Relapsed or Refractory Mantle cell lymphoma: Treatment Strategies and Emerging Therapies

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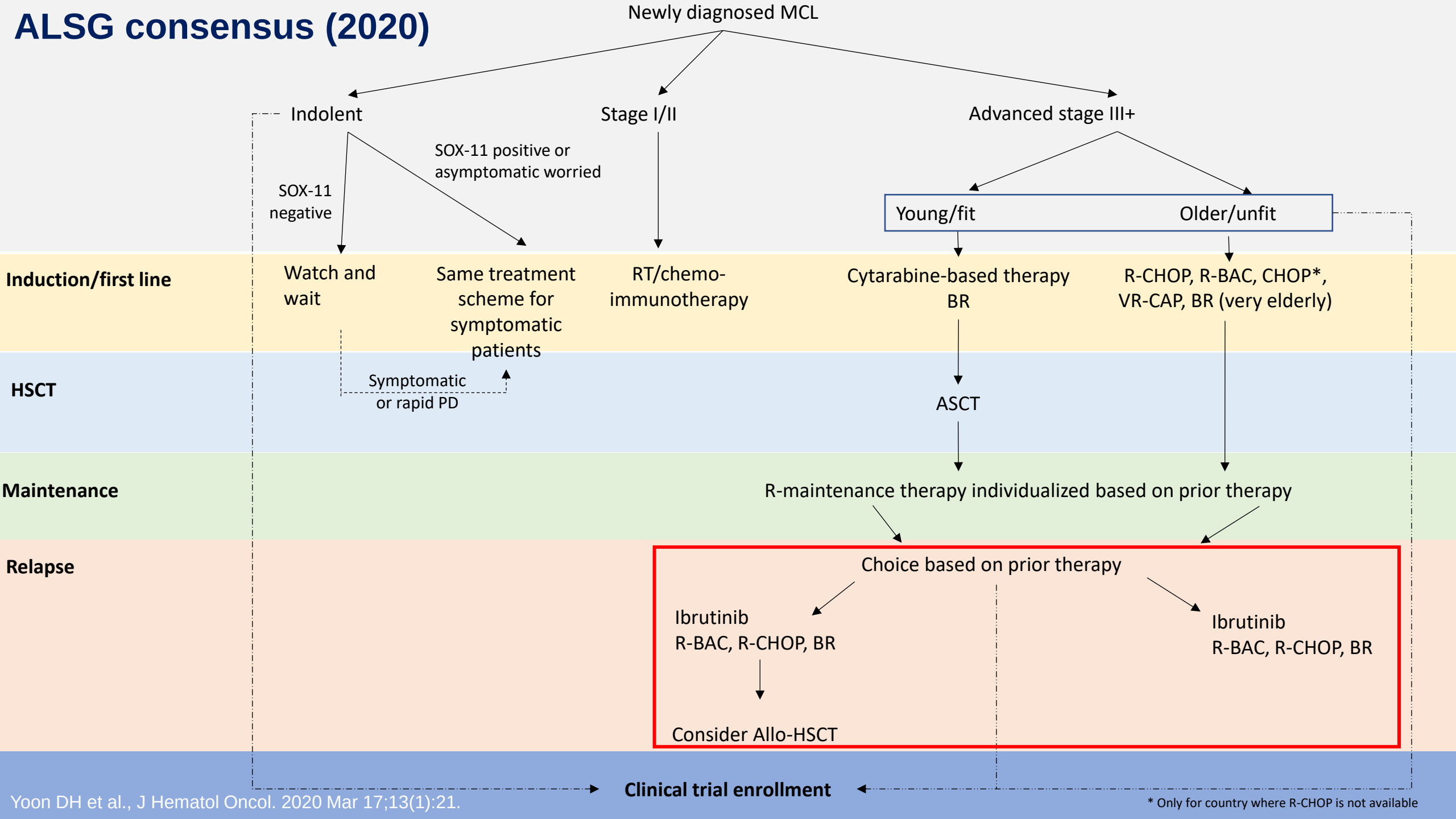
Disclosures

- **Honoraria: Celltrion, Roche, Janssen, Amgen, Celgene, Boryung, Samyang, Kirin Pharm and Takeda**
- **Consulting or Advisory Role: GC Cell, Abclone and GI-cell**
- **Research funding: Abbvie, Celltrion, Samyang and Beigene**

ALSG consensus (2020)



Yoon DH et al., J Hematol Oncol. 2020 Mar 17;13(1):21.

* Only for country where R-CHOP is not available

ESMO guidelines for RRMCL (2017)

- **Young patients ≤ 65 years**
  - Targeted approaches
  - Immunochemotherapy
  - Discussion about allo-SCT
- **Elderly patients > 65 years**
  - Targeted approaches
  - Immunochemotherapy
  - Discussion about R maintenance or radioimmunotherapy
- **Compromised patient**
  - Targeted approaches
  - Immunochemotherapy

Higher relapse

Targeted approaches: ibrutinib, lenalidomide, temsirolimus, bortezomib

Alternatively, repeat previous therapy (long remission)

Annals of Oncology 28 (Supplement 4): iv62–iv71, 2017

cBTKi is moving to frontline therapy

TRIANGLE

Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network

Martin Dreyling, Jeanette Doorduijn, Eva Giné, Mats Jerkeman, Jan Walewski, Martin Hutchings, Ulrich Mey, Jon Riise, Marek Trneny, Vibeke Vergote, Ofer Shpilberg, Maria Gomes da Silva, Sirpa Leppä, Linmiao Jiang, Stephan Stilgenbauer, Andrea Kerkhoff, Ron D Jachimowicz, Melania Celli, Georg Hess, Luca Arcaini, Carlo Visco, Tom van Meerten, Stefan Wirths, Pier Luigi Zinzani, Urban Novak, Peter Herhaus, Fabio Benedetti, Kristina Sonnevi, Christine Hanoun, Matthias Hänel, Judith Dierlamm, Christiane Pott, Wolfram Klapper, Döndü Gözel, Christian Schmidt, Michael Unterhalt, Marco Ladetto, Eva Hoster**

Summary

Background Adding ibrutinib to standard immunochemotherapy might improve outcomes and challenge autologous stem-cell transplantation (ASCT) in younger (aged 65 years or younger) mantle cell lymphoma patients. This trial aimed to investigate whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT. We also investigated whether standard treatment with ASCT is superior to a treatment adding ibrutinib but without ASCT.

Lancet 2024; 403: 2293-306
Published Online May 2, 2024
https://doi.org/10.1016/S0140-6736(24)00184-3

See Comment page 2264

*Contributed equally

ECHO

Original Reports | Hematologic Malignancy

Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma

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DOI https://doi.org/10.1200/JCO-25-00690

ABSTRACT

PURPOSE The combination of the Bruton tyrosine kinase inhibitor ibrutinib with bendamustine-rituximab for first-line treatment of mantle cell lymphoma (MCL) prolonged progression-free survival (PFS), but without improvement in overall survival (OS), likely because of toxicity. Acalabrutinib was shown to be efficacious and less toxic than ibrutinib in a head-to-head trial in chronic lymphocytic leukemia and therefore might lead to better outcomes in MCL.

METHODS Patients 65 years and older with previously untreated MCL received acalabrutinib (100 mg twice daily) or placebo (until disease progression or unacceptable toxicity), plus six cycles of bendamustine (90 mg/m² once daily; days 1 and 2) and rituximab (375 mg/m² as a single dose; day 1) followed by rituximab maintenance in responding patients for 2 years. Crossover to acalabrutinib at disease progression was permitted. The primary end point was PFS per the independent review committee; overall response rate and OS were secondary end points.

RESULTS In total, 598 patients were randomly assigned, with 299 in each arm. At a median follow-up of 49.8 months using the reverse Kaplan-Meier method, the median PFS was 66.4 months in the acalabrutinib arm and 49.6 months in the

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Data Supplement
Protocol

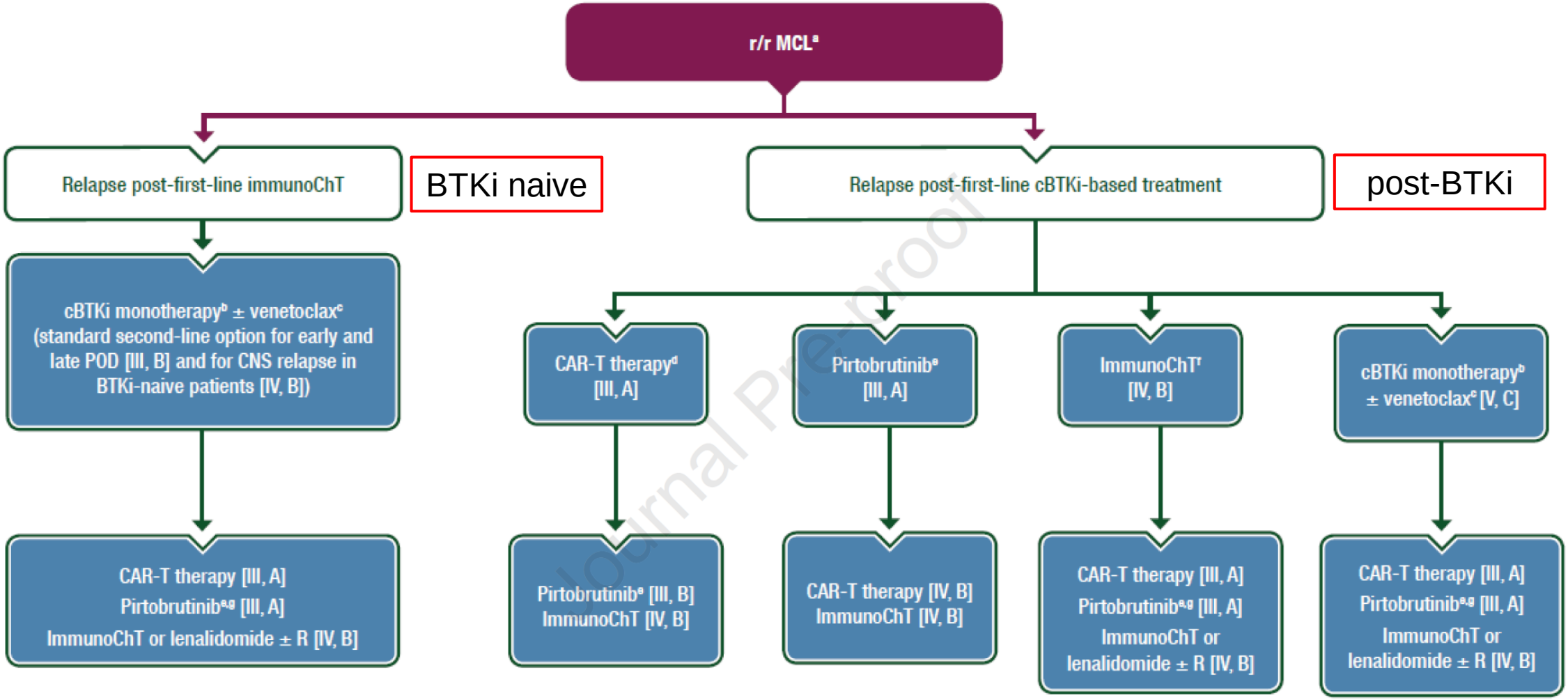
Accepted April 24, 2025
Published May 1, 2025

J Clin Oncol 00:1-9

View Online Article

Lancet. 2024 May 25;403(10441):2293-2306
J Clin Oncol. 2025 May 1:JCO2500690

ESMO guidelines for RRMCL (2025)



Eyre TA et al., Annals of Oncology (2025), doi: https://doi.org/10.1016/ j.annonc.2025.07.014

NCCN guidelines

v5.2021

- **Second-line and subsequent therapy**
- Preferred Regimens (in alphabetical order)
  - BTK inhibitors
    - Acalabrutinib
    - Ibrutinib ± rituximab
    - Zanubrutinib
  - Lenalidomide + rituximab
- Useful in certain circumstances
  - Bendamustine + rituximab (if not previously given)
  - + others like RBAC, R-DHAX, R-GemOx….
- **Second-line consolidation**
  - Allo-SCT (non-myeloablative or myeloablative)
- **Third-line therapy**
  - Brexucabtagene autoleucel
    (only after chemoimmunotherapy and BTK inhibitor)

v2.2025

NCCN guidelines

v5.2021

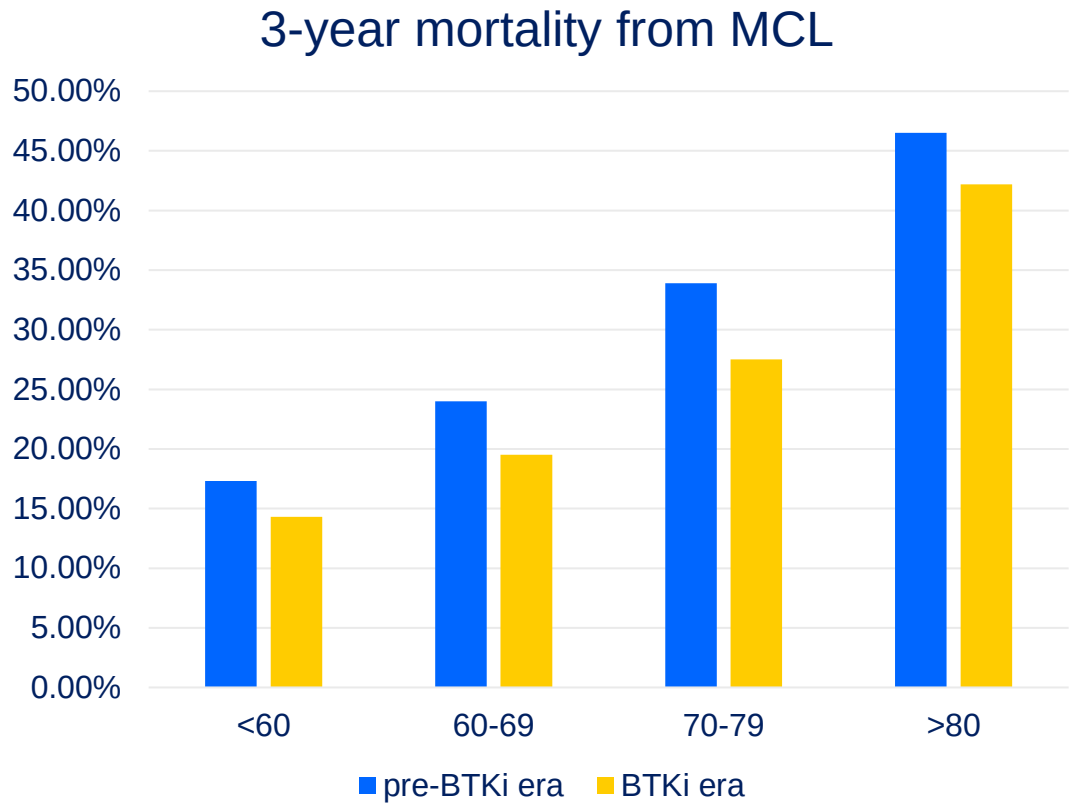
- **Second-line and subsequent therapy**
- Preferred Regimens (in alphabetical order)
  - BTK inhibitors
    - Acalabrutinib
    - Ibrutinib ± rituximab
    - Zanubrutinib
  - Lenalidomide + rituximab
- Useful in certain circumstances
  - Bendamustine + rituximab (if not previously given)
  - + others like RBAC, R-DHAX, R-GemOx….
- **Second-line consolidation**
  - Allo-SCT (non-myeloablative or myeloablative)
- **Third-line therapy**
  - Brexucabtagene autoleucel
    (only after chemoimmunotherapy and BTK inhibitor)

v2.2025

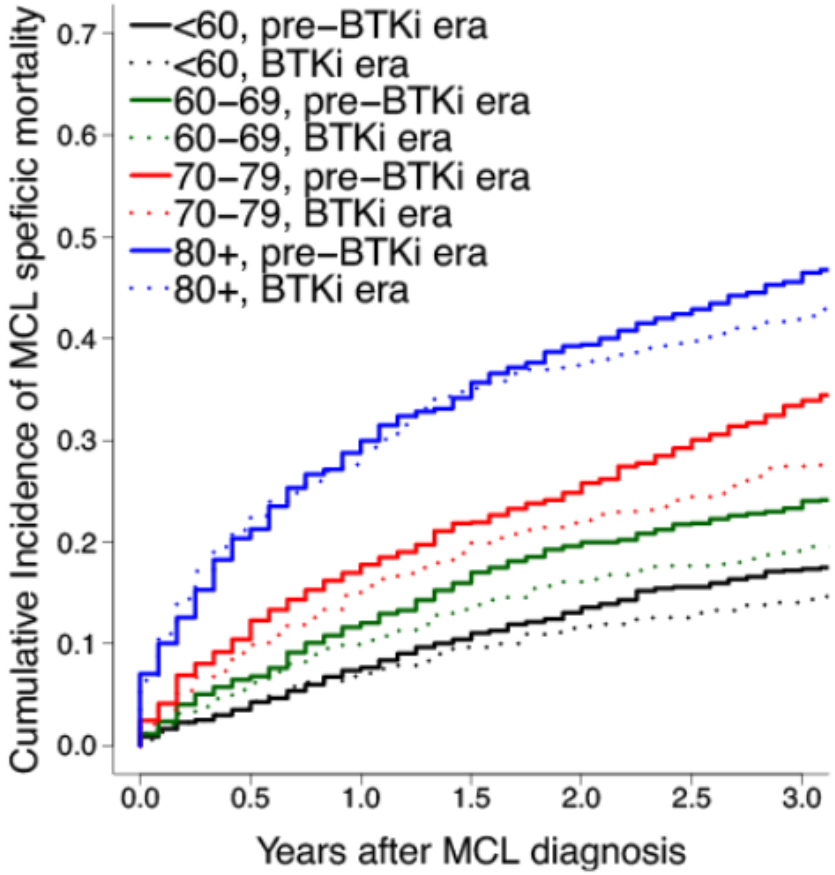
- **Second-line and subsequent therapy**
- Preferred Regimens (in alphabetical order)
  - Covalent BTKi (continuous): Acala or Zanubrutinib
  - Lenalidomide + rituximab
- Other recommended regimen
  - Covalent BTKi (continuous): Ibrutinib ± rituximab
- Useful in certain circumstances
  - Bendamustine + rituximab (if not previously given)
  - + others like RBAC, R-DHAX, R-GemOx….
- PD after prior cBTKi
  - Non-covalent BTKi (continuous): Pirtobrutinib
  - CAR T-cell therapy: Brexu-cel or Liso-cel
- PD after CAR T-cell therapy and pirtobrutinib or ineligible for CAR T-cell therapy
  - Glofitamab (category 2B)

Improved survival in the era of BTKi: SEER data

- **Pre-BTKi era (2007-2011, n=3424) vs. BTKi era (2014-2018, n=4201)**

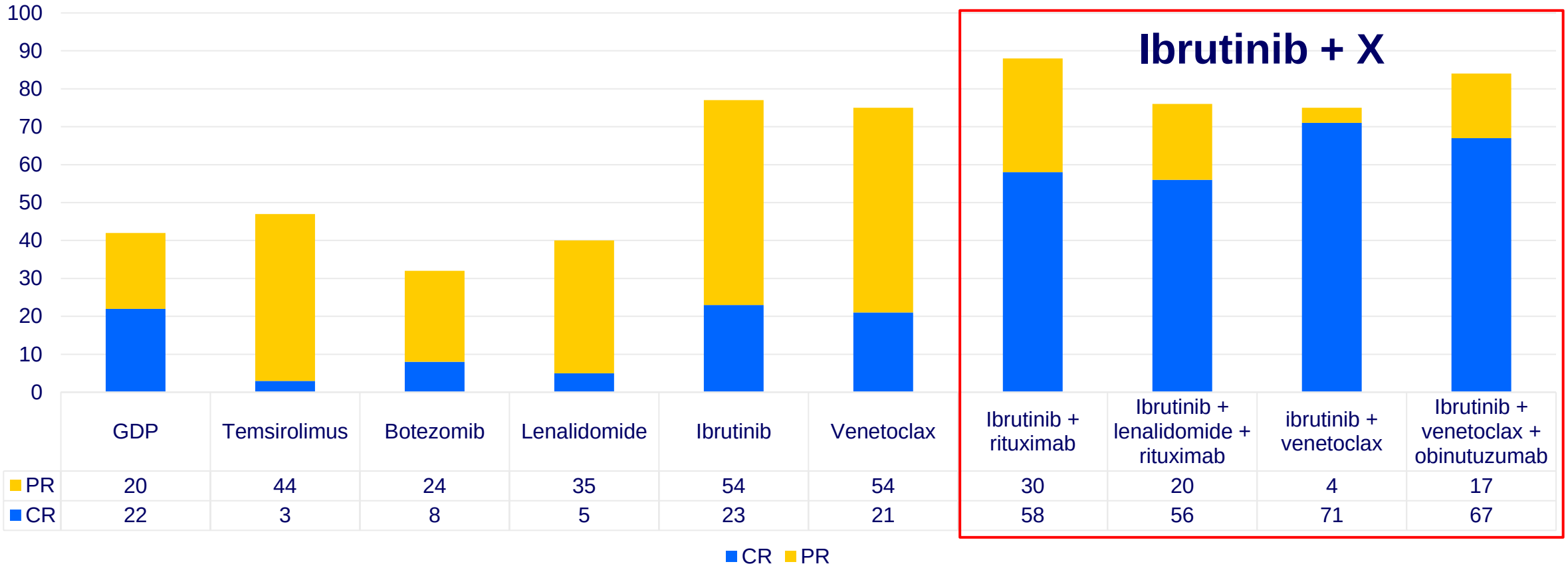


HR	0.8	0.78	0.76	0.87
95% CI	(0.62-1.04)	(0.34-0.94)	(0.65-0.90)	(0.75-1.02)



Blood Adv. 2022 Jun 3;6(11):3339–3342

Overall response rates for therapeutics for R/R MCL



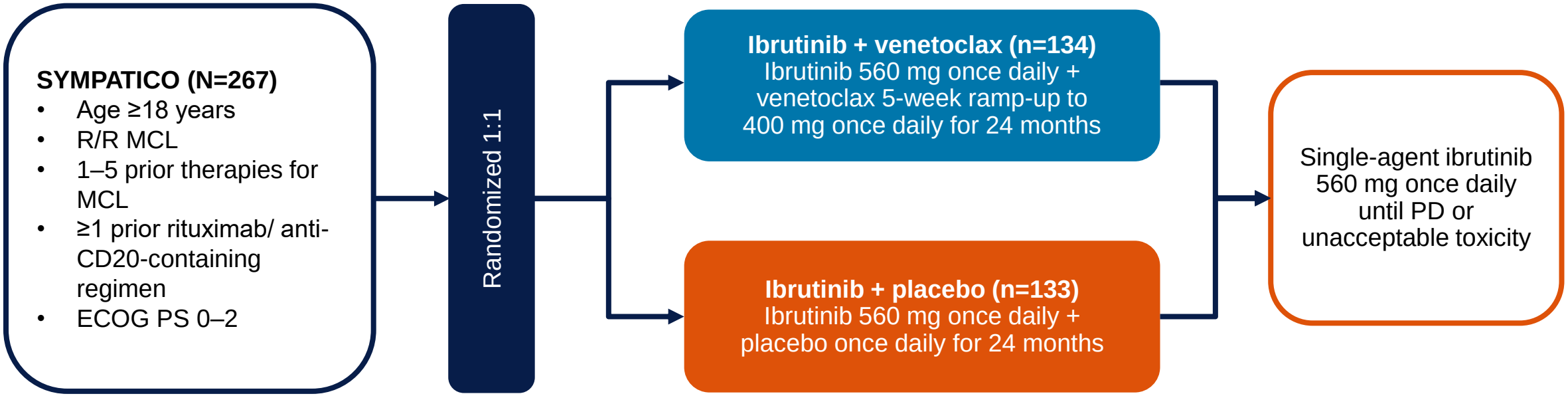
	GDP	Temsirolimus	Botezomib	Lenalidomide	Ibrutinib	Venetoclax	Ibrutinib + rituximab	Ibrutinib + lenalidomide + rituximab	ibrutinib + venetoclax	Ibrutinib + venetoclax + obinutuzumab
PR	20	44	24	35	54	54	30	20	4	17
CR	22	3	8	5	23	21	58	56	71	67

* Data from each trial

GDP: Ann Oncol. 2007 Feb;18(2):370-5; Temsirolimus phase 3, Lancet. 2016;387:770–778; Bortezomib; J Clin Oncol. 2006;24:4867–4874; update of PINNACLE study Ann Oncol. 2009;20: 520–525; Bortezomib + R; Haematologica. 2011;96(7):1008-1014; Lenalidomide: MCL-002; SPRINT, randomized phase 2 Lancet Oncol. 2016;17(3):319-331; Lenalidomide + R, Lancet Oncol. 2012;13(7):716-723; Ibrutinib, phase 3, Lancet. 2016;387:770–778; Ibrutinib+R, phase 2 update, Br J Haematol 2018 May 22. doi:10.1111/bjh.15411; Venetoclax, phase 1 J Clin Oncol. 2017;35(8): 826-833; ibrutinib+lenalidomide+rituximab, Lancet Haematol. 2018;5(3):e109-e116; ibrutinib+venetoclax, NEJM 2018;378:1211-1223 Blood 2020, epub, ibrutnib+venetoclax+obinutuzumab

Ibrutinib Combined With Venetoclax in Patients With RR-MCL: Primary Analysis Results From the Randomized Phase 3 SYMPATICO Study

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study



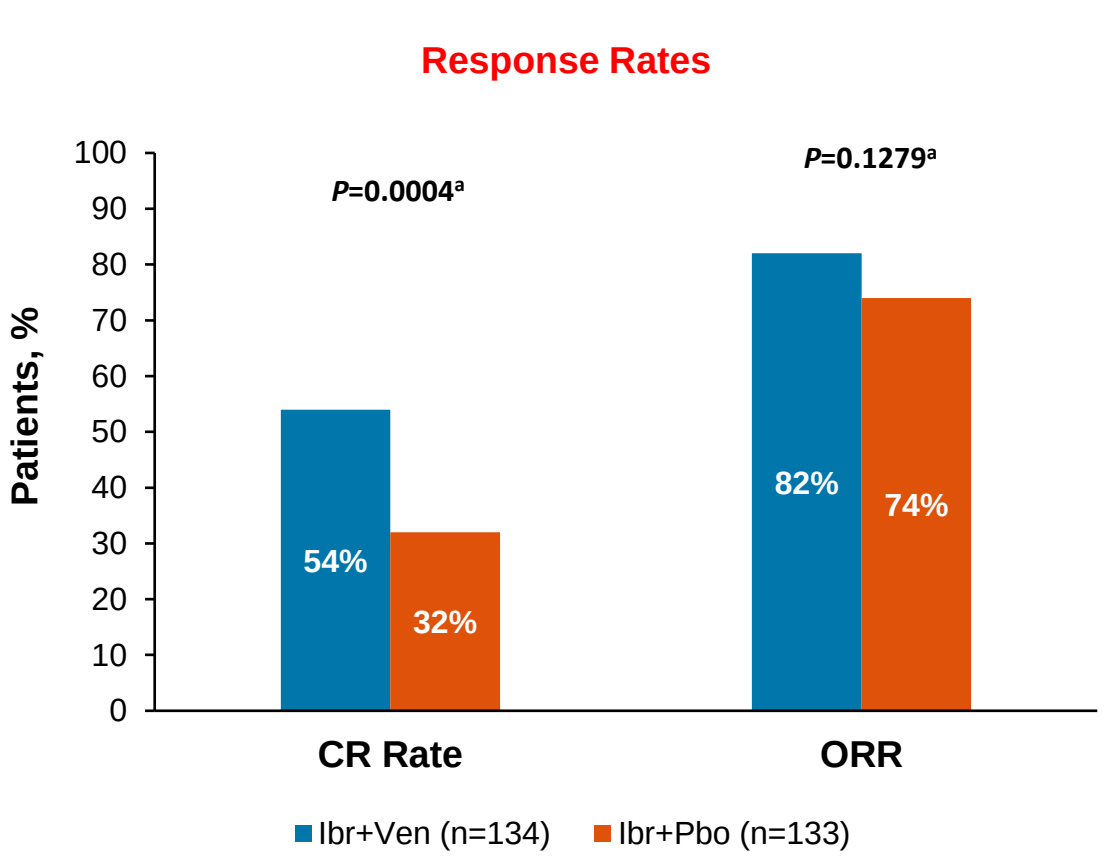
Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

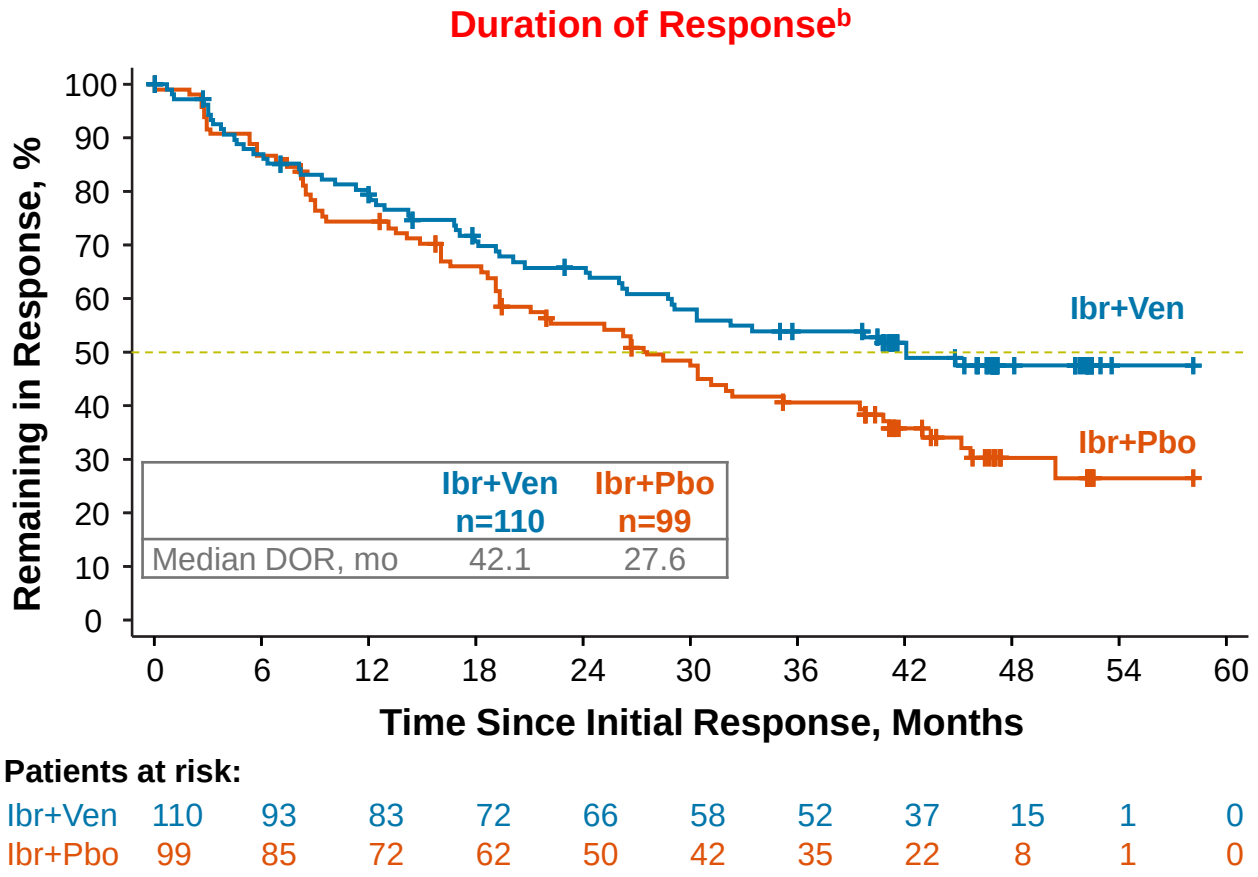
- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria

- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

Michael Wang et al., *Blood* (2023) 142 (Supplement 2): LBA-2.

CR rate was significantly improved with ibrutinib + venetoclax



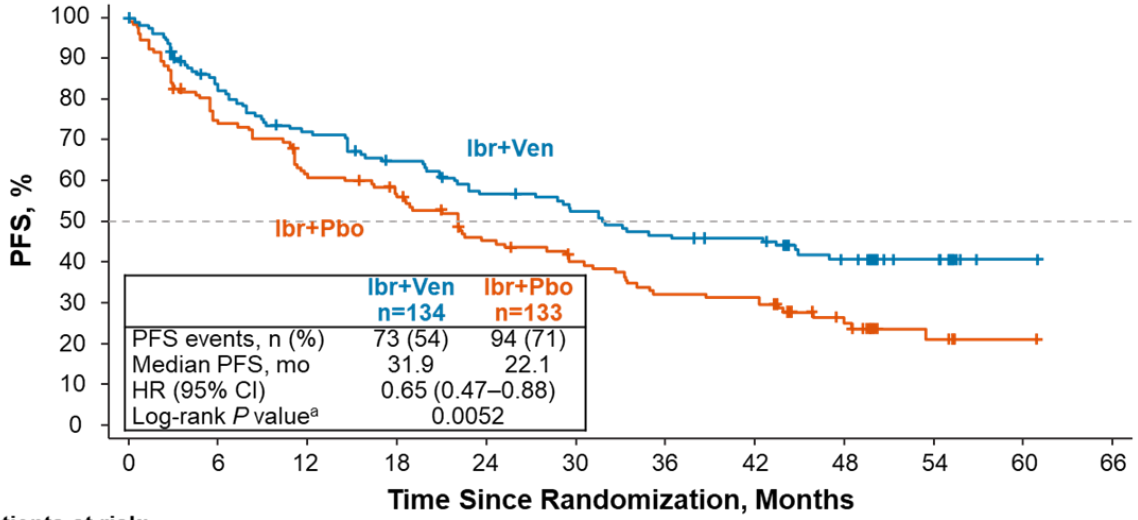


Patients at risk:

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

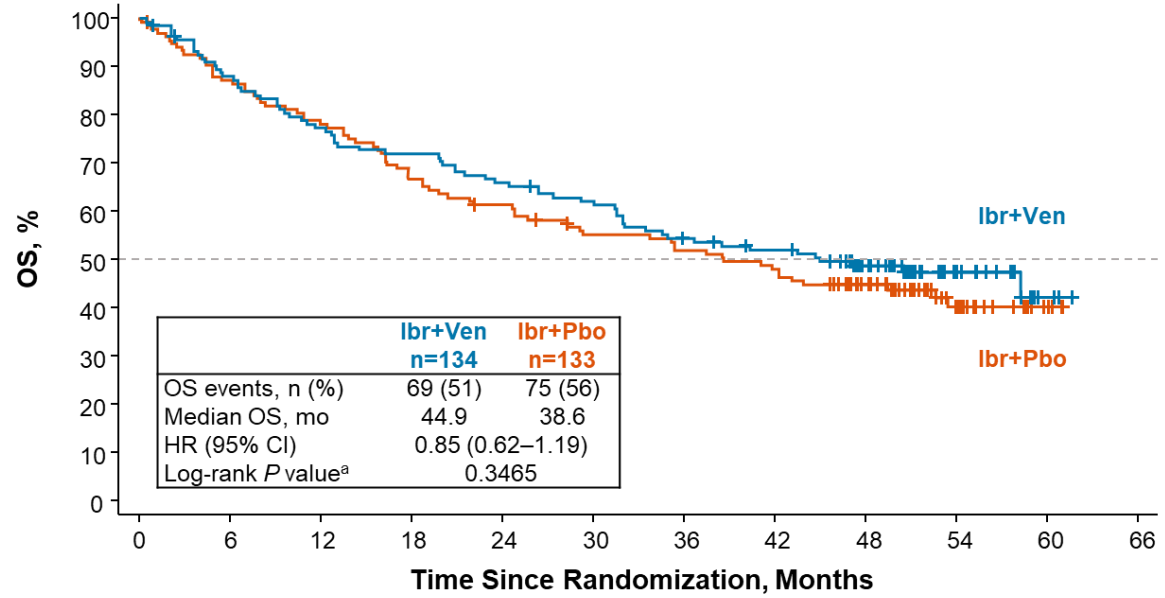
Michael Wang et al., *Blood* (2023) 142 (Supplement 2): LBA-2.

Significantly improved PFS and numerically higher OS in ibrutinib + venetoclax arm



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



Patients at risk:

Ibr+Ven	134	116	102	95	87	81	70	65	48	20	3	0
Ibr+Pbo	133	115	103	88	80	70	66	61	46	20	4	0

Michael Wang et al., *Blood* (2023) 142 (Supplement 2): LBA-2.

Ibrutinib + venetoclax seems to be tolerable

- Safety was consistent with known AEs of each single agent
- Median overall treatment duration:
  - Ibrutinib + venetoclax, 22.2 months (range, 0.5–60.4)
  - Ibrutinib + placebo, 17.7 months (range, 0.1–58.9)

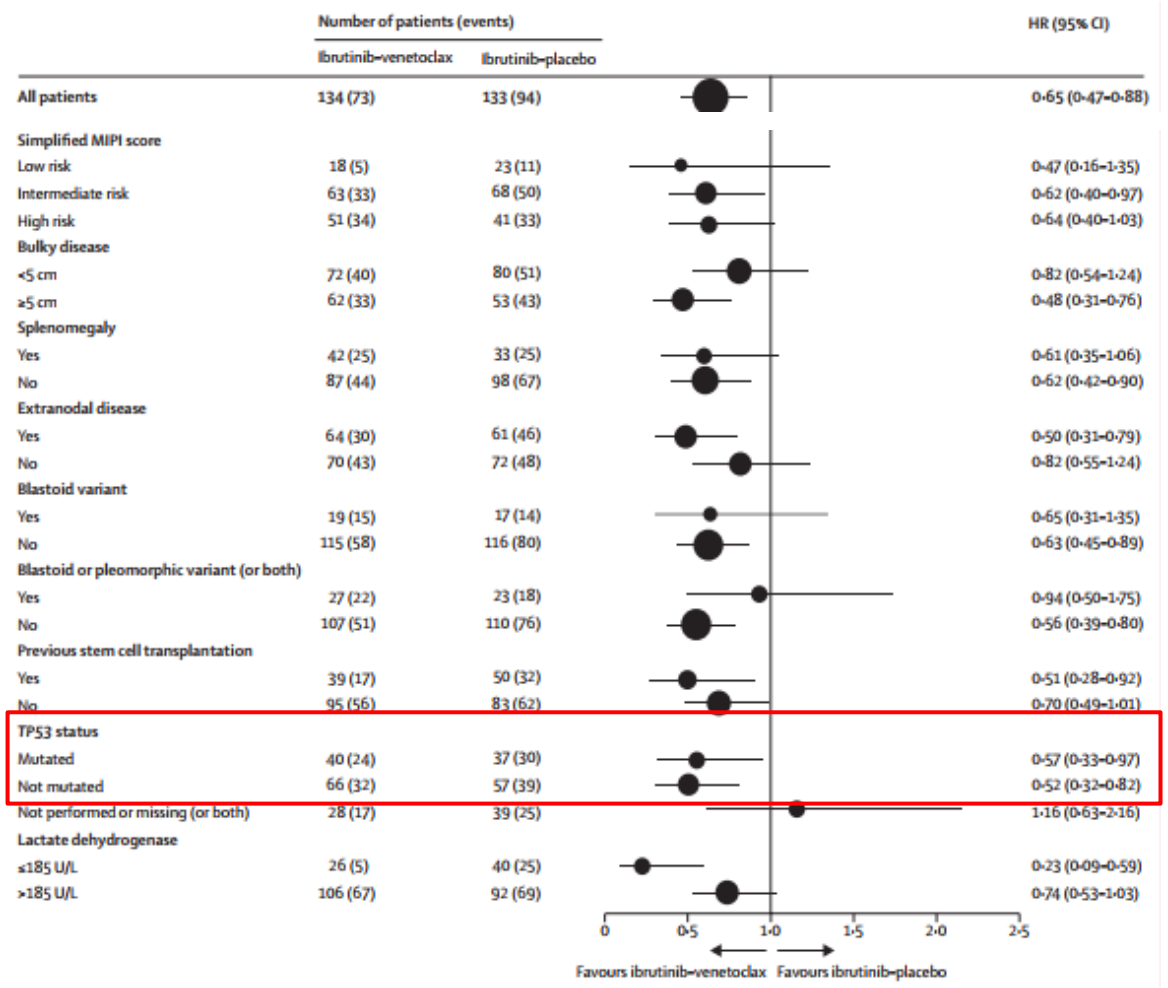
AE, n (%)	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=132
Grade ≥3 AEs	112 (84)	100 (76)
Serious AEs	81 (60)	79 (60)
AEs leading to discontinuation	41 (31)	48 (36)
Ibrutinib only	11 (8)	10 (8)
Venetoclax/placebo only	2 (1)	7 (5)
Both	28 (21)	31 (23)
AEs leading to dose reduction	48 (36)	29 (22)
Ibrutinib only	17 (13)	14 (11)
Venetoclax/placebo only	14 (10)	7 (5)
Both	17 (13)	8 (6)
AEs leading to death	22 (16)	18 (14)
Ibrutinib-related[a]	3 (2)	2 (2)
Venetoclax/placebo-related[a]	0	1 (1)
Tumor lysis syndrome		
Laboratory	7 (5)	3 (2)
Clinical	0	0

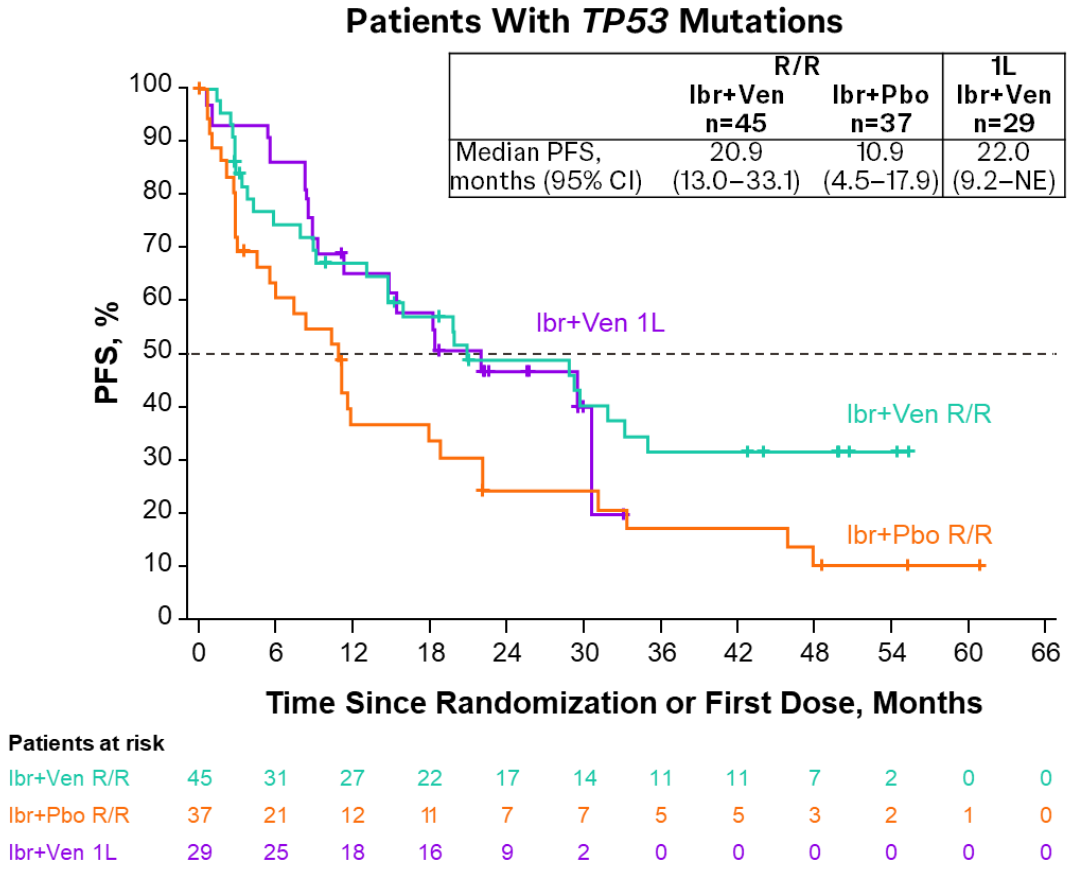
AE, n (%)	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=132
Most frequent any-grade AEs[b]		
Diarrhea	87 (65)	45 (34)
Neutropenia	46 (34)	19 (14)
Nausea	42 (31)	22 (17)
Fatigue	39 (29)	36 (27)
Anemia	30 (22)	16 (12)
Pyrexia	28 (21)	26 (20)
Cough	27 (20)	36 (27)
Muscle spasms	11 (8)	32 (24)
Most frequent grade ≥3 AEs[c]		
Neutropenia	42 (31)	14 (11)
Pneumonia	17 (13)	14 (11)
Thrombocytopenia	17 (13)	10 (8)
Anemia	13 (10)	4 (3)
Diarrhea	11 (8)	3 (2)
Leukopenia	10 (7)	0
MCL[d]	9 (7)	16 (12)
Atrial fibrillation	7 (5)	7 (5)
COVID-19	7 (5)	1 (1)
Hypertension	6 (4)	12 (9)

[d]Worsening of MCL not meeting protocol criteria for progressive disease

Michael Wang et al., *Blood* (2023) 142 (Supplement 2): LBA-2.

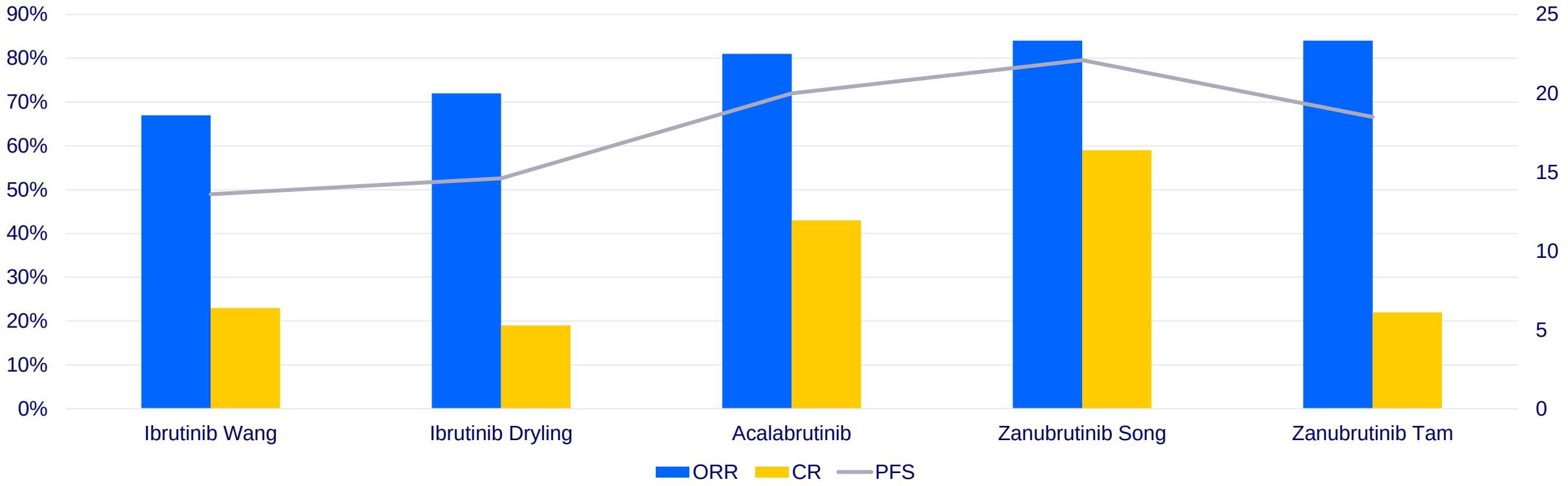
Ibrutinib + venetoclax seems to work better regardless of *TP53* Mutations





Michael Wang, abstract 7007 ASCO 2024; Lancet Oncol. 2025 Feb;26(2):200-213

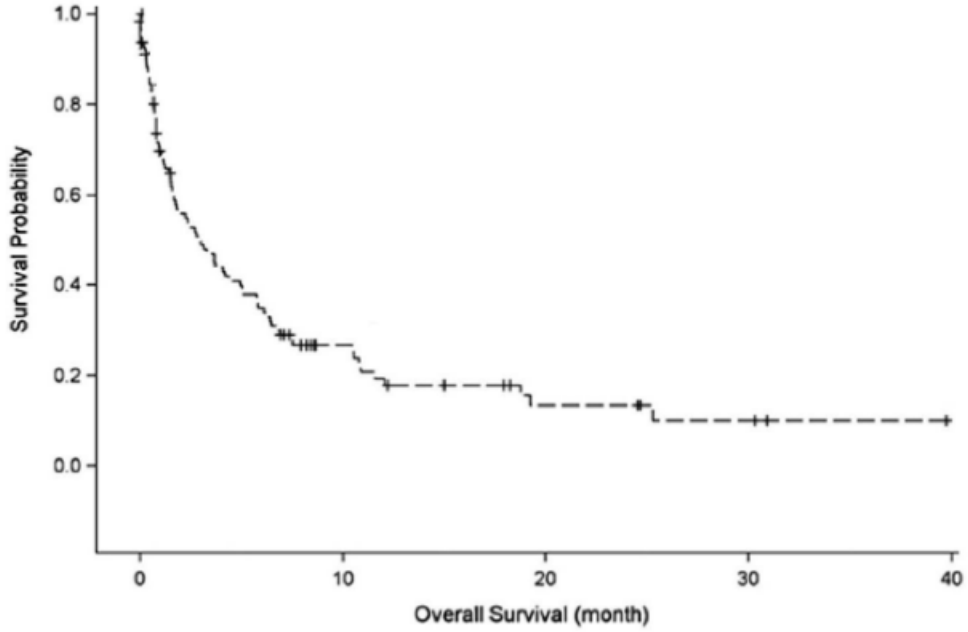
Ibrutinib, acalabrutinib and zanubrutinib

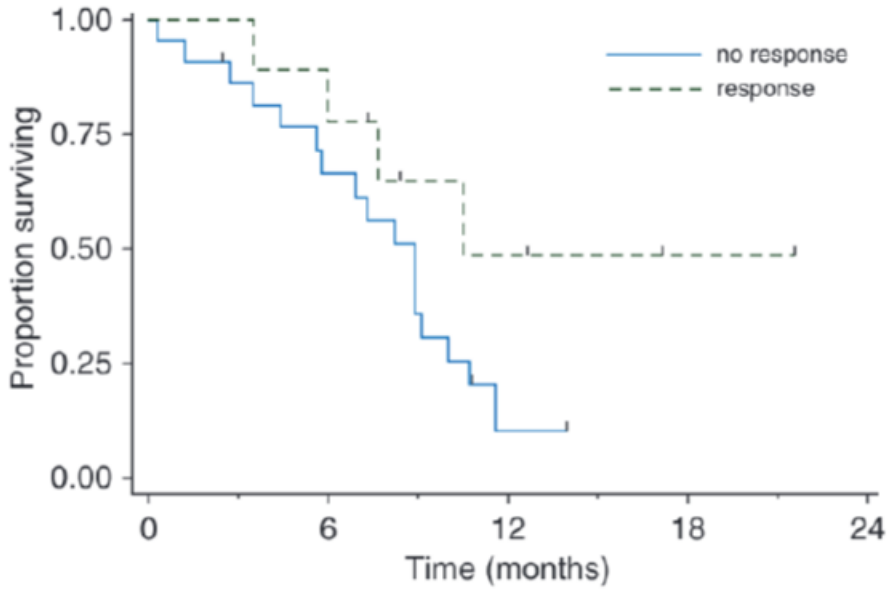


Ibrutininib Dryiling: 280 patients were included; 139 were treated with ibrutinib and 141 with temsirolimus;
Zanubrutinib Tam: 48 MCL patients were included in the study, 37 of whom had R/R MCL.

Outcomes in MCL are Poor Following Covalent BTK Inhibitor Progression

- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
- BTK C481-mutations are uncommon; bypass alterations & epigenetic changes implicated in some patients[7]
- *Overall survival* following covalent BTK inhibitor therapy is poor[3,4]





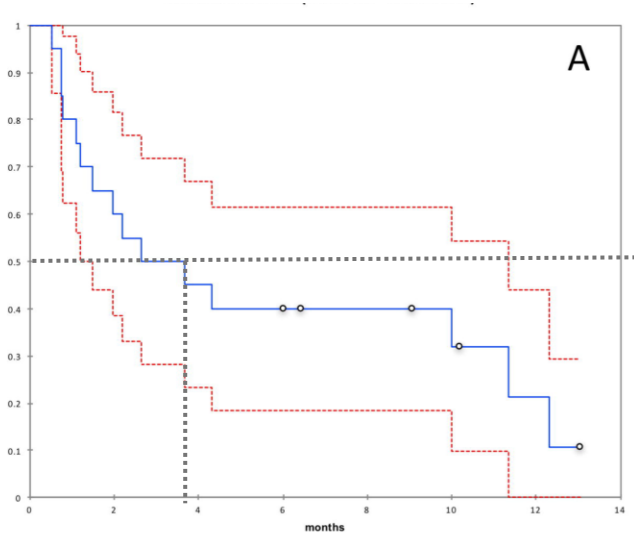
Figures adapted from Martin et al, 2016 (left) and Cheah et al, 2015 (right). [1]Hershkovitz-Rokah et al. *Br J. Haemtol.* 2018;181:306-19. [2]Wang et al. *N. Engl. J. Med.* 2013;369:507-16. [3]Cheah et al. *Ann. Oncol.* 2015;26:1175-79. [4]Martin et al. *Blood.* 2016;127:1559-63. [5]Dreyling et al. *Lancet.* 2016;387:770-8. [6]Epperla et al. *Hematol. Oncol.* 2017;35:528-35. [7]Ondrisova L and Mraz M, *Front. Oncol.* 2020;10. [8]O'Brien et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:648-57. [9]Byrd et al. *Blood.* 2019;130(Suppl 1):4326. [10]Tam et al. *Blood.* 2020;136:2038-50.

Wang et al, ASH 2021 abstract 381

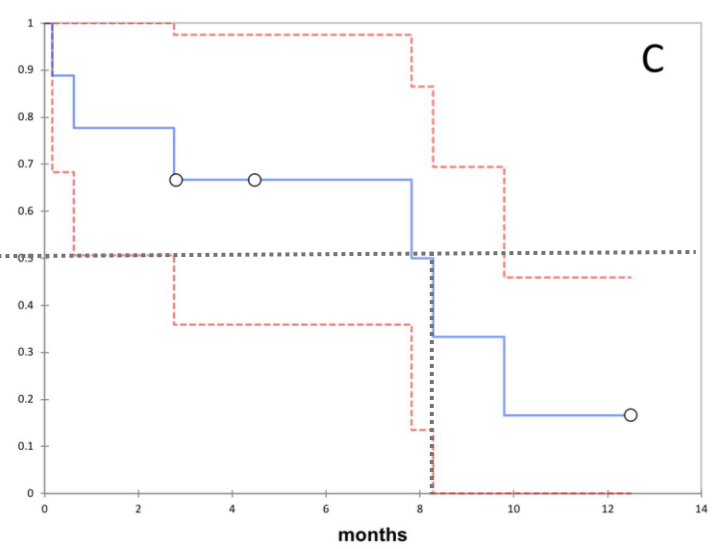
Venetoclax in those with BTKi-refractory
Still some respond, but limited DoR

UK CUP, n=20
ORR 53% with CRR 18%

mPFS = 3.2 mo

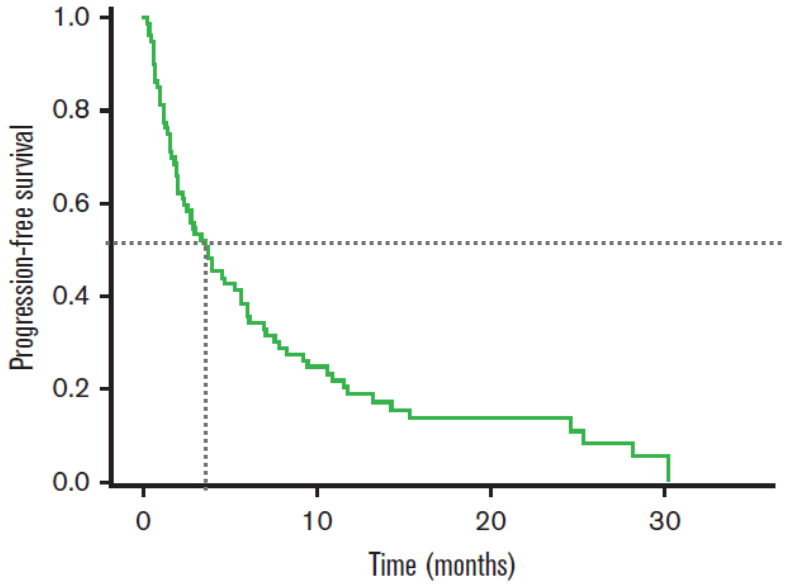


mDoR = 8.1 mo



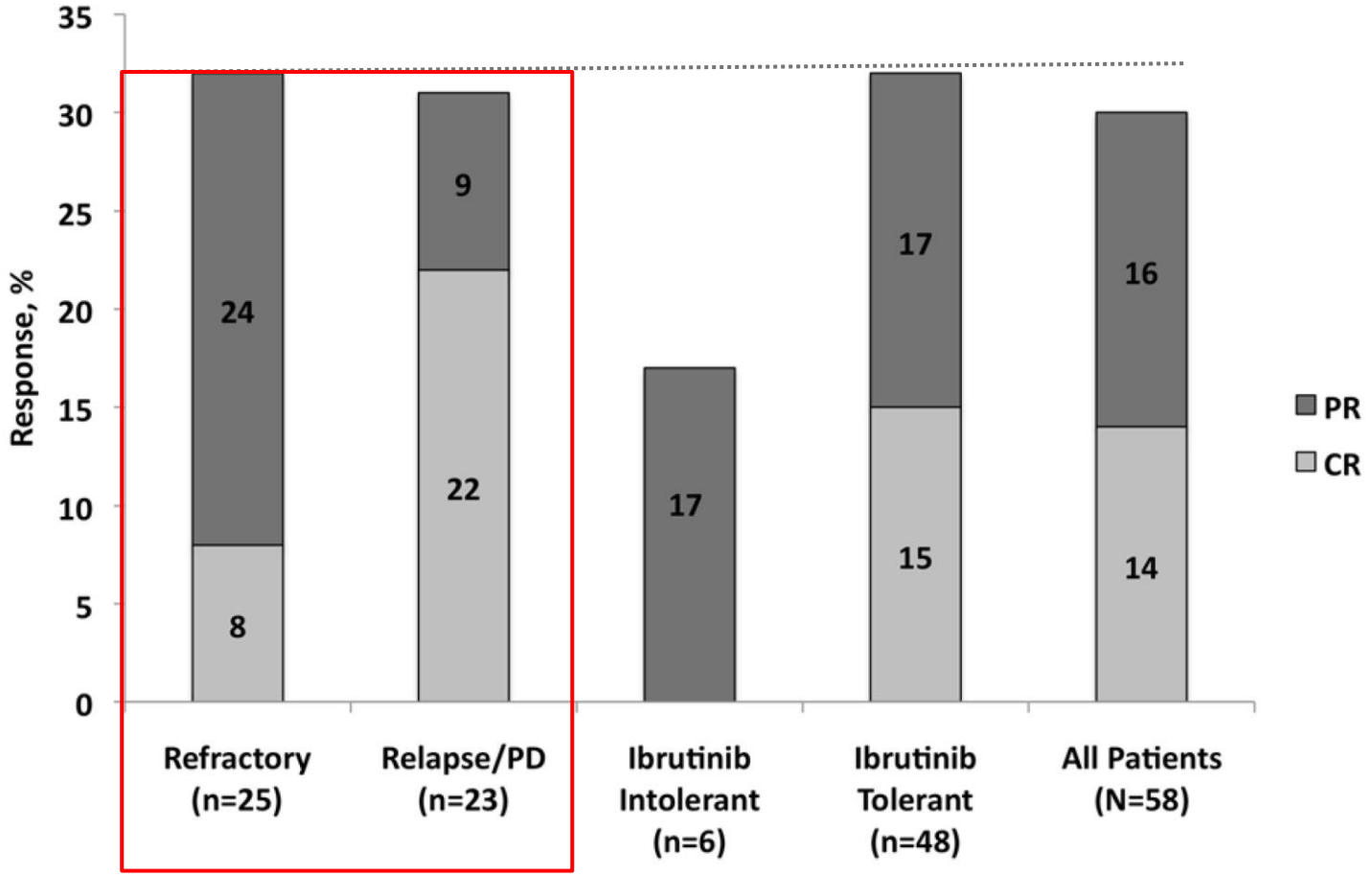
US multicenter retrospective study (n=81)
ORR 40%

Median PFS 3.7 mo



Eyre T, et al. Haematologica. 2019 Feb;104(2):e68-e71; Blood Adv, 7 (13) (2023), pp. 2983-2993

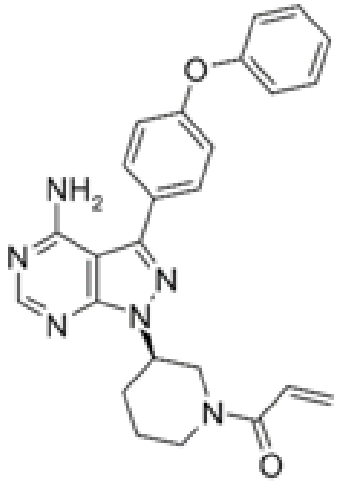
Observational study of lenalidomide in patients with rrMCL refractory/intolerant to ibrutinib (MCL-004)



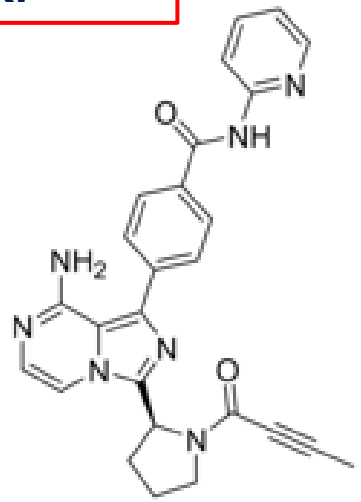
ORR < 30% with mDoR of 20 weeks

Wang et al., J Hematol Oncol 2017;10(1):171

Covalent BTKi

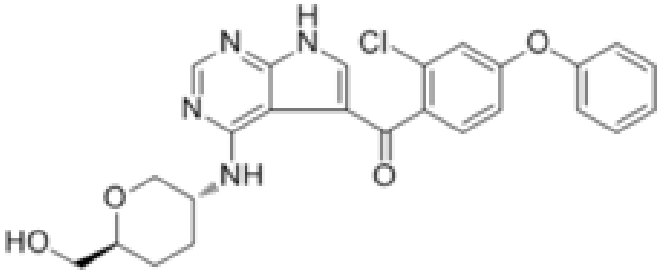


Ibrutinib

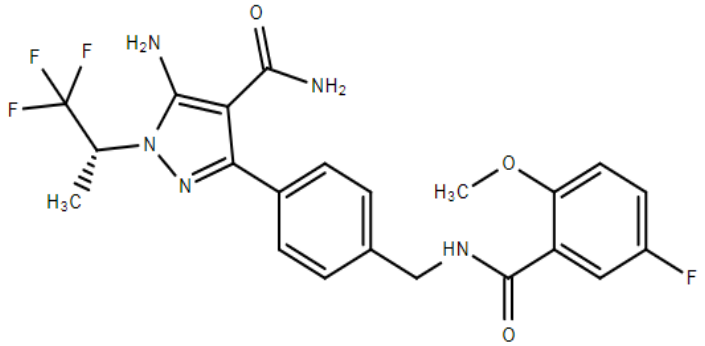


Acalabrutinib

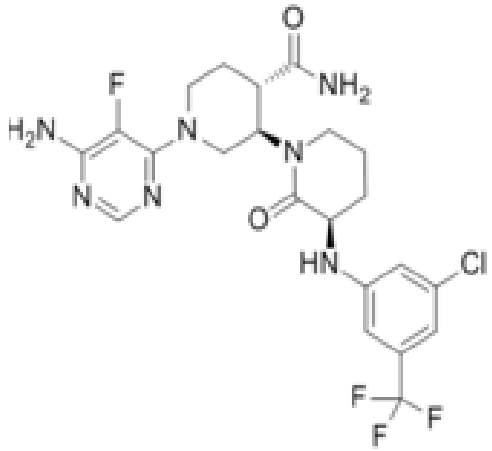
Non-covalent BTKi



ARQ-531
(nemtabrutinib)



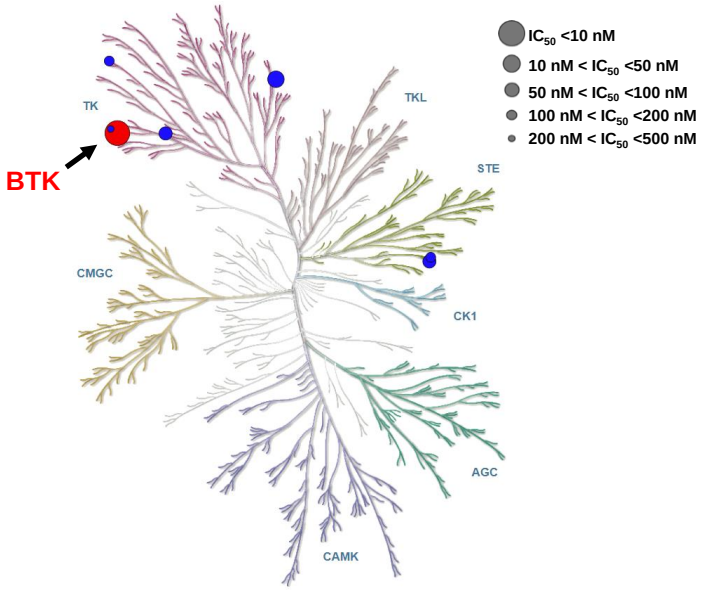
LOXO-305 (pirtobrutinib)



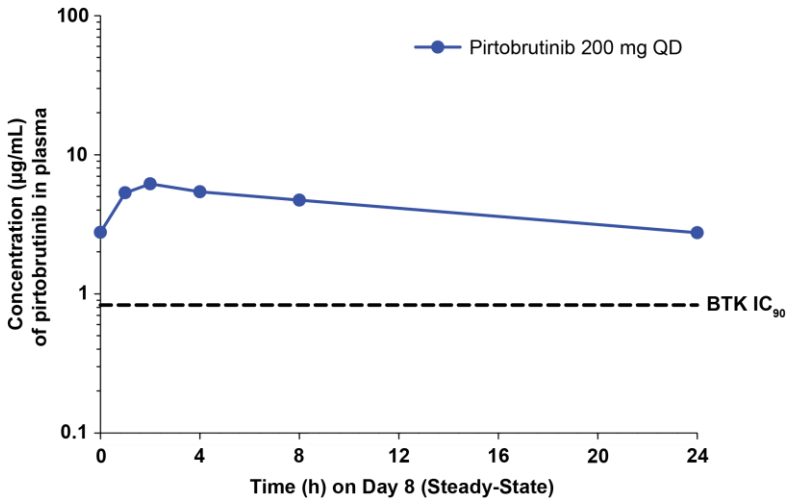
SNS-062
(vecabrutinib)

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

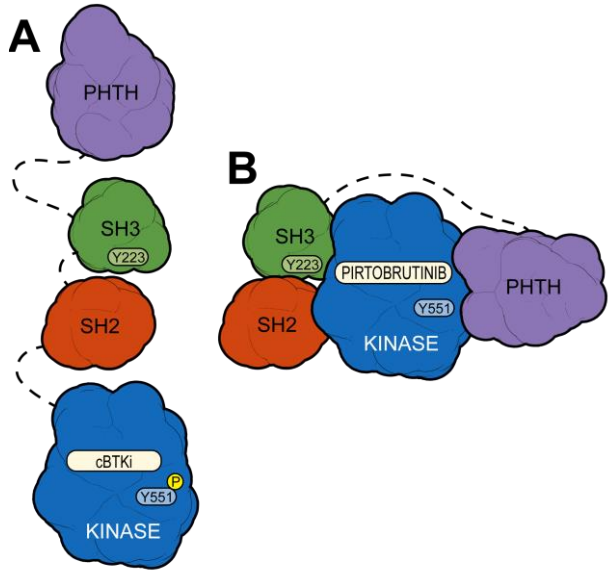
Highly selective for BTK[3,7]



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.

J Clin Oncol. 2023 Aug 20;41(24):3988-3997

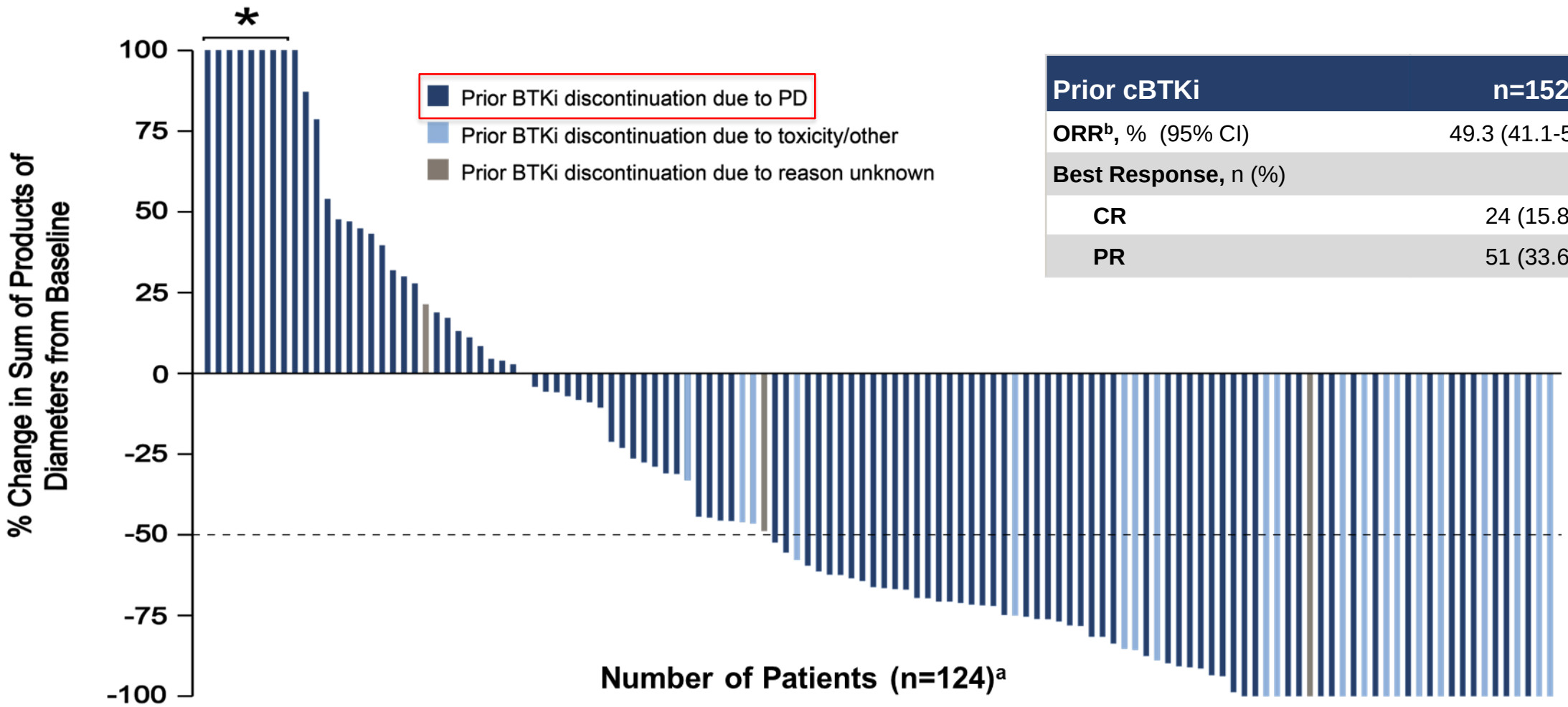
Baseline Characteristics of Patients with MCL

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Median age, years (range)	70 (46-88)	67 (60-86)
Male, n (%)	120 (79)	10 (71)
Histology, n (%)		
Classic/leukemic	120 (79)	11 (79)
Pleomorphic/Blastoid	32 (21)	3 (21)
ECOG PS, n (%)		
0	93 (61)	5 (36)
1	56 (37)	8 (57)
2	3 (2)	1 (7)
sMIPI score, n (%)		
Low risk (0-3)	30 (20)	3 (21)
Intermediate risk (4-5)	79 (52)	5 (36)
High risk (6-11)	43 (28)	6 (43)
Bulky Lymphadenopathy (cm), n (%)		
<5	94 (62)	8 (57)
≥5	36 (24)	5 (36)
No Measurable Lymph Node	22 (15)	1 (7)
Bone marrow involvement, n (%)		
Yes	81 (53)	4 (29)
No	71 (47)	10 (71)
Median number of prior lines of systemic therapy, n (range)	3 (1-9)	2 (1-3)

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Prior therapy, n (%)		
BTK inhibitor	152 (100)	0 (0)
Anti-CD20 antibody	147 (97)	14 (100)
Chemotherapy	137 (90)	14 (100)
Immunomodulator	26 (17)	1 (7)
Stem cell transplant	33 (22)	7 (50)
Autologous	30 (20)	7 (50)
Allogeneic	7 (5)	0 (0)
BCL2 inhibitor	24 (16)	0 (0)
CAR-T	13 (9)	0 (0)
PI3K inhibitor	6 (4)	1 (7)
Reason discontinued any prior BTKi[a], n (%)		
Progressive disease	128 (84)	-
Toxicity / Other	21 (14)	-
Unknown	3 (2)	-
TP53 Mutation status, n (%)		
Yes	30 (20)	3 (21)
No	30 (20)	4 (29)
Missing	92 (61)	7 (50)
Ki-67 index, n (%)		
<30%	18 (12)	2 (14)
≥30%	45 (30)	6 (43)
Missing	89 (59)	6 (43)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. Total percentages may not sum to 100% due to rounding.

Pirtobrutinib Efficacy in Patients with MCL who Received Prior cBTKi



Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

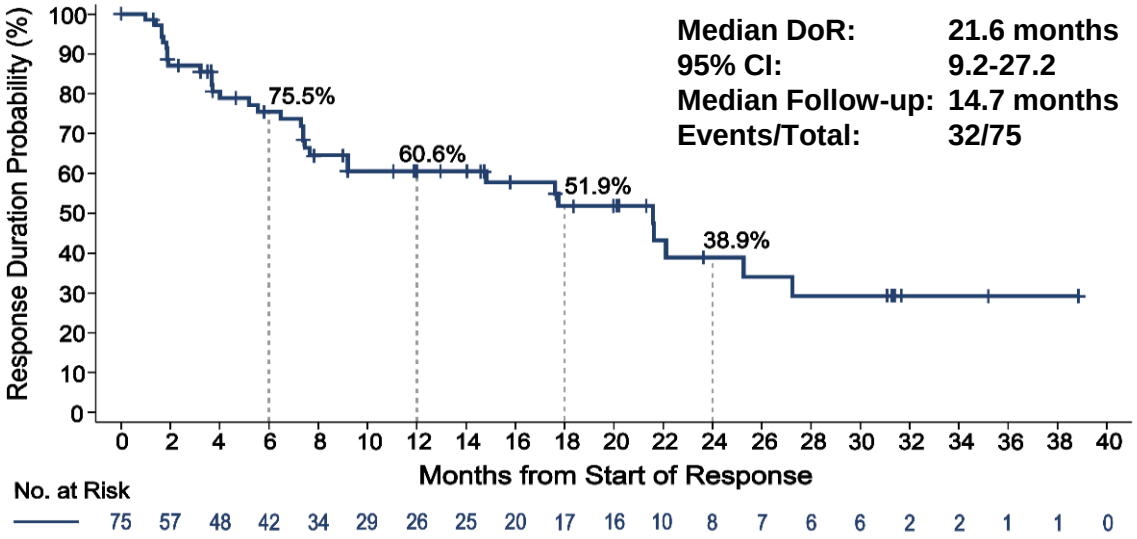
Median Time to First Response was 1.8 months (range: 0.8-13.8)

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Patients with >100% increase in SPD. [a]Data for 28/152 patients who received prior cBTKi are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [b]ORR is the number of patients with best response of CR or PR divided by the total number of patients; 13 patients with a best response of not evaluable (NE) are included in the denominator. Response status per Lugano 2014 criteria based on IRC assessment.

Cohen et al.; ASH 2023

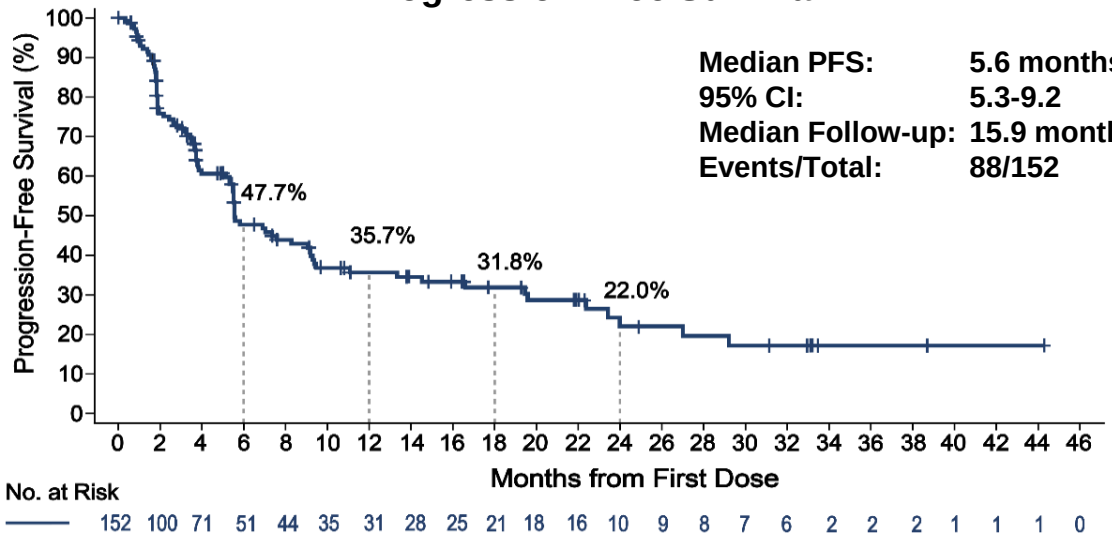
Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL

Duration of Response



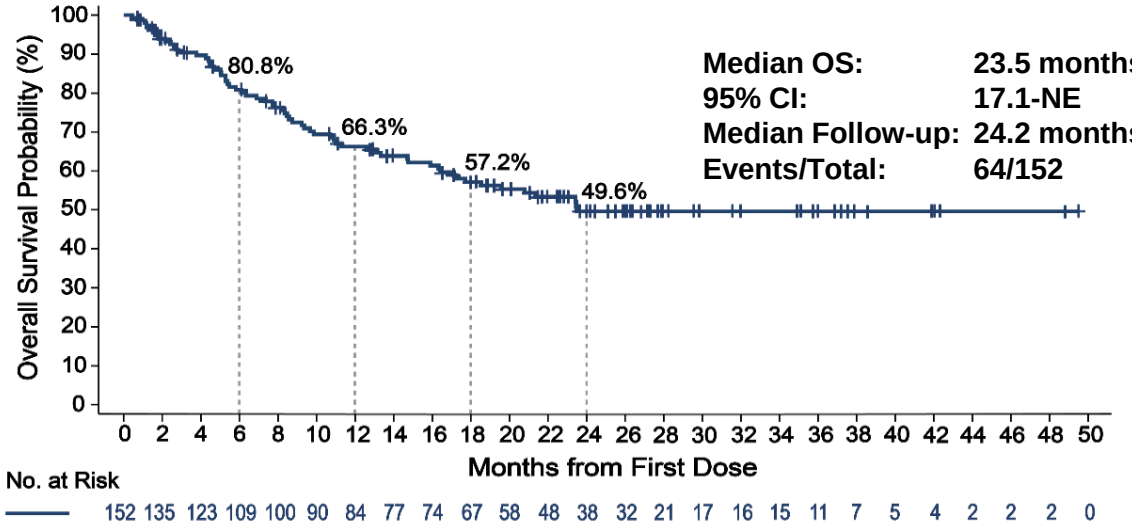
Median DoR: 21.6 months
95% CI: 9.2-27.2
Median Follow-up: 14.7 months
Events/Total: 32/75

Progression-Free Survival



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

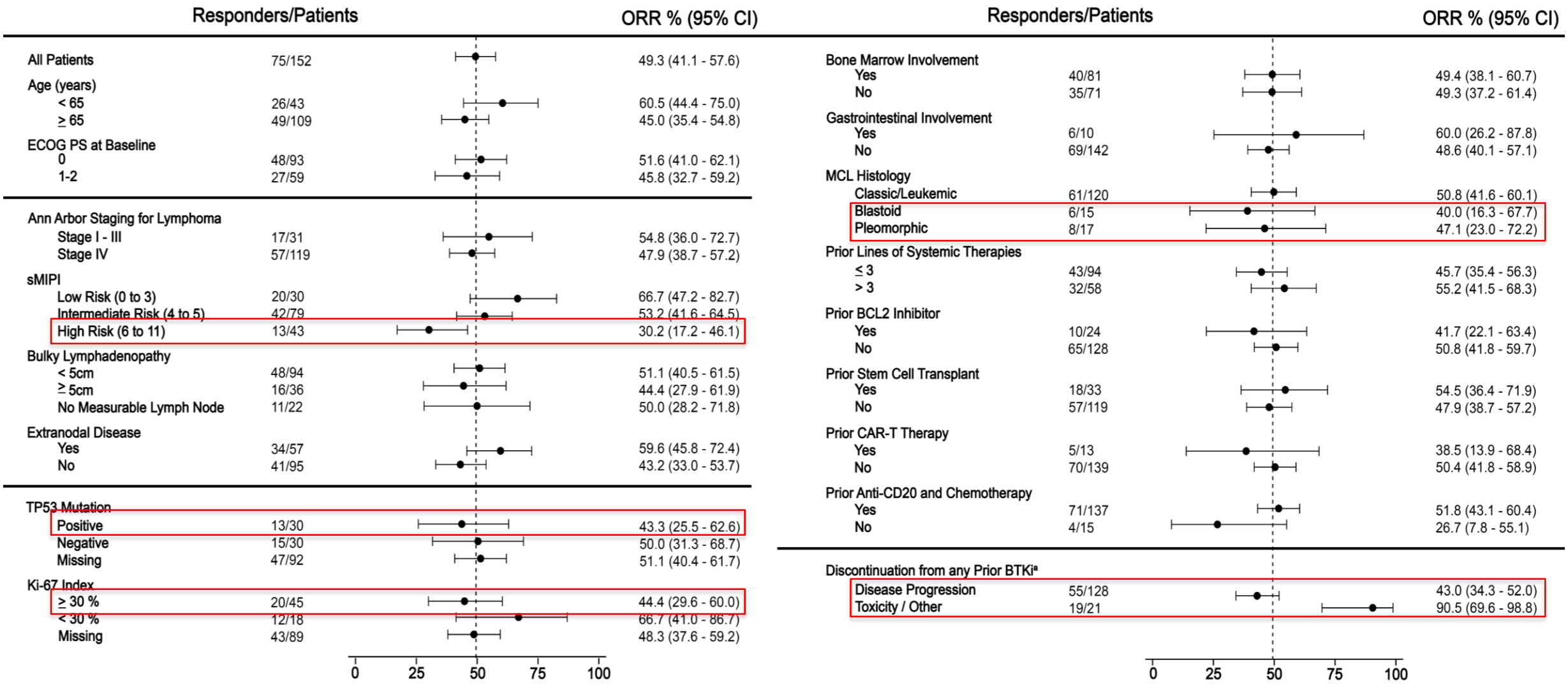
Overall Survival



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

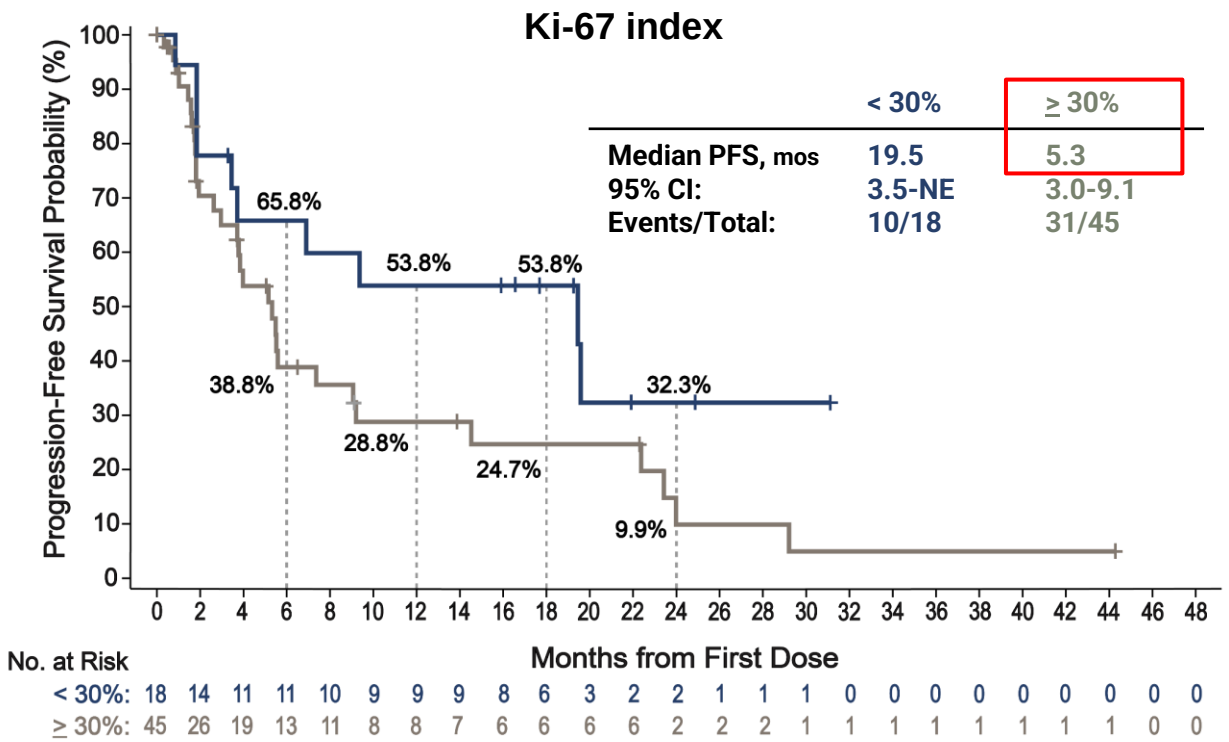
Cohen et al.; ASH 2023

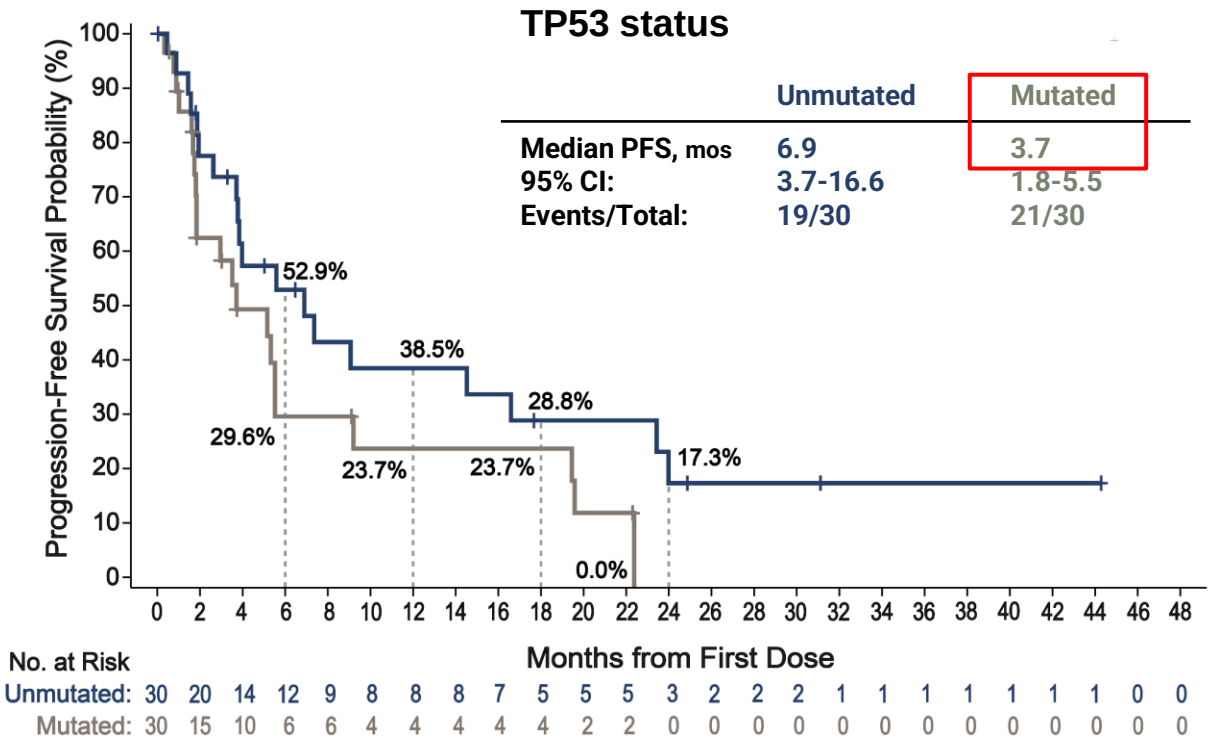
Overall Response Rate in Prior cBTKi Patients with MCL, Including High-Risk Subgroups



Data reported in the forest plot is overall response rate by prespecified patient characteristic subgroups. Two-sided 95% CI were calculated using the exact binomial distribution. [a]In the event more than one reason was noted for discontinuation, disease progression took priority. Response status per Lugano 2014 criteria based on IRC assessment.

Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL by High-Risk Subgroups





	Median DoR (95% CI)	Median OS (95% CI)
Ki-67		
< 30%	17.7 (1.9-N.E.)	N.E. (9.4-N.E)
≥ 30%	21.6 (5.6-27.2)	23.4 (13.1-N.E.)

	Median DoR (95% CI)	Median OS (95% CI)
TP53		
Unmutated	14.8 (1.9-N.E.)	N.E (10.7-N.E.)
Mutated	17.6 (1.7-N.E.)	15.9 (7.8-N.E)

Cohen et al.; ASH 2023

Pirtobrutinib Safety Profile in MCL Patients

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Platelet Count Decreased	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

Median time on treatment was 5.5 months for the MCL cohort
Discontinuations due to TRAEs occurred in 3% (n=5) of patients with MCL
Dose reductions due to TRAEs occurred in 5% (n=8) of patients with MCL

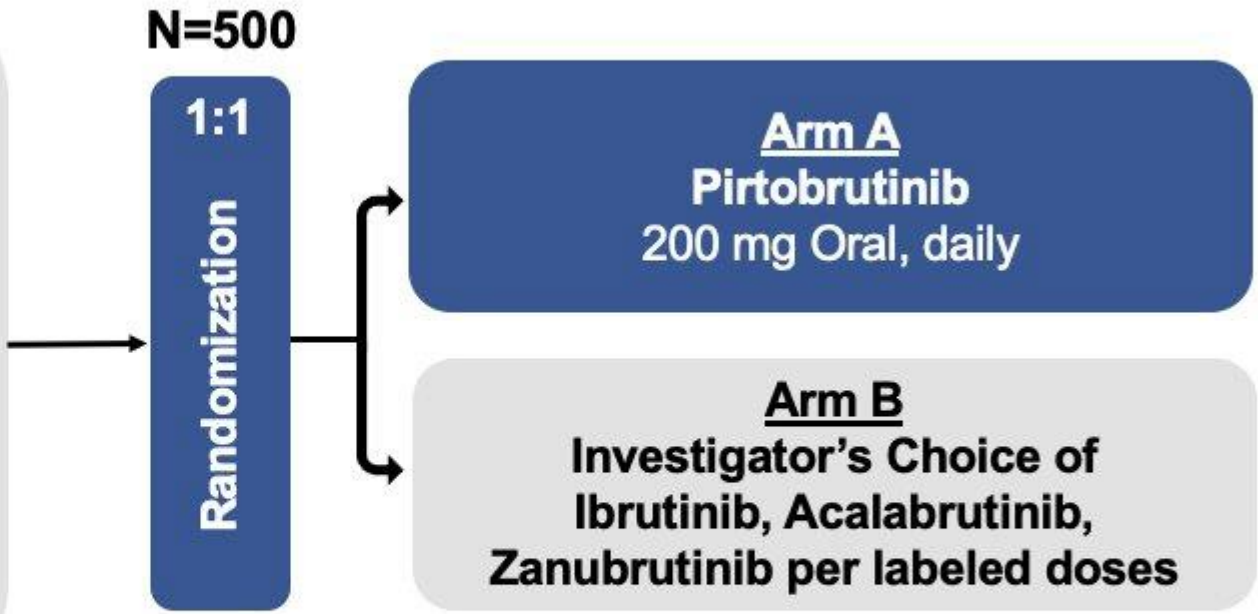
[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of all preferred terms including infection and COVID-19. [c]Aggregate of contusion, bone contusion, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hemorrhage or hematoma. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, treatment-related AEs leading to discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).

Cohen et al.; ASH 2023

BRUIN MCL-321 is a randomized, open-label, global, phase 3 study (NCT04662255)

Key Inclusion Criteria

- Confirmed diagnosis of MCL
- ≥1 prior (non-BTKi) line of systemic therapy for MCL
- Measurable disease per Lugano criteria
- Radiographically / histologically confirmed PD on the most recent line of therapy or relapse
- ≥18 years of age and ECOG 0-2



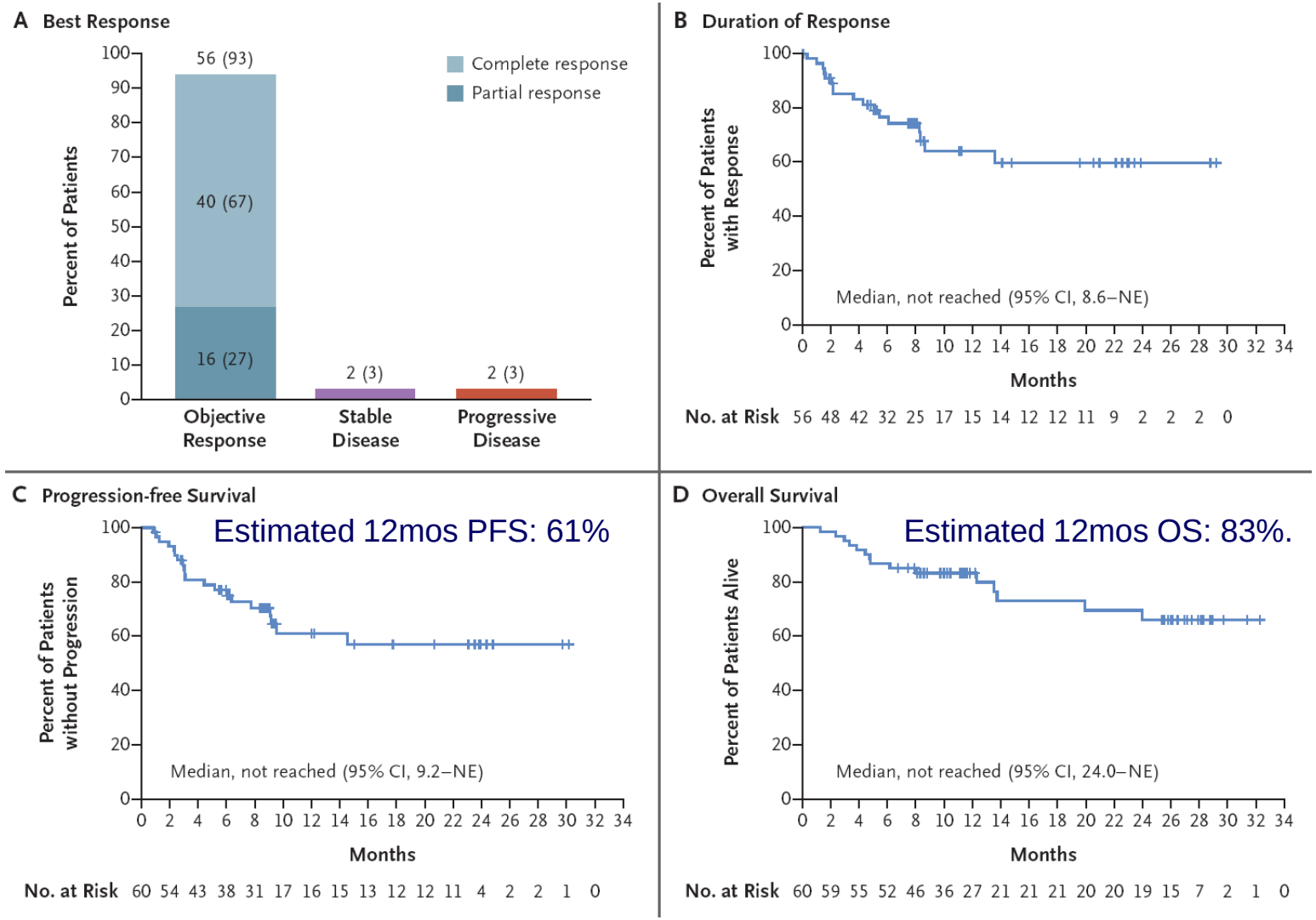
Stratification factors

- sMIPI risk group (low / intermediate vs high)
- Intended comparator BTK inhibitor (ibrutinib vs acalabrutinib / zanubrutinib)
- Number of prior lines of therapy (1 vs ≥ 2)

CAR T-cell therapy in R/R MCL (ZUMA-2)

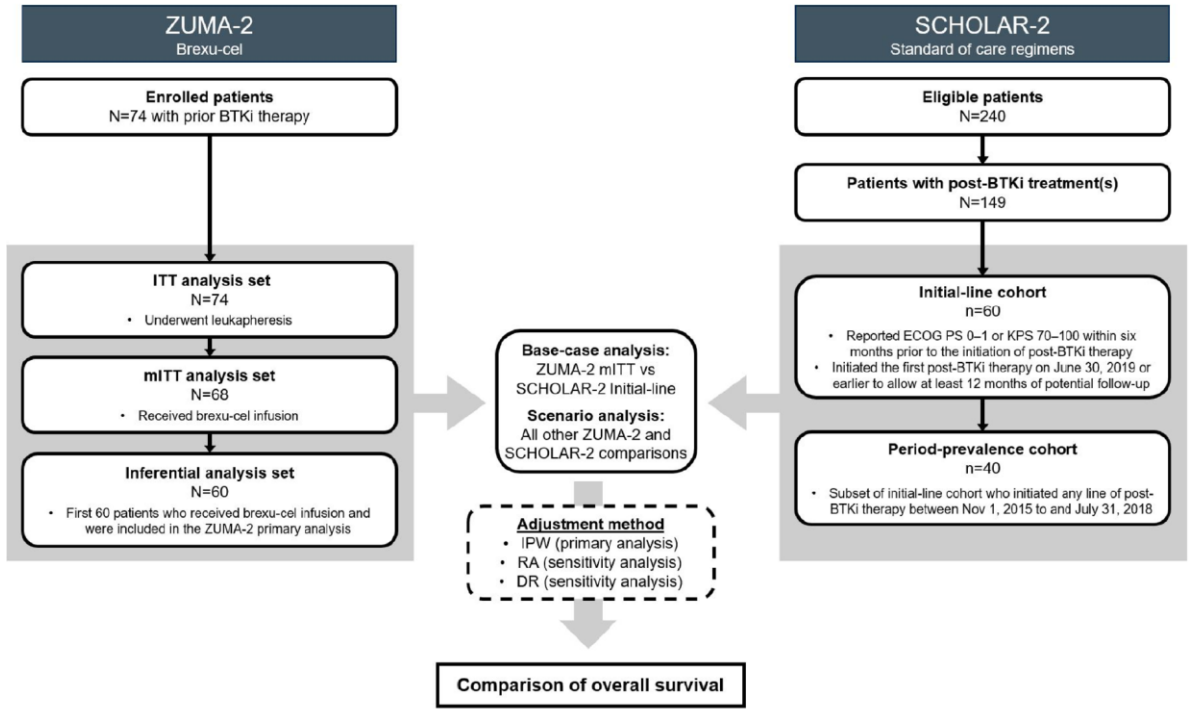
Brexucabtagene autoleucel (Tecartus®, KTE-X19)

- During manufacturing, B-cell depletion is performed before viral transduction and followed by an additional positive T-cell selection for enrichment
- N=68 pts
  - 17 patients (25%) had blastoid histology, 6 had *TP53* mt, and 32 exhibited Ki-67 ≥ 50%.
  - median 3 prior LOT (81% with ≥ 3 LOT).
  - Previous BTKi therapies: 100%, 72% refractory to BTKi.

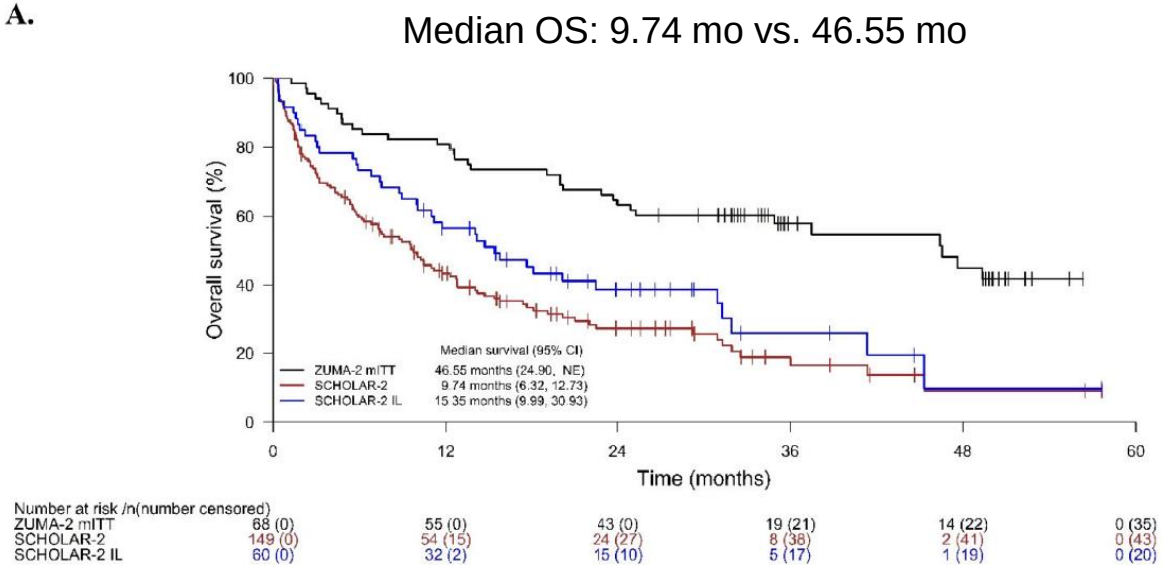


Wang et al., N Engl J Med 2020;382:1331-42.

Indirect treatment comparison of brexucabtagene autoleucel (ZUMA-2) versus standard of care (SCHOLAR-2) in relapsed/ refractory mantle cell lymphoma



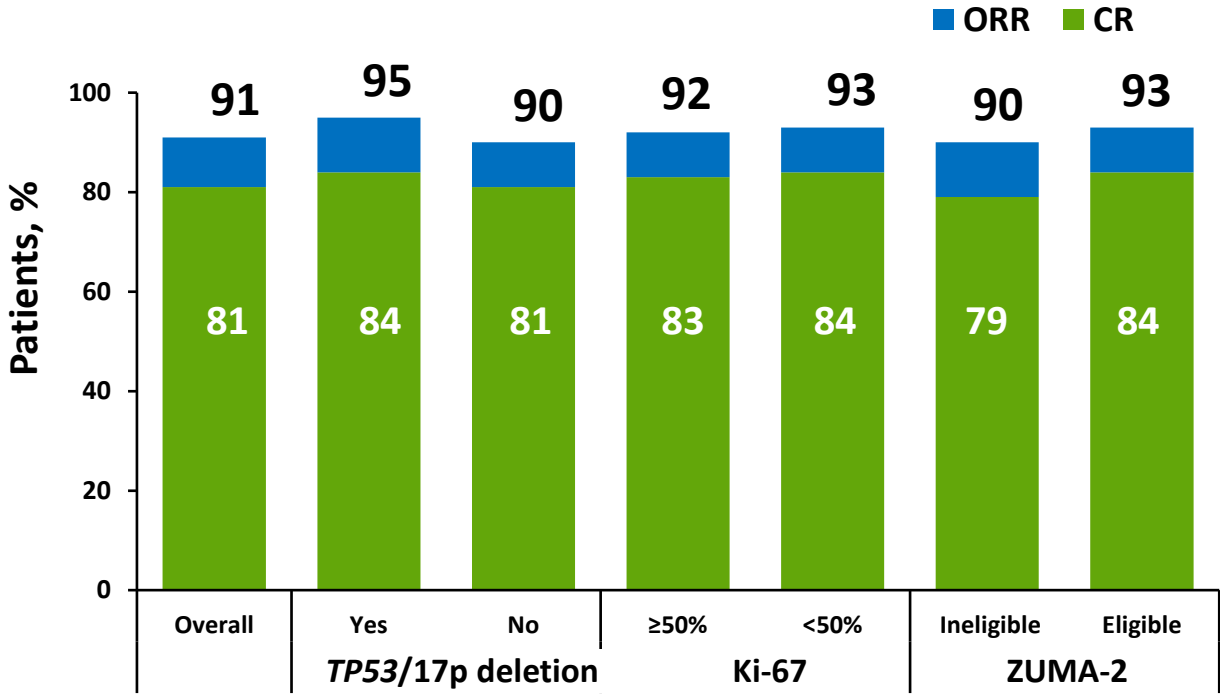
Median OS: 9.74 mo vs. 46.55 mo



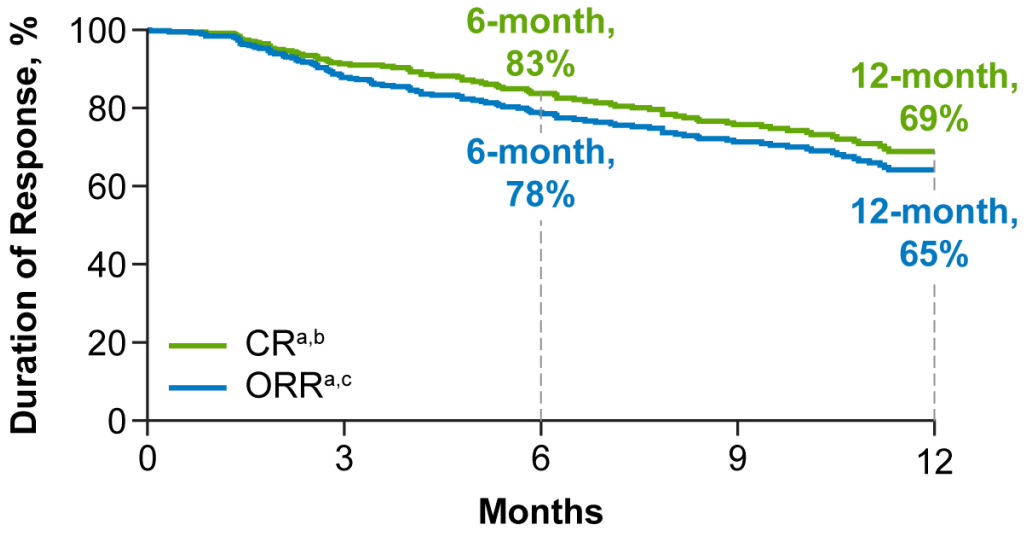
Leuk Lymphoma. 2024 Jan;65(1):14-25

Real world outcomes of Brexu-cel from CIBMTR

ORR and CR Rate



Kaplan–Meier Estimates for DOR

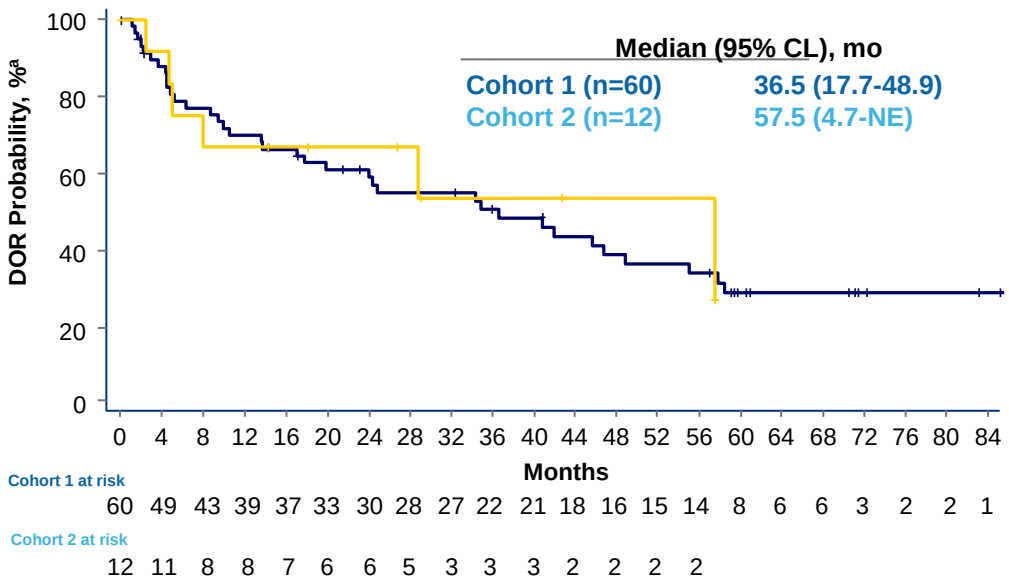


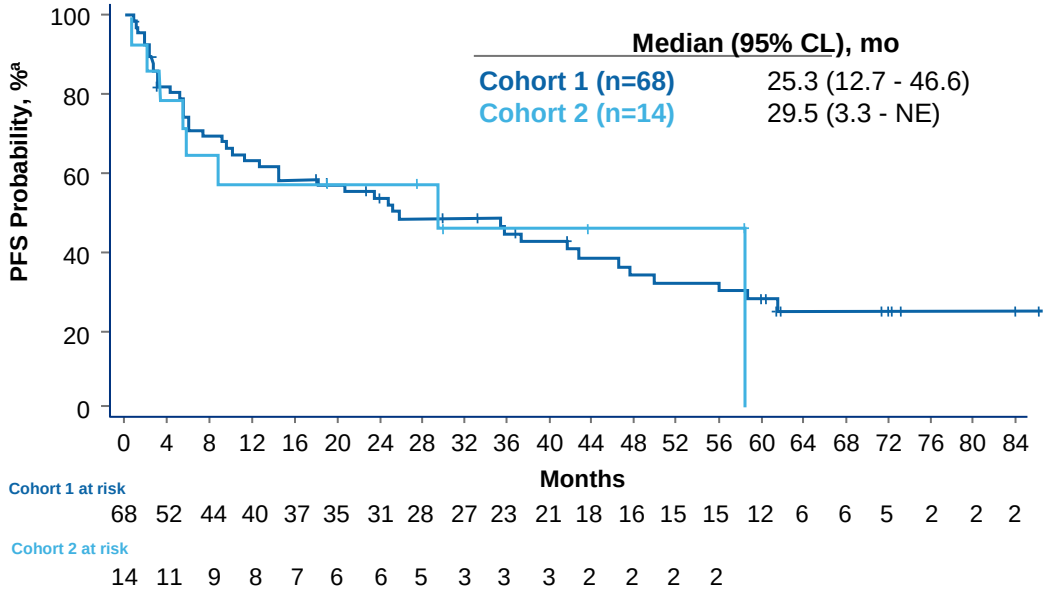
No. at risk					
Patients with CR	347	290	209	168	71
Patients with ORR	388	311	219	176	75

- ORR and CR rates were consistent across high-risk subgroups
- Median DOR was not yet reached

[a] Subsequent cellular therapy and HCT without previously documented relapse or disease progression were censored; median follow-up was 12.3 months (range, 2.9-28.6). [b] Among patients who achieved CR as best response.
[c] Among patients who achieved CR/PR as best response.
CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplant; ORR, overall response rate; PR, partial response.

ZUMA-2 5-year outcomes



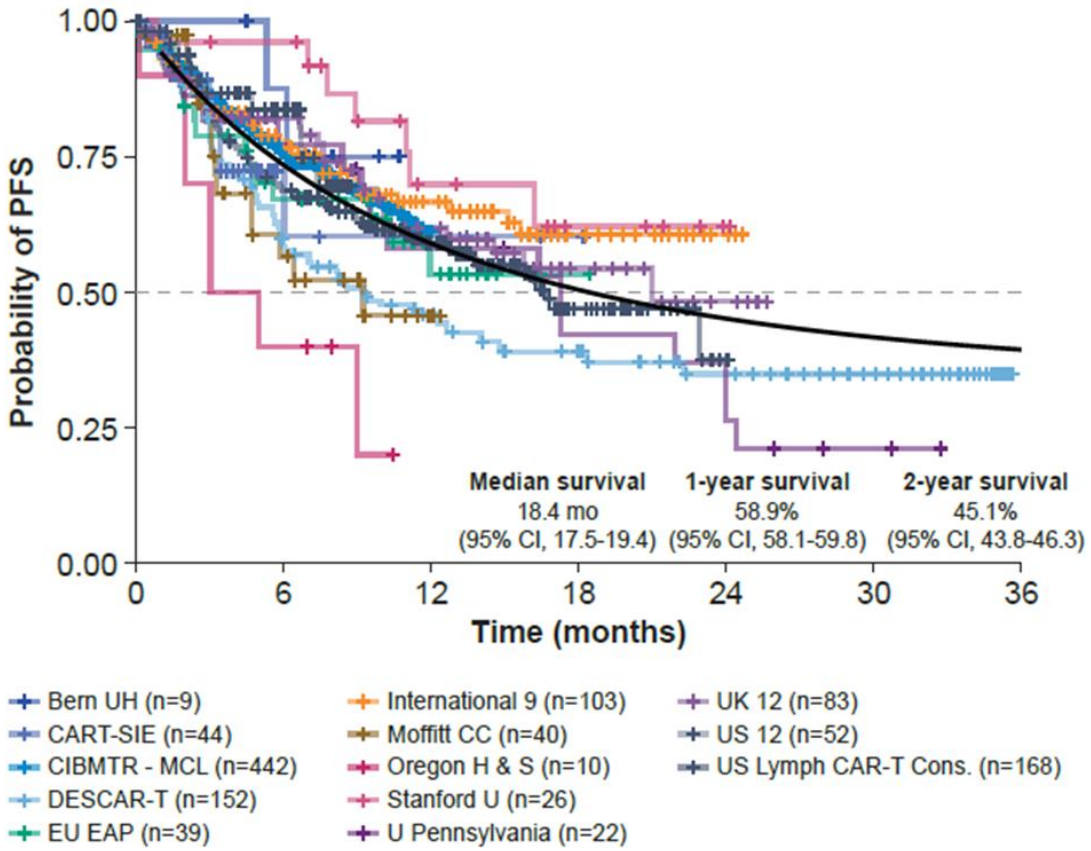


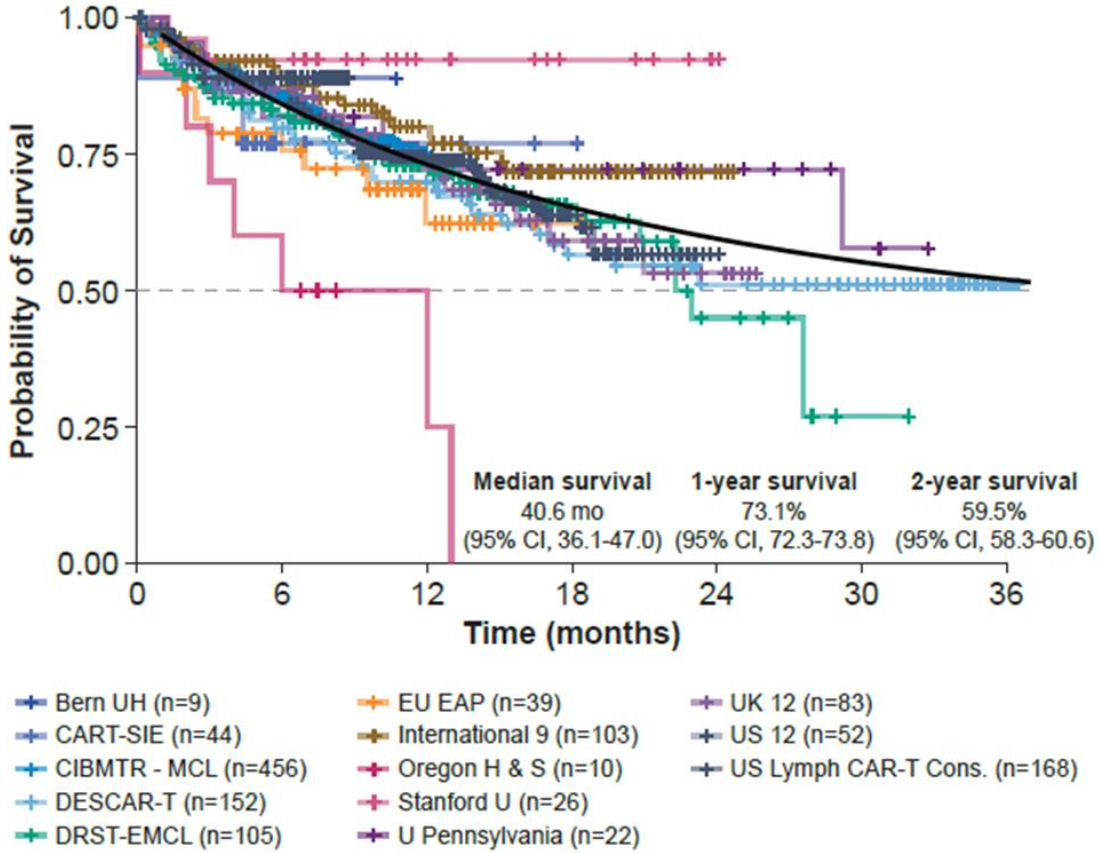
- In Cohort 1, median investigator-assessed DOR was 36.5 months (95% CI, 17.7-48.9; n=60) with 17 patients in ongoing response at data cutoff, all CR

- Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1

Wang *et al.* ASH 2024 (Abstract 4388; poster/oral presentation)

Real-World Outcomes of Brexu-cel in Patients with RRMCL: A Systematic Literature Review and Meta-Analysis



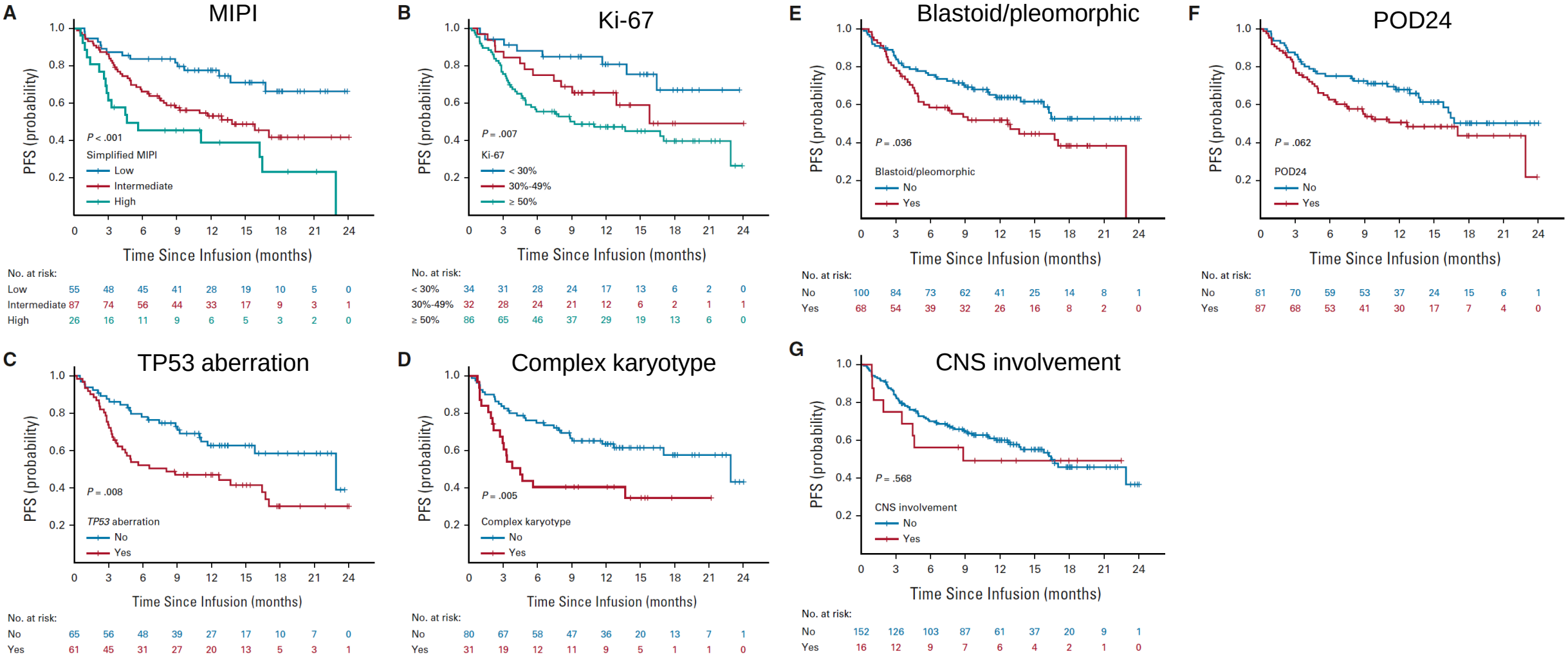


The estimated **median PFS** was **18.4** months
The **1-year PFS** probability was **58.9%**
The **2-year PFS** probability was **45.1%**

The estimated **median OS** was **40.6** months
The **1-year OS** probability was **73.1%**
The **2-year OS** probability was **59.5%**

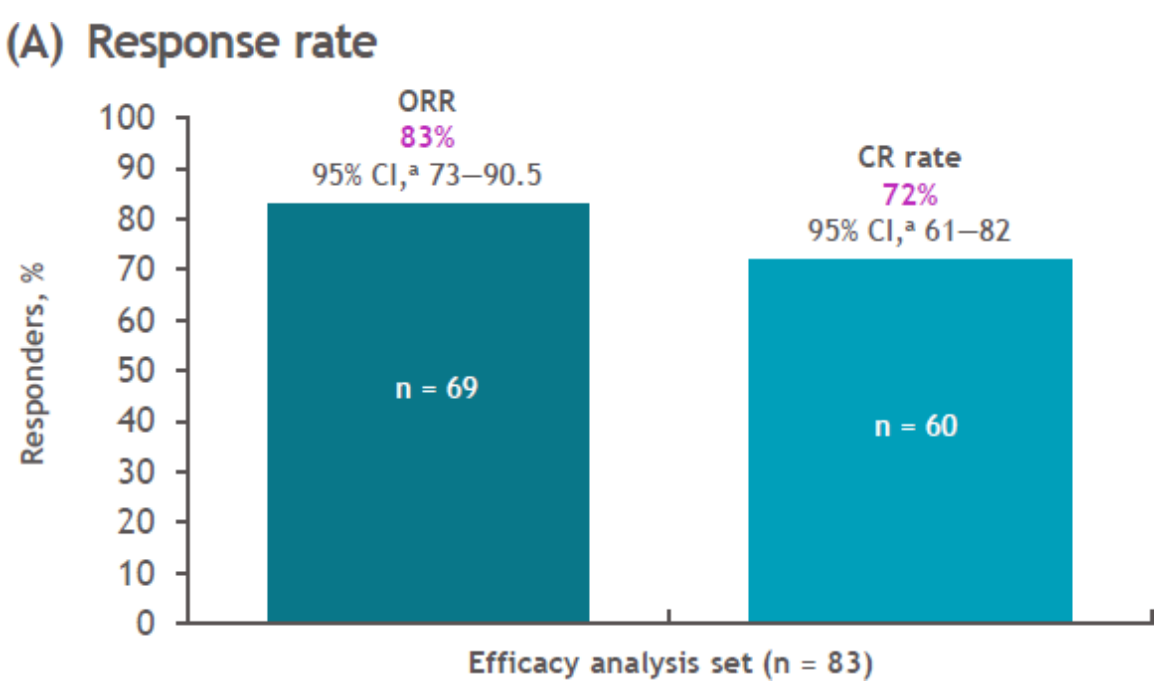
Oluwole *et al.* EHA 2025 (Abstract PF954; poster presentation)

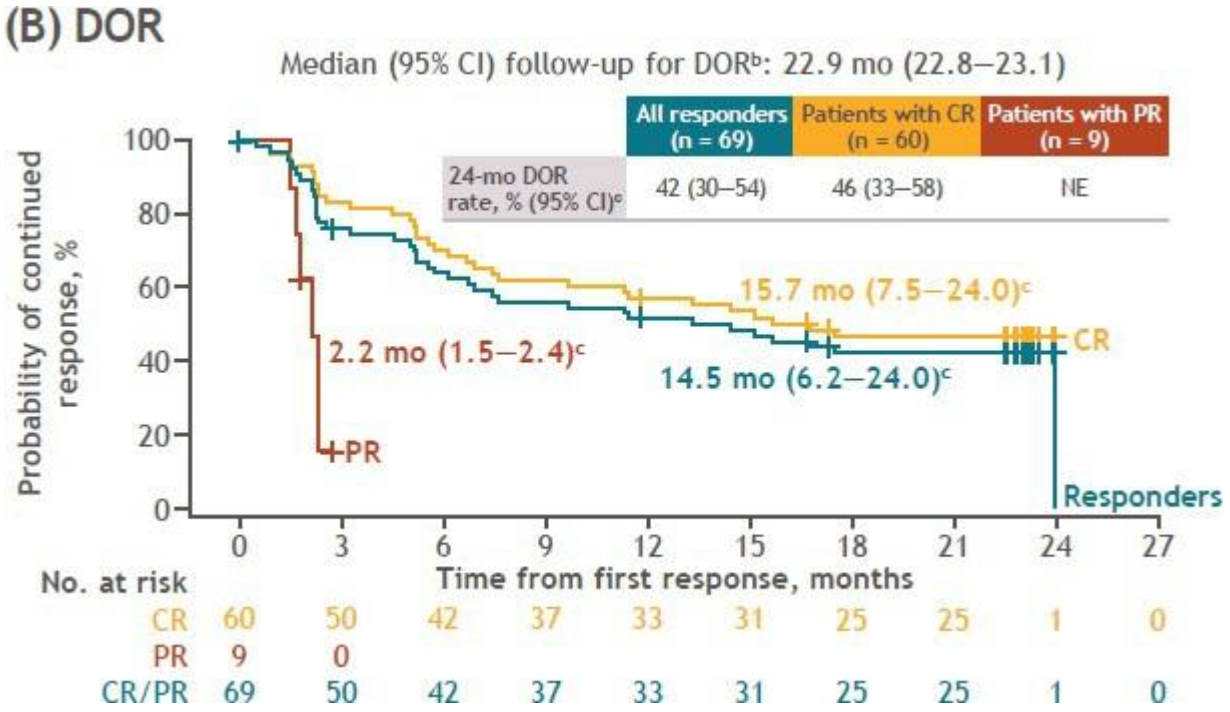
Brexu-cel for RRMCL in Standard-of-Care Practice: Results From the US Lymphoma CAR T Consortium



J Clin Oncol. 2023 May 10;41(14):2594-2606

Liso-cel for MCL (Transcend NHL-001)





- Liso-cel continued to show clinically meaningful and durable disease control with high efficacy, including unchanged response rates, durable responses (**Figure 3**), and sustained PFS (**Figure 4**) and OS (**Figure 5**), consistent with primary analysis results[1]

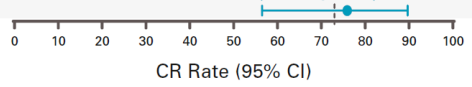
All percentages are rounded to whole numbers except those with ".5%". Data on KM curves are expressed as median (95% CI).
[a]Two-sided 95% exact Clopper-Pearson CIs; [b]Reverse KM was used to obtain median follow-up and its 95% CI; [c]KM method was used to obtain 2-sided 95% CIs.
CI, confidence interval; KM, Kaplan-Meier; NE, not evaluable.

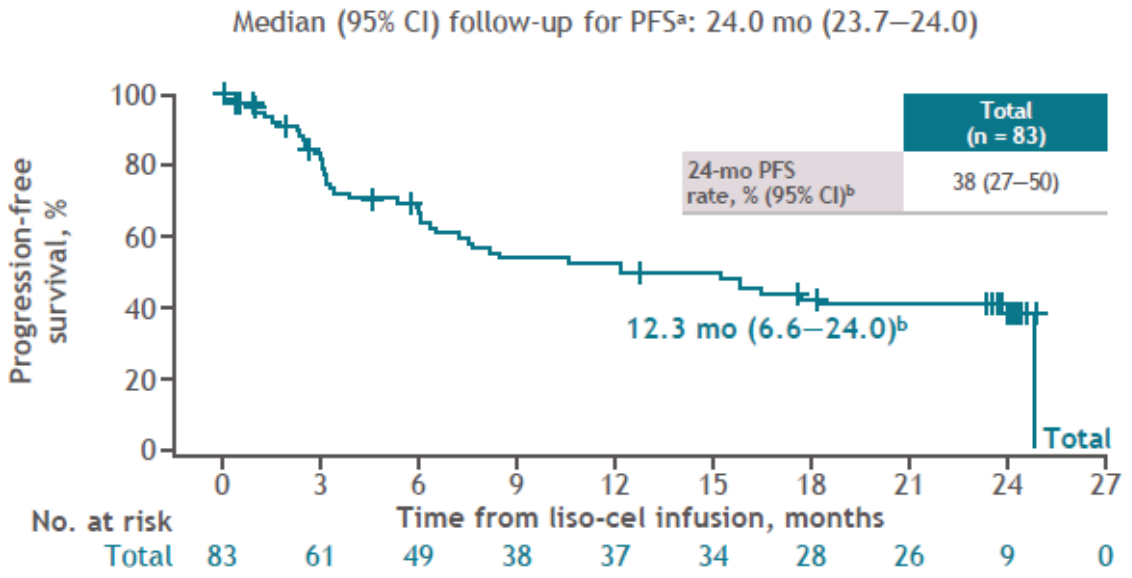
1. Wang M, et al. *J Clin Oncol* 2024;42:1146–1157.

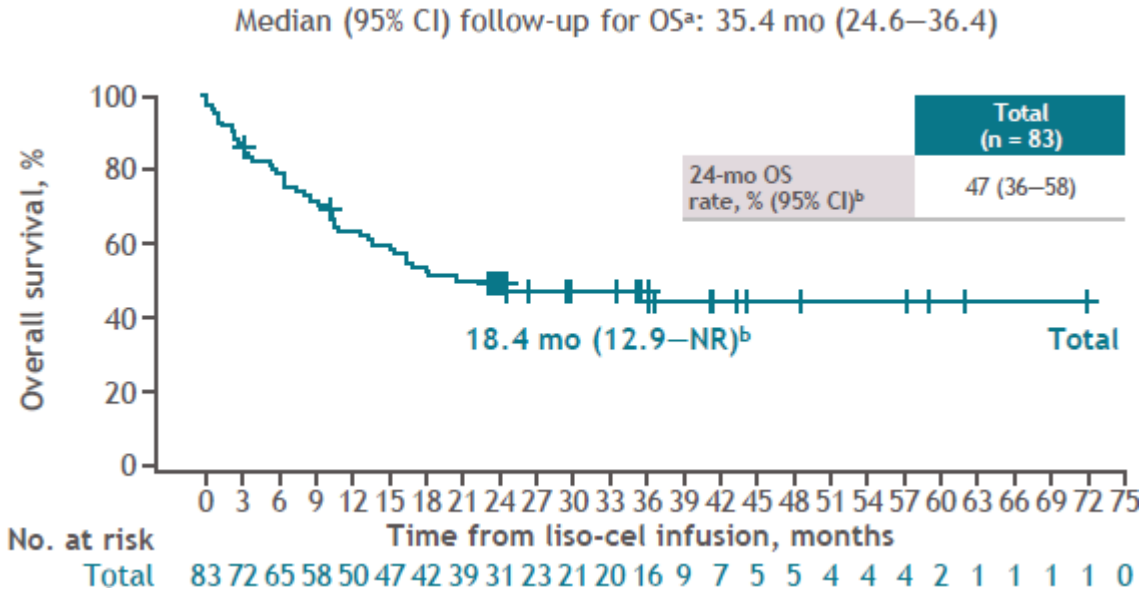
Wang M, et al. ASTCT 2025. Poster number 240

Liso-cel for MCL (Transcend NHL-001)

Characteristic	Evaluable Patients (n)	Patients With CR (n)	CR Rate (95% CI)
Age, years			
≥65	60	45	75.0 (62.1 to 85.3)
<65	23	15	65.2 (42.7 to 83.6)
≥75	16	11	68.8 (41.3 to 89.0)
<75	67	49	73.1 (60.9 to 83.2)
Sex			
Female	20	17	85.0 (62.1 to 96.8)
Male	63	43	68.3 (55.3 to 79.4)
Previous HSCT			
Yes	27	22	81.5 (61.9 to 93.7)
No	56	38	67.9 (54.0 to 79.7)
Secondary CNS lymphoma			
Yes	7	6	85.7 (42.1 to 99.6)
No	76	54	71.1 (59.5 to 80.9)
Response to last therapy			
Refractory	58	38	65.5 (51.9 to 77.5)
Relapsed	25	22	88.0 (68.8 to 97.5)
Chemotherapy response			
Refractory	24	13	54.2 (32.8 to 74.4)
Sensitive	59	47	79.7 (67.2 to 89.0)
Previous BTKi exposure			
Refractory to BTKi	45	29	64.4 (48.8 to 78.1)
Not refractory to BTKi	35	28	80.0 (63.1 to 91.6)
Ki-67 proliferation index			
<30%	14	8	57.1 (28.9 to 82.3)
≥30%	62	47	75.8 (63.3 to 85.8)
Unknown	7	5	71.4 (29.0 to 96.3)
TP53 mutation status			
Yes	19	11	57.9 (33.5 to 79.7)
No	32	27	84.4 (67.2 to 94.7)
Not tested	29	20	69.0 (49.2 to 84.7)
Indeterminate	3	2	66.7 (9.4 to 99.2)
Blastoid morphology			
Yes	27	17	63.0 (42.4 to 80.6)
No	45	37	82.2 (67.9 to 92.0)
Not tested	11	6	54.5 (23.4 to 83.3)
sMIPI risk category			
Low risk	34	28	82.4 (65.5 to 93.2)
Intermediate/high risk	49	32	65.3 (50.4 to 78.3)
LDH			
≥ULN, U/L	39	28	71.8 (55.1 to 85.0)
<ULN, U/L	44	32	72.7 (57.2 to 85.0)
SPD			
≥Median cm^2	38	24	63.2 (46.0 to 78.2)
<Median cm^2	40	33	82.5 (67.2 to 92.7)
Bridging therapy			
Yes	54	38	70.4 (56.4 to 82.0)
No	29	22	75.9 (56.5 to 89.7)







ORR = 84% (27/32); CR = 59% (19/32)

1% CRS (no G3-5), 9% G3 neurologic events (no G4-5)

J Clin Oncol. 2024 Apr 1;42(10):1146-1157
Wang M, et al. ASTCT 2025. Poster number 240

TARMAC: Combination of time-limited ibrutinib and tisagenlecleucel in RR-MCL

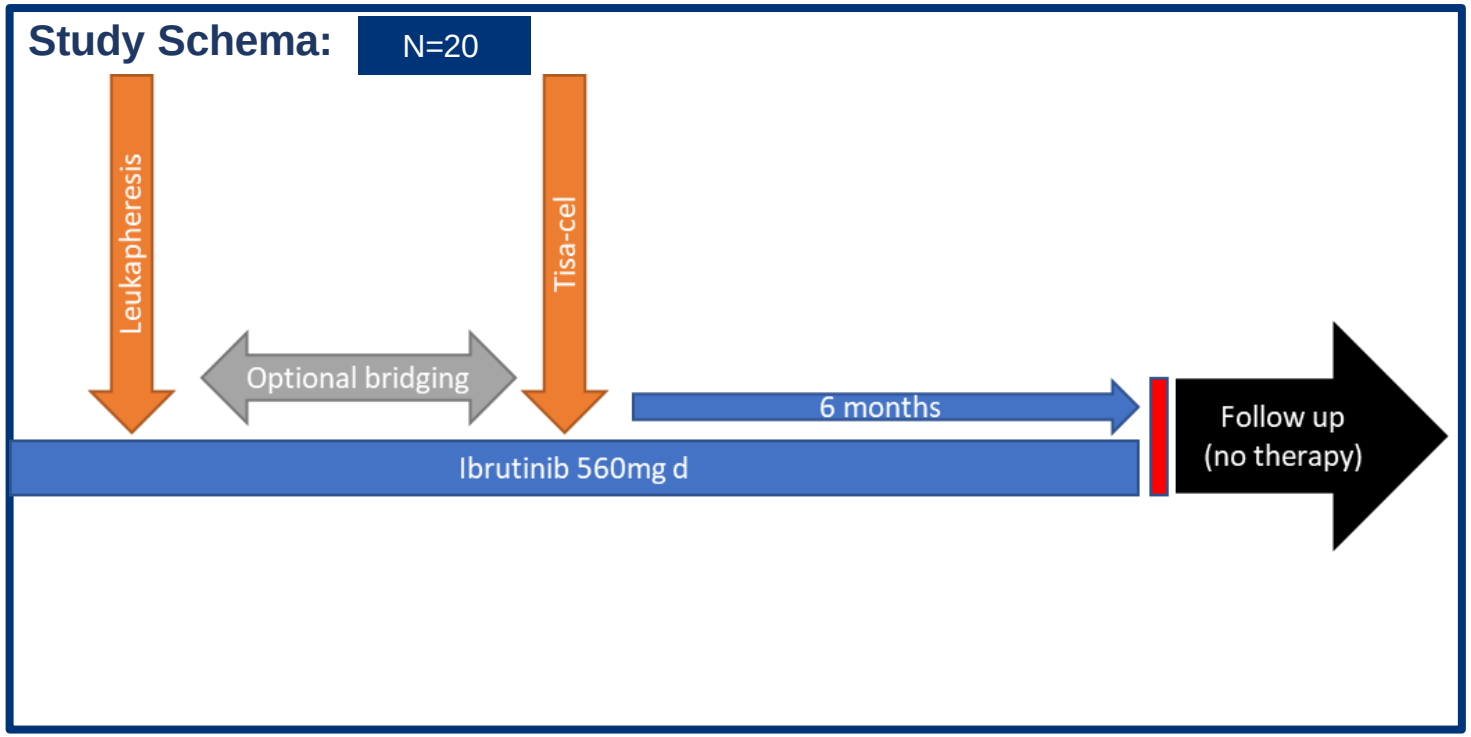
STUDY OVERVIEW

Key inclusion criteria:

- MCL[1]
  - Relapse after 1 line *or*
  - Insufficient response to induction[2]
- ≥18yo
- Radiographically assessable or bone marrow phase disease

Key exclusion criteria:

- Prior allogeneic transplant
- Active CNS involvement



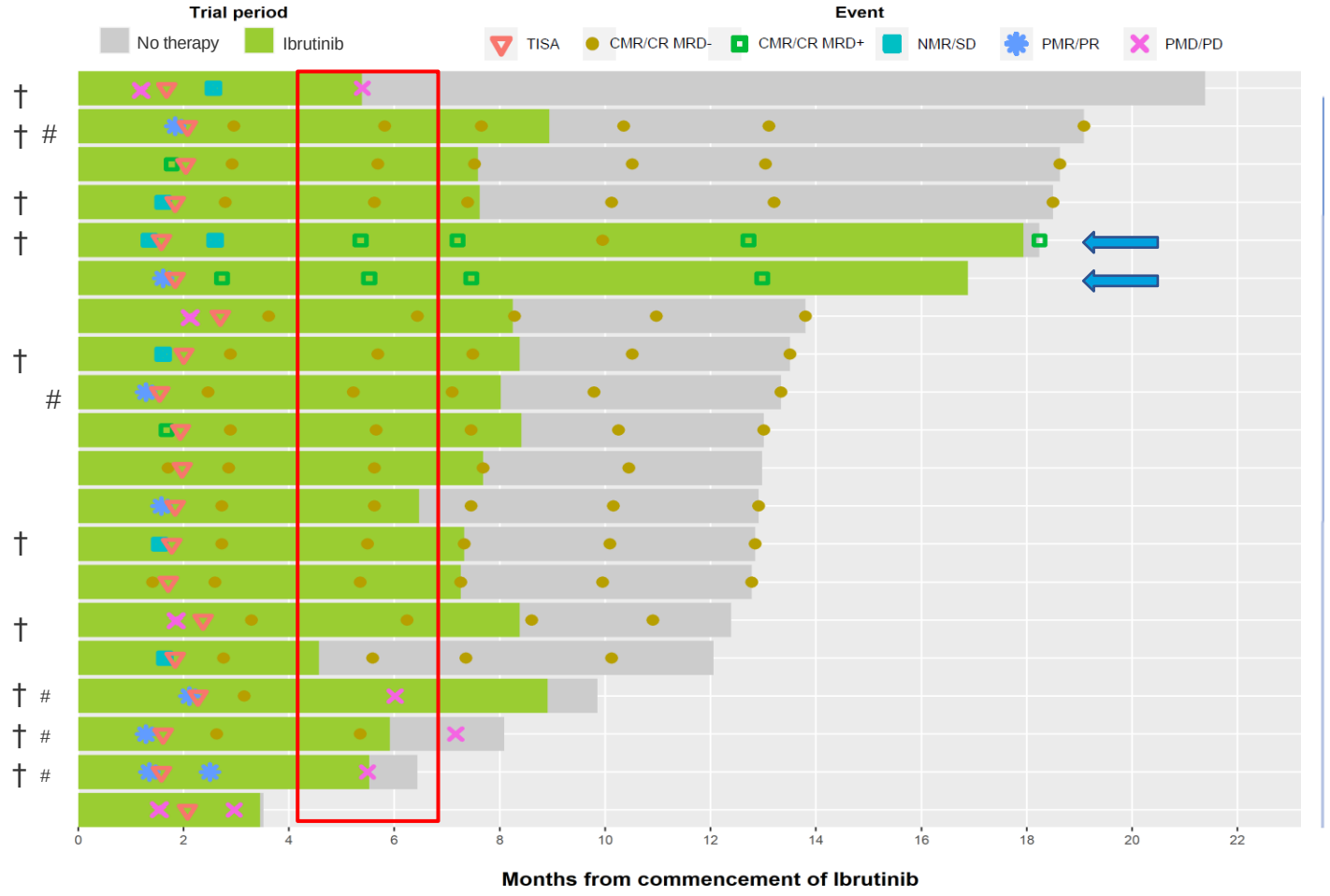
Primary endpoint: Complete response rate at 4 months post tisagenlecleucel[3]
Key secondary endpoints: Safety, objective response rate, progression free survival, duration of response, overall survival, subgroup analysis based on *TP53* status

Alternative hypothesis: CR rate of ≥40% at M4
Null hypothesis:
Ibrutinib naïve: CR rate of 9% at M4 and 20% overall with ibrutinib
Ibrutinib exposed: CR rate of ~20% with chemotherapy

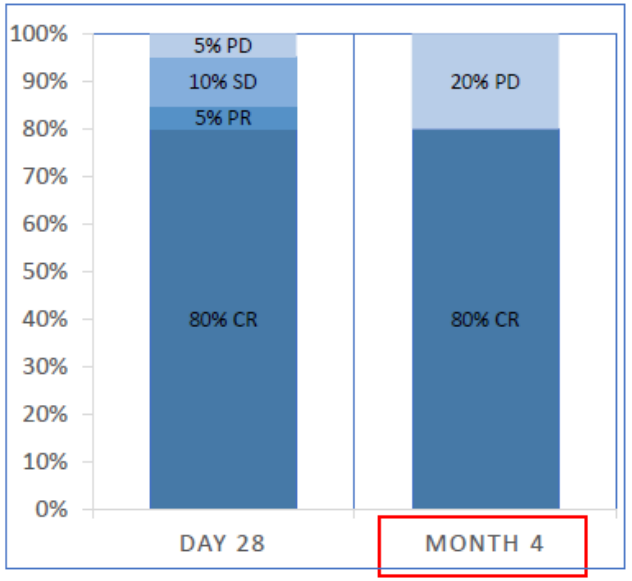
Adrian Minson et al., Blood. 2024 Feb 22;143(8):673-684.

TARMAC

Primary endpoint – response at 4 months



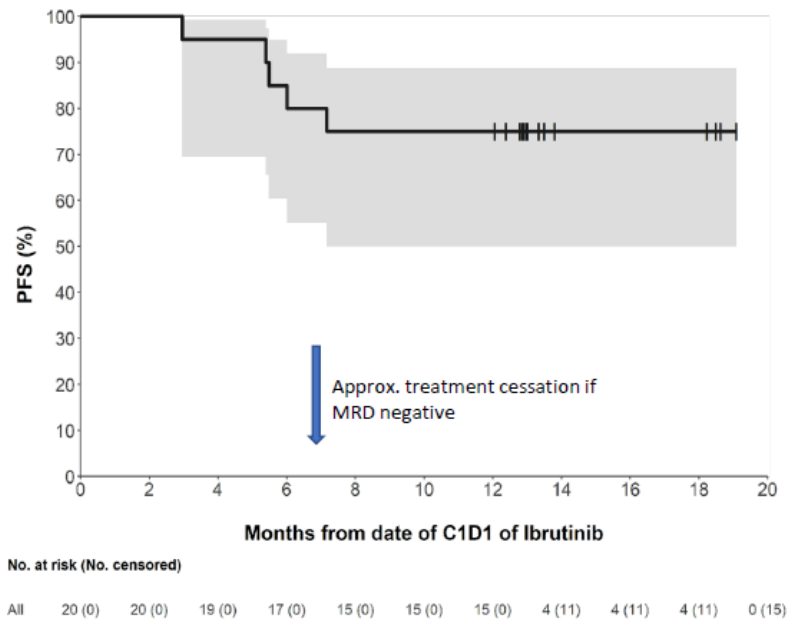
Efficacy endpoint (n=20)	Rate
Complete response rate[1]	80%



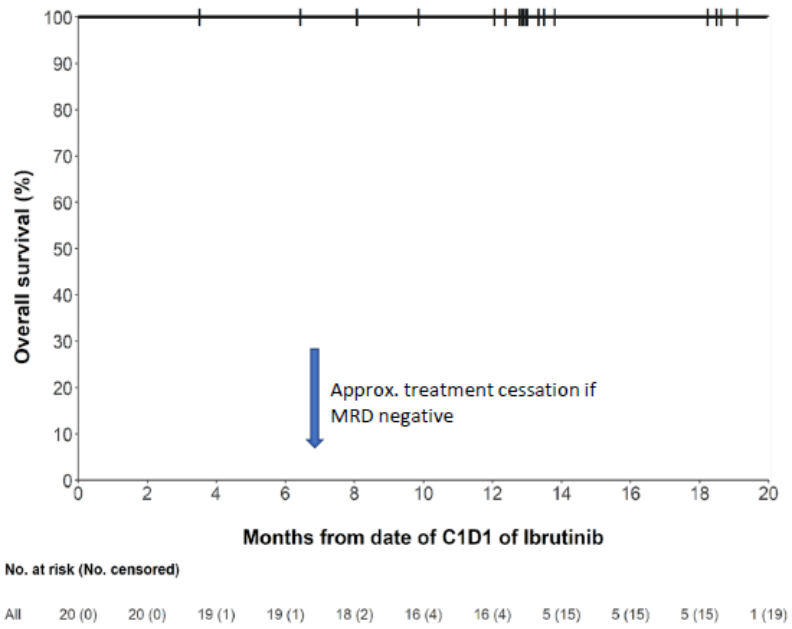
Adrian Minson et al., Blood. 2024 Feb 22;143(8):673-684.

TARMAC
Survival outcomes

PFS



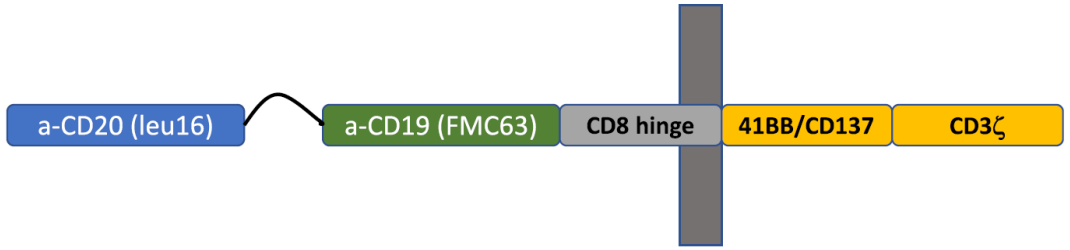
OS



	N=20
Median follow up, mo (range)	13.0 (3.5-21.4)
Median PFS	Not reached (7.2-NE)
6 month event-free rate, % (95% CI)	85 (60-95)
12 month event-free rate, % (95% CI)	75 (50-89)

Adrian Minson et al., Blood. 2024 Feb 22;143(8):673-684.

LV20.19 CAR T-Cells for Relapsed, Refractory Mantle Cell Lymphoma

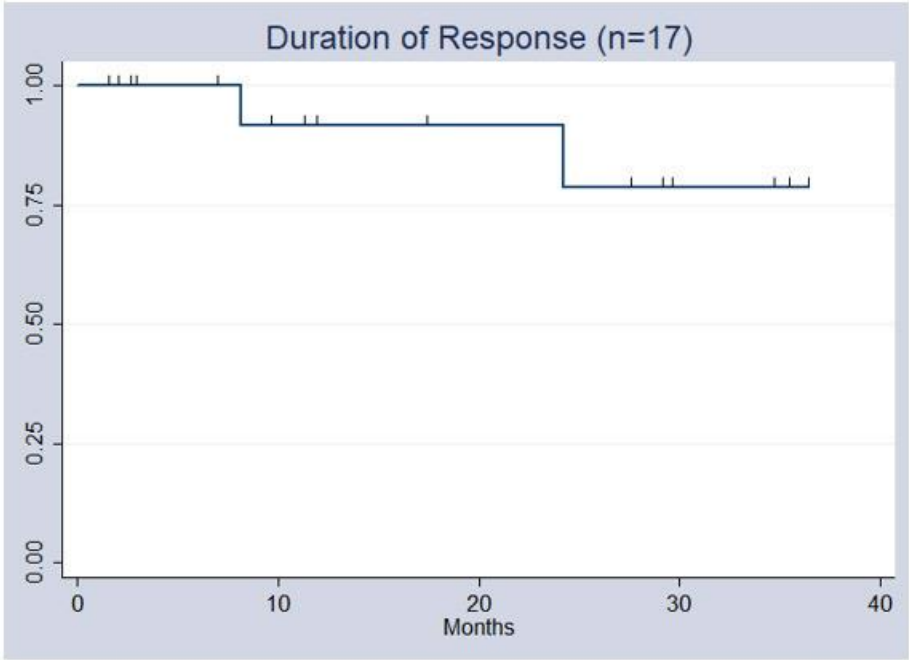


Grade 3-4 CRS in 1 (5%) patient
Grade 3-4 neurotoxicity in 3 (14%) patients.
ORR 82% with 64% CR rate
ORR 100% with 92% CR rate at RP2D

Table 1: Clinical characteristics of MCL patients receiving LV20.19 CAR T-cells

	MCL patients (n=17)
Median Age, years	63 (50-74)
Male % (n)	88% (15)
Prior auto-HCT % (n)	41% (7)
Prior allo-HCT % (n)	12% (2)
BTKi exposed % (n)	94% (16)
BTKi progressed % (n)	76% (13)
Non-covalent BTKi progressed % (n)	35% (6)
Median Prior Lines (including transplant)	4 (3-8)
Complex Cytogenetics	3 patients
p53 aberrations (not uniformly assessed)	3 patients with p53 deletion 4 patients with p53 somatic mutation

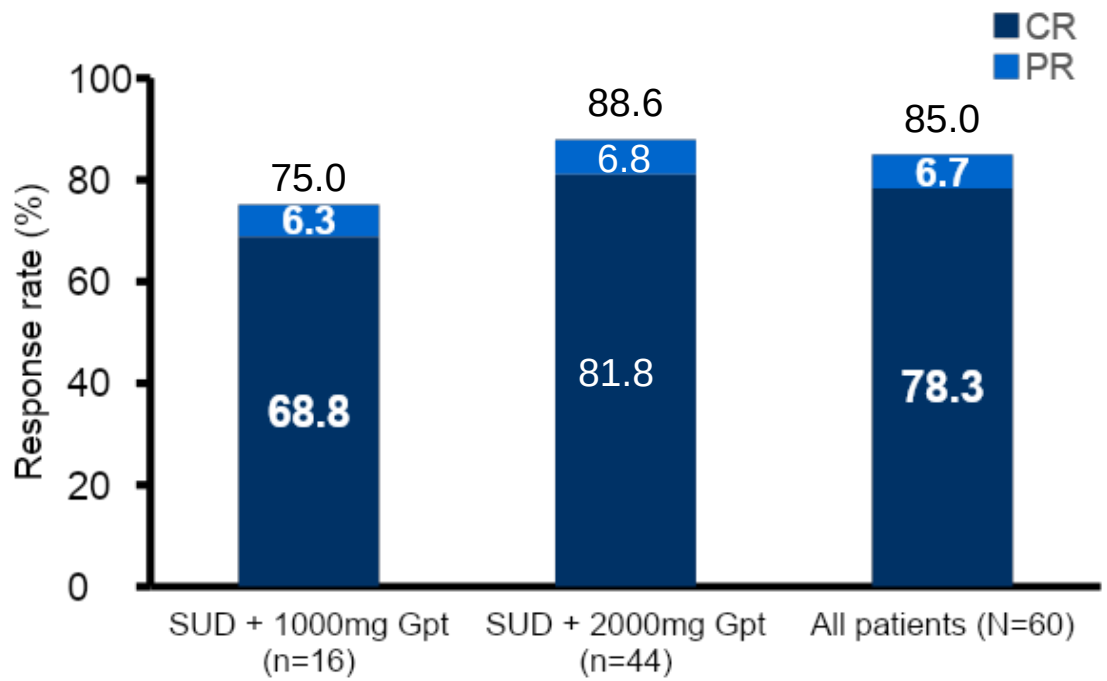
Figure 1



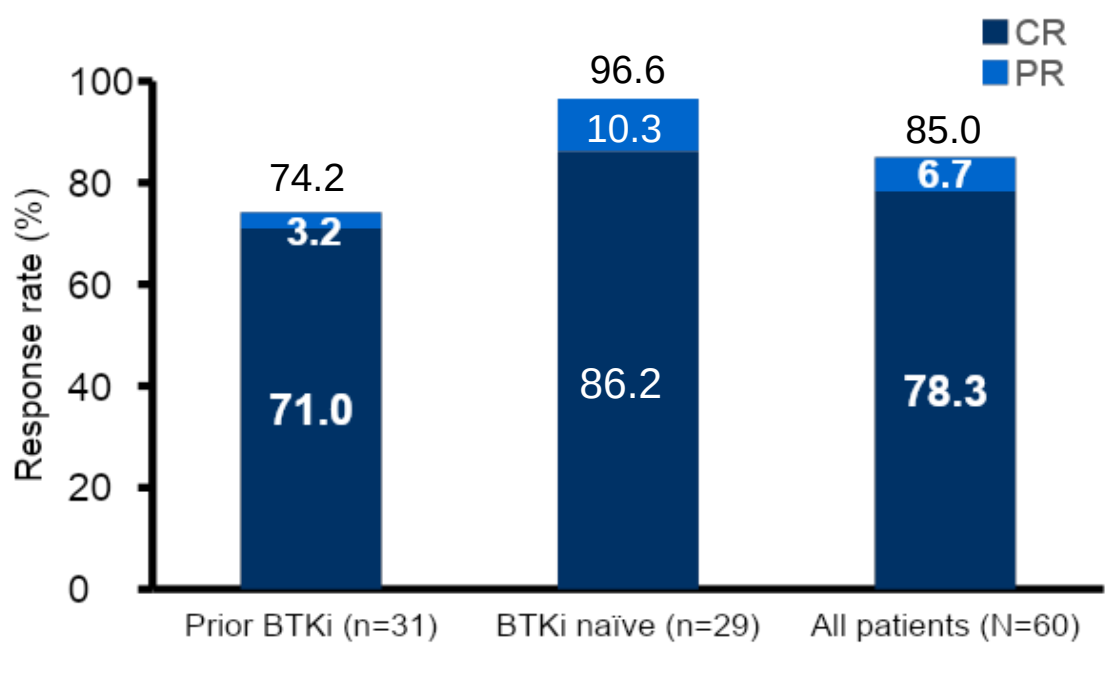
Nat Med. 2020 Oct;26(10):1569-1575 ; Blood. 2023;142(suppl 1):1024

Glofitamab in RRMCL: Results From a Phase I/II Study

All patients



Patients with prior BTKi



- **Median time to first response among responders (n=51): 42 days (95% CI: 42.0–45.0)**
- **High response rates in the overall population and in both BTKi-naïve patients and those with prior BKTi therapy**

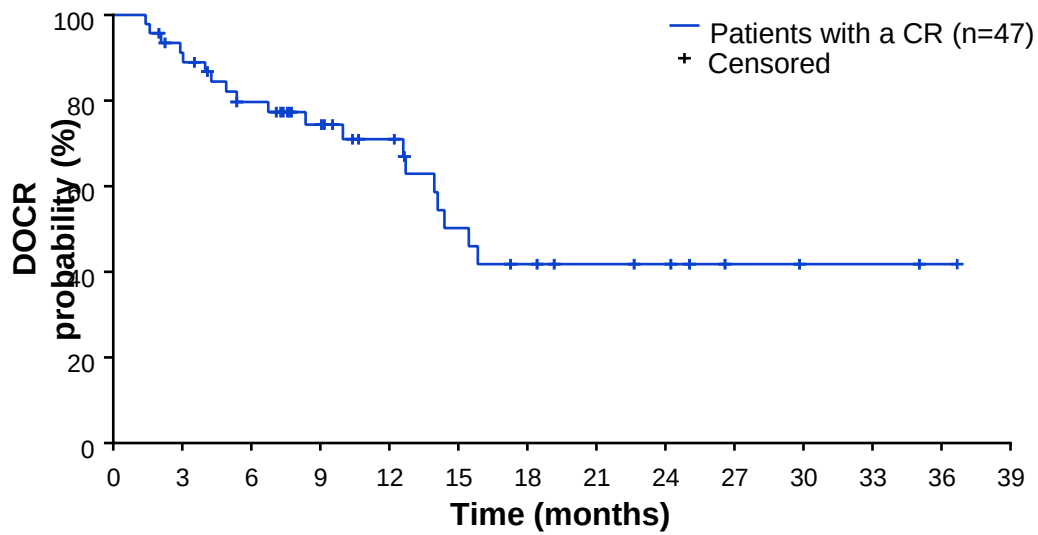
Clinical cut-off date: September 04, 2023. Response rates shown for the efficacy-evaluable population.
*Investigator-assessed.
BTKi, Burton's Tyrosine Kinase inhibitor; CI, confidence interval; CR, complete response; Gpt, obinutuzumab pretreatment; PR, partial response; SUD, step-up dosing.

1. Cheson BC, et al. J Clin Oncol 2014;20:3059–68;
2. Philips T, et al. J Clin Oncol 2024; doi:10.1200/JCO.23.02470 (online ahead of print);
3. Philips T, et al. ASCO 2024; oral presentation (abstract #7008).

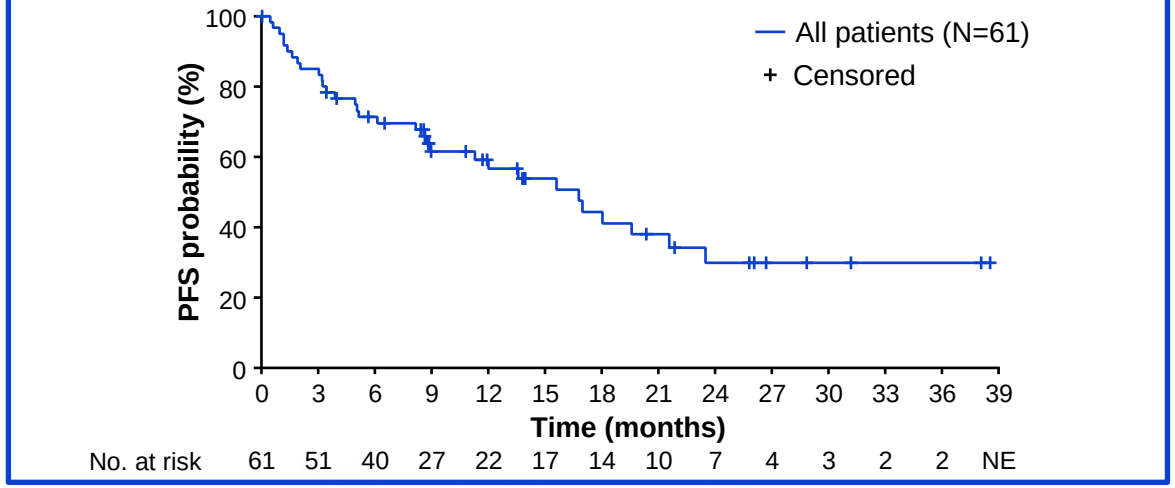
Glofitamab in RRMCL: Results From a Phase I/II Study

Outcomes	Prior BTKi n=22	All patients n=47
Median DOCR, months (95% CI)	**12.6 (5.4–NE)**	15.4 (12.7–NE)
12-month DOCR rate, % (95% CI)		71.0 (56.8–85.2)
Median PFS, months (95% CI)	**8.6 (3.4–15.6)**	16.8 (8.9–21.6)
Median OS, months (95% CI)	**21.2 (9.0–NE)**	29.9 (17.0–NE)

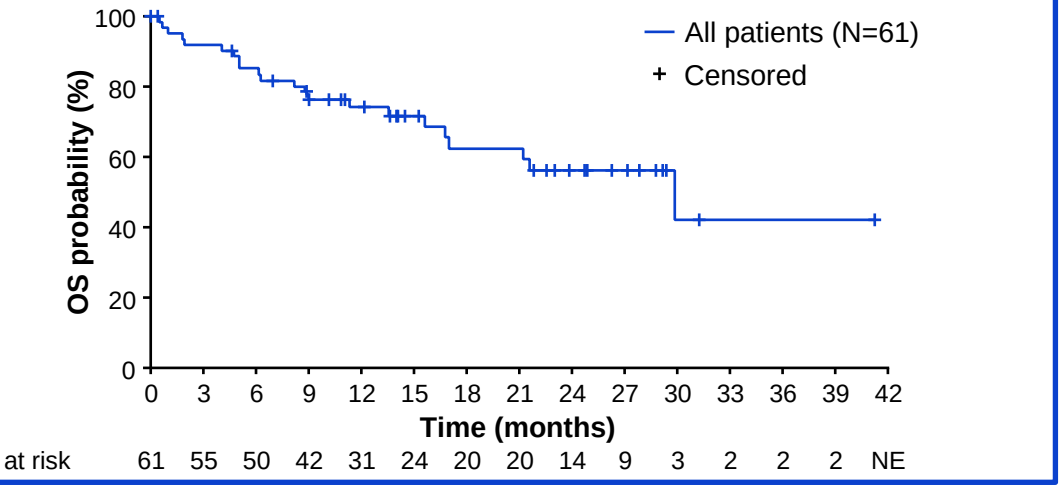
DOCR*



PFS[1]



OS†[1]

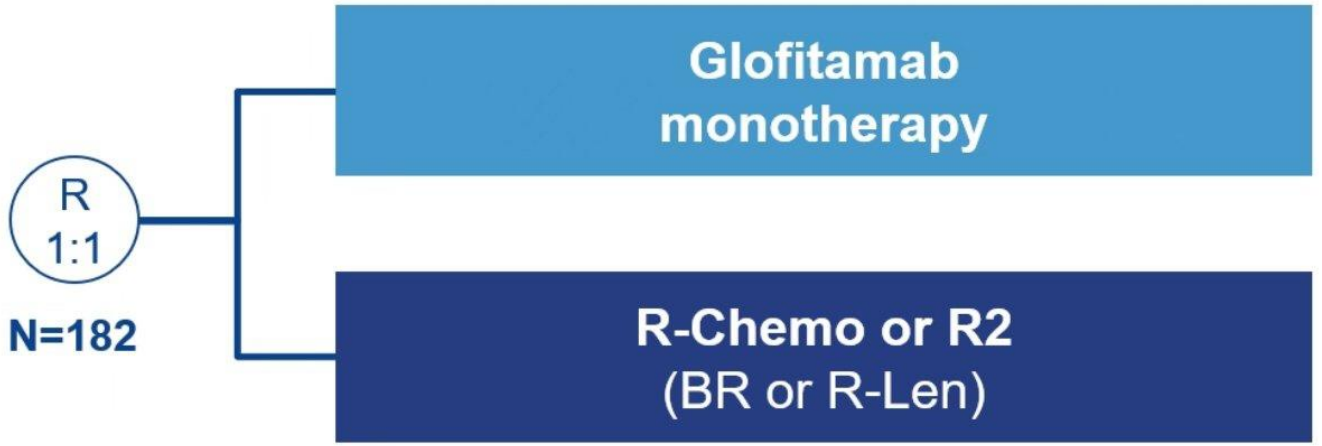


J Clin Oncol. 2025 Jan 20;43(3):318-328

GLOBRYTE: A Phase III, Open-label, Multicenter Randomized Study Evaluating Glofitamab As A Single Agent Versus Investigator's Choice in Patients With R/R MCL

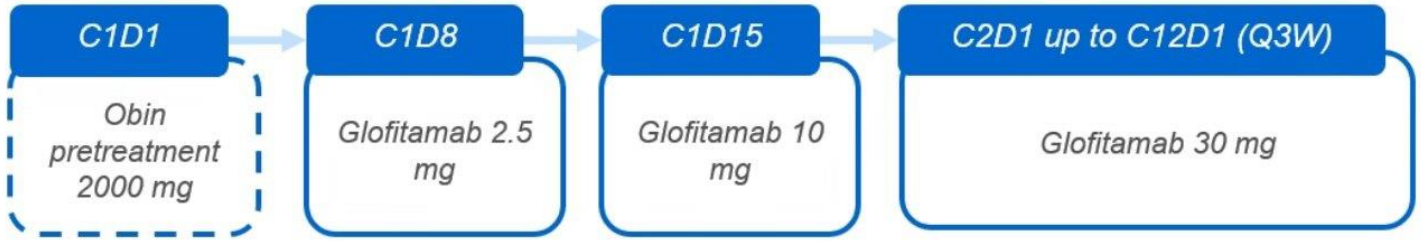
Key Inclusion Criteria

- Histologically confirmed MCL with documentation of either overexpression of cyclin D1 or the presence of t(11:14)
- Relapsed or refractory disease
- Prior therapy must have included a BTKi
- At least 1 bi-dimensionally measurable (1.5 cm) nodal lesion, or 1 bi-dimensionally measurable (1 cm^3) extranodal lesion, as measured on computed tomography scan



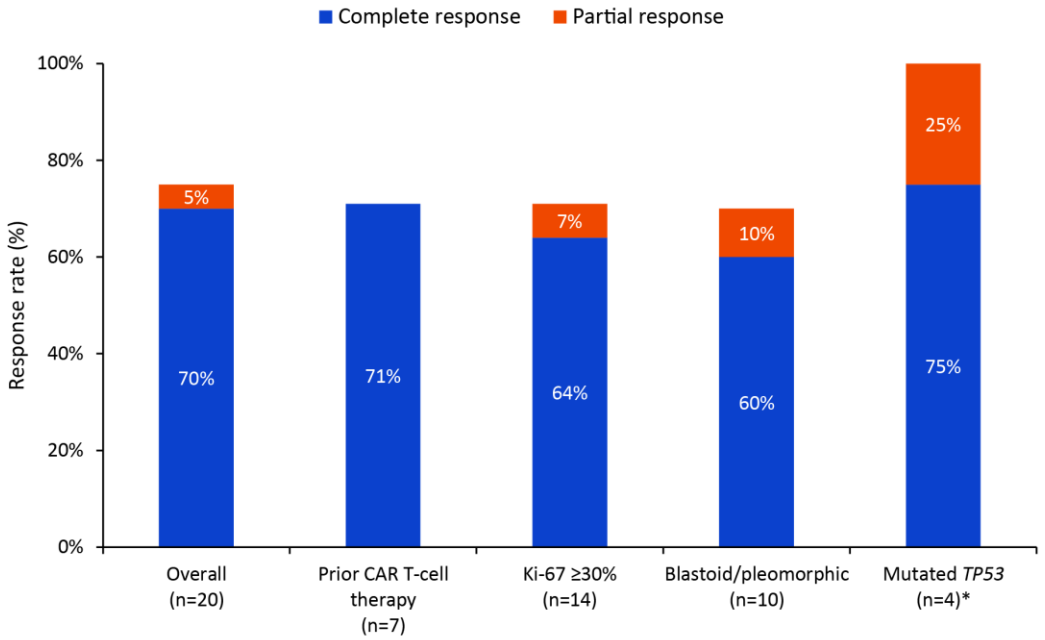
Other Study Details

- **Primary EP:** PFS by IRC
- **Secondary EPs**: ORR, CR, OS, PFS (INV), DOR, DOCR
- **Exploratory EPs:** QOL, PK/PD/ADAs, Biomarkers, Safety
- **Stratification factors:** 2L vs 3L+, outcome of last line of therapy (relapsed vs refractory)
- Mandatory hospitalization after Dose 1
- **Crossover to glofitamab permitted on confirmed progression**



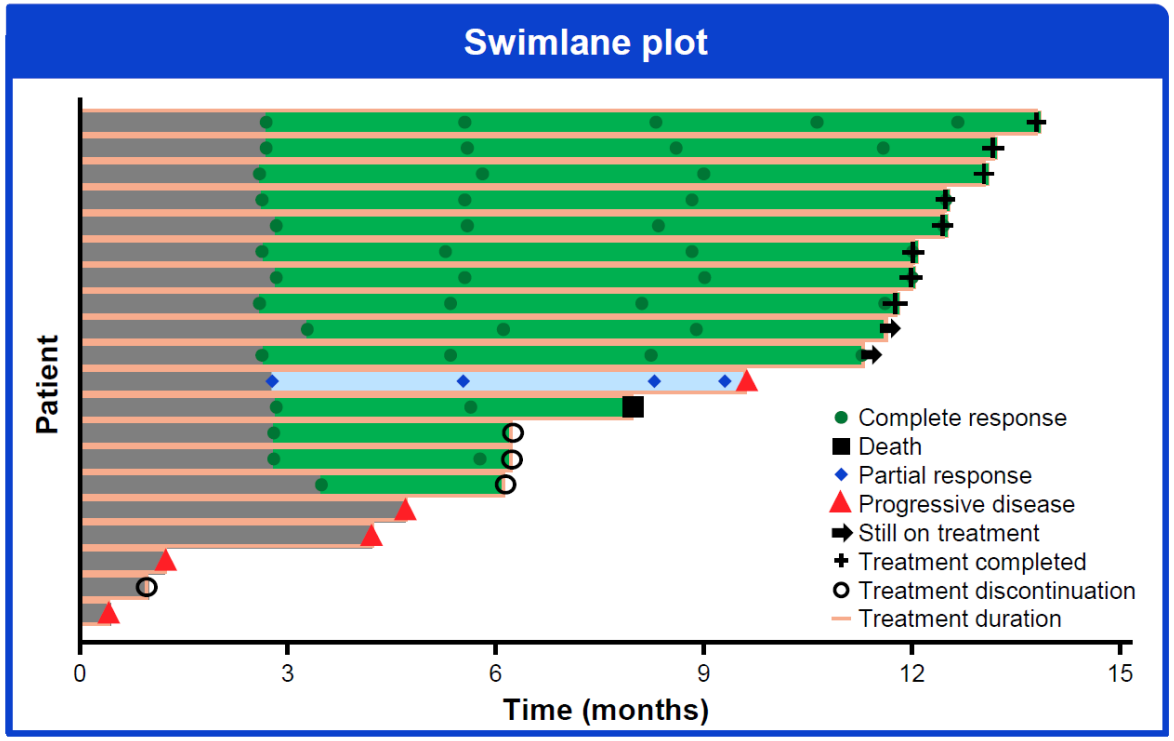
Mosunetuzumab + Polatuzumab vedotin Phase 1b/II for BTKi RRMCL

Figure: Best overall response rates in high-risk MCL subgroups



*The *TP53* status of 10 patients was unknown or not done, therefore these patients were not included in this analysis.

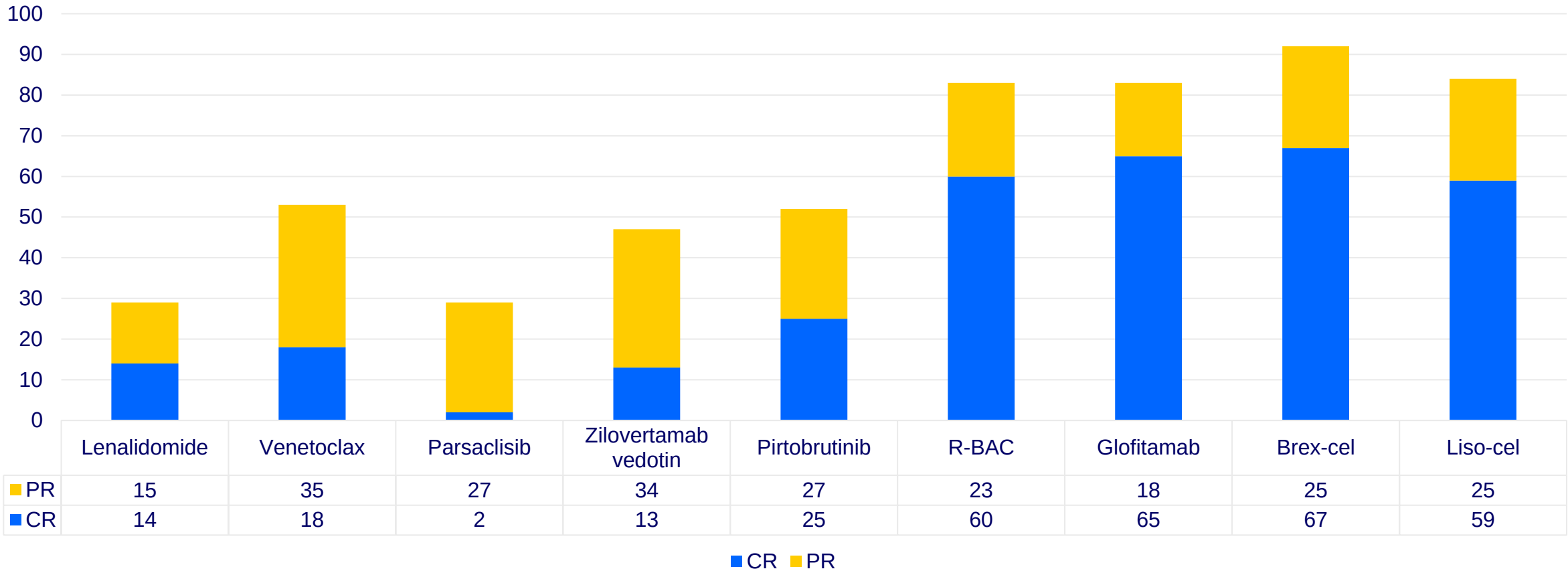
CAR, chimeric antigen receptor; Ki, kinase inhibitor; MCL, mantle cell lymphoma; *TP53*, tumor protein 53



Median DoR: 13.3 mo (95% CI: 13.3-NE)

Michael Wang et al., ASH 2023 Abstract 734

Overall response rates for therapeutics for R/R MCL after covalent BTKi



	Lenalidomide	Venetoclax	Parsaclisib	Zilovertamab vedotin	Pirtobrutinib	R-BAC	Glofitamab	Brex-cel	Liso-cel
PR	15	35	27	34	27	23	18	25	25
CR	14	18	2	13	25	60	65	67	59

* Data from each trial

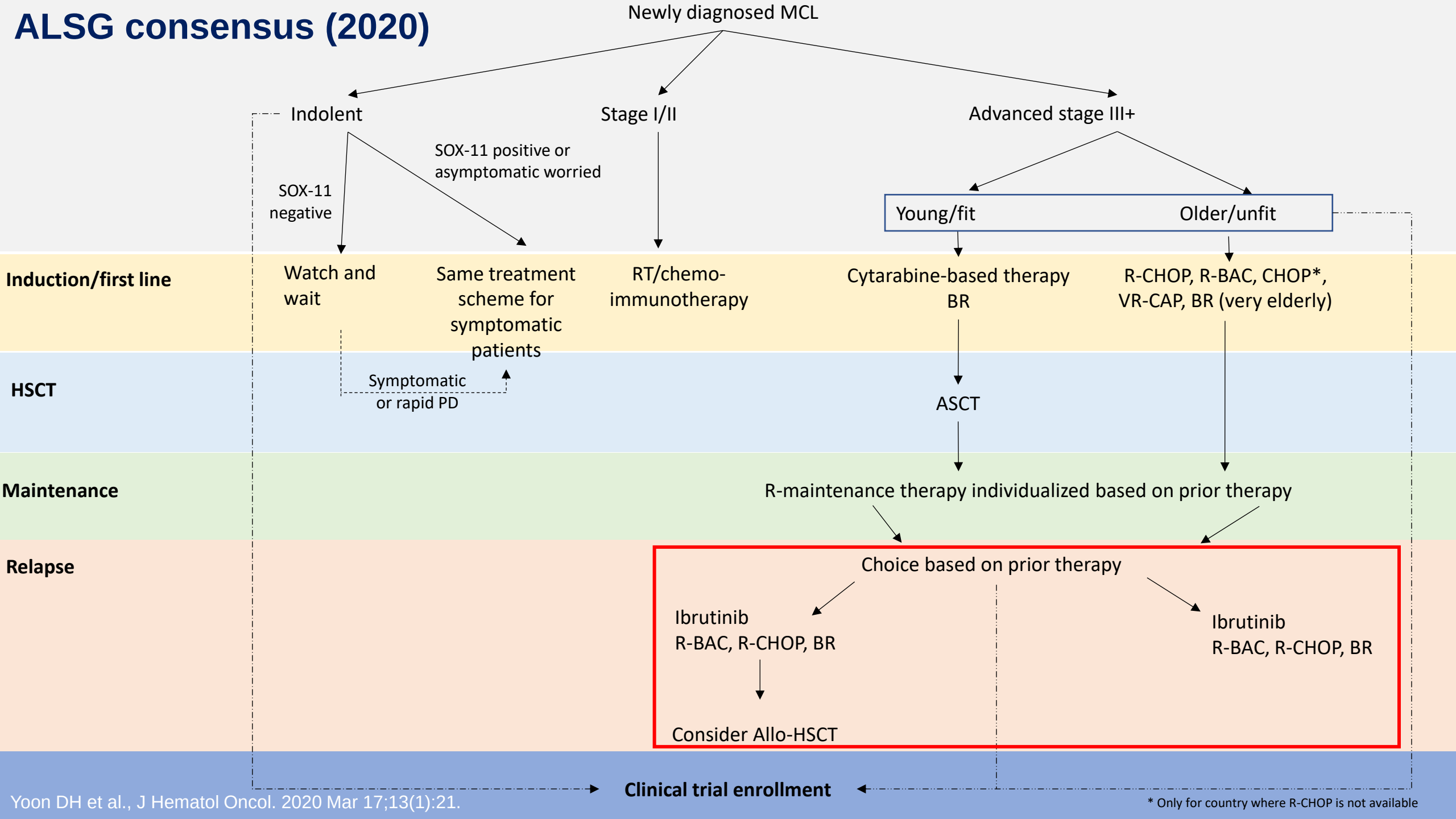
Lenalidomide: Wang et al., J Hematol Oncol 2017;10(1):171; Venetoclax: Eyre T, et al. Haematologica. 2019 Feb;104(2):e68-e71; Parsaclisib, Zinzani et al., ASH 2020, abstract 2044; Pirtobrutinib, Wang et al, ASH 2021 abstract 381; Zilovertamab vedotin: Wang et al., ASH 2020, abstract 121; R-BAC, McCulloch et al., Br J Haematol. 2020 May;189(4):684-688); Glofitamab, Blood (2021) 138 (Supplement 1): 130; Brex-cel, Wang et al., N Engl J Med 2020;382:1331-42; Liso-cel, ASH 2020 abstract 118

Novel agents under active investigation for R/R MCL

Name	Target and mechanism
NX-2127, BGB-16673	BTK-targeting PROTACs
Epcoritamab	Bispecific antibody targeting CD20 and CD3; given subcutaneously
JNJ-80948543	Trispecific antibody targeting CD79b, CD20, and CD3
CART	CAR T-cells targeting CD19/CD20,130 CD79b,121 BAFF, SOX11, and ROR1. Efforts to improve the persistence of CART by modulating BCL2 and FOXO1 are being explored.
Sonrotoclax (BGB11417)	BCL2 antagonist
PRT-343 (NCT03886831)	PRMT5 inhibitor
LP-284135	DNA-damaging agent that induces double-stranded DNA breaks. It has elevated potency in cancer cells with homologous recombination repair defects.
KIN-8194	Dual BTK/HCK inhibitor
Luxeptinib (CG-806)137	Dual BTK/SYK inhibitor
TIGIT ab	Anti-TIGIT antibody
Miscellaneous	CDK inhibitors, MALT1, BAFF, ROR1

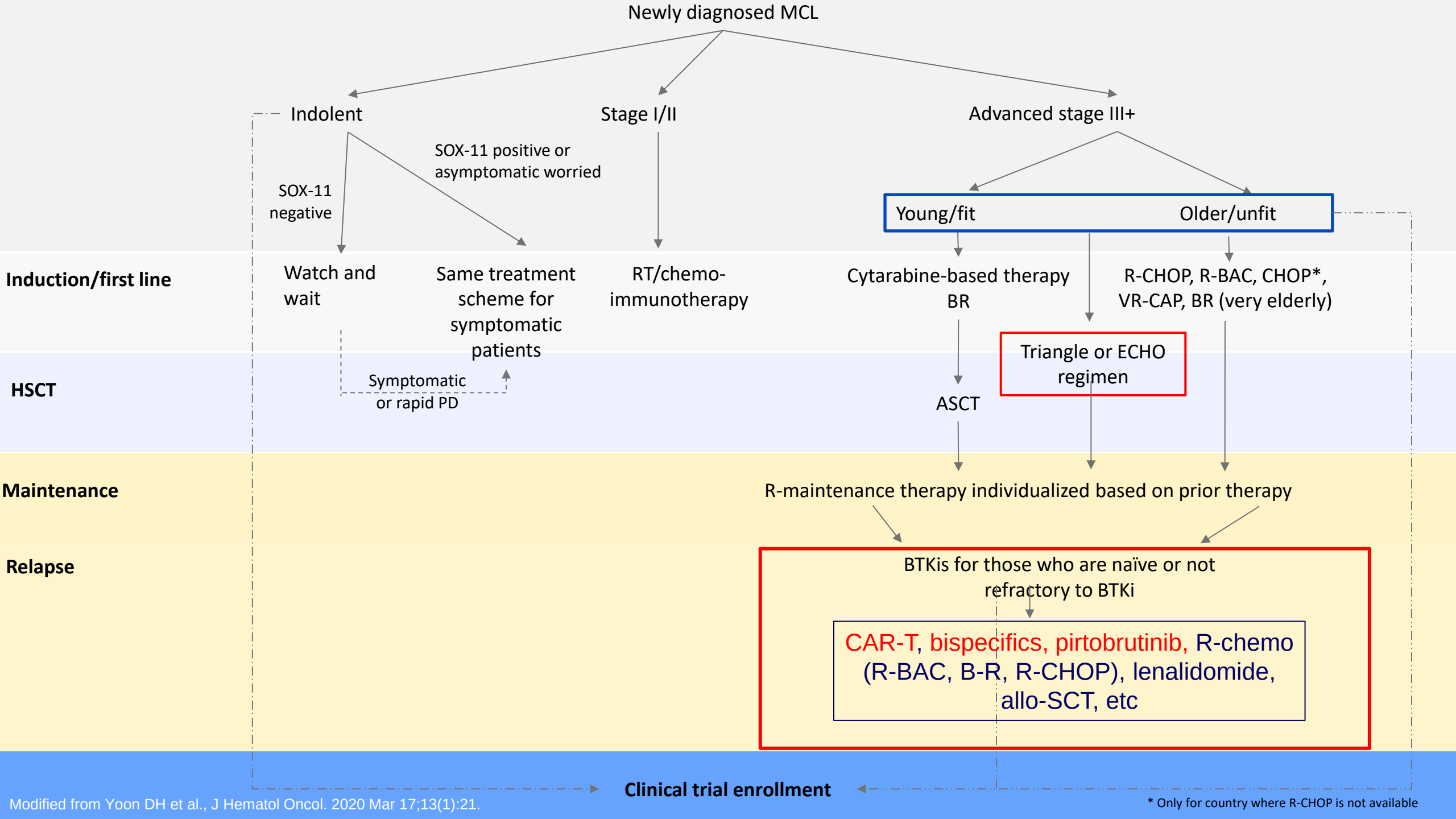
Blood. 2025 Feb 13;145(7):683-695

ALSG consensus (2020)



Yoon DH et al., J Hematol Oncol. 2020 Mar 17;13(1):21.

* Only for country where R-CHOP is not available

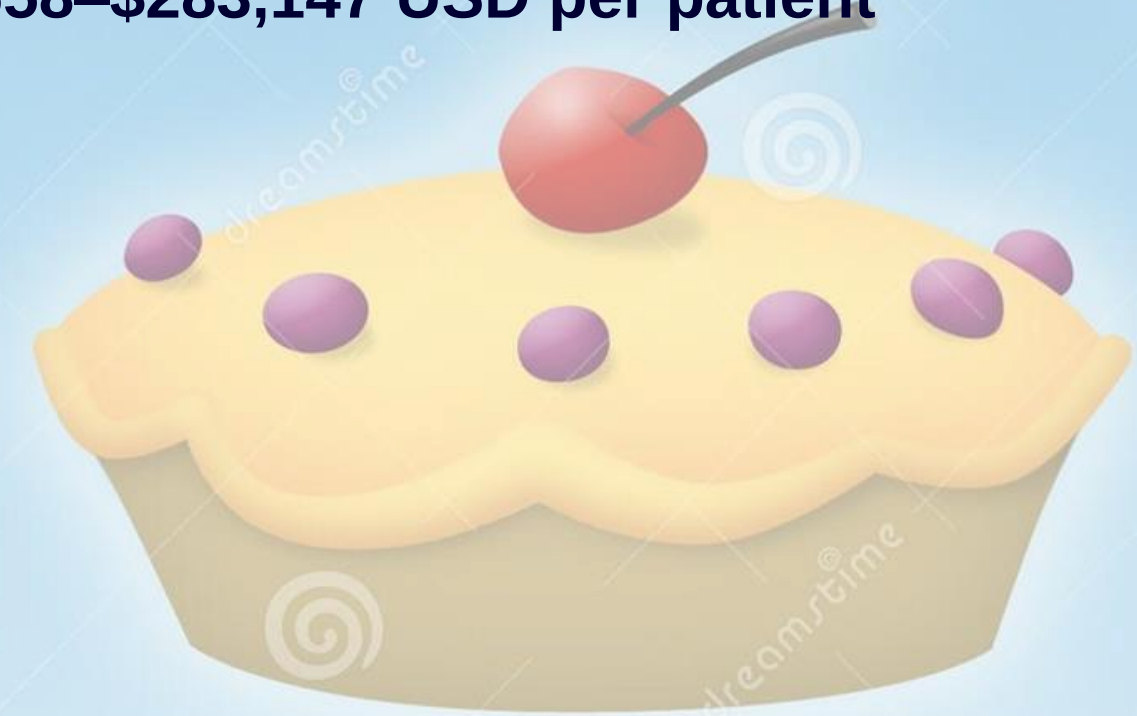

Newly diagnosed MCL
Indolent
Stage I/II
Advanced stage III+
SOX-11 positive or asymptomatic worried
SOX-11 negative
Young/fit
Older/unfit
Induction/first line
Watch and wait
Same treatment scheme for symptomatic patients
RT/chemo-immunotherapy
Cytarabine-based therapy BR
R-CHOP, R-BAC, CHOP*, VR-CAP, BR (very elderly)
Triangle or ECHO regimen
HSCT
Symptomatic or rapid PD
ASCT
Maintenance
R-maintenance therapy individualized based on prior therapy
Relapse
BTKis for those who are naïve or not refractory to BTKi
CAR-T, bispecifics, pirtobrutinib, R-chemo (R-BAC, B-R, R-CHOP), lenalidomide, allo-SCT, etc
Clinical trial enrollment
Modified from Yoon DH et al., J Hematol Oncol. 2020 Mar 17;13(1):21.
* Only for country where R-CHOP is not available

Summary

- **Treatment is evolving with the addition of novel therapeutics**
  - BTK inhibitors: most actively investigated agents for R/R MCL
    - Covalent BTKi: Ibrutinib + acalabrutinib, zanubrutinib → moving to the 1st-line therapy
    - Non-covalent BTKi: pirtobrutinib
  - Venetoclax: moderate efficacy as a single agent
    - Novel combinations: eg., ibrutinib + venetoclax
  - Bispecifics such as glofitamab
  - CAR-Ts: Brexu-cel or liso-cel
  - R-BAC: toxic but effective even after BTKi
- **Challenges**
  - Limited number of randomized trials to guide therapy
  - Still limited options in our clinic

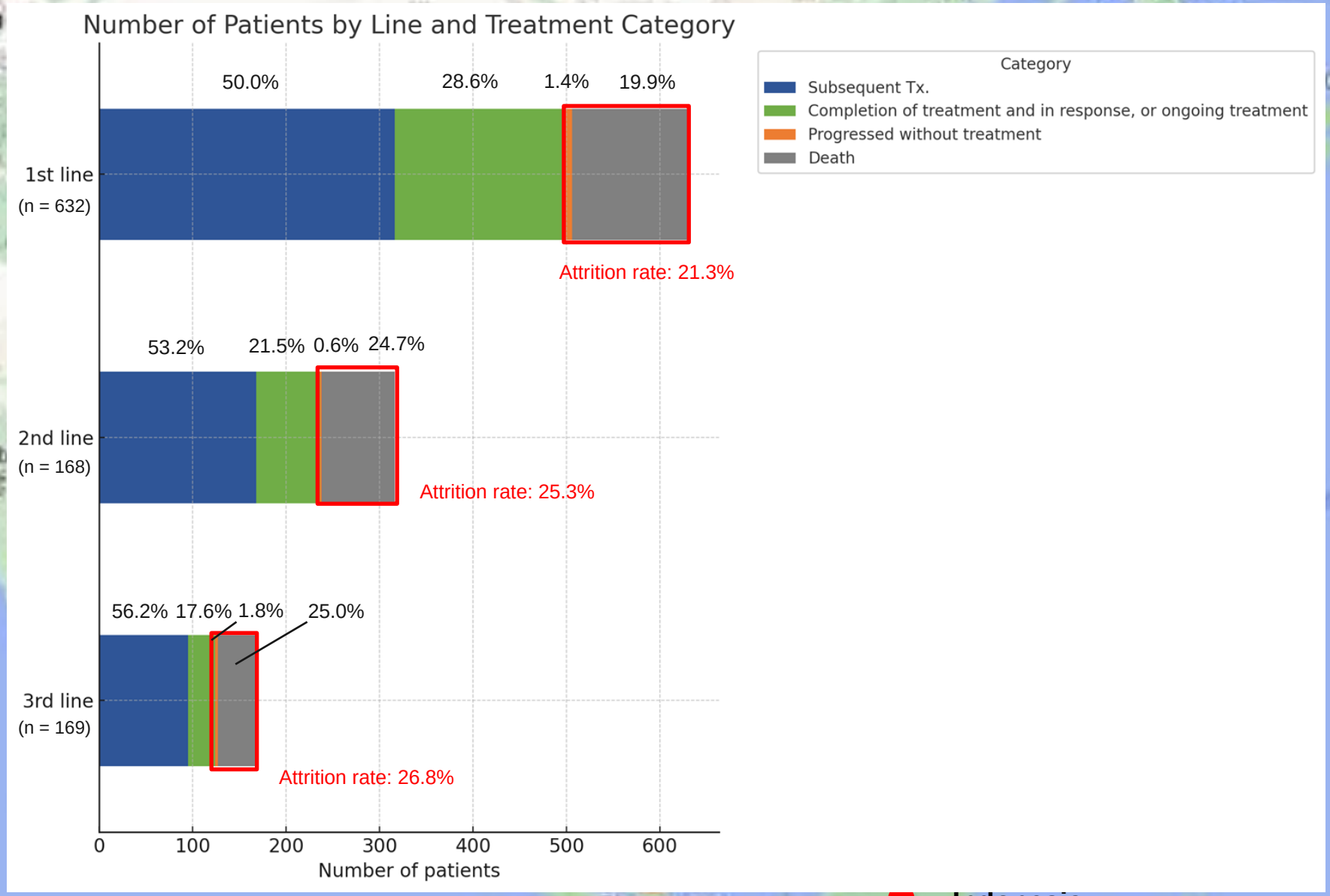
Real challenge for use = $$$

- **Pirtobrutinib: $247,000 to $260,000 USD per year**
- **CAR-Ts: Brexu-cel: $410,000 USD, Liso-cel: $447,227 USD**
- **Glofitamab: $226,658–$283,147 USD per patient**



- **B-R and 2-year R maintenance:** $65,000 to $70,000 USD

Attrition rate from AP MCL registry




SAVE THE DATE !!
The Eastern Breeze Symposium
on Malignant Lymphoma
Celebrating 20 Years:
Korean Society of Hematology Lymphoma Working Party
October 30-31, 2026
Grand Walkerhill Seoul, Korea


ZOEY