

IN PURSUIT OF *YOUR CURE.*

Mantle Cell Lymphoma in 2026: Frontline Strategies, BTK Inhibitors, and Emerging Approaches

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SINTOMA 2026

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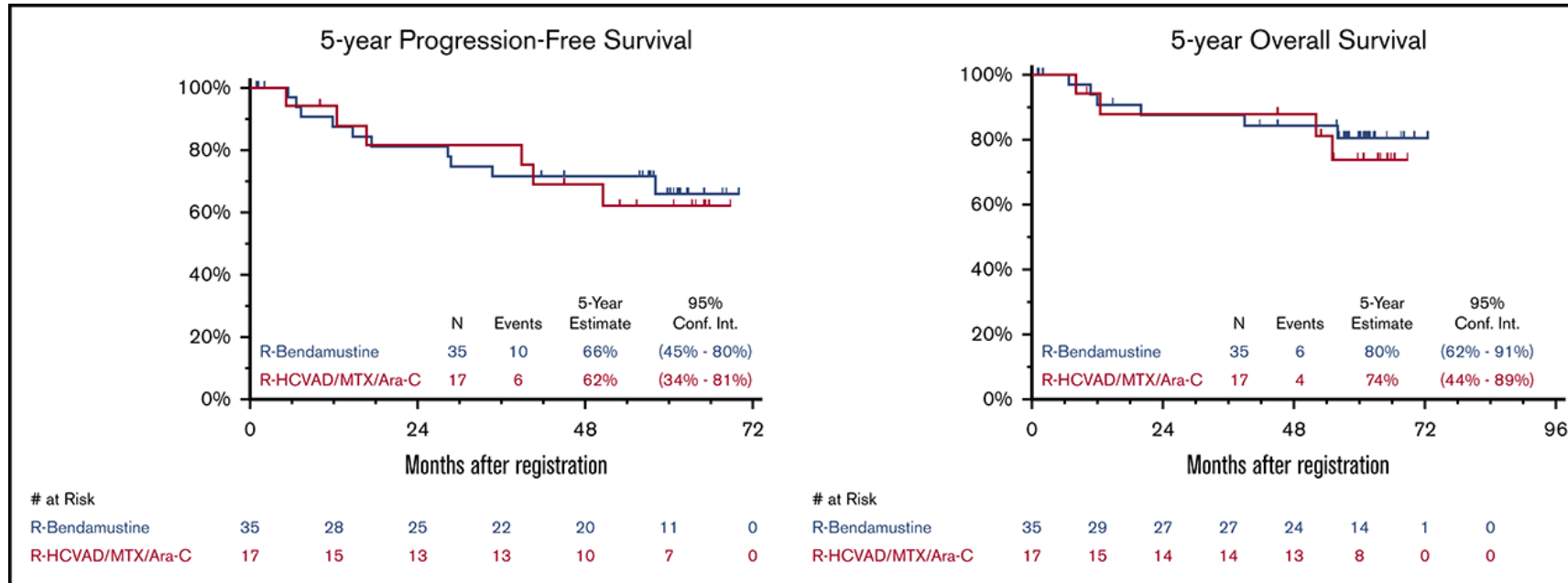


Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

- Consulting: Amgen, Kite, SeaGen, Epizyme, Janssen, BeOne, Abbvie, Incyte, TG Therapeutics, ADC Therapeutics, Lilly, Genentech, Nurix Therapeutics, Astra Zeneca
- Research Funding: Loxo/Lilly, BeOne, Incyte

SWOG 1106 – R-HCVAD vs BR

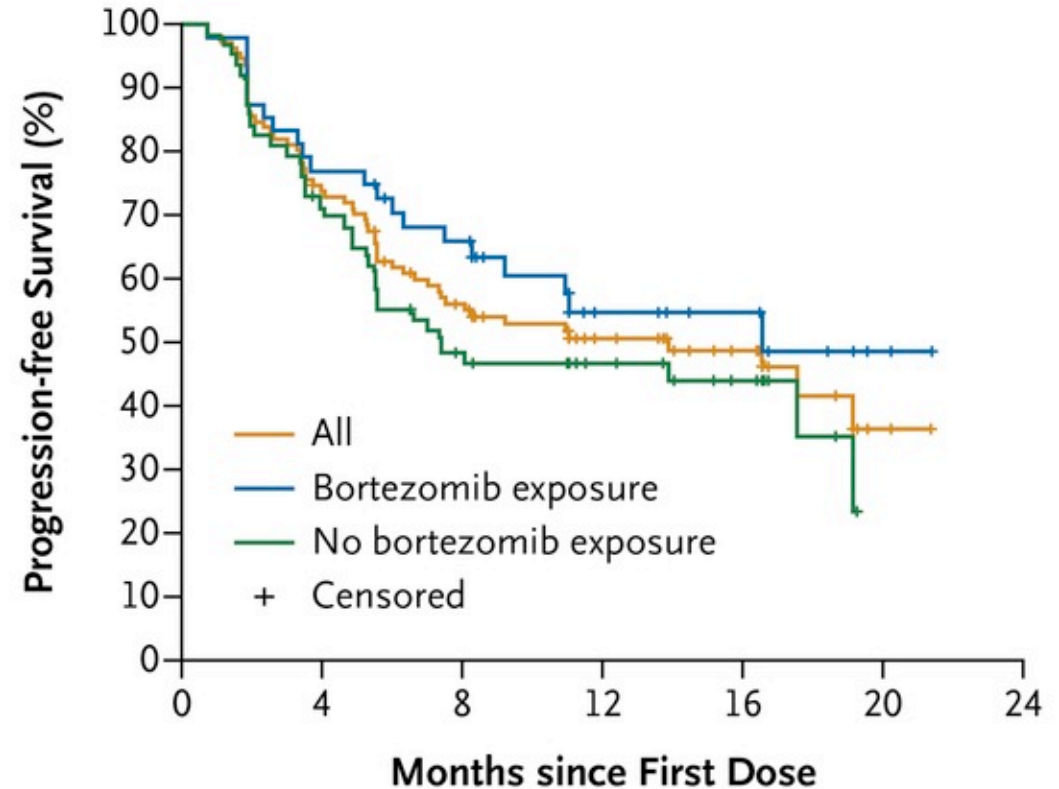


	H-CVAD	BR
ORR	94.1%	82.9%
CR	40%	35%
PR	43%	59%
Failure to collect stem cells	5	2
Negative MRD	100% (n=2)	78% (n=9)

Ibrutinib in MCL

■ Ph 2, ibrutinib

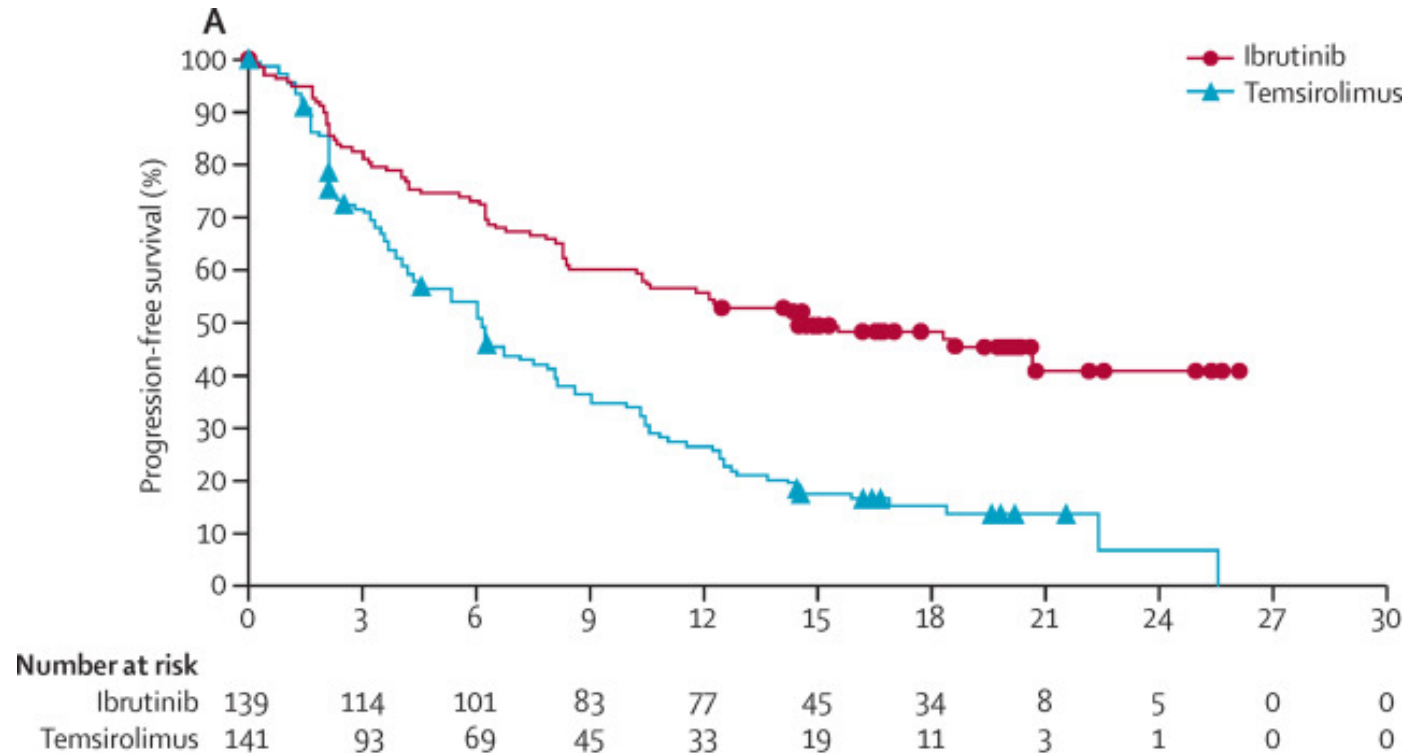
- n=111, median previous tx 3
- mF/U 15.3 mos
- ORR 68%
 - CR 21%
- DOR 17.5 mo
- mPFS 13.9 months



Ibrutinib in MCL

■ RAY study - Ph 3, ibrutinib v temsirolimus

- n=280, median previous tx 2
- mF/U 20 mos
- ORR 77 v 47 %
 - CR 23 v 3%
- DOR 23 v 6 mo
- mPFS 15.6 v 6.2 months
- Trend OS

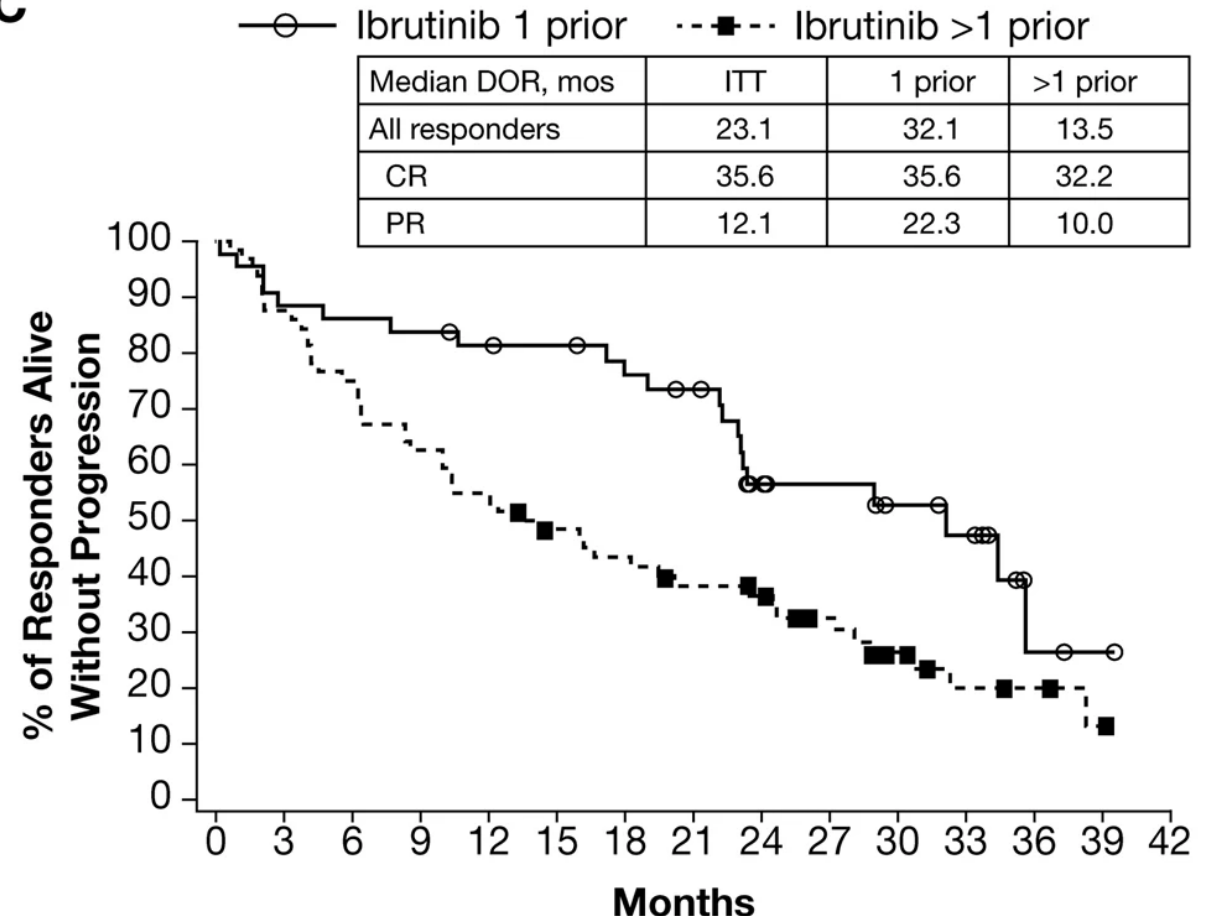


Ibrutinib in MCL

■ RAY study - Ph 3, ibrutinib v temsirolimus

- n=280, median previous tx 2
- mF/U 38 mos
- mPFS 15.6 v 6.2 months
- Longer on less tx lines
- PD main cause d/c
 - Less d/t AE w ibr

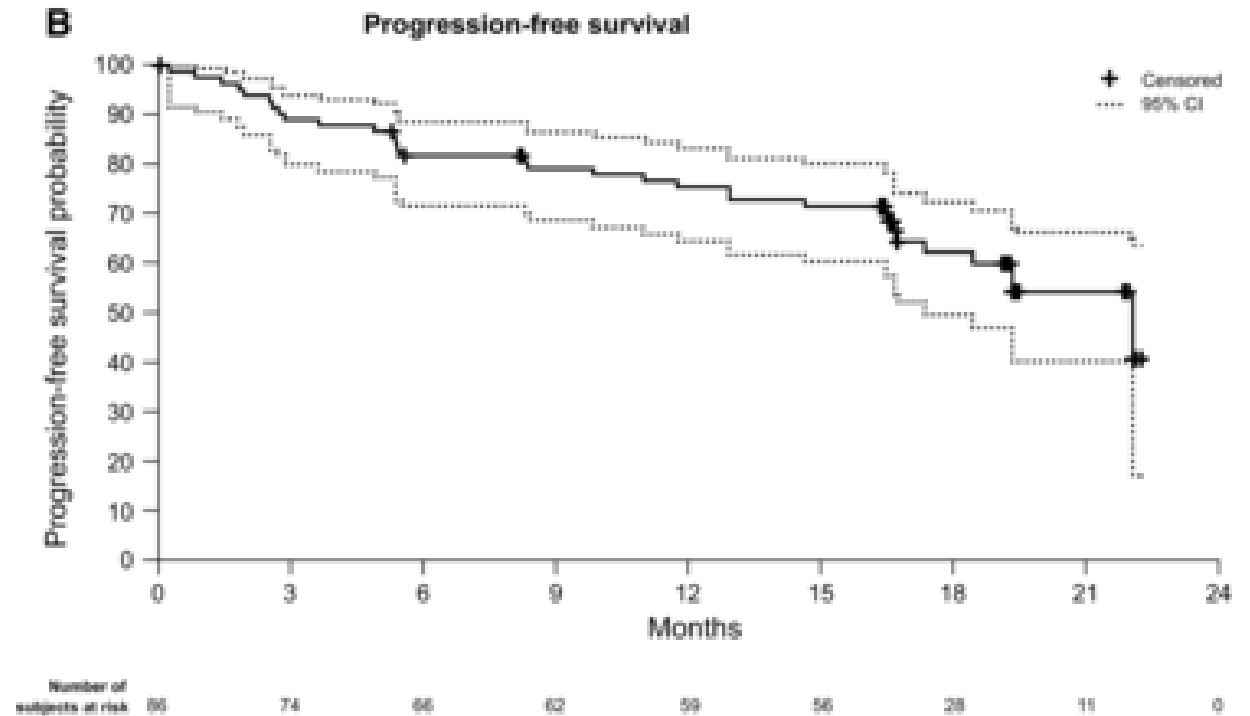
C




Zanubrutinib in MCL

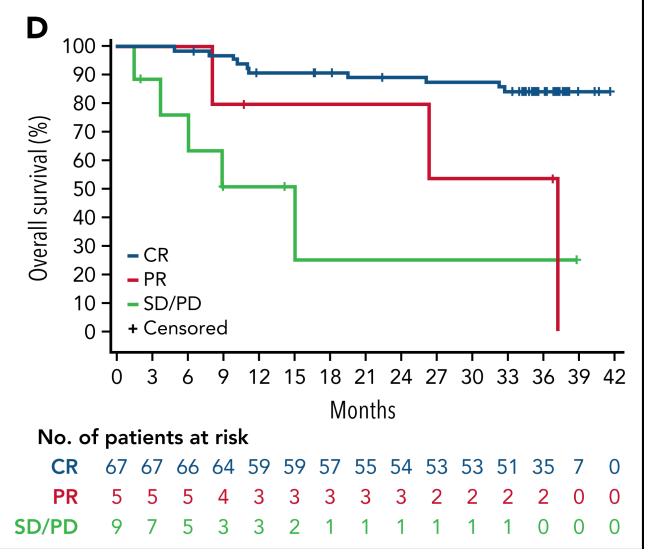
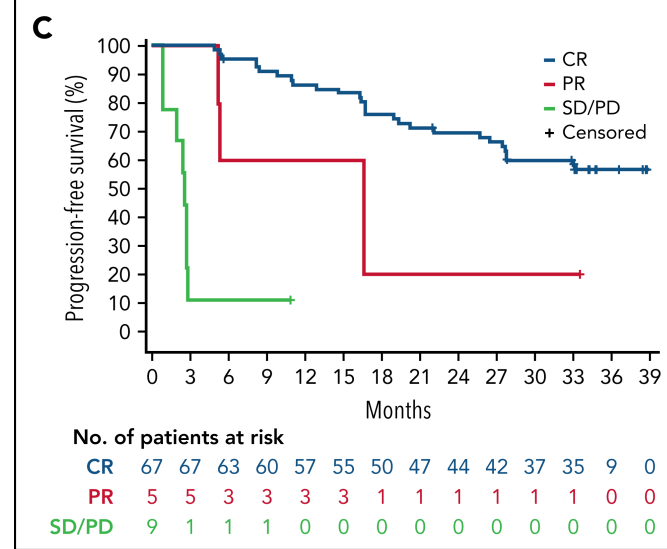
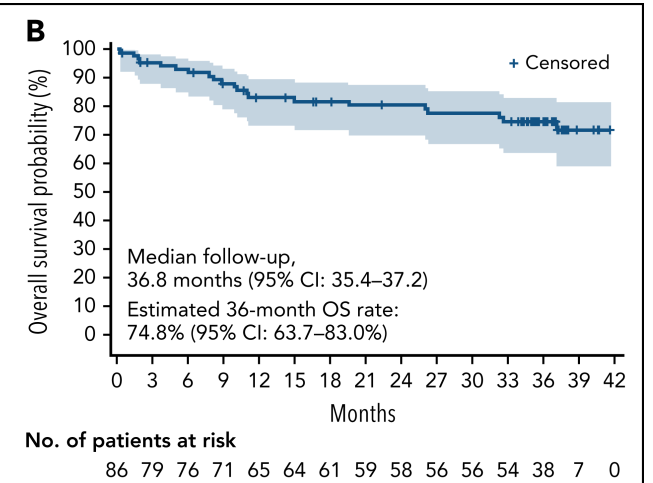
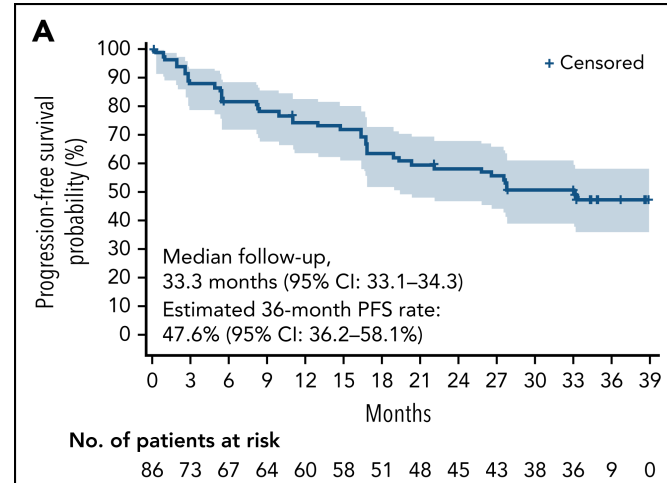
■ Ph 2

- n=86, median previous tx 2
- mF/U 18.4 mos
- ORR 84%
 - CR 68.6%
- DOR 19.5 mo
- mPFS 22.1 months



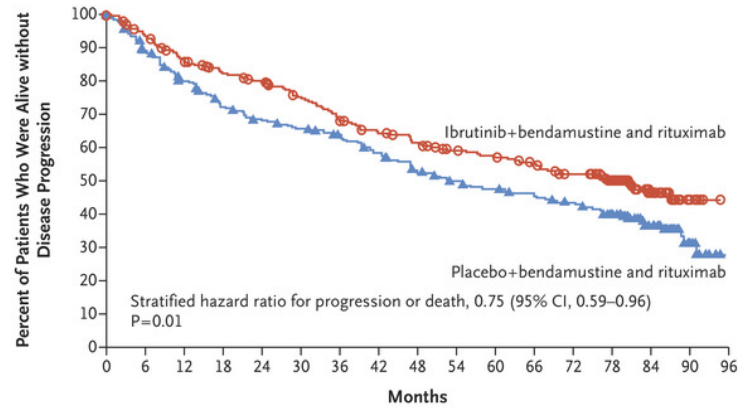
Zanubrutinib in MCL

	Response	PFS	
		2 years	3 years
Phase 2 86 Patients with R/R MCL Median follow-up 35.3 months	ORR 84% CR 78%	58%	48%
	Median DOR	OS	
	Not reached (95% CI: 24.9 months to NE)	2 years	3 years
		80%	75%
	Zanubrutinib was well tolerated		
	<ul style="list-style-type: none"> Few discontinuations (9.3%) due to AEs Majority of AEs: low-grade severity No atrial fibrillation/flutter No second primary malignancies 		



SHINE - BR +/- ibrutinib

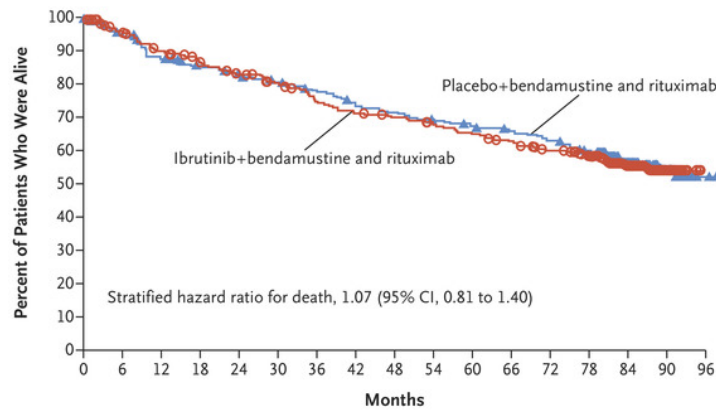
A Progression-free Survival



No. at Risk

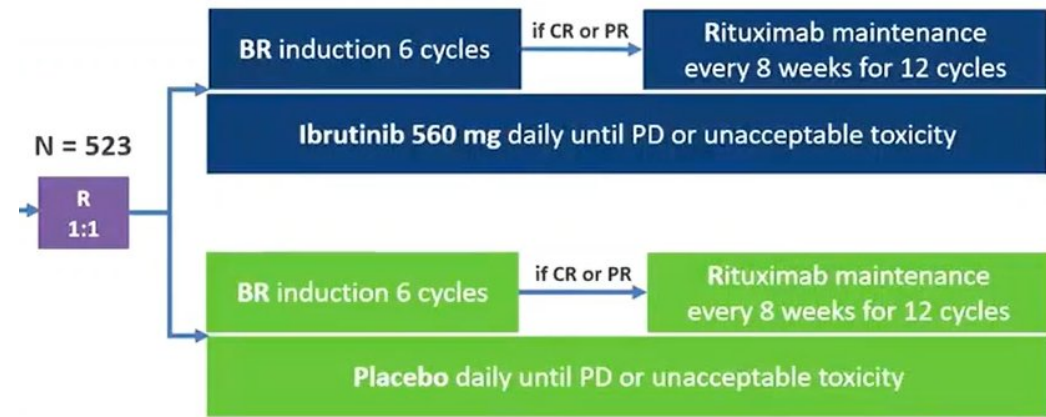
Ibrutinib+bendamustine and rituximab	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo+bendamustine and rituximab	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

B Overall Survival

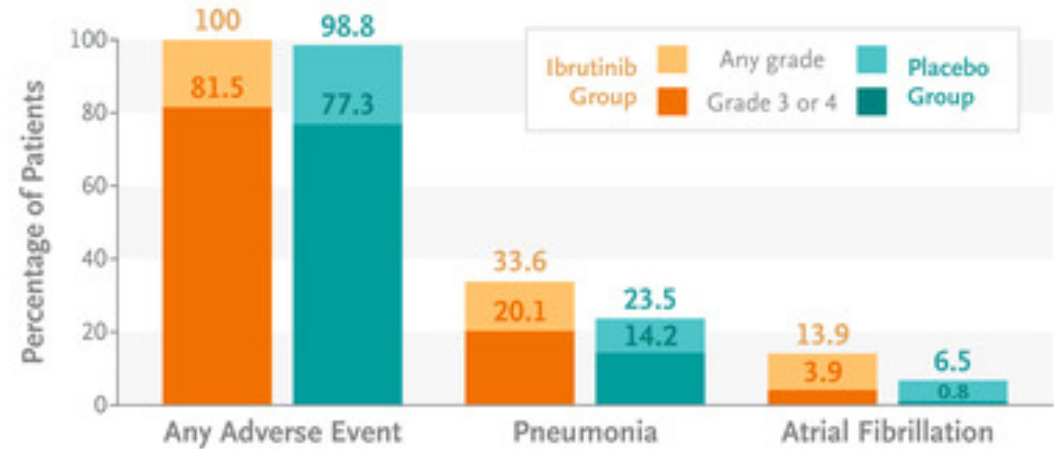


No. at Risk

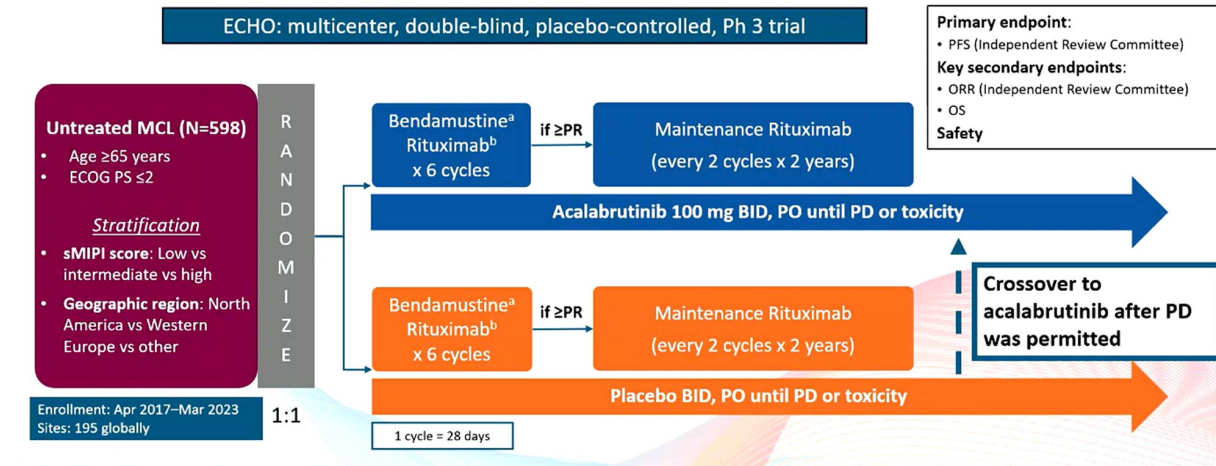
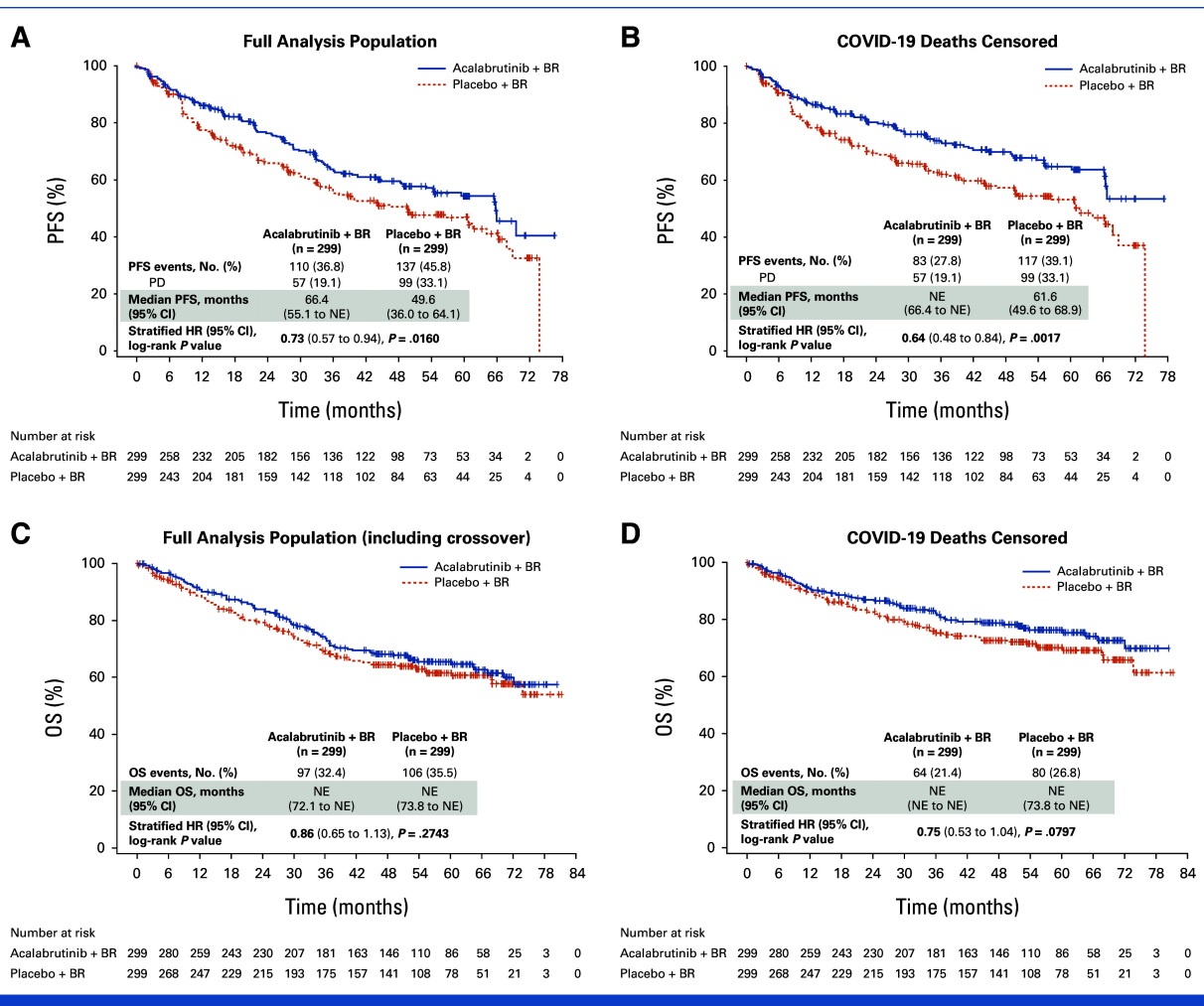
Ibrutinib+bendamustine and rituximab	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo+bendamustine and rituximab	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2



Adverse Events during Treatment



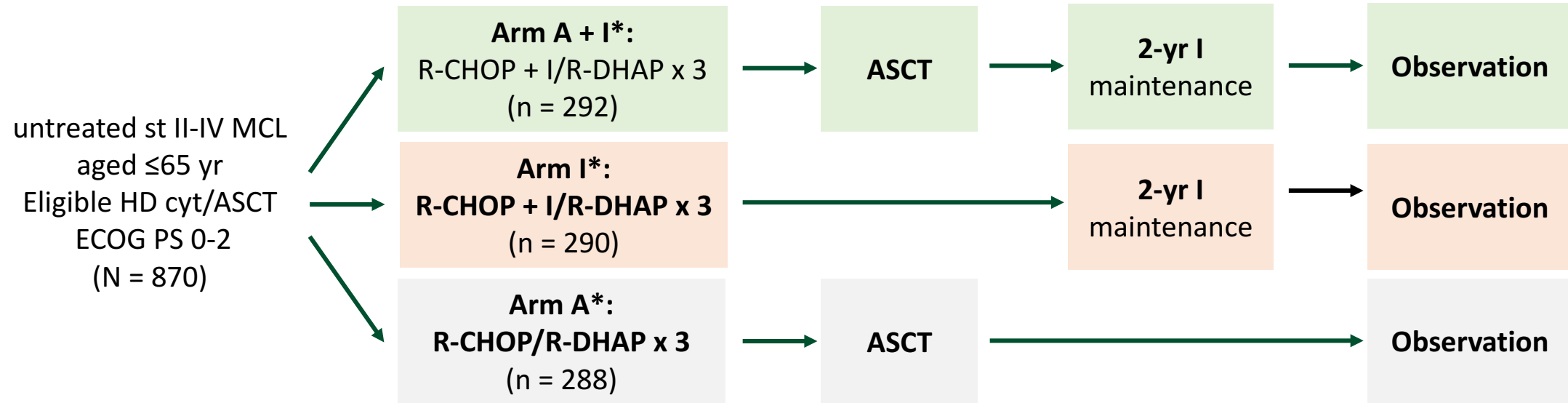
ECHO - BR +/- acalabrutinib



AE of Interest, n (%)	Acala + BR (n = 297)		Pbo + BR (n = 297)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Atrial fibrillation	18 (6.1)	11 (3.7)	13 (4.4)	5 (1.7)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Major bleeding	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Infections	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Second primary malignancies	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)

Ibrutinib in MCL

■ Ph 3, TRIANGLE

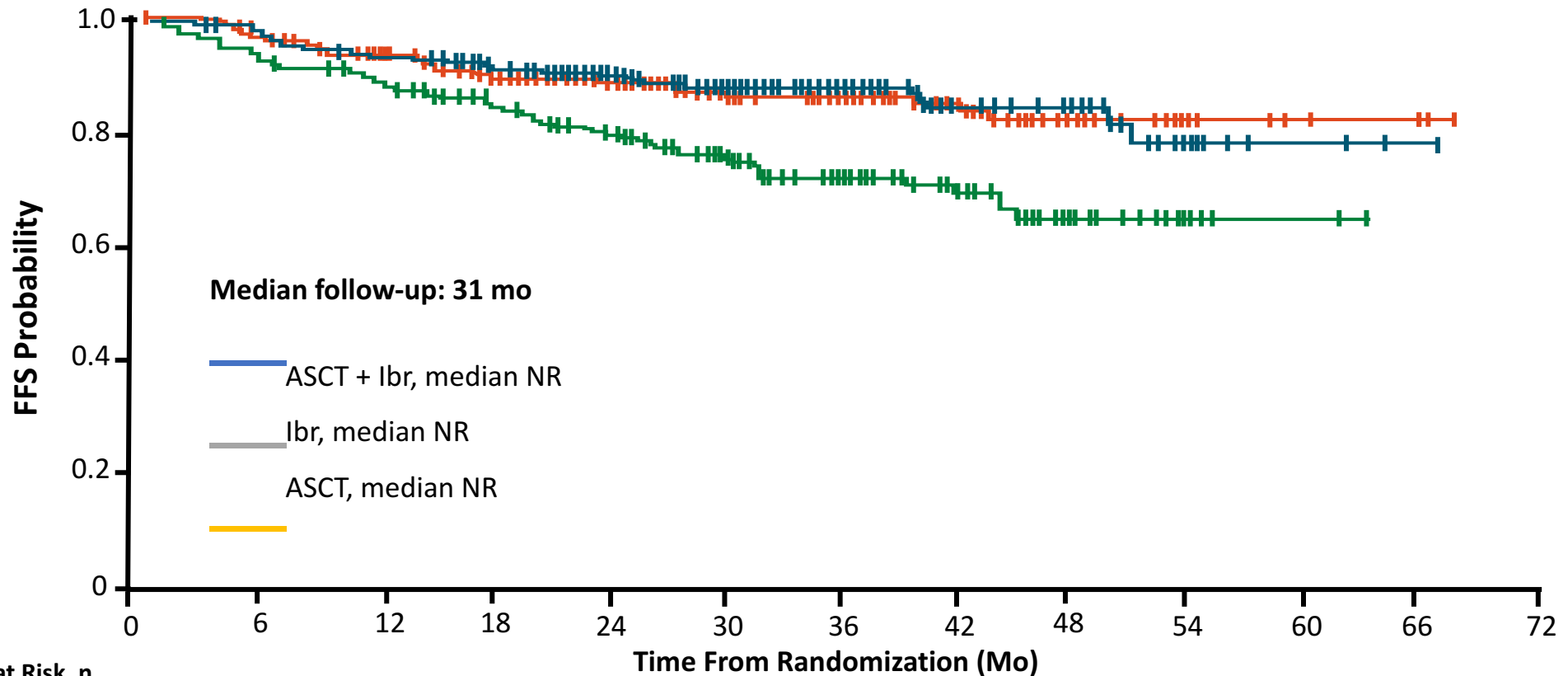


*R maintenance was added following national guidelines in all 3 arms (arm A + I: 57%; arm I: 54%; arm A: 58%).

- Primary endpoint: FFS
- Secondary endpoints: response rates, PFS, RD, OS, safety

Ibrutinib in MCL

■ FFS TRIANGLE



Patients at Risk, n

	0	6	12	18	24	30	36	42	48	54	60	66	72
ASCT + Ibr	292	270	253	226	184	137	109	65	40	17	3	1	
Ibr	290	269	257	229	180	133	100	68	34	16	4	3	
ASCT	288	252	237	206	162	126	85	54	27	12	2	0	

TRIANGLE — long-term follow-up (4-yr OS)

Updated readout, ASH 2024

- Median follow-up: 55 months (n=870 untreated MCL, ≤65 yr, transplant-eligible)
- FFS still superior with ASCT+I vs ASCT alone (82% vs 70%; HR 0.64, p=0.0026)
- Ibrutinib arm (I) ≈ ASCT+I — no FFS difference (HR 0.83, p=0.21)
- 4-yr OS: I 90%, ASCT+I 88%, ASCT alone 81%
- **ASCT alone is inferior to ibrutinib-containing arms in OS**
- High-risk benefit from A+I: Ki-67 >50% (HR 0.62), blastoid (HR 0.57), p53 >50% (HR 0.68)
- Toxicity penalty: Gr ≥3 blood/lymph 54%, infections 34% in A+I

90%

4-yr OS
ibrutinib arm

88%

4-yr OS
ASCT + I

81%

4-yr OS
ASCT alone

0.64

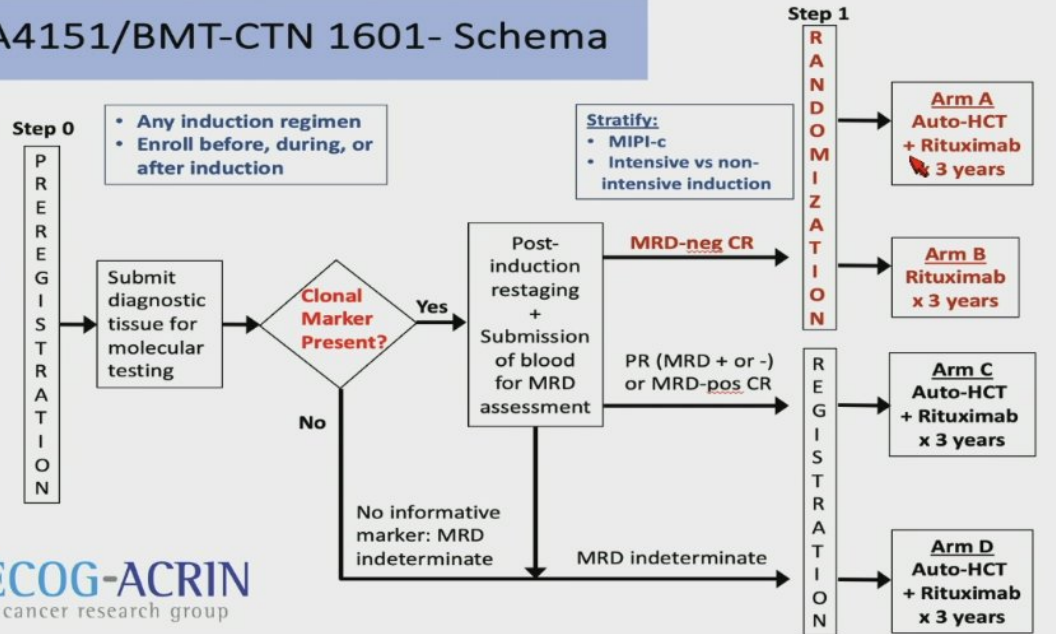
FFS HR
A+I vs A

Practice-changing implication

Ibrutinib + R-CHOP/R-DHAP with 2-yr maintenance is a new standard; ASCT may be safely omitted in younger MCL — pending OS A+I vs I.

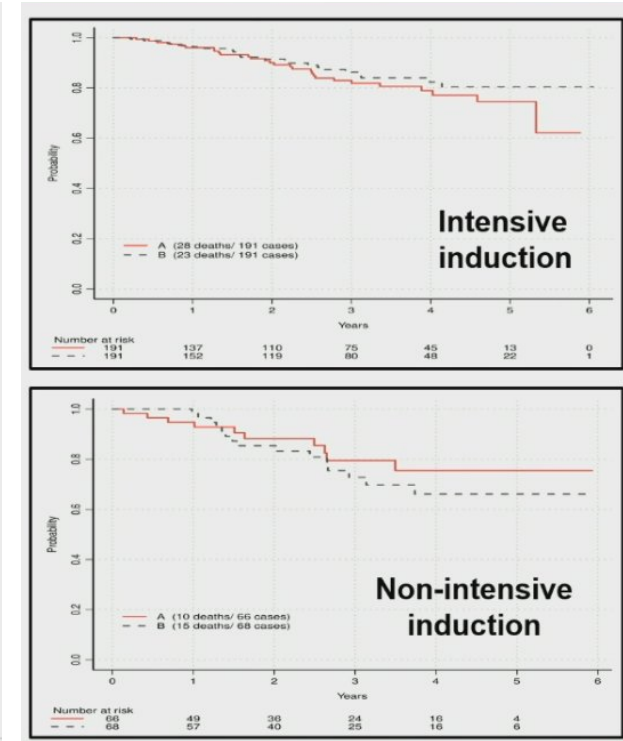
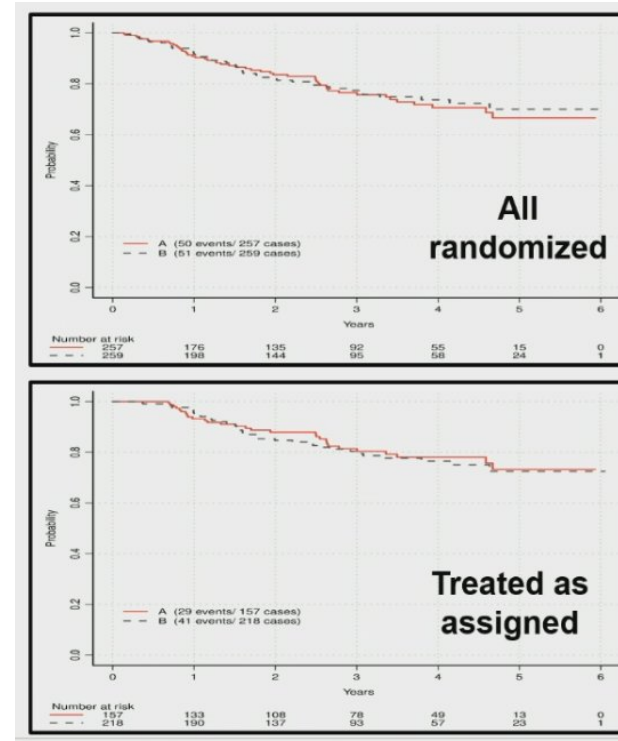
ASCT in MCL – ECOG-ACRIN 4151

EA4151/BMT-CTN 1601- Schema

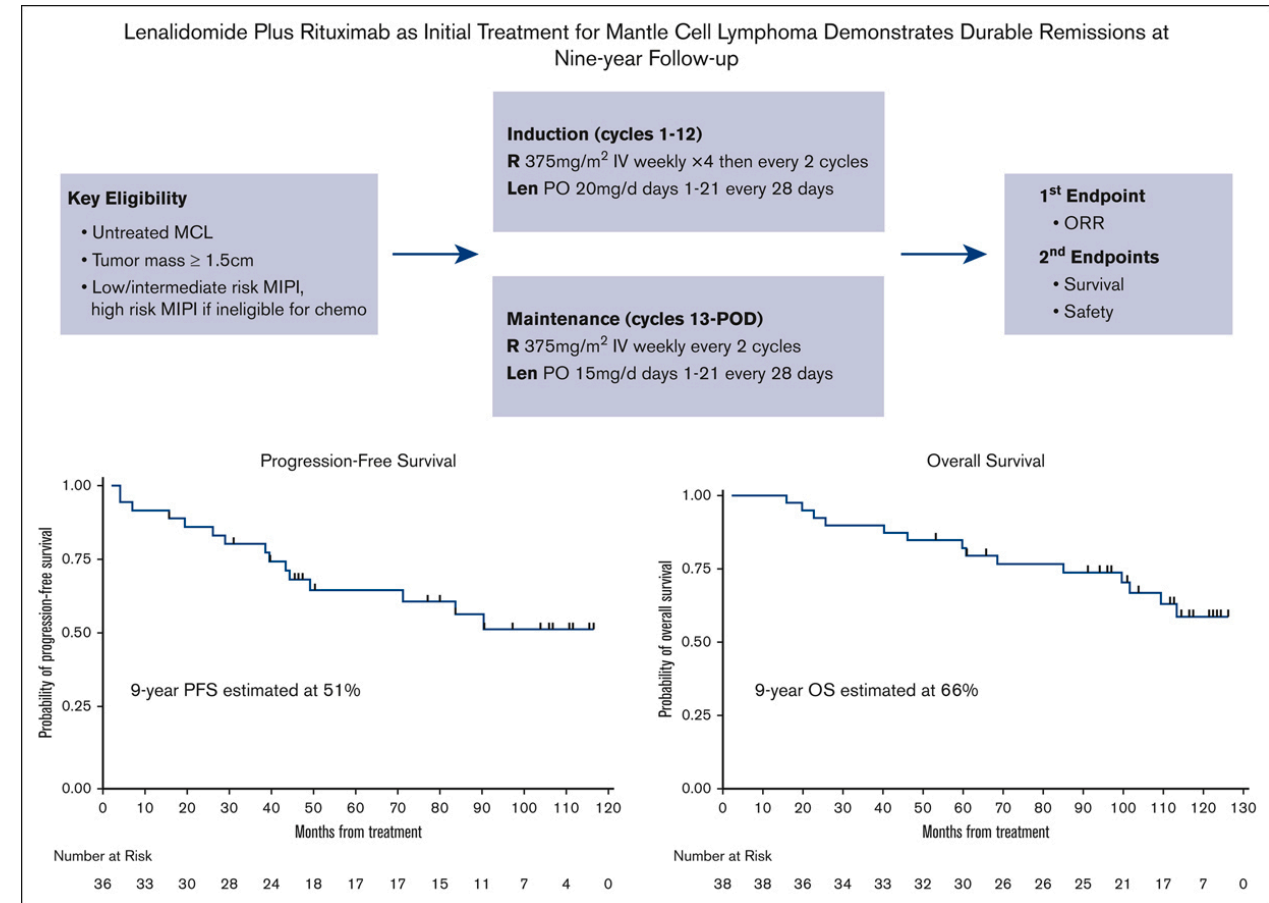
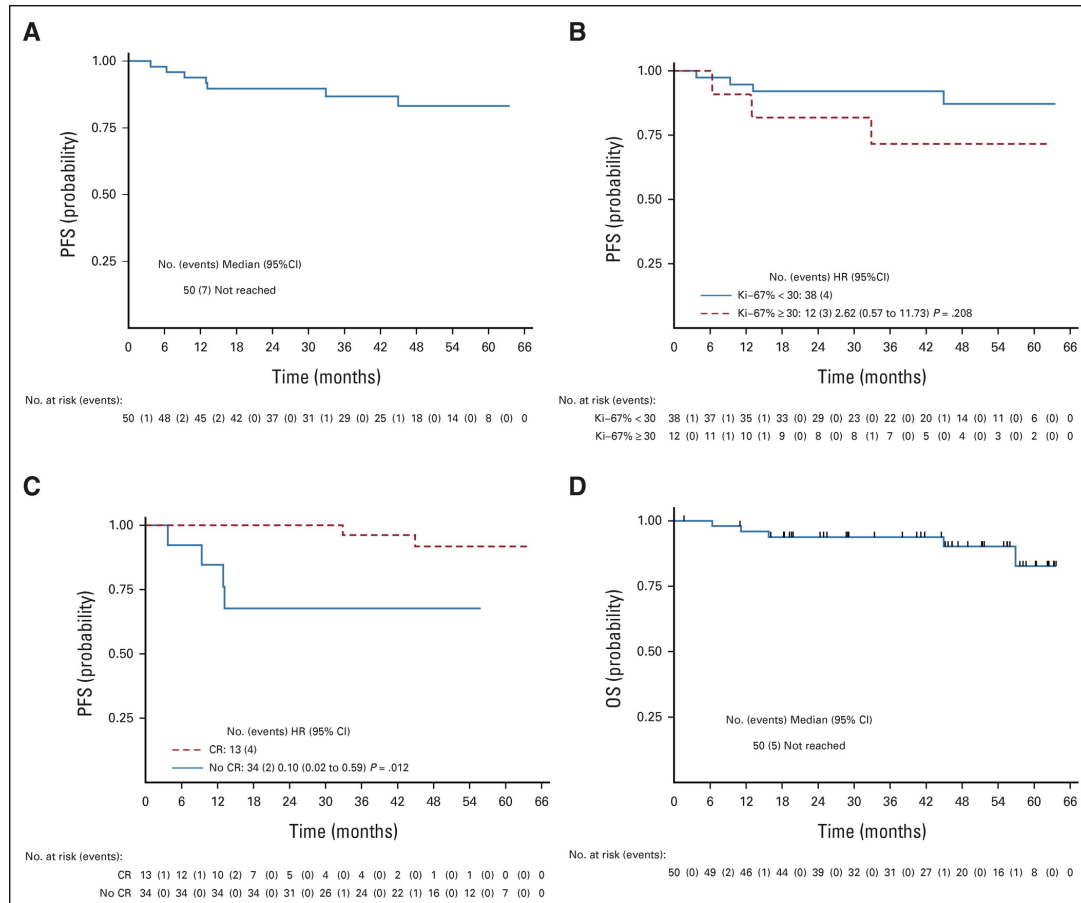


PFS

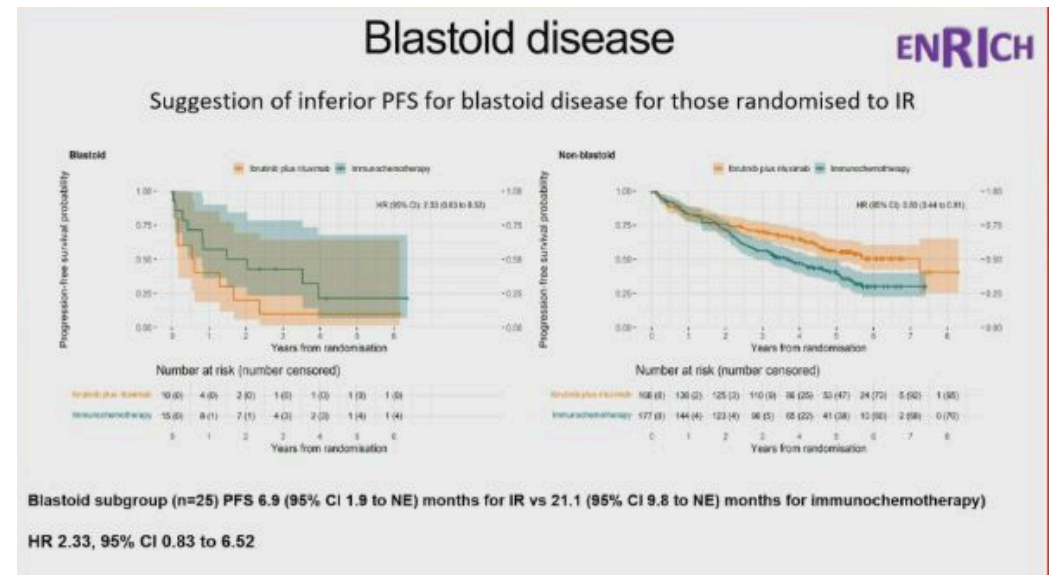
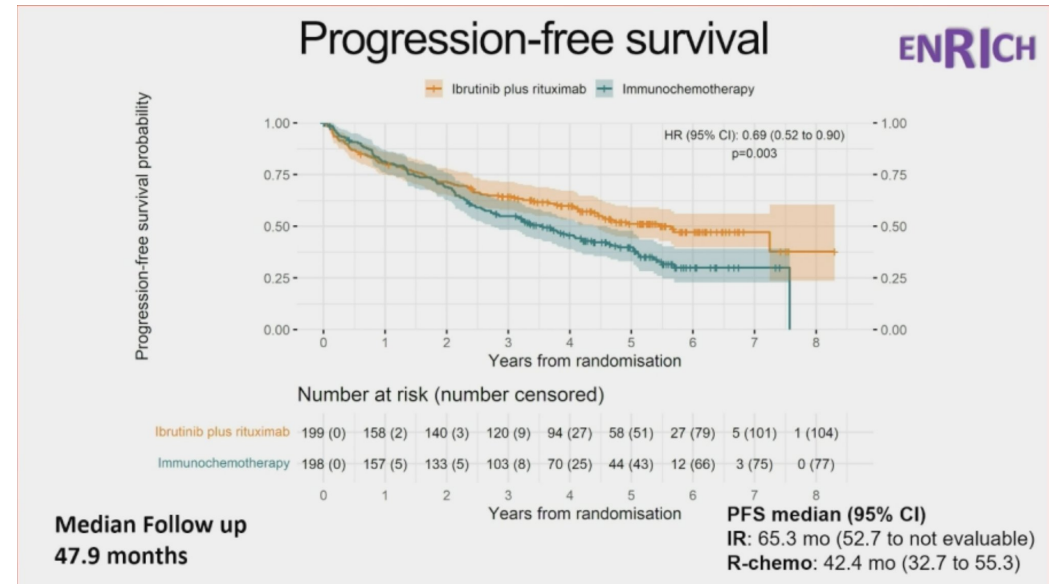
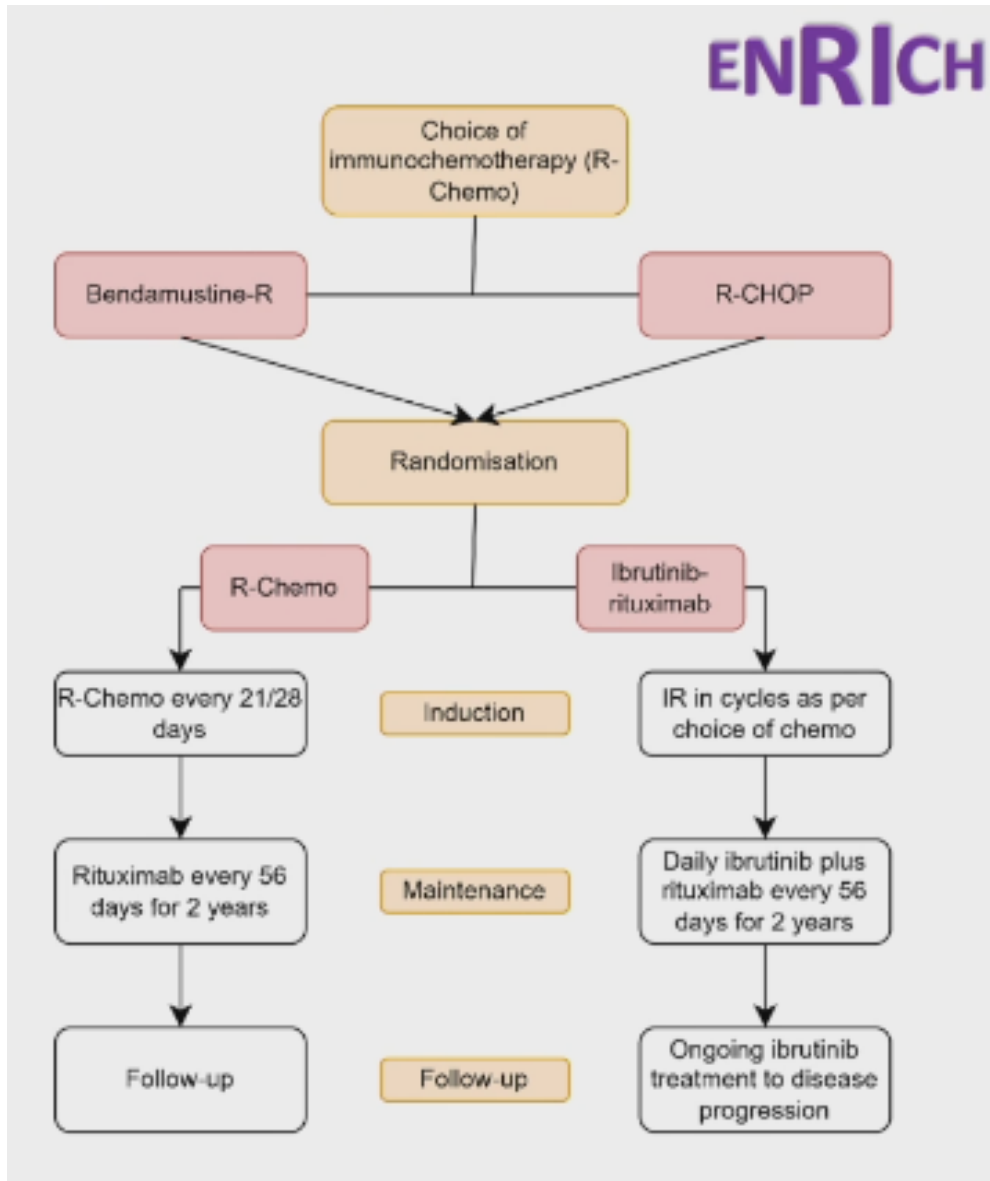
OS



■ First line therapy – R-ibrutinib, R-lenalidomide



BTKi in 1L – ENRICH – R-Ibrutinib vs R-chemo



ENRICH — ibrutinib + rituximab vs R-chemo in older MCL

Phase 2/3, age ≥60, untreated MCL

- n=397 (IR 199 vs R-chemo 198); 66 sites, UK + Nordic countries
- Investigator-chosen comparator: R-CHOP (n=53) or BR (n=145)
- IR: ibrutinib 560 mg daily + R x6–8, then R maintenance q8wk x2 yr; ibrutinib until PD
- Median follow-up 47.9 months (IQR 27.1–63.3)

- Median PFS: IR 65.3 mo vs R-chemo 42.4 mo — HR 0.69 (95% CI 0.52–0.90), p=0.0034

- **Benefit driven by R-CHOP subgroup — HR 0.37 (0.22–0.62); BR subgroup HR 0.91 (0.66–1.25) ≈ neutral**

- Gr ≥3 AEs: IR 67% vs R-chemo 70%; IR — less heme tox (17%), more cardiac

65.3

mPFS (mo)
IR arm

42.4

mPFS (mo)
R-chemo

0.69

PFS HR
overall

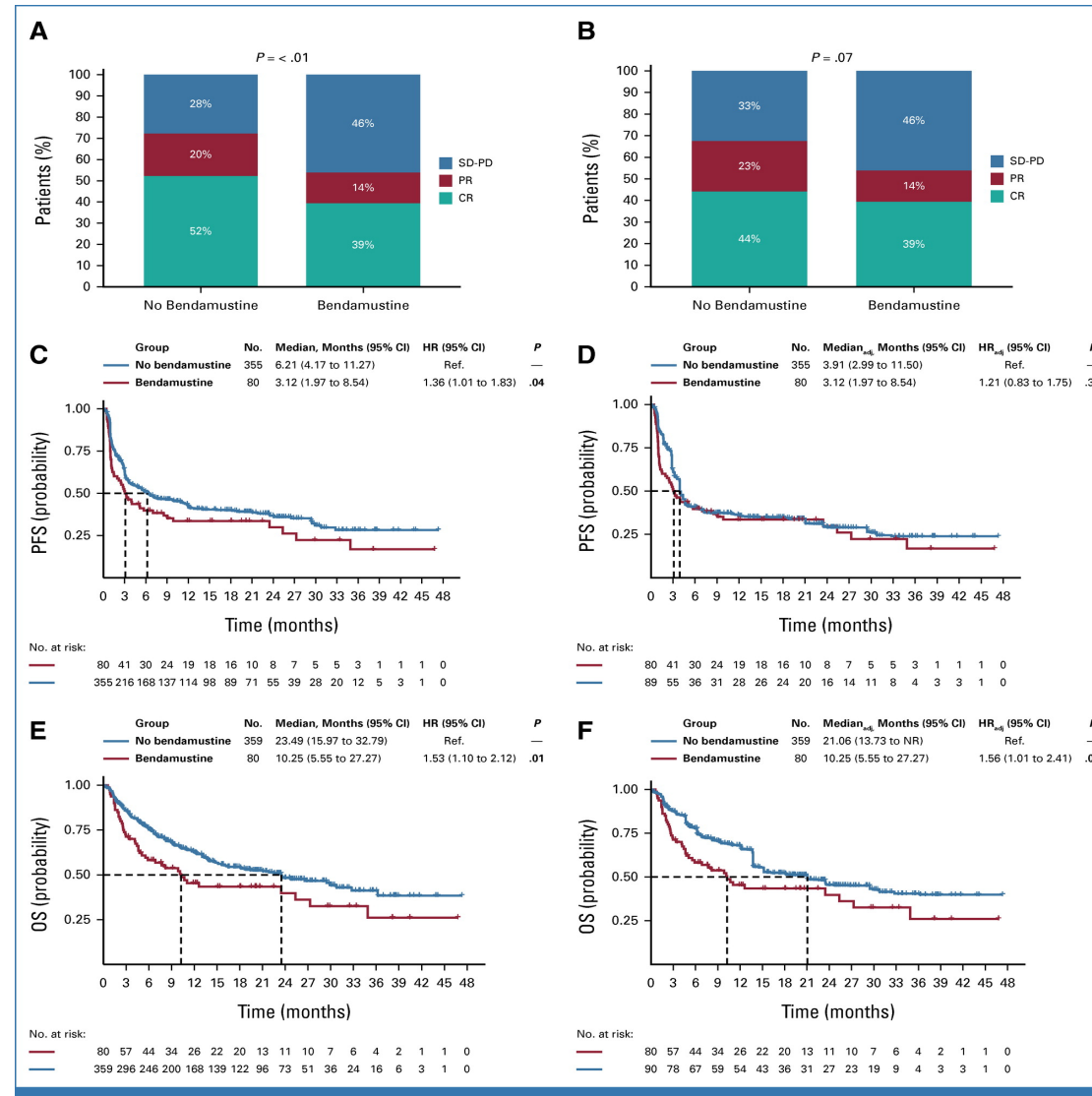
0.37

PFS HR
vs R-CHOP

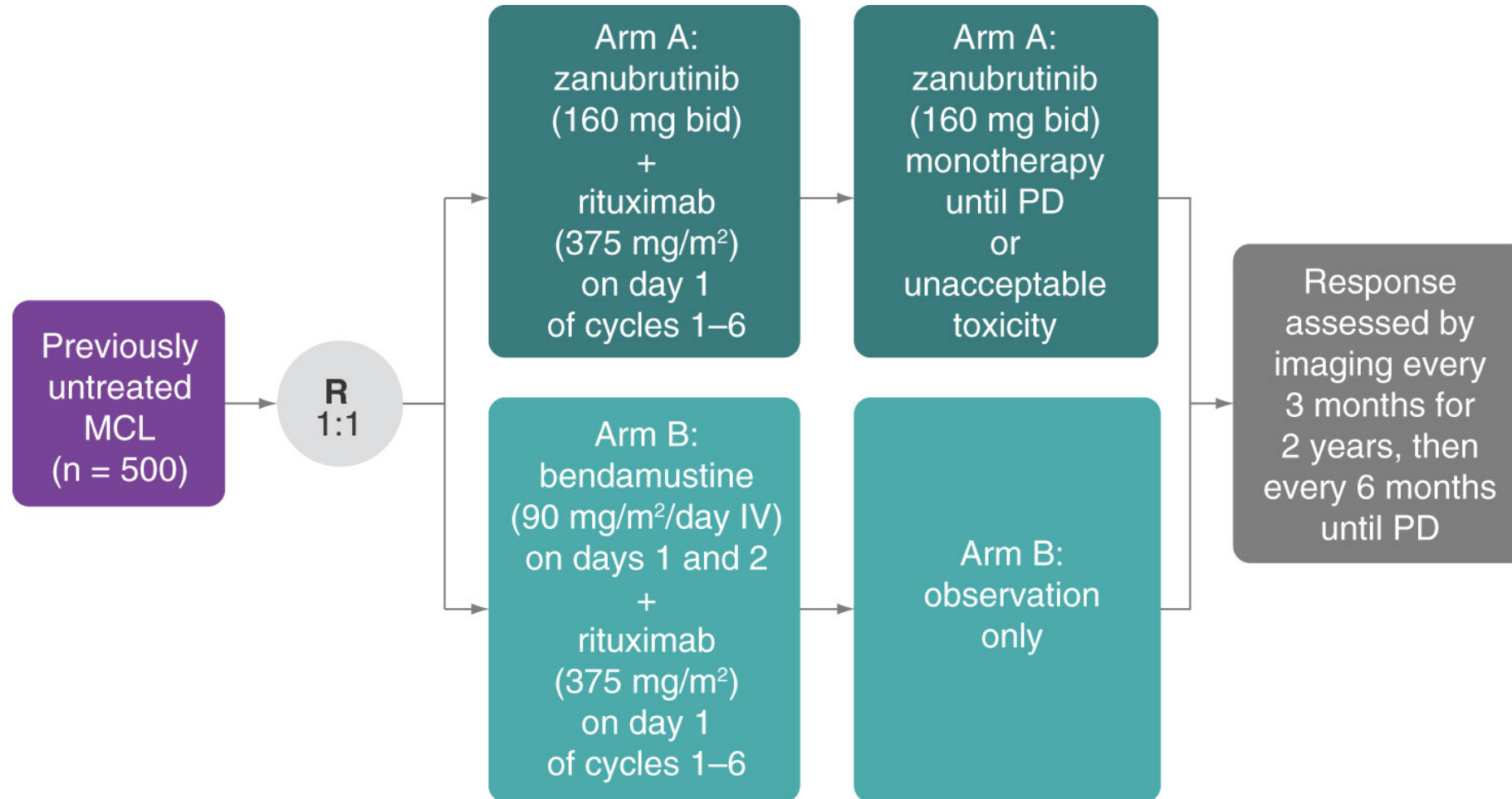
Practice takeaway

IR is a new 1L standard option for older MCL — especially as an R-CHOP alternative. BR remains competitive; choice now turns on toxicity profile and downstream CAR-T plans.

Bendamustine impact on CAR-T



BTKi in 1L – MANGROVE – R-Zanubrutinib vs R-bendamustine



BOVen frontline — TP53-mutated MCL

Zanubrutinib + obinutuzumab + venetoclax — chemo-free, MRD-driven

- Multicenter Ph 2, untreated TP53-mutated MCL
- n=25; median age 65; 60% blastoid/pleomorphic; median Ki-67 50%
- Zanu 160 mg BID continuous + obin 1000 mg + ven (ramp-up to 400 mg)
- **MRD-guided fixed duration — discontinue when CR + uMRD (10^{-6}) achieved**
- **18/25 (72%) completed 24 cycles — all in CR; PB uMRD-5 100% (17/17), uMRD-6 71% (12/15) → protocol discontinuation**
- 2-yr PFS 72% • 2-yr disease-specific survival 91% • 2-yr OS 76%
- Compares favorably to historical chemoimmunotherapy in TP53-mut (mPFS ~11 mo, mOS ~22 mo)
- Safety: diarrhea 64% (mostly Gr 1-2), COVID 56%, neutropenia 32% Gr ≥3

96%

ORR
(n=25)

88%

CR rate

72%

2-yr
PFS

76%

2-yr
OS

Bottom line

BOVen rescues outcomes in TP53-mutated MCL — a population historically chemorefractory with mOS <2 yr. MRD-guided, fixed-duration, chemo-free.

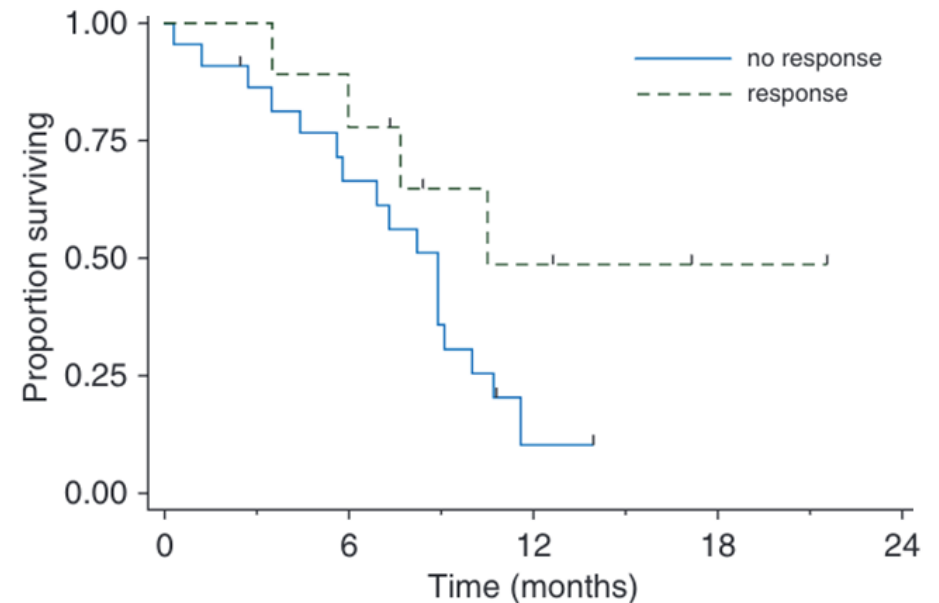
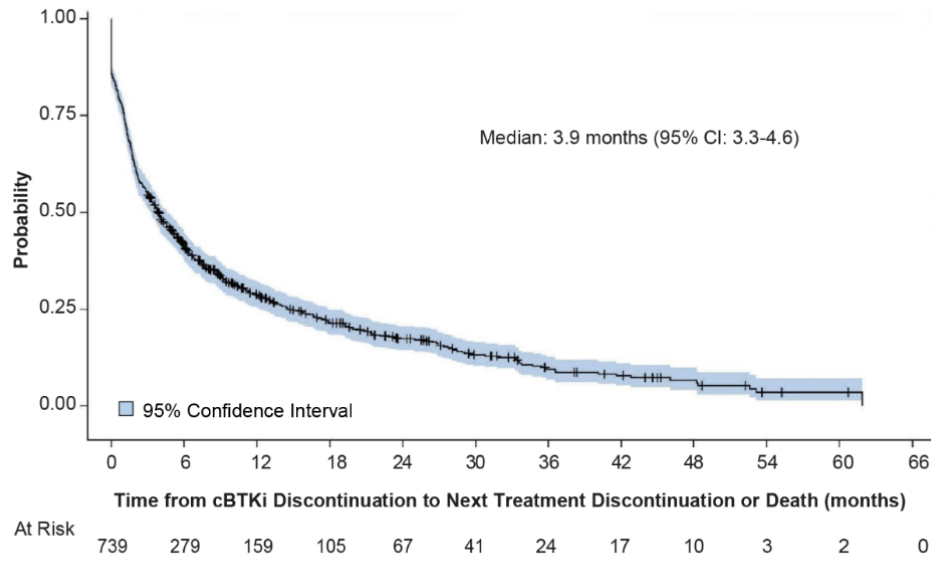
cBTKi failures

What's next

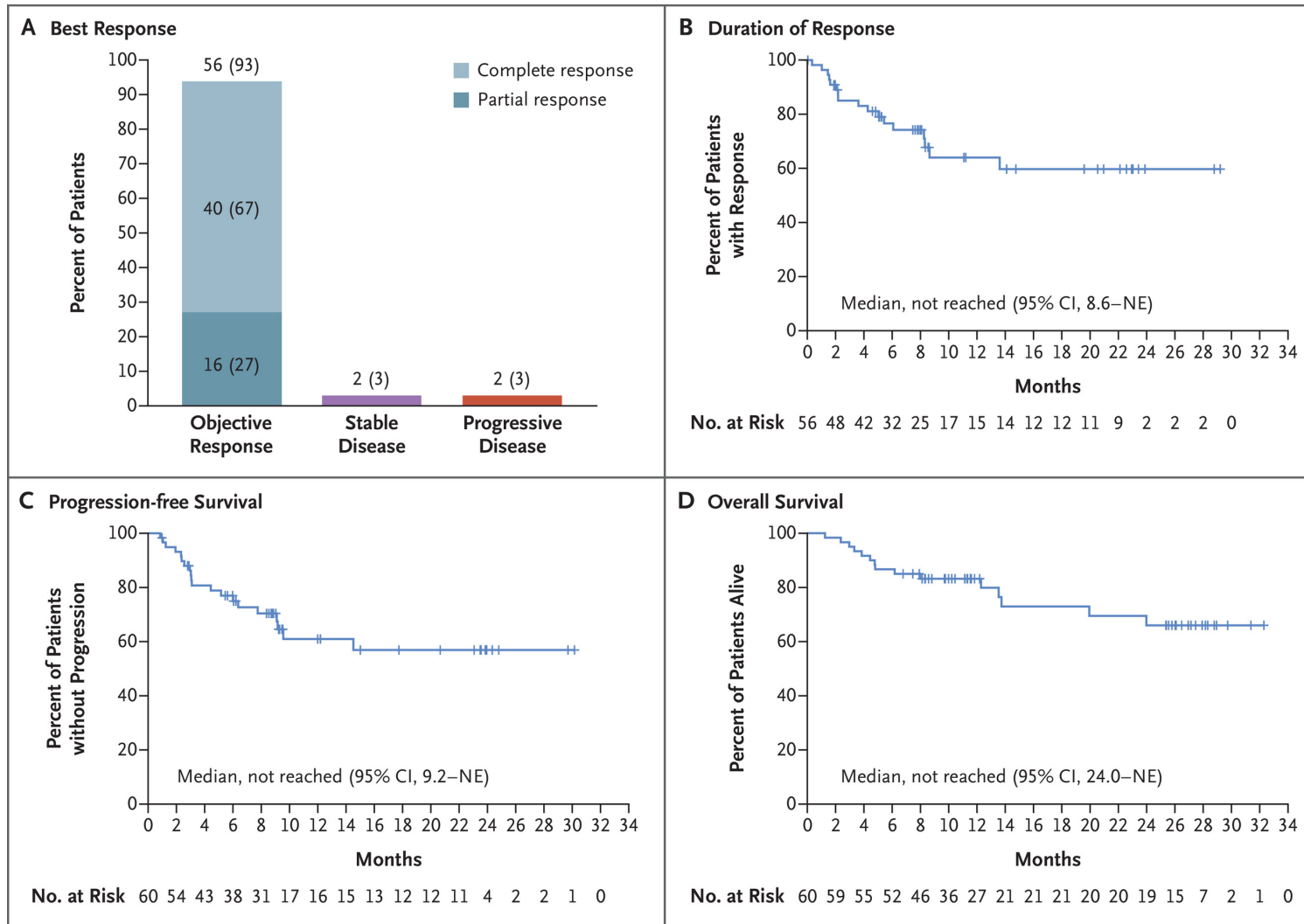
Outcomes were poor after cBTK failure in MCL

- BTK resistance poorly understood
- C481S-mutations uncommon
 - bypass alterations & epigenetic changes
- Poor survival

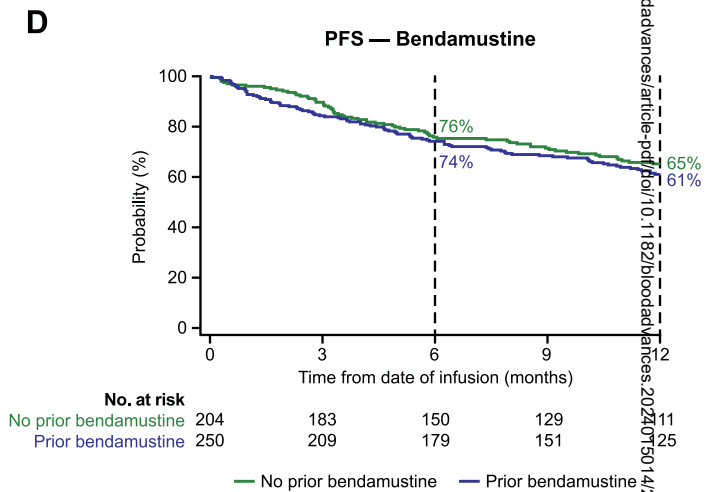
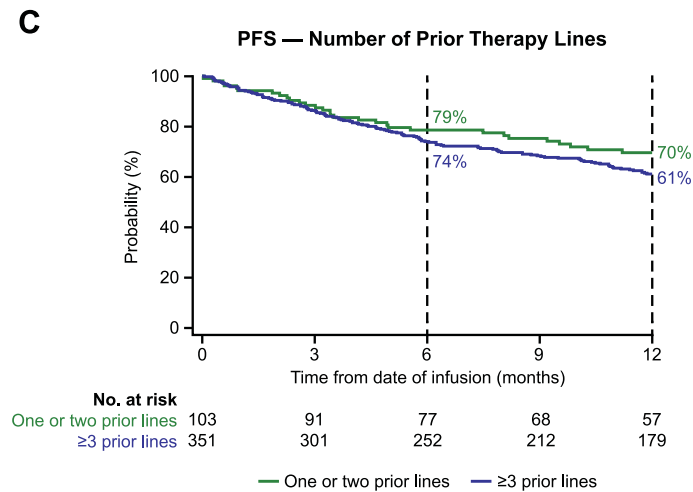
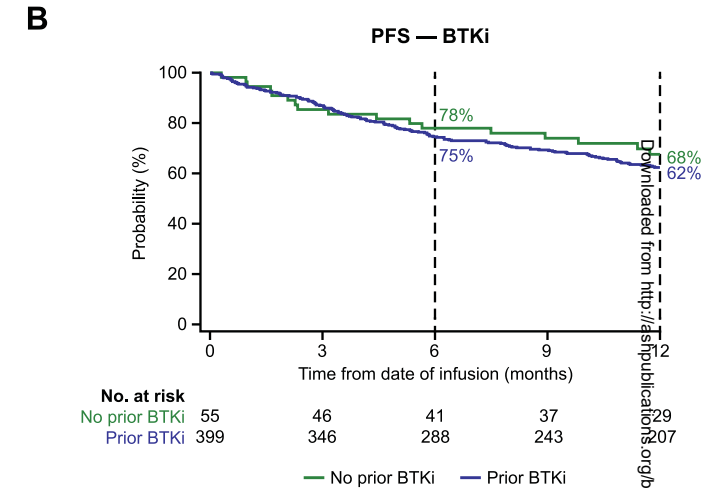
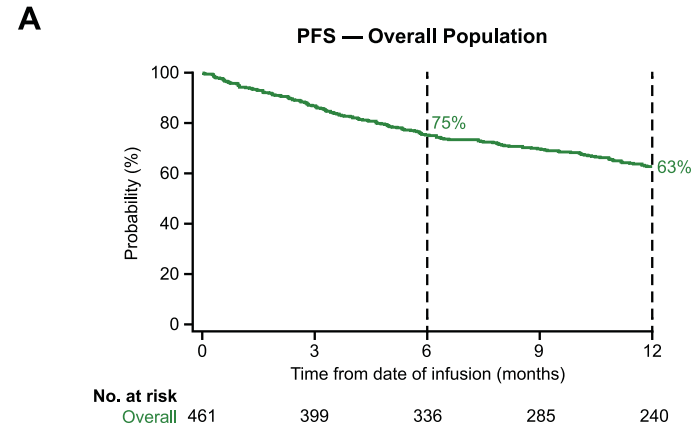
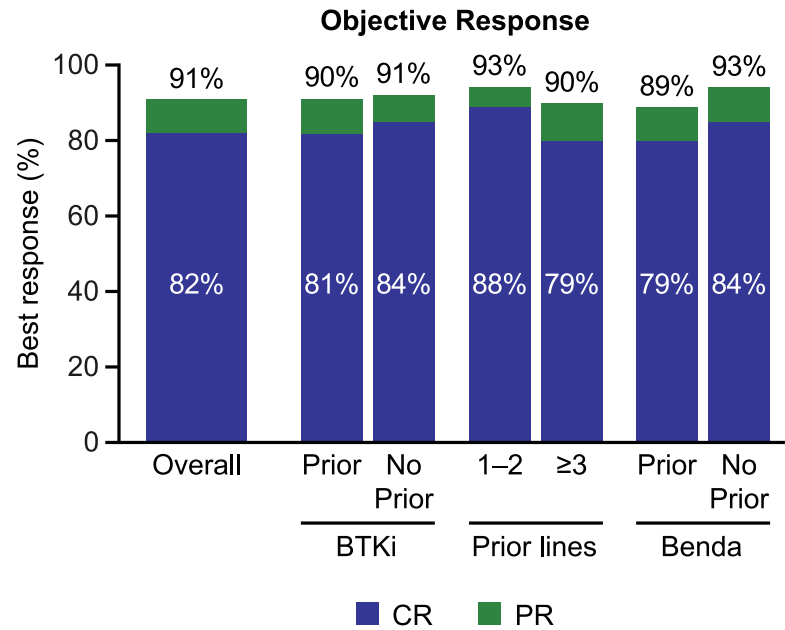
Time from cBTKi Discontinuation to Subsequent Treatment Failure or Death



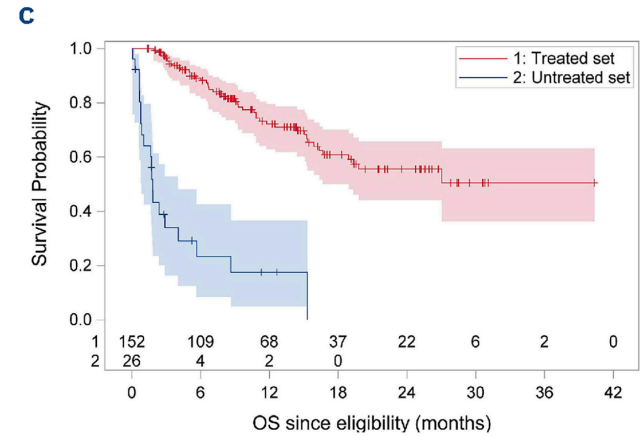
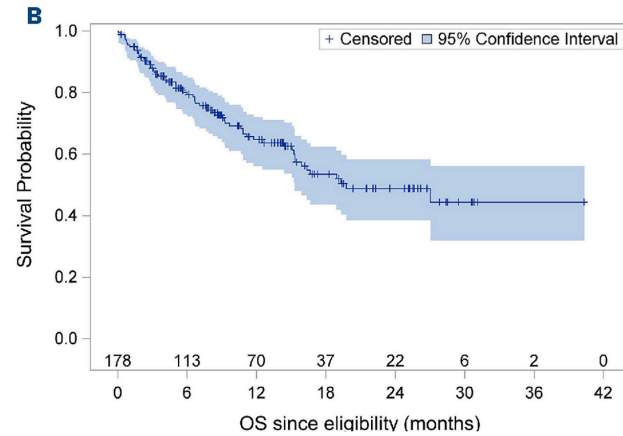
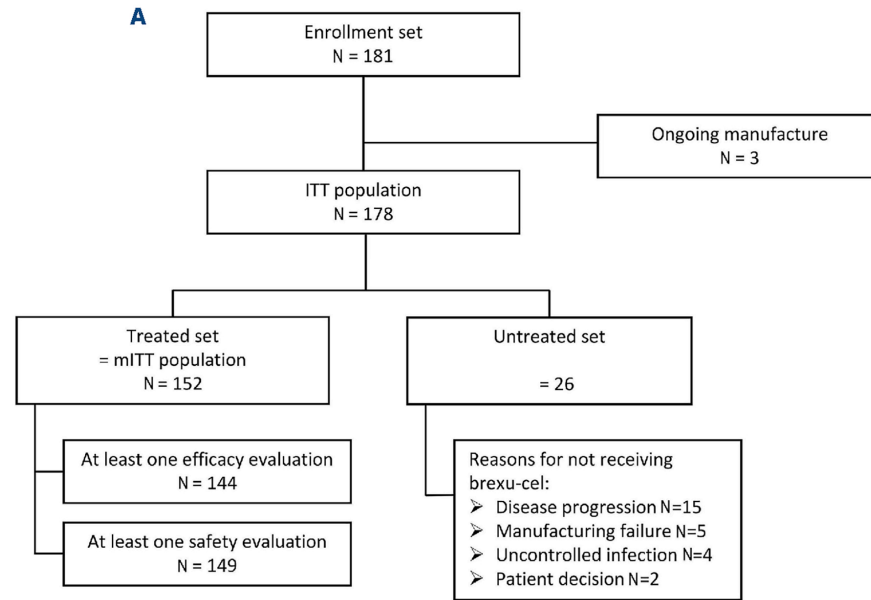
CAR-T cell therapy – brexucabtagene autoleucel



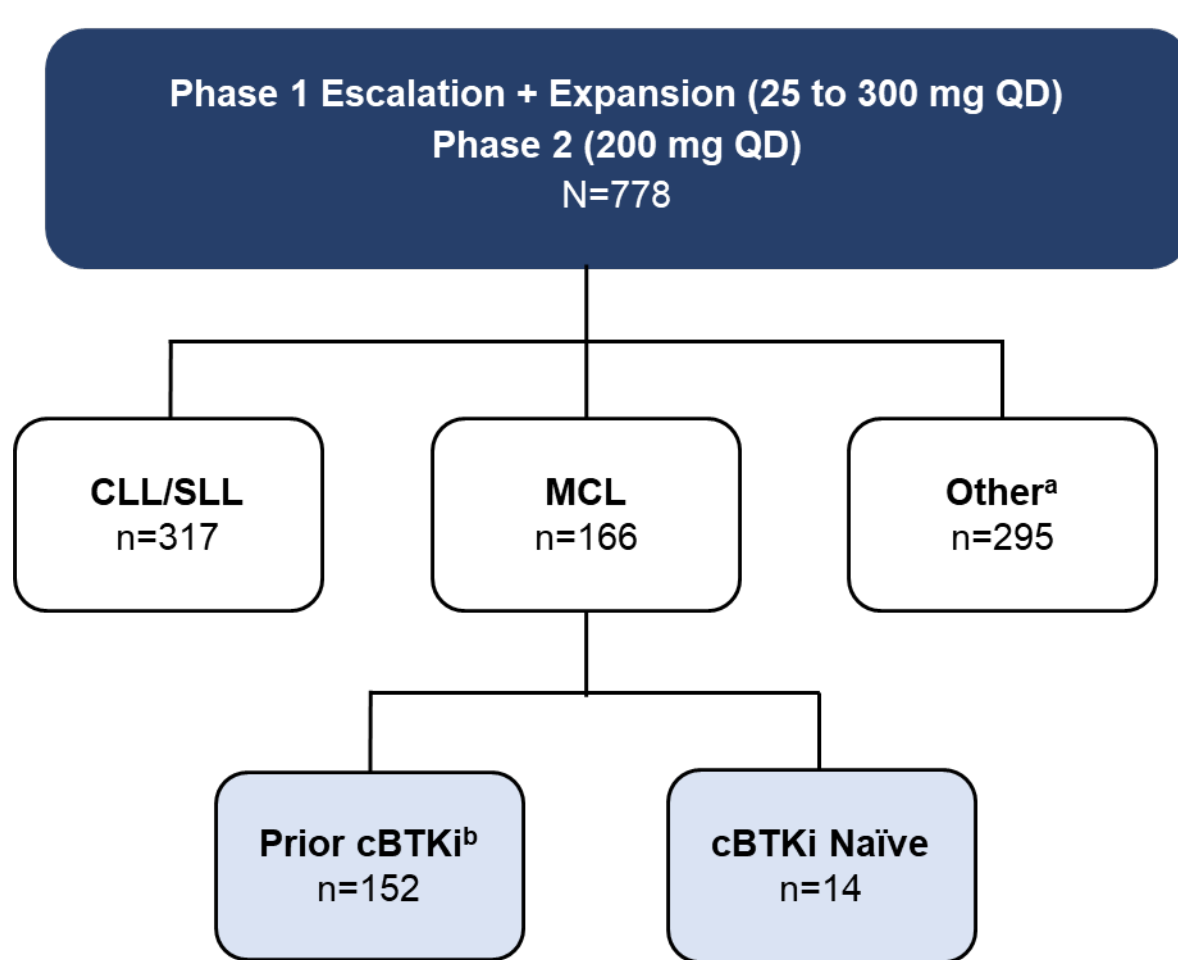
CAR-T cell therapy – brexucabtagene autoleucel



CAR-T cell therapy – brexucabtagene autoleucel ITT



BRUIN – Pirtobrutinib Ph 1-2 in NHL



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

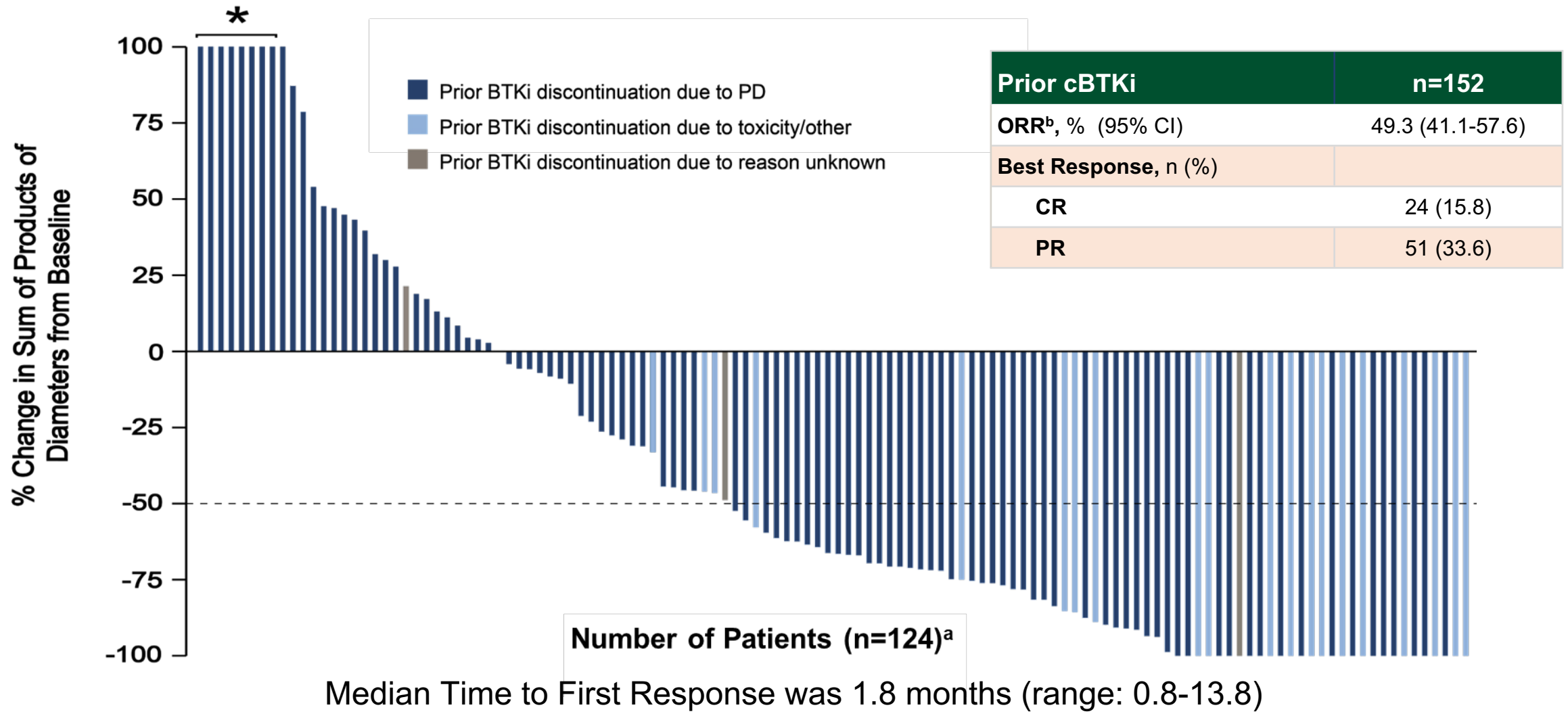
Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

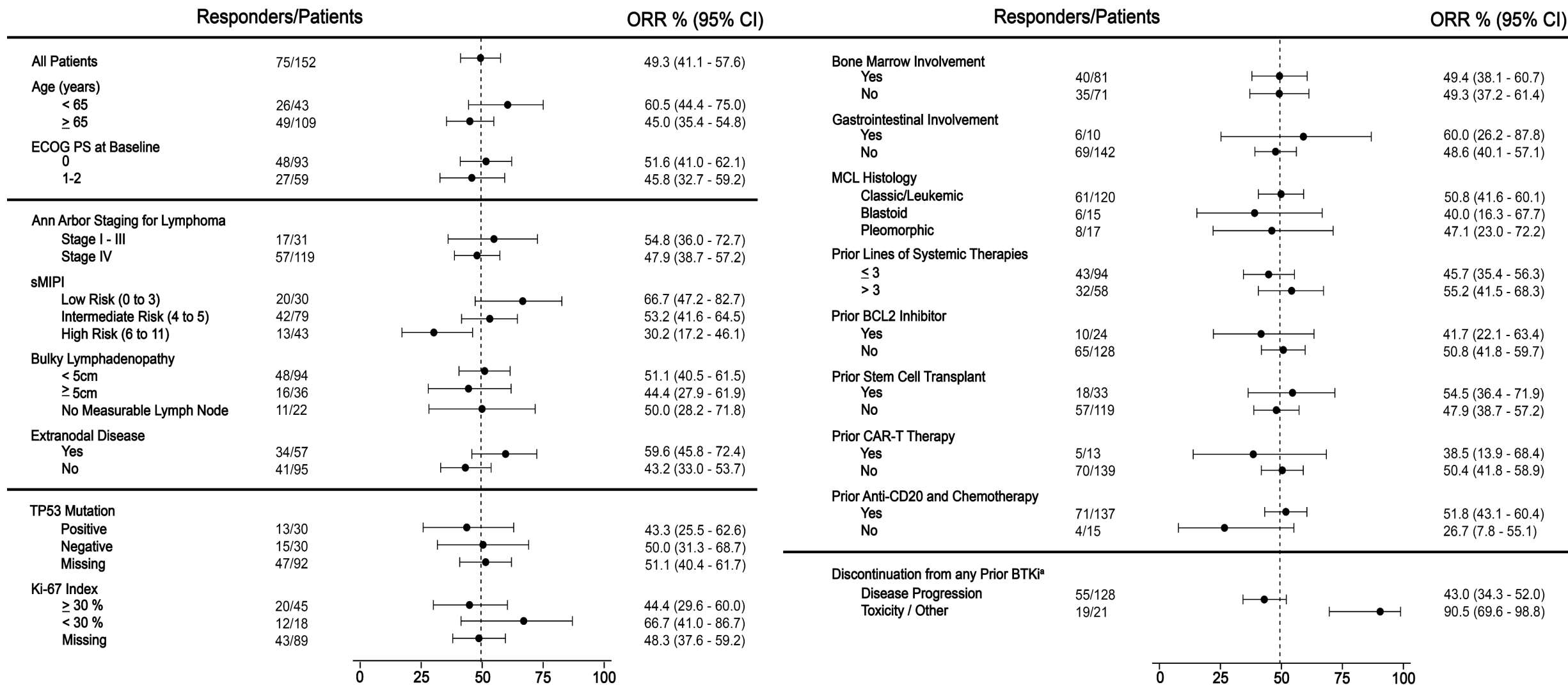
Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

BRUIN – Pirtobrutinib in R/R MCL – Prior BTKi

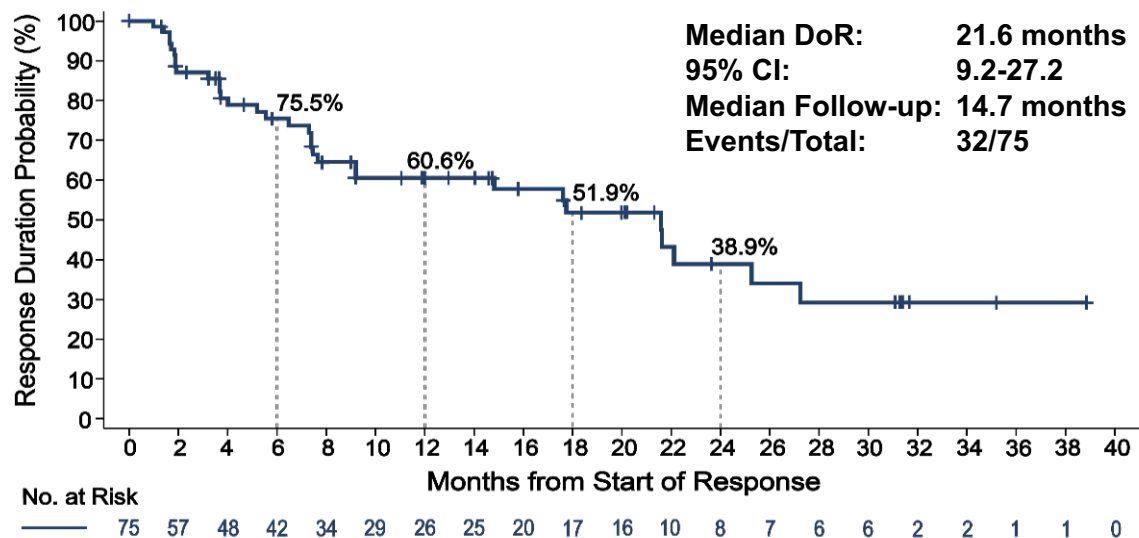


BRUIN – Pirtobrutinib in R/R MCL – Prior BTKi

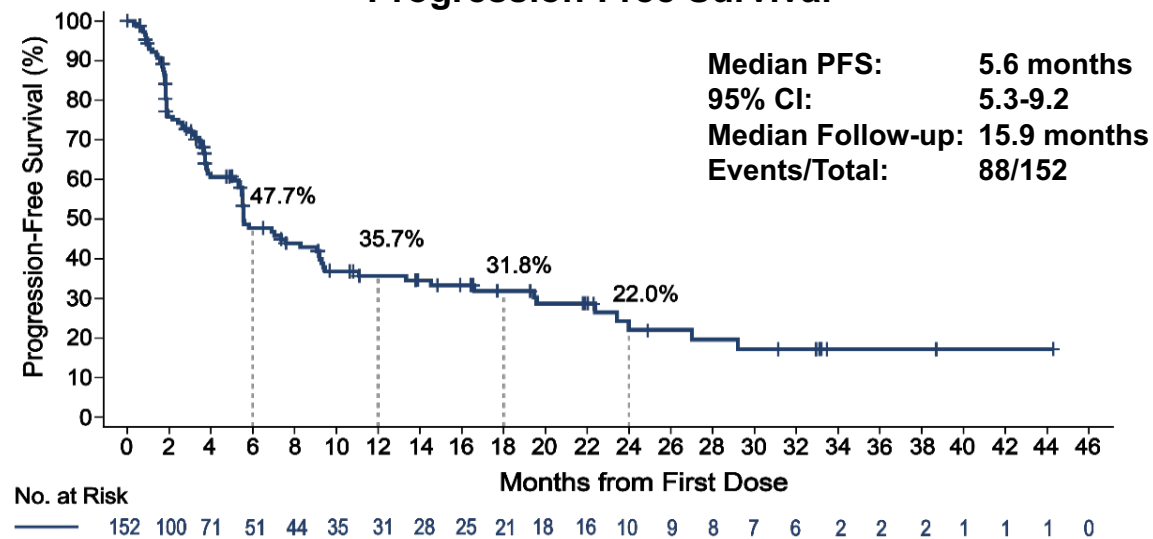


BRUIN – Pirtobrutinib in R/R MCL – Prior BTKi

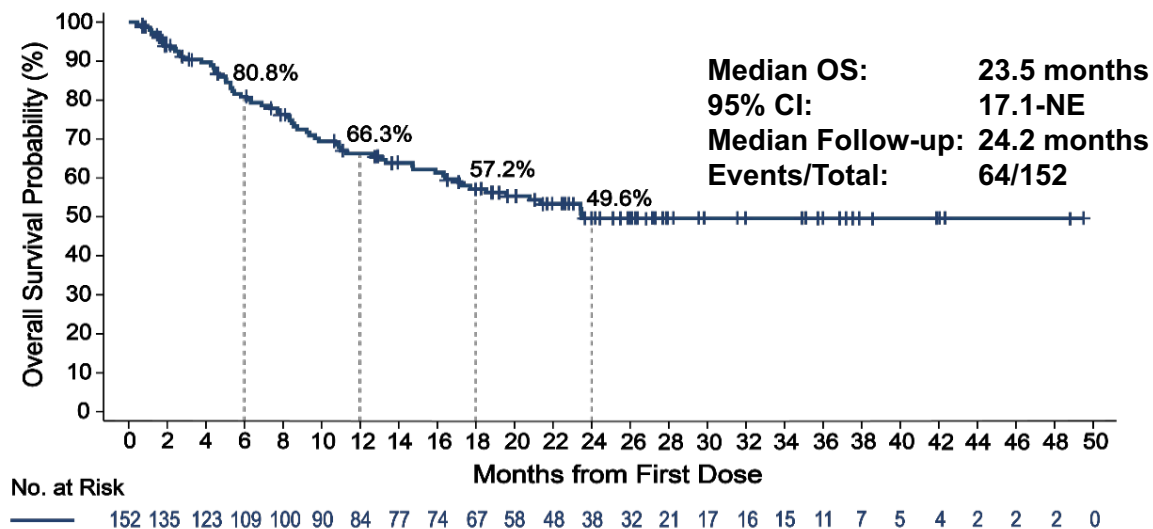
Duration of Response



Progression-Free Survival



Overall Survival



BRUIN – Pirtobrutinib in MCL

Adverse Event	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
	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	42.8	19.9	15.7	3.6
Bruising	16.3	0.0	11.4	0.0
Rash	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter	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

Sonrotoclax — FDA approved May 13, 2026

First-in-class next-generation BCL2 inhibitor

- Accelerated approval — adults with R/R MCL after ≥ 2 prior lines including a BTK inhibitor
- $\sim 10\times$ more potent and more selective than venetoclax (preclinical)
- Dose: 320 mg PO daily after 4-week ramp-up (TLS mitigation)

- BGB-11417-201 — Ph 1/2, single-arm, n=125 (efficacy n=103, safety n=115); mFU 14.2 mo

- CR 15.5% (95% CI 9.1–24.0); mPFS 6.5 mo
- Chinese subpop ORR 62% (n=34)

52%

ORR (IRC)
95% CI 42–62

15.8 mo

Median DOR
95% CI 7.4–NE

1.9 mo

Median time
to response

61%

ORR if < 3
prior lines

In a post-BTKi population where historical ORR ~ 25 –40% and median OS < 12 months

Safety (n=115)

Gr ≥ 3 neutropenia 19% • Pneumonia 10% • TLS (any/Gr ≥ 3) 7% / 7% • SAE 37% • D/C for AE 14%

Sonrotoclax — where it fits & what is next

Sequencing in R/R MCL after BTKi

- Post-cBTKi outcomes historically dismal (mOS ~6–10 mo)
- Pirtobrutinib — ORR 49%, mDOR 21.6 mo, mPFS 5.6 mo (BRUIN)
- Brexu-cel — ORR 91%, durable, but access/eligibility limited
- Sonrotoclax — oral, non-covalent target, ORR 52%, mDOR 15.8 mo
- Active across high-risk subsets — TP53-mut, blastoid, prior BCL2i
- Practical edge over venetoclax: shorter ramp-up, fewer interruptions, low Gr ≥3 TLS in schema

Pipeline & combinations

- **BGB-11417-101 R/R MCL cohort: sonro + zanu (n=51)**
At RP2D 320 mg: ORR 80%, CR 61%
24-mo DOR rate 80.1% (95% CI 49.4–93.3)
No DLTs; MTD not reached
- CELESTIAL-RRMCL (Ph 3): sonro + zanu vs zanu in R/R MCL
- 1L MCL: sonro + zanu + obinutuzumab — fixed-duration, chemo-free
- Sonro + pirtobrutinib in R/R MCL — ongoing

Bottom line

Sonrotoclax adds a third oral salvage option (alongside pirtobrutinib and CAR-T) for post-BTKi MCL — and is the most likely backbone for next-gen chemo-free, fixed-duration MCL regimens.

Glofitamab in R/R MCL — CD20×CD3 bispecific

Phase 1/2 NP30179 — fixed-duration, post-BTKi

- n=60 evaluable; median 2 prior lines (1–5); 73% refractory to last
- 52% had prior BTKi; 94% of those were BTKi-refractory
- Fixed-duration: 12 cycles, with obinutuzumab pretreatment (Gpt 1000–2000 mg)
- Median DOCR: 15.4 months; majority of CRs ongoing at cut-off
- Post-BTKi subgroup: ORR 74%, CR 71%, mPFS 8.6 mo, mDOCR 12.6 mo
- CRS 70% (mostly Gr 1/2); lower with 2000 mg Gpt (64%) vs 1000 mg (88%)

85%

ORR
(all patients)

78%

CR rate
(all patients)

16.8 mo

Median PFS
all patients

74%

ORR if
prior BTKi

Where it fits

Post-BTKi salvage — likely after CAR-T (or instead of CAR-T when leukapheresis/manufacturing/access is a barrier). Sequencing with sonrotoclax and pirtobrutinib still being defined.

BTK degraders — bexobrutideg & BGB-16673

Beyond inhibition: targeted protein degradation of BTK

- Mechanism: bivalent small molecule recruits E3 ligase → BTK ubiquitinated and degraded
- **Active regardless of BTK kinase function or C481/non-C481 resistance mutations**
- Active after both cBTKi AND ncBTKi (pirtobrutinib) failure

- Bexobrutideg (NX-5948, Nurix) — Ph 1a/b NX-5948-301
- BGB-16673 (BeOne) — Ph 1 CaDAnCe-101 in R/R CLL
- *MCL cohorts enrolled in both trials — no dedicated MCL efficacy abstract yet at ASH 2025*

- CaDAnCe-104 (BGB-16673 + sonro / zanu / mosun / glofit) — MCL arm ongoing

ASH 2025 — CLL data side-by-side

	Bex (NX-5948)	BGB-16673
CLL n (Ph 1a/1)	47	68
ORR	83%	85%
ORR at RP2D	83% (600 mg)	94% (200 mg)
mPFS / 18-mo PFS	22.1 mo	66% @ 18 mo
Median FU	16.6 mo	19.8 mo

Why this matters for MCL

If a tumor has escaped cBTKi → ncBTKi → BCL2i, the BTK pathway can still be exploited via degradation. Likely future role: 4th-line+ or rational combination backbone.

How I treat MCL in 2026

Frontline

- **TP53 wild-type, classic histology (non-blastoid/non-pleomorphic)**
 - cBTKi
 - ± anti-CD20
 - *Consider BR for rapid response if needed — but recognize CAR-T impact*
- **TP53-mutated, blastoid, or pleomorphic**
 - BOVen (zanu + obinutuzumab + venetoclax)
 - *Avoid chemotherapy — mostly chemorefractory; bendamustine especially harmful*

Relapsed / refractory

- **Early CAR-T (brexu-cel) preferred**
 - Pirtobrutinib
- **Post-CAR-T relapse — evolving landscape**
 - Pirtobrutinib
 - Sonrotoclax
 - Glofitamab bispecific
 - BTK degraders coming (bexobrutideg, BGB-16673)

Decision framework

Risk stratify upfront: TP53, Ki-67, morphology → choose chemo-free path → preserve T-cell fitness → sequence CAR-T early in relapse → use novel oral agents (sonrotoclax, pirtobrutinib) and bispecifics to fill gaps.

Summary

- BTKi very effective class in MCL
 - Toxicity profile acceptable and manageable
 - cBTKi very early on
- Moving away from chemotherapy
 - Responses no longer very poor after cBTKi failure
- CAR-T very effective
 - Access extremely limited
- Pirtobrutinib and sonrotoclax highly active in MCL
 - Even heavily pre-treated, previous BTKi, high-risk
 - Excellent tolerability

Thank you!

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