Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

EHA 2025

MAILAND, ITALIEN

12. – 15. Juni 2025

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Christian Buske
Universitätsklinikum Ulm

Morbus Waldenström & Marginalzonen-Lymphom

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – EHA 2025 Mailand, Italien wird in Kooperation mit fünf unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	Universitätsklinikum Ulm
Beratungs-/ Gutachtertätigkeit	Gilead Sciences, Janssen, Roche, Pfizer, BeiGene, Celltrion, AbbVie, Incyte, Regeneron, MorphoSys, Novartis, Sobi, Lilly
Besitz von Geschäftsanteilen, Aktien oder Fonds	-
Patent, Urheberrecht, Verkaufslizenz	-
Honorare	Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron, Sobi, Lilly
Finanzierung wissenschaftlicher Untersuchungen	Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen, Bayer
Andere finanzielle Beziehungen	-
Immaterielle Interessenkonflikte	-

Kapitel 1

Morbus Waldenström: was tun nach Ibrutinib/Zanubrutinib – Versagen?

BTK - Degrader

UPDATED EFFICACY & SAFETY OF THE BRUTON TYROSINE KINASE (BTK) DEGRADER BGB-16673 IN PATIENTS WITH RELAPSED/REFRACTORY WALDENSTRÖM MACROGLOBULINEMIA (WM): ONGOING PHASE (PH) 1 CADANCE-101 STUDY RESULTS

S231

Anna Maria Frustaci et al.

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for WM

- Met IWWM-7 criteria for treatment
- ≥2 prior therapies, includ. anti-CD20 monoclonal antibody & cBTK inhibitor (US & EU only)
- ECOG PS 0-2
- Adequate organ function

Key objectives: part 1

- **Primary:** safety[c] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, & preliminary antitumor activity[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, **WM**, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle[b]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, **WM**)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, **WM**, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, **WM**)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor–naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1:** Post BTK inhibitor, R/R CLL/SLL
- **Cohort 2:** Post BTK inhibitor, R/R MCL
- **Cohort 3:** Post BTK inhibitor, R/R WM
- **Cohort 4:** Post BTK inhibitor, R/R MZL
- **Cohort 5:** R/R FL
- **Cohort 6:** R/R non-GCB DLBCL
- **Cohort 7:** Post BTK inhibitor, R/R RT

[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to CTCAE v5.0. [d]Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks.
BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; IWWM, International Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; QD, daily; PD, pharmacodynamics; PK, pharmacokinetics; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, Richter transformation; WM, Waldenström macroglobulinemia.

Baseline Patient Characteristics

Heavily pretreated with high rate of poor risk mutations

	Total (N=36)
Age, median (range), years	72.0 (49-81)
Male, n (%)	22 (61.1)
ECOG PS, n (%)	
0	17 (47.2)
1	17 (47.2)
2	2 (5.6)
Hemoglobin, median (range), g/L	102 (60-146)
Hemoglobin ≤110 g/L, n/N with known status (%)	25/34 (73.5)
Neutrophils, median (range), 10^9/L	2.6 (0.2-7.4)
Neutrophils ≤1.5×10^9/L, n/N with known status (%)	11/33 (33.3)
Platelets, median (range), 10^9/L	153.5 (14.0-455.0)
IgM, median (range), g/L	35.1 (0.3-92.6)

	Total (N=36)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	31/35 (88.6)
CXCR4 mutation present	19/35 (54.3)
BTK mutation present	11/31 (35.5)
TP53 mutation present	16/31 (51.6)
No. of prior lines of therapy, median (range)	3 (1-11)
Prior therapy, n (%)	
cBTK inhibitor	36 (100)
Anti-CD20 antibody	36 (100)
Chemotherapy	34 (94.4)
Proteasome inhibitor	11 (30.6)
BCL2 inhibitor	9 (25.0)
ncBTK inhibitor[b]	7 (19.4)
Discontinued prior BTK inhibitor due to PD, n (%)	30 (83.3)

Data cutoff: March 3, 2025.

[a]Confirmed by central laboratory. [b]All seven patients with ncBTK inhibitor exposure were also exposed to a cBTK inhibitor.

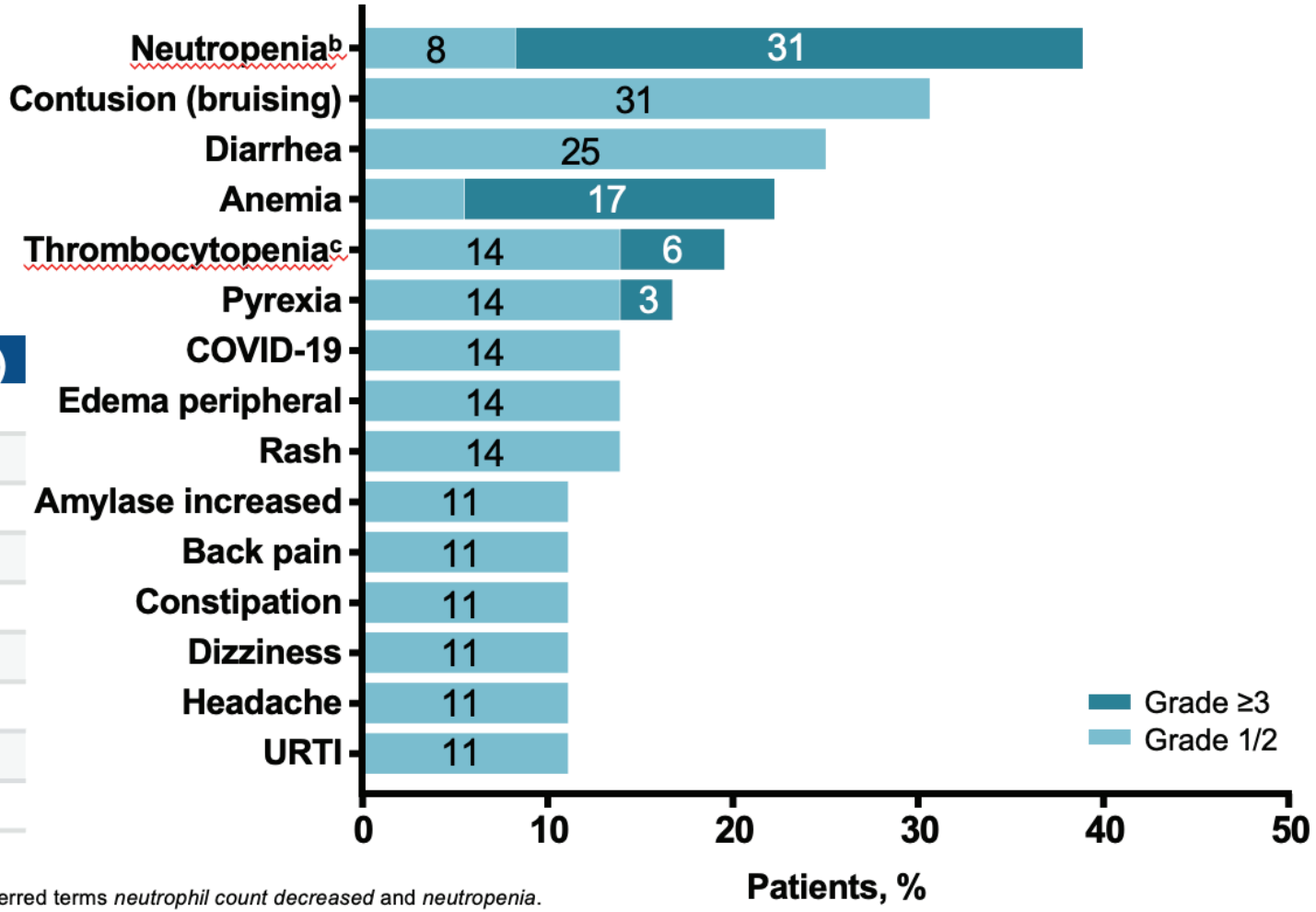
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent BTK; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, immunoglobulin M; ncBTK, noncovalent BTK; PD, progressive disease; WM, Waldenström macroglobulinemia.

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

Well tolerated with no treatment-related TEAEs leading to death

- Most common TEAEs were neutropenia in 39% and contusion (bruising) in 31% of patients
- No atrial fibrillation, febrile neutropenia, or pancreatitis

Patients, n (%)	Total (N=36)
Any TEAE	32 (88.9)
Any treatment-related	25 (69.4)
Grade ≥3	22 (61.1)
Treatment-related grade ≥3	14 (38.9)
Serious	12 (33.3)
Treatment-related serious	4 (11.1)
Leading to death[a]	1 (2.8)
Treatment-related leading to death	0
Leading to treatment discontinuation	2 (5.6)



Data cutoff: March 3, 2025. Median follow-up: 8.2 months (range, 0.6-30.6 months).
[a]Septic shock (200-mg dose level), note in the context of PD. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
[c]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
IgM, immunoglobulin M; PD, progressive disease; PR, partial response; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Overall Response Rate

High response rates across all risk groups

- Responses were observed at all dose levels and in patients with prior chemoimmunotherapy (25/30), cBTK inhibitor (27/32), or ncBTK inhibitor (4/4)

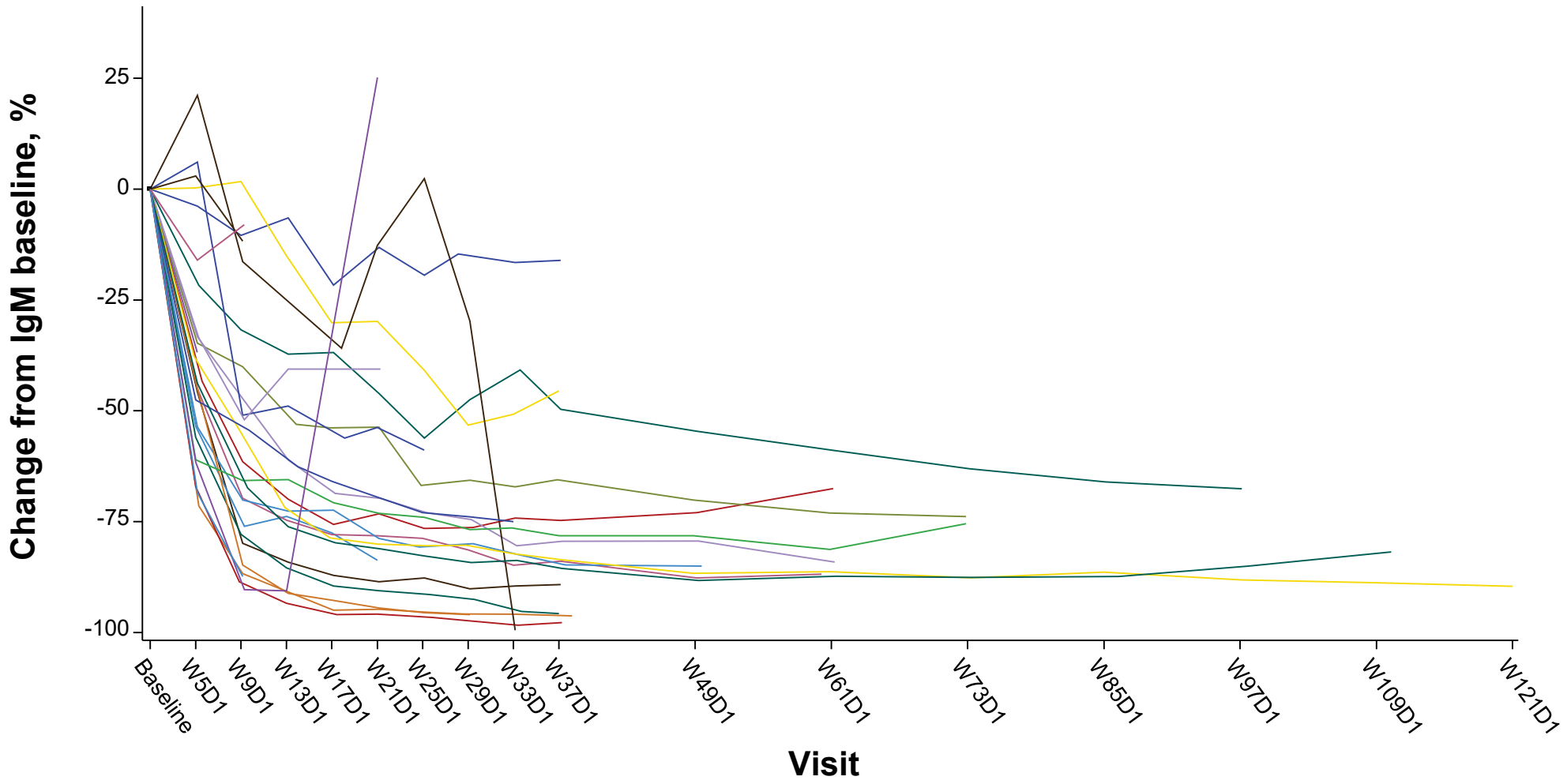
	Total (N=32)[a]
Best overall response, n (%)	
VGPR	10 (31.3)
PR	14 (43.8)
MR	3 (9.4)
SD	3 (9.4)
PD	1 (3.1)
Discontinued prior to first assessment	1 (3.1)
ORR, n (%)[b]	27 (84.4)
Major response rate, n (%)[c]	24 (75.0)
Disease control rate (DCR), n (%)[d]	30 (93.8)
Time to first response, median (range), months[e]	1.0 (0.9-3.7)

Mutation status, n/N tested (%)	ORR (N=32)[a]
BTK	
Mutated	11/11 (100)
Unmutated	15/19 (78.9)
Unknown	1/2 (50.0)
MYD88	
Mutated	25/28 (89.3)
Unmutated	2/3 (66.7)
Unknown	0/1 (0)
CXCR4	
Mutated	16/17 (94.1)
Unmutated	11/14 (78.6)
Unknown	0/1 (0)
TP53	
Mutated	15/15 (100)
Unmutated	11/15 (73.3)
Unknown	1/2 (50.0)

[a]Efficacy-evaluable population; 4 patients were too early in treatment course to be response-evaluable. [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.
BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; MR, minor response; ncBTK, noncovalent Bruton tyrosine kinase; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

IgM Decreased in All Patients

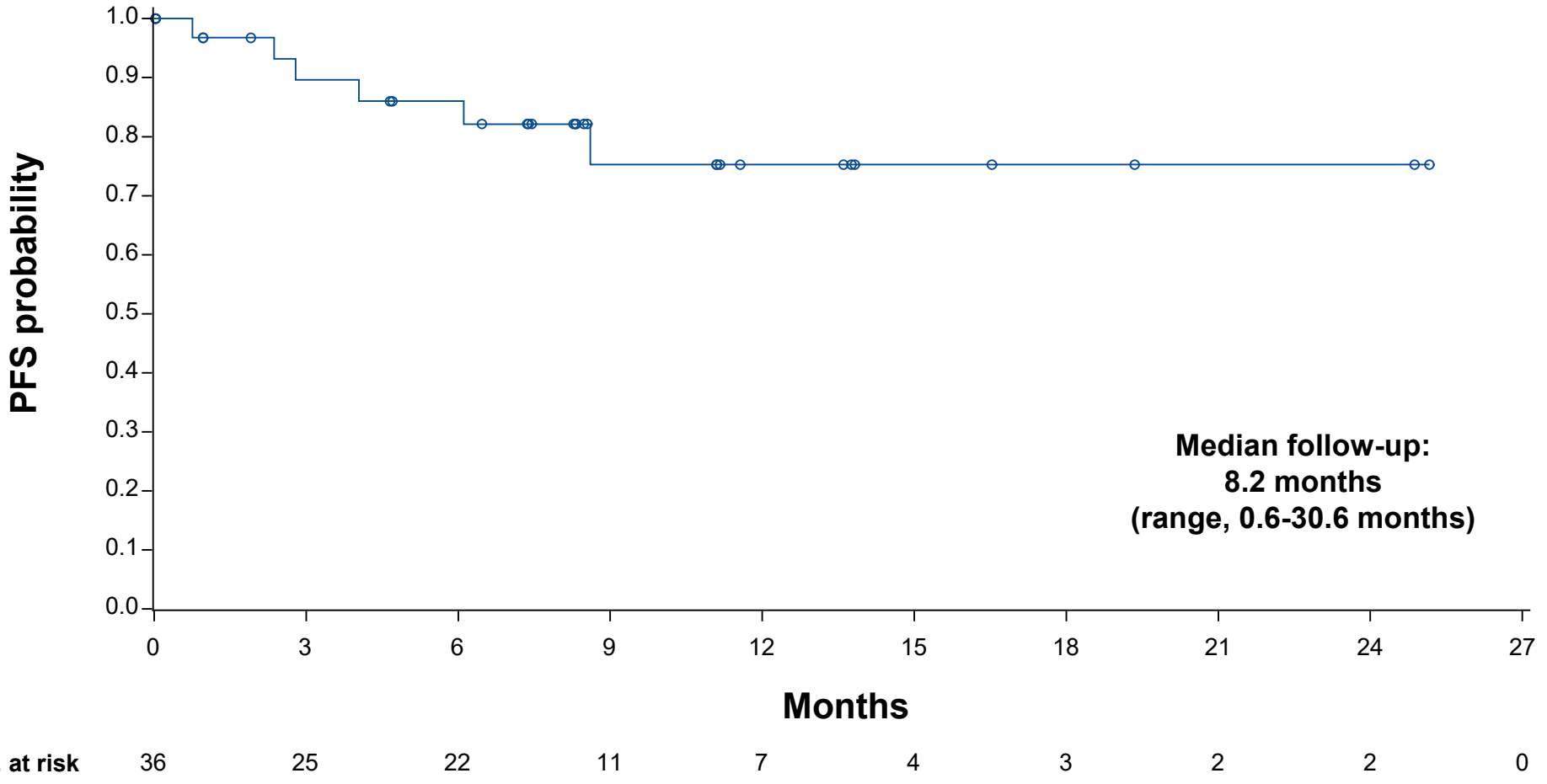
Rapid decline in IgM at all dose levels



Patient with rapid IgM increase had *BTK, MYD88, CXCR4*, and *TP53* mutations at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment.

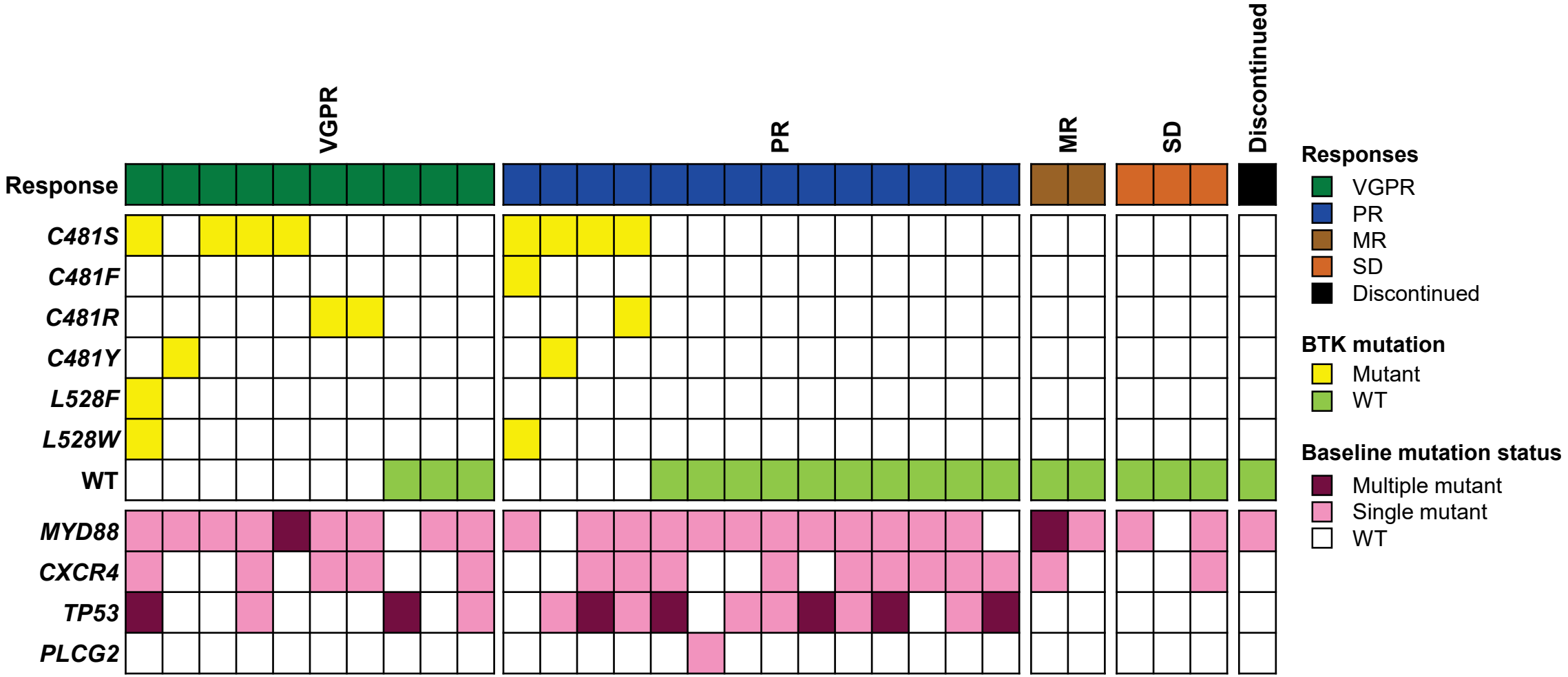
D, day; IgM, immunoglobulin M; W, week.

Median PFS Was Not Reached



PFS, progression-free survival.

Responses Occurred Regardless of Baseline Mutations (Best Overall Response vs Baseline Mutation)[a]



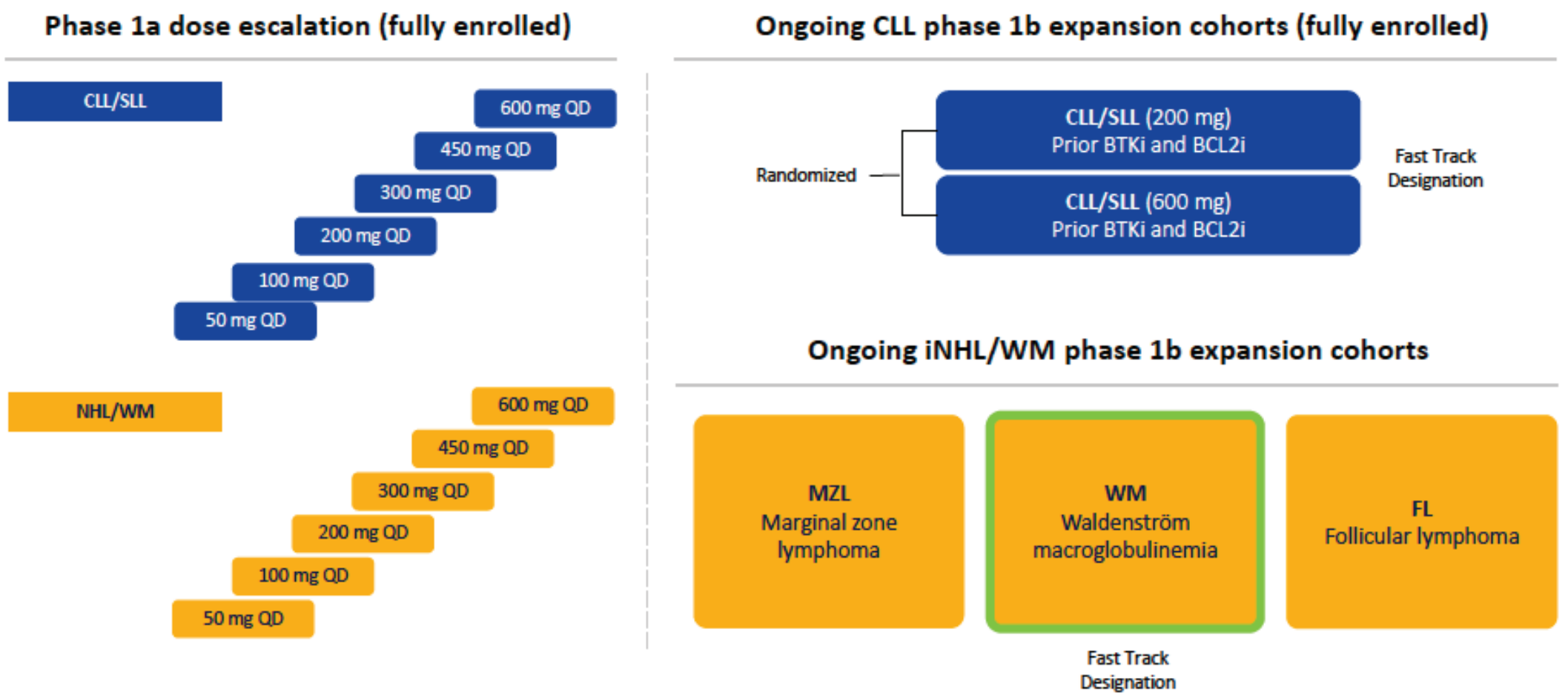
[a]Genomic mutations were centrally assessed by targeted next-generation sequencing.
BTKi, Bruton tyrosine kinase inhibitor; MR, minor response; NE, not evaluable; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

BEXOBRUTIDEG (NX-5948), A NOVEL BRUTON'S TYROSINE KINASE DEGRADER, SHOWS HIGH CLINICAL ACTIVITY AND TOLERABLE SAFETY IN AN ONGOING PHASE 1A/B STUDY IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

PS1883

Dima El-Sharkawi et al.

Figure 2. NX-5948-301 Trial Design



Results

Table 1. Patient Demographics and Baseline Disease Characteristics – Patients with WM

Characteristics	Patients with WM (n=22)
Median age, years (range)	72.5 (58–86)
Male, n (%)	18 (81.8)
ECOG PS, n (%)	
0	8 (36.4)
1	14 (63.6)
CNS involvement, n (%)	2 (9.1)
Median prior lines of therapy (range)	3 (2–5)
Previous treatments[a], n (%)	
BTKi	22 (100.0)
ncBTKi	4 (18.2)
BCL2i	1 (4.5)
BTKi and BCL2i	1 (4.5)
Chemo/chemo-immunotherapies	21 (95.5)
Mutation status[b], n (%)	
MYD88	15 (68.2)
CXCR4	5 (22.7)

[a]Patients could have received multiple prior treatments; [b]Mutation status was gathered from historic patient records

Data cutoff: 12 Mar 2025

Table 3. TEAEs in ≥10% of Overall Population or Grade ≥3 TEAEs in ≥1 Patient or any SAEs

TEAEs, n (%)	Patients with WM (n=22)		
	Any grade	Grade ≥3	SAEs
Petechiae	6 (27.3)	–	–
Diarrhea	5 (22.7)	–	–
Purpura/contusion[a]	4 (18.2)	–	–
Neutropenia[b]	4 (18.2)	1 (4.5)	–
Thrombocytopenia[c]	4 (18.2)	1 (4.5)	–
Upper respiratory tract infection	4 (18.2)	–	–
Anemia	3 (13.6)	2 (9.1)	–
Headache	3 (13.6)	–	–
Rash[d]	3 (13.6)	–	–
COVID-19[e]	3 (13.6)	–	–
Fall	3 (13.6)	1 (4.5)	1 (4.5)
Lower respiratory tract infection	2 (9.1)	1 (4.5)	–
Arthralgia	2 (9.1)	–	–
Cough	2 (9.1)	–	–
Peripheral edema	2 (9.1)	–	–
Pneumonia[f]	2 (9.1)	–	–
Influenza	1 (4.5)	1 (4.5)	1 (4.5)
Influenzal pneumonia	1 (4.5)	1 (4.5)	1 (4.5)
Sepsis	1 (4.5)	1 (4.5)	1 (4.5)
Hypertension	1 (4.5)	1 (4.5)	–
Subdural hematoma[g]	1 (4.5)	–	1 (4.5)
Fatigue[h]	1 (4.5)	–	–

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [f]Aggregate of 'pneumonia' and 'pneumonia klebsiella'; [g]Grade 1 AE in a patient on concurrent anti-coagulation; [h]Fatigue was transient

Data cutoff: 12 Mar 2025

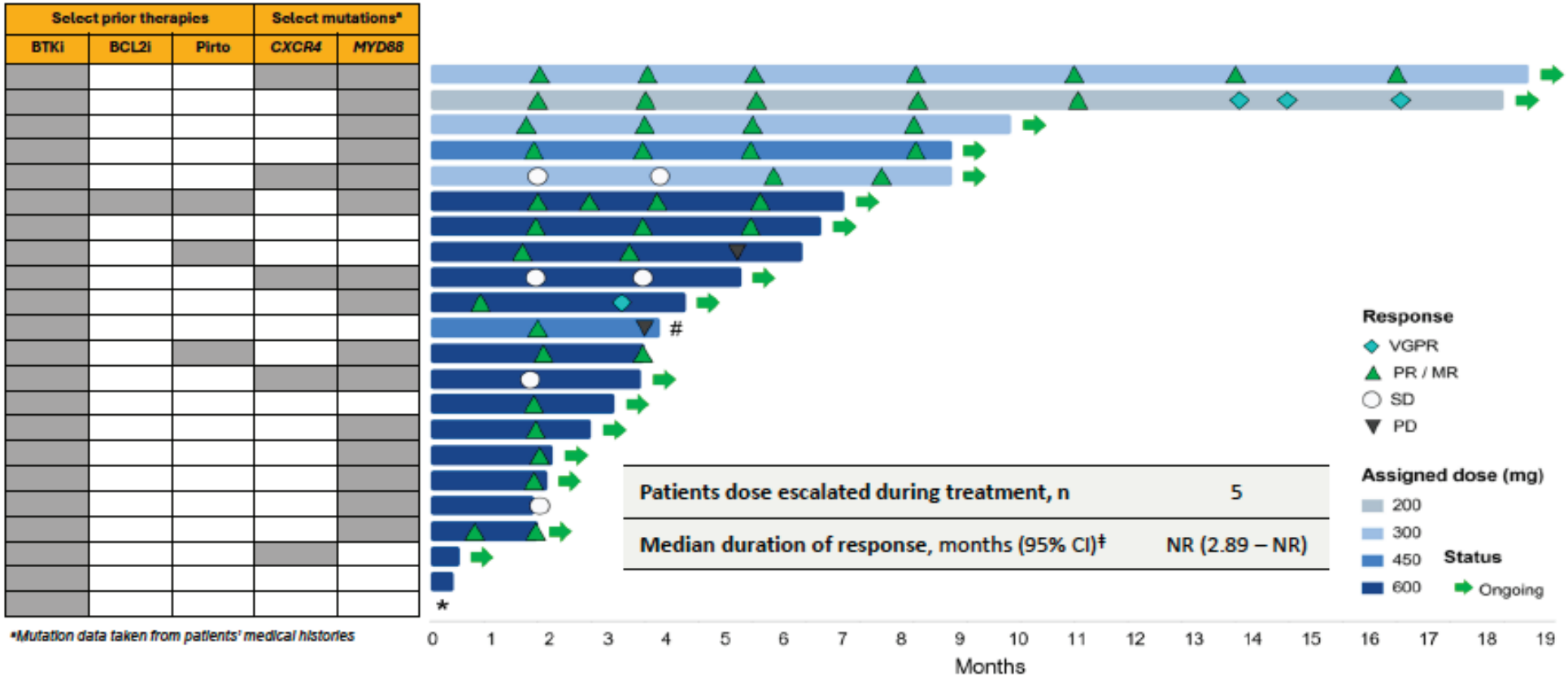
Table 2. Bexobrutideg Overall Response Assessment in Patients with WM: Phase 1a/1b

WM response-evaluable patients	Primary response analysis[b] ≥1 response assessment(s) at 8 weeks (n=19)
Objective response rate (ORR),[a] %	84.2
Best response, n (%)	
CR	0 (0.0)
VGPR	2 (10.5)
PR	11 (57.9)
MR	3 (15.8)
SD	3 (15.8)
PD	0 (0.0)
Median follow-up, months[c] (range)[d]	3.7 (1.9–18.9)

[a]Objective response rate includes CR + PR + MR; [b]Patients who progressed prior to their first response assessment and patients who discontinued for any reason after their first response assessment are included in the denominators; [c]Kaplan-Meier estimate; [d]Observed values

Data cutoff 12 Mar 2025

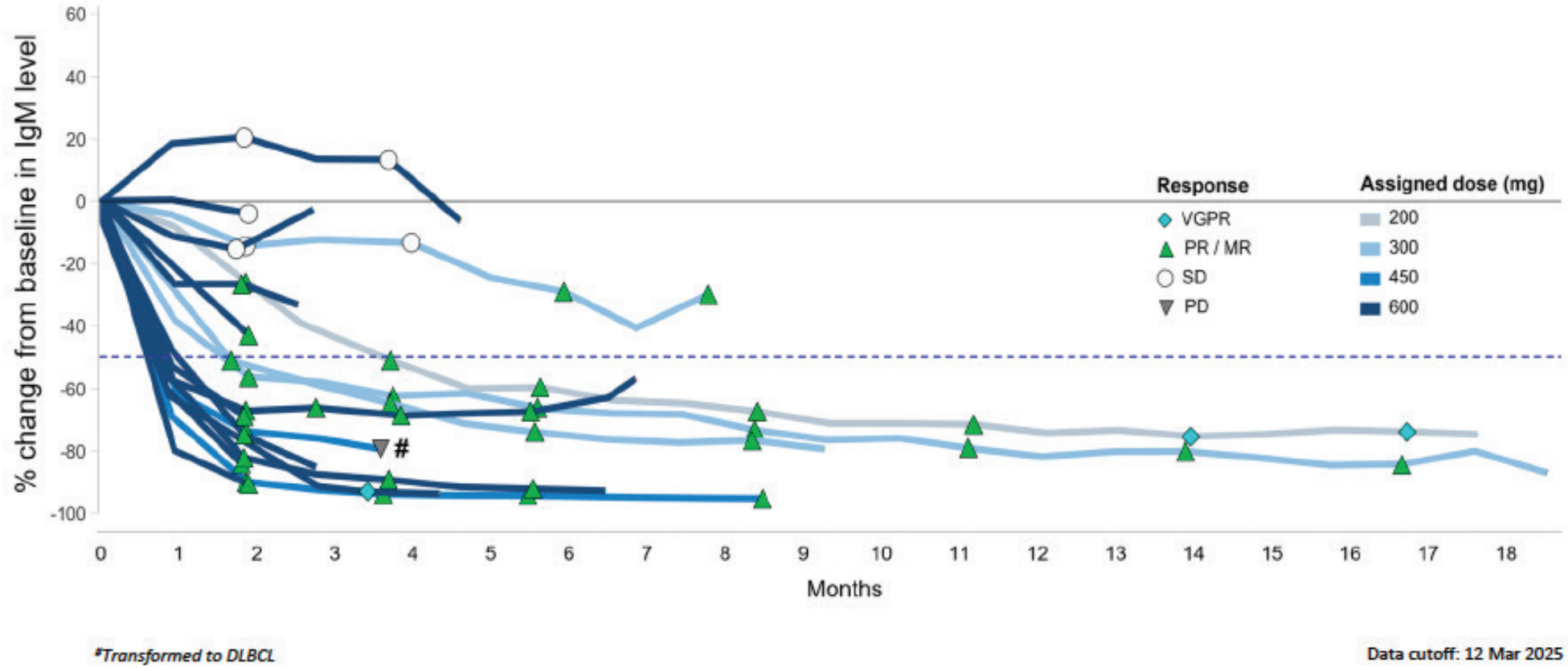
Figure 3. Durable Responses Regardless of Prior Therapy or Mutation Status (n=22)



*Ineligible, identified post 1st dose; #Transformed to DLBCL; ‡Based on Kaplan-Meier estimate

Data cutoff: 12 Mar 2025

Figure 4. Percent Change in IgM Levels from Baseline in Patients with WM



#Transformed to DLBCL

Data cutoff: 12 Mar 2025

Kapitel 2

Morbus Waldenström: was tun nach Ibrutinib/Zanubrutinib – Versagen?

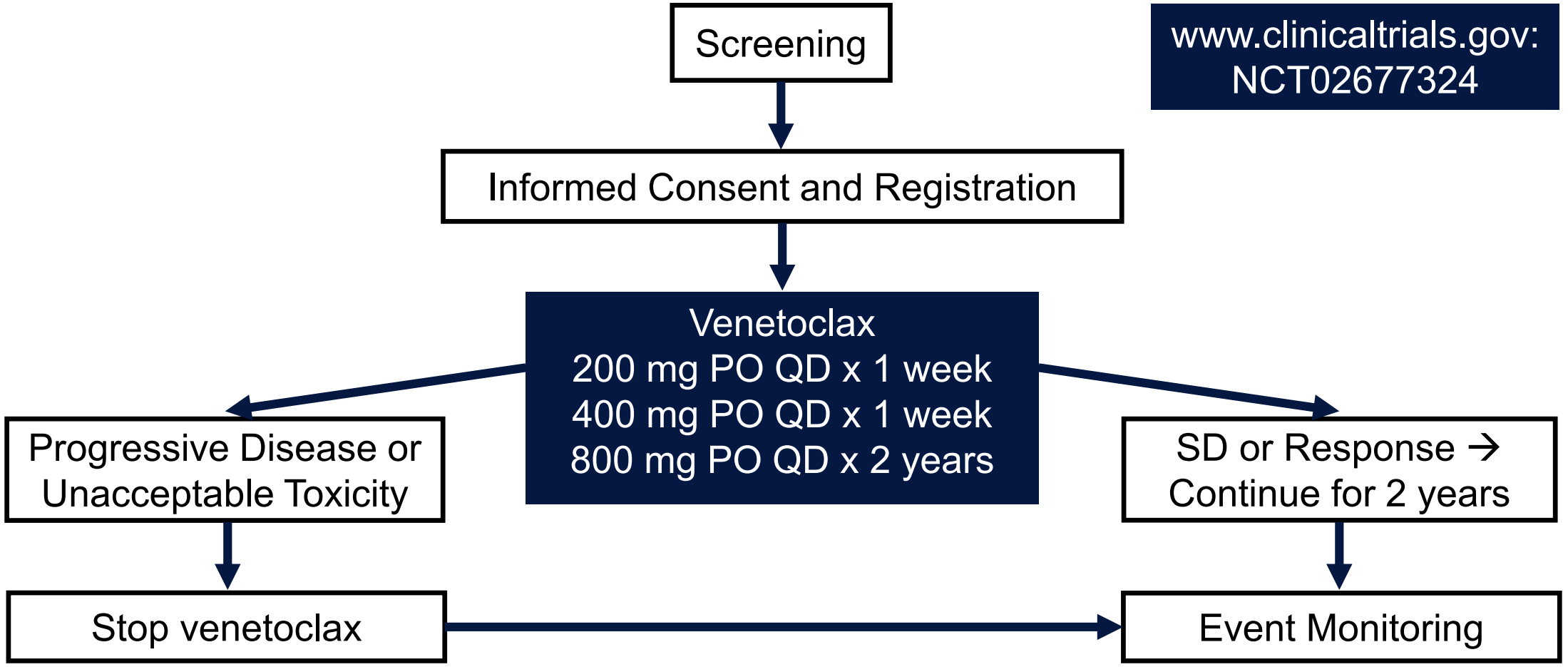
Venetoclax?

LONG-TERM FOLLOW-UP OF VENETOCLAX MONOTHERAPY IN PREVIOUSLY TREATED PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

PS1881

Jorge Castillo et al.

Schema


Screening
www.clinicaltrials.gov:
NCT02677324
Informed Consent and Registration
Venetoclax
200 mg PO QD x 1 week
400 mg PO QD x 1 week
800 mg PO QD x 2 years
Progressive Disease or
Unacceptable Toxicity
SD or Response →
Continue for 2 years
Stop venetoclax
Event Monitoring

Patients' characteristics

Variable	n=32
Age WM diagnosis	58
Age IBR initiation	66
Male sex	56%
Serum IgM level	3,512
Hemoglobin level	10.6
Platelet count	216
B2-microglobulin level	3.6

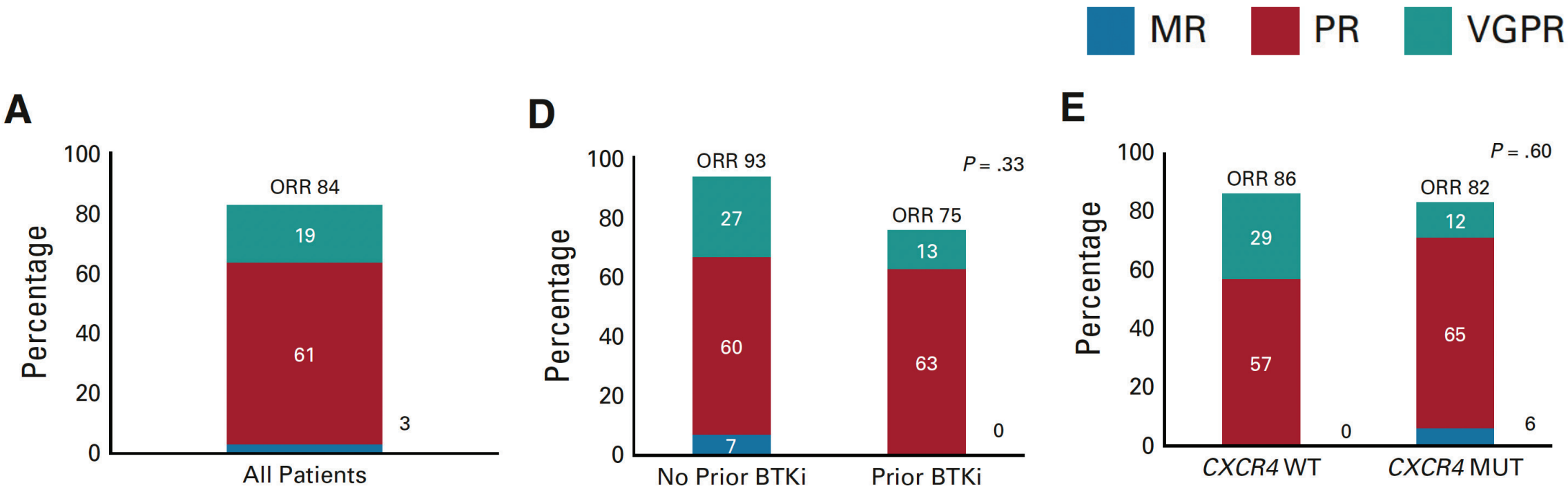
Variable	n=32
BM involvement	35%
Adenopathy ≥1.5 cm	28%
Splenomegaly ≥15 cm	25%
Low IPSSWM	38%
Intermediate IPSSWM	25%
High IPSSWM	38%
CXCR4 mutation	53%

Castillo et al. J Clin Oncol 2022

Previous Treatment

Prior therapies	
Median No. of prior therapies (range)	2 (1-10)
≥ 3 prior therapies, No. (%)	12 (38)
Previous anti-CD20 monoclonal antibodies, No. (%)	28 (88)
Previous proteasome inhibitors, No. (%)	21 (66)
Previous BTKi, No. (%)	16 (50)
Previous chemotherapy, No. (%)	15 (47)
Refractory to most recent therapy, No. (%)	11 (34)

Response to therapy



Safety

Adverse events	Grade 3	Grade 4	Total Grade 3-4
Neutropenia	8	6	14
Febrile neutropenia		1	1
Anemia	1		1
Lymphopenia	1		1
Diarrhea	1		1
Constipation	1		1
URI	1		1
ALK phos increased	1		1
Laboratory TLS	1		1

Castillo et al. J Clin Oncol 2022

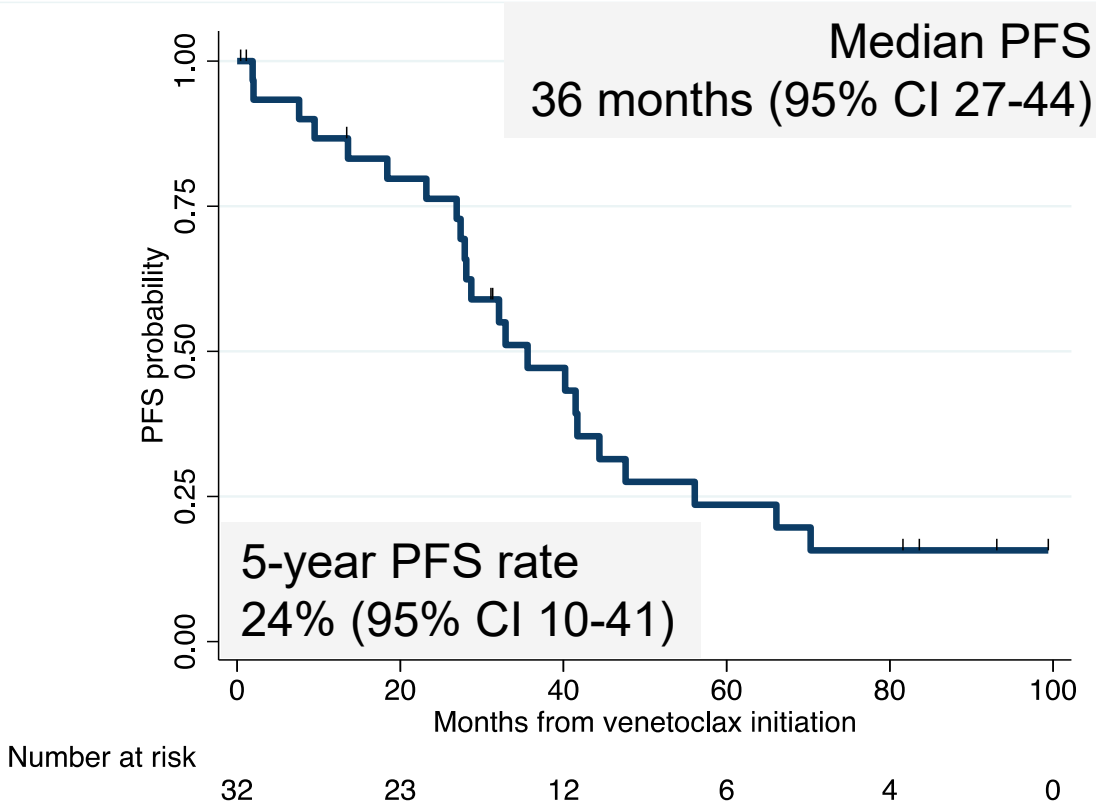
Not observed:

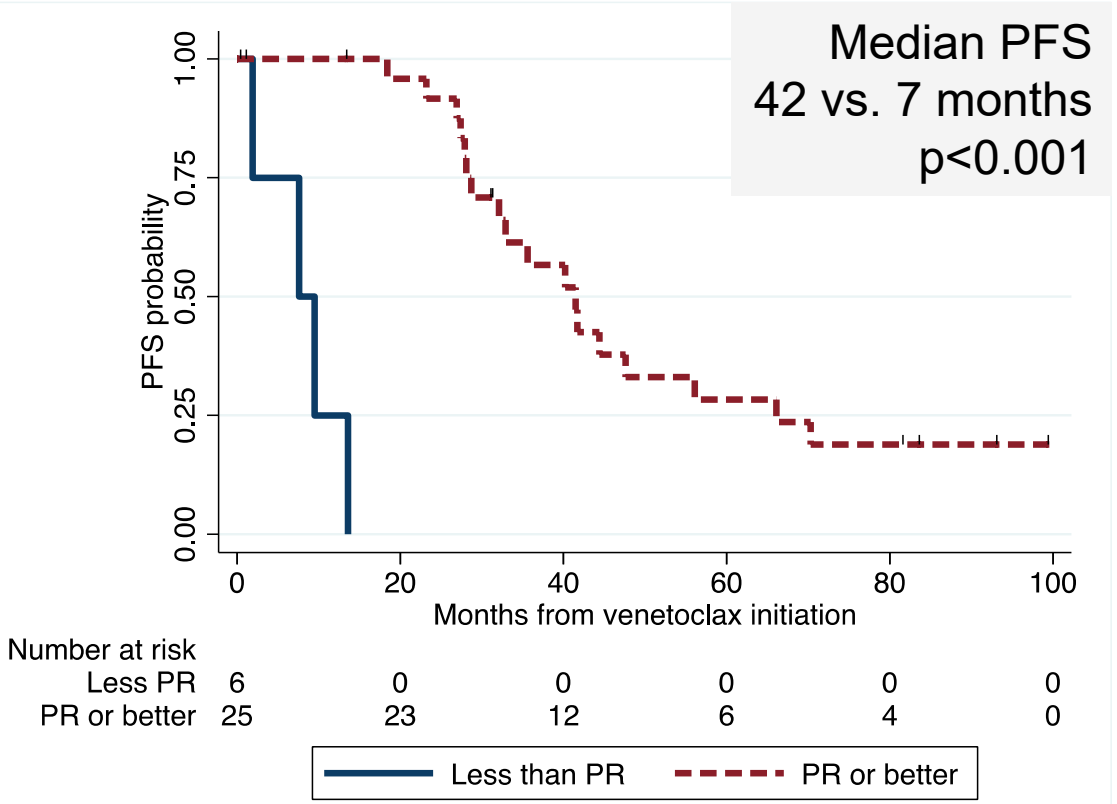
- IgM flare
- IgM rebound
- Neuropathy
- Arrhythmia
- Myeloid neoplasms

Long-term follow-up

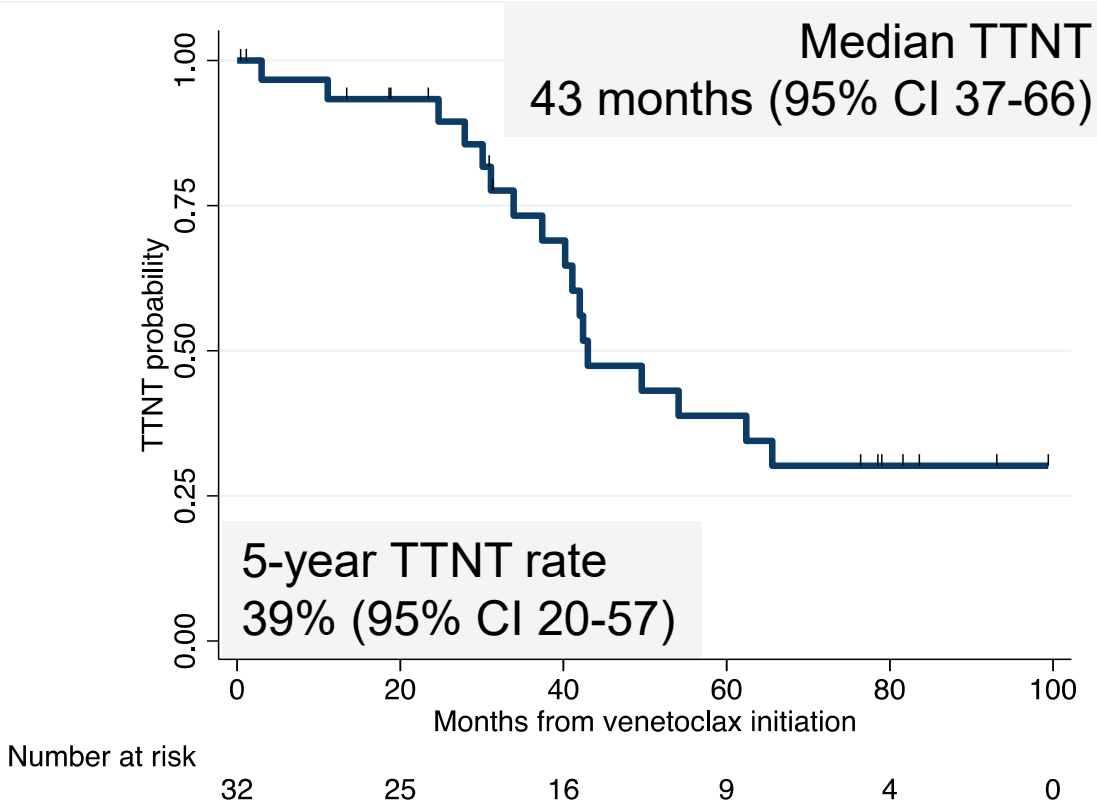
- Median follow-up: 81 months (95% CI 71-86)
- 23 patients experienced a progression event
- 17 patients began a new treatment (9 received venetoclax)
- 3 patients have died (2 WM progression, 1 unknown)

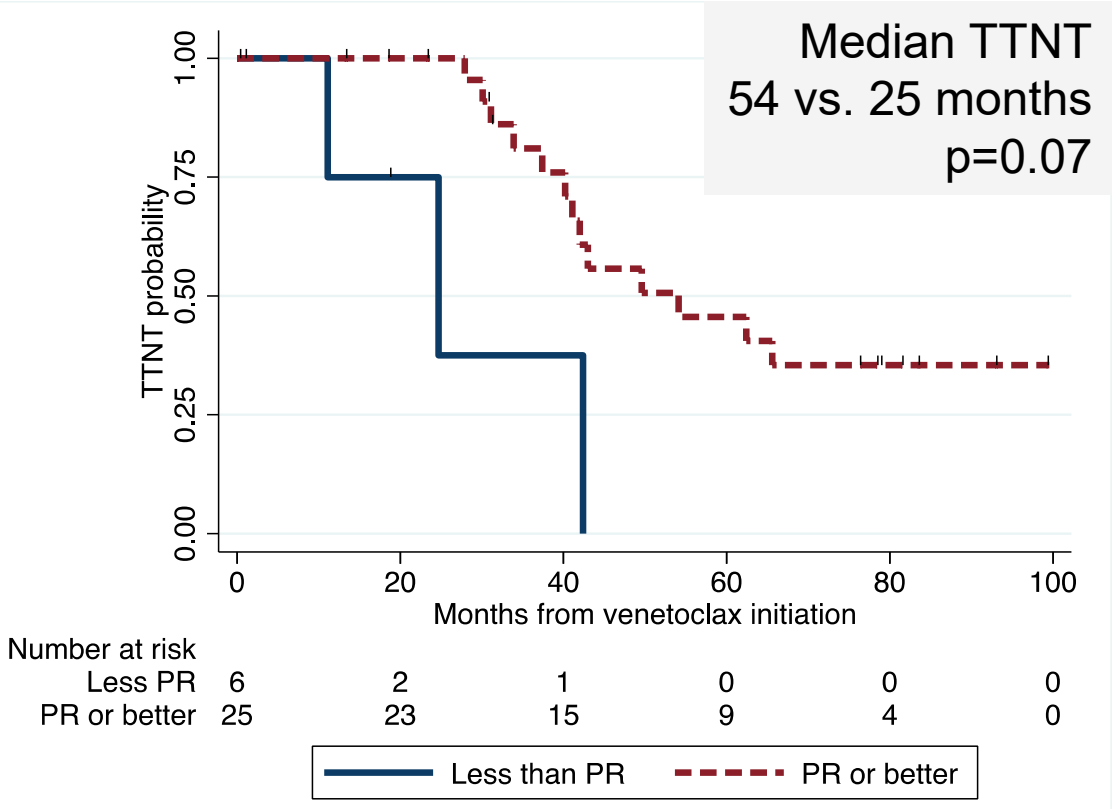
Progression-free survival



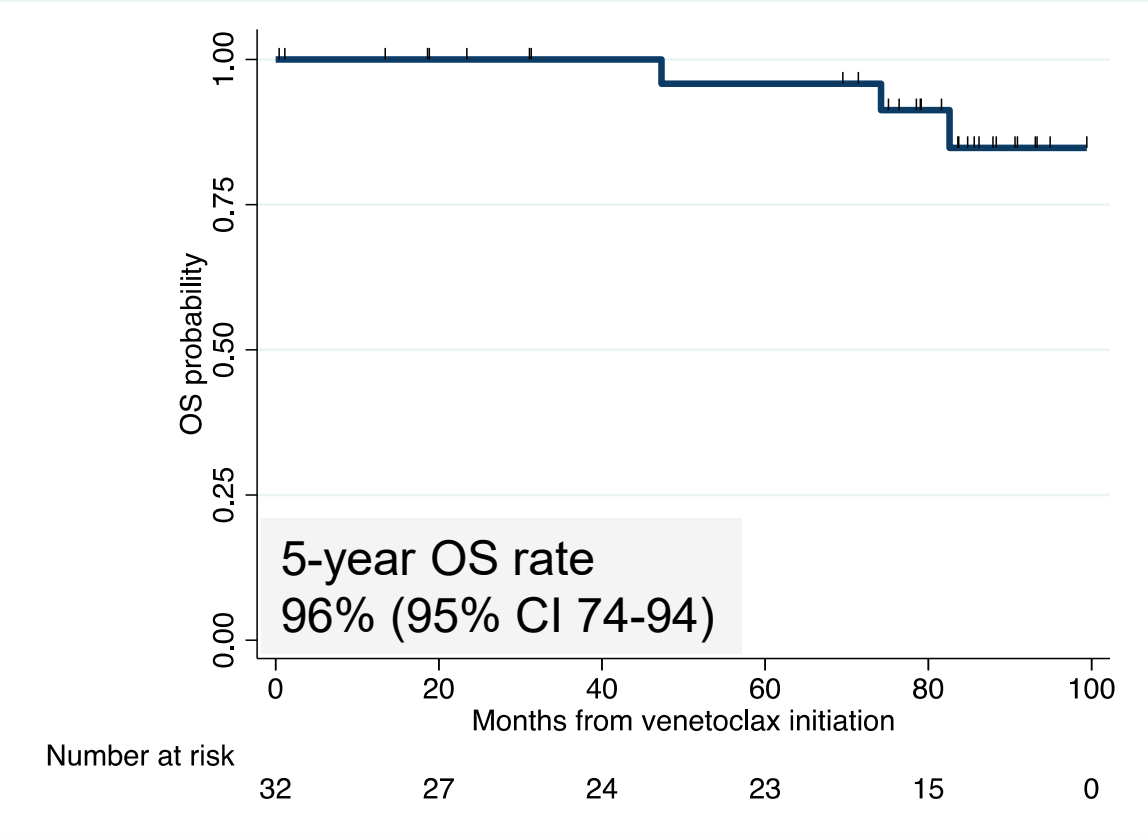


Treatment-free survival





Overall survival



Bone marrow biopsies were performed at baseline and at 6, 12 and 24 months

No acquired *BCL2* mutations tested by PCR assays in CD19-selected bone marrow cells were observed.

Re-treatment

9 patients (27%) received venetoclax upon disease progression

- 6 venetoclax monotherapy (4 PR, 1 VGPR, 1 NR)
- 2 venetoclax plus zanubrutinib (1 VGPR, 1 SD)
- 1 venetoclax plus acalabrutinib (1 VGPR)

Kapitel 3

Morbus Waldenström: was tun nach Ibrutinib/Zanubrutinib – Versagen?

Retrospektive Daten

LONG-TERM OUTCOMES IN WALDENSTRÖM MACROGLOBULINEMIA (WM) PATIENTS WHO DISCONTINUE BRUTON'S TYROSINE KINASE INHIBITOR (BTKI) THERAPY

PS1890

Karan Chohan et al.

Results

Aims:

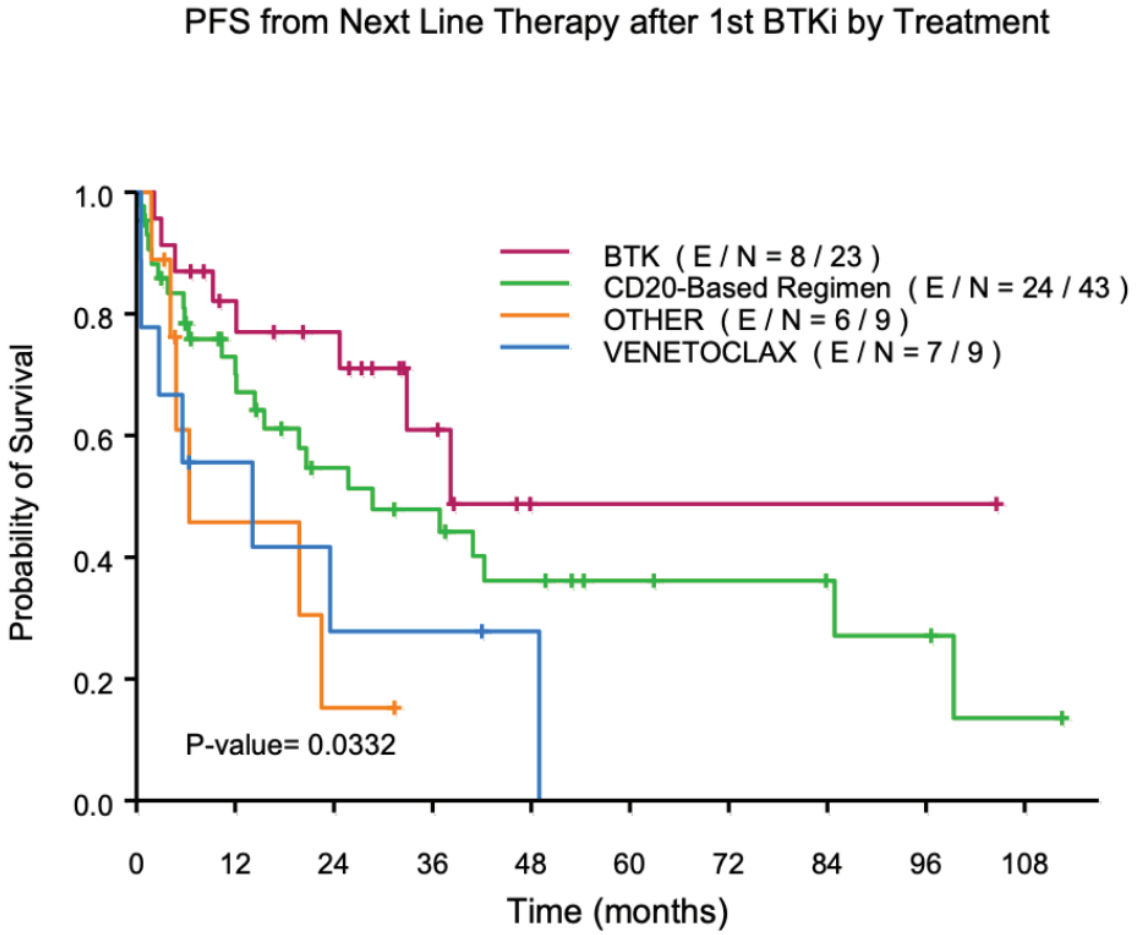
Given the dearth of real-world data, we aimed to evaluate the long-term outcomes of patients (pts) following BTKi discontinuation.

Methods:

We retrospectively analyzed data from all pts treated with BTKi at MD Anderson Cancer Center for frontline or relapsed/refractory (R/R) WM between 1/2014 to 3/2024. Outcomes were determined relative to first BTKi therapy; International Waldenstrom Macroglobulinemia Foundation (IWMF) criteria were used to assess clinical response.

Summary/Conclusion:

Following first BTKi therapy, pts can achieve prolonged survival (median >8 years) regardless of reason for discontinuation. Our analysis suggests that use of an alternate BTKi-based regimen as next line therapy has a PFS advantage; however, when first BTKi is discontinued due to disease progression, CD20-based regimens and venetoclax provide comparable outcomes to that of alternate BTKis. Prospective randomized studies are needed to further inform selection of the best post-BTKi therapy.



Kapitel 4

MZL: geht es ohne Chemotherapie?

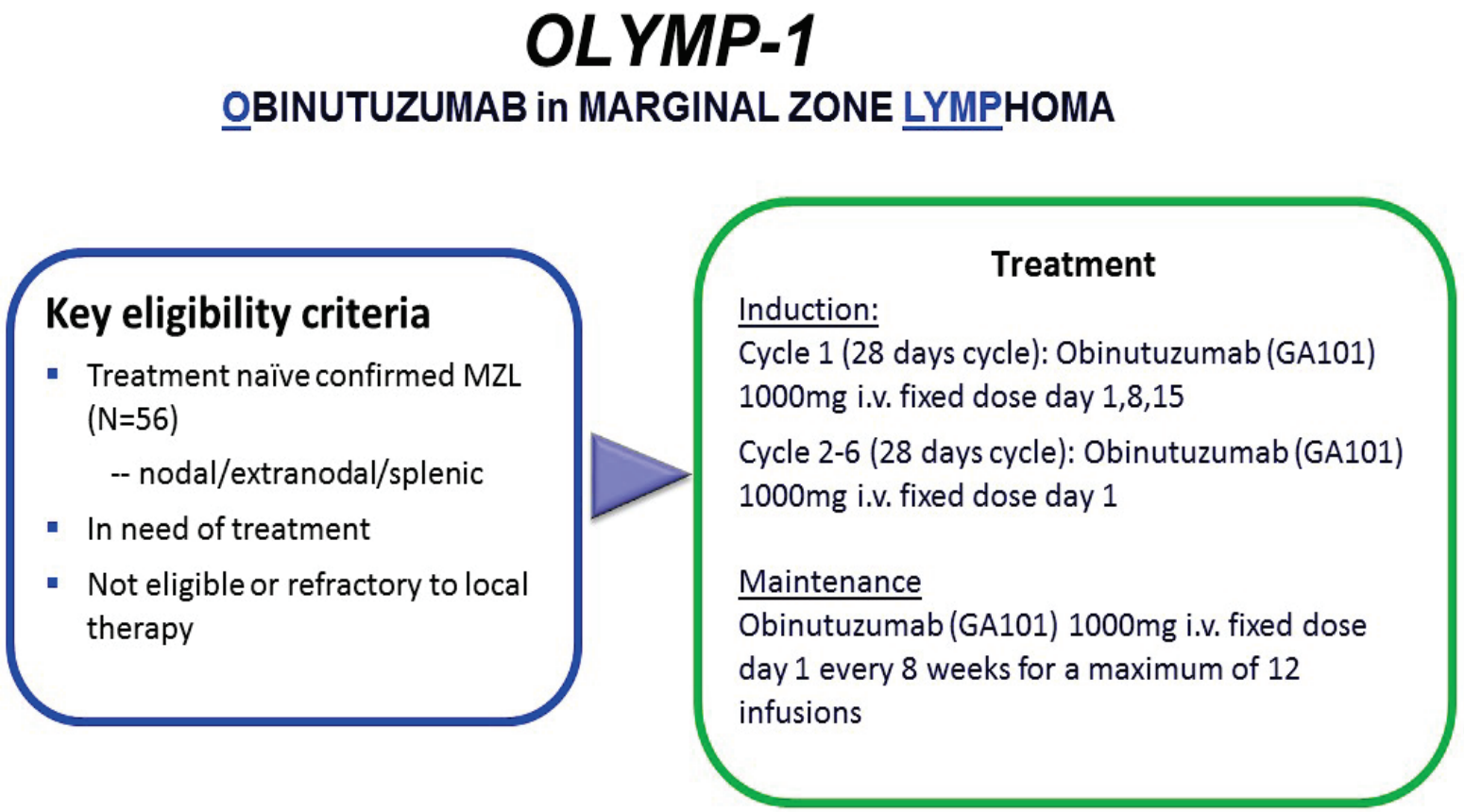
Obinutuzumab als Monotherapie

OBINUTUZUMAB SINGLE AGENT FOR THE FIRST LINE TREATMENT OF MARGINAL ZONE LYMPHOMA: RESULTS OF THE PROSPECTIVE MULTICENTER PHASE II OLYMP-1 TRIAL OF THE GERMAN LYMPHOMA ALLIANCE (GLA)

PS1873

Christian Buske et al.

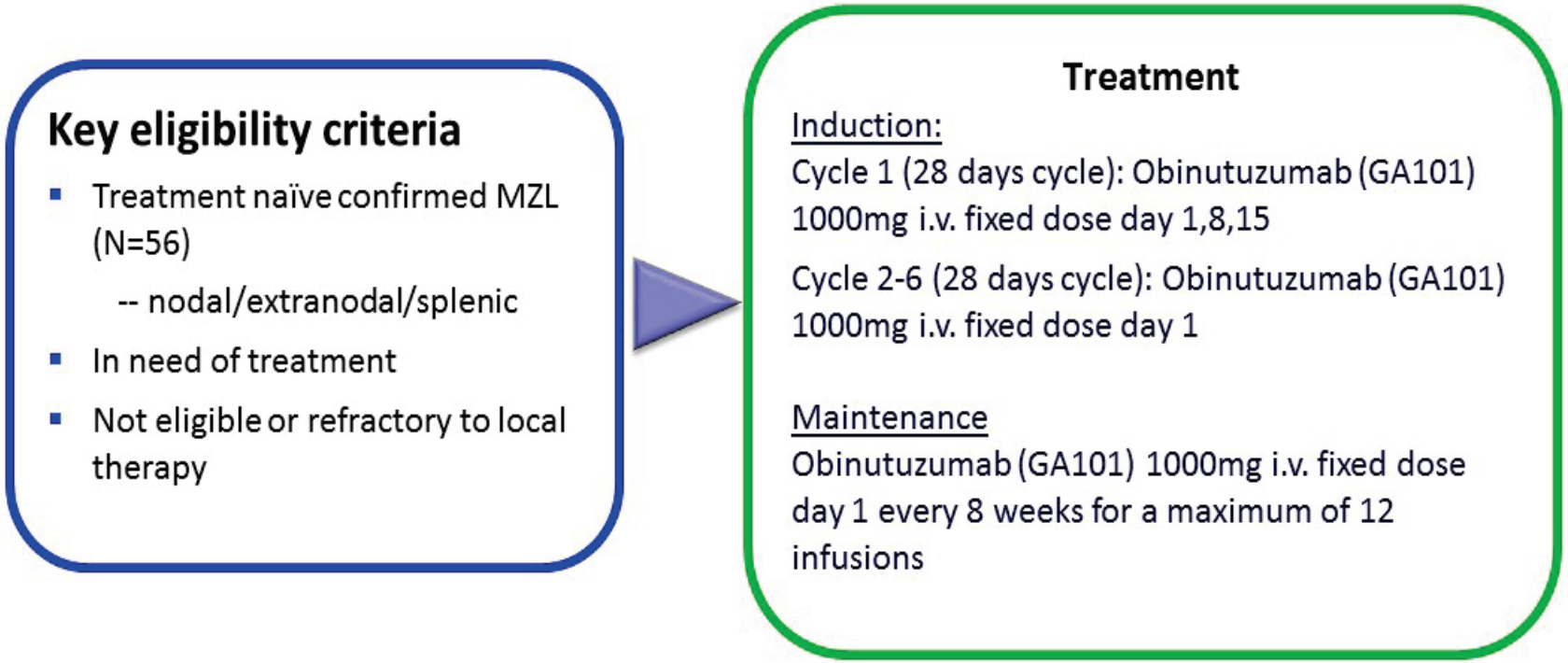
OLYMP-1 | Study Design



Primary Endpoint:
CR rate (CRR) (determined after induction therapy)

OLYMP-1

OBINUTUZUMAB in MARGINAL ZONE LYMPHOMA



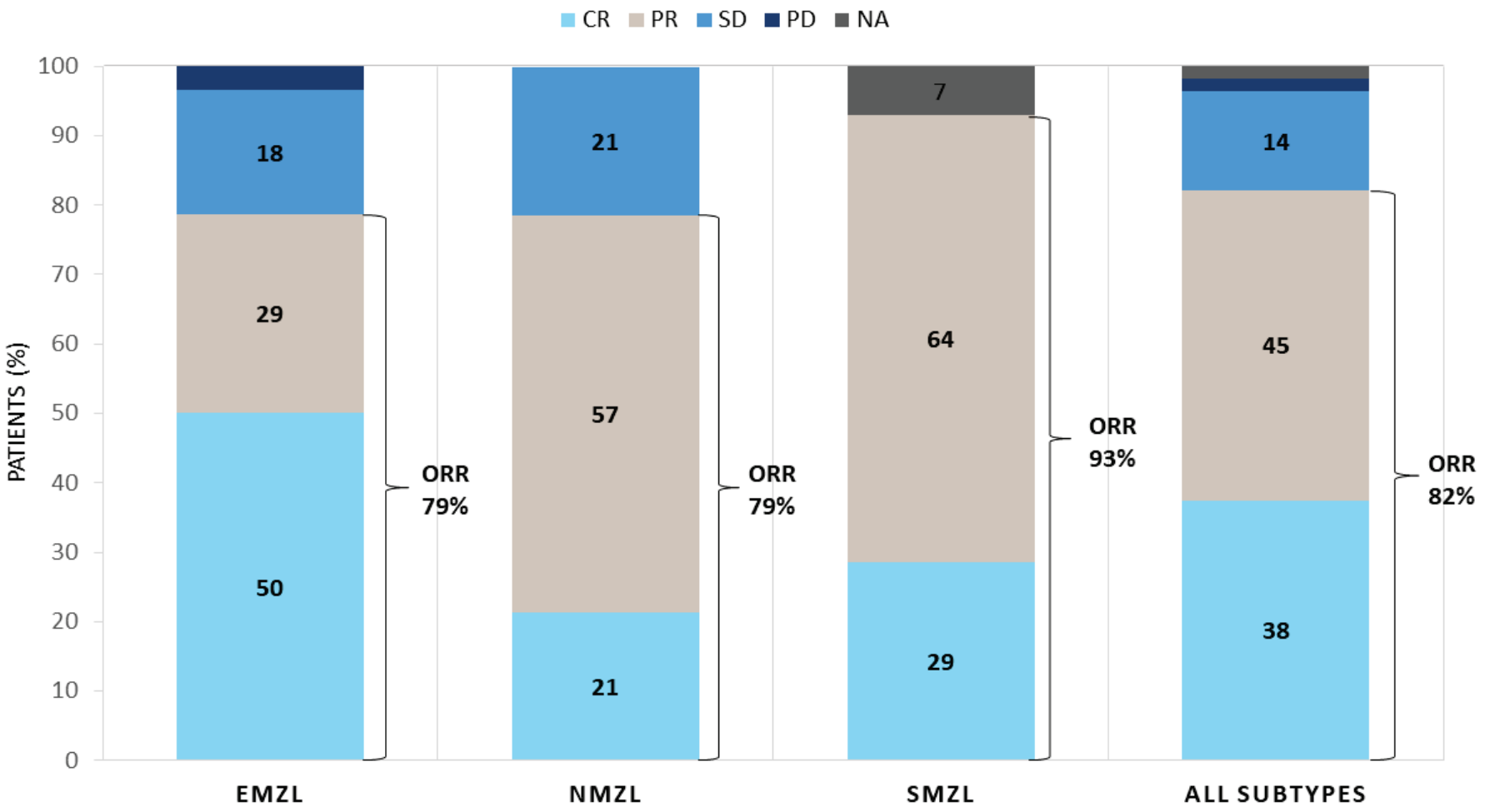
Primary Endpoint:

CR rate (CRR) (determined after induction therapy)

Patient characteristics and Adverse Events

Responses

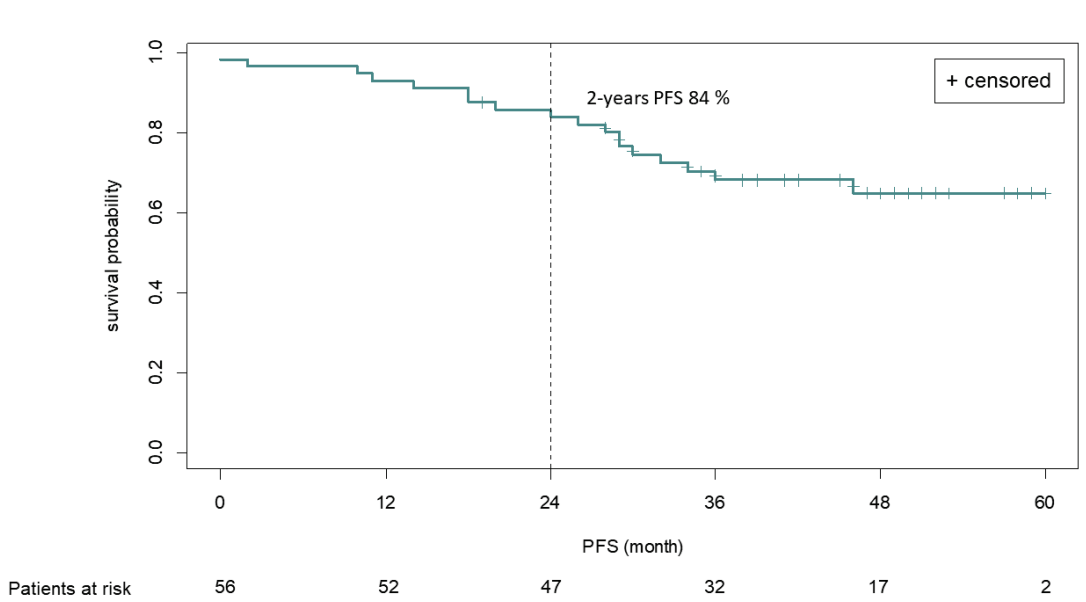
Best Response



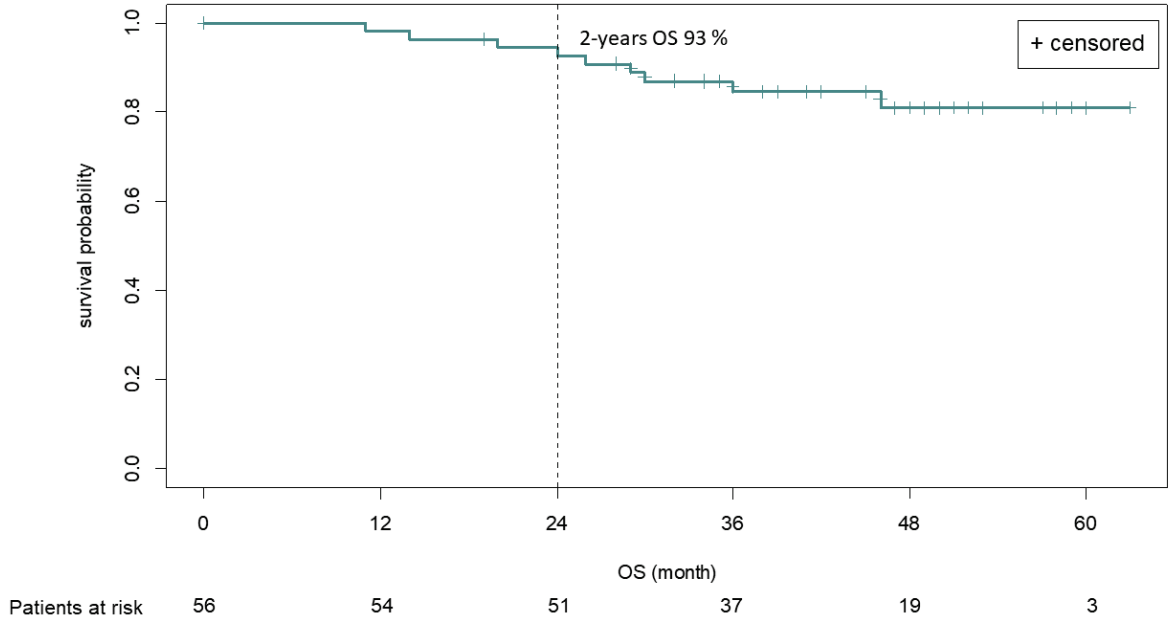
Median time to best response was 6 months

Responses

PFS



OS



93% progression free patients at two years

Causes of death (n=7):

- 4 caused by COVID-19 infection
- 2 by pneumonia
- 1 by secondary malignancy (lung cancer)

CONCLUSIONS

These data underline, that Obinutuzumab single agent is highly active and generally well tolerated in MZL with 93% of patients without progression within the first two years, and induction of CR in every second patient with EMZL. Nearly all deaths were caused by infections, reflecting patient recruitment of this trial in the COVID-19 pandemic but also underlining the increased risk for fatal infections upon prolonged anti-CD20 treatment in this lymphoma subtype. Long-term follow-up is needed to see whether remissions are deepening and continuous over time, thereby supporting chemotherapy free approaches in MZL.

Zusammenfassung | Take-Home-Messages

- Mehrere neue Therapieoptionen nach cBTKi Versagen beim Morbus Waldenström am Horizont:
  - Venetoclax ist im Rezidiv gut verträglich (keine klinisches TLS) und auch bei CXCR4-mutierten WM Patienten wirksam
  - BTK Degrader zeichnen sich nach ersten Daten durch eine hervorragende Verträglichkeit und rasche und hohe Wirksamkeit aus.
  - In retrospektiven Daten sind auch Rituximab-basierte Chemotherapien nach cBTKI Versagen eine Option

- Chemotherapiefreie Ansätze wie Obinutuzumab – Monotherapie erreichen beim MZL in der Ersttherapie hervorragende Krankheitskontrolle

Alle Kurzpräsentationen sind online unter

www.lymphome.de/eha2025

Für den Inhalt verantwortlich:

Prof. Dr. med. Christian Buske

Universitätsklinikum Ulm

Lymphom Kompetenz KOMPAKT

Kompetenznetz Maligne Lymphome

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

EHA 2025

MAILAND, ITALIEN

12. – 15. Juni 2025

Das Informationsprojekt wird unterstützt von:

abbvie

AstraZeneca

GSK

HEXAL
A Sandoz Brand

Lilly

Die Firmen hatten keinen Einfluss auf die Inhalte.