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UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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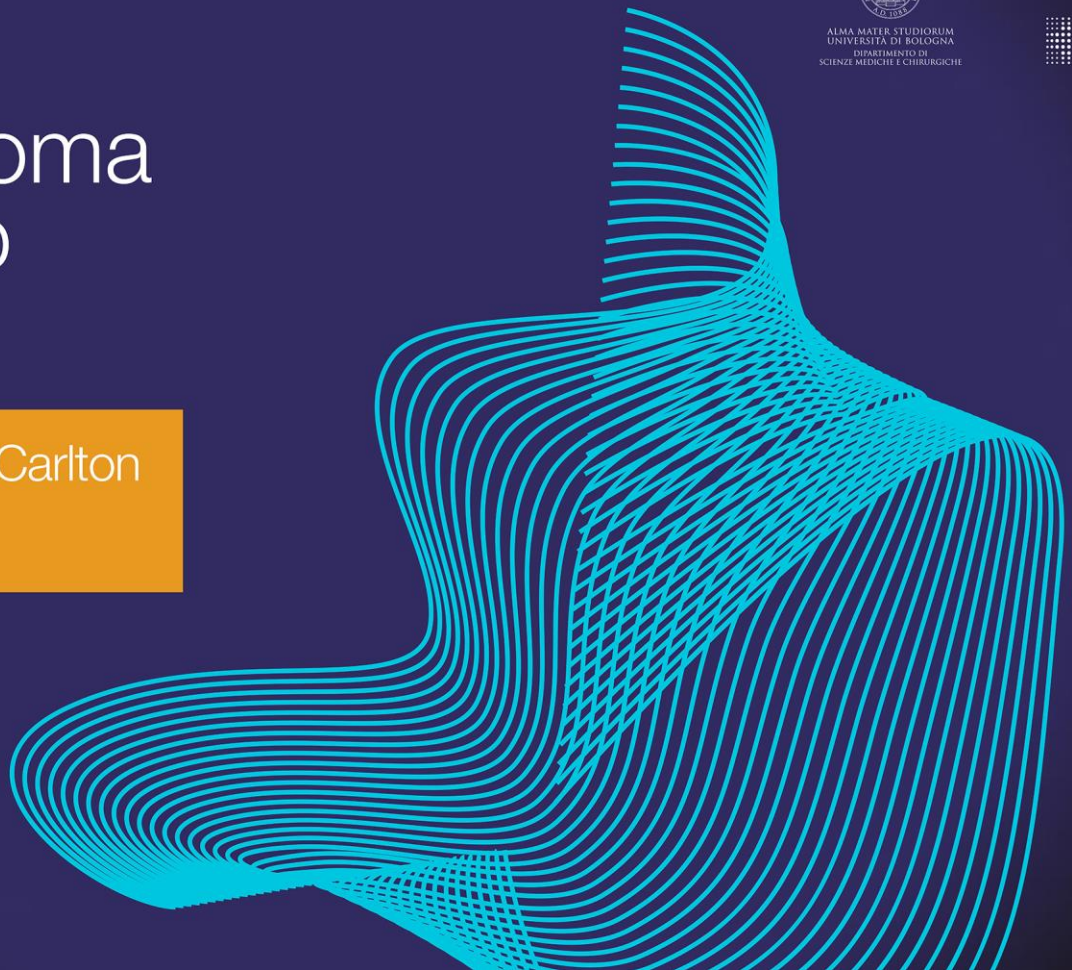
Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

CAR-T as 3rd-line or Later Therapy of Large B-Cell Lymphomas: JULIET Study

Coat of arms of Bologna

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Coat of arms of UPenn

Disclosures

Disclosures of Prof. Stephen J. Schuster, M.D.

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						X	
AstraZeneca						X	
BeiGene						X	
Caribou Biotech						X	Steering committee
Fate Therapeutics							Safety DSMB
Genentech/Roche	X					X	Steering committee
Genmab	X					X	Steering committee
Incyte/Morphosys						X	Honoraria for presentation
Kite Pharmaceuticals						X	
Legend Biotech						X	Steering committee
Novartis						X	Steering committee
Mustang Biotech						X	
Nordic Nanovector						X	Steering committee
Takeda							Honoraria for presentation

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) **Timing of CAR-T Therapy**
   - *second- vs. third-line outcomes*
   - *disease status at the time of CAR-T and its impact on outcome*
2) **Lymphodepletion before CAR-T Infusion**
   - *is fludarabine-cyclophosphamide required?*
3) **Response Assessments after CAR-T Infusion**
   - *timing of response assessments and outcomes*
4) **Immune Reconstitution**
   - *is persistent B-cell aplasia necessary for PFS in NHL?*
5) **CAR-T Products: R-WE**

Disclaimers: These impressions are based on my own personal experiences and observations in the clinical research and practice settings, as well as on impressions gained from the literature and from discussions with other clinicians and investigators. These opinions should not be considered as dogma, but rather as current impressions that may require further validation through additional experience and formal clinical investigation.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) Timing of CAR-T Therapy

- second- vs. third-line outcomes

Patient Characteristics in the Pivotal Trials of Axi-cel

Variable	ZUMA-1 (axi-cel)	ZUMA-7 (axi-cel group)
Primary end point	Overall response rate	Event-free survival
Patient characteristics		
No. of patients	111 (total cohort) 101 (infused cohort)	180
Median age (range) — yr	58 (23–76)	58 (21–80)
Age ≥65 years — no. (%)	24 (24)	51 (28)
Study eligibility		
Disease status	Refractory or relapse ≤12 mo after ASCT; no impending organ compromise	Refractory or relapse at ≤12 mo, ASCT-eligible; no impending organ compromise
Bridging therapy	Glucocorticoids only	Glucocorticoids only (36% received)
CD19-positive — no./total no. (%)	74/82 (90)	144/180 (80)

Variable	ZUMA-1 (axi-cel)	ZUMA-7 (axi-cel group)
Histologic type		
DLBCL, NOS — no. (%)	77 (76)	126 (70)
HGBL, DH — no./total no. (%)	NR	31/180 (17)
HGBL, NOS — no. (%)	0	0
FL grade 3B — no. (%)	0	0
PMBL — no. (%)	8 (8)	0
Other or missing — no. (%)	0	23 (13)
Transformed lymphoma — no. (%)	16 (16)	19 (11)
Disease status at study entry		
Refractory to any therapy	80 (79) *	133 (74)
Relapsed	21 (21)	47 (26)
Previous ASCT	21 (21)	NA

Variable	ZUMA-1 (axi-cel)	ZUMA-7 (axi-cel group)
Progressive disease before CAR T-cell therapy — no. (%)	1 (1)	2 (1)
Received CAR T-cell infusion — no. (%)	101 (91)	170 (94)
Median time from enrollment to CAR T-cell infusion — days	Approx. 17	29
CAR T-cell dose	2×10^6 cells/kg	2×10^6 cells/kg
Clinical outcomes		
Response — %	82	83
Complete response — %	54	65
Median follow-up — months	27.1	25
2-Yr progression-free survival — %	Approx. 40	46
2-Yr overall survival — %	51	61

*** In ZUMA-1, only 2 (3%) patients were primary refractory**; 59 (77%) patients were refractory to ≥ second-line therapy.

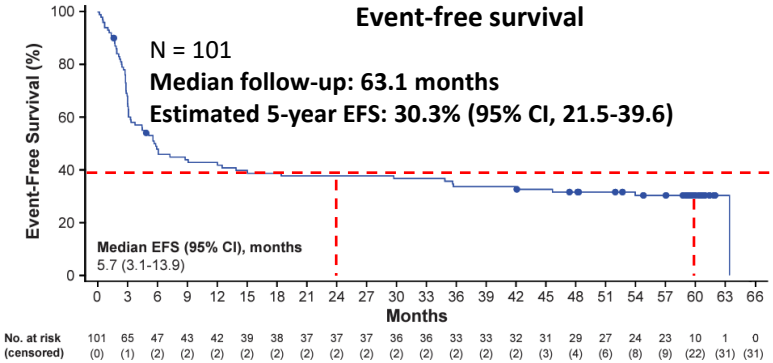
Table adapted from:
Roschewski et al. N Engl J Med. 2022;386(7):692-696.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) Timing of CAR-T Therapy

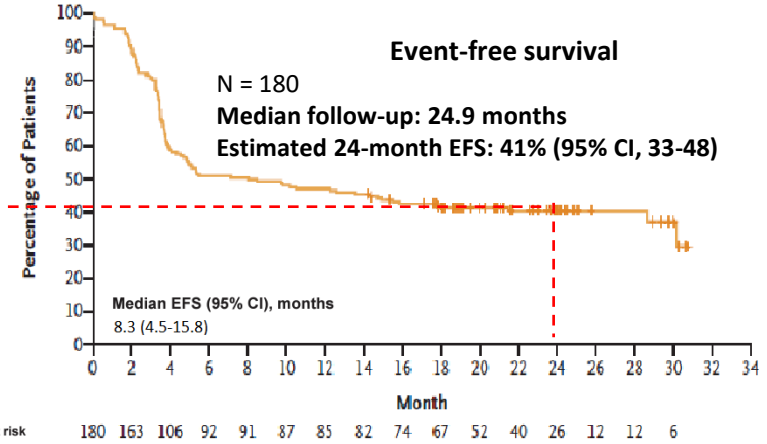
- second- vs. third-line outcomes

ZUMA-1[1,2]: axi-cel as ≥ 3rd-line therapy for LBCL refractory to second or later therapy, relapsed ≤ 12 months after ASCT, or primary refractory



EFS, time from axi-cel infusion until disease progression, initiation of new anticancer therapy, excluding stem-cell transplantation, or any-cause death. Median time from enrollment to CAR T-cell infusion was approximately 17 days.

ZUMA-7[3]: axi-cel as 2nd-line therapy for primary refractory or relapsed ≤ 12 months of 1st therapy



EFS, time from randomization to disease progression, initiation of new anticancer therapy, any-cause death from, or best response of stable disease at day 150 assessment. Median time from enrollment to CAR T-cell infusion was approximately 29 days.

[1]Neelapu SS, et al. N Engl J Med. 2017;377(26):2531-2544; [2]Neelapu SS, et al. Blood. 2023;Epub ahead of print; [3]Locke FL, et al. N Engl J Med. 2022;386(7):640-654.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) Timing of CAR-T Therapy

- second- vs. third-line outcomes

Patient Characteristics in the Pivotal Trials of Liso-cel

TRANSCEND NHL 001[1]: liso-cel as ≥ 3rd-line therapy for LBCL relapsed after or refractory to second or later therapy

TRANSFORM[2]: liso-cel as 2nd-line therapy for primary refractory or relapsed within ≤ 12 months of 1st therapy

	TRANSCEND (≥ 3rd-line)[1]	TRANSFORM (2nd-line)[2,3]
Sample size	N = 177 (*dose level 2**)	N = 92
Age in years, median (range)	63 (18-79)	60 (20-74)
Age ≥ 65 years	71 (40%)	36 (39%)
Diagnosis DLBCL NOS	94 (53%)	53 (58%)
Sum of product diameter, cm^2	***median* 22.6 (IQR, 9.1–67.2)**	***median* 11.4 (range, 1-120)**
Sum of product diameter ≥ 50 cm^2	**48 (27%)**	**10 (11%)**
Pre-LDC LDH ≥ 500 U/L	**36 (20%)**	**10 (11%)**
Chemotherapy-refractory	**123 (69%)****	**25 (27%)*****

*Dose level 2: 100 × 10^6 CAR^+ T cells (50 × 10^6 $CD8^+$ and 50 × 10^6 $CD4^+$ CAR^+ T cells)

**Includes primary refractory disease and relapsed, refractory disease (*i.e.*, refractory to subsequent lines of treatment)

***Chemotherapy refractory is defined as SD or PD to last chemotherapy containing regimen prior to liso-cel

[1]Abramson, et al. Lancet. 2020;396(10254):839-852; [2]Kamdar, et al. Lancet. 2022; 399: 2294-308; [3]Abramson, et al. Blood. 2023; 141(14):1675-1684.

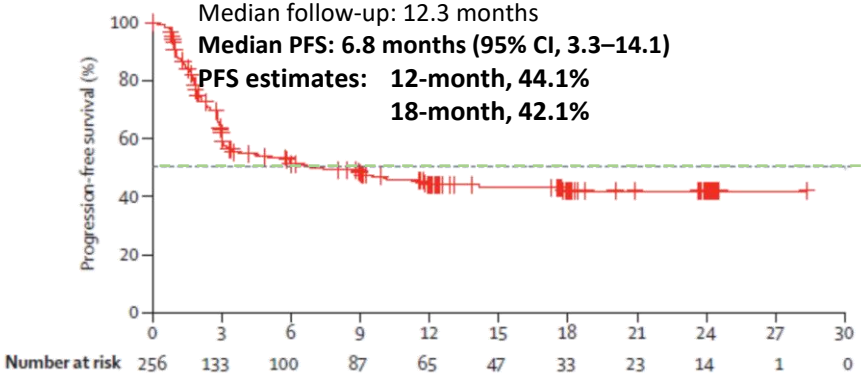
CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) Timing of CAR-T Therapy

- second- vs. third-line outcomes

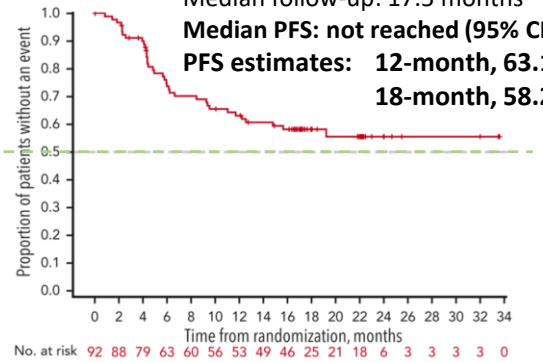
TRANSCEND NHL 001[1]: liso-cel as ≥ 3rd-line therapy for LBCL relapsed after or refractory to second or later therapy

Progression-free survival
N = 256
Median follow-up: 12.3 months
Median PFS: 6.8 months (95% CI, 3.3–14.1)
PFS estimates: 12-month, 44.1%
18-month, 42.1%



TRANSFORM[2]: liso-cel as 2nd-line therapy for primary refractory or relapsed within ≤ 12 months of 1st therapy

Progression-free survival
N = 92
Median follow-up: 17.5 months
Median PFS: not reached (95% CI, 12.6–NR)
PFS estimates: 12-month, 63.1%
18-month, 58.2%



PFS, time from randomization to PD, or death from any cause, whichever occurs first.

[1]Abramson et al. Lancet. 2020;396(10254):839-852; [2]Abramson, et al. Blood. 2023; 141(14):1675-1684.

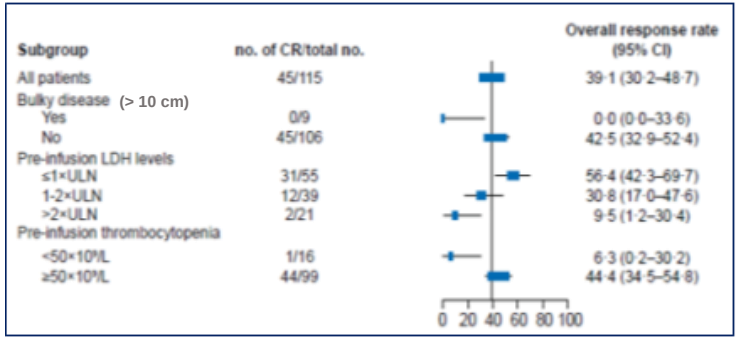
CAR-T as 3rd-line or Later Therapy: Lessons from JULIET

1) Timing of CAR-T Therapy: *disease status at infusion and outcome*

JULIET: Multivariable and Subgroup Analyses

Multivariable analysis		
Predictive Factors from Univariable Analysis	**Responders/Patients**	**Odds Ratio (95% CI)**
LDH		
≤ x ULN	**29/55**	**2.74 (0.71-10.56)**
>2 x ULN	**4/21**	
>1 - 2 x ULN	**11/39**	**0.97 (0.23-4.06)**
>2 x ULN	**4/21**	
Thrombocytopenia		
CTCAE grades 0 - 2	**43/99**	**7.23 (0.84-62.31)**
CTCAE grades 3 - 4	**1/16**	

- **Lab analytes are defined as the closest time before or on the day of infusion**
  - **93% of values fell on the day of infusion**
- **Thrombocytopenia: grade 4, <25; grade 3, 25-50; grade 2, 50-75; grade 1, 75-LLN × 10^9/L**



Univariable Factors Analyzed	
• LDH (≤1 × ULN vs >2 × ULN)	• IFNγ
• LDH (>1–2 × ULN vs >2 × ULN)	• IL10
• CRP (high vs low/normal)	• IL12
• Platelets at baseline (grade 0–2 vs grade 3/4)	• P70
• Lymphocytes before LD chemo. (grade 3/4 vs grade 0)	• IL6
• Lymphocytes before LD chemo. (grade 1/2 vs grade 0)	• IL8
• Ferritin (high vs low/normal)	• IL13
• ECOG PS (0 vs 1)	• TNFα
• Age group (<65 years ≥65 years)	
• Metabolic tumor volume (<100 vs ≥100 mL)	
• IPI risk (≥2 vs <2 risk factors)	

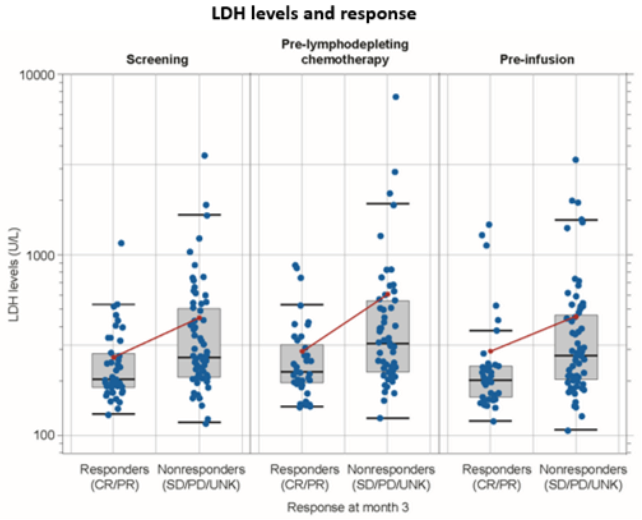
Schuster SJ, *et al*. Lancet Oncol. 2021;22(10):1403-1415.

CAR-T as 3rd-line or Later Therapy: Lessons from JULIET

1) Timing of CAR-T Therapy

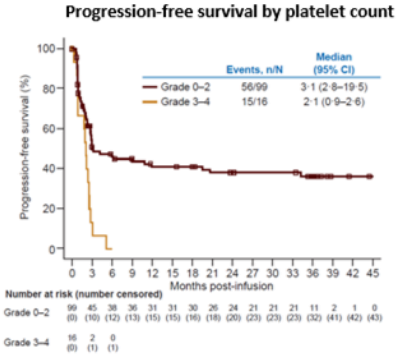
- disease status at the time of CAR-T and outcome

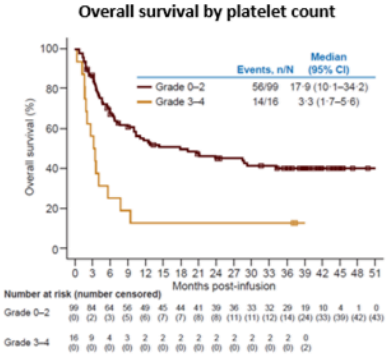
LDH Level



- **The horizontal line within each box represents the median, the lower and upper borders of each box represent the IQR, and the horizontal lines outside each box show the range (excluding outliers).**
- **Red lines denote mean values.**

Platelet Count



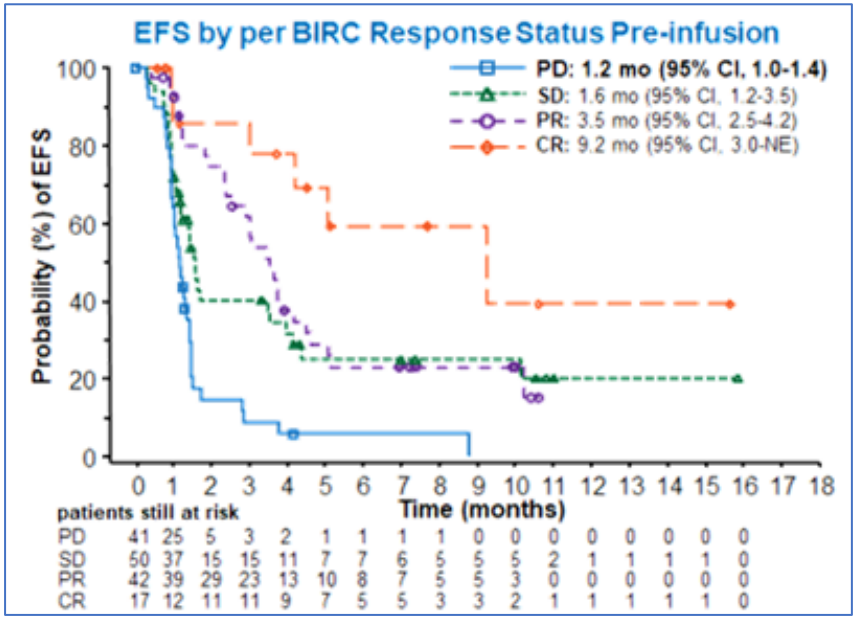


Schuster SJ, *et al. Lancet Oncol.* 2021;22(10):1403-1415.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

1) Timing of CAR-T Therapy

- disease status at the time of CAR-T and outcome



Multivariate Logistic Regression Model for Post-Infusion Best Overall Response (CR/PR vs SD/PD/UNK) in Arm A (second-line CAR-T)

	Odds Ratio Estimates		
Variable	Point Estimate	95% Wald Confidence Limits	
CR/PR before infusion vs. SD/PD before infusion at mean cell dose	7.75	3.23	18.62

The odds ratio is the odds of having a best overall response of CR/PR vs. SD/PD/UNK; *i.e.*, an odds ratio >1 means patients are more likely to have a best overall response of CR/PR.

Bishop *et al.* LBA-6. ASH 2021;
Bishop *et al.* N Engl J Med. 2021 Dec 14. Epub

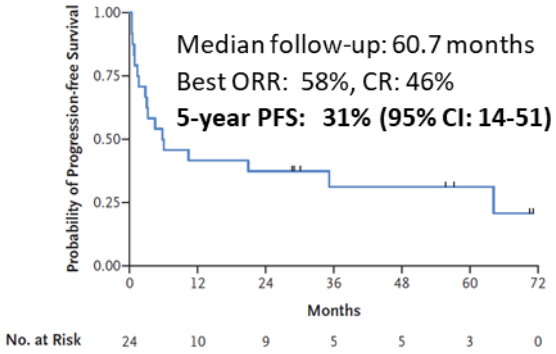
EFS time is relative to date of tisagenlecleucel infusion; median time from pre-infusion disease assessment to infusion was 10 days (range, 2-57; Q1-Q3, 8-15).
EFS events defined as PD/SD after day 71 from randomization or death at any time.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

2) Lymphodepletion before CAR-T Infusion

- is fludarabine-cyclophosphamide required?

UPenn CTL019 trial



Median follow-up: 60.7 months
Best ORR: 58%, CR: 46%
5-year PFS: 31% (95% CI: 14-51)

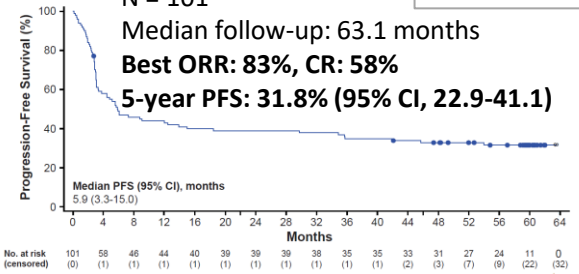
Lymphodepletion Regimens	% use
Bendamustine 70-90 mg/m2 x 2 days	42%
Cyclophosphamide 1 g/m2 bolus	8%
Cyclophosphamide 300 mg/m2 q12 hours x 6 doses	16%
Cyclophosphamide 300 mg/m2/24 hours x 4 days	3%
Radiation 2200-4000 cGy + cyclophosphamide 750mg/m2	8%
Radiation 400 cGy + cyclophosphamide 1g/m2	5%
EPOCH-like (etoposide 50 mg/m2/24 hours x 3-4 days, doxorubicin 10 mg/m2/24 hours x 3-4 days, vincristine 0.5 mg/m2/24 hours x 3-4 days, cyclophosphamide 750 mg/m2 bolus)[1]	13%
Cyclophosphamide 250 mg/m2 + fludarabine 25 mg/m2 x 3 days	3%
Carboplatin 375 mg/m2 + gemcitabine 750 mg/m2	3%

Chong EA, Ruella M, Schuster SJ. N Engl J Med 2021;384(7):673-674.

Zuma-1 trial

Lymphodepletion Regimen
Cyclophosphamide-Fludarabine
(500 mg/m² - 30 mg/m² daily x 3 days)

N = 101
Median follow-up: 63.1 months
Best ORR: 83%, CR: 58%
5-year PFS: 31.8% (95% CI, 22.9-41.1)



Neelapu SS, et al. Blood. 2023; Epub ahead of print

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

2) Lymphodepletion before CAR-T Infusion

- is fludarabine-cyclophosphamide required?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas

G. Ghilardi[1,2,3†], E. A. Chong[1,2,3†], J. Svoboda[1,2,3], P. Wohlfarth[4], S. D. Nasta[1,3], S. Williamson[5], J. D. Landsburg[1,3], J. N. Gerson[1,3], S. K. Barta[1,2,3], R. Pajarillo[1,2,3], J. Myers[5], A. I. Chen[5], L. Schachter[5], R. Yelton[1,2], H. J. Ballard[1,3], A. Hodges Dwinal[5], S. Gier[2,3], D. Victoriano[2,3], E. Weber[1,3], E. Napier[1,3], A. Garfall[2,3], D. L. Porter[1,3], U. Jäger[4], R. T. Maziarz[5], M. Ruella[1,2,3†] & S. J. Schuster[1,2,3*†]

[1]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia; [2]Center for Cellular Immunotherapies and Cellular Therapy and Transplant, University of Pennsylvania, Philadelphia; [3]Division of Hematology-Oncology, Hospital of the University of Pennsylvania, Philadelphia, USA; [4]Medical University of Vienna, Division of Hematology and Hemostaseology, Department of Medicine I Wien, Comprehensive Cancer Center, Vienna, Austria; [5]Oregon Health & Science University Knight Cancer Institute, Adult Blood and Marrow Stem Cell Transplant & Cell Therapy Program, Portland, USA

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

2) Lymphodepletion before CAR-T Infusion

- is fludarabine-cyclophosphamide required?

ORIGINAL ARTICLE

Bendamustine is safe and effective for lymphodepletion

- Retrospective comparison of fludarabine/cyclophosphamide and bendamustine as lymphodepletion prior to tisagenlecleucel
- University of Pennsylvania; Oregon Health & Science University; University of Vienna
- **Bendamustine, n = 90; Fludarabine/Cyclophosphamide n = 42; patient characteristics balanced between LD as shown below**

Characteristics	Total population N = 132 (100%)	Flu/Cy n = 42 (31.8%)	Benda n = 90 (68.2%)	p
Sex				
Female	50 (37.9%)	16 (38.1%)	34 (37.8%)	0.972
Male	82 (62.1%)	26 (61.9%)	56 (62.2%)	
Age at infusion (median – [IQR])	65 [56-70]	67 [56-73]	65 [56-70]	0.222
Diagnosis				
DLBCL NOS	66 (50.0%)	27 (64.3%)	39 (43.3%)	0.128
HGBCL NOS	5 (3.8%)	1 (2.4%)	4 (4.4%)	
tFL	47 (35.6%)	12 (28.6%)	35 (38.9%)	
HGBCL with MYC + BCL2 and/or BCL6 rearrangements	14 (10.6%)	2 (4.8%)	12 (13.3%)	
ECOG PS				
0-1	124 (93.9%)	39 (92.9%)	85 (94.4%)	0.722
≥2	8 (6.1%)	3 (7.1%)	5 (5.6%)	
Renal function				
Normal	108 (81.8%)	32 (76.2%)	76 (84.4%)	0.252
Reduced	24 (18.2%)	10 (23.8%)	14 (15.6%)	
Previous ASCT				
No	104 (78.8%)	31 (63.8%)	73 (81.1%)	0.339
Yes	28 (21.2%)	11 (26.2%)	17 (18.9%)	

Characteristics	Total population N = 132 (100%)	Flu/Cy n = 42 (31.8%)	Benda n = 90 (68.2%)	p
No. of previous lines of therapy (median [IQR])	3 [3-4]	3 [2-4]	3 [3-4]	0.569
Serum LDH (N=131)				
Normal	68 (51.9%)	20 (47.6%)	48 (53.9%)	0.500
Elevated	63 (48.1%)	22 (52.4%)	41 (46.1%)	
Pre-LD CRP (N=54)				
Normal	34 (63.0)	13 (65.0)	21 (61.8)	0.812
Elevated	20 (37.0)	7 (35.0)	13 (38.2)	
Pre-LD Ferritin (N=52)				
Normal	28 (53.8)	11 (55.0)	17 (53.1)	0.895
Elevated	24 (46.2)	9 (45.0)	15 (46.9)	
Bulky disease (>10cm)				
No	119 (90.2%)	36 (85.7%)	84 (92.2%)	0.242
Yes	13 (9.8%)	6 (14.3%)	7 (7.8%)	
Bridging therapy				
No	27 (20.5%)	11 (26.2%)	16 (17.8%)	0.264
Yes	105 (79.5%)	31 (73.4%)	74 (82.2%)	

Ghilardi G, *et al*. Ann Oncol. 2022;S0923-7534(22)01722-7.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

2) Lymphodepletion before CAR-T Infusion

ORIGINAL ARTICLE

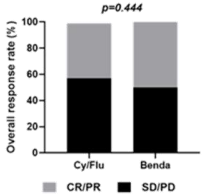
- is fludarabine-cyclophosphamide required?

Bendamustine is safe and effective for lymphodepletion

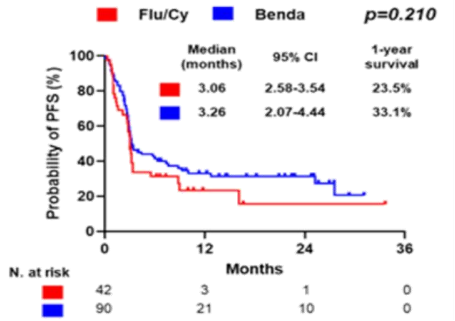
Bendamustine, n = 90
Fludarabine/Cyclophosphamide n = 42

Clinical Outcomes

Response Rates

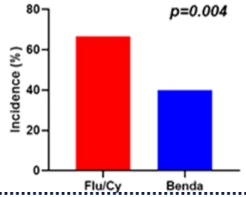


Progression-free survival

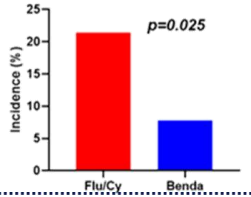


Toxicities

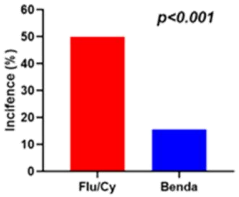
CRS of any grade



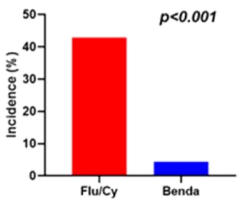
ICANS of any grade



Infections of any grade



Neutropenic fever



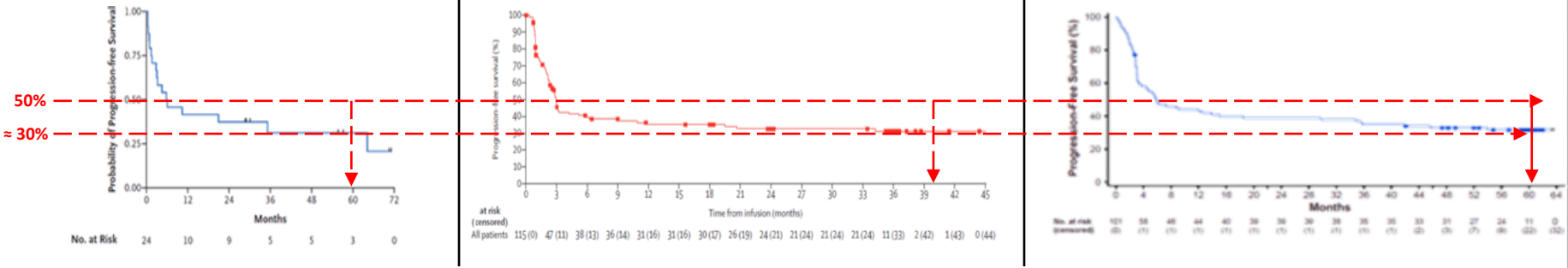
Ghilardi G, *et al*. Ann Oncol. 2022;S0923-7534(22)01722-7. doi:10.1016/j.annonc.2022.05.521

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

3) Response Assessments after CAR-T Infusion

- response assessments and long-term outcomes

UPenn CTL019 Trial[1]	JULIET Trial[2]	ZUMA-1 Trial[3]
n = 24	n = 115	n = 101
Median follow-up: 63.7 months	Median follow-up: 40.3 months	Median follow-up: 63.1 months
Best ORR: 58%, CR: 46%	**Best ORR: 53%, CR: 39%**	**Best ORR: 83%, CR: 58%**
5-year PFS: 31% (95% CI: 14-51)	**3-year PFS estimate: ~31%**	**5-year PFS: 31.8% (95% CI: 22.9-41.1)**



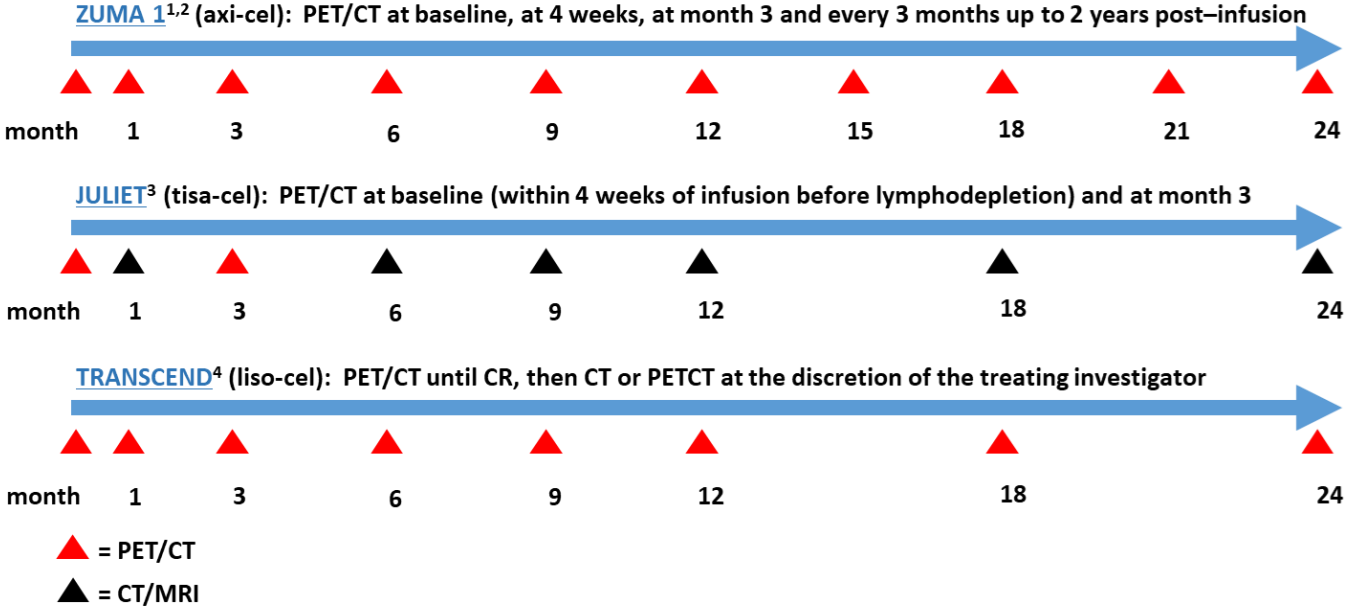
[1]Chong EA, Ruella M, Schuster SJ. N Engl J Med 2021;384(7):673-674; [2]Schuster S. J. et al. Lancet Oncol. 2021; 22(10): 1403-1415; [3]Neelapu SS, et al. Blood. 2023; Epub ahead of print.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

3) Response Assessments after CAR-T Infusion

- response assessments and long-term outcomes

PET/CT Requirements in Registrational Trials of 3rd- or Later-Line CAR-T



[1]Neelapu SS, *et al.* N Engl J Med (2017) 377:2531-44; [2]Locke FL, *et al.* Lancet Oncol (2019) 20:31-42; [3]Schuster SJ, *et al*. N Engl J Med (2019) 380(1):45-56; [4]Abramson J, *et al.* Lancet (2020) 396:839-52.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

3) Response Assessments after CAR-T Infusion

- response assessments and long-term outcomes

PET/CT Use in 3 Registrational CAR-T Clinical Trials

1. PET/CT detects more late response conversions than CT

	JULIET[1]	ZUMA-1[2]	TRANSCEND[3,6]
Response evaluable pts*, n	68	101	192
Median time to response (CR or PR)	0.9 months (range, 0.7-3.3)	0.9 months (range, 0.8-6.2)	1 month (range, 0.7-8.9)

*imaging with measurable disease after completion of bridging chemotherapy and prior to CAR-T

2. PET/CT or CT response assessment at Month-1 is not prognostically useful due to subsequent conversions of PR to CR

PR conversions to CR	JULIET[4] (Month-1 CT)	ZUMA-1[5] (Month-1 PET/CT)
Month-1 Partial Response, n/total CR (best response)	12/37 (32%)	33/55 (60%)
Median time from PR to CR conversion	2 months (range, 1-17.0)	not reported (most by 6 months; as late as 15 months)

*JULIET used CT for Month-1 response assessment; ZUMA-1 and TRANSCEND used PET/CT for Month-1 response assessment

[1]https://www.fda.gov/media/107296; [2]https://www.fda.gov/media/108377; [3]https://www.fda.gov/media/145711;
[4]Schuster SJ, *et al*. N Engl J Med (2019) 380(1):45-56; [5]Locke FL, *et al.* Lancet Oncol (2019) 20:31-42; [6]Abramson J, *et al.* Lancet (2020) 396:839-52.

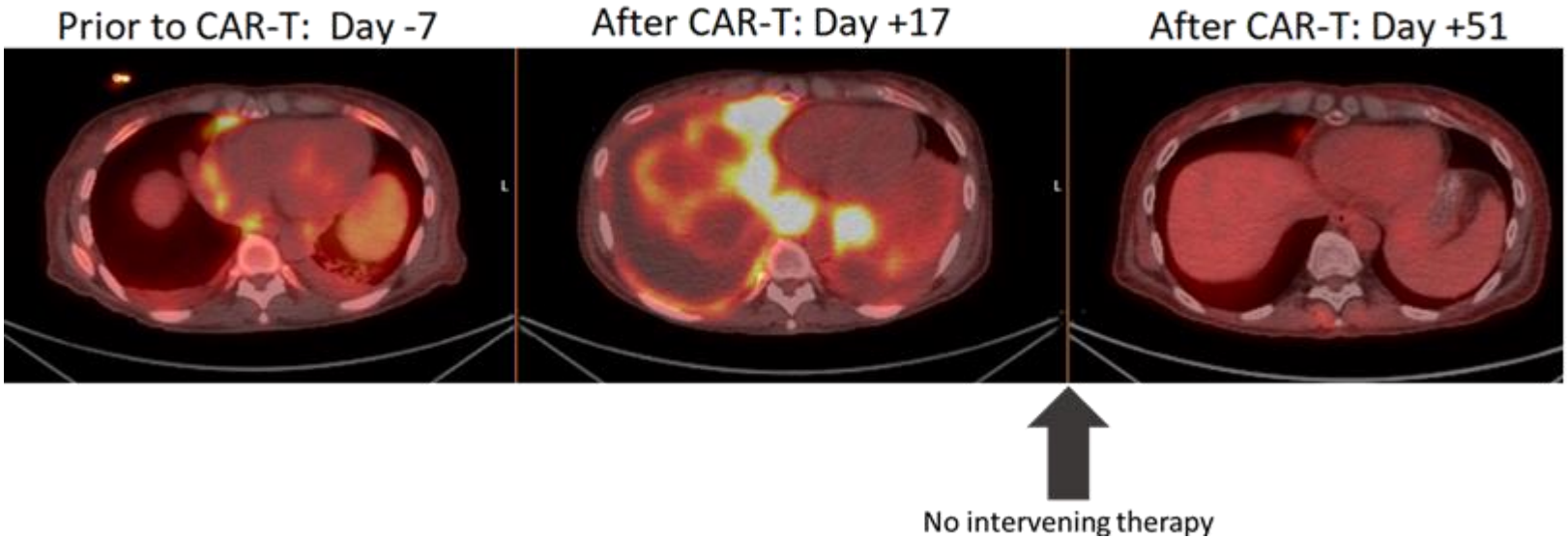
CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

3) Response Assessments after CAR-T Infusion

- response assessments and long-term outcomes

Case: Pseudoprogression during Early Response Assessment

53-year-old woman with refractory large cell transformation of marginal zone lymphoma.



CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

4) Immune Reconstitution: B cell recovery

- is persistent B-cell aplasia related to PFS in NHL?

UPenn CTL019 trial

B-cell counts and immunoglobulin levels in patients in remission for ≥ 1 year

	Normalized N (%)	Median time to normal	Interquartile range	N (%) patients with < 2 x LLN, median follow-up
B cells detectable*	11/16 (69)	11.7 mo	5.8-19.6 mo	5/16 (31), 24.0 mo follow-up
IgM ≥ 40 mg/dL	11/16 (69)	11.7 mo	8.8-22.6 mo	5/16 (31), 55.5 mo follow-up
IgG ≥ 650 mg/dL†	6/16 (38)	11.7 mo	5.8-14.2 mo	5/16 (31), 28.8 mo follow-up
IgA ≥ 50 mg/dL	9/16 (56)	14.0 mo	0-40.1 mo	7/16 (44), 55.4 mo follow-up

*detectable: two consecutive measurements of B cell counts ≥ 2%

† Of note, although a total of 6 patients started IVIg after CTL019, one of these patients was not in remission for over 1 year. Patients in long-term CR who received IVIg (N=5) after CTL019 are included in the total number of patients assessed. Patients who received IVIg are not included in the group of patients whose serum IgG normalized, nor are they included in numerator for the percent of patients with low serum IgG at last follow-up.

- ~ 1/2 of patients in CR recover B cells within 1 year
- ~ 3/4 of patients in CR recover B cells within 2 years
- ~ 2/3 recover immunoglobulins within 2 years

Chong EA, Ruella M, Schuster SJ. N Engl J Med 2021;384(7):673-674.

Zuma-1 trial

B-cell counts over time in patients with ongoing responses

n (%)	Ongoing Response (n=29)
B cells tested at Baseline	23 (79.3)
No B cells	11 (47.8)
With B cells	12 (52.2)
B cells tested at Month 3	27 (93.1)
No B cells	21 (77.8)
With B cells	5 (18.5)
Undetermined	1 (3.7)
B cells tested at Month 6	24 (82.8)
No B cells	19 (79.2)
With B cells	5 (20.8)
Undetermined	–
B cells tested at Month 9	25 (86.2)
No B cells	10 (40.0)
With B cells	15 (60.0)

n (%)	Ongoing Response (n=29)
B cells tested at Month 12	26 (89.7)
No B cells	13 (50.0)
With B cells	13 (50.0)
B cells tested at Month 15	27 (93.1)
No B cells	10 (37.0)
With B cells	17 (63.0)
B cells tested at Month 18	23 (79.3)
No B cells	7 (30.4)
With B cells	16 (69.6)
B cells tested at Month 24	25 (86.2)
No B cells	7 (28.0)
With B cells	18 (72.0)

- ~ 1/2 of patients in ongoing response have B cells at 1 year
- ~ 3/4 of patients in ongoing response have B cells at 2 years

Neelapu SS, et al. Blood. 2023; Epub ahead of print.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

4) Immune Reconstitution: T cell recovery

UPenn CTL019 trial (N-24)

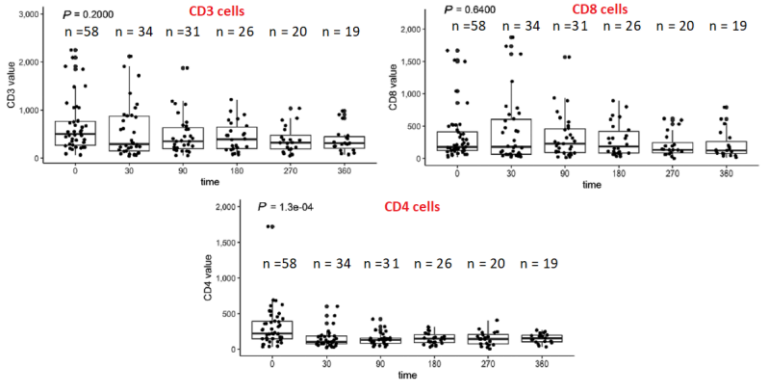
T-cell counts in patients in remission for ≥ 1 year

	% Low T cell counts N (%)	Median time to normal	Interquartile range	Longest time to normal
CD3 count ≥ 900 /uL	11/16 (69)	4.6 mo	3.9-4.9 mo	8.9 mo
CD4 count ≥ 560 / uL	11/16 (69)	4.8 mo	4.1-7.4 mo	14.4 mo
CD8 count ≥ 260 / uL	8/16 (50)	4.7 mo	4.0-5.4 mo	8.9 mo

All patients in CR ≥ 1 year recovered normal CD3, CD4 and CD8 T-cell counts

Chong EA, Ruella M, Schuster SJ. N Engl J Med 2021;384(7):673-674.

Moffitt Cancer Center axi-cel data (N=85)



- **After axi-cel, CD4 T cells decreased from baseline and were persistently low with 1-year median CD4 count 155 cells/µL (n=19, range: 33– 269).**
- **36.5% of patients had infections within 30 days after axi-cel, and 44.3% had infections between days 31 and 360.**

Logue J, et al. Haematologica 2021;106(4):978-986.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

5) CAR-T Products: R-WE

Axicabtagene ciloleucel *vs*. Tisagenlecleucel: R-WE

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

5) CAR-T Products: Selected R-WE

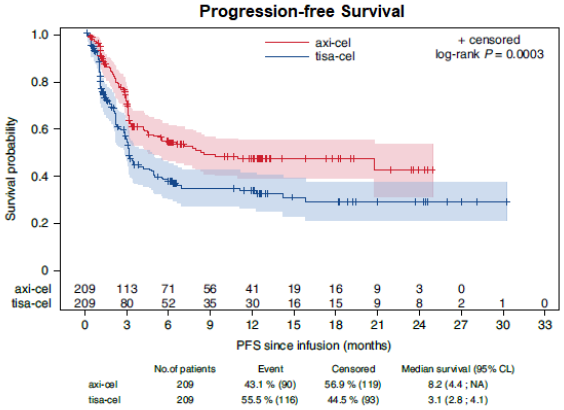
	Axi-cel			Tisa-cel		
reference	(2)	(3)	(4)	(1)	(3)	(4)
N	1,343	209	134	362	209	127
Median follow-up, (range)	11.8 months (0.1-39)	11.7 months	8.2 months (IQR 6-14)	15.8 months	11.7 months	12.4 months (IQR 6-20)
ORR, %	74%	80%*	60%	59.4%	66%*	54%
CR, %	56%	60%*	42%	39.5%	42%*	34%
PFS rate, % (95% CI)	18-month 42% (39-45)	12-month 46.6%*	12-month 41%	12-month 33.5% (28-39)	12-month 33.2%*	12-month 33%
DOR rate, % (95% CI)	18-month 61% (57-65)	12-month 53.8%	median DOR 12.4 months	12-month 52.1% (43-60)	12-month 41.8%	median DOR 14.1 months
OS rate, % (95% CI)	18-month 52% (49-55)	12-month 63.5%*	12-month 51%	12-month 60.3% (54-66)	12-month 48.8%*	12-month 47%
CRS, grade ≥3, %	NR	5.3%	8%	5.2%	9.1%	6%
ICANS, grade ≥3, %	NR	13.9%*	18%*	6.1%	2.9%*	5%*

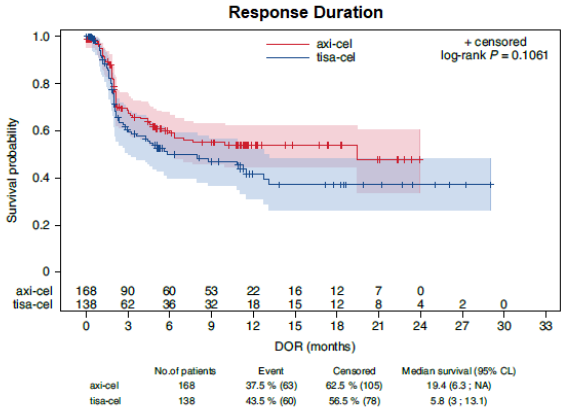
[1]Landsburg DJ, et al. Blood. 2021;138(Sup. 1):429; [2]Locke FL, et al. Blood; 2021;138(Sup. 1):530; [3]Bachy E, et al. Nat Med. 2022;28:2145-2154; [4]Kwon M, et al. Haematologica. 2023;108(1):110-121.

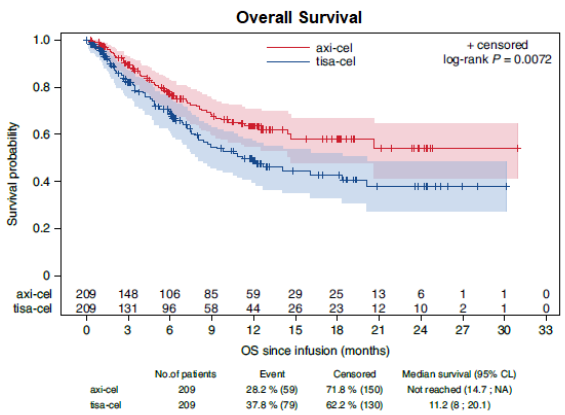
CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

5) CAR-T Products: Selected R-WE

DESCAR-T Registry: a real-world comparison of tisa-cel and axi-cel







Bachy E, et al. Nat Med. 2022;28:2145-2154.

CAR-T as 3rd-line or Later Therapy: Lessons from Long-term Follow-up

Conclusions:

1) *Timing of CAR-T Therapy*
   - **At current follow-up, EFS outcomes for large B-cell lymphoma patients receiving 2nd-line CAR-T are probably improved compared with patients receiving 3nd-line CAR-T; more importantly, earlier application of CAR-T may save patients other additional potentially toxic therapies.**
   - **Uncontrolled tumor growth, high serum LDH, and bulky disease pre-infusion bode poor outcomes for ≥ 3rd-line CAR-T in large B-cell lymphomas.**
2) *Lymphodepletion before CAR-T Infusion*
   - **Fludarabine-cyclophosphamide is *not* required, but randomized trials are needed to define the best lymphodepletion regimens.**
3) *Response Assessments after CAR-T Infusion*
   - **Survival statistics rather than response rates should be used to assess CAR-T efficacy.**
4) *Immune Reconstitution*
   - **Persistent B-cell aplasia after CAR-T is not required for remission in large B-cell lymphomas; most patients in remission recover B cells.**
   - **Patients who achieve complete remission after CAR-T for large B-cell lymphomas can reconstitute their immune system.**

Disclaimers: These impressions are based on personal experiences and observations in the clinical research and practice settings, as well as on impressions gained from the literature and from discussions with other clinicians and investigators. These opinions should not be considered as dogma, but rather as current impressions that may require further validation through additional experience and formal clinical investigation.

CAR-T as 3rd-line or Later Therapy of Large B-Cell Lymphomas

Molte Grazie

Questions or Comments