TORINO

DIPARTIMENTO DI BIOTECNOLOGIE MOLECOLARI E SCIENZE PER LA SALUTE

AULA ARISTOTELE

Via Nizza, 52

17 LUGLIO 2019

ROAD MAP CAR-T

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

2019 MOTORE SANITÀ
Gestire il Cambiamento

Progressi terapeutici nei linfomi aggressivi: la terapia CART

Umberto Vitolo

Hematology

University Hospital

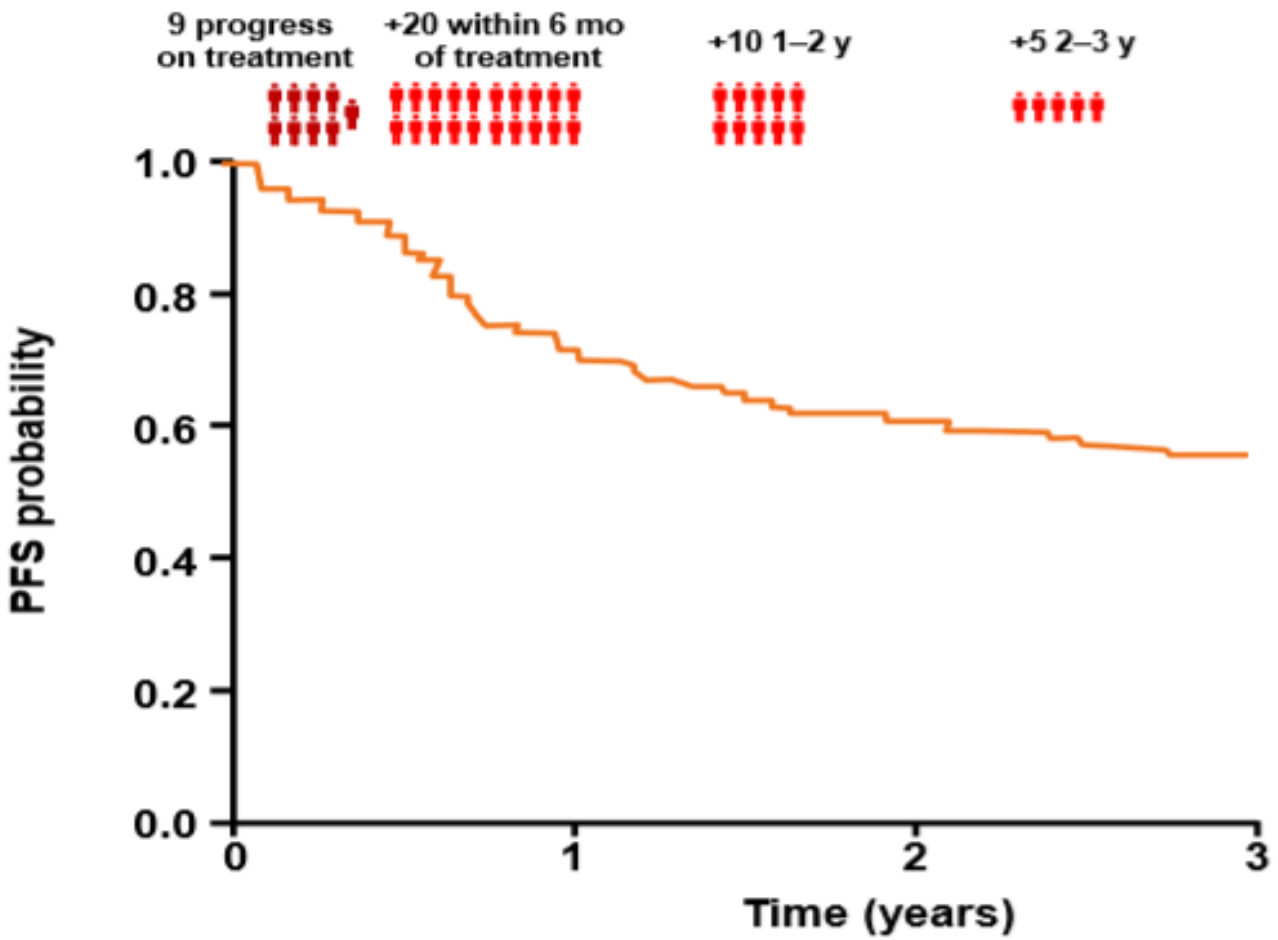
Città della Salute e della Scienza

Torino, Italy

Disclosures – Umberto Vitolo

Research Support/P.I.	Roche, Celgene
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Conferences/Educational Activities	Janssen, Roche, Celgene, Takeda, Gilead, Sandoz
Scientific Advisory Board	Janssen, Celgene, Roche, Novartis, Gilead

DLBCL: 40% of all NHL, median age 65 years, curable disease



In GELA-LNH 98.5 – all patients After 3 years:

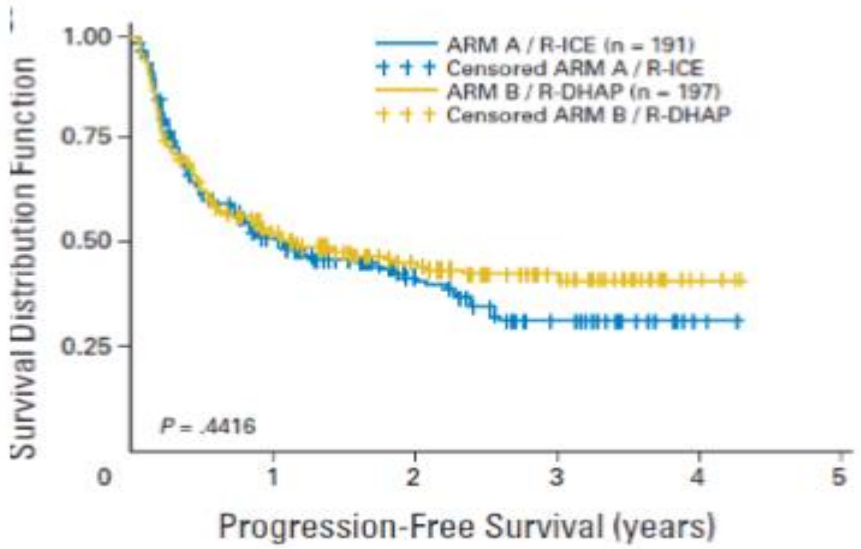
56/100 patients were progression-free and may be cured

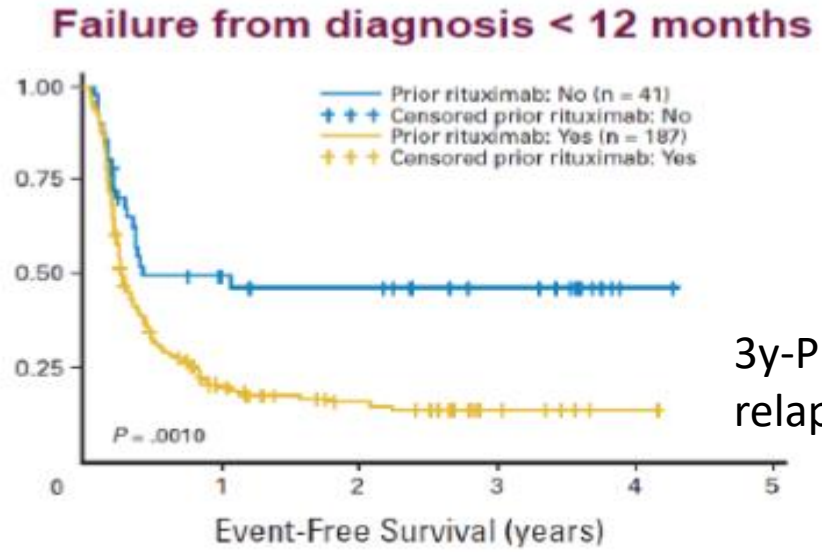
44/100 patients had progressed or died

GELA LNH-98.5: 87% of all progressions occurred in the first 3 years

Coiffier B, et al. Blood 2010; 116:2040–2045.

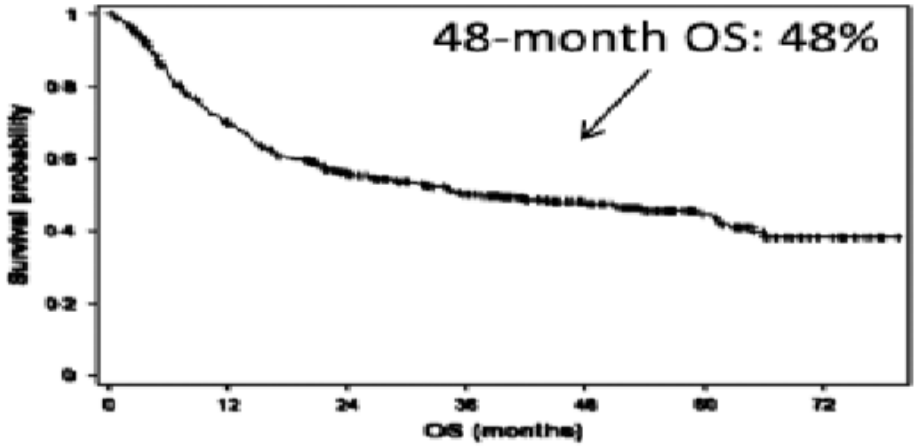
High-dose chemoimmunotherapy + ASCT: CORAL trial



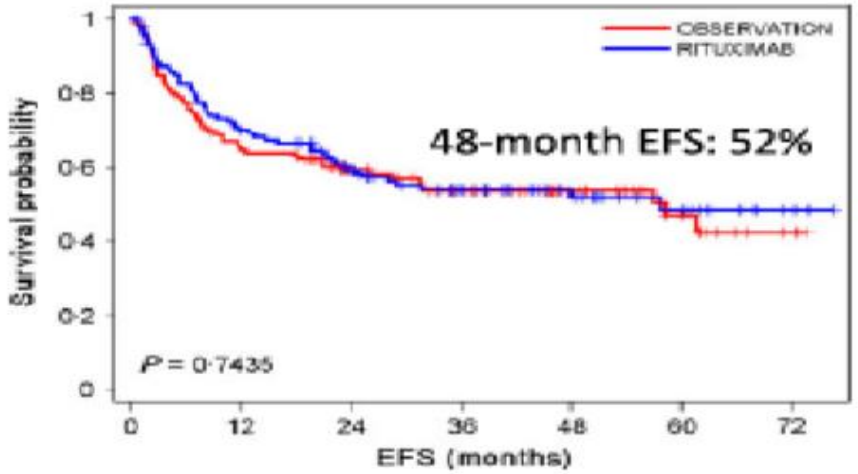


3y-PFS early relapse 23%

OS from **first** randomisation



EFS from **second** randomisation



Gisselbrecht C et al, J Clin Oncol 2010; Gisselbrecht C and Van Den Este E, Br J Haematol 2018

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

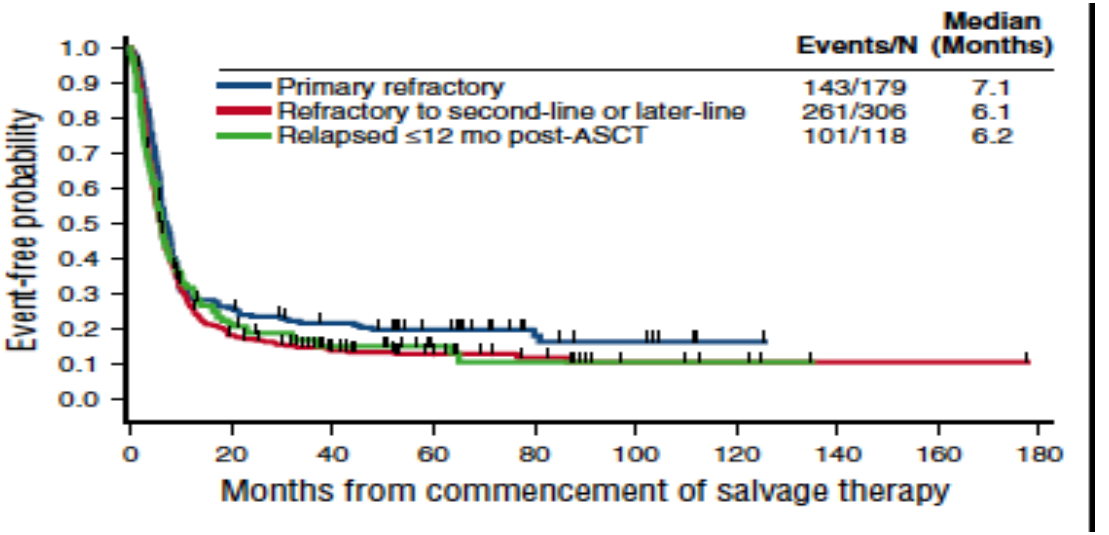
blood

BLOOD, 19 OCTOBER 2017 • VOLUME 130, NUMBER 16

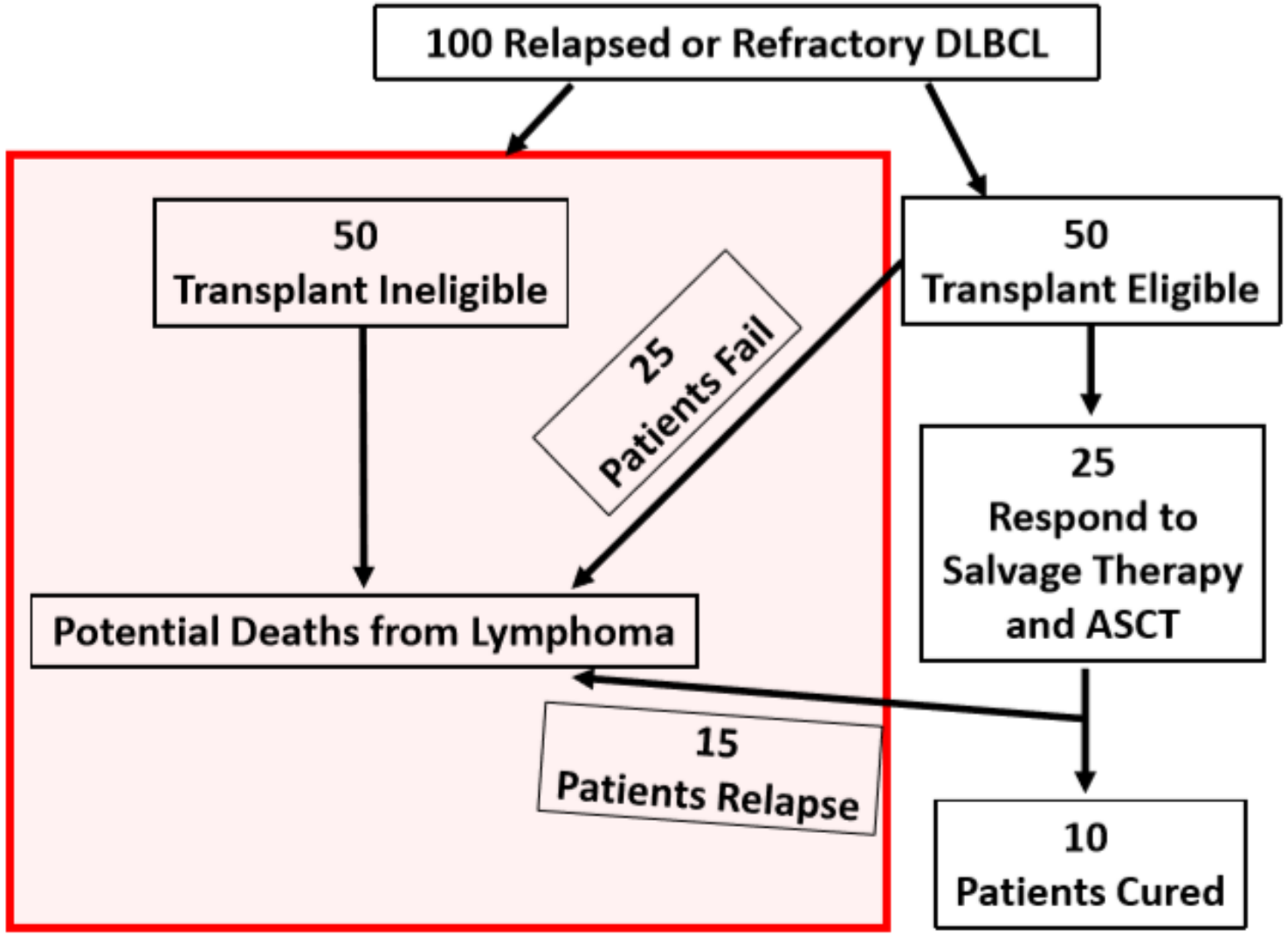
Large retrospective analysis of outcomes in 636 refractory DLBCL

How did these patients with refractory DLBCL respond to the next line of therapy?

- ✓ ORR 26% (CR 7%)
- ✓ Median OS 6.3 months



Outcome of current therapeutic approach in RR DLBCL



*Estimates based on Gisselbrecht et al. J Clin Onc 2010 28:27, 4184-4190.
*Assumes all patients received rituximab as part of primary therapy

Chimeric Antigen Receptor T-cell Therapy (CAR-T)
Redirecting the Specificity of T Cells

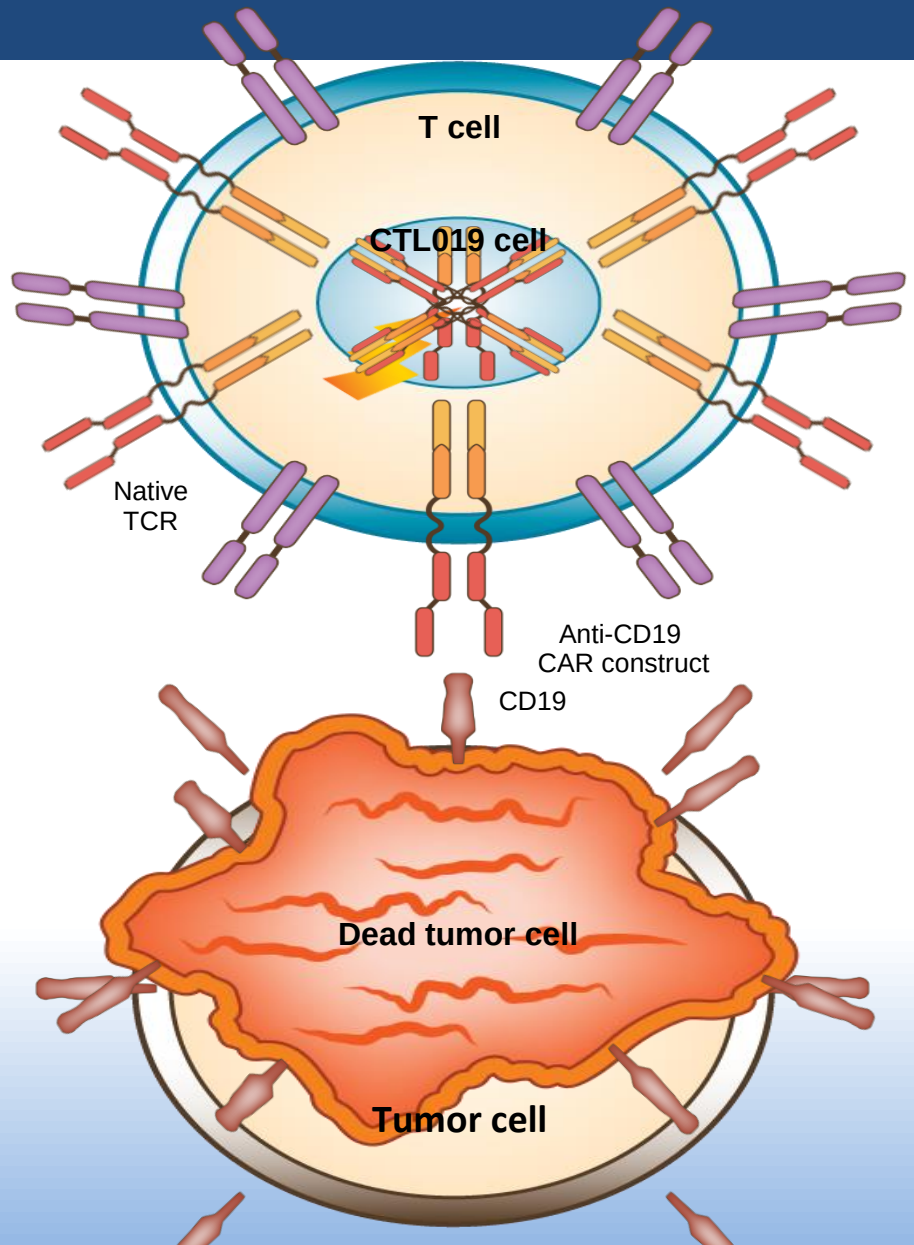
- Different transduction systems to get CARs into T cells:

→Retroviral transduction

→Lentiviral transduction

versus

→ non viral transduction (Sleeping Beauty)



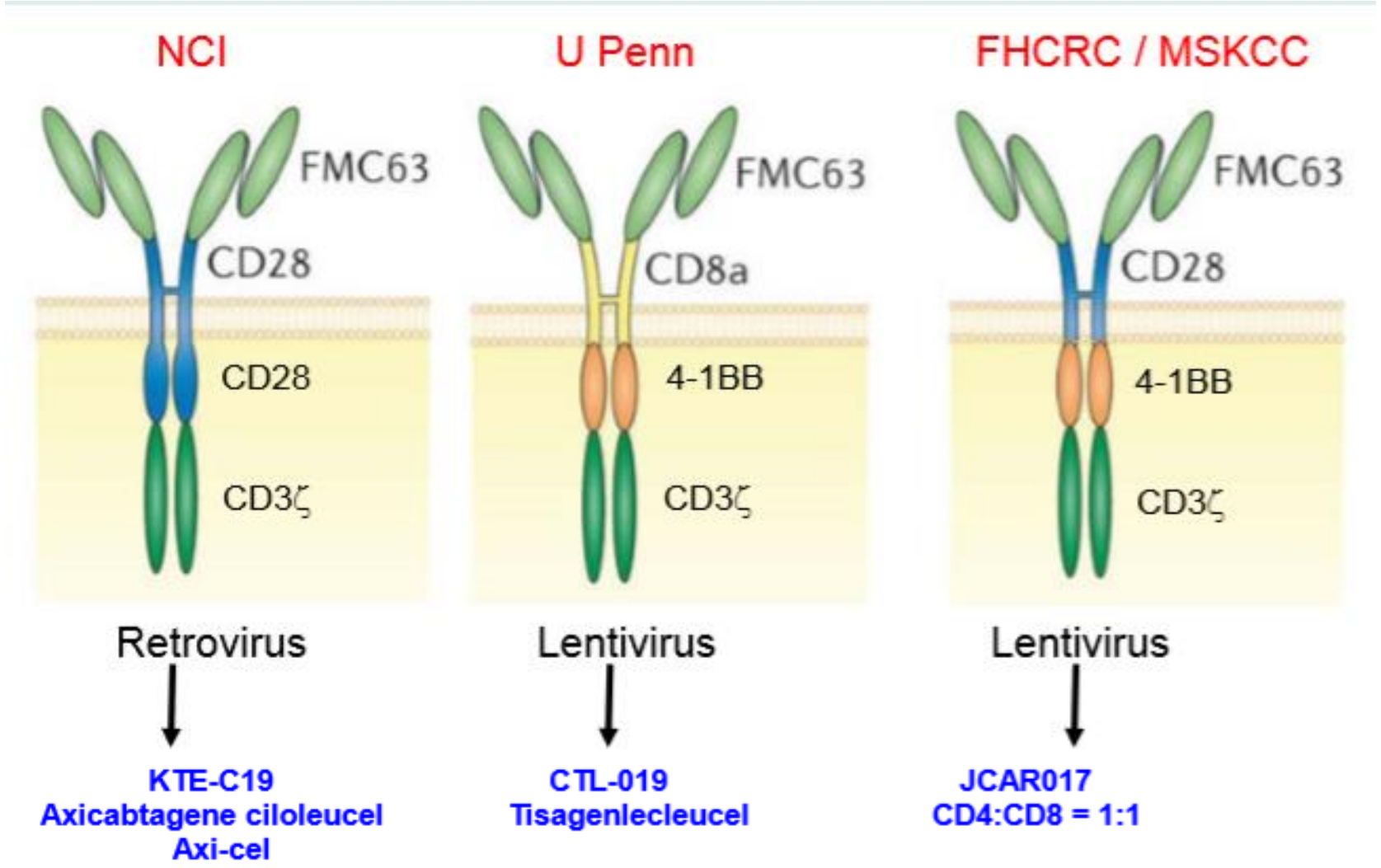
CD19 CAR-T products in pivotal trials in NHL

Antigen-binding (CD19) domain

CD8-alpha hinge and transmembrane

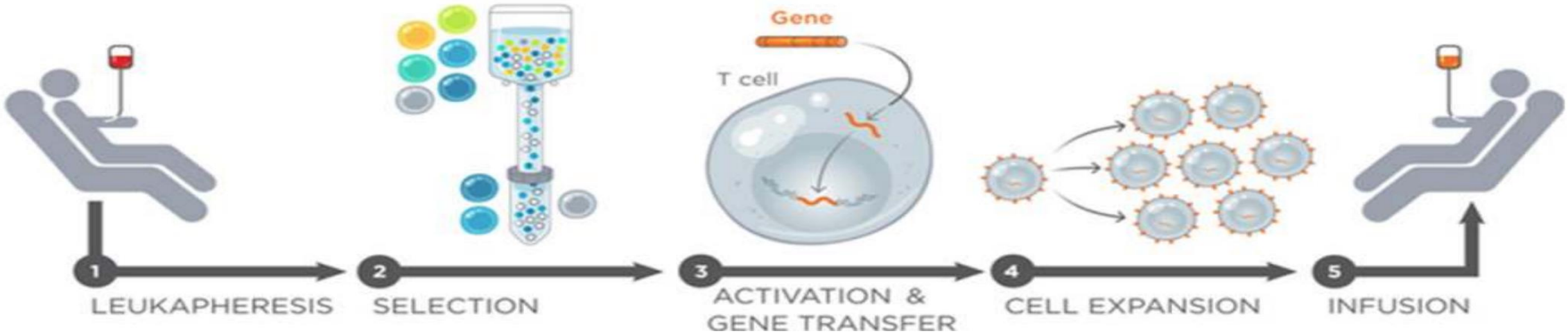
Costimulatory domain

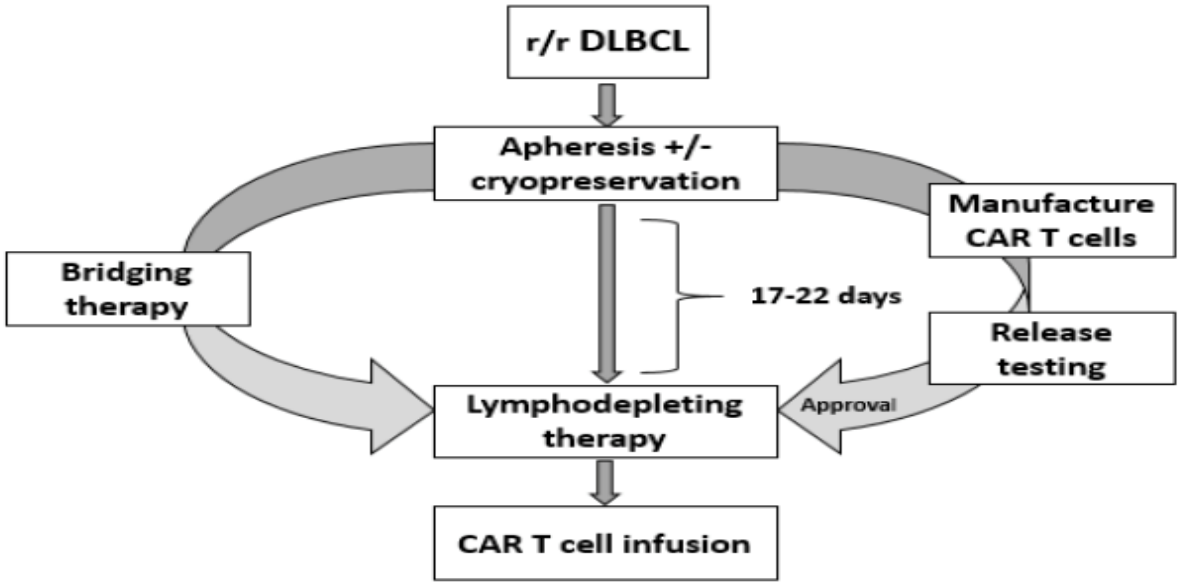
CD3-zeta signaling domain



Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

CAR-T manufacturing process





T cells are separated and transduced ex vivo using a lentivirus encoding for CAR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

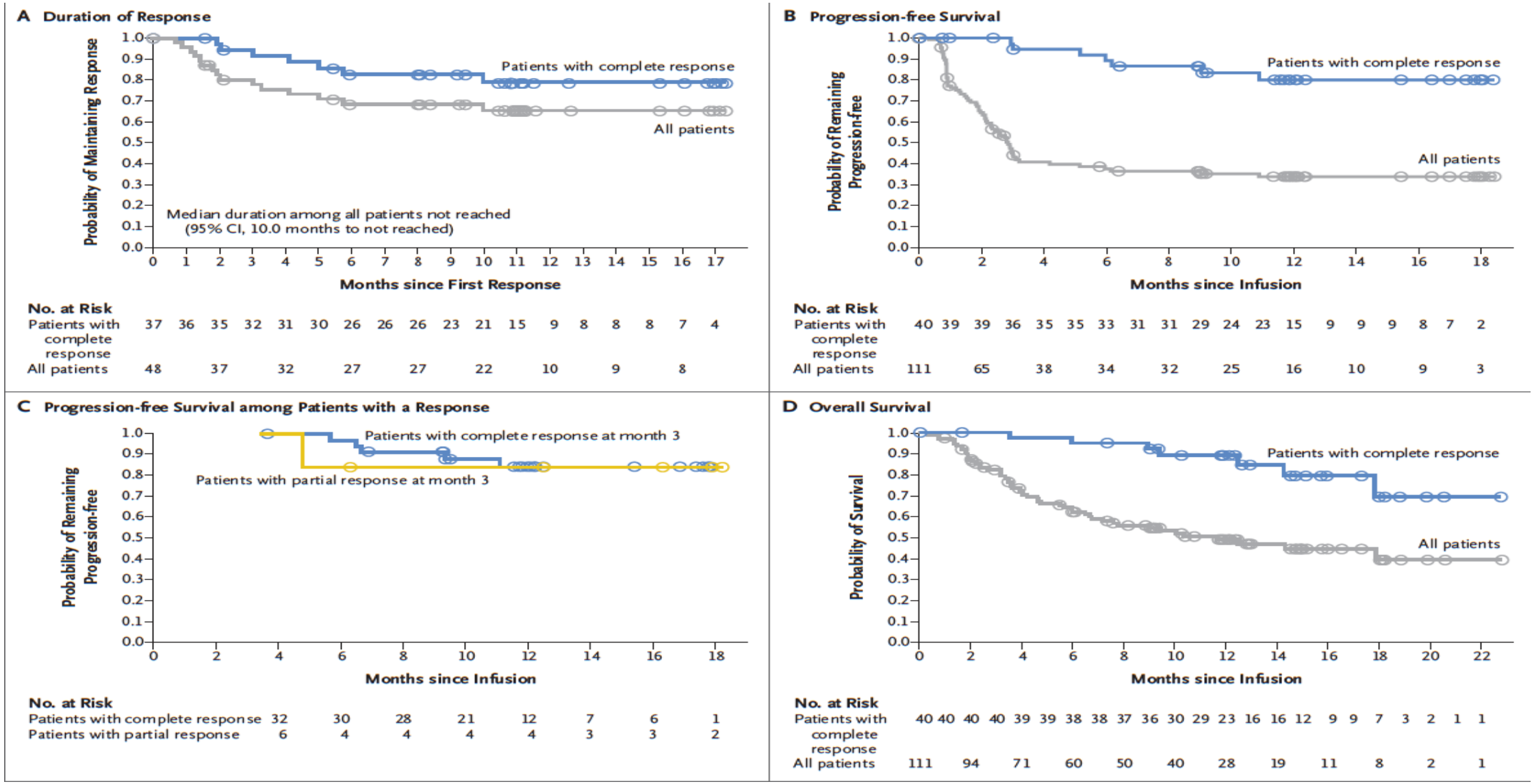
JULIET study. CTL019
Shuster SJ et al, NEJM 2019

238 screened patients
111 treated

	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	79
Transformed follicular lymphoma, %	19
Double/triple hits in *CMYC/BCL2/BCL6* genes, %	17[a]
Cell of origin[b]	
Germinal/Nongerminal center B-cell type, %	57/41
Number of prior lines of antineoplastic therapy, %	
2/3/4-6	44/31/21
IPI ≥ 2 at study entry, %	72
Refractory/relapsed to last therapy, %	55/45
Prior auto-SCT, %	49
Bridging chemotherapy, n	102
Lymphodepleting chemotherapy, n	103

[a] *CMYC* + *BCL2*, n = 10; *CMYC* + *BCL2* + *BCL6*, n = 5; *CMYC* + *BCL6*, n = 4.
[b] Determined by the Choi algorithm.

JULIET study. ORR 52%; ORR (3 mo) 38%; ORR (6 mo) 33%



Shuster SJ et al, NEJM 2019

JULIET study. Special Interest Adverse Events

	(N = 111)		
AESI[a]	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	58	14	8
Neurological events	21	7	5
Prolonged cytopenia[c]	44	16	16
Infections	34	18	2
Febrile neutropenia	15	13	2

[a] Occurring within 8 weeks of tisagenlecleucel infusion. [b] Cytokine release syndrome was graded using the Penn scale. [c] At day 28.

	Patients (N = 111)
Time to onset, median (range), days[a]	3 (1-9)
Duration, median (range), days[a]	7 (2-30)
Hypotension that required intervention, %	26
High-dose vasopressors	6
Intubated, %	7
Anticytokine therapy, %	16
Tocilizumab	15
Corticosteroids	11

[a] Calculated based only on patients who had cytokine release syndrome (n = 64), excluding 1 patient who had onset on day 51.

Tocilizumab administered according to a protocol-specific treatment algorithm (CRS graded per the Penn scale[1])

- 3% of patients with grade 2 CRS
- 50% with grade 3 CRS
- 100% with grade 4 CRS

No deaths due to tisagenlecleucel, CRS or cerebral edema

The most common neurological events were:

- Confusional state (8% any grade; 2% grade 3)
- Encephalopathy (6% any grade; 1% grade 3 and 4% grade 4)

Shuster SJ et al, NEJM 2019

The NEW ENGLAND JOURNAL of MEDICINE

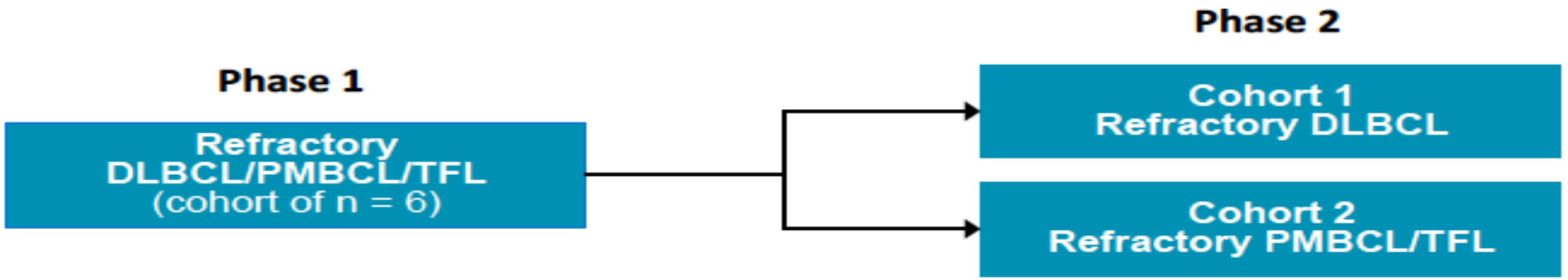
ORIGINAL ARTICLE

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

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

ZUMA-1 study AXI-cel

111 enrolled patients
101 treated



Eligibility criteria

- Aggressive NHL: DLBCL, PMBCL, TFL
- Chemotherapy-refractory disease: no response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 mAb and anthracycline
- ECOG PS 0-1

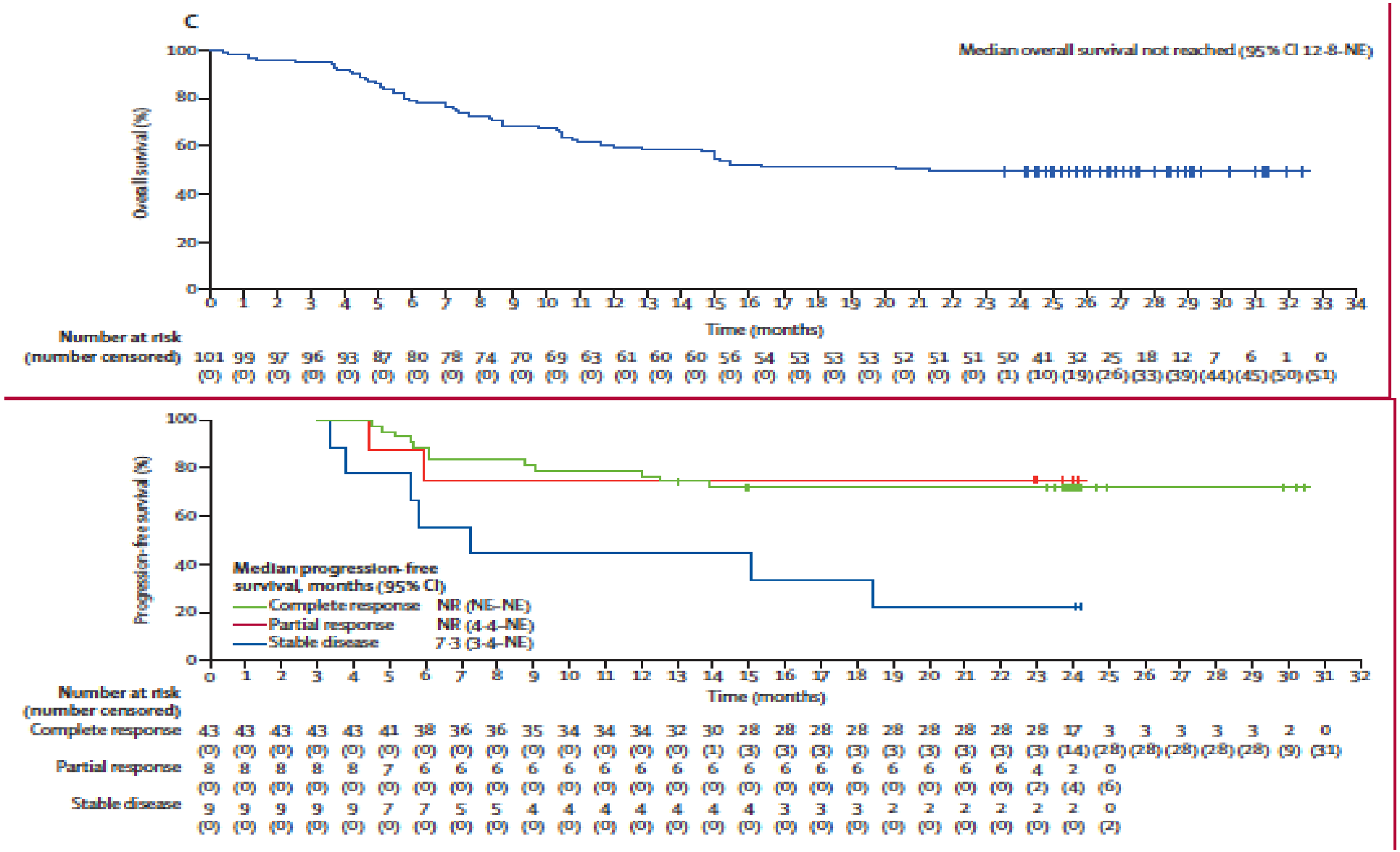
Primary end point

- Phase 2: Objective response rate (ORR)

Key secondary end points

- DOR, OS, safety, levels of CAR T and cytokines

ZUMA-1 study. ORR 83%, median DO 11.1 months



Locke FL et al, Lancet Oncol 2019

ZUMA-1: Summary of Adverse Events

‡

AE, n (%)	Primary Analysis N = 101	Updated Analysis N = 108
Grade ≥ 3 AE	96 (95)	105 (97)
Grade ≥ 3 SAE	43 (43)	50 (46)
Grade ≥ 3 CRS	13 (13)	13 (12)
Grade ≥ 3 NE	28 (28)	33 (31)
Grade 5 AE	3 (3)[a]	4 (4)[b]

- Since the primary analysis with ≥ 6 months of follow-up, there have been no new axi-cel–related CRS, NE, or Grade 5 AEs
- Most patients experienced hypogammaglobulinemia and B cell aplasia; 8% had IVIG support at any point on study

Tox AFTER 6 months

- Infections (8 patients) were the most common new-onset treatment-emergent SAE
- All of the above SAEs had resolved as of the data cut-off

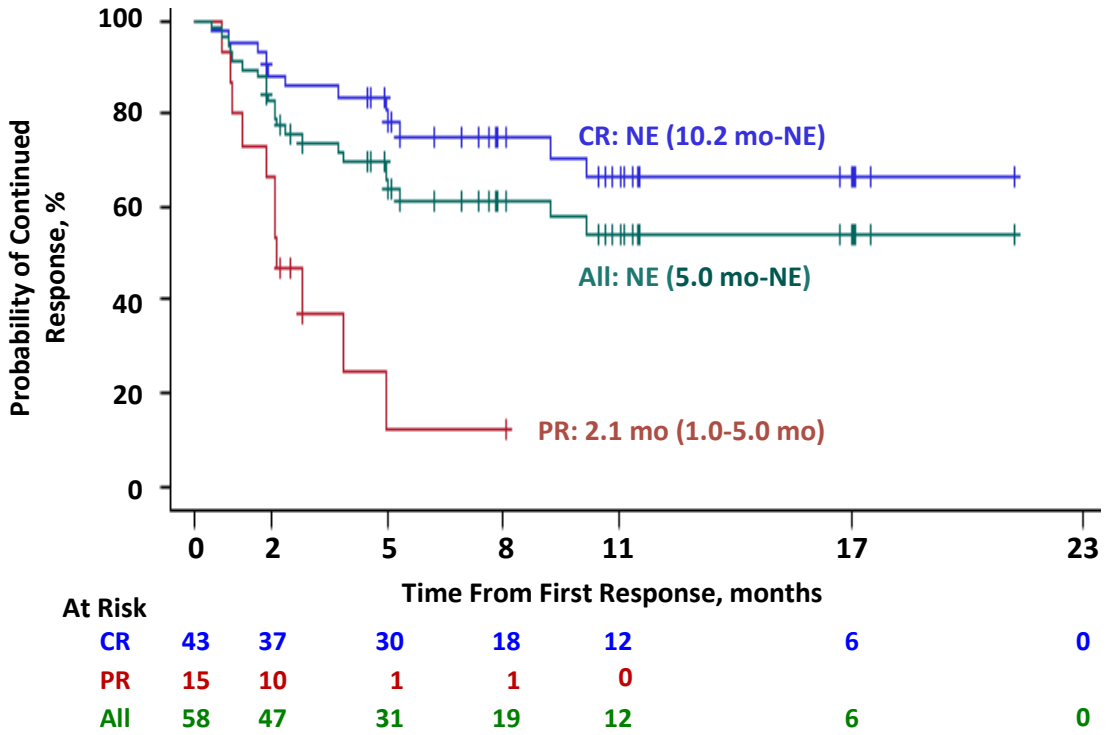
AE, adverse event; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; NE, neurologic event; SAE, serious AE.

[a]As previously reported, Grade 5 AEs occurred in 3 patients. Axi-cel–related, 2 (2%; HLH and cardiac arrest); axi-cel–unrelated, 1 (1%; pulmonary embolism). [b]The additional Grade 5 AE presented here is the previously reported[1] phase 1 event of intracranial hemorrhage unrelated to axi-cel.

1. Locke FL, et al. *Mol Ther*. 2016.25:285-295.

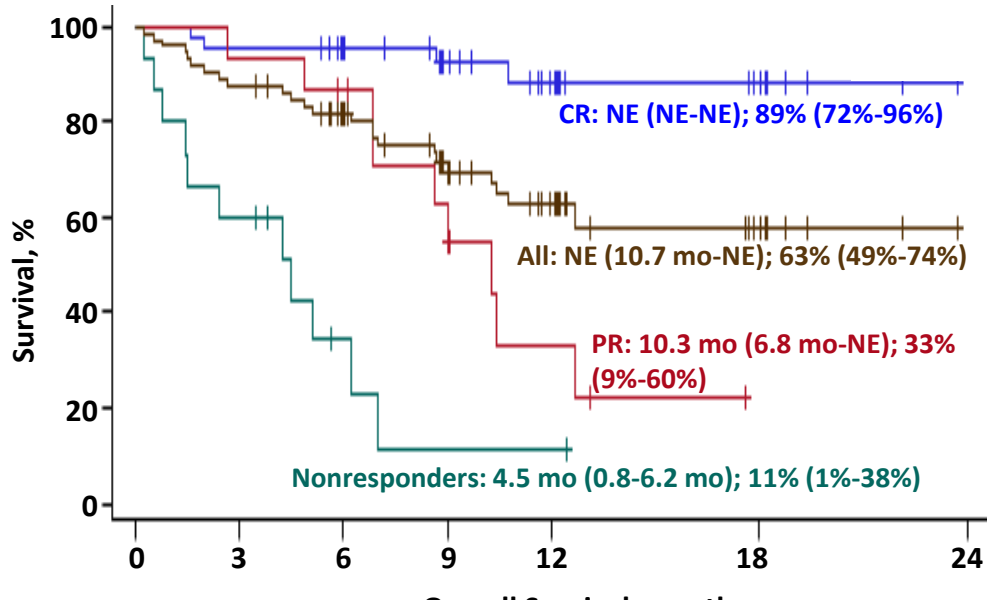
TRANSCEND-NHL-001 JCAR017: Duration of Response and OS 73 patients

DOR (median follow-up 8 mo)



At Risk							
CR	43	37	30	18	12	6	0
PR	15	10	1	1	0		
All	58	47	31	19	12	6	0

OS (median follow-up 12 mo)



At Risk							
All	73	64	50	37	22	8	0
CR	43	41	35	28	18	8	0
PR	15	14	12	8	3	0	
Non-responder	15	9	3	1	1	0	

88% of patients with a CR at 3 months stayed in CR at 6 months;
93% of patients in CR at 6 months had ongoing response

Data in graphs are median DOR (95% CI).
NE, not estimable.
Abramson J, et al. ASCO 2018. abstract 7505.

Axi-cells in Real World Experience

Leukapheresed N=295

7 pts non-conforming cell therapy product
12 pts died to lymphoma
1 non measurable disease
1 infection

Lymphodepleting CT N=274

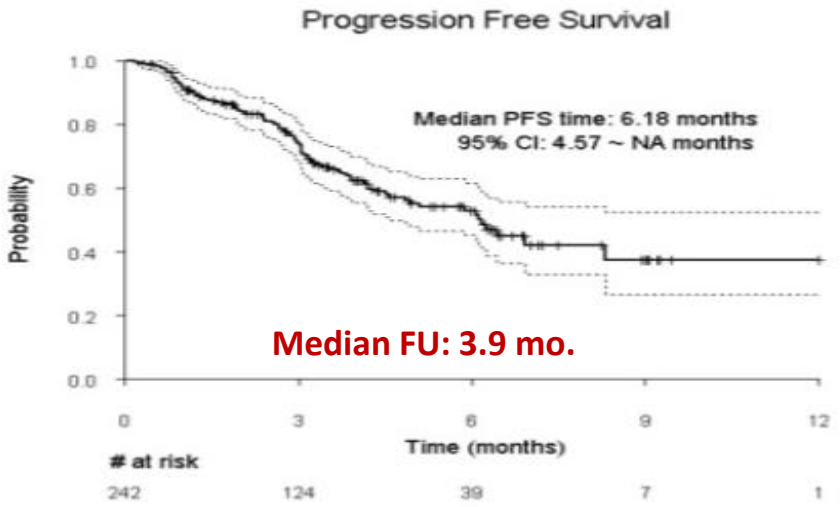
Median Time from LK to CT: 21.5 days
55% of pts received bridging therapy

Axi-Cel 2 x 10^6 CARTcells/Kg N=274

	SOC Axi-cel N = 274 (mITT)
All Grades of CRS*, N (%)	240 (92%)
Grade ≥ 3 CRS, N (%)	18 (7%)
Median time to onset of CRS	3 days
All Grades of NT**, N (%)	181 (69%)
Grade ≥ 3 NT, N (%)	85 (33%)
Median time to onset of NT	6 days

7 toxic deaths: 1 HLH, 1 CRES, 5 infections

	SOC Axi-cel Evaluable	SOC Axi-Cel
Median follow up, months		3.9
Day 30 ORR, N (%)	238	191 (80)
Day 30 CR, N (%)		113 (47)
Best ORR at Day 90, N (%)	248[a]	201 (81)
Best CR at Day 90, N (%)		142 (57)



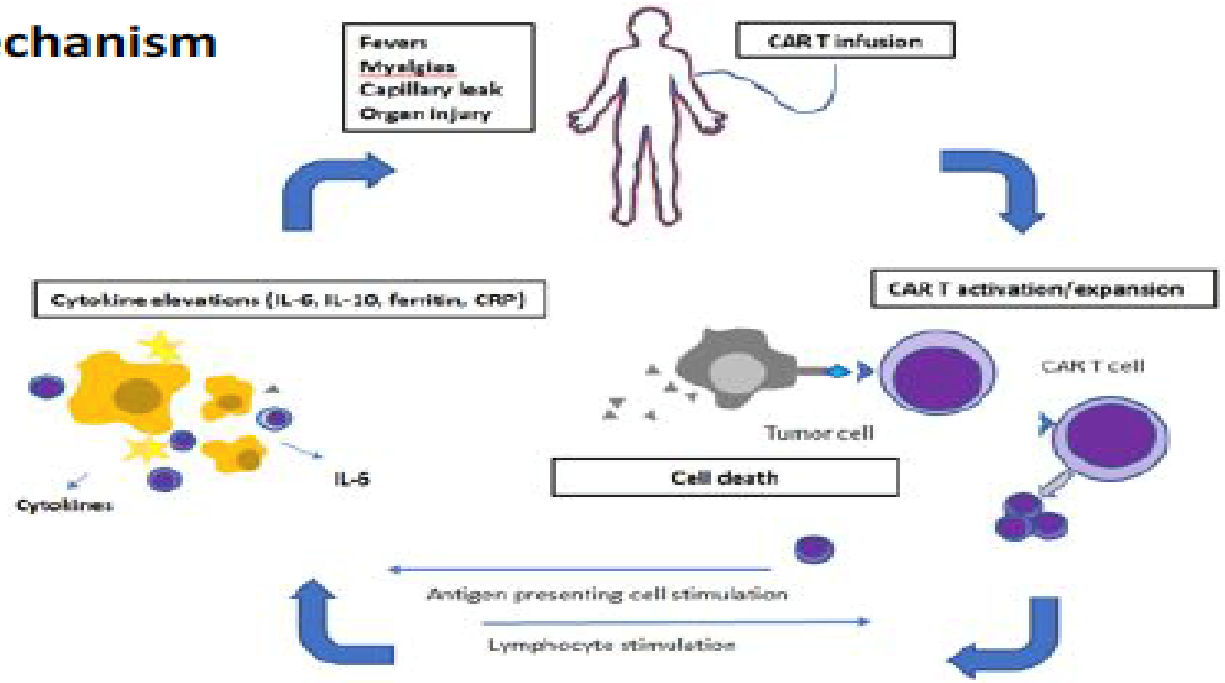
Nastoupil L et al, ASH 2018

WHAT IS CYTOKINE RELEASE SYNDROME?

G	PENN GRADING SCALE[1]
1	Mild reaction: treated with supportive care such as antipyretics, antiemetics
2	Moderate reaction: some signs of organ dysfunction related to CRS and not attributable to any other condition. Need for IV therapies (not including fluid resuscitation for hypotension)
3	More severe reaction: symptoms related to organ dysfunction related to CRS; hypotension treated with intravenous fluids (defined as multiple fluid boluses for blood pressure support) or low-dose vasopressors, coagulopathy requiring FFP/cryo, and hypoxia requiring supplemental O2
4	Life-threatening complications such as hypotension requiring high-dose Vasopressors or hypoxia requiring mechanical ventilation

1. Porter DL *et al. Sci Transl Med*. 2015

Mechanism



Symptoms

Onset 1-14 days after infusion, duration 1-10 days
Fevers come first and get very high (105ºF/41ºC)
Myalgias, fatigue, anorexia, capillary leak, hypoxia, hypotension

Management

Supportive care
Anti-cytokine interventions

NEUROLOGIC TOXICITY

Mechanism

T cell vs. cytokine mediated (endothelial activation)

CAR T cells are seen in the CSF[1-5]

Symptoms

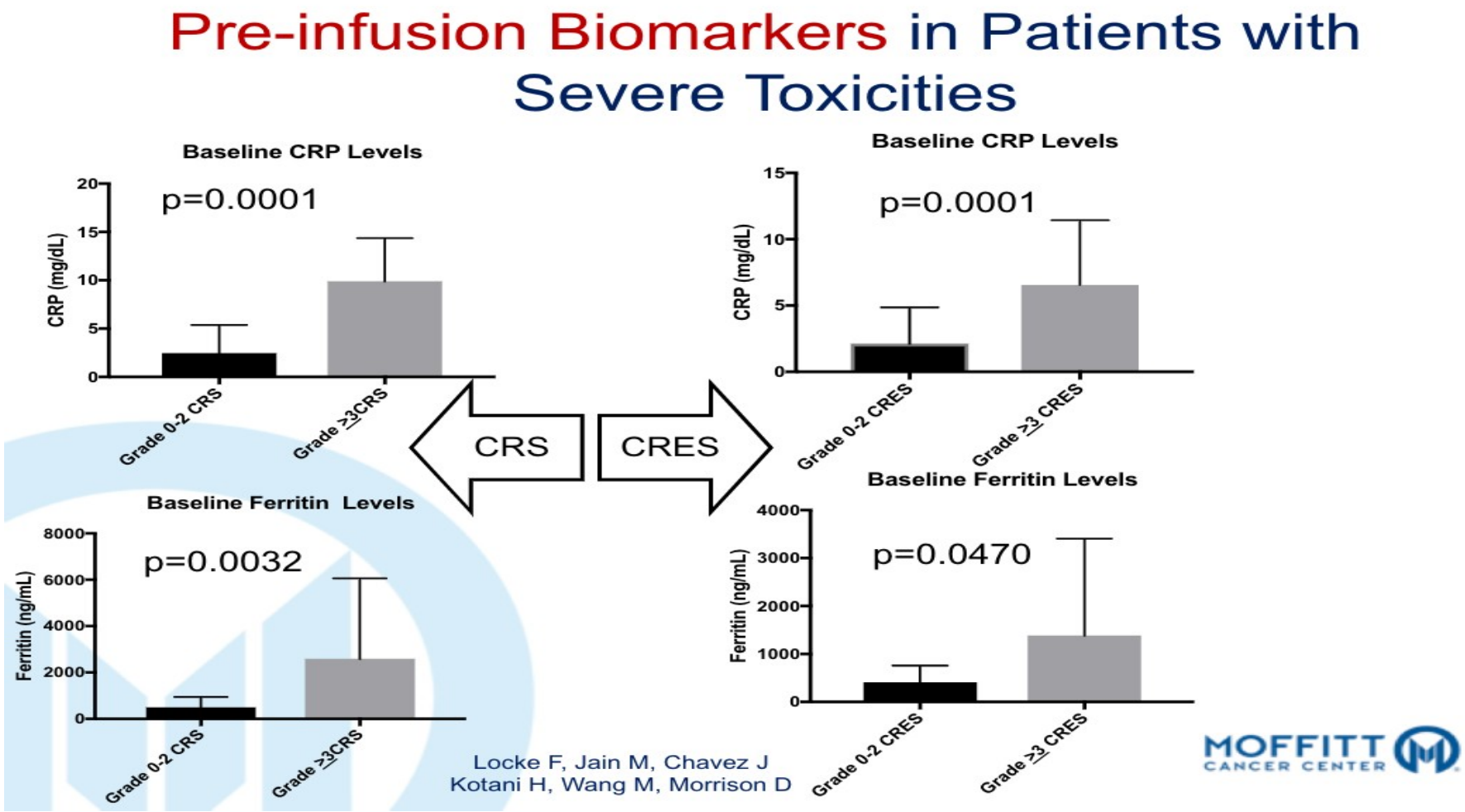
Aphasia, delirium, encephalopathy, seizures

Management

No clear response to anti-cytokine treatment

[1]Maude et al. NEJM 2014
[2]Davila et al. SciTranMed 2014
[3]Lee et al. The Lancet 2015
[4]Kochendorfer et al. JCO 2015
[5]Turtle et al. JCI 2016
[6]Gust et al. Cancer Discovery 2017

Axi-cells in Real World: Predictors of Response, Resistance and Toxicity



Faramand R et al, ASH 2018

CD19-targeted CAR-T cells: Late Effects

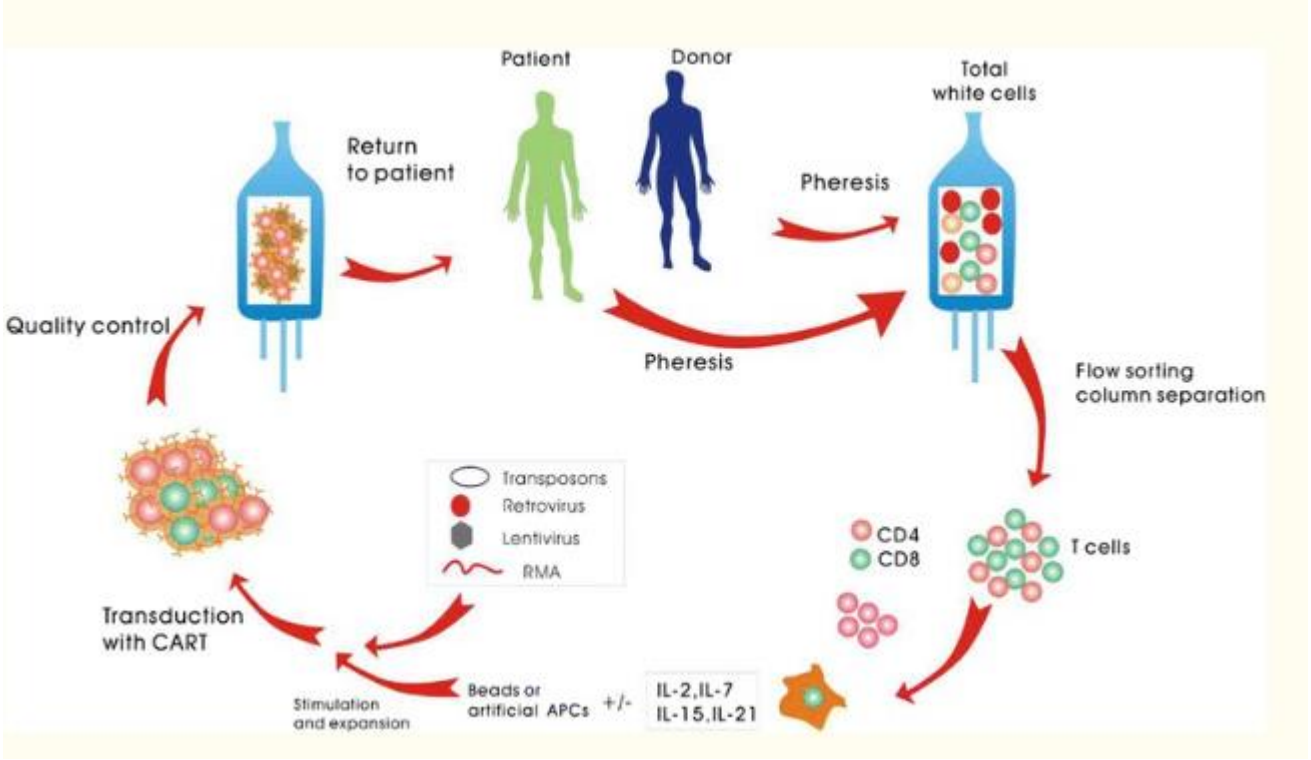
Clinical characteristics	N = 59 (%), median FU after CAR-T 23 months
Median age	60 (range, 34 – 73)
NHL/CLL	42 (71%) / 17 (29%)
Median prior lines	4 (range, 1 – 8)
One CAR T infusion	35 (59%)
Two/Three CAR T infusions	22 (37%); 2 (3%)
Salvage Therapy after CAR T	29 (49)

Adverse Events	
Cytopenia beyond 90 days	**25%**
Subsequent malignancies	**14%**
Neuropsychiatric disordes	**8%**
Cardiovascular Events	**8%**
Severe hypogammaglobulinemia	**41%**
Hospital admission due to infections	**46%**

3/59 pts died of non-relapse causes
(2 due to infection after allo HCT, and 1 due to duodenal ulcer and gut perforation)

Cordeiro A et al, ASH 2018

CART therapy: future prespectives



- ✓ **Allogenic CART**
- ✓ **NK CART**
- ✓ **New targets CART**

(CAR-T cells targeting CD22. Studies evaluating the safety and efficacy of T cells transduced with bivalent lentiviral vector (CD19/CD22.BB.z) expressing CD19/CD22 are currently conducted in patients with selected r/r B-cell malignancies (NCT03289455, NCT03233854, NCT03448393).

CART nei DLBCL : problemi aperti

Vantaggi

- Terapia paziente specifica
- Possibilità terapeutica per pazienti altrimenti a prognosi infausta
- 35-40% vivi e senza malattia a più di 18 mesi
- Effetti collaterali acuti gravi in una minoranza di pazienti e gestibili da un team multidisciplinare addestrato
- Mortalità molto contenuta inferiore al trapianto allogenico

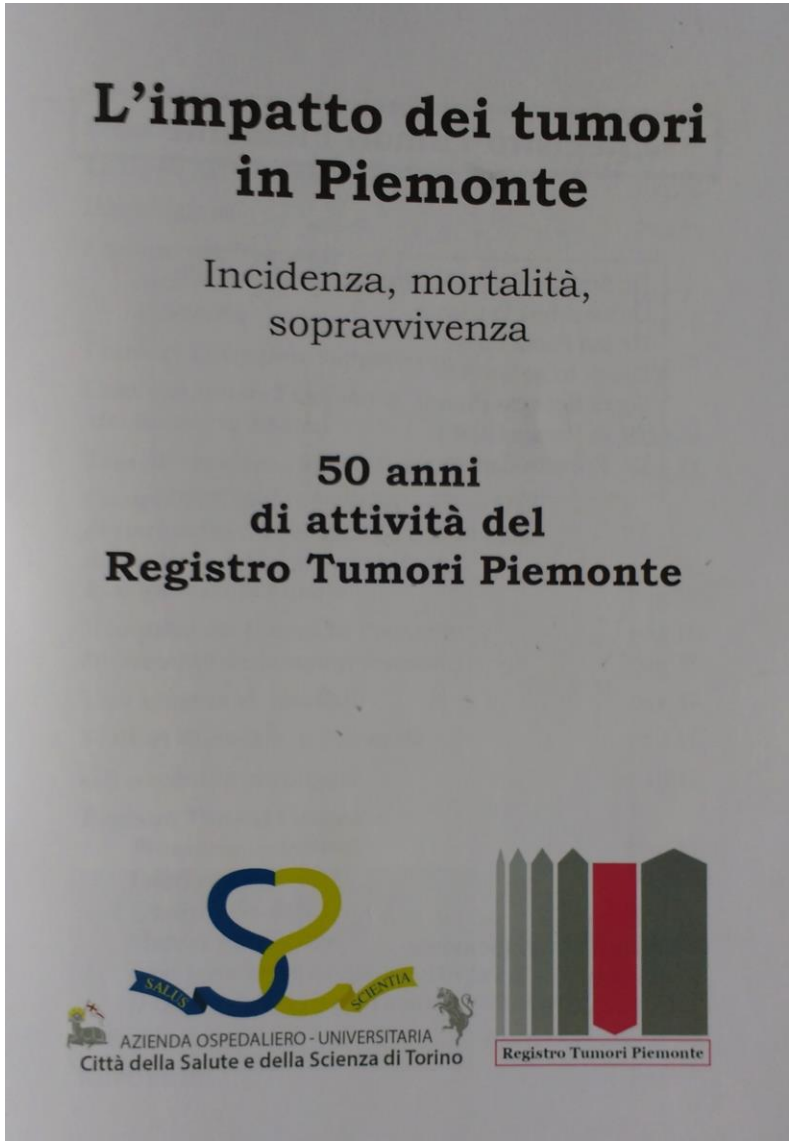
Punti aperti da superare/migliorare

- Individuare i fattori clinici e biologici che determinano la non risposta e i metodi per superarli
- Necessità di ottima selezione dei pazienti per aumentare l'efficacia e ridurre la tossicità
- Il profilo di tossicità dei prodotti non è uguale e necessita di conoscenze specifiche
- Al momento terapia che richiede la somministrazione e la gestione in centri specialistici e con esperienza
- Necessità di utilizzo di varie risorse ospedaliere (terapia intensiva, aferesei, criopreservazione etc)
- Facilitazione dei percorsi
- Costi

Possibili criteri di selezione dei pazinti con Linfoma a grandi cellule eleggibili al trattamento CART in corso di discussione

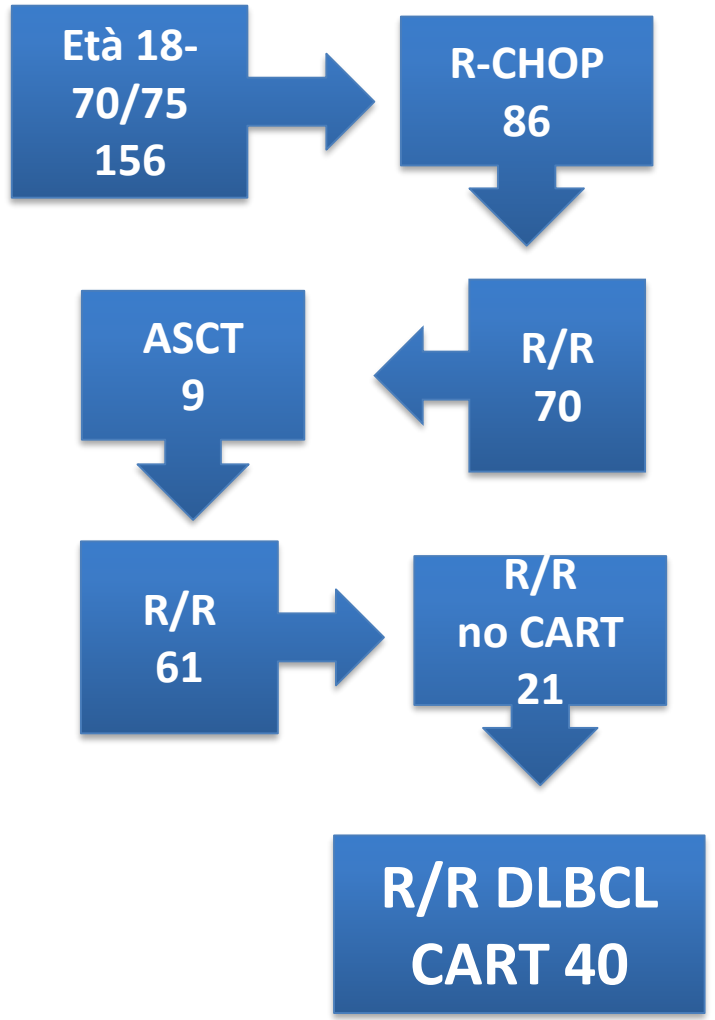
- Età ≤70 o ≤75 anni (da valutare con appropriata scala geriatrica o comorbidità)
- Performance status 0-1
- Malattia non rapidamente progressiva
- Adeguata funzione d'organo
  - Frazione di eiezione > 45%
  - Adeguata funzionalità renale, polmonare ed epatica
- Assenza di infezioni in atto
- Assenza di malattia attiva a livello del sistema nervoso centrale
- Malattia non rapidamente progressiva
- Conta totale linfocitaria > 300
- Livelli di ferritina < 3000

Ipotesi di necessità di trattamento CART nei DLBCL in regione Piemonte



Numero di nuove diagnosi di DLBCL (con referto istologico) nella popolazione residente in Piemonte nel biennio 2013-2014, per sesso e classe d'età. Dati del Registro Tumori Piemonte - CPO

Classi d'età	F	M	TOTALE
0-19	1	0	1
20-24	1	3	4
25-29	4	3	7
30-34	2	5	7
35-39	6	6	12
40-44	5	7	12
45-49	6	15	21
50-54	20	18	38
55-59	13	25	38
60-64	16	34	50
65-69	35	44	79
70-74	43	46	89
75-79	72	45	117
80-84	59	39	98
85+	30	25	55
TOT	313	315	628



Conclusioni

- ✓ I pazienti con DLBCL ricaduti/refrattari hanno urgentemente bisogno di nuove e più efficaci terapie
- ✓ Le CAR-T cells sono in grado di indurre un alto tasso di risposte e durature nel 40% dei pazienti trattati
- ✓ I pazienti elegibili alla terapia con CART devono essere identificati con attenzione
- ✓ CRS e la neurotossicità sono gestibili se riconosciute precocemente e trattate da uno staff esperto
- ✓ Riconosciuti fattori clinici quali malattia bulky, elevati livelli di ferritina sembrano correlare con tossicità e risposta
- ✓ Studi futuri permetteranno di migliorare l'efficacia delle CART e ridurne la tossicità

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Lymphoma Team Hematology Torino

U. Vitolo

C. Boccomini

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E. Santambrogio

F.Vassallo

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Città della Salute e della Scienza di Torino

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