44° CONVEGNO NAZIONALE di Studi di Medicina Trasfusionale
Rimini | Palacongressi, 3-5 maggio 2022
SIMTI

CAR-T cell: indicazioni consolidate e nuove indicazioni in ambito oncoematologico

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Ematologia,

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Fondazione IRCCS Istituto Nazionale dei Tumori
Sistema Sanitario Regione Lombardia

La sottoscritta **CHIAPPELLA ANNALISA**

in qualità di relatore

ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 Febbraio 2017

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- **Advisory Board:** Celgene/BMS, Clinigen, Gilead Sciences, Ideogen, Janssen-Cilag, Roche, SecuraBIO, Takeda
- **Educational Activities/Lecture Fees:** Astrazeneca, Celgene-BMS, Clinigen, Gilead-Sciences, Incyte, Janssen-Cilag, Novartis, Roche, SecuraBIO, Takeda

CD19-Directed CAR T-Cell Products for NHL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]	Brexucabtagene Autoleucel[4]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z
FDA approval status	▪ **Adults with R/R DLBCL, HGBCL, transformed FL, primary mediastinal B-cell lymphoma** ▪ **Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy** ▪ **Adults with R/R follicular lymphoma after ≥ 2 lines of systemic therapy**	▪ **R/R pediatric ALL** ▪ **R/R DLBCL, HGBCL, transformed FL** ▪ **R/R FL**	▪ **R/R DLBCL, HGBCL, FL grade 3B, PMBCL**	▪ **R/R MCL**
AIFA approval status	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including**: ○ DLBCL NOS ○ DLBCL arising from follicular lymphoma ○ Primary mediastinal large B-cell lymphoma ○ High-grade B-cell lymphoma	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including: ○ DLBCL NOS ○ DLBCL arising from follicular lymphoma ○ High-grade B-cell lymphoma		▪ **R/R MCL**

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Lisocabtagene Maraleucel PI. 4. Brexucabtagene autoleucel PI.

Outline of the discussion

- Pivotal trials results in aggressive B-cell lymphomas
  - Long term results
- Real world data in aggressive B-cell lymphomas
- Recent and future indications

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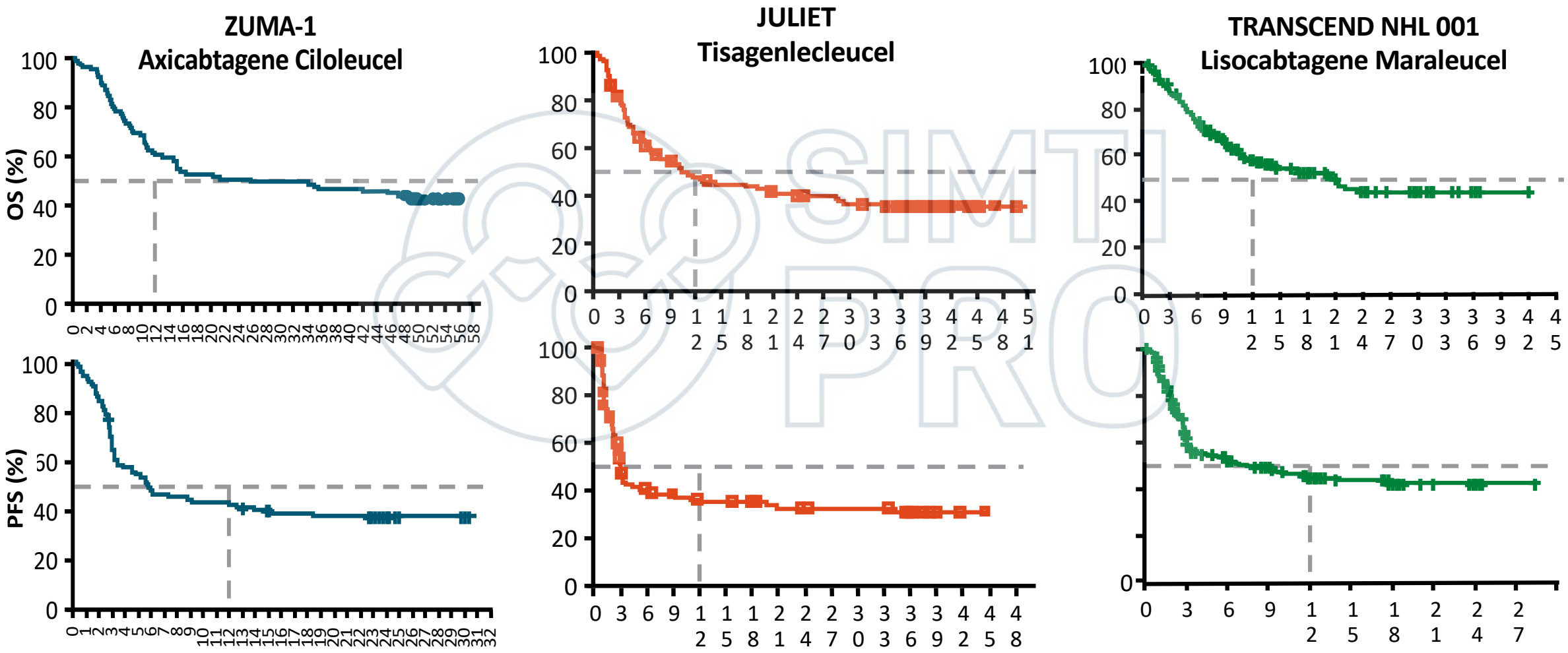
Pivotal Anti-CD19 CAR T-Cell Therapy Trials

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6 to 6.0 x 10^8/kg	50 to 150 x 10^6
Lymphodepletion	Flu/Cy 30/500 x 3 days	Flu/Cy 25/250 x 3 days, or bendamustine x 2 days	Flu/Cy 30/300 x 3 days
	ZUMA-1[1,2]	**JULIET[3]**	**TRANSCEND NHL 001[4]**
Study phase	II	II	I
Patient population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL
Patients apheresed/ treated, n	111/101	165/111	344/269*
Bridging therapy	None allowed in pivotal trial, often used in standard practice	92%	59%
ORR, %	82%	52%	73%
CR, %	54%	40%	53%

*256 included in the efficacy-evaluable set.

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

Pivotal Anti-CD19 CAR T-Cell Therapy Trials



1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

Key Toxicities With CAR T-Cell Therapy for DLBCL: CRS and Neurotoxicity

	ZUMA-1[1]	JULIET[2]	TRANSCEND[3]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
N treated	101	111	269
CRS, %	93†	58*	42†
Grade ≥ 3 CRS, %	13†	22*	2†
NT, %	64	21	30
Grade ≥ 3 NT, %	28	12	10

Additional CAR-T cells toxicities:

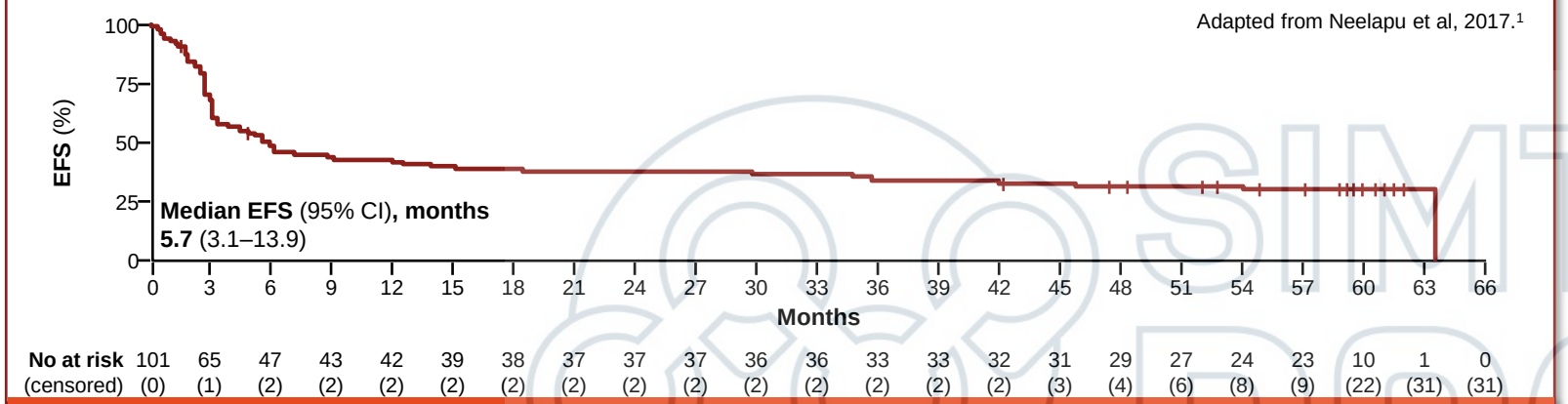
- Long term cytopenias
- Macrophage activation-like syndrome
- Immunosuppression

*Per Penn scale. †Per Lee Scale.

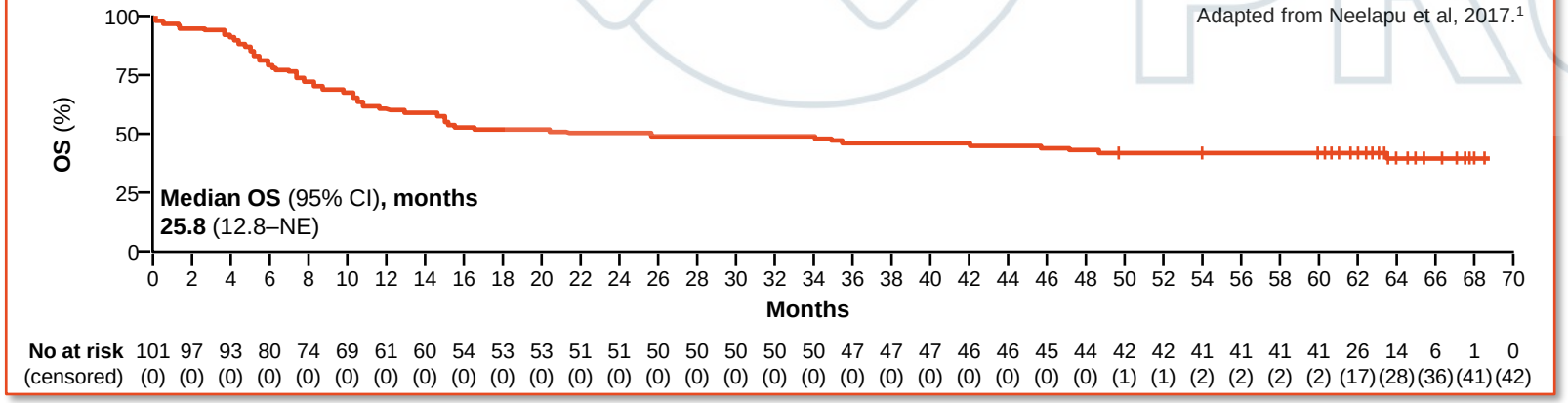
1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.
Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. Hematol Oncol. 2019;37(suppl 1):48. Mehta. Lancet Rheumatol. 2020;2:358.

Axicabtagene ciloleucel for R/R DLBCL: Long-term results from ZUMA-1 trial

24-month EFS rate was 38%[1]



5-year OS rate was 43% (64% if CR)[1]



ORR: (n=101): 83%[1]
CR: 58%[1]

Grade ≥3 CRS = 11%[1]
Grade ≥3 ICANS = 28%[1]

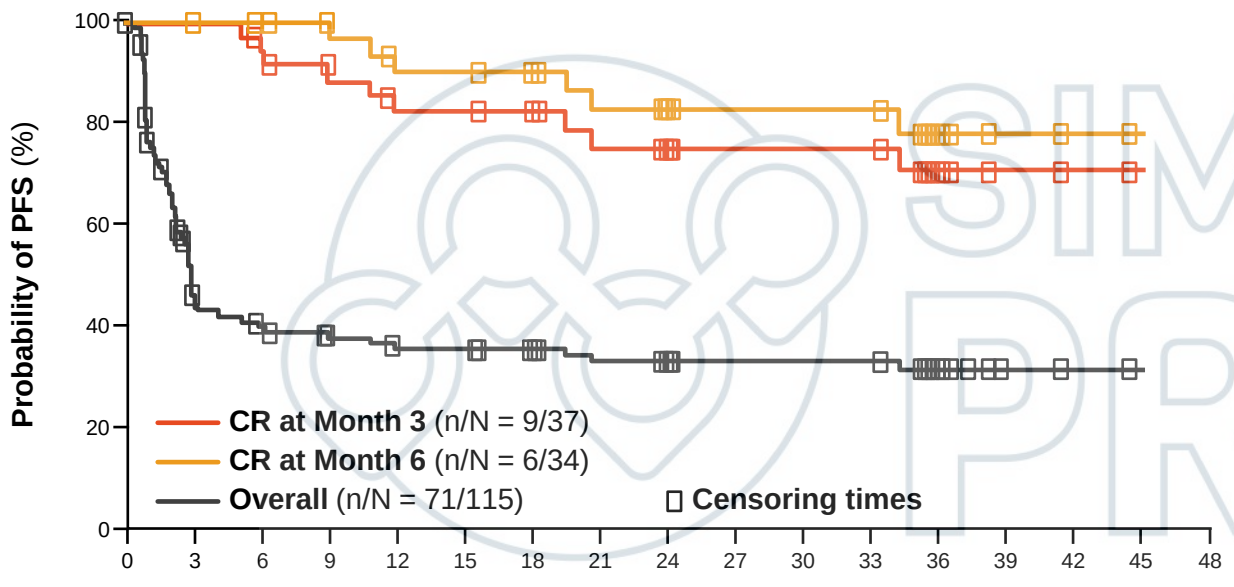
n (%)[2]	N=101
Patients who died	**59** (58)
Primary cause of death	
Progressive disease	**45** (45)
Other	**9** (9)
AEs	**4** (4)
Secondary malignancy	**1** (1)

AE, adverse event; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; ICANS, immune effector cell-associated neurotoxicity syndrome; NE, not estimable; ORR, overall response rate; OS, overall survival, R/R, relapsed/refractory.

1. Neelapu SS, et al. N Engl J Med. 2017;377:2531–44; 2. Jacobson CA, et al. Presented at the 63rd American Society of Hematology Annual Meeting, 11–14 December 2021, Atlanta, GA: Abstract 1764.

Tisagenlecleucel for R/R DLBCL: Long-term results from JULIET trial

PFS



Number of patients still at risk

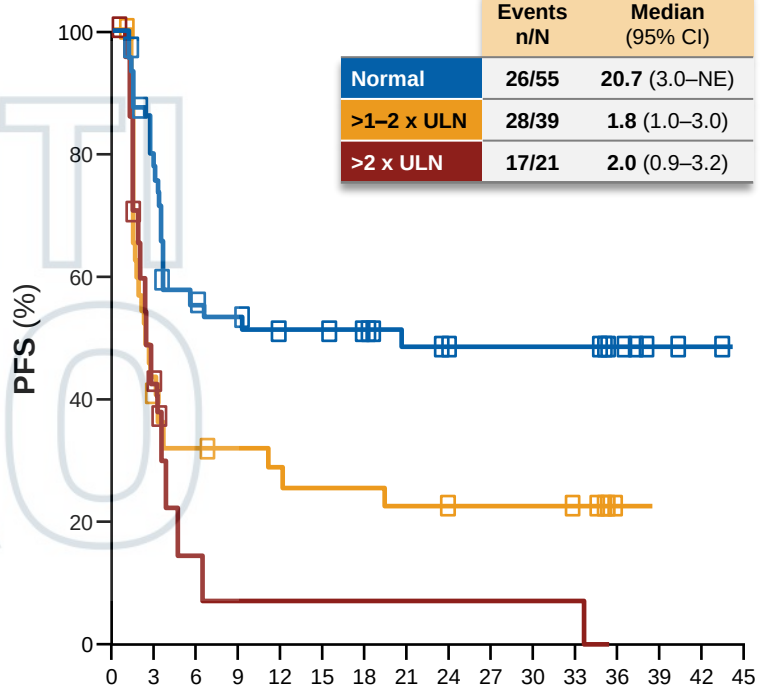
CR at month 3	37	37	33	31	26	26	25	21	20	17	17	17	7	2	1	0
CR at month 6	34	34	33	32	27	27	26	22	21	18	18	18	8	2	1	0
Overall	115	47	38	38	31	31	30	26	24	21	21	21	11	2	1	0

Median follow-up: 40.3 months

Adapted from Schuster et al, 2021.

PFS at 36 months: 31% for all patients and 78% for patients in CR at 3 months

PFS according to LDH



	Events n/N	Median (95% CI)
Normal	26/55	**20.7** (3.0–NE)
>1–2 x ULN	28/39	**1.8** (1.0–3.0)
>2 x ULN	17/21	**2.0** (0.9–3.2)

Adapted from Schuster et al, 2021.

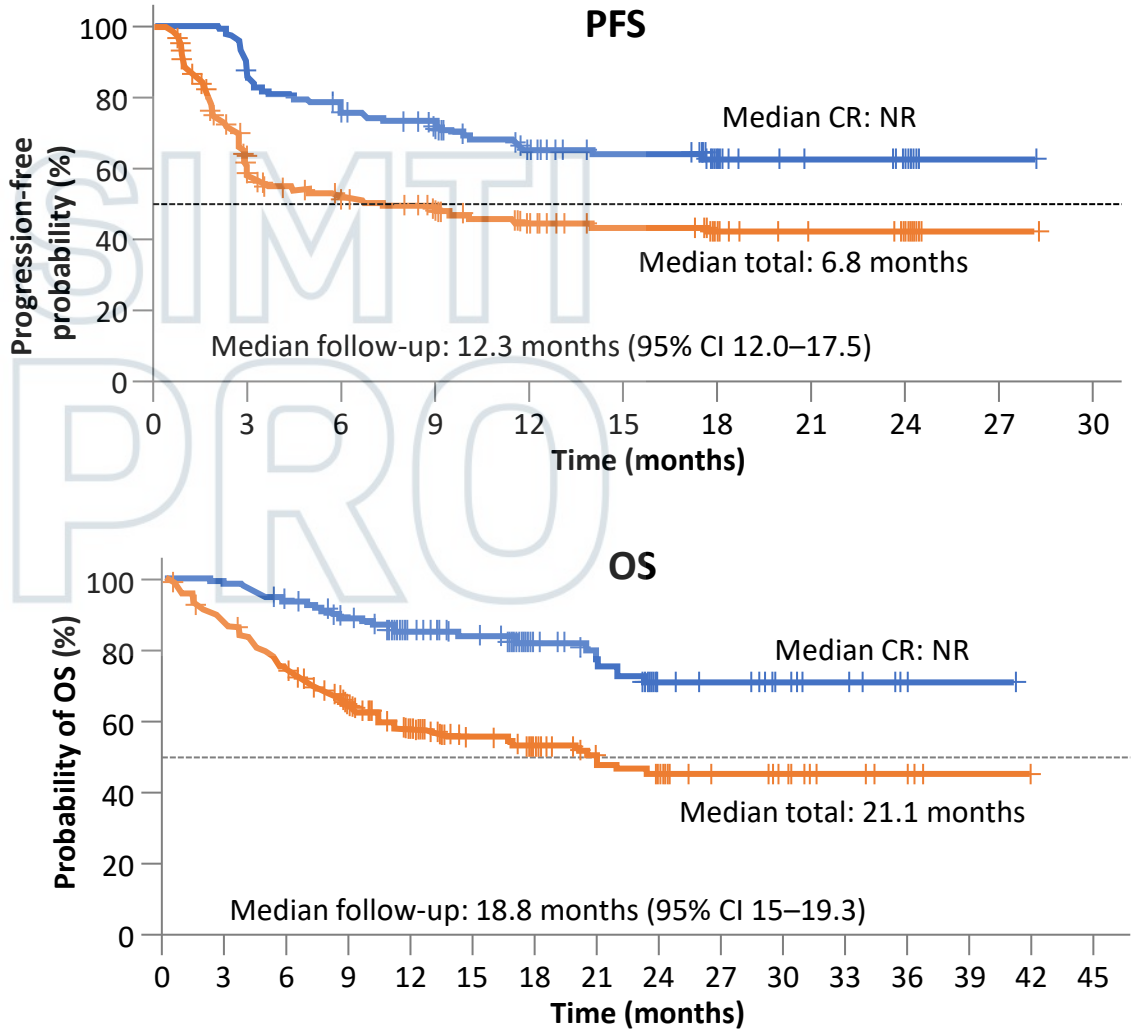
CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; Mo, Months; NE, not estimable; n/N, number of events/number at risk; PFS, progression-free survival; R/R, relapsed/refractory; ULN, upper limit of normal.

Schuster SJ, et al. Lancet Oncol. 2021;22:1403–15 and Supplementary appendix.

TRANSCEND-NHL-001: PFS and OS of patients with R/R DLBCL receiving liso-cel

Characteristics	Patients (N = 269)
Age, median (range), years	63 (54-70)
Double-/triple-hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Prior lines, median (range), n	3 (2–4)
Chemorefractory, range, n	181 (67)
Prior HSCT, n (%)	94 (35)

Best response	Patients (N = 256)
Best ORR, %	73
Best CR, %	53
12-month DOR, %	55



CNS, central nervous system; HSCT, haematopoietic stem cell transplant; R/R, relapsed/refractory.

Abramson JS, et al. Lancet. 2020;396:839-52.

Outline of the discussion

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- Real world data in aggressive B-cell lymphomas
- Recent and future indications

Axi-cells in Real World Experience

original reports

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

Loretta J. Nastoupil, MD[1]; Michael D. Jain, MD, PhD[2]; Lei Feng, MD[1]; Jay Y. Spiegel, MD[3]; Amin Ghobadi, MD[4]; Yi Lin, MD, PhD[5]; Saurabh Dahiya, MD[6]; Matthew Lunning, DO[7]; Lazaros Lekakis, MD[8]; Patrick Reagan, MD[9]; Olalekan Oluwole, MBBS[10]; Joseph McGuirk, DO[11]; Abhinav Deol, MD[12]; Alison R. Sehgal, MD[13]; Andre Goy, MD[14]; Brian T. Hill, MD, PhD[15]; Khoan Vu, MD[16]; Charalambos Andreadis, MD, MSCE[16]; Javier Munoz, MD, MS[17]; Jason Westin, MD[1]; Julio C. Chavez, MD, MS[2]; Amanda Cashen, MD[4]; N. Nora Bennani, MD[5]; Aaron P. Rapoport, MD[6]; Julie M. Vose, MD[7]; David B. Miklos, MD, PhD[3]; Sattva S. Neelapu, MD[1]; and Frederick L. Locke, MD[2]

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

CONTEXT

Key Objective

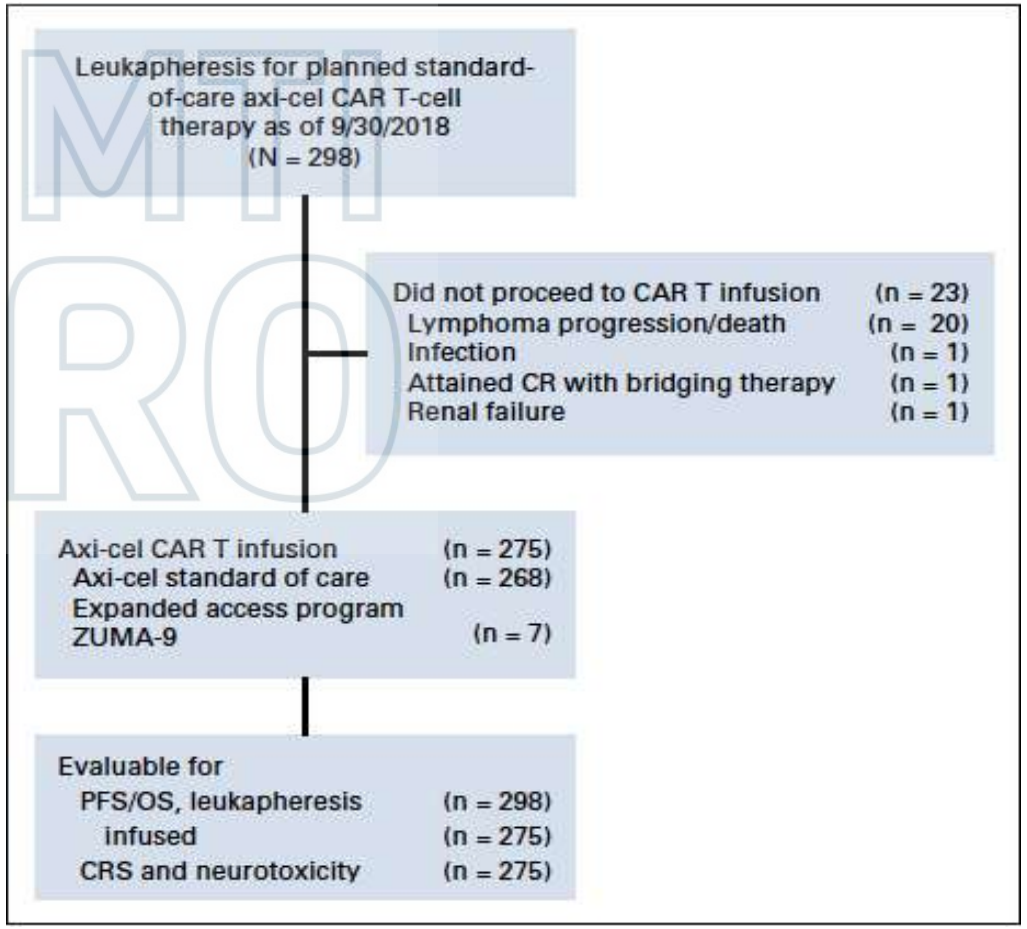
Seventeen US centers set out to delineate the characteristics and outcomes of 298 patients apheresed with intention to be treated with commercially available axicabtagene ciloleucel, an autologous anti-CD19 CAR T-cell.

Knowledge Generated

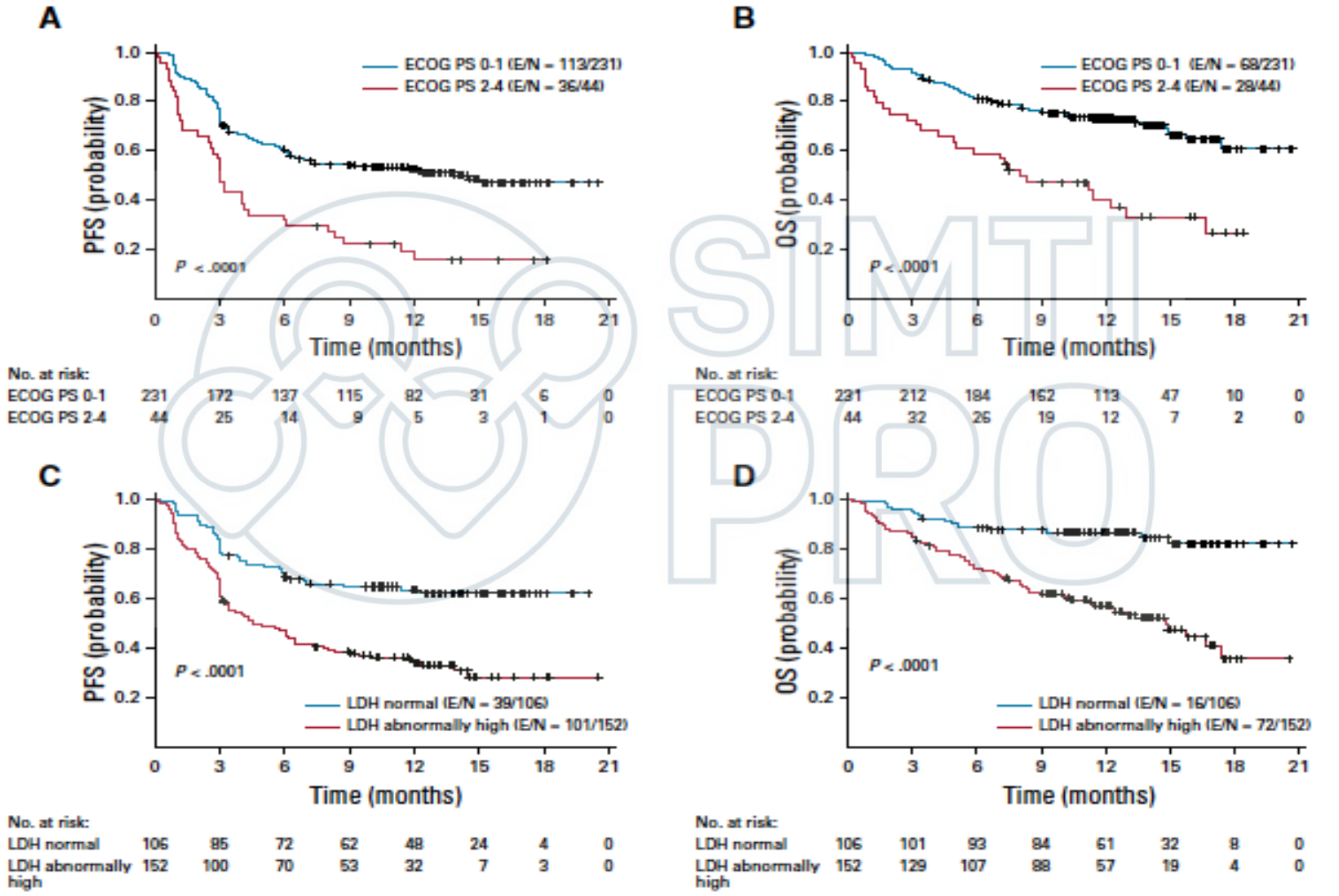
Practice patterns varied from the registrational ZUMA-1 trial. 43% of patients had comorbidities or characteristics that would have deemed them ineligible. Despite this, safety and efficacy outcomes were comparable to ZUMA-1. We identified patient and disease characteristics associated with outcomes.

Relevance

Our findings suggest favorable outcomes reported in prospective trials with axicabtagene ciloleucel can be achieved across multiple centers in the United States using commercial product as a standard of care.

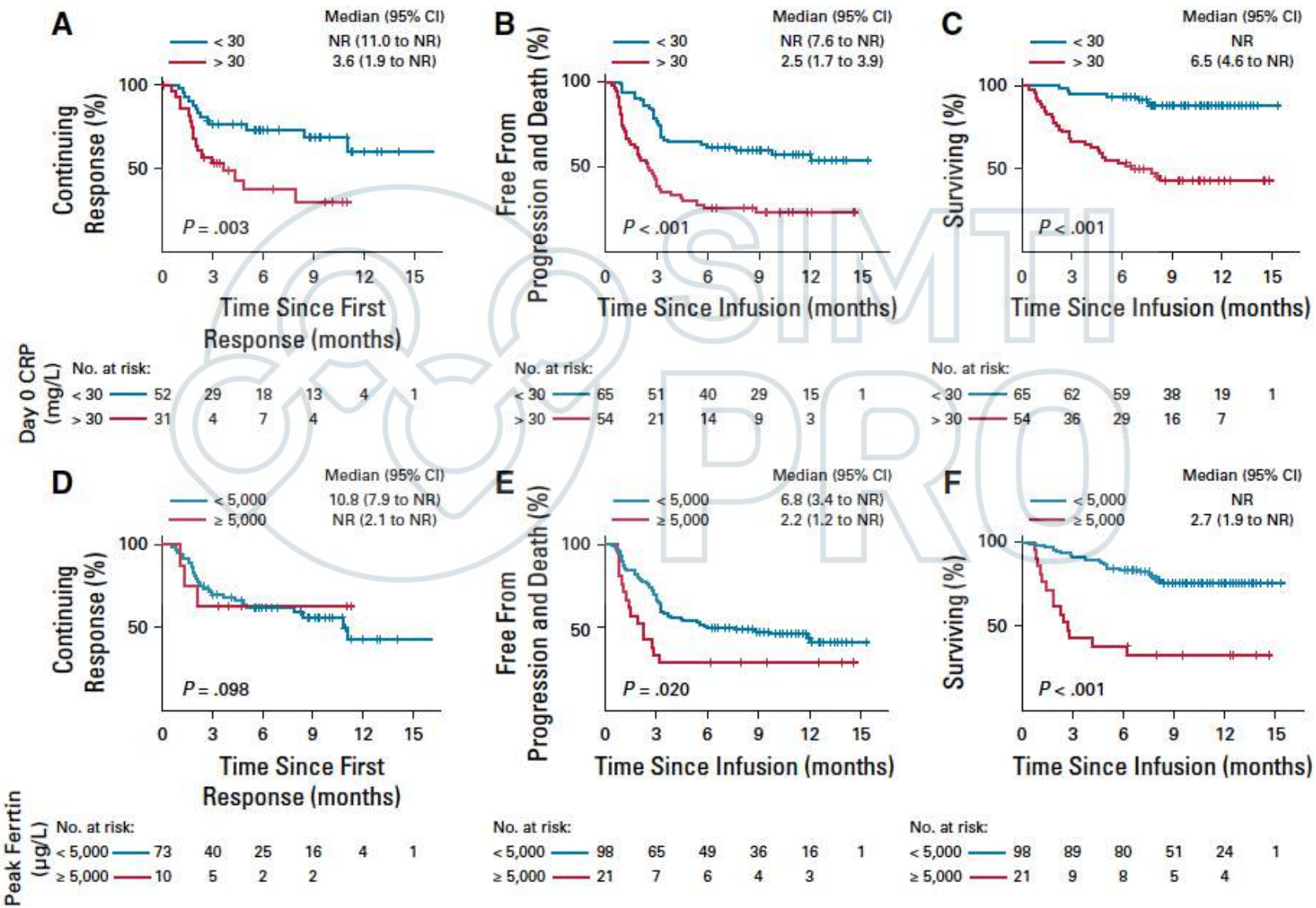


Predictors of response: LDH values and ECOG PS



Nastoupil LJ, J Clin Oncol 2020

Predictors of response: CRP and ferritin levels



Jacobson CA, J Clin Oncol 2020

Predictors of response and toxicity

Predictors of Improved Response	
Patient	▪ Low tumor burden, LDH, pretreatment inflammatory markers ▪ Absence of medical comorbidities ▪ Lack of need for bridging therapy
T-cells	▪ Proportion of CCR7+ and other early memory T-cells in the CAR product ▪ Faster doubling time in vitro ▪ Higher CAR T-cell peak to tumor burden ratio
Tumor	▪ Absence of CD58 mutations, MYC overexpression ▪ Low tumor MDSCs ▪ High TILs

Predictors of Increased Toxicity	
Pretreatment	▪ High tumor burden, pretreatment LDH, pretreatment inflammatory markers ▪ ? High pretreatment monocyte levels
Post-treatment	▪ High peak CAR T-cell, cytokine levels ▪ Markers of DIC (including fibrinogen levels) ▪ Early CRS

Nastoupil. JCO. 2020;38:3119. Locke. Blood Adv. 2020;4:4898. Du. Biomark Res. 2020;8:13. Jaeger. ASH 2020. Abstr 1194. Majzner. ASH 2020. Abstr 556.

Patient selection is primarily guided by the AIFA approved indications

- **Age 18-70 → 75!**
- **Histotypes according to product specification**
- **Active uncontrolled infections → no use**
- **ECOG > 1 → no use**
- HBV/HCV/HIV active infection → no use
- Venous thrombosis in the last six months → no use
- **Active CNS** disorder or primary CNS lymphoma → no use
- Previous allo-SCT → no use
- Inadequate renal (eGFR > 60 ml/min), hepatic, pulmonary or cardiac function (LVEF >50%)
- Prior anti-CD19 therapy → repeat biopsy to prove the presence of CD19
- ANC > 1000, Hb > 8, PLTS > 75.000, ALC >100

Patient selection: INT experience

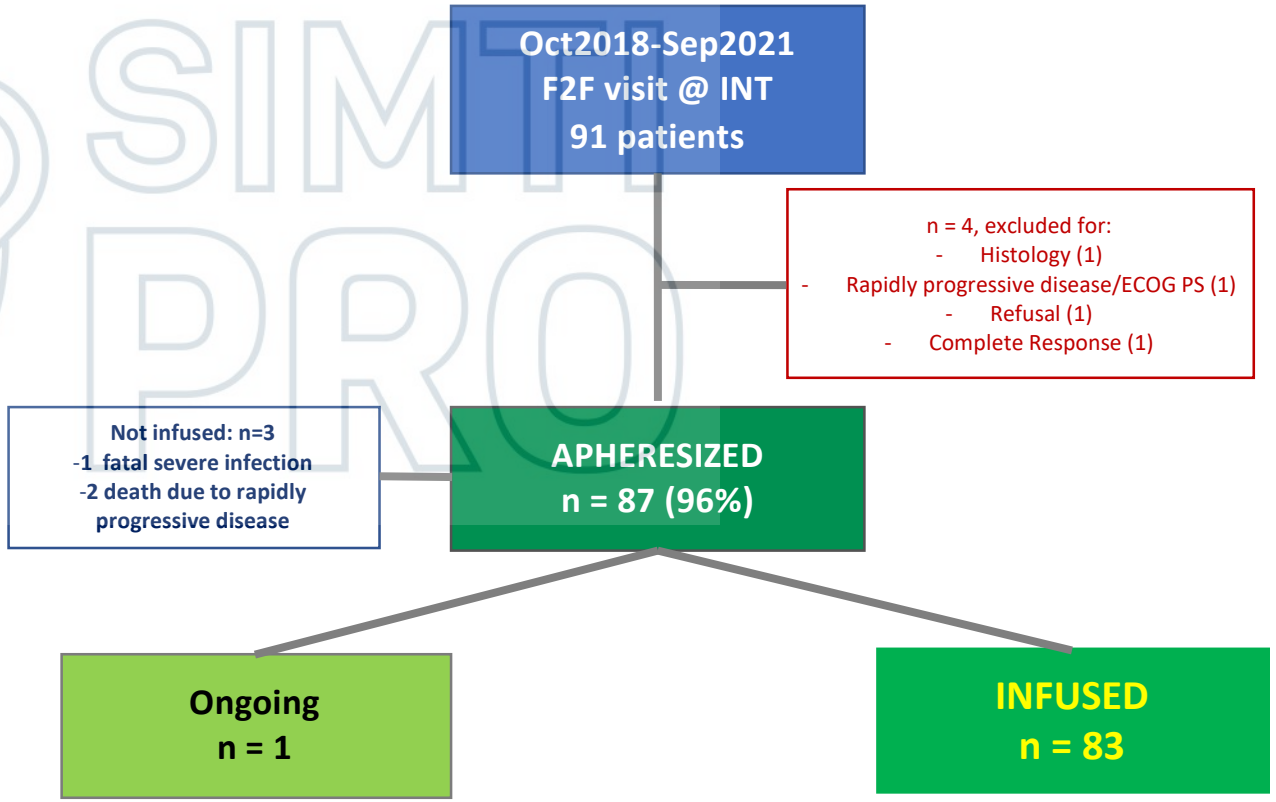
FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Sistema Sanitario Regione Lombardia

CAR-T program @ INT (Oct2018-Sep2021)
5 clinical trials, 9 EAP, 4 NPP, 65 commercial products

n = 83 (48%) not eligible
- Histology (2, 2%)
- CNS involvement (4, 5%)
- Comorbidities (44, 53%)
- Rapidly progressive disease/ECOG PS (30, 36%)
- Eligible to ASCT (3, 4%)

Oct2018-Dec 2019 89 pre-evaluation forms 24 eligible	27%
Jan2020-Dec2020 47 pre-evaluation forms 36 eligible	76%
Jan2021-Sep2021 34 pre-evaluation forms 31 eligible	91%



Speaker experience

CAR-T SIE study

Principal Investigator: Prof Paolo Corradini
Sponsor: Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy

A multicenter prospective observational study on Chimeric Antigen Receptor (CAR) T-cell therapy for lymphoma: monitoring feasibility, efficacy, toxicity and biomarkers in a real life setting

All Italian qualified centers for CAR-T treatment

Società Italiana di Ematologia

Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Sanitario Regione Lombardia

REAL-LIFE CAR-T CELL TREATMENT IN LARGE B-CELL LYMPHOMAS INDICATES THAT AXI-CEL AND TISA-CEL HAVE SIMILAR OUTCOMES, BUT LONG-TERM CYTOPENIA IS AN EMERGING PROBLEM.

Chiappella A[1], Guidetti A[1,2], Dodero A[1], Bramanti S[3], Zinzani PL[4], Santoro A[3], Casadei B[4], Di Rocco A[5], Carrabba M[6], Chiusolo P[7], Martino M[8], Barbui AM[9], Tisi MC[10], Saccardi R[11], Perriello VM[12], Orciuolo E[13], Botto B[14], Russo D[15], Miceli R[16], Ljevar S[16], Carniti C[1] and Corradini P[1,2] on behalf of Italian Society of Hematology (SIE)

Patient Flow: March 2019-June 2021

208 patients leukapheresed

n = 17 (8%), not infused for:
- Rapidly progressive disease (11)
- Severe infection (4)
- Persistent complete response (1)
- Manufacturing failure (1)

INFUSED
n = 191 (92%)

Axi-cel
n = 92 (48%)

Tisa-cel
n = 99 (52%)

Chiappella A, et al. 63rd Annual Meeting of the American Society of Hematology ; December 13, 2021; Abstract No. 3867.

REAL-LIFE CAR-T CELL TREATMENT IN LARGE B-CELL LYMPHOMAS INDICATES THAT AXI-CEL AND TISA-CEL HAVE SIMILAR OUTCOMES, BUT LONG-TERM CYTOPENIA IS AN EMERGING PROBLEM.

Clinical characteristics, 191 infused patients

	N = 191, median age 53 (19-70)
Histotype • PMBCL • DLBCL nos • HGBCL	35 (18%) 134 (70%) 22 (12%)
Stage III/IV	127 (69%)
Lines of prior therapy, median	3 (2-12)
Prior ASCT	58 (30%)
Primary refractory	132 (69%)
Bridging therapy	177 (93%)
radiotherapy	45 (25%)
chemotherapy +/- immunotherapy	115 (65%)
radiotherapy + chemotherapy	17 (10%)

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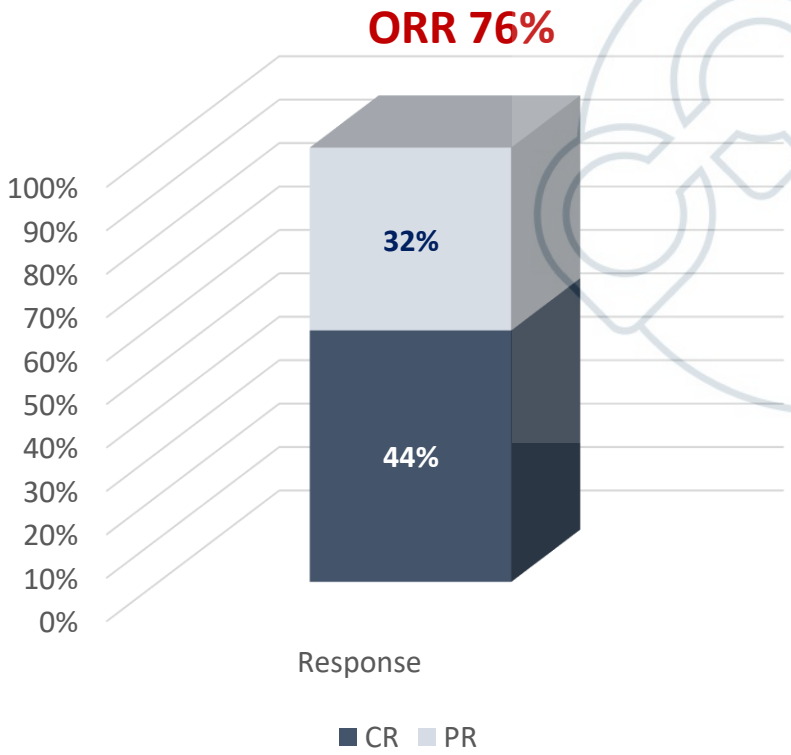
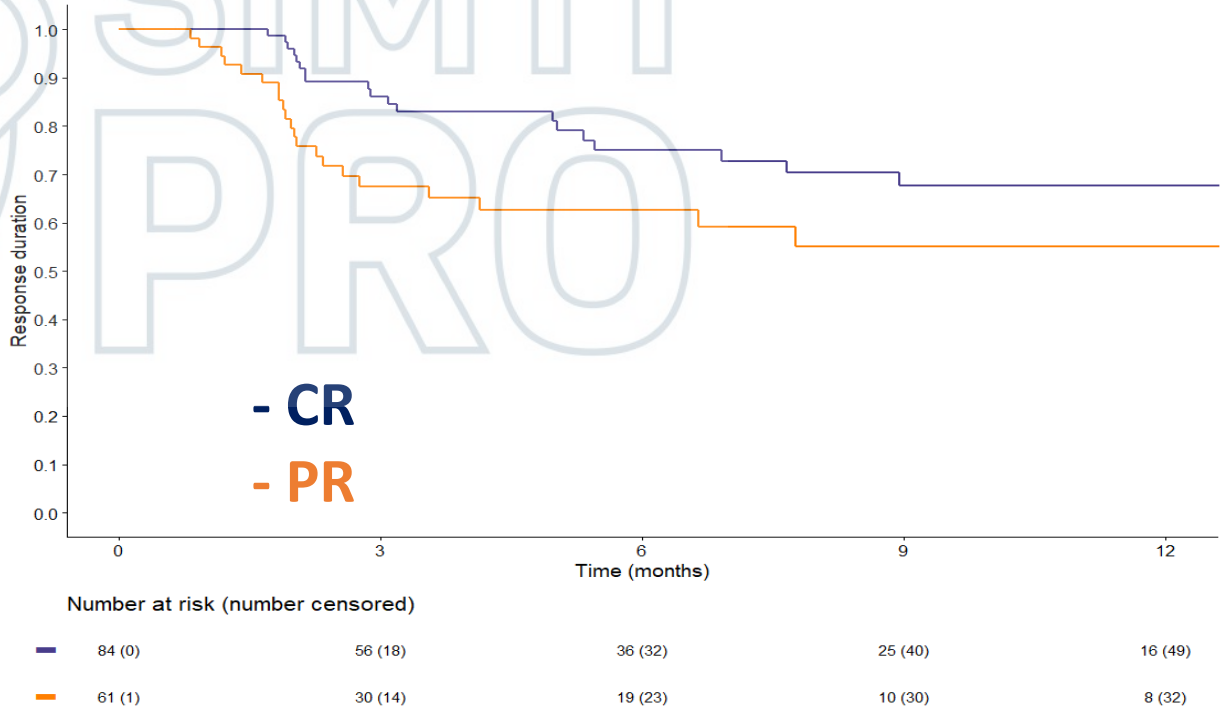
Response rate

191 infused patients evaluable for response at 30-days after the infusion



Median DOR not reached for CR and PR patients;

CR patients did better than PRs (p=0.04)



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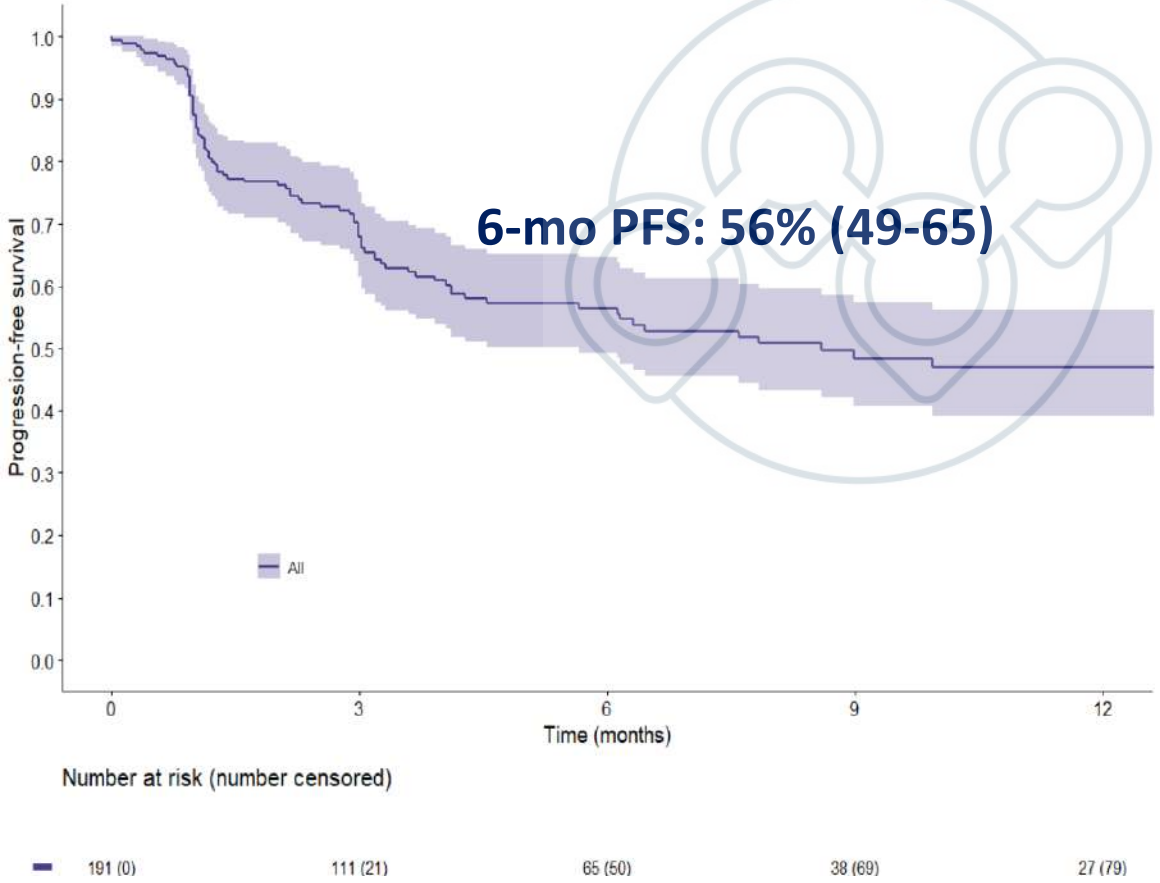
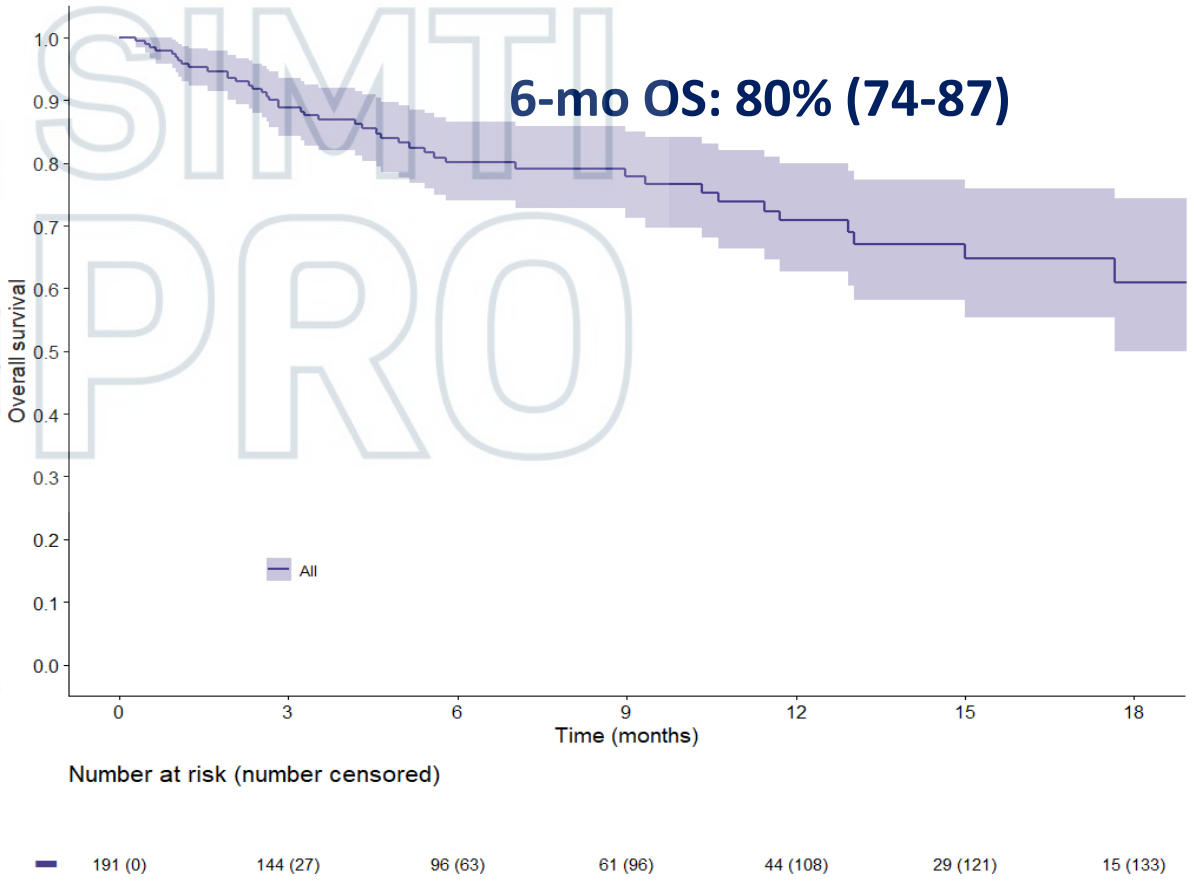
Progression Free Survival (PFS) and Overall Survival (OS)

Median follow-up time for infused patients: 7.66 months (IQR: 4.14-14.74)





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Società Italiana di Ematologia

Safety

N = 191	0	All grade	Grade ≥3
CRS	41 (21%)	150 (79%)	9 (5%)
ICANS	146 (76%)	45 (24%)	15 (8%)

N = 191	Yes	No
Tocilizumab	108 (57%)	83 (43%)
Steroids	62 (33%)	129 (67%)

ICU admission: 24 (13%) patients

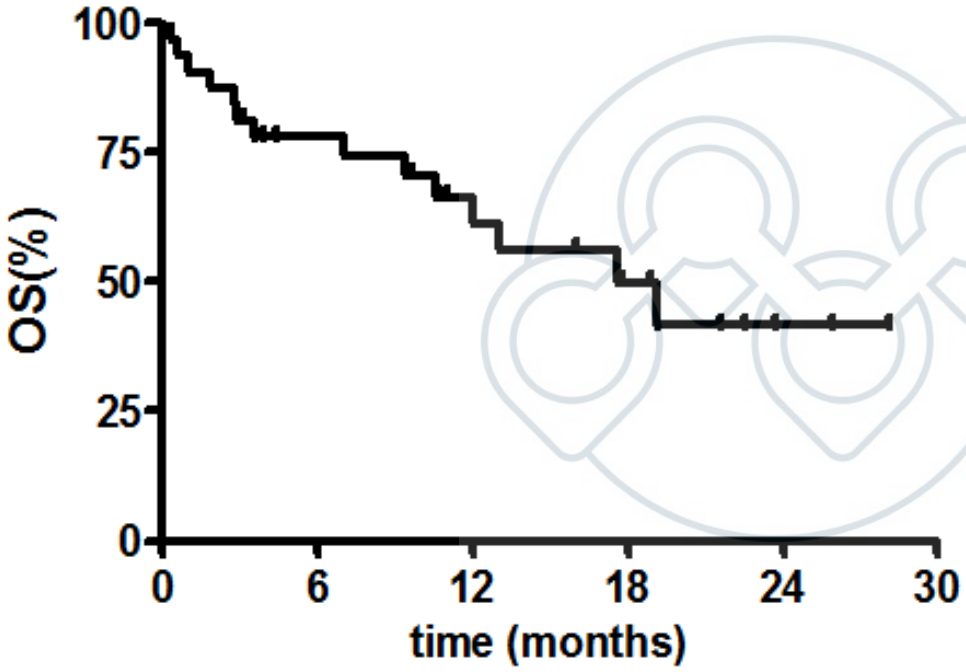
Cytopenia beyond 90 days: 59/179 (33%) patients

No toxic deaths related to CAR-T; 43 deaths recorded, lymphoma-related

Chiappella A, et al. 63rd Annual Meeting of the American Society of Hematology ; December 13, 2021; Abstract No. 3867.

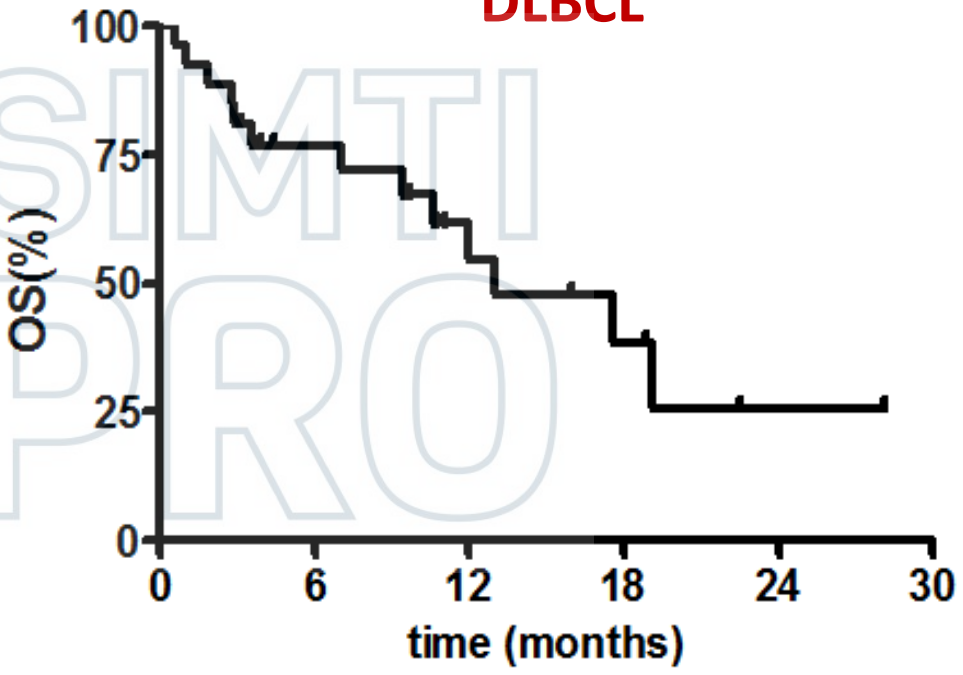
Outcome after CAR-T failure: INT experience
n=32 relapses (n=26 DLBCL, n=6 PMBCL)

DLBCL + PMBCL



1 year 61%, 2 years 41%

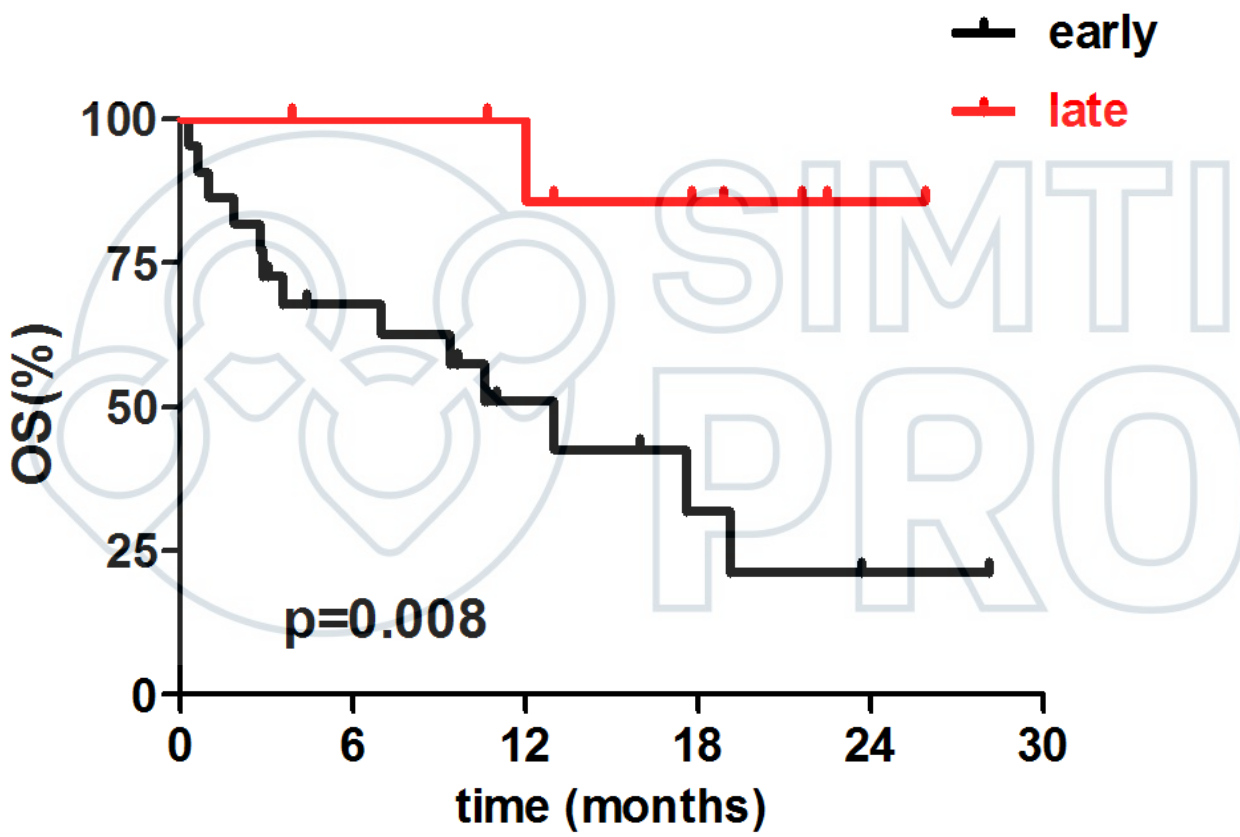
DLBCL



1 year 54%, 2 years 25%

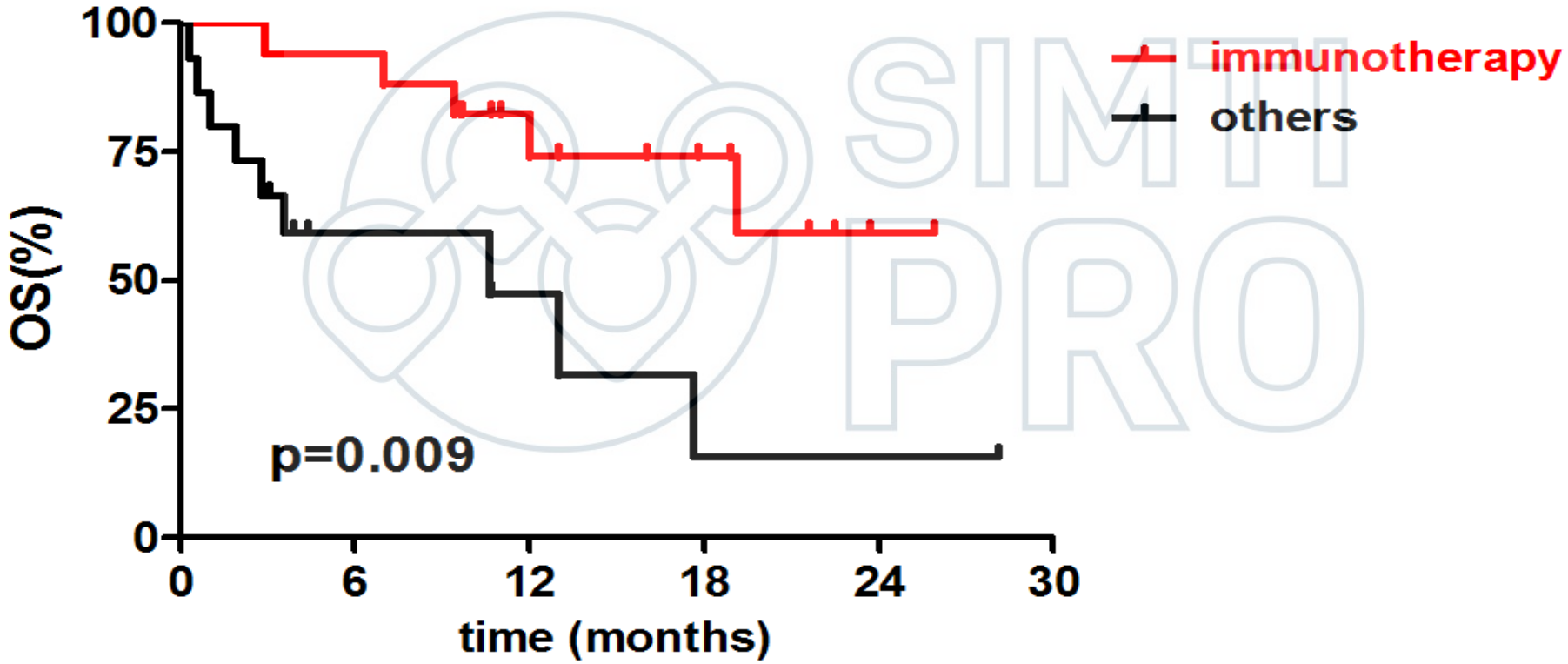
Early vs late CAR-T failure: INT experience

n=32 relapses (n=22 “early” ≤ 90 days, n= 10 “late” > 90 days)



CAR-T failure treatment: INT experience

Immunotherapies: n=17 (n=14 bispecific antibodies, n=3 anti-PD1 antibodies)
Others: n= 15 (n=10 no therapies, n=5 chemotherapy or lenalidomide)



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- Pivotal trials results in aggressive B-cell lymphomas
  - Long term results
- Real world data in aggressive B-cell lymphomas
- Recent and future indications

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

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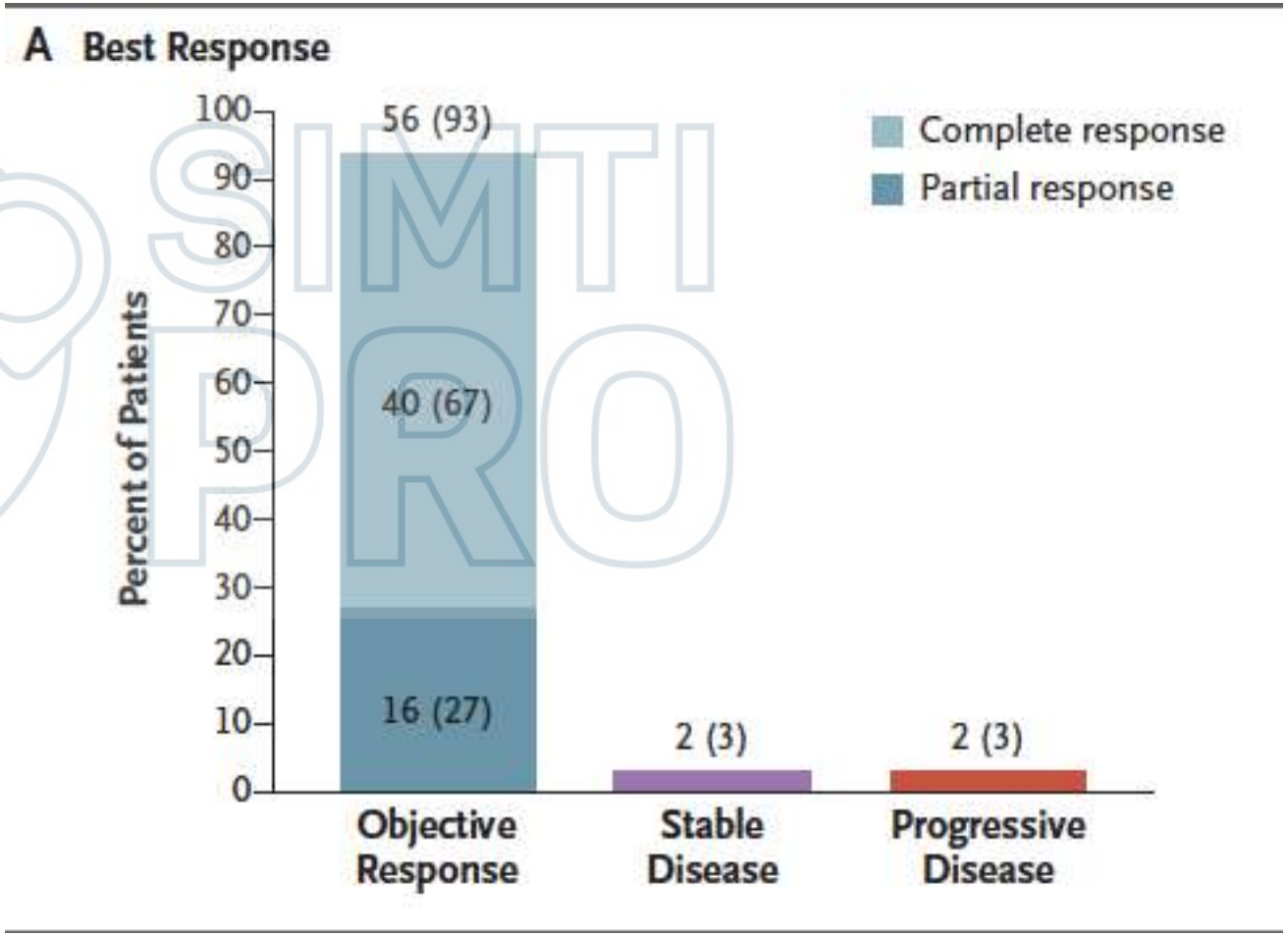
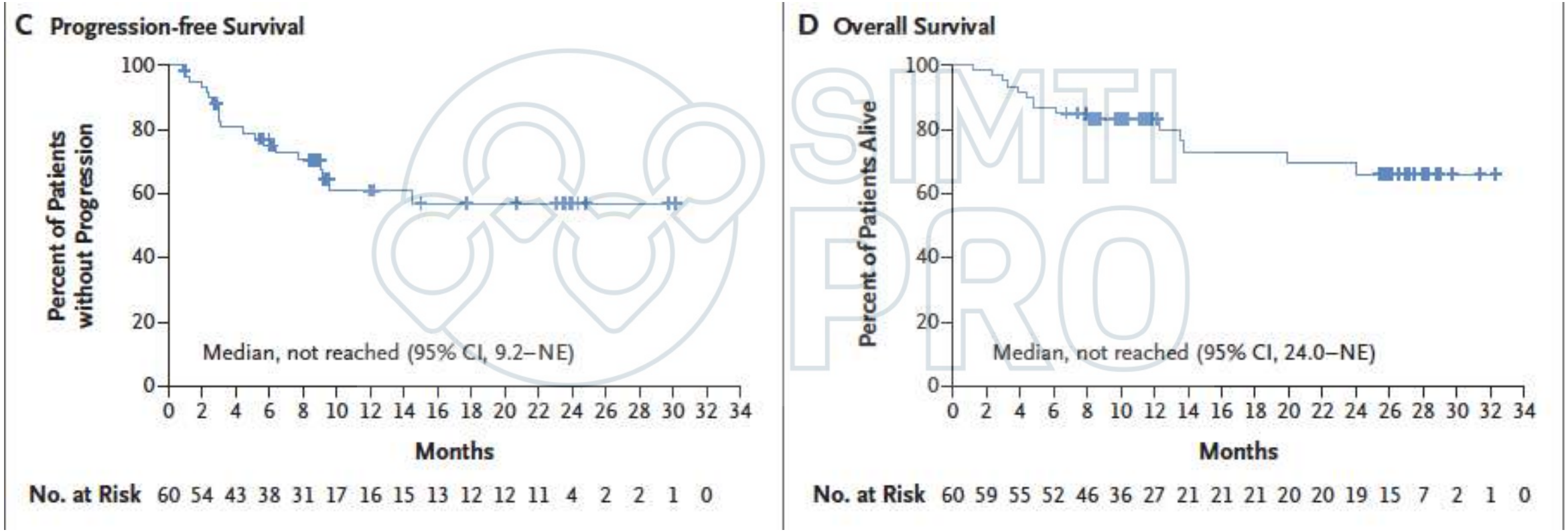


Wang. NEJM. 2020;382:1331.

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

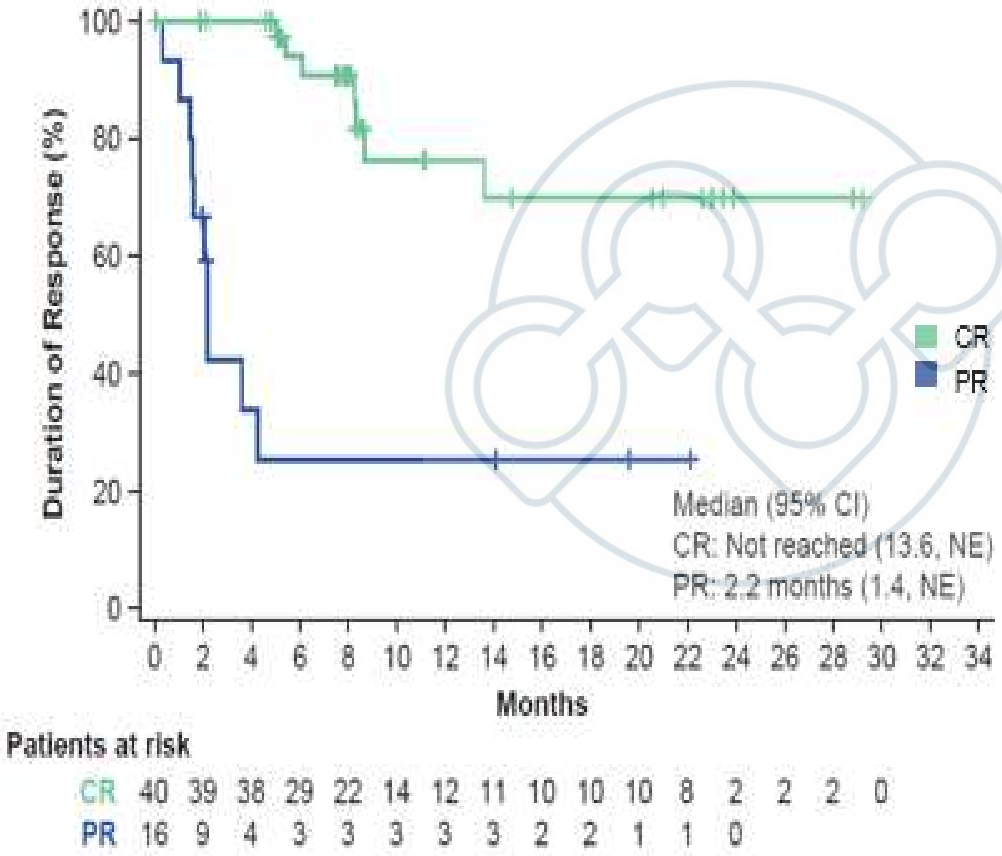
- Multicenter, single-arm, open-label phase II trial of brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma (N = 68 received agent)

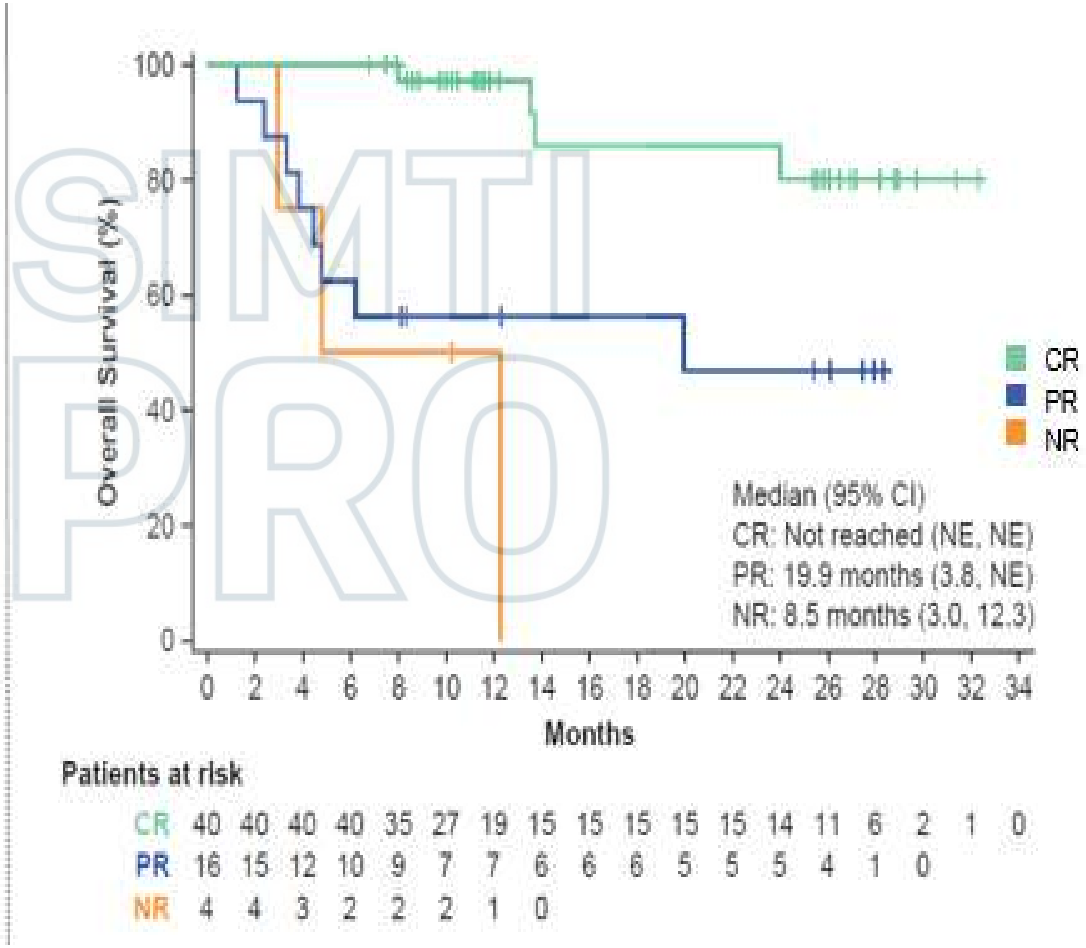


Wang. NEJM. 2020;382:1331.

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

- Survival by best response: 78% of patients with a CR remain in remission





Wang. NEJM. 2020;382:1331.

REAL-WORLD EVIDENCE OF BREXUCABTAGENE AUTOLEUCEL FOR THE TREATMENT OF RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

Characteristic	Apheresis (N=28)	Infusion (N=19)
Gender, number (%)		
- Male	25 (89)	17 (89)
- Female	3 (11)	2 (11)
Age, median years (range)	67 (47-79)	67 (51-78)
- <65	9 (32)	6 (32)
- ≥65	19 (68)	13 (68)
Prior lines, median (range)	3 (2-6)	2 (2-6)
- >2 prior lines	16 (57)	8 (42)
Primary refractory*, patients (%)	7 (25)	4 (21)
Previous autologous stem cell transplant, n (%)	12 (43)	6 (32)
Previous allogeneic stem cell transplant, n (%)	3 (11)	2 (11)
Previous BTK inhibitor therapy		
- Ibrutinib	28 (100)	19 (100)
- LOXO-305	2 (7)	0
Prior bendamustine therapy	13 (46)	8 (42)
Prior rituximab maintenance	10 (36)	6 (32)
Morphology at apheresis, patients (%)		
- Classical	14/26 (54)	11/17 (65)
- Blastoid	10/26 (38)	6 /17(35)
- Pleomorphic	2/26 (8)	0

Characteristic	Apheresis (N=28)	Infusion (N=19)
TP53 status at apheresis, patients (%)		
- Mutated	3/13 (23)	2/10 (20)
- Unmutated	10/13 (77)	8/10 (80)
Ki67 index > 30% at apheresis	16/18 (89)	11/13 (85)
Stage at apheresis, patients (%)		
- I-II	5 (18)	3 (16)
- III-IV	23 (82)	16 (84)
Simplified MIPI at apheresis, patients (%)		
- Low	6 (21)	3 (16)
- Intermediate	5 (18)	4 (21)
- High	17 (61)	12 (63)
Extranodal disease at apheresis, patients (%)	18 (64)	14 (74)
LDH at apheresis >ULN, N (%)	13 (46)	8 (42)
ECOG at apheresis, patients (%)		
- 0	12 (43)	7 (37)
- 1	13 (46)	11 (58)
- 2	3 (11)	1 (5)

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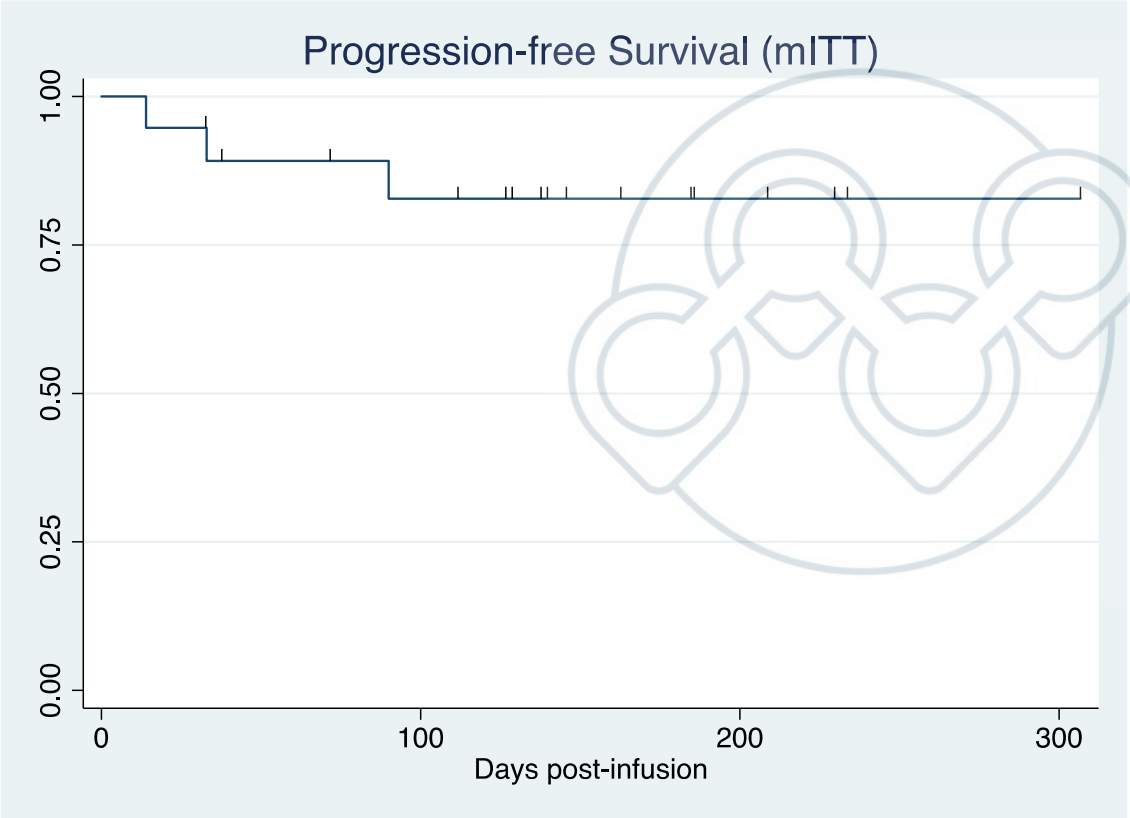
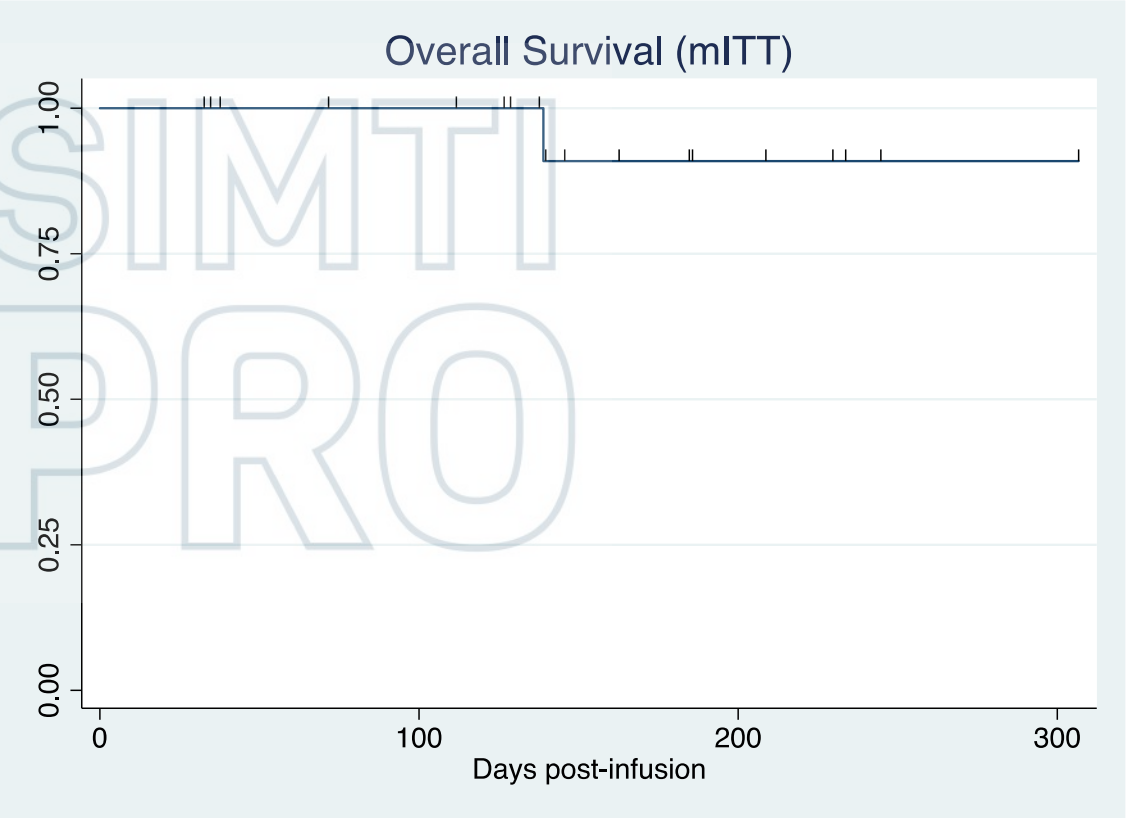
REAL-WORLD EVIDENCE OF BREXUCABTAGENE AUTOLEUCEL FOR THE TREATMENT OF RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

PFS and OS for infused patients





mITT, modified intention-to-treat

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ZUMA-5: Axicabtagene Ciloleucel for Patients With Relapsed/Refractory FL or MZL

Patients with R/R FL (grade 1-3a) or MZL (nodal or extranodal), ≥ 2 prior lines of therapy including anti-CD20 mAb + alkylating agent (N = 146)

→ **Conditioning CT**: **Fludarabine** 30 mg/m^2 + **Cyclophosphamide** 500 mg/m^2 Days -5, -4, -3

→ **CAR T-Cells**: **Axi-Cel** 2 x 10^6 cells/kg Day 0

→ ***Followed for safety up to 15 yrs***

Patients with SD but no relapse > 1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

Characteristic	Axi-Cel		
	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Median age, yrs (range)	60 (34-79)	66 (48-77)	61 (34-79)
▪ ≥ 65 yrs, n (%)	38 (31)	13 (59)	51 (35)
Male, n (%)	73 (59)	10 (45)	83 (57)
ECOG PS 1, n (%)	46 (37)	9 (41)	55 (38)
Stage III/IV disease, n (%)	106 (85)	20 (91)	126 (86)
≥ 3 FLIPI, n (%)	54 (44)	14 (64)	68 (47)
High tumor bulk by GELF,* n (%)	64 (52)	8 (36)	72 (49)

Characteristic	Axi-Cel		
	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Median prior tx, n (range)	3 (1-10)†	3 (2-8)	3 (1-10)
▪ ≥ 3	78 (63)	15 (68)	93 (64)
▪ PI3K inhibitor	34 (27)	9 (41)	43 (29)
Refractory disease,‡ n (%)	84 (68)	16 (73)	100 (68)
POD24§ from first anti-CD20 mAb tx, n (%)	68 (55)	11 (52)	79 (55)
Prior ASCT, n (%)	30 (24)	3 (14)	33 (23)

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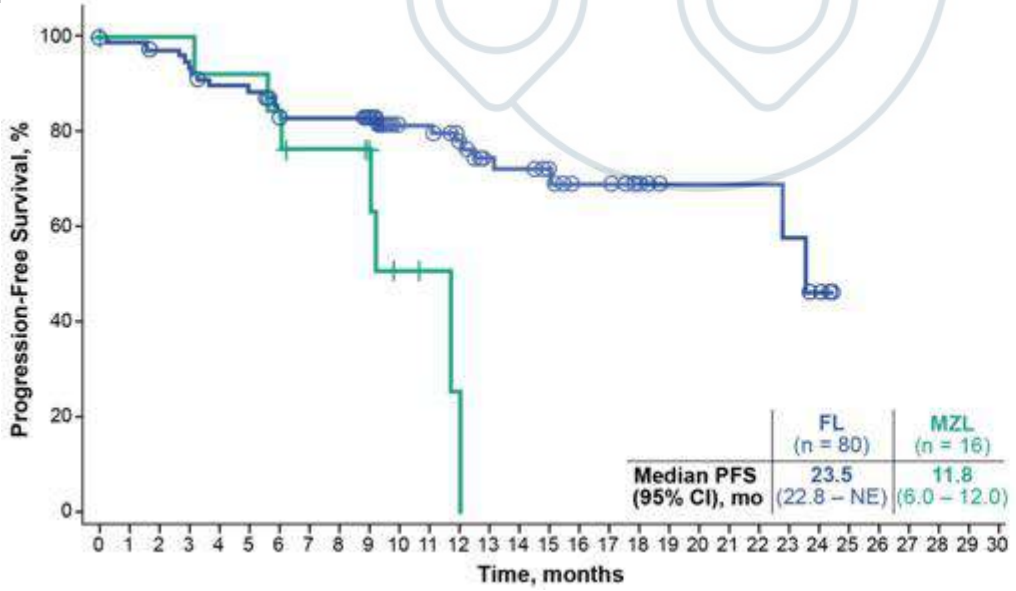
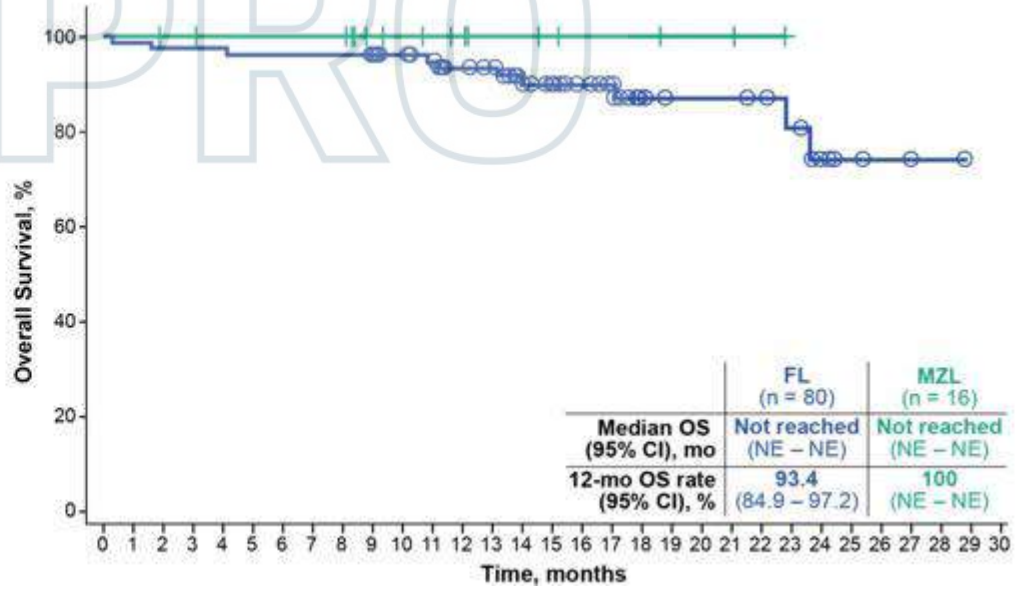
ZUMA-5: Axicabtagene Ciloleucel for Patients With Relapsed/Refractory FL or MZL

IRRC-Assessed Response,*† n (%)	Axi-Cel		
	FL (n = 84)	MZL (n = 20)	Overall (N = 104)
ORR	79 (94)	17 (85)	96 (92)
CR	67 (80)	12 (60)	79 (76)
PR	12 (14)	5 (25)	17 (16)
SD	3 (4)	0	3 (3)
ND	2 (2)	3 (15)	5 (5)

DoR by Best Response (95% CI)	FL	
	CR (n = 67)	PR (n = 12)
Median DoR, mos	NE (20.8-NE)	2.8 (2.1-8.2)
12-mo DoR rate, %	87.0 (75.6-93.3)	13.6 (1.0-42.6)

DoR by Best Response (95% CI)	MZL	
	CR (n = 12)	PR (n = 5)
Median DoR, mos	10.6 (3.1-NE)	8.1 (NE-NE)
12-mo DoR rate, %	NE (NE-NE)	0 (NE-NE)





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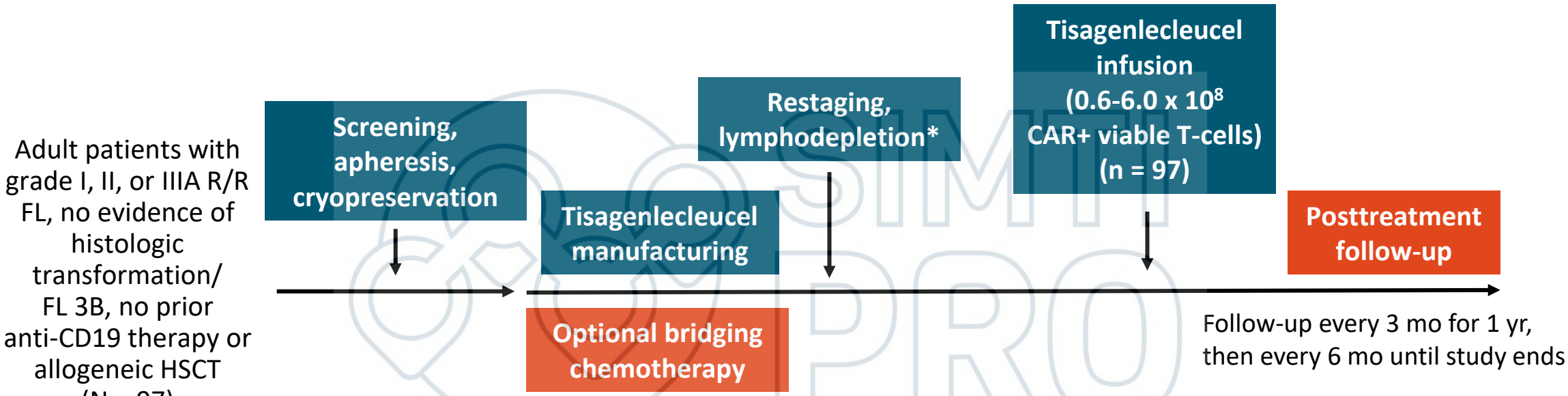
ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

- Single-arm phase II study of tisagenlecleucel for patients with R/R FL (N = 97 at interim analysis)



*Lymphodepleting therapy: fludarabine 25 mg/m^2/day IV for 3 days + cyclophosphamide 250 mg/m^2/day IV for 3 days or bendamustine 90 mg/m^2/day IV for 2 days.

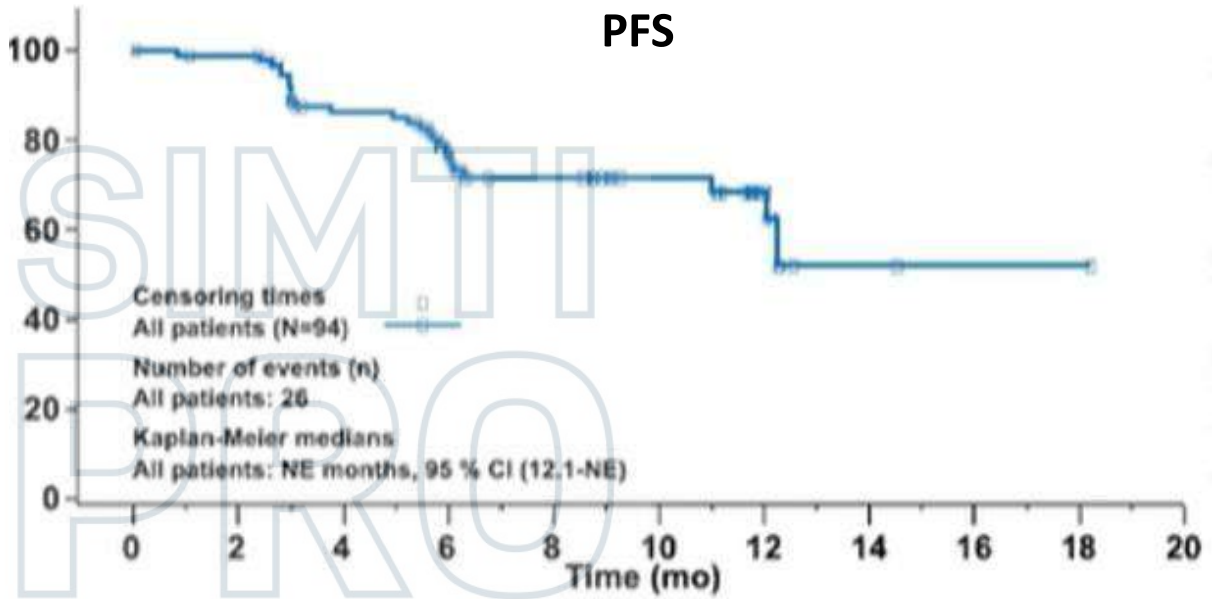
- Primary endpoint: CRR by IRC
- Secondary endpoints: ORR, DoR, PFS, OS, safety, cellular kinetics

Schuster. ASCO 2021. Abstr 7508.

ELARA: Tisagenlecleucel for Patients With Relapsed/Refractory FL

- Median follow-up for efficacy was 10.9 mo (range 4.3-19.7)

Response, %	Evaluable Patients (n = 94)
Investigator assessed	
▪ CRR	69.1
▪ ORR	90.4
IRC-assessed	
▪ CR	66.0
▪ PR	20.2
▪ ORR (CR + PR)	86.2



- Median DoR, PFS, and OS were not reached
- Responding patients had a 79% (95% CI: 66%-87%) probability of remaining in response for ≥6 mo
- 38.7% (12/31) of patients achieving PR converted to CR: 11 occurred between Mo 3 and 6

Schuster. ASCO 2021. Abstr 7508.

Take home messages

- **CAR-T cells are living drugs**: pharmacology of CAR-T is very different from inert drugs
- **Patient selection** is a critical step
- Consider CAR-T therapy and **refer early**
- Maintain clear communication with **CAR-T team** during all steps
- Collection of **real life data** is important

Aknowledgments

CAR-T Team @INT

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Radiologia	Rodolfo Lanocita, Davide Scaramuzza
Cardiologia	Fabio Turazza, Irina Arendar
Referente statistico	Rosalba Miceli, Silva Ljevar

All the Referral centers, patients, families and nurses

All the CAR-T teams: