Navigating Mantle Cell Lymphoma in the Era of Targeted Therapy

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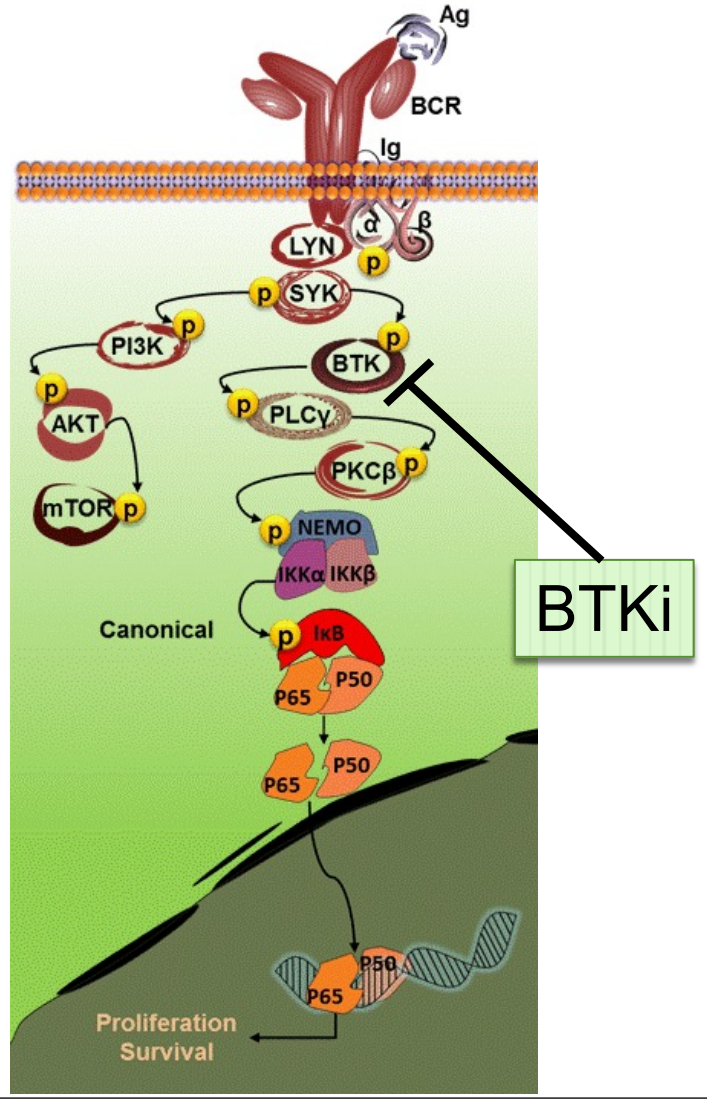
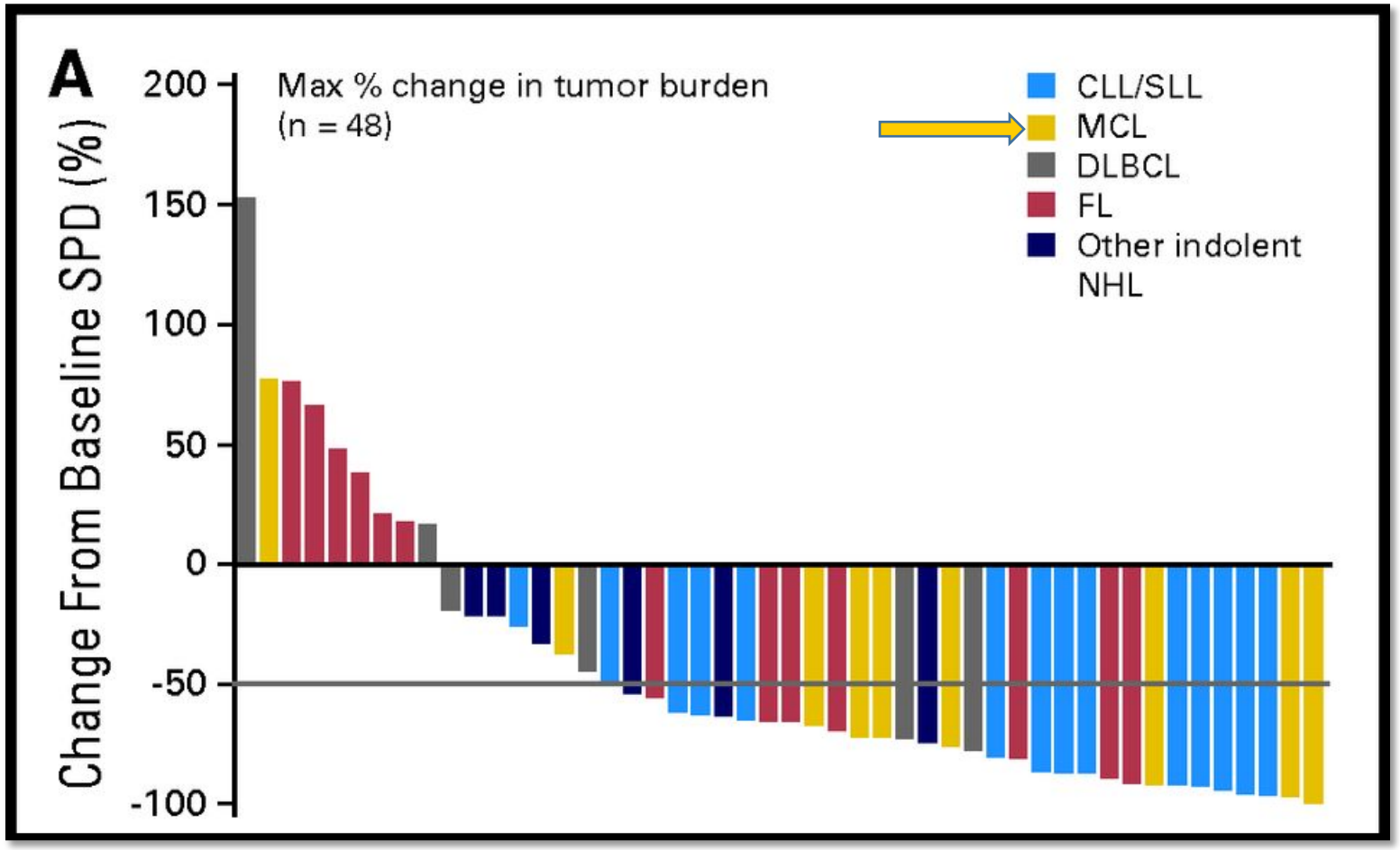
19th Annual New Orleans Summer Cancer Meeting
Sunday July 21, 2024
New Orleans, LA

The BCR signaling pathway



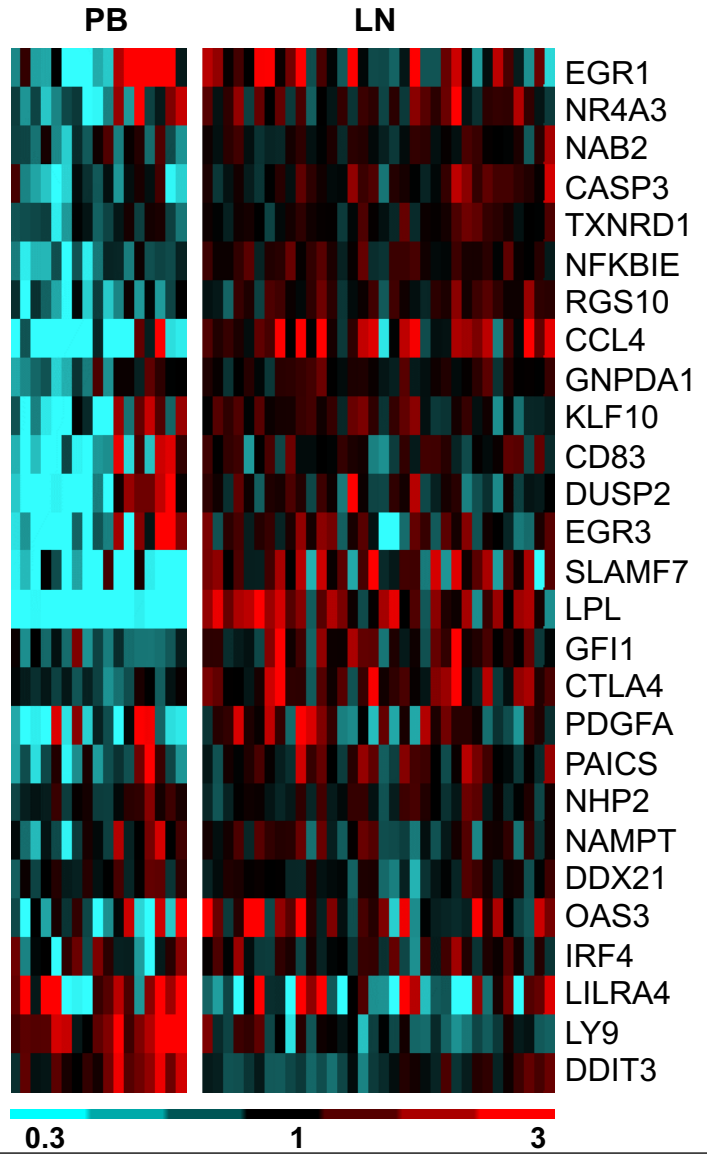
Saba & Wiestner.
Curr Opin Hematol. 2014

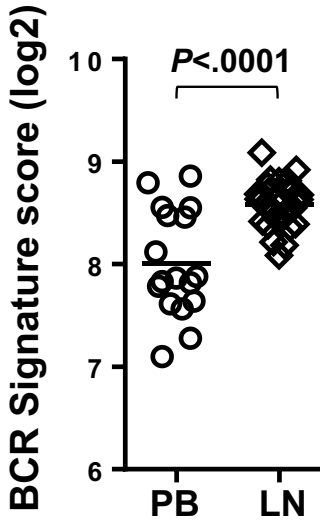
Ibrutinib, Phase 1 in Relapsed/Refractory Lymphoma

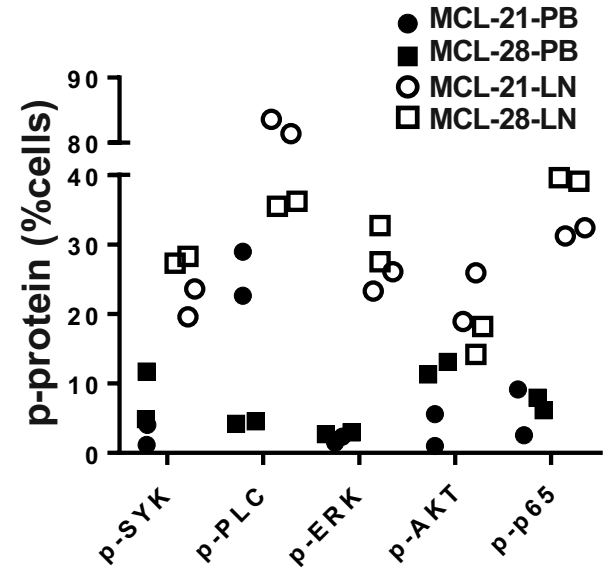


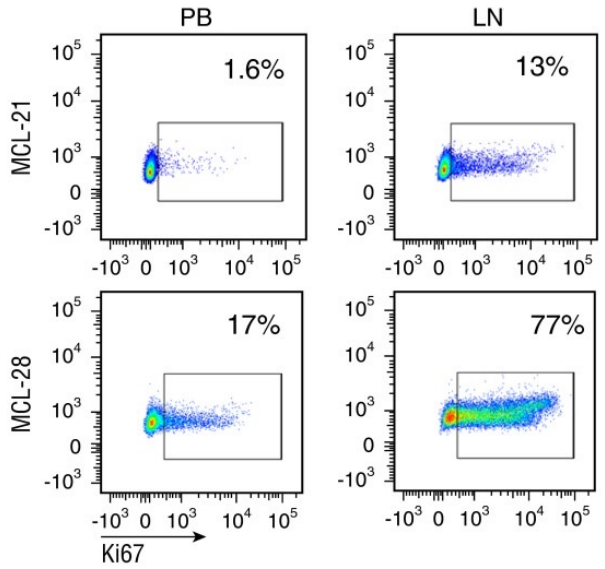
Advani et al, JCO 2012

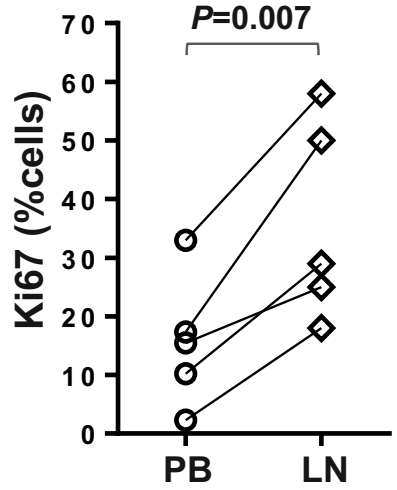
MCL in LN display higher BCR activity than in blood









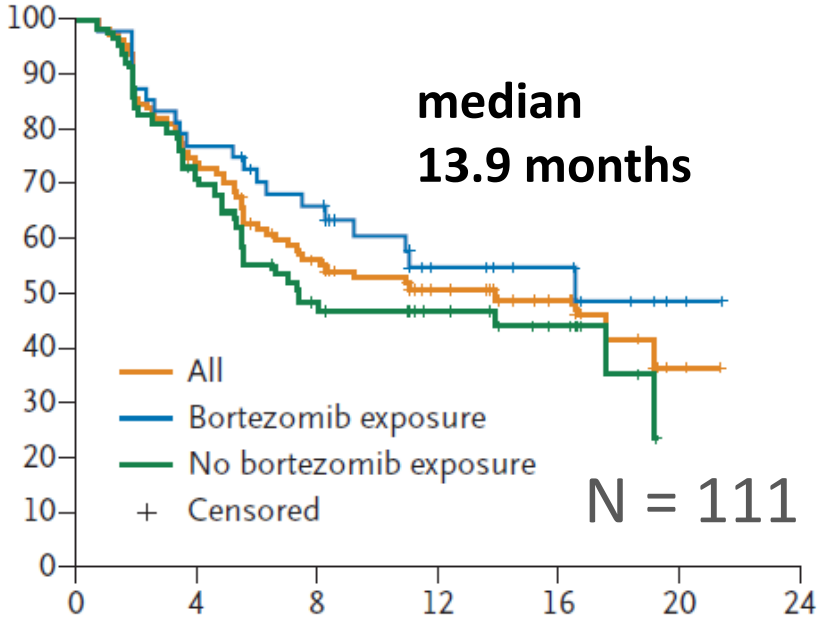


Saba et al. Blood 2016

Ibrutinib, Phase 2 in R/R MCL

- ORR 68%, CR 21%

Progression free survival

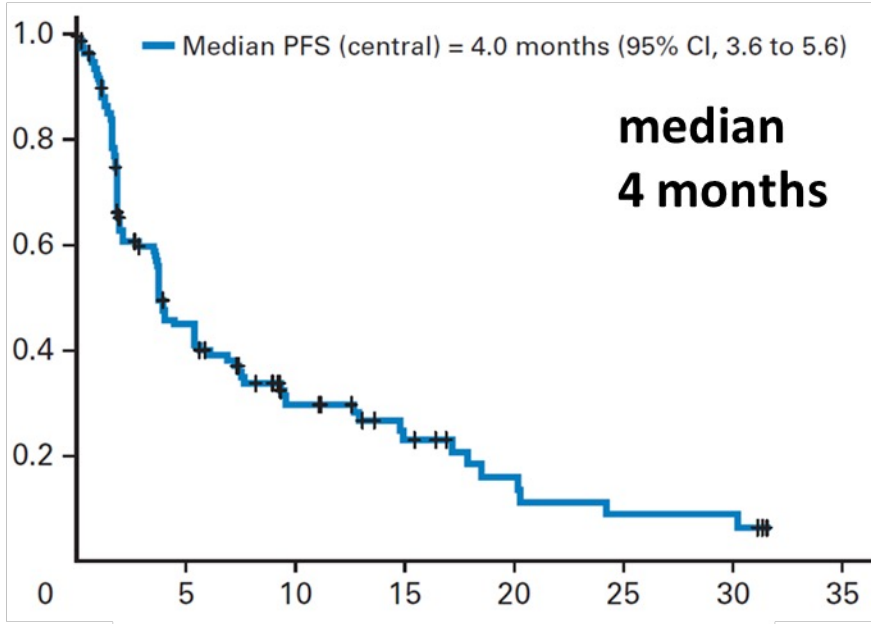


Months on study

Wang et al, NEJM 2013

- ORR 28%, CR 7.5%

Progression free survival

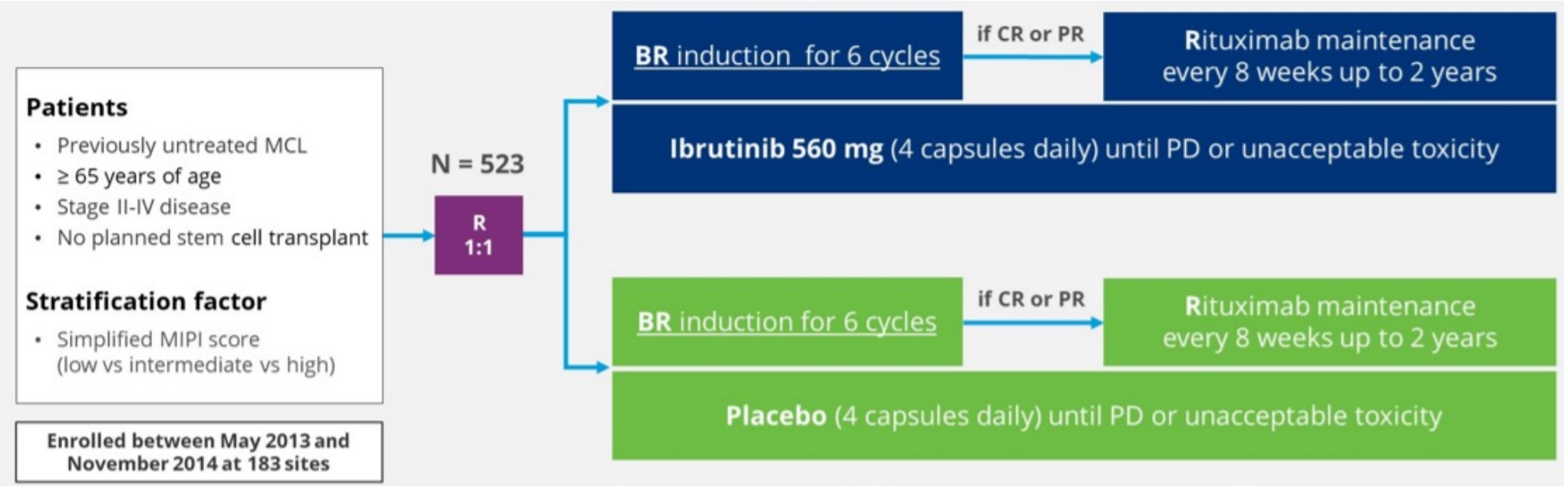


Revlimid, months on study

Goy et al, JCO 2013

SHINE: First-line Ibrutinib + BR Followed by R Maintenance in Older Patients With MCL

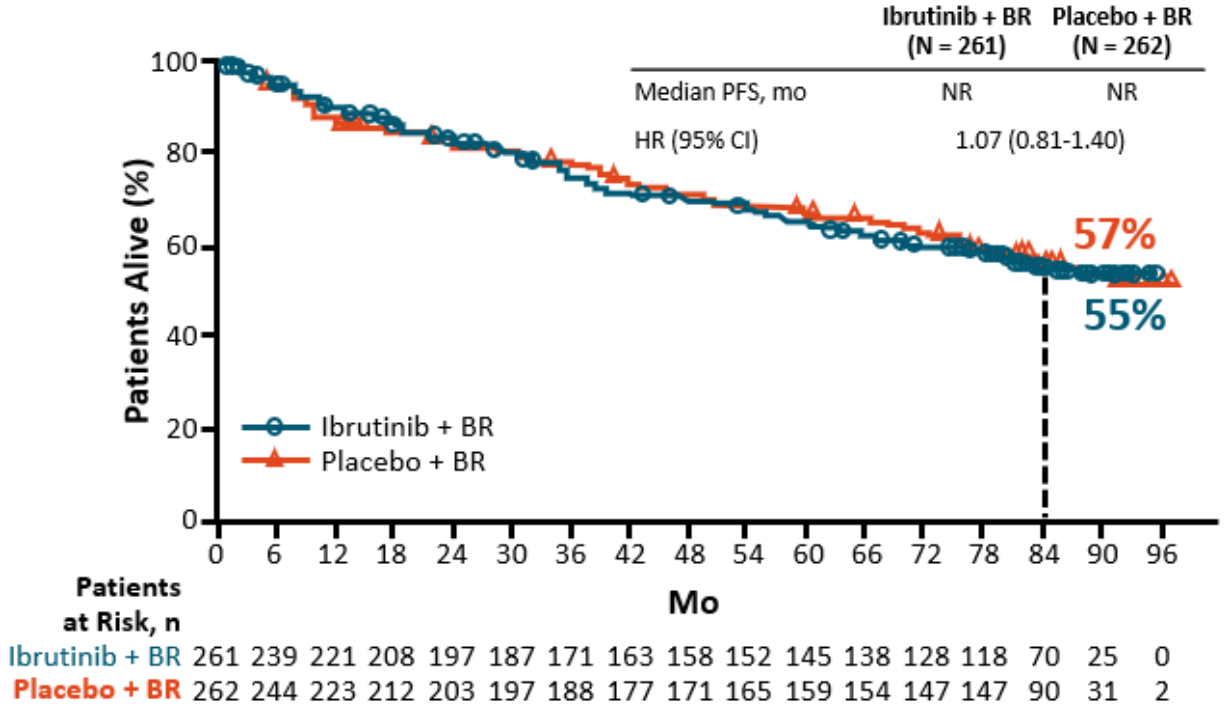
Multicenter, double-blind, placebo-controlled, phase 3 trial



- **Primary endpoint:** investigator-assessed PFS (in ITT)
- **Key secondary endpoints:** ORR, time to next treatment, OS, safety

Wang et al. NEJM 2022

SHINE: Primary Endpoint of Improved PFS was met. No Improvement in OS.



Median PFS, Mo	Ibrutinib + BR	Placebo + BR	HR (95% CI)
Patients with blastoid/ pleiomorphic histology	25.6	10.3	0.66 (0.32-1.35)
Patients with *TP53* mutation†	28.8	11.0	0.95 (0.50-1.80)

Efficacy Outcome	Ibrutinib + BR (n = 261)	Placebo + BR (n = 262)
ORR, %	**89.7**	**85.5**
▪ CR	65.5	57.6
▪ PR	24.1	30.9

- **Median follow-up**: **84.7 mo (7.1 yr)**
- Ibrutinib + BR and R maintenance showed:
  - Significant improvement in median PFS by 2.3-yr for ibrutinib arm vs the placebo arm (6.7 vs 4.4 years)
  - 25% reduction in risk of PD or death

Wang et al. NEJM 2022

SHINE: TEAEs of Clinical Interest

TEAEs of Interest With BTK Inhibitors, %	Ibrutinib + BR (n = 259)		Placebo + BR (n = 260)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any bleeding	42.9	3.5	21.5	1.5
Major bleeding	5.8	--	4.2	--
Atrial fibrillation	13.9	3.9	6.5	0.8
Hypertension	13.5	8.5	11.2	5.8
Arthralgia	17.4	1.2	16.9	0

- TEAEs of interest with BTK inhibitors typically not treatment limiting
- Other events similar with ibrutinib vs placebo: SPMs, 21% vs 19%; MDS/AML, 2 vs 3 patients

Wang et al. NEJM 2022

Single Agent Covalent BTKi Activity in R/R MCL

BTKi	Phase	N	#PT	Resp. Criteria	ORR (CR)	mPFS (mo)	mOS (mo)
Ibrutinib	2	111	3	Cheson (2007)	68 (21)	13.9	22.5
Acalabrutinib*	2	124	2	Lugano (2014)	81 (48)	22	59
Zanubrutinib*	2	86	2	Lugano (2014)	84 (59)	33	N/R
Orelabrutinib	2	106	NR	Lugano (2014)	88 (28)	NR	NR

*Head-to-head studies between these regimen are lacking. Therefore, direct comparisons cannot be made. * denotes FDA approved agents.*

Wang et al. NEJM 2013; Le Gouill et al. EHA 2022; Song Y, et al. Blood. 2022; Song et al. ASH 2020

ECHO: First-line Acalabrutinib + BR Followed by R Maintenance in Older Patients with MCL

Multicenter, double-blind, placebo-controlled, phase 3 trial

Primary endpoint:
- PFS (IRC)

Key secondary endpoints:
- ORR (IRC)
- OS
- 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

RANDOMIZE

1:1

Enrollment: Apr 2017–Mar 2023
Sites: 195 globally

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

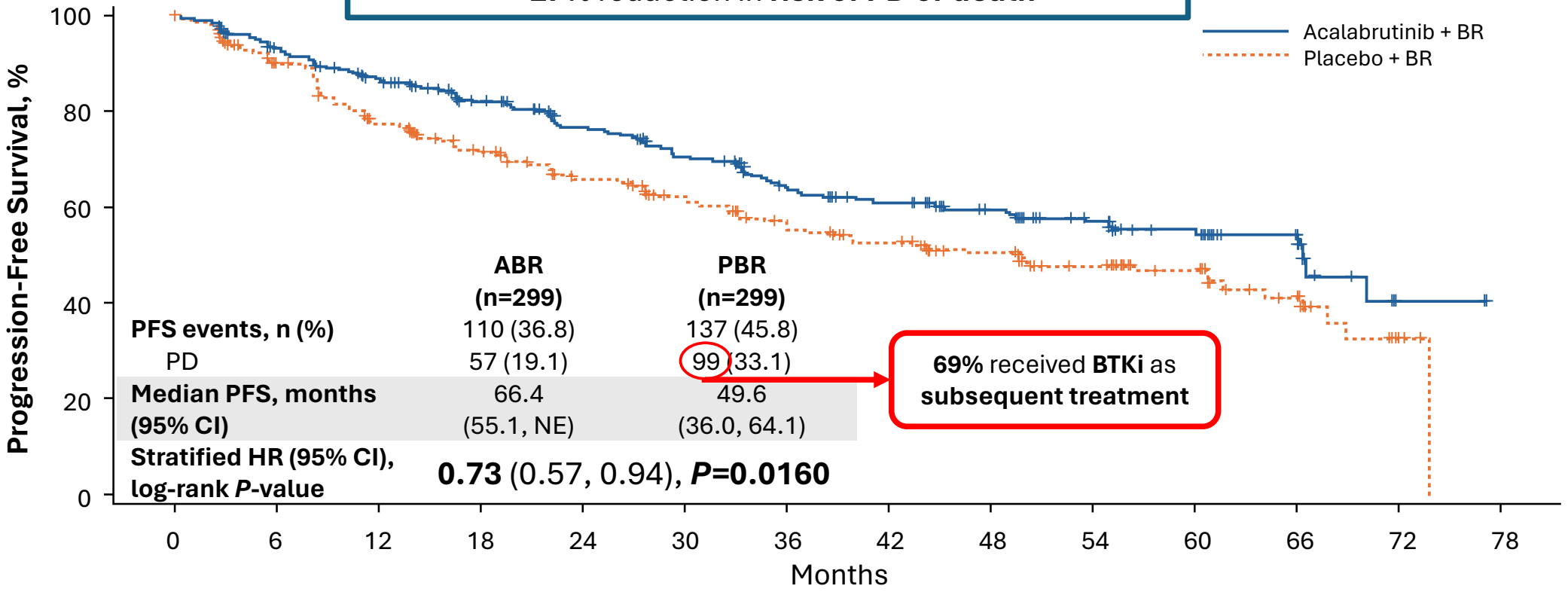
1 cycle = 28 days

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

Wang et al. EHA 2024

ECHO Met the Primary End Point of PFS Superiority

- **Significant improvement in median PFS by ~17 mo**
  - **27%** reduction in **risk of PD or death**[a]



	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

69% received **BTKi** as **subsequent treatment**

Number at risk

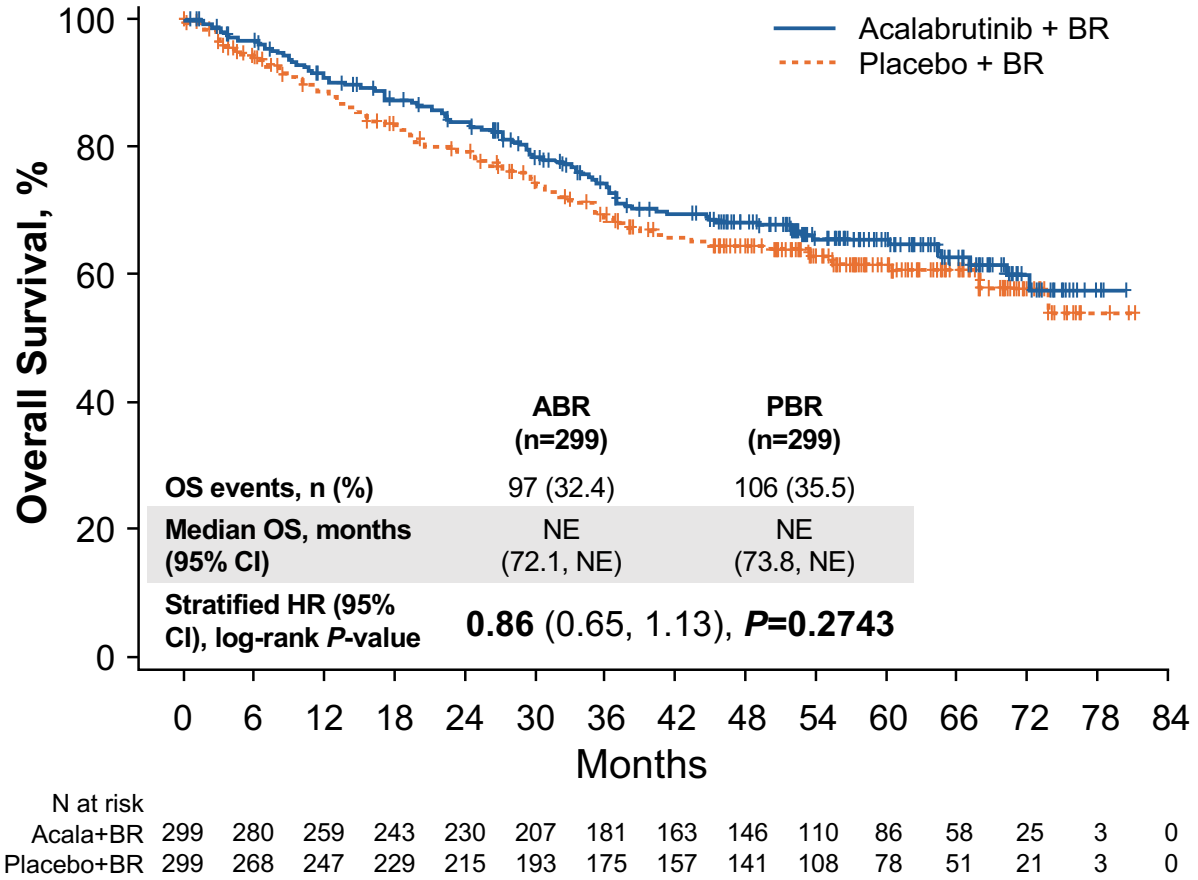
Acala + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Wang et al. EHA 2024

Trend Toward Improvement in OS, But Not Significant

Prespecified Sensitivity Analysis

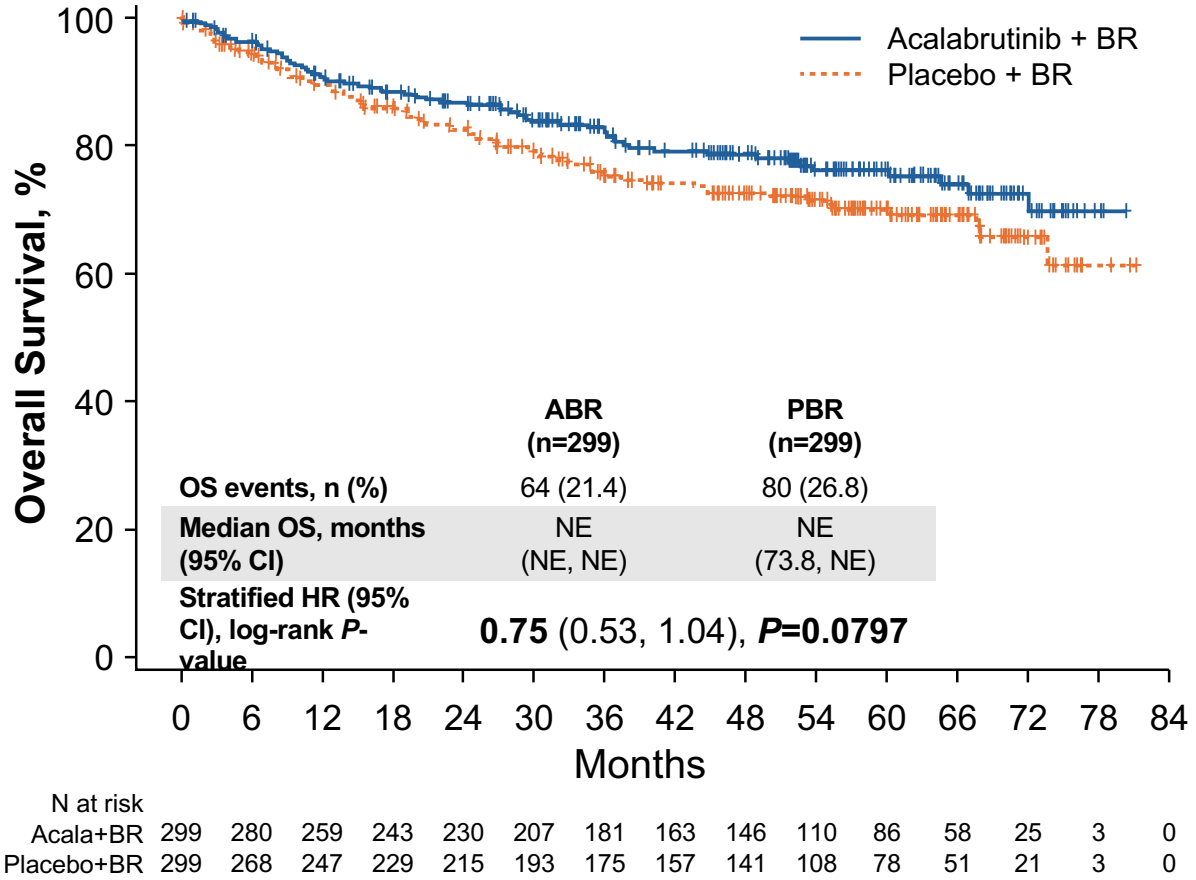
Full analysis population (including crossover)



	ABR (n=299)	PBR (n=299)
OS events, n (%)	97 (32.4)	106 (35.5)
Median OS, months (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.86** (0.65, 1.13), ***P*=0.2743**	

N at risk															
Acala+BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo+BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

COVID-19 deaths censored

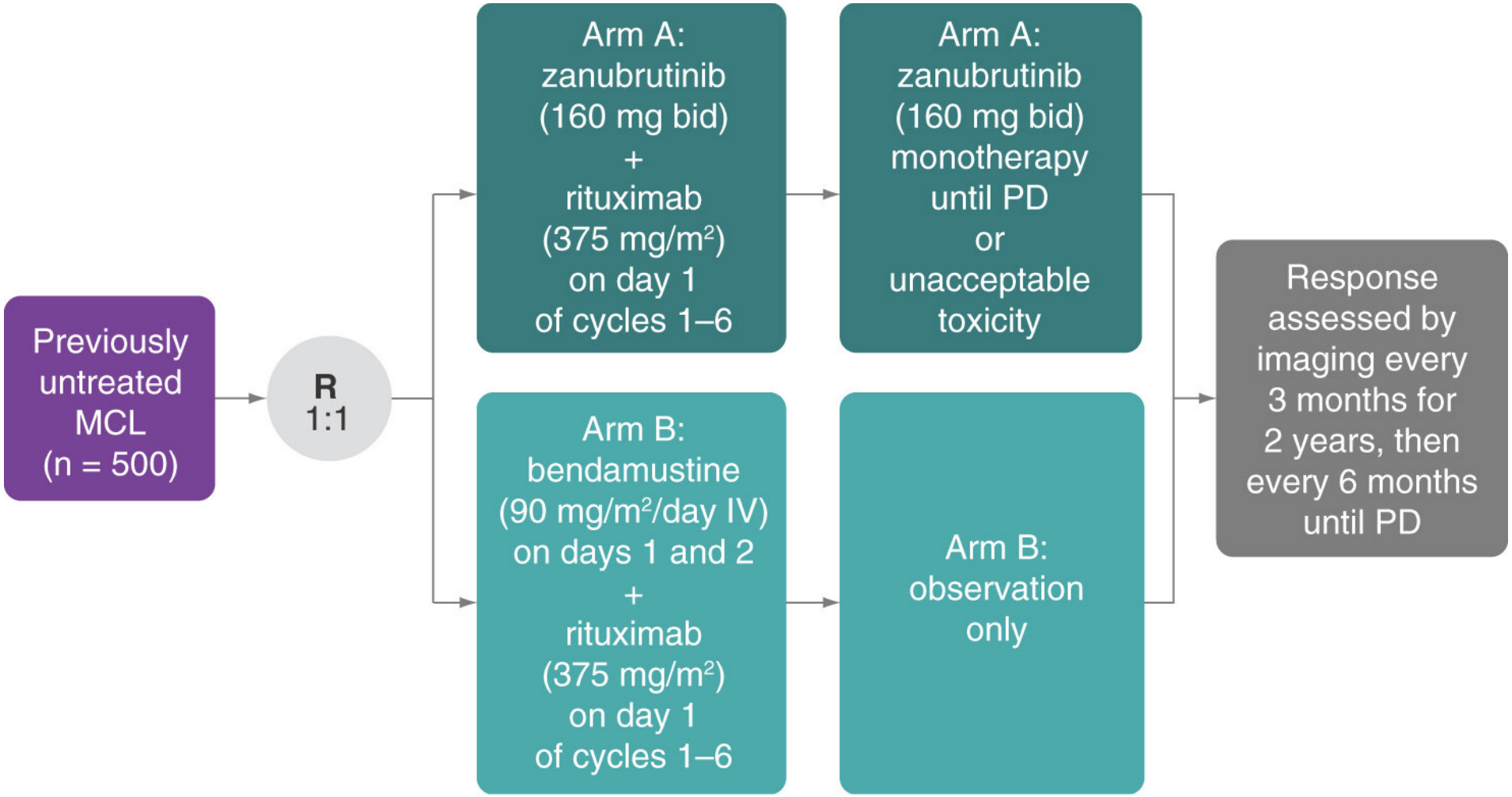


	ABR (n=299)	PBR (n=299)
OS events, n (%)	64 (21.4)	80 (26.8)
Median OS, months (95% CI)	NE (NE, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.75** (0.53, 1.04), ***P*=0.0797**	

N at risk															
Acala+BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo+BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

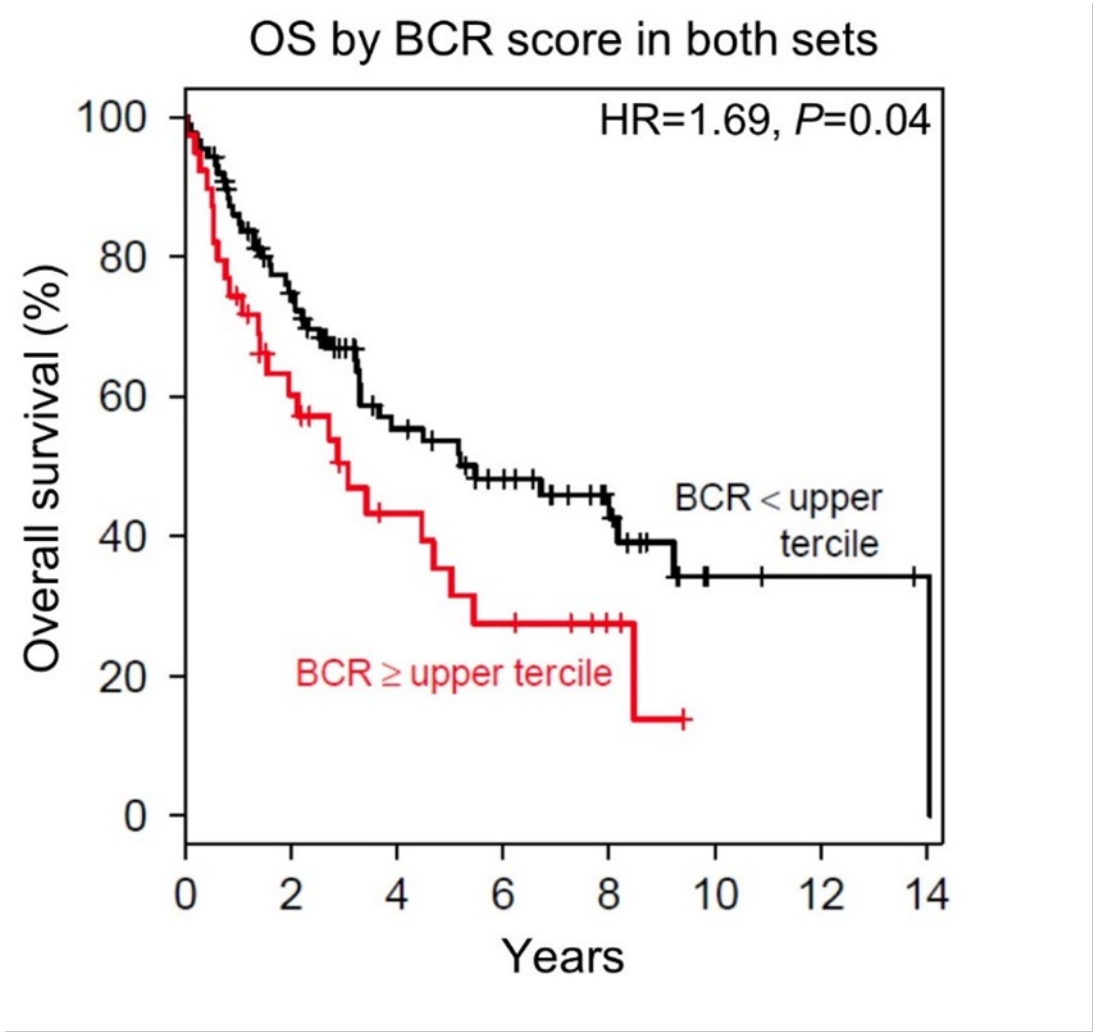
Wang et al. EHA 2024

A Phase III Study of Zanu+R *Vs.* BR in Transplant-Ineligible, Untreated MCL



Dreyling et al. Future Oncol. 2020. Clinical Trial Registration: NCT04002297

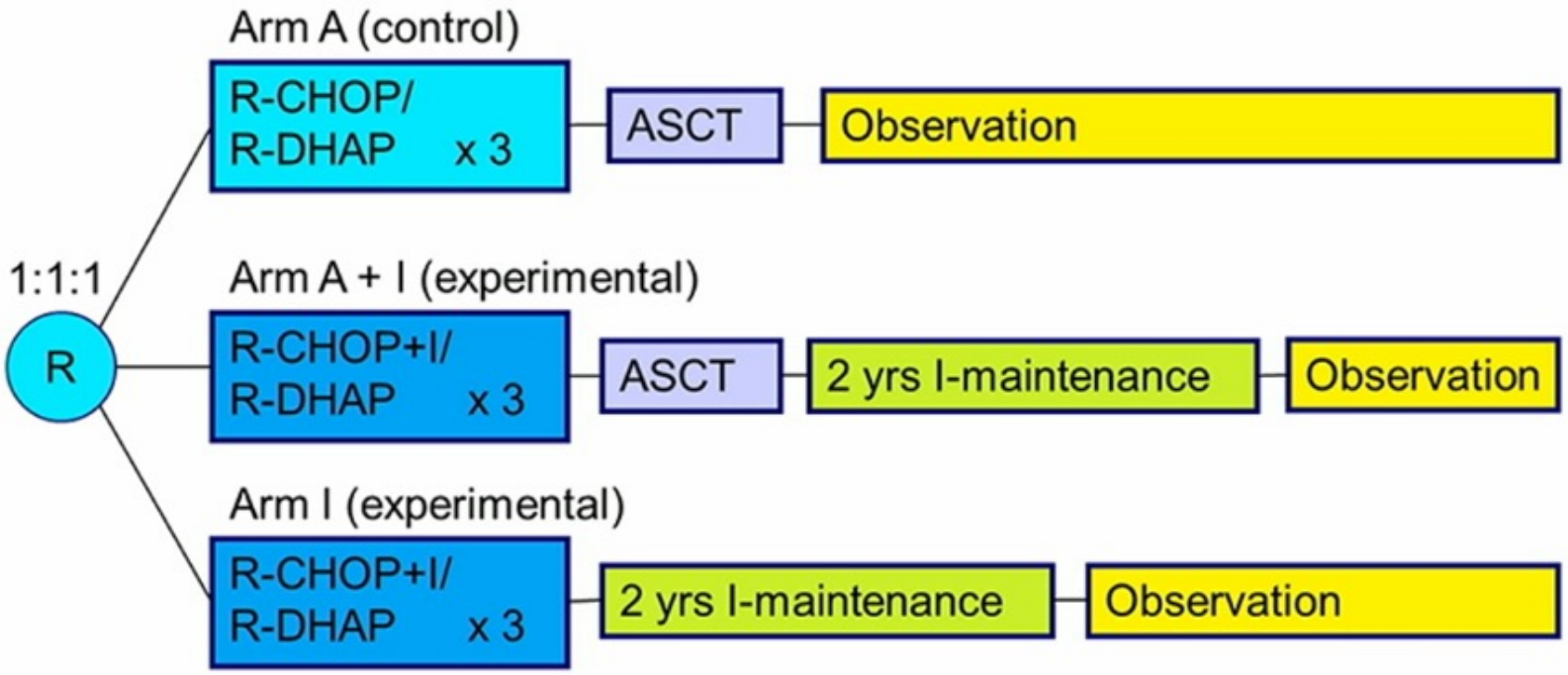
Strength of BCR signaling is associated with resistance to chemotherapy in MCL



Saba et al. Blood 2016

BTKi +Aggressive Induction?

TRIANGLE: Study Design



- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling et al. ASH 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Mantle Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

INDUCTION THERAPY	
Aggressive induction therapy	**Preferred regimens** (in alphabetical order) • LyMA regimen: RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) x 4 cycles followed by RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for non-PET CR • NORDIC regimen: Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine • Rituximab, bendamustine[c] followed by rituximab, high-dose cytarabine[e] • TRIANGLE regimen: Alternating RCHOP + covalent BTKi[g]/RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (category 2A for ibrutinib; category 2B for acalabrutinib[j] or zanubrutinib) **Other recommended regimen** • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[d] (NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR) • RBAC500 (rituximab, bendamustine,[c] cytarabine)
Less aggressive induction therapy	**Preferred regimens** • Bendamustine + rituximab[e] • VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) • RCHOP[f] • Lenalidomide (continuous) + rituximab **Other recommended regimen** • Acalabrutinib[g,j] (continuous) + rituximab

MAINTENANCE AFTER HDT/ASCR OR AGGRESSIVE INDUCTION THERAPY
• Covalent BTKi[g] x 2 years[h] (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib) + rituximab every 8 weeks x 3 years

-Value
IR 0.52, =0.0008
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-Value
IR 1.77, =0.9979
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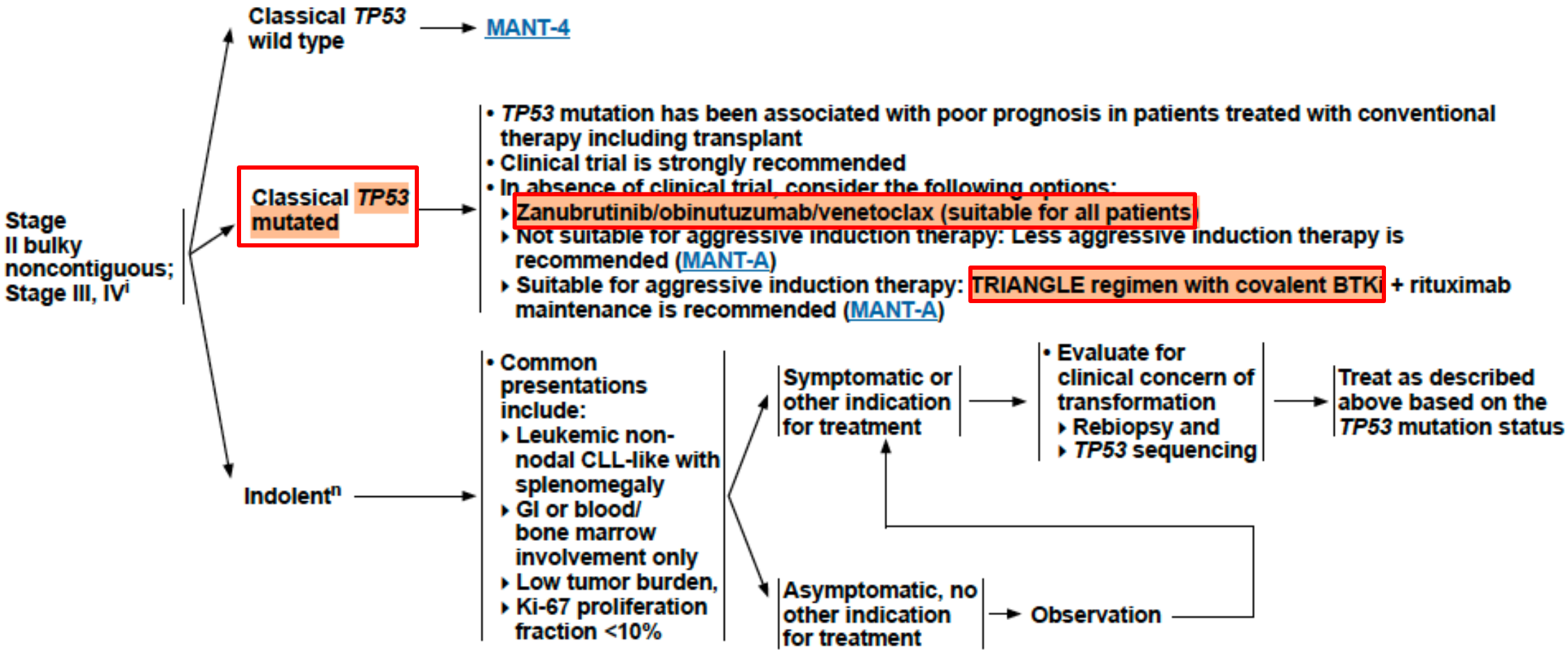
Dreyling et al. ASH 2022

MANAGEMENT AND FOLLOW-UP[m]



BOVen Frontline Combination in TP53^{mut} MCL

Phase II, investigator-initiated, multicenter, single arm study

MCL (N=25)
- Previously untreated
- TP53^{mut}
- ECOG: 0-2

BOVen (28D cycles x 2Y minimum)
- Zanu 160 mg PO BID
- Obin 1000 mg IV D1, 8, 15 of C1; D1 of C2-8
- Ven ramp up initiated C3D1 (target 400 mg daily)

Primary endpoint:
2Y PFS

Patients

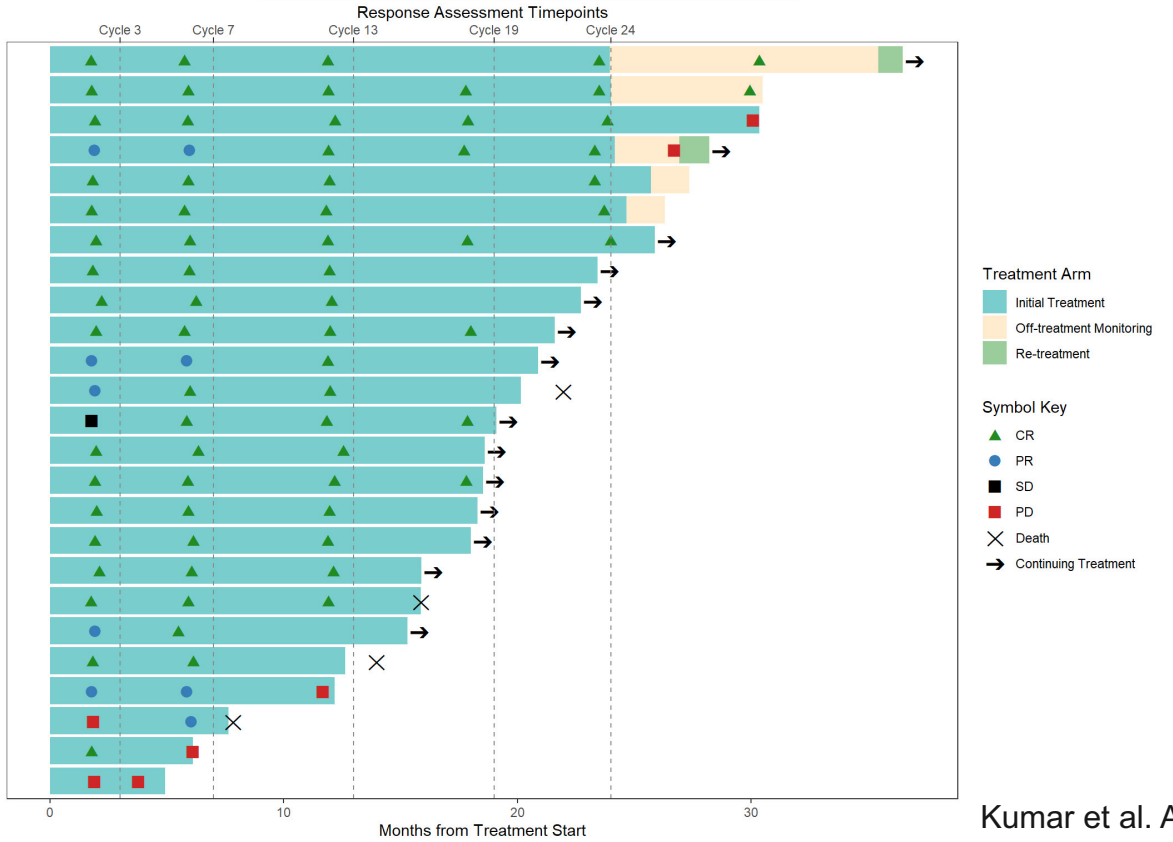
Median age: 65 years (range, 29-82)
Stage IV: 100%; TP53^{mut}: 100%; MIPI-high: 68%
Median F/U: 16.1 months

Safety (G3-4)

Neutropenia (12%), IRR (8%), COVID-19 (8%), diarrhea (4%), transaminitis (4%), thrombocytopenia (4%), and rash (4%)

Efficacy

Best ORR: 95% (CR, 88%)
PFS (84% at 1Y, 75% at 16 mo)
OS (96% at 1Y, 87% at 16 mo)



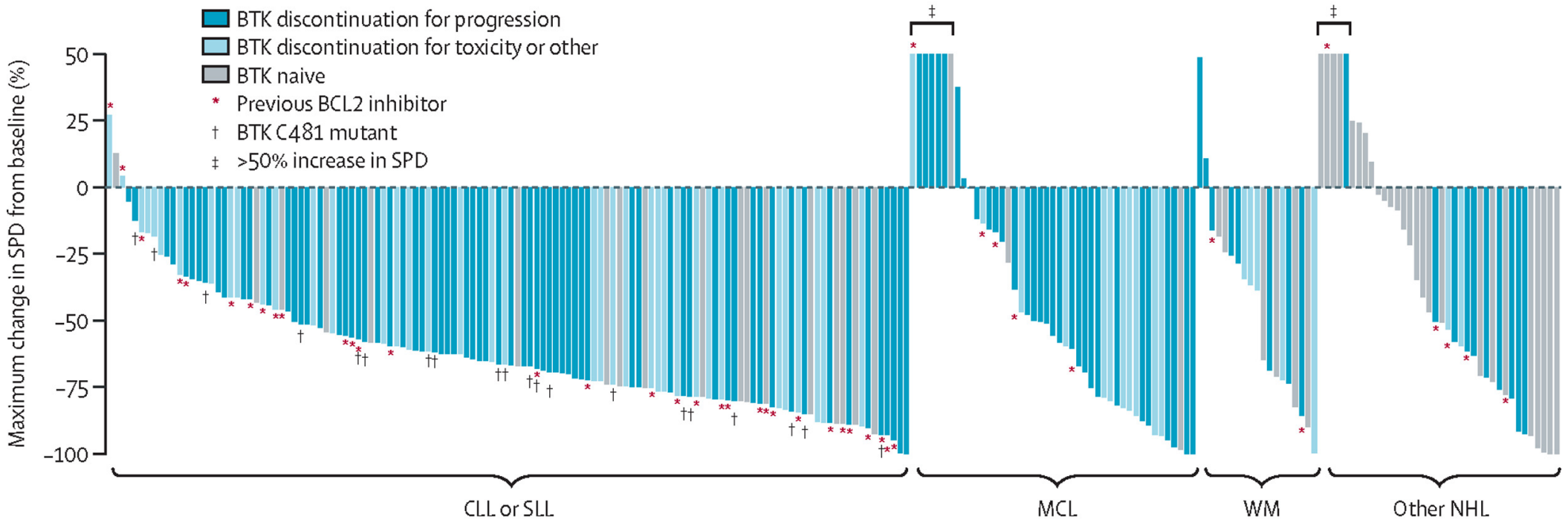
Kumar et al. ASH 2023

FDA-Approved BTKis

Variable	Ibrutinib[a]	Acalabrutinib[b]	Zanubrutinib[c]	Pirtobrutinib[d]
Binding to BTK	Covalent	Covalent	Covalent	Noncovalent
Dose schedule	QD	BID	QD or BID	QD
Use after progression on cBTKi	No	No	No	Yes
Use after intolerance to cBTKi	N/A	Yes	Yes	Yes
CLL/SLL	+	+	+	+
MCL	-	+	+	+
MZL	-	-	+	-
WM	+	-	+	-
FL	-	-	+	-

[a]Ibrutinib: CLL/SLL, WM.
[b]Acalabrutinib: CLL/SLL, R/R MCL.
[c]Zanubrutinib: CLL/SLL, WM, R/R MZL after least 1 anti-CD20-based regimen, FL in combination with obinutuzumab after 2 or more lines of systemic therapy.
[d]Pirtobutinib: R/R CLL/SLL and R/R MCL after at least 2 lines of systemic therapy, including a cBTKi (MCL), and cBTKi and BCL2i (CLL/SLL).

Pirtobrutinib in R/R B-cell malignancies (BRUIN): a Phase 1/2 study



- N=152, all BTKi exposed
- Median # prior therapy: 3 (range 1-9)
- TP53 mutation: 71%
- Median on treatment time: 12 months
- ORR 49.3% (CR 15.8%)

Low rates of TEAEs:

- Hemorrhage (Grade ≥3: 2.4%), A-Fib/Flutter (All Grade 3.6%)
- Discontinuation due to a TRAE: 3%

Cohen et al. ASH 2023; Wang et al. ASH 2022; Mato et al. Lancet 2021

Glofitamab Monotherapy in R/R MCL

Updated Analysis from a Phase I/II Study

Study design[1]

- Multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with Obinutuzumab pre-treatment

Glofitamab IV administration

- Fixed-duration treatment: maximum 12 cycles

Population characteristics

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS 0 or 1

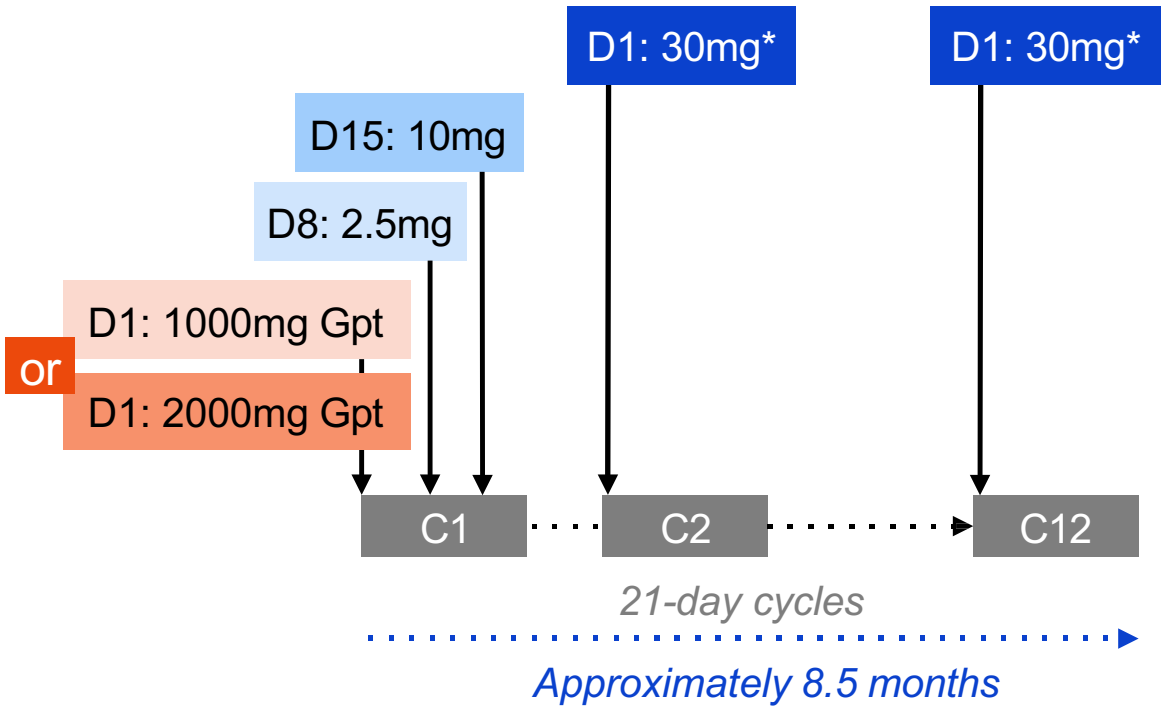
CRS mitigation

- Obinutuzumab pretreatment (1000mg or 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Clinical cut-off date: September 04, 2023.
*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.
C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous.

1. NCT03075696. Available at: https:www.clinicaltrials.gov.

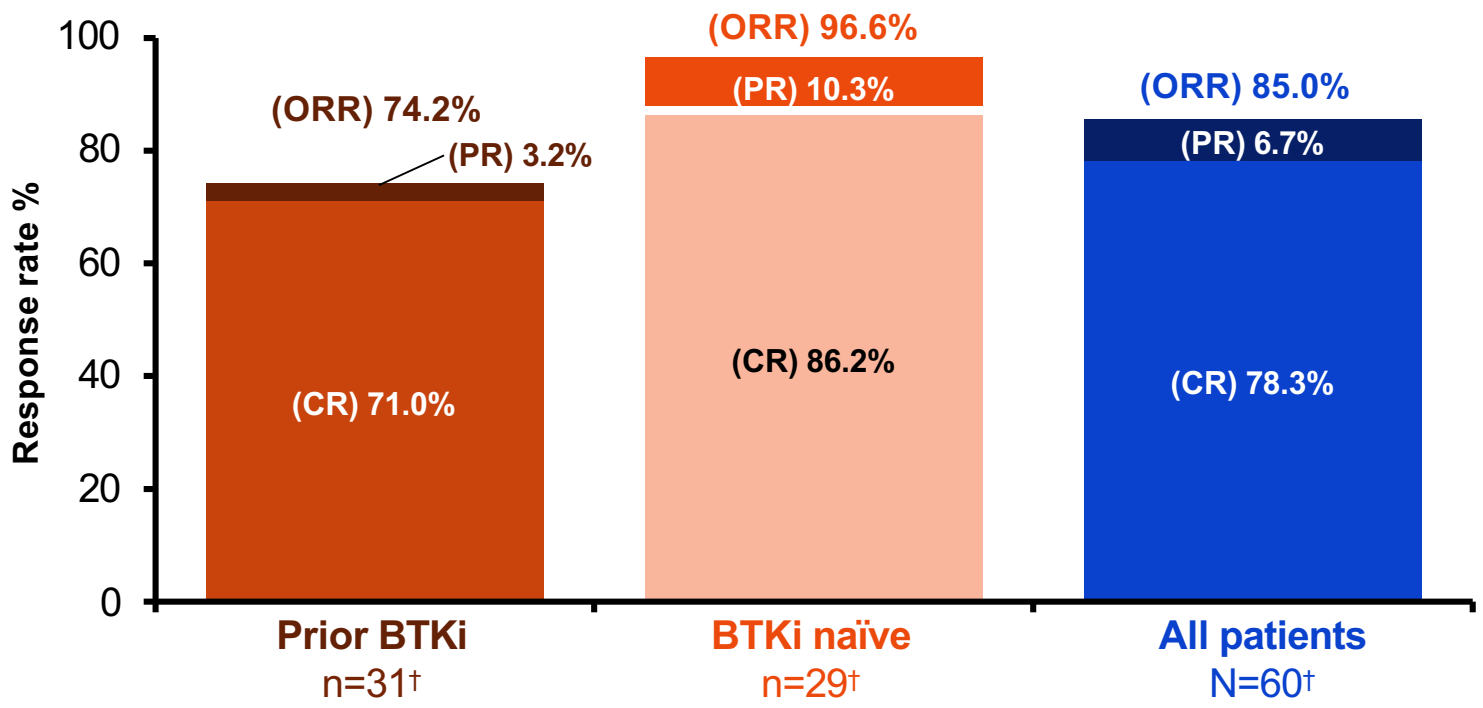
Dosing schedule



Phillips et al. EHA 2024

High Response Rates with Glofitamab

Response rates* in patients with R/R MCL



- Median time to first response among responders (n=51): **42 days** (95% CI: 42.0–45.0)

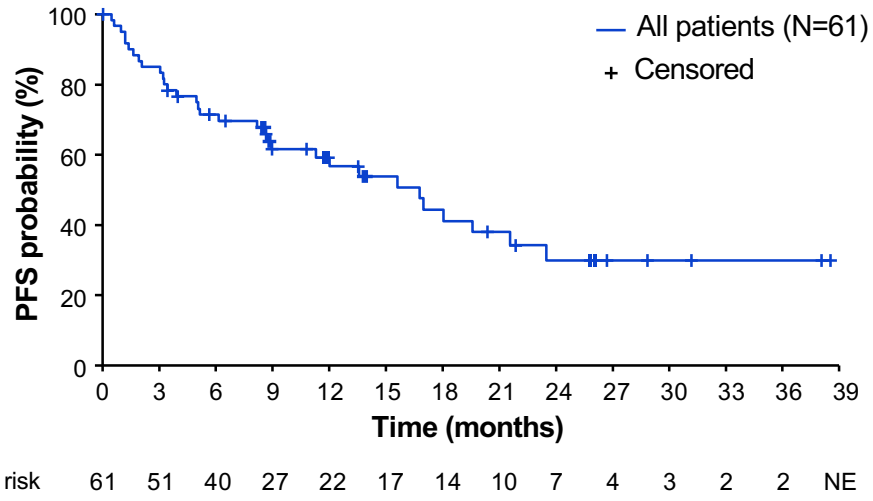
High CR and OR rates were observed in the overall population and in both BTKi-naïve patients and those with prior BKTi therapy

Clinical cut-off date: September 04, 2023.
*Investigator-assessed. †Efficacy evaluable population.
CI, confidence interval; ORR, overall response rate; PR partial response.

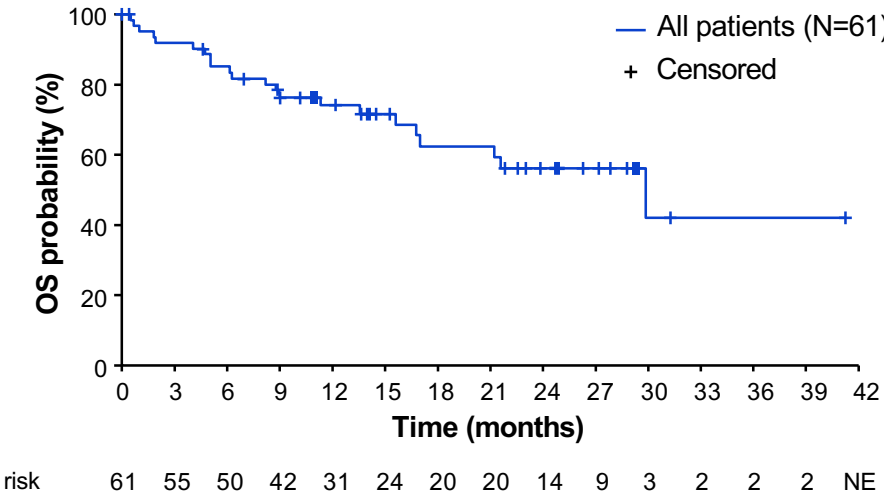
Phillips et al. EHA 2024

Median PFS and OS

PFS



OS†



	Prior BTKi n=32*	All patients N=61*
Median PFS follow-up, months (95% CI)	26.1 (13.5–31.2)	19.6 (11.9–26.1)
Median PFS, months (95% CI)	8.6 (3.4–15.6)	16.8 (8.9–21.6)
15-month PFS rate, % (95% CI)	33.0 (14.8–51.1)	54.0 (40.1–67.8)

	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	21.2 (9.0–NE)	29.9 (17.0–NE)
15-month OS rate, % (95% CI)	55.0 (36.5–73.6)	71.4 (59.3–83.5)

Clinically significant PFS and OS at 15 months were achieved with fixed-duration glofitamab

Clinical cut-off date: September 04, 2023.
*ITT population. †At the time of analysis, 22 patients had died, the majority due to PD (n=7) or COVID-19 (n=7); other causes of death were pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1), and unknown/other (n=5). All patients who died due to COVID-19 had achieved a CR.
OS, overall survival; PD, progressive disease; PFS, progression-free survival.

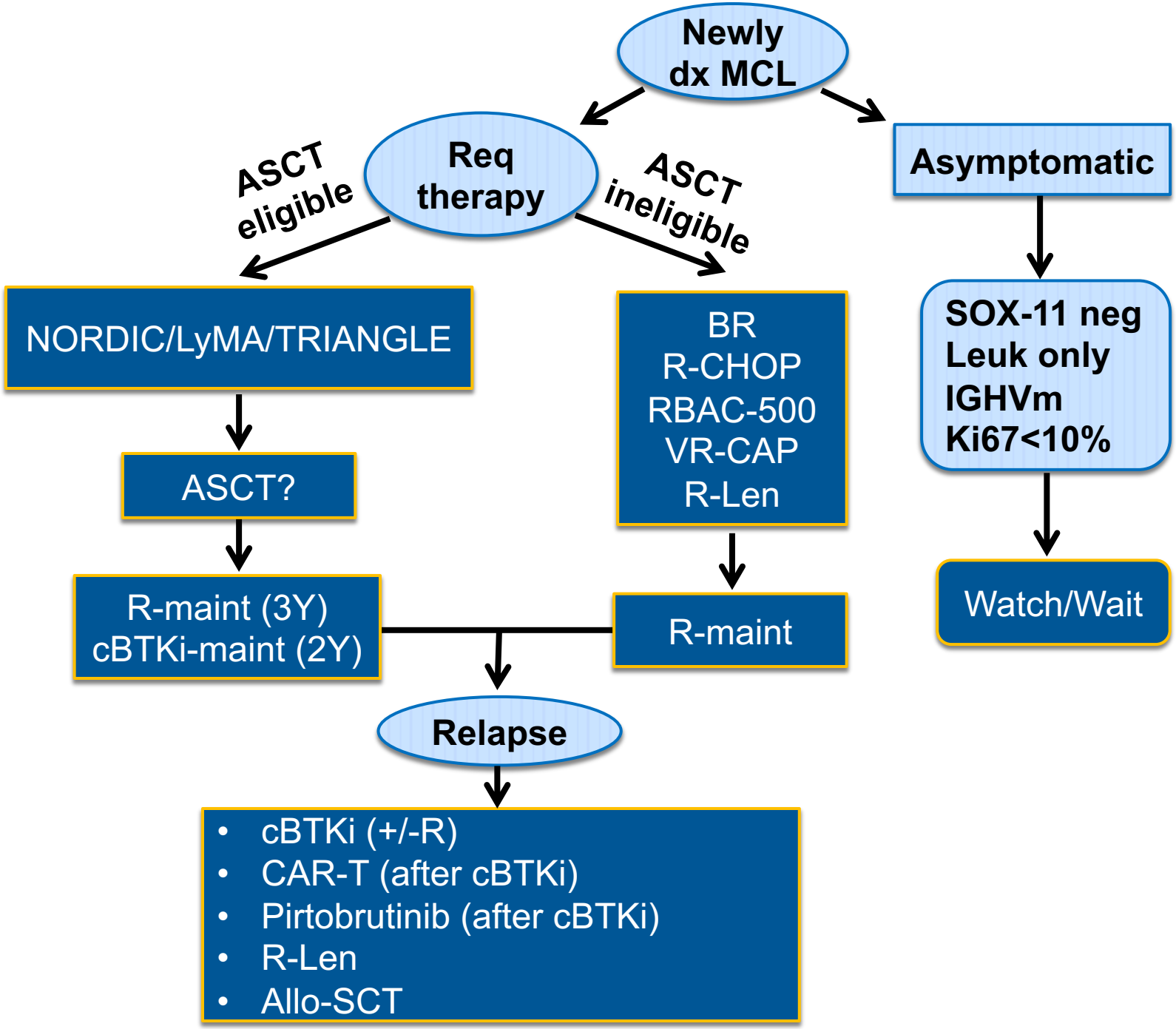
CRS and ICANS

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Any grade CRS*	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
Serious AE of CRS†	11 (68.8)	12 (27.3)	23 (38.3)

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
CRS management			
Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Corticosteroid	8 (50.0)	10 (22.7)	18 (30.0)
Toci + steroids	6 (37.5)	7 (15.9)	13 (21.7)
ICU admission	5 (31.3)	4 (9.1)	9 (15.0)
ICANS (derived) related to glofitamab			
Any grade	2 (12.5)	1 (2.3)	3 (5.0)
Grade 1	1 (6.3)	1 (2.3)	2 (3.3)
Grade 2	1 (6.3)	0	1 (1.7)

The majority of CRS events were Grade 1/2, and a lower incidence of CRS was observed in the 2000mg versus 1000mg cohort

On May 31, 2024, Glofitamab received Breakthrough Therapy Designation from FDA for the treatment of patients with R/R MCL after at least two systemic therapies.


Newly dx MCL
Req therapy
ASCT eligible
ASCT ineligible
Asymptomatic
NORDIC/LyMA/TRIANGLE
BR
R-CHOP
RBAC-500
VR-CAP
R-Len
SOX-11 neg
Leuk only
IGHVm
Ki67<10%
ASCT?
R-maint (3Y)
cBTKi-maint (2Y)
R-maint
Watch/Wait
Relapse
cBTKi (+/-R)
CAR-T (after cBTKi)
Pirtobrutinib (after cBTKi)
R-Len
Allo-SCT

Thank you

Lymphoma Questions?

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