Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

18th ICML LUGANO

17. – 21. Juni 2025

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Expert:innen berichten zu Lymphomen & Leukämien

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Mantelzell-Lymphom (MCL)

Mantle cell lymphoma
Disclosures

https://bureaucracyincts.eu

Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
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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**

Mantle cell lymphoma
Overview

- prognosis
- First line in elderly patients
- future concepts in relapsed patients

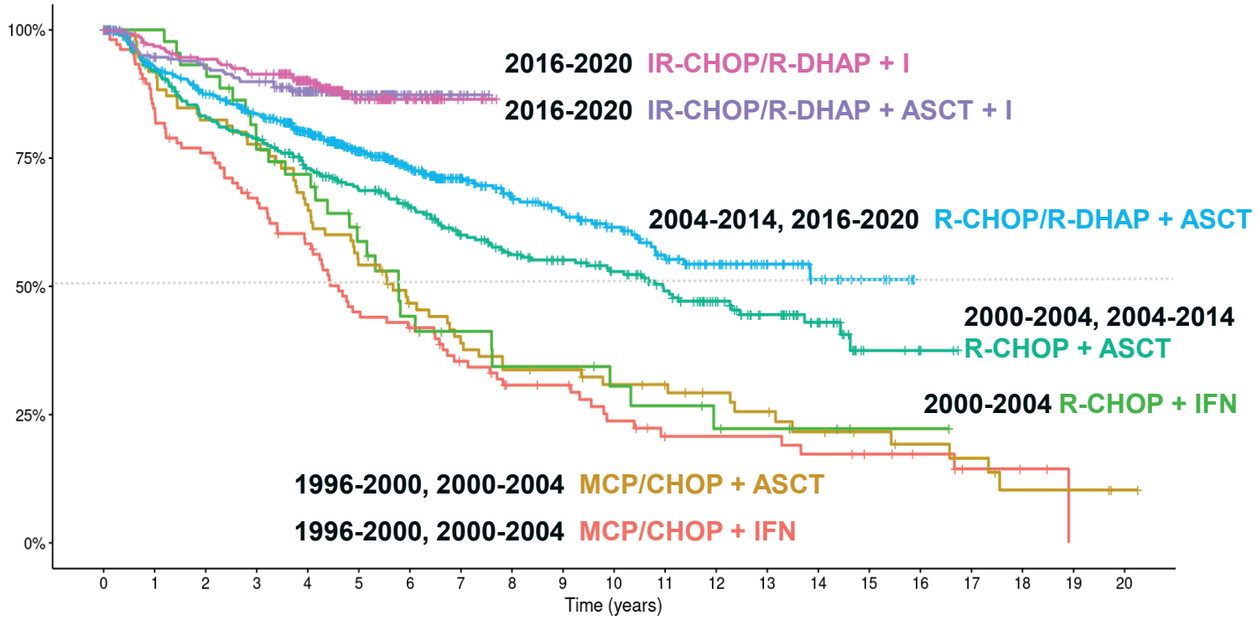
Background: GLSG and European MCL network trials

six practice-changing randomized phase III trials since 1996

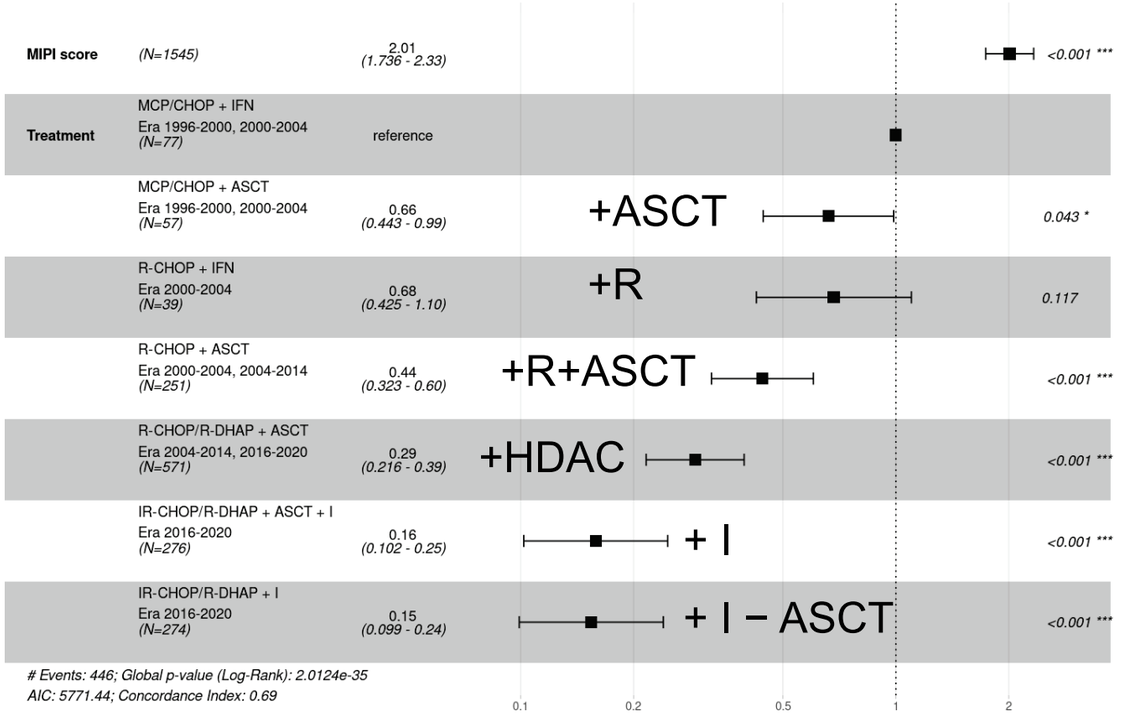
chemotherapy +/-ASCT (y)	immunochemotherapy		
+/-ASCT (y)	+/- high-dose cytarabine + ASCT (y) +/- fludarabine, +/- rituximab maintenance (e)	+/-ibrutinib +/- ASCT (y)	

Results: Survival trends – younger: impact of treatment

By eras and treatment



Treatment effects

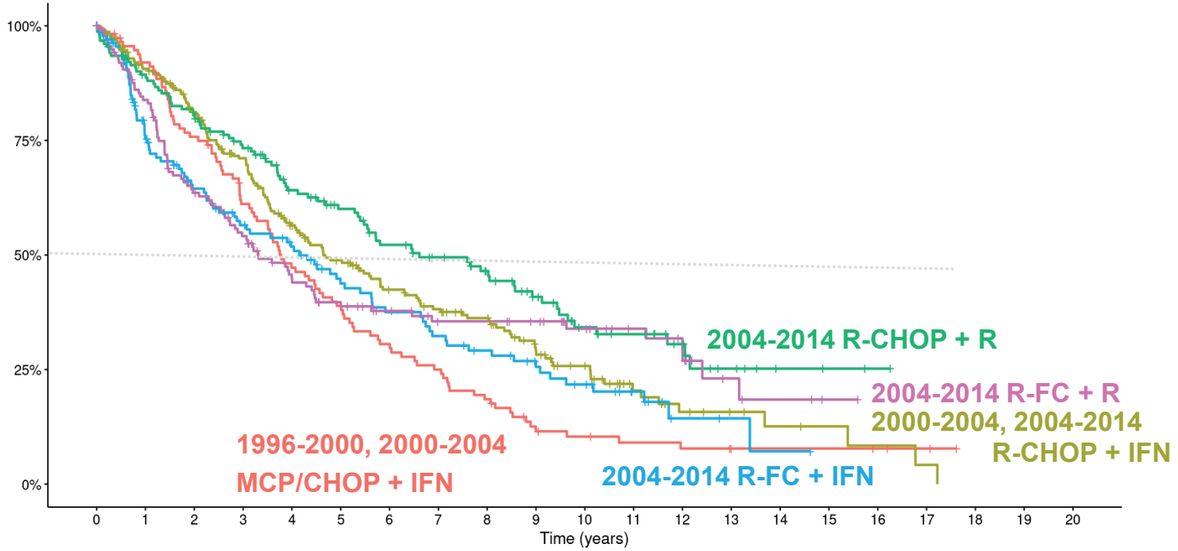


- Adding rituximab, ASCT, high-dose cytarabine, and ibrutinib to chemotherapy improved OS

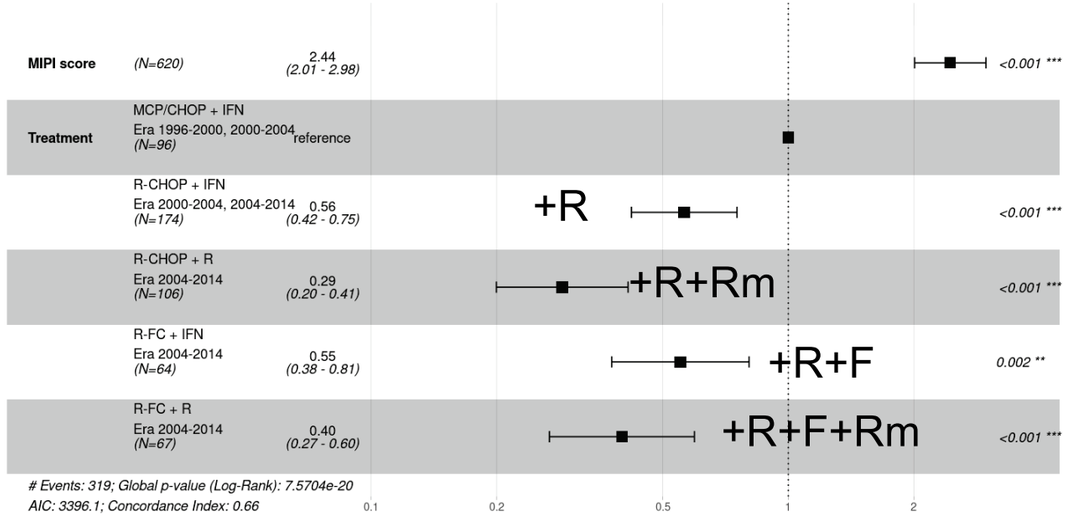
ASCT: autologous stem cell transplantation, R: rituximab during induction, HDAC: high-dose cytarabine during induction, I: ibrutinib during induction and as 2-years maintenance

Results: Survival trends – older: impact of treatment

By eras and treatment



Treatment effects



- Adding rituximab during induction and as maintenance improved OS

R: rituximab during induction, Rm: rituximab maintenance, F: fludarabine-containing induction

European MCL Network
Study generation 2024

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	< 65 years	> 60 years	> 65 years		
+ chemo	*MCL younger:* R-CHOP/DHAP =>ASCT R-CHOP+I/DHAP =>ASCT => I R-CHOP+I/DHAP => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	BR +/- BTKi ⇒ Rituximab M +/- BTKi	*VR-BAC:* R-BAC ⇒ Venetoclax ⇒ (only high risk)	
vs. chemo	*CARMAN (high risk):* R-Ibrutinib => CAR-T vs. R-Ibrutinib + chemo	*ENRICH:* R-CHOP/Benda vs R-Ibrutinib	BR vs. BTKi-R	*OASIS 2:* R-Ibrutinib +/- Venetoclax	*MCL elderly 3:* BR (Ibrutinib) vs R-Venetoclax-Ibrutinib

Relapse

Ibrutinib/ Bortezomib	Ibrutinib +/- ABT-199	Pirtobrutinib + Glofitamab

ECHO Study Design

ECHO (NCT02972840): multicenter, double-blind, placebo-controlled, phase 3 trial

Primary endpoint:
- PFS (independent review committee)

Key secondary endpoints:
- OS
- ORR (independent review committee)

Safety

Untreated MCL (N=598)
- Age ≥65 years
- ECOG PS ≤2

Stratification
- **sMIPI score:** Low vs intermediate vs high
- **Geographic region:** North America vs Western Europe vs other

Enrollment: April 2017 to March 2023
Sites: 195 globally

RANDOMIZE 1:1

Bendamustine[a] Rituximab[b] x 6 cycles → **if ≥PR** → Maintenance Rituximab (every 2 cycles x 2 years) → **Acalabrutinib 100 mg BID, PO until PD or toxicity**

Bendamustine[a] Rituximab[b] x 6 cycles → **if ≥PR** → Maintenance Rituximab (every 2 cycles x 2 years) → **Placebo BID, PO until PD or toxicity**

Crossover to acalabrutinib after PD was permitted

1 cycle = 28 days

Data cutoff date: February 15, 2024
Median time on study: 44.9 months

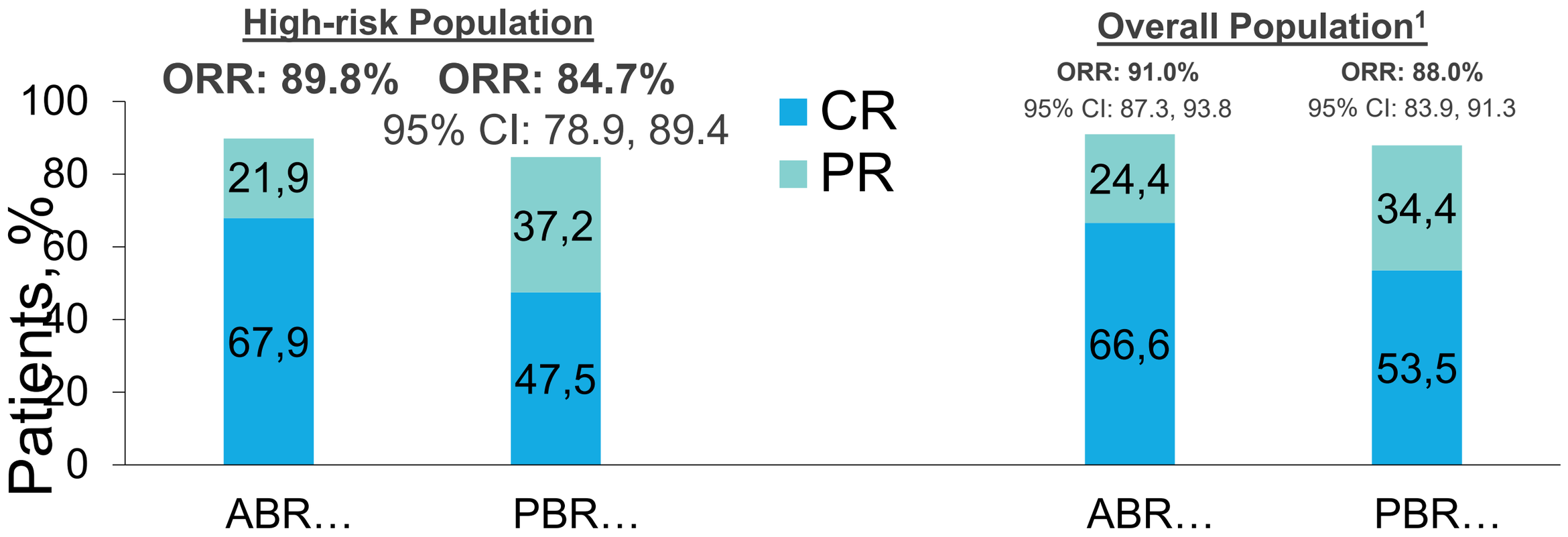
[a]Bendamustine 90 mg/m^2 on days 1 and 2
[b]Rituximab 375 mg/m^2 on day 1

High-risk disease defined as any of the following:
- **High-risk MIPI (6–11)**
- ***TP53* mutation**
- **Ki-67 index ≥30%**
- **Blastoid/pleomorphic histology**

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response; sMIPI, simplified MCL International Prognostic Index.

ECHO High Risk Analysis

Best Response of CR Significantly Higher With ABR in Patients With High-risk MCL



	ORR	CR
Difference (ABR vs PBR)	5.1%	20.4%
95% CI	-1.7, 12.1	10.4, 30.0
P-value	.1382	**<.0001**

	ORR
Difference (ABR vs PBR)	3.0%
95% CI	-2.0, 8.1
P-value	.2196

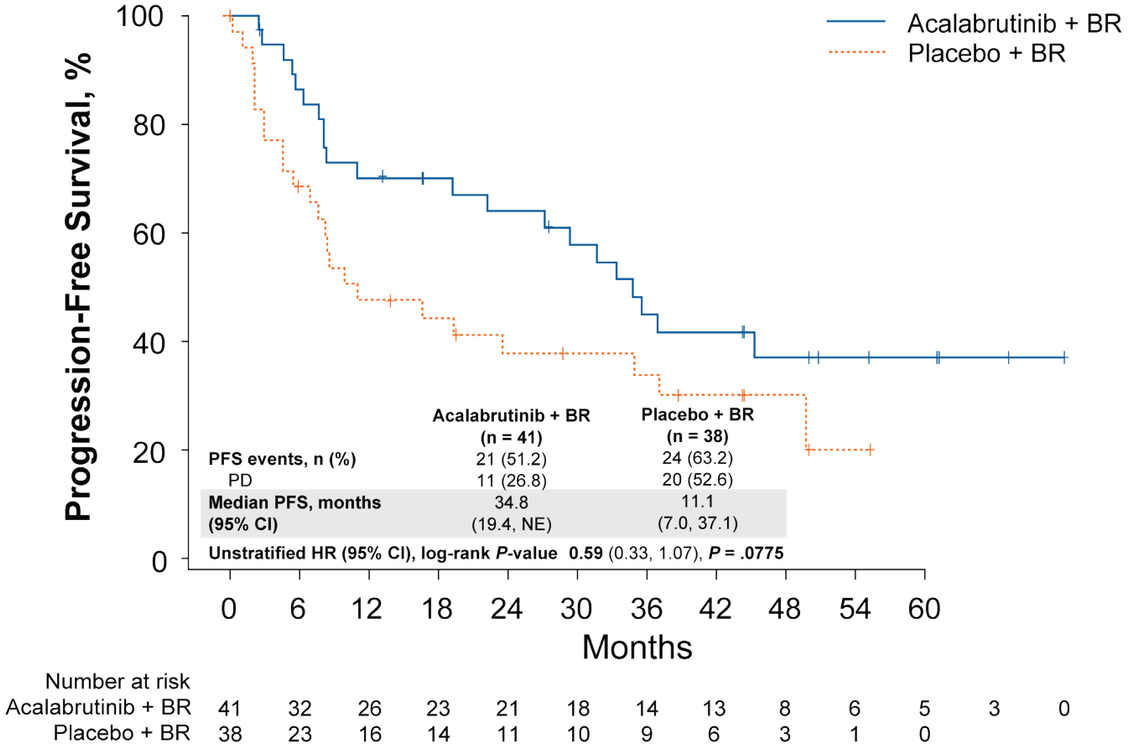
ABR, acalabrutinib-bendamustine-rituximab; CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PBR, placebo-bendamustine-rituximab; PR, partial response.

1. Wang M, et al. *J Clin Oncol*. 2025:101200JCO2500690. doi: 10.1200/JCO-25-00690. Online ahead of print.

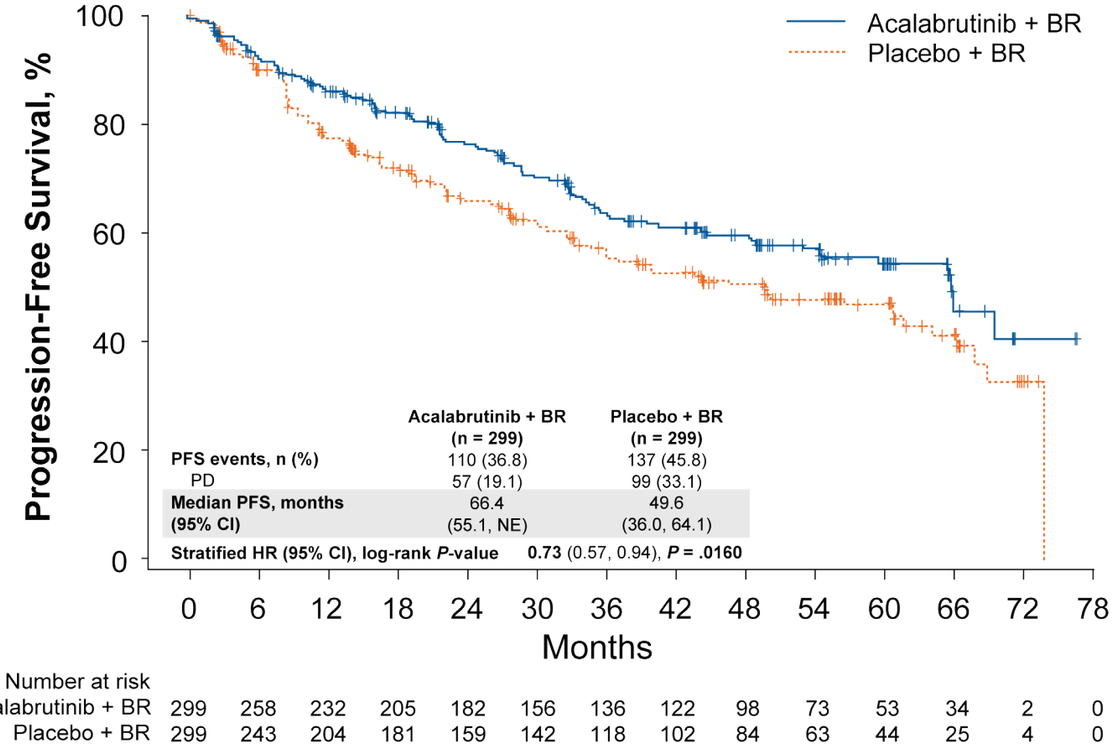
ECHO High Risk Analysis

PFS in Patients With Blastoid/Pleomorphic Histology

PFS in Patients With Blastoid/Pleomorphic Histology



PFS in Full Analysis Population[1]



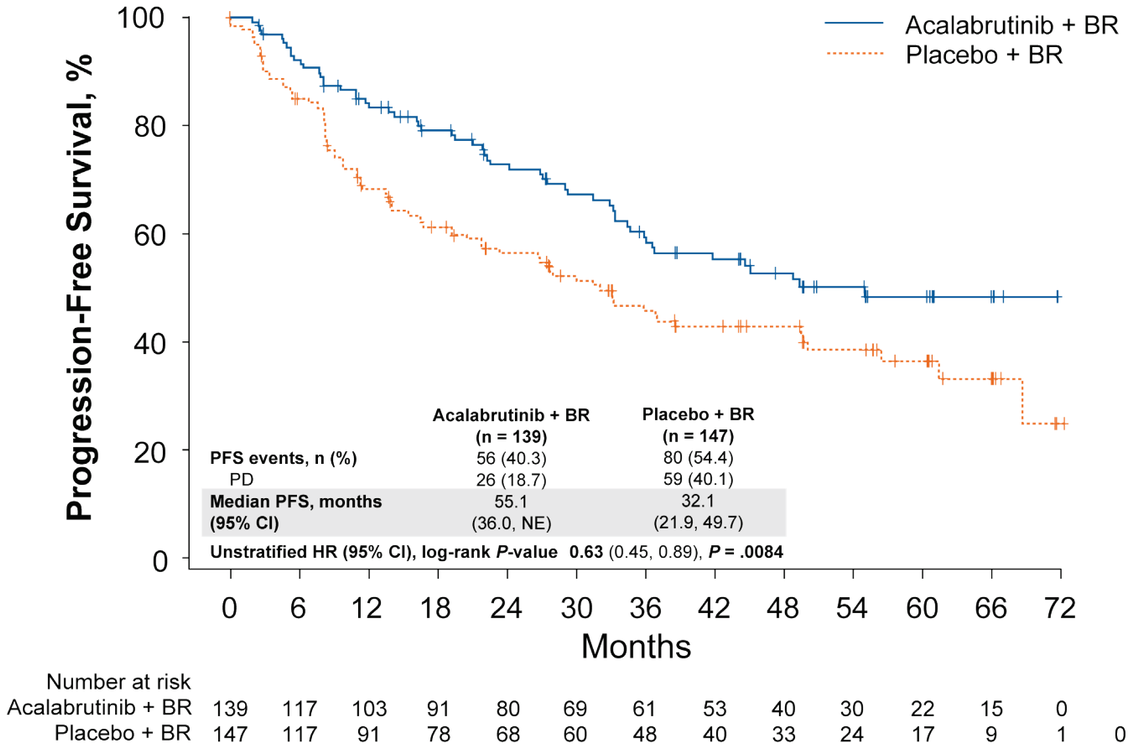
- Sample size in this subgroup was small; the difference in median PFS was ~24 months

ABR, acalabrutinib-bendamustine-rituximab; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo-bendamustine-rituximab; PD, progressive disease; PFS, progression-free survival.

1. Wang M, et al. *J Clin Oncol*. 2025:101200JCO2500690. doi: 10.1200/JCO-25-00690. Online ahead of print.

Significantly Longer PFS With ABR in Patients With Ki-67 Index ≥30%

PFS in Patients With Ki-67 Index ≥30%



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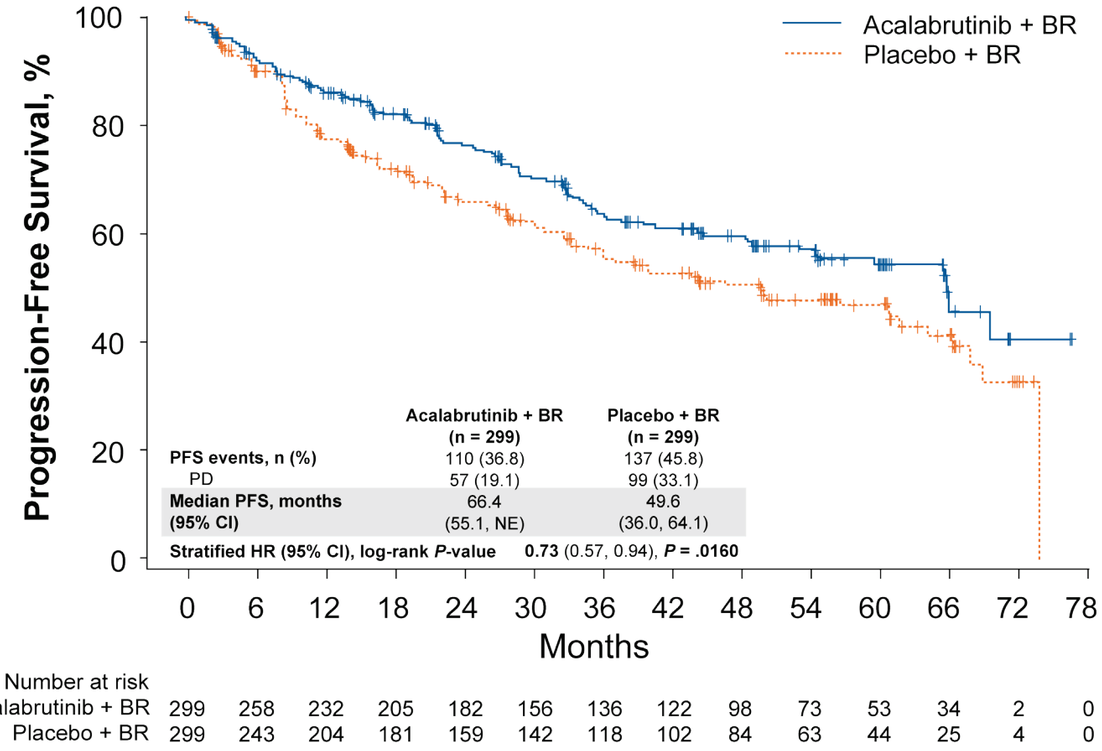

ABR, acalabrutinib-bendamustine-rituximab; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo-bendamustine-rituximab; PD, progressive disease; PFS, progression-free survival.

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ECHO High Risk Analysis

European MCL Network
Study generation 2024

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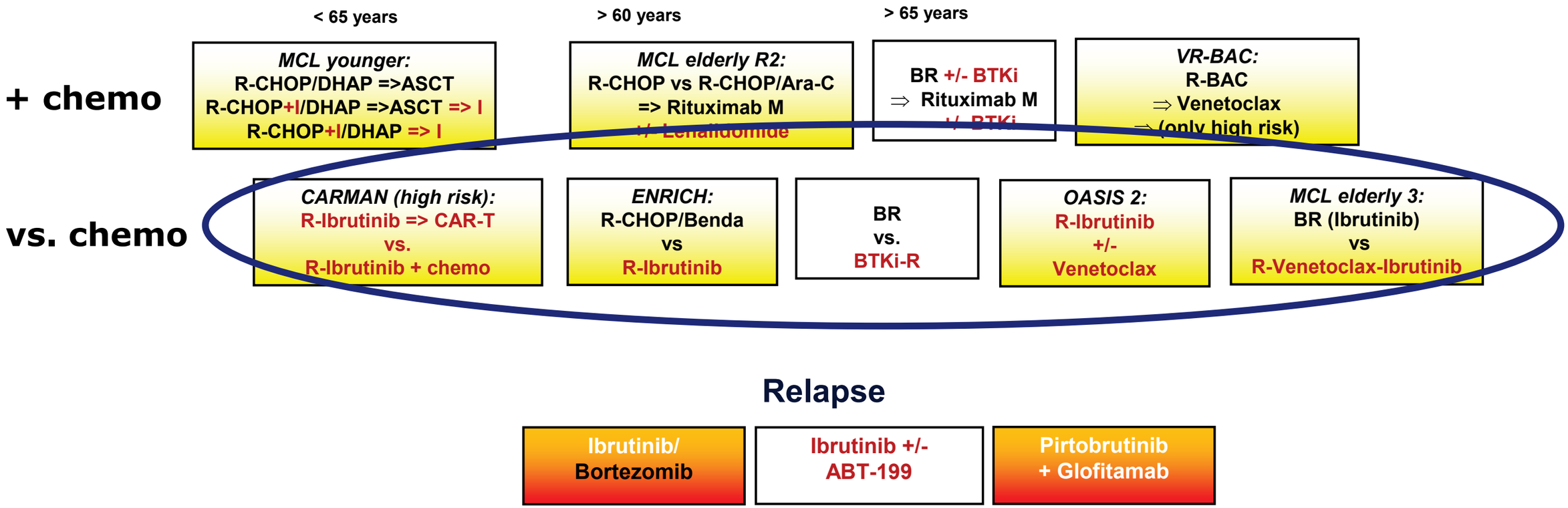
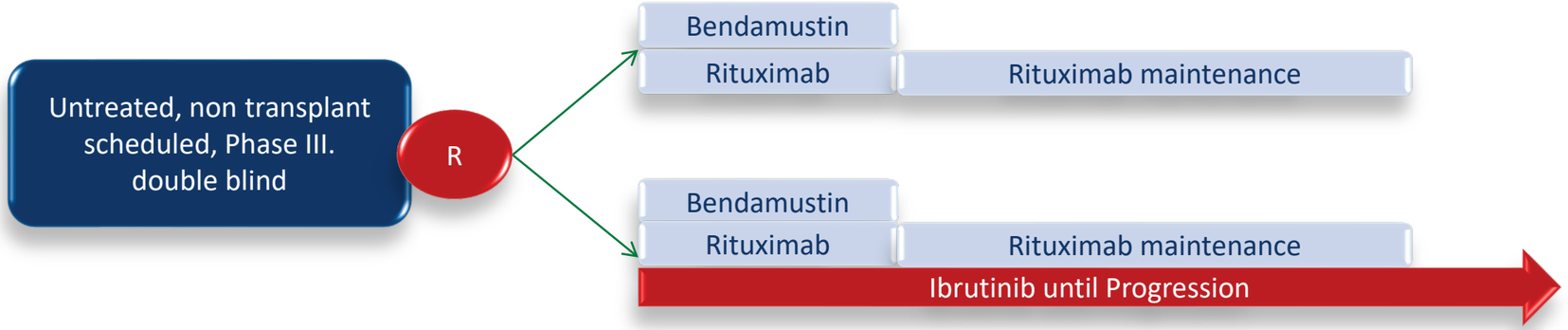


Relapse

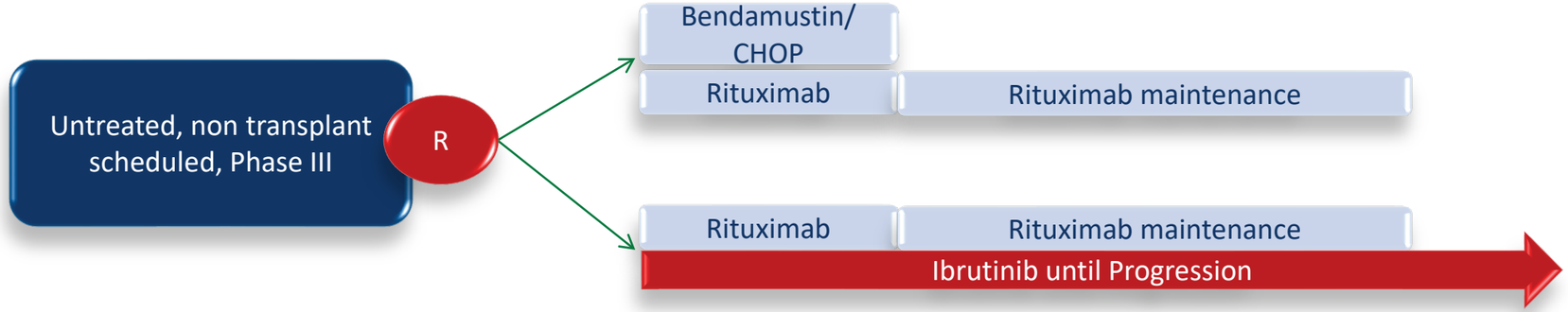
Ibrutinib/ Bortezomib	Ibrutinib +/- ABT-199	Pirtobrutinib + Glofitamab

SHINE



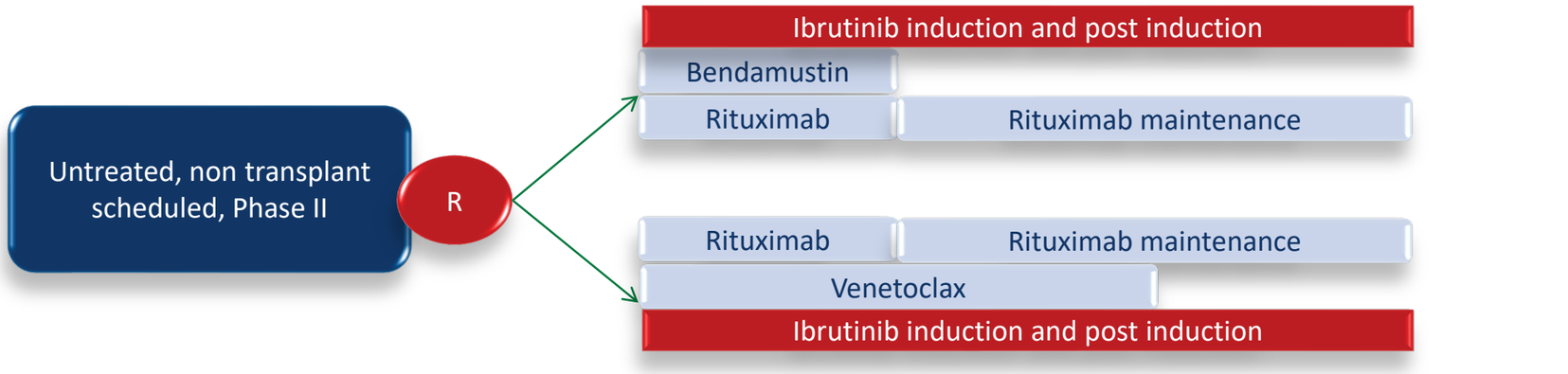
Addition of I beneficial?

ENRICH



Chemo-free as good as CIT?

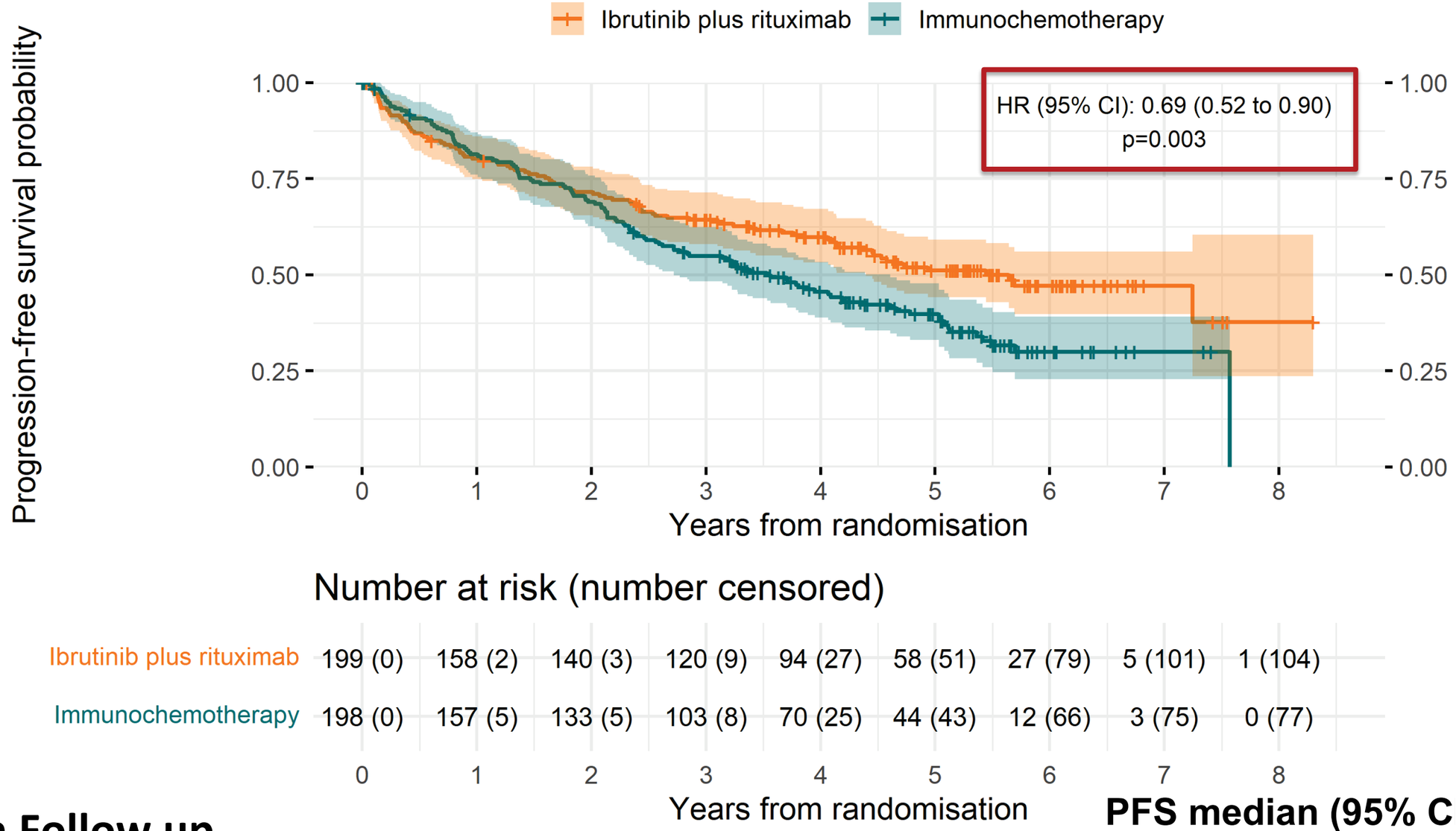
MCL elderly III



Best chemo free combo? → cessation possible?

Progression-free survival

ENRICH



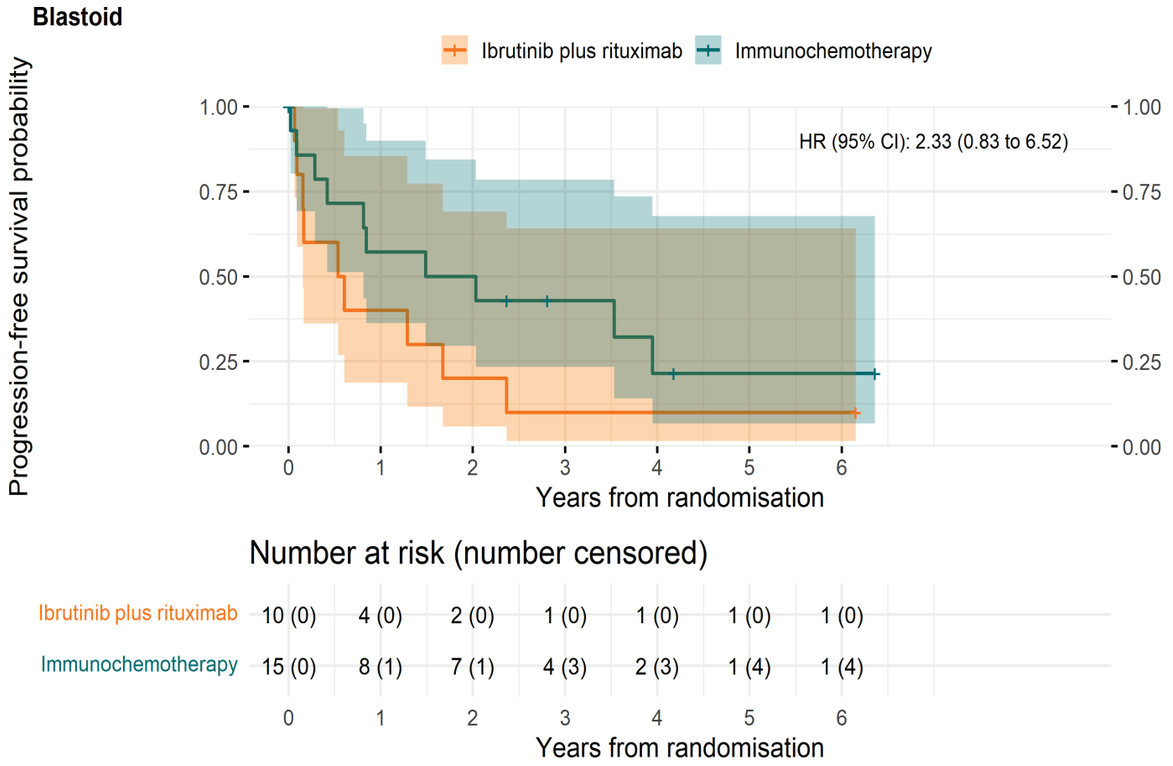
Median Follow up
47.9 months

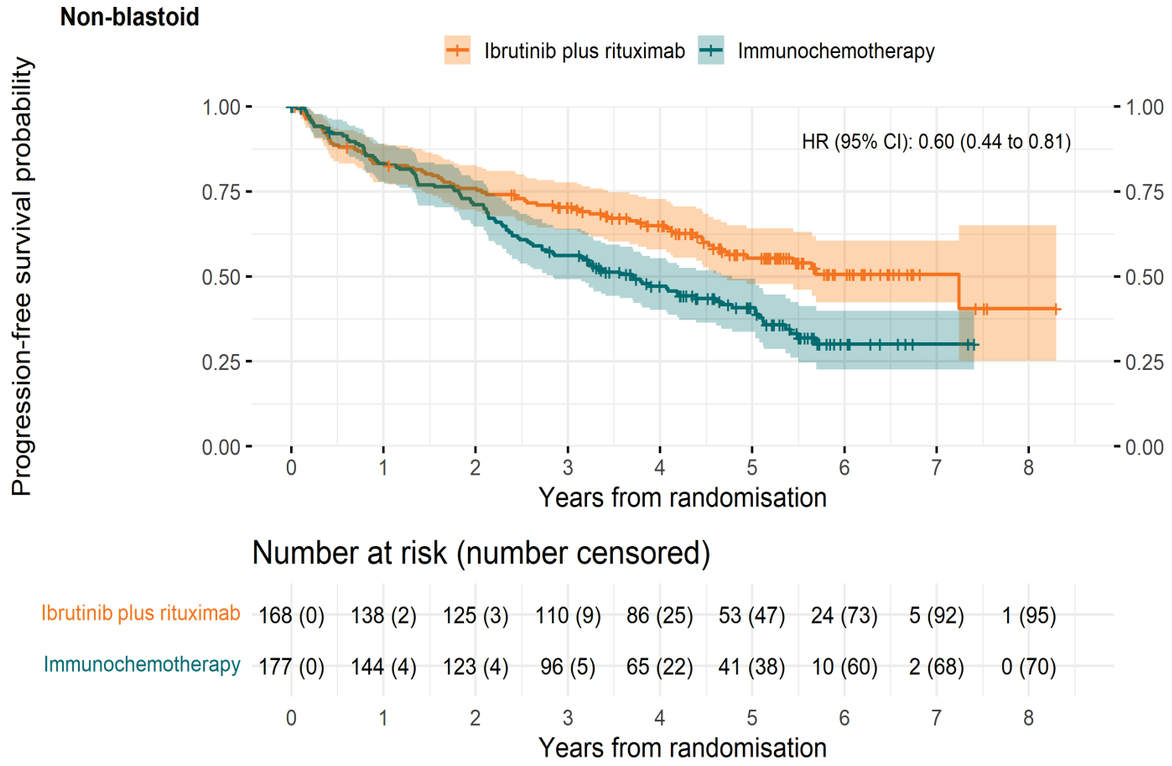
Lewis, ICML 2025, #047

PFS median (95% CI)
IR: 65.3 mo (52.7 to not evaluable)
R-chemo: 42.4 mo (32.7 to 55.3)

Blastoid disease

Suggestion of inferior PFS for blastoid disease for those randomised to IR

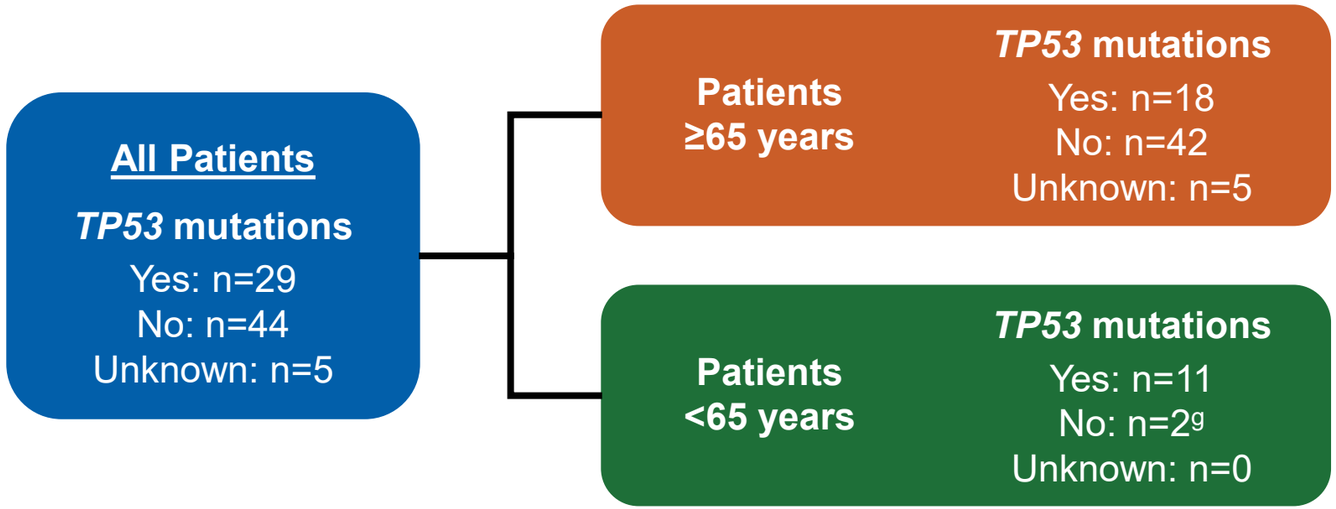




Blastoid subgroup (n=25) PFS 6.9 (95% CI 1.9 to NE) months for IR vs 21.1 (95% CI 9.8 to NE) months for immunochemotherapy)

HR 2.33, 95% CI 0.83 to 6.52

SYMPATICO[a] Included an Open-Label, Single-Arm Cohort for Patients With TN MCL Who Were Older and/or Had *TP53* Mutations[b]



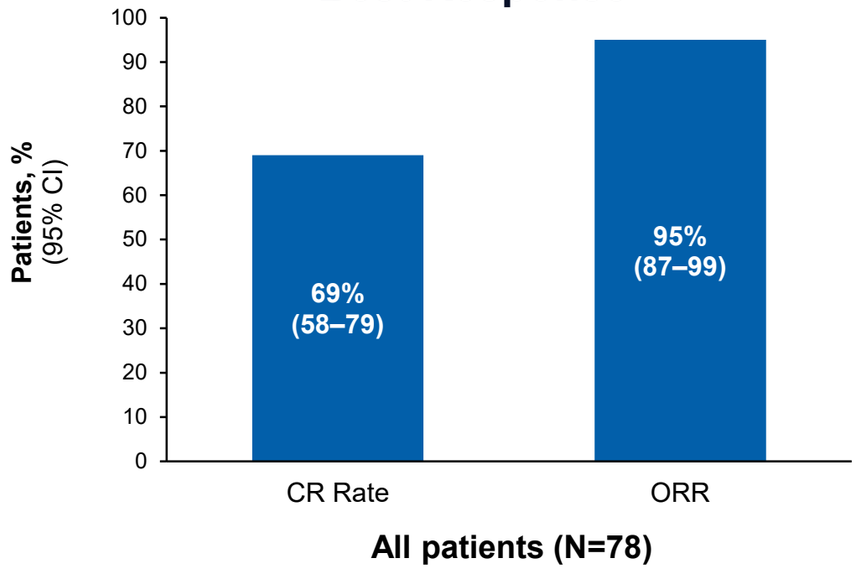
Treatment Disposition, n (%)	Ibrutinib	Venetoclax
Discontinued	**52 (67)**	**39 (50)**
PD[f]	18 (23)	17 (22)
AE	15 (19)	11 (14)
Ongoing single-agent	**26 (33)**	**0**

- **Median time on study:** 40.5 months (range, 0.6+ to 46.9)
- **Median treatment duration:** 24.0 months (range, 0.3–46.9)

[a]NCT03112174. [b]Somatic mutations in exons 1–11 of *TP53* were evaluated by next-generation sequencing, with a variant allele fraction cutoff of 2%. [c]560 mg once daily. [d]5-week ramp-up to 400 mg once daily. [e]560 mg once daily until PD or unacceptable toxicity. [f]PD per protocol criteria or clinical PD. [g]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

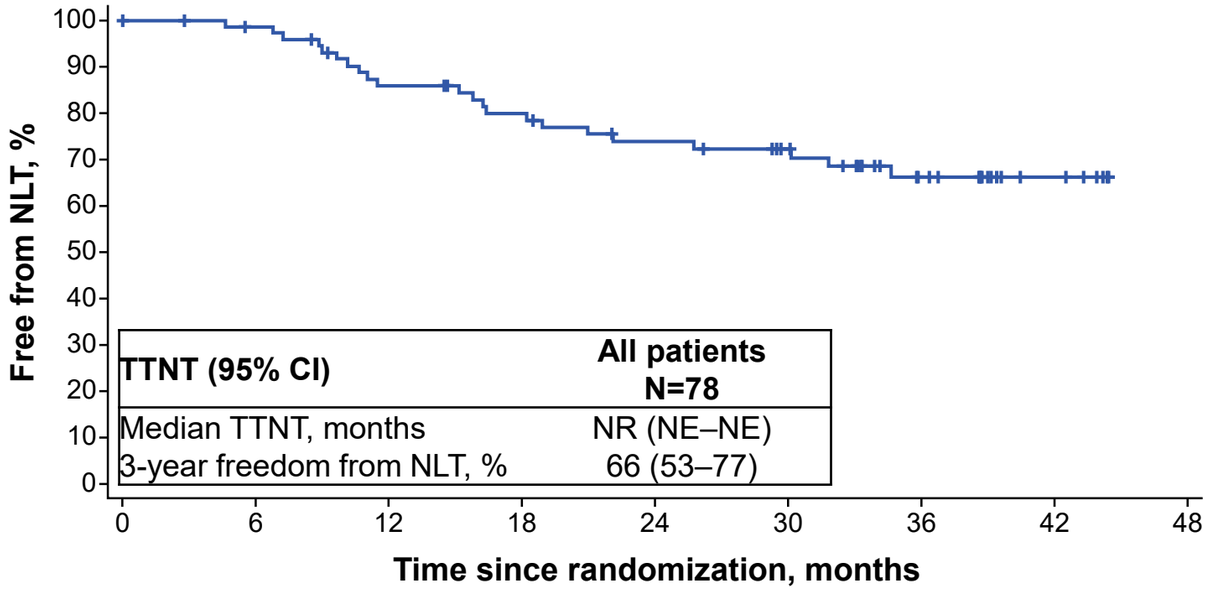
Ibrutinib + Venetoclax Met the Primary Endpoint for CR Rate and Showed Promising ORR and TTNT in Patients With TN MCL

Best Response



Outcome (95% CI)	DOCR n=54	DOR n=74
Median, months	37.1 (34.0–NE)	37.1 (30.3–NE)

TTNT



TTNT (95% CI)	All patients N=78
Median TTNT, months	NR (NE–NE)
3-year freedom from NLT, %	66 (53–77)

Patients at risk:

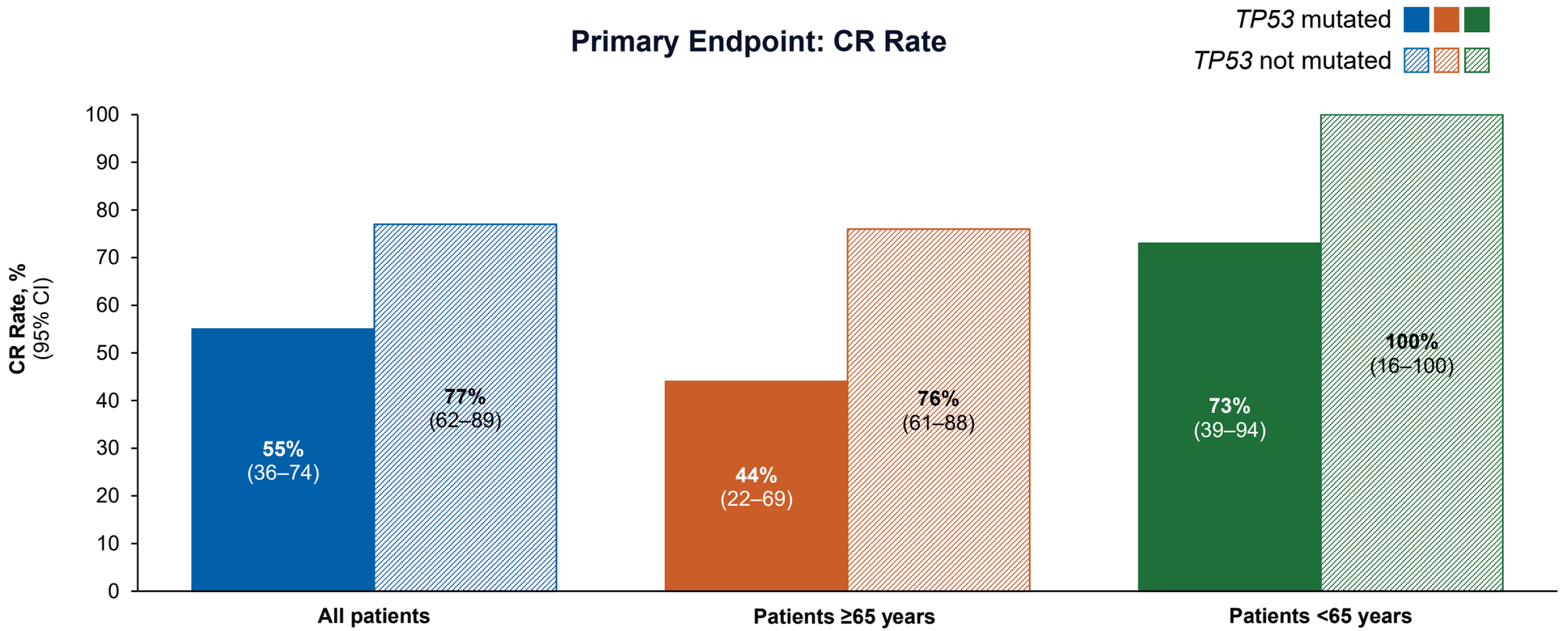
Total	78	72	60	54	47	40	27	7	0

- Among patients with CR, MRD-negative remission[a] was achieved in:
  - 13 of 22 evaluable patients (59%) in bone marrow
  - 26 of 34 evaluable patients (76%) in peripheral blood

CR, complete response; DOCR, duration of complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; NLT, next line treatment; NR, not reached; ORR, overall response rate; TTNT, time to next treatment.

[a]MCL cells <0.05% by 8-color flow cytometry.

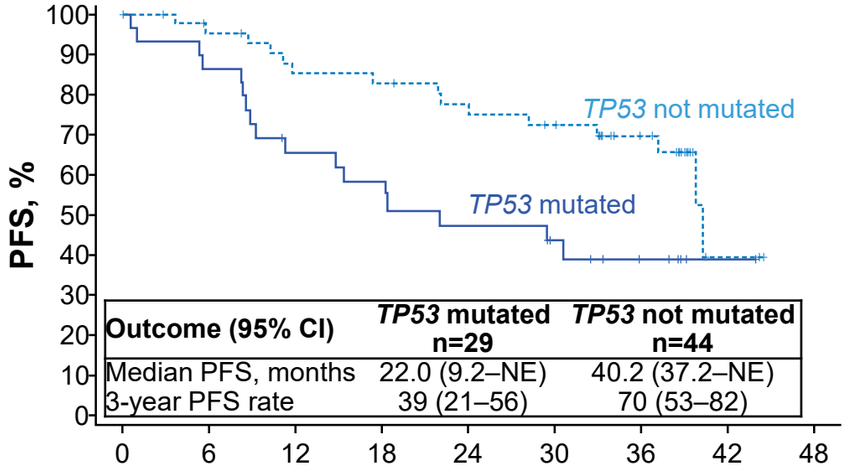
Ibrutinib + Venetoclax Also Improved Response Rates in Patients With *TP53* Mutations Overall and Across Subgroups by Age



[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

Encouraging PFS and OS with Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations Across Age Subgroups

All Patients



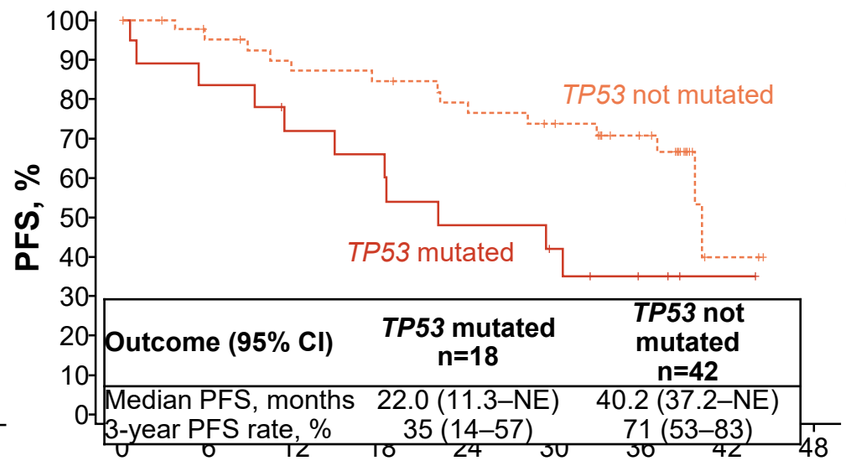
Outcome (95% CI)	*TP53* mutated n=29	*TP53* not mutated n=44
Median PFS, months	22.0 (9.2–NE)	40.2 (37.2–NE)
3-year PFS rate	39 (21–56)	70 (53–82)

Number of patients at risk:

TP53 mutated	29	25	18	16	13	9	5	1	0
TP53 not mutated	44	39	34	33	30	27	18	2	0

- 3-year OS rates (95% CI) in all patients
  - *TP53* mutated: 68% (47–82)
  - *TP53* not mutated: 86% (71–93)

Patients ≥65 years



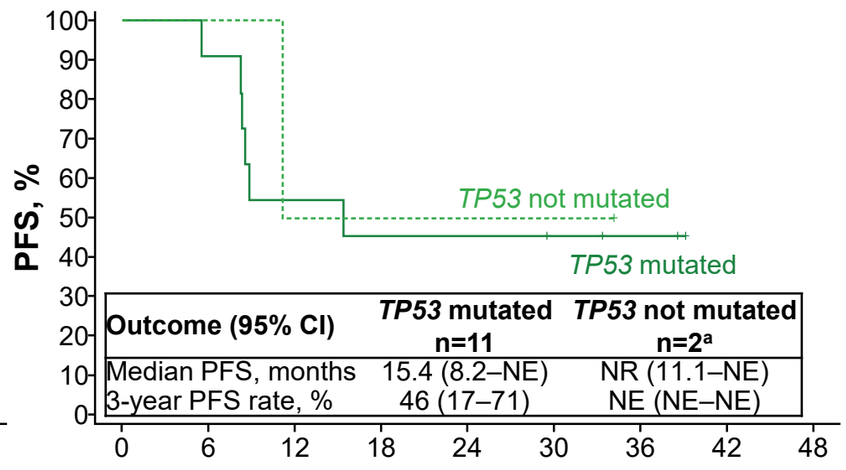
Outcome (95% CI)	*TP53* mutated n=18	*TP53* not mutated n=42
Median PFS, months	22.0 (11.3–NE)	40.2 (37.2–NE)
3-year PFS rate, %	35 (14–57)	71 (53–83)

Number of patients at risk:

TP53 mutated	18	15	12	11	8	6	3	1	0
TP53 not mutated	42	37	33	32	29	26	18	2	0

- 3-year OS rates (95% CI) in patients ≥65 years
  - *TP53* mutated: 66% (39–83)
  - *TP53* not mutated: 85% (70–93)

Patients <65 years



Outcome (95% CI)	*TP53* mutated n=11	*TP53* not mutated n=2[a]
Median PFS, months	15.4 (8.2–NE)	NR (11.1–NE)
3-year PFS rate, %	46 (17–71)	NE (NE–NE)

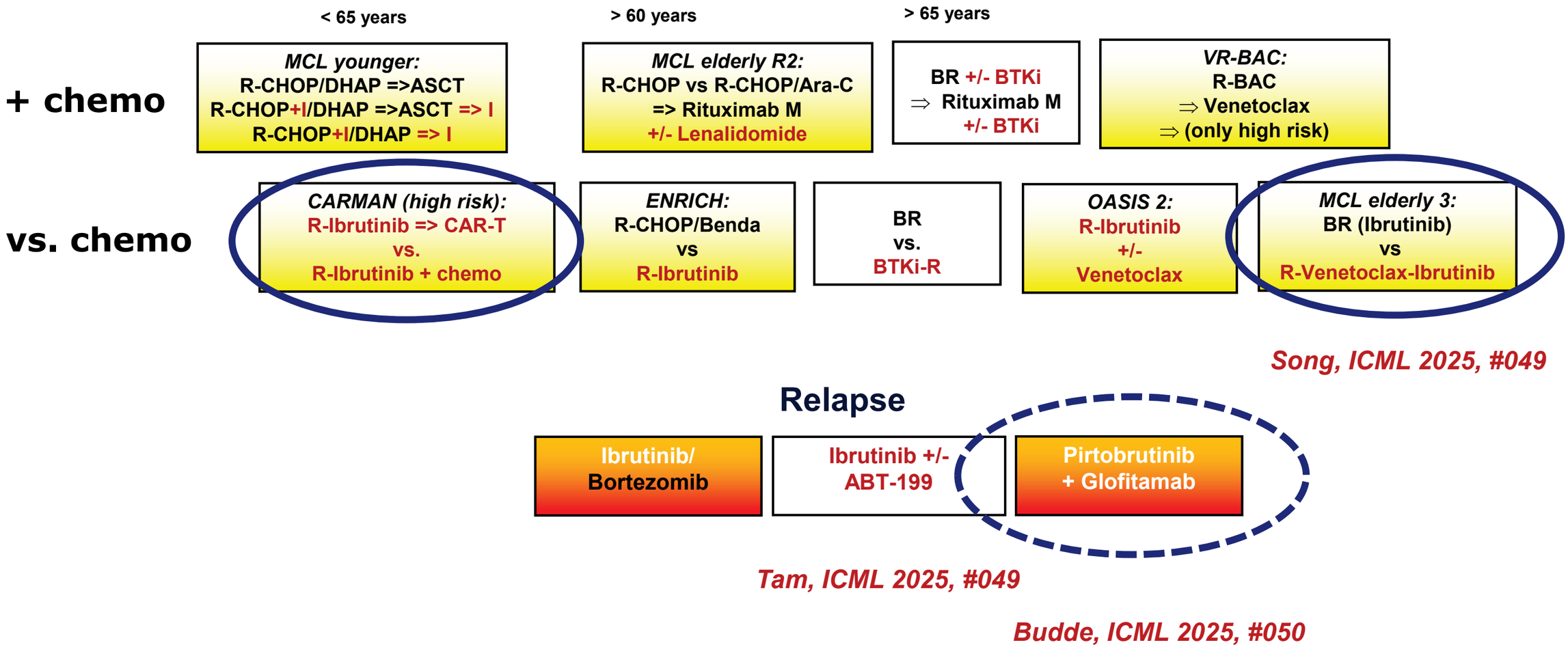
Number of patients at risk:

TP53 mutated	11	10	6	5	5	3	2	0	0
TP53 not mutated	2	2	1	1	1	1	0	0	0

- 3-year OS rates (95% CI) in patients <65 years
  - *TP53* mutated: 73% (37–90)
  - *TP53* not mutated: 100% (100–100)

[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

European MCL Network
Study generation 2025



Song, ICML 2025, #049

Relapse

Tam, ICML 2025, #049

Budde, ICML 2025, #050

Study design: Phase II dose expansion

Key inclusion criteria

- R/R MCL
- ECOG PS 0–2
- ≥2 prior therapies (including an anti-CD20 antibody, anthracycline or bendamustine therapy, and BTKi)

Objectives

- Primary: best ORR[1] by IRC
- Secondary: best ORR by INV, CR rate, DOR, DOCR, PFS, OS and safety

Mosun-Pola fixed duration administration (NCT03671018)

Mosun

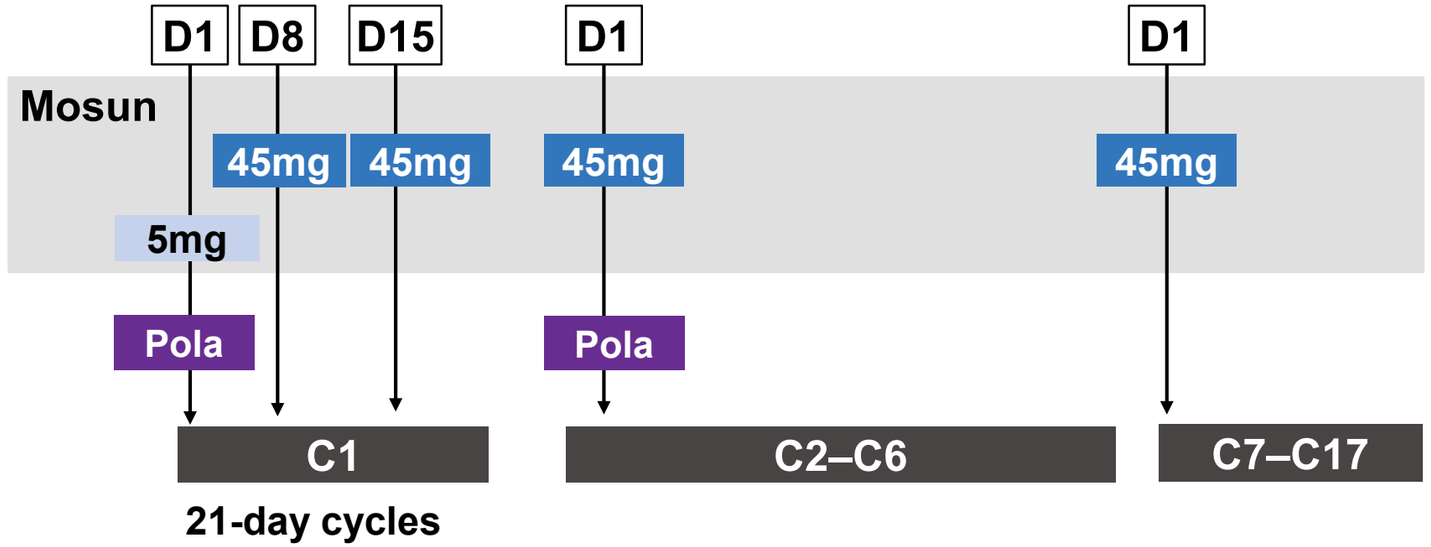
- SC administered in 21-day cycles with step-up dosing in C1; total of 17 cycles

Pola

- 1.8mg/kg IV on D1 of C1–6

No mandatory hospitalization

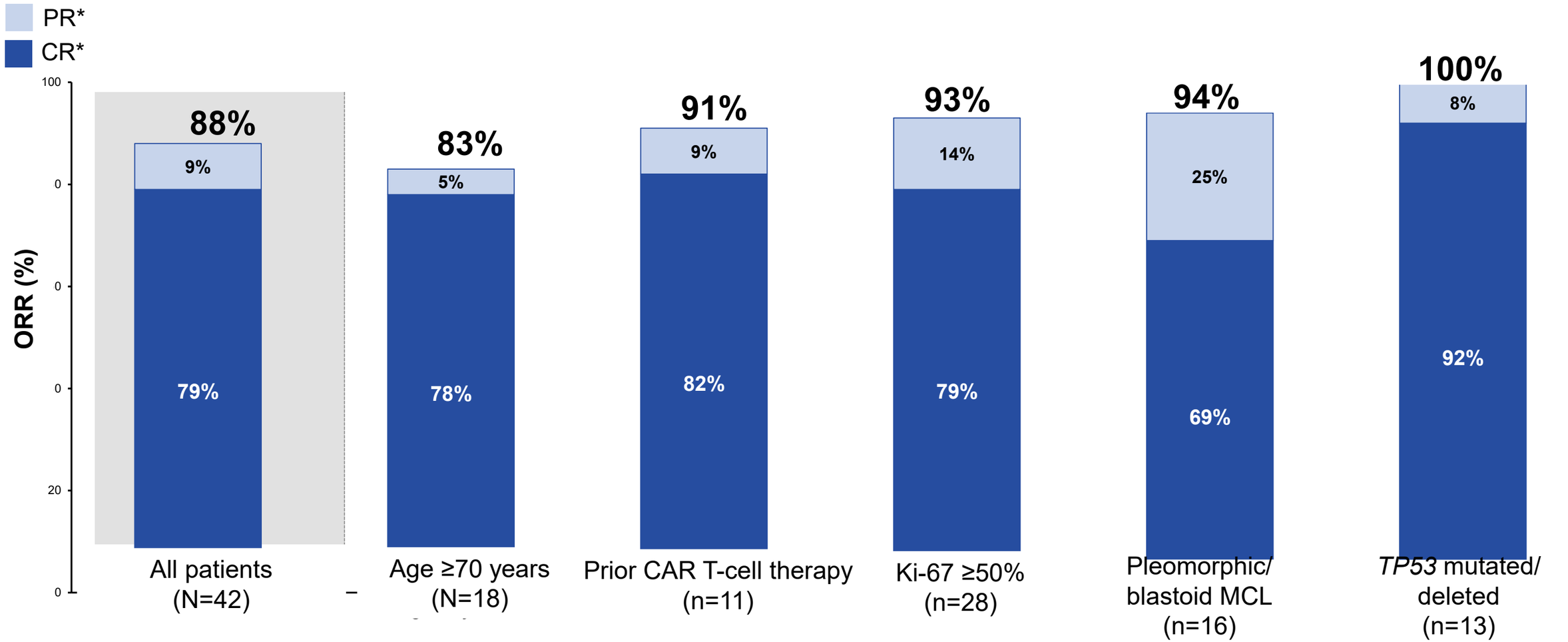
Corticosteroid premedication was given prior to each dose in C1*



*From C2 and beyond, premedication was optional for patients who did not experience CRS in the previous cycle; corticosteroid premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.
C, cycle; CR, complete response; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; CRS, cytokine release syndrome; DOCR, duration of complete response; DOR, duration of response; IRC, independent review committee; IV, intravenous; INV, investigator; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SC, subcutaneous.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Response rates

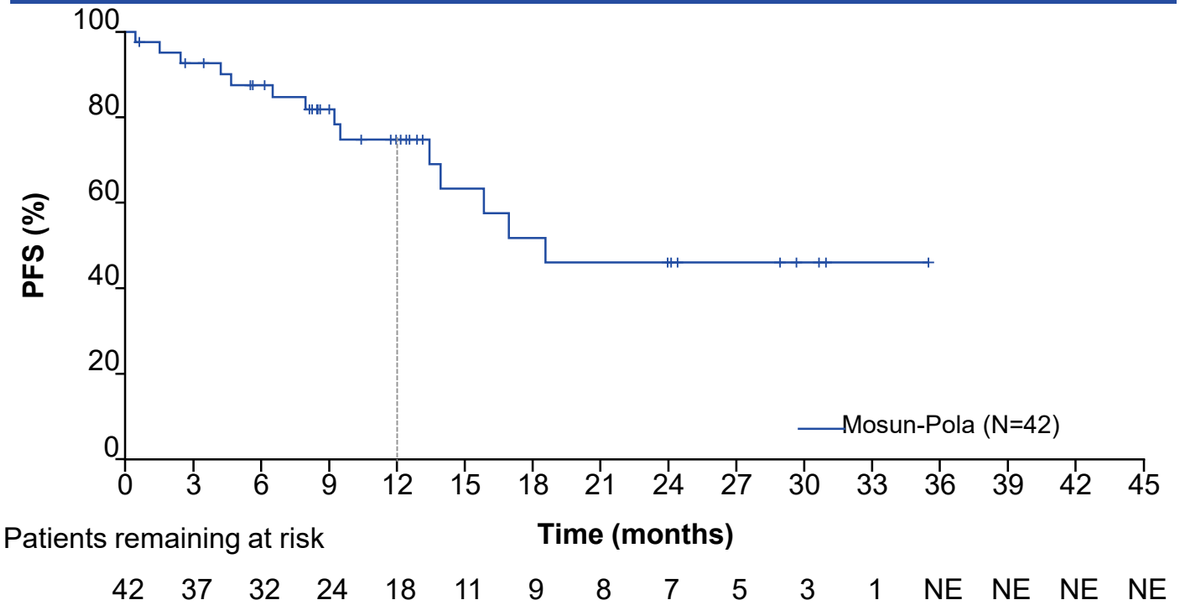


Efficacy was consistent across high-risk subgroups

CCOD: November 8, 2024. *IRC-assessed.

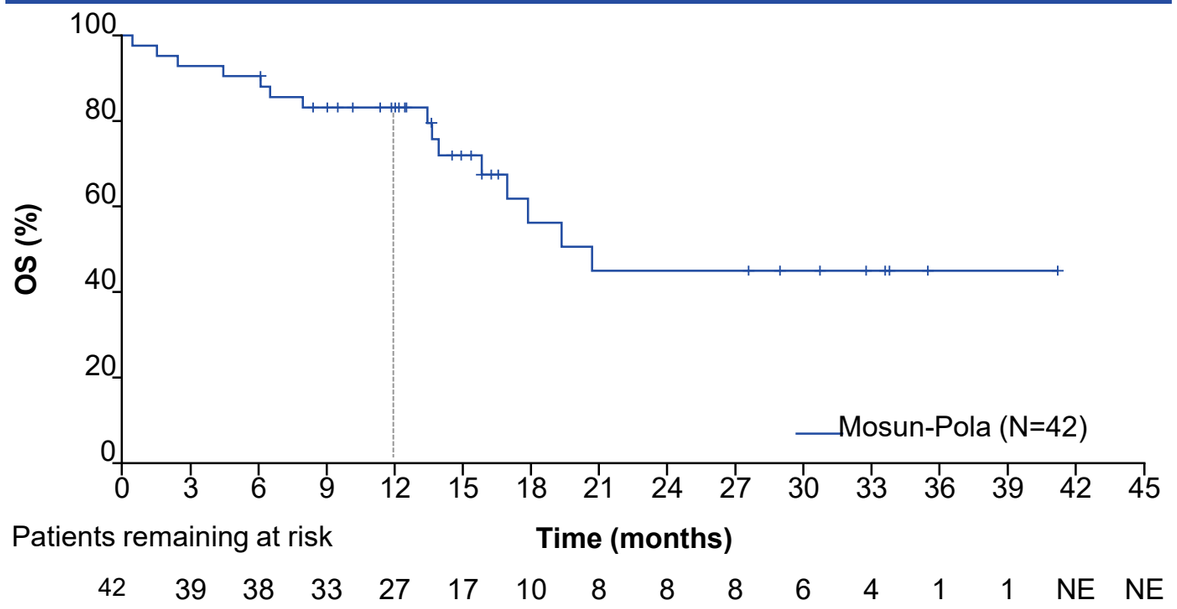
PFS and OS

Progression-free survival*



Patient population	n=42
Median PFS, months (95% CI)	18.6 (13.9–NE)
12-month rate, % (95% CI)	74.8 (60.2–89.4)

Overall survival



Patient population	n=42
Median OS, months (95% CI)	20.7 (17.0–NE)
12-month rate, % (95% CI)	83.1 (71.7–94.5)

Mosun-Pola demonstrated promising PFS and OS

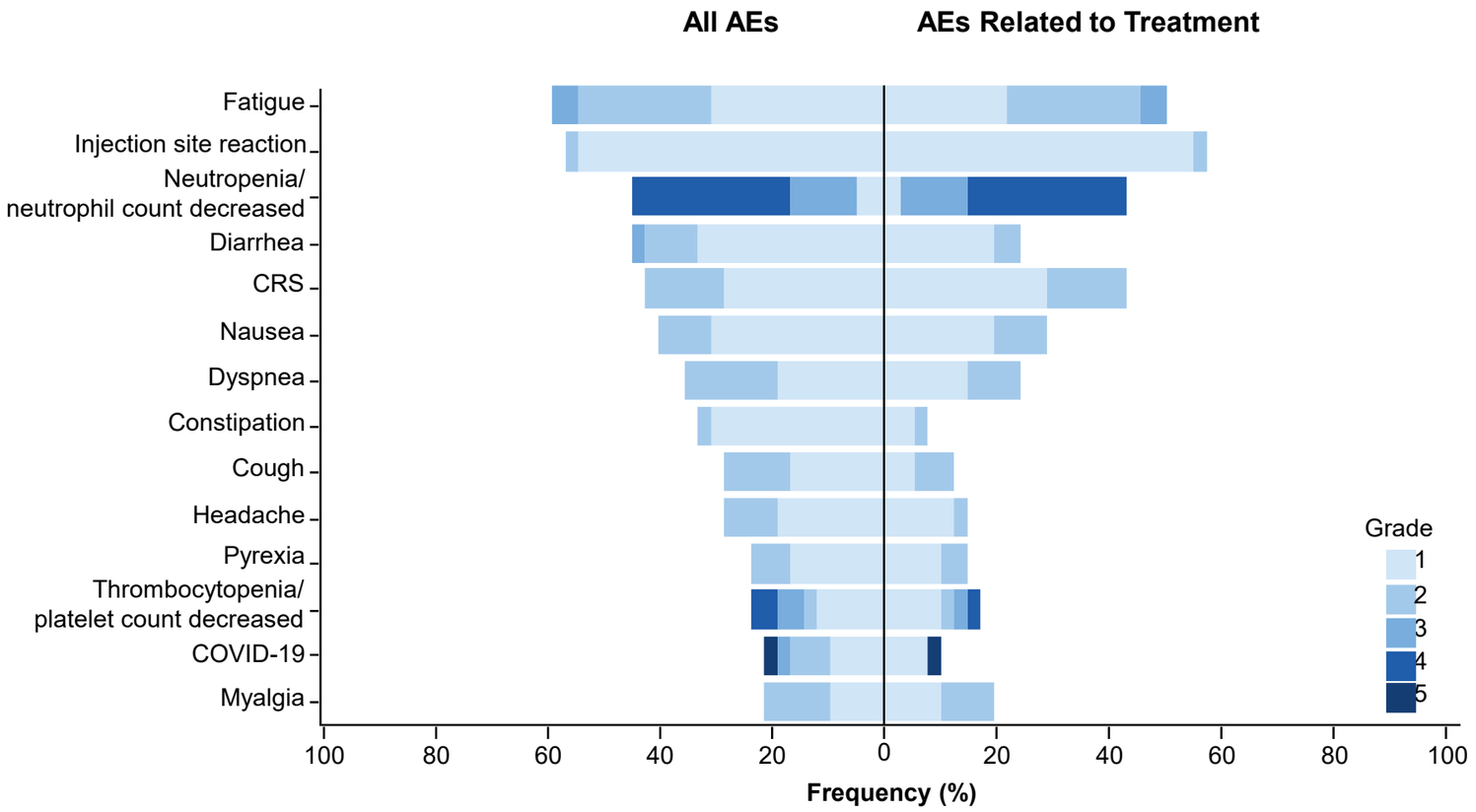
CCOD: November 8, 2024. *IRC-assessed.

Safety summary

n (%)	N=42
AE	42 (100)
Treatment-related	39 (93)
Grade 3–4 AE	29 (69)
Treatment-related	25 (60)
Serious AE	26 (62)
Treatment-related	17 (41)
Grade 5 (fatal) AE	5 (12)*
Treatment-related	1 (2)†
AE leading to treatment discontinuation	10 (24)‡
Treatment-related	5 (12)

Median number of cycles:
- Mosun: 15 (range, 1–17)
- Pola: 6 (range, 1–6)

AEs occurring in ≥20% of patients by grade



CCOD: November 8, 2024. *Gr 5 events: COVID-19 pneumonia (n=3), and one each of pneumonia and West Nile virus encephalitis. †COVID-19 pneumonia (n=1). ‡Not treatment-related: COVID-19 pneumonia (n=2, Gr 5), and one each of pneumonia (Gr 3), vascular dementia (Gr 3), colorectal cancer (Gr 3, Mosun-discontinuation) and cough (Gr 2, Mosun-discontinuation); Mosun-Pola-related: one each of uveitis (Gr 3), pneumonitis (Gr 3, Pola-discontinuation), and upper respiratory tract infection (Gr 2, Mosun-discontinuation); Mosun-related: *Clostridioides difficile* colitis (n=1, Gr 3, Mosun-discontinuation); Pola-related: peripheral neuropathy (n=2, Gr 2, Pola-discontinuation). AE, adverse event; COVID-19, coronavirus disease 19; Gr, grade.

Mantle cell lymphoma
Take home messages

LMU KLINIKUM

- Improved prognosis in younger patients
- BTKi-chemo standard in first line (elderly high risk)
- R-Ibrutinib in low risk patients
- In studies: BTKi combinations

  (Ibru/Ven, Zanu/Sonro, Oreo/Len/R)
- relapsed patients; new combinations (Pola/Mosu)

Studientreffen 2024, München

Alle Kurzpräsentationen sind online unter

www.lymphome.de/icml2025

Für den Inhalt verantwortlich:

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LMU Klinikum München

Lymphom
Kompetenz
KOMPAKT

KML KONGRESSE

Expert:innen berichten zu
Lymphomen & Leukämien

Kompetenznetz
Maligne Lymphome

18th ICML LUGANO
17. – 21. Juni 2025

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