LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

Milano, Hilton Milan Hotel
27 gennaio 2025

Responsabili Scientifici
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Quali Strategie per il «Bridging»

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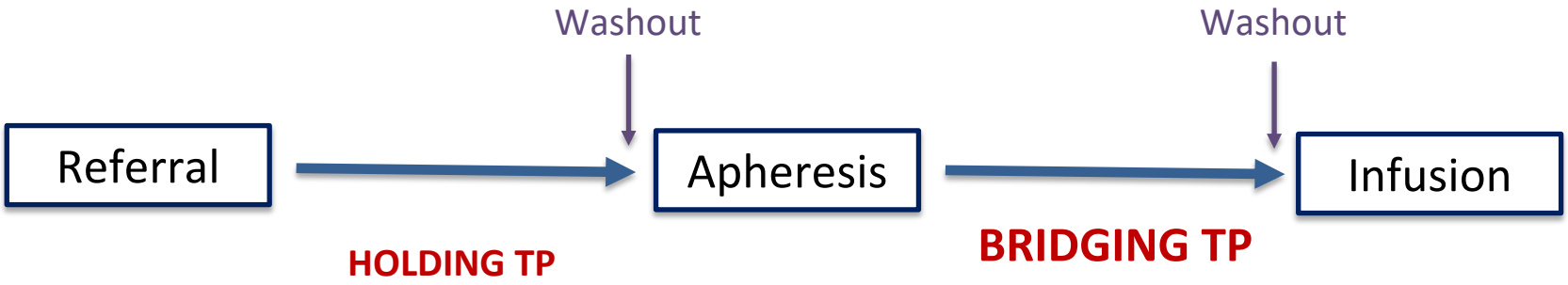
Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite-Gilead					x	x	
Novartis					x		x
Celgene-BMS						x	
Abbvie					x	x	
Janssen					x	x	
Lilly					x		
Beigene						x	
Roche					x	x	
Incyte							x
Takeda						x	

Bridging Therapy - The Balance Between Efficacy and Toxicity



Low toxicity (Ly ≥ 100/mmc)
T-cell fitness (no Benda)
Effective

Low toxicity (Plt, PMN, infection, organ failure)
Effective (able to reduce the tumor burden → LDH, MTV, CR/PR..)

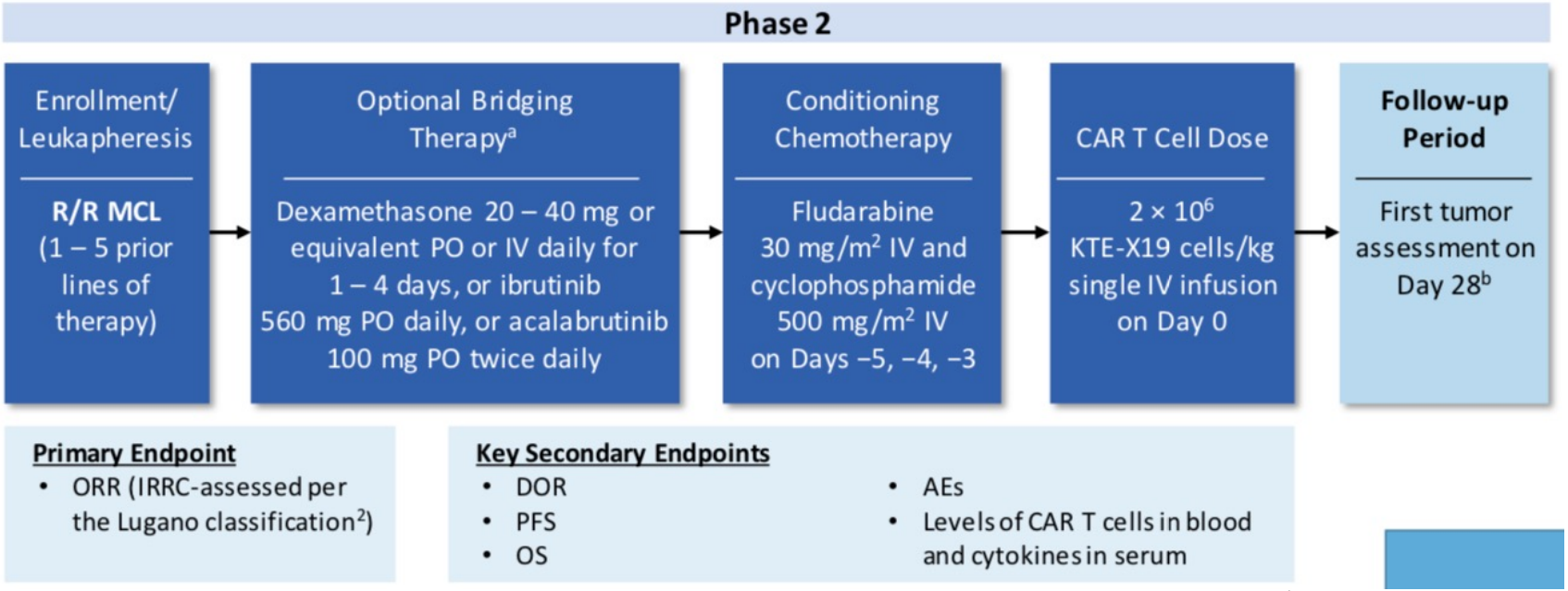
Bridging Therapy - The Balance Between Efficacy and Toxicity

- Which pts benefit from BT?
- How to choose the best BT?

- Predict time to CAR T-cell infusion
- Disease burden
- Prior treatment
- Comorbidities
- Potential toxicity

Chemotp +/- Immunotp +/- Small molecules +/- RT +/- Steroids

Bridging Therapy – ZUMA 2



a. BT therapy may be considered for any subject, particularly those with high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1000 leukemic phase mantle cells/mm3 in the peripheral circulation); BT has to be completed ≤ 5 days before initiating LD, PET-CT was require post BT.

Modified from Wang ML, Abs 1120 ASH2020

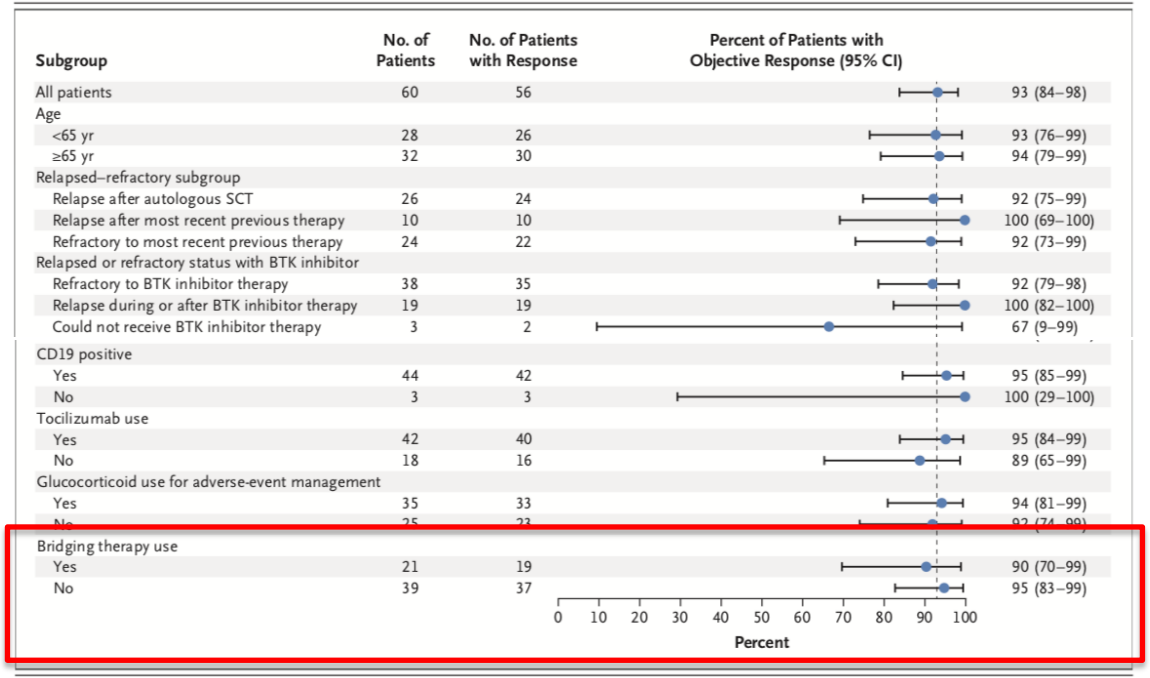
Bridging Therapy – ZUMA 2

Table S3. Bridging Therapies

Characteristic	N = 68
Any bridging therapy, n (%)	25 (37)
Ibrutinib*	14 (21)
Acalabrutinib†	5 (7)
Dexamethasone	12 (18)
Methylprednisolone	2 (3)
Both BTKi and corticosteroids, n (%)	6 (9)
Ibrutinib + corticosteroid	4 (6)
Acalabrutinib + corticosteroid	2 (3)

* Of the 14 patients who received ibrutinib, 9 were refractory to prior ibrutinib and 1 was refractory to prior acalabrutinib.
† Of the 5 patients who received acalabrutinib for bridging, 1 was refractory to prior ibrutinib, and 3 were refractory to prior acalabrutinib.

«The majority of the 17 pts who had assessments both before and after BT had an increase in the median tumor burden after the receipt of BT».



Wang ML et al, N Engl J Med 2020;382:1331-42.

Bridging Therapy – TRANSCEND 001

Leukapheresed ITT set
(N = 104)

Did not receive CAR T cells[a] (n = 12)
Died[b] (n = 9)
No longer met eligibility criteria[c] (n = 3)

Received nonconf

No PET-positive di
baseline

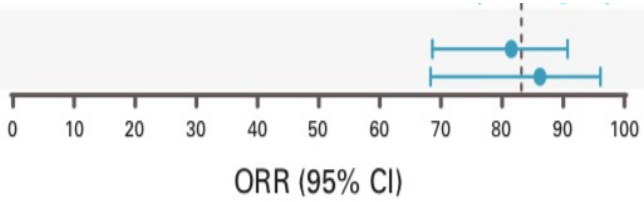
No PET scan repea
therapy

Primary analysis set[c] (n = 74)

Cel–Treated
(N = 88)
(66)
(71)
(5)
(24)

A

Characteristic	Evaluable Patients (n)	Patients With Objective Response (n)	ORR (95% CI)
Bridging therapy			
Yes	54	44	81.5 (68.6 to 90.7)
No	29	25	86.2 (68.3 to 96.1)



Wang M et al, J Clin Oncol 2023;42:1146-1157

Bridging Therapy – RWE: US Lymphoma CART Consortium

Bridging Therapy	All Patients Who Underwent Leukapheresis[a] (N = 189)
Total, No.	128
BTKi-based, No.	31
BTKi with or without steroid	17
BTKi + CD20 mAb with or without steroid	6
BTKi + chemo with or without CD20 mAb	5
BTKi + radiation with or without CD20 mAb with or without steroid	3
Venetoclax-based, No.	10
Venetoclax with or without CD20 mAb	9
Venetoclax + chemo with or without CD20 mAb	1
BTKi + venetoclax-based, No.	17
BTKi + venetoclax with or without CD20 mAb with or without steroid	13
BTKi + venetoclax + R-chemo	1
BTKi + venetoclax + radiation with or without steroid	3
Chemo with or without CD20 mAb with or without steroid, No.	38
Chemo with or without CD20 mAb + radiation with or without steroid, No.	6
Lenalidomide-based, No.	6
Lenalidomide with or without CD20 mAb	3
Lenalidomide + radiation with or without CD20 mAb with or without steroid	2
Lenalidomide + R-chemo	1
Radiation with or without steroid with or without CD20 mAb, No.	12
Steroid and/or CD20 mAb, No.	8

68%

Response to bridging therapy, No. (%)	
CR	6 (6)
PR	26 (27)
SD	26 (27)
PD	37 (39)
Not assessed/unknown	33

ORR: 33%

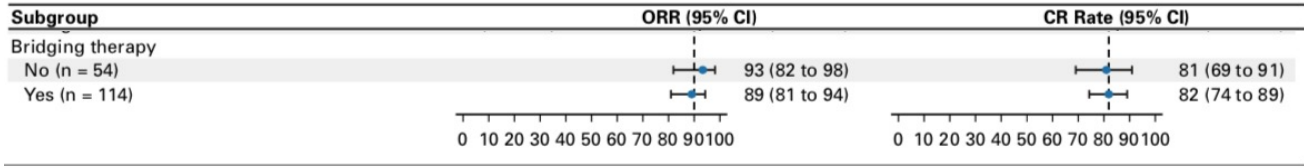
Wang Y, J Clin Oncol 2022; 41:2594-2606.

Bridging Therapy – RWE: US Lymphoma CART Consortium

Characteristic	No Bridging Therapy (n = 54)	Bridging Therapy (n = 114)	*P* Value
Age, years, median (range)	67.5 (49-82)	67 (34-89)	.866
ECOG PS ≥ 2, No. (%)	2 (4)	16 (14)	.059
Simplified MIPI, No. (%)			.104
Low risk (0-3)	23 (43)	32 (28)	
Intermediate risk (4-5)	26 (48)	61 (54)	
High risk (6-11)	5 (9)	21 (18)	
Ki-67, No. (%)			.002
< 30%	17 (36)	17 (16)	
30%-49%	13 (28)	19 (18)	
≥ 50%	17 (36)	69 (66)	
Blastoid/pleomorphic, No. (%)	13 (24)	55 (48)	.003
TP53 aberration, No. (%)	9 (22)	52 (61)	< .001
Complex karyotype, No. (%)	6 (15)	25 (35)	.023
Prior lines of therapy	3 (1-10)	3 (1-10)	.510
POD24, No. (%)	24 (44)	63 (55)	.190

Wang Y, J Clin Oncol 2022; 41:2594-2606.

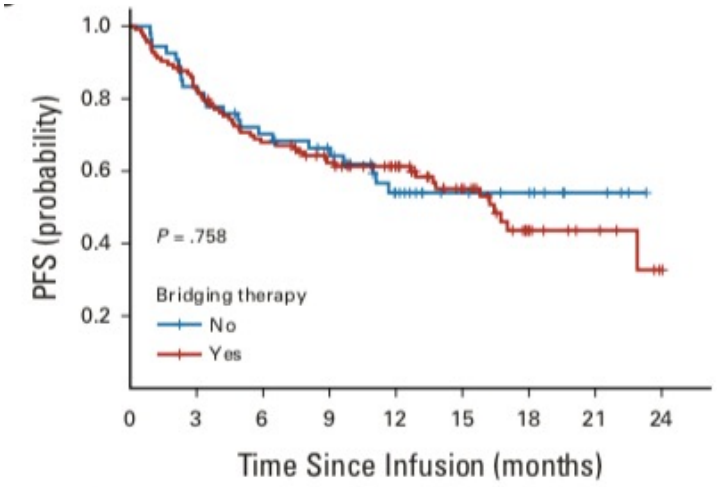
Bridging Therapy – RWE: US Lymphoma CART Consortium



		Grade 3 CRS		Grade 3 ICANS	
Characteristic	**No.**	**No. (%)**	***P***	**No. (%)**	***P***
ZUMA-2 eligibility			.196		.795
Eligible	39	1 (3)		11 (28)	
Ineligible, BTKi- or anthracycline-/ bendamustine-naïve	26	1 (4)		8 (31)	
Ineligible, disease status or comorbidities	103	11 (11)		35 (34)	
Bridging therapy			1.000		.009
No	54	4 (7)		10 (19)	
Yes	114	9 (8)		44 (39)	

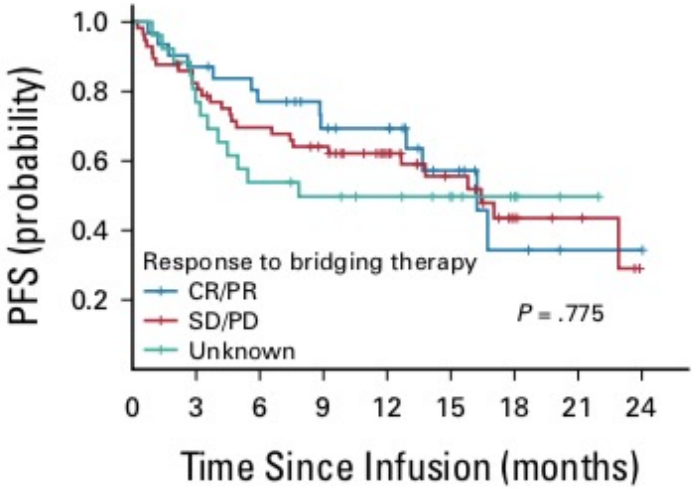
Wang Y, J Clin Oncol 2022; 41:2594-2606.

Bridging Therapy – RWE: US Lymphoma CART Consortium



No. at risk:

No	54	45	37	31	18	11	9	4	0
Yes	114	93	75	63	49	30	13	6	1



No. at risk:

CR/PR	31	27	23	18	16	8	3	1	1
SD/PD	57	46	38	33	23	15	6	4	0
Unknown	26	20	14	12	10	7	4	1	0

Wang Y, J Clin Oncol 2022; 41:2594-2606.

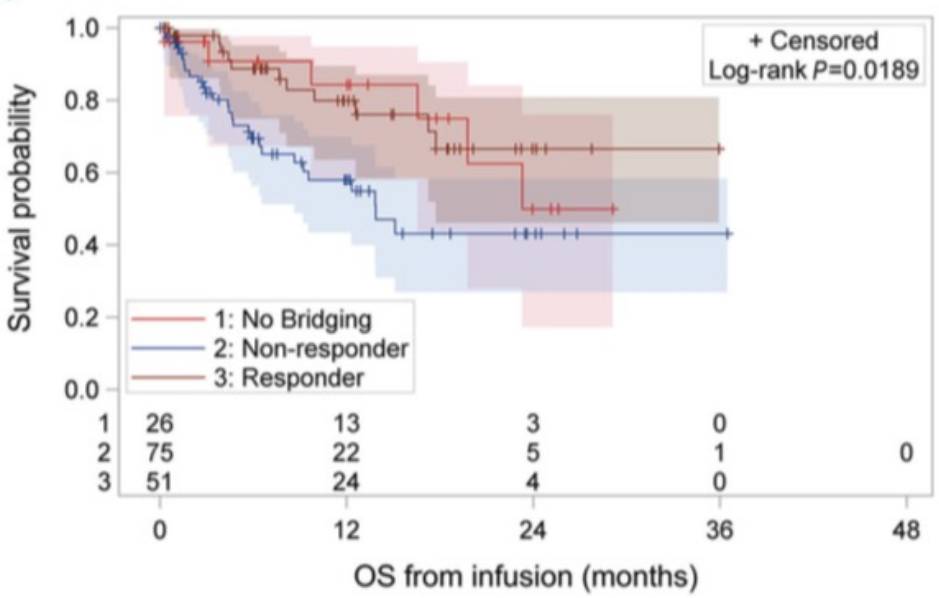
Bridging Therapy – RWE: DESCART

	Patient without bridge or holding N=27		Patients with bridge only N=63		Patients with holding then bridge N=62	
Number or prior lines of therapy**						
Median (min ; max)	3.0 (2 ; 8)		3.0 (2 ; 9)		3.0 (1 ; 6)	
Prior autologous transplant	8	(29.6%)	23	(36.5%)	29	(46.8%)
Previous BTK inhibitor therapy						
IBRUTINIB	25	(92.6%)	61	(96.8%)	54	(87.1%)
ACALABRUTINIB	2	(7.4%)	2	(3.2%)	0	(0.0%)
ZANUBRUTINIB	0	(0.0%)	0	(0.0%)	0	(0.0%)
Bridging therapy	0	(0.0%)	63	(100.0%)	62	(100.0%)
Type of treatment***						
Monoclonal antibody	0	-	45	(71.4%)	37	(59.7%)
Other immunotherapy	0	-	0	(0.0%)	0	(0.0%)
Chemotherapy	0	-	43	(68.3%)	34	(54.8%)
Radiotherapy	0	-	6	(9.5%)	4	(6.5%)
IMiD	0	-	5	(7.9%)	5	(8.1%)
Epigenetic modifiers agents	0	-	0	(0.0%)	0	(0.0%)
Kinase inhibitor	0	-	12	(19.0%)	24	(38.7%)
Corticosteroids	0	-	8	(12.7%)	5	(8.1%)
Other anti-cancer therapy	0	-	14	(22.2%)	21	(33.9%)
Disease status before CAR-T infusion						
Complete Response	0	-	6	(9.5%)	9	(14.5%)
Partial Response	0	-	15	(23.8%)	21	(33.9%)
Stable Disease	0	-	9	(14.3%)	8	(12.9%)
Progressive Disease	0	-	29	(46.0%)	19	(30.6%)
Not Evaluated	0	-	4	(6.3%)	4	(6.5%)
Missing	0	-	0	(0.0%)	1	(1.6%)

126/152 (83%)

Herbaux C, Hematologica 2024.

Bridging Therapy – RWE: DESCART



	Subjects	Event	Censored	Median survival (95% CI)
No Bridging	26	23.1 % (6)	76.9 % (20)	23.3 (16.6 - NA)
Non-responder	75	37.3 % (28)	62.7 % (47)	13.9 (8.6 - NA)
Responder	51	21.6 % (11)	78.4 % (40)	Not reached (17.7 - NA)

The need of BT and the response after it are significantly associated with OS from infusion (OS at 12 mo: 58% vs 80% vs 84%)

Herbaux C, Hematologica 2024.

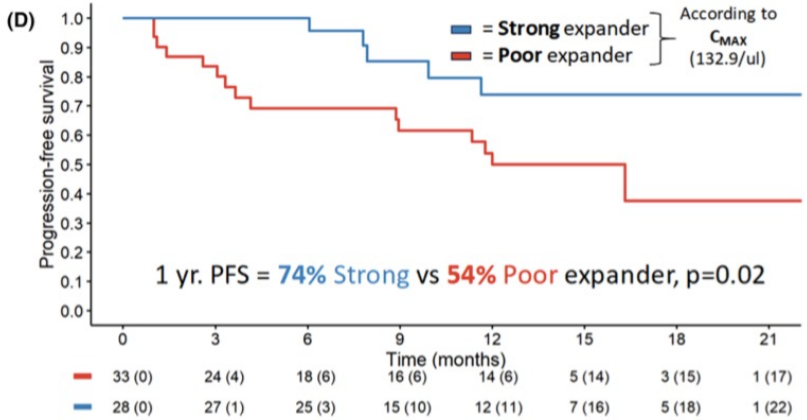
Bridging Therapy – RWE: CART-SIE

	Global population N=106pts.	**In vivo expansion** N=61pts.
BTKi	37	23
Bendamustine	11	4
Venetoclax	11	6
Immuno-chemotherapy	15	10
Radiotherapy	4	3
IMiDS	5	1
No bridging	23	14
No response	68 (72%)	41(67%)

Stella F, et al. Br J Hematol 2025.

Bridging Therapy – RWE: CART-SIE

C_{MAX}	Odds-ratio	95%CI	p-value
Histology (Blastoid)	0.34	0.04-2.05	0.2
MIPI (High)	0.23	0.04-1.03	0.03
Bridging (Yes)	0.23	0.03-0.88	0.03
AUC_{0-30}	**Odds-ratio**	**95%CI**	**p-value**
MIPI (High)	0.2	0.05-0.74	0.02
Bridging (Yes)	0.1	0.02-0.48	0.002



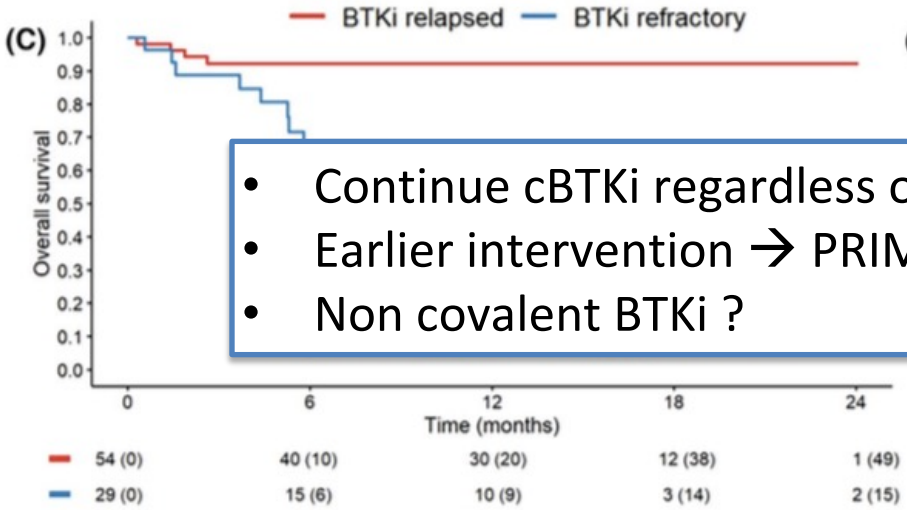
BT correlated with the in vivo expansion of CAR T-cells

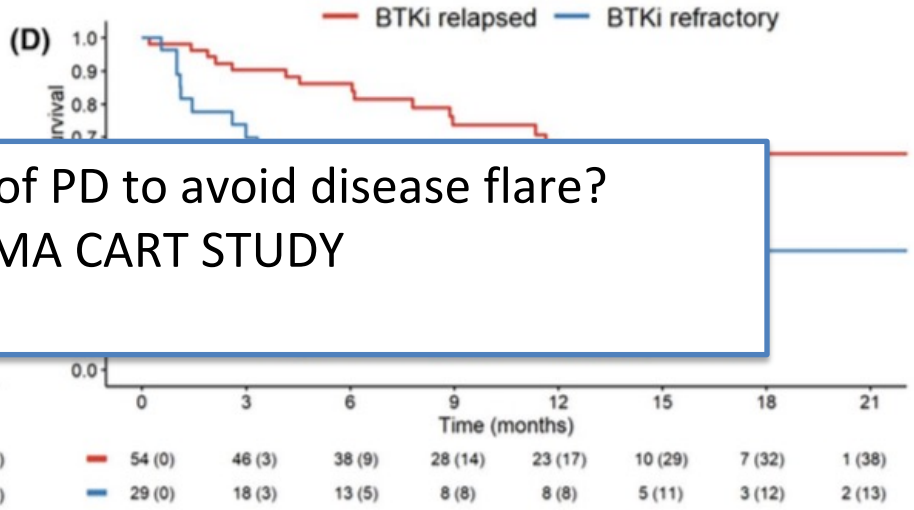
Stella F, et al, Br J Hematol 2025.

Conclusions

- No standard approach for BT, in particular in cBTKi refractory patients
- RT provides rapid cytoreduction and has retained efficacy for chemorefractory disease. Moreover has known immunomodulatory properties, raising the possibility of immune synergy with CAR T → can be an option for localized bulky disease
- Non–cross-reactive immunochemotherapy? Although R-BAC is a valuable third-line option after covalent BTKi, use of bendamustine before/after apheresis is generally discouraged.
- Other experimental non-chemotherapeutic approaches (Zilovertamab? Glofitamab?)

Conclusion – is continuing with covalent BTK a good option?





- Continue cBTKi regardless of PD to avoid disease flare?
- Earlier intervention → PRIMA CART STUDY
- Non covalent BTKi ?

Stella F, et al, Br J Hematol 2025.

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