LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

Milano, Hilton Milan Hotel
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Responsabili Scientifici
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Le Cart nel BTK refrattario: risultati degli studi

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS			x		x	X	x
KITE					x	X	x
BMS					x	X	
ROCHE						X	

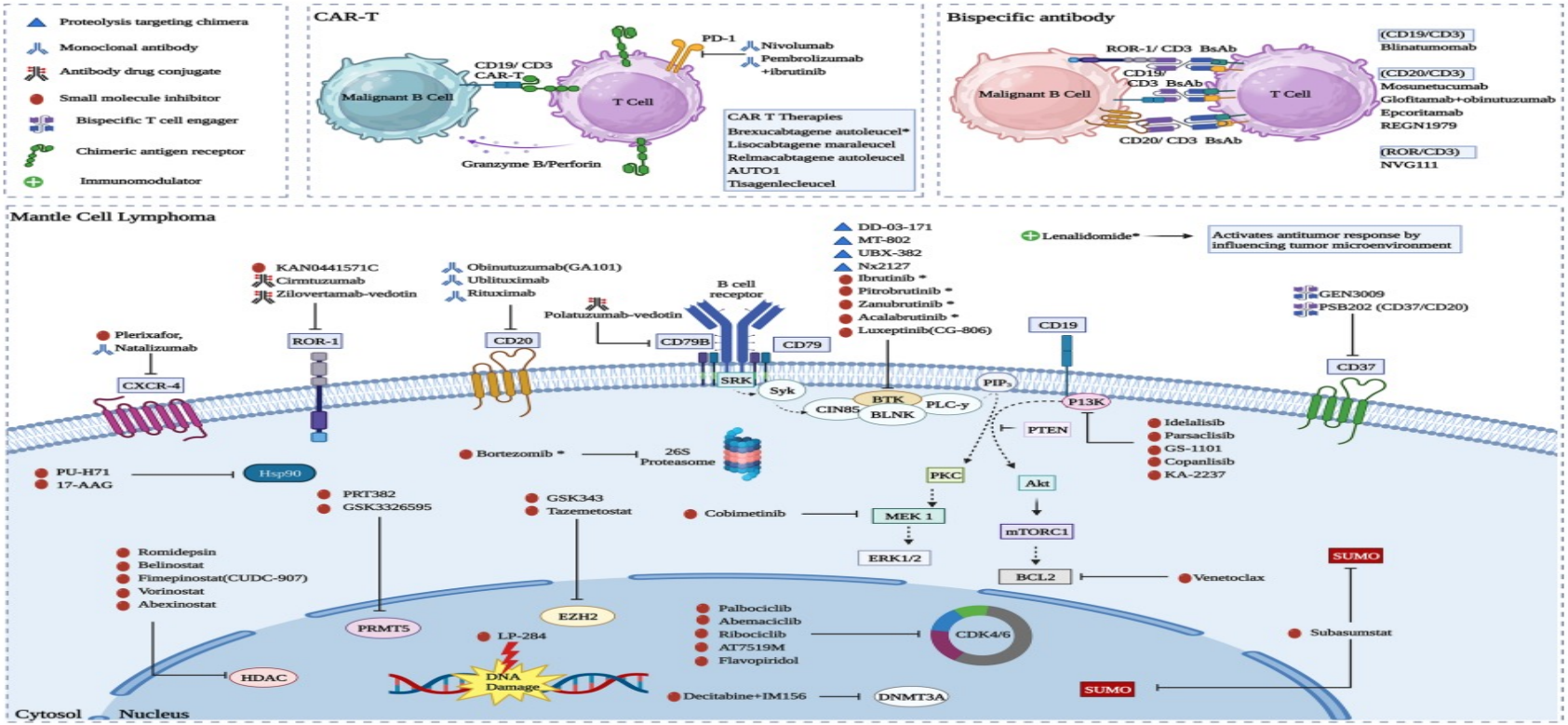


Fig. 1 A summary of various MCL-targeting agents, including BTKi and other small molecular inhibitors, antibody–drug conjugates, chimeric antigen receptor T cells, bispecific antibodies, and other immune modulators

Jain et al. Journal of Hematology & Oncology (2023)

Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up

Outcomes With Ibrutinib: Overall, by Best Response, and by Prior LOT

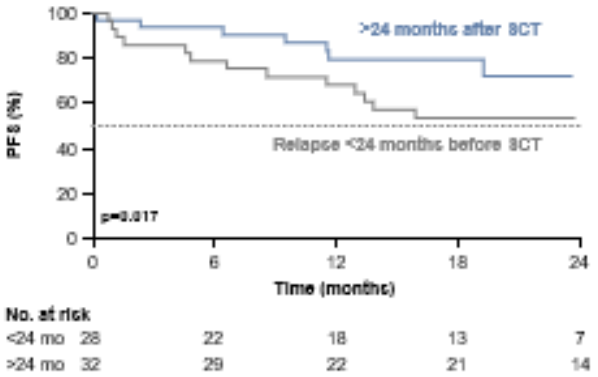
Endpoint	Overall (N = 370)	Prior Lines of Treatment	
		1 (n = 99)	>1 (n = 271)
PFS, median (95% CI), mo	**12.5 (9.8-16.6)**	**25.4 (17.5-51.8)**	**10.3 (8.1-12.5)**
Patients with CR (n = 102)	68.5 (51.7–NE)	NR (38.0–NE)	67.7 (41.7–NE)
Patients with PR (n = 156)	12.6 (10.3–16.6)	24.2 (13.9–36.5)	10.5 (8.3–12.9)
Overall response rate, n (%)	**258 (69.7)**	**77 (77.8)**	**181 (66.8)**
CR	102 (27.6)	37 (37.4)	65 (24.0)
PR	156 (42.2)	40 (40.4)	116 (42.8)
SD	43 (11.6)	11 (11.1)	32 (11.8)
PD	56 (15.1)	8 (8.1)	48 (17.7)
NE/UN	8 (2.2)	1 (1.0)	7 (2.6)
Missing	5 (1.4)	2 (2.0)	3 (1.1)
DOR, median (95% CI), mo	**21.8 (17.2–26.4)**	**35.6 (23.2–66.5)**	**16.6 (12.9–21.3)**
Patients with CR (n = 102)	66.4 (49.5–NE)	NR (35.6–NE)	65.6 (40.0–NE)
Patients with PR (n = 156)	10.3 (6.6–14.8)	22.1 (10.6–34.4)	8.3 (6.2–10.8)
OS, median (95% CI), mo	**26.7 (22.5–38.4)**	**61.6 (36.0–NE)**	**22.5 (16.2–26.7)**
Patients with CR (n = 102)	NR (NE–NE)	NR (74.3–NE)	NR (NE–NE)
Patients with PR (n = 156)	23.6 (20.7–32.2)	36.0 (21.8–55.6)	22.6 (17.2–26.9)

CI = confidence interval; CR = complete response; DOR = duration of response; LOT = line of treatment; NE = not estimable; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PD = progressive disease; PR = partial response; SD = stable disease; UN = unknown.

Poor Outcomes in Patients With POD24 After First-line Chemotherapy and ASCT

Retrospective analysis of patients with MCL who received ibrutinib after first-line chemotherapy and ASCT (N=66; EBMT registry)

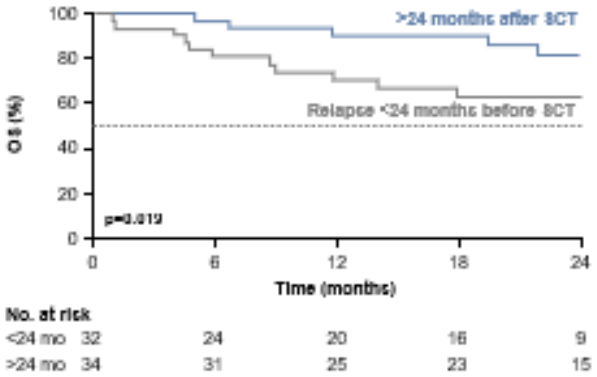
PFS after start of ibrutinib



No. at risk					
<24 mo	28	22	18	13	7
>24 mo	32	29	22	21	14

	POD24	POD≥24	All patients
2-year PFS, %	53	72	62

OS after start of ibrutinib



No. at risk					
<24 mo	32	24	20	16	9
>24 mo	34	31	25	23	15

	POD24	POD≥24	All patients
2-year OS, %	68	80	72

median duration of response was 10.1 months

Allogeneic stem cell transplantation in patients with mantle cell lymphoma: results from the MANTLE-FIRST study on behalf of Fondazione Italiana Linfomi

Table 1. Patient characteristics.

Variable	Status	*N* (%)
Age at diagnosis	Median (range)	52 (35–69)
Age at 1st relapse	Median (range)	54 (37–69)
	>60 years	14 (25)
Gender	Male	42 (76)
Morphology	Blastoid	10 (18)
Ki 67 ($n = 30$)	≥30%	20 (67)
Ann Arbor stage ($n = 53$)	III	4 (8)
	IV	49 (92)
MIPI ($n = 49$)	Low	24 (49)
	Intermediate	15 (31)
	High	10 (20)
Upfront therapy	R HyperCVAD	17 (31)
	R CHOP/R DHAP	11 (20)
	Nordic/R HDS	27 (49)
Auto-SCT	Yes, front line	43 (78)
Time to 1st relapse, months	Median (range)	29 (4-94)
	Early POD (24 m)	25 (45)
	Refractory	4 (7)
2nd line therapy	R-Bendamustine	5 (9)
	R-BAC	22 (40)
	Ibrutinib	12 (22)
	Others[a]	16 (29)
Response to 2nd line therapy	ORR	39 (71)
	CR	32 (58)
Relapse/progression after 2nd line therapy	yes	29 (53)
3rd line therapy ($n = 21$)	R-Bendamustine	4 (19)
	R-BAC	8 (38)
	Ibrutinib	6 (29)
	Others[b]	3 (14)

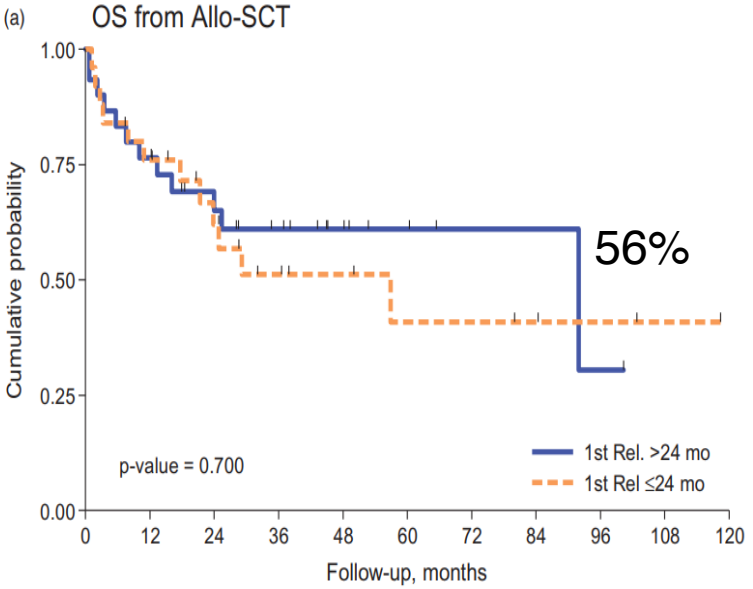
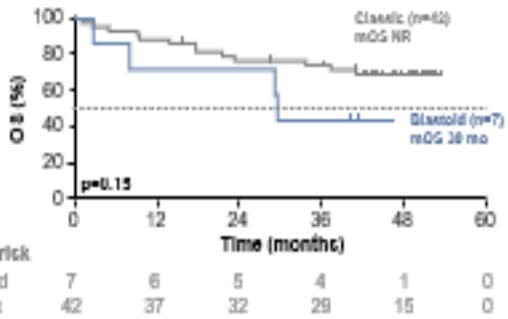
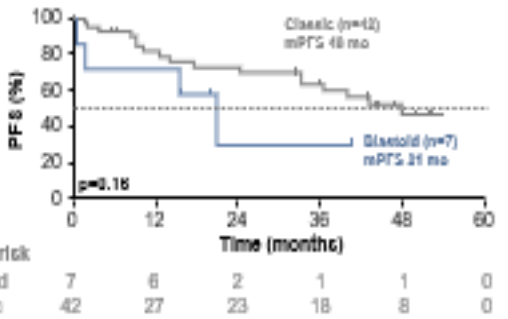
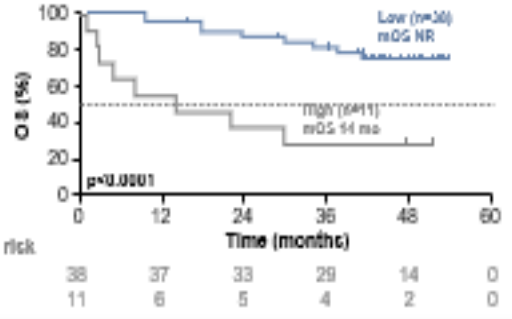
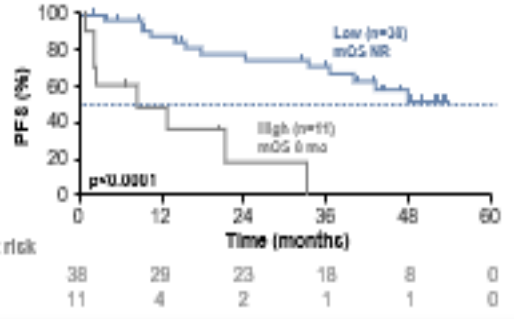


Table 2. Transplant characteristics.

Variable	Status	*N* (%)
Age at allo-SCT	Median (range)	56 (38–70)
	>60 years	16 (29)
HCT-CI (Sorror)	Low (0)	21 (43)
	Intermediate (1–2)	15 (31)
	High (≥ 3)	13 (26)
Disease status at allo-SCT	CR	35 (64)
	PR	16 (29)
	SD/PD	4 (7)
N. prior lines before allo-SCT	2	35 (64)
	3	12 (22)
	>3	8 (14)
Bridging therapy to allo-SCT	Bendamustine-based	31 (56)
	Ibrutinib	15 (27)
	Others[a]	9 (16)
Timing of allo-SCT	At 1st relapse	35 (64)
	At 2nd relapse (and beyond)	20 (36)
	Time from diagnosis, months	40 (11–137)
	Time from 1st relapse, months	11 (5–96)
Donor type	Sibling	24 (44)
	MUD	30 (56)
Matching	HLA identical	26 (48)
	Mismatched	16 (30)
	Haploidentical	12 (22)
Donor gender	Female	19 (35)
CMV status patient/donor	CMV pos/neg	7 (13)
	CMV pos/pos	33 (60)
Source	PBSC	49 (89)
	Bone Marrow	6 (11)
Conditioning	RIC	44 (80)
	Myeloablative	11 (20)
Engraftment	Time to neutrophil engraftment, days (median, range)	16 (7–49)
	Time to platelet engraftment, Days (median, range)	17 (7–181)
Infections	Grades I and II	15 (38)
	Grades III–V	24 (62)
Cumulative incidence of acute GVHD	Yes	25 (46)
	Grades III and IV	6/24 (25)
Cumulative incidence of chronic GVHD	Yes	21 (40)
	Extensive	9/20 (45)

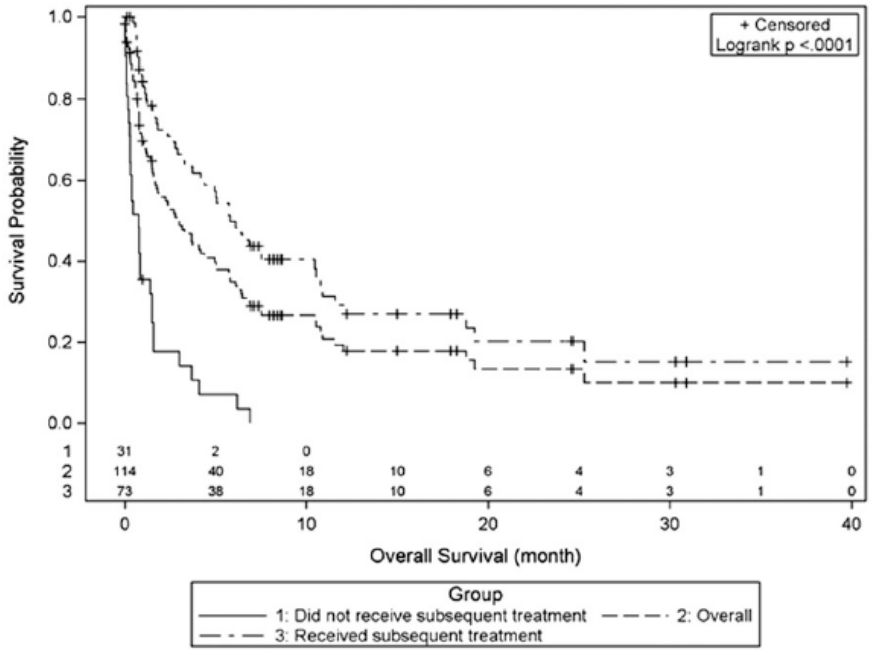
NRM 23%, PFS 53%,
NRM was significantly higher in the case of aGVHD , > 2 prior lines of therapy, age > 60 years.
The use of BTKi as a bridge to allo-SCT did not increase the toxicity and allowed a good control of disease.

High-risk feature

High-risk feature	OS	PFS
MCL morphology (classic vs. blastoid)		
Ki-67 index (low <50% vs. high ≥50%)		

Median OS following ibrutinib cessation : 2,9 months

114 patients in 15 centers



Martin P et al, Blood 2016

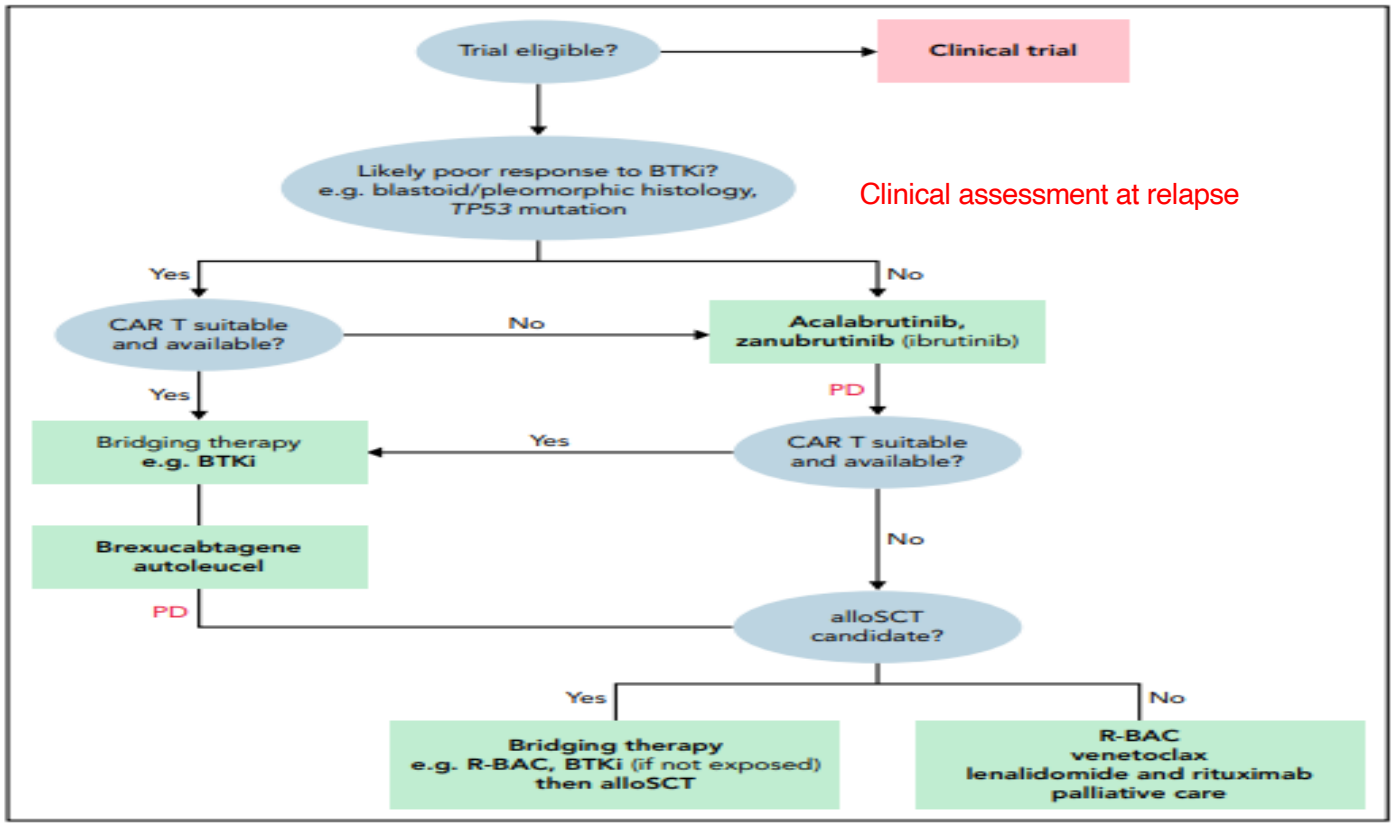
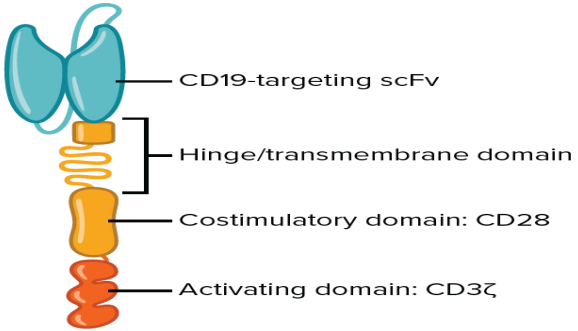


Figure 1. Treatment algorithm for patients with R/R MCL.

Toby A. Eyre,1 Chan Y. Cheah,2,3 and Michael L. Wang

Table 2. Selected studies assessing outcomes of patient who received therapy for MCL after relapsing while treated with BTKi

Treatment	Reference	Study	N	Median age, y	High risk*	Median prior lines therapy	Response to prior BTKi	Response to treatment	Transplant consolidation	Outcomes, mo
Assorted (lenalidomide 26%, cytarabine 18%, bendamustine 16%, bortezomib 10%)	54	Retrospective multicenter†	73	67	48%	4 (1-11)	ORR 50% CR 11%; median DOI 4.7 m	ORR 26% CR 7%	5 (6.8%)	Median OS 5.8
Lenalidomide ± anti-CD20 ± chemotherapy	67	Observational multicenter‡	58	71	NA	4 (1-13)	ORR 45% CR 14%; median DOI 4.3 mo	ORR 29% CR 14%	NA	Median DOR 5
Venetoclax monotherapy	68	Retrospective multicenter	20	69	55%	3 (2-5)	ORR 55% CR 15% median DOI 4.8 mo	ORR 53% CR 18%	1 (5.0%)	Median PFS 3.2; median OS 9.4
Venetoclax monotherapy	69	Retrospective single center	24§	69	67%	5 (1-11)	"66% BTKi resistant"	ORR 50% CR 21%	—	Median PFS 8; median OS 13.5
R-BAC	71	Retrospective multicenter	36	66	58%	2 (1-6)	ORR 68% CR 32%; median PFS 9.2 mo	ORR 83% CR 60%	12 (33.3%)	Median PFS 10.1; median OS 12.5
Brexucabtagene autoleucel	77	Phase 2	74	65	NA	3 (1-5)	ORR 38%	ORR 93% CR 67%	—	1-y PFS 61% 1-y OS 83%
Lisocabtagene maraleucel	53	Phase 1	41	67	NA	3 (1-7)	ORR 66%	ORR 84% CR 59%	—	NA
Pirtobrutinib	85	Phase 1/2	61	69	NA	3 (2-4)	NA	ORR 52% CR 25%	NA	NA
Zilovertamab vedotin	86	Phase 1	15	70‖	NA	4 (1-24)‖	NA	ORR 47% CR 13%	NA	NA



ZUMA-2 Study Design

Phase 2

Enrollment/ Leukapheresis	Optional Bridging Therapy*	Conditioning Chemotherapy	CAR T Cell Dose	Follow-Up Period
R/R MCL	Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily	Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3	2×10^6 KTE-X19 cells/kg single IV infusion on Day 0	First tumor assessment on Day 28†

Day -5 · Day 0 · Day 7

Manufacturing (median 16 days after apheresis)

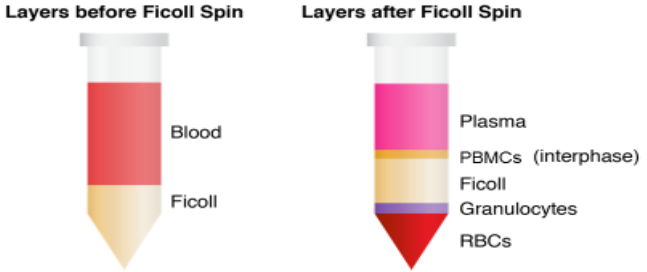
Hospitalization period

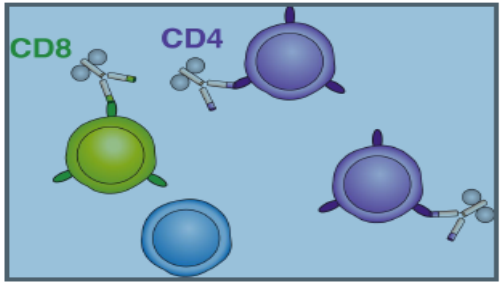
CLP Process

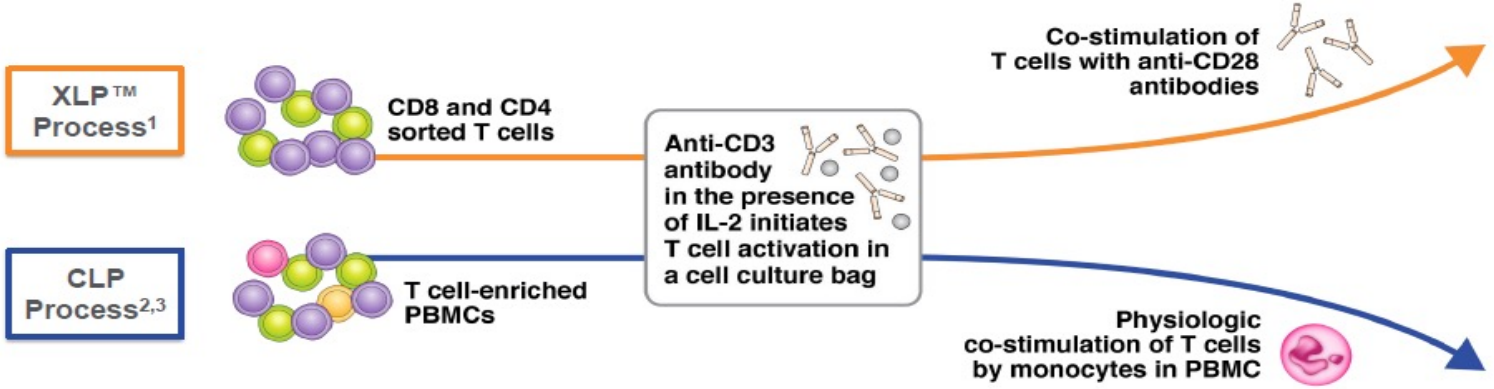
The T cell containing peripheral blood mononuclear cells (PBMC) fraction is enriched for mononuclear cells using Ficoll-based separation in a closed automated system[1]

XLP™ Process

Enrichment of T cells by positive selection for CD4 and CD8 positive cells to remove blast and tumor cells[2,3]







Patients Characteristics	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)

R/R MCL defined as:
- Disease progression after last regimen or
- Failure to exhibit a CR or PR to the last regimen

1-5 prior therapies that must have included:
- **An anthracycline- or bendamustine-containing chemotherapy AND**
- **Anti-CD20 monoclonal antibody therapy AND**
- **Ibrutinib or acalabrutinib**

- ≥ 1 measurable lesion
- Age ≥ 18 years
- ECOG of 0 or 1
- Adequate renal, hepatic, pulmonary, and cardiac function
- ALC ≥ 100 mm^3

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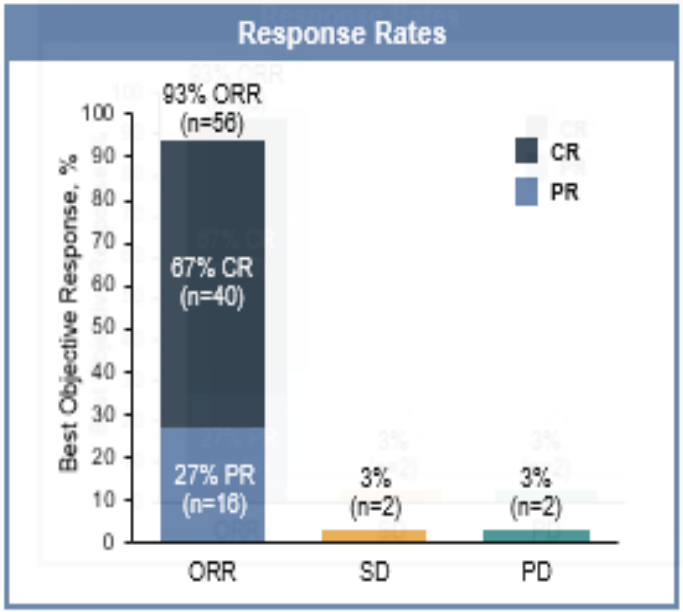
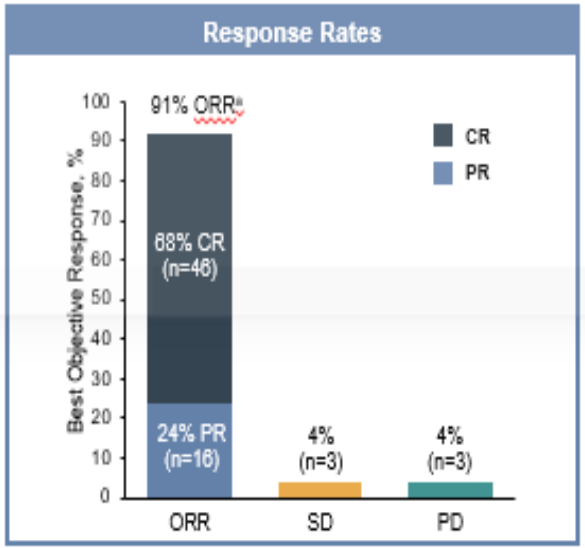
- Prior allo
- Prior CD19-targeted therapy
- Prior CAR
- Clinically significant infection
- CNS involvement



	Efficacy Evaluable N=60
Median follow-up, months (range)	12.3 (7.0–32.3)
Median time to response, months (range)	
Initial response	1.0 (0.8–3.1)
CR	3.0 (0.9–9.3)
Patients who initially had PR/SD and subsequently had a CR, n (%)	24/42 (57)
PR to CR	21/42 (50)
SD to CR	3 (7)

- ORR by IRRC assessment was 93% (95% CI, 84–98) and CR rate was 67% (95% CI, 53–78)

3-Year Analysis:
ORR in the All-Treated Population (Primary Endpoint)

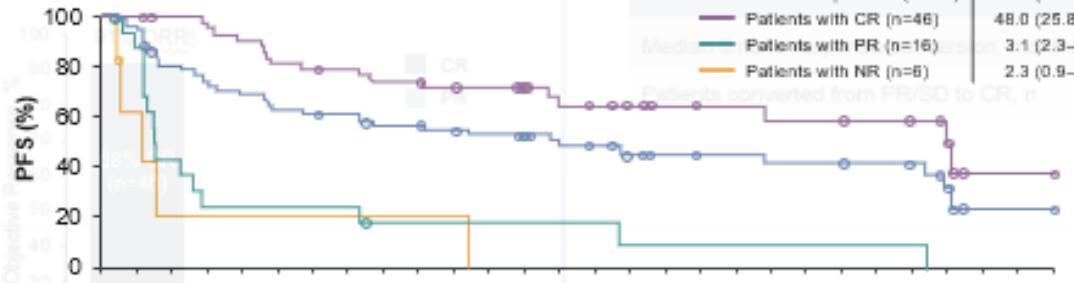


	Patients N=68
Median time to response conversion, months	2.3
Patients converted from PR/SD to CR, n	25

- ORR by IRRC assessment was 91% (95% CI, 81.8–96.7) and CR rate was 68% (95% CI, 55.2–78.5)

PFS[1]

	Median PFS, months (95% CI)	24-Month PFS Rate, % (95% CI)
All-treated patients (N=68)	25.8 (9.6–47.6)	52.9 (39.9–64.3)
Patients with CR (n=46)	48.0 (25.8–NE)	71.8 (55.7–82.9)
Patients with PR (n=16)	3.1 (2.3–5.6)	18.8 (4.6–40.2)
Patients with NR (n=6)	2.3 (0.9–NE)	ND



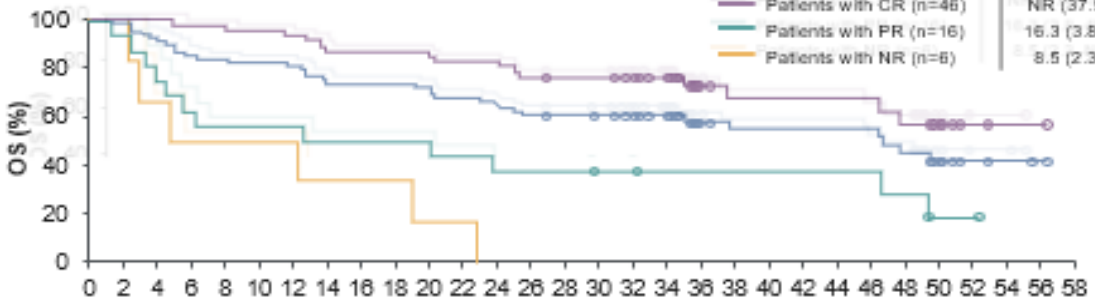
No. at risk

All-treated patients	68	62	51	47	44	40	39	35	34	33	31	31	29	28	22	18	17	14	12	11	11	10	10	9	4	1	1	0
Patients with CR	46	45	43	42	39	35	34	33	31	31	29	28	22	18	17	14	12	11	11	10	10	9	9	8	4	1	1	0
Patients with PR	16	14	7	4	4	4	4	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0	0	0
Patients with NR	6	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- **Primary Analysis**: Median PFS was not reached after a median follow-up of 12.3 months[2]
- **3-Year Analysis**: Median PFS in the all-treated populations was 25.8 months[1a]
  - 24-month PFS rate of 52.9%[1a]

OS[1]

	Median OS, months (95% CI)	30-Month OS Rate, % (95% CI)
All-treated patients (N=68)	46.6 (24.9–NE)	60.3 (47.7–70.8)
Patients with CR (n=46)	NR (37.5–NE)	76.1 (61.0–86.0)
Patients with PR (n=16)	16.3 (3.8–49.3)	37.5 (15.4–59.8)
Patients with NR (n=6)	8.5 (2.3–NE)	ND



No. at risk																													
All-treated patients	68	67	62	58	56	56	55	50	50	50	47	46	43	41	40	39	35	28	19	17	17	17	17	17	14	9	4	2	1	0
Patients with CR	46	46	46	45	44	44	43	40	40	40	39	38	37	35	34	34	30	24	15	13	13	13	13	13	11	8	3	2	1	0
Patients with PR	16	15	12	10	9	9	9	8	8	8	7	7	6	6	6	5	5	4	4	4	4	4	4	4	3	1	1	0	0	0
Patients with NR	6	6	4	3	3	3	3	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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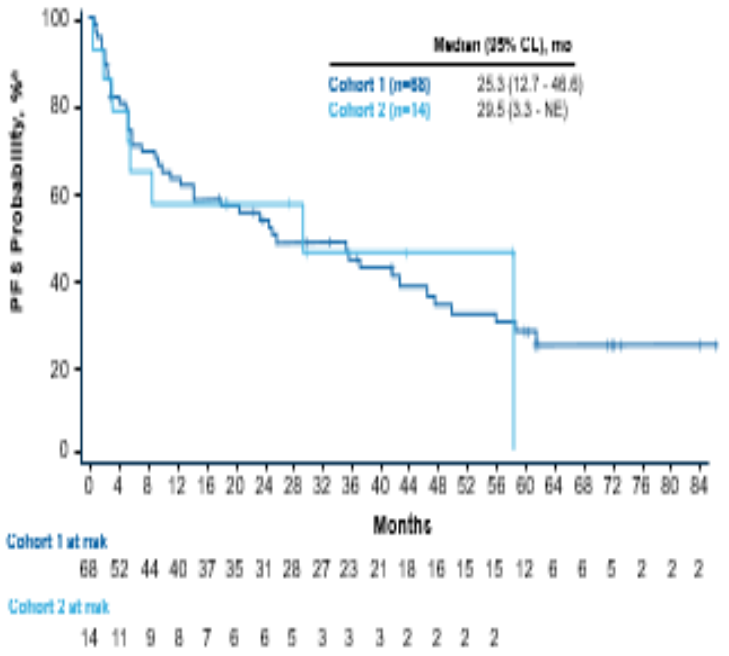
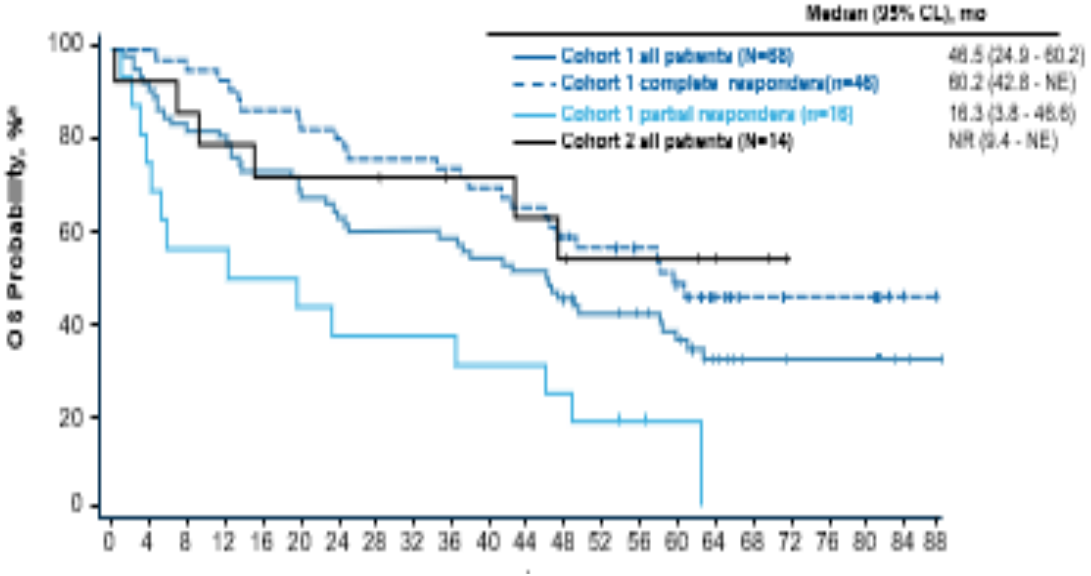
- **Primary Analysis**: Median OS was not reached after a median follow-up of 12.3 months[2]
- **3-Year Analysis**: Median OS was 46.6 months (95% CI, 24.9–NE)[1a]

Five-Year Outcomes of Patients With Relapsed/Refractory Mantle Cell Lymphoma Treated With Brexucell in ZUMA-2 :PFS

- Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1 (**Figure 5**)
- In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month PFS rate was 46% (95% CI, 17.3-70.5; N=14; **Figure 5**)



Five-Year Outcomes of Patients With Relapsed/Refractory Mantle Cell Lymphoma Treated With Brexucell in ZUMA-2 : OS



- In Cohort 1, the median OS was 46.5 months (95% CI, 24.9-60.2) and 60-month OS rate was 39% (95% CI, 26.7-50.1; **Figure 6**)
- In Cohort 2, median OS was not reached (95% CI, 9.4-NE) and 60-month OS rate was 54% (95% CI, 23.8-76.2; **Figure 6**)

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

Rates of Grade ≥3 CRS and neurological events were 15% and 31% no cases of Grade 5 CRS or neurological events

The 5-year rates of PD-related death and non-PD–related death were 40% (24/60) and 22% No cases of secondary T-cell malignancies

TEAE,[a] n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any TEAE	68 (100)	14 (100)
Grade ≥3	67 (99)	13 (93)
Any brexu-cel–related TEAE	66 (97)	14 (100)
Grade ≥3	54 (79)	10 (71)
TEAEs in ≥40% of patients in either cohort		
Any pyrexia	64 (94)	13 (93)
Grade ≥3	9 (13)	3 (21)
Any anaemia	46 (68)	7 (50)
Grade ≥3	35 (51)	6 (43)
Any neutrophil count decreased	37 (54)	6 (43)
Grade ≥3	36 (53)	6 (43)
Any hypotension	36 (53)	11 (79)
Grade ≥3	15 (22)	8 (57)
Any platelet count decreased	35 (51)	5 (36)
Grade ≥3	26 (38)	5 (36)
Any chills	28 (41)	6 (43)
Grade ≥3	0	0

TEAE,[a] n (%) (cont.)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any white blood cell count decreased	28 (41)	7 (50)
Grade ≥3	28 (41)	7 (50)
Any fatigue	26 (38)	7 (50)
Grade ≥3	1 (1)	0
Any hypoxia	26 (38)	7 (50)
Grade ≥3	14 (21)	2 (14)
Any tremor	24 (35)	7 (50)
Grade ≥3	0	2 (14)
Any nausea	22 (32)	7 (50)
Grade ≥3	1 (1)	0
Any decrease in appetite	15 (22)	7 (50)
Grade ≥3	0	0
Any confusional state	14 (21)	6 (43)
Grade ≥3	8 (12)	1 (7)
Any dyspnea	14 (21)	6 (43)
Grade ≥3	2 (3)	3 (21)

- In Cohort 1, the most common Grade ≥3 AEs were neutrophil count decreased (53%), anaemia (51%), and white blood cell count decreased (41%; **Table 3**)
- In Cohort 1, the most common Grade ≥3 AEs were neutrophil count decreased (53%), anaemia (51%), and white blood cell count decreased (41%; **Table 3**)

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"Chiedo scusa alle grandi domande
per le piccole risposte"
(Wislawa Szymborska)