Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Amy Sparwasser, Stock-Fotografie-ID: 1455291856

ASH 2025

ORLANDO | 06.-09. Dezember 2025

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Prof. Dr. med. Christian Buske
Universitätsklinikum Ulm

Morbus Waldenström (WM) Marginalzonen-Lymphom (MZL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2025 wird in Kooperation mit acht unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	--
Beratungs-/ Gutachtertätigkeit	Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron, Sobi, Lilly, Cellectar
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, Cellectar
Finanzierung wissenschaftlicher Untersuchungen	Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen, Bayer, AbbVie
Andere finanzielle Beziehungen	--
Immaterielle Interessenkonflikte	--

Kapitel 1

Stellenwert der R-Chemotherapie beim Morbus Waldenström

Final Analysis of the ECWM-1 trial of the European Consortium for Waldenström‘s Macroglobulinemia

Abstract # 223

Morel et al.

Dexamethasone, Rituximab and Cyclophosphamide with Bortezomib is a rapidly acting and highly efficient first-line treatment in Waldenström' Macroglobulinemia: Final analysis of *ECWM-1 trial* of the European Consortium for Waldenström's Macroglobulinemia (ECWM)

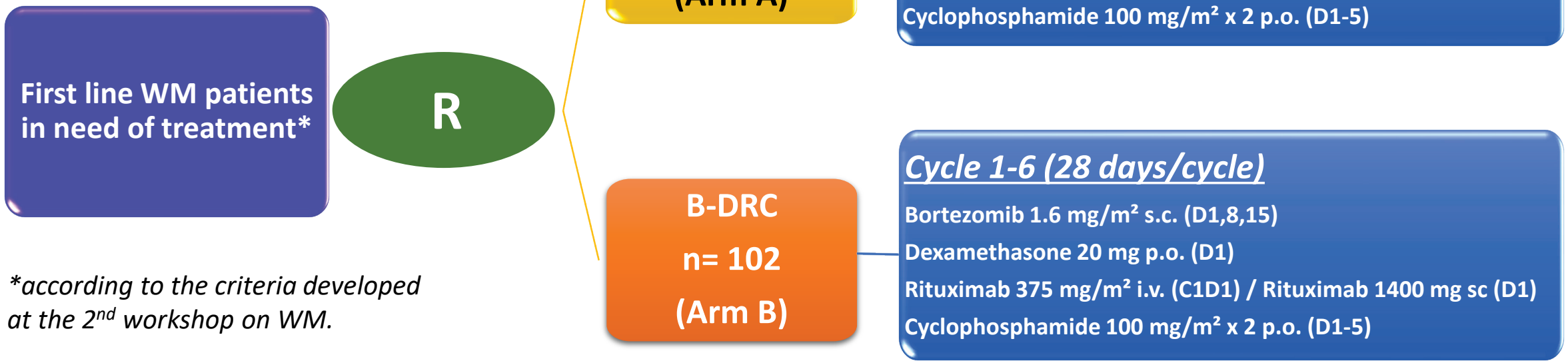
Pierre Morel, MD, Christian Buske, MD, Alexander Grunenberg, MD, Efstathios Kastritis, MD, Lydia Montes MD, Cecile Tomowiak, MD4 Roman Hajek, MD, PhD, Andreas Viardot, MD, Olivier Tournilhac, MD, Therese Aurran, MD, Florian Bouclet, MD, Hacene Zerazhi, MD, Benedicte Hivert, MD, Damien Roos Weil, MD, PhD, Sophie de Guibert, MD, Lena Brandefors, MD, PhD, Ramon Garcia-Sanz, MD, Maria Gomes da Silva, MD, Eva Kimby, MD, PhD, Birgit Schmelzle, Dajana Kaszynski, Melanie Verlay, Caroline Skrzypczak, Jens Dreyhaupt, Rainer Muche and Meletios A Dimopoulos, MD, PhD

on behalf of the European Consortium for Waldenström's Macroglobulinemia (ECWM)

UNIVERSITÄTS KLINIKUM ulm

ECWM-1 | Sponsor: University Hospital Ulm

Study Design



**according to the criteria developed at the 2nd workshop on WM.*

Study design and sample Size:

- 90% power at a 0.05 significance level to detect a difference of **0.15 (0.65 [DRC] to 0.80 [B-DRC]) in 2-year PFS** (i.e. hazard ratio=0.518).
- Sequential design with 3 sequential tests → **106 events**

ECWM-1: BASELINE PATIENT CHARACTERISTICS

	DRC (n=100)	B-DRC (n=102)
Age, years median (IQR) > 65 years > 75 years	68.2 (59.4 - 72.8) 61 (61 %) 18 (19%)	67.9 (60.1 - 67.0) 62 (61%) 26 (26%)
Gender, n (%) Male Female	 67 (67%) 33 (33%)	 68 (67%) 34 (33%)
ISSWM, n (%) Low Intermediate High	Eval. pts: 92 14 (15%) 30 (33%) 48 (52%)	Eval. pts: 100 12 (12%) 41 (41%) 47 (47%)
ECOG, n (%) 0 1 2	Eval. pts: 97 57 (59%) 35 (36%) 5 (5%)	Eval. pts: 100 51 (51%) 45 (45%) 4 (4%)
Lymphadenopathy, n (%)	Eval. pts: 95 41 (43%)	Eval. pts: 101 42 (42%)
BM infiltration, % median (IQR)	Eval. pts: 78 36 % (22 - 54)	Eval. pts: 81 35% (19,0 -53,5)

	DRC (n=100)	B-DRC (n=102)
IgM g/l, median (IQR) Serum IgM >70 g/l, %	Eval. pts: 97 31.9 (17.8 - 54.6) 1.0%	Eval. pts: 102 30.6 (17.2 - 48.0) 2.0%
Hb g/dl median (IQR)	Eval. pts: 97 9.7 (7.1 - 15.4)	Eval. pts: 101 9,8.0 (8.5 - 11.3)
Genotypes: n (%) $MYD88^{L265P}/CXCR4^{WT}$ $MYD88^{L265P}/CXCR4^{MUT}$ $MYD88^{L265P}/CXCR4^{n.a.}$ $MYD88^{WT}/CXCR4^{WT}$	Eval. pts: 57 33 (58%) 19 (33%) 1 (2%) 4(7%)	Eval. pts: 56 40 (71%) 10 (18%) 2 (4%) 4(7%)

ECWM-1 : first analysis

- **First analysis:**

original reports

Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia

Christian Buske, MD[1]; Meletios A. Dimopoulos, MD, PhD[2]; Alexander Grunenberg, MD[3]; Efstathios Kastritis, MD[2]; Cecile Tomowiak, MD[4]; Béatrice Mahé, MD[5]; Xavier Troussard, MD[6]; Roman Hajek, MD, PhD[7]; Andreas Viardot, MD[3]; Olivier Tournilhac, MD[8]; Therese Aurran, MD[9]; Stephane Lepretre, MD[10]; Hacene Zerazhi, MD[11]; Benedicte Hivert, MD[12]; Veronique Leblond, MD, PhD[13]; Sophie de Guibert, MD[14]; Lena Brandefors, MD, PhD[15]; Ramon Garcia-Sanz, MD[16]; Maria Gomes da Silva, MD[17]; Eva Kimby, MD, PhD[18]; Birgit Schmelzle, MSc[1]; Dajana Kaszynski, MSc[1]; Jens Dreyhaupt, PhD[19]; Rainer Muche, PhD[19]; and Pierre Morel, MD[20]

- 204 patients registered patients,
  - 2 patients excluded.
  - DRC arm (Arm A): 100 patients
  - B-DRC arm (Arm B): 102 patients

Median follow-up: 27.5 months.
53 events

Results

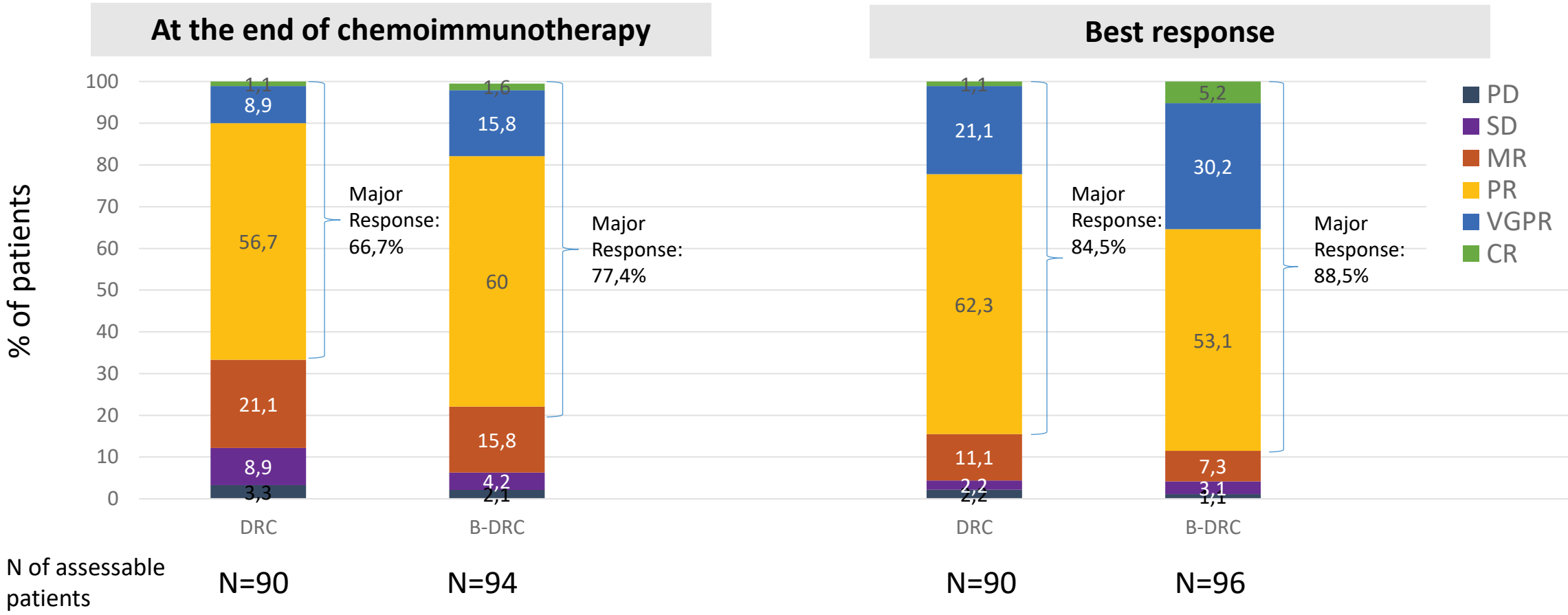
- Adding bortezomib to DRC is associated with
  - Deep remission,
  - Shortened time to response
  - No additional relevant toxicity compared to DRC alone,
  - Potential risk of neurotoxicity should be taken into account

Buske C et al J Clin Oncol 2023

ECWM-1: Final Analysis

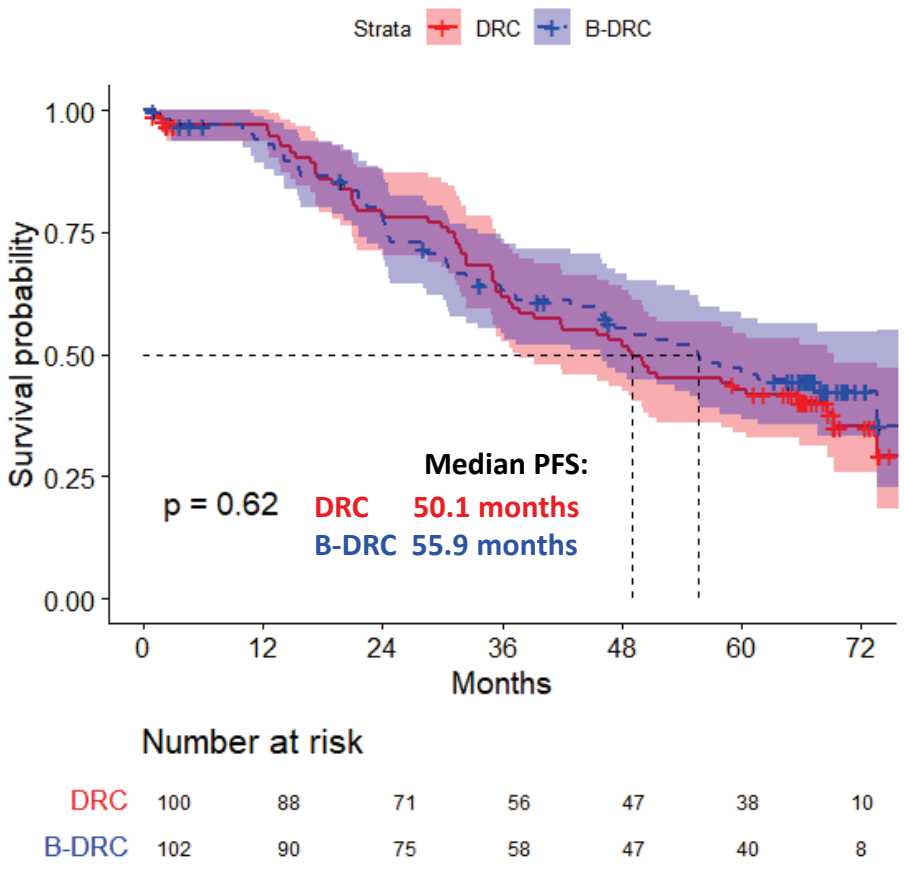
- Stopping date: April 2024
- Median follow-up (of alive patients): **68.8 months** (IQR: 64.2-77.3)
- **114 events**
  - 104 progressions
  - 10 patients have died without progression
  - 20 additional patients have died after progression.

ECWM-1: Response rates

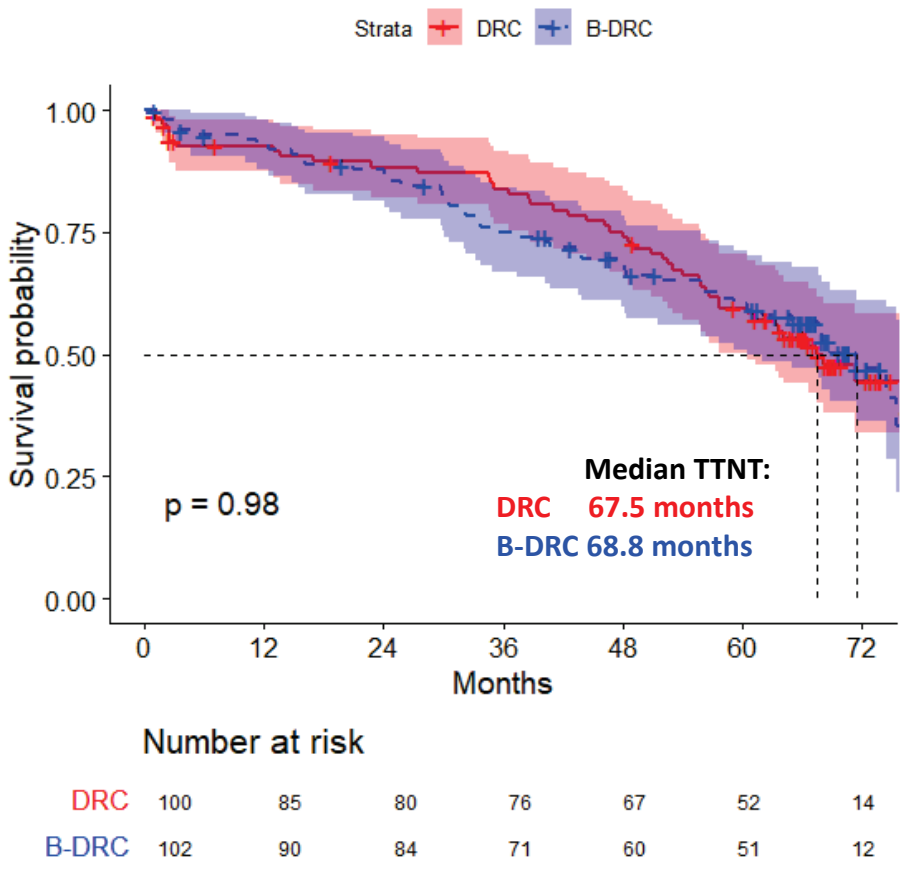


ECWM-1: PFS and TTNT

Progression-Free Survival

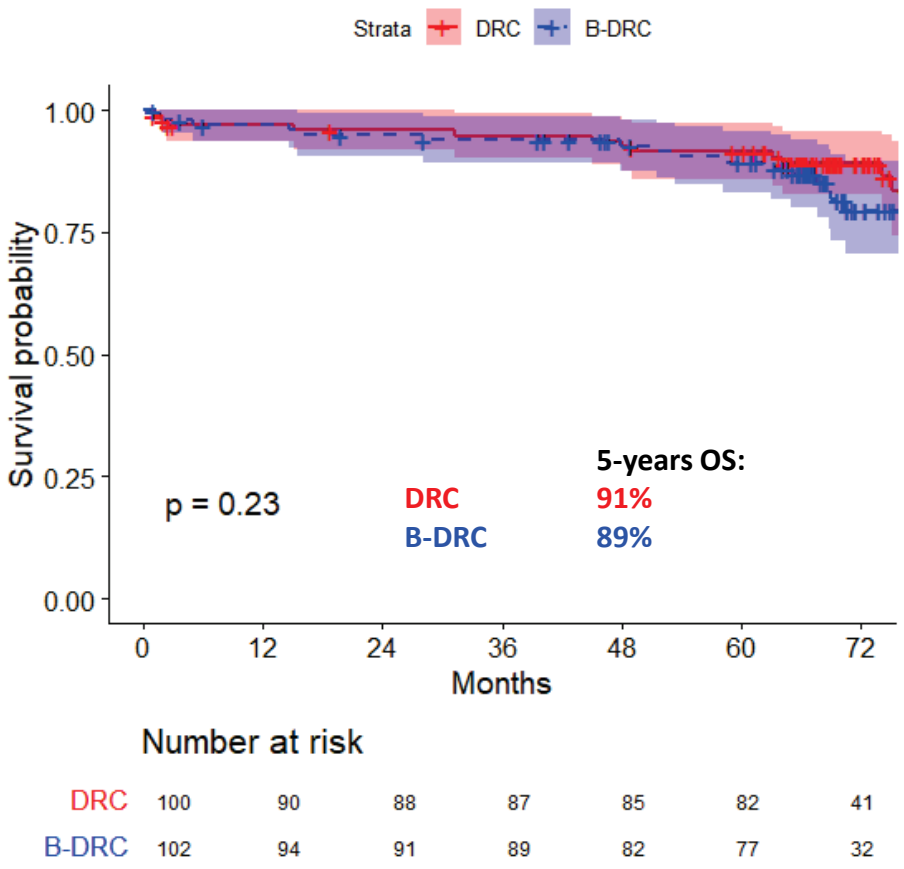


Time to Next Treatment

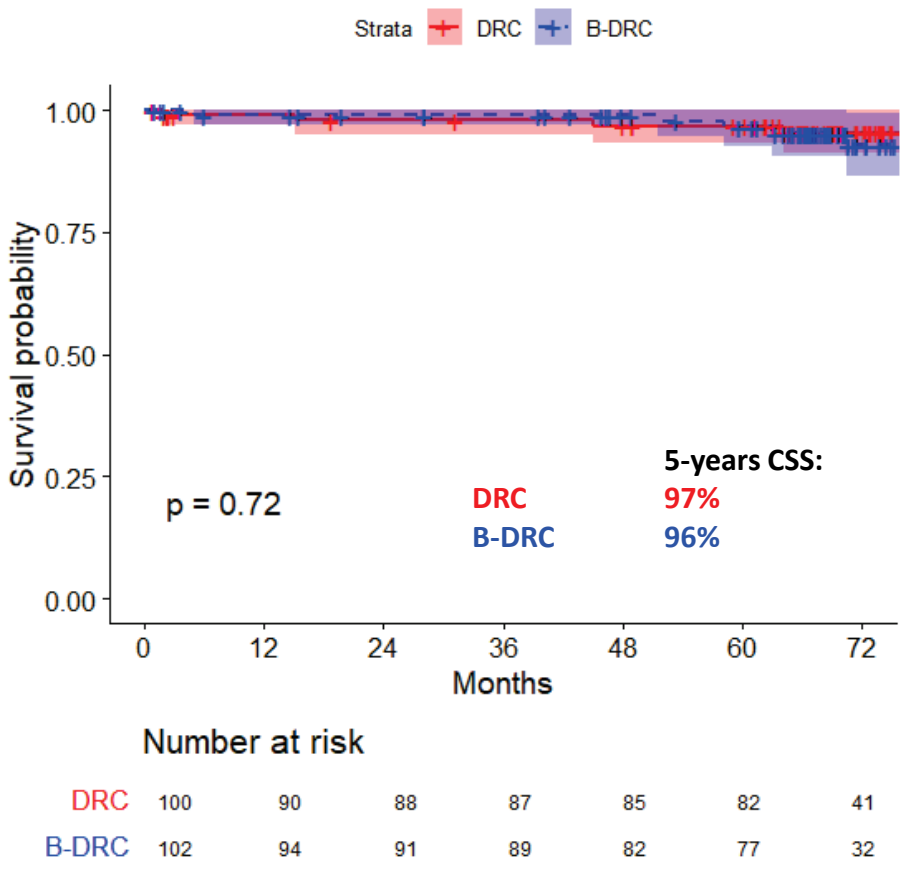


ECWM-1: OS and Cause-specific Survival

Overall

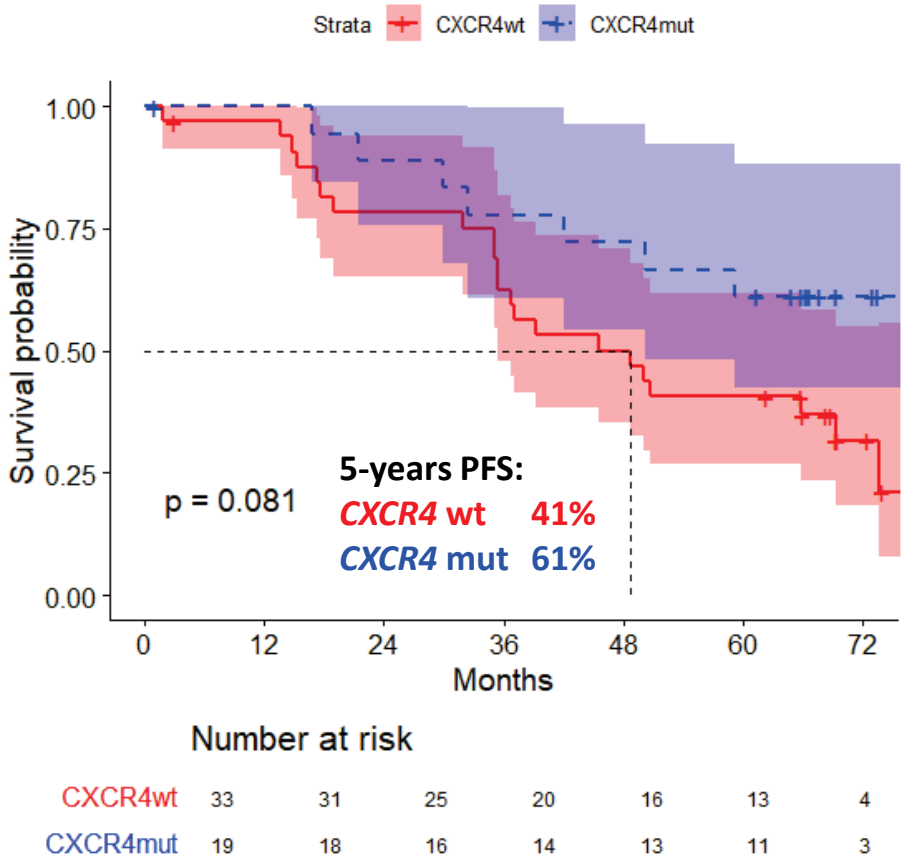


Cause-Specific

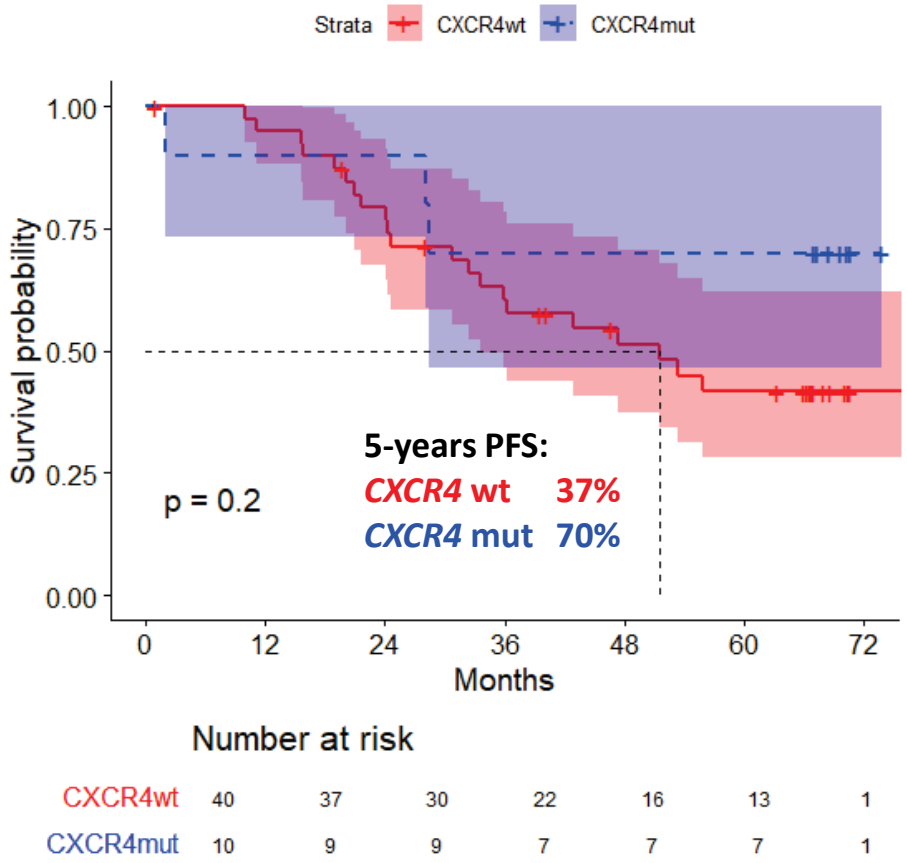


ECWM-1: PFS according to the CXCR4 mutational status

DRC arm A



B-DRC arm B



ECWM-1: Safety

Immediate safety

	Total number of events	Total number of patients	DRC Arm A (number of patients*)	B-DRC Arm B (number of patients*)
Adverse events	1373	189	92	97
Grade≥3 adverse events		101	49	52
SAE		41	27	14
Toxic death		3	2	1
Drug-related sensory neuropathies	71		20 events	51 events (including 4 grade 3)

*** unless otherwise specified**

Long-term safety:

- Second malignancy: 15 patients (**7.5%**).
  - DRC arm A: 10 patients
  - B-DRC arm B: 5 patients

High VGPR/CR rate with pirtobrutinib plus venetoclax in previously treated Waldenström macroglobulinemia

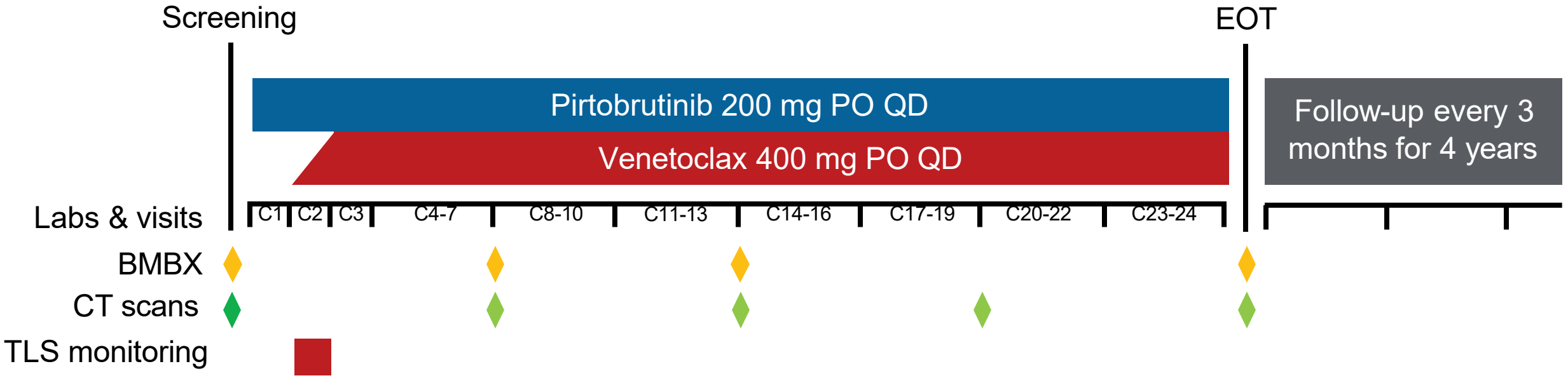
Abstract # 225

Castillo et al.

Treatment schema

Key inclusion criteria
18+ years
Diagnosis and need for treatment per IWWM2
MYD88 L265P
1+ previous therapy

Key exclusion criteria
CNS involvement
Pregnancy
Active HIV, HBV, HCV infection
Previous non-covalent BTK inhibitor



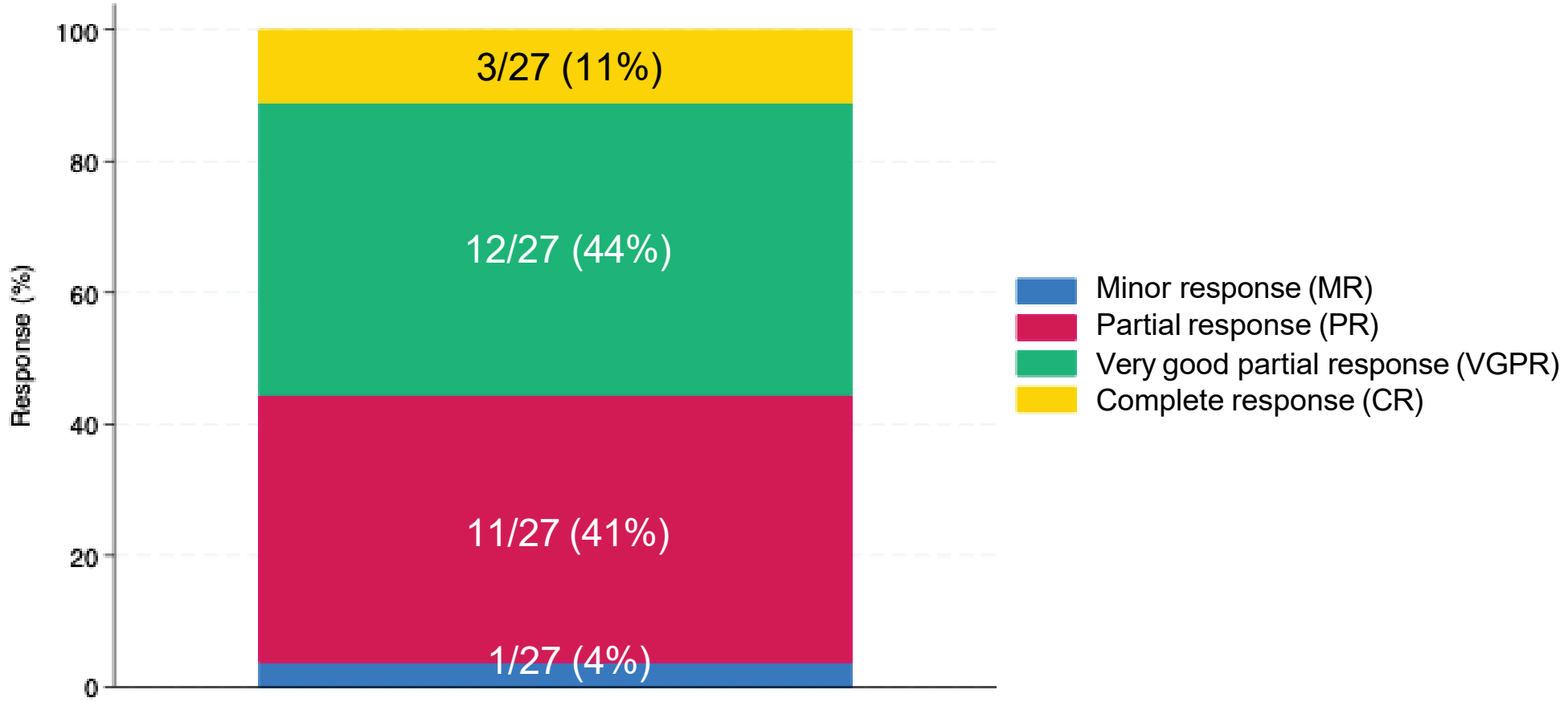
Baseline characteristics

n=27 patients who completed 6 months on study

Characteristic	Number/Median	Percentage/Range
Median age (years)	69	55-80
Female sex	12	44%
Number of previous lines	1	1-3
Covalent BTKi exposure	14	52%
Covalent BTKi resistant	10/14	71%
Median serum IgM level (mg/dl)	2,552	551-7,249
Median hemoglobin (g/dl)	9.4	6.6-13.3
Median platelet count (k/ul)	206	22-402
CXCR4 mutations	12	44%
TP53 mutations	5	19%
Median BM involvement	70%	10-95%
Lymphadenopathy ≥1.5 cm	11	41%
Splenomegaly ≥15 cm	3	11%

Response to therapy

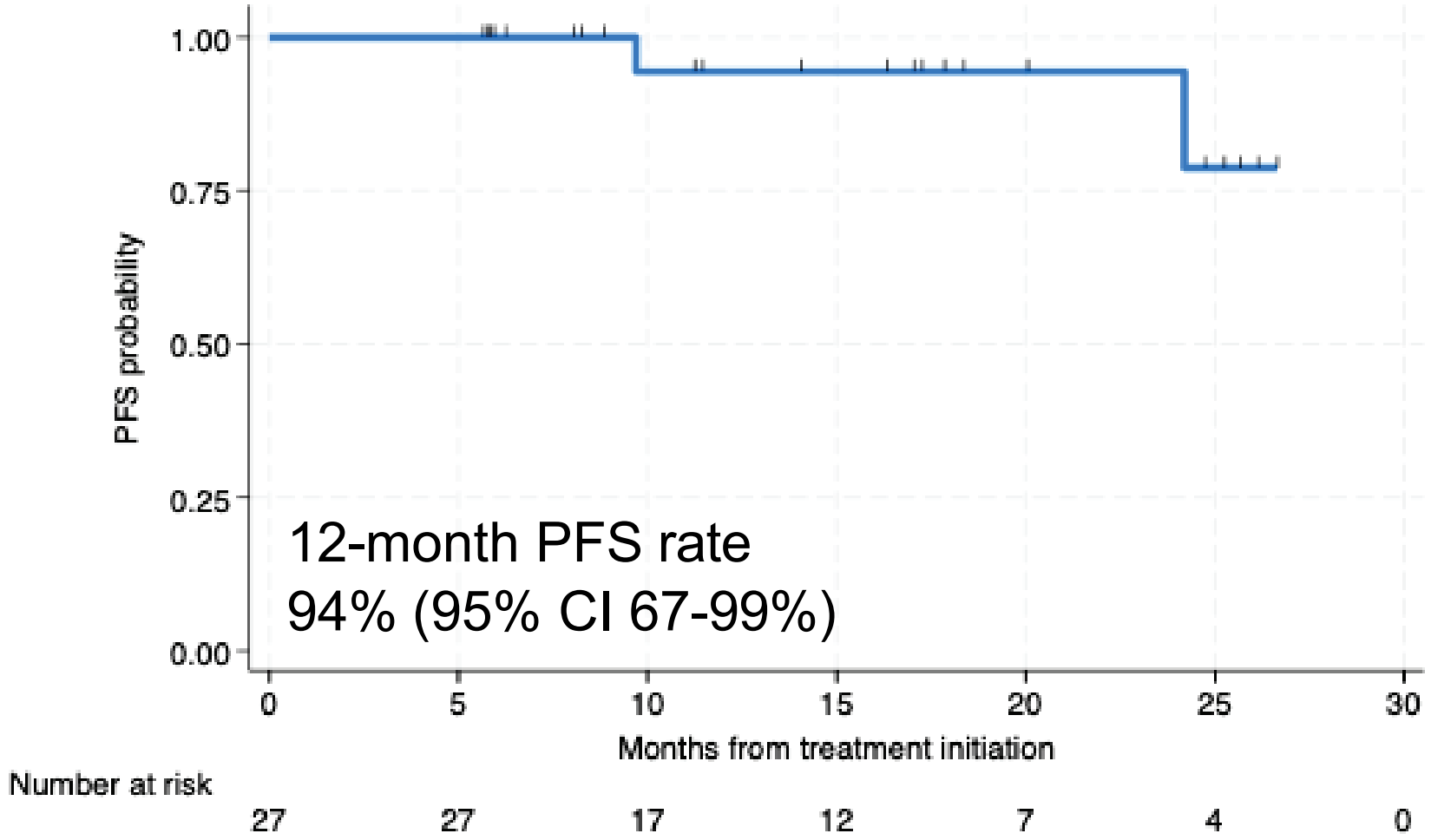
Median follow-up
11 months (95% CI 8-18)



VGPR/CR rate 56% (15/27)

Progression-free survival

Median follow-up
11 months (95% CI 8-18)



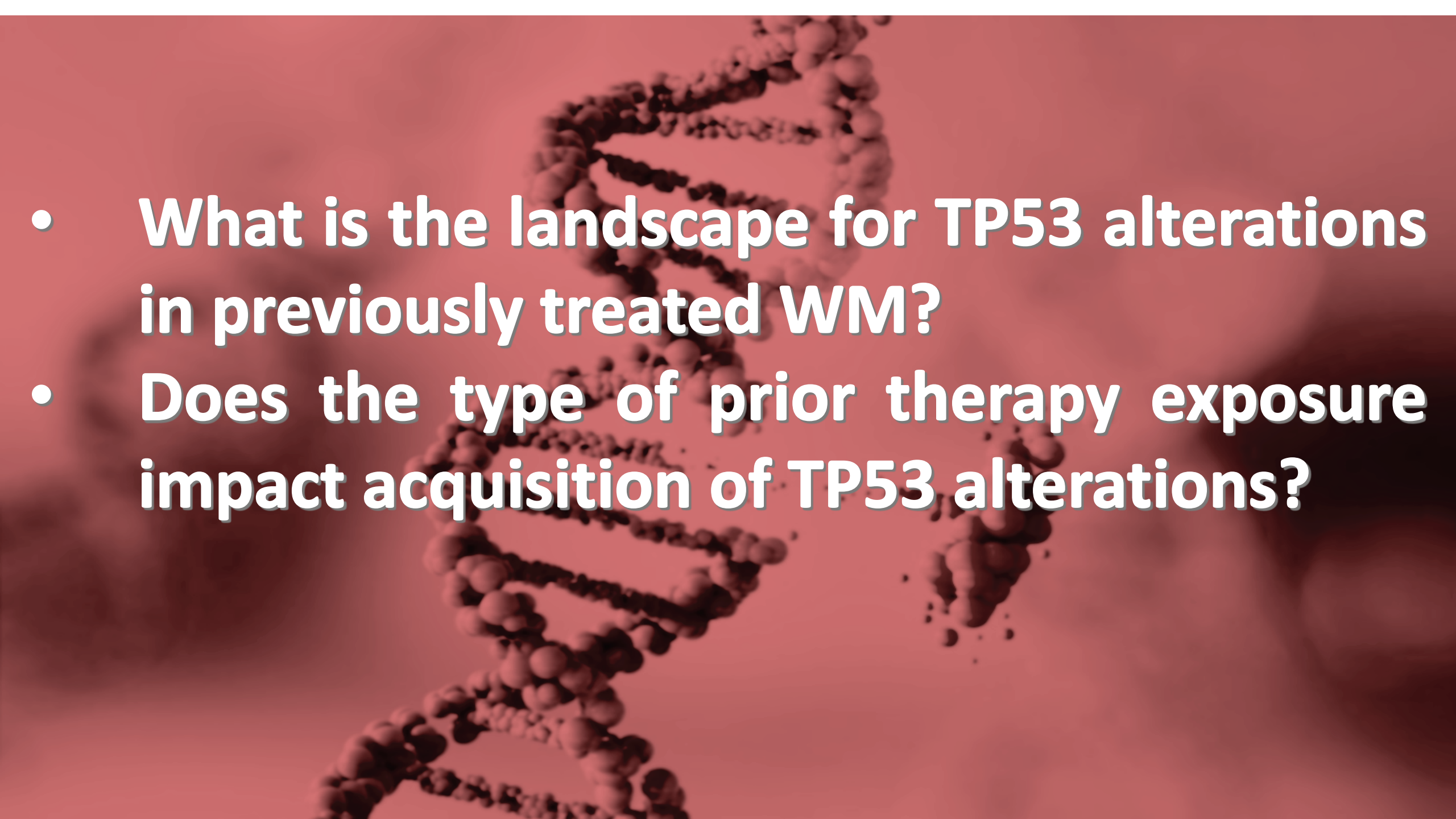
Safety profile

	Grade 2	Grade 3	Grade 4
Thrombocytopenia	1		2
Neutropenia		10	1
Anemia	3	3	
AST elevation		2	
URI	11	1	
Headache	5	1	
Diarrhea	4	1	
Musculoskeletal pain	2	1	
Lung infection		1	
Reflux/indigestion	7		
Fatigue	3		
Nausea/vomiting	3		
UTI	2		
Hyperphosphatemia	2		
Rash	2		
Abdominal pain	1		
Weight gain	1		
Pruritus	1		
Conjunctivitis	1		

DOUBLE-HIT ALTERATIONS OF TP53 IDENTIFY ULTRA HIGH-RISK DISEASE IN PREVIOUSLY TREATED, MYD88 MUTATED WALDENSTROM MACROGLOBULINEMIA

Abstract # 224

Tsakmaklis et al.



- What is the landscape for TP53 alterations in previously treated WM?
- Does the type of prior therapy exposure impact acquisition of TP53 alterations?

Methods and Patient Characteristics

Factor	Level	Value
N		164
Age at Diagnosis		57.8 (33.4-86.7)
Age at Bone Marrow Biopsy		64.9 (36.7-88.5)
Sex	Female	64 (39%)
	Male	100 (61%)
Hemoglobin (g/dL)		11.2 (6.9-15)
IgM (mg/dL)		3070 (28-8880)
Bone marrow involvement (%)		42.5 (5-95)
CXCR4 Status	WT	89 (54.3%)
	MUT	75 (45.7%)
Lines of therapy		1.5 (1-9)
Time from diagnosis (years)*		6.18 (0.04-22.8)
Time from first treatment* (years)		4.43 (0.04-22.7)

Group	Treatment	N	% of patients
Chemotherapy	Alkylating agents (AA)	70	85.4
N=82	Nucleoside analogues (NA)	28	34.1
	AA or NA	66	80.5
	AA and NA	16	19.5
Non-chemotherapy	Proteasome inhibitors (PI)	74	90.2
N=82	BTK inhibitors (BTKi)	25	30.5
	PI + BTKi	17	20.7
	Rituximab alone	65	79.3

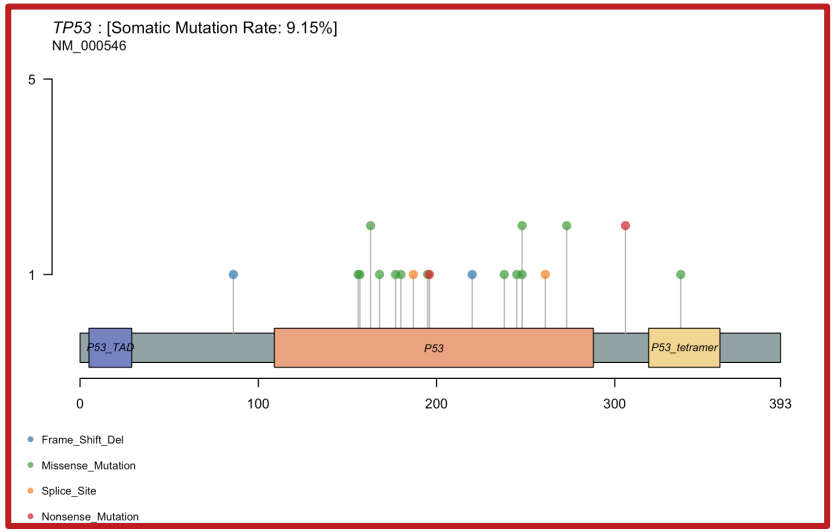
- **WES performed on DNA from CD19$^+$ BM LPC and PB CD19$^-$ cells (germline) from 164 previously treated WM patients.**
- **Analysis restricted to patients with ≥5% MYD88 VAF to ensure adequate tumor content.**
- **Median target coverage was 115X and 625X for germline and tumor samples, respectively.**

* To study biopsy

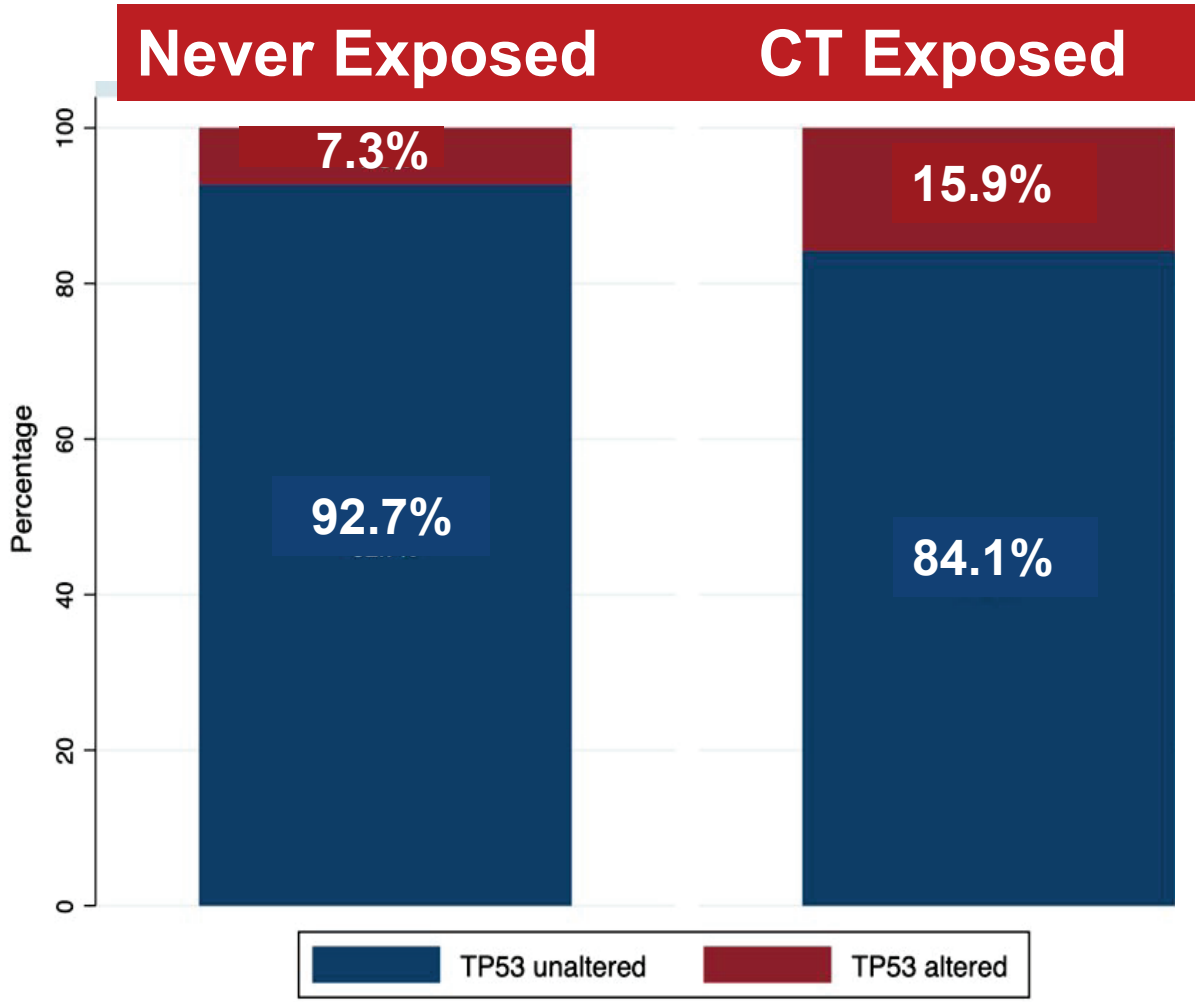
TP53^{ALT} in 19/164 (12%) of Previously Treated WM Patients

Sample	Variant	Type	TP53 VAF	MYD88 VAF	TP53 VAF / MYD88 VAF	Impacts binding domain?	Chr17 Status	TP53^{ALT} Status
PT019	R156G	Missense mutation	0.339	0.429	0.790	Y	Intact	Double-hit
PT019	G245D	Missense mutation	0.398	-	0.928	Y	Intact	-
PT019	R248Q	Missense mutation	0.005	-	0.012	Y	Intact	-
PT024	E180K	Missense mutation	0.014	0.381	0.037	Y	Del	Double-hit
PT024	X187_splice	Splice donor variant	0.036	-	0.094	Y	Del	-
PT024	R273C	Missense mutation	0.015	-	0.039	Y	Del	-
PT024	R306*	Nonsense mutation	0.053	-	0.139	N	Del	-
PT024	R337C	Missense mutation	0.042	-	0.110	N	Del	-
PT036	R306*	Nonsense mutation	0.593	0.527	1.125	N	UPD	Double-hit
PT048	C238G	Missense mutation	0.944	0.445	2.121	Y	UPD	Double-hit
PT050	X261_splice	Splice site	0.04	0.655	0.061	Y	Intact	Single-hit
PT064	Y163C	Missense mutation	0.45	0.438	1.027	Y	Del	Double-hit
PT064	V157F	Missense mutation	0.278	-	0.635	Y	Del	-
PT076	A86Hfs*37	Frameshift	0.052	0.09	0.578	Y	Intact	Single-hit
PT105	H168R	Missense mutation	0.351	0.343	1.023	Y	Del	Double-hit
PT128	R248Q	Missense mutation	0.452	0.476	0.950	Y	Intact	Single-hit
PT133	R273C	Missense mutation	0.606	0.678	0.894	Y	Del	Double-hit
PT178	Y163C	Missense mutation	0.79	0.677	1.167	Y	UPD	Double-hit
PT181	P177L	Missense mutation	0.089	0.33	0.270	Y	Intact	Single-hit
PT181	Y220Mfs*27	Frameshift	0.021	-	0.064	Y	Intact	-
PT199	R196*	Nonsense mutation	0.209	0.169	1.237	Y	Del	Double-hit
PT221	R248W	Missense mutation	0.283	0.233	1.215	Y	Del	Double-hit
PT251	I195T	Missense mutation	0.272	0.521	0.522	Y	Intact	Single-hit
PT069	WT	WT	NA	0.473	NA	Y	Del	Single-hit
PT127	WT	WT	NA	0.388	NA	Y	Del	Single-hit
PT104	WT	WT	NA	0.346	NA	Y	Del	Single-hit
PT070	WT	WT	NA	0.318	NA	Y	Del	Single-hit

- **TP53^{MUT} only (N=5); del17p only (N=4); TP53 double-hit (N=10).**
- **19 unique TP53 variants were observed; 4 variants occurred in >1 patient (R248Q, R273C, R306*, and Y163C).**



TP53 ALT Were More Common in CT- vs. Non-CT-Exposed Patients



p=0.088

Multivariate Logistic Regression

Term	p-value	OR
Prior AA or NA	0.102	2.89
CXCR4 Mutated	0.118	2.28
Age at Biopsy	0.589	1.01
>1 Prior Therapy	0.945	0.96
Actively Progressing	0.909	1.06

Double-hit TP53^{ALT}

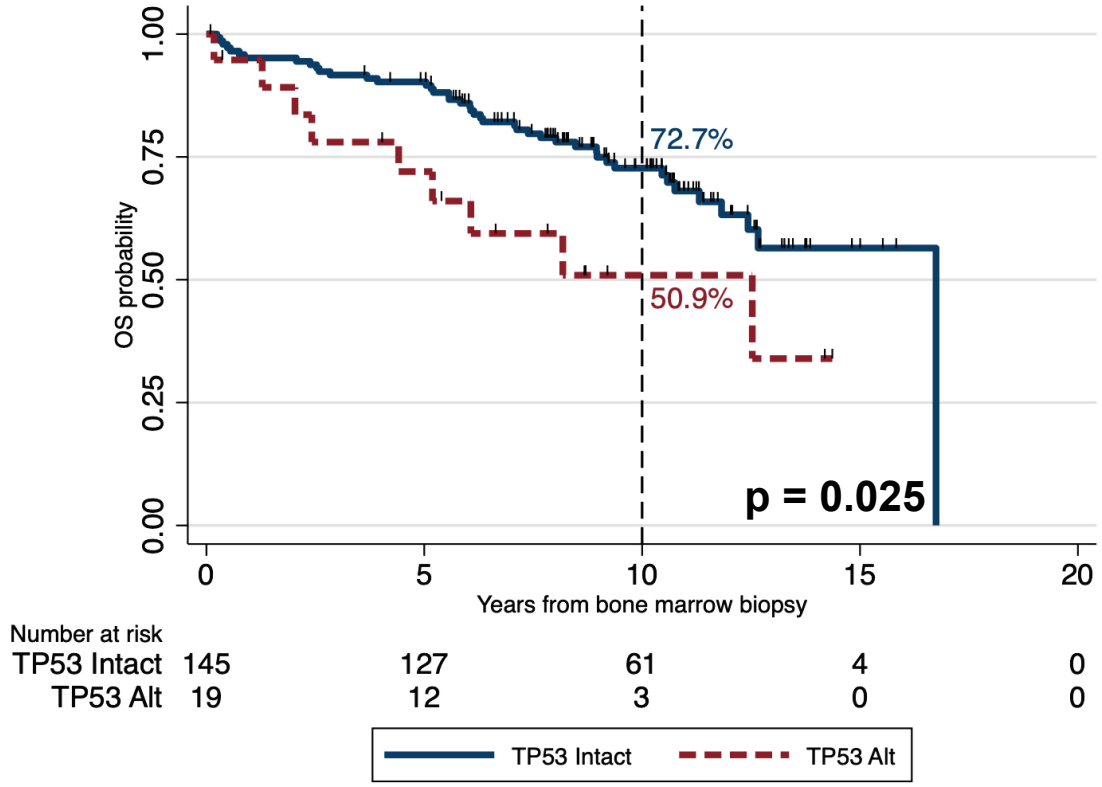
18.8% who received both AA and NA

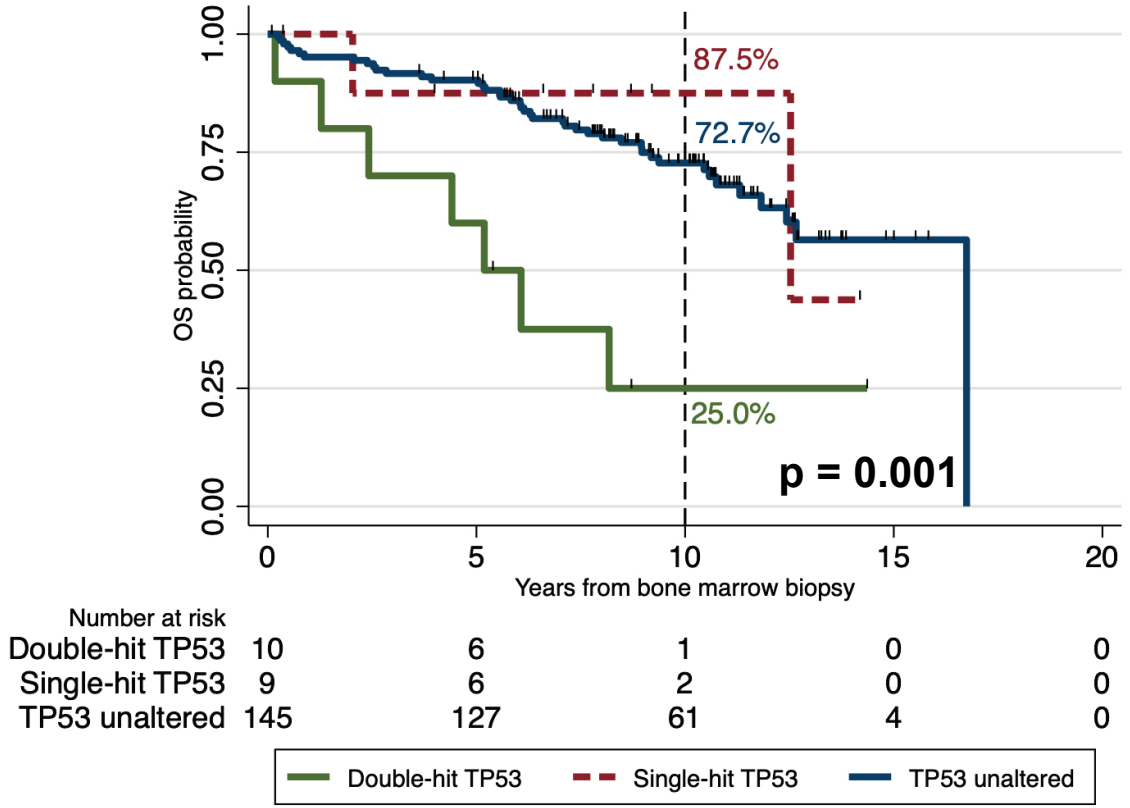
6.1% who received either AA or NA

3.6% who received no CT

p=0.069

TP53 Double-hit is Associated with inferior OS in previously treated WM patients





Median follow-up 10 yrs (95% CI 9.2-10.7 yrs) from study biopsy

Kapitel 2

Patientenpräferenzen bei der Behandlung des Morbus Waldenström

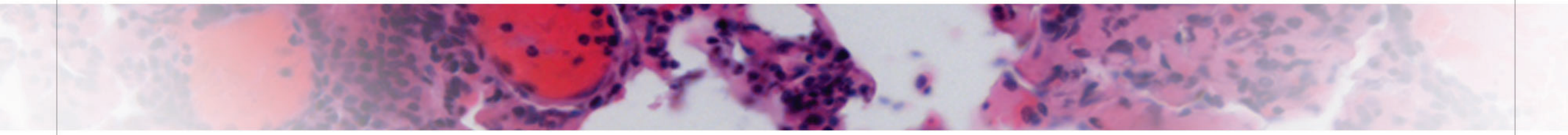
WM-VOICE study: An International Discrete Choice Experiment on Treatment Preferences in 1,455 Patients with Waldenström Macroglobulinemia

Abstract # 519

Becking et al.

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



WM-VOICE study

An International Discrete Choice Experiment on Treatment Preferences in 1,455 Patients with Waldenström Macroglobulinemia

WM-VOICE

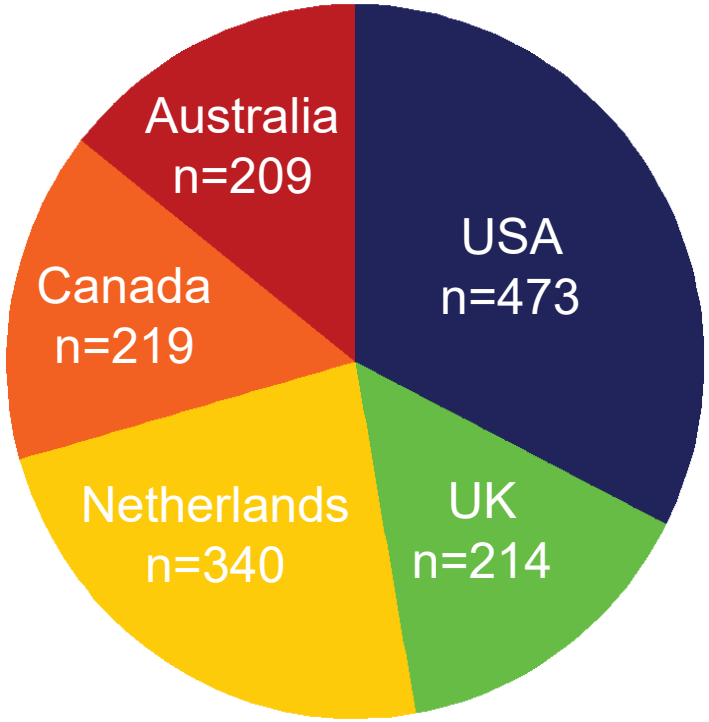
Anne-Marie L. Becking, MD, PhD student
Amsterdam UMC, Department of Hematology

This work is supported by the International Waldenstrom's Macroglobulinemia Foundation (IWMF).
Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the IWMF.

WM-VOICE: respondents

Accrual (Oct ‘24 – Feb ‘25)

Total DCE respondents: N = 1,455



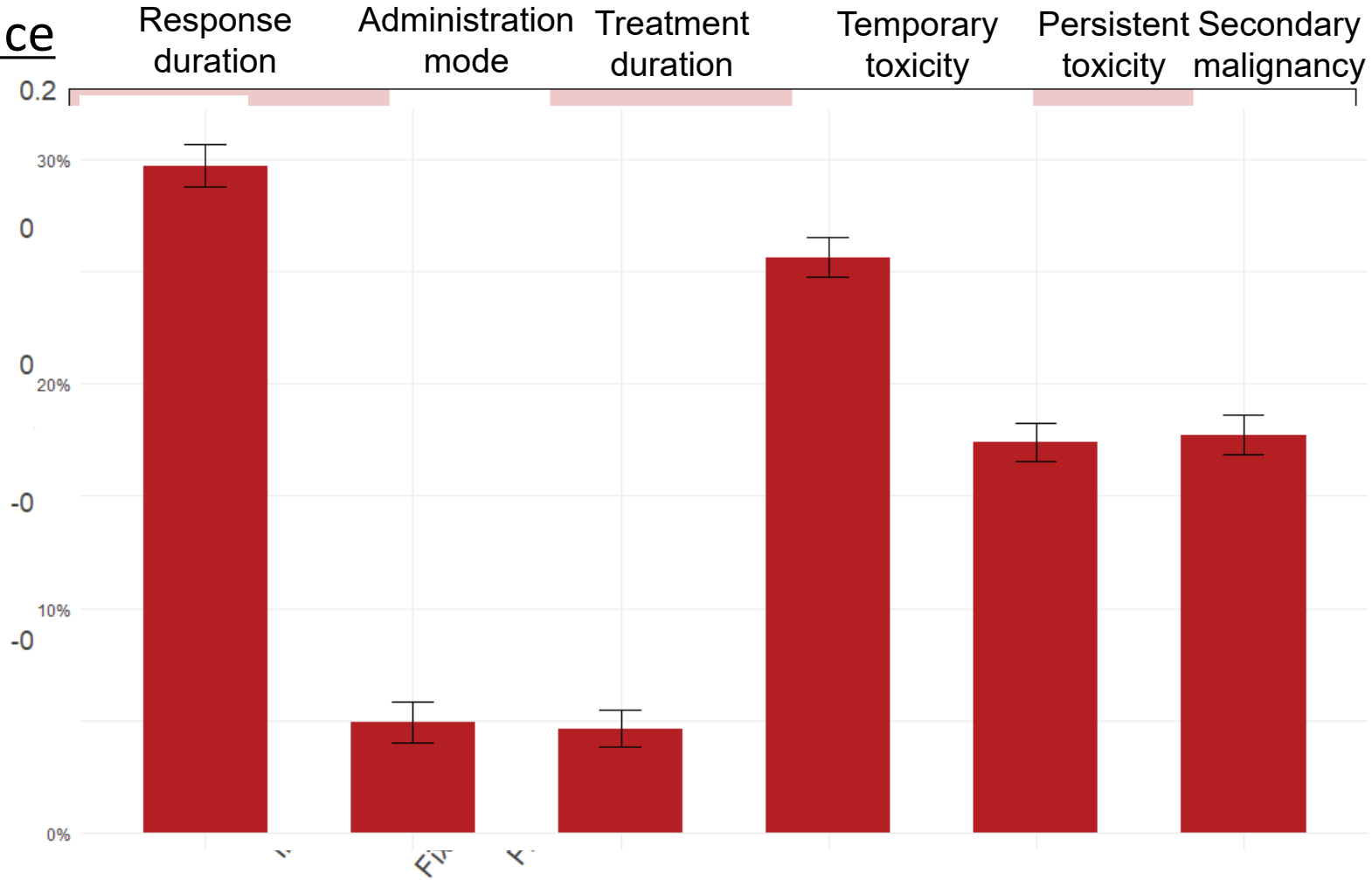
Baseline characteristics

Sex, male:	818 (56%)
Age:	61-70 yrs (33%)
	71-80 yrs (42%)
Med time since WM diagnosis:	6 yrs (IQR 3-10)
Previously treated:	1,155 (79%)
Med no. of Tx lines:	1 (IQR 1-2)
Prior chemotherapy:	849 (58%)
Prior rituximab:	847 (58%)
Prior BTK inhibitors:	456 (31%)

WM-VOICE: DCE results

Conditional relative importance

Average marginal effects



Conclusion

- WM-VOICE first to study international WM patient treatment preferences
- 6 treatment properties identified, significantly influencing choices
  - Strong similarity across 5 Western countries
- Patient choices mainly driven by long response duration and avoidance of severe toxicity
  - Administration mode (iv vs. oral) and treatment-free interval less influential
- Could support shared-decision making, drug development and trial design

Kapitel 3

Bedeutung des PET/CT für die Bestimmung des Ansprechens beim Marginalzonenlymphom

Utility of 18F-FDG PET/CT for response assessment in marginal zone lymphomas: preliminary results of the IELSG44 international study

Abstract # 1810

Ceriani et al.

Background

- Controversial role of 18F-FDG PET/CT in MZL
- Routine use not recommended by current Lugano classification
- IELSG44/PIMENTO multicenter retrospective study designed to assess PET role in MZL:
  - staging
  - response assessment
  - outcome prediction

Results

357 patients from 21 centers in 4 countries

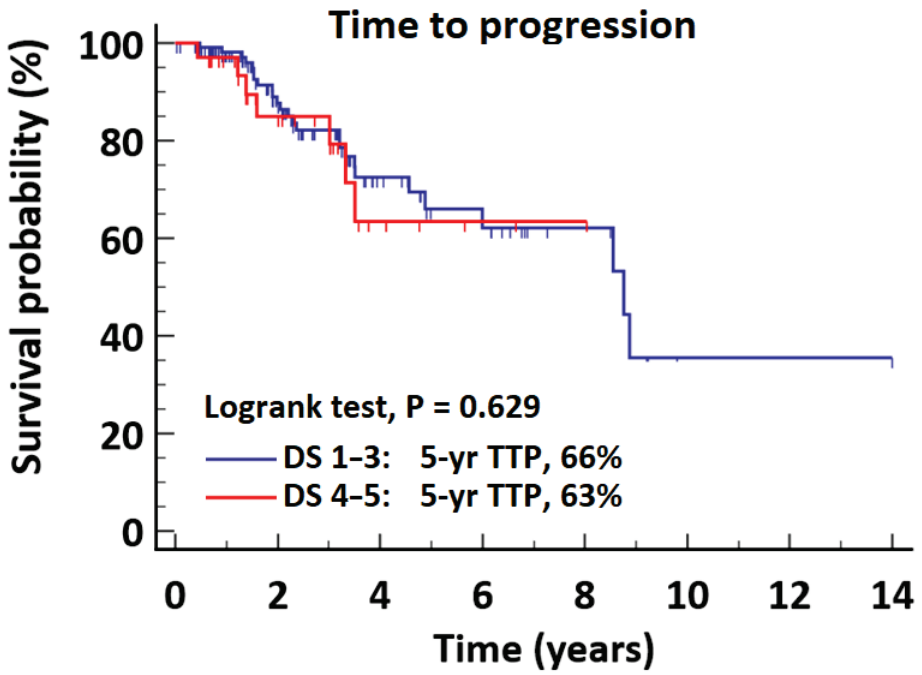
- 307 with baseline PET/CT scans
- 68 with post-treatment PET scans
- 162 with both baseline and end-of-therapy PET/CT

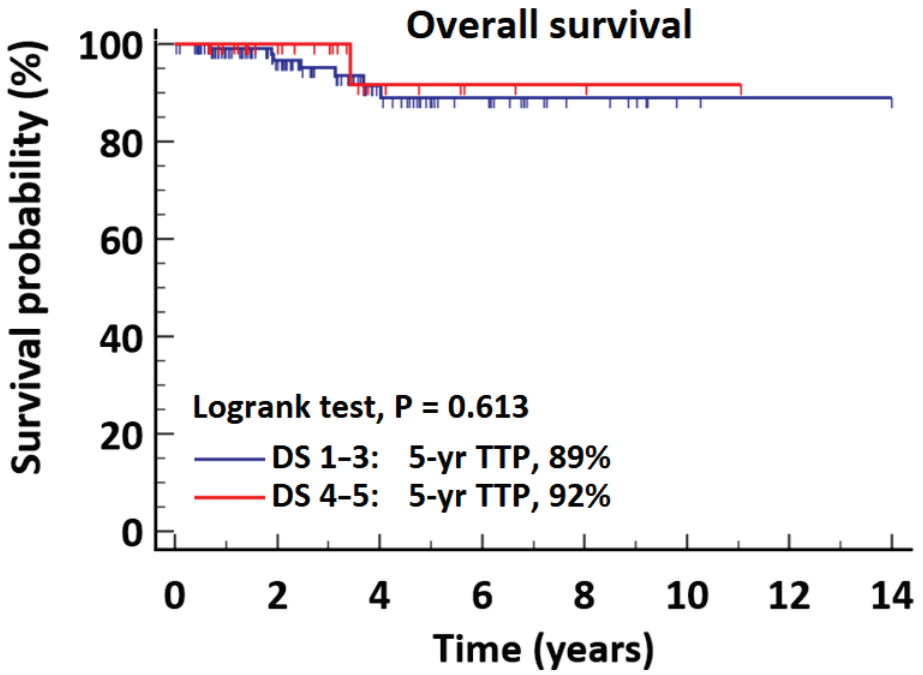
156/162 with clinical follow-up data and scans available for central review

- 88 extranodal MZL
- 43 nodal MZL
- 21 splenic MZL
- 4 MZL, not otherwise specified

Results (cont.)

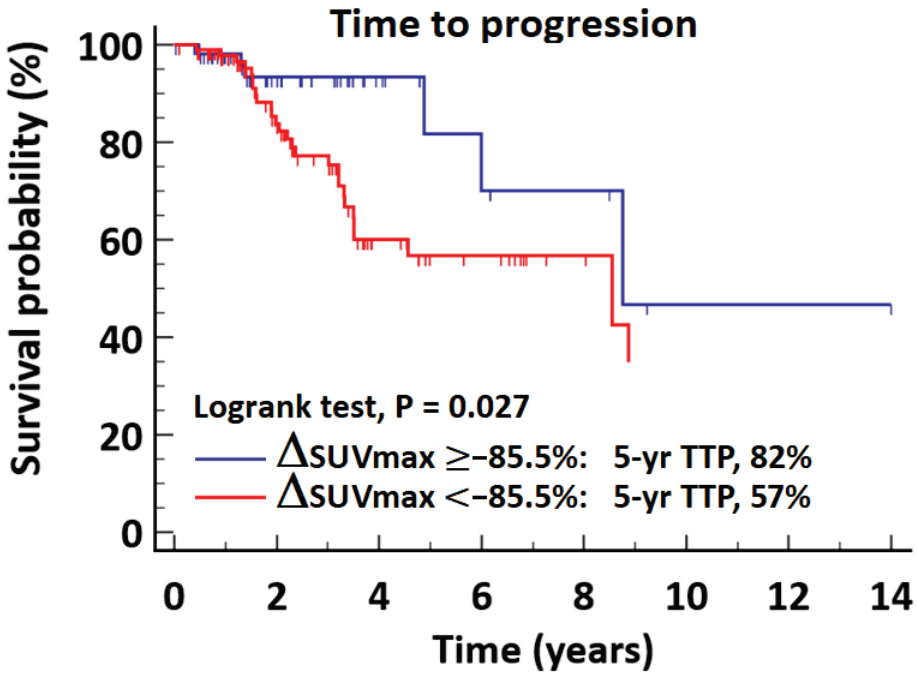
- median follow-up: 2.7 years (IQR: 1.4–4.5)
- CMR defined as DS 1–3 did not predict outcome





Results (cont.)

- Post-treatment reduction in SUVmax did not predict outcomes with conventional thresholds (-66% and -70%) in the entire cohort, but it was predictive of progression regardless of baseline SUV with the ROC-defined cutoff (-85.5%)



Zusammenfassung | Take-Home-Messages

Morbus Waldenström:

- DRC plus/minus Bortezomib ist eine hocheffektive und gut verträgliche Erstlinientherapie, die eine mediane Zeit bis zur nächsten Therapie von fast 70 Monaten und ein lymphomspezifisches Überleben von 96%/97% nach 5 Jahren erzielt

- Pirtobrutinib/Venetoclax ist eine vielversprechende zeitlich begrenzte chemotherapiefreie Therapie, die nach ersten Daten sehr gut verträglich ist und tiefe Remissionen bei der Mehrzahl der Patienten erzielen kann

- Therapien mit Alkylanzien und Nukleosidanaloga könnten mit einer höheren Rate an TP53 Alterationen assoziiert sein

- Double hit TP53 Alterationen sind in einer retrospektiven Analyse mit einem deutlich schlechteren Therapieergebnis verbunden

- Für Patienten ist vor allem eine geringe Toxizität sowie eine lange Ansprechdauer der Behandlung entscheidend für die Akzeptanz einer Therapie

Marginalzonenlymphom:

- Die Rolle des PET/CTs für die Beurteilung des Ansprechens kann derzeit nicht als gesichert gelten

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2025

Für den Inhalt verantwortlich:

Prof. Dr. med. Christian Buske

Universitätsklinikum Ulm

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

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