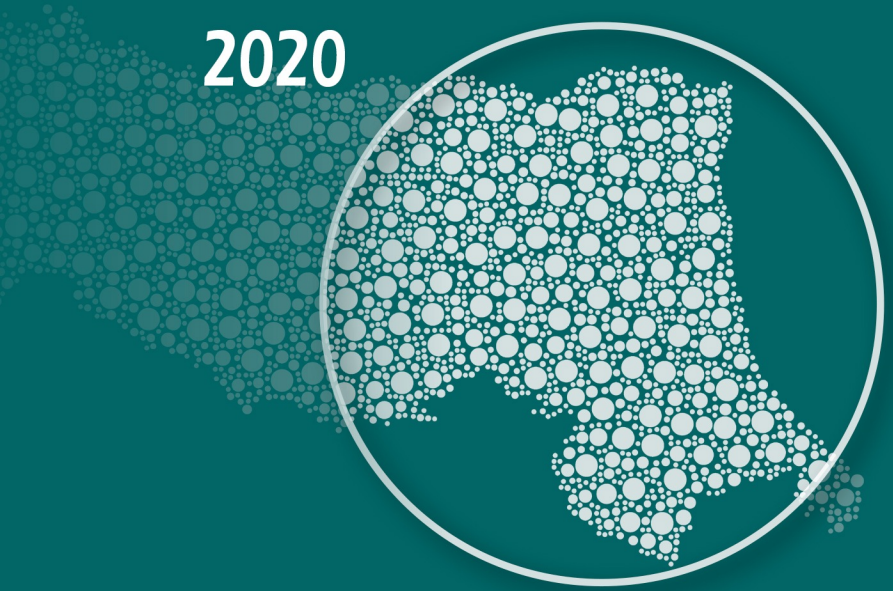


Progetto Ematologia Romagna

Quali sono i pazienti candidabili?

Beatrice Casadei

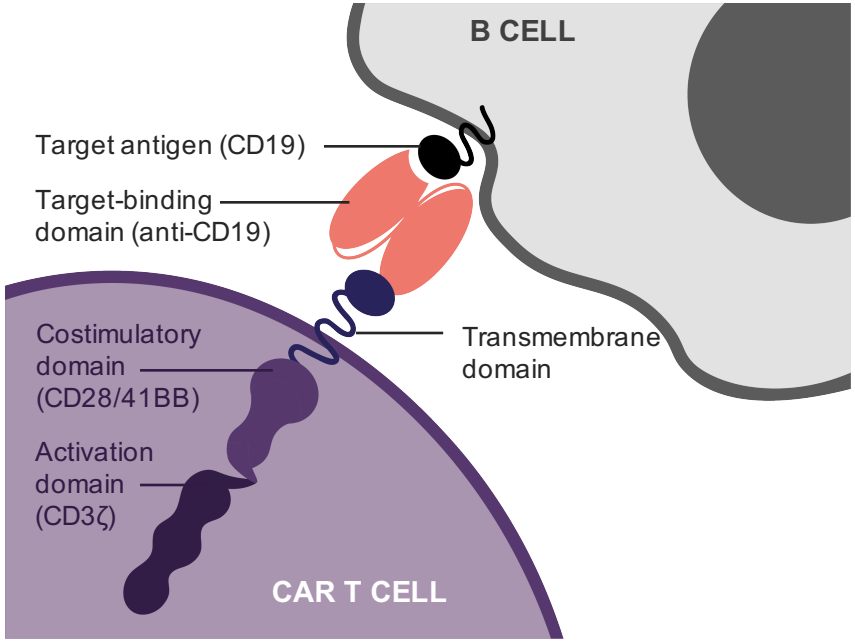
Relatore: Beatrice Casadei

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

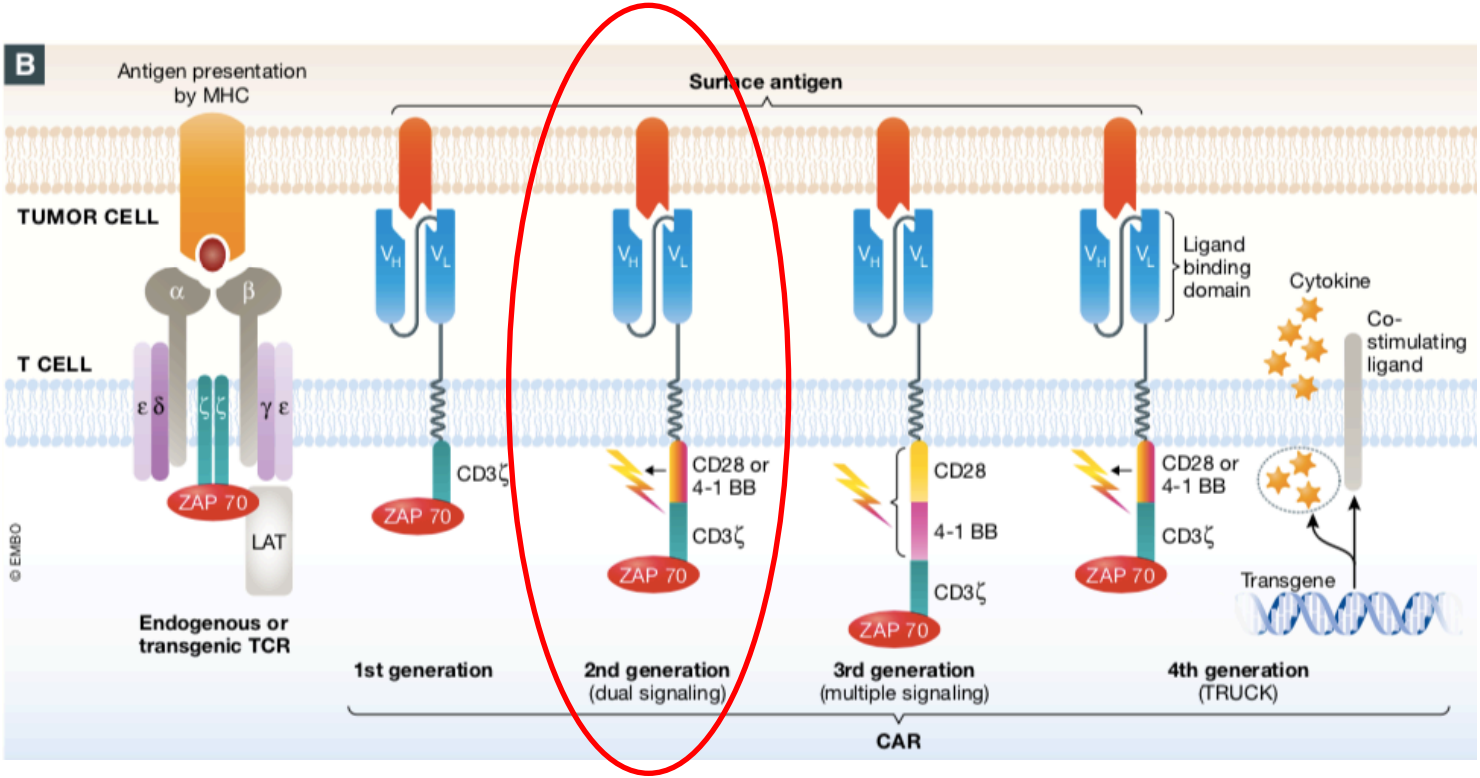
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazione ad Advisory Board: TAKEDA, KITE-GILEAD, JANSSEN
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)

ANTI-CD19 CAR-T CELLS

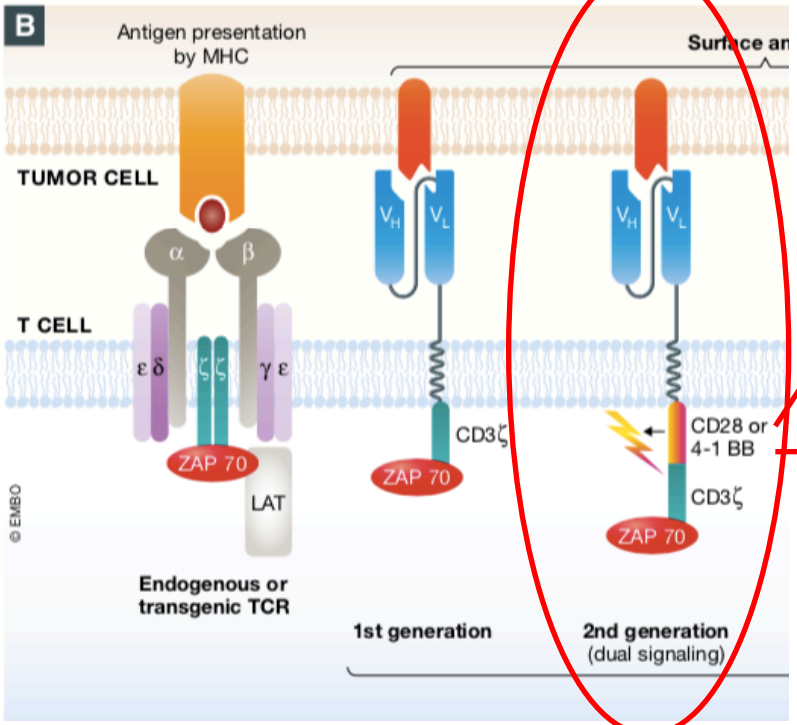
- Patient's own T cells are engineered to express an **anti-CD19 CAR** using a retroviral vector
- The **target-binding domain** identifies and binds to the CD19 surface antigen of B cells
- Upon binding, the **CD3ζ activation** and **CD28/41BB costimulatory domains** activate the CAR T cells
- Activated CAR T cells release inflammatory cytokines and chemokines and destroy the CD19-expressing B cells



CAR: Chimeric Antigen Receptor



CAR: Chimeric Antigen Receptor



CD28: Axicabtagene ciloleucel

4-1BB: Tisagenlecleucel

AIFA APPROVED CAR-T CELLS

Tisagenlecleucel (Tisa-cel)
Approvazione AIFA il 7 agosto 2019:

a. Pazienti pediatrici e giovani adulti fino a 25 anni di età affetti da leucemia acuta linfoblastica B refrattaria, in recidiva post-trapianto o in seconda o ulteriore recidiva.

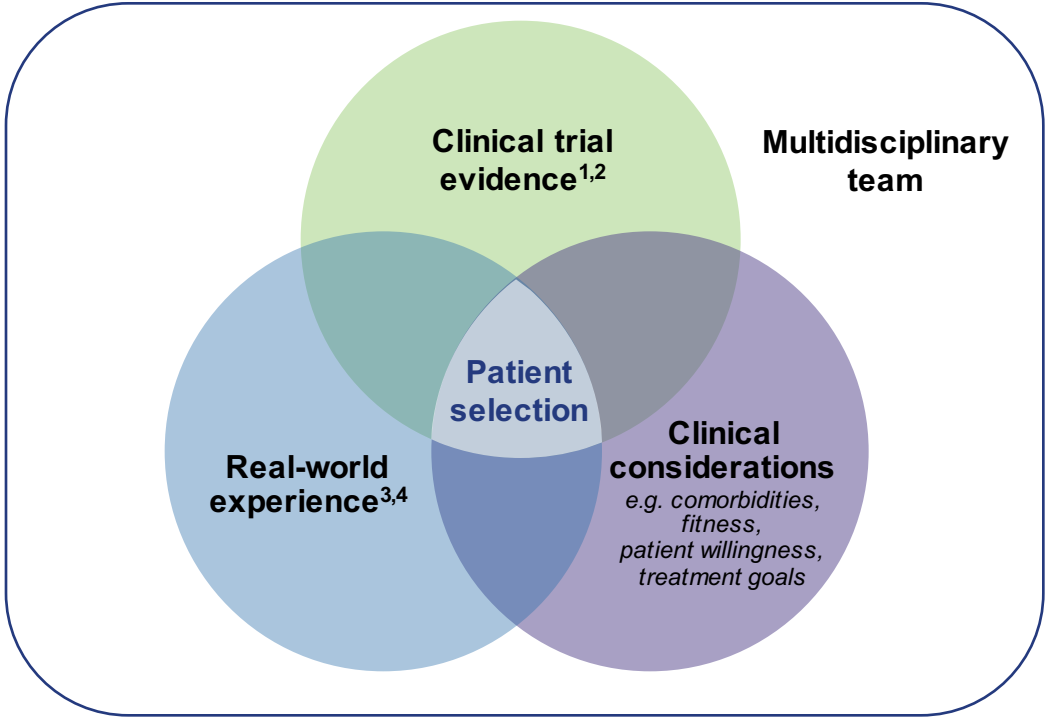
b. Pazienti adulti affetti da DLBCL in recidiva o refrattario a due o più linee di terapia sistemica.

Axicabtagene ciloleucel (Axi-cel)
Approvazione AIFA il 4 novembre 2019:

a. Pazienti affetti da DLBCL, ricaduti o refrattari ad almeno due precedenti linee di terapia sistemica

b. Pazienti affetti da PMBCL ricaduto o refrattario ad almeno due precedenti linee di terapia sistemica

PATIENT SELECTION IS INFLUENCED BY DIFFERENT FACTORS



1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531–2544; 2. Schuster et al, N Engl J Med 2019;380:45-563.
3. Nastoupil L, et al. *Blood.* 2018;132:91; 4. Jacobson CA, et al. *Blood.* 2018; 132:92; 5.

JULIET: ELIGIBILITY CRITERIA

Tisagenlecleucel (Tisa-cel)

KEY INCLUSION CRITERIA
DLBCL including DH/TH; TFL
Age ≥ 18 years
At least 2 lines of therapy including **rituximab** AND an **anthracycline**-containing regimen
Pts had relapsed after or were ineligible for ASCT
ECOG 0 or 1
Absolute neutrophil count ≥ 1,000/µL; Absolute **lymphocyte count ≥ 300/µL**; Platelet count ≥ 50,000/µL Hb ≥ 8 gr/dL
Adequate organ function

KEY EXCLUSION CRITERIA
PMBCL, T-cell rich/histocyte rich DLBCL, primary cutaneous DLBCL, EBV–positive DLBCL of the elderly, Richter's transformation, or Burkitt lymphoma
History of deep vein thrombosis or pulmonary embolism within 6 months of enrolment
History or presence of CNS disorder or CNS lymphoma
History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression within the last 2 years
Infection with HIV or HBV or HCV
Prior allo-SCT or anti-CD19 directed therapy

1. Schuster et al, N Engl J Med 2019;380:45-56.

ZUMA-1: ELIGIBILITY CRITERIA

Axicabtagene ciloleucel (Axi-cel)

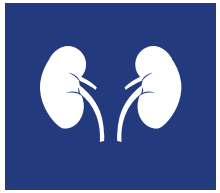
KEY INCLUSION CRITERIA
DLBCL NOS, T cell/histiocyte rich DLBCL; DLBCL associated with chronic inflammation; EBV+ DLBCL of the elderly; leg type DLBCL; DH/TH; **PMBCL** and **TFL****
Age ≥ 18 years
At least 2 lines of therapy including **rituximab** AND an **anthracycline**-containing regimen
Refractory disease: progressive or stable disease as the best response to the most recent chemotherapy or disease progression or relapse within 12 months after ASCT
ECOG 0 or 1
Absolute neutrophil count ≥ 1,000/µL; Absolute lymphocyte count **≥ 100/µL**; Platelet count ≥75,000/µL
Adequate organ function

KEY EXCLUSION CRITERIA
Richter's transformation, or Burkitt lymphoma
History of deep vein thrombosis or pulmonary embolism within 6 months of enrolment
Presence of suspicion of an infection
History or presence of CNS disorder or CNS lymphoma
History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression within the last 2 years
Infection with HIV, HBV or HCV
Prior allo-SCT or anti-CD19 directed therapy

1. Neelapu SS, *et al. N Engl J Med* 2017; 377:2531–2544

** Defined By WHO 2008

ADEQUATE ORGAN FUNCTION



Renal[1,2]

Creatinine clearance ≥60 mL/min (Cockcroft–Gault)

Cardiac[1,2]

Cardiac EF ≥50%[1] or 45%[2],
No evidence of pericardial effusion
No clinically significant ECG findings

Hepatobiliary[1,2]

Serum ALT/AST ≤2.5 ULN

Total bilirubin ≤1.5 mg/dL (except for Gilbert's syndrome)

Pulmonary[1,2]

No significant pleural effusion

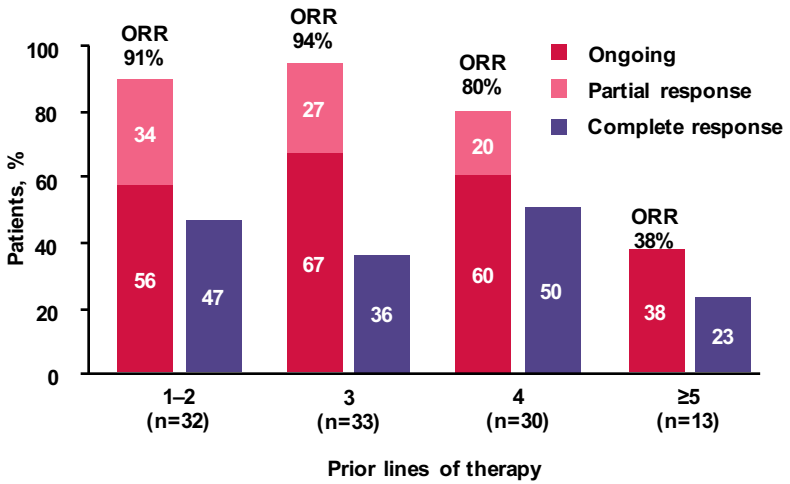
Baseline oxygen saturation ≥92% AA

Patients with inadequate renal, hepatic, pulmonary or cardiac function are likely to be more vulnerable to the consequences of CAR T-cell therapy-associated AEs

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531–2544
2. Schuster et al, N Engl J Med 2019;380:45-56

Patients With ≥5 Lines of Therapy Demonstrated a Trend For Lower Clinical Efficacy and Higher Rates of AEs Versus 1–4 Lines

Response rates by prior lines of therapy



Summary of safety by prior lines of therapy

	Prior lines of therapy before enrolment on ZUMA-1			
Grade ≥3 AE, n (%)	1–2 (n=32)	3 (n=33)	4 (n=30)	≥5 (n=13)
SAEs related axi-cel	11 (34)	9 (27)	7 (23)	7 (54)
CRS[1]	5 (16)	3 (9)	3 (10)	2 (15)
NEs[2]	9 (28)	11 (33)	6 (20)	7 (54)

- Rates of Grade ≥3 CRS were similar across prior lines of therapy
- There was a trend for higher rates of Grade ≥3 SAEs and neurologic events for patients with ≥5 prior lines of therapy

[1]CRS was graded per Lee et al.
[2] Neurologic events were graded per CTCAE v 4.03.
Locke et al, Lancet Oncology 2018

REAL WORLD SETTING RESULTS

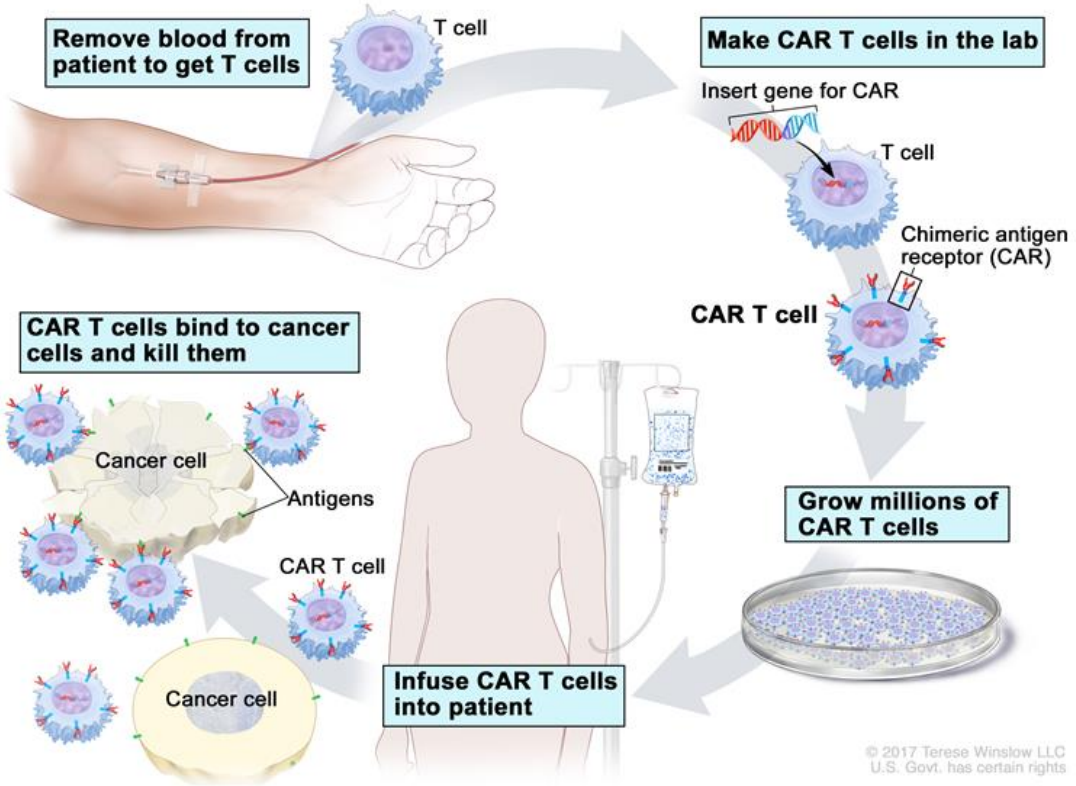
Predictor of response:

- low CRP and ferritin at day 0 *(Jacobson C.A. et al ASH 2018, Abstract 627; Sesques et al, Am J Hematol 2020)*
- high absolute lymphocyte count at apheresis *(Jacobson C.A. et al ASH 2018, Abstract 627)*
- Serum LDH above the UNL and number of previous treatment lines above four *(Sesques et al, Am J Hematol 2020)*
- ECOG, PS 2-4 was associated to inferior outcome *(Jacobson C.A. et al ASH 2018, Abstract 627)*

Predictors of toxicity:

- high peak CRP (for neurotoxicity) and high peak ferritin (for both neurotoxicity and CRS) *[Jacobson C.A. et al ASH 2018, Abstract 627]*

Patient Selection Is Influenced By Factors Beyond Clinical Trial Evidence



Patient Selection Is Influenced By Factors Beyond Clinical Trial Evidence

Comorbidities[1]

Patients should be **relatively fit** and **without serious comorbidities** that would make the potential adverse events profile prohibitive

Similar to determining whether a patient would be medically fit for a stem cell transplant

Willingness to travel to another centre[1]

Location of nearest CAR T-cell treatment centre for in-patient care and post treatment follow-up

If a patient does not live in proximity to a centre, arrangements to facilitate treatment should be considered

Presence of home support network[1,]

Does the patient have **appropriate carer support** in place during the acute period (30 days) after infusion?

Due to the potential for neurological events, patients should refrain from driving until at least 8 weeks after infusion or until resolution of neurological adverse events

Patients may need to rely on somebody to help with transportation

Long-term treatment goals (long-term or palliative care?)[1]

CAR T cells are **not to be given with palliative intent**

1. Cassaday RD. *Cell Therapy Next.* 13 December 2018

SINTESI CRITERI DI RIMBORSABILITA' AIFA
ISTOLOGIA

DLBCL NOS
- GCB and ABC
- DLBCL trasformato da linfoma follicolare
- DLBCL EBV+, NOS (*Axi-Cel*)
- DLBCL primitivo della cute/leg type (*Axi-Cel*)
- DLBCL associato ad infiammazione cronica (*Axi-Cel*)
- DLBCL HHV8 positivo (*Axi-Cel*)
- DLBCL primary effusion (*Axi-Cel*)
- Linfoma a cell B con caratteristiche intermedie tra DLBCL and cHL (*Axi-Cel*)

HGBCL
- High grade B-cell lymphoma, NOS
- High grade B-cell lymphoma con riarrangiamento di MYC e BCL2 and/or BCL6

PMBCL (*Axi-Cel*)

LAL-B (*Tisa-Cel*)

DLBCL
- Linfoma a cell B ricco in cell T/istiociti
- Linfoma plasmoblastico
- Linfoma a grandi cell B con riarrangiamento di IRF4
- Linfoma a grandi cell B ALK1 positivo
- Linfoma a grandi cell B intravascolare

Sindrome di Richter

DLBCL primitivo del SNC

Linfoma di Burkitt

SINTESI CRITERI DI RIMBORSABILITA' AIFA

CARATTERISTICHE DEL PAZIENTE

DIAGNOSI

✓ **DLBCL** o **PMBCL**:
- Recidivanti/refrattari all'ultima chemioterapia di salvataggio
- Recidivanti dopo il trapianto di cellule staminali

ETÀ

✓ **≥18 ≤70 anni**

ECOG PS

✓ ECOG PS **0-1**

✗ **≥2**

ASPETTATIVA DI VITA

✓ aspettativa di vita **>12 settimane**

PRECEDENTI TERAPIE SISTEMICHE

✓ **≥2** precedenti terapie sistemiche che comprendano rituximab e antracicline

ASCT/ALLO-SCT

✗ candidabili ad ASCT

✗ precedente allo-SCT

✓ recidiva dopo ASCT

COMORBIDITÀ

HBV/HCV E HIV

✗ **infezione attiva HBV/HCV** o **HIV+**

INFEZIONI E MALATTIE INFIAMMATORIE[2]

✗ **infezioni attive o malattie infiammatorie non risolte**

PATOLOGIE AUTOIMMUNI

✗ **patologie autoimmuni con danno d'organo terminale**

✗ **terapia sistemica immunosoppressiva** o ***disease modifying***

nei due anni precedenti

TROMBOSI VENOSA PROFONDA O EMBOLIA POLMONARE

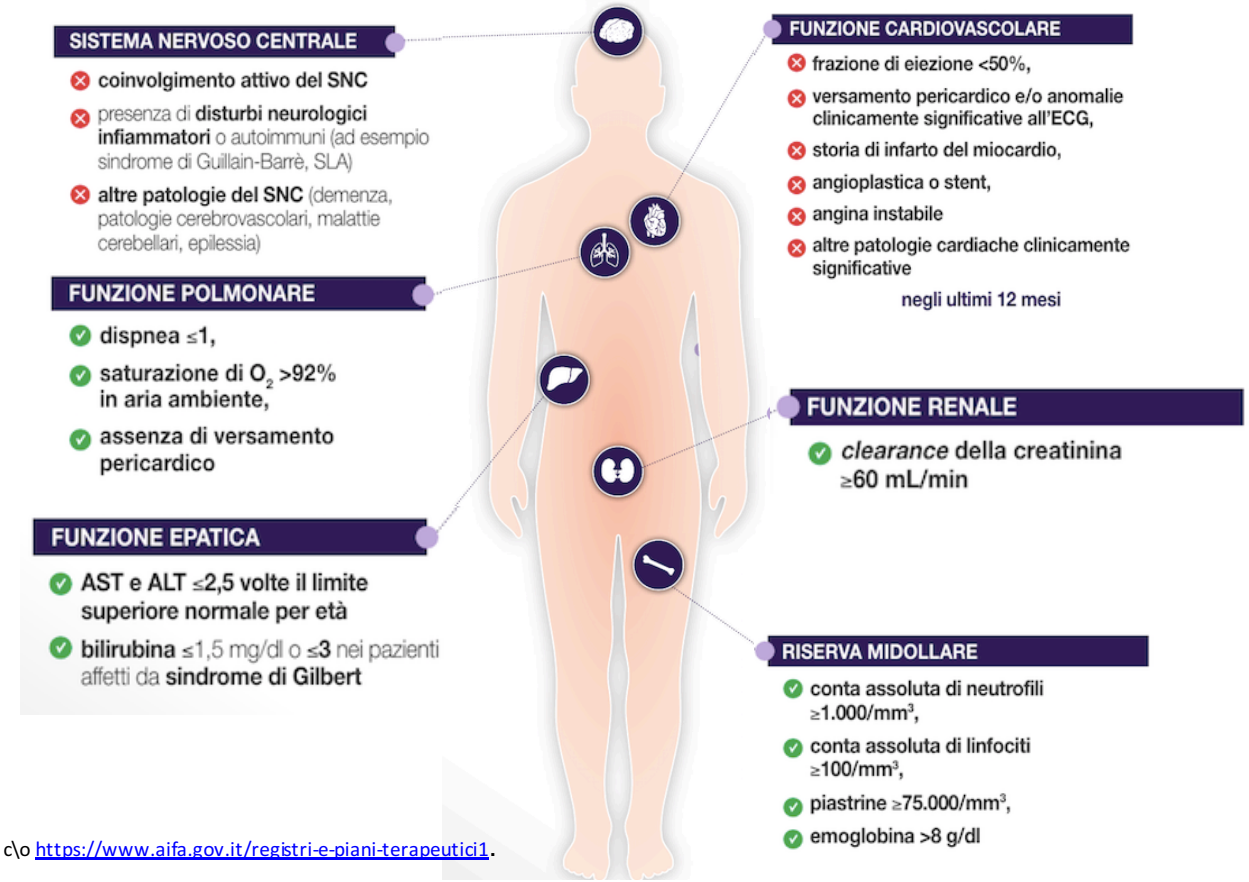
✗ storia di trombosi venosa profonda

✗ embolia polmonare

negli **ultimi 6 mesi**

Schede di monitoraggio AIFA reperibili c\o https://www.aifa.gov.it/registri-e-piani-terapeutici1.
Modificate da scheda "criteri di elegibilità/rimborsabilità di Axi-cel"

SINTESI CRITERI DI RIMBORSABILITA' AIFA



Schede di monitoraggio AIFA reperibili c\o https://www.aifa.gov.it/registri-e-piani-terapeutici1.

TAKE HOME MESSAGES

- Patient selection is primarily guided by the Axi-cel and Tisa-cel RCP and AIFA Reimbursement Criteria
  - -- Age
  - -- Histology
  - -- Previous lines
  - -- Adequate organ function and comorbidities
- Number of previous treatment lines above four is associated with inferior outcome → **CONNECT THE PATIENT TO THE REFERRAL CENTER AS SOON AS POSSIBLE!**
- Performance status is associated with inferior outcome → **CONNECT THE PATIENT TO THE REFERRAL CENTER AS SOON AS POSSIBLE!**
- The patient need a caregiver or the presence of home support network due to potential adverse events after CAR-T cells infusion

KTE-X19 USO NOMINALE

Yes	No	Inclusion Criterion
		Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14)
		Received at least one prior regimen for MCL. Prior therapy must have included: a. Anthracycline or bendamustine-containing chemotherapy, and b. Anti-CD20 monoclonal antibody therapy, and c. Treatment with BTKi: ibrutinib, acalabrutinib, or a BTKi in a clinical trial for r/r MCL. Subjects with BTKi intolerance are eligible if they meet following inclusion criteria.
		Relapsed or refractory disease, defined by the following: a. Disease progression after last regimen, or b. Failure to achieve a partial response (PR) or CR to the last regimen
		Magnetic resonance imaging (MRI) of the brain showing no evidence of central nervous system (CNS) lymphoma
		Subjects who have had allo-SCT are eligible if they meet all of the following criteria: a. Allo-SCT performed ≥ 6 months prior to enrollment b. If Donor lymphocyte infusion (DLI) was administered, must be ≥ 6 months prior to enrollment c. No GVHD therapies within 4 weeks of enrollment. These include any corticosteroids, calcineurin inhibitors, methotrexate, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibody (eg, anti-CD20 monoclonal antibodies, anti-tumor necrosis factor [TNF], anti-interleukin 6 [IL-6] or anti-interleukin 6 receptor [IL-6R]), or any investigational agents received in a clinical trial for acute or chronic GVHD. d. No evidence of acute GVHD Grade II to Grade IV by Glucksberg criteria or severity B-D by IBMTR index within 4 weeks of enrollment
		Toxicities due to prior therapy must be stable and have recovered to ≤ Grade 1 (except for clinically non-significant toxicities, such as alopecia).
		Age 18 years or older
		Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
		Absolute neutrophil count (ANC) ≥ 500/uL
		Platelet count ≥ 50,000/uL

Yes	No	Inclusion Criterion
		Absolute lymphocyte count ≥ 100/uL
		Adequate renal, hepatic, pulmonary, and cardiac function defined as: a. Creatinine clearance (as estimated by Cockcroft Gault formula) ≥ 60 ml/min b. Serum alanine aminotransferase/aspartate aminotransferase (ALT)/(AST) ≤ 5 x upper limit of normal (ULN) c. Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome d. Left ventricular ejection fraction ≥ 50%, no evidence of clinically relevant pericardial effusion as determined by an echocardiogram (ECHO) and no clinically significant electrocardiogram (ECG) findings e. No clinically significant pleural effusion f. Baseline oxygen saturation > 92% on room air

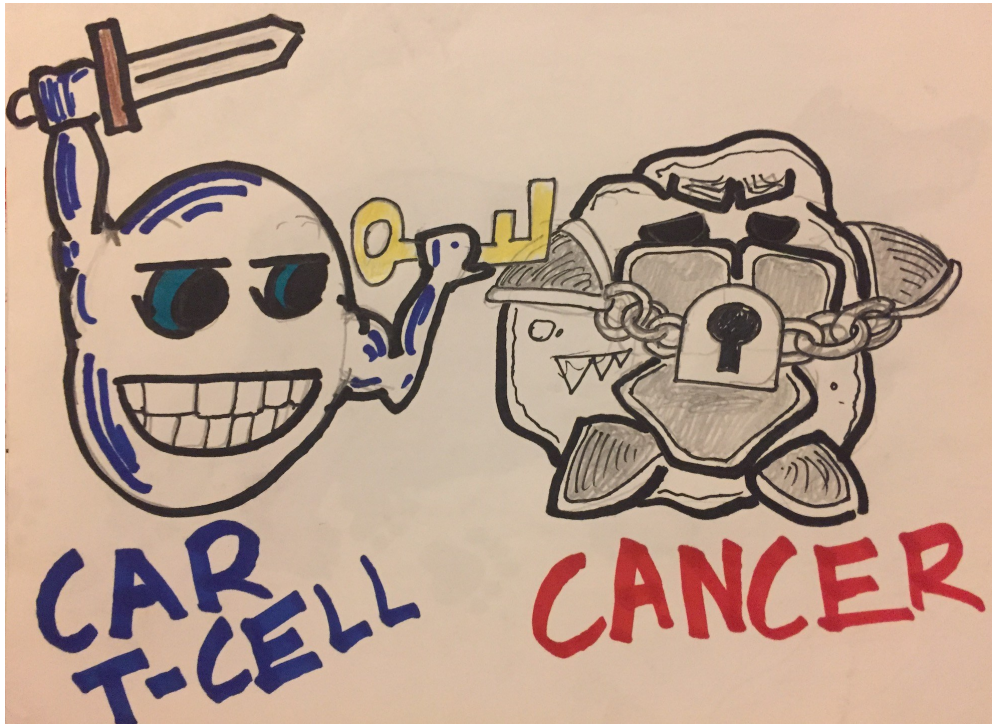
Wang et al, N Engl J Med 2020;382:1331-42.DOI: 10.1056/NEJMoa1914347

KTE-X19 USO NOMINALE

Yes	No	Exclusion Criterion
		Auto-SCT within 6 weeks prior to enrollment
		History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
		Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment
		Active infection with HIV, hepatitis B or hepatitis C virus. A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing. A history of HIV infection is permitted if the viral load is undetectable (less than 50 copies/ml) under antiretroviral therapy
		Presence of any in-dwelling line or drain (eg, percutaneous nephrostomy tube, in-dwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs (if inserted for indication other than active CNS disease treatment) and dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted. In-dwelling stents (eg, ureteral stents or hepatic stents) inserted to relieve obstruction from lymphadenopathy from underlying MCL are permitted.
		Subjects with detectable cerebrospinal fluid (CSF) malignant cells or brain metastases or with a history of CNS lymphoma, CSF malignant cells, or brain metastases
		History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement
		History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, active arrhythmias (including paroxysmal atrial fibrillation requiring intermittent therapy), or other clinically significant cardiac disease within 12 months of leukapheresis
		Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
		History of symptomatic deep vein thrombosis (DVT) or pulmonary embolism requiring systemic anticoagulation within the last 6 months of leukapheresis

Yes	No	Exclusion Criterion
		Primary immunodeficiency
		Any medical condition likely to interfere with assessment of safety or efficacy of KTE-X19 treatment
		History of severe, immediate hypersensitivity reaction to any of the agents used
		Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen
		Women of childbearing potential who are pregnant or breastfeeding
		Subjects of both sexes who are not willing to practice birth control from the time of leukapheresis through 6 months after the completion of KTE-X19 infusion
		History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

Wang et al, N Engl J Med 2020;382:1331-42.DOI: 10.1056/NEJMoa1914347



GRAZIE PER L'ATTENZIONE