyclophosphamide … CD-R
  - Bendamustine…….…. Benda-R
  - Anthracyclines ……. CHOP-R
  - Bortezomib…… BD-R

ORR >80%
PFS >3 yr

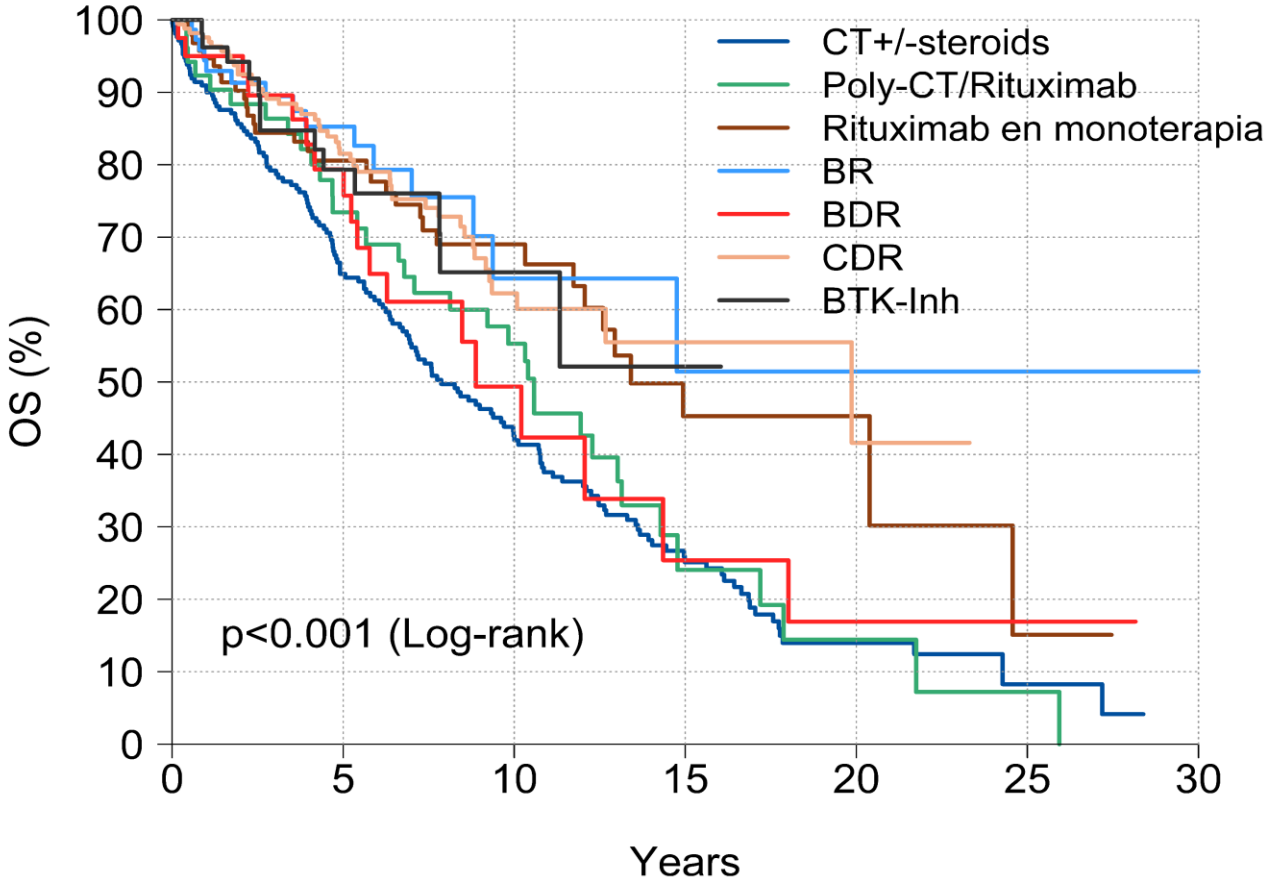
- **Monotherapy:**
  - Rituximab alone
  - Chlorambucil
  - Oral Fludarabine

Survival of WM in Spain according to first line regimen

Disease-Specific Survival

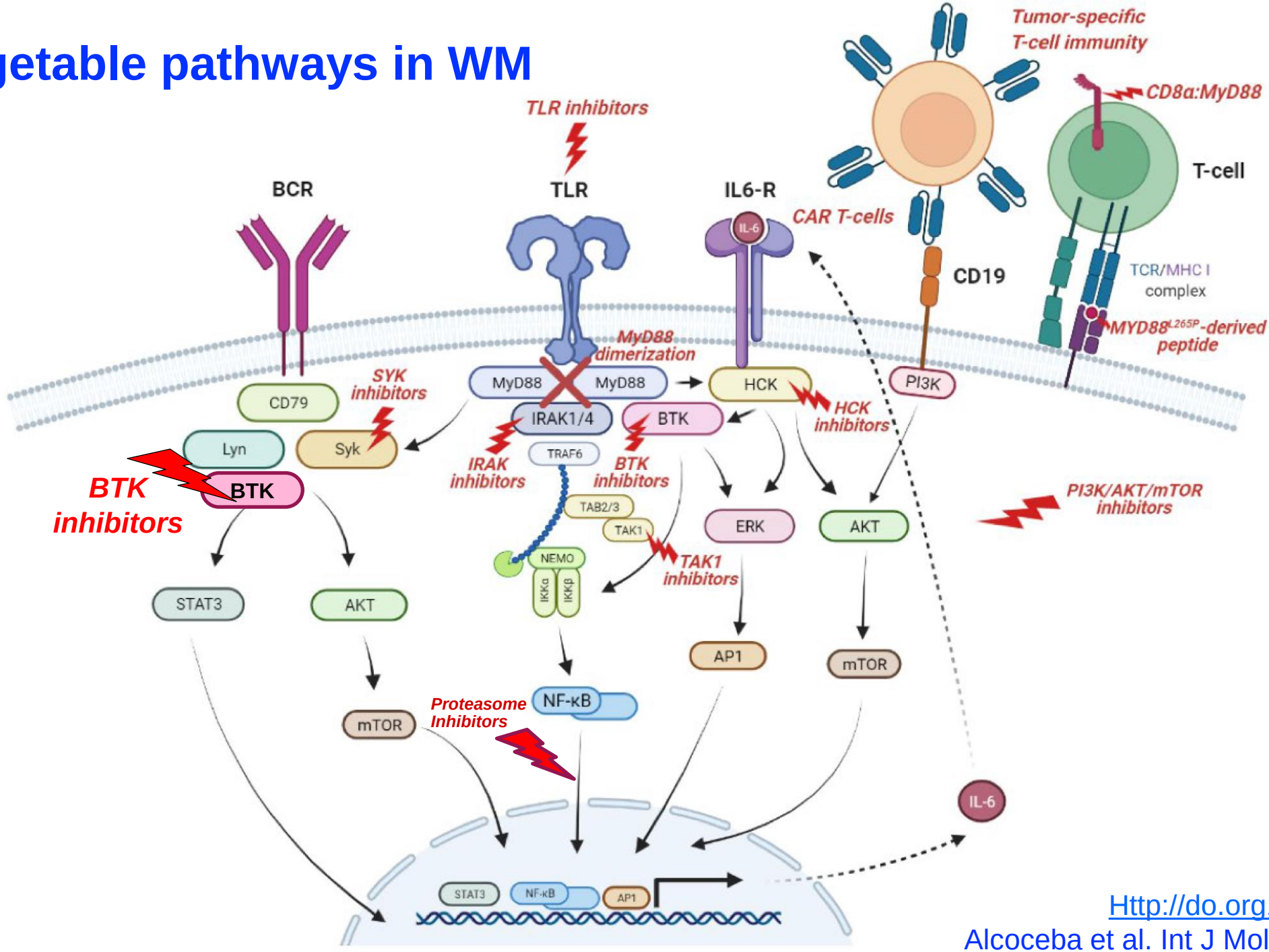


Overall Survival



Askari et al, IWWM-12, Prague, 2024

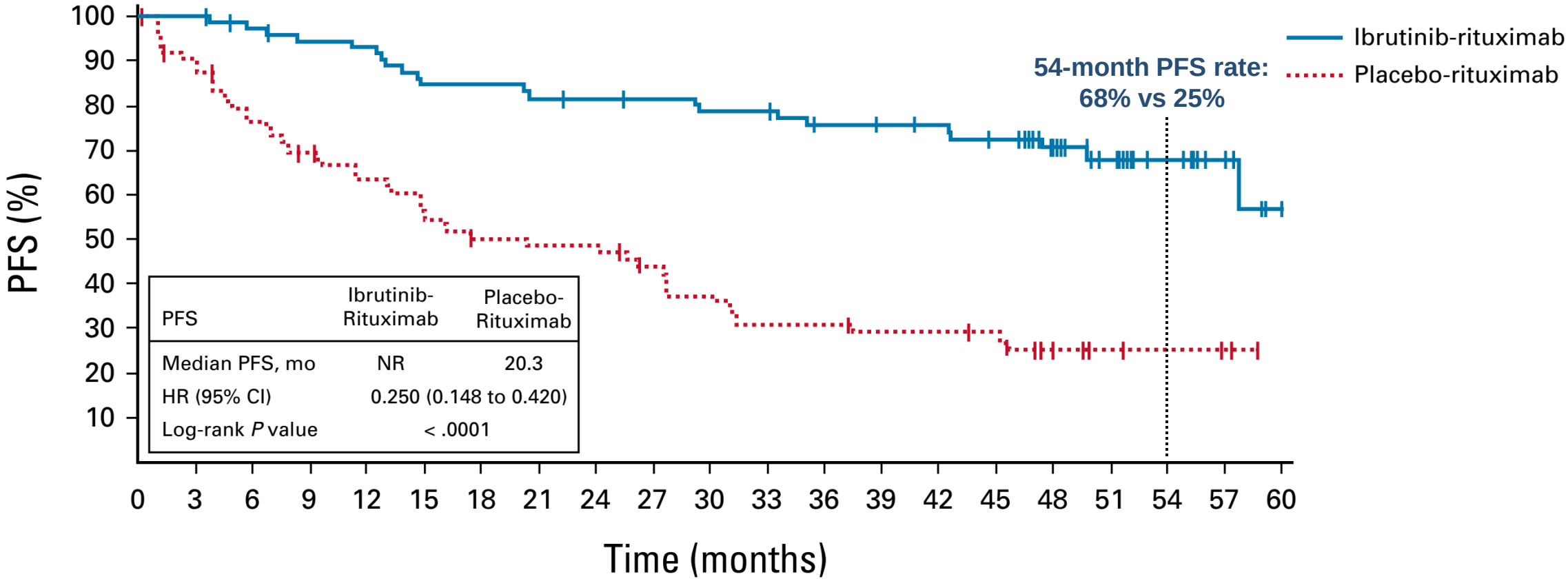
Targetable pathways in WM



Http://do.org10.3390/ijms23105570

Alcoceba et al. Int J Mol Sci. 2022 16;23:5570.

Median progression-free survival was not reached with 5 years of Ibrutinib-RTX – ITT population



No. at risk:

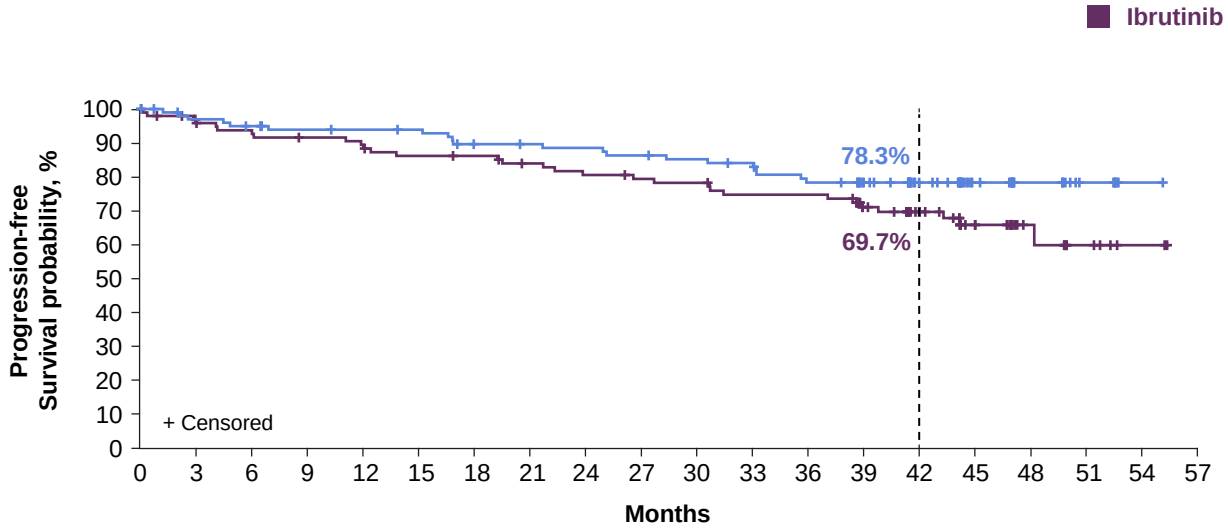
Ibrutinib-rituximab	75	73	69	67	66	60	60	58	57	56	54	54	46	48	47	44	32	22	15	7
Placebo-rituximab	75	64	54	48	43	39	33	32	31	27	23	19	19	17	17	15	7	4	3	2

Buske et al., J Clin Oncol 2022 Jan 1;40(1):52-62[12]

ASPEN – Long-term follow-up

Progression-Free and Overall Survivals in ITT Population

Progression-Free Survival[a]

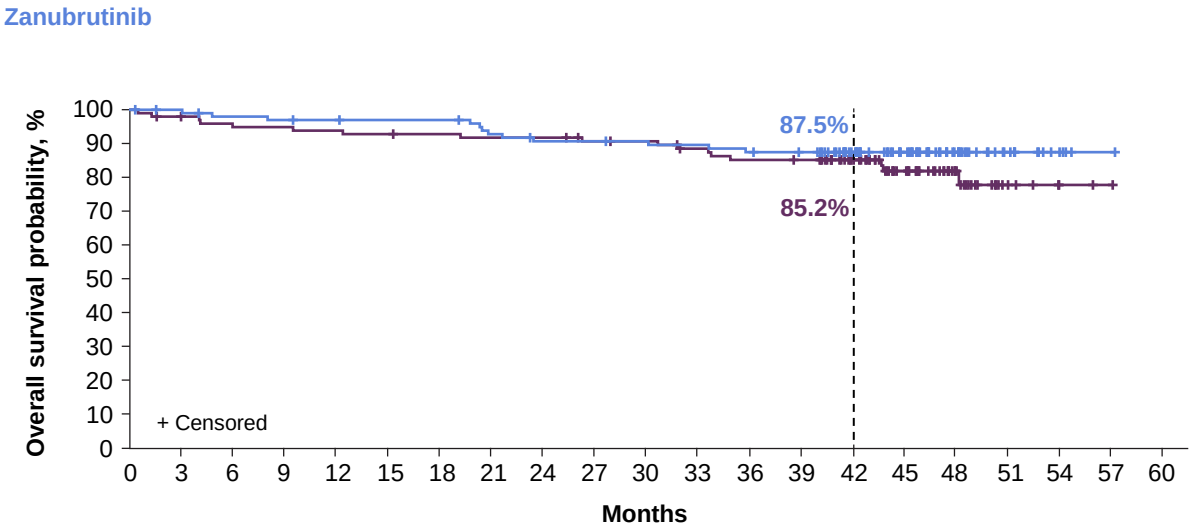


No. of Patients at Risk:

Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

	Zanubrutinib	Ibrutinib
Events, n (%)	20 (19.6)	30 (30.3)
HR (95% CI)	0.63 (0.36, 1.12)	

Overall Survival[a]



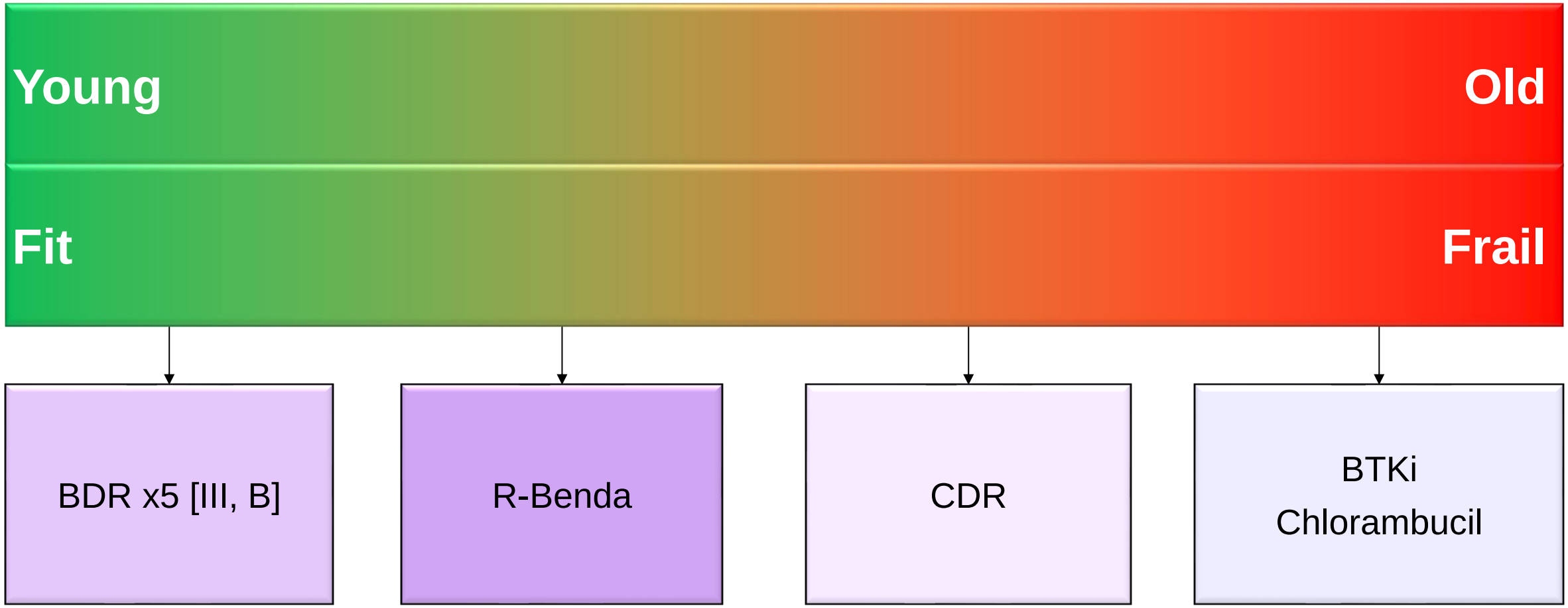
No. of Patients at Risk:

Zanubrutinib	102	100	97	96	95	94	94	89	86	86	85	84	82	80	65	49	27	13	5	1	0
Ibrutinib	99	96	93	92	91	90	89	88	88	85	84	80	77	76	62	43	21	7	3	1	0

	Zanubrutinib	Ibrutinib
Events, n (%)	12 (11.8)	17 (17.2)
HR (95% CI)	0.75 (0.36, 1.59)	

Images adapted from Dimopoulos MA et al. JCO 2023
Data cutoff: October 31, 2021. [a]By investigator assessment.
CI=confidence interval, HR=hazard ratio, ITT=intention-to-treat, OS=overall survival, PFS=progression-free survival.
Dimopoulos MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

Symptomatic Waldenström Macroglobulinemia: 1st line



BDR: Bortezomib, Dexamethasone & Rituximab; R-Benda: Rituximab & Bendamustine; CDR: cyclophosphamide, dexamethasone y Rituximab; BTKi: Bruton Tyrosine Kinase Inhibitors

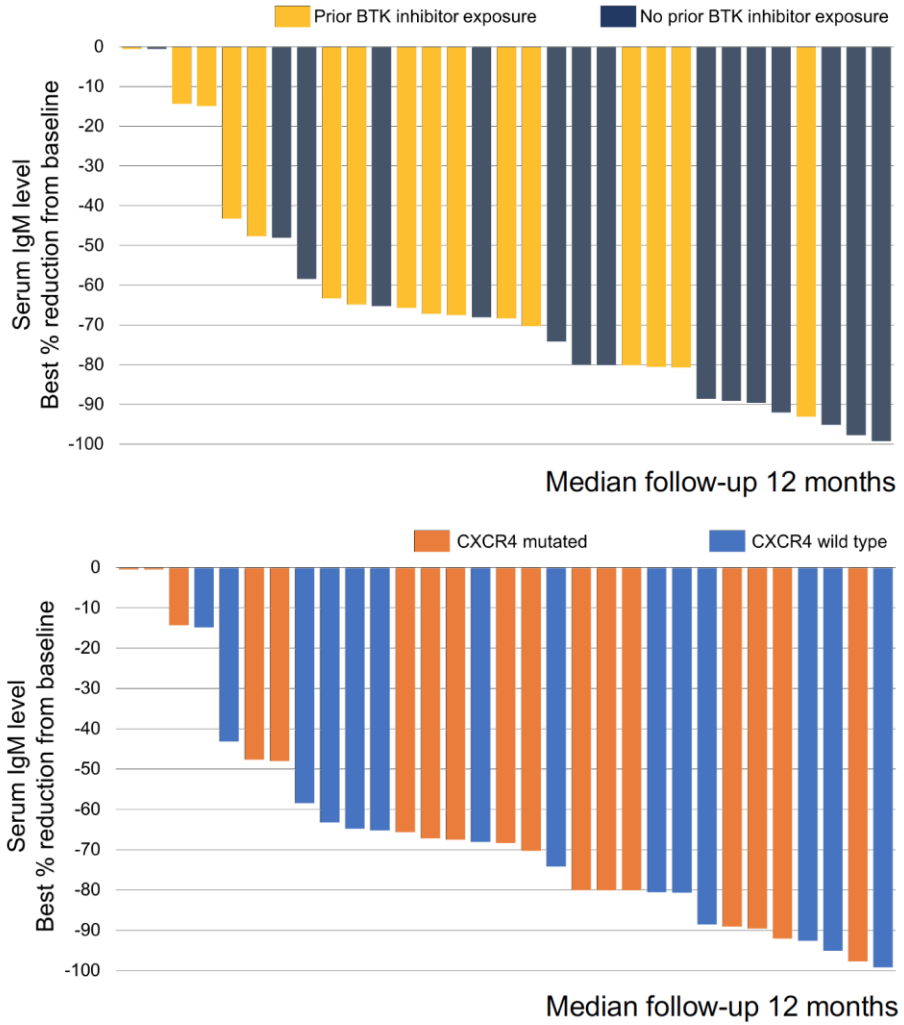
García-Sanz R, Opinión personal

Other possibilities

Venetoclax

Multicenter Prospective Phase II Study in Patients with Previously Treated WM

- 200 mg/day D1-7 → 400 mg/day D8-14 → 800 mg/day, max 2y.
- 30 sWM, 66y (39-80), 57% men. MYD88^{L265P} 100%, CXCR4^{WHIM} 53%.
- Prior therapies 2 (1-10), 50% with prior BTK-i exposition.
- VGPR 17%, PR 63%, mR 7% and SD in 13% (no PD)
- **ORR 87% & MRR 80%.**
- ORR in refractory vs. relapsed diseas: 57% vs. 95% (p=0.01).
- Time to response was 9w; slower with for BTK-i exposed (19 vs. 6w; p=0.02).
- No clinical TLS, only one case of laboratory TLS
- **G3-4 neutropenia** occurred in 11 patients, responding to G-CSF.
- Other G3 AEs were <5%



Castillo et al, Blood 2018 132:2888

Safety and Efficacy Results of a Phase 1 Study of the Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) for Relapsed/Refractory Waldenström Macroglobulinemia

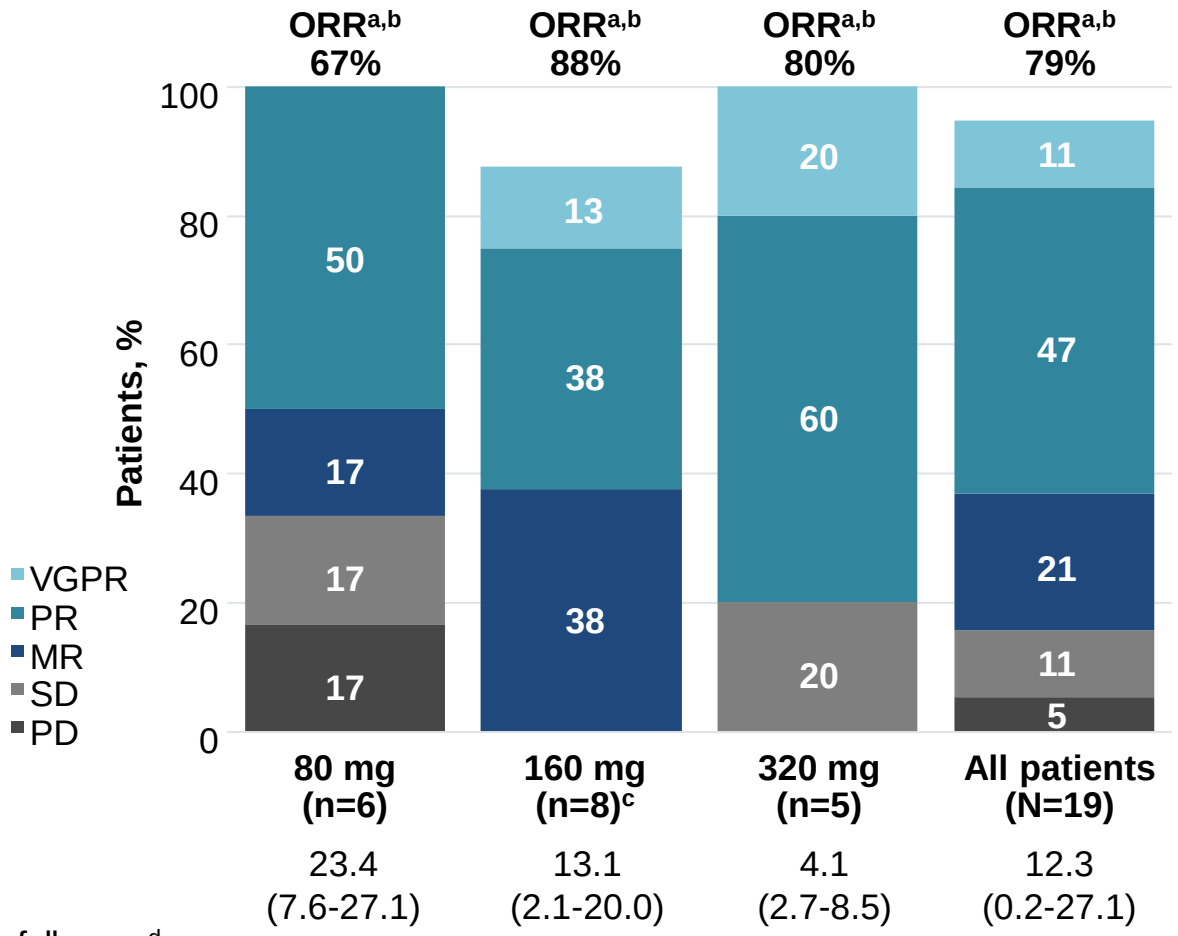
Ramón García-Sanz,[1] Chan Y. Cheah,[2-4] Constantine S. Tam,[5] Mazyar Shadman,[6,7] Sophie Leitch,[8] Christopher D'Angelo,[9] Lydia Scarfo,[10] Yiqian Fang,[11] Sheel Patel,[12] Wei Ding,[12] Haiyi Guo,[11] Peter Browett,[13]

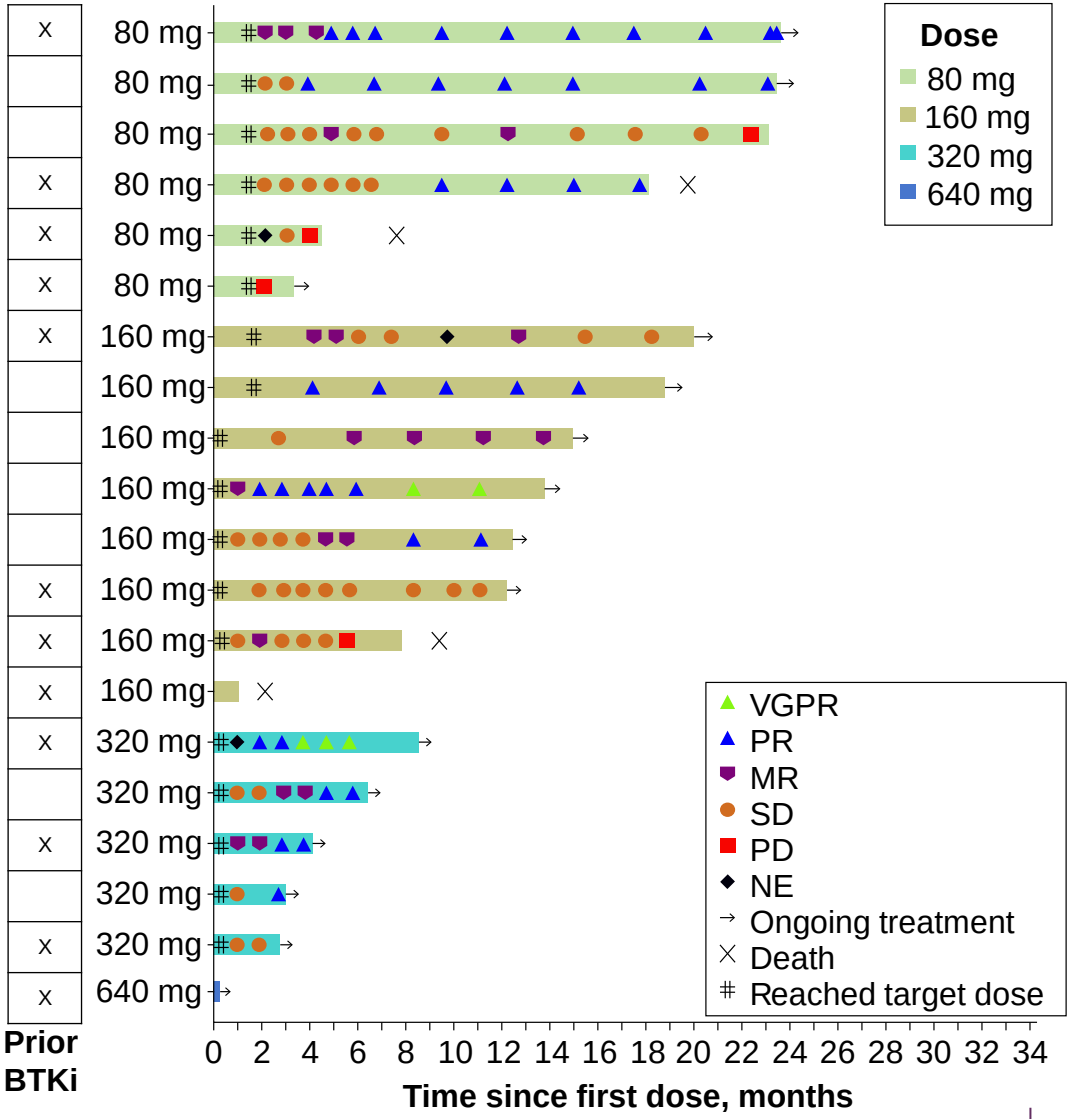
[1]Hospital Universitario de Salamanca, Salamanca, Spain; [2]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [6]Fred Hutchinson Cancer Center, Seattle, WA, USA; [7]University of Washington, Seattle, WA, USA; [8]Te Whatu Ora Health New Zealand, Waitemata, Auckland, New Zealand; [9]University Of Nebraska Medical Center, Omaha, NE, USA; [10]Università Vita Salute and IRCCS Ospedale San Raffaele, Milano, Italy; [11]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [12]BeiGene USA, Inc, San Mateo, CA, USA; [13]Auckland City Hospital, Grafton, Auckland, New Zealand

Presented at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12); October 17-19, 2024; Prague, Czech Republic

Data originally presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain. Abstract P1110

Promising Single-Agent Antitumor Activity Across Dose Levels





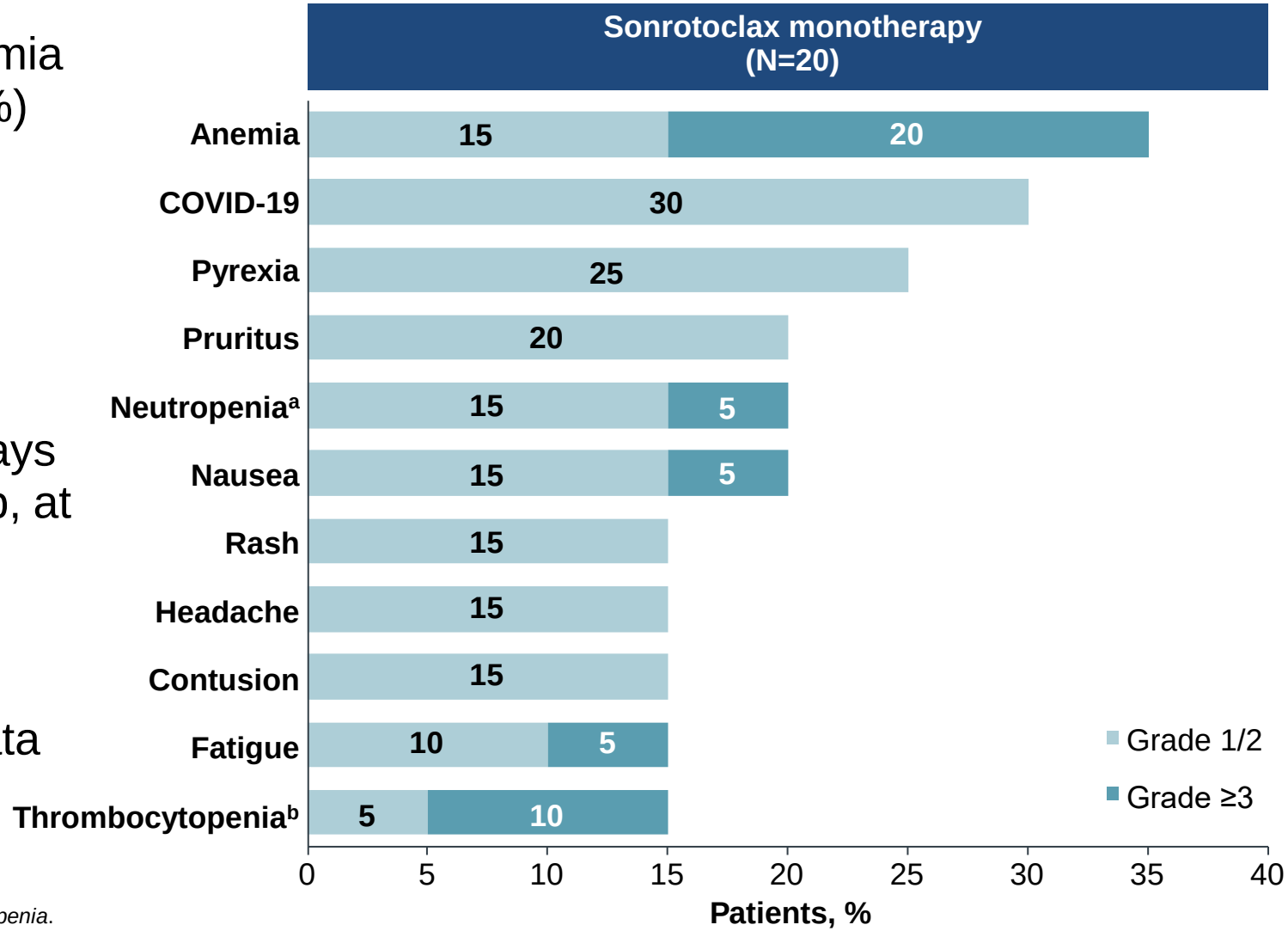
[a] Responses were assessed per modified Owens 2013 criteria. [b] ORR was defined as response of MR or better. [c] One patient (160-mg dose) died due to a COVID-19 infection before a post-baseline response assessment. [d] For all patients as treated (N=20).

BTKi, BTK inhibitor; MR, minor response; NE, not evaluable; VGPR, very good partial response.

García-Sanz et al, presented at the XIIth international Workshop of WM, Prague, sep 2024

TEAEs in ≥3 Patients

- Most common any-grade TEAEs: anemia (35%), COVID-19 (30%), pyrexia (25%)
- Most common grade ≥3 TEAE: anemia (20%)
- No laboratory or clinical TLS
- One DLT in at (160-mg dose): grade 3 febrile neutropenia; resolved after 2 days without dose reduction during ramp-up, at the dose of sonrotoclax 10 mg
- Dose escalation is ongoing at 640 mg, with no MTD reached at the time of data cut-off

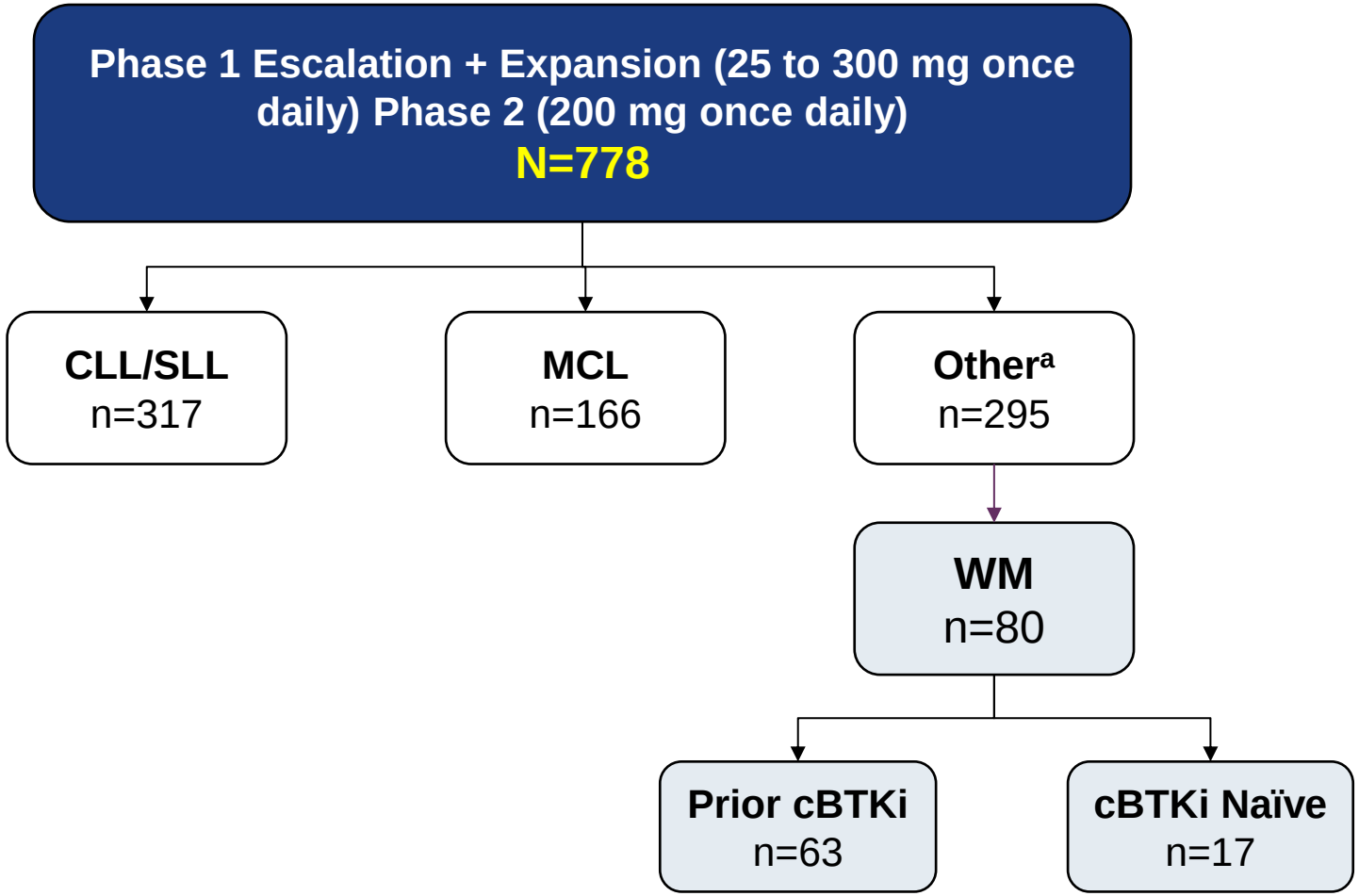


[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
TEAE: treatment-emergent adverse events. TLS: Tumor lysis syndrome. DLT: dose limnitinbg toxicity; MTD Maximum tolerable dose

García-Sanz et al, presented at the XIIth international Workshop of WM, Prague, sep 2024

Pirtobrutinib: non-covalent BTKi

Phase 1/2 BRUIN study: Design, Eligibility and enrollment



Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

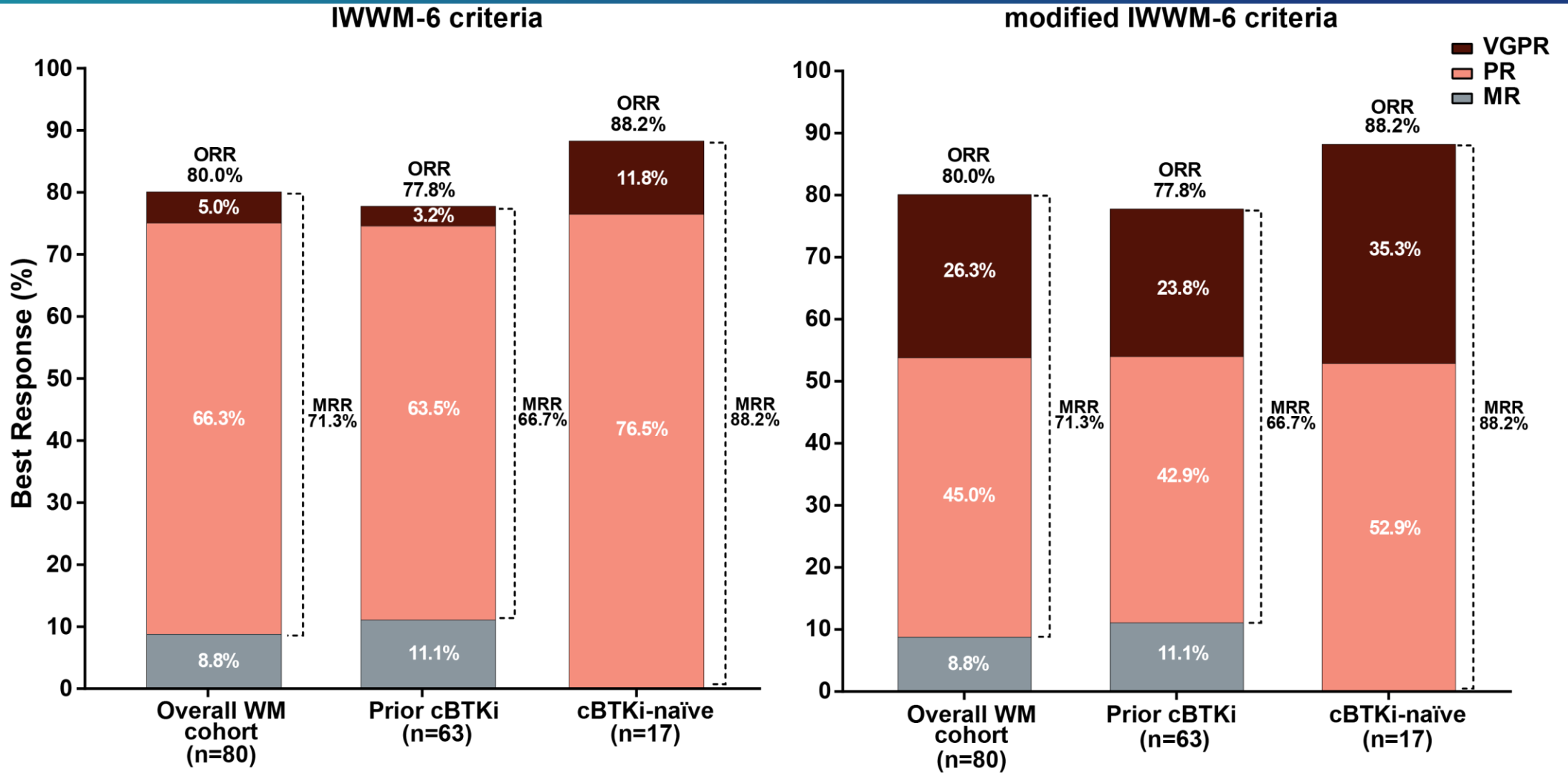
Key Endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Investigator-assessed ORR and MRR assessed by IWWM-6 and modified IWWM-6 criteria, PFS, OS, and Duration of Major Response

Updated data with a median study follow-up of 22 months

Data cutoff date of 05 May 2023. [a]Other includes DLBCL, follicular lymphoma, marginal zone lymphoma, B-cell prolymphocytic leukemia, hairy cell leukemia, primary central nervous system lymphoma, Richter transformation, and other transformations. Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IWWM, International Workshop on Waldenstrom macroglobulinemia; MCL, mantle cell lymphoma; MRR, major response rate; MTD, maximum tolerated dose; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose; SLL, small lymphocytic lymphoma; WM, Waldenstrom macroglobulinemia.

Pirtobrutinib Efficacy in WM Patients

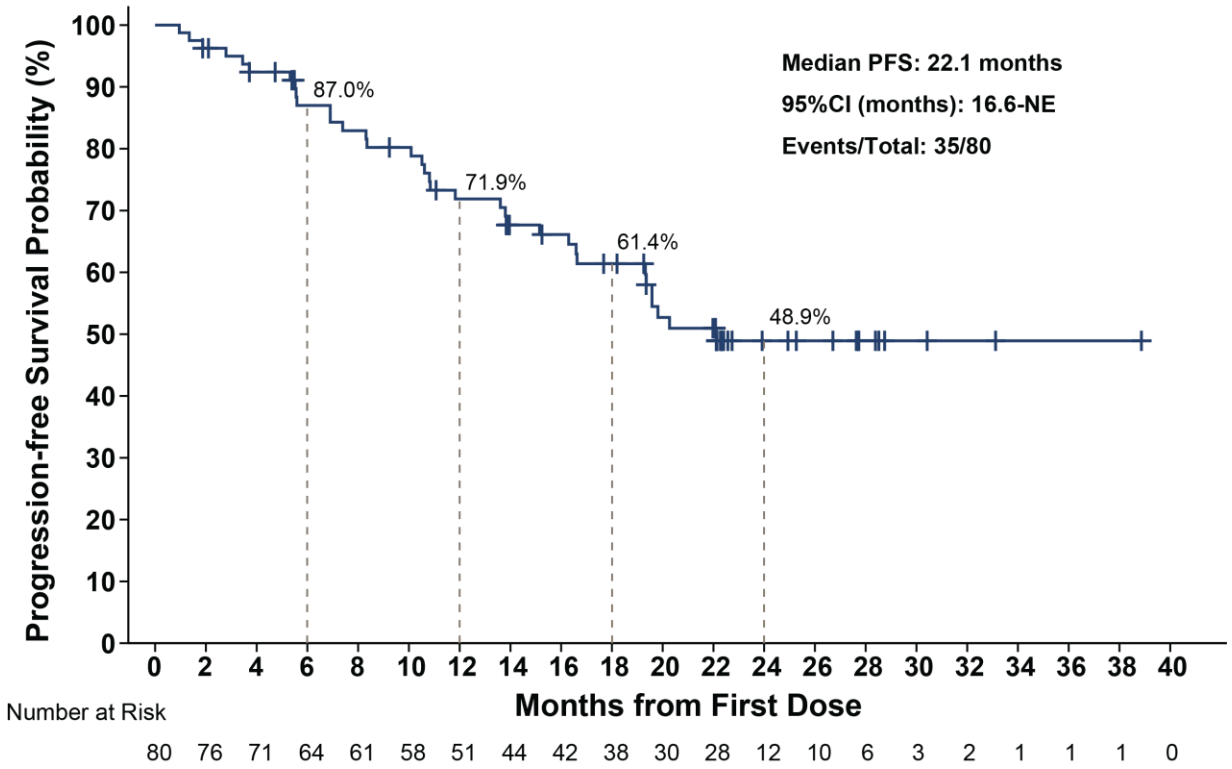


Data cutoff date of 05 May 2023. Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; IWWM-6, Sixth International Workshop on Waldenström Macroglobulinemia; MR, minor response; MRR, major response rate; ORR, overall response rate; PR, partial response; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Palomba et al, presented at the XIIth international Workshop of WM, Prague, sep 2024

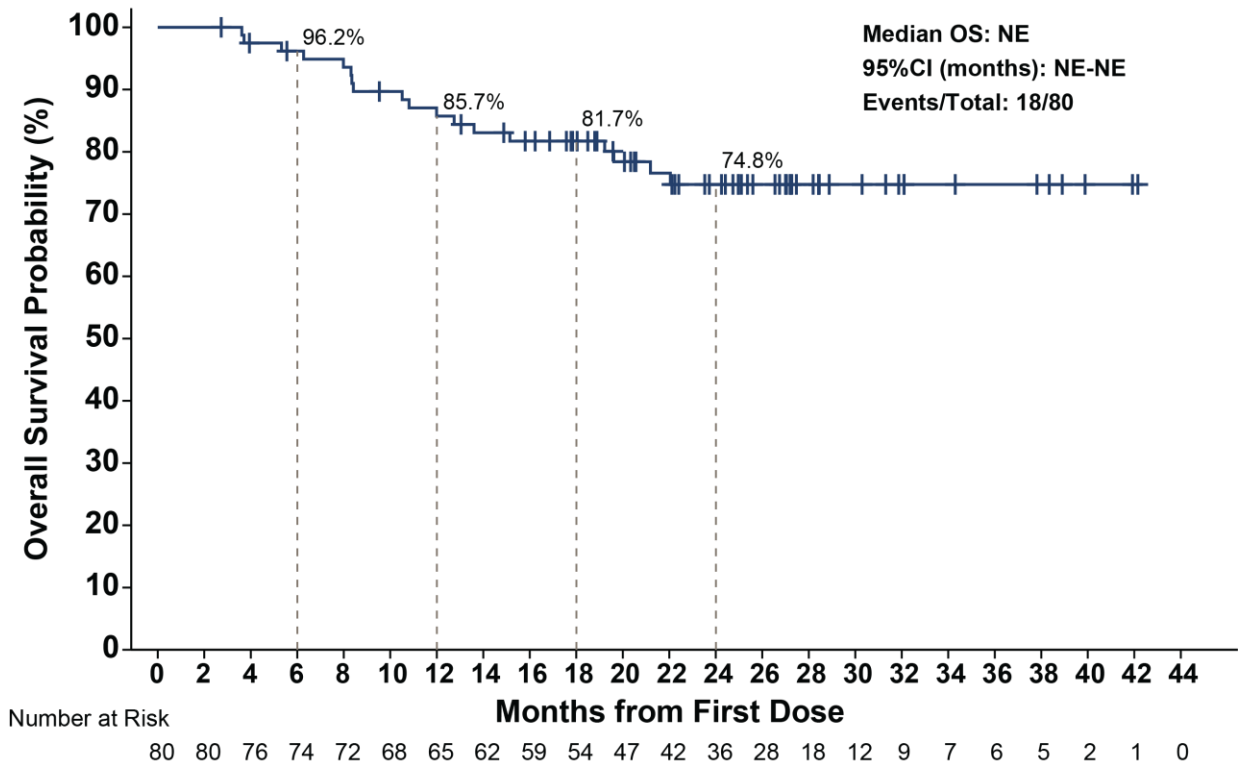
Pirtobrutinib Progression-Free Survival and Overall Survival

Progression-Free Survival



- The median follow-up was 22 months (IQR, 19.3–26.7)
- The PFS rate at 18 months was 61.4% (95%CI, 49.1-71.6)

Overall Survival

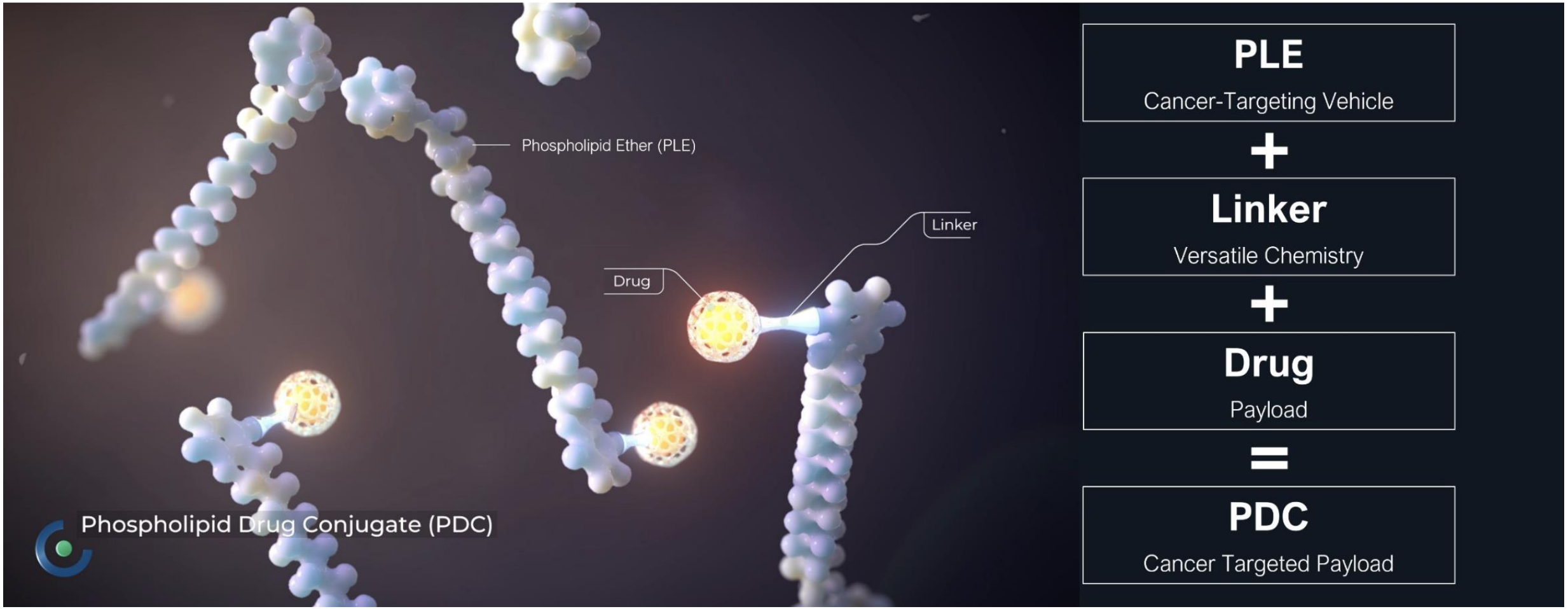


- The median follow-up was 25 months (IQR, 19.6-28.4)
- The OS rate at 18 months was 81.7% (95% CI 71.1–88.7)

Data cutoff date of 05 May 2023.

Palomba et al, presented at the XIIth international Workshop of WM, Prague, sep 2024

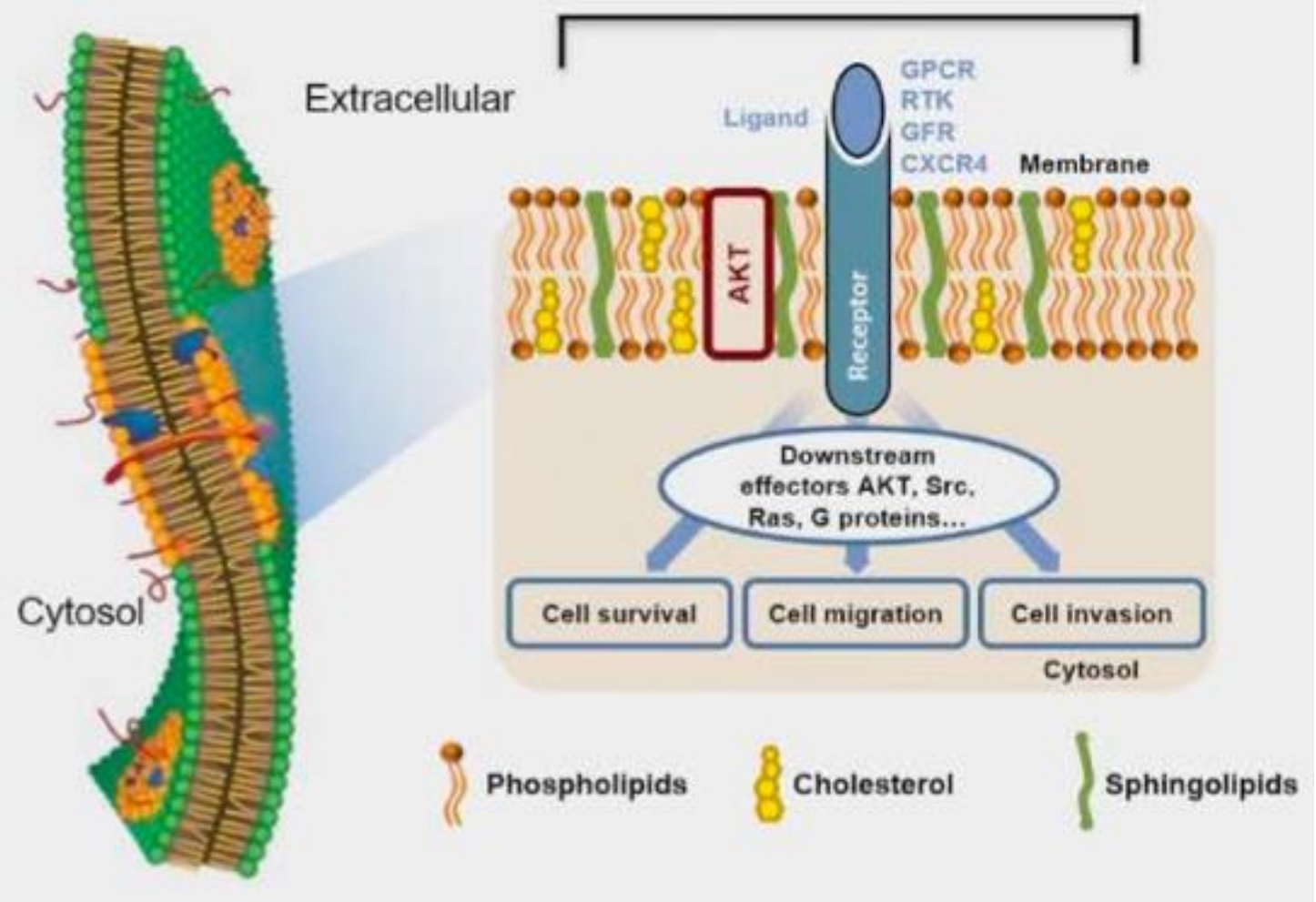
CLOVER WaM
IOPOFOSINE i-132 clinical profile



https://www.cellectar.com/platform

(Islas Lipídicas) Lipid Rafts: Novel Approach to Targeting Cancer

- Highly ordered, tightly regulated microdomains, enriched in colesterol and sphingolipids
- Signaling hubs: coalesce GPI-anchored proteins, signaling proteins and receptors
- Facilitators of (anaerobic) beta-oxidation
- Upregulation and stabilization in cancer:
  - Normal cells = nanostructures (~25nm)
  - Cancer cells = coalesced raft (100uM)
  - Stabilized (days vs microseconds)



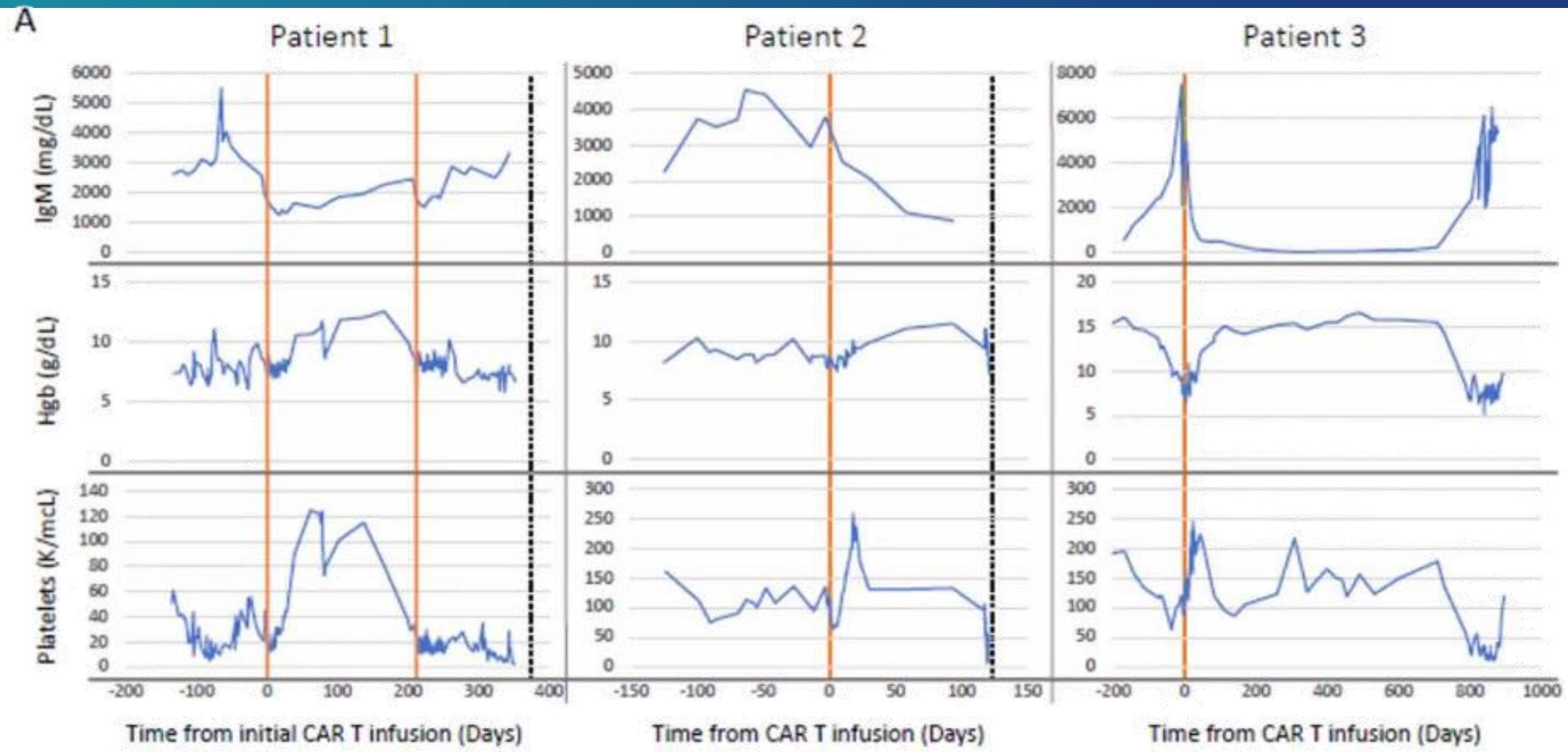
Ailawadhi et al. *Blood* (2024) 144 (Suppl 1): 861. https://doi.org/10.1182/blood-2024-200277

CLOVER-WaM: Efficacy Analysis

Endpoint	(n=55)
Response rates, n **(%)**	
MRR: CR, VGPR, PR	31 **(58.2%)**
ORR: CR, VGPR, PR, MR	46 **(83.6%)**
CBR: CR, VGPR, PR, MR, SD	54 **(98.2%)**
CR/VGPR	4 **(7.3%)**

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; IgM, immunoglobin M; mF/U, median follow-up; MR, minor response; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, standard deviation; VGPR, very good partial response

CD19-directed autologous CAR-T cells (MSKCC 1928z)

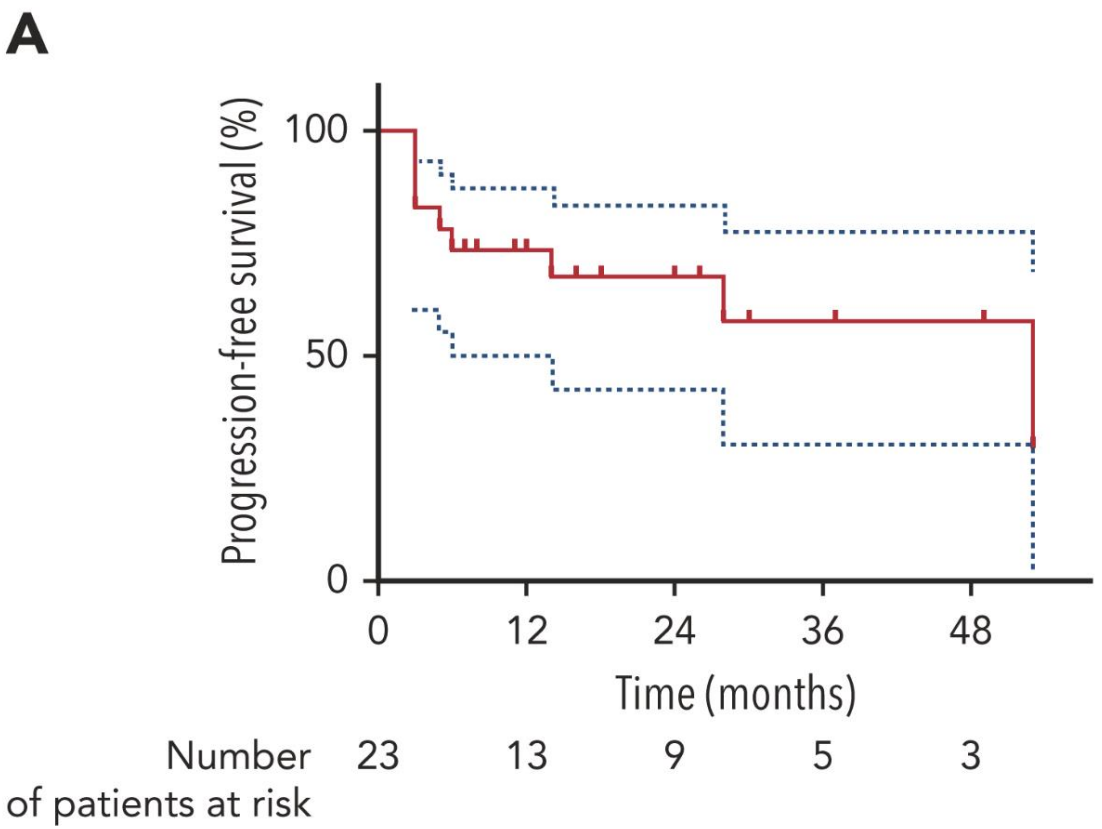


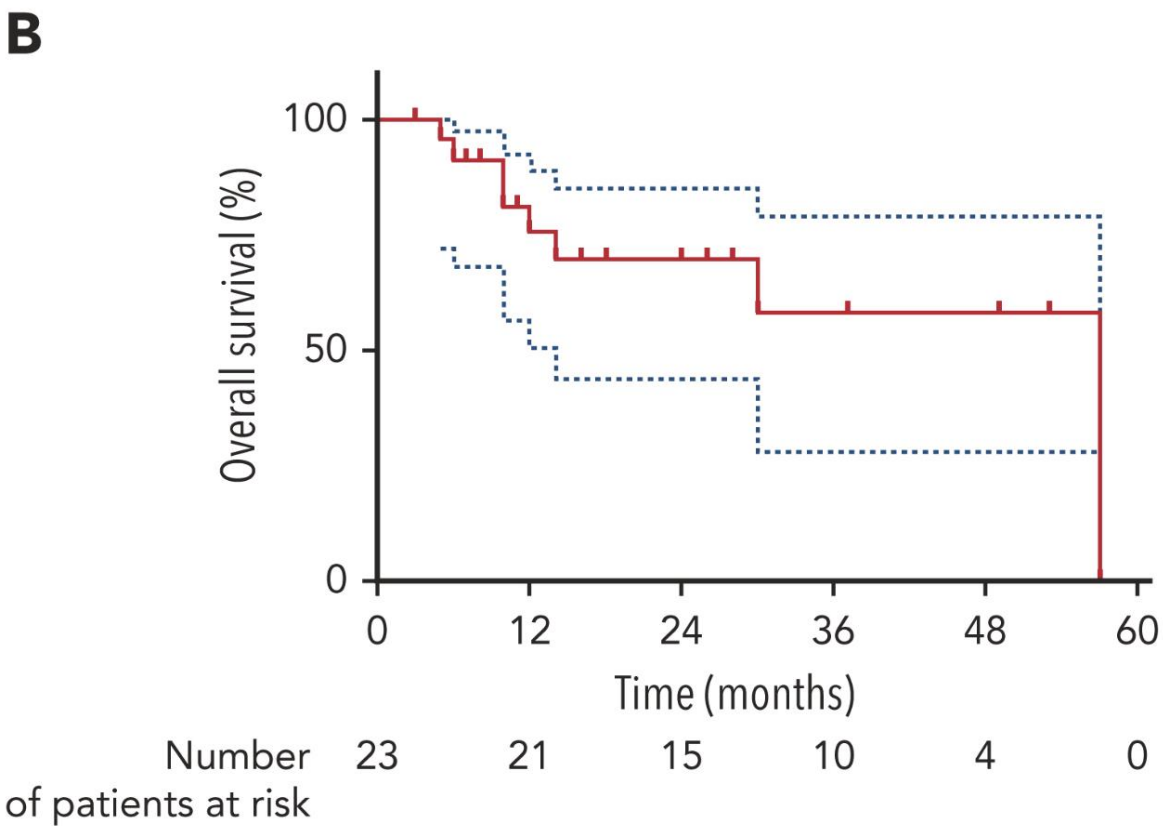
CAR: chimeric antigen receptor; CD: cluster differentiation; MSKCC: Memorial Sloan Kettering Cancer Centre

Palomba L, *et al. J Immunother Cancer* 2022; 10:e004128.

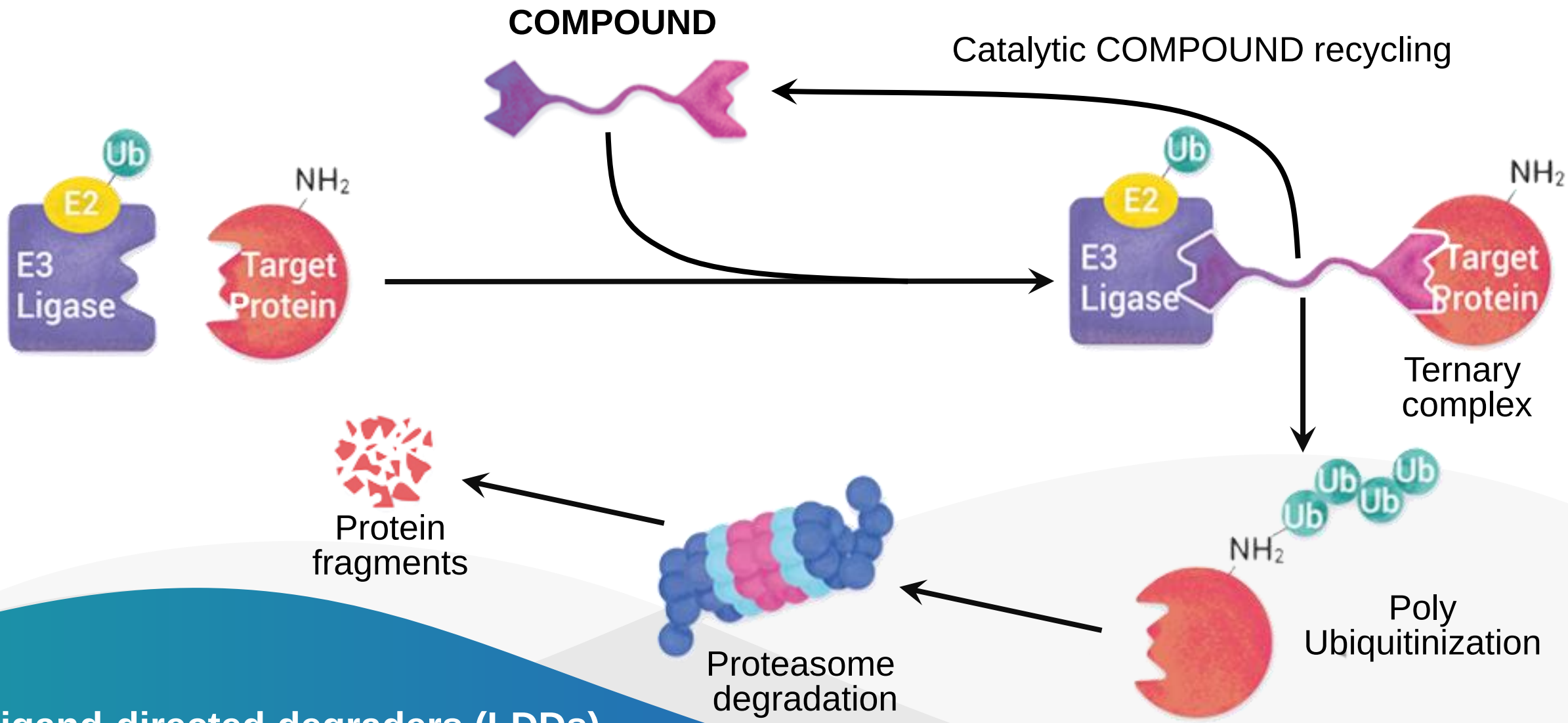
Transformed WM: Outcomes after CAR T-cell infusion

N=23 (19 France; 4 USA). Best overall response rate: 96%, CR: 87%





Durot et al. Blood. 2024; 143:2804-2807. http://doi.org/10.1182/blood.2024024452. PMID: 38669635.



Ligand-directed degraders (LDDs)
Degrader Antibody Conjugates (DACs)
Proteolysis-Targeting Chimeras: PROTAC
Chimeric Degradation Activation Compounds (CDAC)

Baseline Patient Characteristics

Heavily pretreated with high rate of WM mutations

	Total, N=27
Age, median (range), years	73.0 (56-81)
Male, n (%)	15 (55.6)
ECOG PS, n (%)	
0	14 (51.9)
1	12 (44.4)
2	1 (3.7)
Hemoglobin , median (range), g/dl	10.3 (6.0-13.5)
Neutrophils, median (range), 10^9/L	2.7 (0.21-7.43)
Ptatelets, median (range), 10^9/L	157 (14-455)
Mutation status,	
n/N with known status (%)[a]	24/26 (92.3)
MYD88 mutation present	12/25 (48.0)
CXCR4 mutation present	11/25 (44.0)
BTK mutation present	13/25 (52.0)
TP53 mutation present	15 (55.6)

	Total N=27
IgM median (range) , g/l	37.4 (2.8-7 4.4)
No. of prior lines of therapy, median (range)	3.0 (2-11)
Prior therapy, n (%)	
cBTK inhibitor	27 (100)
Chemotherapy	25 (92 6)
Proteasome inhibitor	9 (33 .3)
BCL2 inhibitor	5 (18.5)
ncBTK inhibitorb	4 (14.8)
Discontinued prior BTK inhibitor due to PD, n (%)	21 (77.8}

Data cut-off: September 2, 2024

a) Confirmed by central laboratory. b) All 4 patients with ncBTK inhibitor exposure were exposed to a cBTKi inhibitor

cBTK: covalent BTKi; IgM: Immunoglobulin M; ncBTK: non covalente BTKi

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

Well tolerated with no AEs leading to treatment discontinuation

- No DLTs[a]
- No cases of atrial fibrillation, hypertension, major hemorrhage,[b] febrile neutropenia, or pancreatitis
- One patient had IgM flare and/or rebound 1 week after starting treatment (went on to develop PR)

Patients, n (%)	Total (N=27)
Any TEAE	25 (92.6)
Any treatment-related	19 (70.4)
Grade ≥3	11 (40.7)
Treatment-related grade ≥3	7 (25.9)
Serious	7 (25.9)
Treatment-related serious	2 (7.4)
Leading to death[c]	1 (3.7)
Treatment-related leading to death	0
Leading to treatment discontinuation	0

	Total (N=27)	
Patients, n (%)	All Grade	Grade ≥3
Neutropenia[d]	8 (29.6)	7 (25.9)
Diarrhea	7 (25.9)	0
Anemia	5 (18.5)	3 (11.1)
Contusion (bruising)	5 (18.5)	0
Rash	5 (18.5)	0
Thrombocytopenia[e]	5 (18.5)	2 (7.4)
Amylase increased	4 (14.8)	0
Dizziness	4 (14.8)	0
Pyrexia	4 (14.8)	1 (3.7)
Arthralgia	3 (11.1)	0
Constipation	3 (11.1)	0
COVID-19	3 (11.1)	0
Fall	3 (11.1)	0
Headache	3 (11.1)	0
Lipase increased	3 (11.1)	1 (3.7)
Muscle spasms	3 (11.1)	0
Petechiae	3 (11.1)	0
Upper respiratory tract infection	3 (11.1)	0

Data cutoff: September 2, 2024. Median follow-up: 5.0 months (range, 0.8-24.6+).

[a] DLTs were only assessed during the first 4 weeks of part 1a. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Septic shock (200-mg dose level), note in the context of PD. [d] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [e] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

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Overall Response Rate

High response rates across all risk groups

- Responses were observed starting at the lowest dose (100 mg; 7/9) and in patients with prior cBTK inhibitor (22/27) or ncBTK inhibitor (4/4)

	Total[a] (N=27)
Best overall response, n (%)	
VGPR	7 (25.9)
PR	13 (48.1)
MR	2 (7.4)
SD	3 (11.1)
Not evaluable	1 (3.7)
Discontinued prior to first assessment	1 (3.7)
ORR, n (%)[b]	22 (81.5)
Major response rate, n (%)[c]	20 (74.1)
Disease control rate (DCR), n (%)[d]	25 (93.0)
Follow-up, median (range), months	5.0 (0.8-24.6)
Time to first response, median (range), months[e]	1.0 (0.9-3.7)

Mutation status, n/N tested (%)	Total[a] (N=27)
BTK	
Mutated	10/11 (90.9)
Unmutated	11/14 (78.6)
Unknown	1/2 (50.0)
MYD88	
Mutated	20/24 (83.3)
Unmutated	1/2 (50.0)
Unknown	1/1 (100)
CXCR4	
Mutated	11/12 (91.7)
Unmutated	10/13 (76.9)
Unknown	1/2 (50.0)
TP53	
Mutated	12/13 (92.3)
Unmutated	9/12 (75.0)
Unknown	1/2 (50.0)

[a] Efficacy-evaluable population. [b] Includes best overall response of MR or better. [c] Includes best overall response of PR or VGPR. [d] Includes best overall response of SD or better.
[e] In patients with a best overall response better than SD.
cBTK, covalent BTK; MR, minor response; ncBTK, noncovalent BTK; VGPR, very good partial response.

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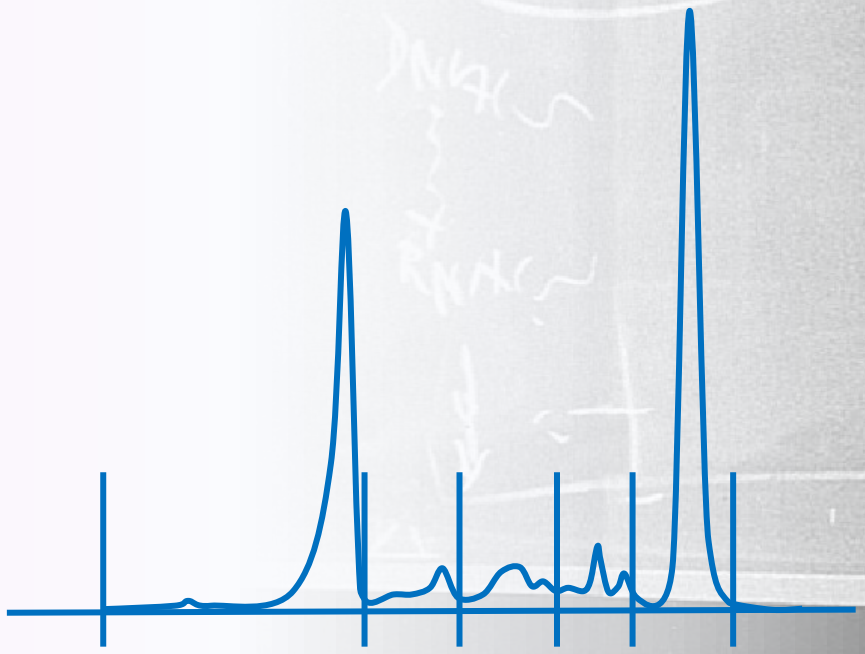
So many possibilities



Waldenström's
Macroglobulinemia

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