



Con il patrocinio di



PADOVA

SALA CONVEGNI VIMM

Via Orus, 2

28 MAGGIO 2019

ROAD MAP CAR-T

**PROSPETTIVE ATTUALI E FUTURE
DELL'USO DELLE CAR-T IN ITALIA**

2019 **MOTORE** 
SANITÀ 
Gestire il Cambiamento

Car-T cells: linfomi a grandi cellule B (DLBCL)

Carlo Visco

Professore Associato

Dipartimento di Medicina, Sezione di Ematologia

AOUI Verona

Epidemiologia regionale

Linfomi non Hodgkin

Registro Tumori del Veneto

[www.registrotumoriveneto.it/registro/incidenza/inc_ven.php]

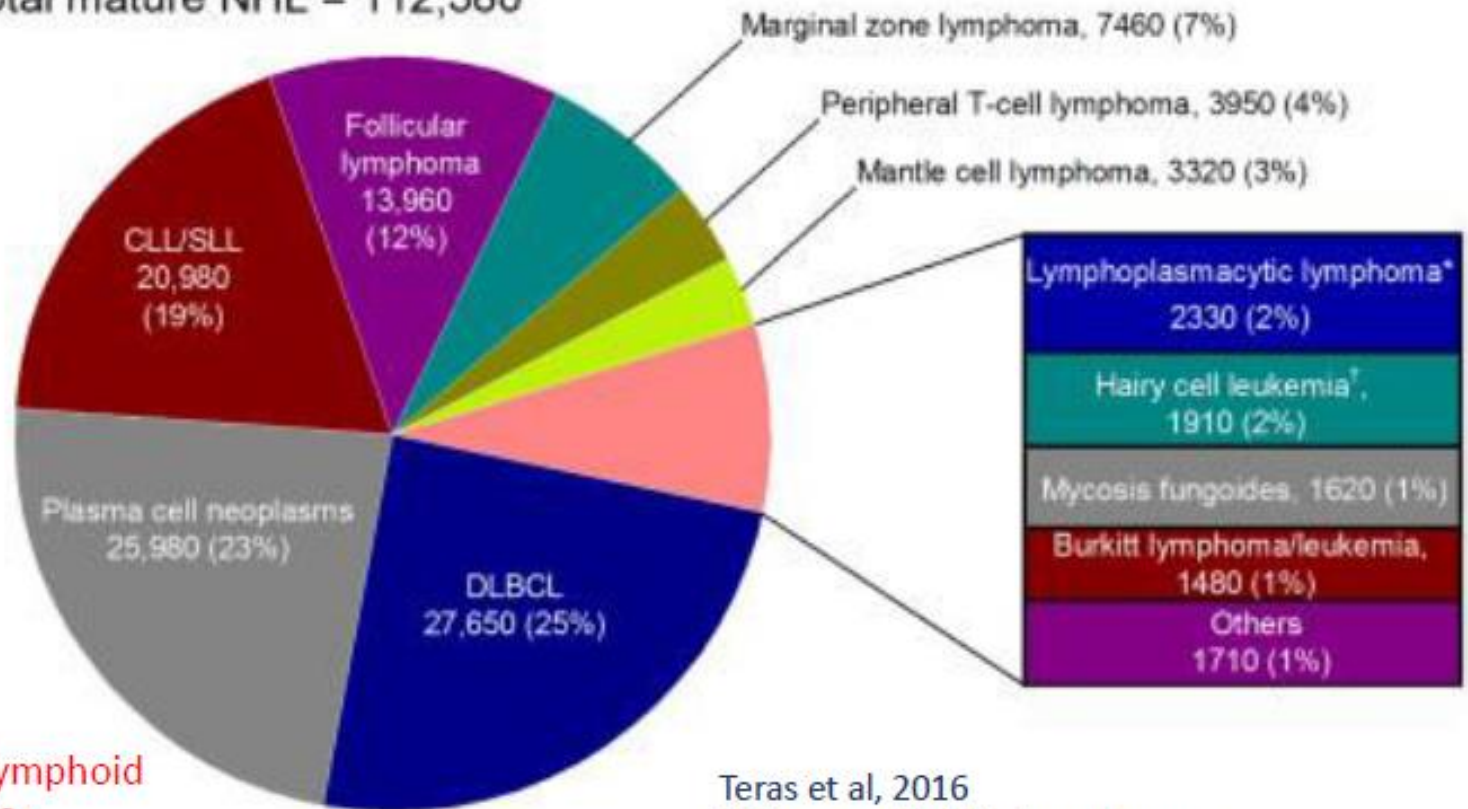
- I linfomi colpiscono prevalentemente la popolazione maschile
- Incidenza maschile: 17.6 casi/100.000/anno;
Incidenza femminile: 12.1 casi/100.000/anno
- Non significative variazioni nelle singole aree geografiche regionali
- Tasso di incidenza appare in lieve riduzione nei maschi, mentre è in aumento nelle femmine in un confronto tra i periodi 1990-1993 e 2004-2006.

Sono attesi circa 750 nuovi casi/anno

Estimated Cases and Distribution of Mature Lymphoid Neoplasm Subtypes

United States, 2016

Total mature NHL = 112,380



500 casi/anno



180 DLBCL/anno

Teras et al, 2016

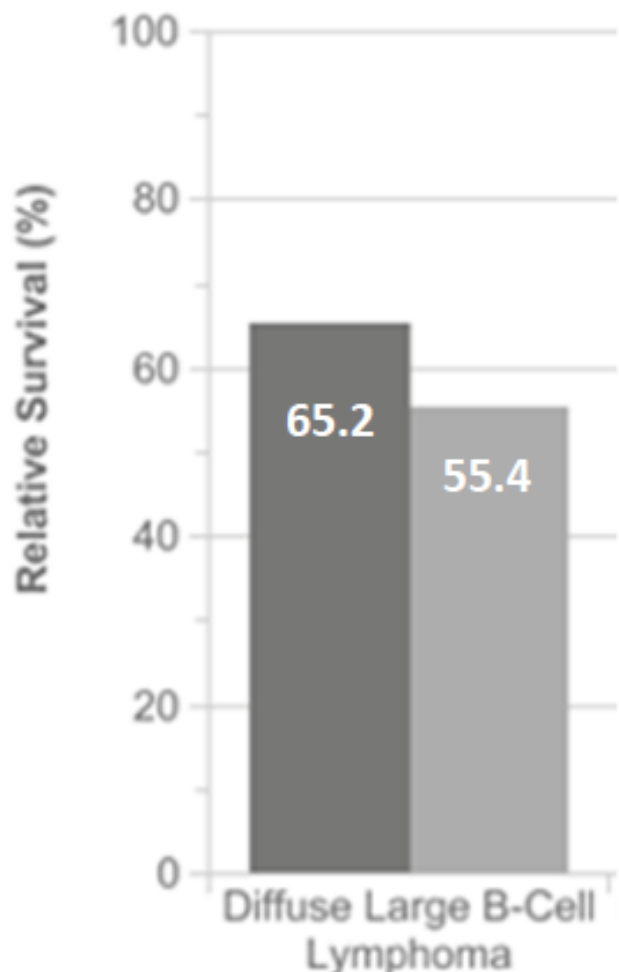
NHL = non-Hodgkin lymphoma;

CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma.

≈ 70% of all mature lymphoid neoplasms are CD19+
 ≈ 45% are CD19+ neoplasms other than DLBCL

DLBCL: Real World Prognosis

- 1- and 5-Year Survival (%), All Ages, 2004-2011



Ideal World Outcomes*

Treatment outcomes for advanced DLBCL

R-CHOP ¹ :	66% 5 year DFS 34% relapse / fail therapy
HD chemo + ASCT ² :	<u>31% salvaged*</u> (3 year EFS) 76% long term remissions
unmet need	≈ 24% of patients with DLBCL

*assumes all relapsed or refractory patients are eligible for high dose chemotherapy and ASCT

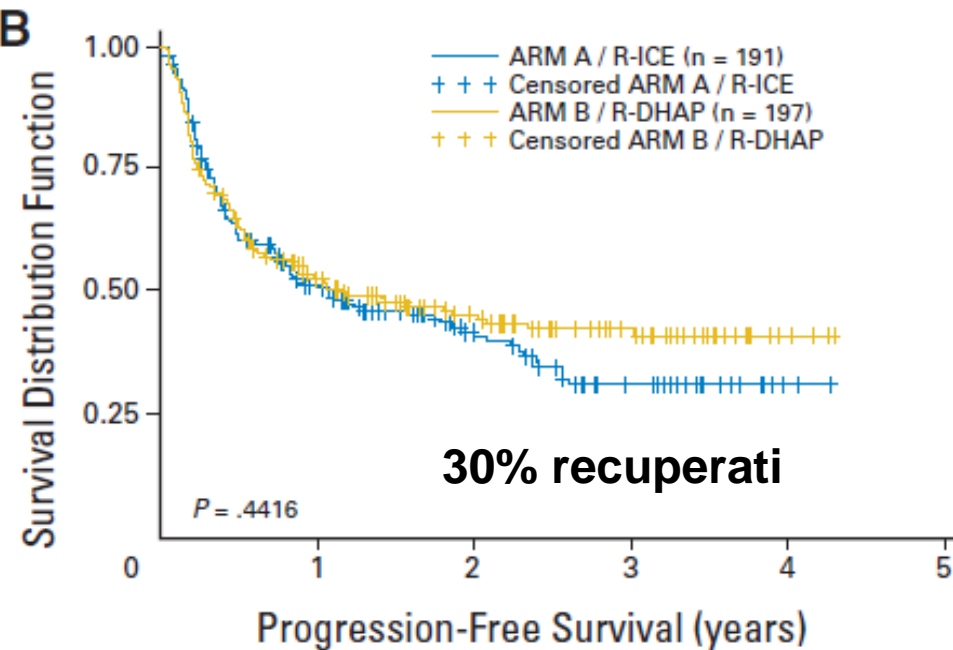
¹J Clin Oncol 2005; 23:4117-4126.

²J Clin Oncol 2010; 28:4184-4190.

DLBCL, diffuse large B-cell lymphoma
DFS, disease-free survival
EFS, event-free survival
ASCT, autologous stem cell transplant

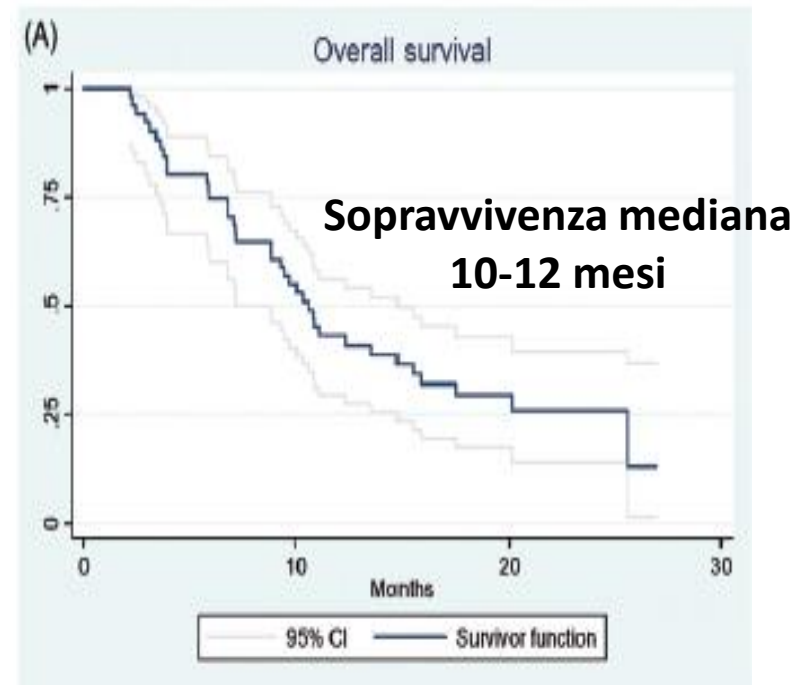
Sopravvivenza nei pazienti con DLBCL recidivato o refrattario dopo R-CHOP nel caso siano:

Eleggibili a trapianto autologo



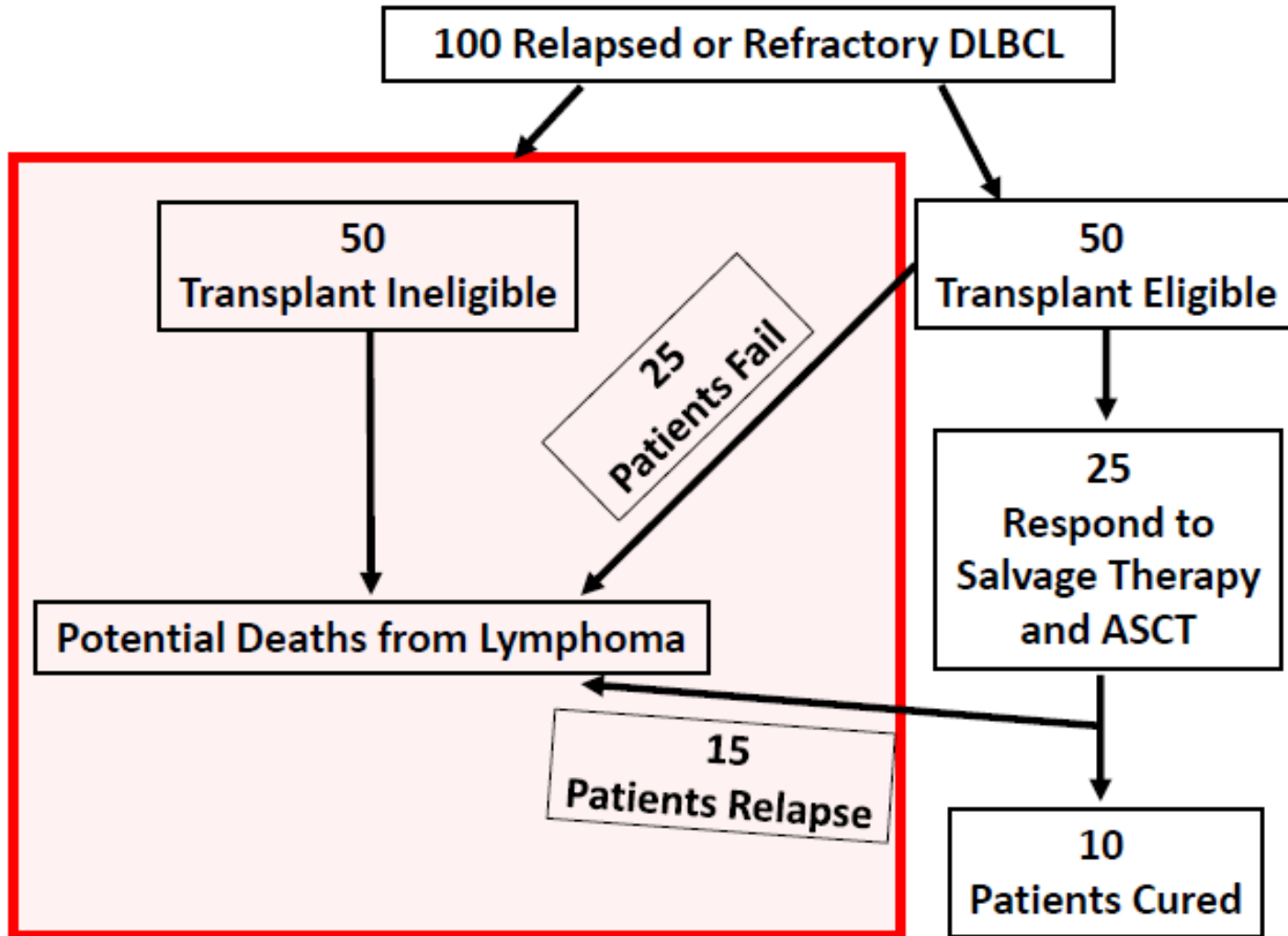
[CORAL study, JCO 2010]

Non elegibili a trapianto autologo



[Arcari et al, Leuk Lymph 2014]

Pazienti con DLBCL recidivati o refrattari, solo il 10% sono curati a lungo termine



*Estimates based on Gisselbrecht et al. J Clin Onc 2010 28:27, 4184-4190.

*Assumes all patients received rituximab as part of primary therapy

Pazienti potenzialmente elegibili a Car-T cells

- Pazienti refrattari o ricaduti dopo terapia di prima linea e non elegibili a trapianto autologo
- Pazienti che falliscono il trapianto autologo o non idonei a trapianto
- Pazienti ricaduti dopo trapianto allogenico*

In Veneto stimati 30+25+2 (57) pazienti/anno

*Il trapianto allogenico è praticabile nel 10% dei pazienti per chemiorefrattarietà, età, comorbidità,



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Yescarta (*axicabtagene ciloleucel*) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (*DLBCL*) and primary mediastinal large B-cell lymphoma (*PMBCL*), after two or more lines of systemic therapy.

Terapia di terza linea



AUTHORISED

This medicine is authorised for use in the European Union.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Kimriah (*tisagenlecleucel*) is indicated for paediatric and young adult patients up to 25 years with B-cell acute lymphoblastic leukaemia (*ALL*) that is refractory, in relapse post-transplant or in second or later relapse.

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (*DLBCL*) after two or more lines of systemic therapy.

Terapia di terza linea



AUTHORISED

This medicine is authorised for use in the European Union.

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE S.S. Neelapu, et al. Dec 10, 2017

ZUMA-1 is a prospective, registrational, single arm, phase 1-2 study at 22 Medical centers in USA and Israel

119 patients enrolled (median age 58, range 34-69)

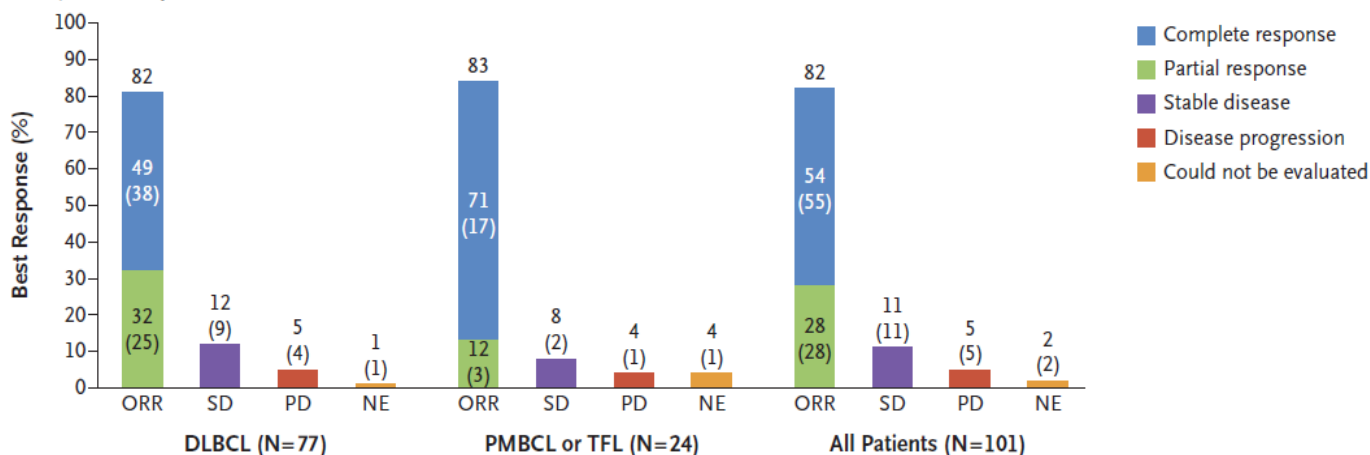
	Phase 1 (n=7)	Phase 2 (n=101)
Previous therapies		
Median (IQR)	3 (3-4)	3 (2-4)
1	0	3 (3%)
2	1 (14%)	28 (28%)
≥3	6 (86%)	70 (69%)
History of primary refractory disease†	1 (14%)	26 (26%)
History of resistance to two consecutive lines	1 (14%)	54 (53%)

Con terapia standard
Risposte complessive 20-30%
Risposte complete 7-10%
Sopravvivenza mediana 2-8 mesi

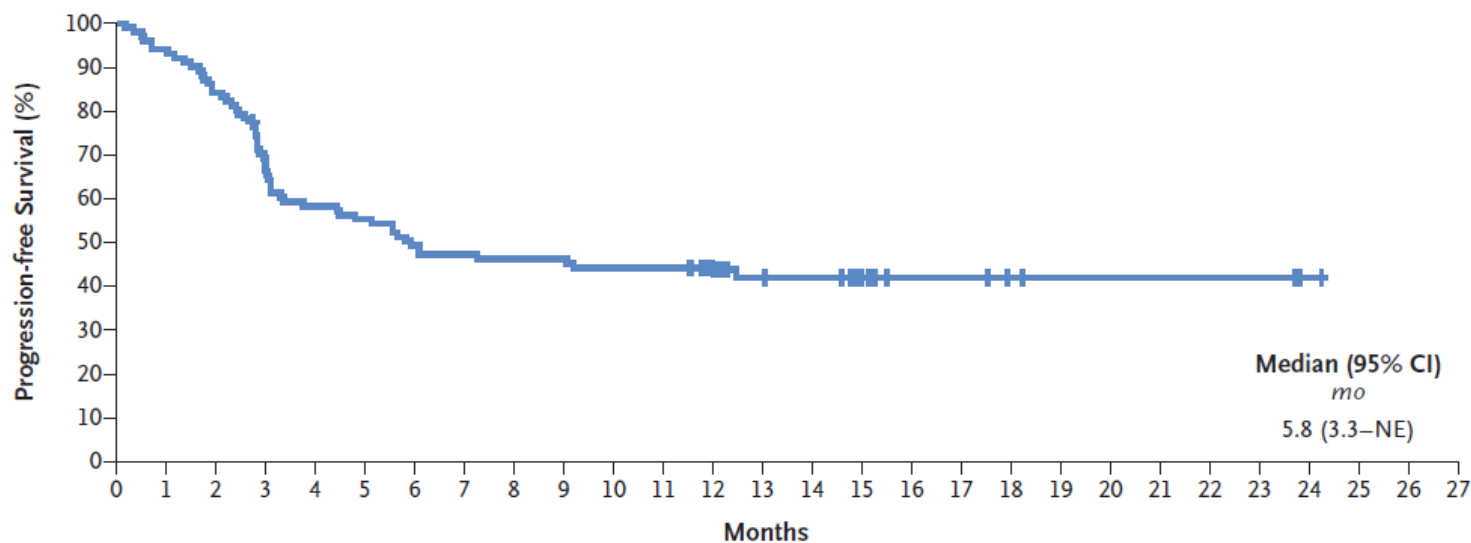
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE S.S. Neelapu, et al. Dec 10, 2017

A Objective Response Rate



Progression-free Survival



No. at Risk

108 101 90 71 61 58 52 50 49 49 47 47 34 21 20 12 6 6 4 3 3 3 3 3 1 0

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE S.S. Neelapu, et al. Dec 10, 2017

During treatment, all 101 patients who had received axi-cel had AE (95% gr ≥ 3)

Event	Any Grade	Grade 1 or 2	Grade ≥ 3
	<i>Number of patients (percent)</i>		
Adverse event			
Any	101 (100)	5 (5)	96 (95)
Pyrexia	86 (85)	72 (71)	14 (14)
Neutropenia	85 (84)	6 (6)	79 (78)
Anemia	67 (66)	24 (24)	43 (43)
Hypotension	60 (59)	46 (46)	14 (14)
Thrombocytopenia	59 (58)	21 (21)	38 (38)
Febrile neutropenia	35 (35)	4 (4)	31 (31)
Encephalopathy	34 (34)	13 (13)	21 (21)
Cytokine release syndrome			
Any	94 (93)	81 (80)	13 (13)
Pyrexia	77 (76)	66 (65)	11 (11)
Hypotension	41 (41)	32 (32)	9 (9)
Hypoxia	22 (22)	13 (13)	9 (9)

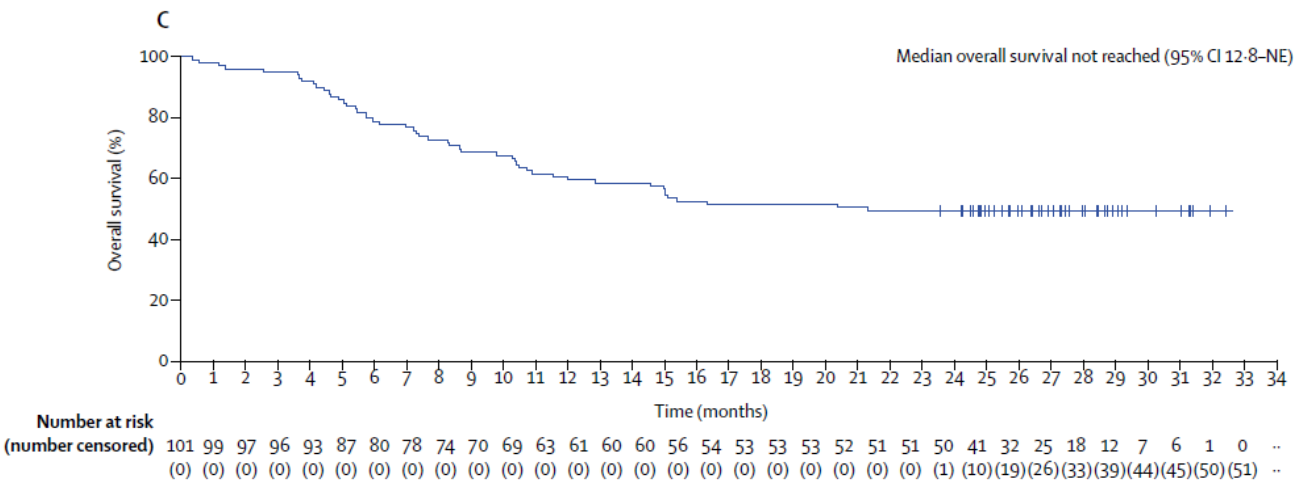
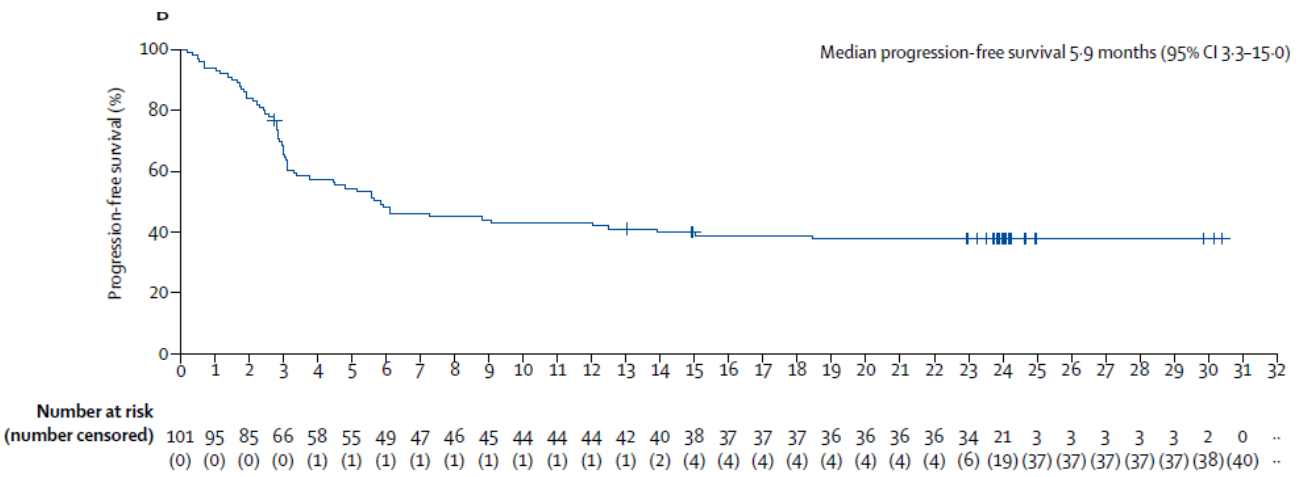
Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial

Lancet Oncol 2019; 20: 31-42

Frederick L Locke, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wieszorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**

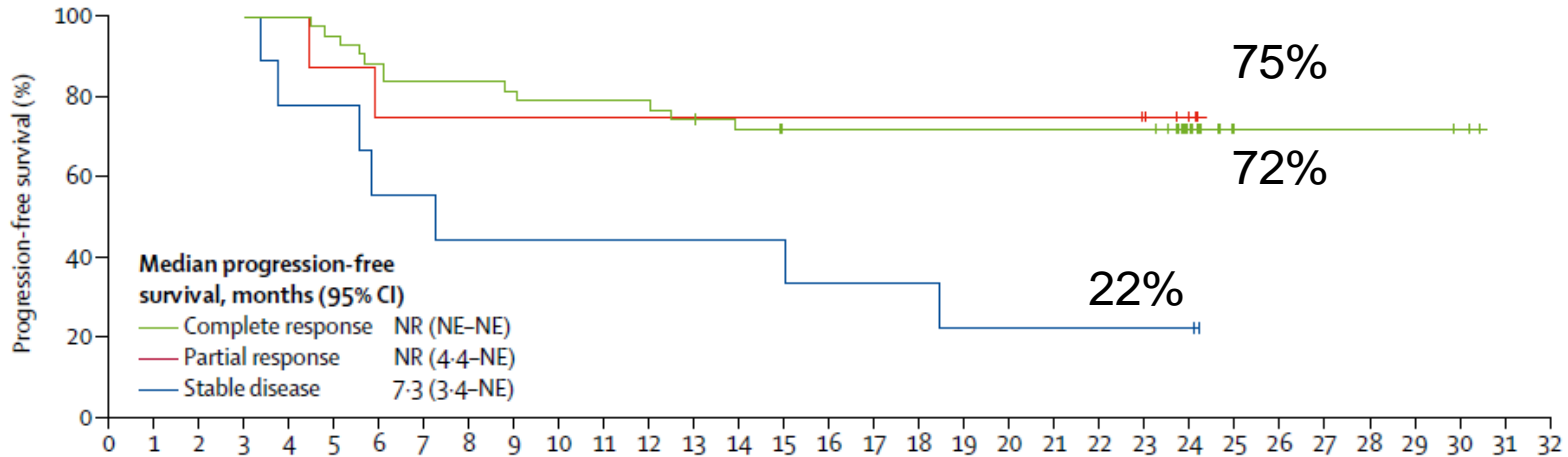
	IRC-assessed (n=101)
Objective response*	75 (74%)
Complete response†	55 (54%)
Partial response	20 (20%)
Ongoing response‡	36 (36%)
Complete response	35 (35%)
Partial response	1 (1%)

Median time to response 1 month
1/3 improved response between m 1 and 6



PFS of patients according to response at 3 months after infusion

A post-hoc analysis



Achievement of partial or complete response after 3 months is predictive of long term response durability

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

Stephen J. Schuster, N Engl J Med 2019;380:45-56.

Characteristic	Patients (N=111)
Median age (range) — yr	56 (22–76)
Age ≥65 yr — no. (%)	25 (23)
No. of previous lines of antineoplastic therapy — no. (%)¶	
1	5 (5)
2	49 (44)
3	34 (31)
4–6	23 (21)
Relapse after last therapy — no. (%)	50 (45)
Refractory diffuse large B-cell lymphoma — no. (%)**	61 (55)
Previous autologous hematopoietic stem-cell transplantation — no. (%)	54 (49)

ZUMA-7: A phase 3 randomized trial of axicabtagene ciloleucel (Axi-Cel) versus standard-of-care (SOC) therapy in patients with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL).

Trial in corso che confronta Car-T cells con trapianto autologo in seconda linea

?%

30%

