QUARTO EVENTO NAZIONALE

SIE incontra i pazienti

Il Futuro delle CAR-T

Beatrice Casadei
IRCSS AOU di Bologna

26 maggio 2025
Bologna, Royal Hotel Carlton

SIE incontra i pazienti

Disclosures of Beatrice Casadei

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

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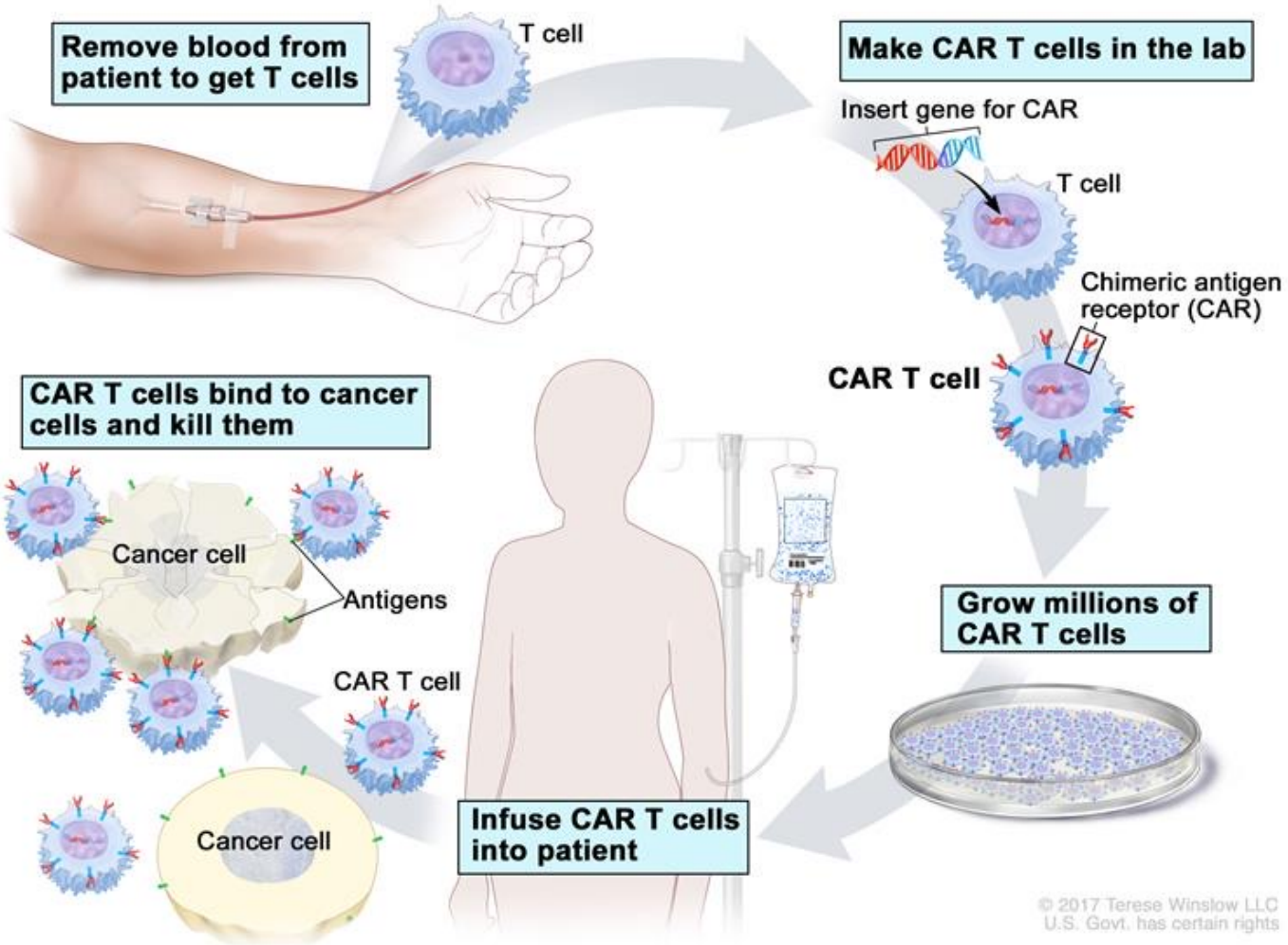
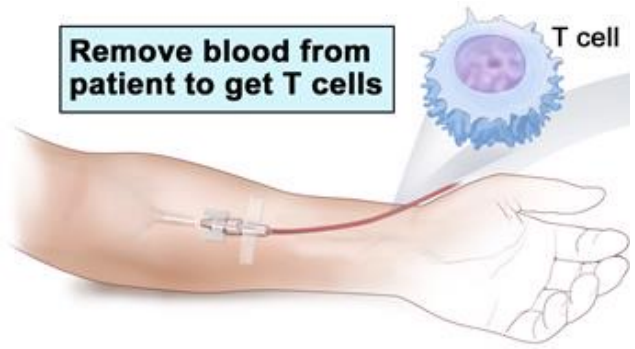
Presente e Futuro delle Terapie CAR-T



Il Presente: CAR-T Autologhe

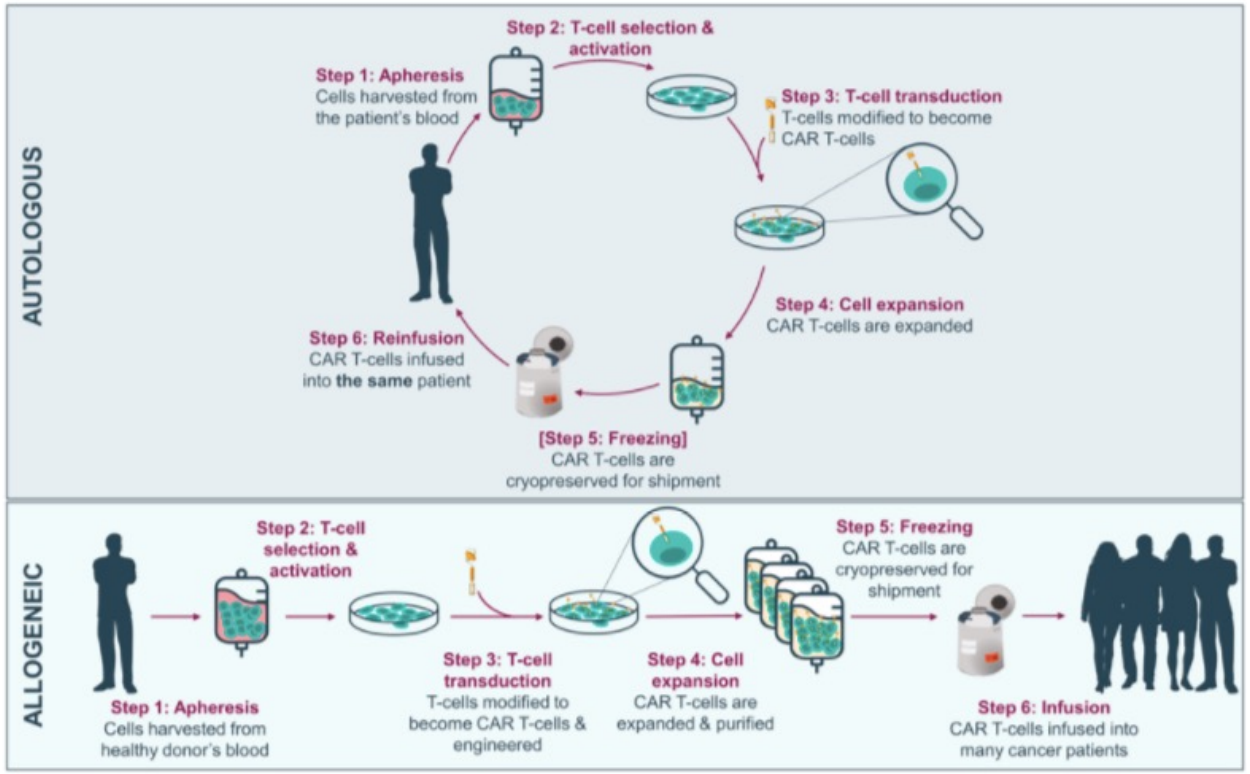
CAR-T autologhe



Pro:
- Immunogenicità limitata
- Ridotti effetti collaterali
- Efficacia

Contro:
- Necessaria linfocitoaferesi (tempo)
- T-cell fitness ridotta nel paz RR
- Ridotta accessibilità

Il Futuro (?): CAR-T Allogeniche



Pro:

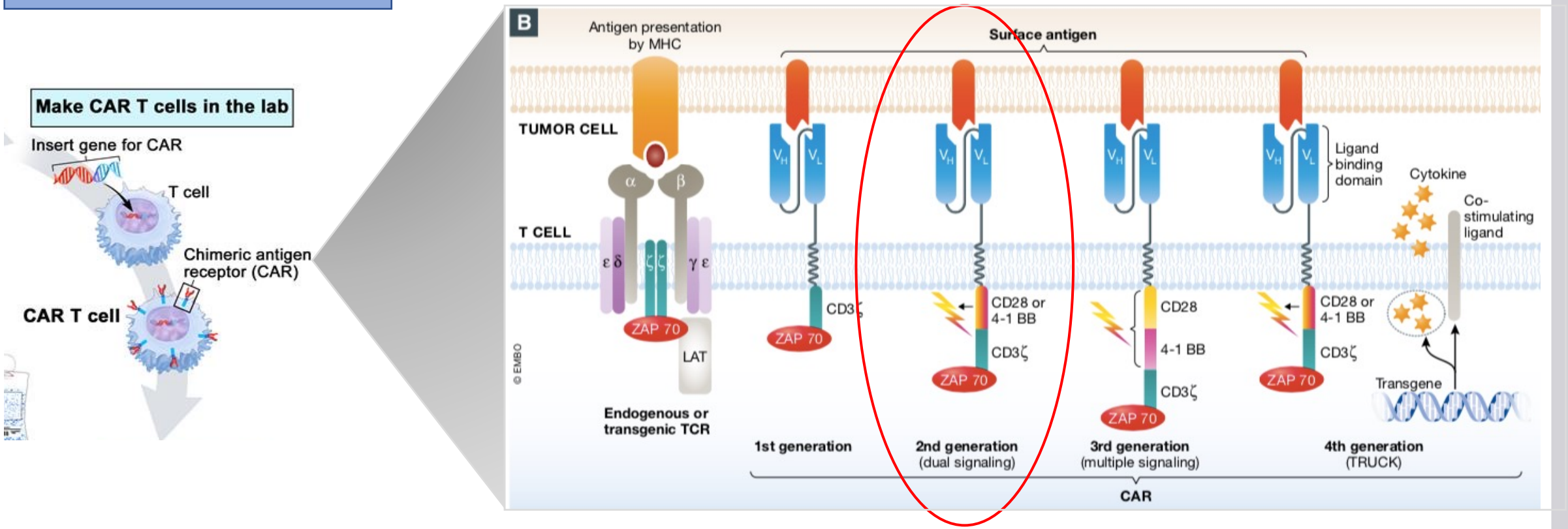
- Off the shelf (pronte all'uso)
- Maggiore accessibilità
- Possibile multiple infusioni
- Source: healthy donor → maggiore fitness dei linfociti T

Contro:

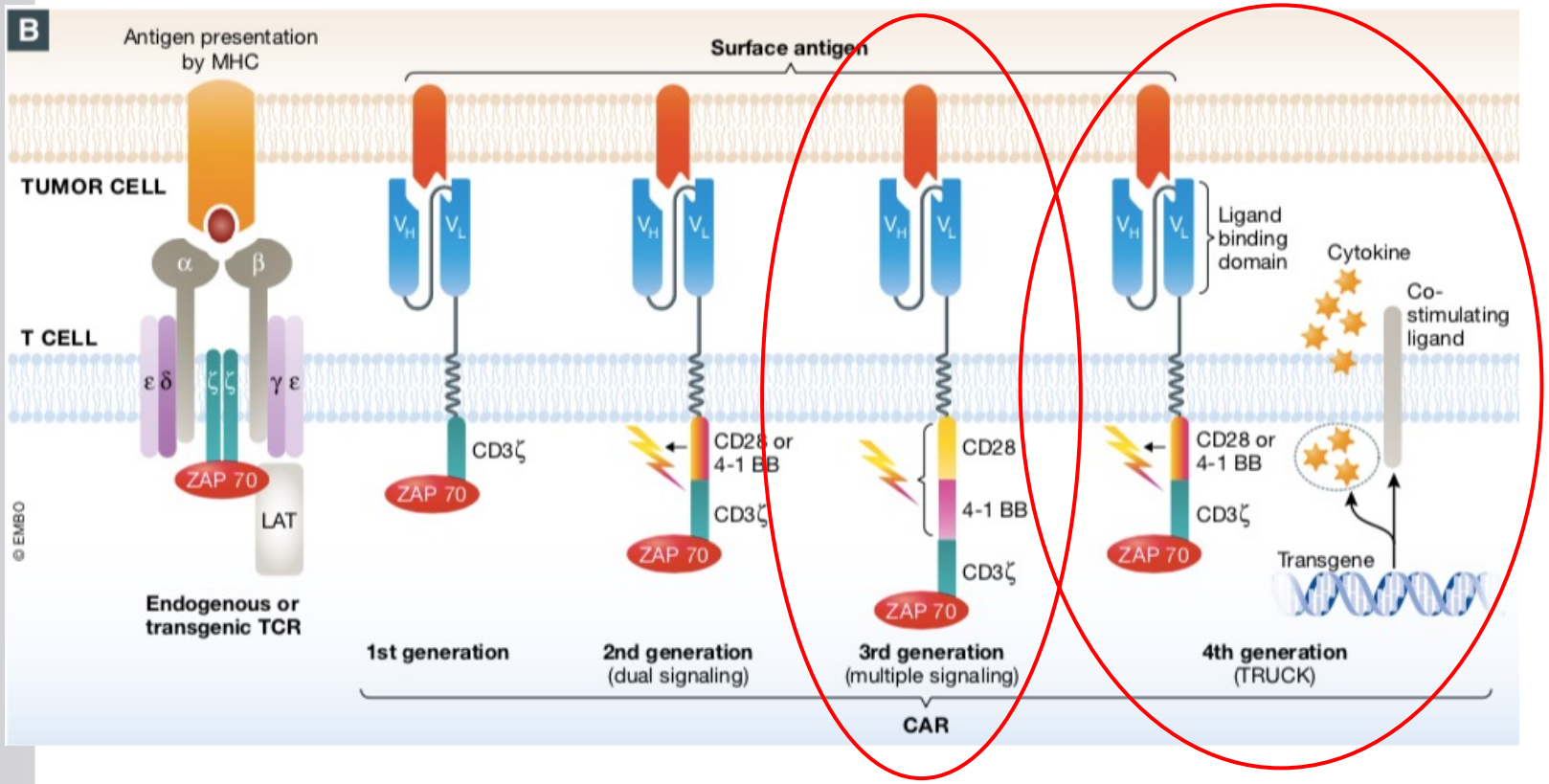
- Rischio di mancato engraftment dei linfociti CAR+
- Rischio di GVHD (TCR knock-out/ NK cells)
- Efficacia simile ma maggiore tasso di infezioni
- Necessari approcci più efficaci per prevenire reazioni immuni e quindi permettere un' epsansione in vivo più consistente e quindi una maggior persistenza delle allo-CART

Il Presente: Costrutto di II Generazione

Costrutti di II generazione



Il Futuro (?): Costrutto di III/IV Generazione



III generazione:

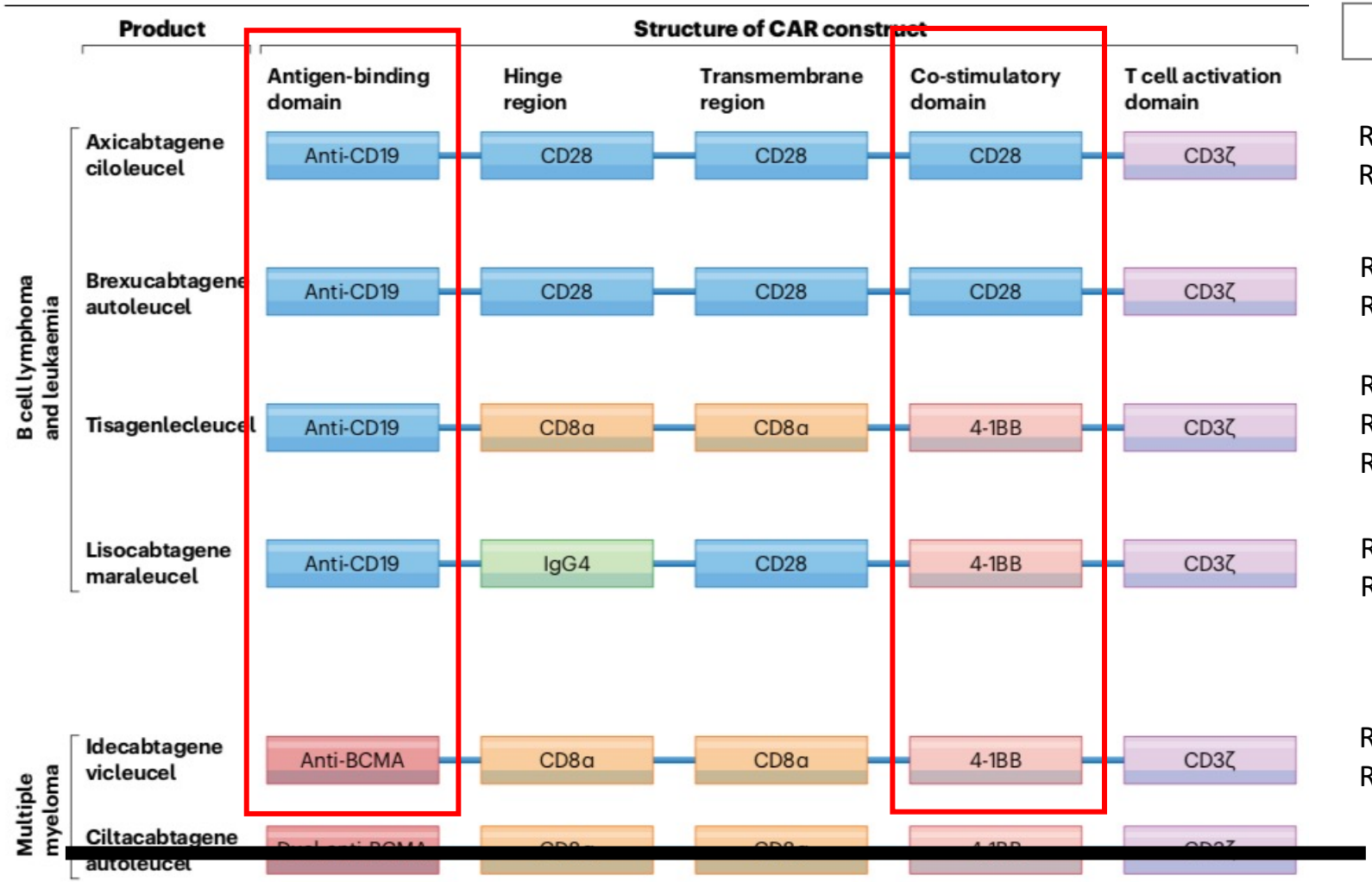
- ++ attivazione linfo T
- Efficacia simile a quelli di II gen
- Tossicità maggiore (+ grave)
- Ongoing trial CLL

IV generazione:

- rilascio di citochine
- ++ attivazione linfo T
- Modulazione microambiente
- Ongoing trial nei tumori solidi

SIE incontra i pazienti

Il Presente della Terapia CAR-T: Prodotti Disponibili e Approvazioni AIFA

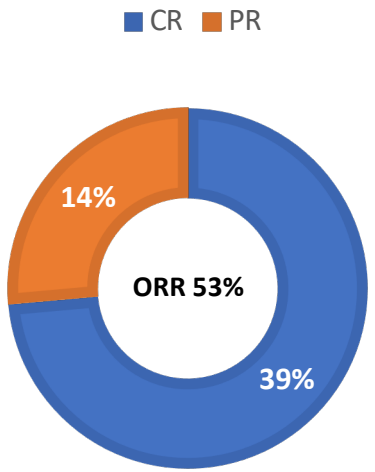


Approvazioni AIFA
RR DLBCL (≥ 2L), HGBCL (≥ 2L), PMBCL (≥ 3L) RR FL (≥ 4L)
RR MCL (≥ 3L) RR B-ALL
RR DLBCL (≥ 3L), HGBCL (≥ 3L) RR FL (≥ 3L) RR B-ALL (< 25aa)
RR DLBCL (≥ 3L), HGBCL (≥ 3L), PMBCL (≥ 3L) RR FLgr 3B (≥ 3L)
RR MM (≥ 2L) RR B-ALL

Modified from Cappell MK et al, Nature 2023

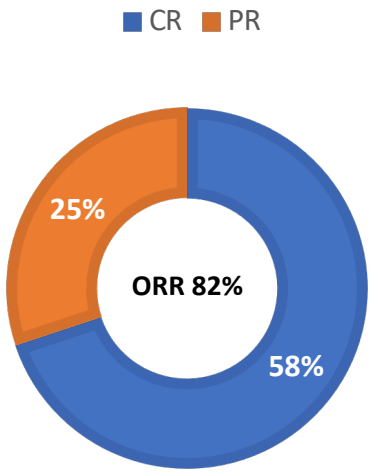
Il Presente : Efficacia nei LBCL (≥ 3L)

TISACEL (JULIET)



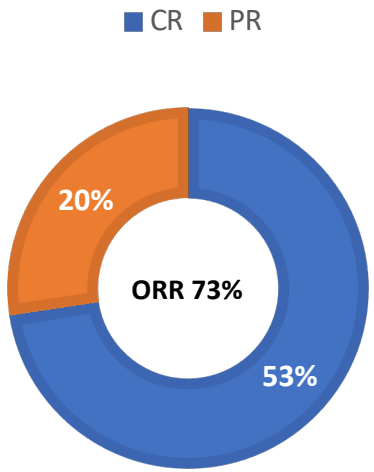
median DOR NR

AXICEL (ZUMA-1)



median DOR 11 mo

LISOCEL (TRANSCEND)



median DOR 23 mo

Schuster SJ, et al. Lancet Oncol 2021; Neelapu SS, et al. Blood 2023; Abramson JS, et al. Blood 2024

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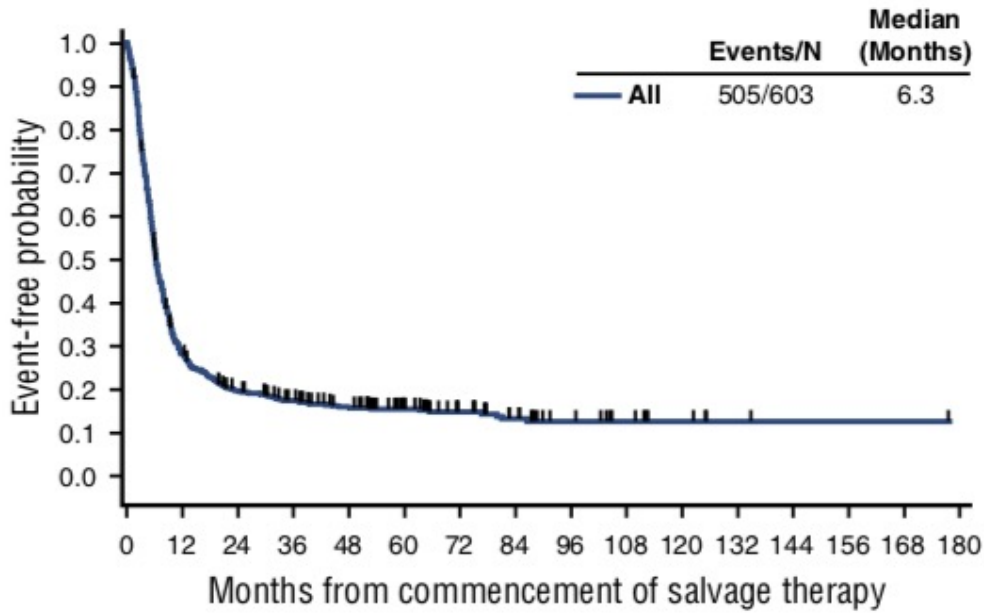
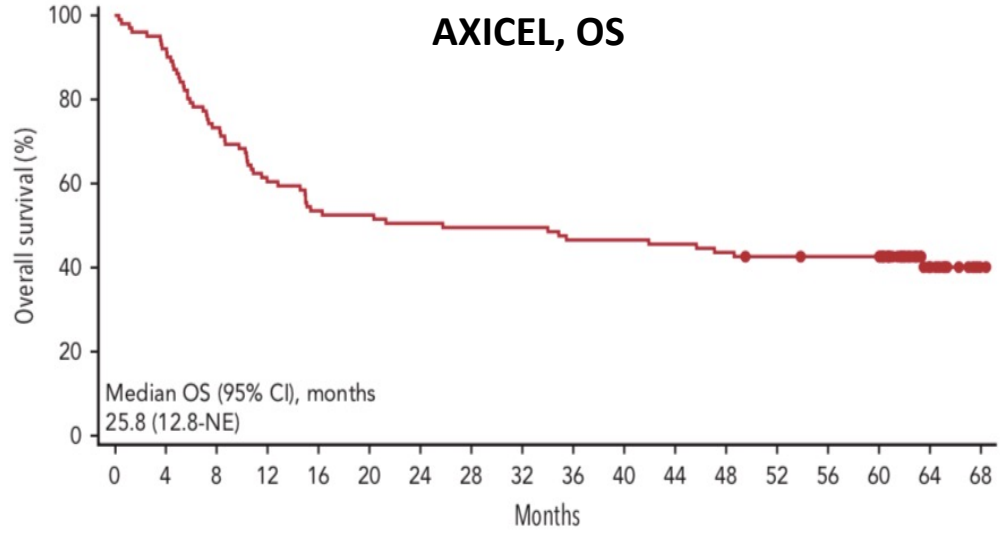
Il Presente: Efficacia nei LBCL (≥ 3L)

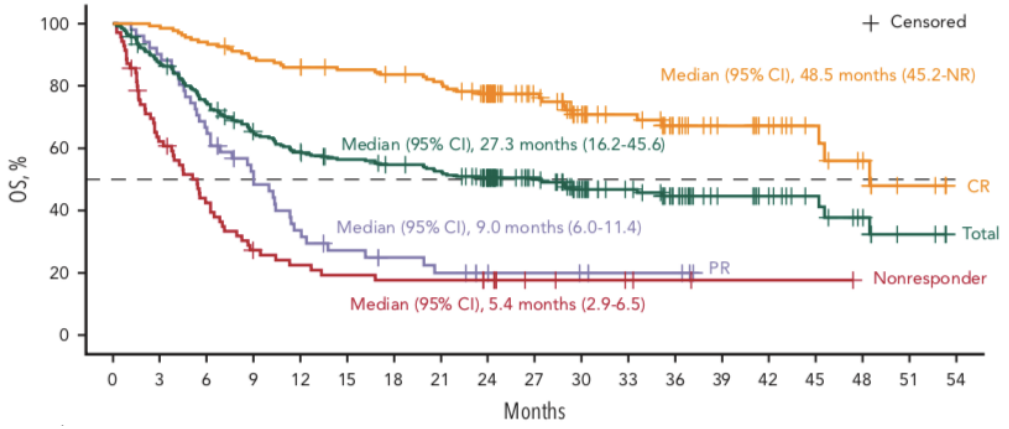
SCHOLAR-1, OS



AXICEL, OS



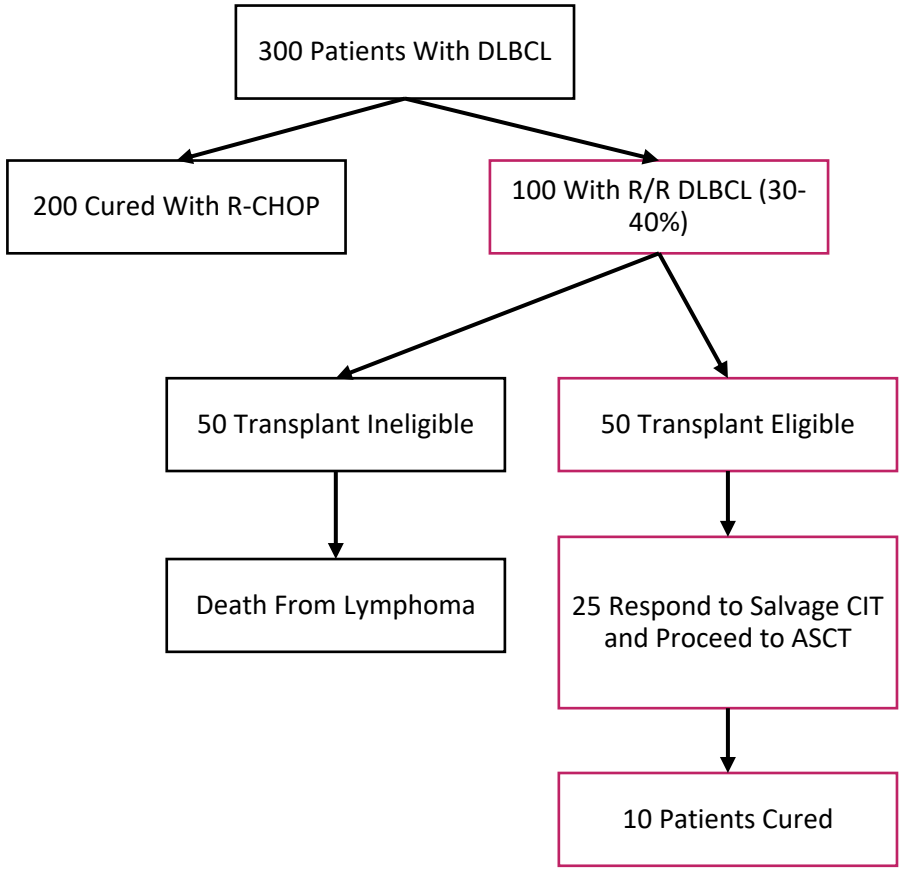
LISOCEL, OS



Crump M et al, Blood 2017; Schuster SJ, et al. Lancet Oncol 2021; Neelapu SS, et al. Blood 2023; Abramson JS, et al. Blood 2024

SIE incontra i pazienti

II Linea nei DLBCL: Background



10-15% dei pz curati con la II linea (SOC)

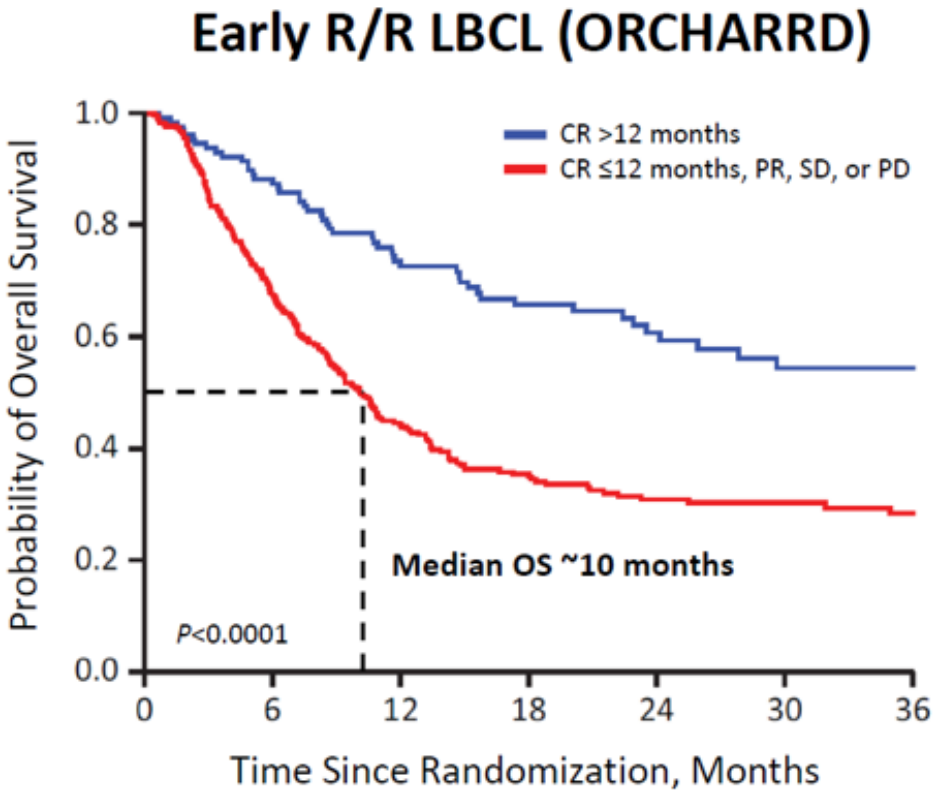


Figure adapted from Friedberg. Hematology Am Soc Hematol Educ Program 2011, van Imhoff GW J Clin Oncol 2017

Il Presente: Efficacia nei DBCL (2L)

TRANSFORM: Lisocel vs SOC

Key eligibility
- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit/NOS)
  - FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count

Screening + leukapheresis → 1:1 Randomization

Bridging therapy allowed[a] (PET[b] LDC[c])

Liso-cel arm (100 × 10^6 CAR$^+$ T cells)

Stratification
- Refractory vs relapsed
- sAAIPI: 0/1 vs 2/3

SOC arm[d]
3 cycles of CT (RDHAP, RICE, RGDP), followed by HDCT + ASCT

Response assessments
- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Primary endpoint
- EFS (per IRC)

Key secondary endpoints
- CR rate, PFS, OS

Other secondary endpoints
- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints
- Cellular kinetics
- B-cell aplasia

Crossover to liso-cel allowed
- Failure to respond by 9 weeks post-randomization
- PD at any time
- Start of new antineoplastic therapy after ASCT

ZUMA-7: Axicel vs SOC

R/R LBCL
N=359
77 sites

Key Eligibility:
- Aged ≥18 y
- LBCL
- R/R ≤12 mo of 1L therapy[a]
- Intended to proceed to HDT-ASCT

Stratification:
- Response to 1L therapy
- Second-line age-adjusted IPI (sAAIPI)

Optional Steroid-Only Bridging (No CHT)

1:1 Randomization

Axi-Cel (n=180)
Conditioning Chemotherapy + Axi-cel

SOC (n=179)
Cycle 1 | Cycle 2 | Cycle 3 (Optional)
Investigator-Selected Platinum-Based Chemoimmunotherapy[b]

Initial Disease Assessment (Day 50)

Responders (CR or PR) Proceed to HDT-ASCT

Nonresponders Additional Treatment Off Protocol[c]

Day 100 Assessment | Day 150 Assessment | LTFU Assessment

Primary Endpoint
- Event-free survival[d] (EFS) by blinded central review

Key Secondary Endpoints
- ORR
- OS

Secondary Endpoints
- PFS
- Safety
- PROs

No Protocol-Specified Crossover

Kamdar M et al, Lancet 2022; Locke F.L. et al, New Engl J Med; 2022

Il Presente: Efficacia nei DBCL (2L)

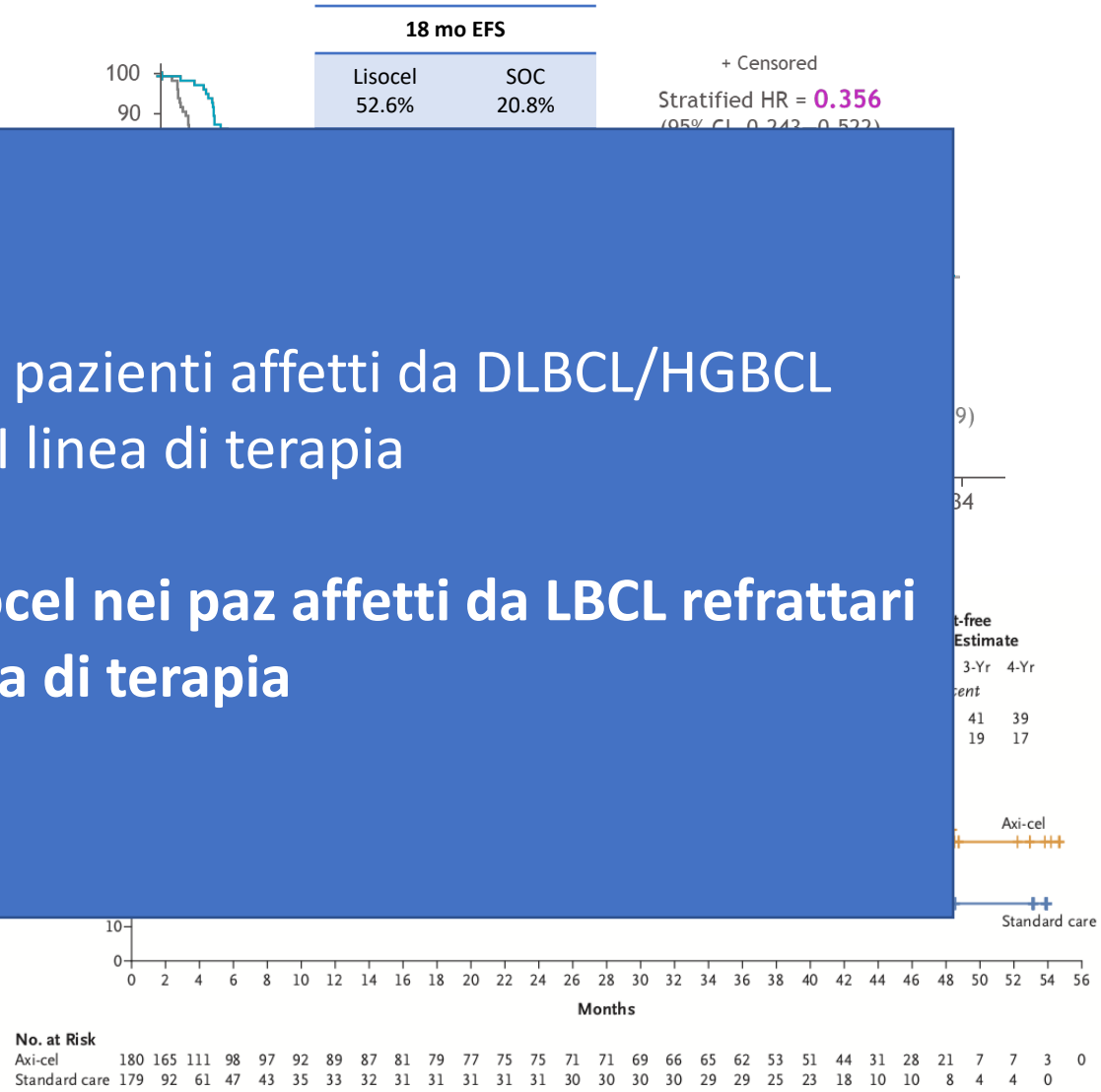
TRANSFORM

Response n (%)	Lisocel (n=92)	SoC (n=92)	p
ORR			
CR			
Survival, mo			
Median PFS			
Median OS			

Response n (%)			
ORR			
CR			
Survival, mo			
Median PFS	14.7	3.7	0.49
Median OS	NR	31.1	0.73

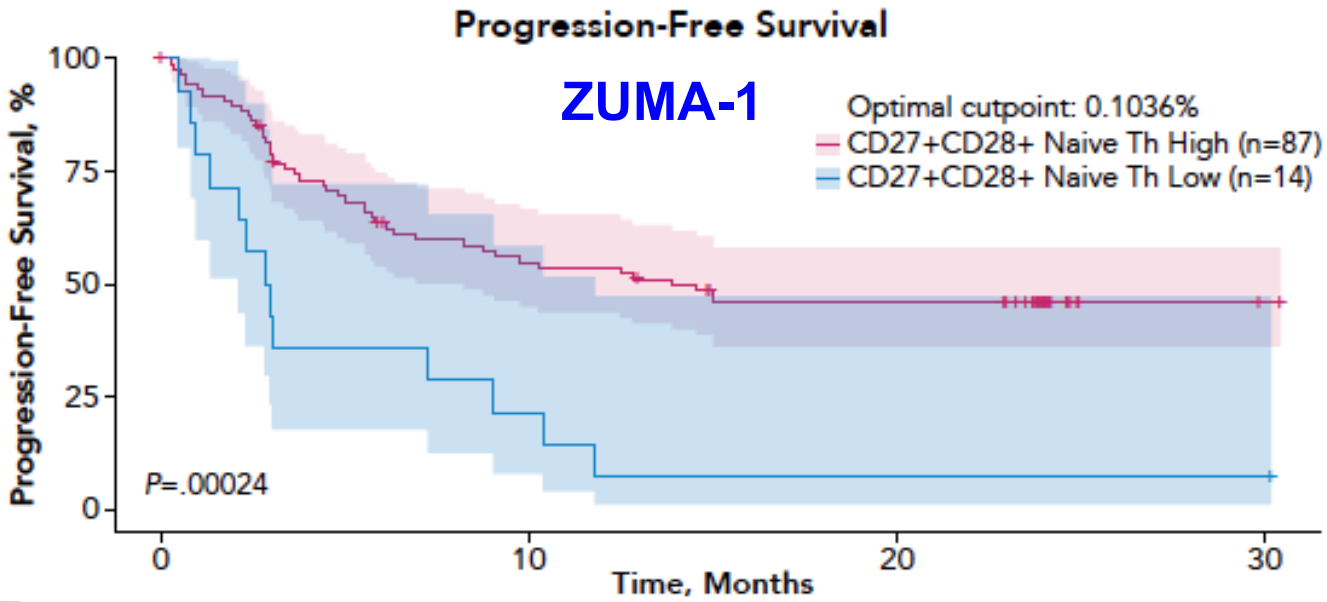
Presente: Axicel approvato nei pazienti affetti da DLBCL/HGBCL refrattari alla I linea di terapia

Futuro: Approvazione AIFA di lisocel nei paz affetti da LBCL refrattari alla I linea di terapia

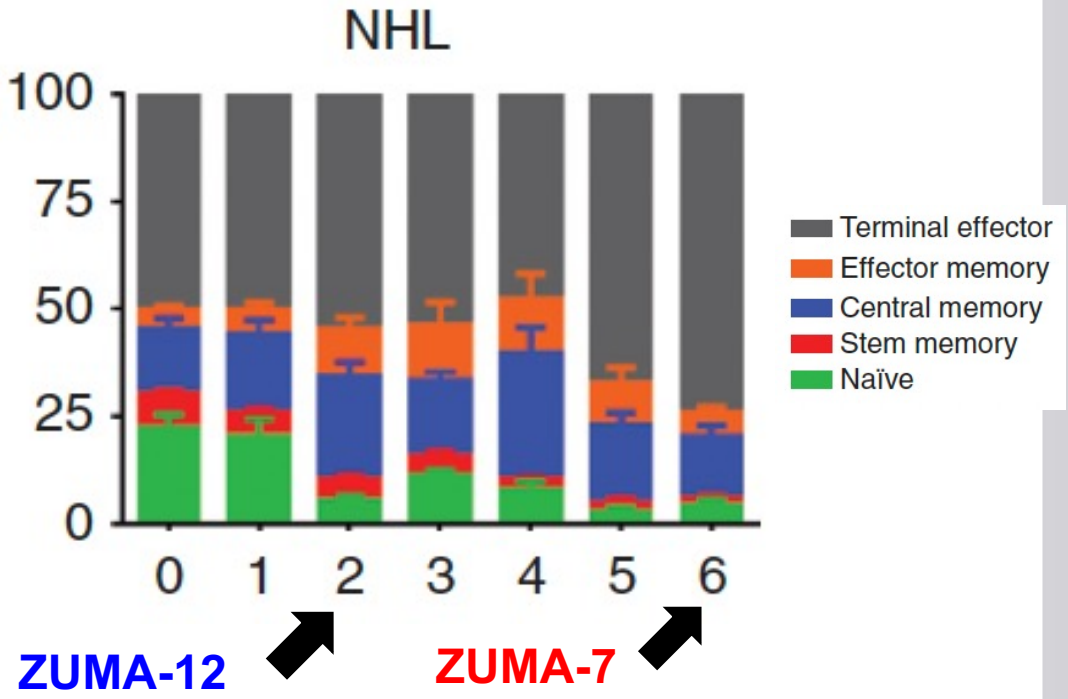


Abramson J et al, Blood 2023; Westin W. et al, New Engl J Med; 2023

La Qualità/Fitness dei Linfociti T nell'Aferesi si Associa ad una Miglior Efficacia



CD27⁺CD28⁺ naïve T cells in apheresis associated with better efficacy

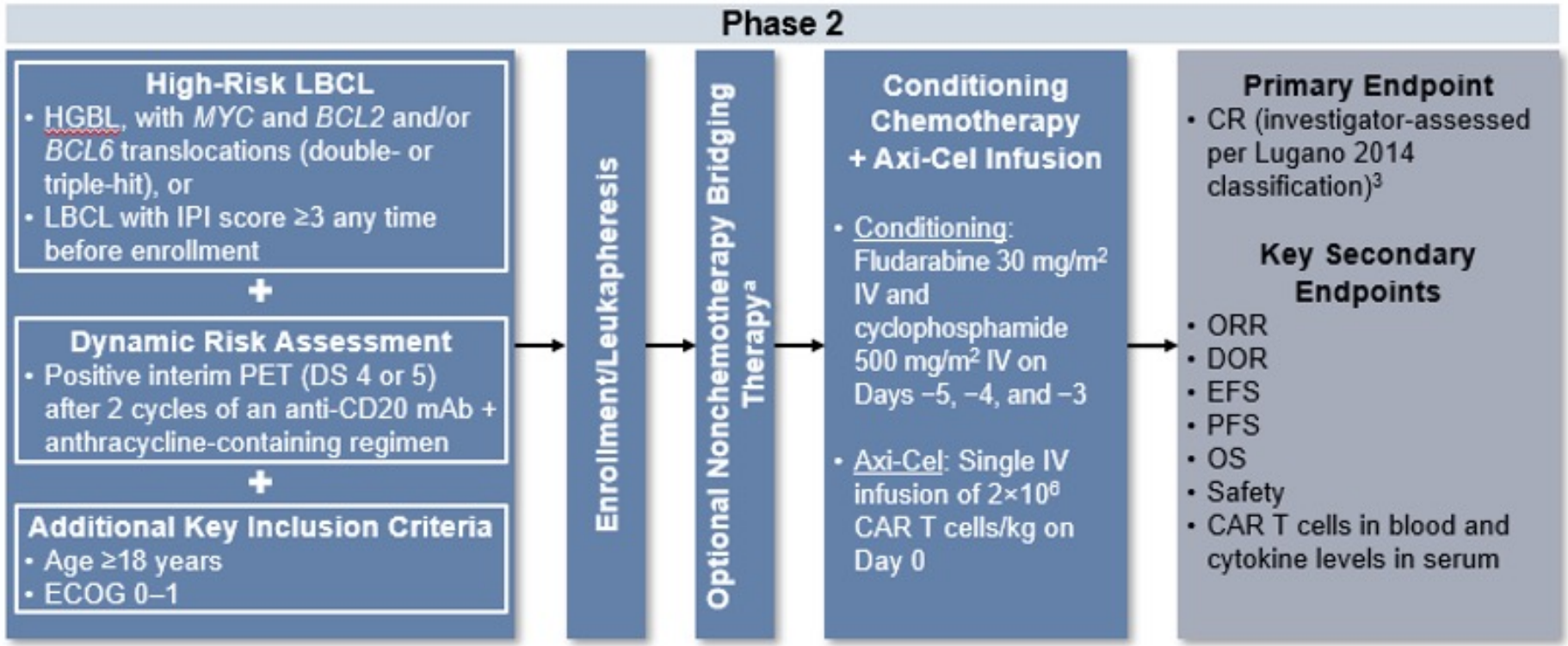


Previous tx impairs immune cell phenotype and fitness

Budka et al, *AACR* 2021, Abstract #CT166

Il Futuro: I Linea nel DLBCL

ZUMA-12: Axi-cel as 1L Therapy in High-Risk LBCL



To assess the efficacy and safety of axi-cel as part of 1L therapy after **an incomplete 1L** treatment regimen of **two cycles** of chemoimmunotherapy in patients with high-risk LBCL

a) Therapies allowed were corticosteroids, localized radiation, and HDMP+R

Neelapu SS, et al. Nat Med 2022

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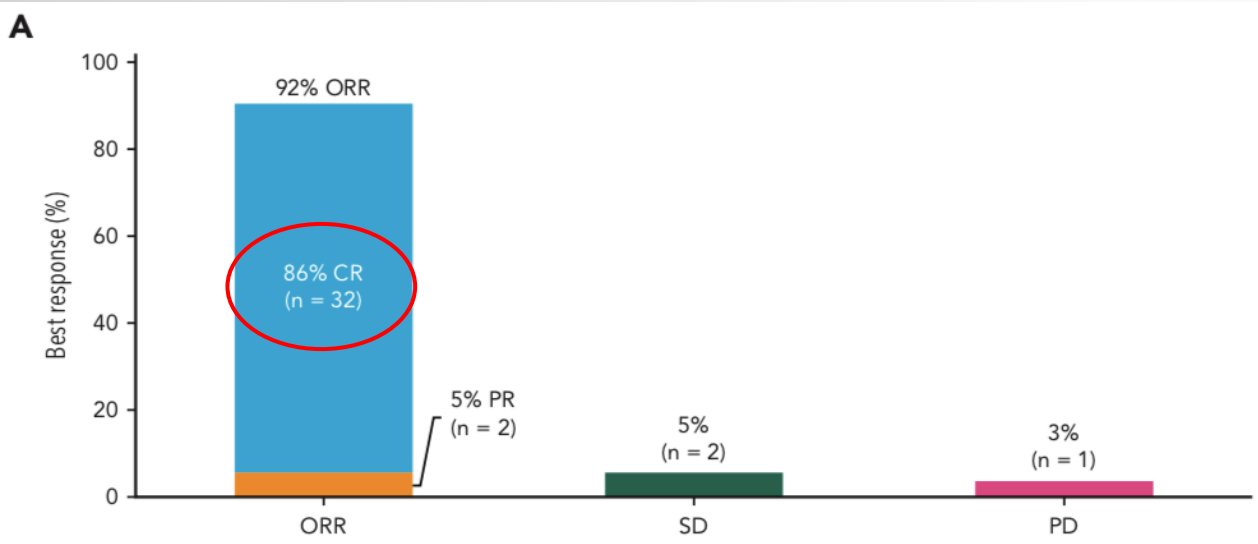
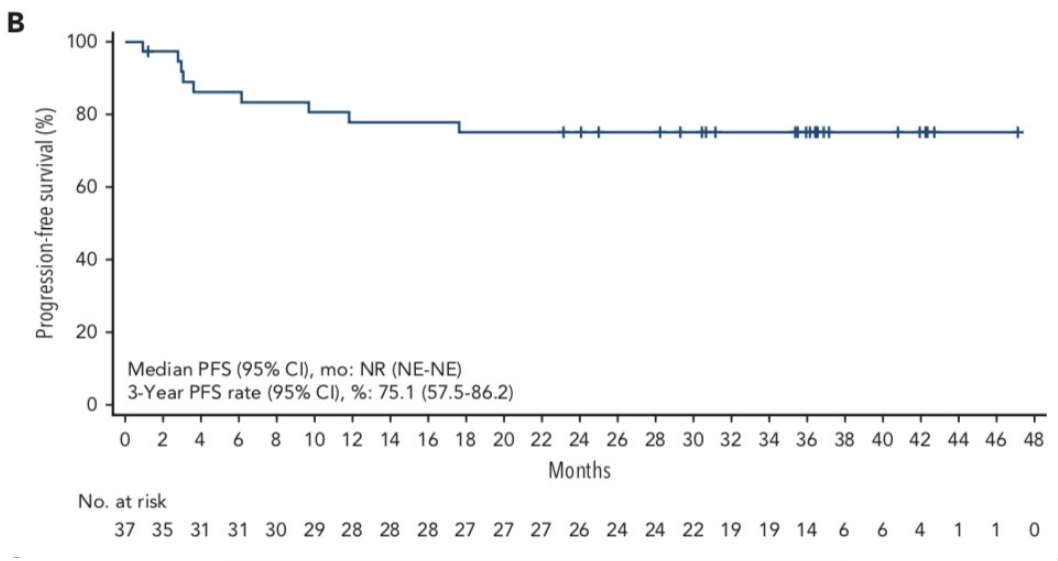
Il Futuro: I Linea nel DLBCL





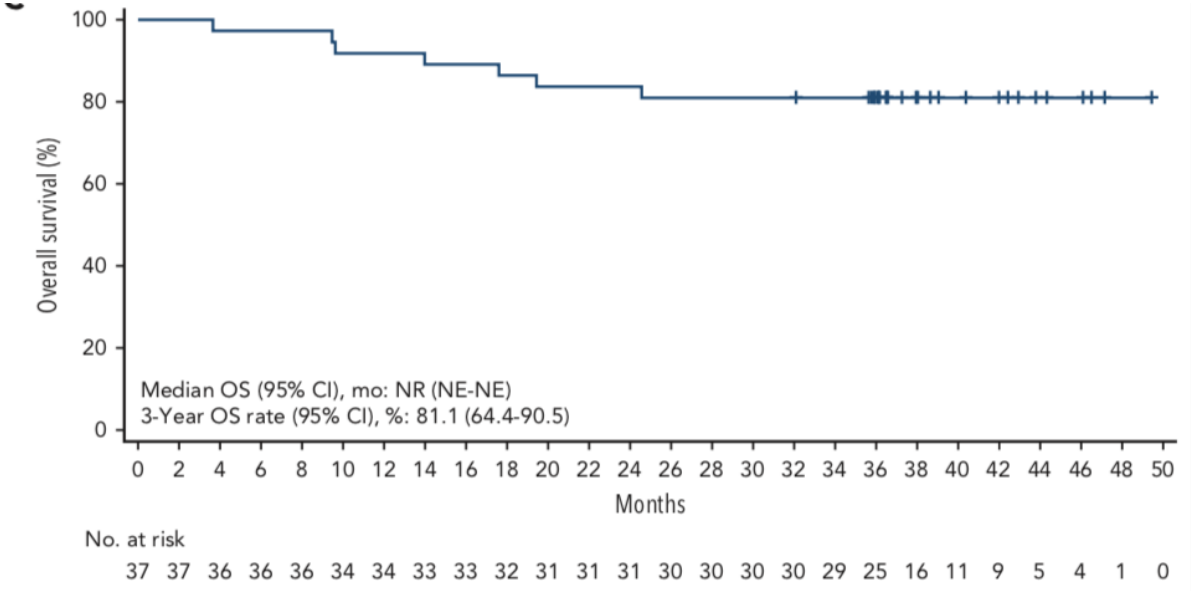


Table 3 | Adverse events of interest occurring in ≥15% of all treated patients, by worst grade

Adverse event[a], *n* (%)	Grade 1	Grade 2	Grade ≥3	Total
Subjects with any CRS[a]	27 (68)	10 (25)	3 (8)	40 (100)
Pyrexia	8 (20)	28 (70)	4 (10)	40 (100)
Hypotension	7 (18)	5 (13)	0 (0)	12 (30)
Chills	9 (23)	1 (3)	0 (0)	10 (25)
Hypoxia	2 (5)	2 (5)	5 (13)	9 (23)
Sinus tachycardia	6 (15)	0 (0)	0 (0)	6 (15)
Subjects with any neurologic events	14 (35)	6 (15)	9 (23)	29 (73)
Confusional state	7 (18)	2 (5)	2 (5)	11 (28)
Encephalopathy	2 (5)	2 (5)	6 (15)	10 (25)
Tremor	8 (20)	2 (5)	0 (0)	10 (25)

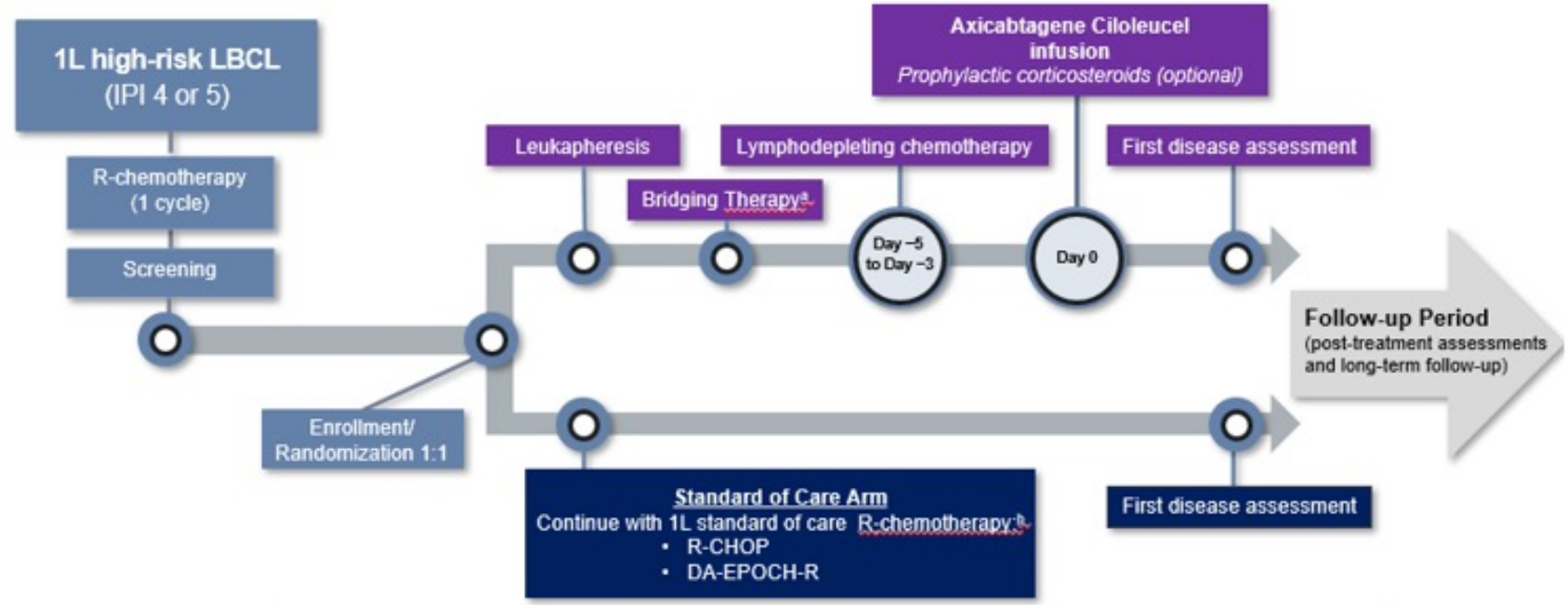
[a]Adverse events include those with onset on or after axi-cel infusion date and coded using MedDRA v.23.1. Neurologic events were identified using the modified blinatumomab registrational study[35]. CRS was graded according to Lee et al.[36]. The severity of all adverse events, including neurologic events and symptoms of CRS, was graded according to CTCAE v.5.0.

Neelapu SS, et al. Nat Med 2022; Chavez JC, et al. Blood 2025

SIE incontra i pazienti

Il Futuro: I Linea nel DLBCL

ZUMA-23: Axi-cel vs SOC for Newly Diagnosed High-Risk LBCL



a) Bridging therapy with R-CHOP or DA-EPOCH-R will be administered during the cell manufacturing period.

https://clinicaltrials.gov/ct2/show/NCT05605899.

Il Presente: Efficacia nei FL (≥3L)

Presente: tisacel e axicel approvati nei pazienti affetti da FL gr 1-3A RR (tisacel ≥3L, axicel ≥4L)

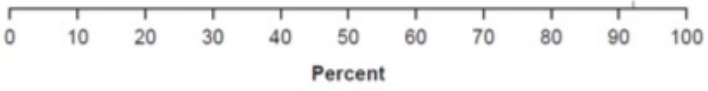
Futuro: Approvazione AIFA di lisocel nei paz affetti da FL gr 1-3A RR (≥3L)

Median fo					
mDOR	NR (fup 29 mo)	mDOR	60 mo	mDOR	NR
mPFS	53 mo	mPFS	57.3 mo	mPFS	NR
mOS	NR	mOS	NR	mOS	NR

Fowler NL et al, Nature Med 2022; Thieblemont C et al, ASH 20204 abs#3034; Neelapu SS et al, ASH 2024 abs#864; Morschhauser F. et al Nature 2024

Il Presente: Efficacia nei FL ad Alto Rischio (≥3L)

	No. of Patients	No. of Patients with a Response	Percent of Patients with Overall Response (95% CI)
Overall	104	96	92 (85–97)
Age, years			
<65	62	58	94 (84–98)
≥65	42	38	90 (77–97)
Sex			
Male	54	51	94 (85–99)
Female	50	45	90 (78–97)
ECOG performance status			
0	63	58	92 (82–97)
1	41	38	93 (80–98)
High tumor burden (GELF criteria)			
Yes	49	47	96 (86–100)
No	55	49	89 (78–96)
Number of prior therapies			
2	32	28	88 (71–96)
3	26	25	96 (80–100)
≥4	46	43	93 (82–99)
Prior PI3K inhibitor			
Yes	35	33	94 (81–99)
No	69	63	91 (82–97)
Prior lenalidomide			
Yes	32	29	91 (75-98)
No	72	67	93 (85-98)
Prior autologous SCT			
Yes	23	21	91 (72–99)
No	81	75	93 (85–97)
Relapse/refractory subgroup			
Relapsed	28	25	89 (72–98)
Refractory	76	71	93 (85–98)
POD24 from initiating first anti-CD20 mAb–containing therapy			
Yes	57	53	93 (83–98)
No	36	33	92 (78–98)
Corticosteroid and/or tocilizumab use			
Yes	63	57	90 (80–96)
No	41	39	95 (83–99)



Jacobson C et al, Lancet Oncol 2022

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Il Futuro: II linea nei FL ad alto rischio

ZUMA 22: AXICEL VS SOC in Subjects With HIGH RISK Follicular Lymphoma (NCT05371093)

Phase 3
R/R FL
(2L POD24 and 3L)
(N≈230)

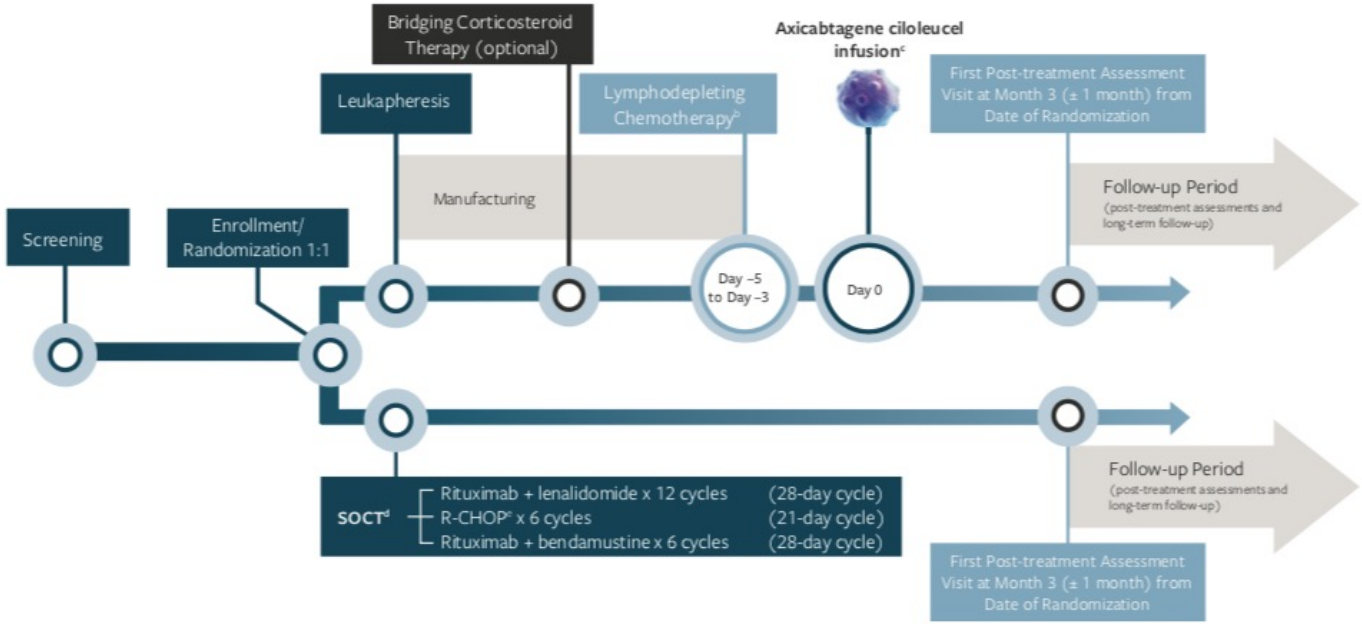
Arm A
Axicabtagene ciloleucel infusion

Arm B
SOCT—investigator's choice of one of the following therapies:
- Rituximab + lenalidomide
- R-CHOP
- Rituximab + bendamustine

Primary End Point
- PFS[a]

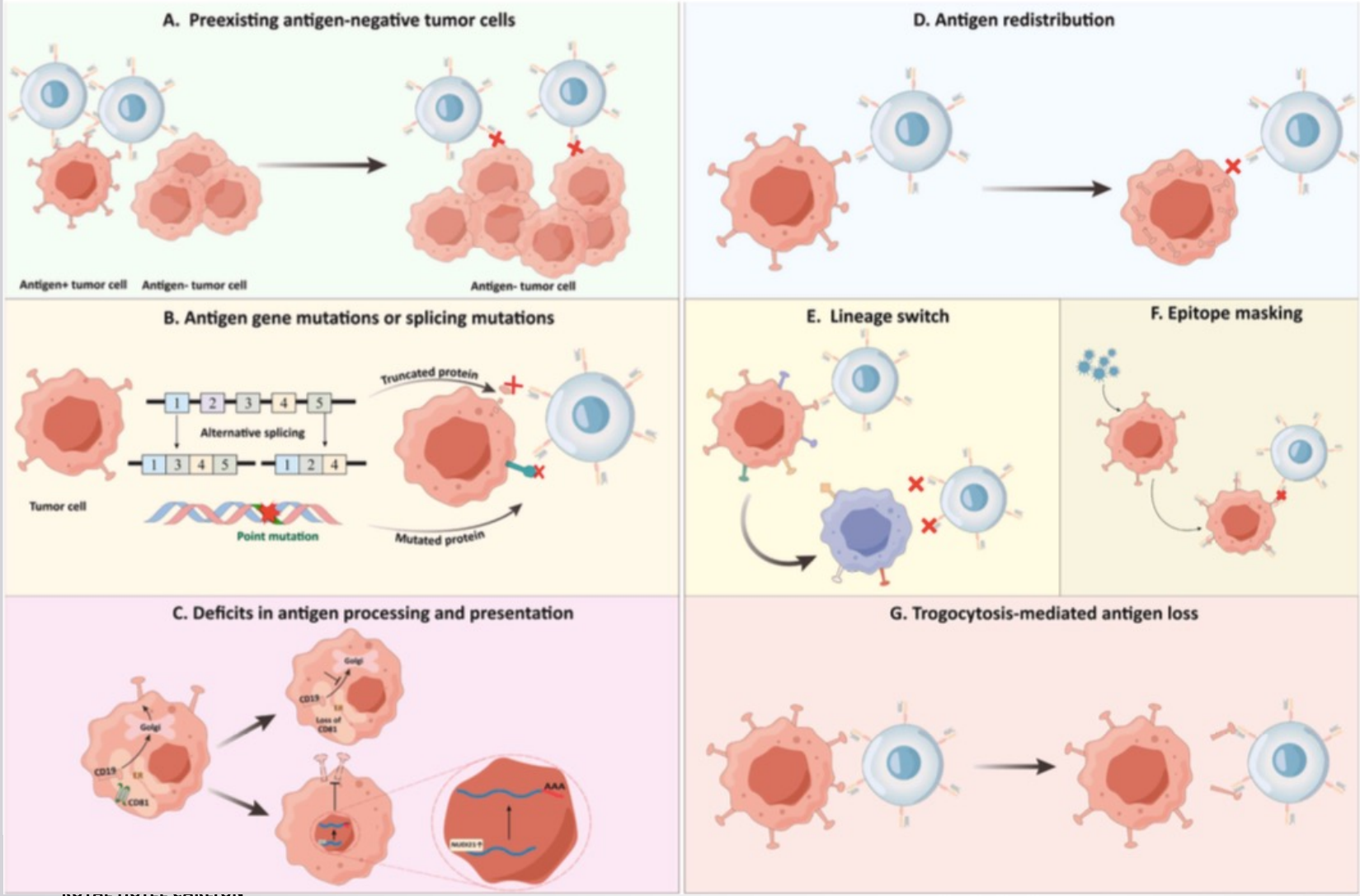
Secondary End Points
- CR rate[a]
- ORR[a]
- DOR[a]
- Duration of CR[a]
- OS
- EFS[a]
- TTNT
- Percentage of participants experiencing TEAEs
- Percentage of participants experiencing clinically significant changes in safety laboratory values
- PROs/QoL
  - —Change from baseline EORTC QLQ-C30
    - Global health status QoL scale
    - Physical functioning domain
  - —Change from baseline NHL-LG20
    - Global health status QoL scale
    - Physical functioning domain
  - —Changes from baseline in the EQ-5D-5L
  - —Changes from baseline in the VAS scores

Treatment Schema[2]



SIE incontra i pazienti

Antigen Escape e Resistenza alla tp CAR-T



Principale meccanismo di resistenza:

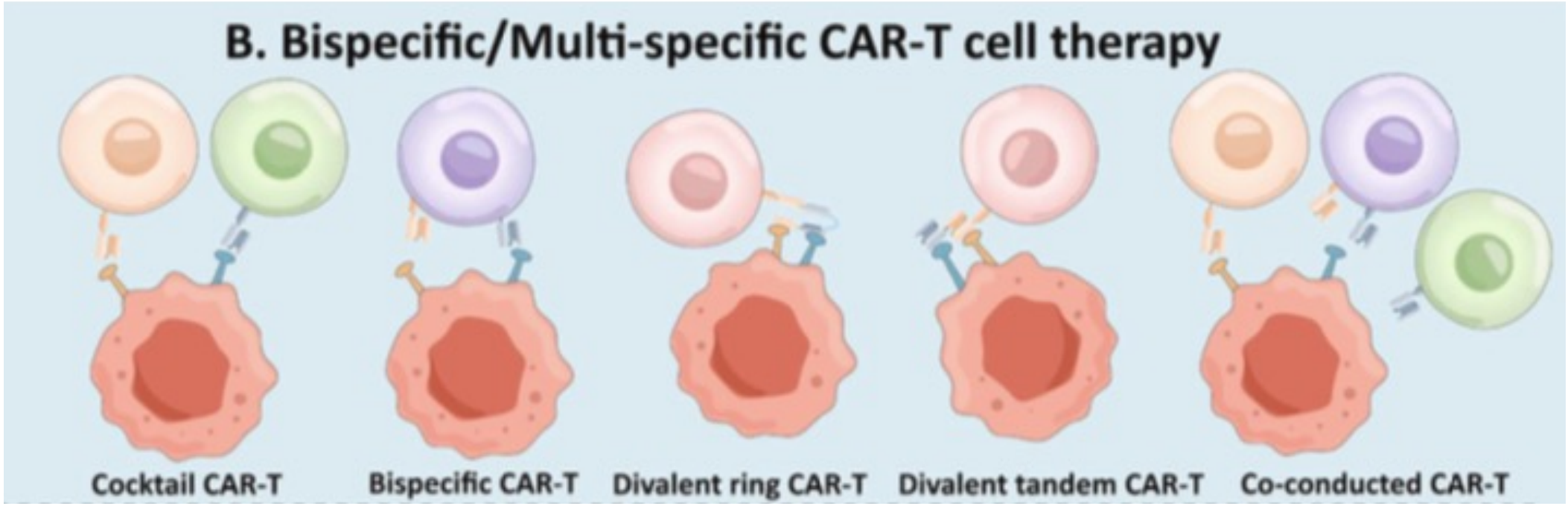
- 20-30% dei linfomi B perde il CD19
- 20-70% delle B-ALL perde il CD19

Altri meccanismi di resistenza:

- T-cell fitness/function/exhaustion
- Immunosuppressive TME
- Tossicità delle CAR T-cell

Lin H et al, Biomedicine and Pharmacotherapy 2024

Il Futuro: CAR-T Dirette Contro Differenti Antigeni



Lin H et al, Biomedicine and Pharmacotherapy 2024

Il Futuro: Terapie di Combinazione (CAR-T +….)

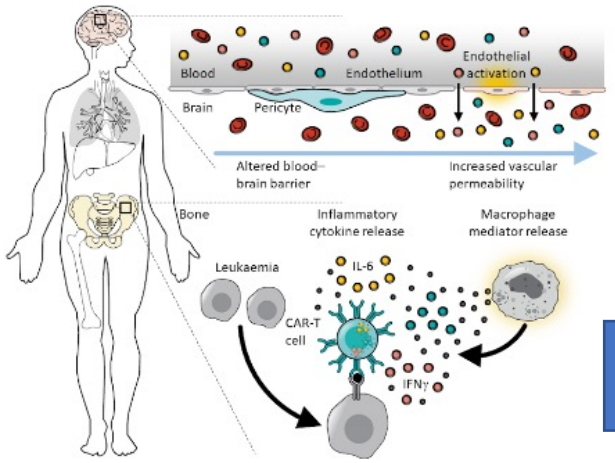
- **LV20.19 CAR T-Cells in Combination With Pirtobrutinib for Relapsed, Refractory B-cell Malignancies** (NCT 05990465)
  - NHLs (FL**,** MZL, MCL; PMBCL, DLBCL, BL)
  - LV20: CAR-T bispecifico anti CD19 anti CD20, costimolazione 41BB
  - Pirtobrutinib 200 mg/die per os almeno 14 giorni pre aferesi, come bridging fino alla linfodeplezione poi ripreso tra i giorni 28-120 post infusione come mantenimento
  - ≥ 2 linee

- **Autologous Cells Derived Anti-CD19 CAR-Engineered T Cells With Concurrent BTK Inhibitor for B Cell Lymphoma** (NCT05020392)
  - anti-CD19 CAR-T VS anti-CD19 CAR-T + BTK inhibitor (Ibrutinib, Zanubrutinib, Orelabrutinib)
  - ≥ 1 linea

SIE incontra i pazienti

Il Presente delle CAR-T: Tossicità Acuta

CRS



Cytokine release syndrome

- Fever, hypotension, hypoxia
- Capillary leak syndrome
- Arrhythmia
- Coagulopathy
- HLH / MAS

Any grade: 40-95%
Gr ≥ 3: 2-20%

AE, adverse event; CRS, cytokine release syndrome; HLH, haemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; IFNγ, interferon gamma; IL, interleukin; MAS, macrophage activation syndrome.

June CH, et al. Science. 2018;359:1361-65.
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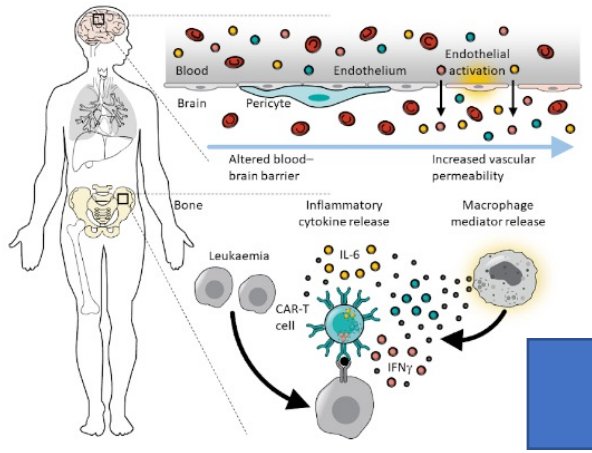
ICANS



Neurological events

- Headache, confusion
- Tremors
- Aphasia
- Paresis
- Seizures
- Cerebral edema

Any grade: 4-70%
Gr ≥ 3: 10-30%

AE, adverse event; CRS, cytokine release syndrome; HLH, haemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; IFNγ, interferon gamma; IL, interleukin; MAS, macrophage activation syndrome.

June CH, et al. Science. 2018;359:1361-65.
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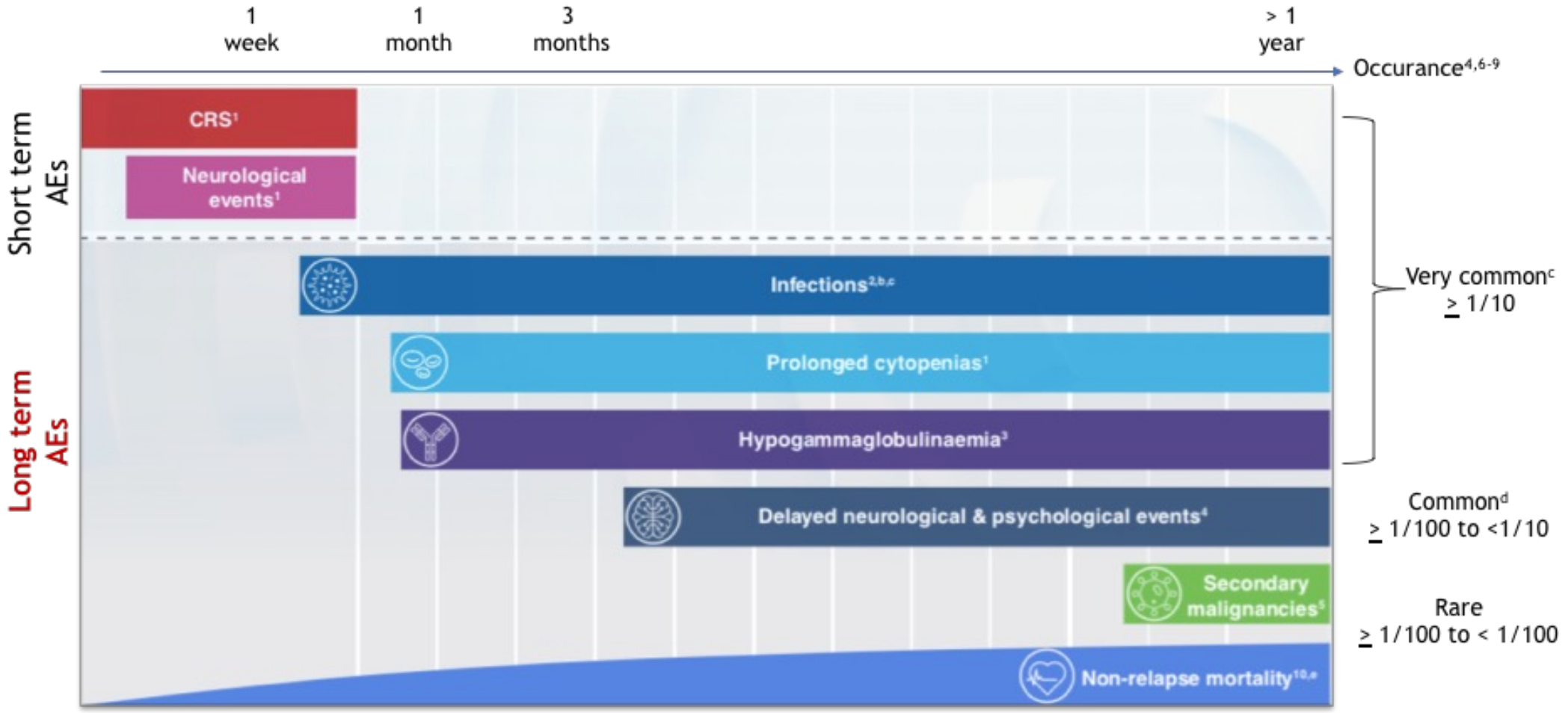
CRS: « supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction»

SIE incontra i pazienti

Il Presente delle CAR-T: Tossicità a Lungo Termine



b Unspecified pathogen, viral, bacterial and fungal infection; c Unspecified pathogen infections, viral infections, and bacterial infections are very common; fungal infections are common; d Delirium and insomnia were very common, anxiety and affective disorder were common; e The overall NRM point estimate across all CAR T studies is 6.8%, with 6.1% for LBCL.

1.Locke FL, et al. New Eng J Med 2022; 2.Baird JH, et al. Blood Adv 2021; 3.Cappell KM, et al. J Clin Oncol 202; 4. Cordeiro A, et al. Biol Blood Marrow Transplant 2020; 5. Barone A, et al. Br J Haematol 2024; 6. The EBMT/EHA CART-cell Handbook 2022; 7. Jain T, t al. Blood 2023; 8.Axicabtagene ciloleucel Smp 2024; 9.Levine BL, et al. Nat Med 2024; 10. Cordas Dos Santos DM, et al. Nat Med 2024

SIE incontra i pazienti

Efficacia e Tossicità: la Gestione Condivisa del Paziente

SIE incontra i pazienti

Il Futuro: Ricerca di Fattori Prognostici di Efficacia e Tossicità

nature medicine

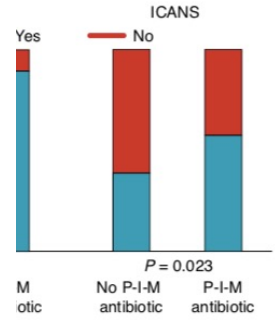
Gut microbior
toxicity follow

Melody Smith[1,2,3,4], Anqi D
Raymone Pajarillo[5,6], John B
Annelie Clurman[1], Emmanu
Jonas Schluter[11], Emily Fo
Elizabeth Halton[3,16], Josel R
Miguel-Angel Perales[1,2], C
Daniel Landsburg[5,20], James
Sergio Giralt[1,2], Saar I. Gill[5,6]
Michel Sadelain[22], Noelle
Jonathan U. Peled[1,2], Andr
and Marco Ruella[5,6,20,26,27]

Study code: **MICROCAR**

NCT05725720

Role of the gut microbiome in the outcome of Diffuse Large B-Cell Lymphoma patients treated with CAR-T cell therapy

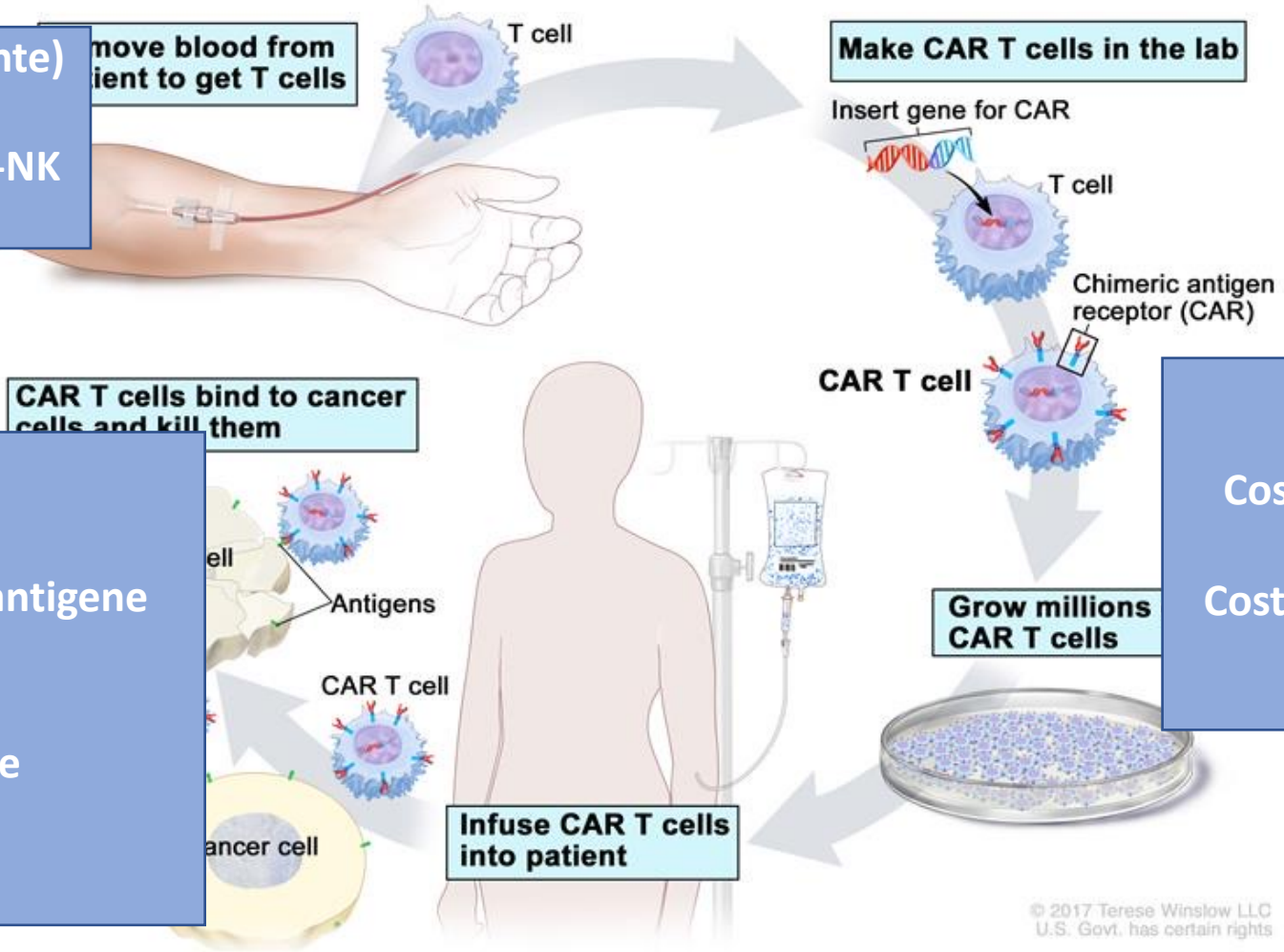


Author (s): Prof. Pier Luigi Zinzani, Patrizia Brigidi, Silvia Turroni, Serafina Guadagnuolo, Beatrice Casadei Francesca Bonifazi, Lisa Argnani

SIE incontra i pazienti

CONCLUSIONI

CAR-T autologhe (presente)
vs
CAR-T allogeniche/CAR-NK (futuro?)



RR
Single agent
Specifiche verso un antigene
Vs
In I linea
In associazione
Bispecifiche
Microbiome

Costrutti di II gen (presente)
vs
Costrutti di III-IV gen (futuro?)

GRAZIE PER L'ATTENZIONE!

UOC EMATOLOGIA
SSD LINFOMI E SDR LINFOPROLIFERATIVE CRONICHE
Prof. Pier Luigi Zinzani

UOC TERAPIE CELLULARI AVANZATE
Dott.ssa Francesca Bonifazi

CAR T- cell TEAM
UO Emolinfopatologia
UO Farmacia Clinica
Lab di Processazione Cellulare
UO Malattie Infettive
UO Med. Trasfusionale ed Aferesi
UO Medicina Nucleare
UO Neurologia
UO Neuroradiologia
UO Terapia Intensiva
UO Radioterapia
Tutto il personale infermieristico dei reparti DSV, BCM, II e I Sezione

CAR-T SPECIALIST