Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

66th ASH Meeting 2024

San Diego & virtuell

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Kompetenznetz Maligne Lymphome

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KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Christian Buske
Universitätsklinikum Ulm

Morbus Waldenström (WM) Marginalzonen-Lymphom (MZL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2024 wird in Kooperation mit sieben 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: Optimierung chemotherapiefreier Konzepte - cBTKi

Abstract 859

Efficacy of first line Bortezomib, Rituximab, Ibrutinib (B-RI) for patients with treatment naive Waldenström's Macroglobulinemia

Christian Buske[1], Efstathios Kastritis[2], Alexander Grunenberg[3], Andreas Viardot[3], Dajana Kaszynski[1], Heike Mund[1], Katja Gutmair[4], Matthias Zingerle[5], Paul Duewel[6], Susanne Saussele[7], Björn Schöttker[8], Ullrich Graeven[9], Martin Dreyling[10], Andrea Kerkhoff[11], Thomas Weber[12], Holger F. Hebart[13], Ralf Ulrich Trappe[14], Lisa Kaiser[1], Elke Runge[1], Jasmin Mark[1], Simone Ferrero[15], Daniela Drandi[16], Falko Fend[17], Irina Bonzheim[17], Eva Hoster[18], Jens Dreyhaupt[19] and Meletios A. Dimopoulos[2] *on behalf of the European Consortium for Waldenström's Macroglobulinemia (ECWM)*

Study Design

Induction *6 months*
- **Bortezomib**: 1.6 mg/ m^2 Day 1,8,15
- **Rituximab**: 375 mg/m^2 i.v (C1D1); 1400 mg absolute s.c (C 2-6 D1)
- **Ibrutinib**: 420 mg p.o. , daily

Maintenance I *24 months*
- **Rituximab**:1400 mg absolute s.c (D1 every 2nd month)
- **Ibrutinib**: 420 mg p.o. , daily

Maintenance II *until PD/Toxicity*
- **Ibrutinib**: 420 mg p.o., daily **until** non-tolerated toxicity or progression

Follow Up *until end of study*

Only for patients with early treatment discontiuation or PD
- Every 3 months for 2 years, afterwards every 6 months until end of study
- After Progression: Survival Follow Up every 6 months until end of study

Study design:
Phase II, single arm, open label, 1st line WM, N = 53 patients

Primary Endpoint:
1Y PFS

Secondary endpoints: response rates, PFS, OS, safety

First Pat In:	Sep 2019
Last Pat In:	Nov 2021
End of Study:	Feb 2027

Baseline Characteristics

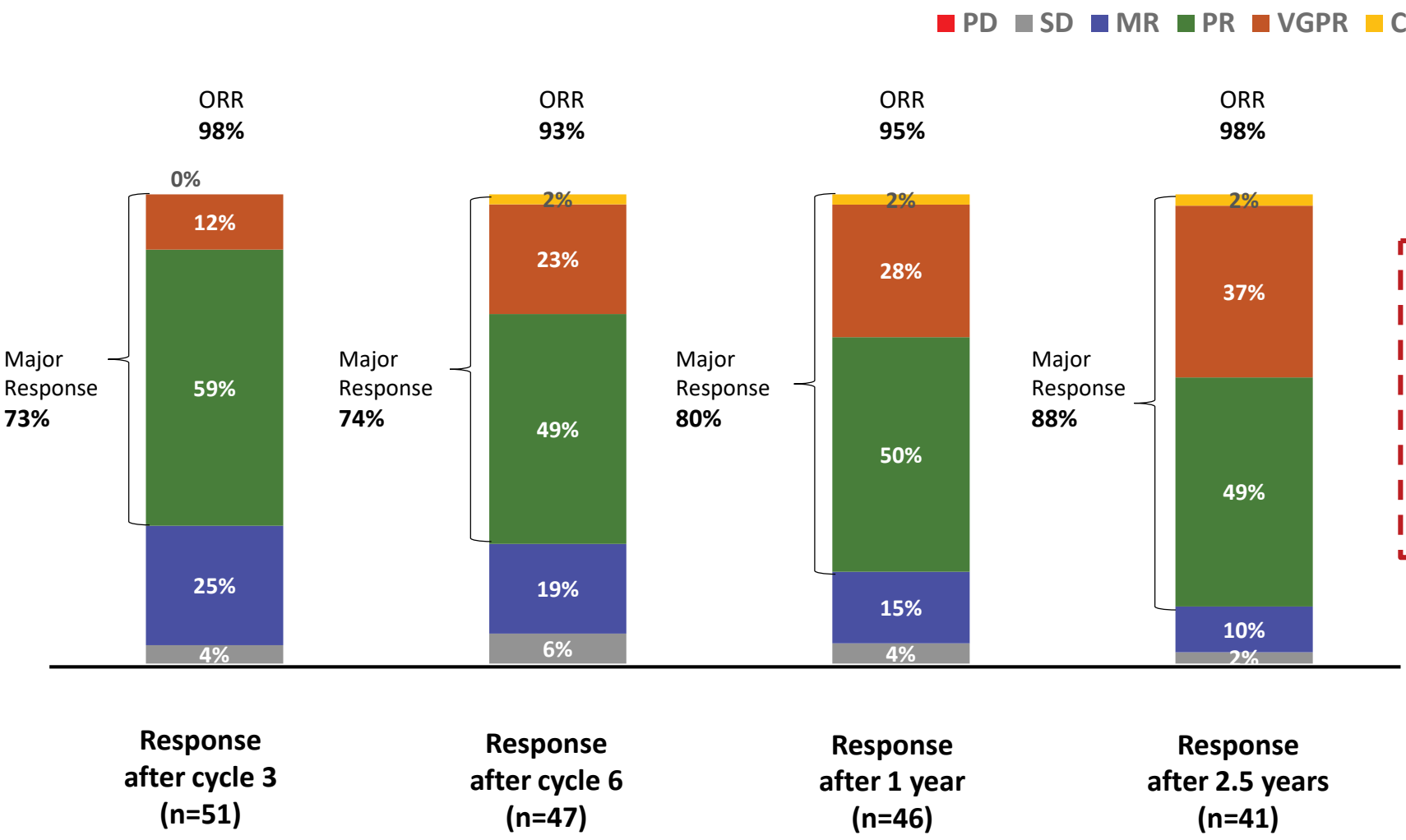
	N=53
Age, years median (range) > 65 years > 75 years	63y (36 - 84) 22 (41.5%) 8 (15.1%)
Gender, n (%) Male Female	 33 (62.3%) 20 (37.7%)
ISSWM*, n (%) Low Intermediate High	 16 (30.2%) 21 (39.6%) 16 (30.2%)
ECOG, n (%) 0 1 2	 34 (64.2%) 18 (34.0%) 1 (1.9%)
Patients with Lymphadenopathy, n (%)	29 (54.7%)
Patients with Splenomegaly (≥13cm), n (%)	12 (22.6%)

	N=53
IgM g/L median (range) (at Baseline or C1D1) Serum IgM >70 g/l, n (%)	33.9 (3.05 - 102.87) 4 (7.4%)
Hb g/dL median (range) Hb <10 g/dl, n (%)	10.1 (7.1 – 14.5) 25 (47.2%)
$ß_2$-Microglobulin > 3 mg/l, n (%)	 33 (62.3%)

Mutational Status	N = 52 (%)
$MYD88^{MT}$ • $MYD88^{MT}/CXCR4^{WT}$ • $MYD88^{MT}/CXCR4^{MT}$	50 (96%) 28 (54%) 22 (42%)
$MYD88^{WT}/CXCR4^{WT}$	2 (4%)
$TP53^{MT}$	3 (6%) 1x $MYD88^{MT}/CXCR4^{WT}$ 2x $MYD88^{MT}/CXCR4^{MT}$

*ISSWM = International Scoring System for WM = Prognostic Index

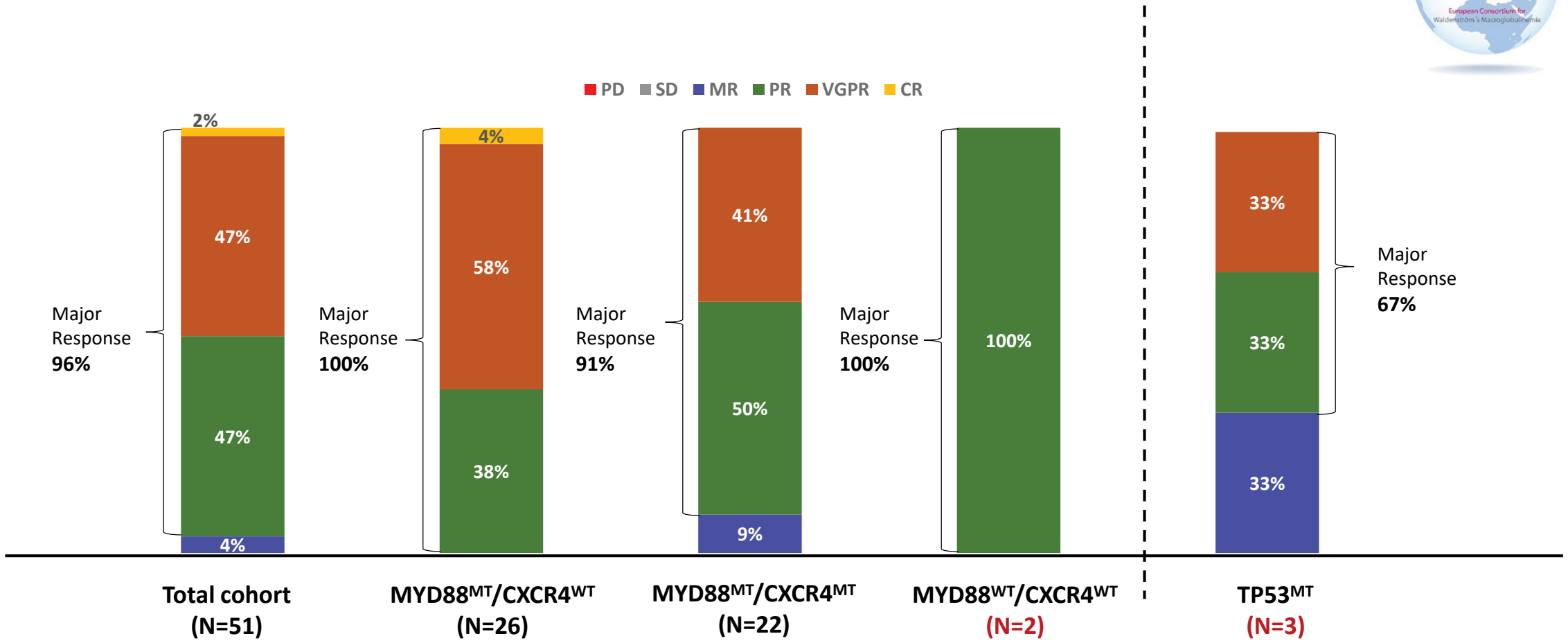
Response Rates



Median time to major response:
⇒ 2.8 months

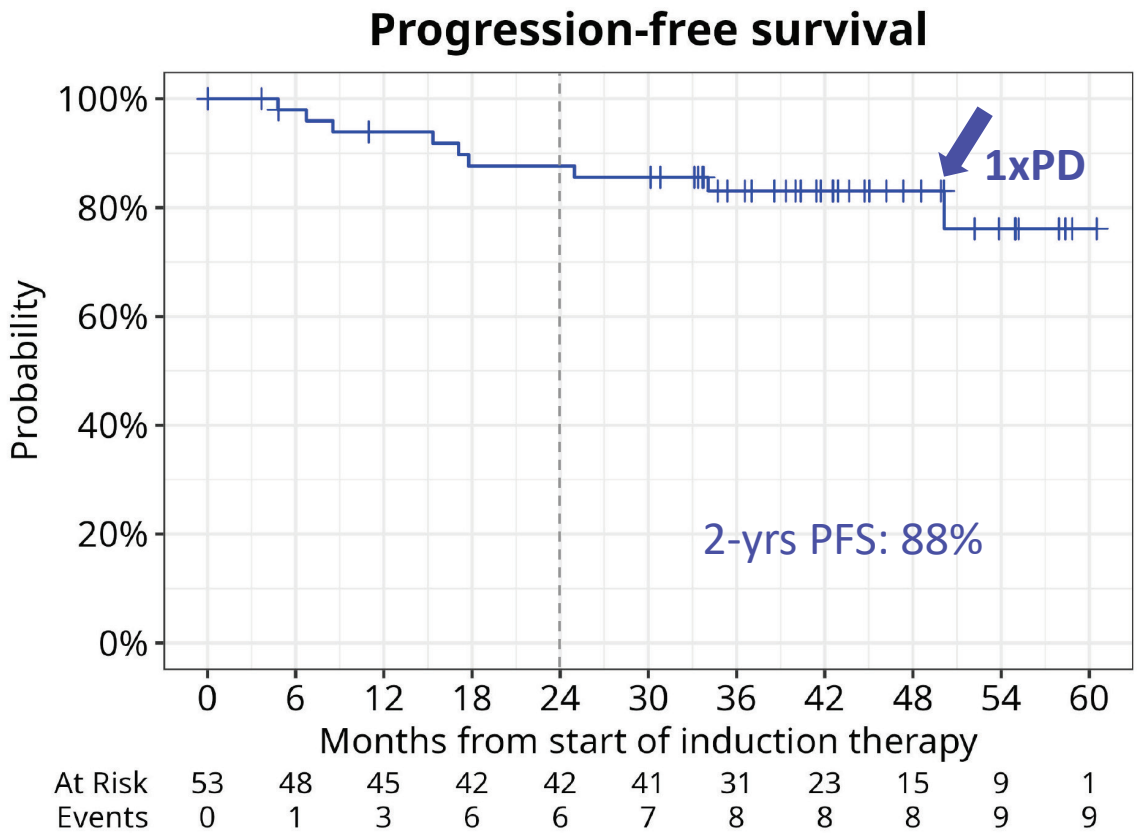
1 year probabillity for Major response:
⇒ 81% (95% CI: 67% - 90%)

Response Rates - Best response



Median time to best response: 6.7 months
1 year probabillity for best response: 69% (95% CI: 54% - 80%)

Progression Free Survival



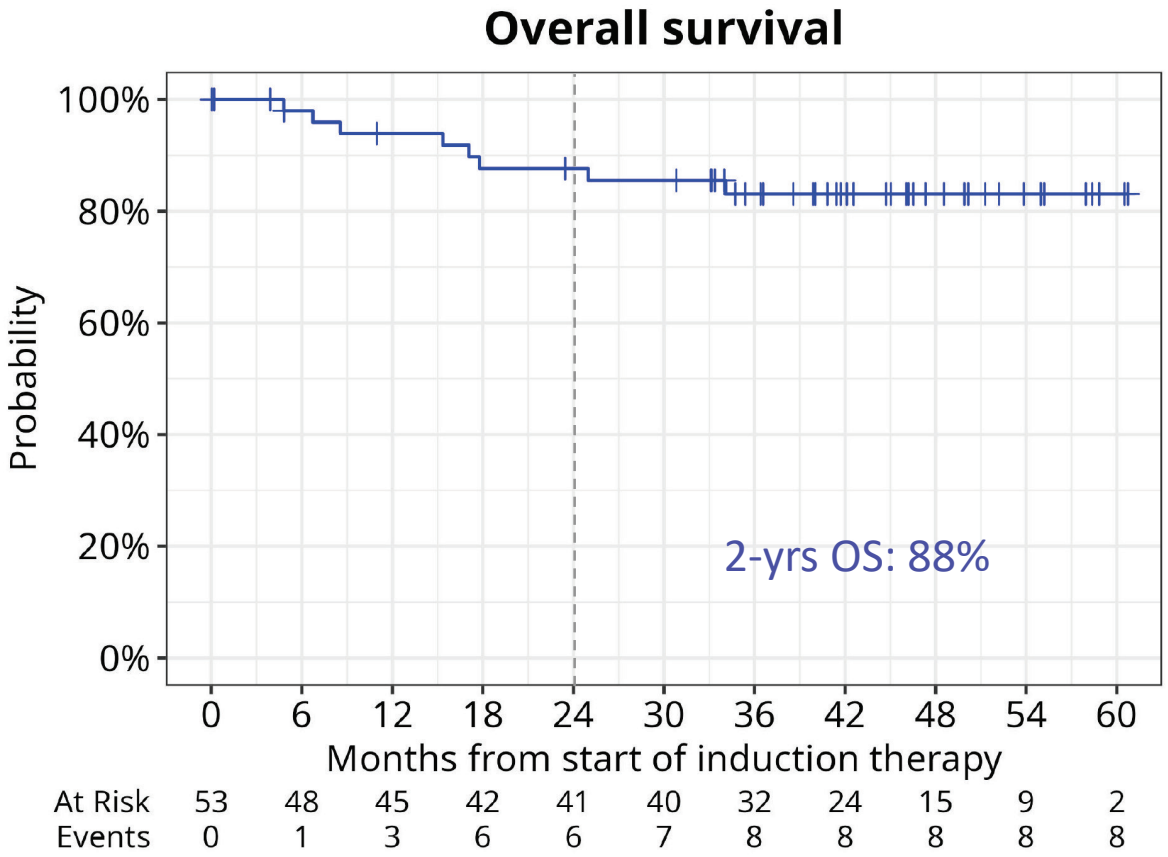
Data cut: 07 Nov 2024

9 Events

Event	N	Histology	Study phase	Best Response
Disease Progression	**1**	MZL	Maintenance II	PR
Deaths	**8**			

Median Follow-up: 43 months

Overall Survival



Median Follow-up: 43 months

8 Events

Deaths	Study phase	Last Response
Lower respiratory tract infection	Induction	PR
Covid 19	Maintenance I	PR
Lower respiratory tract infection with septic shock	Maintenance I	PR
Covid 19	Maintenance I	VGPR
Covid 19	Maintenance I	VGPR
Covid 19	Maintenance I	PR
Covid 19	Maintenance I	VGPR
Covid 19	Maintenance II	PR

Safety Profile

	Total subjects (n=53)
Number of patients with any AE	51 (96.2%)
Most common AEs (all grades) Diarrhoea COVID-19 COVID-19 Pneumonia Peripheral sensory neuropathy	Total n=51 (96.2%) 20 (39.2%) 18 (35.3%) 12 (23.5%) 12 (23.5%)
Most common AEs (≥3 grade) COVID-19 pneumonia Hypertension COVID-19 Neutropenia	Total n=35 12 (34.3%) 4 (11.4%) 3 (8.6%) 3 (8.6%)
Newly developed Neuropathy Grade 1 Grade 2 Grade ≥ 3	 11 (resolved: 8) 6 (resolved: 5) 0

Kapitel 2

Liquid Biopsy beim Morbus Waldenström

Abstract 4352

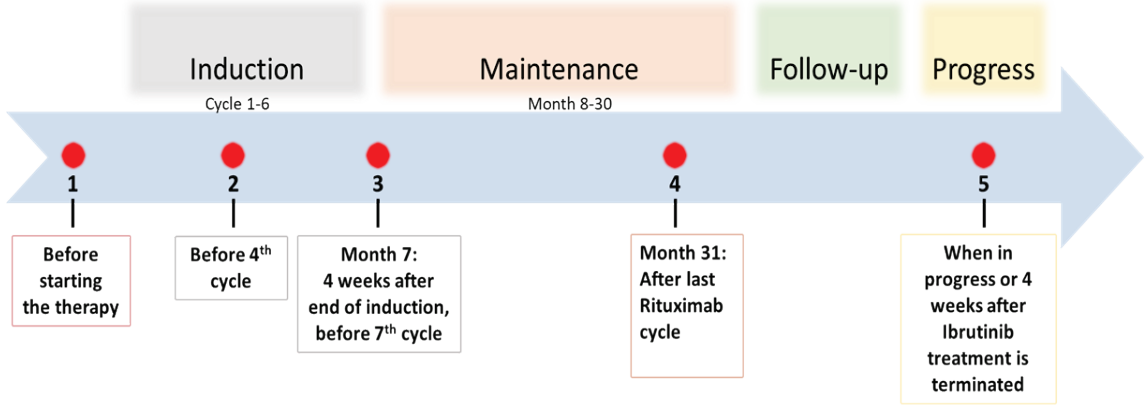
Determining the Mutational Landscape of Waldenström's Macroglobulinemia By Liquid Biopsy: Results of the Prospective ECWM-2 Trial of the European Consortium for Waldenström's Macroglobulinemi

P. NAKOV, D. DRANDI, L. KAISER, D. KASZYNSKI, A. GRUNENBERG, J. MARK, E. RUNGE, M. DIMOPOULOS, E. KASTRITIS, T. BAGRATUNI, C. BUSKE, C. POTT, S. FERRERO and M. KHOUJA on behalf of the European Consortium for Waldenström's Macroglobulinemia

Biosampling und Methodik

ECWM-2 Studie

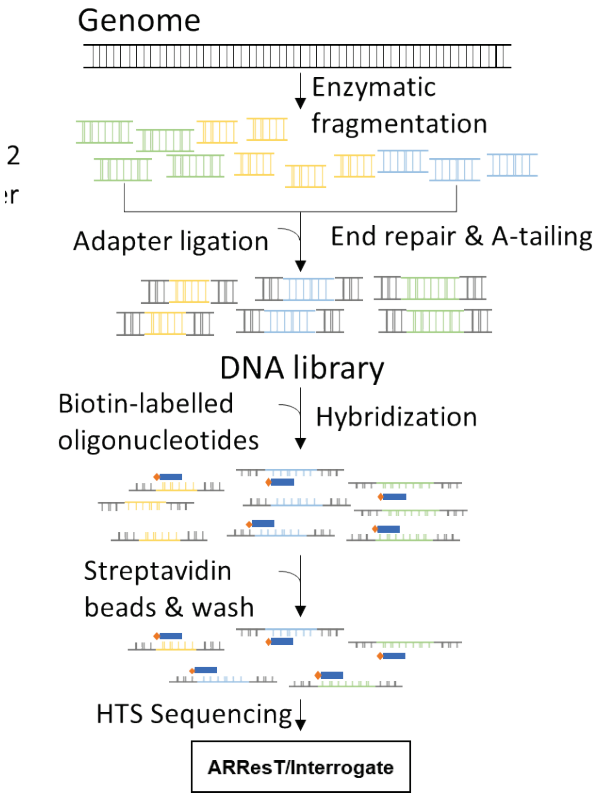
Timeline



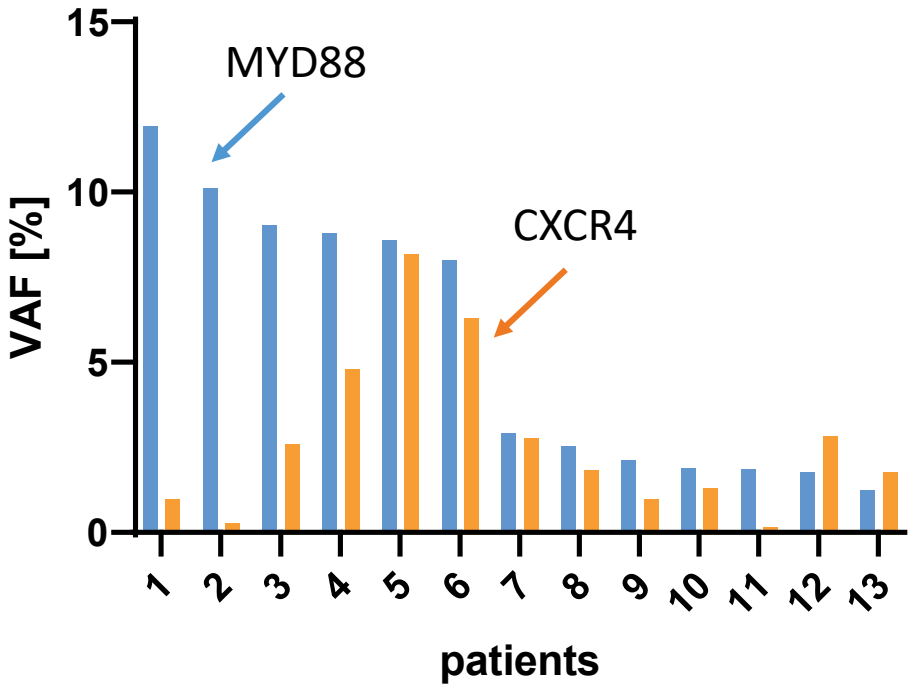
EC-NDC

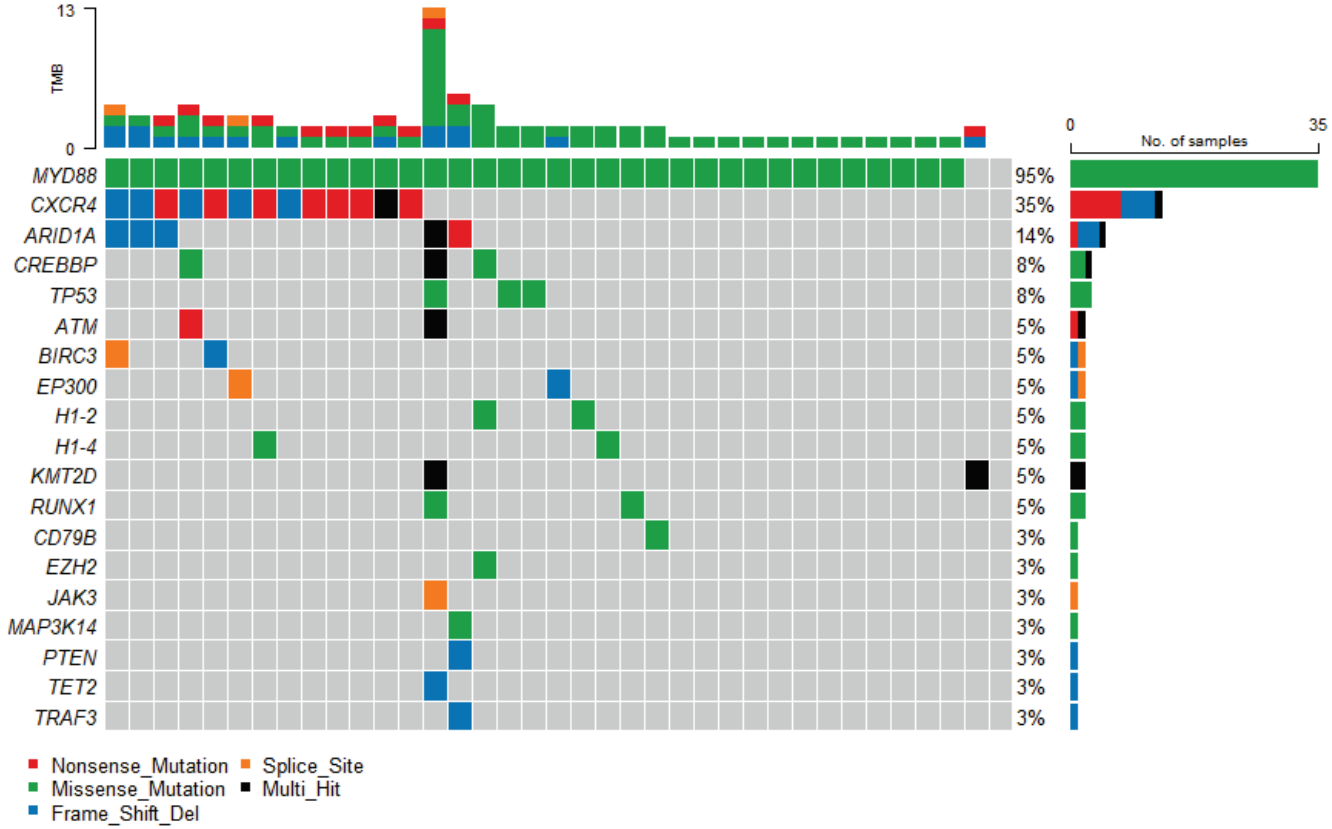
A targeted capture-based NGS assay targeting 72 genes and covering IG/TR loci for genotyping andclonality assessment and CNV profiling

Principle:

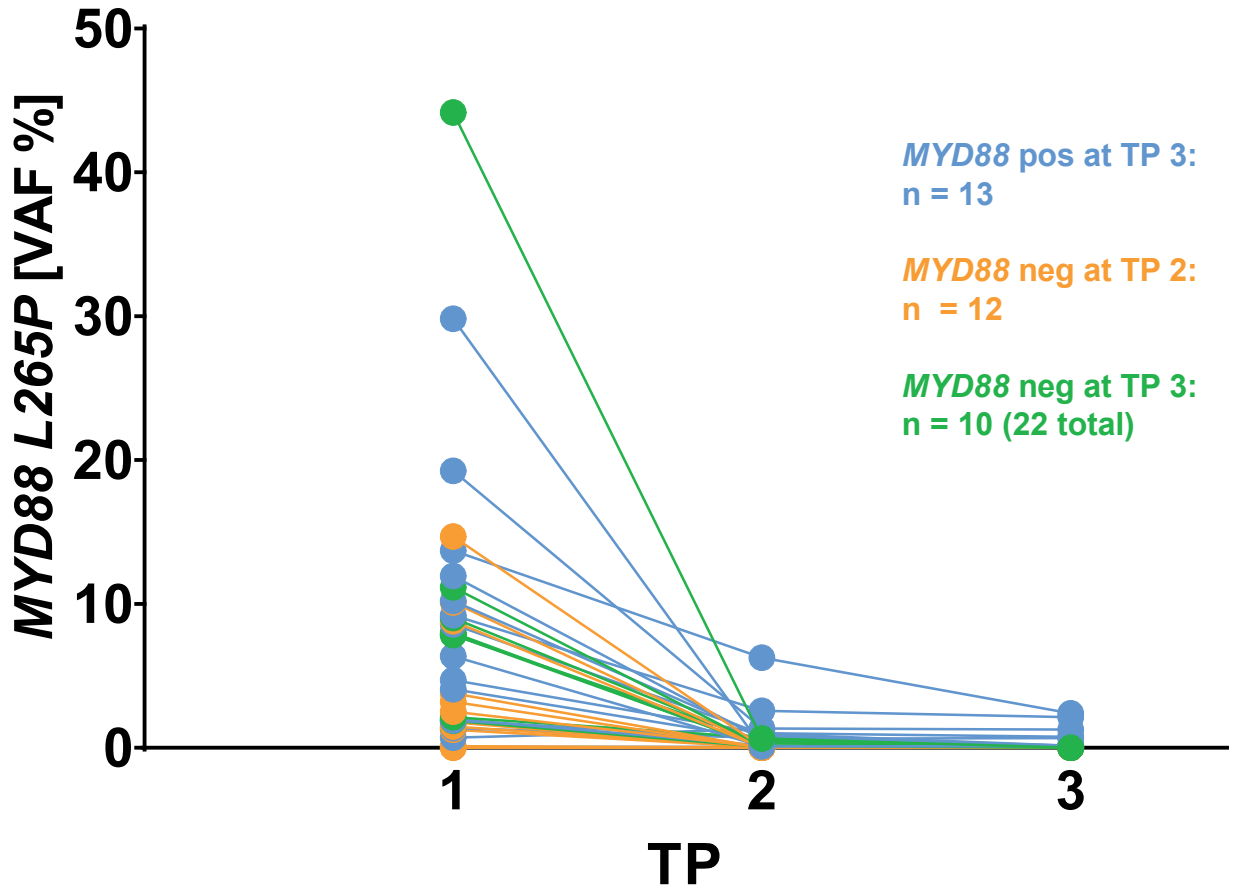


Detektion der „mutational landscape“ (Plasma – cfDNA) beim Morbus Waldenström





Rascher Abfall der MYD88 Tumorlast unter Therapie



Kapitel 3

Morbus Waldenström: Optimierung chemotherapiefreier Konzepte - BTK Degrader

Abstract 860

Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients with Relapsed or Refractory Waldenström Macroglobulinemia: Results from the Phase 1 CaDAnCe-101 Study

John F. Seymour,, *Constantine S. Tam, Chan Y. Cheah, Ricardo D. Parrondo, John N. Allan, MD, Judith Trotman,, Ranjana H. Advani, Herbert A. Eradat, Pier Luigi Zinzani, Masa Lasica, Steven P. Treon, Xiangmei Chen, Kunthel By, Shannon Fabre, Daniel O. Persky, Amit Agarwal and Anna Maria Frustaci*

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

- Histologically confirmed, meeting IWWM-7 criteria for treatment
- ≥2 prior therapies, including anti-CD20 monoclonal antibody and cBTK inhibitor (US and EU only)
- ECOG PS 0-2
- Adequate organ function

Key study objectives for part 1

- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and 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 meeting other criteria for treatment discontinuation. [c] Safety was assessed according to CTCAE v5.0; DLTs were assessed during the first 4 weeks of part 1a. [d] Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks. cBTK, covalent BTK; GCB, germinal center B cell; RT, Richter transformation.

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)
Platelets, median (range), 10^9/L	157 (14-455)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	24/26 (92.3)
CXCR4 mutation present	12/25 (48.0)
BTK mutation present	11/25 (44.0)
TP53 mutation present	13/25 (52.0)

	Total (N=27)
IgM, median (range), g/L	37.4 (2.8-74.4)
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 inhibitor[b]	4 (14.8)
Discontinued prior BTK inhibitor due to PD, n (%)	21 (77.8)

Data cutoff: September 2, 2024.

[a] Confirmed by central laboratory. [b] All 4 patients with ncBTK inhibitor exposure were exposed to a cBTK inhibitor.

cBTK, covalent BTK; IgM, immunoglobulin M; ncBTK, noncovalent BTK.

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

Patients, n (%)	Total (N=27)	
	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*.

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)

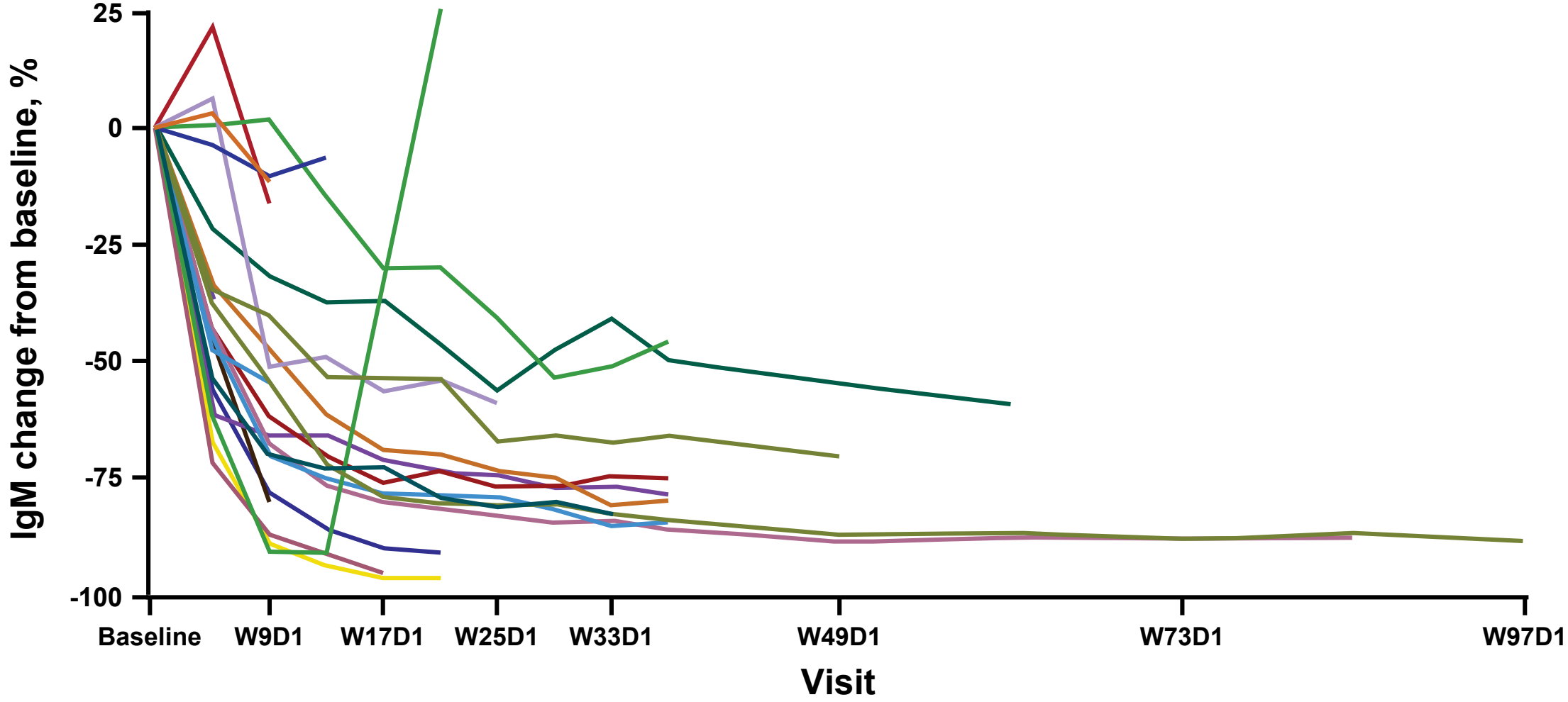
	Total[a] (N=27)
Best overall response, n (%)	
VGPR	7 (25.9)
PR	13 (48.1)
MR	2 (7.4)
SD	3 (11.1)
Not evaluable	1 (3.7)
Discontinued prior to first assessment	1 (3.7)
ORR, n (%)[b]	22 (81.5)
Major response rate, n (%)[c]	20 (74.1)
Disease control rate (DCR), n (%)[d]	25 (93.0)
Follow-up, median (range),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

IgM Decreased in All Patients

Rapid decline in IgM at all dose levels



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

Kapitel 4

MZL: bi-spezifische Antikörper?

Abstract 862

Efficacy and Safety of Odronextamab in Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL): Data from the R/R MZL Cohort in the ELM-2 Study

Tae Min Kim, *Seok-Goo Cho, Michal Taszner, Geoffrey Chong, Jingxian Cai, Amulya Uppala, Aafia Chaudhry, Hesham Mohamed, Srikanth Ambati and John N. Allan*

Efficacy and Safety of Odronextamab in Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL): Data from the R/R MZL Cohort in the ELM-2 Study

Tae Min Kim[1], Seok-Goo Cho[2], Michal Taszner[3], Geoffrey Chong[4], Jingxian Cai[5], Amulya Uppala[5], Aafia Chaudhry[5], Hesham Mohamed[5], Srikanth Ambati[5], John N. Allan[6]

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ClinicalTrials.gov ID: NCT03888105

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Medical writing support was provided by Cassady Collins, MPH, of Callisto, a division of OPEN Health Communications (London, UK), and funded by Regeneron Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP) guidelines (www.ismpp.org/gpp-2022).

Presented at the 66th American Society of Hematology 2024 (ASH 2024) Annual Meeting and Exposition, December 7–10, 2024, San Diego, CA, USA

ELM-2 study design: R/R MZL cohort

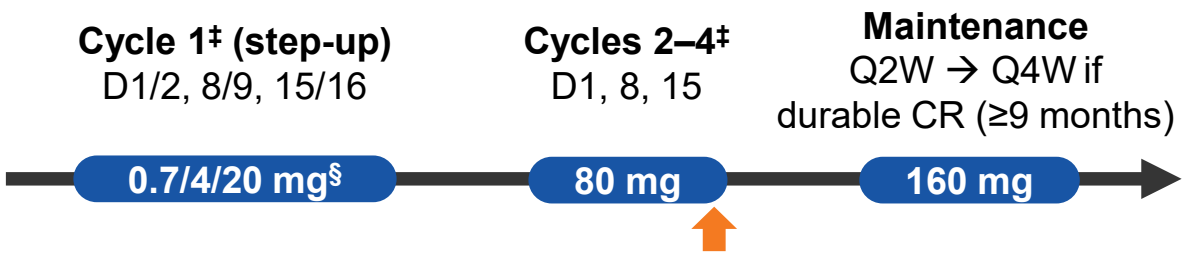
- Phase 2, open-label, multicohort, multicenter study of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105)

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

*Per World Health Organization 2017 classification;[1] †According to Lugano criteria;[2] ‡Each cycle = 21 days; §The study initiated with a Cycle 1 step-up regimen of 1/20 mg. This was modified to 0.7/4/20 mg to further mitigate the risk of CRS. Premedication administered during Cycle 1 step-up included dexamethasone, diphenhydramine, and acetaminophen.
B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; CRS, cytokine release syndrome; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent central review; IVIg, intravenous immunoglobulin; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PJP, *Pneumocystis jirovecii* pneumonia; QXW, once every X weeks; R/R, relapsed/refractory.

1. Beham-Schmid C. *Memo* 2017;10(4):248–54; 2. Cheson BD, et al. *J Clin Oncol* 2014;32(27):3059–68.

Baseline characteristics

Patient and disease characteristics		Overall (n=42)*	Extranodal (n=21)	Nodal (n=15)	Splenic (n=5)
Median age (range), years		63.5 (34–82)	59.0 (34–82)	66.0 (38–80)	73.0 (52–80)
Age, %	*≥65 / ≥75*	47.6 / 23.8	33.3 / 19.0	66.7 / 26.7	60.0 / 40.0
Male, %		45.2	42.9	46.7	40.0
Ann Arbor stage III/IV, %		83.3	76.2	93.3	80.0
Bulky disease, %		9.5	14.3	0	20.0
Race, %	*White / Asian / Black or African American / Not reported*	47.6 / 38.1 / 4.8 / 9.5	33.3 / 57.1 / 4.8 / 4.8	60.0 / 26.7 / 6.7 / 6.7	80.0 / 0 / 0 / 20.0
ECOG PS, %	*0 / 1*	45.2 / 54.8	42.9 / 57.1	46.7 / 53.3	40.0 / 60.0
IPI score, %	*3 / 4–5*	19.0 / 9.5	23.8 / 0	13.3 / 20.0	20.0 / 20.0
Median number of prior lines of therapy (range)		2 (1–8)	2 (1–8)	2 (1–4)	2 (2–4)
Number of prior lines,† %	*≥2 / ≥3 / ≥4 / ≥5*	83.3 / 31.0 / 19.0 / 2.4	76.2 / 38.1 / 19.0 / 4.8	93.3 / 20.0 / 13.3 / 0	100 / 40.0 / 40.0 / 0
Primary refractory, %		33.3	38.1	33.3	20.0
Refractory to last line of therapy, %		64.3	57.1	80.0	60.0
Refractory to anti-CD20 antibody in any line, %		47.6	52.4	53.3	20.0
Double refractory to alkylator/anti-CD20 antibody in any line, %		33.3	42.9	33.3	0
Prior BTKi, %		28.6	19.0	33.3	60.0
Prior bendamustine, %		33.3	33.3	40.0	20.0
Prior ASCT, %		7.1	9.5	6.7	0
POD24, %		50.0	57.1	60.0	0

Data cut-off date: August 15, 2024.

*MZL type was unknown in one patient; †Eligibility criteria initially required patients with MZL to have progressed after ≥1 prior line of systemic therapy, but the protocol was updated such that progression after ≥2 prior lines of systemic therapy was required; seven patients who received the 1/20 mg step-up regimen had received only one prior line of therapy.

ASCT, autologous stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; CD, cluster of differentiation; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; MZL, marginal zone lymphoma; POD24, progression of disease within 2 years.

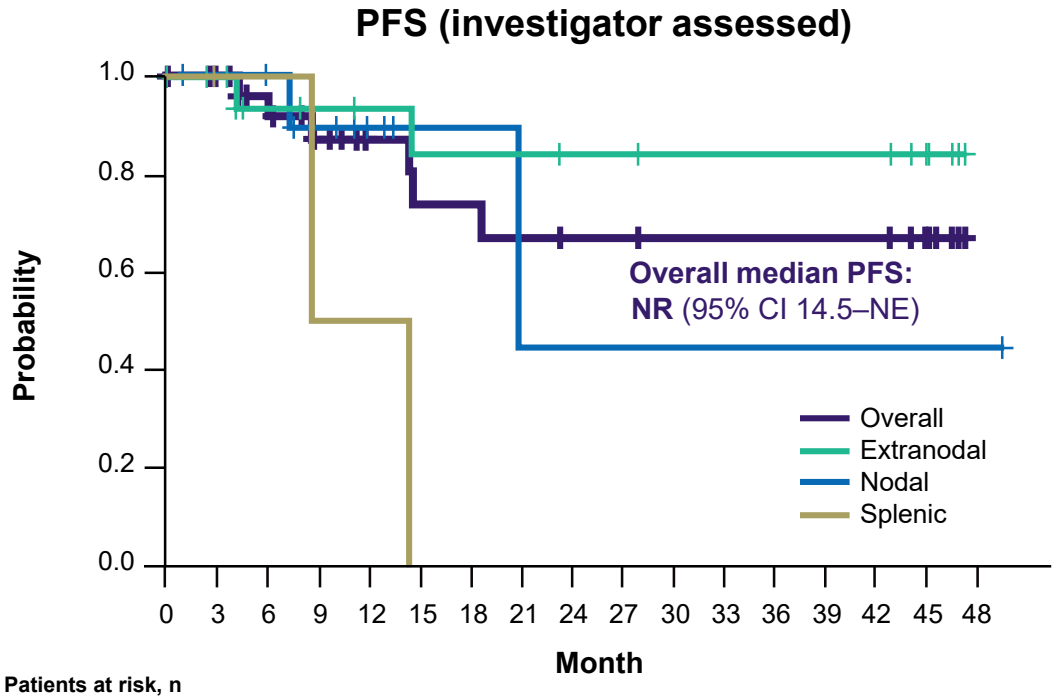
All responders achieved CR

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

- Median follow-up for efficacy population: 11.1 months (95% CI 6.2–42.8)†

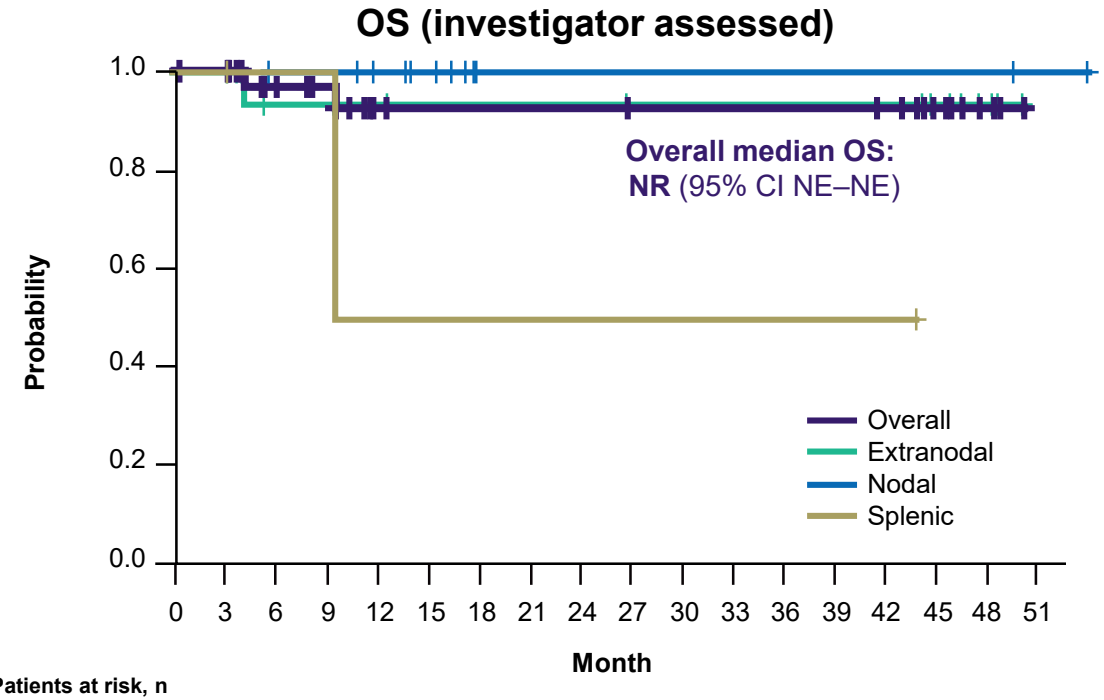
Data cut-off date: August 15, 2024.
*Responses per local investigator assessment in patients who had the opportunity for response assessment at 12 weeks. †Duration of efficacy follow-up calculated based on reverse Kaplan–Meier PFS (investigator assessed).
CI, confidence interval; ORR, objective response rate; PFS, progression-free survival.

Neither median PFS nor median OS were reached



Patients at risk, n

Overall	35	28	23	18	13	11	11	10	9	9	8	8	8	8	8	5	0
Extranodal	19	16	12	11	10	9	9	9	8	8	7	7	7	7	7	4	0
Nodal	12	10	9	6	2	2	2	1	1	1	1	1	1	1	1	1	0
Splenic	3	2	2	1	1	0											



Patients at risk, n

Overall	35	34	25	22	15	14	14	14	14	13	13	13	13	13	12	8	3	0
Extranodal	19	19	12	12	11	10	10	10	10	9	9	9	9	9	9	7	3	0
Nodal	12	11	10	7	2	2	2	2	2	2	2	2	2	2	1	1	0	
Splenic	3	3	2	2	1	1	1	1	1	1	1	1	1	1	1	1		

12-month PFS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
87.5 (65.9–95.8)	93.3 (61.3–99.0)	88.9 (43.3–98.4)	50.0 (0.6–91.0)

12-month OS rate (95% CI):

Overall	Extranodal	Nodal	Splenic
92.2 (71.8–98.0)	93.3 (61.3–99.0)	100 (100–100)	50.0 (0.6–91.0)

Data cut-off date: August 15, 2024. Efficacy per local investigator assessment.
CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

AEs of interest: CRS and ICANS

	0.7/4/20 mg			
	Overall (n=23)	Extranodal (n=10)	Nodal (n=9)	Splenic (n=4)
CRS (any grade), n (%)	13 (56.5)	5 (50.0)	5 (55.6)	3 (75.0)
Grade 1	8 (34.8)	5 (50.0)	2 (22.2)	1 (25.0)
Grade 2	5 (21.7)	0	3 (33.3)	2 (50.0)
Grade 3	0	0	0	0
Grade ≥4	0	0	0	0
Median time to onset CRS (range), hours	4.0 (−6.0–64.0)	4.0 (−6.0–18.7)	3.6 (0.0–64.0)	3.0* (3.0–3.0)
Median CRS duration (range), hours	6.2 (1.0–29.0)	5.5 (1.4–29.0)	6.0 (1.0–16.8)	6.7* (6.7–6.7)
Systemic steroid for CRS management, n (%)	8 (34.8)	2 (20.0)	3 (33.3)	3 (75.0)
Tocilizumab for CRS management, n (%)	7 (30.4)	2 (20.0)	3 (33.3)	2 (50.0)

- 0.7/4/20 mg step-up regimen:
  - CRS events all Grade 1/2 and generally confined to Cycle 1
  - CRS events resolved within a median of 6.2 hours (range 1.0–29.0) with supportive measures
- No ICANS events reported

Data cut-off date: August 15, 2024. CRS per Lee DW, et al. 2019 criteria.[1]
*Only one patient was evaluable for this data point.
AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
1. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25(4):625–38.

AEs of interest: Infections

Patients with any infection TEAE, n (%)	All safety-evaluable patients			
	Overall (n=42)	Extranodal (n=21)	Nodal (n=15)	Splenic (n=5)
Any grade	29 (69.0)	17 (81.0)	9 (60.0)	3 (60.0)
Grade 1	4 (9.5)	3 (14.3)	1 (6.7)	0
Grade 2	15 (35.7)	8 (38.1)	5 (33.3)	2 (40.0)
Grade 3	9 (21.4)	5 (23.8)	3 (20.0)	1 (20.0)
Grade 4	1 (2.4)	1 (4.8)	0	0
Grade 5	0	0	0	0

- Most frequent infections: COVID-19* (19.0%), cytomegalovirus reactivation† (11.9%), upper respiratory tract infection† (9.5%), and herpes zoster† (9.5%)
- Infection incidence was broadly similar across extranodal, nodal, and splenic subtypes
- No treatment discontinuations due to treatment-related infections
- No Grade 5 infections
- COVID-19* infection was reported in eight patients overall (Grade 3/4, n=2; no Grade 5)

Data cut-off date: August 15, 2024.
*Incidence of COVID-19 equates to incidence of coronavirus infection (HLT), as all preferred-term infection events reported under this HLT were COVID-19 related; †Preferred term description per NCI-CTCAE v5.0.
CMV surveillance was done by PCR testing in blood during screening, at Week 6, Week 12, Week 24, and at other timepoints when clinically indicated
AEs, adverse events; HLT, high-level term; MZL, marginal zone lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Conclusions

- Odronextamab showed promising clinical efficacy with a generally manageable safety profile in heavily pretreated patients with R/R MZL
  - ORR, 77.1% (100% of responses were CRs)
  - ORR and CR rates were comparable across MZL subtypes and similar to rates reported in the R/R FL cohort in ELM-2
- Responses were durable, with median DOR and median DOCR not yet reached with a median of 11 months of follow-up
- The safety profile of odronextamab in patients with R/R MZL was consistent with that observed in other indolent B-NHL, with no new safety signals
  - All CRS events were Grade 1/2, and no ICANS events were reported
  - Most common Grade ≥3 TEAEs were neutropenia (23.8%), ALT increased (16.7%), AST increased (16.7%) and anemia (11.9%)
- Enrollment in a Phase 3 trial of odronextamab-lenolidomide versus R2, including patients with R/R MZL, is ongoing (OLYMPIA-5; NCT06149286)

ALT, alanine aminotransferase; AST, aspartate aminotransferase B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; CRS, cytokine release syndrome; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; MZL, marginal zone lymphoma; ORR, objective response rate; R2, lenalidomide-rituximab; R/R, relapsed/refractory, TEAE, treatment-emergent adverse event

Kapitel 5

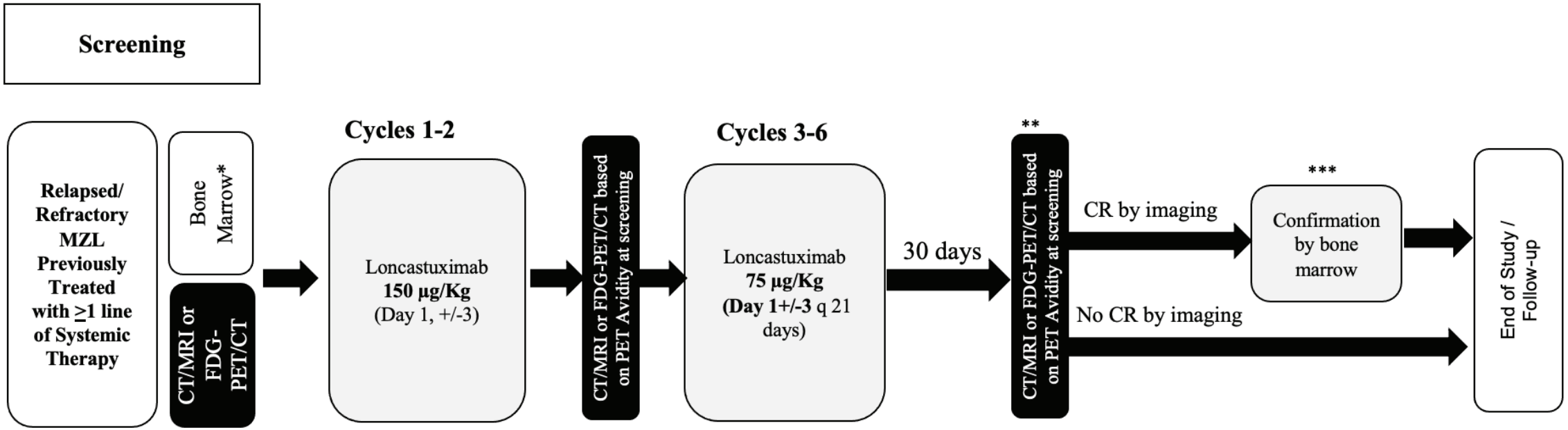
MZL: ADC? - Loncastuximab

Abstract 3032

Limited Duration Loncastuximab Tesirine Induces a High Rate of Complete Responses in Patients with Relapsed/Refractory Marginal Zone Lymphoma - Report of First Planned Interim Futility Analysis of a Multicenter Phase II Study

Izidore S. Lossos, *Geoffrey Shouse, Alvaro J Alencar, Safia Sawleh, David S. Lessen, Craig H. Moskowitz, Jennifer Rose Chapman-Fredricks, Isildinha M. Reis, Russ Kuker and Juan Pablo Alderuccio*

A phase 2, Open-label, Study Evaluating Safety and Efficacy of the Loncastuximab in Relapsed/refractory MZL



Patient Demographics

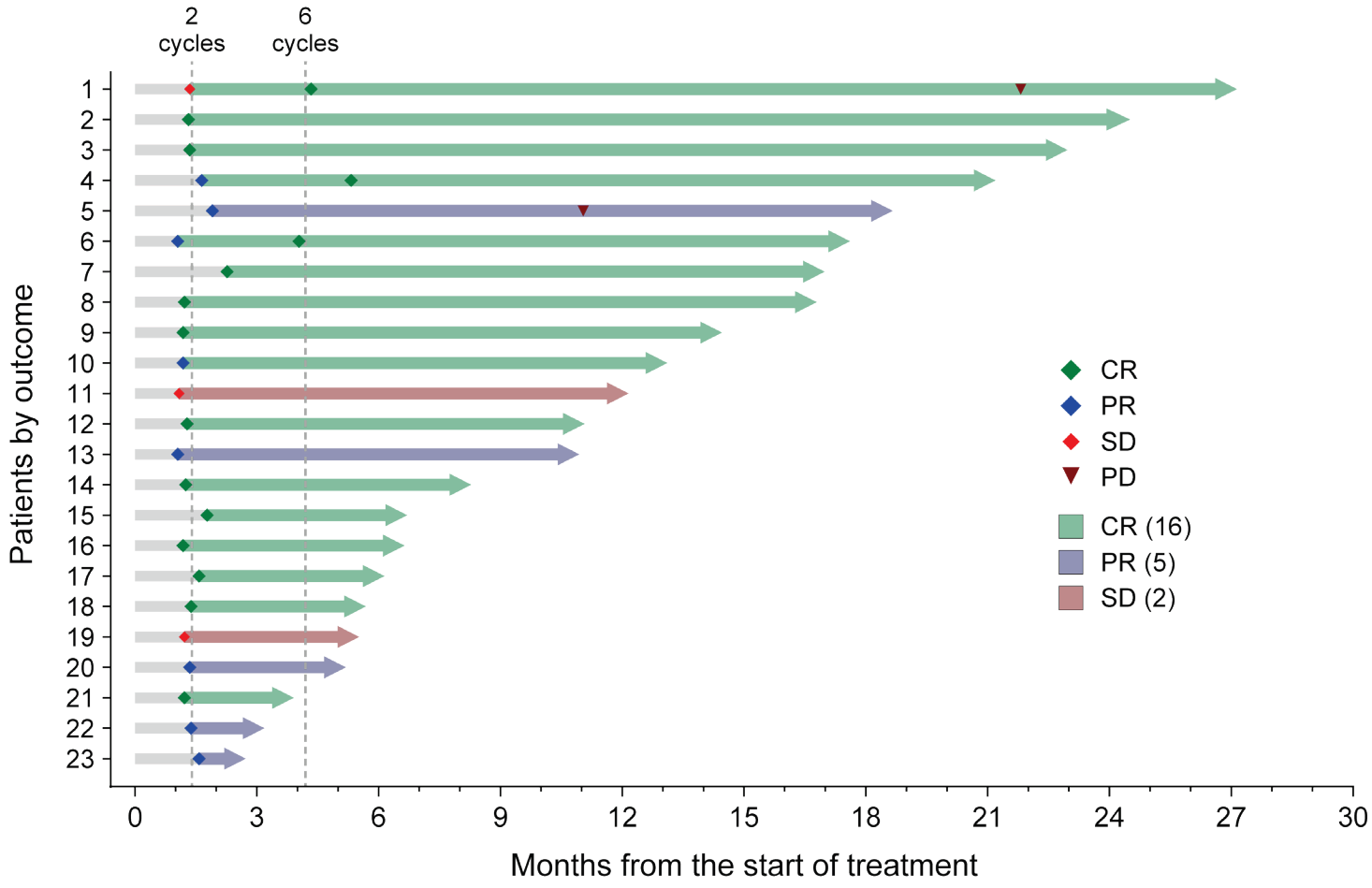
- A total of 23 patients were enrolled from July 2022 to October 2024

Characteristic	Patients (N = 23)
Age, median (range)	65 (45-82)
Gender (M:F)	8:15
MZL type, n (%) EMZL NMZL SMZL	 14 (61) 7 (30) 2 (9)
Stage, n (%) I III IV	 4 (17) 2 (9) 17 (74)

Characteristic	Patients (N = 23)
ECOG PS 0-1, n (%)	23 (100)
POD24, n (%)	11 (48)
Median previous lines of treatment (range)	2 (1-4)
Relapsed, n (%)	14 (61)
Refractory, n (%)	9 (39)
Previous treatments,[a] n (%) Rituximab XRT R-CHOP BR BTKi R^2 RICE	 8 (35) 7 (30) 7 (30) 6 (26) 4 (17) 3 (13) 2 (9)

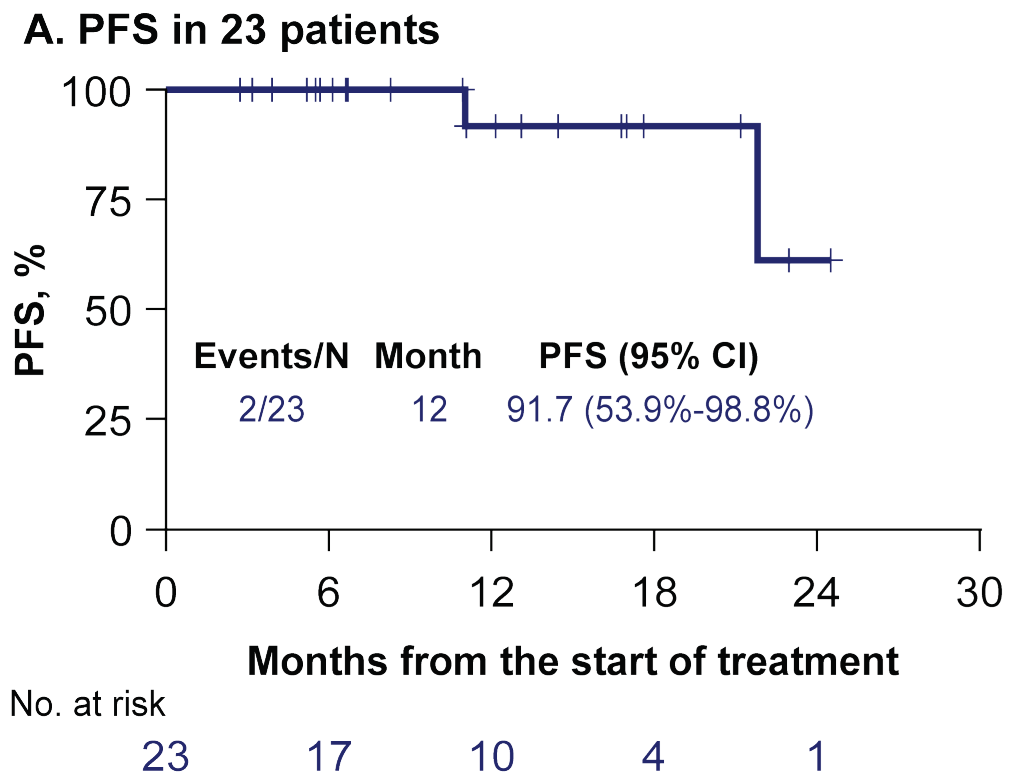
Efficacy

- As of October 15, 2024, 23 patients were evaluable for response
- **The overall response rate was 91% (21/23 patients), with a CR rate of 70% (16/23 patients) and with 2 patients still on treatment**
- Lonca led to CR in 7 of 11 patients (64%) with POD24 who were assessed for response; 1 patient who had progressed after CAR-T achieved a CR with Lonca

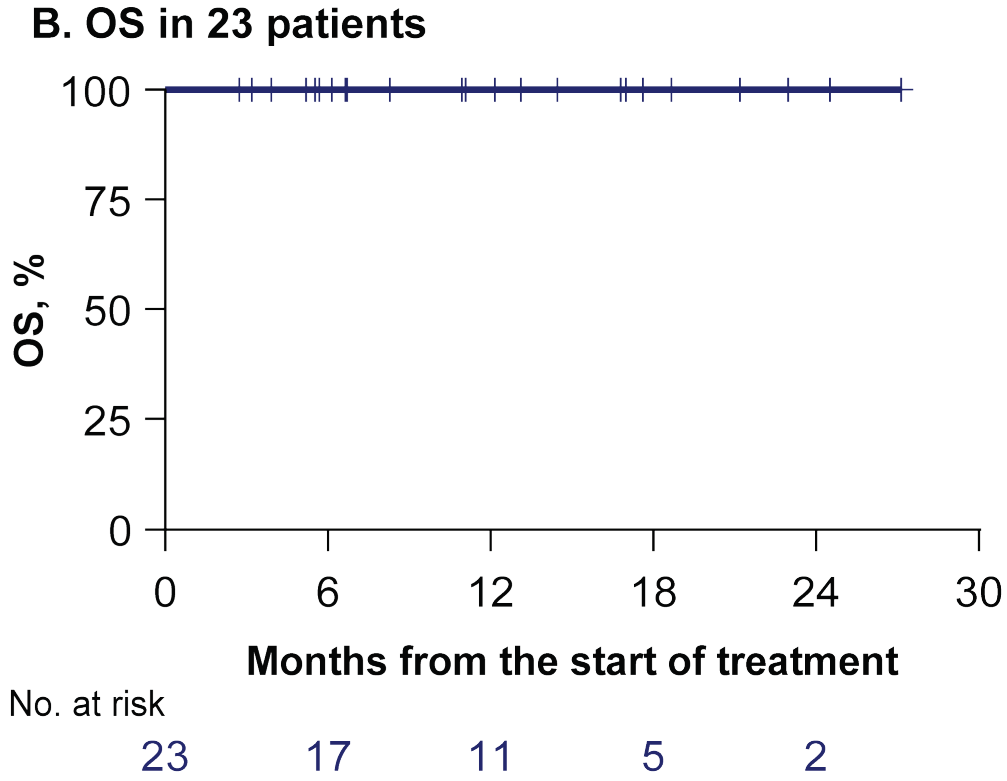


Progression-free and Overall Survival

- The estimated PFS rate at 12 months was 91.7%



- No patients have died during treatment



Safety

- Generally, Lonca was well tolerated, and the observed safety was consistent with the known profile
- All 23 patients experienced expected AE, most commonly grade 1 or 2
- Grade 3 and 4 AEs were observed in 15 and 1 (neutropenia) patients, respectively
- 3 patients needed dose reduction
- 1 patient discontinued treatment after cycle 4 because of cholestatic hepatitis
  - Patient clinically fully recovered with normalization in LFT abnormalities

TEAE, n (%)	Patients (N = 23)		
	Any grade	Grade 3	Grade 4
Maculopapular rash	15 (65.2)	1 (4.3)	0
Increased AST	15 (65.2)	0	0
Increased ALT	14 (60.8)	2 (8.7)	0
Increased ALP	11 (47.8)	3 (13.0)	0
Neutropenia	10 (43.4)	3 (13.0)	1 (4.3)
Local edema	10 (43.4)	0	0
Photosensitivity	7 (30.4)	1 (4.3)	0
Anemia	7 (30.4)	1 (4.3)	0
Urinary infection	3 (13.0)	1 (4.3)	0
Lung infection	2 (8.7)	0	0
Pleural effusion	2 (8.7)	0	0
Anorexia	1 (4.3)	1 (4.3)	0
COVID-19	1 (4.3)	0	0
Weight loss	1 (4.3)	1 (4.3)	0

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function tests; Lonca, loncastuximab tesirine; TEAE, treatment-emergent adverse event.

Zusammenfassung | Take-Home-Messages

- Die Kombination Proteasom-Inhibitor/cBTKi ist hocheffektiv beim Morbus Waldenström
- Erste Daten zeigen eine hohe Effektivität von BTK Degradern auch beim Morbus Waldenström
- Bi-spezifische AK induzieren hohe Raten an kompletten Remissionen beim R/R MZL (längeres Follow-up für Safety und PFS notwendig)
- Das ADC Loncastuximab über 6 Zyklen erreicht ebenfalls hohe CR – Raten bei vorbehandelten MZL mit guter Verträglichkeit

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2024

Für den Inhalt verantwortlich:

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Lymphom Kompetenz KOMPAKT

KML KONGRESSE

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