Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

65th ASH Meeting 2023

San Diego & virtuell

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Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Martin Dreyling
Klinikum der Universität München

Mantelzell-Lymphom (MCL)

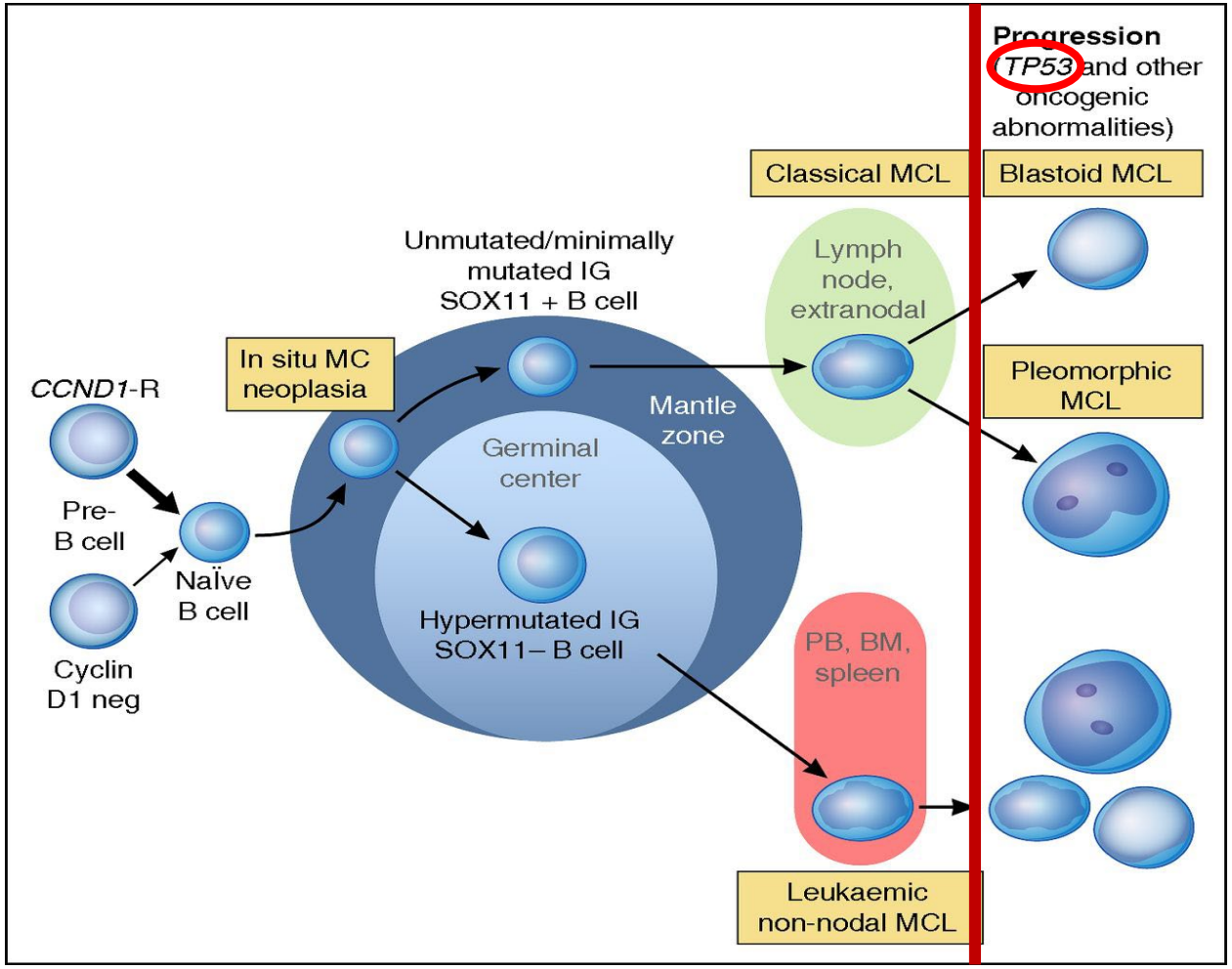
Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2023 wird in Kooperation mit acht unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche**
Scientific Advisory Board	**Abbvie, Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche**

Mantelzell-Lymphom

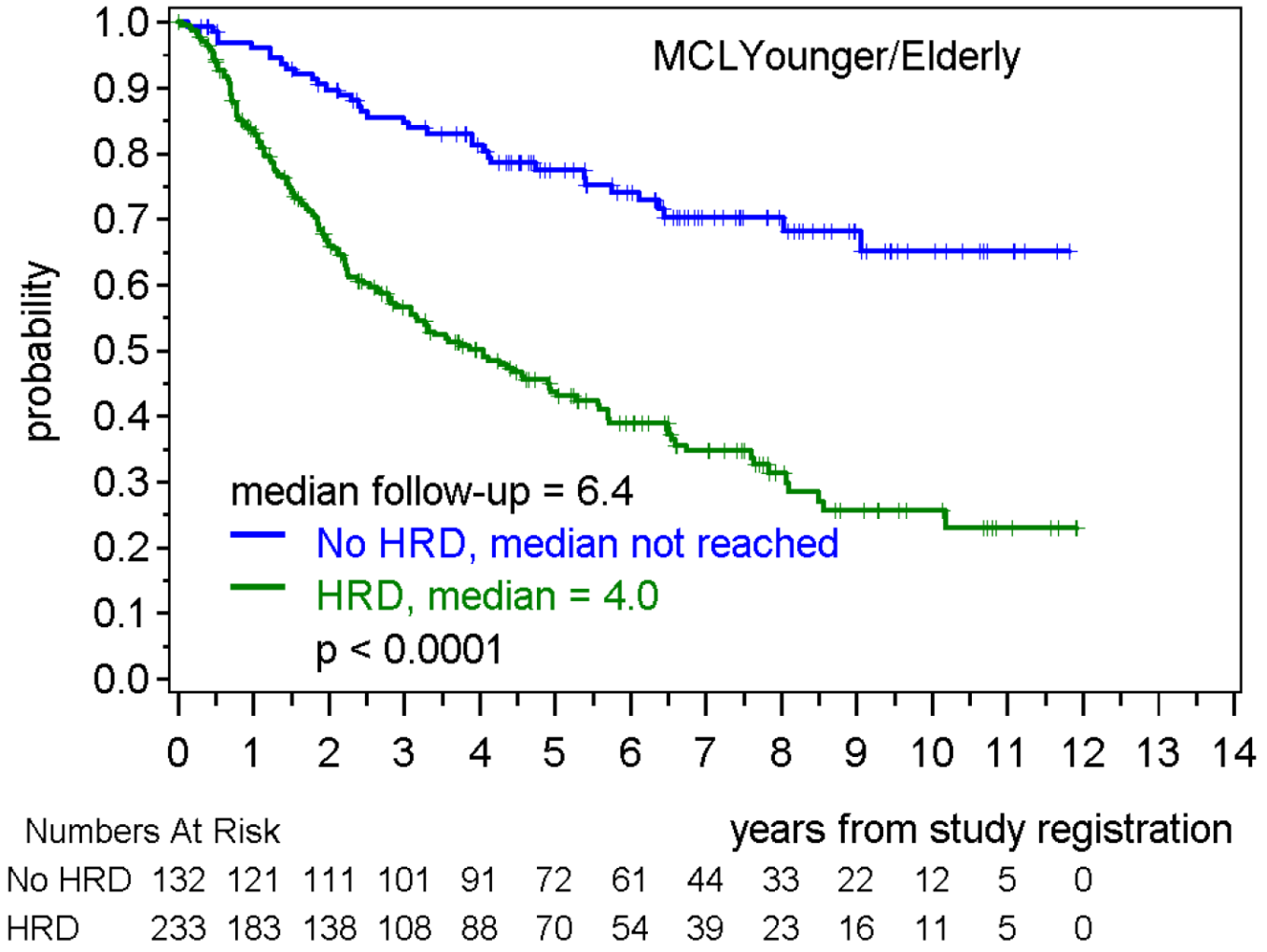
Spektrum der Erkrankung



Dreyling, Ann Oncol 2017

Hochrisiko Mantelzell-Lymphom

Gesamt-Überleben (n=465)



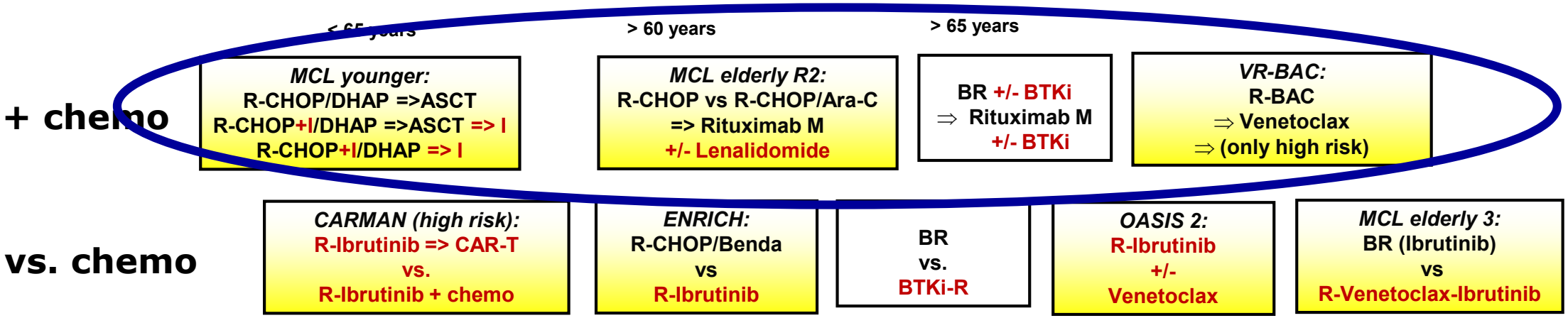
Scheubeck, Leukemia 2023

Kapitel 1

Erstlinientherapie.

Immun-Chemotherapie & targeted Therapie

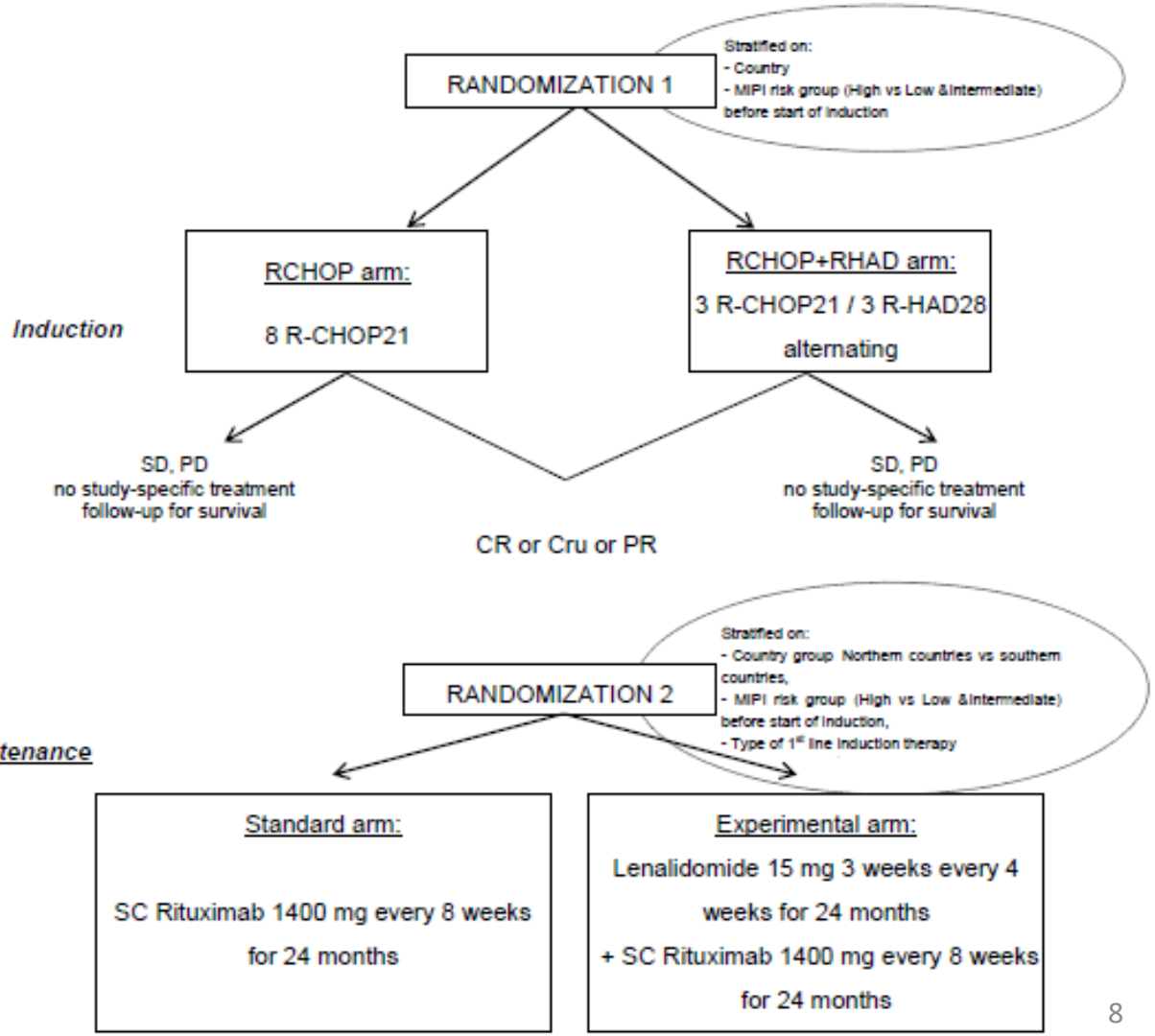
European MCL Network
Study generation 2023



Relapse

MCL-R2 Elderly: study design

Response assessment according to Cheson 1999 criteria

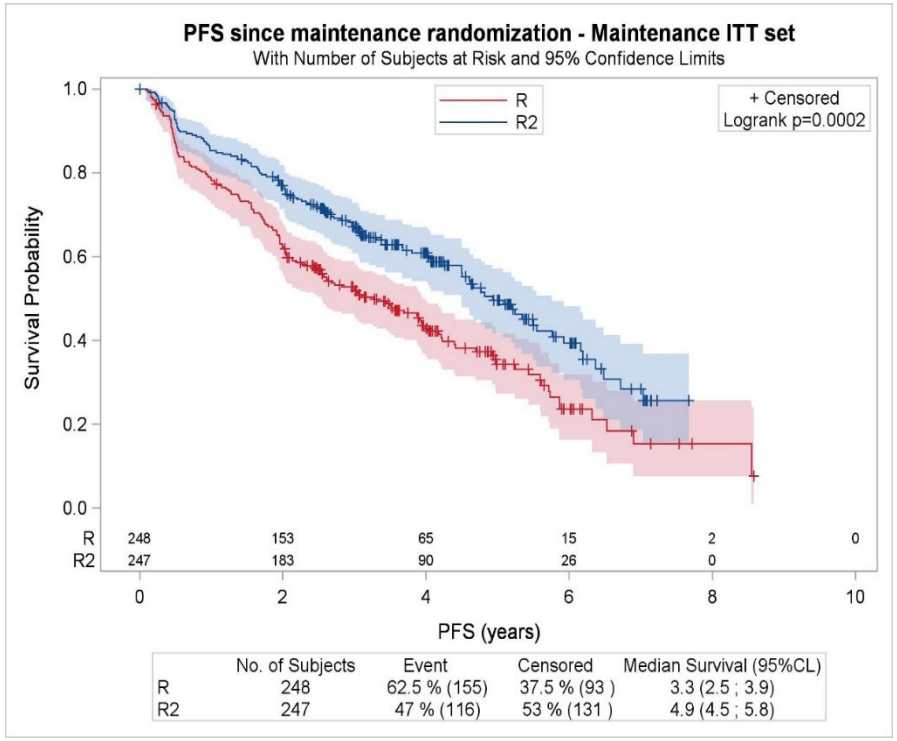


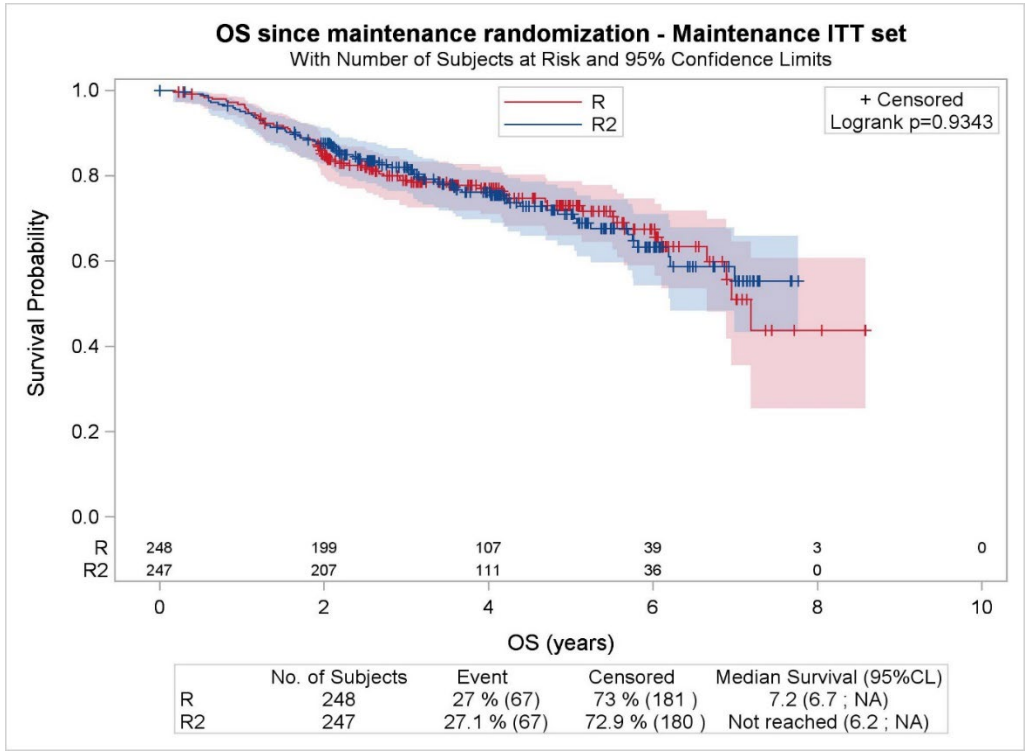
Follow-up: for progression death and SPM until the end of the study

MCL-R2 Elderly: safety maintenance

SAE all grade during maintenance phase – Maintenance Safety set	R N=250	R2 N=238
Blood and Lymphatic System Disorders	70 (121 events)	144 (520 events)
Neutropenia > grade 2	48 (66 events)	124 (344 events)
Anemia > grade 2	1 (1 event)	9 (9 events)
Infections and Infestations	60 (100 events)	105 (183 events)
SPM	36 (47 events)	45 (80 events)
Death for Toxicity	1	3

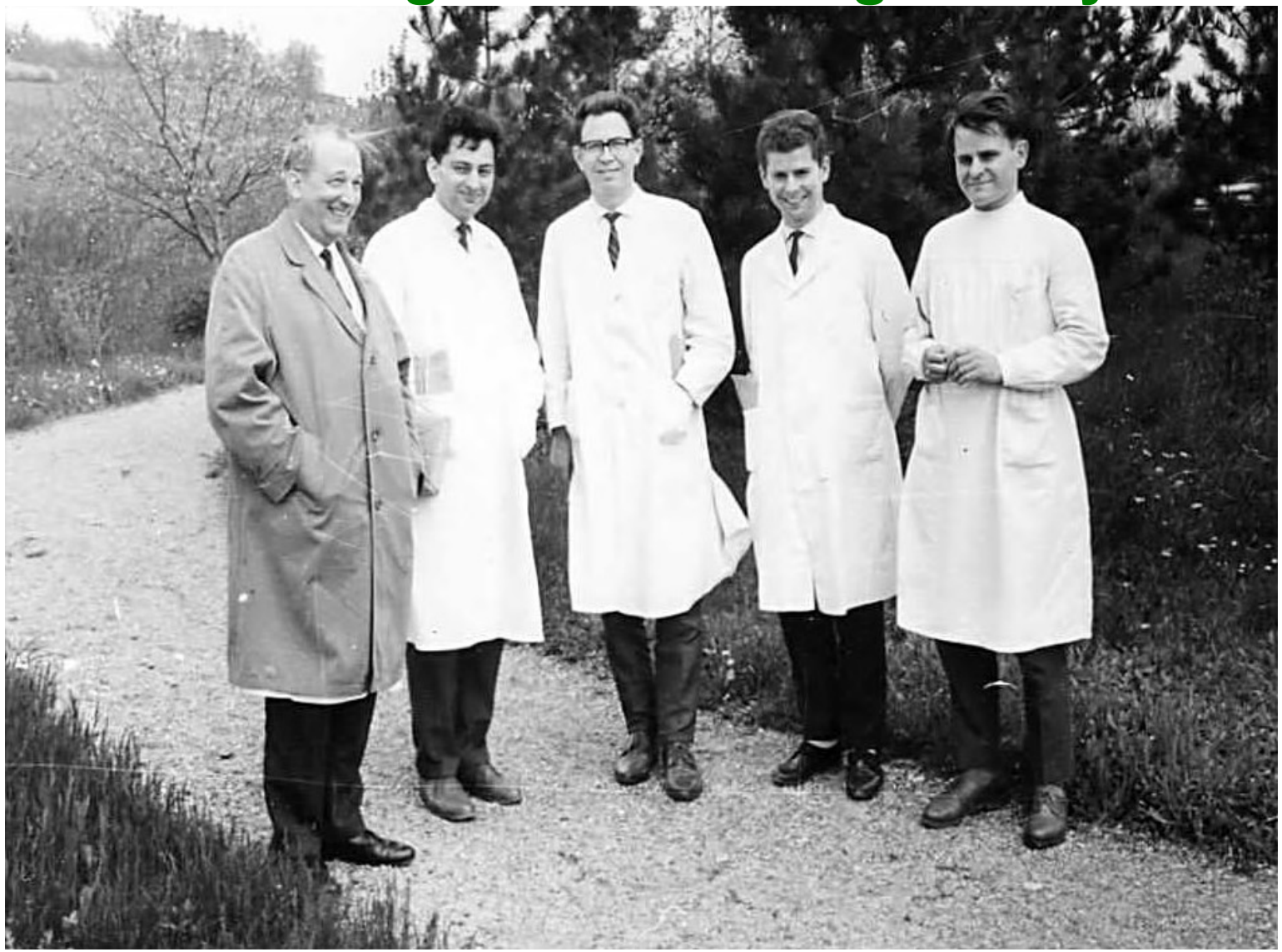
MCL-R2 Elderly: PFS analysis





Bendamustine:

An ‘agent’ with a long history



- **synthesis : W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)**
- **Published in Journal für Praktische Chemie, Vol. 20, issue 3-4, 1963**

Study Schema

N=33

REGISTRATION

Induction[1]

Rituximab 375 mg/m^2 IV d 1 Q 28 days x 6 cycles[2]

Bendamustine 90 or 70 mg/m^2 IV d 1, 2 Q 28 days x 6 cycles[3]

Cycle 1: Venetoclax titration to 200 mg PO d 1-28[4]

Cycle 2-6: Venetoclax 400 mg PO d 1-10 of 28 day cycle

Response

Per Investigator Discretion

Maintenance[4]

Rituximab 375 mg/m^2 IV or SQ every 8 weeks x 12 doses or 24 months (whichever comes first)

Progression

Off Study

GCSF prophylaxis was required with each cycle

[1] Interim safety analysis for TLS after first 19 pts who receive venetoclax.
[2] If first 2 cycles of IV rituximab tolerated, may use SQ.
[3] 70 mg/m^2 allowed per investigator discretion for subjects over 75 years of age.
[4] After EOT, subjects responding to therapy may receive maintenance rituximab (every 8 weeks for 12 doses over 24 months) per physician and patient preference

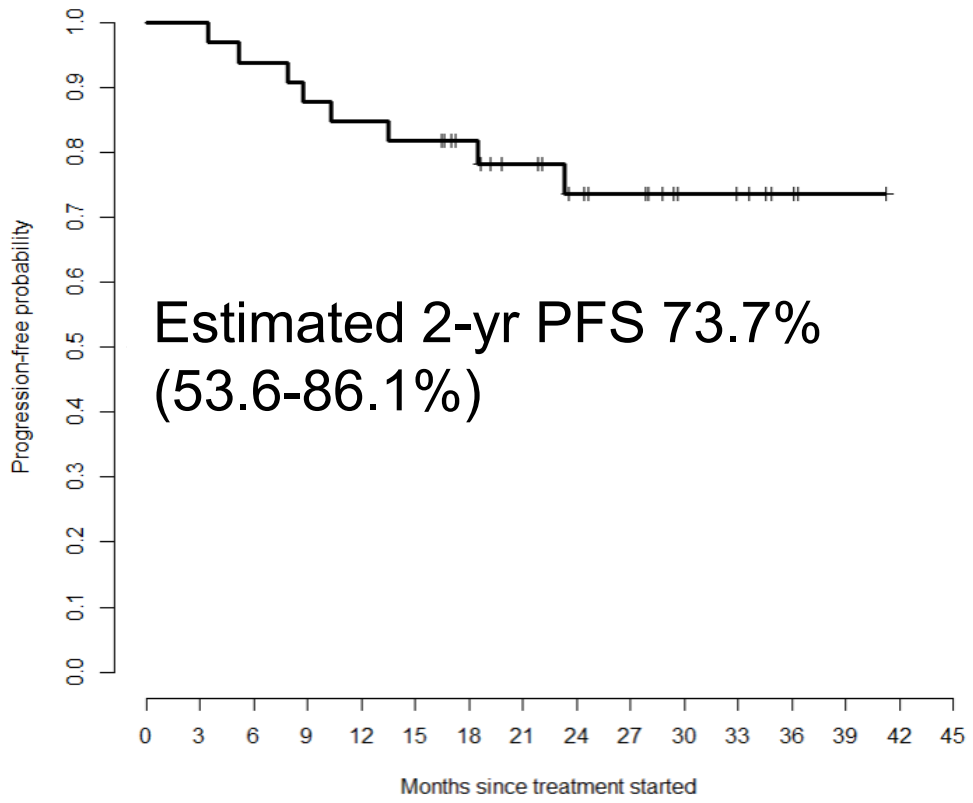
Treatment Details

- 7 (21%) of subjects were treated with bendamustine 70 mg/m^2
- Laboratory TLS was seen in 2 of 33 subjects during C1 only
  - NO clinical TLS was seen
- Dose adjustments or delays occurred in 36% and 67% of subjects respectively
- 22 (66.7%) of subjects completed all 6 cycles
  - Reasons for treatment discontinuation prior to 6 cycles include:
    - AE (n=6)
    - Death (n=1)
    - Investigator Discretion (n=1)
    - Progression (n=1)
    - Other (n=2)

Survival

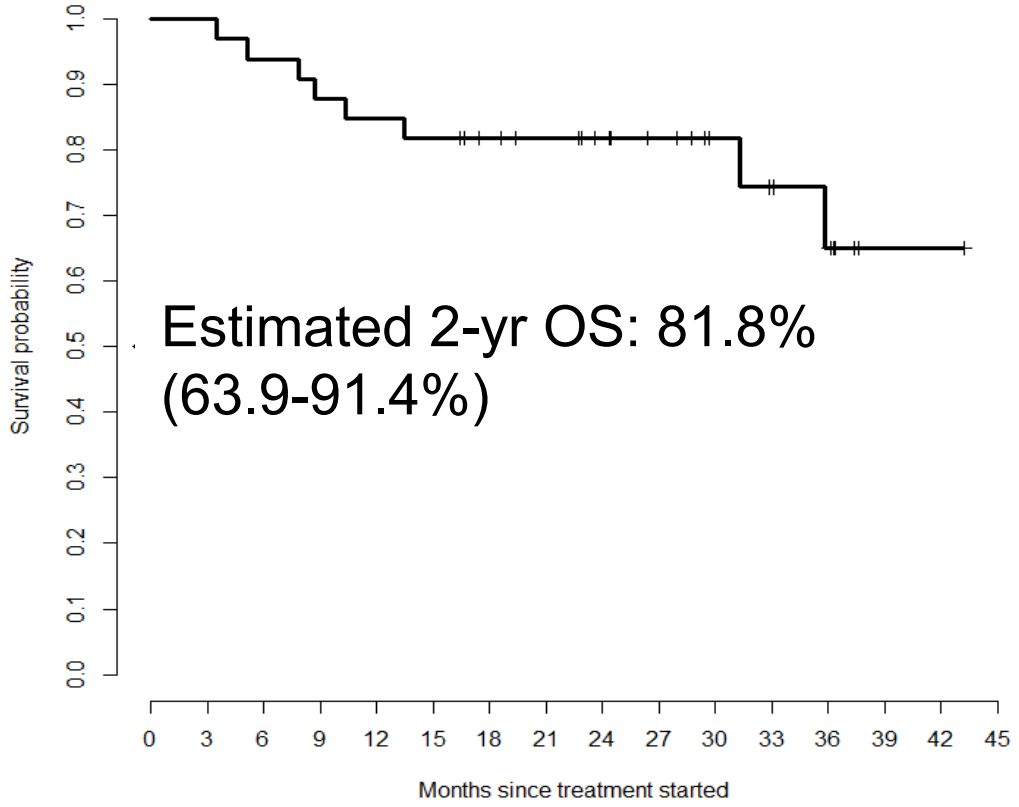
Updated August 2023

Progression-Free Survival



Estimated 2-yr PFS 73.7%
(53.6-86.1%)

Overall Survival



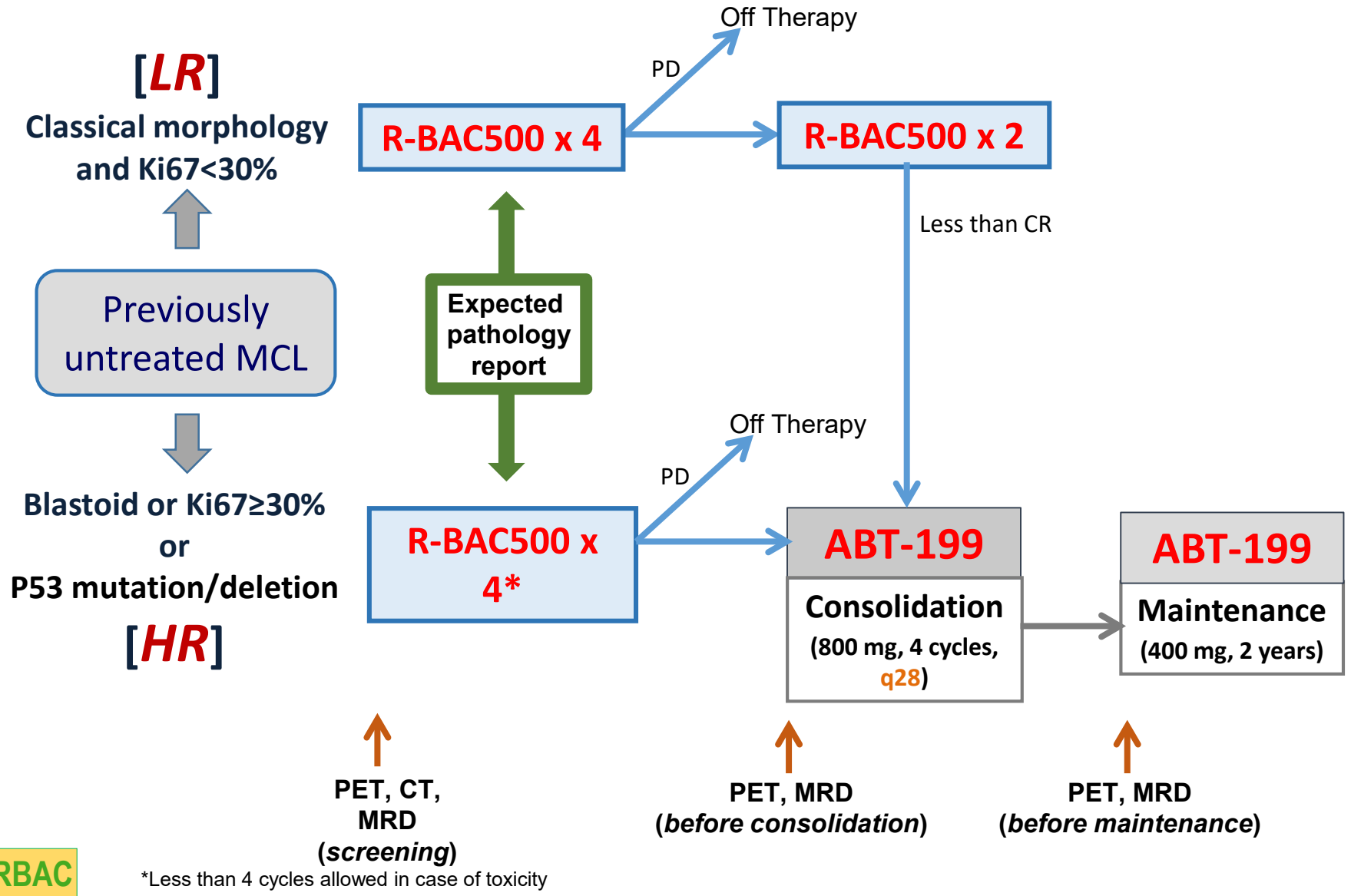
Estimated 2-yr OS: 81.8%
(63.9-91.4%)

* Median (Q1, Q3) follow up of 28.7 (22.8, 36.1)

FONDAZIONE ITALIANA LINFOMI

Study Design

www.filinf.it



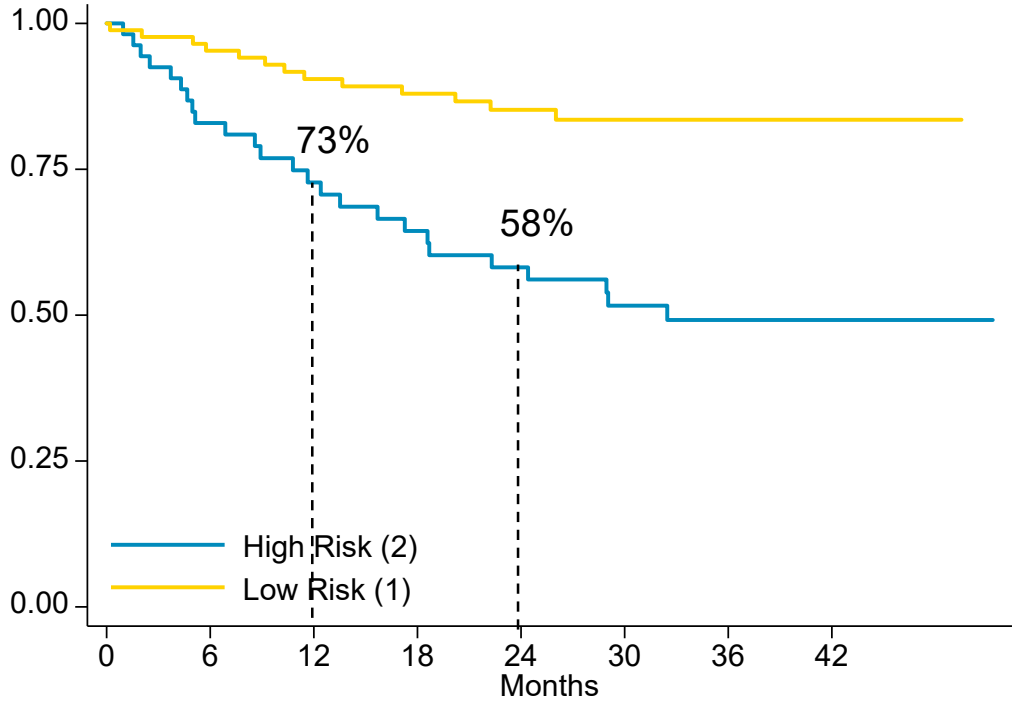
V-RBAC

*Less than 4 cycles allowed in case of toxicity

FONDAZIONE ITALIANA LINFOMI

Progression-free Survival by risk group

www.filinf.it

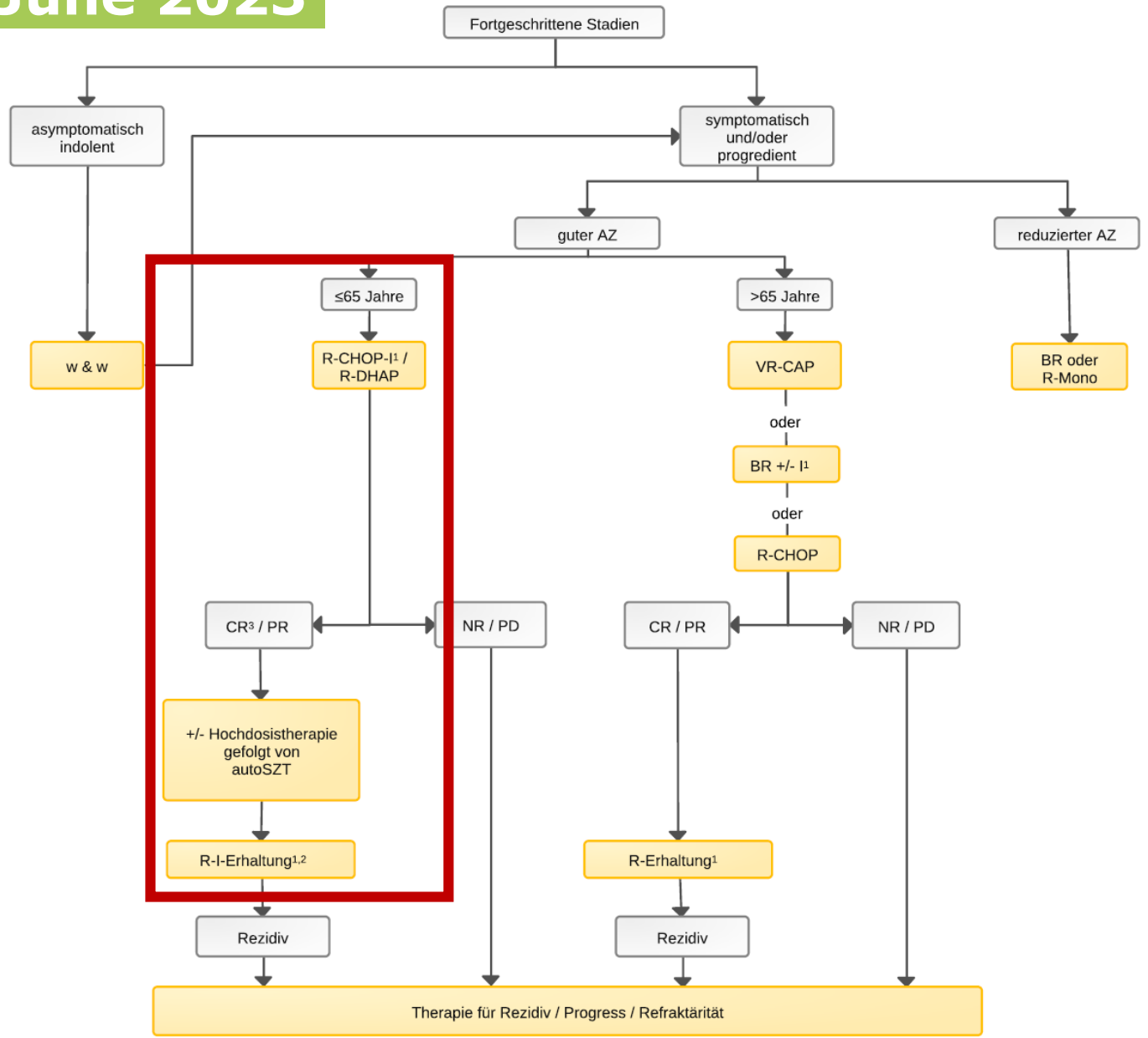


At risk:								
High Risk (2)	54	42	35	31	28	22	15	10
Low Risk (1)	86	81	73	70	56	42	26	13

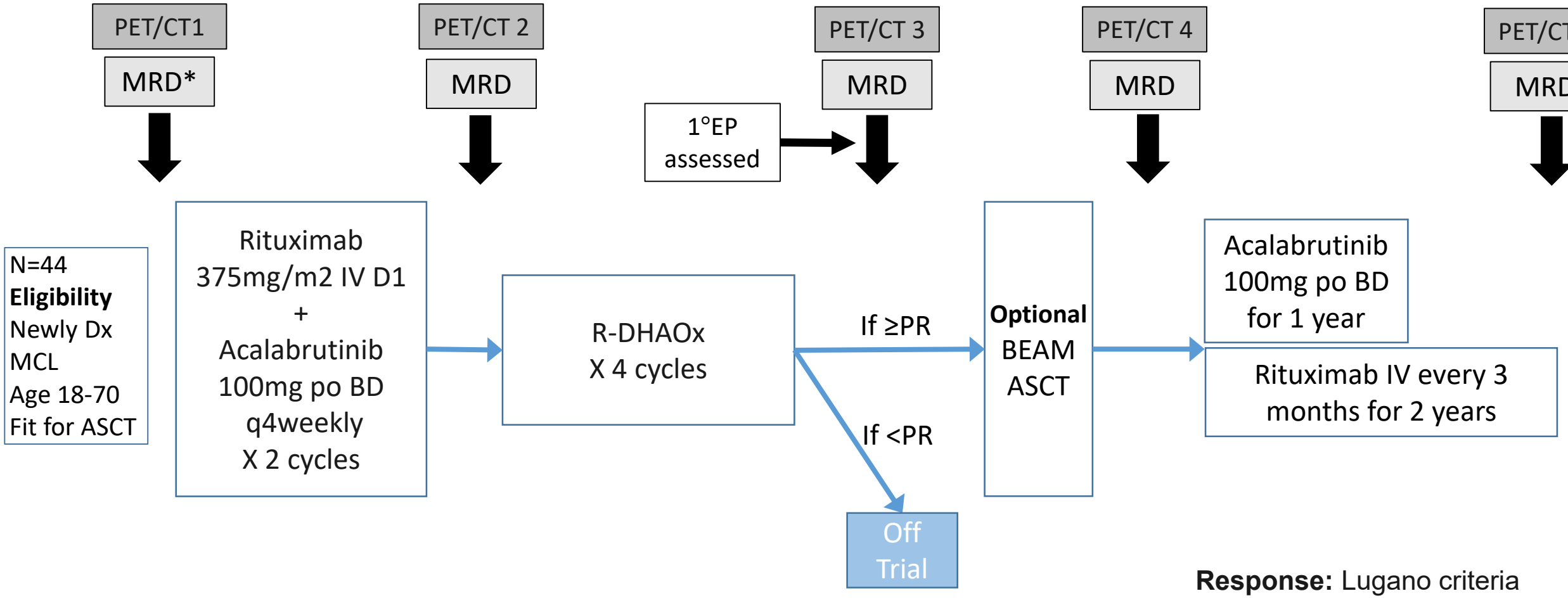
Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Low Risk (1)				
12	0.9046	0.0321	0.8182	0.9511
24	0.8519	0.0396	0.7534	0.9133
High Risk (2)				
12	0.7274	0.0624	0.5929	0.8289
24	0.5819	0.0701	0.4329	0.7046

V-RBAC

Mantle cell Lymphoma
Onkopedia June 2023



NHL33 WAMM Study schema: Single-arm Phase II study

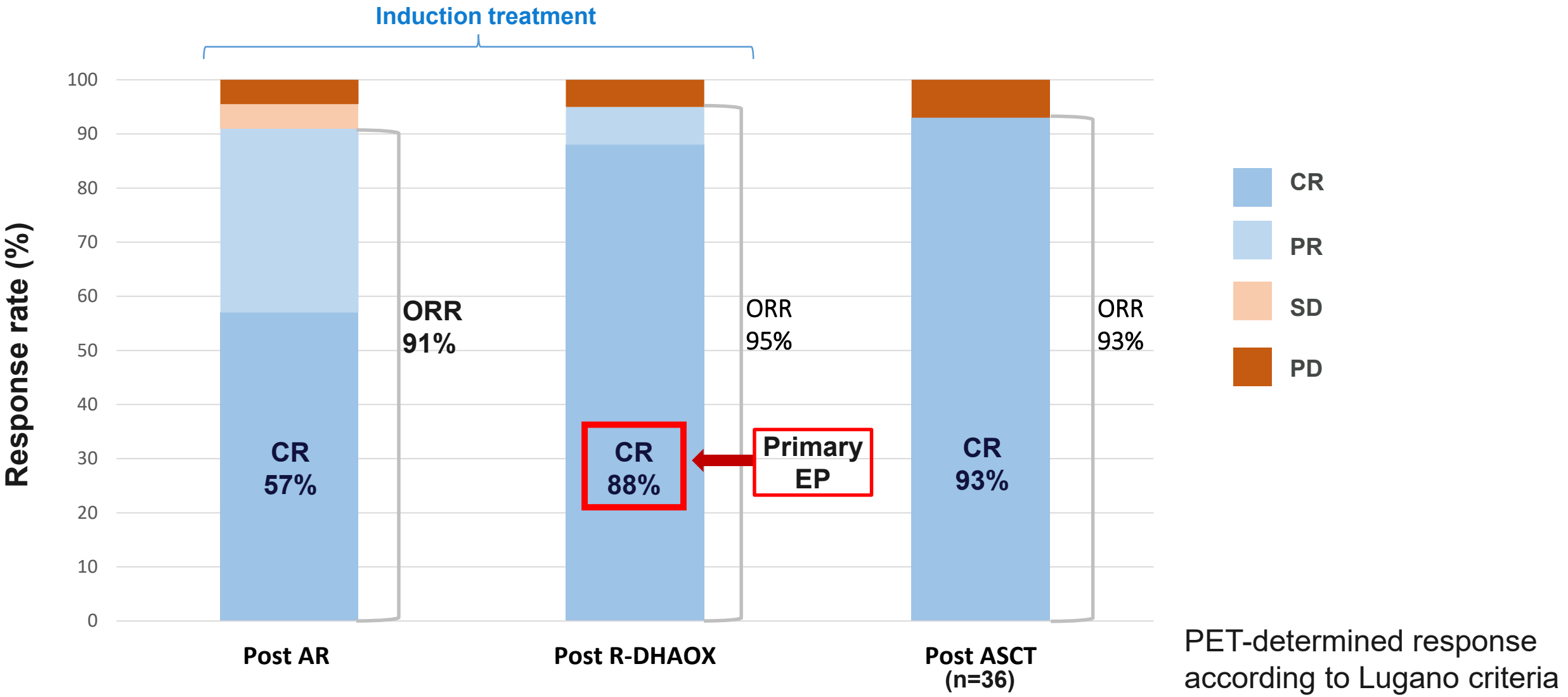


Primary EP: PET CR rate in the absence of prohibitive toxicity after R-DHAOx
Secondary Endpoints: ORR, Toxicity, PFS, OS, MRD, Stem cell mobilisation, QOL

Response: Lugano criteria
MRD: Peripheral blood LymphoTrack® NGS based IGH clonality assay

ALLG NHL33 WAMM study primary report.
ASH 2023 San Diego Abstr # 735

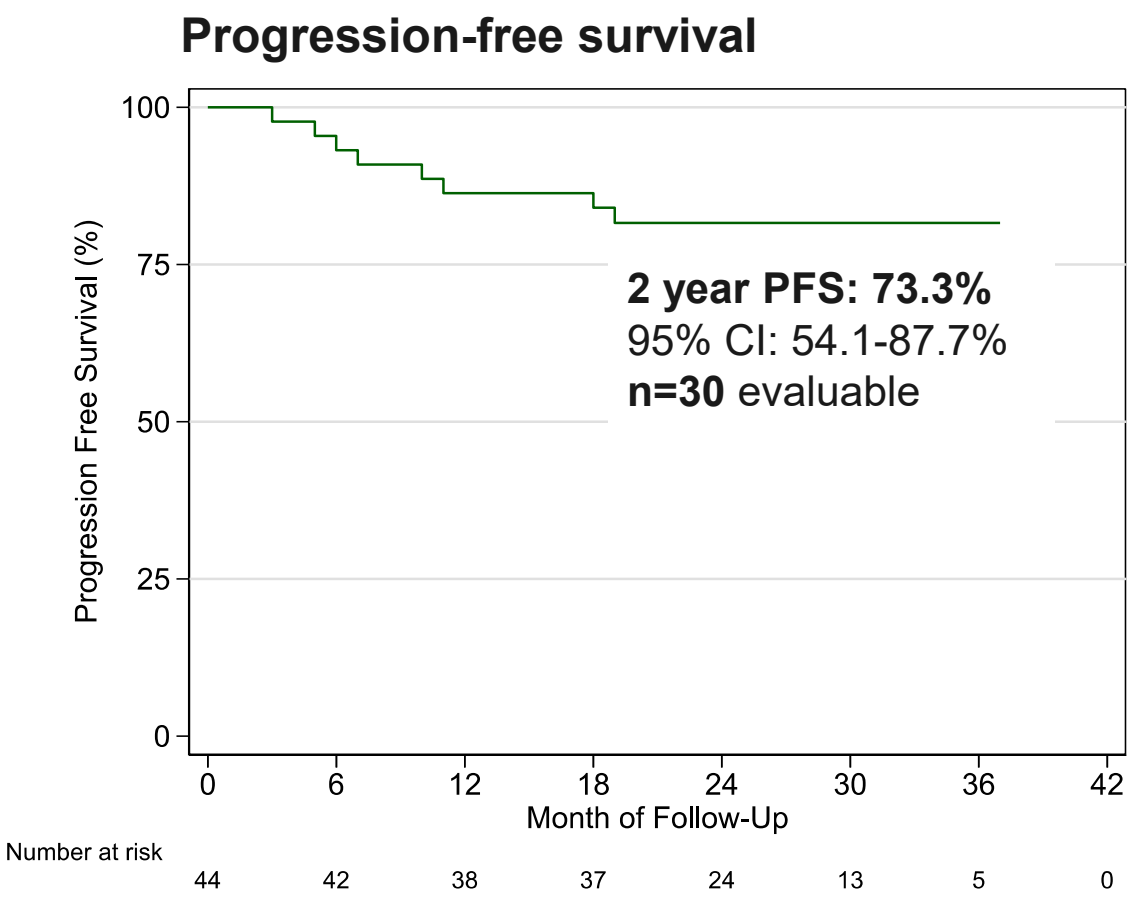
NHL33 WAMM: Primary endpoint and overall response rates

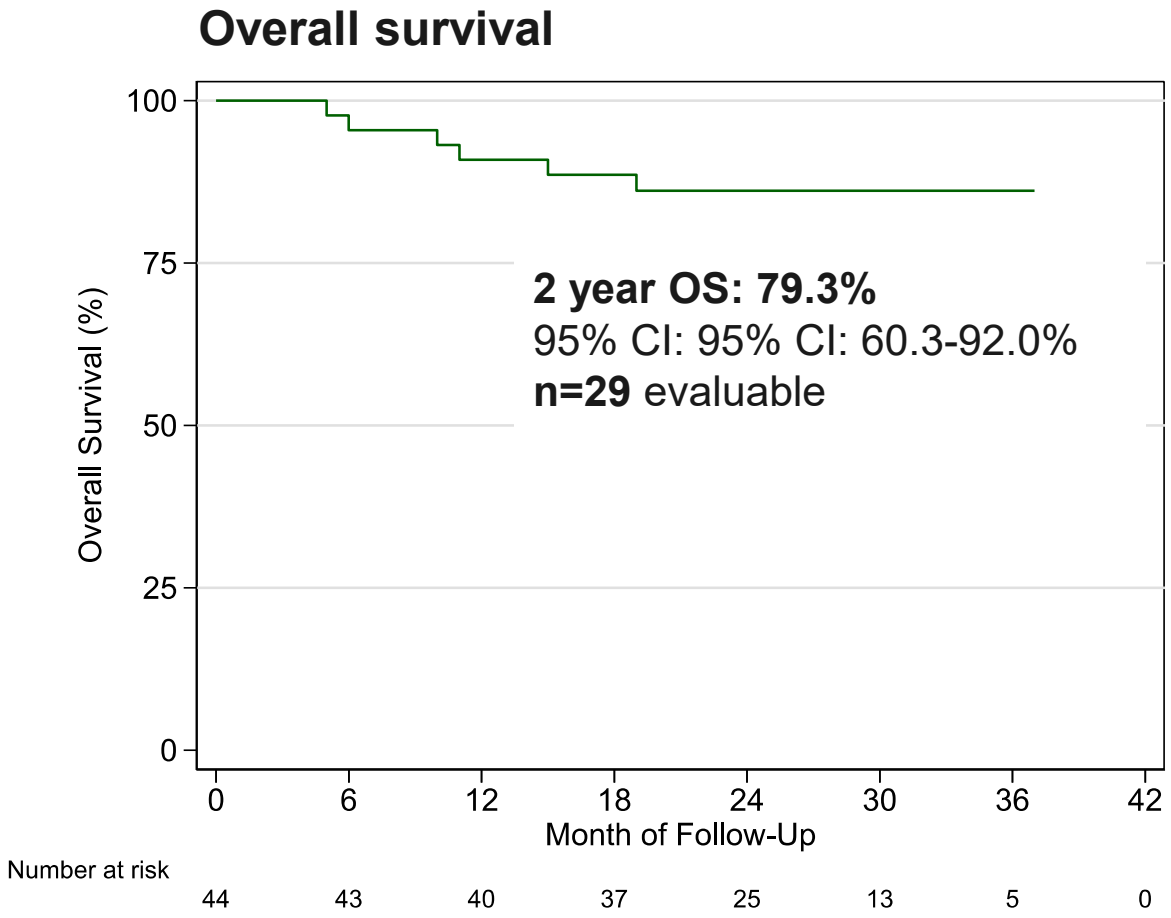


PET-determined response according to Lugano criteria

ALLG NHL33 WAMM study primary report.
ASH 2023 San Diego Abstr #735

NHL33 WAMM: PFS and OS





With median follow-up of 25 months (range 5-37) there were 7 progression events and 6 deaths (5 due to PD, 1 COVID pneumonitis).

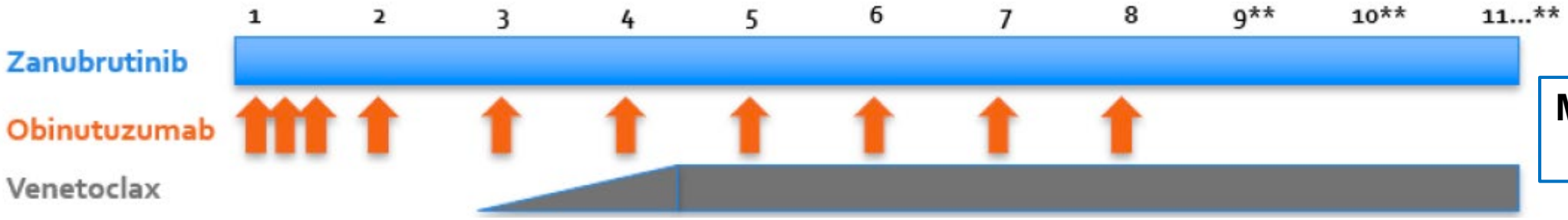
ALLG NHL33 WAMM study primary report.
ASH 2023 San Diego Abstr #735

Kapitel 2

Erstlinientherapie.

(keine Immun-Chemotherapie &) targeted Therapie

Phase II Multicenter Study of BOVen



Minimum of 24 cycles

Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

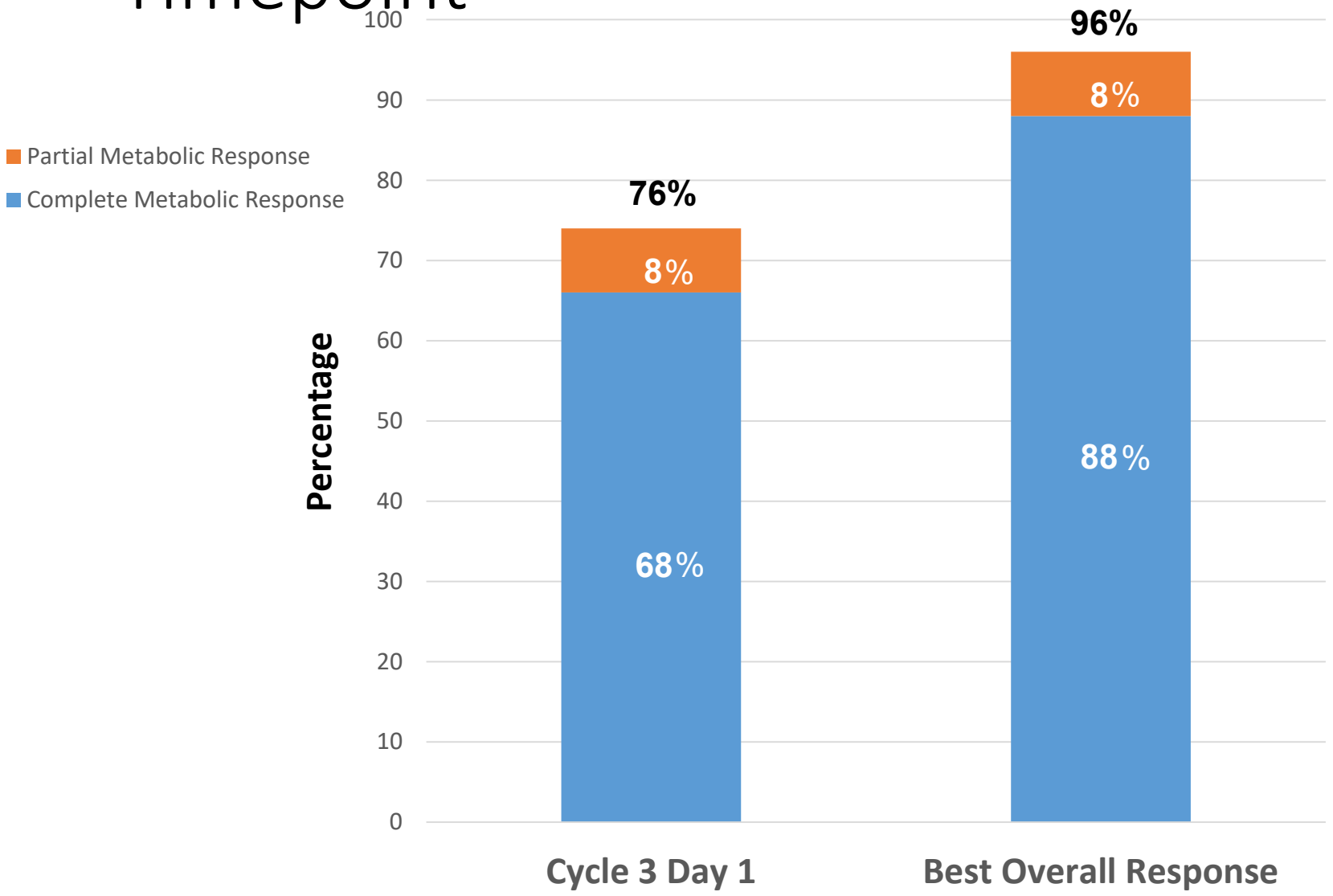
Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- ***TP53* mutation (of any variant allele frequency)**
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

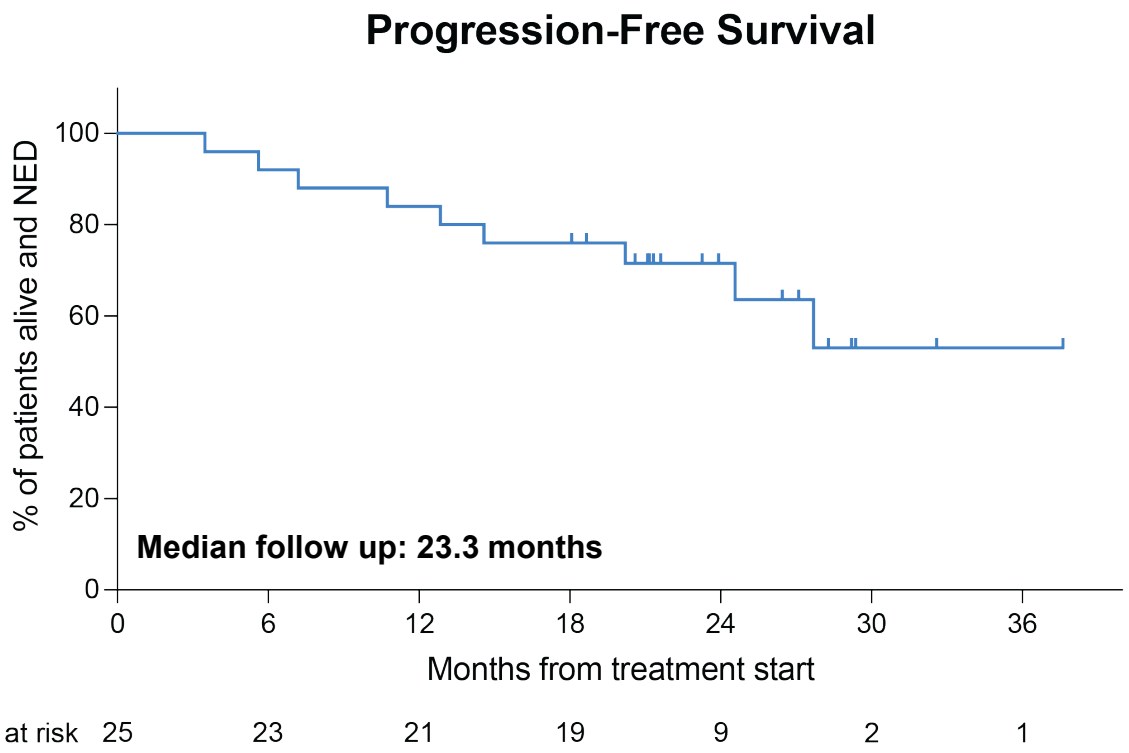
- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

Response Rates By Timepoint

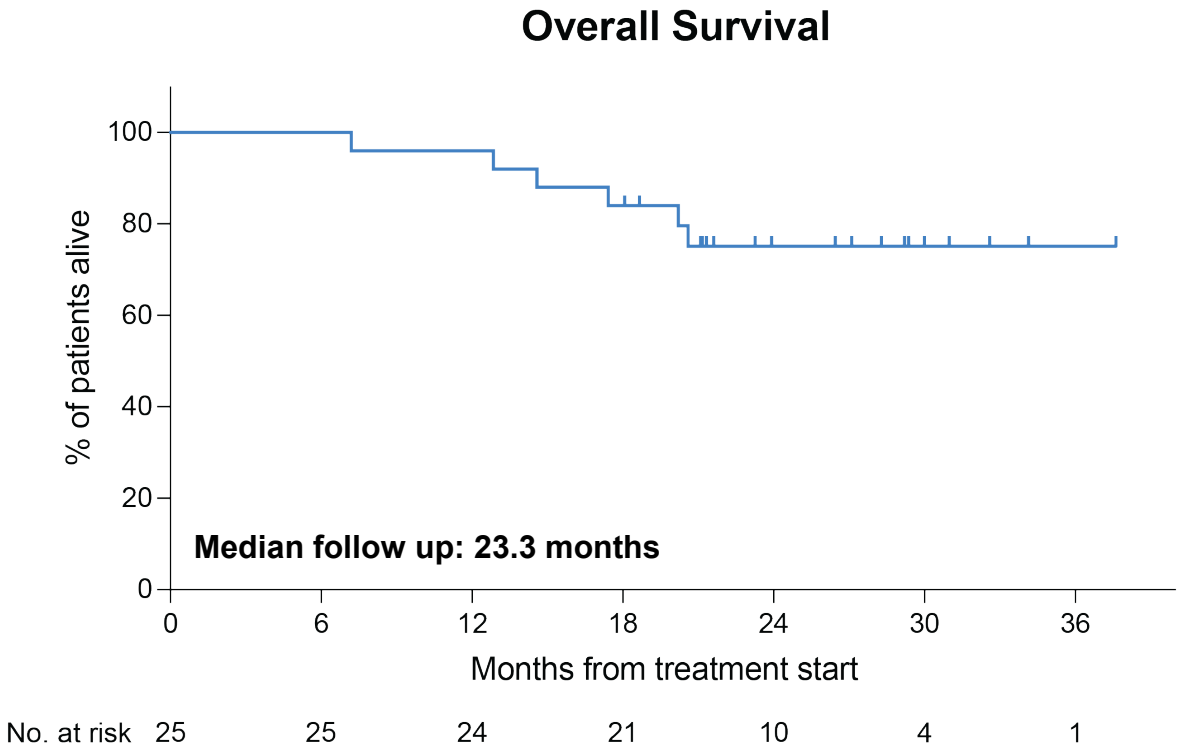


- **High Metabolic Response Rates after 2 cycles of Zanu+Obin**
- **High Overall Metabolic Response Rate with Zanu+Obin+Ven**

Progression-Free and Overall Survival Outcomes



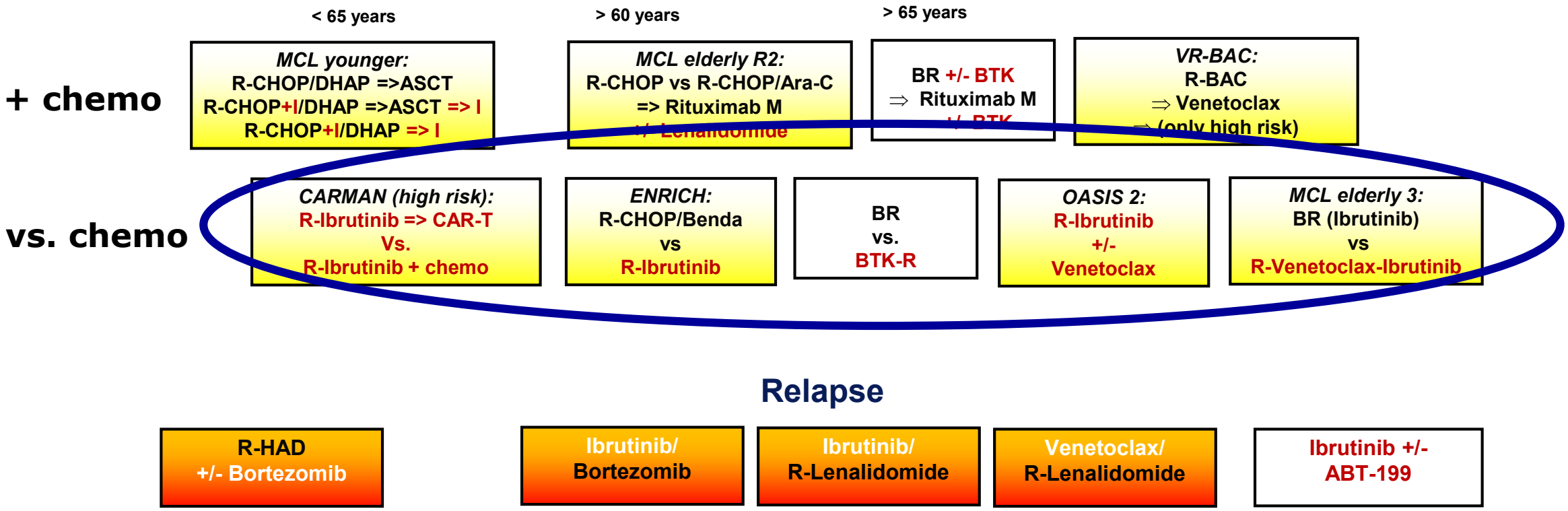
2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached



2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Primary PFS Endpoint is Met:
11 patients progression-free at 2 years

European MCL Network
Study generation 2023



Relapse

Kapitel 2

Rezidiertes Mantelzell-Lymphom:

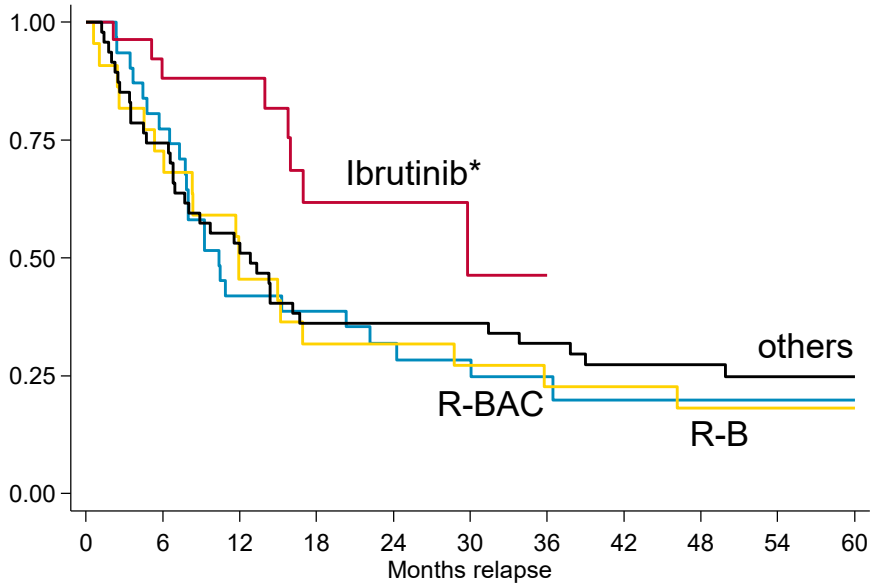
Targeted Therapie

Ibrutinib in relapsed MCL (POD 24)

Overall survival

MANTLE-FIRST

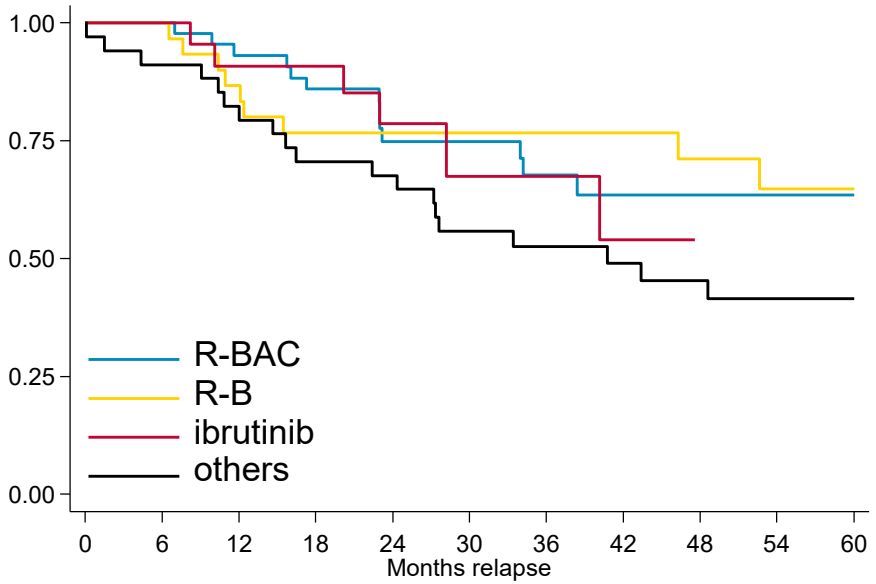
Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

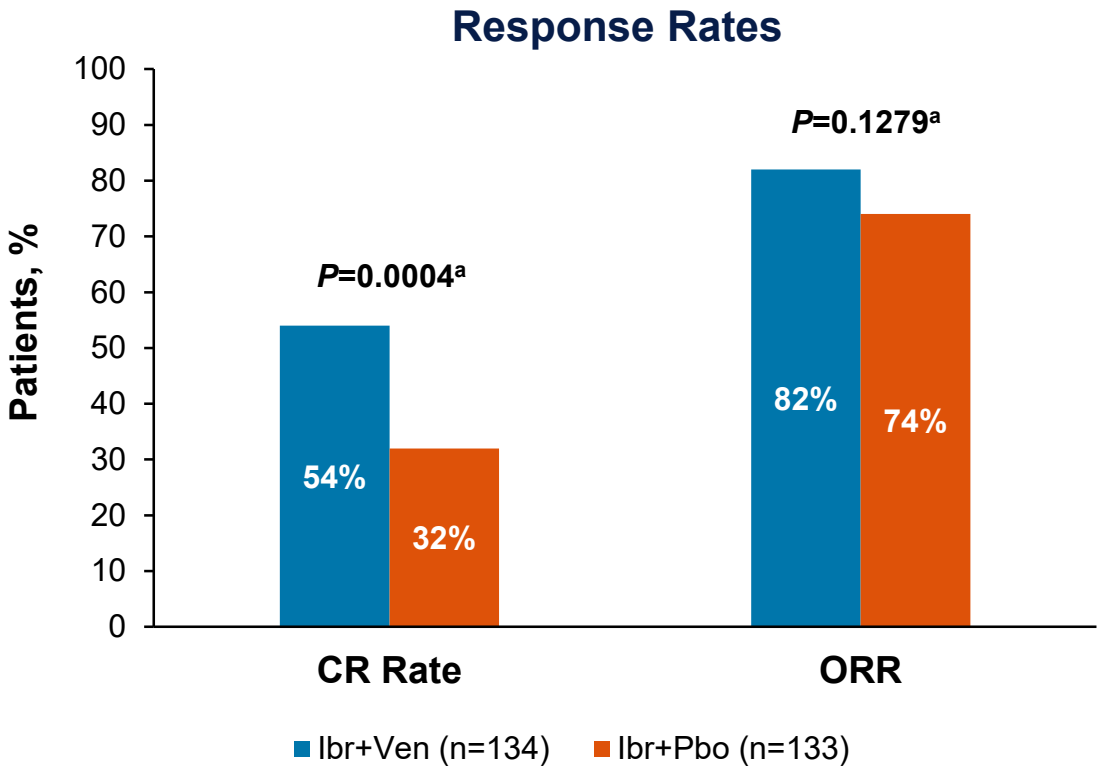
Late-POD

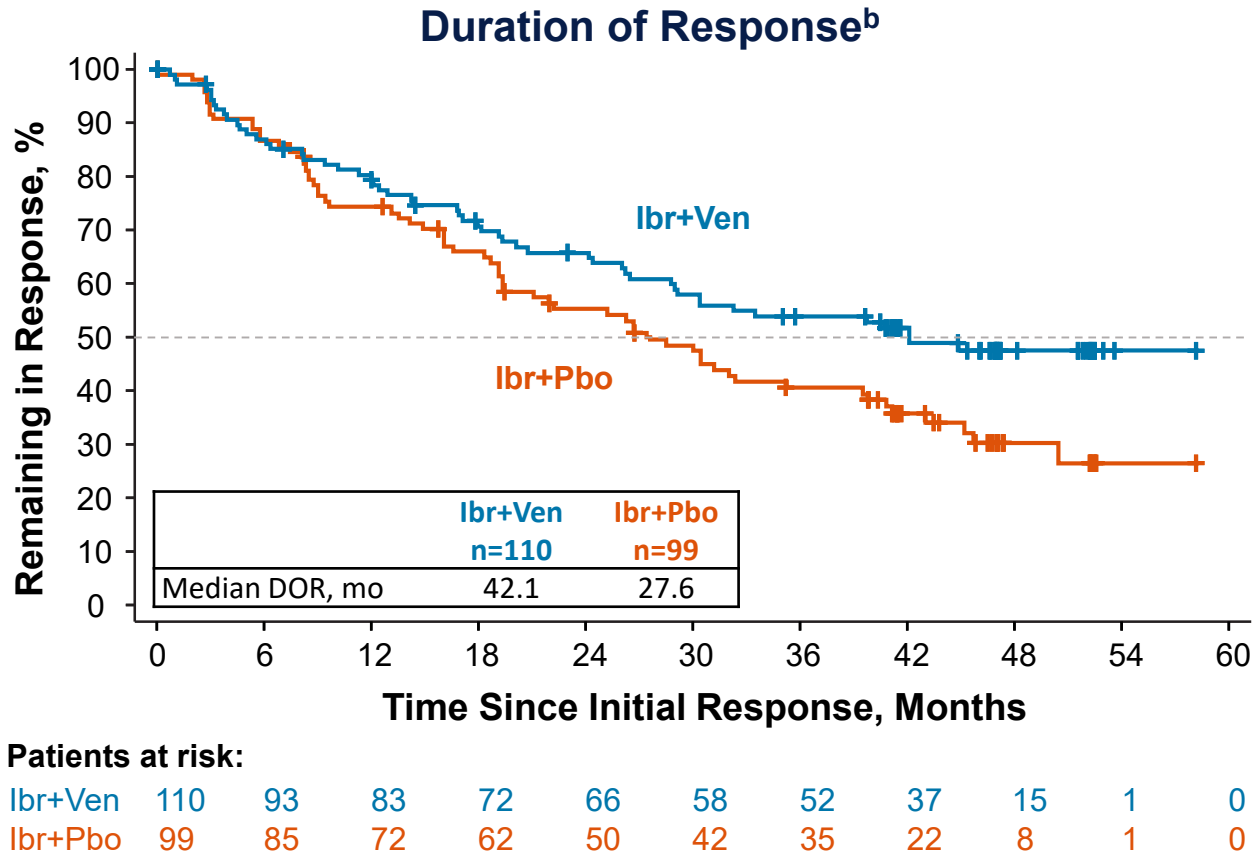


At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

Visco, Leukemia 2021

CR Rate Was Significantly Improved With Ibrutinib + Venetoclax





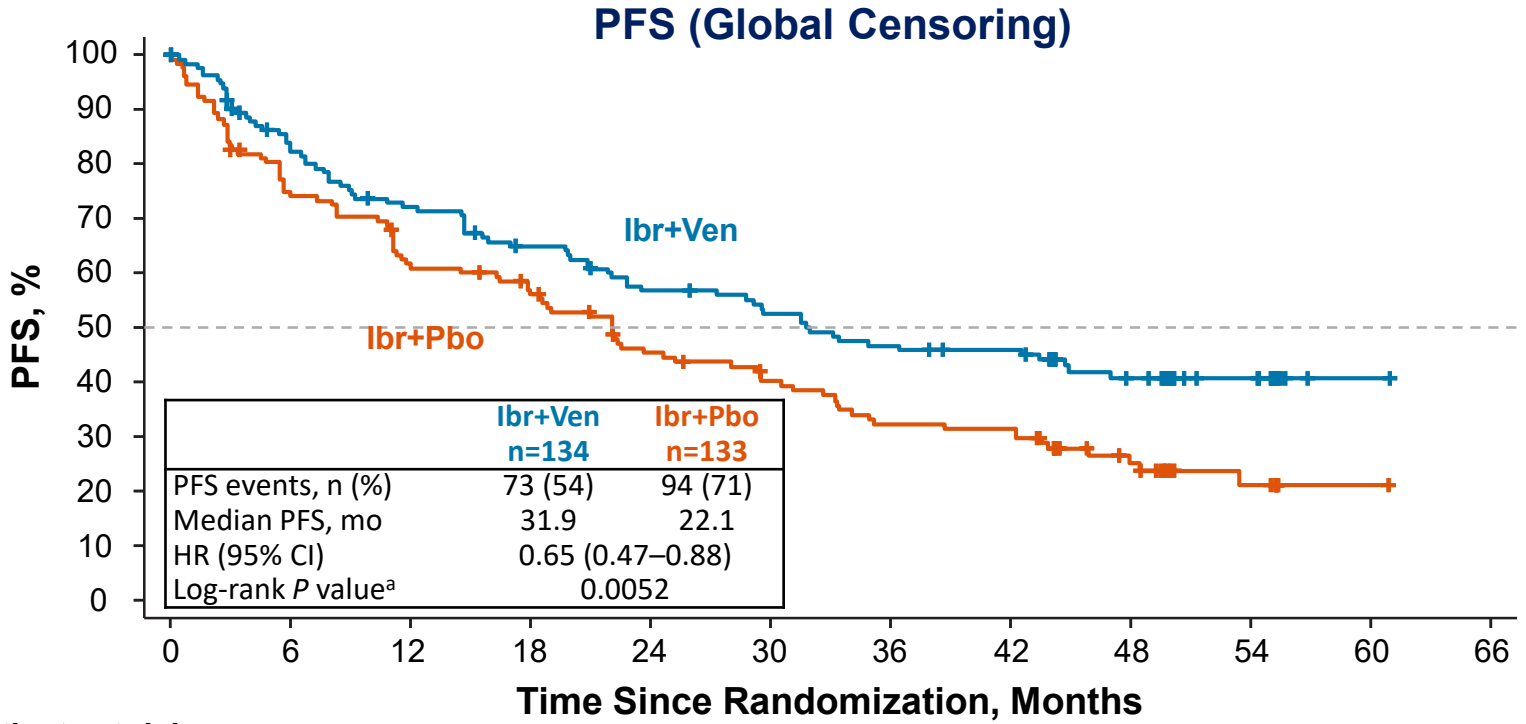
Patients at risk:

Ibr+Ven	110	93	83	72	66	58	52	37	15	1	0
Ibr+Pbo	99	85	72	62	50	42	35	22	8	1	0

DOR, duration of response.

[a]*P* values were determined by stratified Cochran-Mantel-Haenszel test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Global censoring (censoring at last non-PD assessment for patients without PD or death).

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



Patients at risk:

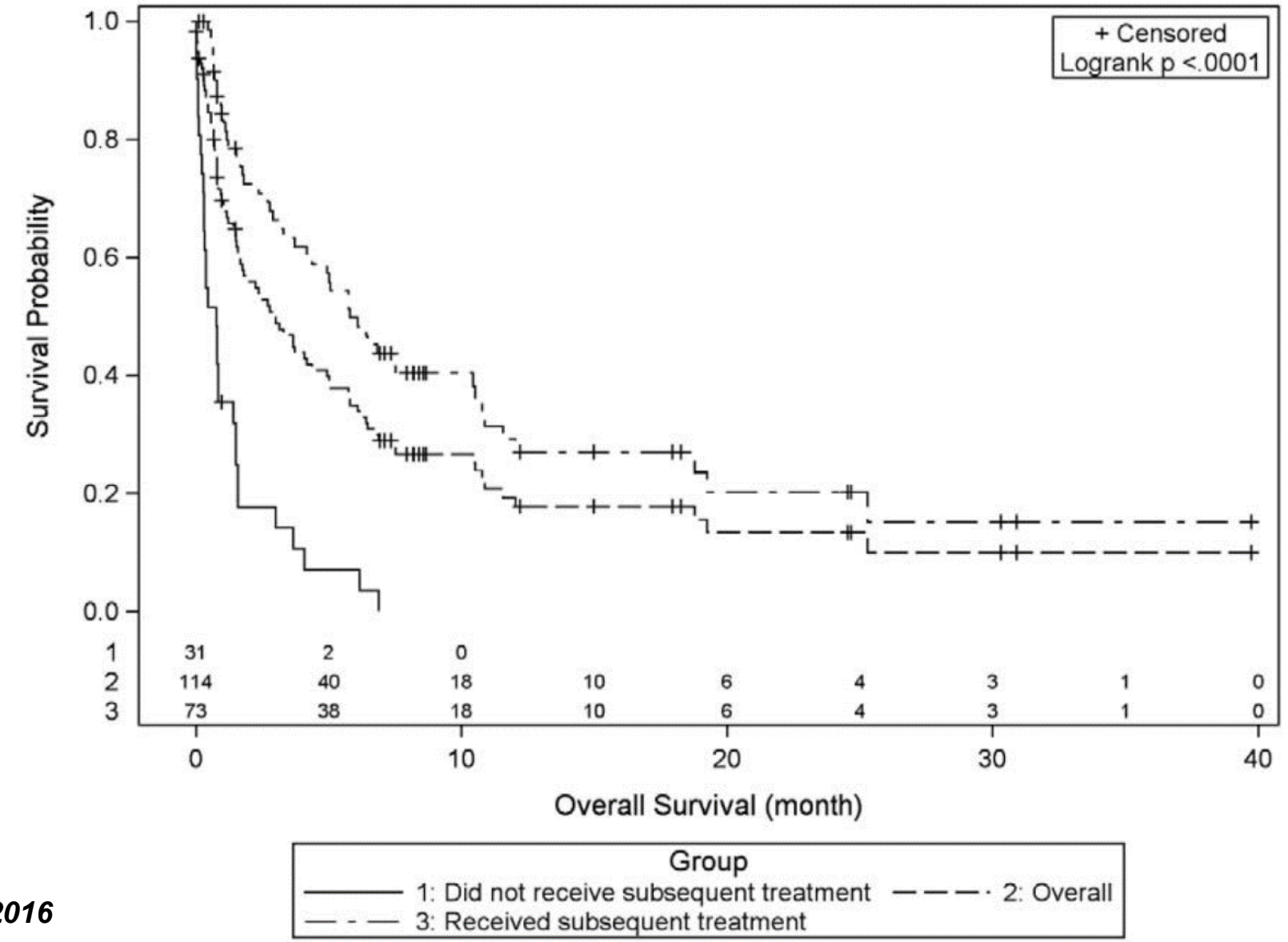
Ibr+Ven	134	107	91	80	69	63	56	53	34	15	1	0
Ibr+Pbo	133	96	79	70	54	46	37	36	18	8	1	0

Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

HR, hazard ratio; Ibr, ibrutinib; Pbo, placebo; Ven, venetoclax.

[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.

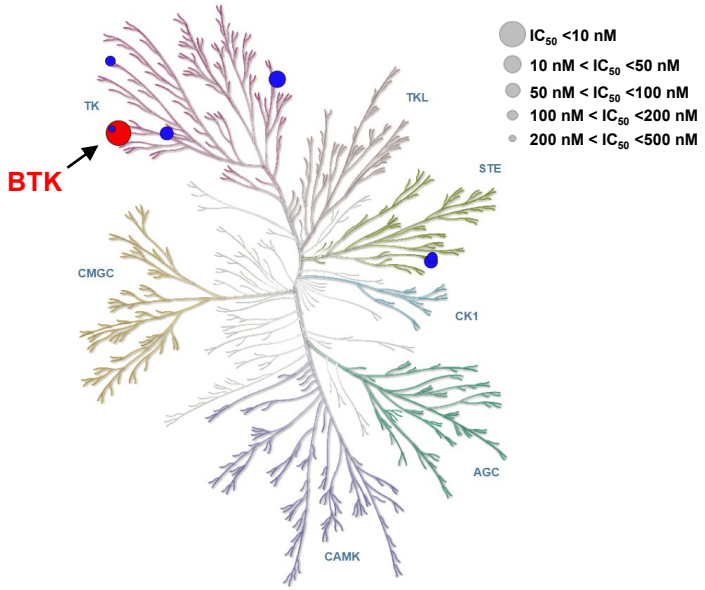
Relapsed mantle cell lymphoma
Failure under ibrutinib



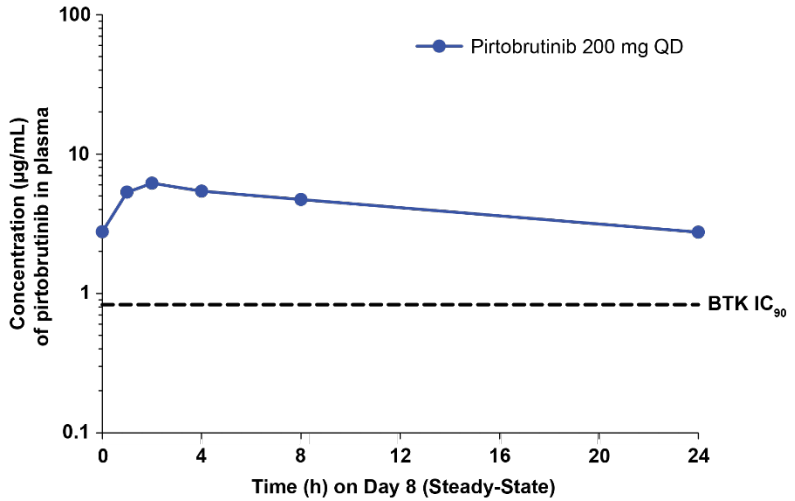
Martin, Blood 2016

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

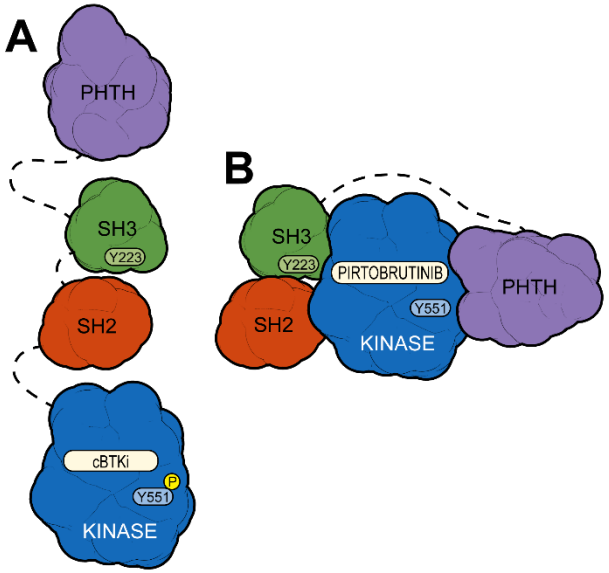
Highly selective for BTK[3,7]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[8]

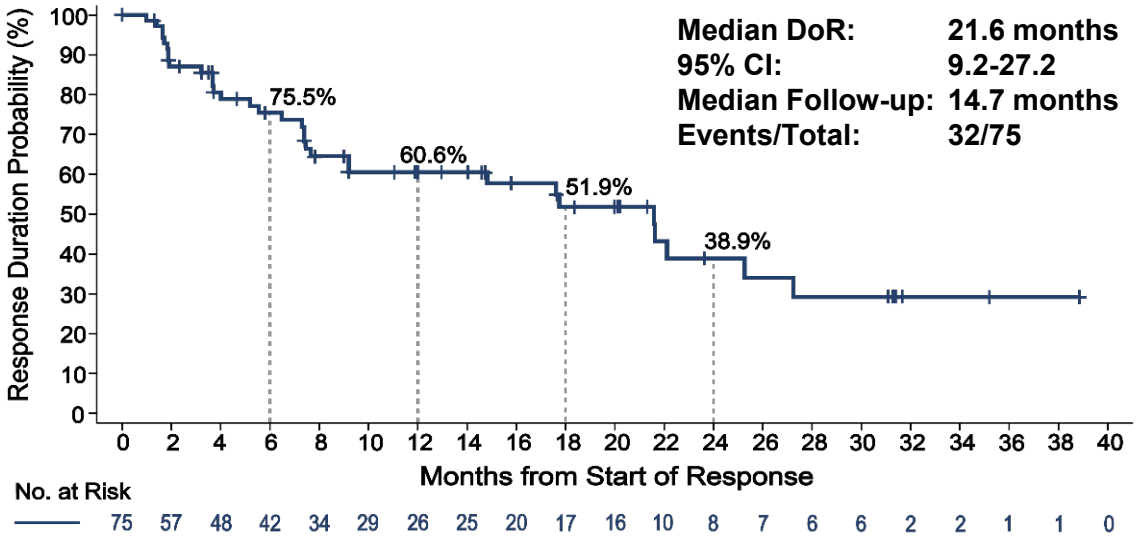


- Inhibits both WT and C481-mutant BTK with equal low nM potency[8]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[8]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[8]

[3]Mato et al. *Lancet* 2021; 397: 892–901. [7]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216. [8]Gomez et al. *Blood*.2023; 142(1):62-72.

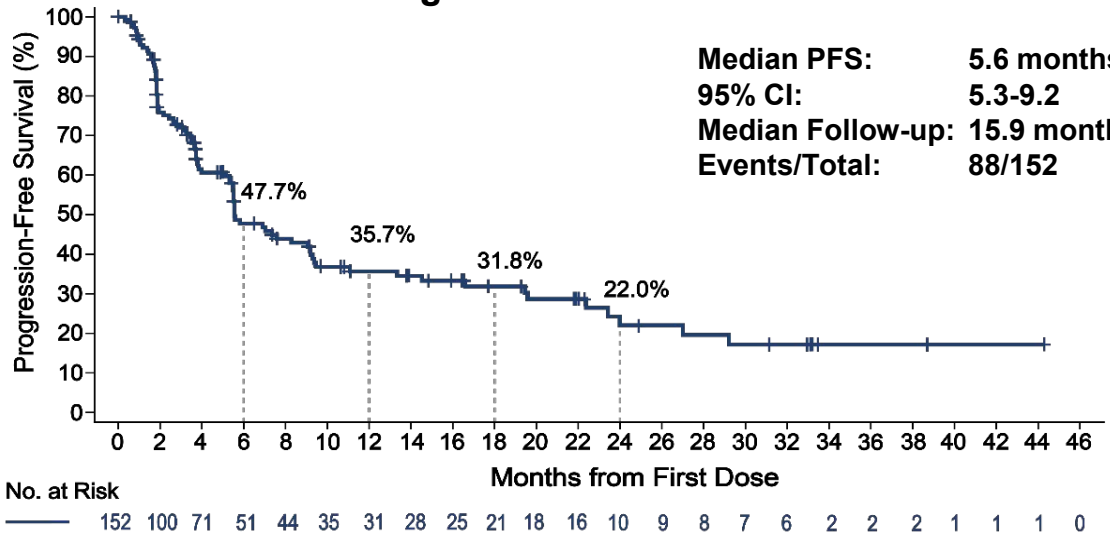
Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL

Duration of Response



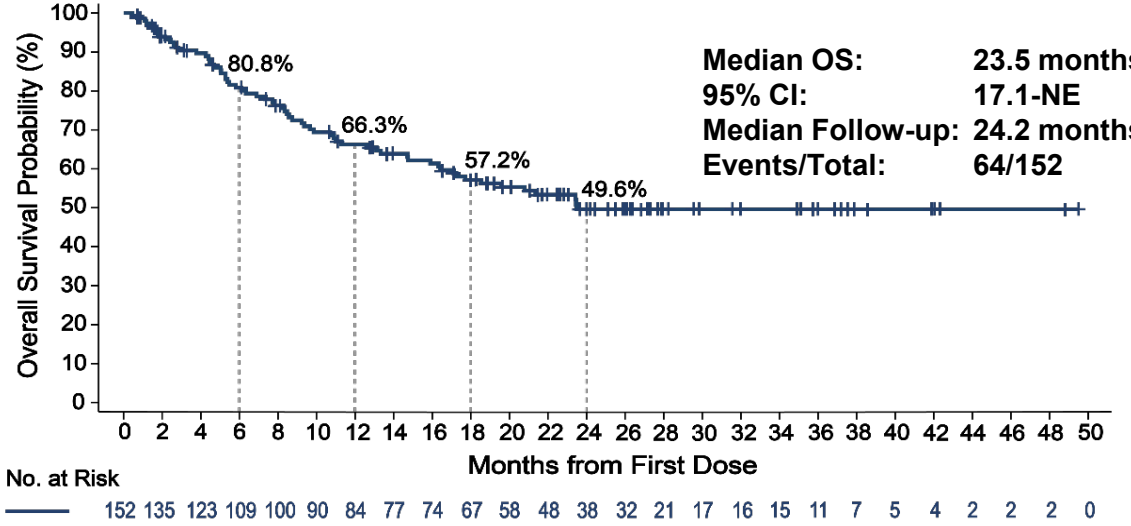
Median DoR: 21.6 months
95% CI: 9.2-27.2
Median Follow-up: 14.7 months
Events/Total: 32/75

Progression-Free Survival



Median PFS: 5.6 months
95% CI: 5.3-9.2
Median Follow-up: 15.9 months
Events/Total: 88/152

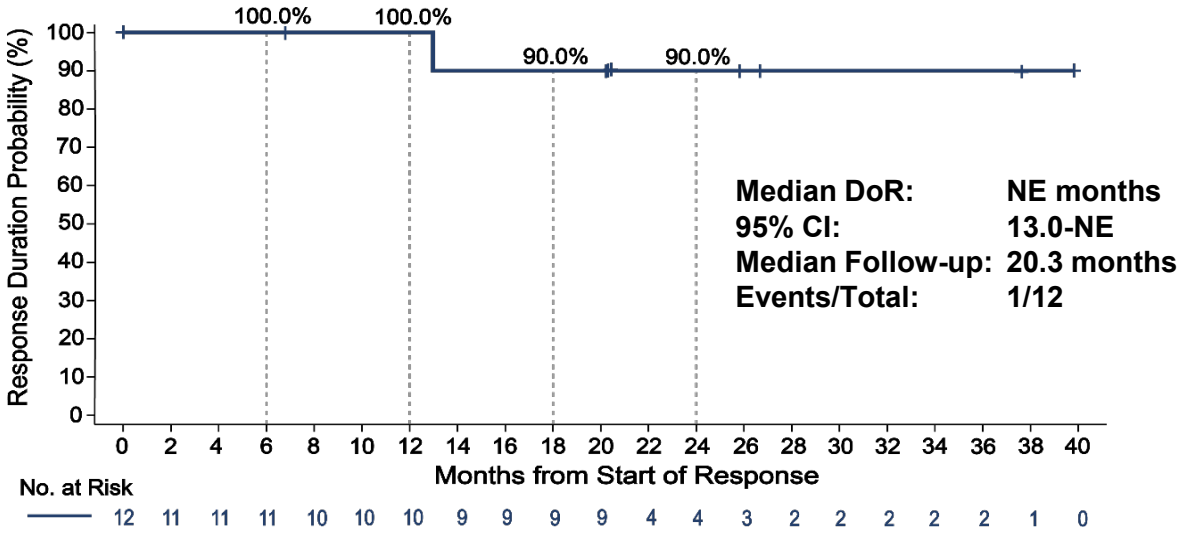
Overall Survival



Median OS: 23.5 months
95% CI: 17.1-NE
Median Follow-up: 24.2 months
Events/Total: 64/152

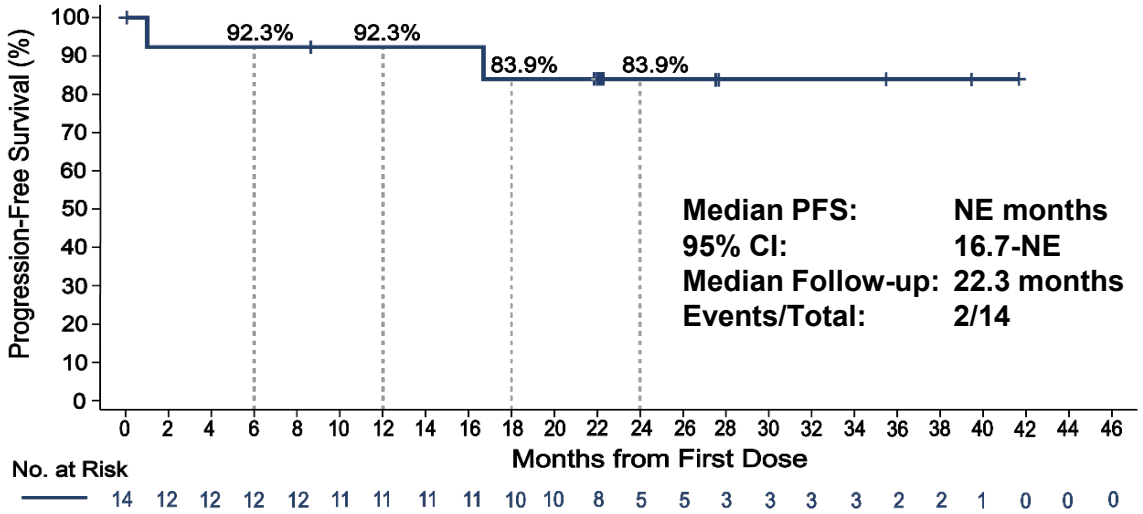
Pirtobrutinib Outcomes in cBTKi Naïve Patients with MCL

Duration of Response



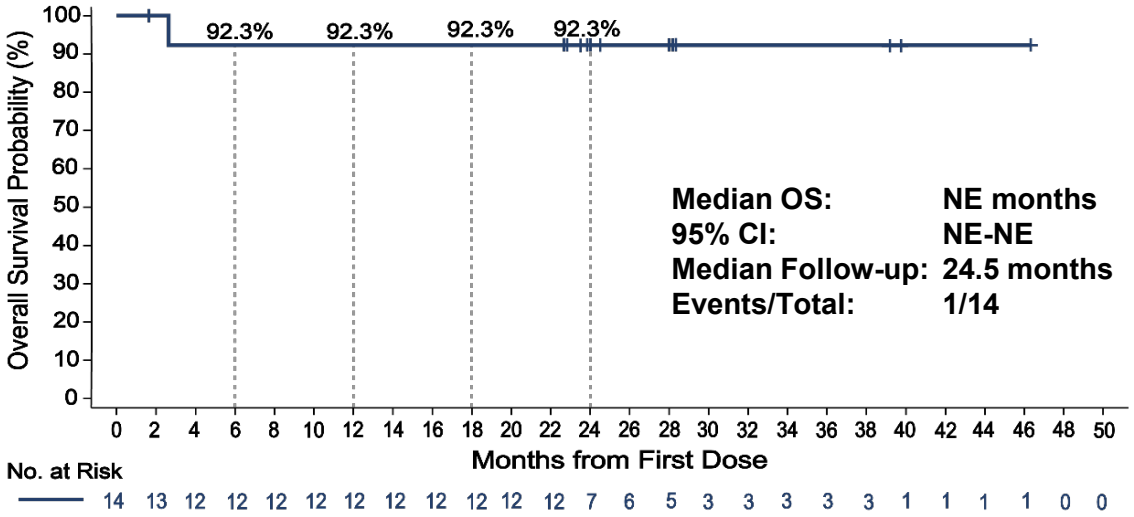
Median DoR: NE months
95% CI: 13.0-NE
Median Follow-up: 20.3 months
Events/Total: 1/12

Progression-Free Survival



Median PFS: NE months
95% CI: 16.7-NE
Median Follow-up: 22.3 months
Events/Total: 2/14

Overall Survival



Median OS: NE months
95% CI: NE-NE
Median Follow-up: 24.5 months
Events/Total: 1/14

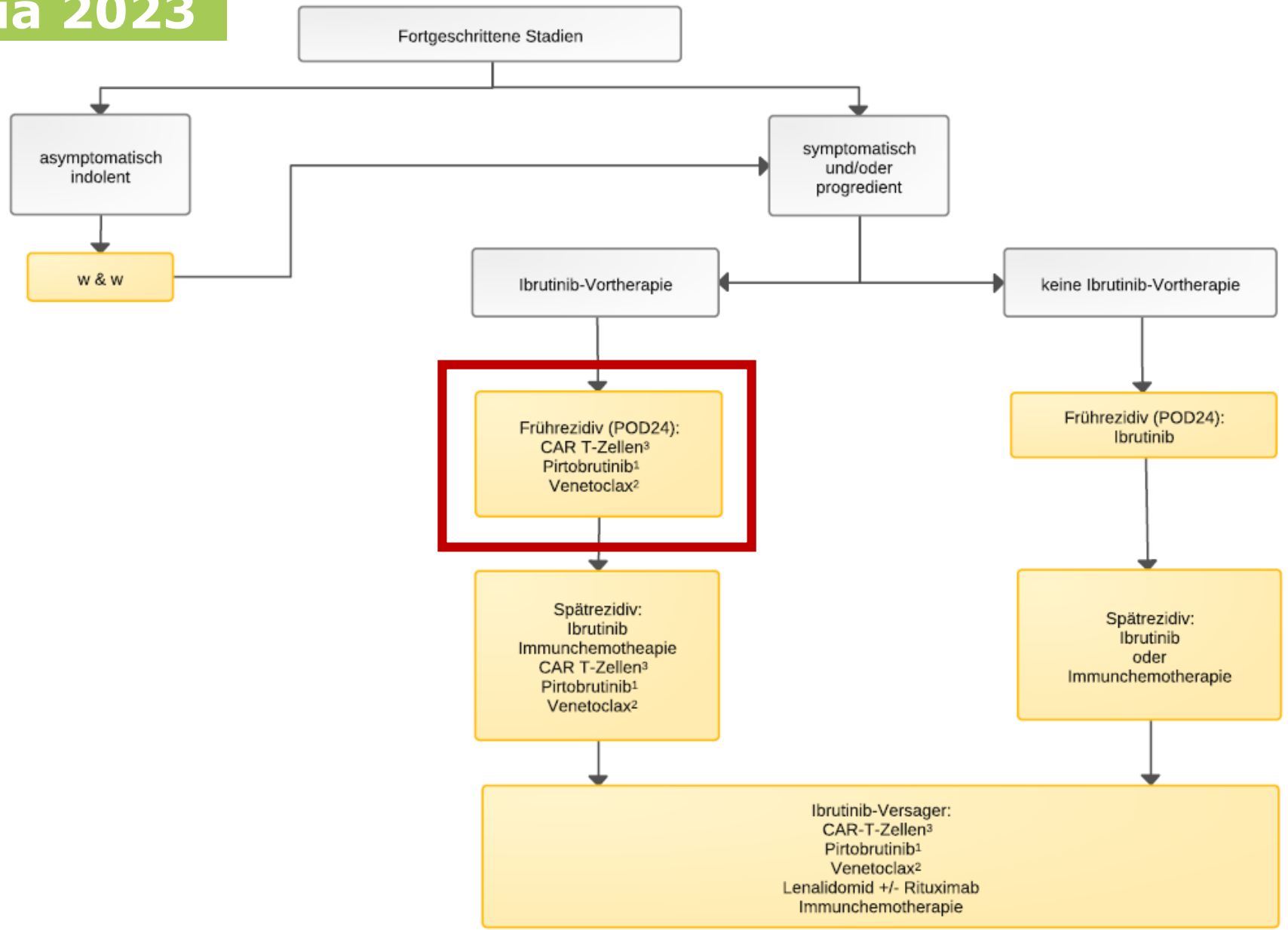
cBTKi Naive Cohort:

- The ORR[a] was 85.7% (95% CI: 57.2-98.2)
  - 6 CR (42.9%) and 6 PR (42.9%)

[a]1 cBTKi-naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment.

Relapsed Mantle cell Lymphoma

Onkopedia 2023



Studientreffen 2022, Berlin

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2023

Für den Inhalt verantwortlich:

Prof. Dr. med. Martin Dreyling

Klinikum der Universität München

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

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