Kompetenznetz Maligne Lymphome

64th ASH Meeting 2022

New Orleans & virtuell

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

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Expert:innen berichten zu Lymphomen & Leukämien

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Morbus Waldenström (WM) Marginalzonen-Lymphom (MZL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2021 wird in Kooperation mit sechs unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	--
Beratungs-/ Gutachtertätigkeit	Roche, Janssen, AbbVie, Novartis, Bayer, Celltrion, Incyte, Beigene, BMS
Besitz von Geschäftsanteilen, Aktien oder Fonds	--
Patent, Urheberrecht, Verkaufslizenz	--
Honorare	Roche, Janssen, AbbVie, Novartis, Bayer, Celltrion, Incyte, Pfizer, Beigene, BMS
Finanzierung wissenschaftlicher Untersuchungen	Roche, Janssen, Bayer, Celltrion, MSD
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

Kapitel 1

Morbus Waldenström

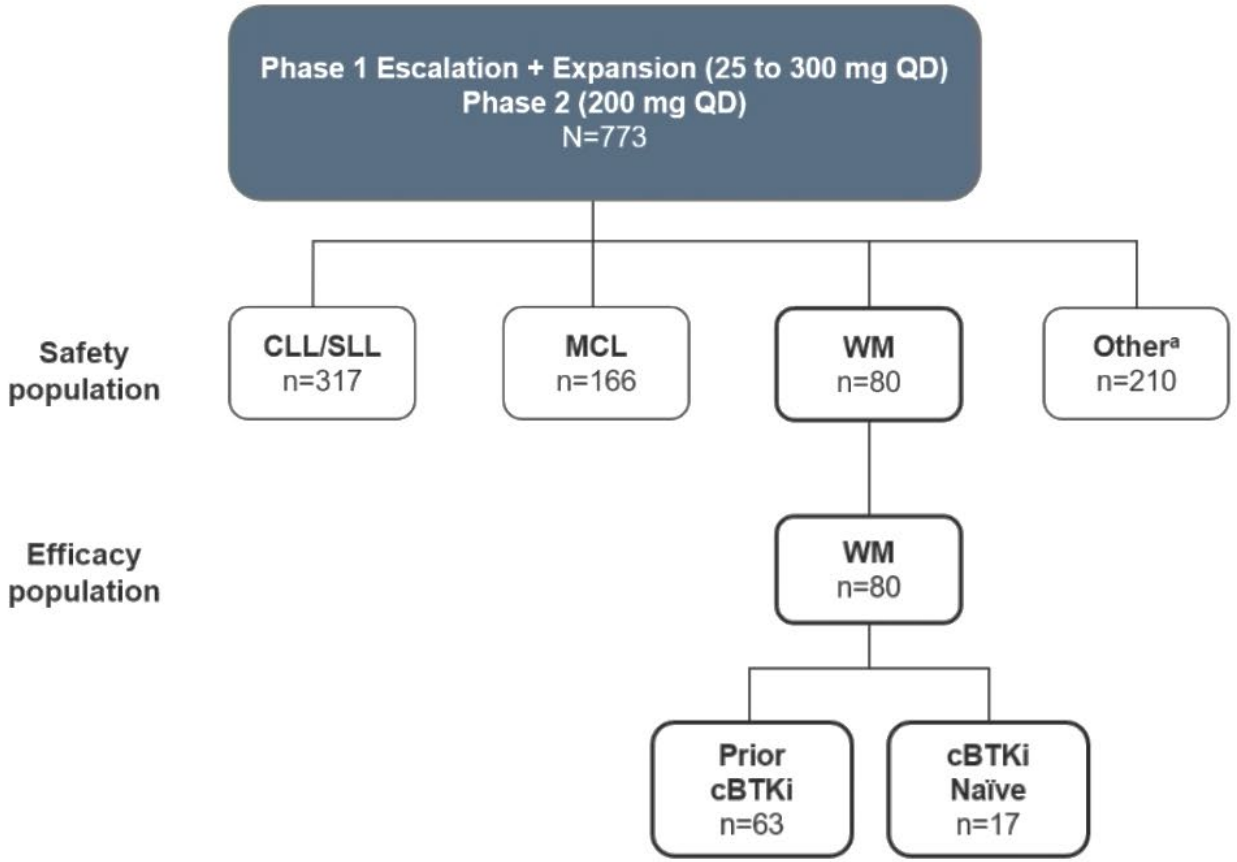
Therapie nach BTK Inhibitor Versagen?

Pirtobrutinib bei BTKi Versagen beim Morbus Waldenström

#229 Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

M.Lia Palomba, et al.

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

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

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR (IWWM6/Modified IWWM6) as assessed by Investigator

cBTKi, covalent Bruton tyrosine kinase inhibitor. Data cutoff date of 29 July 2022. [a]Other includes DLBCL, Richter transformation, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

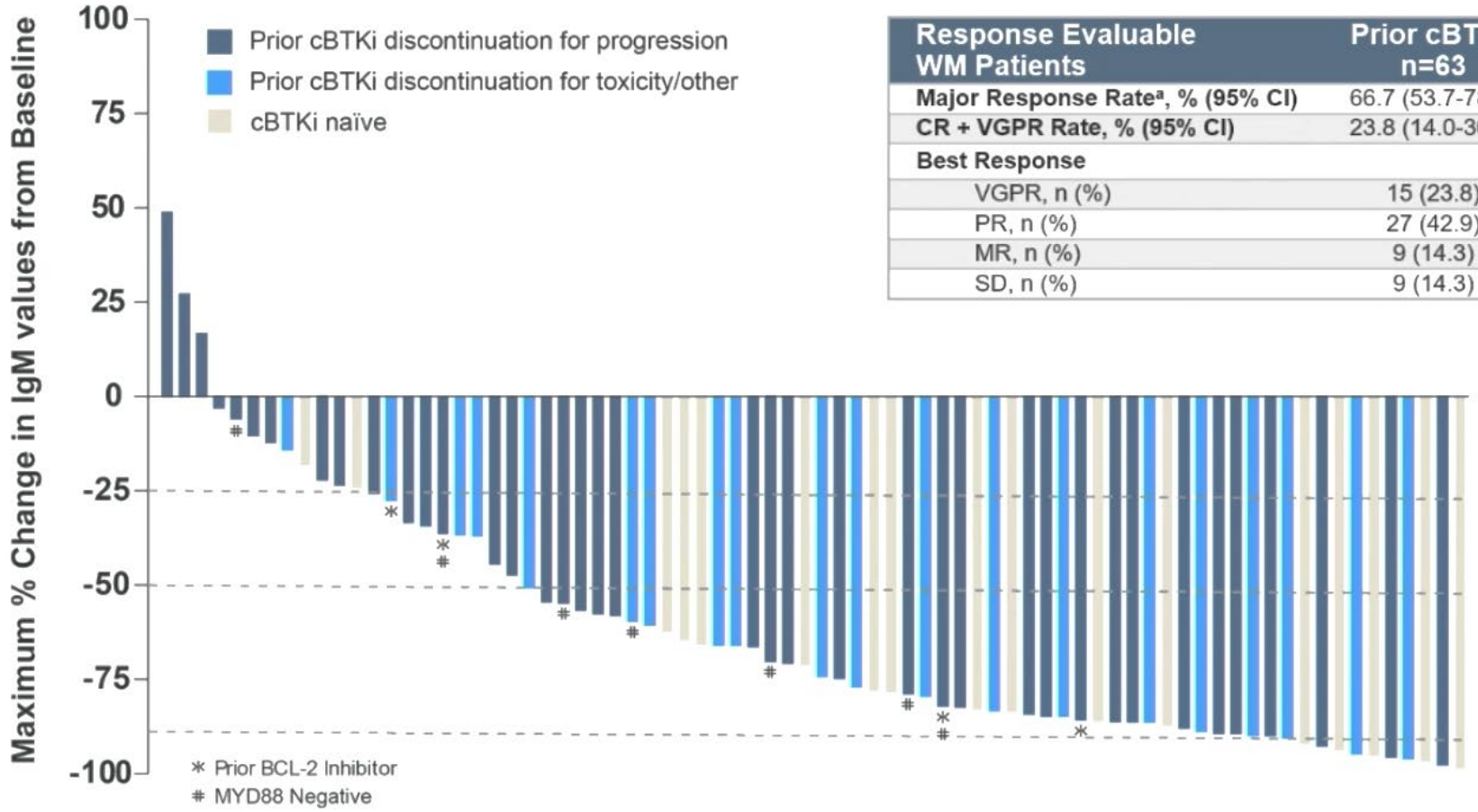
WM Patient Characteristics

Characteristics	Prior cBTKi n=63	cBTKi Naïve n=17
Median age (range), years	69 (42-84)	68 (47-83)
Male, n (%)	42 (67)	10 (59)
ECOG PS, n (%)		
0	34 (54)	9 (53)
1	28 (44)	8 (47)
2	1 (2)	0 (0)
Median number prior lines of systemic therapy (range)	3 (1-11)	2 (1-4)
Prior therapy, n (%)		
cBTK inhibitor	63 (100)	0 (0)
Chemotherapy	52 (83)	17 (100)
Anti-CD20 antibody	58 (92)	16 (94)
CIT + BTK inhibitor	50 (79)	0 (0)
PI3K inhibitor	3 (5)	0 (0)
Immunomodulator	6 (10)	2 (12)
BCL2 inhibitor	4 (6)	0 (0)
Autologous stem cell transplant	4 (6)	0 (0)
Other systemic therapy	31 (49)	6 (35)
Reason discontinued any prior BTK inhibitor[a,b], n (%)		
Progressive disease	41 (65)	-
Toxicity/Other	21 (33)	-

	Prior cBTKi n=63	cBTKi Naïve n=17
WM IPSS score, n (%)		
Low	13 (21)	1 (6)
Intermediate	38 (60)	14 (82)
High	10 (16)	2 (12)
Missing	2 (3)	0 (0)
IgM, median (min, max)	2.46 (0.1, 8.0)	2.59 (0.6, 6.1)
≤7 g/dL, n (%)	61 (97)	17 (100)
>7 g/dL, n (%)	2 (3)	0 (0)
β-2 Microglobulin, median, (min, max)	4.00 (1.6, 95.3)	3.36 (2.4, 11.8)
≤3 mg/L, n (%)	20 (32)	3 (18)
>3 mg/L, n (%)	41 (65)	14 (82)
Missing, n (%)	2 (3)	0 (0)
Peripheral blood cytopenias, n (%)		
Hemoglobin ≤11.5 g/dL	42 (68)	12 (71)
Platelet count ≤100 × 10^9/L	11 (18)	3 (18)
MYD88 genotype[c], n (%)		
Negative	7 (11)	0 (0)
Positive	52 (83)	9 (53)
Missing	4 (6)	8 (47)
CXCR4 genotype[c], n (%)		
Negative	11 (18)	0 (0)
Positive	9 (14)	0 (0)
Missing	43 (68)	17 (100)
Extramedullary disease, n (%)		
Lymphadenopathy	37 (59)	10 (59)
Splenomegaly	18 (29)	3 (18)

cBTKi, covalent Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; IPSS, International Prognostic Scoring System. Data cutoff date of 29 July 2022. Total % may be different than the sum of the individual components due to rounding. [a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]One patient had unknown reason for prior BTKi discontinuation. [c]Molecular characteristics were determined locally and are presented based on data availability.

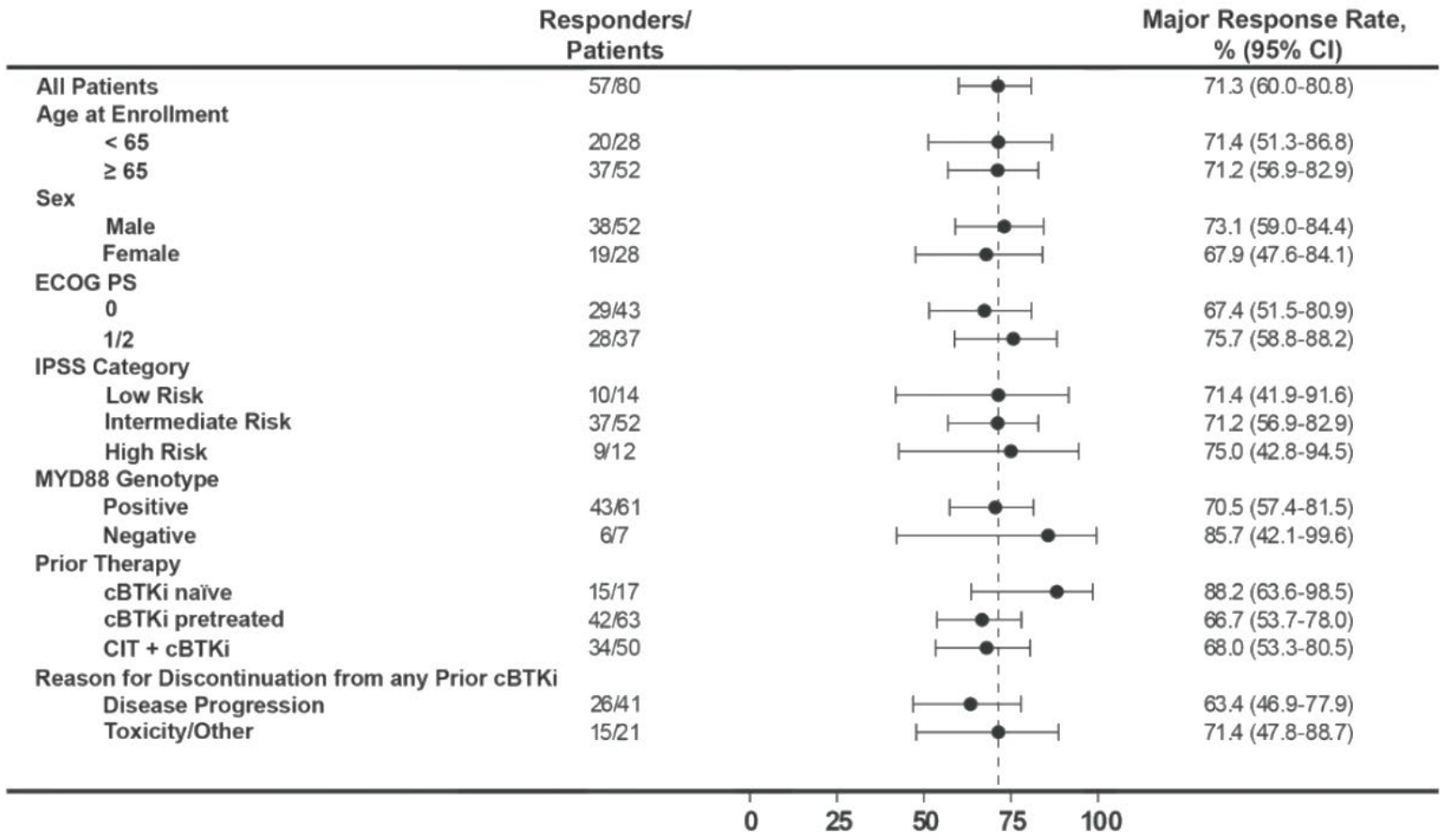
Pirtobrutinib Efficacy in WM Patients



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)

Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding.

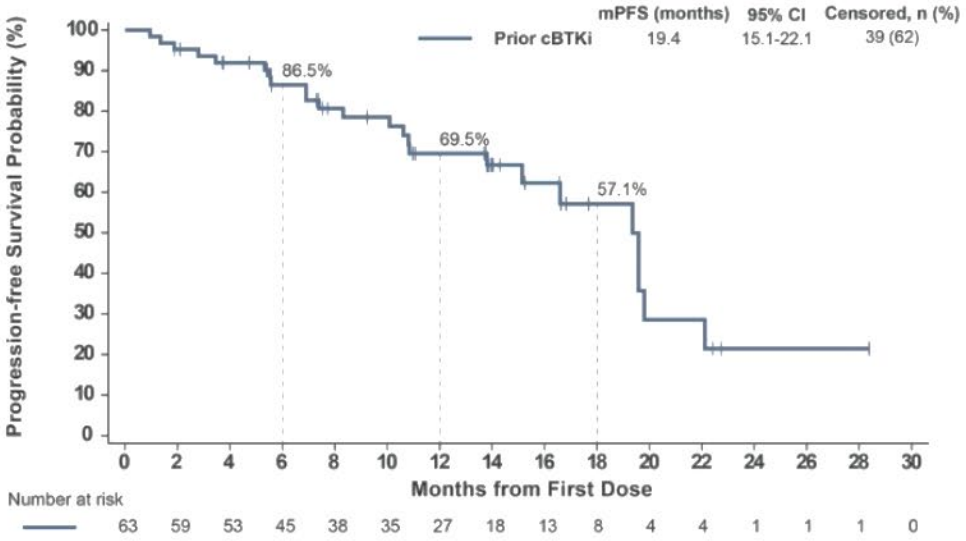
Major Response Rate in WM Subgroups



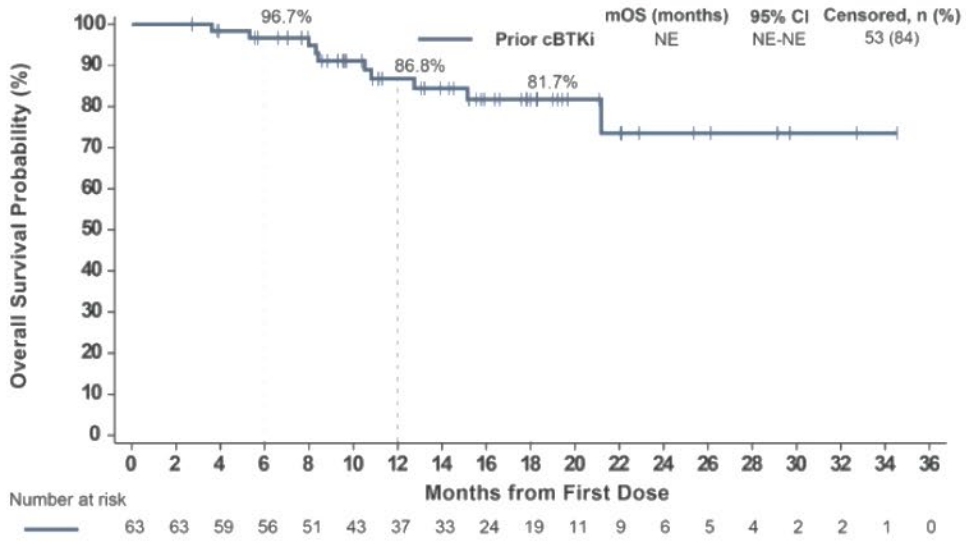
Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Progression-Free Survival and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

Kapitel 2

Morbus Waldenström

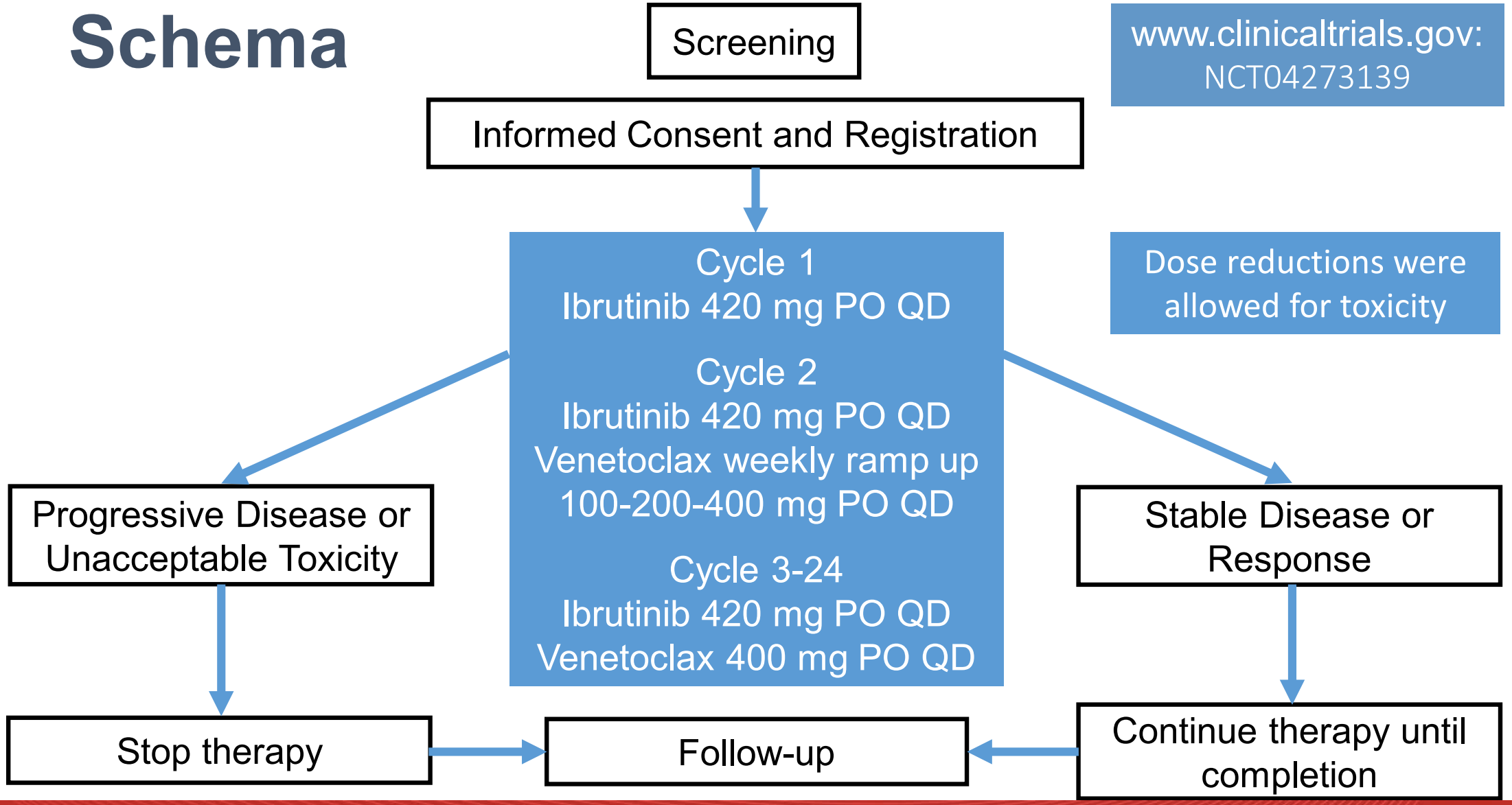
Chemotherapiefreie Ansätze zeitlich begrenzt?

Ibrutinib Therapie zeitlich begrenzt

#231 Ibrutinib and Venetoclax in Previously Untreated Waldenström Macroglobulinemia

Jorge J. Castillo, et al.

Schema

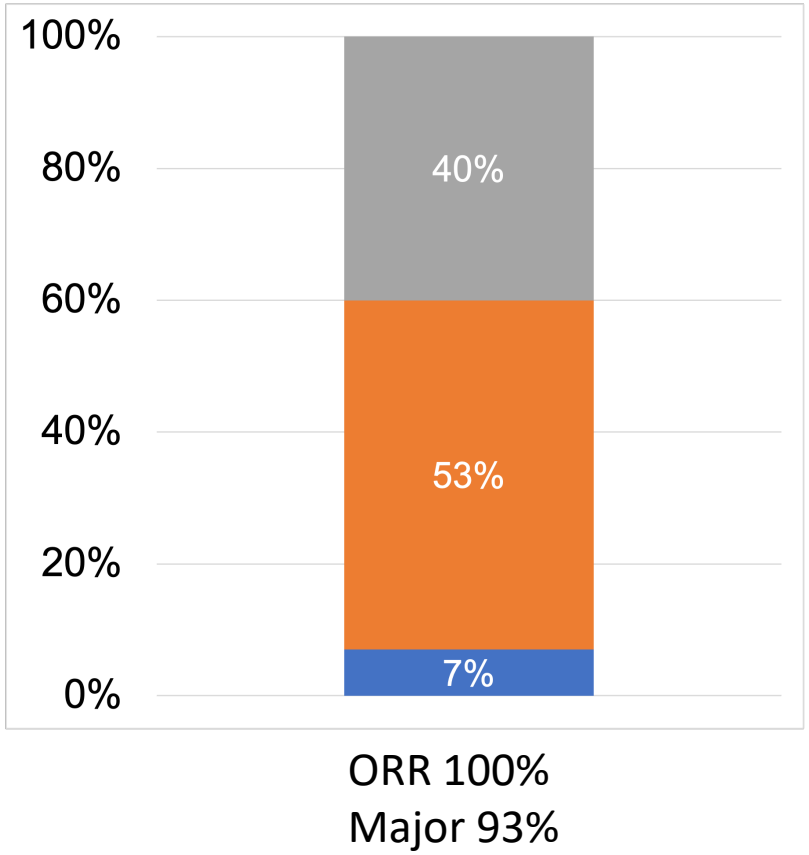

Screening
www.clinicaltrials.gov: NCT04273139
Informed Consent and Registration
Cycle 1
Ibrutinib 420 mg PO QD
Cycle 2
Ibrutinib 420 mg PO QD
Venetoclax weekly ramp up
100-200-400 mg PO QD
Cycle 3-24
Ibrutinib 420 mg PO QD
Venetoclax 400 mg PO QD
Dose reductions were allowed for toxicity
Progressive Disease or Unacceptable Toxicity
Stable Disease or Response
Stop therapy
Follow-up
Continue therapy until completion

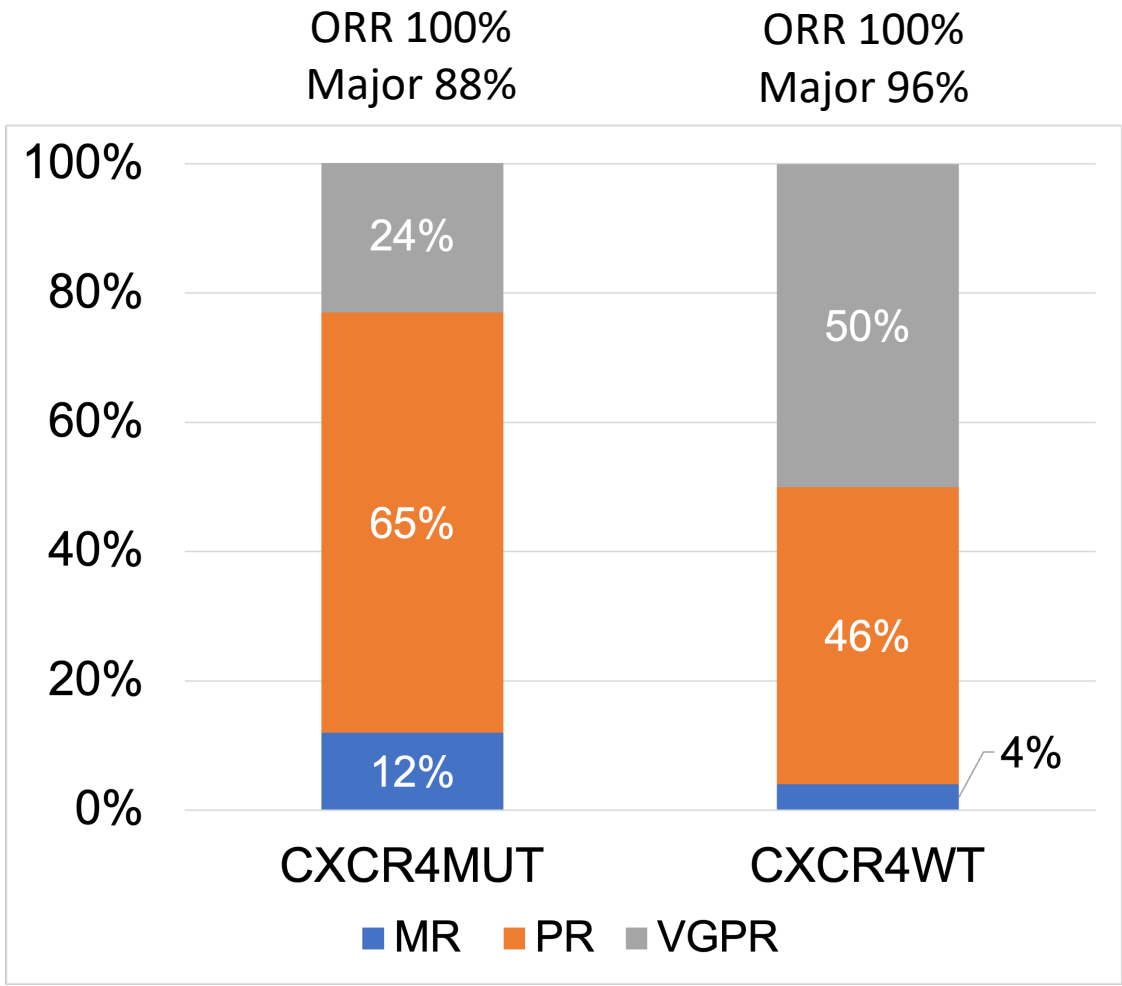
Patients' characteristics

Variable	n=45
Age IVEN initiation	67 (39-81)
Male sex	30 (67%)
Serum IgM level (mg/dl)	4297 (572-9211)
Serum IgG level (mg/dl)	567 (110-8303)
Hemoglobin level (g/dl)	10.2 (7.5-15.3)
Platelet count (k/ul)	274 (75-596)
B2-microglobulin level (mg/l)	3.9 (1.7-12)
BM involvement	60% (5-90%)

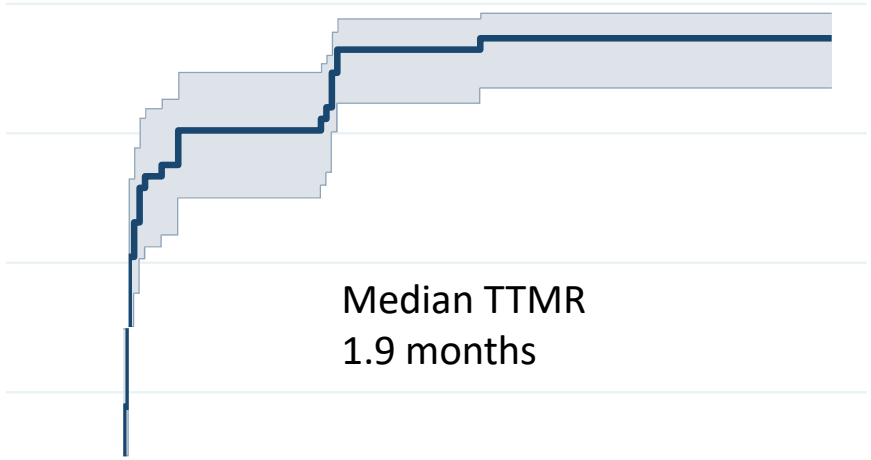
Variable	n=45
Adenopathy ≥1.5 cm	25 (56%)
Splenomegaly ≥15 cm	13 (29%)
Acquired VWD	9 (20%)
Detectable cryoglobulins	3 (7%)
Low IPSSWM	9 (20%)
Intermediate IPSSWM	16 (36%)
High IPSSWM	19 (43%)
CXCR4 mutation	17 (38%)

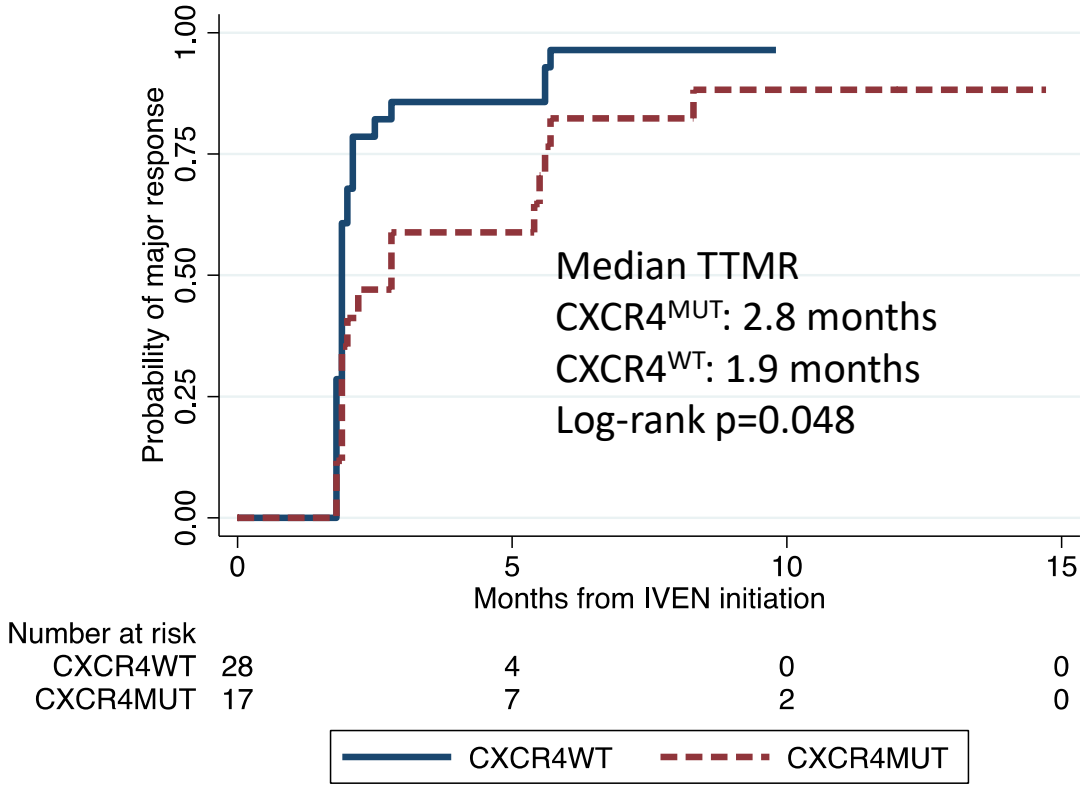
Response to therapy





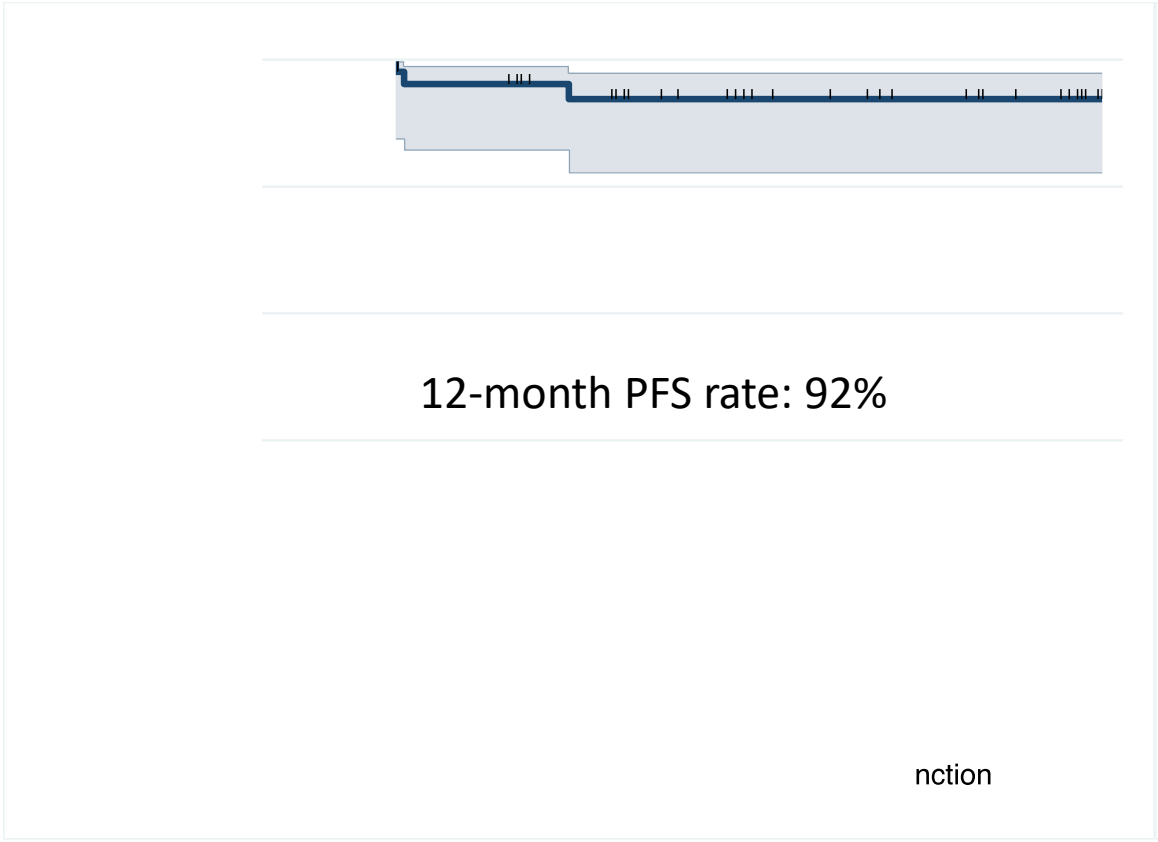
Time to major response





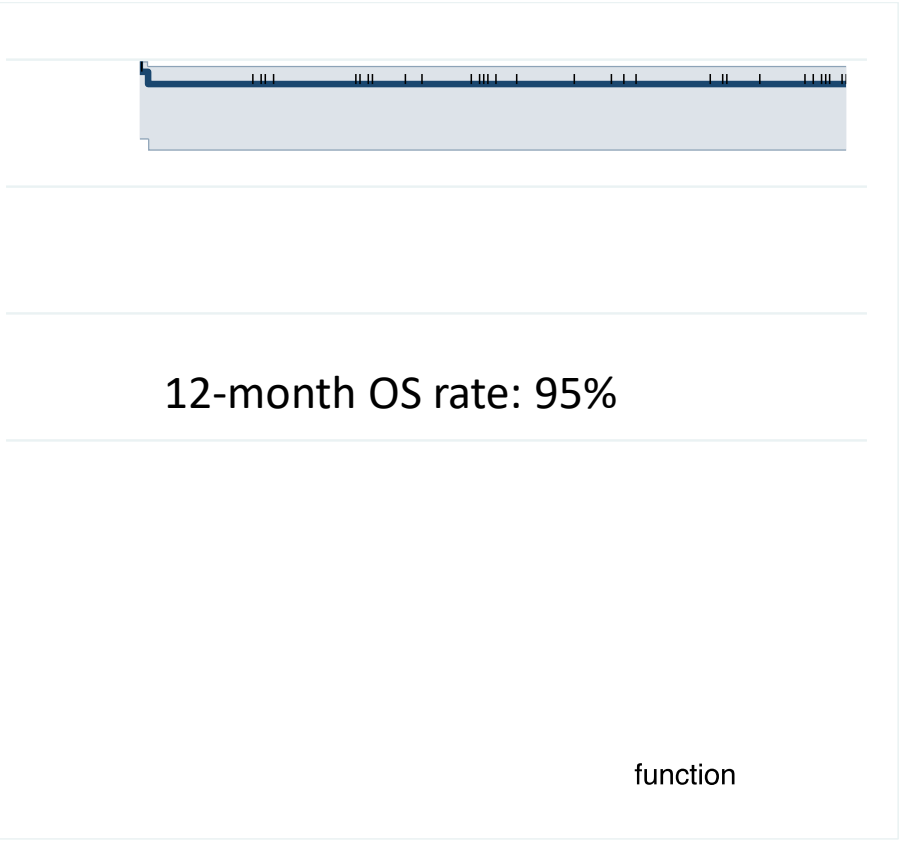
Survival analysis

Median follow-up: 11 months



12-month PFS rate: 92%

nction



12-month OS rate: 95%

function

Safety

Adverse events observed in ≥3 patients and of clinical importance

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

Kapitel 3

Marginalzonenlymphom

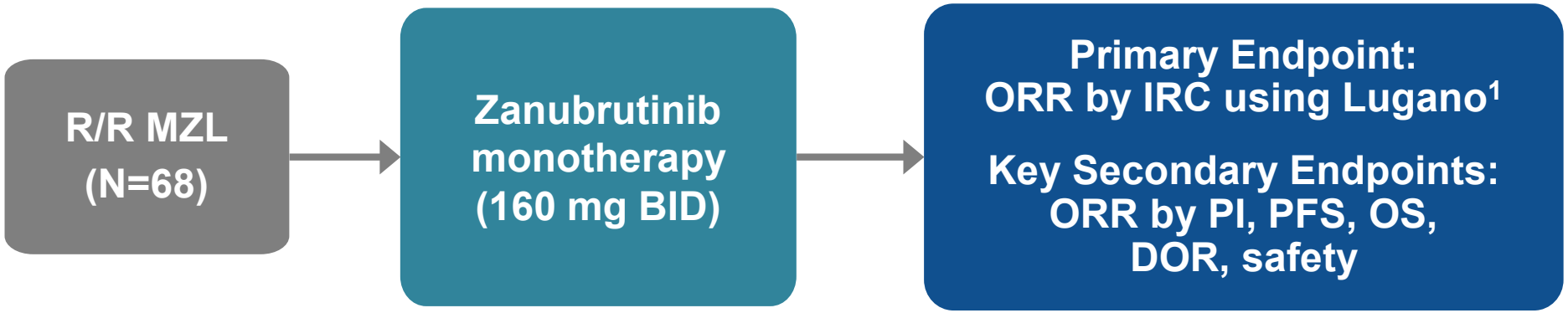
Langzeitergebnisse Zanubrutinib beim MZL?

Zanubrutinib als zugelassene Substanz beim r/r MZL

#234 Long-Term Efficacy and Safety of Zanubrutinib in Patients with Relapsed/Refractory (R/R) Marginal Zone Lymphoma (MZL): Final Analysis of the Magnolia (BGB-3111-214) Trial

Stephen Opat, et al.

MAGNOLIA (BGB-3111-214) Study Design
A Phase 2, Multicenter, Open-Label, Single-Arm Study



- Patients with R/R MZL who received ≥1 CD20-directed regimen
- Response based on the Lugano classification for NHL[1]
  - PET-based criteria for patients with IRC-confirmed FDG-avid disease
  - CT-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Biomarker correlative sub-study by the Australasian Leukaemia and Lymphoma Group

CT, computerized tomography; DOR, duration of response; FDG, fluorodeoxyglucose; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PI, principal investigator.

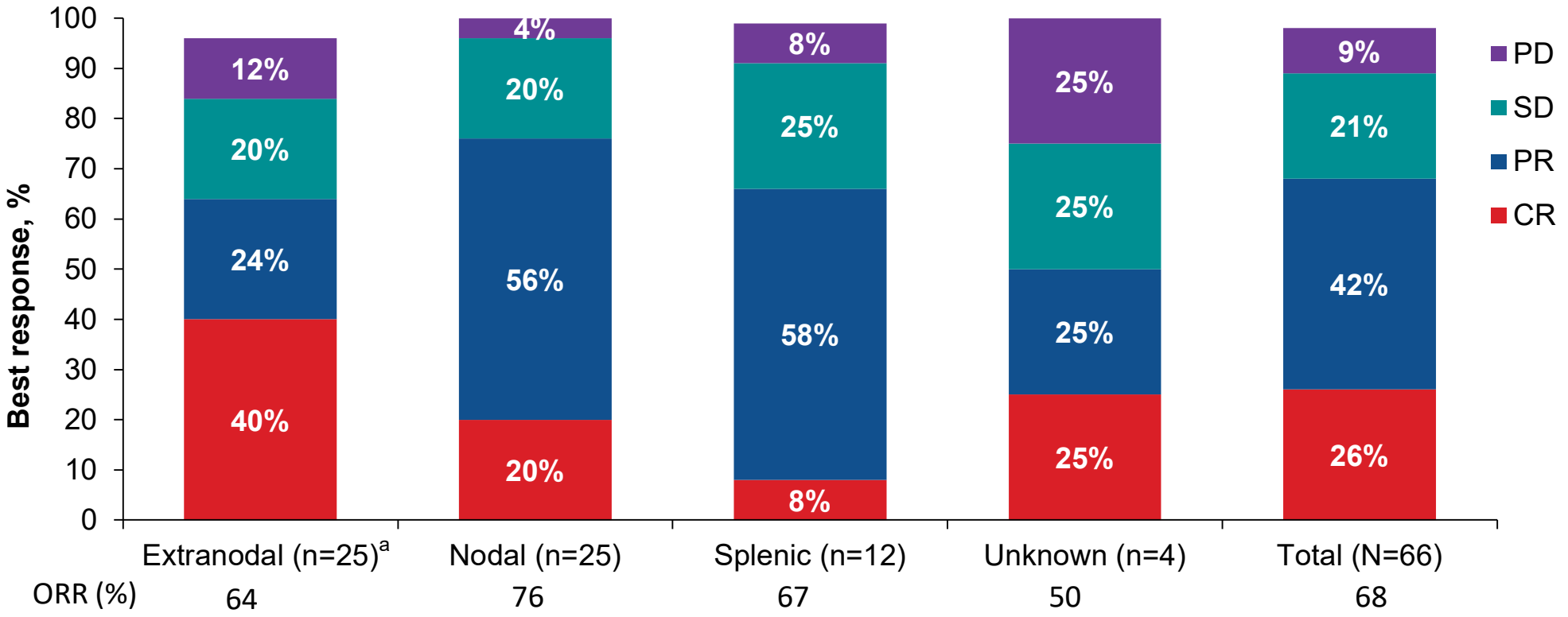
1. Cheson et al. *J Clin Oncol* 2014;32(27):3059-3067.

Baseline Demographics and Disease History

Characteristics, n (%)	Total (N=68)
Median age (range), years	70 (37-95)
≥65	41 (60)
≥75	19 (28)
Male	36 (53)
ECOG PS 0/1[a]	63 (93)
MZL subtypes	
Extranodal	26 (38)
Nodal	26 (38)
Splenic	12 (18)
Unknown	4 (6)
Disease status	
Relapsed	44 (65)
Refractory	22 (32)
Stage III/IV	59 (87)
FDG-avid (by IRC)	61 (90)
Extranodal site involvement	53 (78)
Bone marrow infiltration	29 (43)
Median prior lines of systemic therapy (range)	2 (1-6)
Immunochemotherapy	61 (90)[b]
Rituximab monotherapy	7 (10)

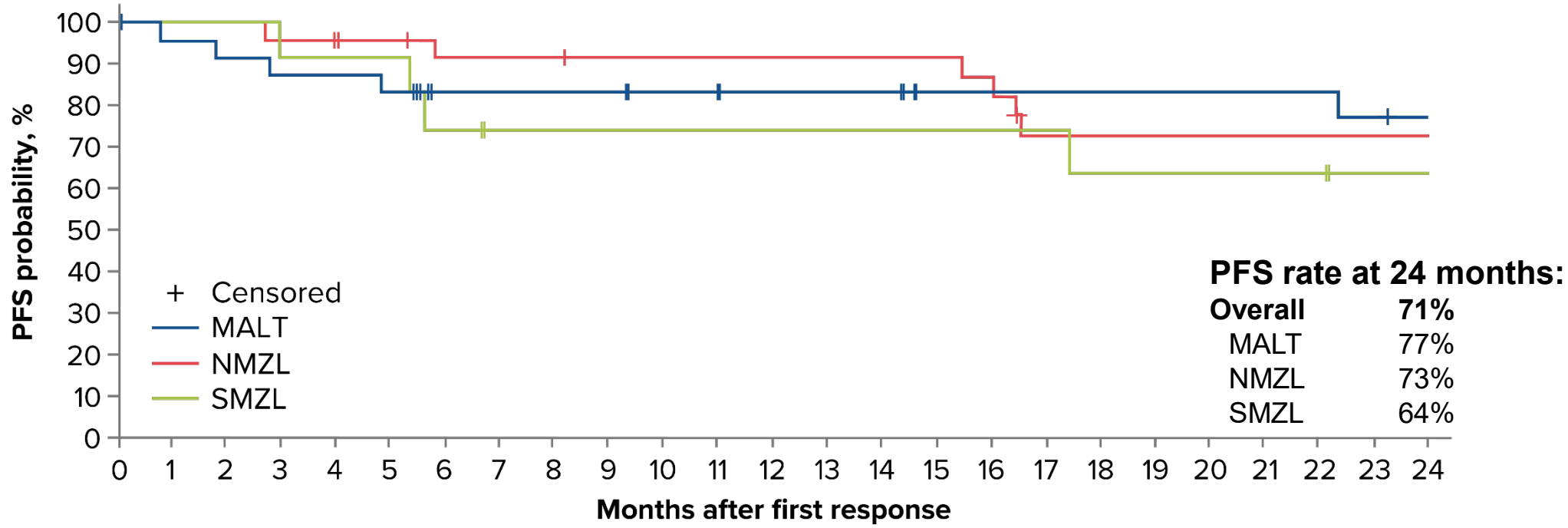
[a]Overall, 43% of patients had ECOG 1/2. [b]Rituximab-based chemotherapy in most patients (n=60; 88%).

Best Overall Response by IRC and MZL Subtypes



[a]One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.

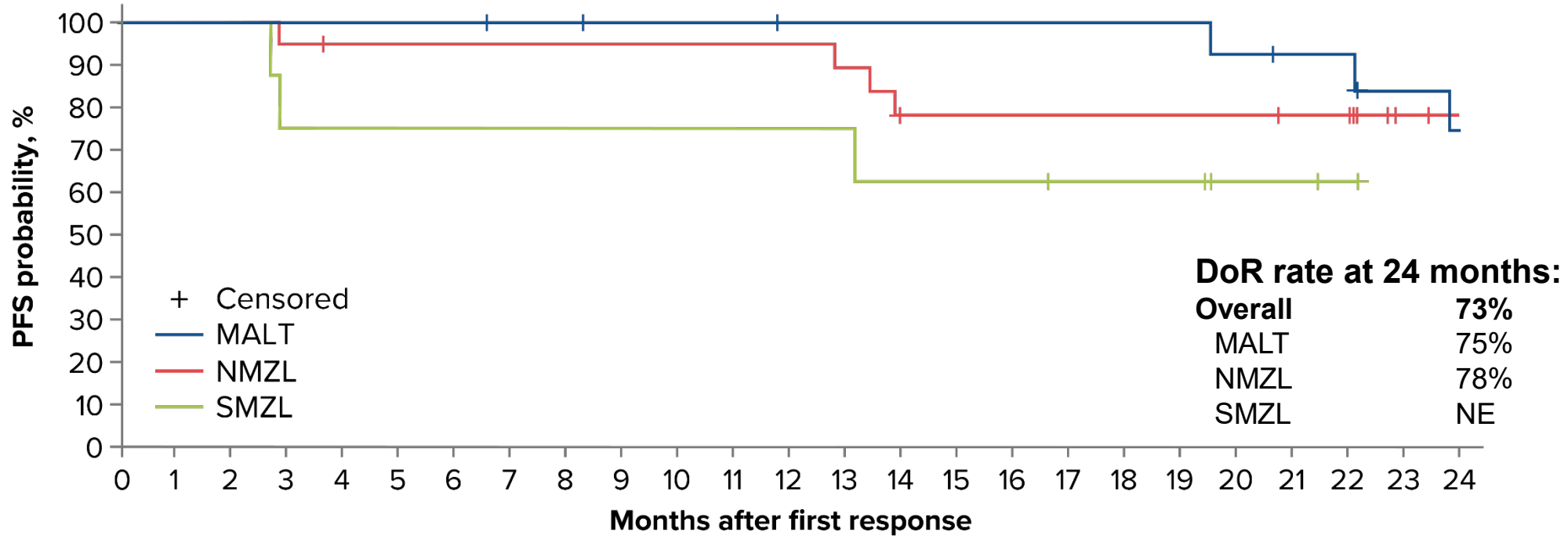
PFS by MZL Subtypes by IRC Assessment



No. at risk

MALT	25	23	22	21	21	20	18	18	18	18	17	17	16	16	16	14	14	14	14	14	14	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	20	20	20	20	20	20	19	15	15	15	15	15	15	15
SMZL	12	12	12	11	11	11	8	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	4	4

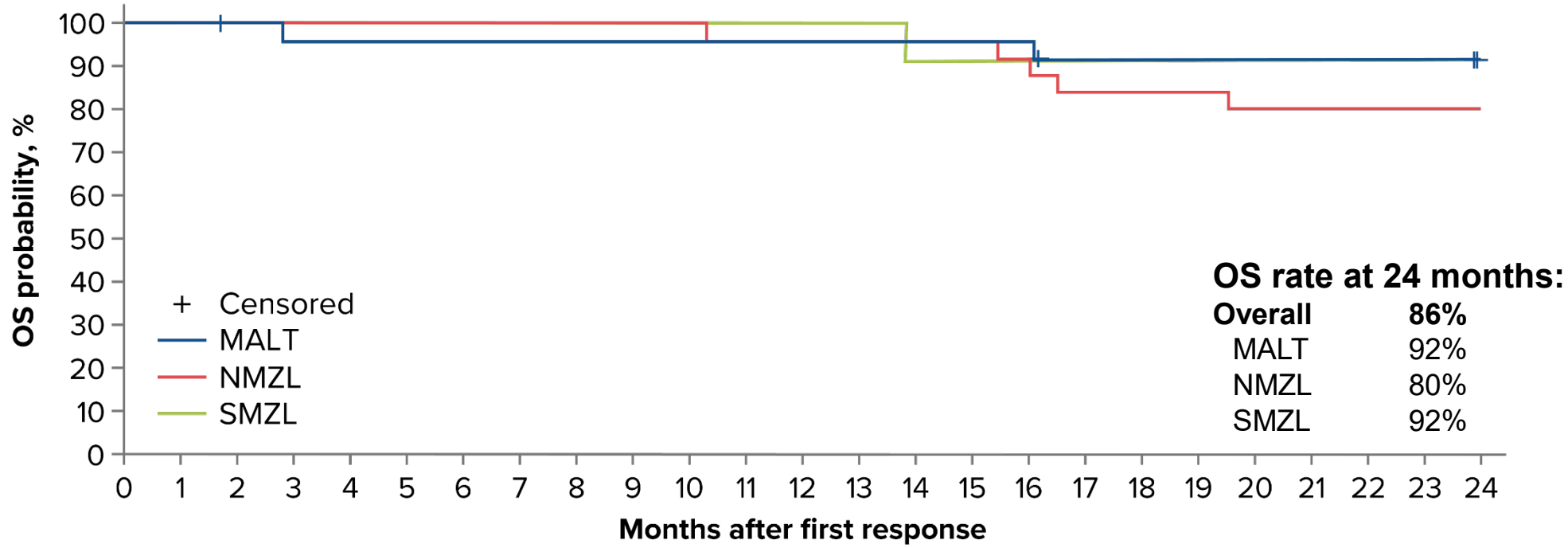
DOR by MZL Subtypes by IRC Assessment



No. at risk

MALT	16	16	16	16	16	16	16	15	15	14	14	14	13	13	13	13	13	13	13	13	12	11	11	9	8
NMZL	19	19	19	18	17	17	17	17	17	17	17	17	17	17	17	16	13	13	13	13	13	12	11	7	6
SMZL	8	8	8	6	6	6	6	6	6	6	6	6	6	6	5	5	5	4	4	4	2	2	1	0	

Overall Survival by MZL Subtypes



No. at risk

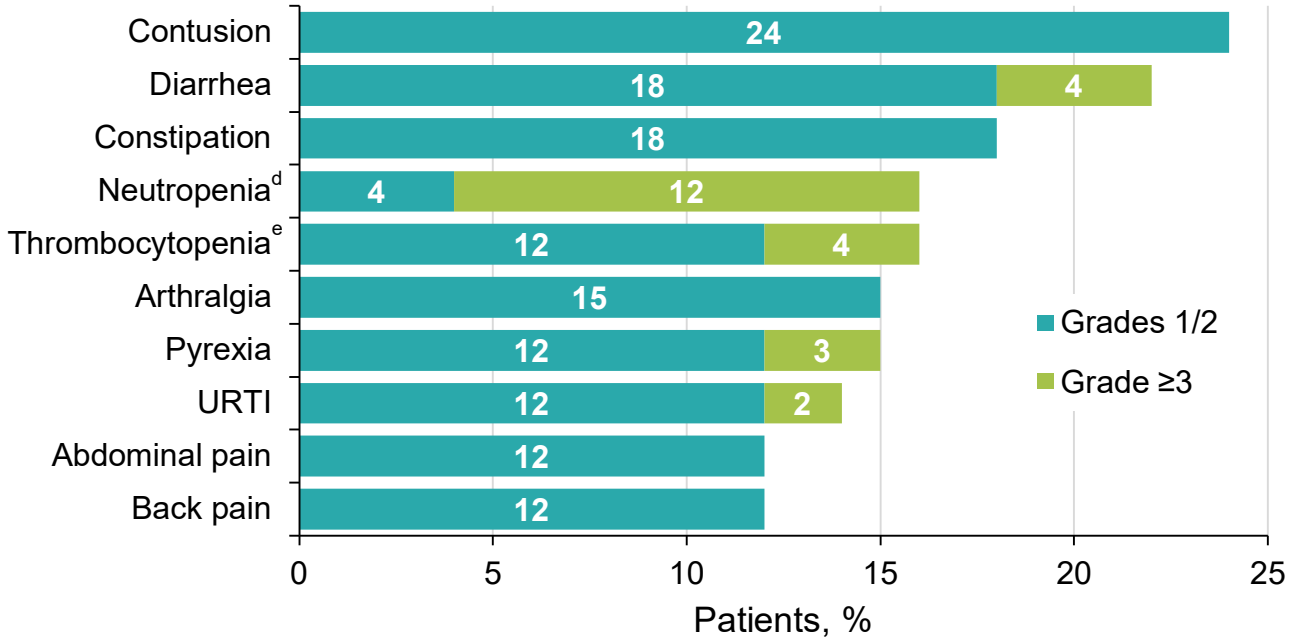
MALT	25	25	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	21	21	21	21	21	21	21	21
NMZL	25	25	25	25	25	25	25	25	25	25	25	24	24	24	24	24	23	21	21	21	20	20	20	20	20
SMZL	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	10

TEAEs in All Patients

Safety Summary

TEAEs, n (%)	N=68
Patients with ≥1 TEAE	68 (100)
Grade ≥3 TEAE	33 (48)
Serious TEAE	30 (44)
Leading to death	5 (7)[a]
Leading to dose interruption	25 (37)[b]
Leading to study drug discontinuation	5 (7)[c]
Leading to dose reduction	0

Most Common TEAEs



[a]Five patients died owing to AEs: COVID-19 pneumonia (n=2); myocardial infarction in a patient with preexisting cardiovascular disease (n=1); acute myeloid leukemia in a patient with prior exposure to an alkylating agent (n=1); septic encephalopathy following radical cystectomy and ileal conduit in a patient with recurrent bladder cancer (in CR at the time of death; [n=1]). [b]Most common AEs leading to dose interruption: COVID-19 pneumonia (n=4), neutropenia (n=3), diarrhea (n=2), lower respiratory tract infection (n=2), pneumonia (n=2), pyrexia (n=2), syncope (n=2), and tonsillitis (n=2). [c]Five patients discontinued owing to AEs: COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); myocardial infarction (n=1); septic encephalopathy (n=1). [d]Includes neutropenia and neutrophil count decreased. [e]Includes thrombocytopenia and platelet count decreased
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

TEAEs of Clinical Interest

TEAEs of interest, n (%)	N=68	
	All grade	Grade ≥3
Infections	38 (56)	15 (22)[a]
Hemorrhage	28 (41)	1 (1.5)[b]
Cardiac		
Hypertension	3 (4)[c]	2 (3)
Atrial fibrillation/flutter	2 (3)[d]	1 (1.5)
Ventricular extrasystole	1 (1.5)[e]	0
Second primary malignancy	5 (7)[f]	3 (4)

[a]Fatal infection: COVID-19 pneumonia (n=2).
[b]Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode.
[c]Two 2 patients had new-onset hypertension; none led to treatment reduction or discontinuation.
[d]Atrial fibrillation in a patient with preexisting atrial fibrillation (21 days after end of treatment owing to disease progression). Patient with atrial flutter recovered spontaneously and continued zanubrutinib.
[e]Ventricular extrasystole in an 83-year-old patient with no known cardiac history, was non-serious, transient, resolved on the same day, and did not lead to treatment modification or discontinuation.
[f]Includes basal cell and squamous cell carcinoma and basal cell carcinoma (with history of skin cancer); papillary thyroid carcinoma; (with preexisting thyroid nodule); recurrent bladder cancer and prostate cancer (with history of bladder cancer); and acute myeloid leukemia (with prior chemotherapy with alkylating agent).

Kapitel 4

Marginalzonenlymphom

Hochrisikopatienten mit MZL?

Frührezidive beim MZL charakterisieren eine Hochrisikogruppe

#795 Early Relapse within 24 Months after Frontline Systemic Therapy (POD24) Is Associated with Worse Survival in Patients with Marginal Zone Lymphoma: A US Multisite Study

Narendranath Epperla, et al.

POD24 beim MZL

Studiendesign - Methoden

- multicenter, retrospective cohort study of MZL patients treated at 8 US medical centers
- patients diagnosed with MZL from 2010-2020
- Patients were grouped into POD24 and non-POD24 groups.
- The primary endpoint was overall survival (OS).
- Secondary endpoints were determining the predictive factors for POD24 and cumulative incidence of histologic transformation in POD24 vs non-POD24 groups.
- Survival analysis according to POD24 was only calculated for patients with events within 24 months (early progressors).
- For patients without early progression, OS was computed starting from the time of systemic therapy.
- Patients who were censored or expired before 24 months were excluded from analysis.

POD24 beim MZL

Therapieergebnisse: Gesamtgruppe und nach Therapie aufgeschlüsselt

Figure 1. OS by POD24 vs nonPOD24

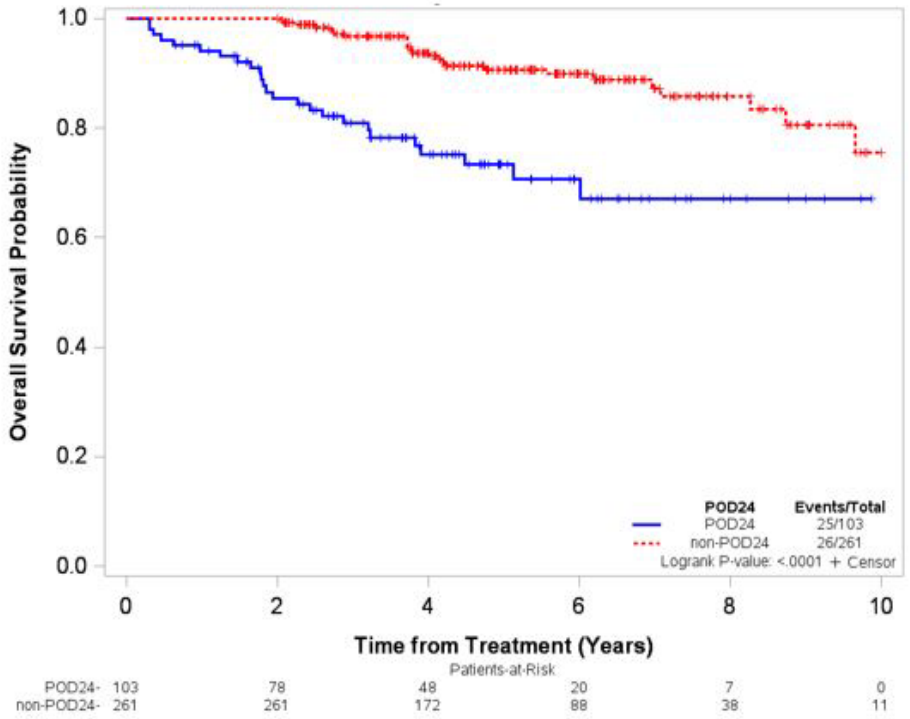
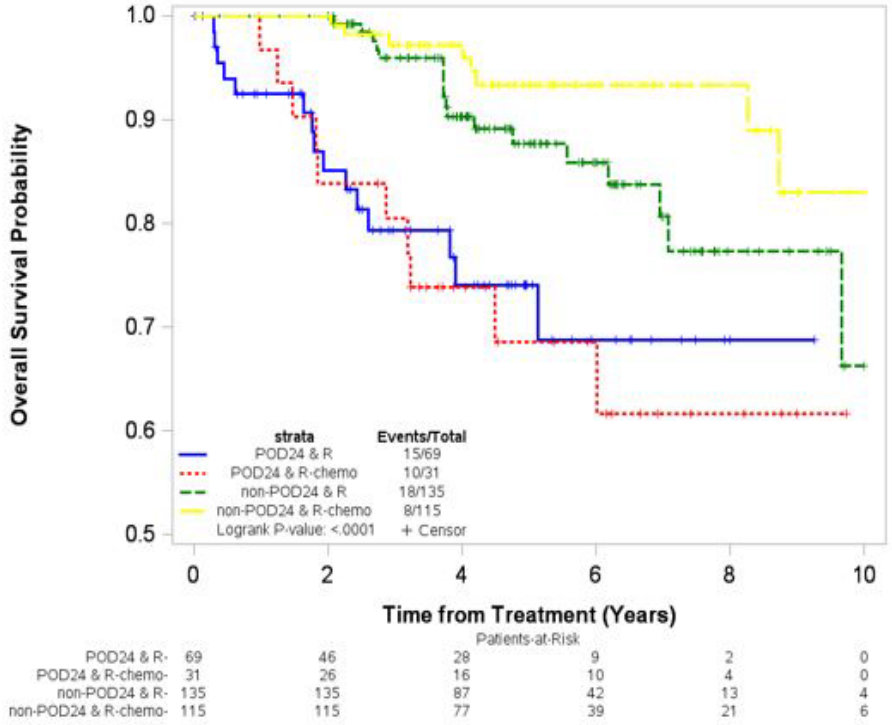


Figure 2. OS by POD24 vs nonPOD24 and treatment modality



Kapitel 5

Marginalzonenlymphom

Welche Bedeutung hat das Vorliegen eines M-Proteins?

M – Protein beim MZL: Implikationen?

#170 Impact of Monoclonal Protein at Diagnosis on Outcomes in Patients with Marginal Zone Lymphoma: A Multicenter Cohort Study

Narendranath Epperla, et al.

M – Protein beim MZL

Studiendesign - Methoden

- multicenter, retrospective cohort study of MZL patients treated at 8 US medical centers
- patients diagnosed with MZL from 2010-2020
- Patients were grouped according to the presence or absence of M-protein detectable by serum protein electrophoresis or immunofixation.
- The primary endpoint was progression-free survival (PFS).
- PFS was defined as the time from the start of first-line therapy until lymphoma relapse/progression or death from any cause, censoring at the last clinical assessment.

M- Protein beim MZL

Therapieergebnisse: Gesamtgruppe und nach Therapie aufgeschlüsselt

Figure 1

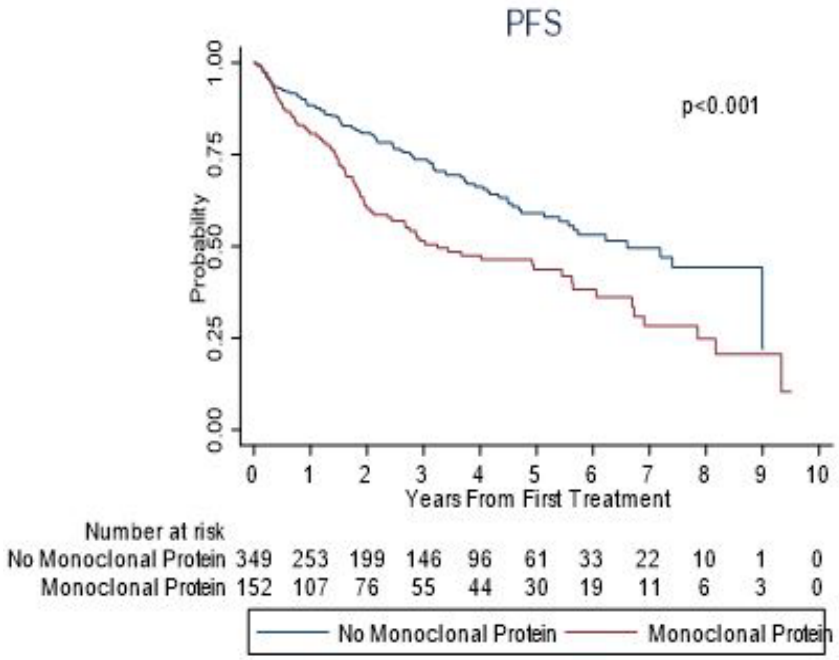
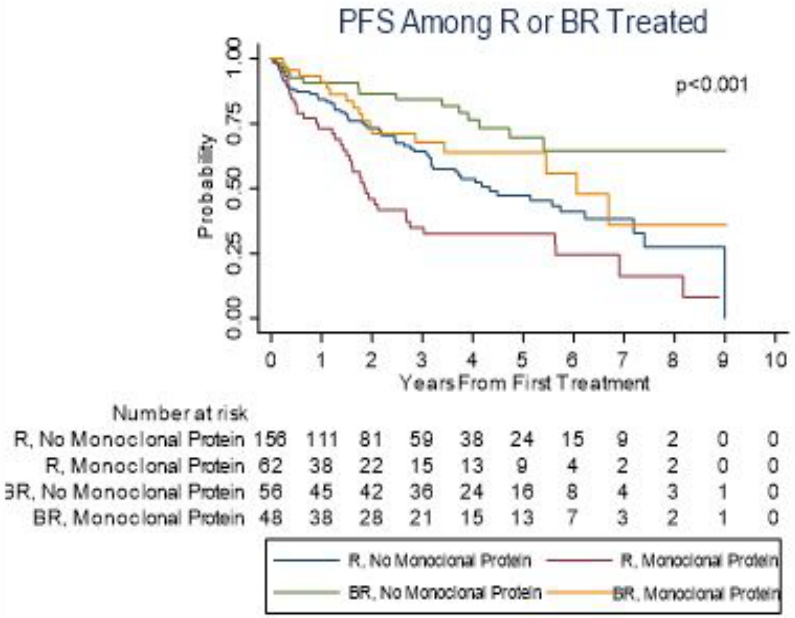


Figure 2



Zusammenfassung | Take-Home-Messages

Morbus Waldenström

- Ibrutinib/Venetoclax als zeitlich begrenzte Therapie ist im Gegensatz zur CLL beim Morbus Waldenström mit tödlichen ventrikulären Arrythmien assoziiert und wird damit nicht weiter bei dieser Erkrankung verfolgt werden.

- Der nicht-kovalente BTK Inhibitor Pirtobrutinib zeigt hohe Aktivität und sehr gute Verträglichkeit bei Waldenström – Patienten nach Versagen auf einen kovalenten BTK Inhibitor.

MZL

- Zanubrutinib zeigt auch nach längerem Follow-up robuste Aktivität und sehr gute Verträglichkeit beim r/r MZL und stellt damit eine wertvolle Bereicherung unserer therapeutischen Möglichkeiten beim MZL da.

- Ähnlich der Beobachtungen beim follikulären Lymphom rezidivieren zwischen 20-30% aller MZL bereits innerhalb von 2 Jahren und sprechen deutlich schlechter auf Therapie an.

- Bei 30% aller MZL Patienten ist ein monoklonales Protein nachweisbar. Diese Patienten sprechen zumindest in einer retrospektiven Analyse schlechter auf eine Rituximab – Monotherapie an als Patienten ohne monoklonales Protein, während dieser Unterschied nach Immunchemotherapie nicht zu sehen ist.

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2022

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