FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Il ruolo delle CAR T e dei nuovi farmaci nei pz rec/ref dopo cBTKi

Maria Chiara Tisi

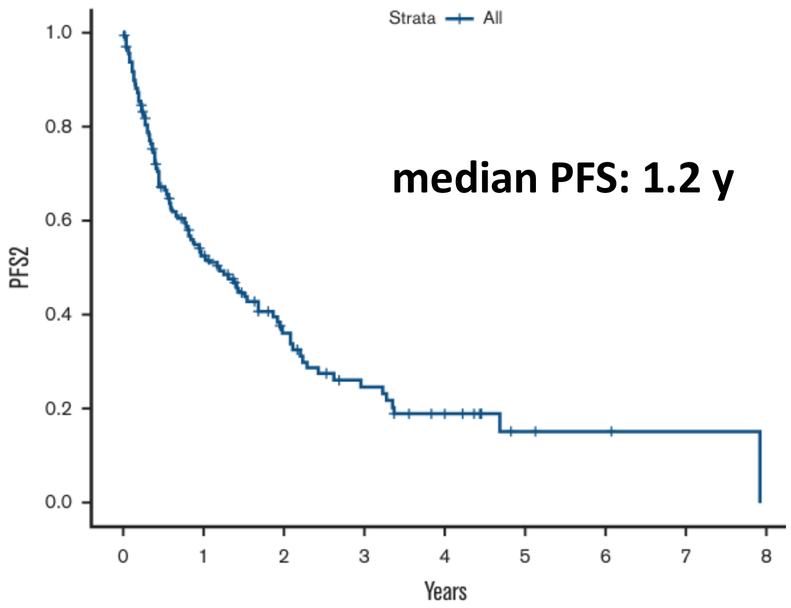
UOC Ematologia - Vicenza

Disclosures of Maria Chiara Tisi

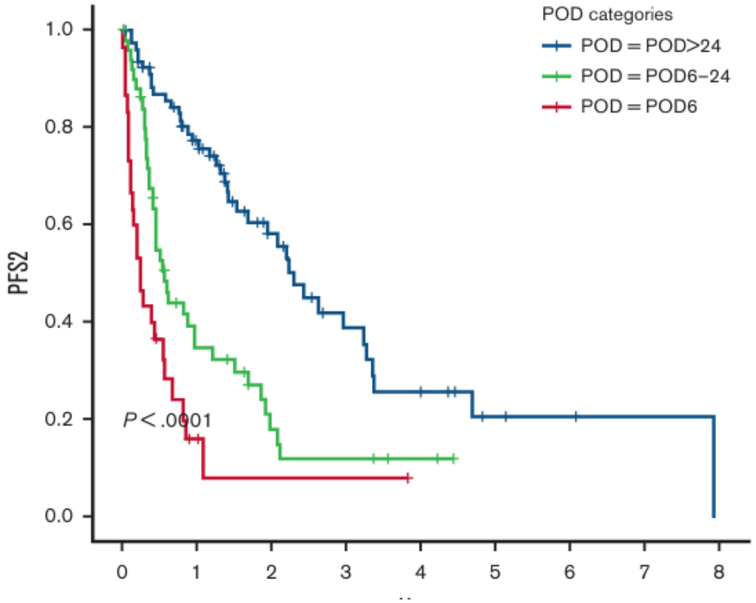
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead Science					x	x	
Novartis					x	x	
BMS					x	x	
Roche					x	x	
Incyte					x		
Lilly					x		
Janssen					x		
SOBI					x	x	
Beigene					x	x	
Abbvie					x	x	

Background - Time to progression of disease and outcomes with second-line BTK inhibitors on r/r MCL

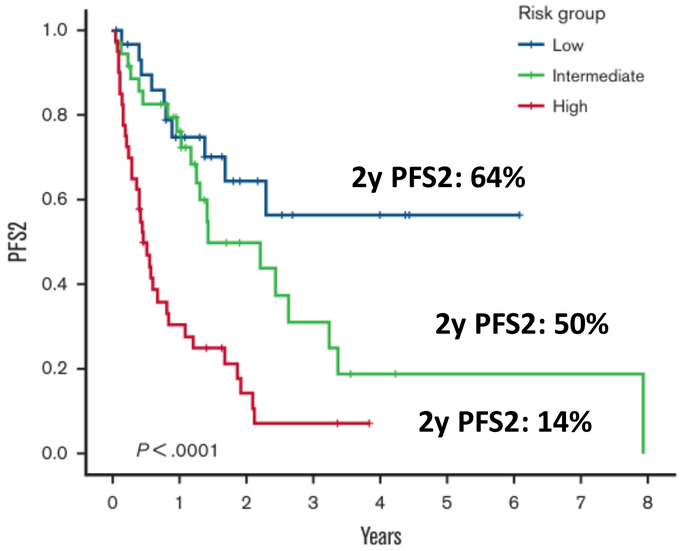
360 pts: 160 main cohort ; 200 validation cohort



median PFS: 1.2 y



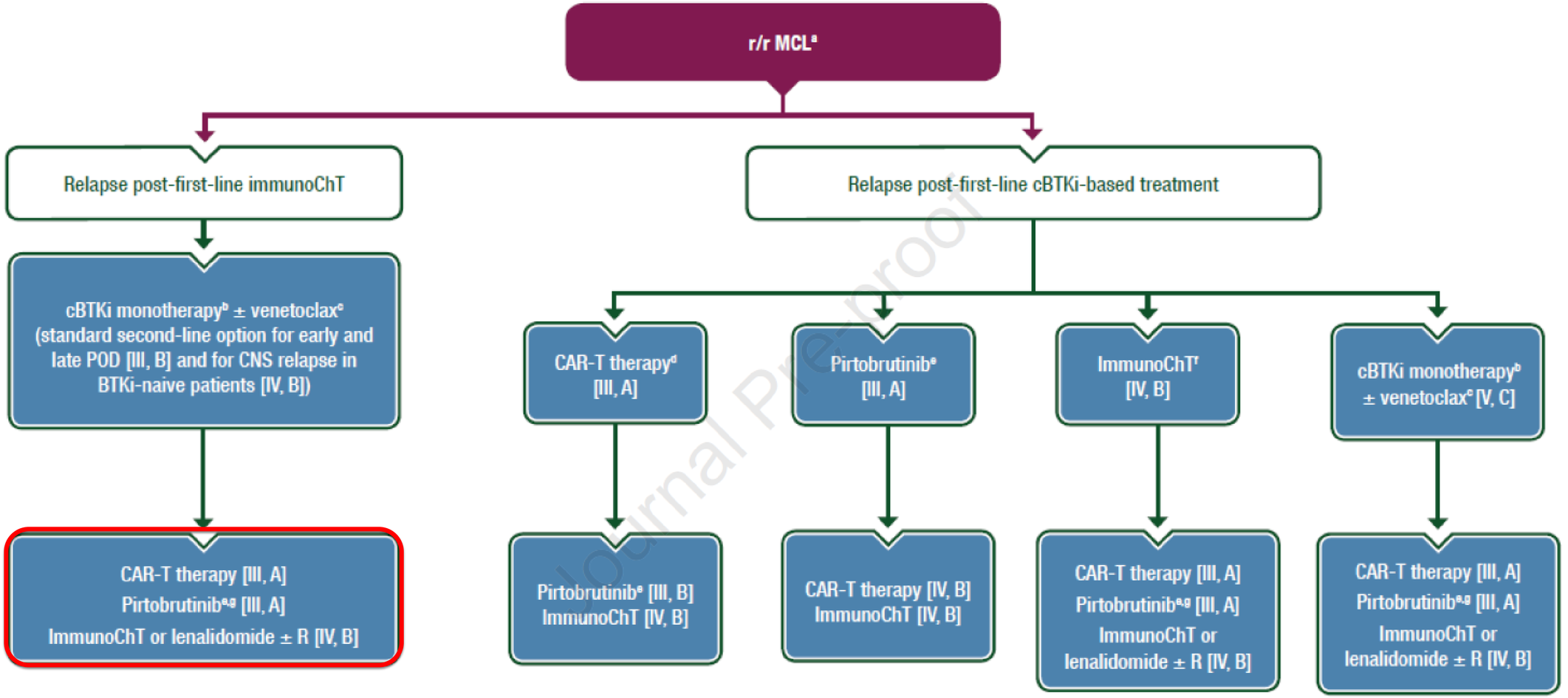
Prognostic index: 2L BTKi MIPI:
1) POD24; 2) KI67; 3) MIPI



The 2L BTKi MIPI identifies patients expected to have limited disease control with 2L BTKis and who may benefit from other therapies

Villa et al, Blood Advances 2023

Management of R/R MCL – ESMO guidelines



Eyre TA et al, Annals of Oncology 2025

CART – ZUMA-2 Brexucel – 5y outcomes

Baseline patient and disease characteristics

Baseline Characteristics

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
≥ 65 years, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG PS, n (%)	
0	44 (65)
1	24 (35)
Bulky disease (≥ 10 cm), n (%)	7 (10)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)*	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)†	38 (56)
MCL morphology, n (%)‡	
Classical	40 (59)
Pleomorphic	4 (6)
Blastoid	17 (25)

Prior therapies

Characteristic	N = 68
Median no. of prior therapies (range)*	3 (1-5)
≥ 3 prior lines of therapy, n (%)	55 (81)
Anthracycline or bendamustine, n (%)	67 (99)
Anthracycline	49 (72)
Bendamustine	37 (54)
BTKi, n (%)	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed/refractory subgroup, n (%)	
Relapsed after autologous SCT	29 (43)
Refractory to last prior therapy	27 (40)
Relapsed after last prior therapy	12 (18)
BTKi relapsed/refractory status, n (%)	68 (100)
Refractory to BTKi	42 (62)
Relapsed on BTKi	18 (26)
Relapsed after BTKi	5 (7)
Intolerant to BTKi†	3 (4)

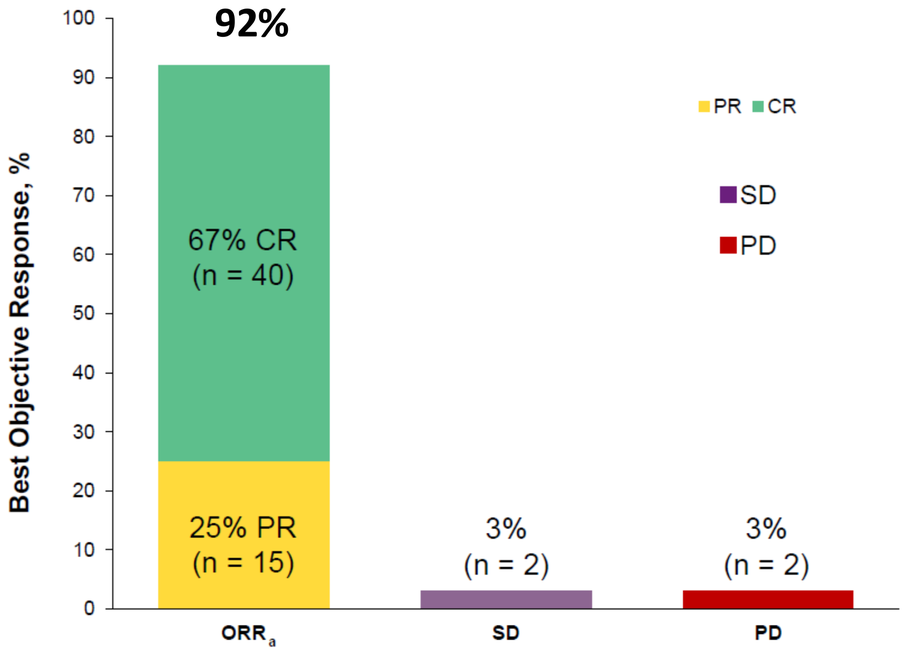
Cohort 1: 2 x 10^6 cells/kg; Cohort 2: 0.5 x 10^6 cells/kg
Cohort 2 did not achieve full enrollment (limited CAR T-cell area under the curve expansion in Cohort 2)

Wang et al, N Engl J Med 2020;
Wang et al, ASH 2024, Abstract 4388

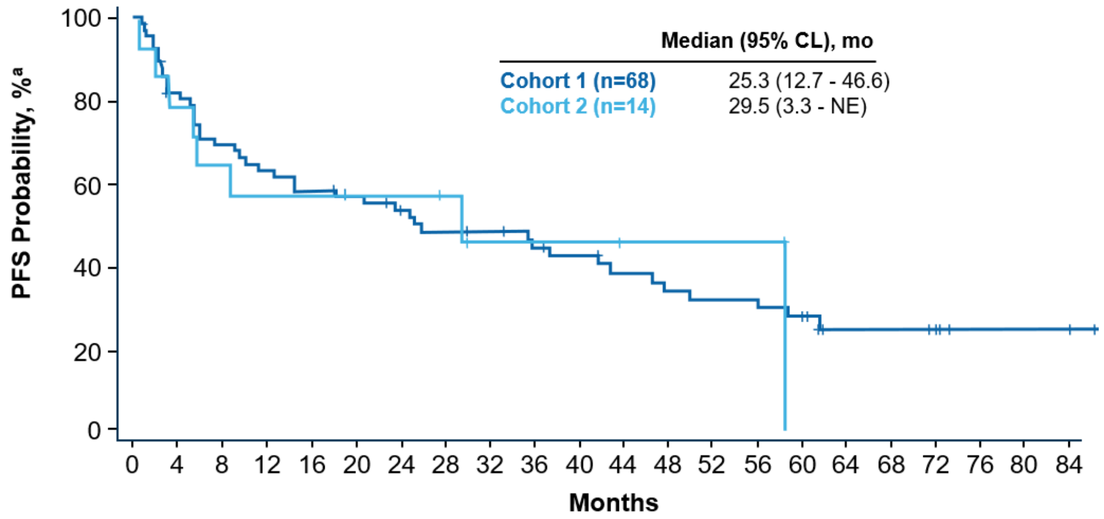
CART – ZUMA-2 Brexucel – 5y outcomes

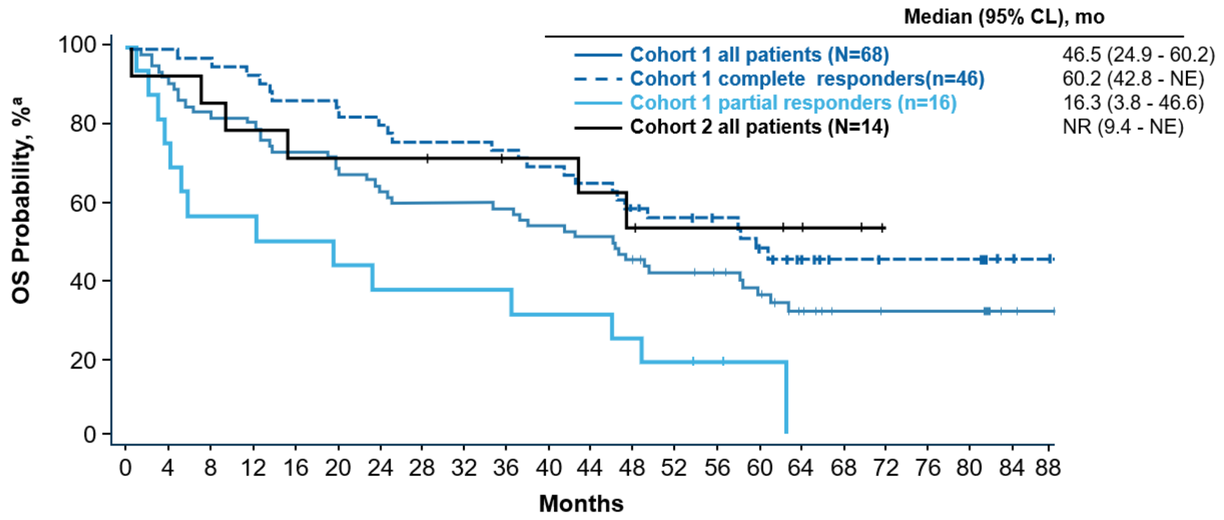
Efficacy and survival

median f-up
Cohort 1: 67.8 months (range, 58.2-88.6)
Cohort 2: 72.3 months (range, 70.1-74.3)



In Cohort 2 primary analysis,
ORR was 93% (95% CI, 66.1-99.8);
64% of patients had a CR and 29% had a PR





Wang et al, N Engl J Med 2020;
Wang et al, ASH 2024, Abstract 4388

CART – ZUMA-2 Brexucel – 5y outcomes

Safety and expansion

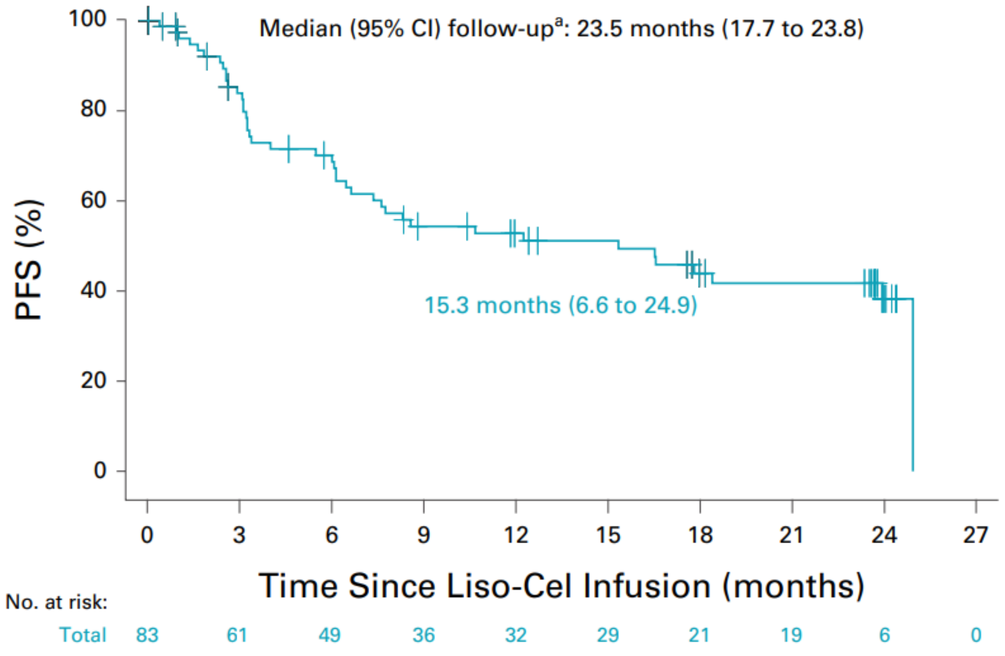
AEs of Interest, n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any CRS[a]	62 (91)	13 (93)
Grade ≥3	10 (15)	2 (14)
Any neurologic event[b]	43 (63)	13 (93)
Grade ≥3	21 (31)	6 (43)
Any thrombocytopenia	50 (74)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any neutropenia	59 (87)	11 (79)
Grade ≥3	58 (85)	11 (79)
Any anemia	47 (69)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any infection	37 (54)	7 (50)
Grade ≥3	26 (38)	3 (21)
Any hypogammaglobulinemia	14 (21)	0
Grade ≥3	1 (1)	0

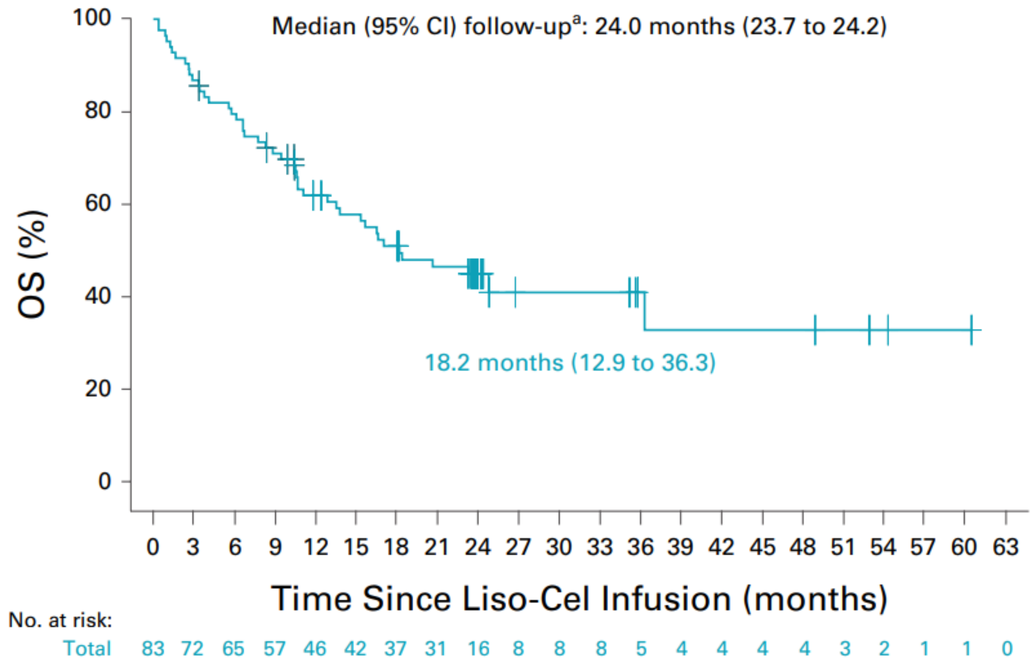
- no cases of Grade 5 CRS or neurological events occurred;
- 5-year rates of PD-related death 40% (24/60)
- 5-year non-PD–related death 22% (13/60)
- On LTFU, 1 patient had 3 ongoing AEs: hypogammaglobulinemia and 2 viral infections that arose prior to LTFU
- Two patients died on LTFU, both due to PD
- No cases of secondary T-cell malignancies were reported in ZUMA-2

Wang et al, N Engl J Med 2020;
Wang et al, ASH 2024, Abstract 4388

CART – TRANSCEND NHL 001 study, Liso-Cel

Of 104 leukapheresed patients, 88 received liso-cel
In the total of 83 pts (efficacy set) ORR was 83.1% and CR was 72.3%





CRS any grade: 61%
CRS grade 3-4: 1%
NEs any grade: 31%
NEs grade 3-4: 9%
No grade 5 CRS or NEs

Palomba et al, ASH 2023, abstr 3505; Wang et al, JCO 2024

CART – RWE – The Italian Experience

Received: 29 October 2024 | Accepted: 11 December 2024
DOI: 10.1111/bjh.19961

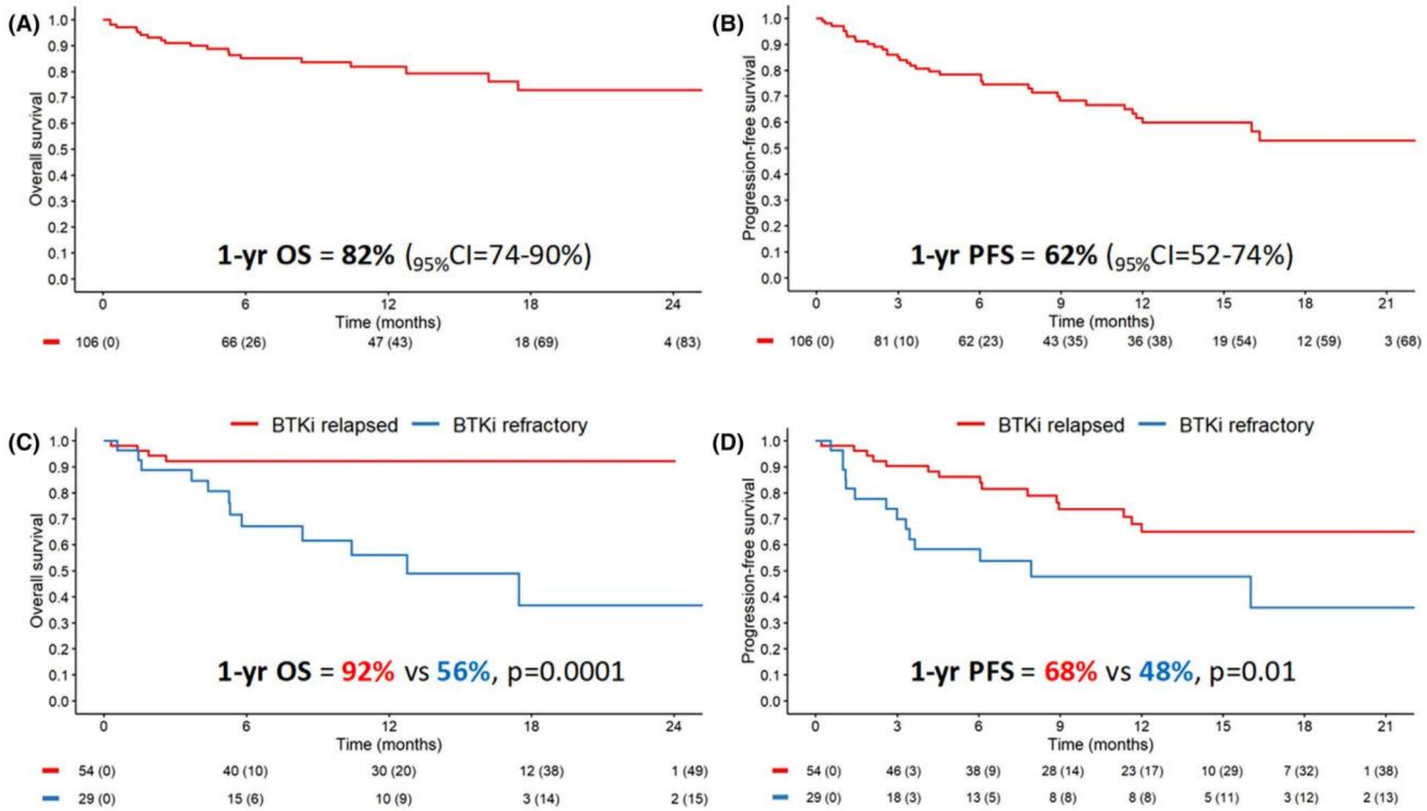
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Haematological Malignancy – Clinical

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

Federico Stella[1,2] | Annalisa Chiappella[2] | Martina Magni[2] | Francesca Bonifazi[3] |



- 106 pts; median age 63 (42-79)
- Previous lines 3 (2–5)

- The best ORR 88%
- CR rate 75%
- ORR at 90 days was 77%

Stella et al, BJHaem, 2024

PIRTOBRUTINIB - the Phase 1/2 BRUIN Study

Cohen et al, ASH 2023; Wang M et al, JCO 2023

Non-Covalent (Reversible) BTK Inhibitor

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)

PIRTOBRUTINIB - the Phase 1/2 BRUIN Study

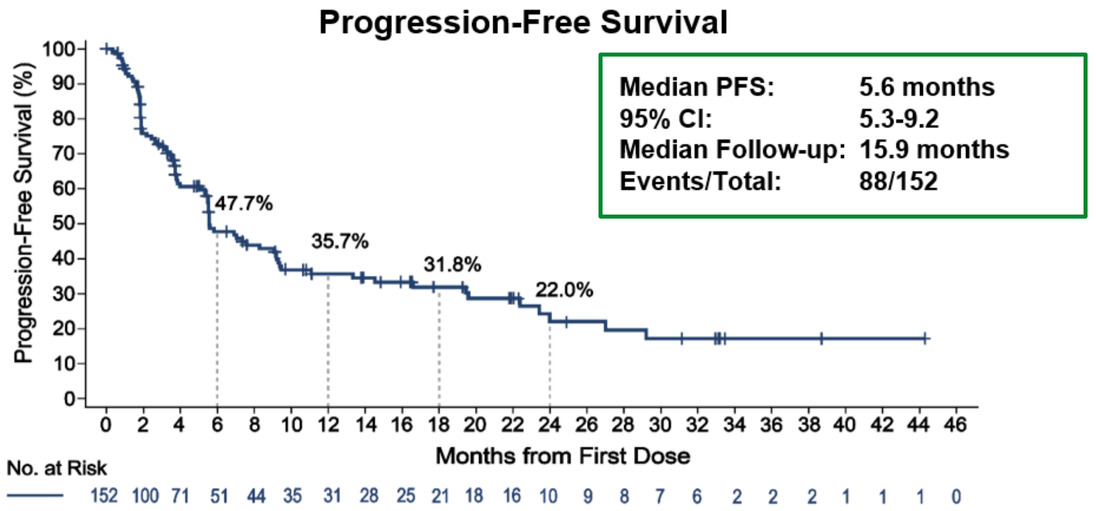
Efficacy and outcomes in prior cBTKi

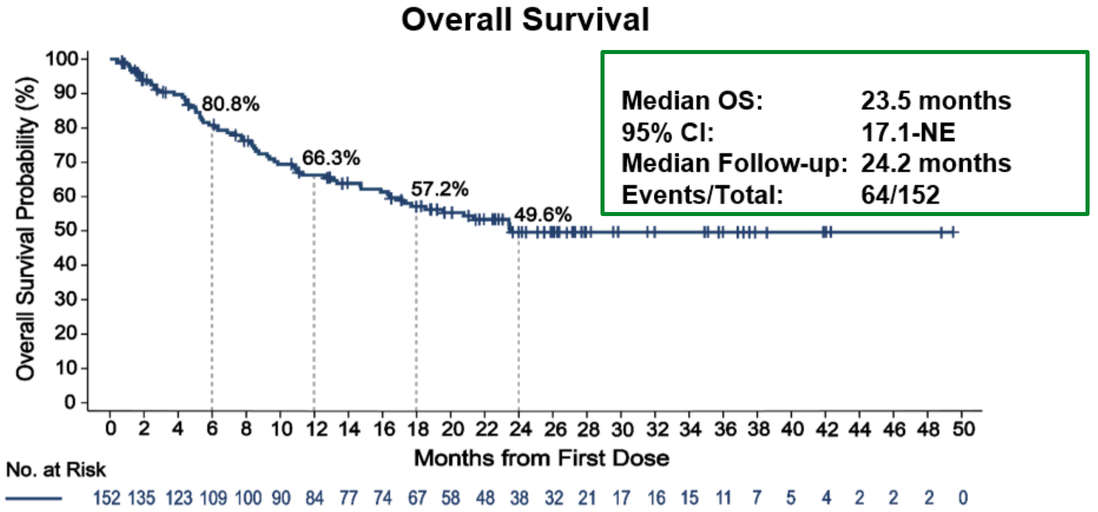
Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

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

cBTKi Naive Cohort:

- ORRa 85.7% (95% CI: 57.2-98.2)
- 6 CR (42.9%) and 6 PR (42.9%)





Cohen et al, ASH 2023; Wang M et al, JCO 2023

PIRTOBRUTINIB - the Phase 1/2 BRUIN Study

Pirtobrutinib Safety Profile

	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

Cohen et al, ASH 2023; Wang M et al, JCO 2023

Bispecific - NP30179 Phase I/II study – Glofitamab in RR MCL

Patients baseline characteristics

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)
MIPI 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)

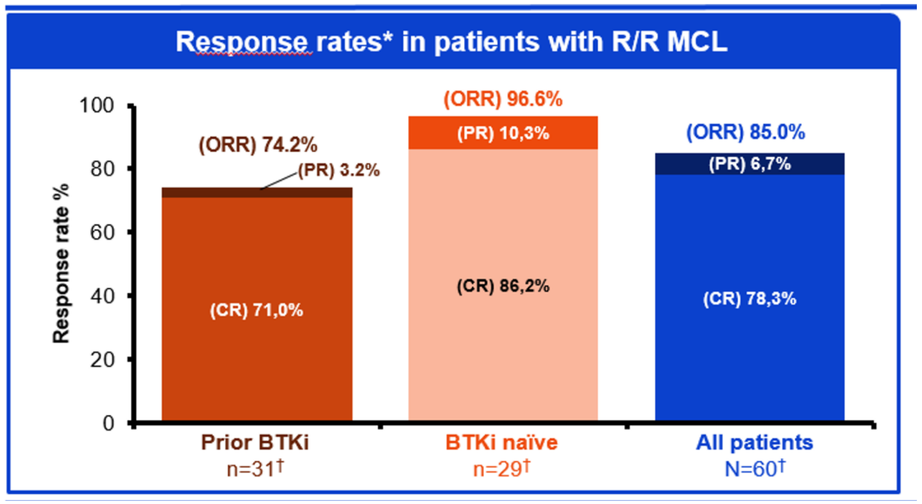
Patients with R/R MCL were heavily pretreated and highly refractory to their last prior therapy

A higher proportion of patients with prior BTKi therapy were refractory to their last prior therapy compared with BTKi-naïve patients

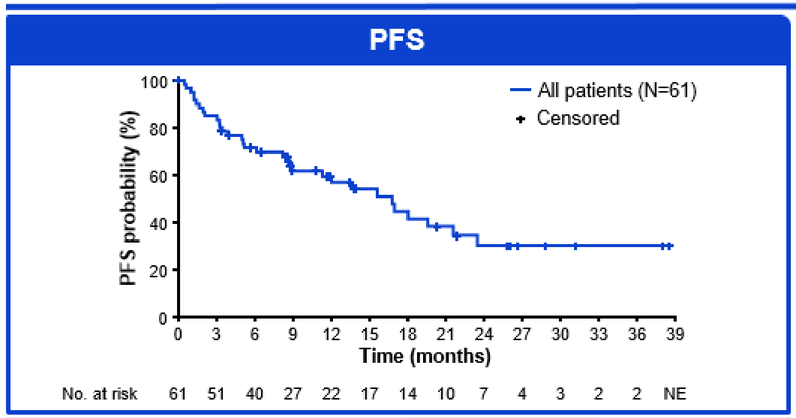
Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024; Philips et al JCO 2024

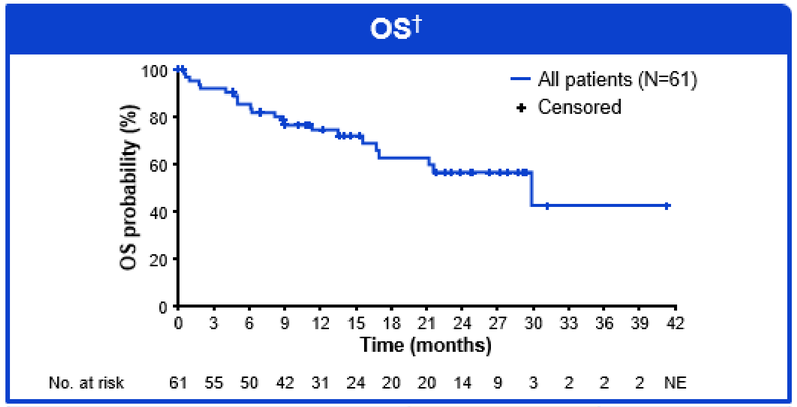
Bispecific - NP30179 Phase I/II study – Glofitamab in RR MCL

Response rates



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





	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)

Median DOR 15 months

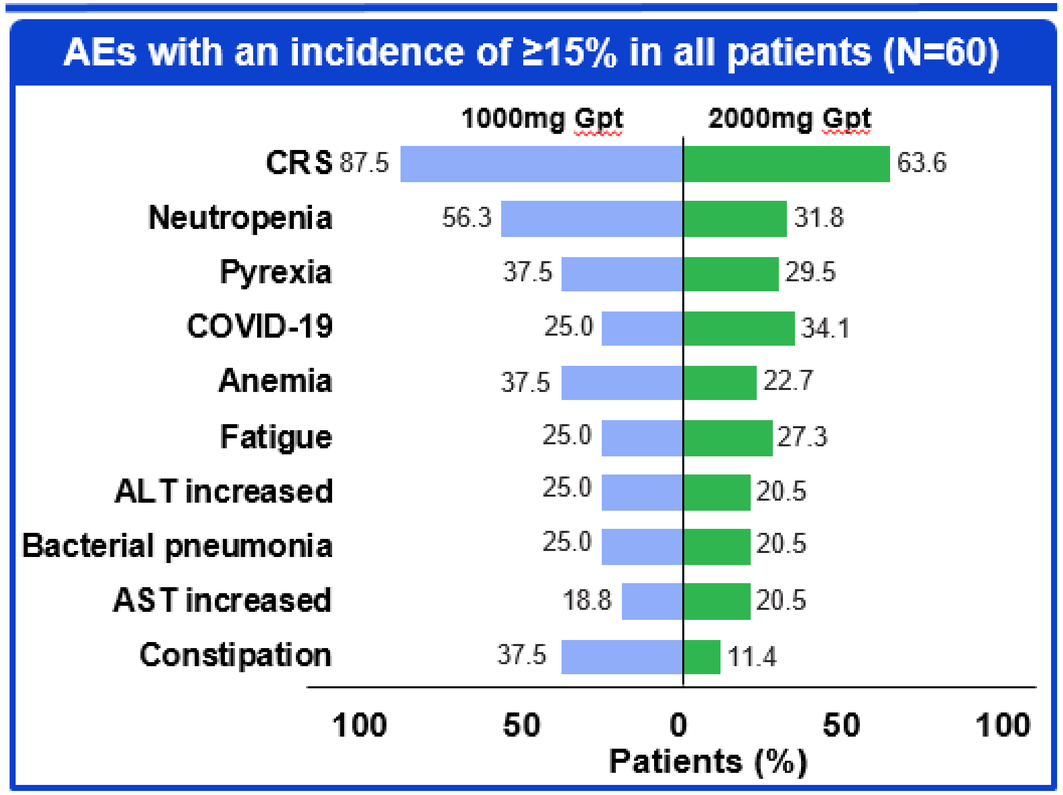
Median follow-up 17 months

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

Bispecific - NP30179 Phase I/II study – Glofitamab in RR MCL

Safety

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



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

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)

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

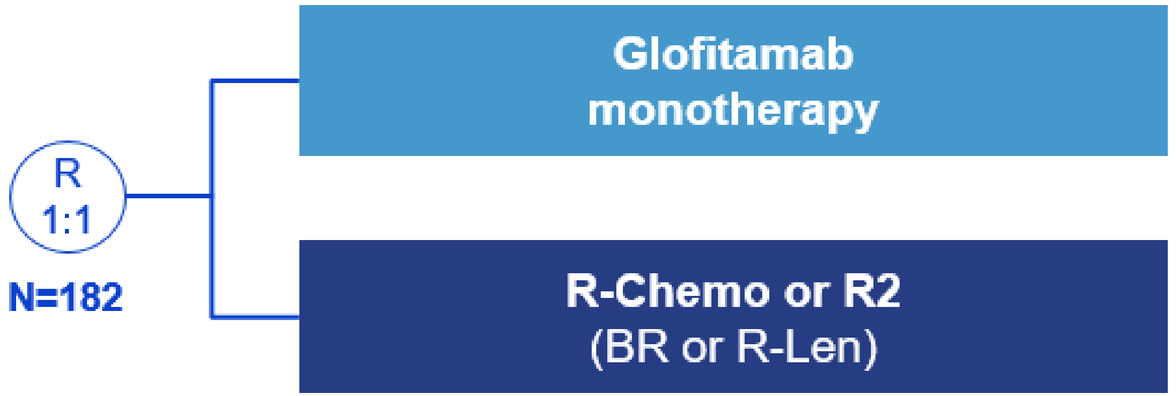
GLOBRYTE[1]: A Phase III, Open-label, Multicenter Randomized Study Evaluating Glofitamab As A Single Agent Versus Investigator's Choice in Patients With R/R MCL

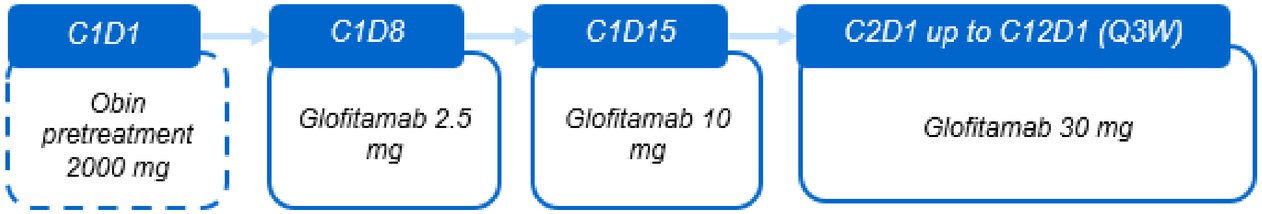
Key Inclusion Criteria

- 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**

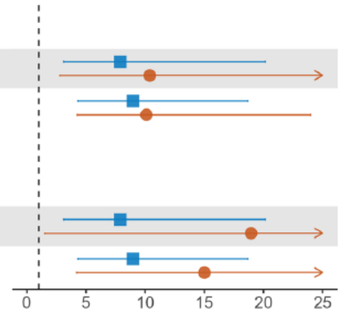




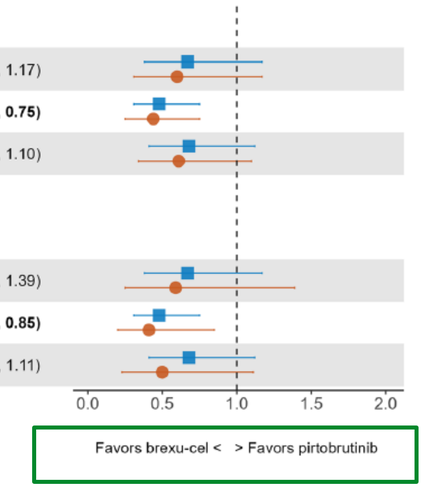
NCT06084936. Available at: https:www.clinicaltrials.gov

MAIC ZUMA-2 vs BRUIN in RR MCL post cBTKi

Comparison	Naive	Matching-adjusted	Odds ratio (95% CI)
Base Case			
ORR	**7.90 (3.10, 20.15)**	**10.39 (2.81, 38.46)**	
CR	**8.98 (4.32, 18.68)**	**10.11 (4.26, 24.00)**	
Sensitivity Analysis			
ORR	**7.90 (3.10, 20.15)**	**18.95 (1.50, 238.71)**	
CR	**8.98 (4.32, 18.68)**	**15.01 (4.20, 53.70)**	



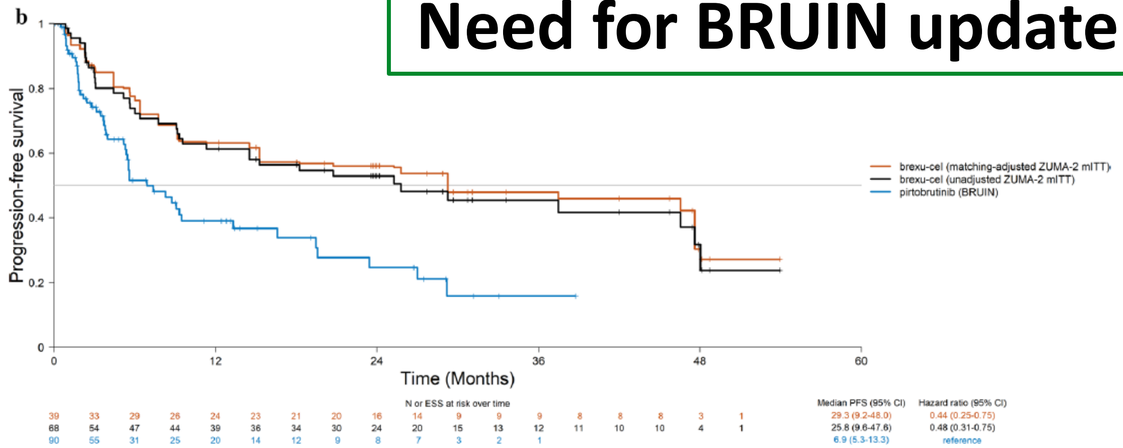
Comparison	Naive	Matching-adjusted	Hazard ratio (95% CI)
Base Case			
DOR	0.67 (0.38, 1.17)	0.60 (0.31, 1.17)	
PFS	**0.48 (0.31, 0.75)**	**0.44 (0.25, 0.75)**	
OS	0.68 (0.41, 1.12)	0.61 (0.34, 1.10)	
Sensitivity Analysis			
DOR	0.67 (0.38, 1.17)	0.59 (0.25, 1.39)	
PFS	**0.48 (0.31, 0.75)**	**0.41 (0.20, 0.85)**	
OS	0.68 (0.41, 1.12)	0.50 (0.23, 1.11)	

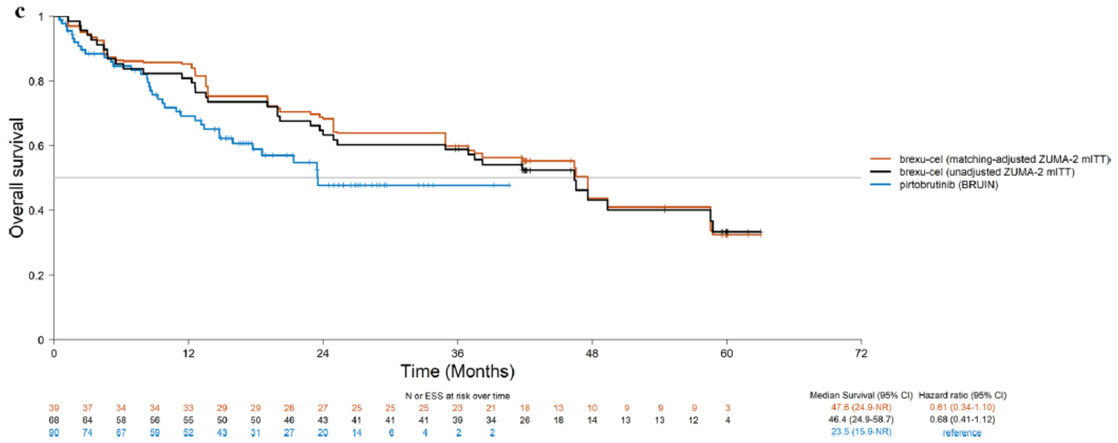


18,9% of pts of BRUIN went on to receive CART therapy

The ability to detect statistically significant differences for outcomes with low starting sample sizes is limited

Need for BRUIN update!





Salles G et al, Adv Ther 2024

Conclusions

- Prognosis of patients with R/R MCL who discontinued cBTKi has been improved by new drugs (CAR-T, noncBTKi, …)
- No direct comparison between drugs (MAIC with low sample size, small numbers of events and some variable/endpoint not included - *Salles G et al, Adv Ther 2024*) - shorter median f-up of BRUIN (23.5 mo vs 47.5 mo)
- Ongoing studies will probably provide more answers

CART

- **Multistep process (referral, leukapheresis, BT, vein to vein time)** ↓
- **Not all selected patients received infusion** ↓
- **Specific toxicity – need for inpatients** ↓
- **Large amount of Real word data** ↑
- **Longer follow-up** ↑
- **Quality of life and economic outcomes** ↓

PIRTOBRUTINIB

- **Immediatily available** ↑
- **Less toxic** ↑
- **No Real word data** ↓
- **Shorter follow-up** ↓
- **QoL** ↑

When choising a treatement consider:

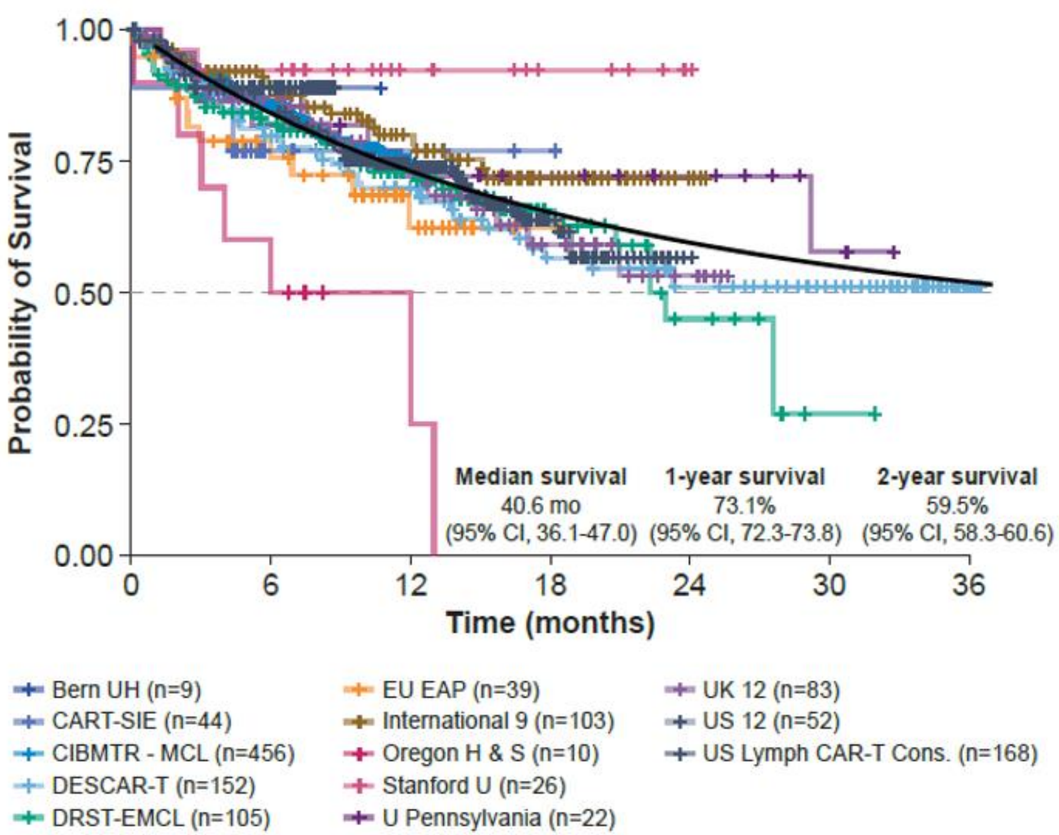
- **tp53 mutation status**
- **Ki67**
- **Response to prior cBTKi**
- **Response to last therapy**
- **Duration on prior cbTKi**
- **Reason for prior BTKi discontinuation (PD vs toxicity)**

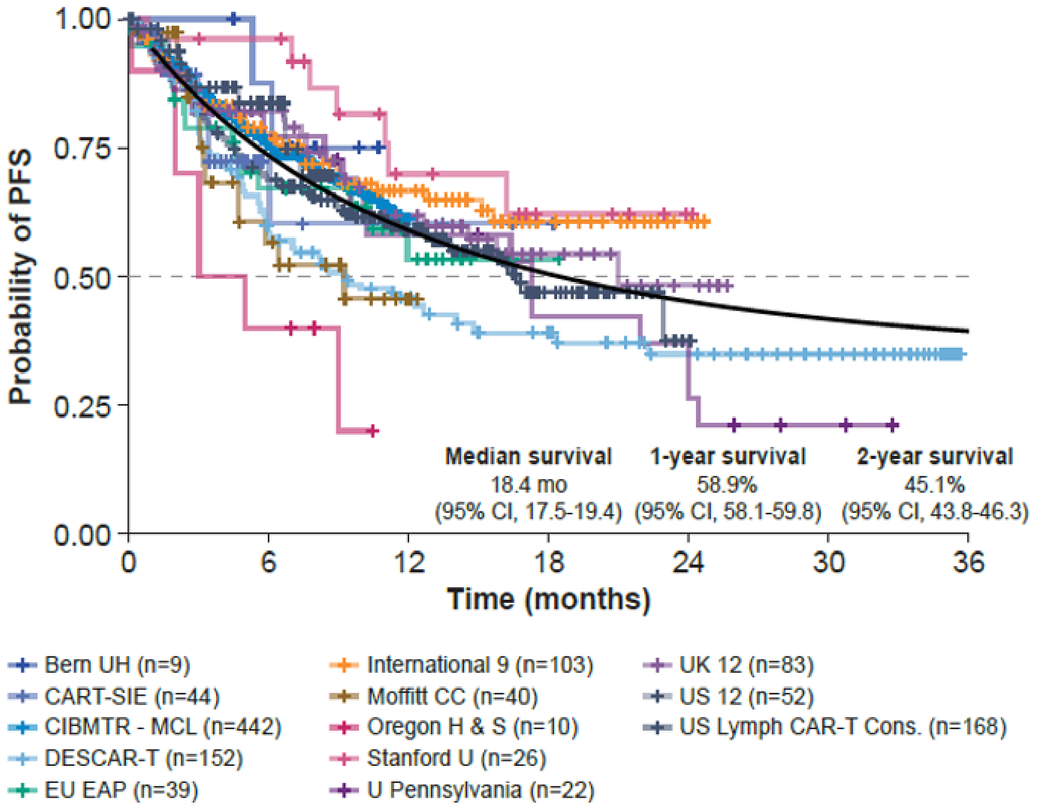
Speaker's opinion


Thank
You

CART – RWE – Meta- Analysis

12 cohorts, 1670 pts per OS e 1591 pts per PFS





ORR was estimated at 88%; CR rate was 76%

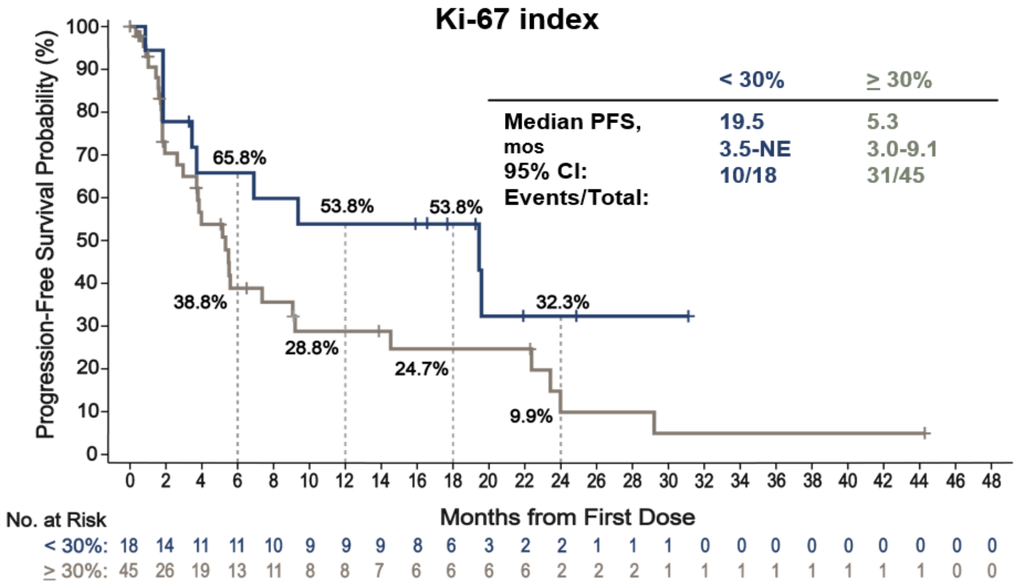
CRS 88%, CRS G>3 12%; ICANS 54%, ICANS G>3 20%

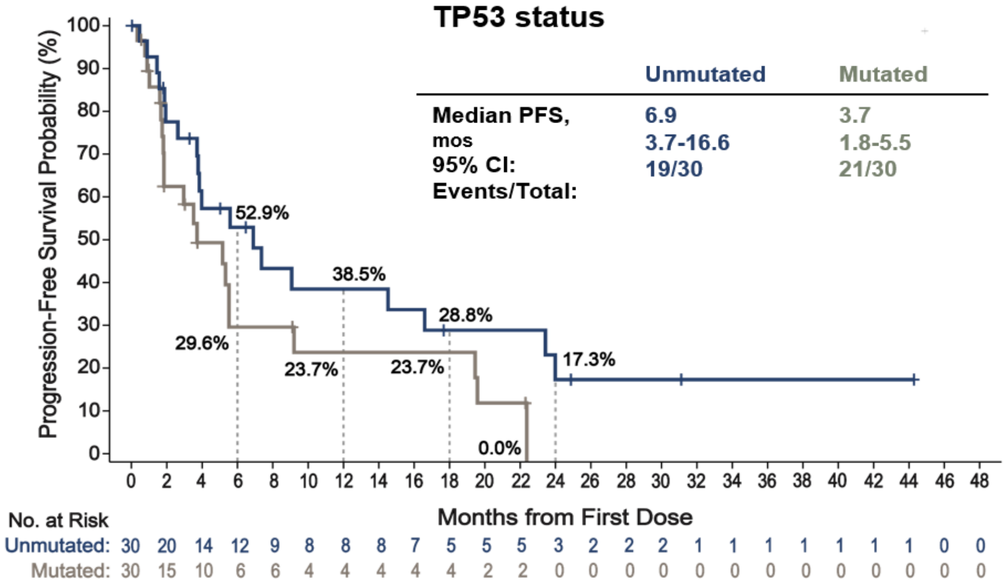
Secondary malignancies of any grade were reported at a pooled estimate of 5%

Olalekan, O, EHA 2025; Abstract PF954; poster presentation

PIRTOBRUTINIB - the Phase 1/2 BRUIN Study

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; Wang M et al, JCO 2023