Il suono DELL' INNOVAZIONE
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Qual è la seconda linea ottimale in MCL...e dopo?

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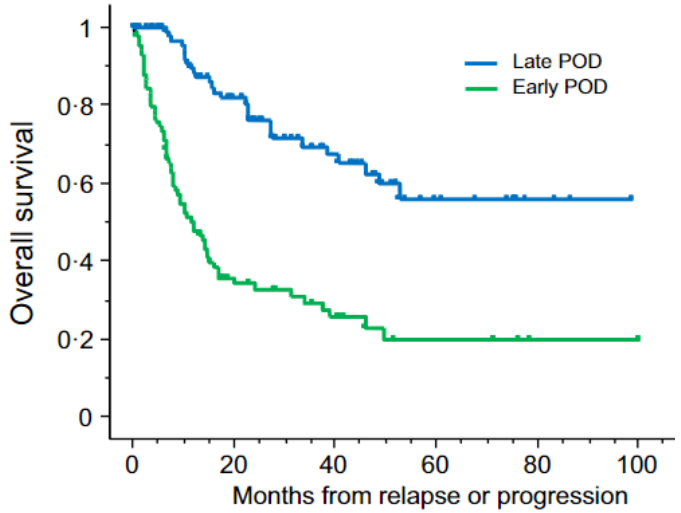
Disclosure Maurizio Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X		X	x	
Beigene						x	
Eli Lilly					X	x	
Recodati Rare disease					X	x	
Incyte			X			X	
Kite Gilead			X		X	x	
Novartis						X	
Janssen							
Roche			X		X	X	
SOBI						X	
Takeda						X	
BMS						x	

Ibrutinib as standard of care for first relapse: Time to POD

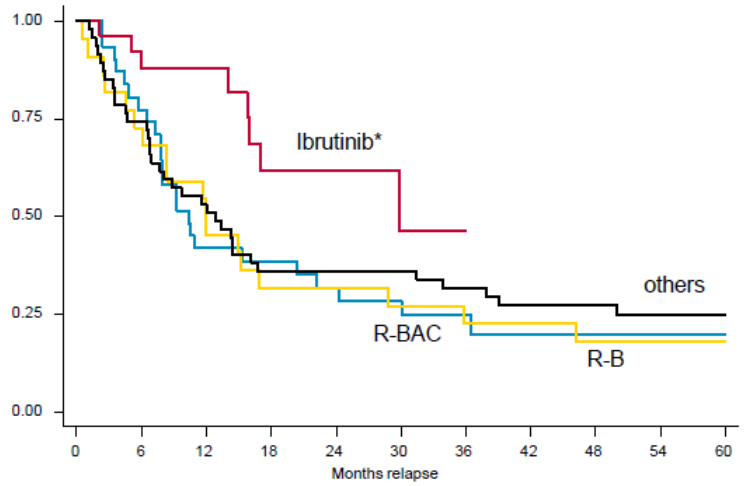
MANTLE-FIRST



At risk:

Early POD	90	24	13	6	1	1
Late POD	98	61	31	11	3	0

Early POD



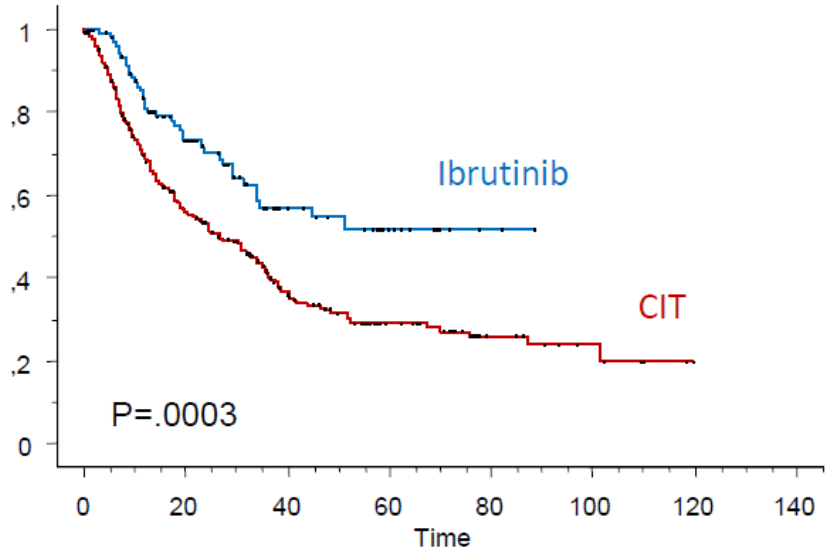
At risk:

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

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

PFS-2

Late POD



Median 26 months for CIT;
NR for Ibrutinib

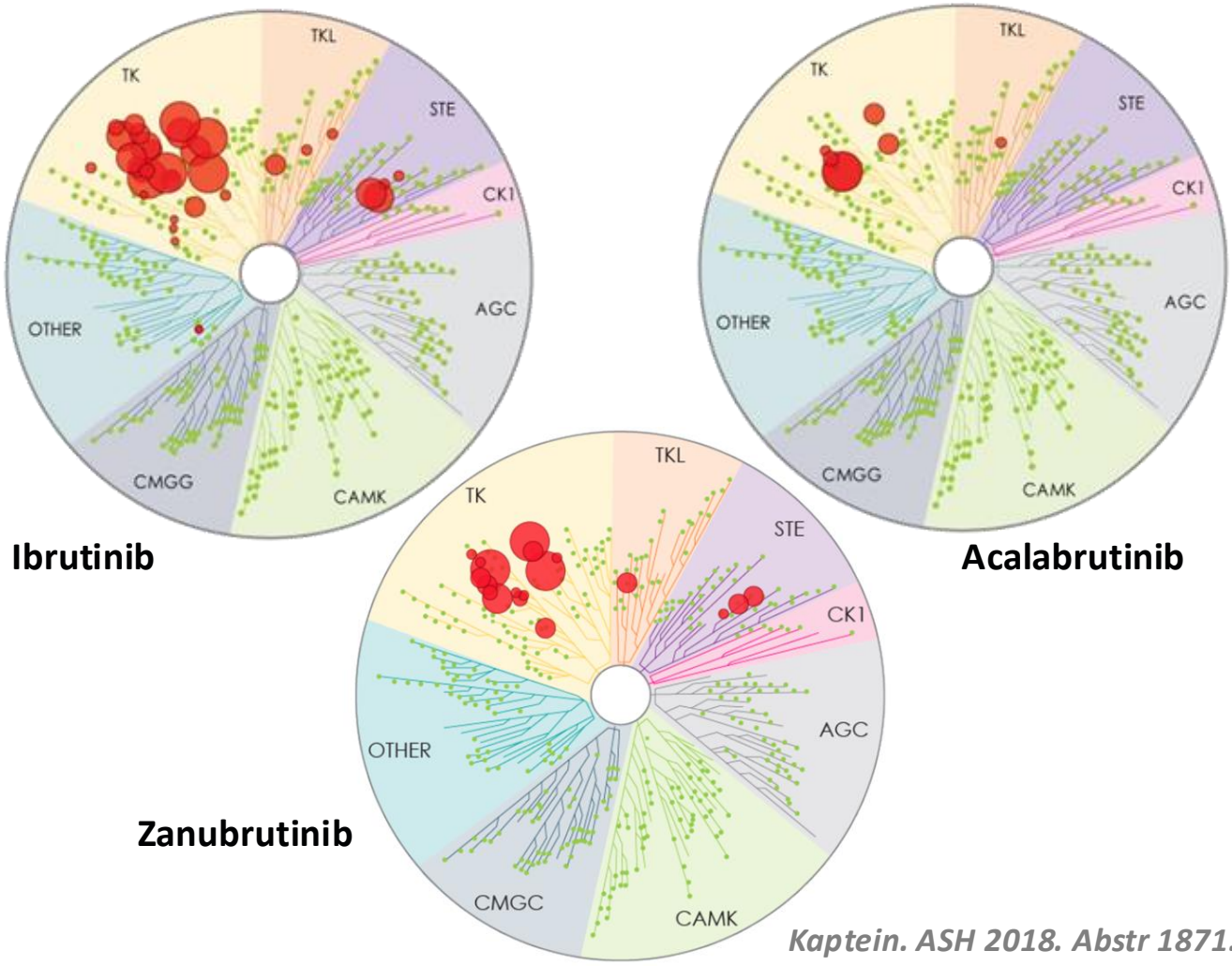
Visco C et al, BJH 2019; Visco C et al, Leukemia 2020; Malinverni C et al, Blood 2024

Kinase Selectivity of BTK Inhibitors

Kinase	IC_{50}/EC_{50} (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kinase Selectivity Profiling at 1 μmol/L (in vitro)

Larger red circles represent stronger inhibition

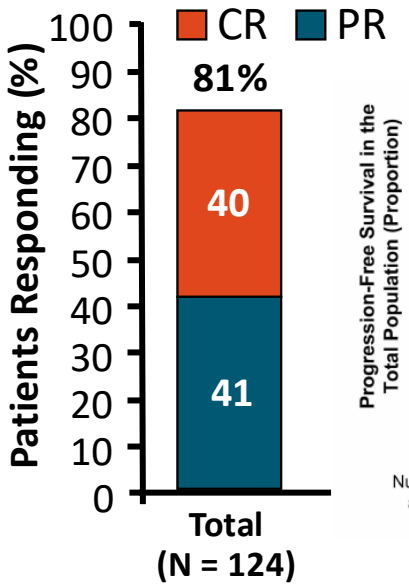


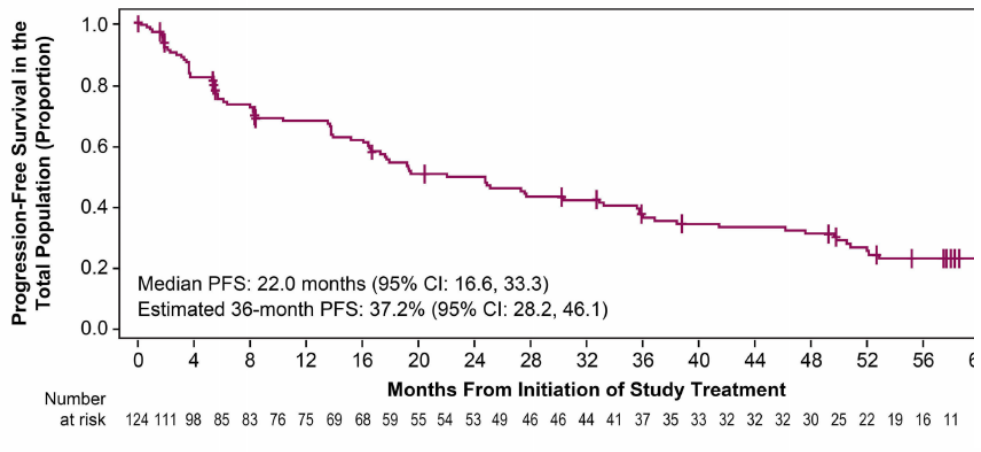
Kaptein. ASH 2018. Abstr 1871.

Phase II ACE-LY-004: Acalabrutinib in Relapsed/Refractory MCL

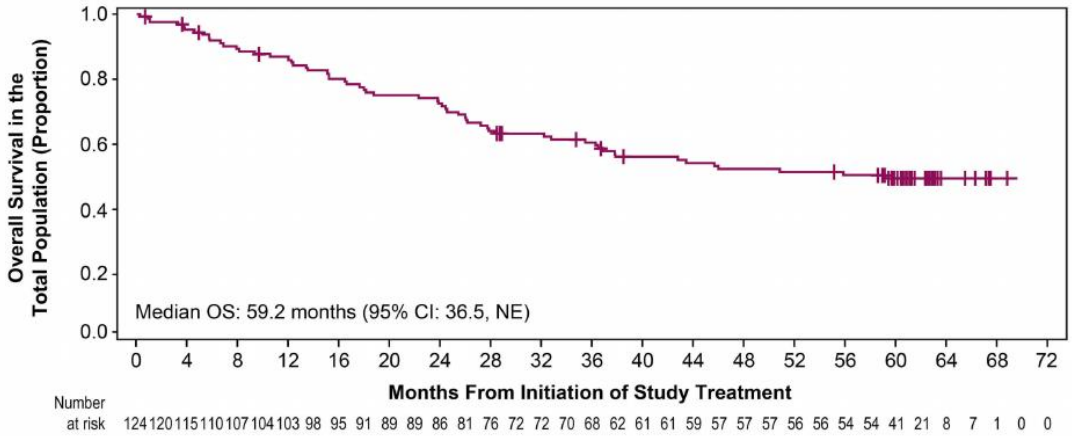
Adult patients with MCL;
1-5 prior lines of tx; ECOG PS 0-2; no notable CVD*;
no concurrent use of warfarin/equivalent vitamin K antagonists, no prior BTK inhibitors
(N = 124)

→ **Acalabrutinib** 100 mg PO BID in 28-day cycles → ***Until PD***





- *Median PFS was 22 months in the overall population*



- *Median OS ws 59.2 months in the overall population*

Le Gouill S et al. Haematologica. 2024

Phase II ACE-LY-004: Acalabrutinib in Relapsed/Refractory MCL

n (%)	Any Grade	Grade 3/4
Atrial fibrillation	**3 (2.4%)**	**0**
Hypertension	**5 (4.0%)**	**2 (1.6%)**
Hemorrhage	**46 (37.1%)**	**5 (4.0%)**
Infections	**84 (67.7%)**	**21 (16.9%)**

n (%)	Acalabrutinib
Discontinuations for PD	77 (62.1%)
Discontinuations for AEs	**15 (12.1%)**
Patients on treatment at data cut-off	18 (14.5%)
Median duration of treatment (range)	17.5 months (0.1–65.3)

- ***Patients discontinue primarily due to disease progression, not because of toxicity.***
- *43.5% of patients continued acalabrutinib for more than 24 months, including 11.3% who continued therapy for more than 60 months.*

Le Gouill S et al. Haematologica. 2024

blood® Regular Article

Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Zanubrutinib 160 mg PO BID

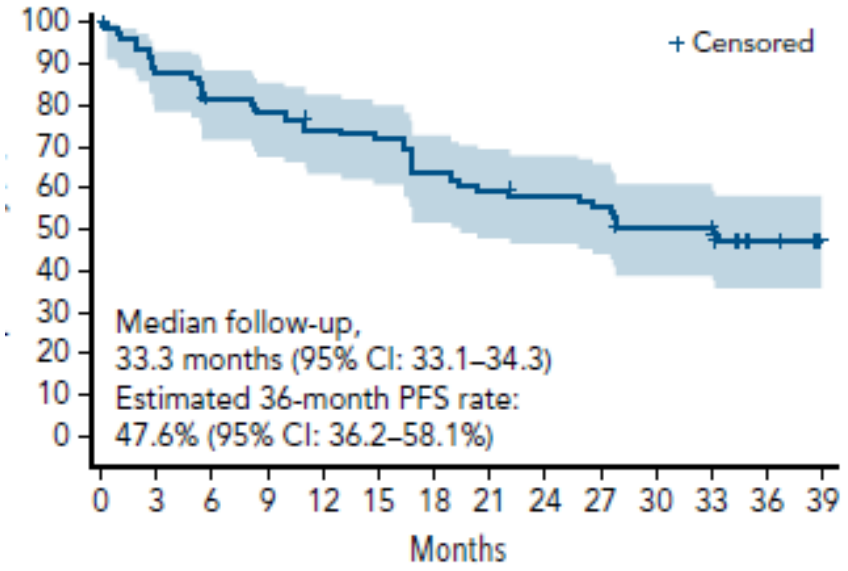
Zanubrutinib monotherapy demonstrates durable clinical benefit in the long-term follow-up of patients with relapsed/refractory MCL

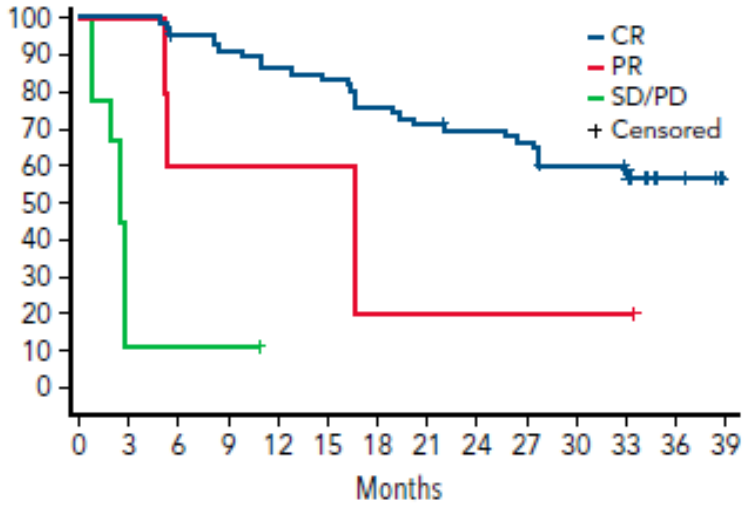
	Response	PFS 2 years	PFS 3 years
Phase 2 86 Patients with R/R MCL Median follow-up 35.3 months	ORR 84% CR 78%	58%	48%
	Median DOR	**OS 2 years**	**OS 3 years**
	Not reached (95% CI: 24.9 months to NE)	80%	75%

Zanubrutinib was well tolerated

- Few discontinuations (9.3%) due to AEs
- Majority of AEs: low-grade severity
- No atrial fibrillation/flutter
- No second primary malignancies

PFS 36-months follow up





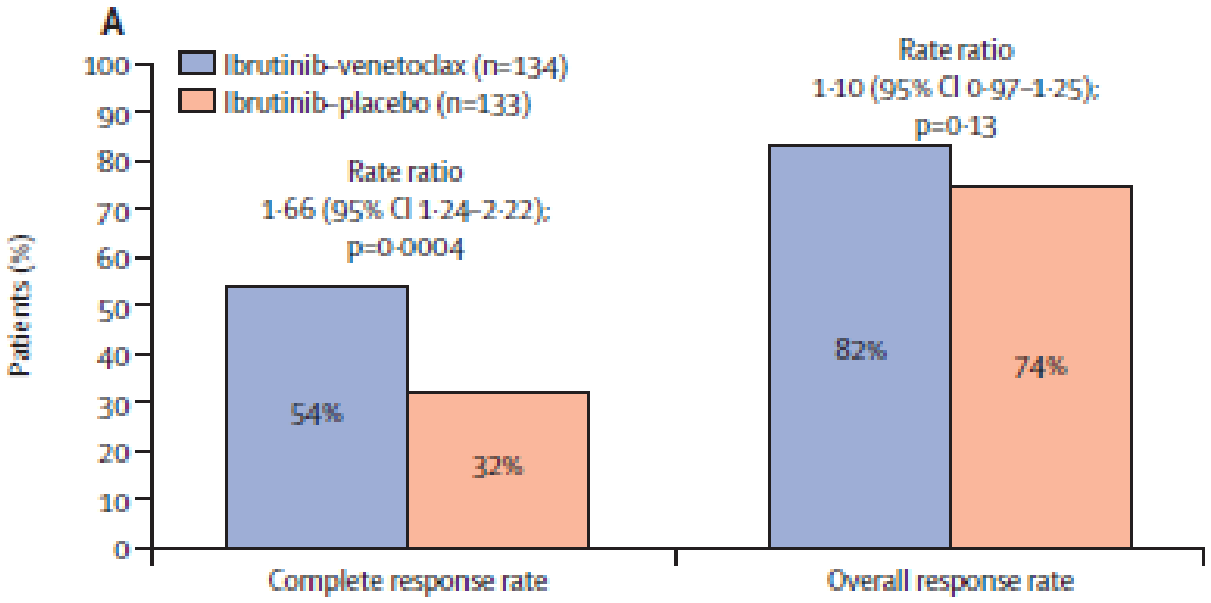
Song Y. et al . Blood . 2022; 139:3149

Adverse Events of Available BTK Inhibitors in MCL

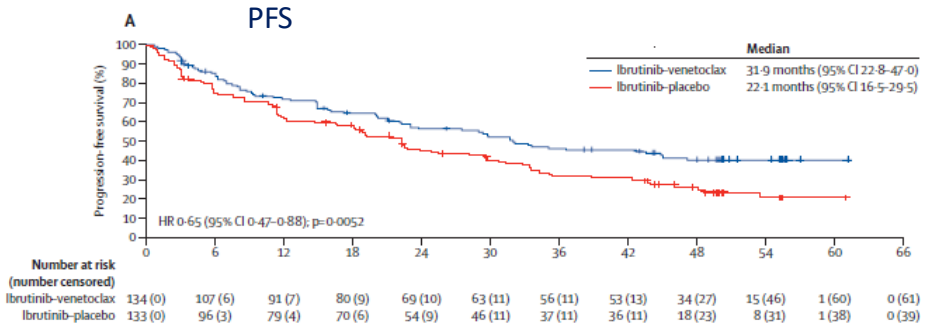
Ibrutinib	Acalabrutinib	Zanubrutinib
Gastrointestinal	**Gastrointestinal**	**Gastrointestinal**
▪ Diarrhea: 51% (grade ≥3: 5%) ▪ Nausea: 31% (grade ≥3: 0%)	▪ Diarrhea: 31% (grade ≥3: 3.2%) ▪ Nausea: 19% (grade ≥3: 0.8%)	▪ Diarrhea: 23% (grade ≥3: 0.8%) ▪ Nausea: NR
Musculoskeletal	**Musculoskeletal**	**Musculoskeletal**
▪ Includes pain, arthralgias, muscle spasms ▪ 11% to 37% of patients (grade ≥3: up to 1%)	▪ Includes myalgia ▪ 21% of patients (grade ≥3: 0.8%)	▪ Includes pain, discomfort, myalgia, back pain, arthralgia, arthritis ▪ 14% of patients (grade ≥3: 3.4%)
Other common AEs	**Other common AEs**	**Other common AEs**
▪ Rash: 25% (grade ≥3: 3%) ▪ Fatigue: 41% (grade ≥3: 5%) ▪ Headache: 13% (grade ≥3: 0%)	▪ Rash: 18% (grade ≥3: 0.8%) ▪ Fatigue: 28% (grade ≥3: 0.8%) ▪ Headache: 39% (grade ≥3: 1.6%)	▪ Rash: 36% (grade ≥3: 0%) ▪ Fatigue: 11% ▪ Headache: 4.2%

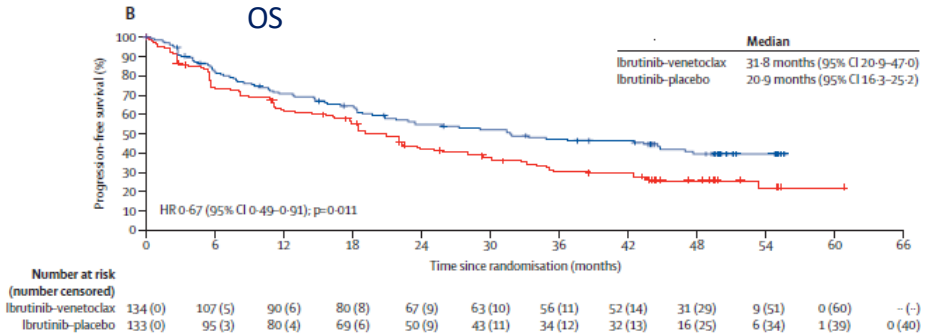
Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

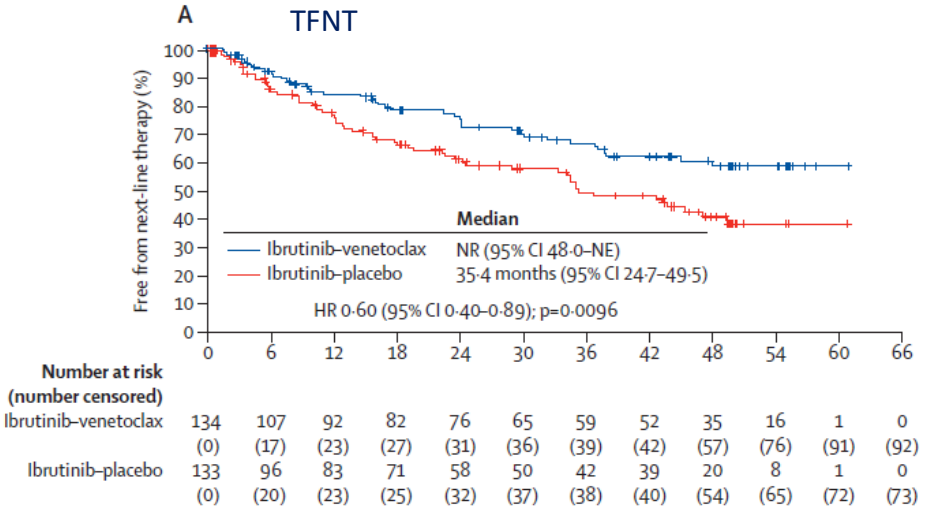
Michael Wang, Wojciech Jurczak, Marek Trneny, David Belada, Tomasz Wrobel, Nilanjan Ghosh, Mary-Margaret Keating, Tom van Meerten, Ruben Fernandez Alvarez, Gottfried von Keudell, Catherine Thieblemont, Frederic Peyrade, Marc Andre, Marc Hoffmann, Edith Szafer-Glusman, Jennifer Lin, James P Dean, Jutta K Neuenburg, Constantine S Tam



Wang M et al. Lancet Oncology 2025

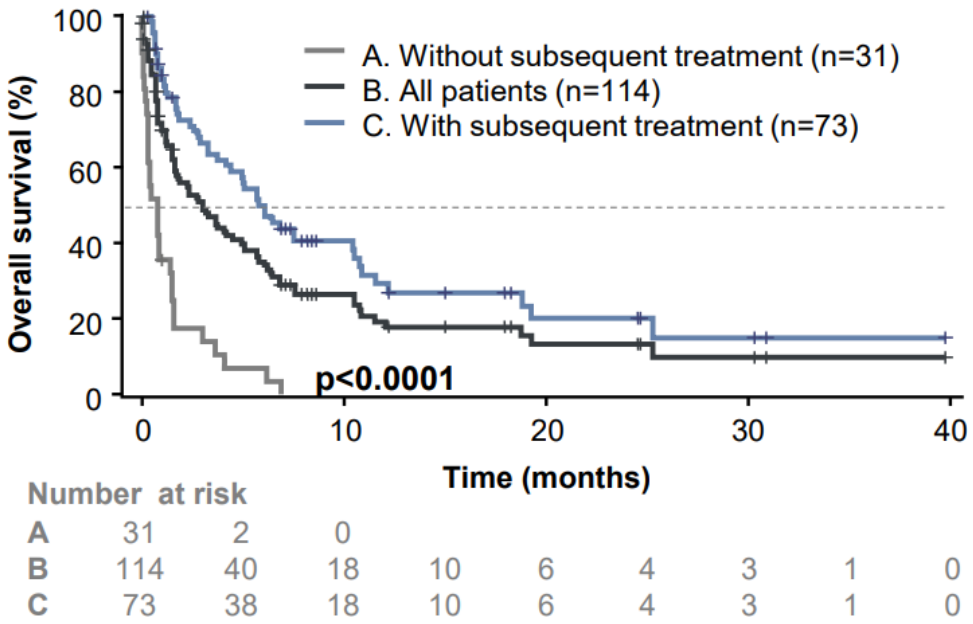






Outcome in MCL is Poor Following Covalent BTK Inhibitor Progression

OS of patients with MCL after ibrutinib cessation (± subsequent therapy) (N=114)



Adapted from Figure 1 in Ref. Martin P, et al. Blood 2016

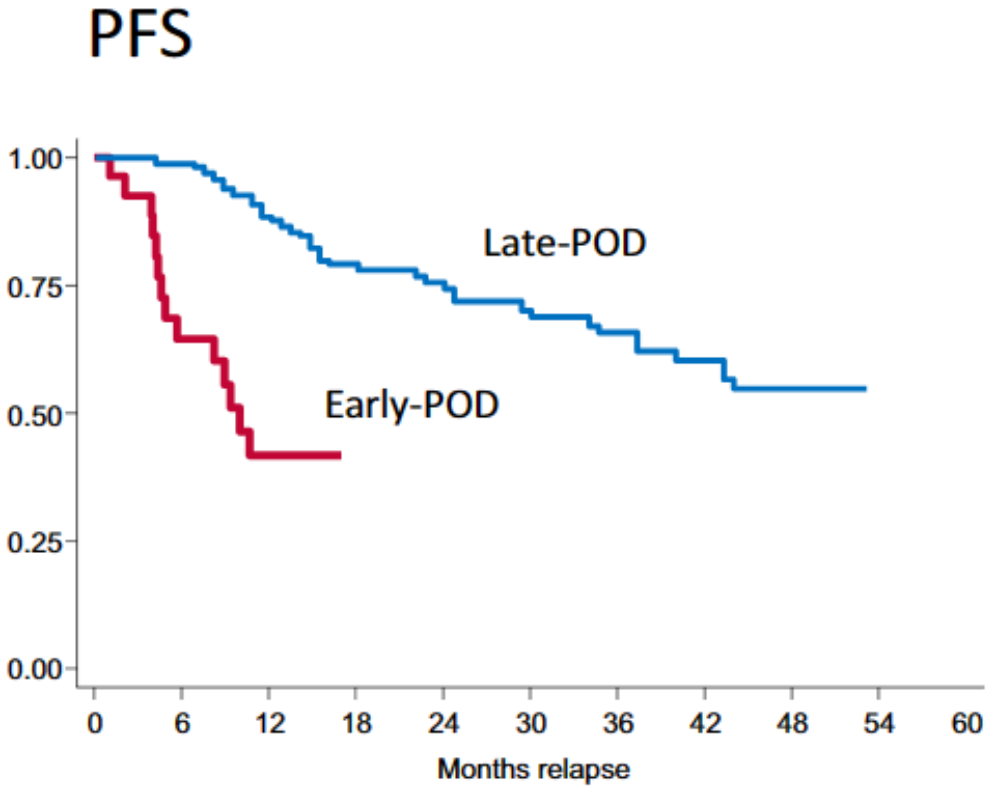
Median OS all patients: 2.9 months[1]

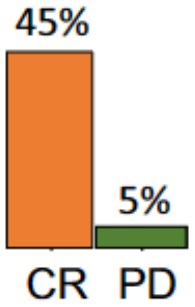
- The main cause of discontinuation is **disease progression***
  - Acquired resistance appeares to be universal[1]
  - Primary resistance to ibrutinib occurs in 1/3 patients[1]
- **Lower activity of ibrutinib in high-risk MCL** (Blastoid, TP53, ki67≥ 50%)*,[2]

Unmet medical needs[1]

Martin P, et al. Blood 2016; 127:1559-1563; 2. Jain P, et al. Br J Haematol 2018; 182:404–411

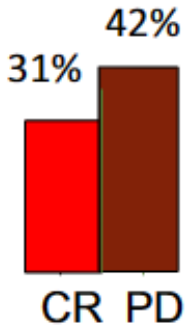
Ibrutinib at first relapse and CAR-T





Late-POD

Standard approach during BTKi
Refer to CAR-T centre if suboptimal response or high-risk features (i.e. TP53 mutation)



Early-POD

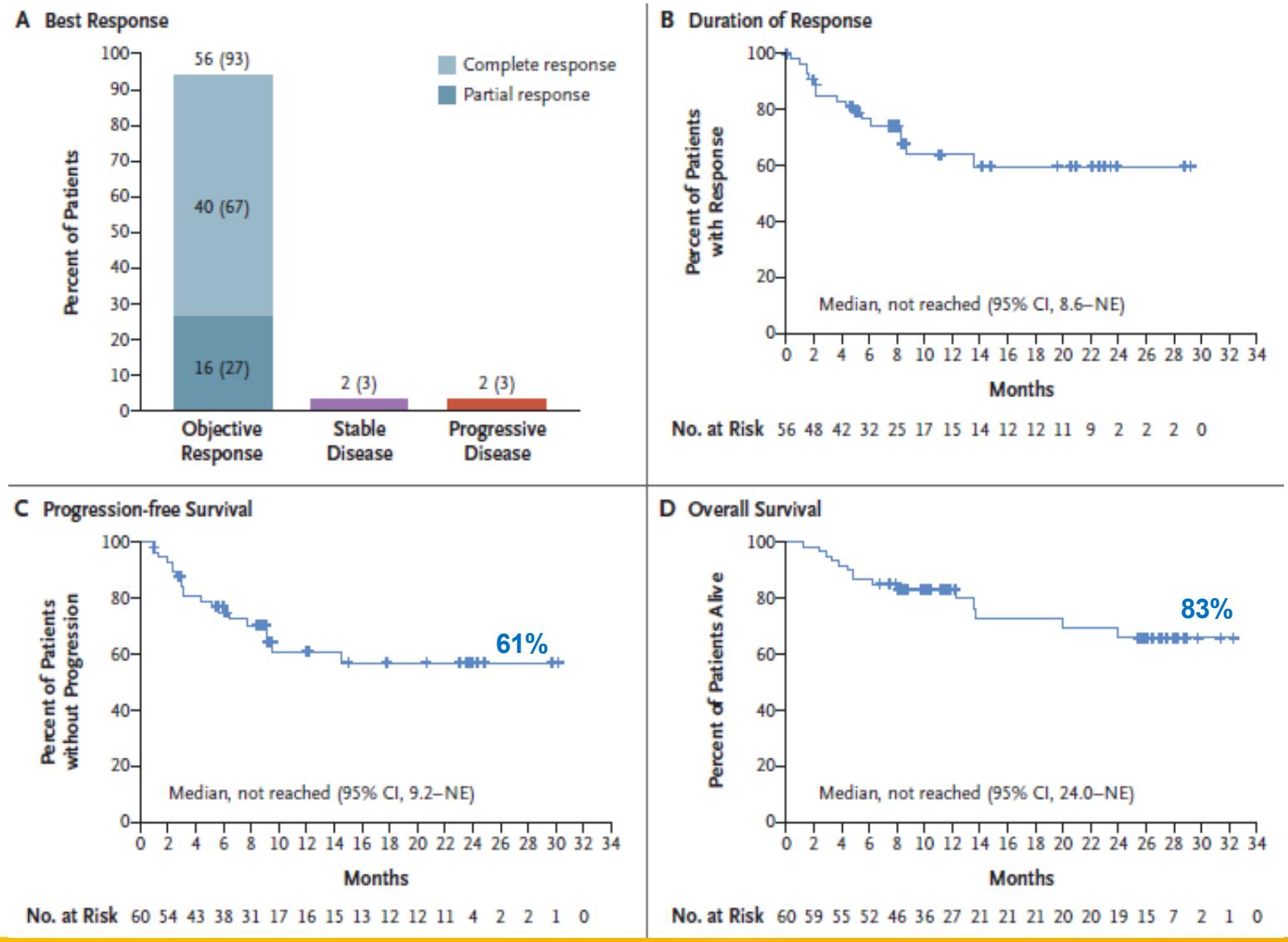
Refer to CAR-T centre at start of therapy
Close clinical monitoring
Restage 8-12 weeks

Patient identification at first relapse (before starting 2L): High risk patients

- Blastoid/pleomorfic morphology
- TP53 mut (including high expression of p53 with immunohistochemistry)
- Ki 67 > 50%
- Bulky > 5 cm
- POD24
- sMIPI high score

Visco, BJH 2023; Eyre BJH 2023

CART- Brexucel: ZUMA 2: phase 2 study

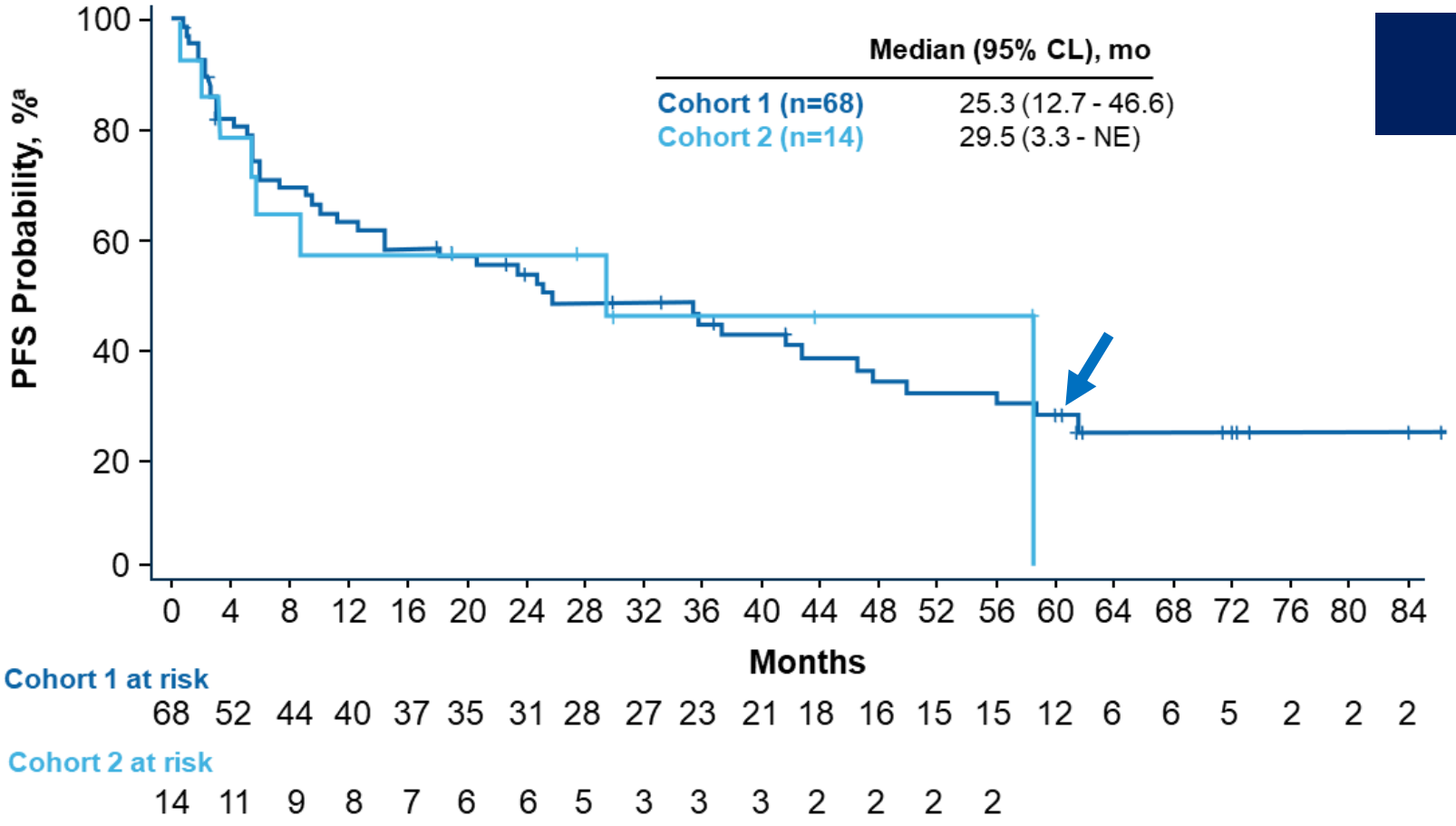


Median follow up: 12.3 months

74 patients enrolled

Wang M, et al. N Engl J Med 2020

Patient disposition for ZUMA-2 Cohorts 1 and 2: follow up 5-years



ORR 93%
CR rate 64%

Median age 65
(38-79)

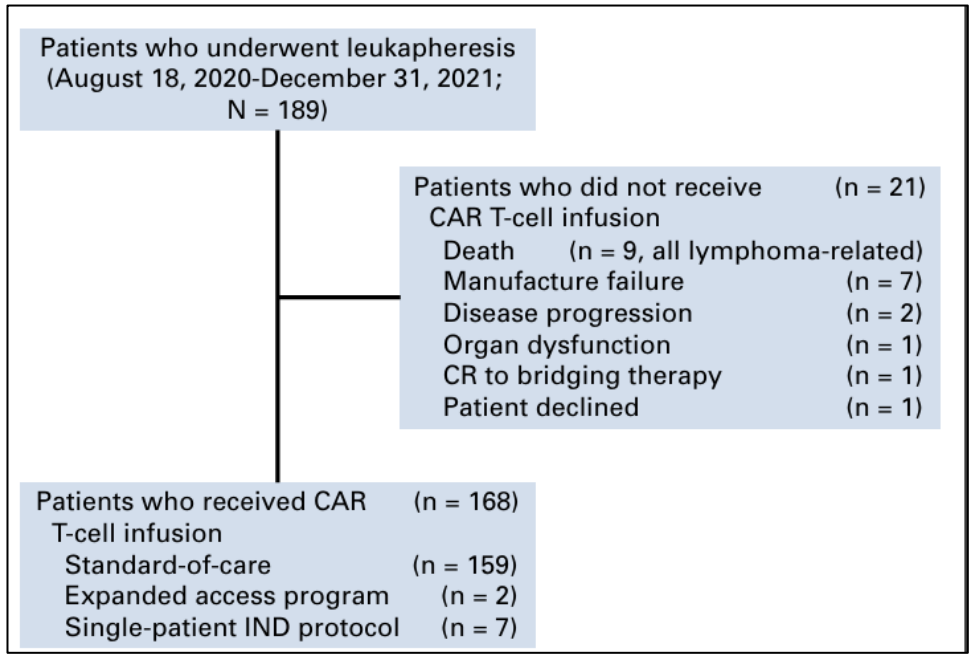
Median follow-up of 5 years

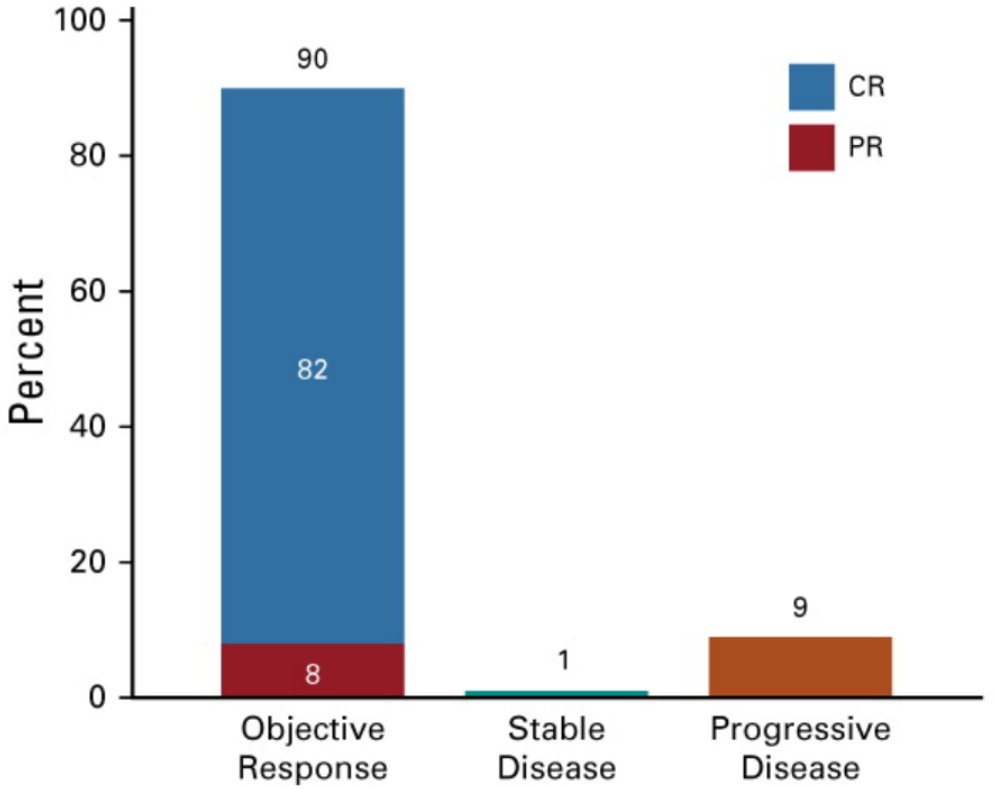
Late-onset toxicities were infrequent; only 3% of treatment-emergent adverse events of interest in ZUMA-2 occurred during this longer follow-up.

Wang M et al, ASH 2024

Brexu-cel for R/R MCL in Standard of Care Practice: results from the US consortium

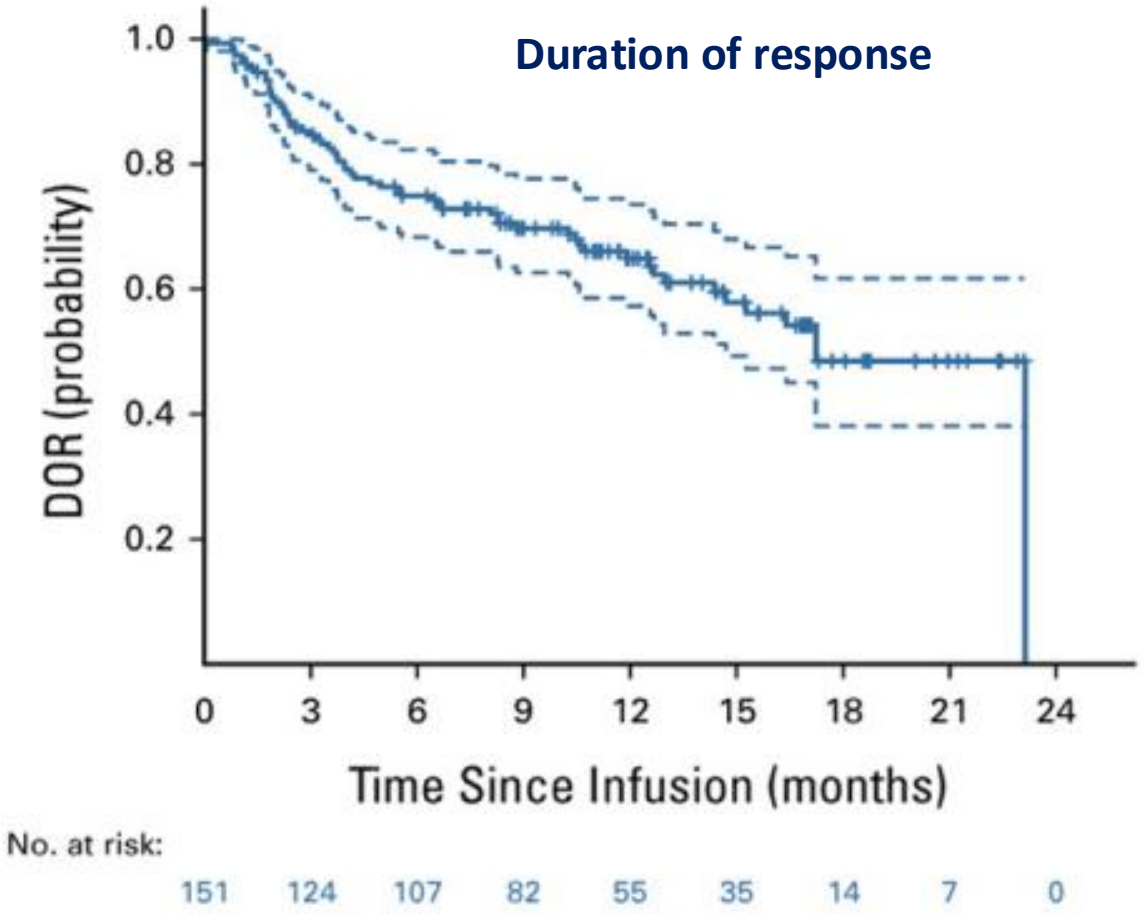
US Lymphoma CAR T Consortium: retrospective, multicenter study in patients receiving KTE-X19 (n= 189)

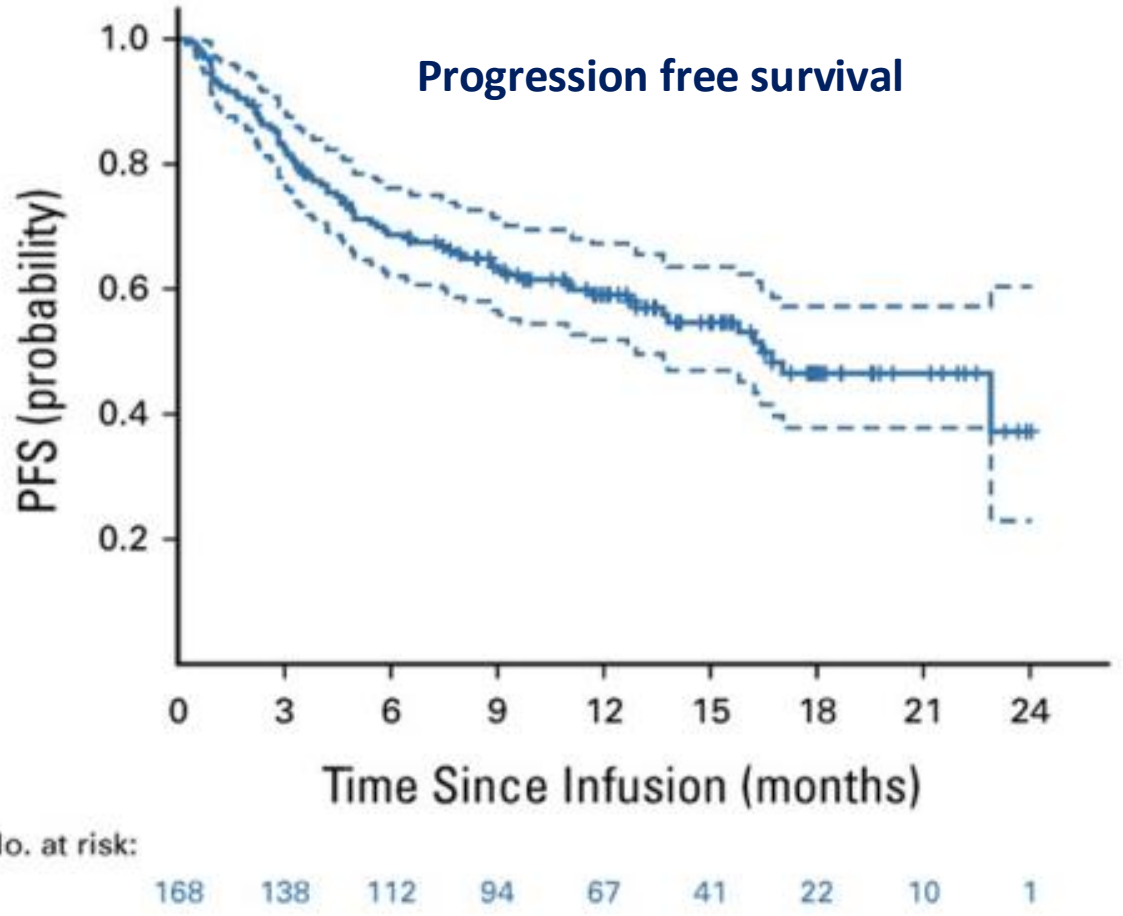




Wang Y, et al. JCO 2023

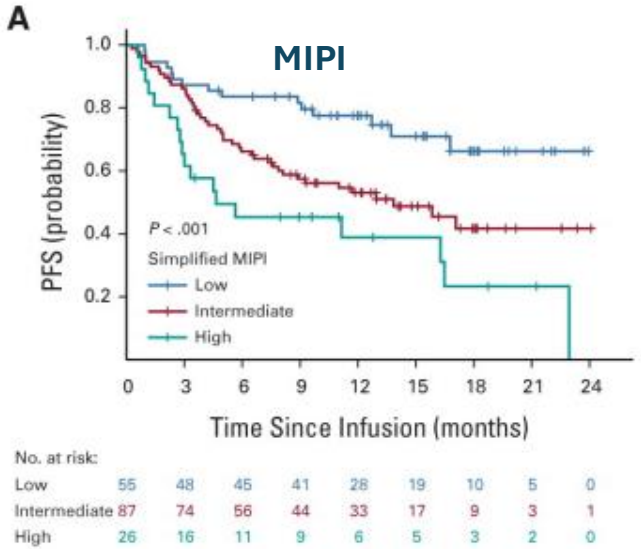
Brexu-cel for R/R MCL in Standard of Care Practice

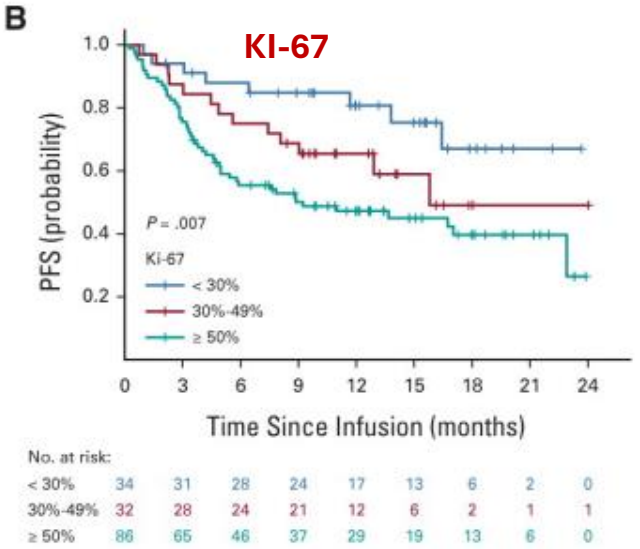


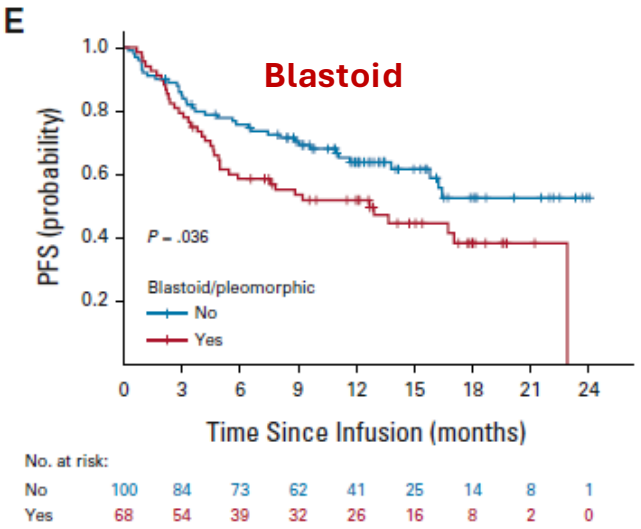


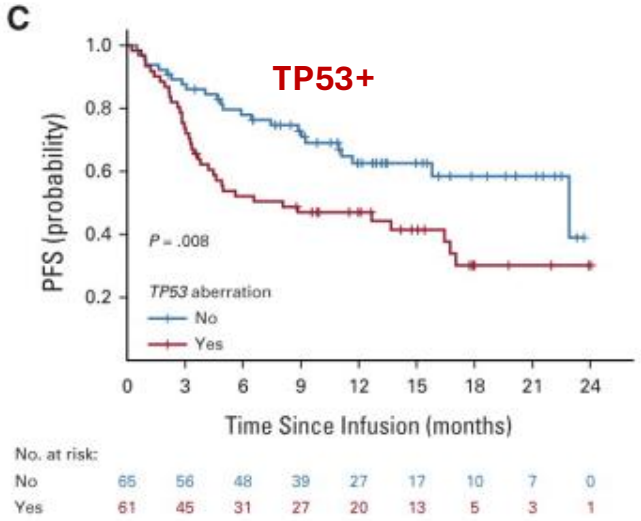
Wang Y, et al. JCO 2023

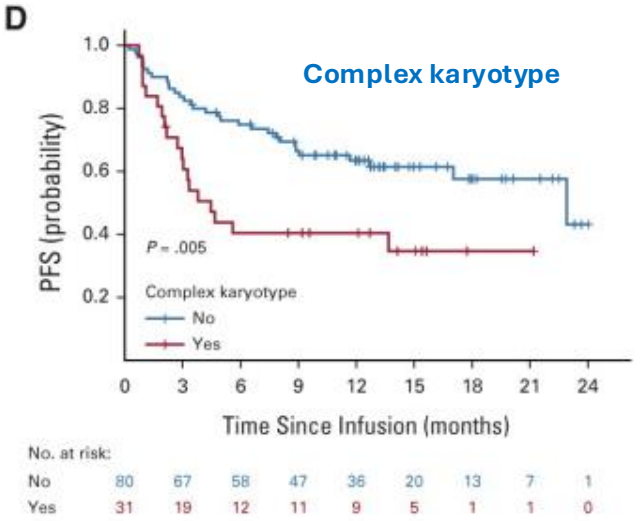
Brexu-cel for R/R MCL in Standard-of-Care Practice

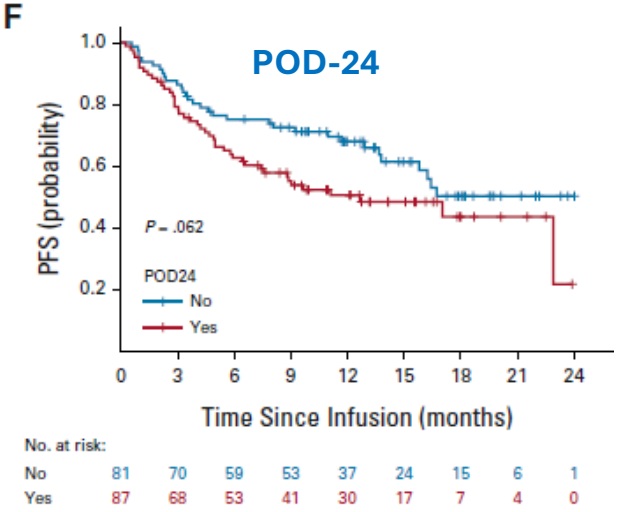








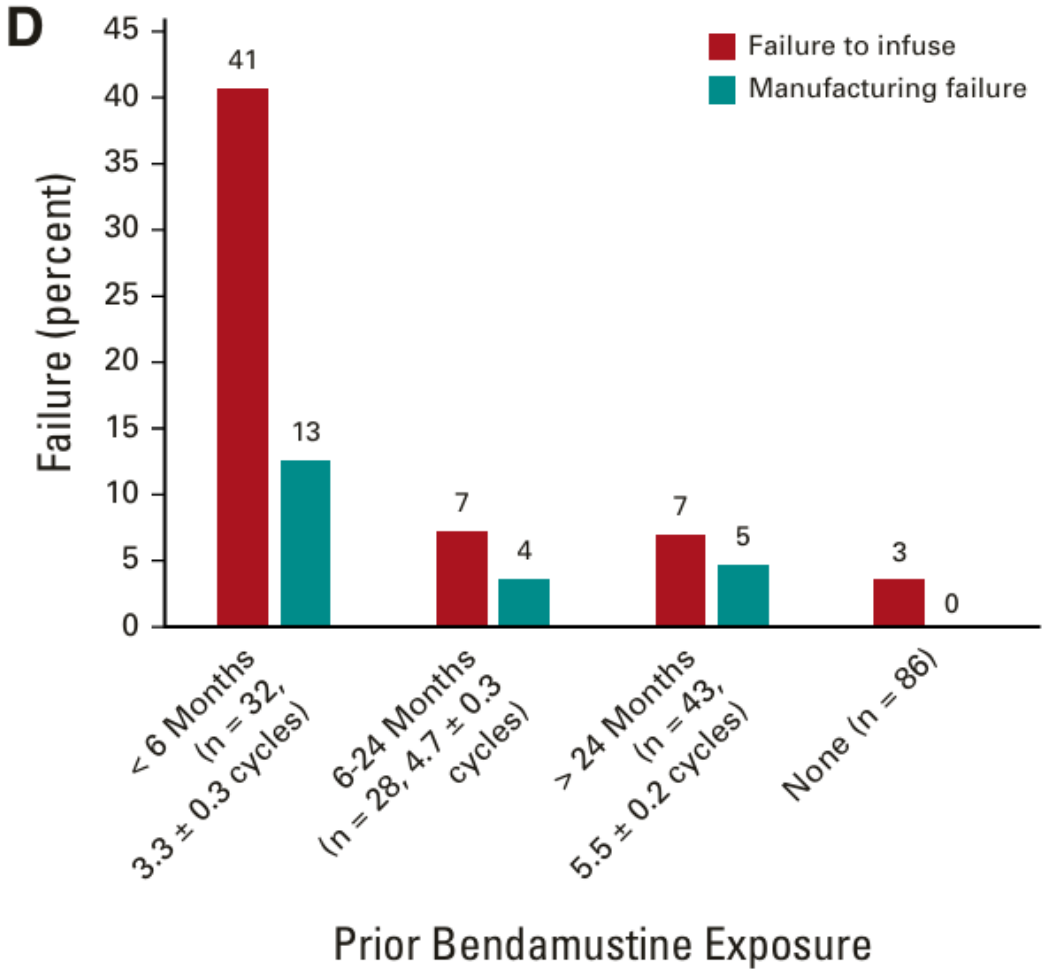


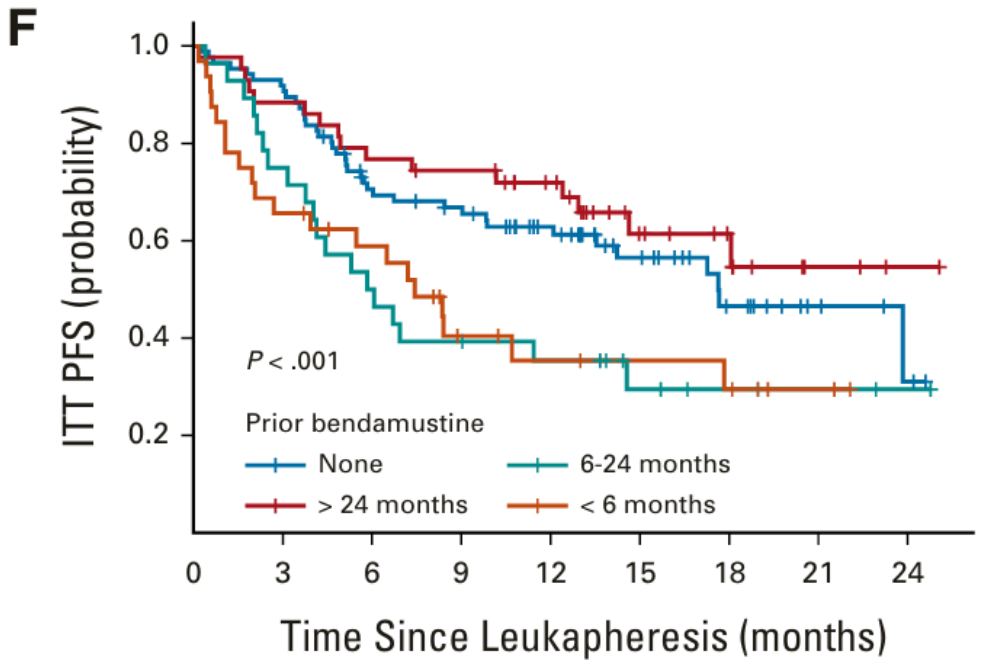


Wang Y et al. JCO 2023

Prior Bendamustine exposure and outcomes

103/189 patients received prior bendamustine





No. at risk:

None	86	79	57	51	39	23	13	5	2
> 24 months	43	38	33	31	25	13	9	3	1
6-24 months	28	21	14	11	9	5	3	2	1
< 6 months	32	21	17	9	7	6	5	2	0

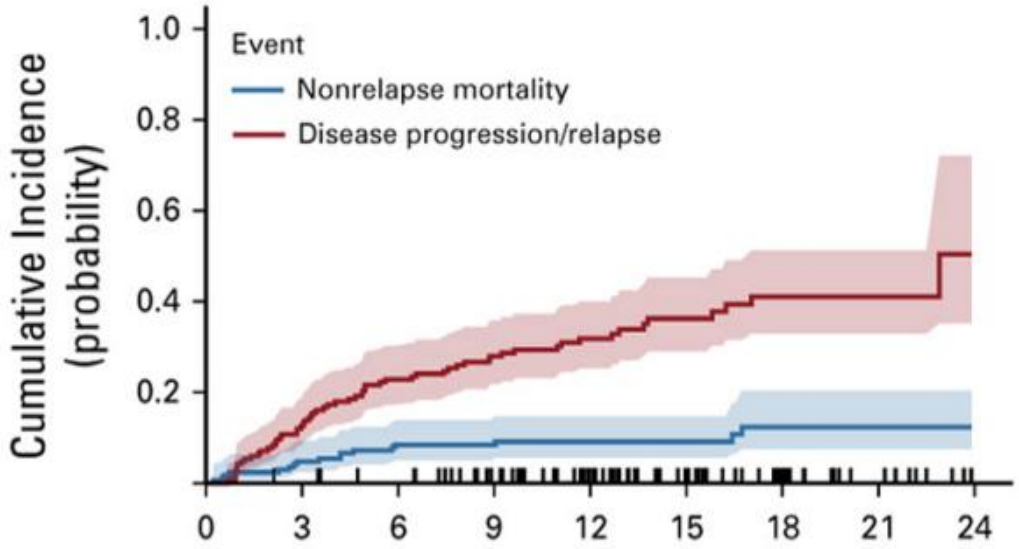
Wang Y, et al. JCO 2023

Short term and long term toxicity

- The incidences of CRS and ICANS were comparable to those reported in ZUMA-2.
- Tocilizumab and corticosteroids use appeared to be more frequent in this Consortium study cohort

	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	86 (91%)	57 (60%)	91%	63%
Max Grade*				
1-2	78 (82%)	24 (25%)	76%	32%
3-4	8 (8%)	33 (35%)	15%	31%
Days to onset	4 (0-11)	6 (1-15)	2 (1-13)	7
Days to max Grade	5 (0-7)	7 (3-15)	-	-
Duration	5 (1-33+)	6 (2-144+)	11	12

- **The non relapse mortality was 9.1% at 1 year**, primarily because of infections.

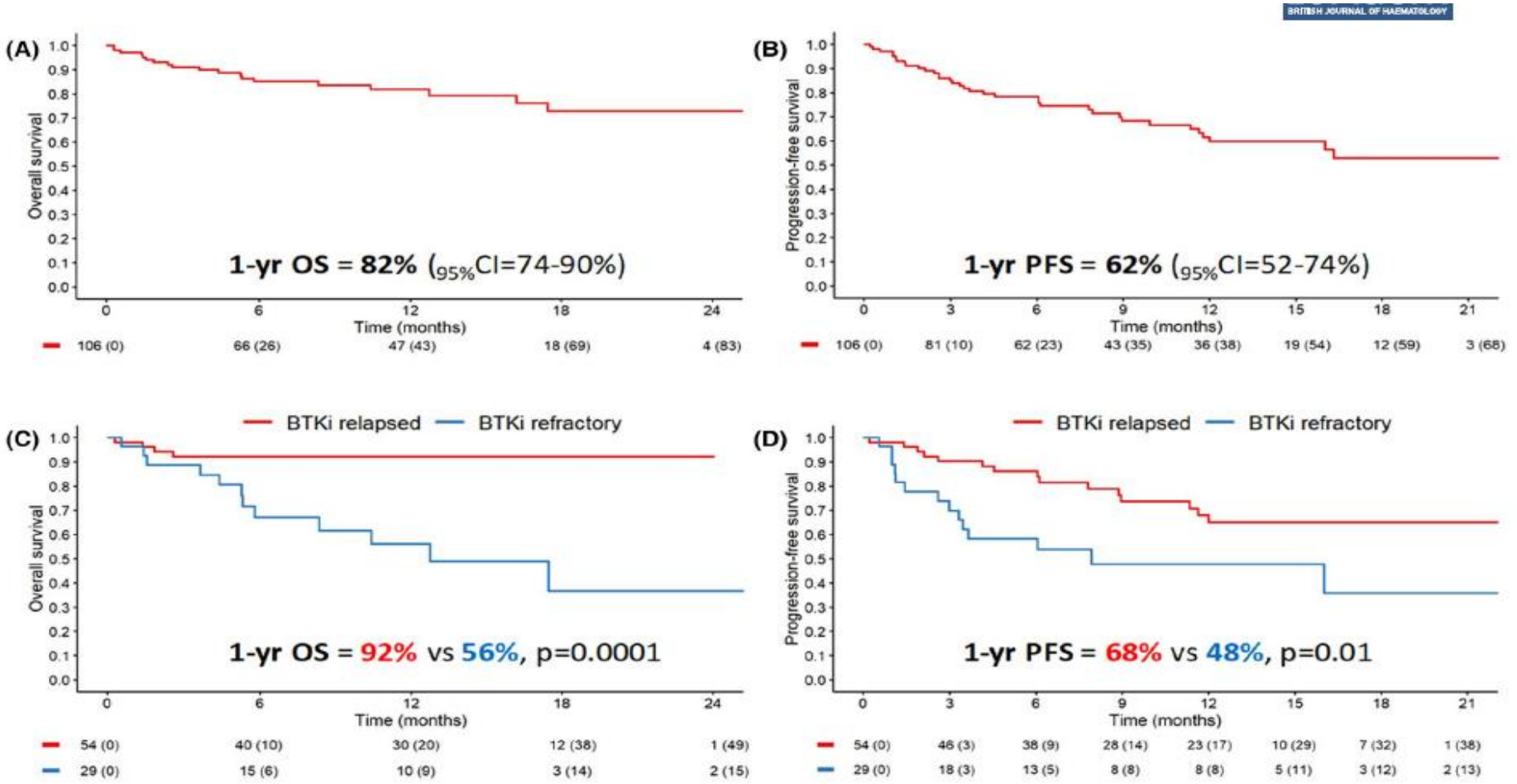


Wang Y, et al. JCO 2023

ORIGINAL PAPER
Transplantation and Cellular Therapy

CART-SIE

Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: Results from CART-SIE study

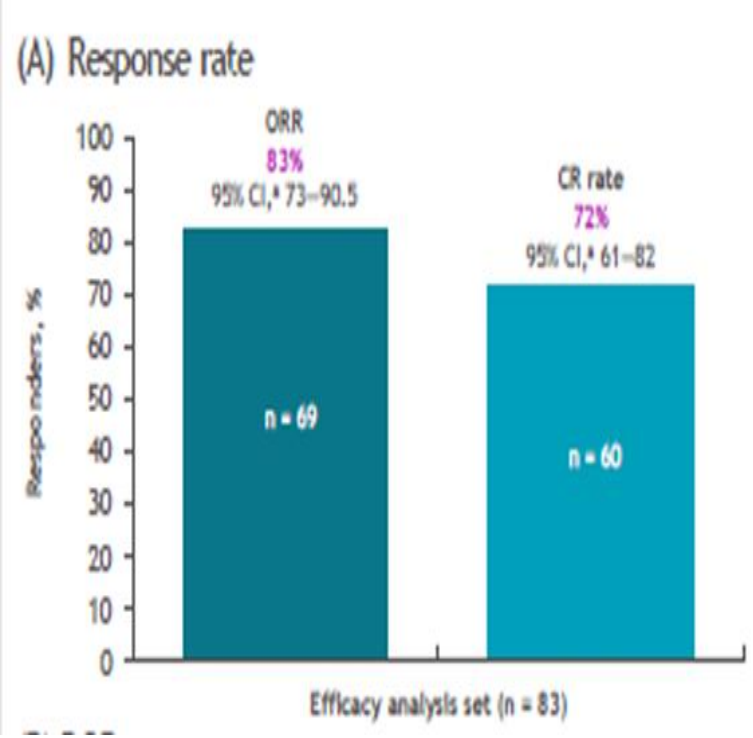


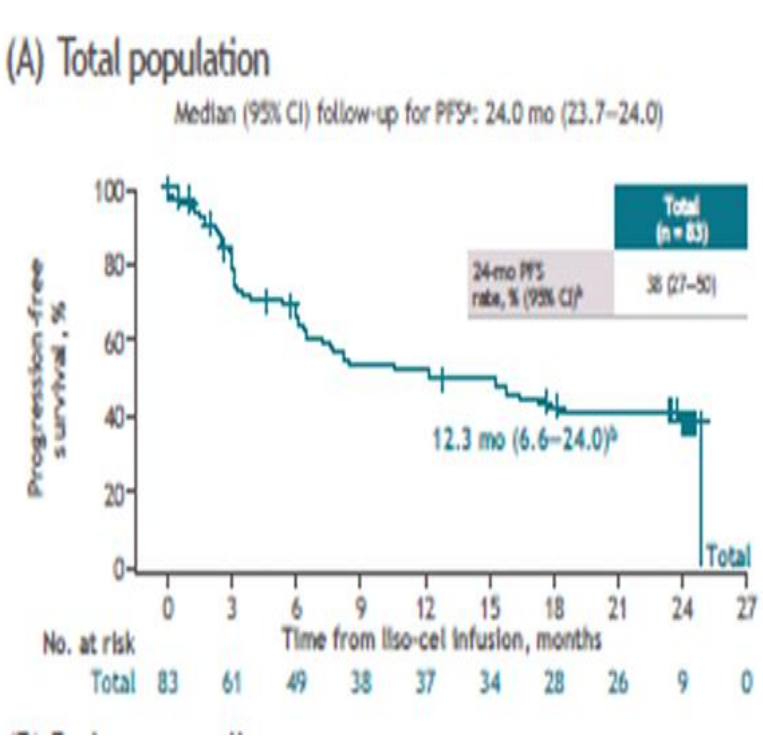
Response @ day + 90:
ORR 77%, CR 70%

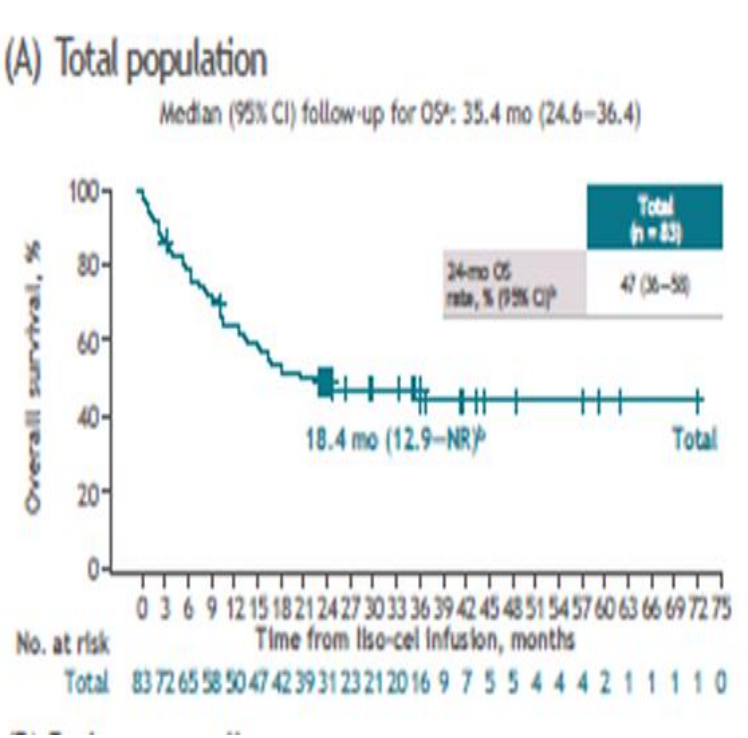
Median follow-up: 12.07 months (IQR: 5.95, 17.86

Stella F. et al, B.J.Hematology 2024

CAR-T: TRANSCEND NHL 001 study, Liso-Cel







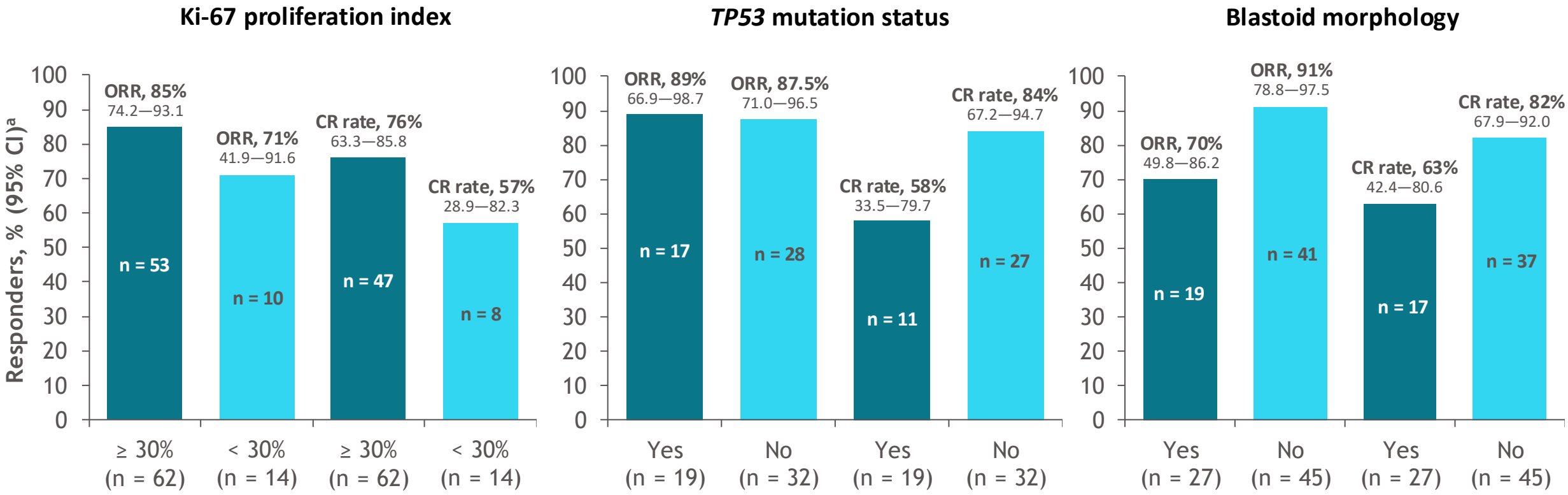
CRS any grade: 61% **CRS grade 3-4: 1%**

NEs any grade: 31% **NEs grade 3-4: 9% No grade 5 CRS or NEs**

Wang et al, JCO 2024

CAR-T: TRANSCEND NHL 001 study, Liso-Cel

ORR and CR rate by high-risk disease feature subgroup (efficacy set)

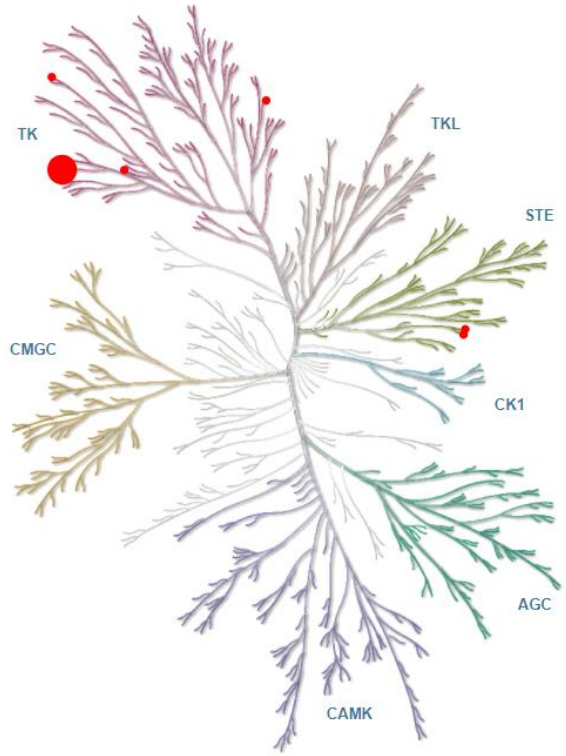


In the total of 83 pts (efficacy set) ORR was 83.1% and CR was 72.3%

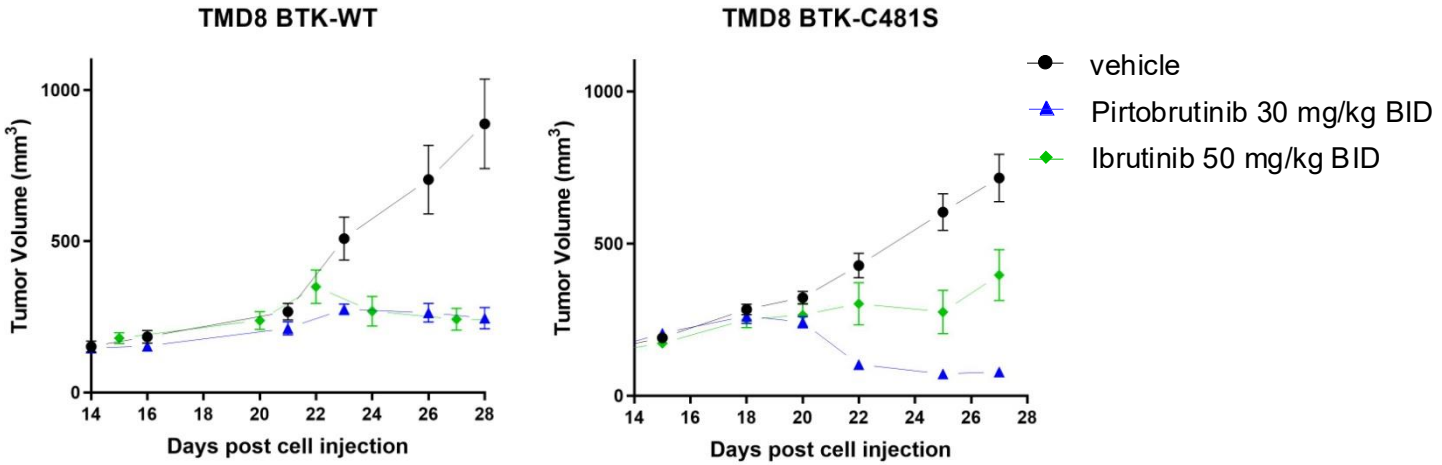
Wang et al, JCO 2024

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

Kinome selectivity[1]
Highly selective for BTK

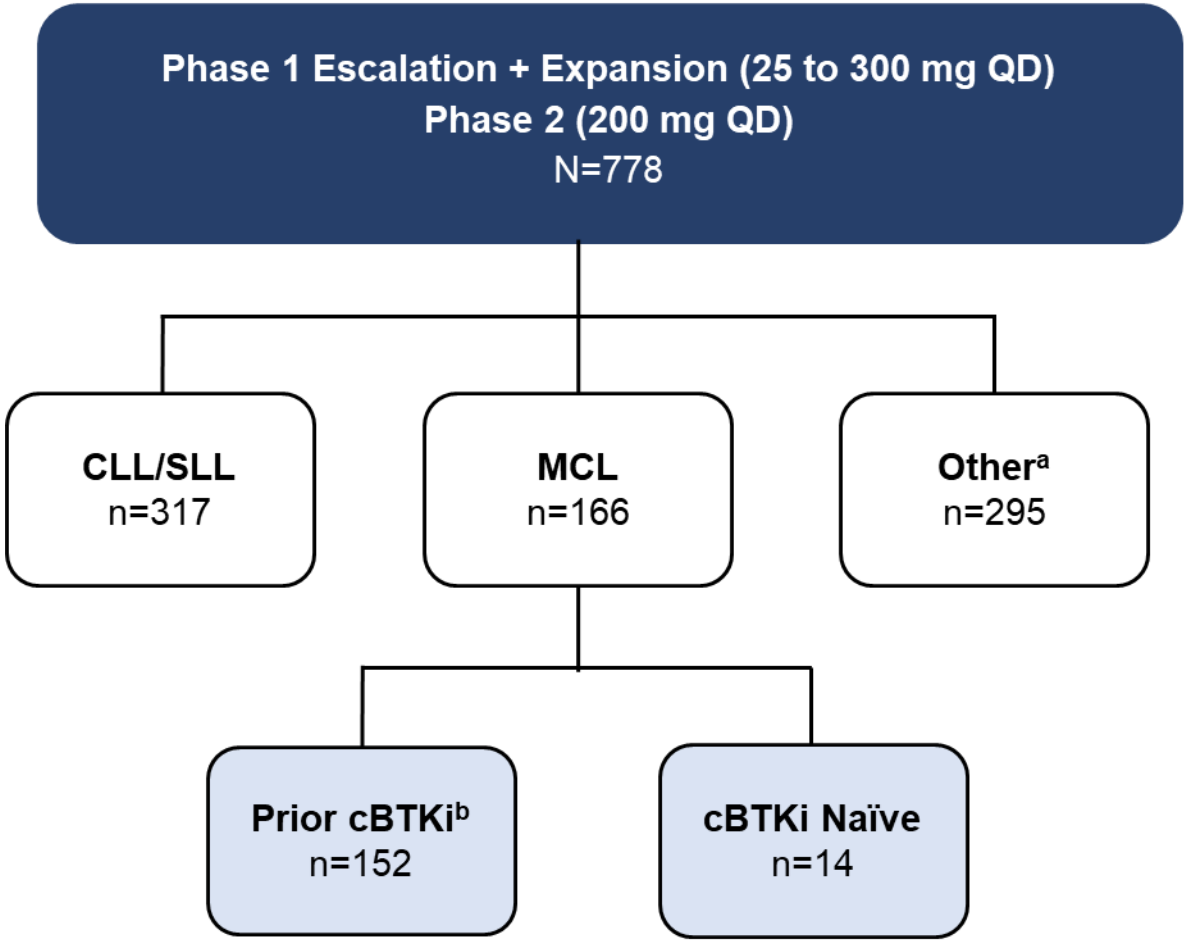


Xenograft models
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

Pirtobrutinib Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



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

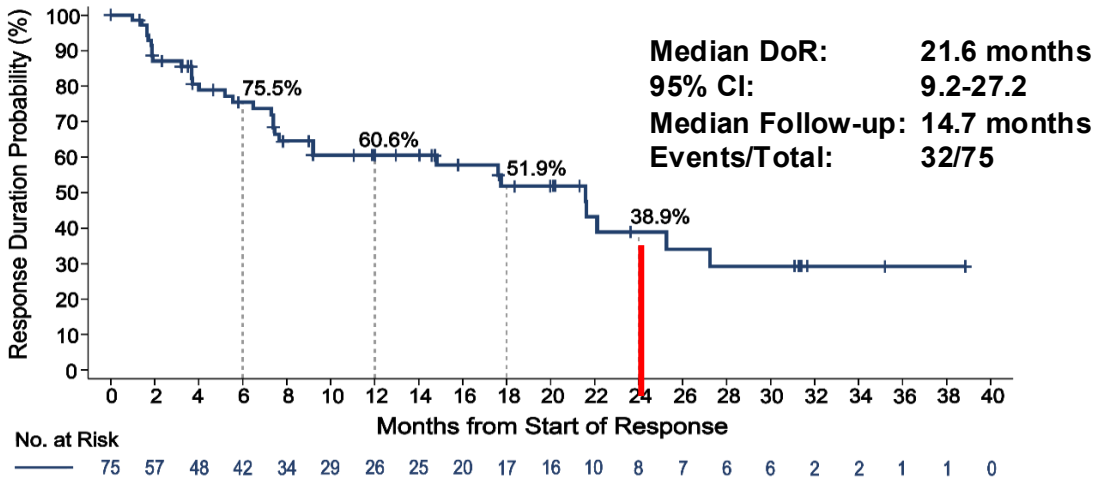
- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

Wang M.L et al.; ASH 2025

Pirtobrutinib phase 1/2 BRUIN Study: outcomes in Prior cBTKi pts with MCL

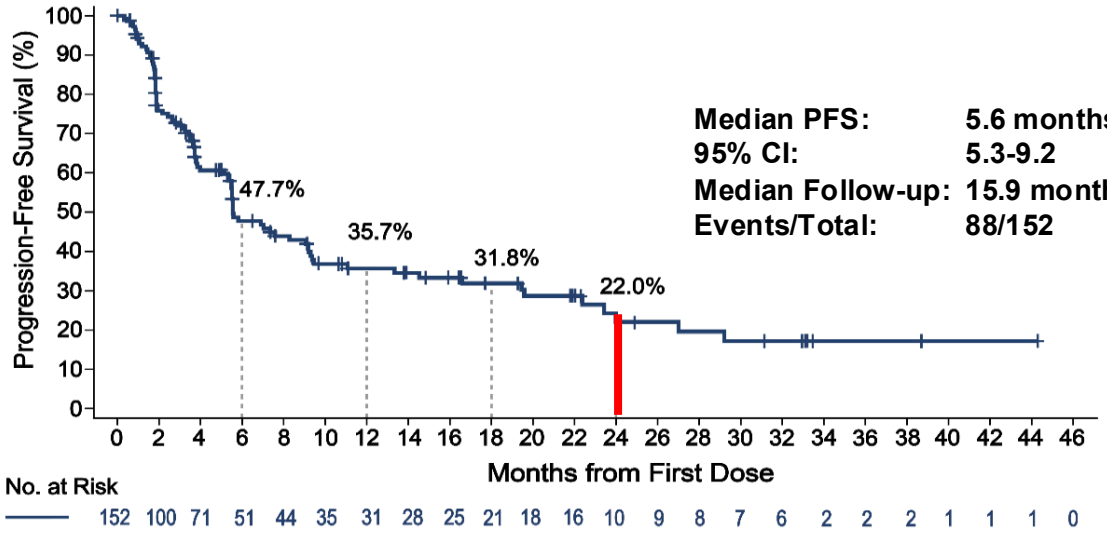
Prior cBTKi	n=152
ORR[b] % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Duration of Response



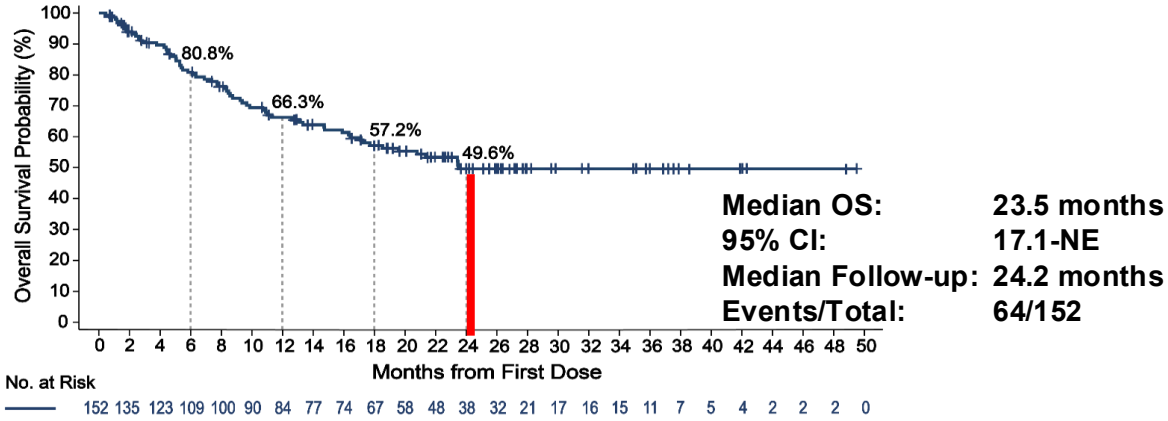
Median DoR: 21.6 months
95% CI: 9.2-27.2
Median Follow-up: 14.7 months
Events/Total: 32/75

Progression-Free Survival



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

Overall Survival



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

Pirtobrutinib Safety Profile

Treatment-Emergent AEs	Pirtobrutinib (n=166)			
	All-cause AEs, %		TRAEs, %	
AEs (≥15%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.9	0.0	13.3	0.0
Dyspnea	18.1	1.2	9.6	0.6
Anemia	18.1	8.4	7.8	3.0
Platelet count decreased	15.1	7.8	7.8	3.0
AEs of interest[a]				
Infections[b]	44.0	21.1	18.1	5.4
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	15.7	0.6	10.2	0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.8	0.6	1.8	0.0
Atrial fibrillation/flutter[f,g]	3.6	1.8	0.6	0.0

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Wang M.L. ASH 2025 oral

Treatment RR- Mantle Cell Lymphoma

The next future……

Glofitamab in RR-MCL: step up dosing

Phase I dose escalation in R/R MCL[1,2]

Glofitamab IV administration

- **Fixed-duration treatment: maximum 12 cycles**
  - Fixed dosing: 0.6mg, 16mg or 25mg Q3W*[1]
  - Step-up dosing: target dose 30mg Q3W†

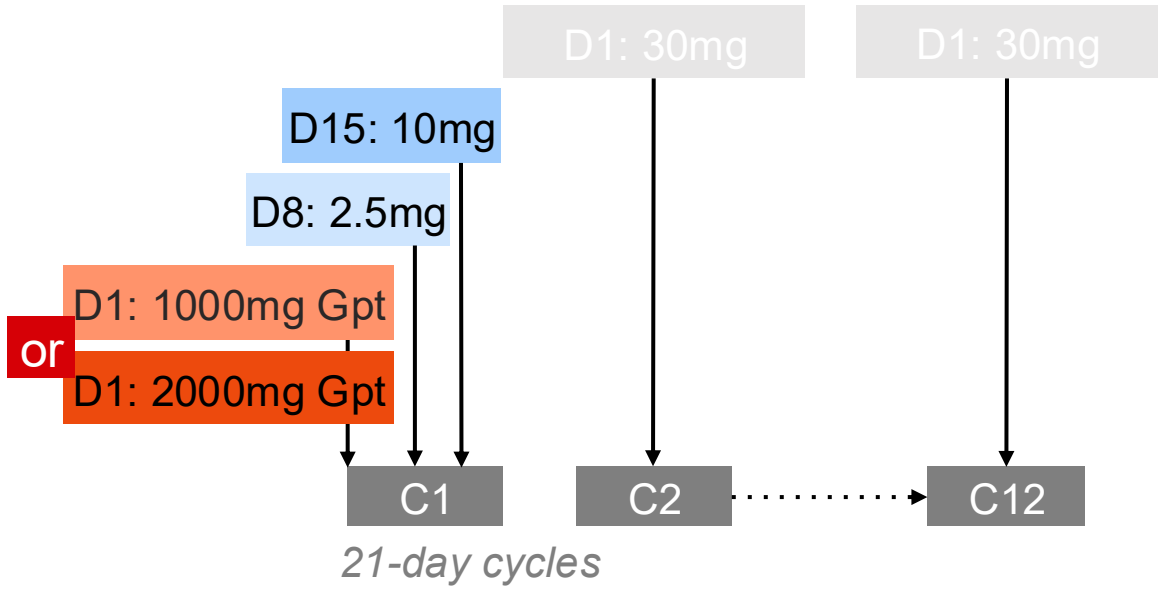
CRS mitigation

- Obinutuzumab pretreatment: 1 x 1000mg or 1 x 2000mg (2000mg option with step-up dosing only)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Population characteristics:

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1

Glofitamab step-up dosing schedule[2]



1. Philips T, et al. ASH 2021; oral presentation (abstract #130).
2. Philips T, et al. ASH 2022; oral presentation (abstract #74).

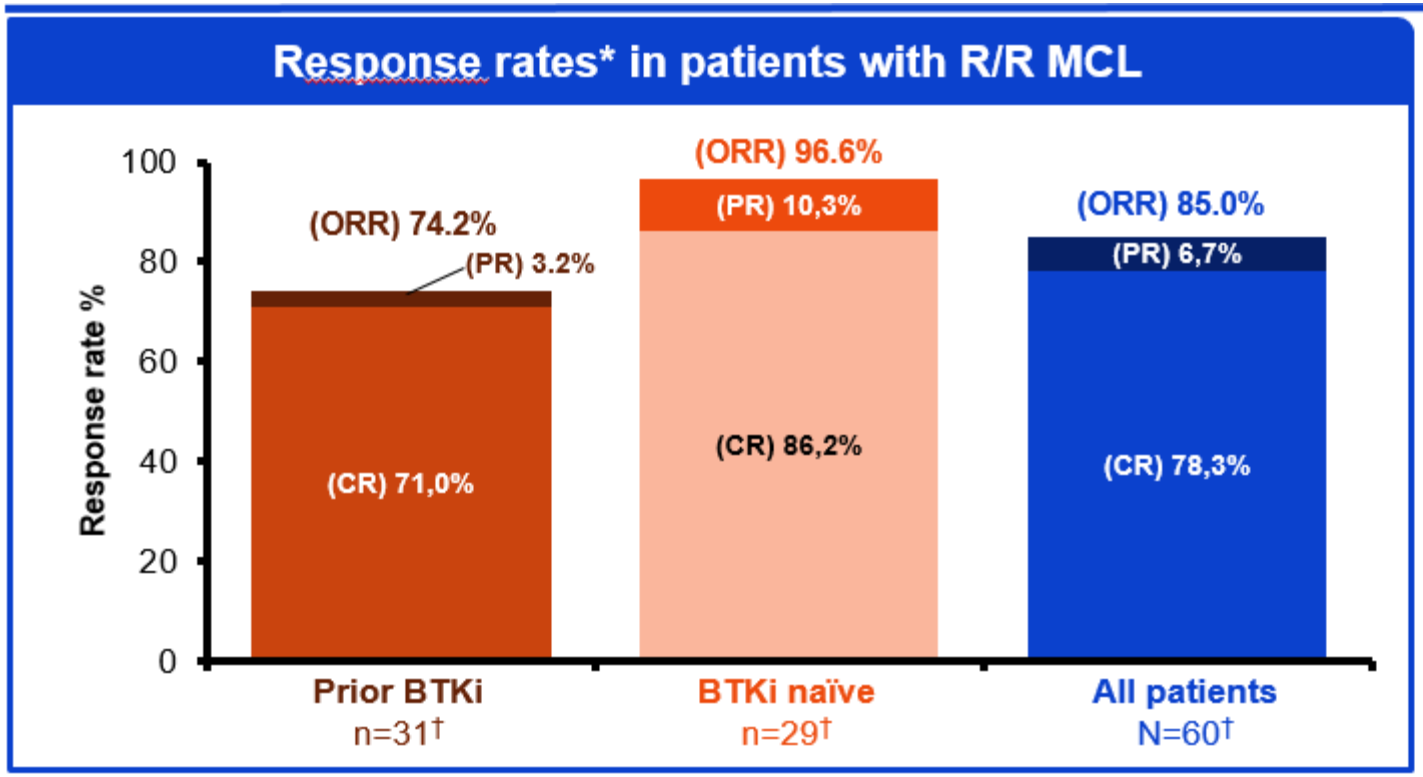
Glofitamab RR-MCL : baseline characteristics by prior BTKi

n (%) of patients unless stated		Prior BTKi (n=31)*	BTKi naïve (n=29)*	All patients (N=60)*
Median age, years (range)		70.0 (41–84)	72.0 (52–86)	72.0 (41–86)
Male		23 (74.2)	21 (72.4)	44 (73.3)
Ann Arbor stage III/IV		28 (90.3)	24 (82.8)	52 (86.7)
MCL IPI score ≥6		7 (22.6)	8 (27.5)	15 (25.0)
Median no. of prior lines (range)		3.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Median time since last prior therapy to first study treatment, months (range)		1.3 (0.1–53.2)	7.4 (1.1–132.5)	2.4 (0.1–132.5)
Median time since last anti-CD20 therapy to first study treatment, months (range)		15.1 (0.7–159.0)	25.1 (1.4–132.5)	16.3 (0.7–159.0)
Refractory status	Refractory to any prior therapy	30 (96.8)	20 (69.0)	50 (83.3)
	Refractory to 1L therapy	17 (54.8)	14 (48.3)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)	44 (73.3)

1. Philips T, et al. ASH 2021; oral presentation (abstract #130).
2. Philips T, et al. ASH 2022; oral presentation (abstract #74).

Glofitamab : Response rates by regimen and prior BTKi

Response rates



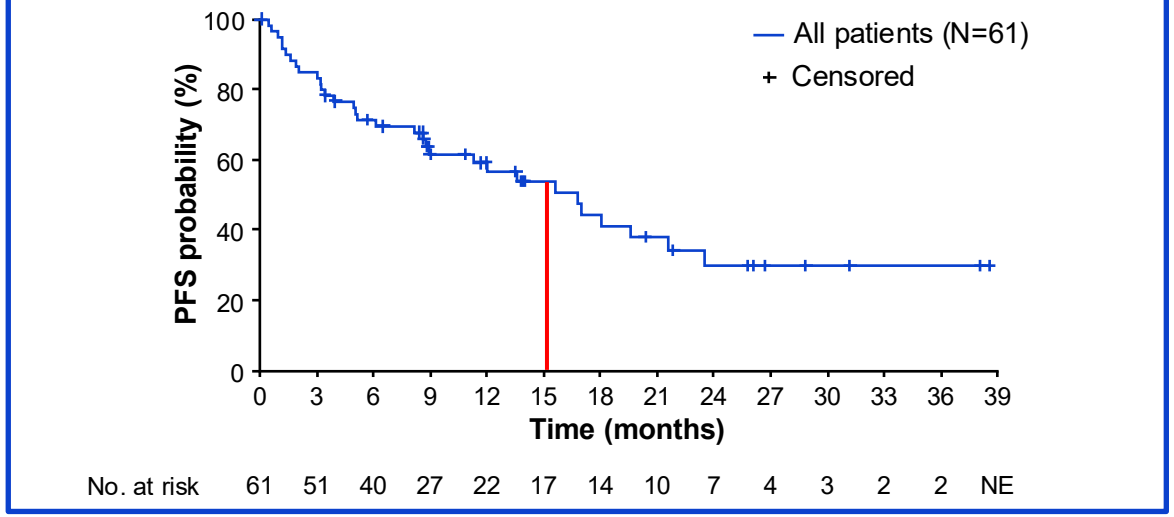
- Median time to first response among responders (n=51): **42 days** (95% CI: 42.0–45.0)

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

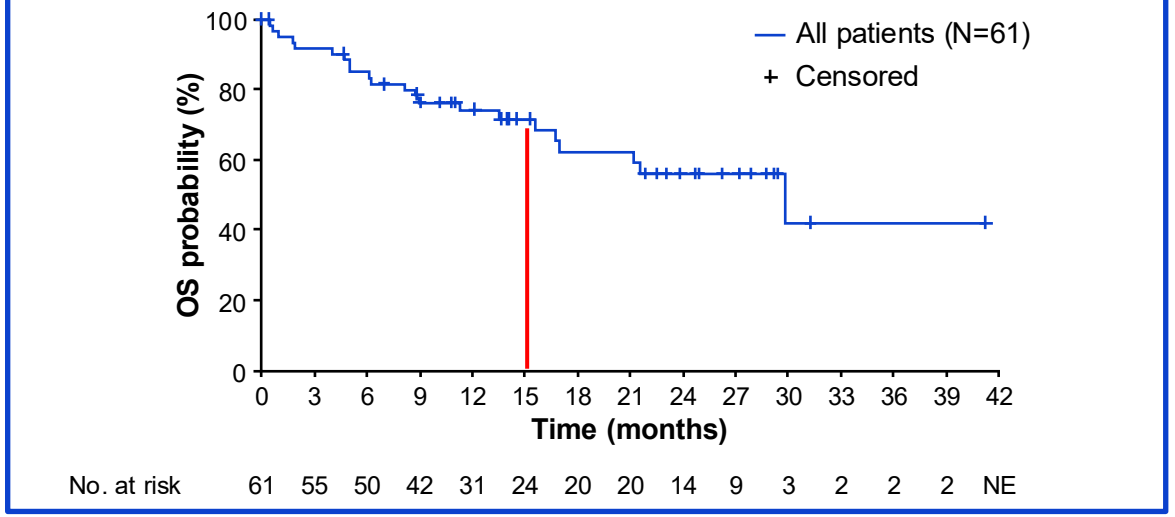
Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024

Glofitamab : Time-to-event endpoints

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)

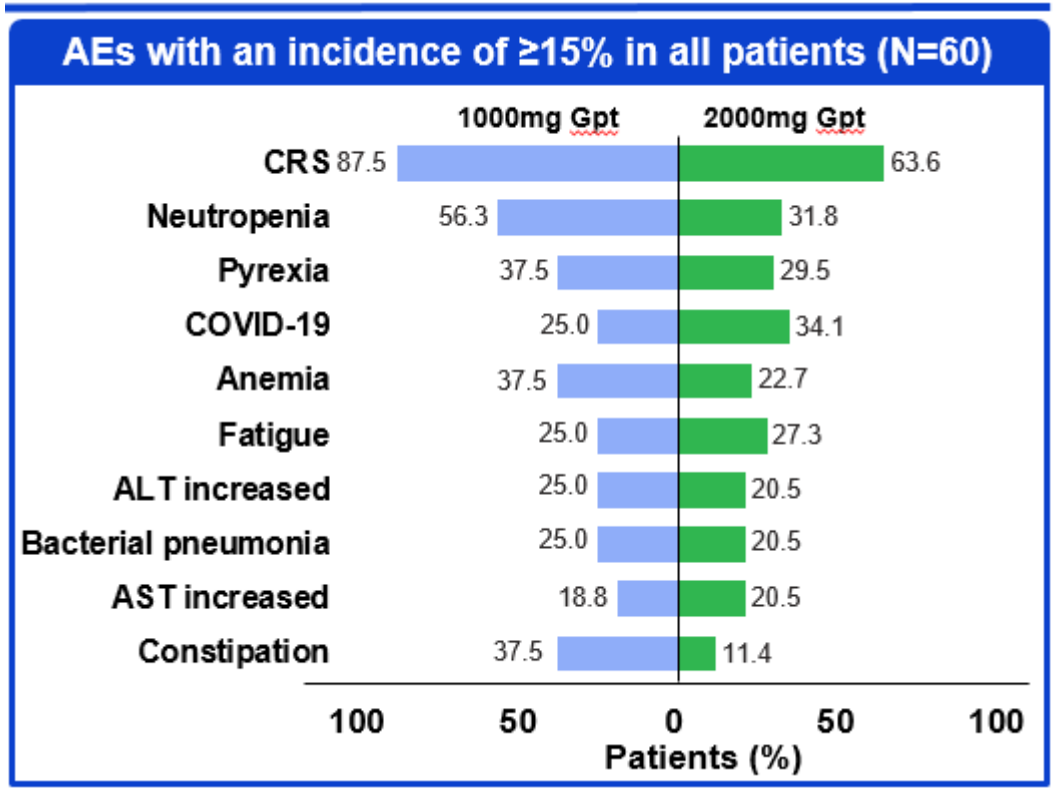
	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	**21.2 (9.0–NE)**	**29.9 (17.0–NE)**
15-month OS rate, % (95% CI)	55.0 (36.5–73.6)	71.4 (59.3–83.5)

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

Philips T, et al. J Clin Oncol October 4, 2024

Bispecific Phase I/II study – Glofitamab in RR MCL

Safety



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)

ICANS any grade (3 pts – 5%) – all G1-G2

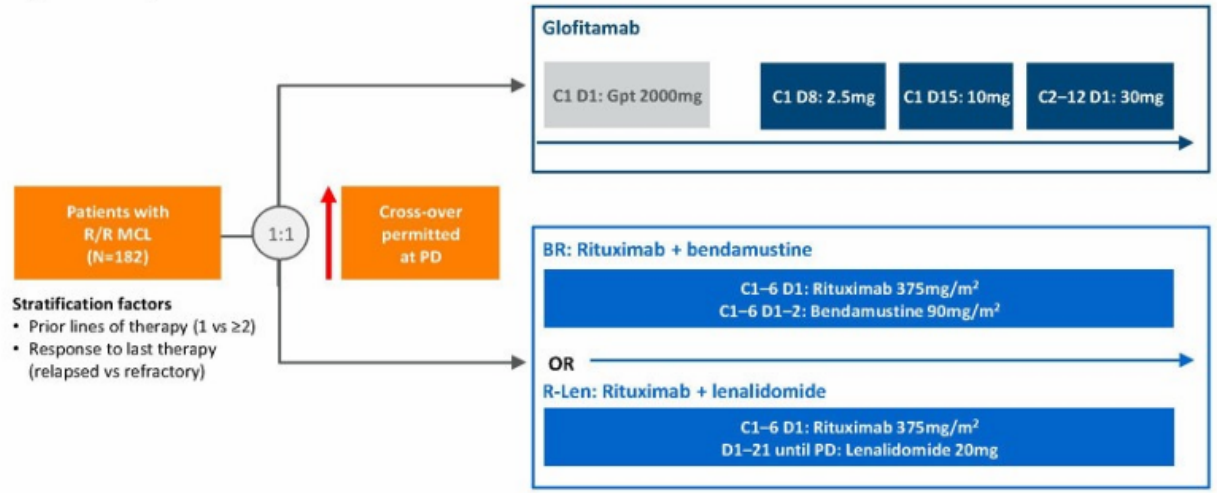
A lower incidence of CRS was observed in the 2000mg versus 1000mg cohort

Philips T, et al. J Clin Oncol October 4, 2024

Future prospectives

GLOBRYTE: A Phase III, Open-Label, Multicenter, Randomized Trial Evaluating Glofitamab Monotherapy in Patients with Relapsed or Refractory Mantle Cell Lymphoma

Figure. Study schema



B, bendamustine; C, cycle; D, day; Gpt, obinutuzumab pretreatment; Len, lenalidomide; MCL, mantle cell lymphoma; PD, progressive disease; R/R, relapsed/refractory; R, rituximab. Relapsed disease is defined as disease progression after the last regimen; refractory disease is defined as failure to achieve a partial response or complete response to the last regimen.

MD01-01_I01_PFIL06

FONDAZIONE ITALIANA LINFOMI

Clinical Protocol

Title

A phase II, multicenter study of GlOfitamab in patients with mantle cell Lymphoma and inaDequate response or relapse following CAR T-cell therapy (GOLD)

Bispecific –Phase Ib/II Study– Mosun-Pola in RR MCL

Patients with Prior-BTKi Treated – Baseline Characteristics

n (%), unless stated	N=20
Median age, years (range)	68 (44–82)
Male sex	15 (75)
ECOG PS score	
0	12 (60)
1	5 (25)
2	3 (15)
Ann Arbor stage III–IV	19 (95)
Extranodal involvement	17 (85)
Elevated LDH	9 (45)
Median lines of prior therapy, n (range)	3 (2–9)
Number of prior lines of therapy	
2	5 (25)
3	6 (30)
≥4	9 (45)

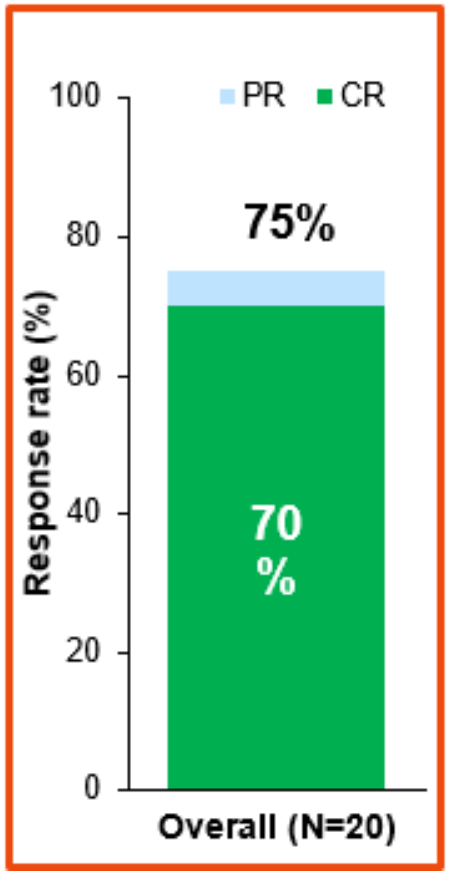
n (%), unless stated	N=20
Prior therapy	
BTKi	20 (100)
CAR T	7 (35)
ASCT	6 (30)
Refractory to last prior therapy	17 (85)
TP53 aberration at study entry	
Mutation/deletion	5/12 (42)*
Wildtype	7/12 (58)
Unknown	8
Ki-67	
≥30%	13 (65)†
≥50%	12 (60)
MIPI score ≥6	8 (40)
Blastoid/pleomorphic	10 (50)
Bone marrow involvement	9 (45)

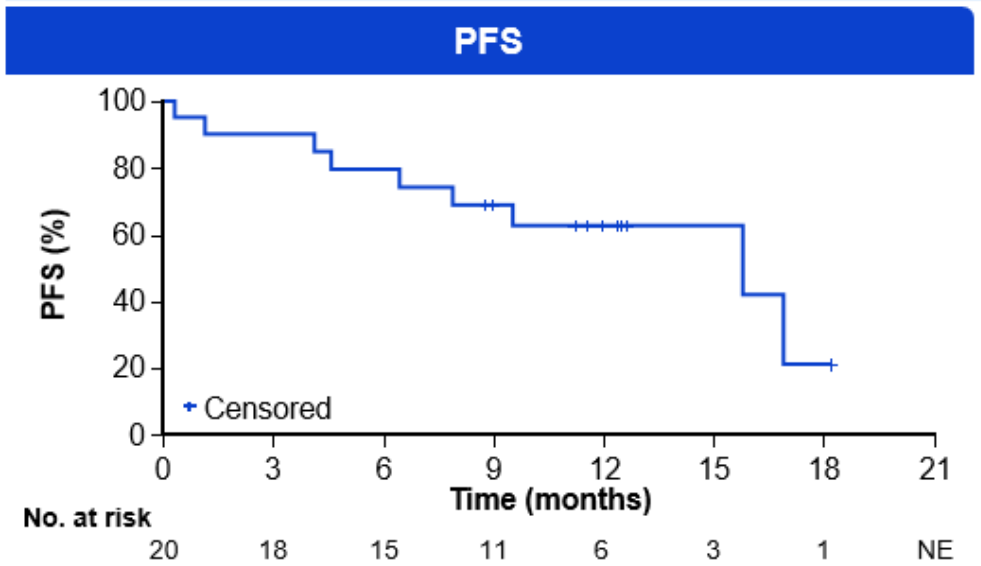
Wang M et al, ASH 2023

Bispecific –Phase Ib/II Study– Mosun-Pola in RR MCL

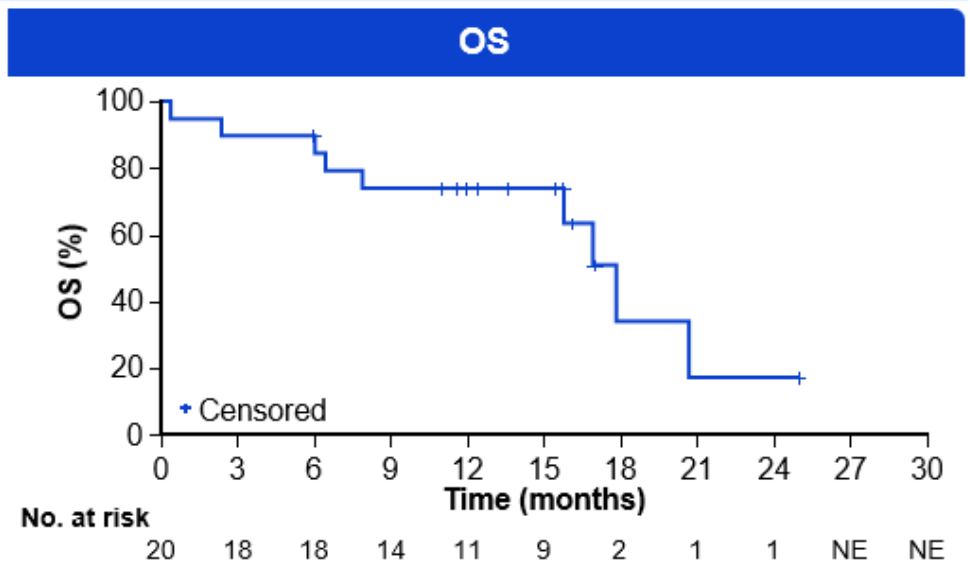
Response and Survival

Median follow-up: 15.8 months





	N=20
Median PFS, months (95% CI)	15.8 (8.0–NE)
9-month event-free rate, % (95% CI)	68.8% (48.1–89.6)



	N=20
Median OS, months (95% CI)	17.9 (15.8–20.7)
9-month event-free rate, % (95% CI)	74.1% (54.5–93.7)

Wang M et al, ASH 2023

Sonrotoclax monotherapy in R/R MCL previously treated with a BTK inhibitor: early results from a phase 1/2 study

	Sonrotoclax	Venetoclax	Differences in Design
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may potentially lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity
Half-life in humans	≈5 hours[2]	26 hours[3]	Short half-life and no accumulation may potentially result in simplified TLS monitoring during sonrotoclax ramp-up

Wang M et al, ASH 2025

BGB-11417-201 (NCT05471843) study design

Eligibility criteria

- Age ≥18 years
- Histologically-confirmed MCL per WHO 2016 classification
- ≥1 line of anti-CD20-based therapy and ≥1 BTK inhibitor
- ECOG PS of 0-2
- No prior BCL2 inhibitor treatment

Study design

Parts 1A + 1B dose escalation and safety expansion

Target dose 1: 160 mg QD (n=10)

Target dose 2: 320 mg QD (n=12)

Safety expansion: up to 2 cohorts at select sonrotoclax target dose levels n≤12 per cohort (including part 1A)

Part 1 endpoints

- Primary: DLTs (part 1A), TEAEs, SAEs, AEs leading to discontinuation, TLS events
- Secondary: preliminary antitumor activity

Part 2 efficacy expansion

Sonrotoclax at RP2D[a] until PD n=103

Part 2 endpoints

- Primary: ORR by IRC (Lugano 2014)
- Secondary: ORR by INV, DOR by IRC and INV, PFS by IRC and INV, TTR by IRC and INV, HR-QOL, OS, safety

Sonrotoclax target doses were achieved after a ~4 week ramp-up that did not require hospitalization or 12- or 24-hour post-dose laboratory monitoring

Wang M et al, ASH 2025

Baseline patient demographics and disease characteristics

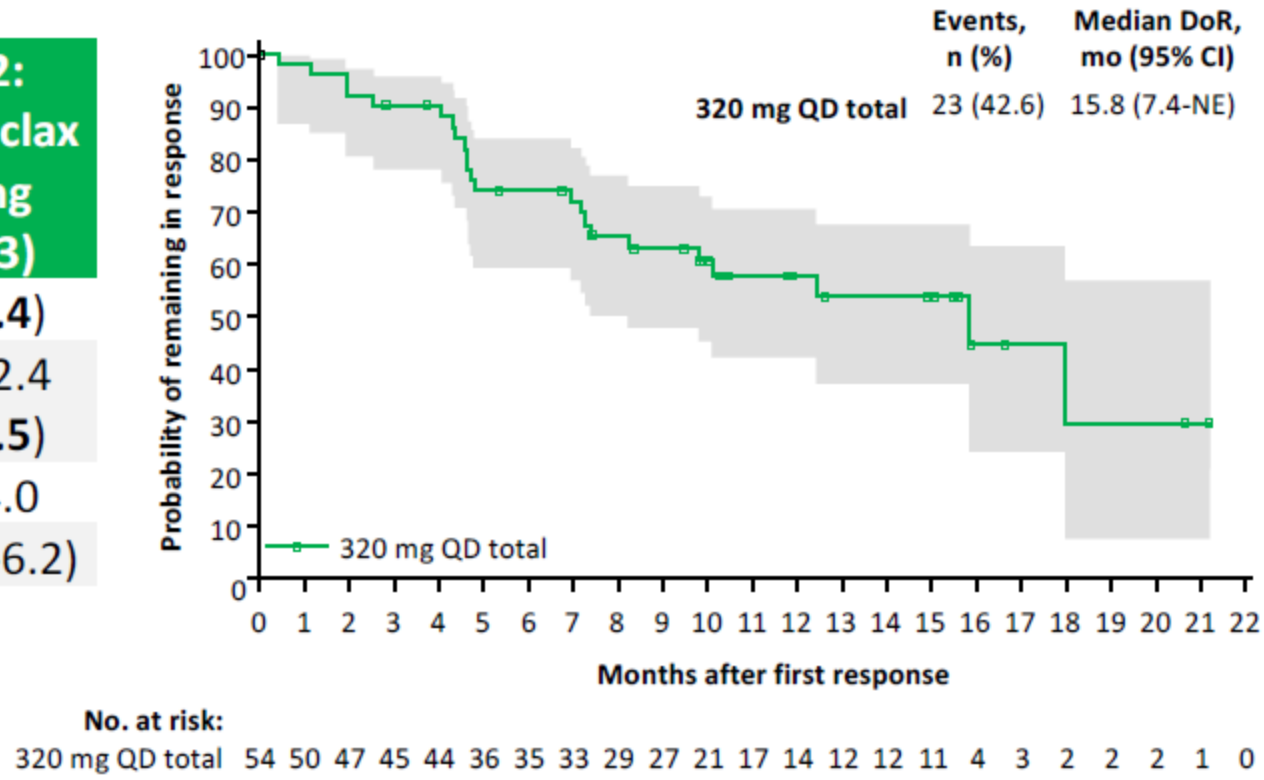
Parameters	Sonrotoclax 320 mg (n=115)
Age, median (range), years	68 (39-85)
≥65 years, n (%)	74 (64.3)
Male, n (%)	87 (75.7)
Race, n (%)	
Asian	45 (39.1)
Black or African American	3 (2.6)
White	61 (53.0)
Other/not reported	6 (5.2)
Ethnicity, n (%)	
Not Hispanic or Latino	87 (75.7)
Hispanic or Latino	25 (21.7)
ECOG performance status, n (%)	
0	34 (29.6)
1	74 (64.3)
2	7 (6.1)
Disease stage at study entry, n (%)	
III	11 (9.6)
IV	90 (78.3)
Disease status to last prior therapy, n (%)	
Refractory[a]	100 (87.0)
Relapsed[b]	14 (12.2)
MIPI, n (%)	
High	39 (33.9)
Intermediate	41 (35.7)

Parameters	Sonrotoclax 320 mg (n=115)
Bulky disease status, n (%)	
LDi ≥5 cm	46 (40.0)
LDi ≥10 cm	12 (10.4)
Bone marrow involvement at baseline, n (%)	58 (50.4)
Ki67 status, n/N with known status (%)	
Positive	92/98 (93.9)
≥30%	41/98 (41.8)
***TP53* mutation, n/N with known status (%)**	27/78 (34.6)
Prior lines of therapy, median (range)	3 (1-8)
≥3 prior lines, n (%)	68 (59.1)
Prior BTK inhibitor treatment, n (%)	115 (100)
≥2 prior BTK inhibitors	22 (19.1)
Prior ASCT, n (%)	17 (14.8)
Prior CAR-T therapy, n (%)	3 (2.6)
Reason for ending last line of anticancer therapy, n (%)	
Progressive disease	79 (68.7)
Treatment completed	17 (14.8)
Toxicity	12 (10.4)
Other	7 (6.1)

Wang M et al, ASH 2025

Efficacy for Sonrotoclax at RP2D 320 mg QD

	Part 2: Sonrotoclax 320 mg (n=103)
ORR, n (%)	54 (**52.4**)
95% CI, %	42.4-62.4
CR rate, n (%)	16 (**15.5**)
95% CI, %	9.1-24.0
TTR, median (range), months	1.9 (1.6-6.2)



Wang M et al, ASH 2025

AlloSCT in RR-MCL?

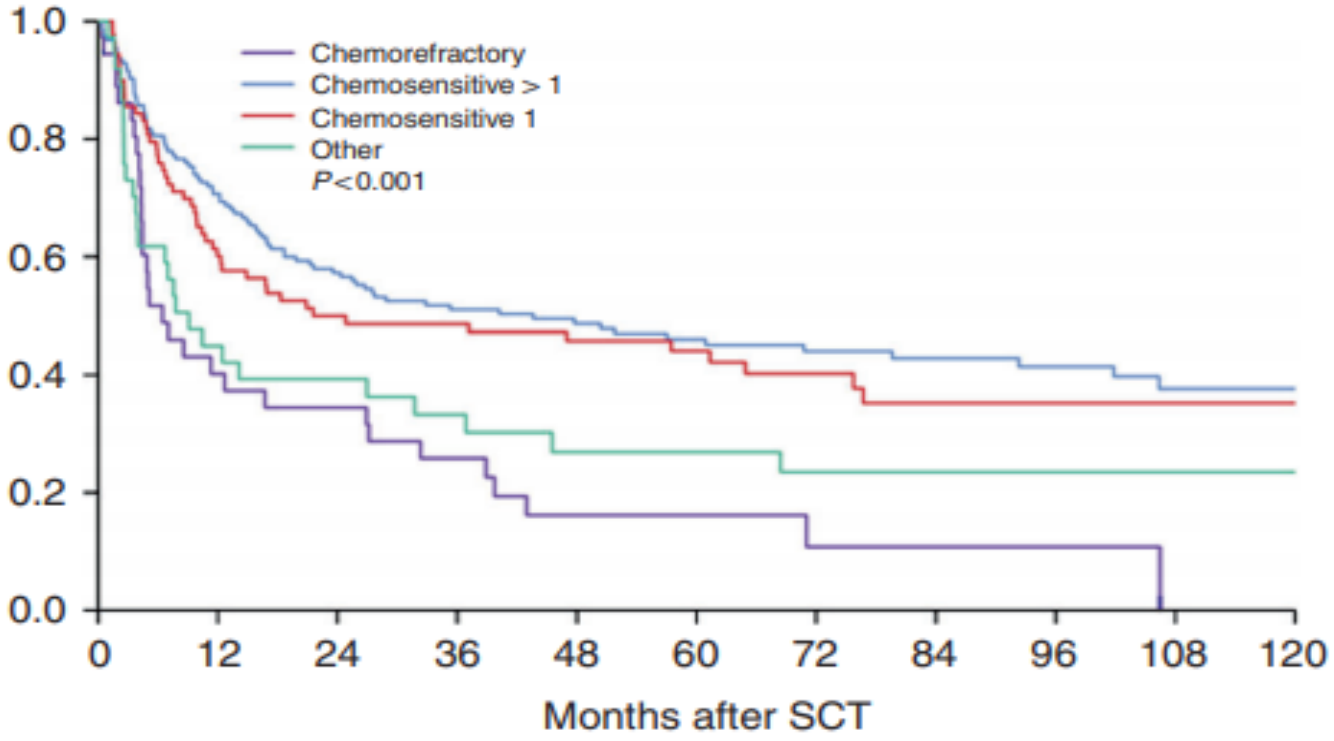
Study	Timing	N° Patients	ORR/CR	Median FU	2-yr NRM	5-yr PFS	5-yr OS	Main Toxicities
Le Gouill et al.	Salvage	70	95%/89%	24mo	32%	≈25%	≈25%	GVHD
Krüger et al.	First line	24	86%/76%	2.8yr		≈67%	≈73%	Stomatitis, infection, GVHD
	Salvage	15	91%/83%	2.8yr		≈67%	≈73%	
Rule et al.	First line	25	92%/60%	60.5mo	13%	56%	76%	Infection, mucositis, GVHD
Fenske et al.	First response	50		48mo	≈30%	55%	62%	
	Salvage	88		37mo	≈25%	24%	31%	
Tessoulin et al.	Salvage	106	97%/86%	45mo	≈30%	≈35%	≈55%	GVHD, infection

Marangon M. et al. Cancers 2021, 13, 291.

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-017-0067-3

ARTICLE

Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party



	PFS	OS
1-YR	51%	62%
4-5 YR	**31%**	**40%**

NRM 100 days 10%
NRM 1 year 24%

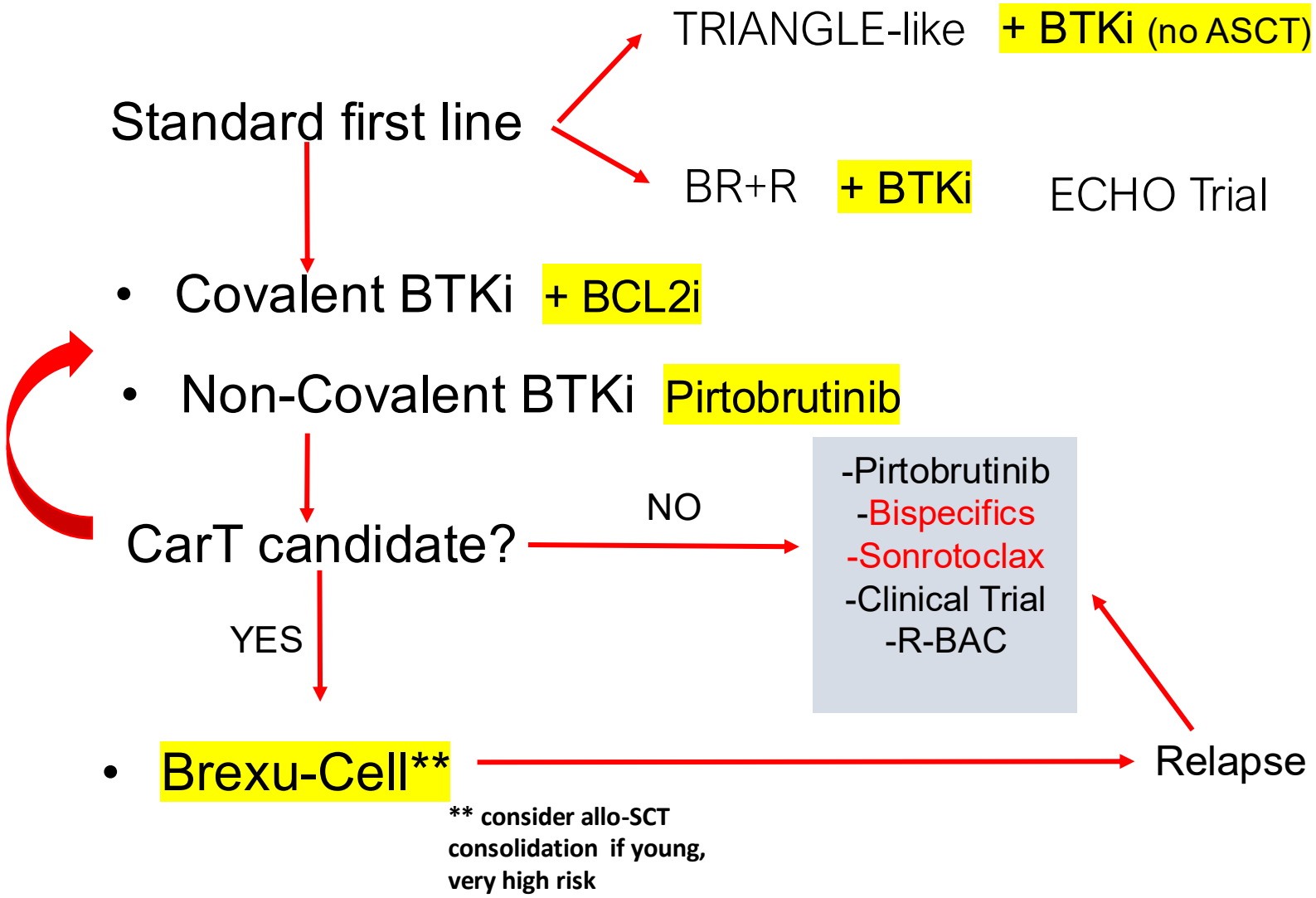
Robinson SP et al, BMT 2018

RR-MCL: Treatment algorithm

Upfront

First relapse

Second relapse or further



Personal opinion

Grazie per l'attenzione ……

SAPIENZA UNIVERSITÀ DI ROMA

FONDAZIONE ITALIANA LINFOMI

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA UNIVERSITARIA POLICLINICO UMBERTO I