LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

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Le CAR-T nella RWE

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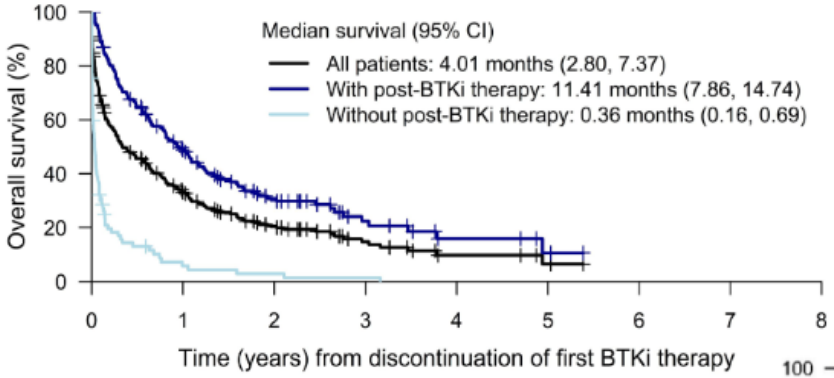
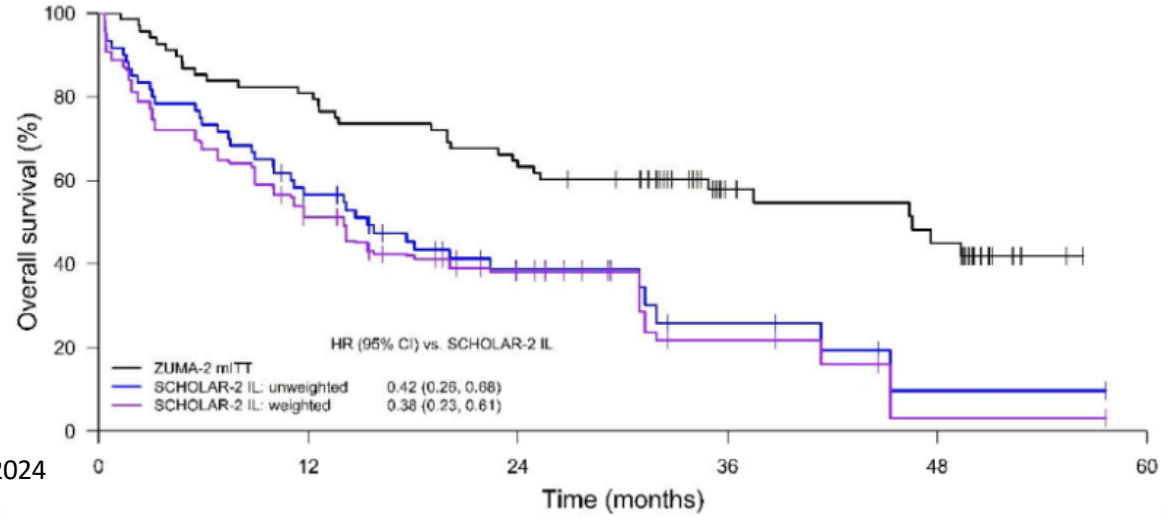
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Conference participation support
BMS					X	X	
Kyte/Gilead					X		
Abbvie							X
Roche							X



The outcome of patients with R/R MCL after BTK-i failure is dismal, and no standard of care is established

Brexucabtagene Autoleucel (brexu-cel) has significantly improved survival rates (ZUMA-2 vs. Scholar-2)



Hess et al. Br J Haematol. 2023; Hess et al. Leuk Lymphoma. 2024

First real-world evidence from a European Early Access Program (EAP) confirmed efficacy and safety of the ZUMA-2 trial

Included all patients with **R/R MCL who underwent apheresis for brexu-cel at 11 European sites** (Spain, **Italy**, Germany, Netherlands) from February 2020 to August 2021.

- **39 underwent apheresis**
- **Manufacturing failure in 3 (8%):**
  - 2 required a 2nd apheresis, 1 a 3rd.
  - 2/3 successfully infused.
- **Turn-around time: 29 days**
- **Infused: 33 (85%)**
- **Non-infused: 6 (15%)**
  - 3 PD
  - 2 CR after bridging
  - 1 infection

Iacoboni, Blood Advances 2022

	Infused (N=33)
Age, median y (range)	67 (47-79)
≥65	23 (70)
Prior lines >2, median (range)	2 (1-8)
Primary refractory, n (%)	7 (21)
Previous auto-HCT, n (%)	12 (36)
Previous allo-HCT, n (%)	5 (15)
Best response to ibrutinib, n (%)	
CR	11 (34)
PR	10 (30)
SD/PD	8 (24)
Not available	4 (12)
Prior bendamustine therapy, n (%)	14 (42)
Morphology, n (%)	
Classical	22 (67)
Blastoid/pleomorphic	9 (27)
Not available	2 (6)

	Infused (N=33)
TP53 status, n (%)	
Mutated	4 (12)
Unmutated	11 (33)
Not available	18 (55)
Ki67 index >30%, n (%)	
Yes	16 (49)
No	3 (9)
Not available	14 (42)
Stage III/IV, n (%)	29 (88)
s-MIPI, n (%)	
Low	8 (24)
Intermediate/high	23 (70)
Not available	2 (6)
Extranodal disease, n (%)	26 (79)
Bone marrow infiltration, n (%)	10 (30)
ECOG, n (%)	
0	15 (45)
≥1	18 (55)
Bridging therapy, n (%)	32 (82)

Iacoboni, Blood Advances 2022

Response Category	EAP n (%)	ZUMA-2 n (%)
Overall Response Rate (ORR)	30 (91%)	56 (93%)
Complete Response (CR)	26 (79%)	40 (67%)
Partial Response (PR)	4 (12%)	16 (27%)
Stable Disease (SD)	1 (3%)	2 (3%)
Progressive Disease (PD)	1 (3%)	2 (3%)

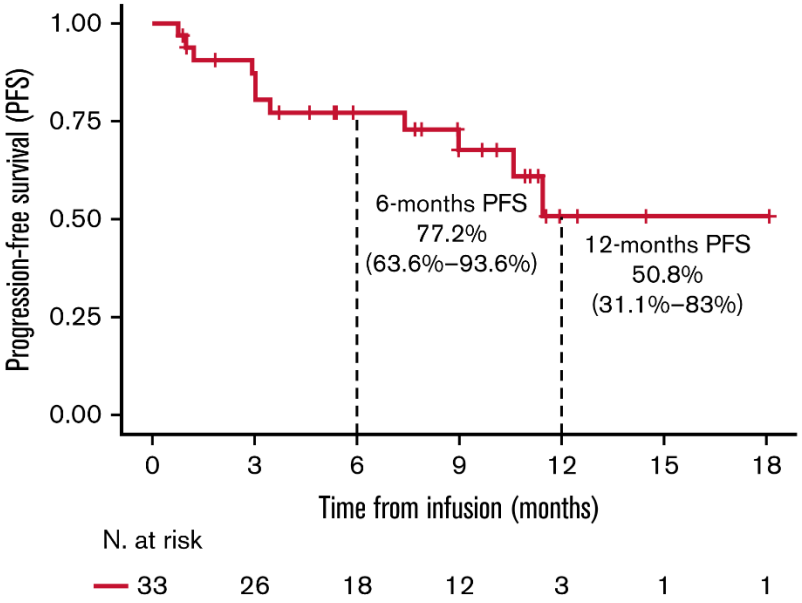
Efficacy results were comparable to ZUMA-2

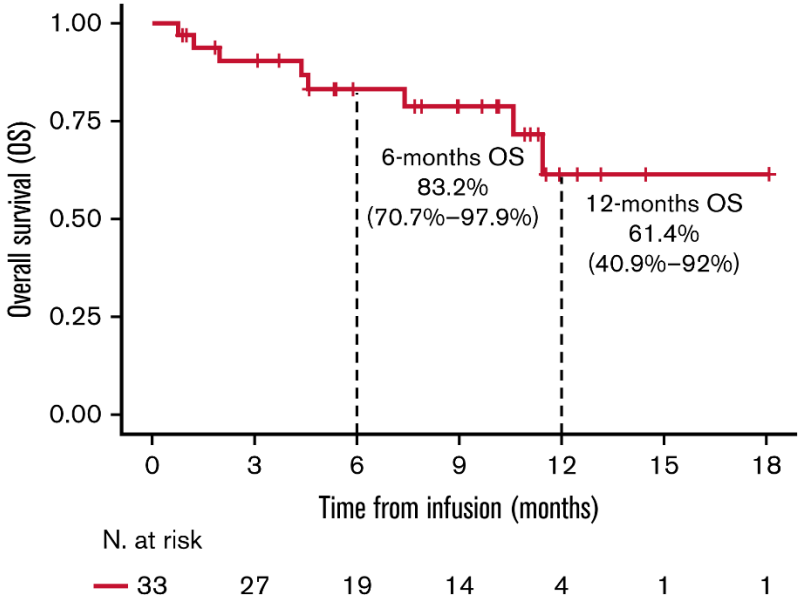
Similarly, safety data were comparable to ZUMA-2

Adverse Event	EAP n (%)	ZUMA-2 (%)
CRS (Any Grade)	30 (91%)	91%
CRS (Grade ≥3)	3 (1%)	15%
ICANS (Any Grade)	21 (64%)	63%
ICANS (Grade ≥3)	12 (36%)	31%

Iacoboni, Blood Advances 2022

Median follow-up 10.1 months (95% CI, 7.9-11.5)
NRM 15% (5 pts: 4 COVID, 1 steroid-related deterioration)





iTT (N = 39) 6-mo PFS and OS: 68% (95% CI, 55-85) and 76% (95% CI, 63-91)

Iacoboni, Blood Advances 2022

Variable	N	Progression-free survival	6-months PFS (95% CI)
Overall	33		77.2 (63.6–93.6)
Age			
<65 years	10		67.5 (43–100)
≥65 years	23		81.5 (66.6–99.7)
Prior lines			
1–2	18		82.5 (66.3–100)
3+	15		71.4 (51.3–99.5)
Previous ASCT			
No	21		74.5 (57.4–96.6)
Yes	12		81.8 (61.9–100)
Morphology			
Classical	22		80.3 (64.6–99.7)
Blastoid/Pleomorphic	9		66.7 (42–100)
***TP53* mutation**			
No mutation	11		100 (67.6–100)
Mutation	4		66.7 (30–100)
Simplified MIPI			
Low/Intermediate	13		100 (86.5–100)
High	18		61.1 (42.3–88.3)
Extranodal disease			
No	7		85.7 (63.3–100)
Yes	26		74.8 (59.1–94.5)
LDH			
≤ULN	19		87.5 (72.7–100)
>ULN	14		64.3 (43.5–95)
ECOG			
0	15		85.7 (69.2–100)
1–2	18		69.6 (50.4–96)
Prior bendamustine			
No	19		76.4 (58.5–99.8)
Yes	14		78.6 (59.8–100)

0% 20% 40% 60% 80% 100%

6m progression-free survival (%)

Variable	N	Overall survival	6-months OS (95% CI)
Overall	33		83.2 (70.7–97.9)
Age			
<65 years	10		88.9 (70.6–100)
≥65 years	23		81 (65.7–99.7)
Prior lines			
1–2	18		81.4 (64.3–100)
3+	15		85.1 (68–100)
Previous ASCT			
No	21		78.7 (62.1–99.7)
Yes	12		90.9 (75.4–100)
Morphology			
Classical	22		79.4 (63.2–99.8)
Blastoid/Pleomorphic	9		87.5 (67.3–100)
***TP53* mutation**			
No mutation	11		100 (67.6–100)
Mutation	4		66.7 (30–100)
Simplified MIPI			
Low/Intermediate	13		100 (86.5–100)
High	18		70.5 (51.7–96.2)
Extranodal disease			
No	7		100 (77.6–100)
Yes	26		78.4 (63.2–97.2)
LDH			
≤ULN	19		93.3 (81.5–100)
>ULN	14		70.7 (50.2–99.6)
ECOG			
0	15		100 (88.2–100)
1–2	18		68.2 (48.5–95.9)
Prior bendamustine			
No	19		76.4 (58.5–99.8)
Yes	14		92.9 (80.3–100)

0% 20% 40% 60% 80% 100%

6m overall survival (%)

Iacoboni, Blood Advances 2022

Real-life Brexu-cel from the US CAR T Consortium: 16 US Institutions

Patients who underwent leukapheresis (August 18, 2020-December 31, 2021; N = 189)

- Patients who did not receive CAR T-cell infusion (n = 21)
  - Death (n = 9, all lymphoma-related)
  - Manufacture failure (n = 7)
  - Disease progression (n = 2)
  - Organ dysfunction (n = 1)
  - CR to bridging therapy (n = 1)
  - Patient declined (n = 1)
- Patients who received CAR T-cell infusion (n = 168)
  - Standard-of-care (n = 159)
  - Expanded access program (n = 2)
  - Single-patient IND protocol (n = 7)

} Out-of-spec products

Wang, JCO 2023

	Leukapheresed (N=189)	Infused (N=168)
Age, median (range)	67 (34–89)	67 (34–89)
ECOG PS ≥2, n (%)	26 (14%)	18 (11%)
Simplified MIPI, n (%):		
Low-Intermediate Risk (0-5)	149 (79%)	142 (84%)
High Risk (6-11)	40 (21%)	26 (15%)
Ki-67 (%):		
30-49	35 (20%)	32 (21%)
≥50	99 (58%)	86 (57%)
Blastoid/pleomorphic, n (%)	81 (43%)	68 (40%)
TP53 aberration, n (%):	69/141 (49%)	61/126 (48%)
Complex karyotype, n (%):	36/126 (29%)	31/111 (28%)
Stage III-IV, n (%)	172 (91%)	151 (90%)
CNS involvement, n (%)	20 (11%)	16 (10%)

	Leukapheresed (N=189)	Infused (N=168)
Bone marrow involved, n (%):	76/131 (58%)	65/118 (55%)
Bulky disease (≥10 cm), n (%)	30 (16%)	24 (14%)
Median prior lines of therapy	3 (1–10)	3 (1–10)
Prior bendamustine, n (%)	103 (54%)	85 (51%)
Prior venetoclax, n (%)	61 (32%)	54 (32%)
Prior auto-SCT, n (%)	53 (28%)	47 (28%)
Prior allo-SCT, n (%)	5 (3%)	5 (3%)
Prior BTKi, n (%):	163 (86%)	144 (86%)
Refractory	146 (77%)	128 (76%)
POD24, n (%)	97 (51%)	87 (52%)
Disease status at CAR-T, n (%):		
Relapsed after last line	104 (55%)	94 (56%)
Refractory to last line	85 (45%)	74 (44%)
Bridging therapy	128 (68%)	-

72% (149 pts) would not have met ZUMA-2 eligibility criteria for comorbidities, CNS disease, prior lines

Wang, JCO 2023

CRS & ICANS

Measurement	CRS	ICANS	CRS in ZUMA-2, %	Neurologic Events in ZUMA-2, %
Total, No. (%)	151 (90)	103 (61)	91	63
Maximum grade, No. (%)				
1-2	138 (82)	49 (29)	76	32
3-4	12 (7)	54 (32)	15	31
5	1 (1)			
Days to onset, median (range)	4 (0-13)	6 (1-18)	2 (1-13)	7
Days to maximum grade, median (range)	5 (0-30)	8 (1-18)	—	—
Duration in days, median (range)	5 (1-33)	6 (1-144+)[a]	11	12
Tocilizumab	129 (77)[b]			
Tocilizumab doses, No., median (range)	2 (1-4)			
Corticosteroids	116 (69)			
Anakinra[c]	28 (17)			
Siltuximab[d]	5 (3)			

ICU admission 20%

Cytopenias

Adverse Event/Management	Day 30, No./n (%)	Day 90, No./n (%)
Hemoglobin < 8 g/dL	13/164 (8)	8/146 (5)
Platelet < 50,000/μL	70/164 (43)	16/146 (11)
ANC < 1,000/μL	54/164 (33)	27/146 (18)
ANC < 500/μL	23/164 (14)	9/146 (6)
Infections[f]	Days 0-30: 35/168 (21)	Days 31-90: 19/164 (12)

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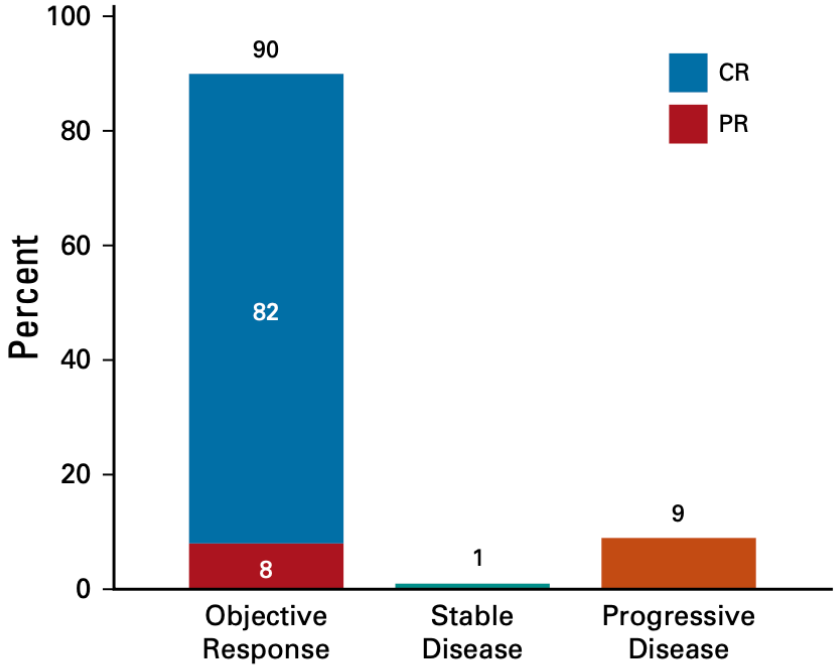
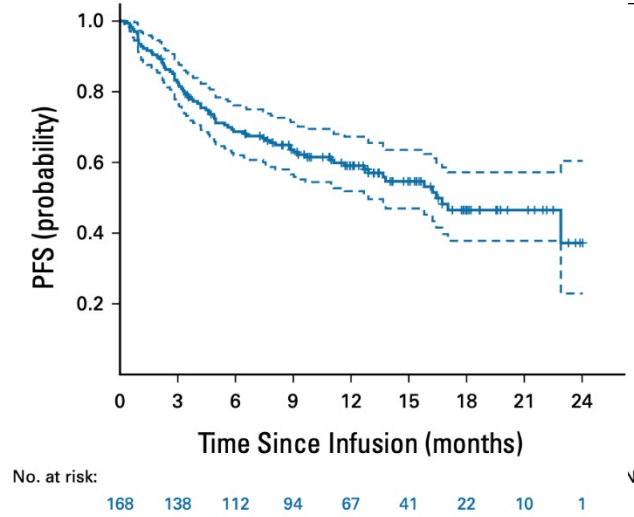
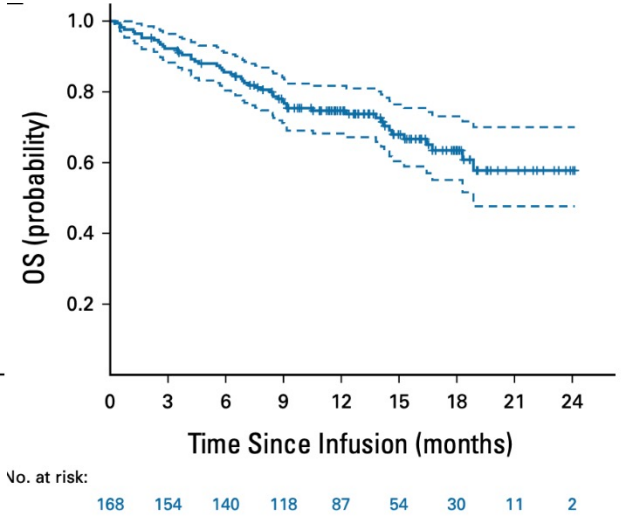
Response rates were similar to ZUMA-2

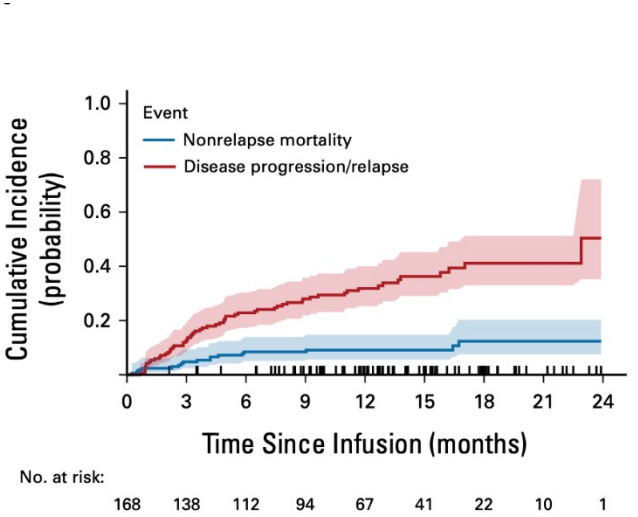


Wang, JCO 2023

median follow-up 14.3 months (95% CI, 12.7 to 15.9)





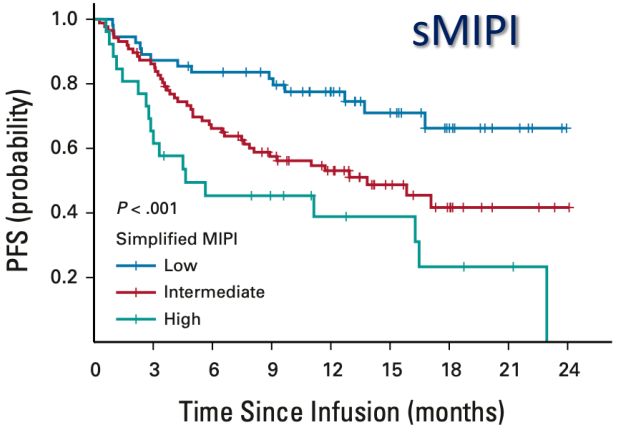


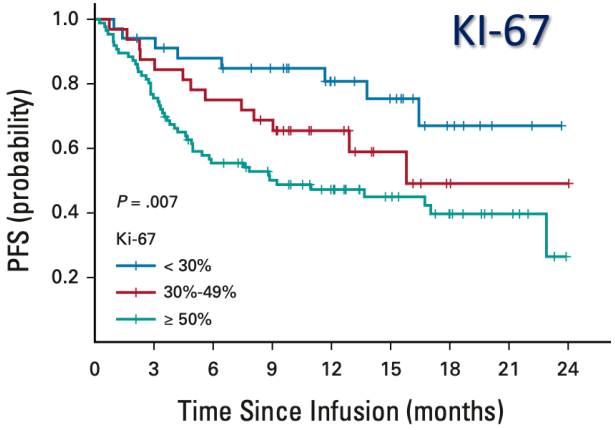
PFS
Median: 16.4 months (95% CI, 12.7 to NE)
6-month: 69% (95% CI, 61 to 75)
12-month: 59% (95% CI, 51 to 66)

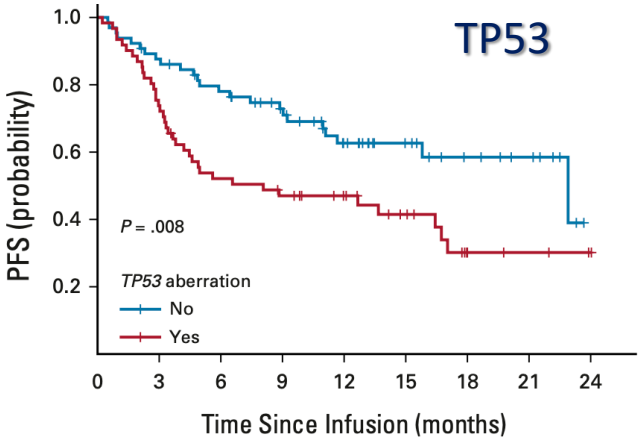
OS
Median: NR (95% CI, 18.7 to NE)
6-month: 86% (95% CI, 79 to 90)
12-month: 75% (95% CI, 67 to 81)

NRM
30-day: 2.4% (95% CI, 0.8 to 5.6)
90-day: 4.8% (95% CI, 2.2 to 8.8)
1-year: 9.1% (95% CI, 5.3 to 14.1)

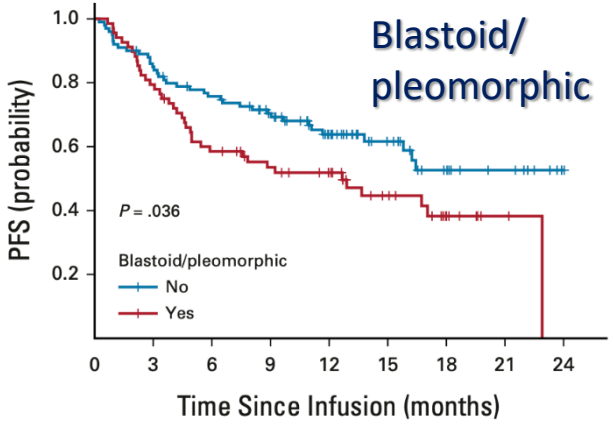
Wang, JCO 2023

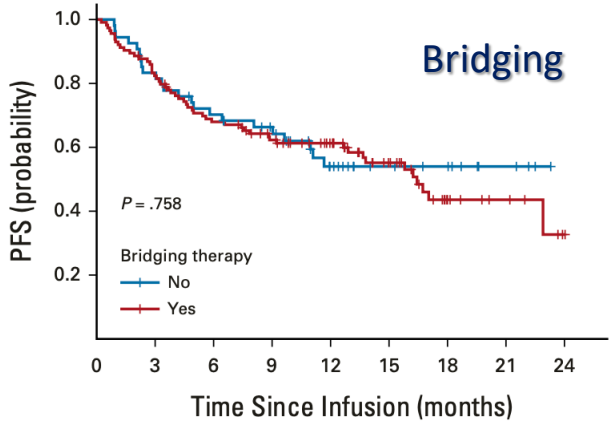






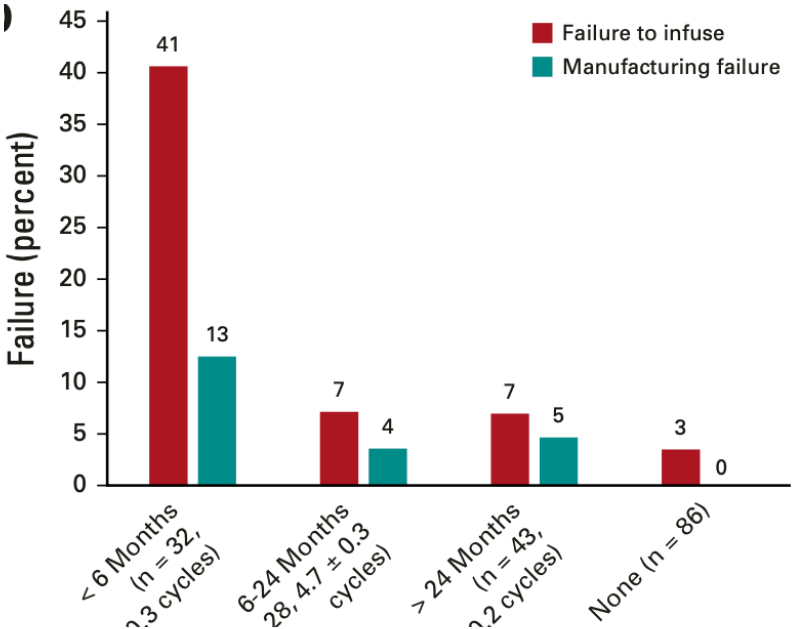
sMIPI, Ki-67, TP53 aberr., blastoid/pleomorphic v. were correlated with shorter PFS.
Bridging was not.

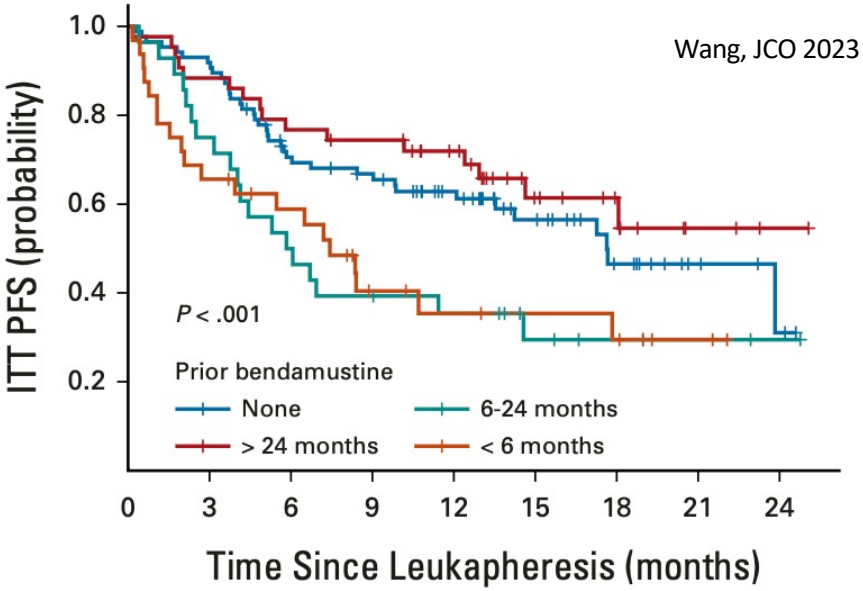




Wang, JCO 2023

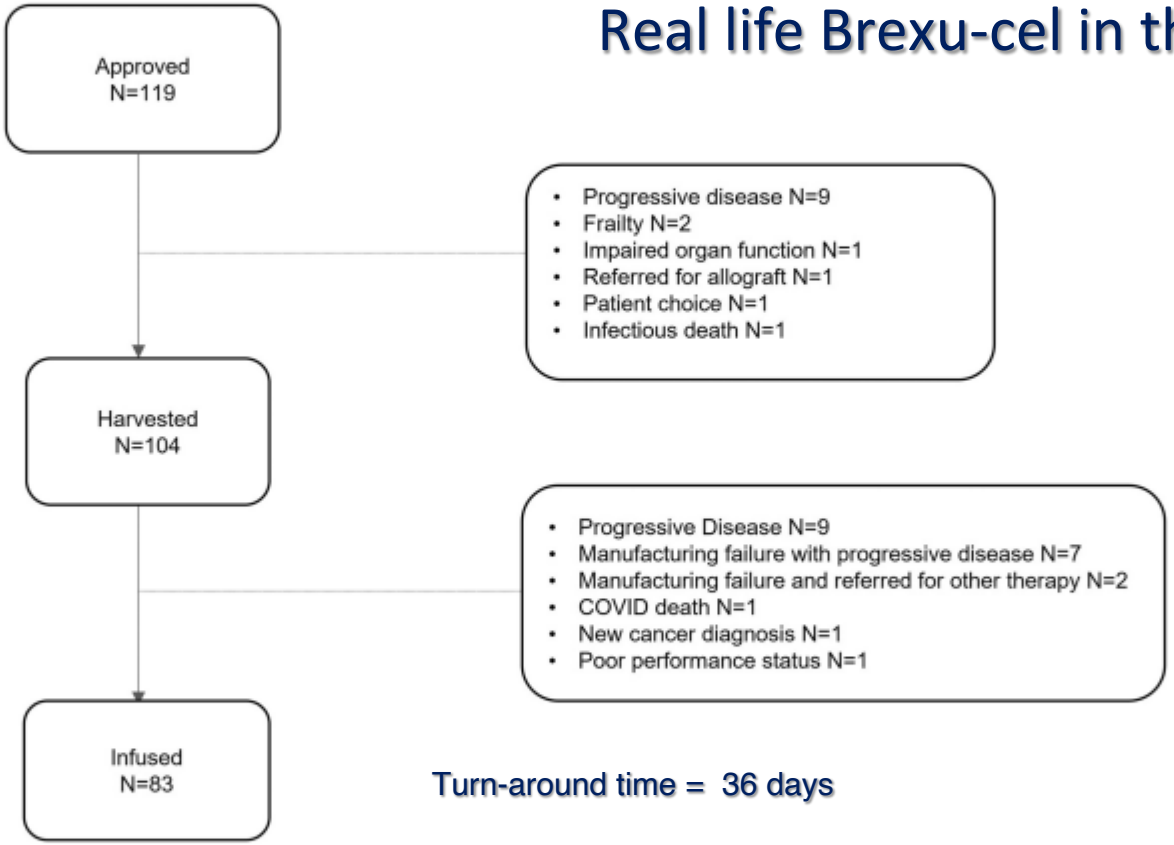
Recent Bendamustine exposure was associated with manufacturing failure, failure to infuse, and shorter PFS and OS





after adjusting for sMIPI and Ki-67, the association was no longer significant

Real life Brexu-cel in the United Kingdom: 12 CAR T centers



Turn-around time = 36 days

O' Reilly, Hemasphere 2024

	Approved (N=119)	Harvested (N=104)	Infused (N=83)
Age, median (range)	68 (41–80)	67.5 (41–78)	68 (41–78)
Previous lines, median (range)	2 (2-7)	2 (2-7)	2 (2-7)
Refractory to all lines, n (%)	14 (12%)	12 (12%)	9 (11%)
Ibrutinib refract, n (%)	35 (30%)	30 (29%)	25 (30%)
Previous ASCT, n (%)	40 (34%)	35 (34%)	29 (35%)
Previous Allo, n (%)	15 (13%)	15 (14%)	14 (17%)
POD24, n (%)	67 (57%)	61 (59%)	45 (55%)
ECOG PS = 1, n (%)	77 (65%)	67 (64%)	50 (60%)
Ki-67 ≥30%, n (%)	49 (78%)	46 (78%)	35 (76%)
Stage III-IV, n (%)	96 (81%)	83 (81%)	64 (77%)
Bulk (>5 cm), n (%)	41 (34%)	38 (37%)	29 (35%)

	Approved (N=119)	Harvested (N=104)	Infused (N=83)
sMIPI High Risk, n (%)	47 (47%)	40 (45%)	31 (45%)
Blastoid/Pleomorphic, n (%):	33 (42%)	29 (41%)	21 (38%)
TP53 aberration, n (%)	31 (53%)	25 (51%)	18 (45%)
Unknown	60	55	43
TP53 mutation, n (%)	21 (38%)	17 (37%)	15 (38%)
Unknown	63	58	44
LDH, median (range)	231 (105–3209)	228 (105–2233)	227 (120–2233)
Most recent bendamustine, n (%)			
<6 months	12 (11%)	12 (12%)	10 (12%)
6–24 months	15 (14%)	15 (15%)	9 (11%)
>24 months	15 (14%)	15 (15%)	14 (17%)
None	65 (61%)	61 (59%)	49 (60%)

O' Reilly, Hemasphere 2024

CRS & ICANS

Toxicity/Management	Incidence
CRS (Any Grade)	77/83 (93%)
CRS (Grade ≥3)	10/83 (12%)
ICANS (Any Grade)	46/83 (55%)
ICANS (Grade ≥3)	19/83 (23%)
Management Strategies	
- Steroid Use	48/83 (58%)
- Median Cumulative Steroid Dose (mg)	195 (10–1416)
- Tocilizumab Use	66/83 (80%)
- Anakinra Use	14/83 (17%)
- Median Anakinra Duration (Days)	11 (3–30)
ICU Admission	22/83 (27%)

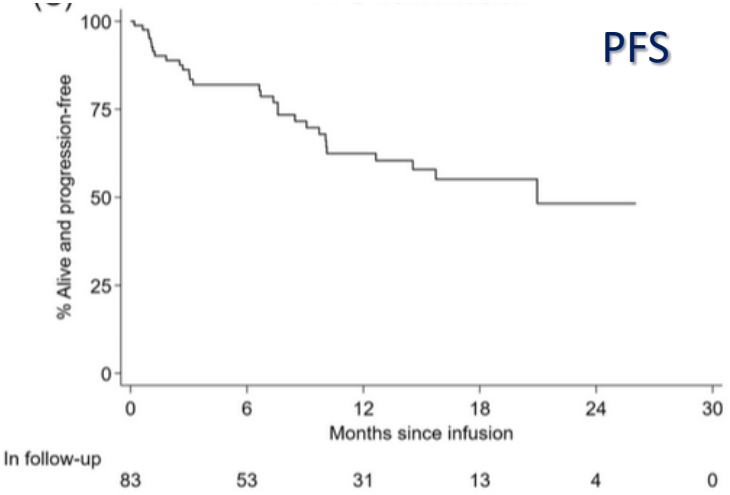
Cytopenias

Cytopenias	Incidence
- 30 days Grade 3/4 Neutropenia	48/81 (59%)
- 30 days Grade 3/4 Thrombocytopenia	49/81 (60%)
- 90 days Grade 3/4 Neutropenia	17/67 (25%)
- 90 days Grade 3/4 Thrombocytopenia	21/67 (31%)

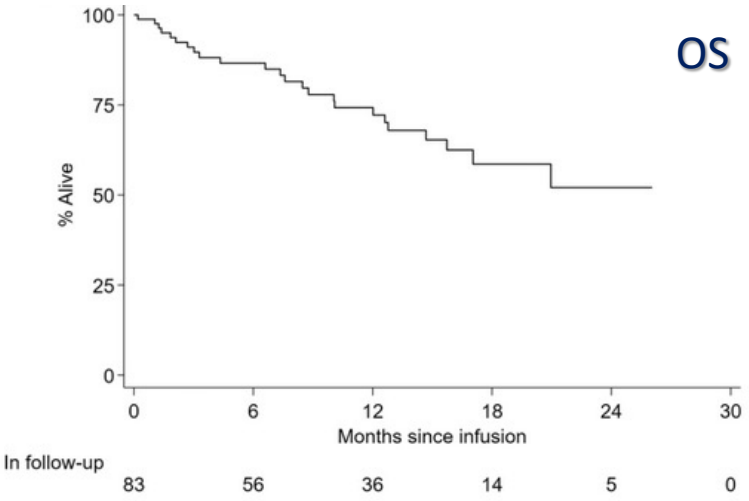
O' Reilly, Hemasphere 2024

Best ORR 87% (CR 81%; PR 6%); median follow-up 13.3 months

PFS



OS



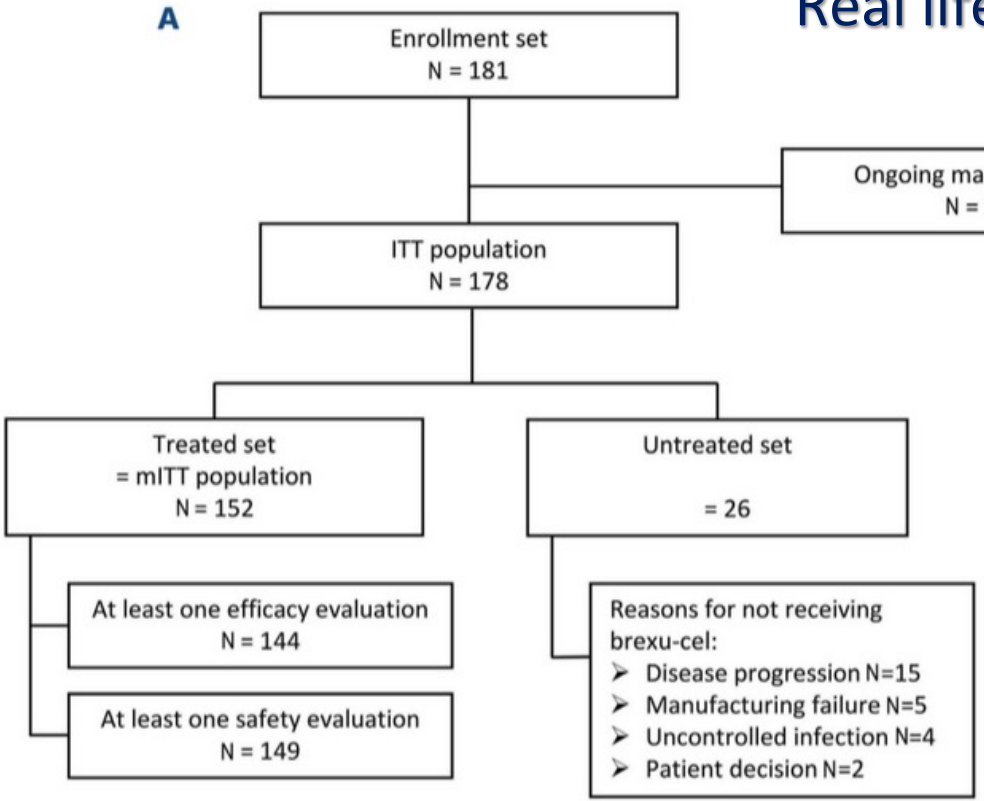
Median PFS: 21 months (95% CI: 10.1–NA)
6-Month PFS: 82% (95% CI: 71–89)
12-Month PFS: 62% (95% CI: 49–73)
ITT cohort median PFS of 11.4 months

Median OS: NR (95% CI: 18.7–NA)
6-Month OS: 87% (95% CI: 76–93)
2-Month OS: 74% (95% CI: 62–83)
NRM 6% at 6mo, 15% at 12 mo, 25% at 2y

on MVA: bulky, male sex, ECOG > 1 pre-LD, and manufacture failure (MF) had negative impact on PFS / OS

O' Reilly, Hemasphere 2024

Real life Brexu-cel in France: DESCAR-T: 24 French centers



71% would not meet ZUMA-2 eligibility criteria for type of bridge and ECOG and prior malignancy

Turn-around time = 39 days

Herbaux et al. Haematologica 2024

	Treated set (N=152)	Untreated set (N=26)
Age, median (min-max)	68.0 (39–83)	66.5 (47–77)
Age ≥65 years	99 (65.1)	16 (61.5)
Age >75 years	19 (12.5)	3 (11.5)
ECOG PS ≥2	17 (12.0)	9 (39.1)
- Missing	10	3
MIPI risk group		
- Low risk: <5.7	27 (19.9)	3 (15.0)
- Intermediate risk: 5.7–6.2	54 (39.7)	5 (25.0)
- High risk: ≥6.2	55 (40.4)	12 (60.0)
- Missing	16	6

	Treated set (N=152)	Untreated set (N=26)
Ki-67 ≥30%	85 (79.4)	11 (78.6)
- Missing	45	12
TP53 mutation	29 (30.2)	6 (42.9)
- Missing	56	12
Blastoid variant	41 (31.1)	3 (16.7)
- Missing	20	8
Prior lines of therapy, median (min-max)	3.0 (1–9)	3.0 (2–9)
Prior transplant		
- Autograft	60 (39.5)	9 (34.6)
- Allograft	9 (5.9)	0 (0)
Bridging therapy	126 (82.9)	15 (57.7)

Herbaux et al. Haematologica 2024

CRS & ICANS

Toxicities	Incidence
CRS (Any Grade)	131/149 (87.9%)
CRS (Grade ≥3)	18/149 (12.1%)
ICANS (Any Grade)	82/149 (55%)
ICANS (Grade ≥3)	23/149 (15.4%)
Management Strategies	
- Tocilizumab Use	112/149 (74.8%)
- Corticosteroid Use	97/149 (64.9%)
- Anakinra Use	17/149 (11.5%)
- Siltuximab Use	8/149 (5.3%)
ICU Admission	
- Total Admissions	46/149 (34.3%)
- Median of Hospitalization	6 days
- CRS-Related Admission	44 cases (26 Grade 2; 18 ≥3)
- ICANS-Related Admission	36 cases (13 Grade 2; 23 ≥3)

Cytopenias, Infections & NRM

Cytopenias at 3 Months	
- Any Grade	24/122 (19.7%)
- Grade ≥3 Neutropenia	13/122 (10.7%)
- Grade ≥3 Thrombocytopenia	1/122 (0.8%)
Infections (Grade ≥3)	
- Total (From Infusion to Day 10)	38/149 (25.5%)
- Bacterial Infections	25/149 (16.8%)
Non-Relapse Mortality	17/152 (11.2%)
Cause of Death	
- Progressive Disease	29/152
- Infectious Events	11/152
- CRS	2/152
- Myelodysplastic Syndrome	2/152
- Unknown Cause	2/152

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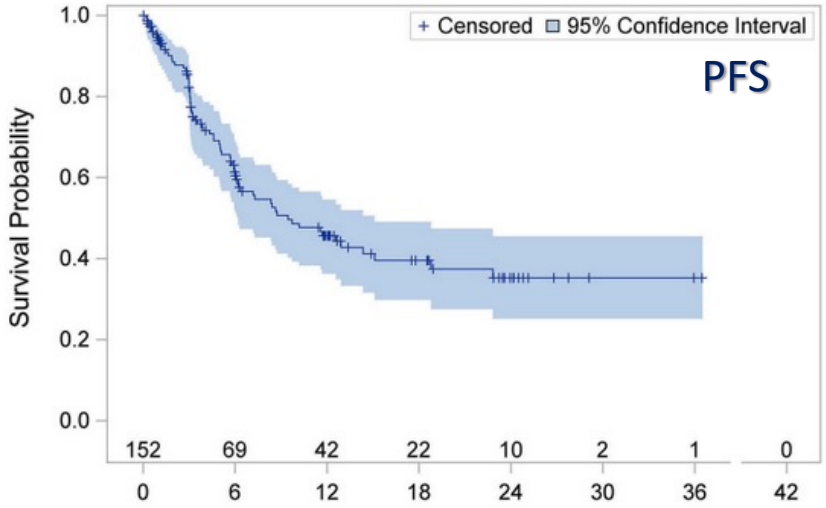
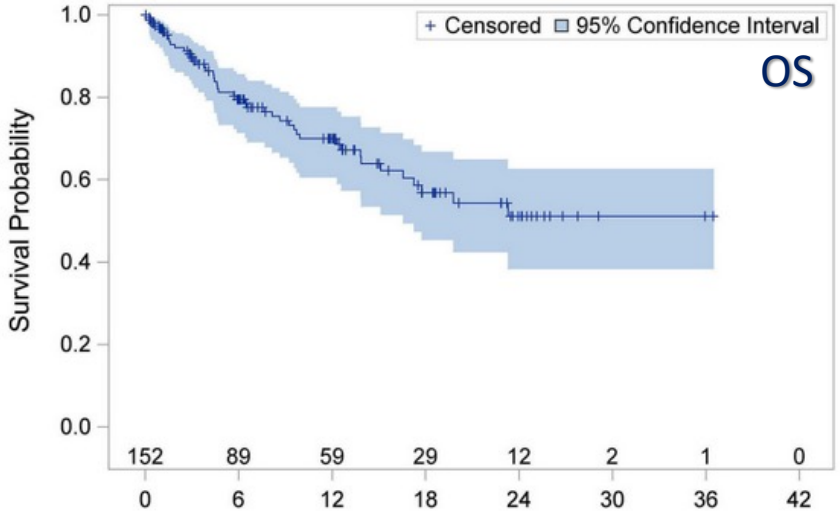
On 144 evaluable patients ORR: 84.7%; CR: 72.2%
Median Follow-Up: 12.2 months (95% CI: 11.8–13.4);





Median PFS: 9.5 months (95% CI: 6.2–15.1)
Estimated PFS at 6 months: 61.3% (95% CI: 52.2–69.3)
Estimated PFS at 12 months: 45.6% (95% CI: 36.2–54.5)

Median OS: Not reached (NR)
Estimated OS at 24 months: 51.1%
median ITT OS 19.8 months (95%CI 15.3-NA)

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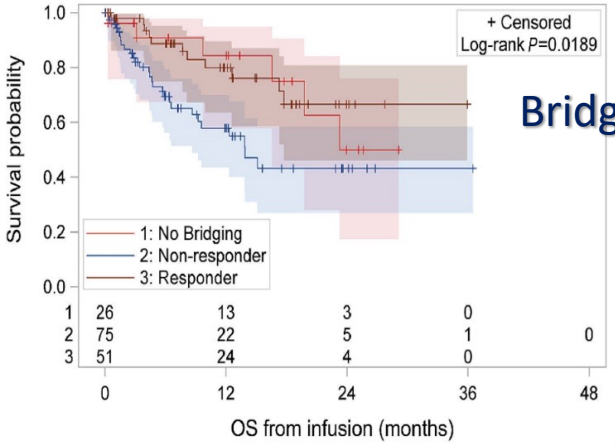
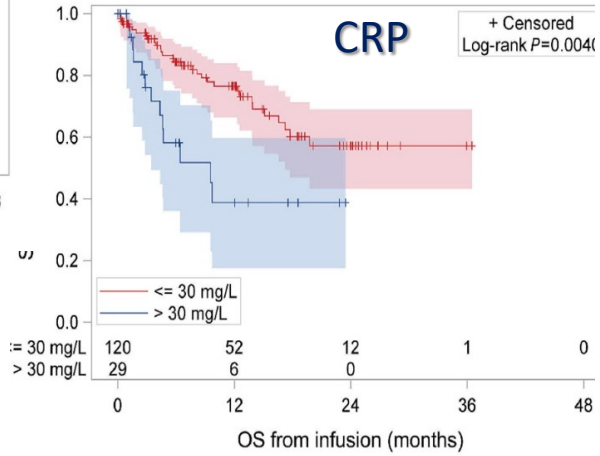
No response to bridging, high CRP and ferritine levels had a negative impact on OS

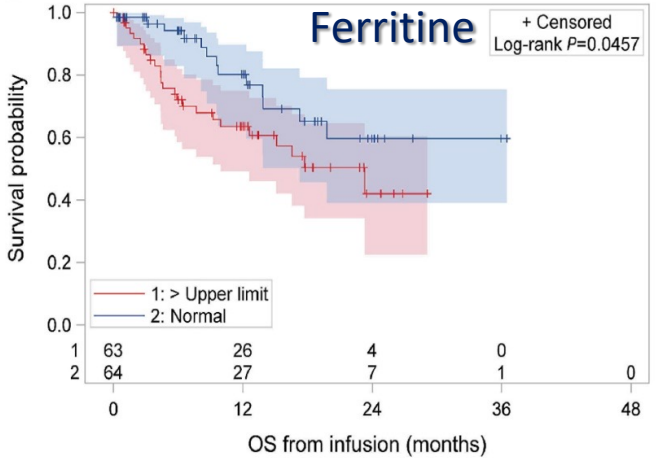
Bridging



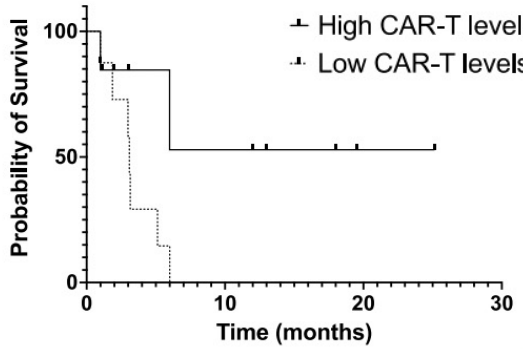
CRP



Ferritine



PFS



High CAR-T cells expansion (>60 CAR+/ul Cmax) associated with longer PFS

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Real life Brexu-cel in Italy, CART-SIE: 20 Italian centers

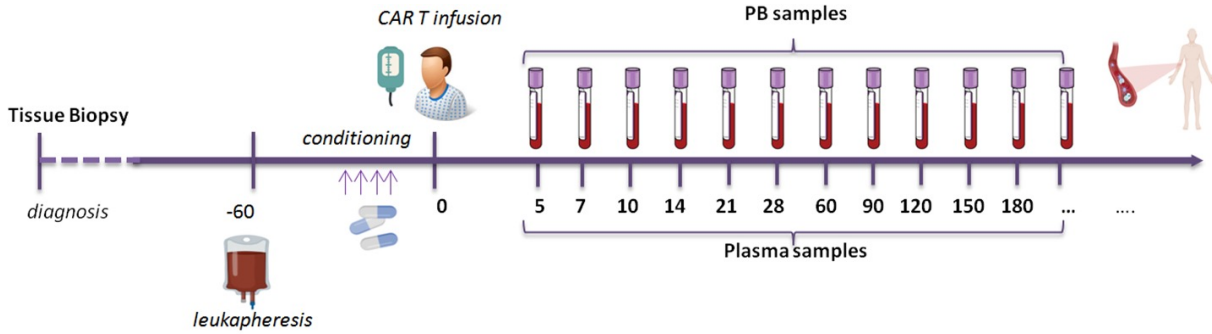
1002 patients enrolled

746 patients evaluable

Axi-cel
49% (n = 368)

Tisa-cel
37% (n = 272)

Brexu-cel
14% (n = 106)



Courtesy of Chiappella A

Characteristic	Global Population (N=106)
Age (median)	63 (42–79)
Histology	
- Classic MCL	74 (70%)
- Blastoid/pleomorphic MCL	32 (30%)
Refractory Disease	56 (53%)
BTKi Relapsed	54 (65%)
BTKi Refractory	29 (35%)
- Missing	23 (22%)
Previous ASCT	61 (58%)
Stage III–IV	96 (92%)
Extranodal Disease	55 (52%)
Bone Marrow Involved	62 (59%)

Characteristic	Global Population (N=106)
Bulky Disease	21 (20%)
LDH Baseline > ULN	25 (25%)
POD24	45 (42%)
sMIPI Risk Group	
- Low	32 (35%)
- Intermediate	18 (20%)
- High	41 (45%)
- Missing	15 (14%)
Bridging Therapy	83 (79%)
No response to Bridging	68 (72%)

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CRS & ICANS

Toxicity/Management	Incidence
CRS (Any Grade)	95%
CRS (Grade ≥3)	21%
ICANS (Any Grade)	48%
ICANS (Grade ≥3)	18%
Management Strategies	
- Tocilizumab Use	84%
- Steroid Use	54%
- ICU Admission	18%

Cytopenias & NRM

Hematological Toxicity	Incidence
- Grade ≥3 Thrombocytopenia	18%
- Grade ≥3 Anemia	1.1%
- Late Grade ≥3 ICAHT	4.4%
Mortality	
- Non-Relapse Mortality at 1 Year	7.3% (Range: 3.2%–14%)
Causes of Death	
- Bacterial Infections	2/7 (29%)
- G5 CRS	1
- G5 ICANS	1
- Cerebrovascular Event	1
- Multi-Organ Failure	2
Secondary Primary Malignancies	
- Diagnosed Cases	3/106 (2.8%)
- Types	2 MDS, 1 Bladder Cancer

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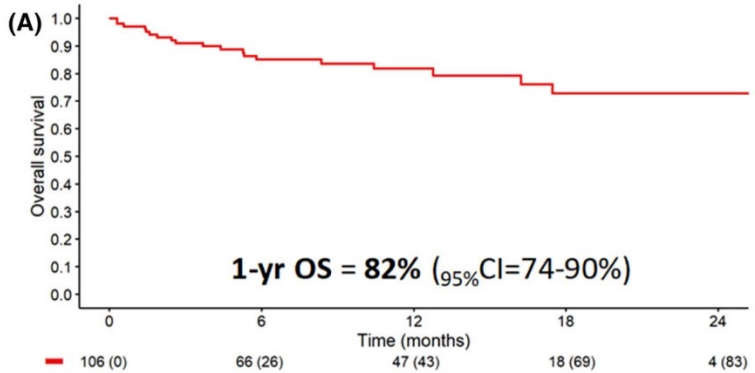
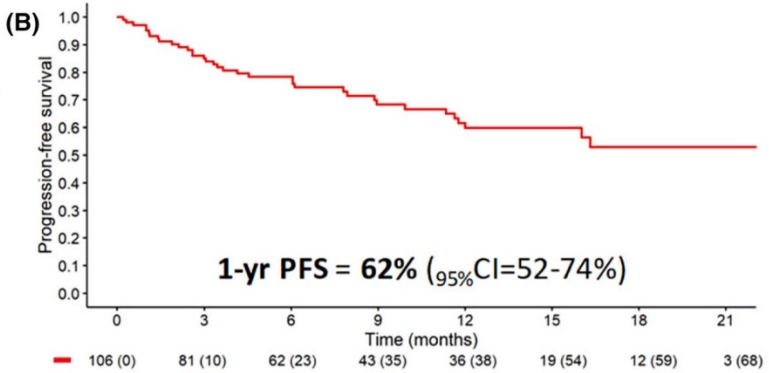
Day 90 ORR 77% (CR 70%); median follow-up = 12.1 months (IQR: 6, 18)





Pre-lymphodepletion LDH and PLT levels were shown to be associated with both PFS & OS; response to bridging didn't impact survival

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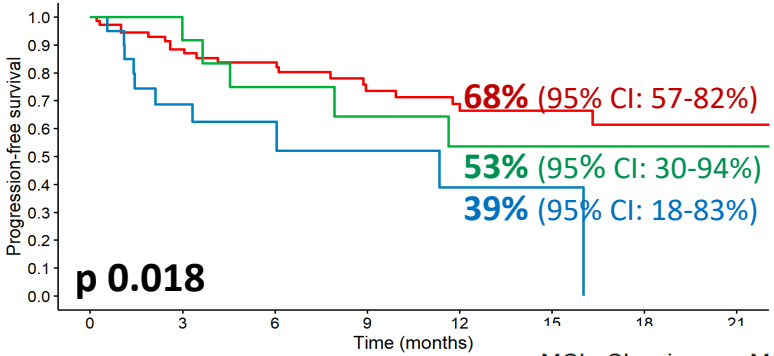
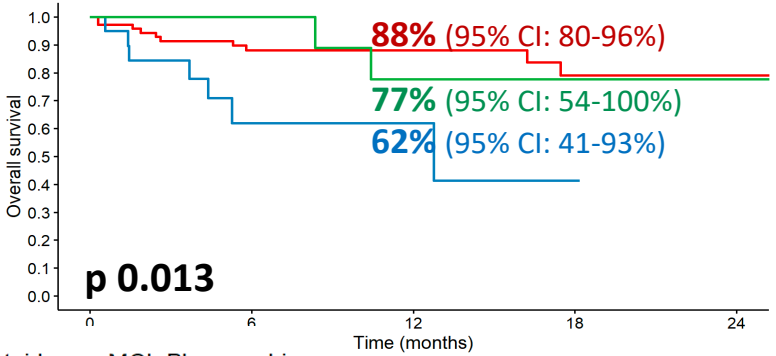
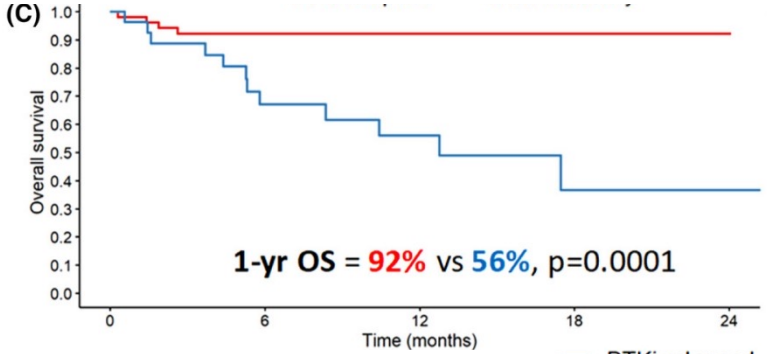
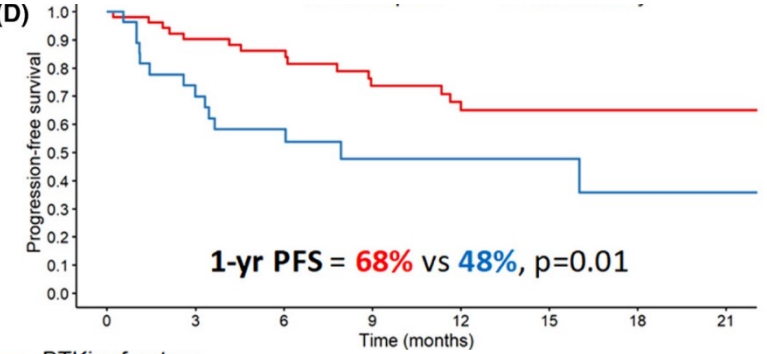
BTKi-refractoriness and blastoid/pleomorphic variant were associated with shorter PFS & OS





MCL_Classic MCL Blastoid MCL Pleomorphic





BTKi relapsed BTKi refractory

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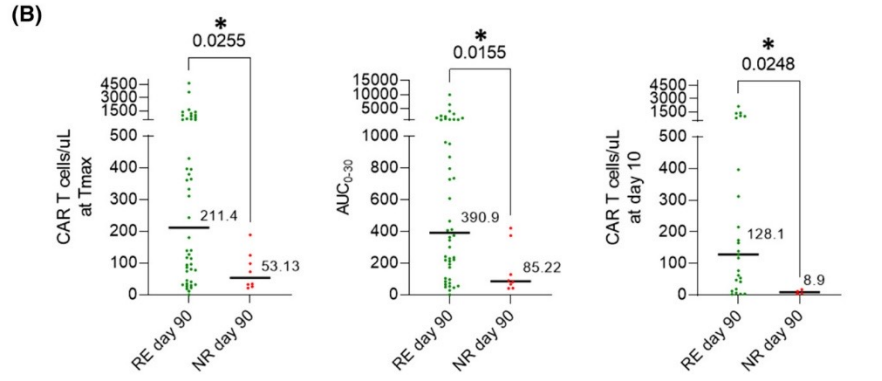
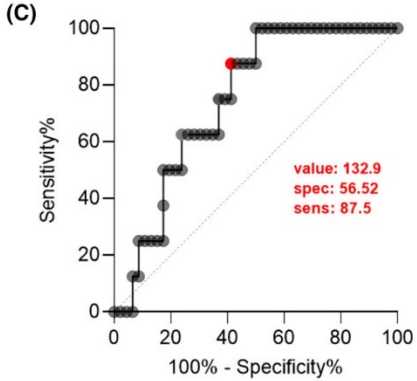
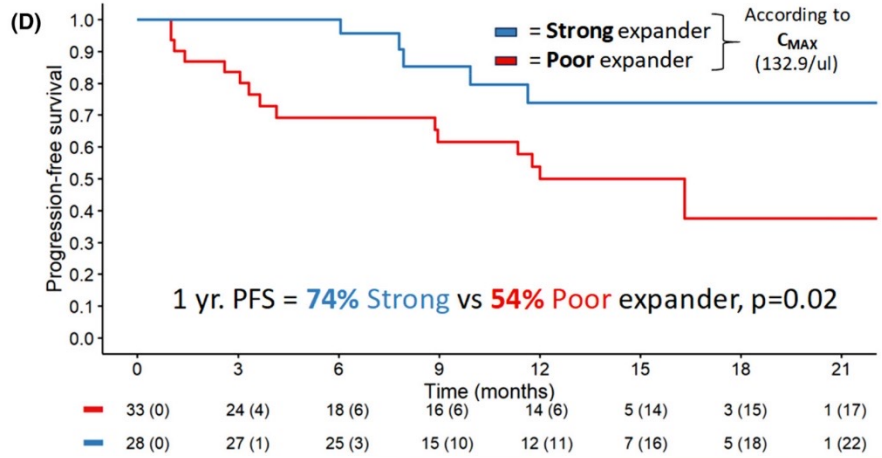
CAR-T cells expansion data available in 57%.

- Responders (CR/PR) at day 90 had higher C10/Cmax/AUC CAR-T cells levels
- Strong expansion = Cmax > 132.9 CAR+/ul was an independent predictor of longer PFS
- Bridging therapy negatively impacted expansion







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Conclusions

- ✓ Real life studies have reproduced similar efficacy and safety results as compared to ZUMA-2
- ✓ Variables negatively impacting PFS and OS differed across studies, including high-risk sMIPI, high ki-67, CRP, ferritine and LDH levels, TP53 aberrations, blastoid/pleomorphic variant, recent exposure to Bendamustine, manufacturing failure
- ✓ strong CAR-T cells expansion predicts longer PFS
- ✓ Rates of drop-out during ”brain to vein” time is probably underestimated (drop-out after approval 30% in UK, after apheresis = globally 11-20%) which underlines the need for a better and early patient selection for a successful treatment