CAR T-CELL THERAPY FOR HEMATOLOGIC MALIGNANCIES: FOCUS ON DIFFUSE LARGE B-CELL LYMPHOMA

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LEARNING OBJECTIVES

- Describe the latest developments in CAR T-cell therapy options for adults and pediatric patients
- Explain short and long-term side-effect management, including CRS and neurotoxicities
- Discuss practical information in considering and treating a patient in a CAR T trial
- Be more prepared to identify resources for professionals as well as for their patients

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CAR T-cell Therapy for Hematologic Malignancies: Focus on Diffuse Large B-cell Lymphoma

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Outline

1. Overview of refractory/relapsed Diffuse Large B-cell Lymphoma
2. Overview of Cancer Immunotherapy
3. CAR-T cell structure and manufacturing
4. Efficacy of multicenter CAR-T cell studies in DLBCL
5. CAR-T cell therapy in pediatric acute lymphoblastic leukemia (ALL)
6. CAR-T cell toxicity and principles of management
7. Patient selection, toxicity management and post CAR-T cell therapy monitoring
8. Future directions

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Overview of Refractory/Relapsed DLBCL

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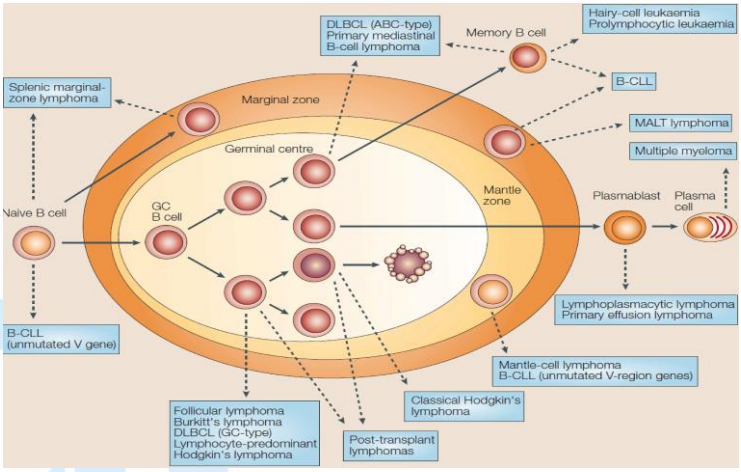
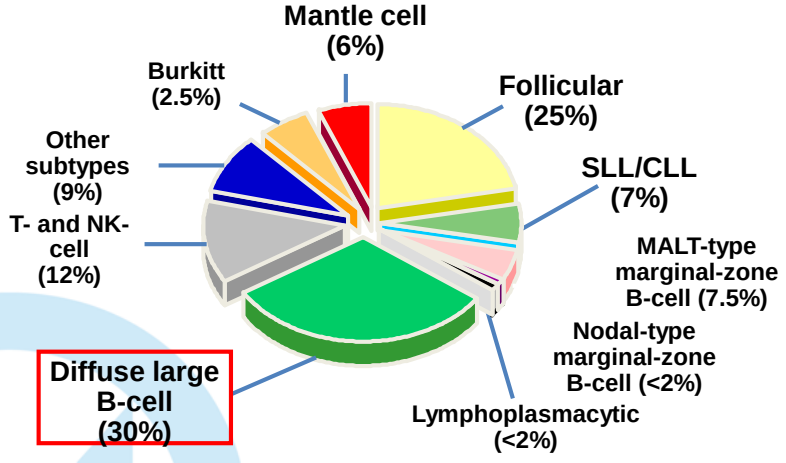
Cell of origin of B-cell lymphomas



Kuppers. Nature Reviews Cancer 2005; (5): 4.

7

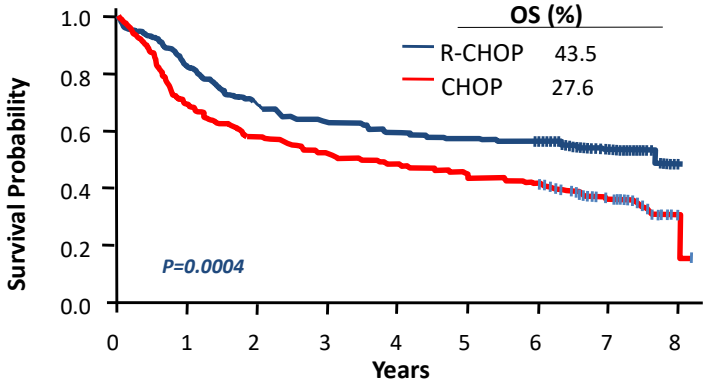
Most Common Subtypes of NHL



Lichtman MA, Beutler E, Kipps TJ, et al, eds. Williams Hematology. 7th ed. New York, NY McGraw-Hill;2006:1408.

8

10 Years Long-Term Follow-Up of DLBCL Elderly Patients Treated With CHOP With or Without Rituximab (LNH 98.5/GELA study)

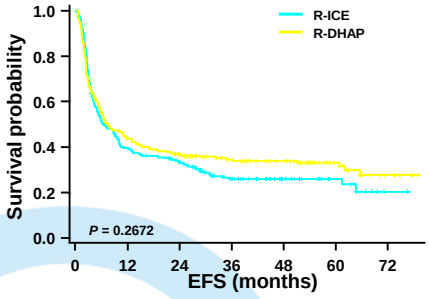


Coiffier et al. *Blood* 2010;116:2040-2045.

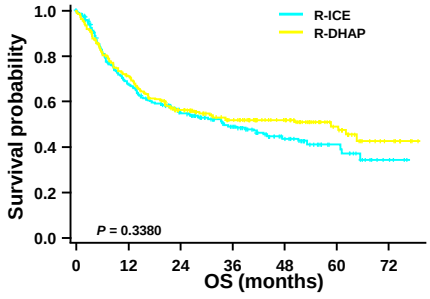
9

Role of Auto HCT in R/R DLBCL: EFS and OS by Induction Treatment: CORAL Study

481 patients randomized in the first part from 24 July, 2003 to 30 June, 2008
245 patients randomized in the second part from 21 October, 2003 to 21 October, 2008



	No. of subjects	Event	Censored	Median
R-ICE	239	71% (170)	29% (69)	6.51
R-DHAP	230	67% (153)	33% (77)	7.49



	No. of subjects	Event	Censored	Median
R-ICE	239	52% (125)	48% (114)	34.53
R-DHAP	230	49% (112)	51% (118)	58.97

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Gisselbrecht C, et al. J Clin Oncol. 2010;28(27):4184-4190.

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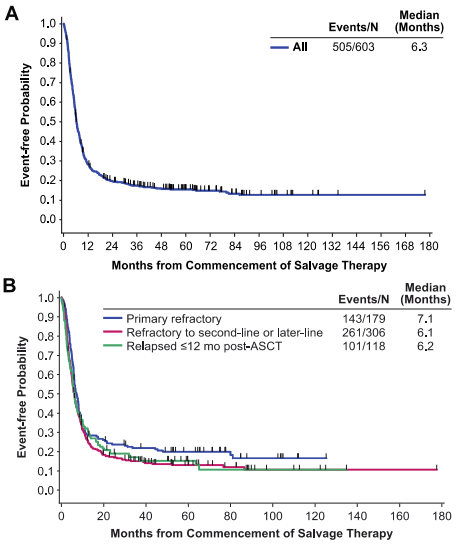
SCHOLAR-1: Outcomes of Patients With Refractory DLBCL

- SCHOLAR-1: Poor outcomes in patients:
  - Progressive disease to R-CHOP
  - Relapse post autologous HCT ≤12 months
  - Refractory to second- or later-line (N = 636)

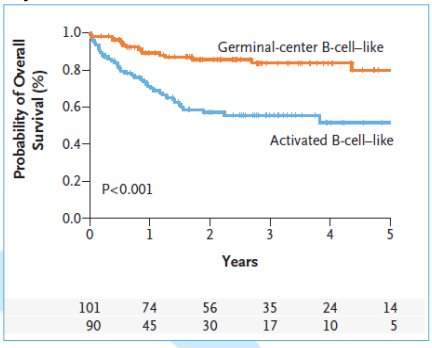


1. Crump M, et al. Blood. 2017;130(16):1800-1808.
2. Neelapu SS, et al. Ann Oncol. 2017;28(suppl 5):412 (abstr 1161P).
Neelapu SS, et al. Blood. 2017;130(suppl 1): 579.

11

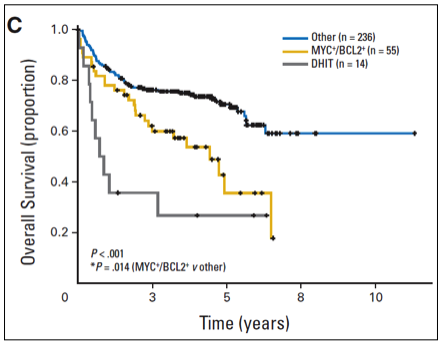
DLBCL is a Molecularly Heterogeneous Disease; Certain Patient Subsets Do Worse

Patients with ABC DLBCL are less likely to be cured by R-CHOP



Lenz G, et al. N Engl J Med. 2008;359(22):2313-2323.

"Double-Hit" (MYC + BCL2) carries worst prognosis



Johnson NA, et al. J Clin Oncol. 2012;30(28):3452-3459.

Additional Unmet Need

- **Primary refractory or first relapse within 12 months**
- **High IPI score at relapse**
- **Transformed lymphoma**
- **Relapse post ASCT**

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Cancer Immunotherapy

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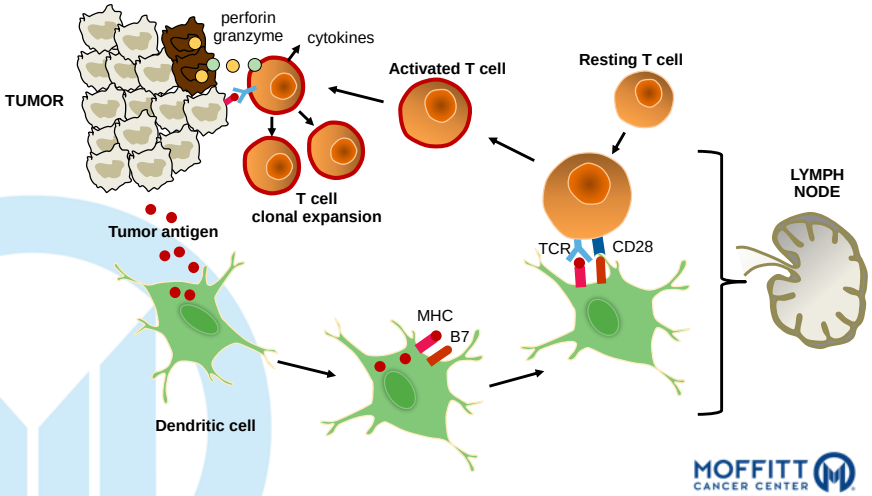
Tumor Immunology: Overview



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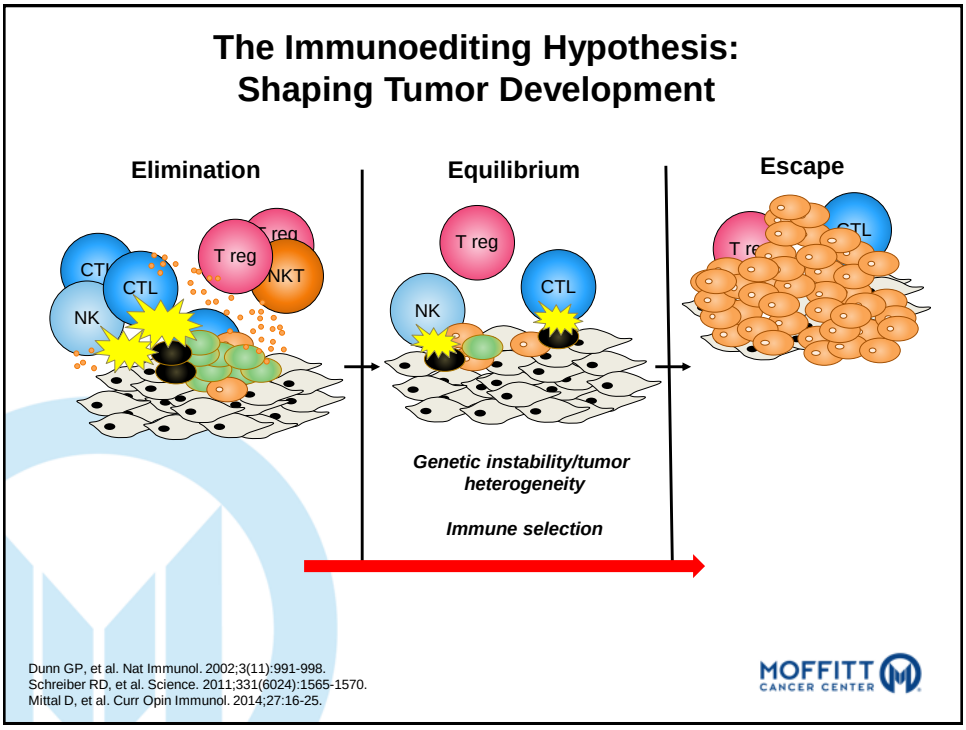
The Immunoediting Hypothesis:
Shaping Tumor Development
Elimination
Equilibrium
Escape
T reg
NKT
CTL
NK
Genetic instability/tumor heterogeneity
Immune selection
Dunn GP, et al. Nat Immunol. 2002;3(11):991-998.
Schreiber RD, et al. Science. 2011;331(6024):1565-1570.
Mittal D, et al. Curr Opin Immunol. 2014;27:16-25.
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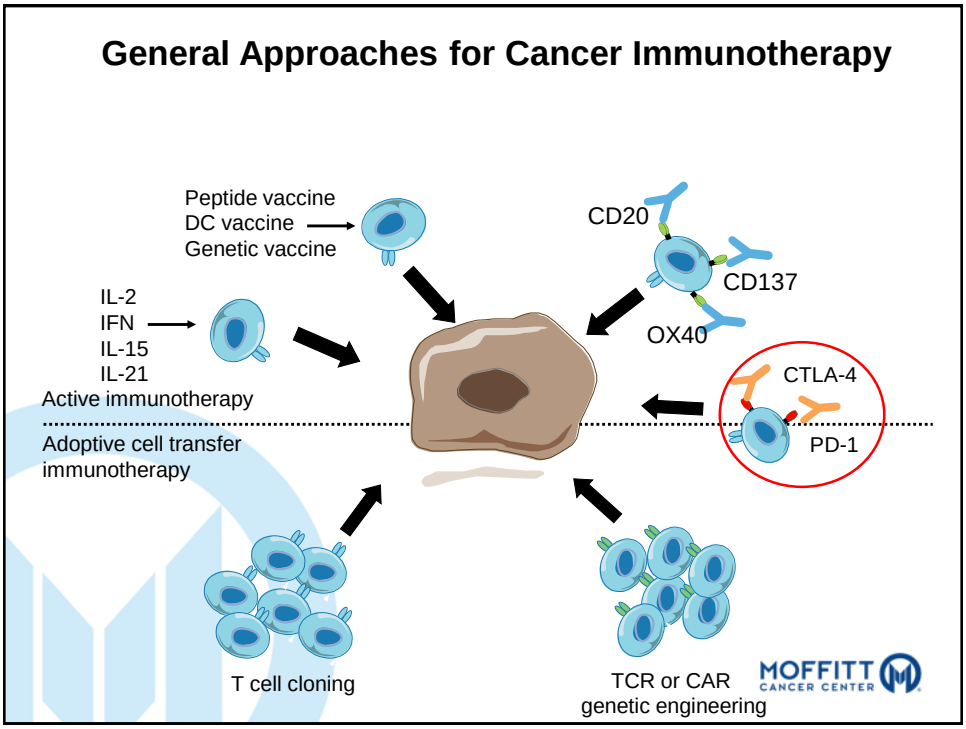
General Approaches for Cancer Immunotherapy
Peptide vaccine
DC vaccine
Genetic vaccine
IL-2
IFN
IL-15
IL-21
Active immunotherapy
Adoptive cell transfer immunotherapy
CD20
CD137
OX40
CTLA-4
PD-1
T cell cloning
TCR or CAR genetic engineering
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CAR T-cell Structure and Manufacturing

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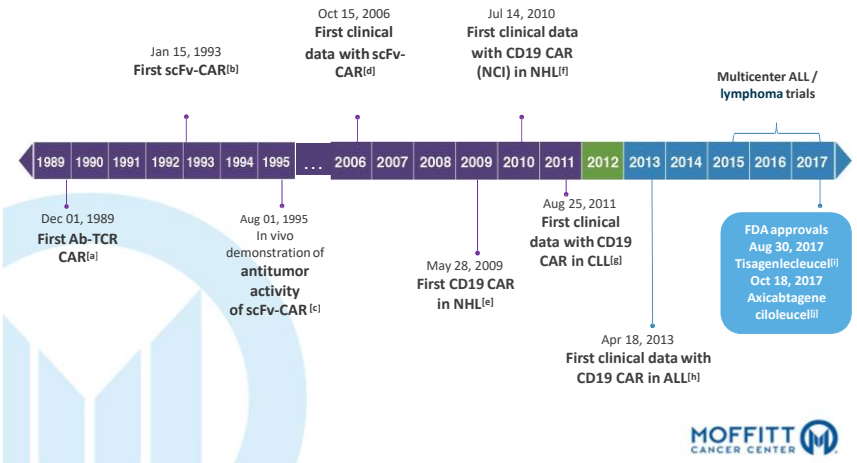
CAR T Development timeline: From Discovery to FDA Approval



a. Gross G, et al. *Proc Natl Acad Sci USA.* 1989; b. Eshhar Z, et al. *Proc Natl Acad Sci U S A.* 1993; c. Hwu P, et al. *Cancer Res.* 1995;55; d. Kershaw MH, et al. *Clin Cancer Res.* 2006; e. Kochenderfer JN, et al. *J Immunother.* 2009; f. Kochenderfer JN, et al. *Blood.* 2010; g. Porter D, et al. *N Engl J Med.* 2011; h. Grupp SA, et al. *N Engl J Med.* 2013;368; i. Kymriah™ PI; j. Yescarta™ PI.

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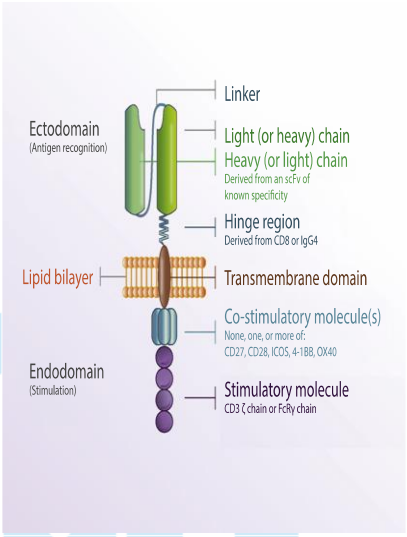
CAR T-cell Anatomy



Antibody-like recognition
+
T-cell activating function

- ***Extracellular***
  - ScFv: antibody single-chain variable fragment
  - Permits antigen recognition
- ***Hinge***
- ***Intracellular***
  - Signaling domains
  - T cell activation

Jackson HJ, et al. Nat Rev Clin Oncol. 2016;13(6):370-383.
Sadelain M. Cell. 2017;171(7):1471.

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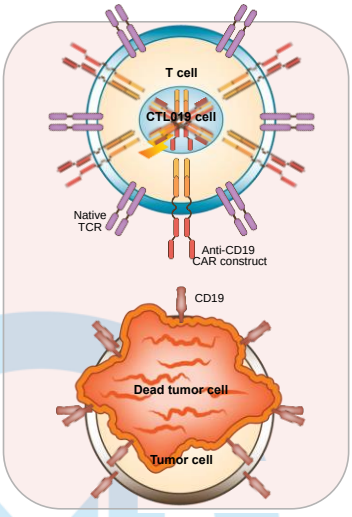
CAR T-cells: Mechanism of Action



- Gene transfer technology is used to express CARs on T cells, conferring novel antigen specificity.
- CAR T cells use T-cell cytotoxic potential to kill tumor cells in an antigen-dependent manner.
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells.

Milone MC, et al. Mol Ther. 2009;17(8):1453-1464.

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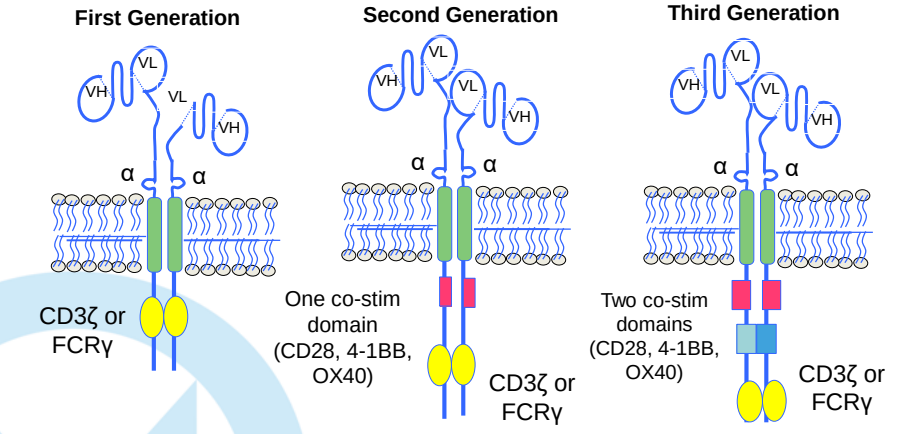
Evolution in CAR T-cell Design



Park JH, Brentjens RJ. J Clin Oncol. 2015;33(6):651-653.

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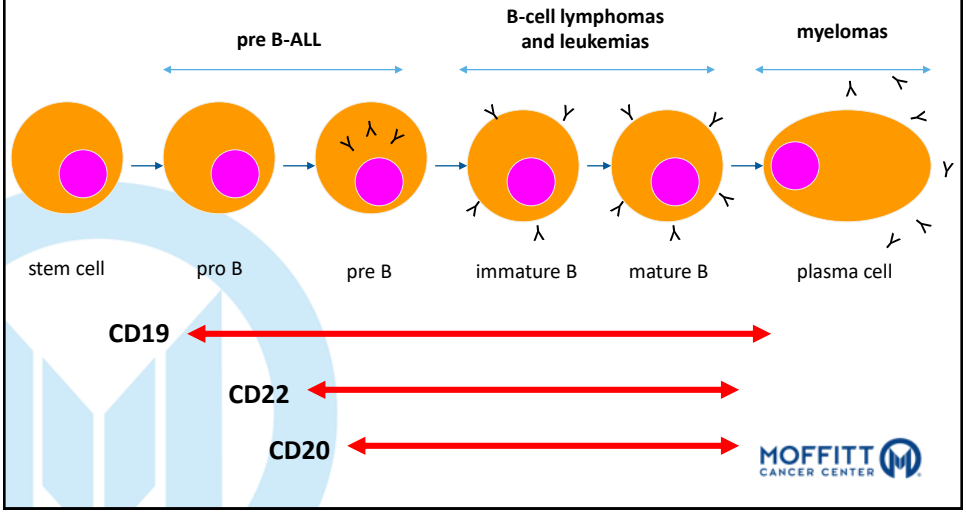
Expression of CD19 and Other B-cell Markers on B-Lineage Cells



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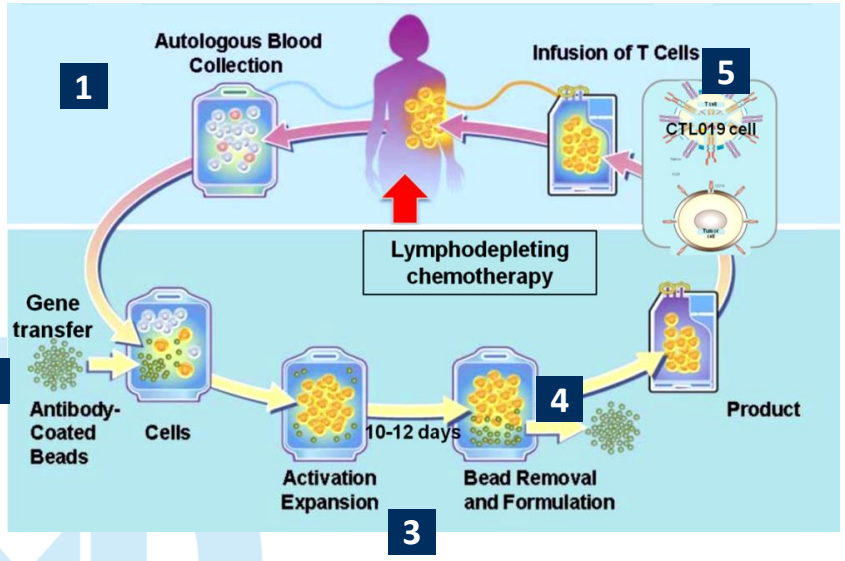
CAR T-cell Manufacturing Process



Images courtesy of David Porter, MD; University of Pennsylvania.

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Efficacy of CAR T-cell Therapy in Refractory DLBCL

- ZUMA-1 trial results
- JULIET trial results
- TRANSCEND trial results

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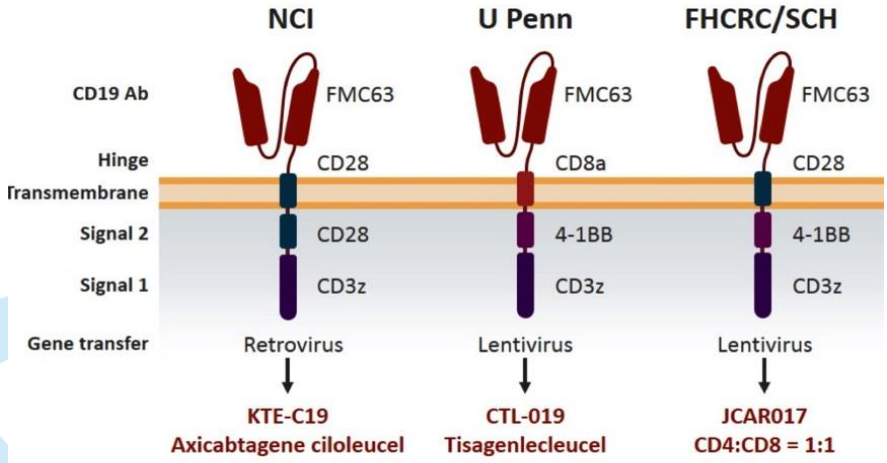
Anti-CD19 CAR T-cell Constructs in Use in Clinical Trials



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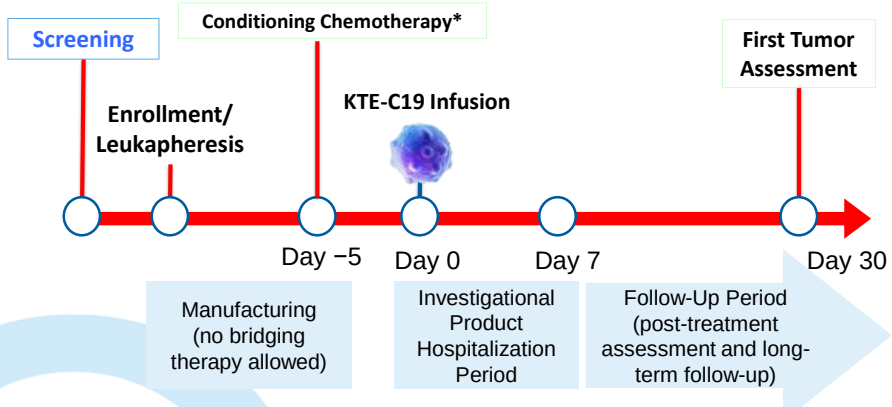
ZUMA-1 Treatment Schema



Manufactured in a closed, streamlined 6- to 8-day process with a total turnaround time ≈ 17.5 days with 100% manufacturing success rate.

*KTE-C19 treatment consists of conditioning chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine on Day −5, Day − 4, Day −3 followed by a target of 2×10^6 CAR T cells/kg (minimum 1×10^6 CAR T cells/kg) on Day 0.

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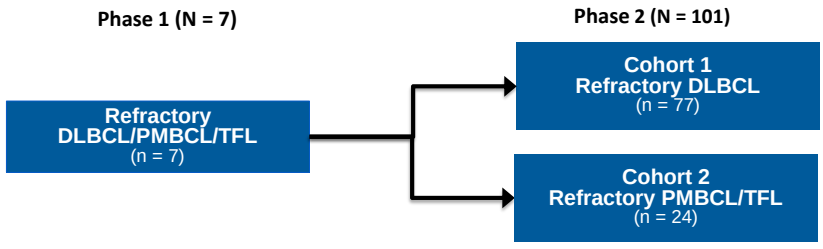
ZUMA-1: Updated Analysis



Key eligibility criteria

- No response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

- **N = 108**
- **Data cutoff: August 11, 2017**
- **Median follow-up: 15.4 months**

Conditioning regimen

- Cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 for 3 days

Axi-cel: 2 × 10^6 CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed

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ASCT, autologous stem cell transplant.

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ZUMA-1: Baseline Characteristics

Characteristic	Phase 1 and 2 N = 108
Median (range) age, years	58 (23 – 76)
≥65 y, n (%)	27 (25)
Male, n (%)	73 (68)
ECOG 1, n (%)	62 (57)
Disease stage III/IV, n (%)	90 (83)
IPI score 3-4, n (%)	48 (44)
≥3 prior therapies, n (%)	76 (70)
Refractory Subgroup Before Enrollment	**Phase 1 and 2 N = 108**
Refractory to second- or later-line therapy, n (%)	80 (74)
Best response as PD to last prior therapy	70 (65)
Relapse post-ASCT, n (%)	25 (23)

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Neelapu SS, et al. Blood. 2017;130(suppl 1):578.

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ZUMA-1: Objective Response

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, months	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49–424) days

Response was evaluated by investigator assessment.
CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

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Neelapu SS, et al. Blood. 2017;130(suppl 1):578.

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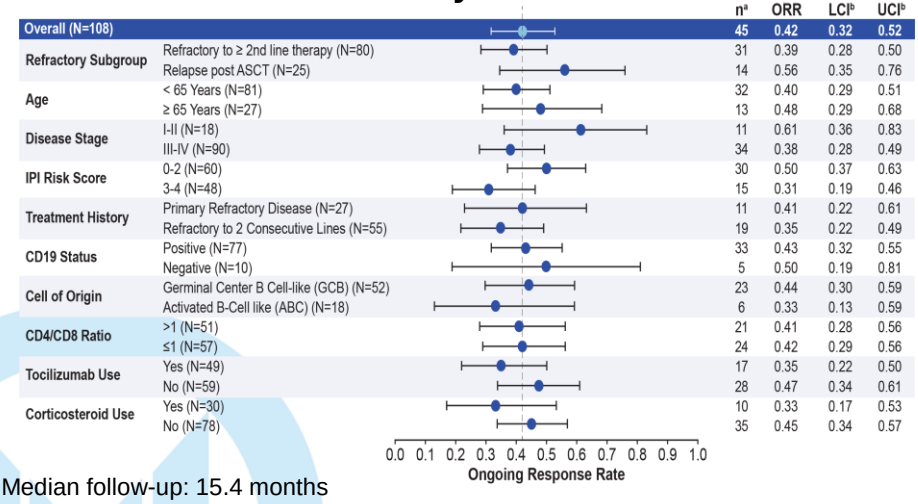
ZUMA-1: Consistent Ongoing Responses (>1 Year) Across Key Covariates



Median follow-up: 15.4 months

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Neelapu SS, et al. Blood. 2017;130(suppl 1):578.

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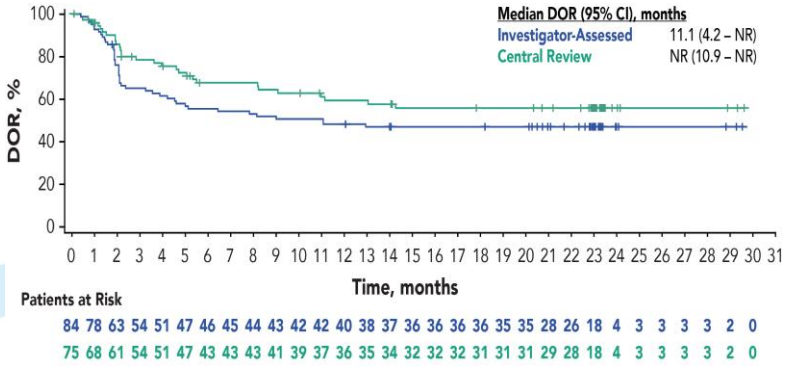
ZUMA-1: 2-year follow up- Duration of Response



- Median duration of CR has not been reached
- There were 10 relapses at 6 months post-infusion

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Locke et al Lancet Oncology 2018.

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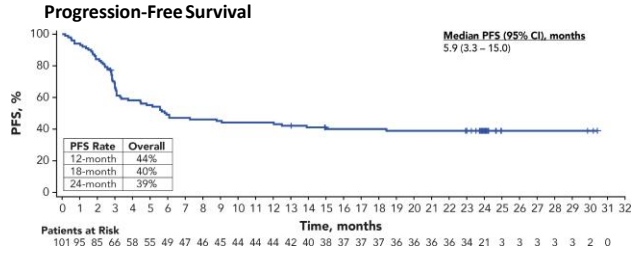
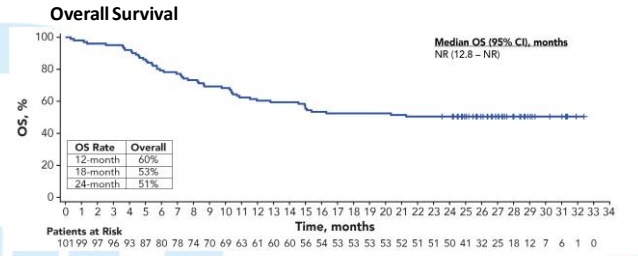
ZUMA-1: Outcomes at Median Follow-Up of 27 months





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Locke et al. Lancet Oncology 2018.

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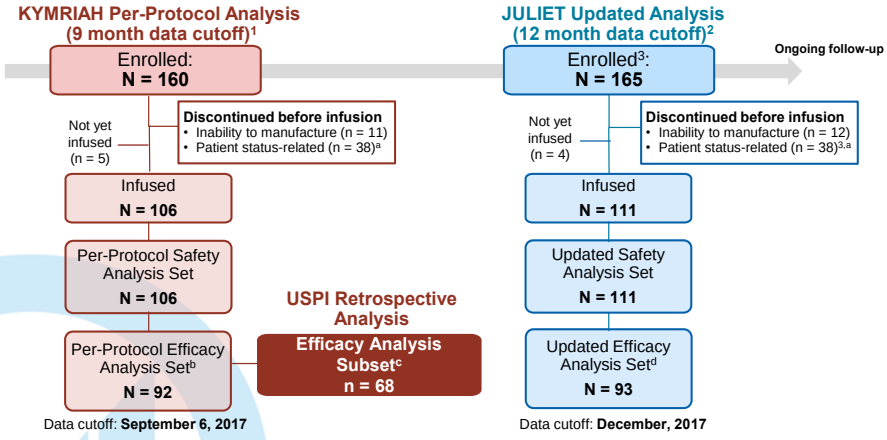
JULIET Trial (CTL019) for Refractory DLBCL



Borchmann P, et al. Presented at: 2018 EHA Congress; June 14-17, 2018; Stockholm, Sweden. Abstract S799.

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JULIET Trial: Demographics and Baseline Disease Status

	Patients (N = 111)
Age, median (range), years	56 (22-76)
e 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[a], %	17
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 e 2 at study entry, %	72
Refractory/relapsed to last therapy, %	55/45
Prior auto-SCT, %	49
Bridging chemotherapy, n	**102**
Lymphodepleting chemotherapy, n	**103**

auto-SCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group.
[a] *CMYC* + *BCL2*, n = 10; *CMYC* + *BCL2* + *BCL6*, n = 5; *CMYC* + *BCL6*, n = 4. [b] Determined by the Choi algorithm.
From Borchmann P, et al. In: Proceedings from the European Hematology Association; June 14-17, 2018; Stockholm, Sweden [abstract S799]. Reprinted with author's permission.

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JULIET: Efficacy ORR and CR

- At data cutoff (21 May 2018), 167 patients were enrolled
- 115 of 167 patients received tisagnenlecleucel infusion
- Main cohort, n=99; Cohort A, n = 16
- 90% received bridging therapy
- 93% received lymphodepleting chemotherapy

- All patients in the main cohort who received tisagenlecleucel infusion and had ≥ 3 months of follow-up
- 99 patients evaluated,
  - ORR: 54% ORR
  - CR: 40%
- Response was consistent across subgroups

Schuster et al. ASH2-18.

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JULIET Efficacy Results:

		N	ORR, n/N (%)	[95% CI]
All patients	All patients	99	53/99 (53.5)	[43.2-63.6]
Age	<65 years	75	38/75 (50.7)	[38.9-62.4]
	≥65 years	24	15/24 (62.5)	[40.6-81.2]
Sex	Female	36	22/36 (61.1)	[43.5-76.9]
	Male	63	31/63 (49.2)	[36.4-62.1]
Prior response status	Refractory to last line	50	21/50 (42.0)	[28.2-56.8]
	Relapsed to last line	49	32/49 (65.3)	[50.4-78.3]
IPI at enrollment	<2 risk factors	27	16/27 (59.3)	[38.8-77.6]
	≥2 risk factors	72	37/72 (51.4)	[39.3-63.3]
Prior anti-neoplastic therapy	≤2 lines	52	27/52 (51.9)	[37.6-66.0]
	3 lines	29	18/29 (62.1)	[42.3-79.3]
	≥4 lines	18	8/18 (44.4)	[21.5-69.2]
Molecular subtype	Activated B-cell	45	25/45 (55.6)	[40.0-70.4]
	Germinal center	51	25/51 (49.0)	[34.8-63.4]
Prior ASCT therapy	No	55	27/55 (49.1)	[35.4-62.9]
	Yes	44	26/44 (59.1)	[43.2-73.7]
Rearrangements in *MYC/BCL2/BCL6* genes	Double/triple hits	17	7/17 (41.2)	[18.4-67.1]
	Other	82	46/82 (56.1)	[44.7-67.0]
Tumor volume	<100 mL	50	28/50 (56.0)	[41.3-70.0]
	≥100 mL	31	11/31 (35.5)	[19.2-54.6]
	Unknown	18	14/18 (77.8)	[52.4-93.6]

Schuster et al. ASH2018.

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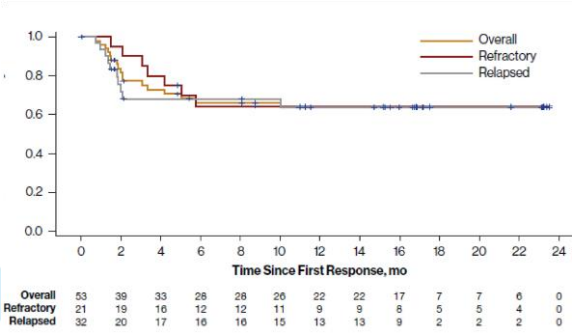
JULIET Efficacy Results:



- The median DOR in the main cohort has not been reached
- No relapses were observed beyond 11 months after infusion
- **54% (13/24) of partially responding patients converted to CR**, including 2 patients 9-12 mo after initial response

Schuster et al. ASH2018.

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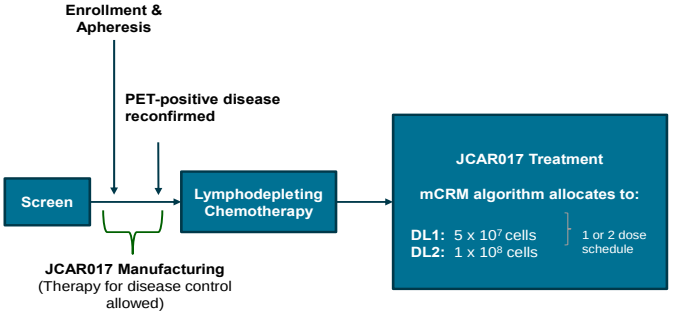
TRANSCEND NHL001: Schema



ELIGIBILITY

- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed indolent)
  - PMBCL
  - FL3B
  - High grade B-cell lymphoma (double/triple hit)
- MCL after 1 line of therapy

Prior allo SCT allowed
Secondary CNS involvement allowed
ECOG 0-2

Abramson JS, et al. J Clin Oncol. 2018;36 (suppl): abstr 7505.

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TRANSCEND: Patients Characteristics

Characteristic	FULL (n = 102)	CORE (n = 73)
Median age (range), years	61 (20-82)	60 (20-82)
≥ 65 years, n (%)	37 (36)	24 (33)
B-NHL Subtype, n (%)		
DLBCL, NOS de novo	63 (62)	53 (73)
Transformed from FL (tFL)	23 (23)	20 (27)
Transformed from MZL (tMZL) /CLL (tCLL)	6 (6)/6 (6)	0
Follicular, grade 3B/PMBCL	1 (1)/3 (3)	0
Molecular Subtype, n (%)		
Double/triple hit[a]	19 (19)	16 (22)
Patient Characteristics, n (%)		
ECOG PS 0-1	93 (91)	73 (100)
IPI 3-5	43 (42)	26 (36)
CNS involvement	2 (2)	1 (1)
Chemorefractory[b]	71 (70)	49 (67)
Prior lines of therapy, median (range)	3 (1-8)	3 (2-8)
Never achieved CR	49 (48)	36 (49)
Any HSCT	41 (40)	28 (38)
Prior autologous	38 (37)	28 (38)
Prior allogeneic	5 (5)	0

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Abramson JS, et al. J Clin Oncol. 2018;36 (suppl): abstr 7505.

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TRANSCEND: ORR in the FULL and CORE Subgroups

High Response Rates in R/R DLBCL

Potential Dose Response Relationship in CORE Patient Population; DL2 Chosen for Pivotal Cohort

	FULL	CORE		
	All Dose Levels (n=102)	All Dose Levels[a] (n=73)	DL1S (n=33)	DL2S (n=37)
ORR (95% CI), %	75 (65-83)	80 (68-88)	79 (61-91)	78 (62-90)
CR (95% CI), %	55 (45-65)	59 (47-70)	55 (36-72)	62 (45-78)

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Abramson JS, et al. J Clin Oncol. 2018;36 (suppl): abstr 7505.

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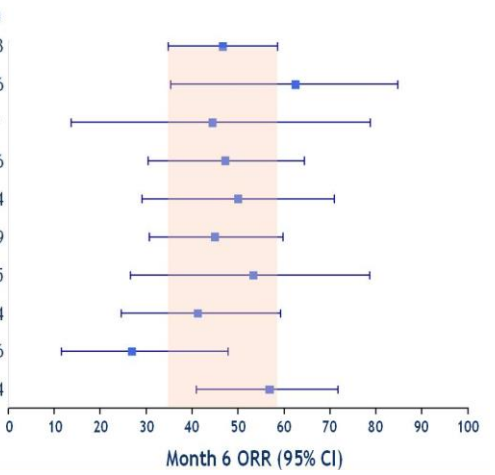
TRANSCEND: Durable Responses in Poor-Risk DLBCL Subsets

Population	ORR (95% CI)	n
CORE patient population[a]	46.6 (34.8-58.6)	73
Double/triple hit	62.5 (35.4-84.8)	16
Double expressor	44.4 (13.7-78.8)	9
Never in CR	47.2 (30.4-64.5)	36
Chemosensitive	50 (29.1-70.9)	24
Chemorefractory	44.9 (30.7-59.8)	49
Relapse < 12 mo from ASCT	53.3 (26.6-78.7)	15
SD/PD to last chemotherapy	41.2 (24.6-59.3)	34
IPI 3-5	26.9 (11.6-47.8)	26
IPI 0-2	56.8 (41-71.7)	44



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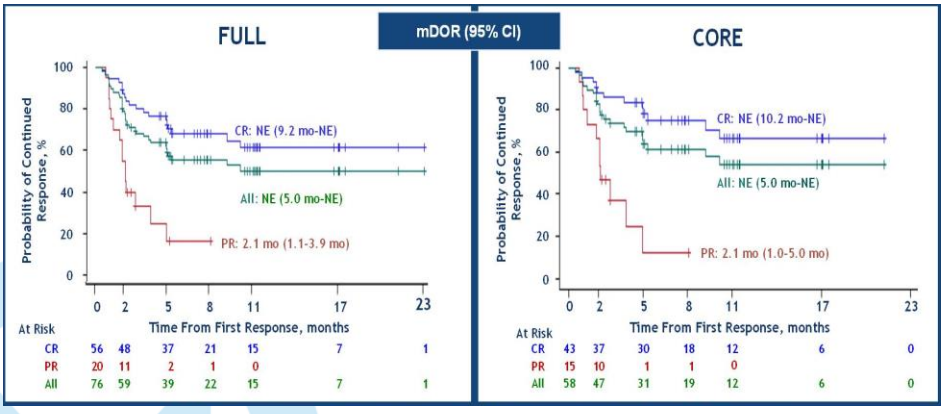
Abramson JS, et al. J Clin Oncol. 2018;36 (suppl): abstr 7505.

41

TRANSCEND: Duration of Response (Median Follow-Up: 8 Months)



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Abramson JS, et al. J Clin Oncol. 2018;36 (suppl): abstr 7505.

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Multicenter Studies With Autologous Anti-CD19 CAR T-cell Therapy for Aggressive B-cell Lymphomas

Study	ZUMA-1 (Locke, 2017)	JULIET (Schuster, 2018)	TRANSCEND (Abramson, 2018)
No of patients enrolled (treated)	111 (101)	165 (111) FDA 68 pts	134 (114- CORE 73)
Median age	58 (23-76)	56 (24-75)	61 (29 – 82)
Median follow-up	15.4 months	14 months	8 months
Costim domain	CD28	4-1BB	4-1BB
Bridging chemoTx	Not allowed	Allowed	Allowed
Conditioning regimen	Flu 30 mg/m^2 x 3d Cy 500 mg/m^2 x 3d	Flu 25 mg/m^{2}x 3d Cy 250 mg/m^2 x 3d or B 90 mg/m^2 x 2d	Flu 30 mg/m^2 x 3d Cy 300 mg/m^2 x 3d
%ORR (%CR)	82 (54)	50 (32)	80 (59)
3-month ORR (CR)	44 (39)	45 (37)	59 (45)
6-month ORR (CR)	41 (36)	50 (32)	47 (41)

Locke, 2017.
Schuster, 2018.
Abramson , 2018.

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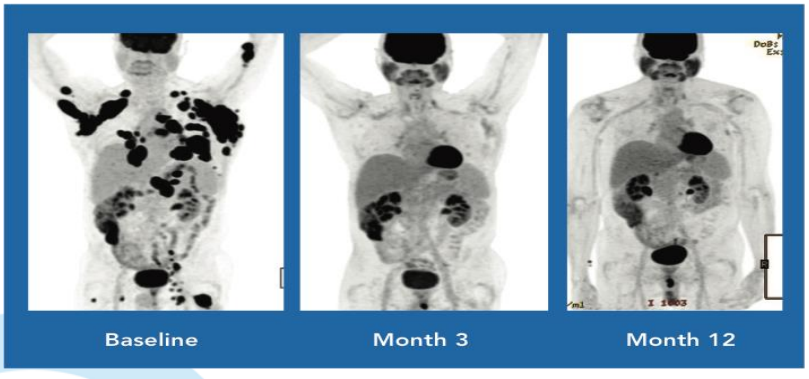
Clinical Efficacy: Case Study



- 62-year-old [redacted] with refractory DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-lenalidomide

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5. CAR T-cell therapy in pediatric B-ALL

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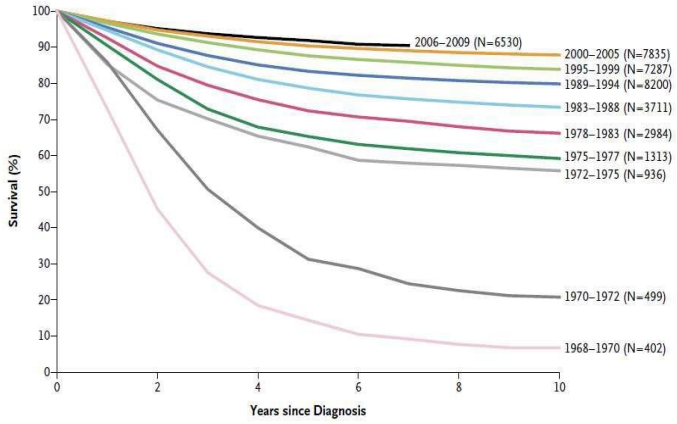
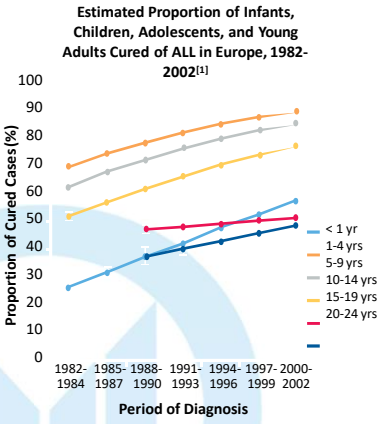
Survival of Children With ALL Treated on Sequential CCG/COG Clinical Trials, 1968-2009

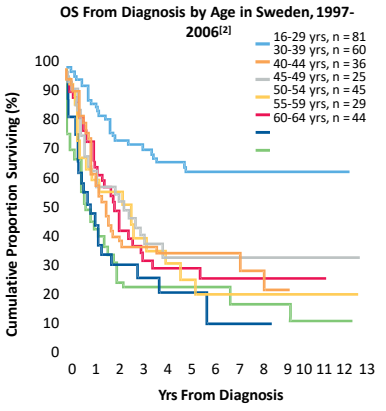


Hunger. NEJM. 2015;373:1541.

46

ALL Cure Rates Decrease With Age





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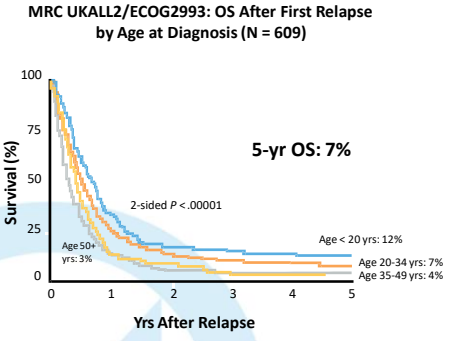
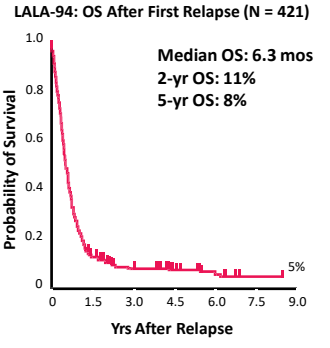
1. Gatta G, et al. Haematologica. 2013;98:744-752.
2.Juliusson G, et al. Cancer. 2011;117:4238-4246.

47

Poor Prognosis of Relapsed ALL





Patients received either autoSCT, alloSCT, or chemotherapy before and after relapse

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Slide credit: clinicaloptions.com

Fielding A, et al. Blood 2007;109:944-950. Tavernier E, et al. Leukemia 2007;21:1907-1914.

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Clinical Efficacy of CD19 CAR T-Cells in Relapsed/Refractory ALL

	T-Cell Product	Median Age, Yrs (Range)	N	T-Cell Dose	CR, n (%)	MRD- CR, n (%)
Adults	19-28z (JCAR015-MSK)	45 (22-74)	50 (45 evaluable)	1-3 x 10^6 CAR T-cells/kg	37 (82)	30 (67)
	19-4-1BBz (CTL019-Upenn)	N/A	12	4 x 10^7 - 1 x 10^9 CAR T-cells	89	--
	19-4-1BBz (JCAR017-FHRC)	N/A	30 (29 evaluable)	2 x 10^5 - 10^7 CAR T-cells/kg	27 (93)	25 (86)
Peds	19-4-1BBz (CTL019-CHOP)	10 (5-22)	53	~ 3 x 10^6 CAR T-cells/kg	50 (94)	45 (85)
	19-28z (KTE-C19-NCI)	14 (5-27)	20	1-3 x 10^6 CAR T-cells/kg	14 (70)	12 (60)

Park J, et al. Blood. 2016;127:3312-3320.

49

ELIANA trial: CTL019 for R/R B-ALL: Study Design

- Multicenter, open-label, single-arm phase II study

Pts aged 3-21 yrs* with B-cell ALL; ≥ 5% BM lymphoblasts; no isolated extramedullary disease relapse, prior CD19-directed therapy, or prior gene therapy (N = 81)

→ Fludarabine 30 mg/m² IV QD for 4 doses Cyclophosphamide 500 mg/m² IV QD for 2 doses

→ **Single-Dose CTL019 2.0-5.0 x 10^6/kg IV if ≤ 50 kg 1.0-2.5 x 10^8 IV if > 50 kg (n = 62†)**

*From 3 yrs at screening to 21 yrs at initial diagnosis.

†14 pts discontinued before infusion: deaths (n = 6), manufacturing failures (n = 5), AEs (n = 3).

- Primary endpoint: ORR (CR + CRi) within 3 mos, assessed by IRC
  - 4-wk maintenance of remission required
- Secondary endpoints: MRD status, DoR, OS, cellular kinetics, safety

Grupp SA, et al. ASH 2016. Abstract 221.

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ELIANA: Efficacy

Outcome	CTL019 (n = 50*)
ORR (CR + CRi) within 3 mos (with MRD < 0.01% in BM), % (95% CI)	82 (69-91)†
Best overall response, % •CR •CRi	 68 14
OS •6 mos, % (95% CI) •Median, mos (95% CI)	 89 (76-95)‡ NE (8.6-NE)‡
Duration of remission •6 mos, % (95% CI) •Median, mos (95% CI)	 62 (36-78) NE (4.8-NE)

*Interim analysis set: first 50 pts infused with CTL019 with 3-mo follow-up. †P < .0001. ‡Full analysis set: all pts infused with CTL019.

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Grupp SA, et al. ASH 2016. Abstract 221.

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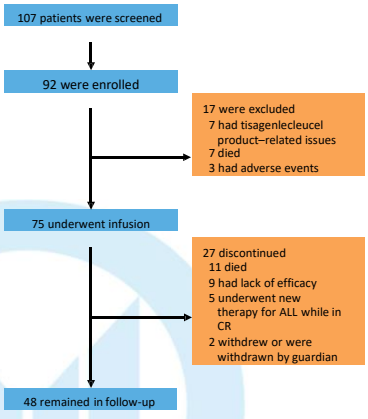
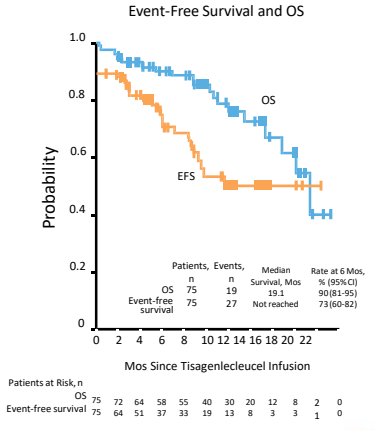
ELIANA: Tisagenlecleucel (CTL019) in Children and Young Adults With R/R B-ALL: EFS/OS





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Maude. NEJM. 2018;378:439.

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CAR T Toxicity

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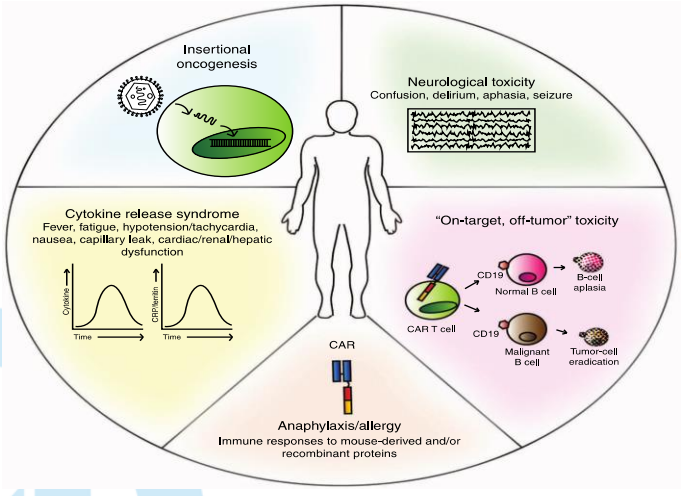
Spectrum of CAR T-Related Toxicities



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Bonifant CL, et al. Mol Ther Oncolytics. 2016;3:16011.

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Two Important Categories of Toxicities Related to CAR T-cell Therapy

- Cytokine Release Syndrome
- Neurotoxicity

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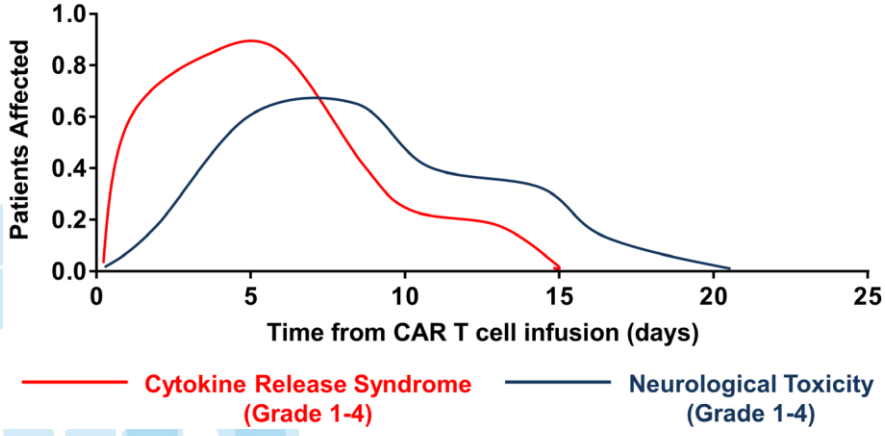
Estimated Timeline of Toxicities After CD19 CAR T-cell Therapy



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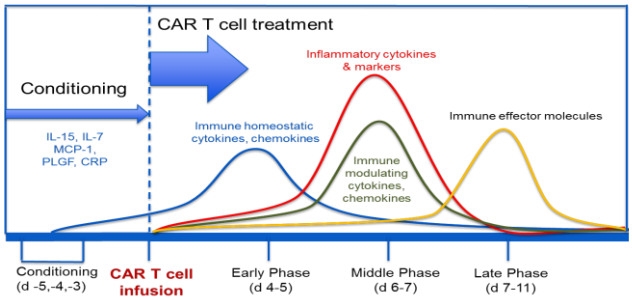
Cytokines Pattern After CAR T-cells infusion



Immune homeostatic cytokines	Inflammatory cytokines and markers	Immune modulating cytokines	Chemokines	Other markers
IL-15	IL-6	IL-13	IL-8	PLGF
IL-7	IL-1α	IL-4	MCP-1	sICAM-1
IL-2	IL-1β	IL-5	MCP-4	sVCAM-1
	IL-17α	IL-10	MIP-1α	VEGF
Immune effectors	TNFα	IFNγ	MIP-1β	VEGF-C
Granzyme A	TNFβ	IL-12p40	IP-10	VEGF-D
Granzyme B	GM-CSF	IL-12p70	TARC	FGF-2
sFASL	CRP	IL-16	Eotaxin	
Perforin	SAA		Eotaxin-3	
			MDC	

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Perez A et al., ASH, 2015.

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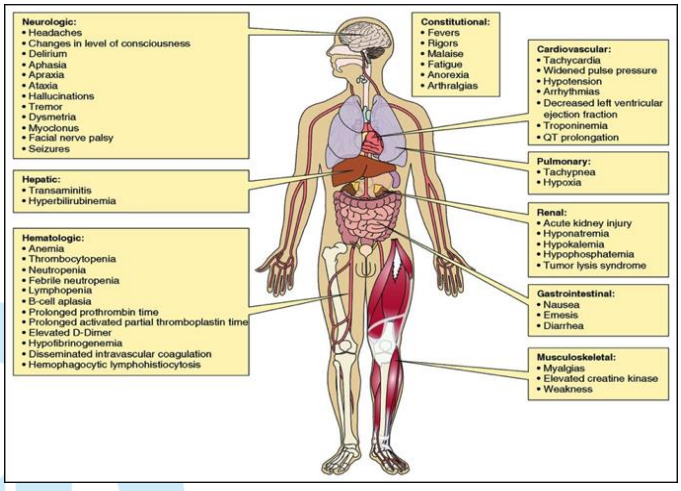
Cytokine Release Syndrome (CRS)



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Brudno and Kochenderfer. Blood, 2017.

58

Neurotoxicity

- Neurotoxicity typically manifests as a toxic encephalopathy
  - Aphasia, confusion, disorientation, agitation, dysphasia, somnolence, tremors, and impaired handwriting
  - In more severe cases, seizures, motor weakness, incontinence, increased intracranial pressure, papilledema, and cerebral edema may also occur
- May last few hours to several days
- Generally reversible although fatal cases have occurred
- Onset may be biphasic
  - 1st phase (days 0-5) – symptoms may appear with other CRS symptoms
  - 2nd phase (after day 5) – starts after CRS symptoms have subsided

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Pathophysiology of Neurotoxicity

- Etiology and Pathophysiology still unclear: possible increased vascular permeability
- No clear evidence of expression of target (CD19) in CNS
- Possible CNS occult disease
- MRI of brain is usually negative
- EEG may show diffuse slowing or electrographic seizures
- CSF is usually positive for CAR T-cells
- Two potential explanations include:
  - Passive diffusion of cytokines
  - Trafficking of T cells into central nervous system (CNS)
  - Increased vascular permeability

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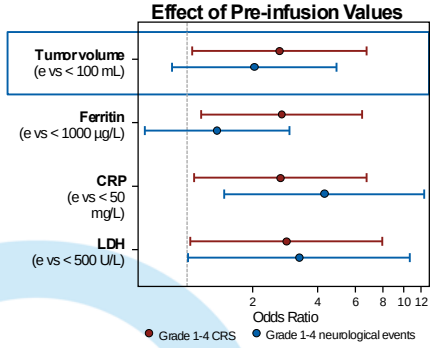
JULIET: Predictors of Toxicity (CRS and Neurotoxicity)



CAR-positive viable T cell dose

- No significant relationship between dose and CRS when accounting for baseline tumor burden
- No relationship observed between dose and neurological events
- No relationship between dose and efficacy

CRP, C-reactive protein; CRS, cytokine release syndrome; LDH, lactate dehydrogenase.
From Borchmann P, et al. In: Proceedings from the European Hematology Association; June 14-17, 2018; Stockholm, Sweden [abstract S799]. Reprinted with author's permission.

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Reported Toxicity Across CAR T-cell Therapy Multicenter Studies

Study	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND* (Abramson, 2017)
No patients enrolled (treated)	111 (101)	141 (85)	NR (91)
Cytokine release syndrome			
Time to onset, median, range	2 days (1–12)	3 days (1–9)	5 days (1–14)
Duration, median, range	8 days (NR)	7 days (3–34)	5 days (NR)
Grade (All)	93%	58%	36%
Grade 3 o 4	13%	23%	1%
Use of tocilizumab	43%	15%	12%
Use of vasopressors	17%	6%	24%
Use of steroids	27%	11%	16%
Admission to ICU	NR	24%	NR
Infections			
All Grades	35%[1]	27%	NR
Grade 3 or 4	31%[1]	13%	NR
Neurotoxicity			
Time to onset, range	5 days (1–17)	NR	10 days (3–23)
Duration, median, range	17 days (NR)	NR	11 days (NR)
All Grades	64%	21%	21%
Grade 3 or 4	28%	12%	15%

Neelapu, 2017.
Schuster, 2017.
Abramson, 2017.

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Principles of CRS Management

- Work-up to exclude infection or other cause
- Fluid resuscitation and vasopressors
- Antipyretics
- Broad spectrum antibiotics
- Supplemental oxygen
- Tocilizumab +/- corticosteroids

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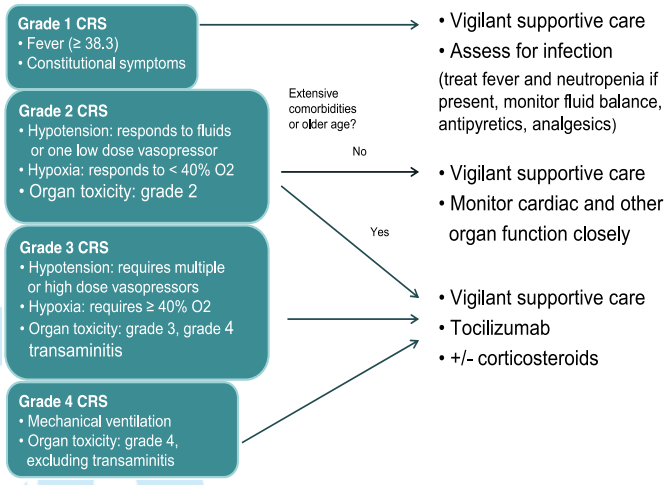
CRS Grading and Management Overview



Lee DW, et al. Blood. 2014;124(2):188-195.

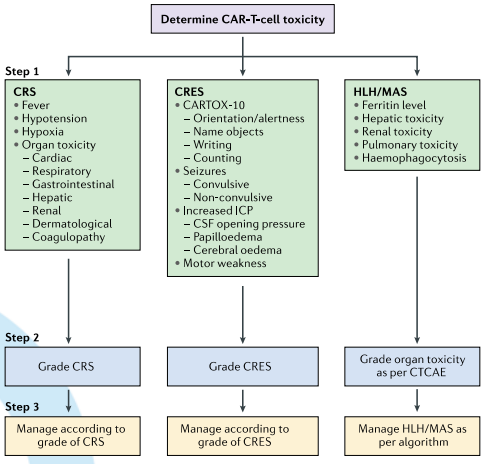
64

Steroids for Treatment of CAR-T Neurologic Toxicities

- For Grade 2 or higher Neurologic Toxicity: Dexamethasone 10mg q6H then taper
- For Grade 4 or higher Neurologic Toxicity: Consider methyprednisolone 1g/day IV until improvement to grade 1 then taper
- Consider antifungal prophylaxis with azoles or echinocandins in patients receiving high dose steroids.

65

Three-Step Approach for CRS and NT: The CARTOX Model



Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15(1):47-62.
et al. Blood 2014.

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CAR T-cell: Patient Selection

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ZUMA-1 Eligibility Criteria is Very Strict: The Label for FDA-Approved Yescarta® (axicabtagene ciloleucel) is Broader

Selected ZUMA-1 Eligibility Criteria

- Chemotherapy-refractory disease: PD or SD as best response to last chemotherapy or relapse ≤12 months of prior ASCT
- Platelet count >75,000 cells/microL
- ANC >1,000 cells/microL
- ECOG PS 0-1
- No history of any CNS disease
- No history of any hepatitis
- No DVT within 6 months

Yescarta® Indications and Usage

"…..indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy…"

- Limitation of Use: Yescarta® (axicabtagene ciloleucel) is not indicated for the treatment of patients with primary central nervous system lymphoma

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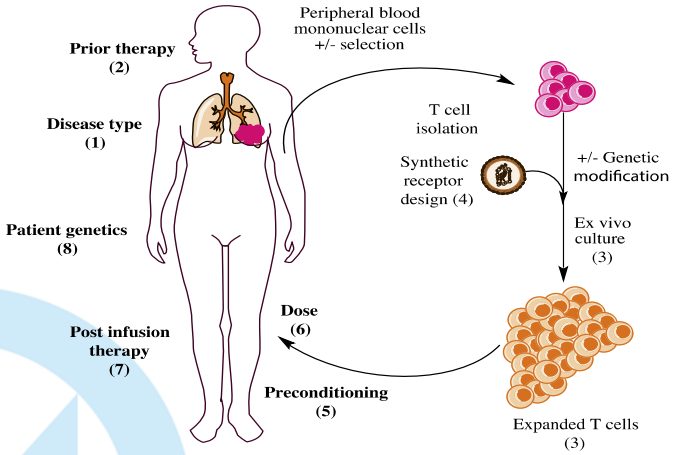
Factors Affecting CAR T Efficacy/Outcomes



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Patient Selection

- Clinical judgment should be used to select patients who will receive this therapy. Using clinical trials criteria may be too strict
- Consider comorbidities and frailty status when indicating CAR T-cell therapy, specially in cases with significant cardiac, pulmonary neurological, renal or liver disease.
- Disease status and degree of aggressiveness
- Social support: Caregiver (especially for the first 4-8 weeks post CART infusion)
- Lodging/Transportation

70

Two CAR T-cell Products FDA Approved for Refractory DLBCL

- *Axicabtagene ciloleucel: Yescarta®*
  - Approved for adults with DLBCL who have failed 2 lines of systemic therapy
- *Tisagenlecleucel: Kymriah®*
  - Approved for patients up to the age of 25 with B-cell precursor ALL
  - Approved for adults with DLBCL who have failed 2 lines of systemic therapy

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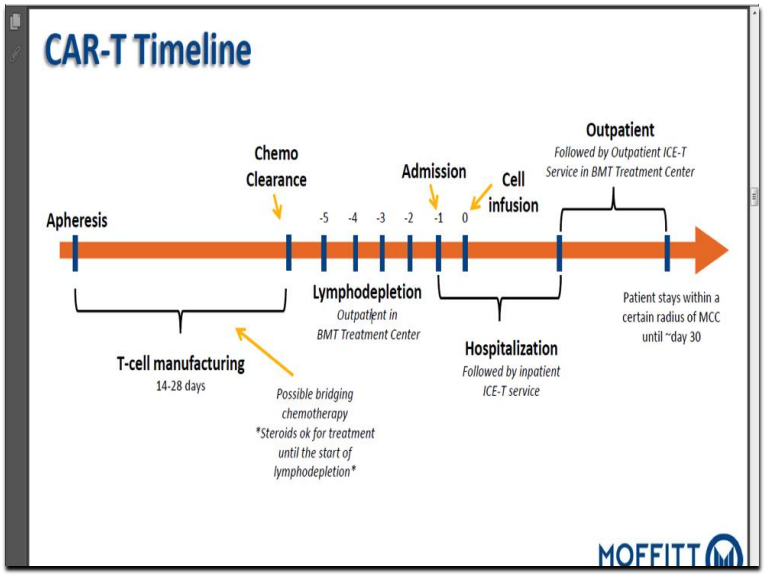

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CASE STUDY: PATIENT Y (AXICABTAGENE CILOLEUCEL)

- Patient is a 47-year old male diagnosed with DLBCL
- Relapsed post R-CHOP followed by ASCT, then Rituxan® + Revlimid®, XRT to large abdominal mass

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Conditioning Chemotherapy

- Palonosetron 0.25 mg IV on *Day -6*
- Fludarabine 30 mg/m^2 on *Days -5, -4, -3*
- Cyclophosphamide 500 mg/m^2 *Days -5, -4, -3*
  - Start allopurinol 300 mg/day on day of chemo to prevent tumor lysis syndrome

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Hospital Course: Patient Y

- Admission on *Day -1* to the Immune and Cellular Therapy (ICE-T) Service
- Start PPx Keppra®(levetiracetam)on day -1 for neurotoxicity
- Start ID PPx (Cipro® [ciprofloxacin], ACV, Fluconazole) on day 0
- CAR-T multidisciplinary treatment team includes MD, PharmD, APP, Social Worker, RN, Case Manager, ID and Neurology Consultants

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Patient Y:
Day 0 CAR-T Infusion

- Patient received NS prior to infusion of cells
- Premedication with Tylenol® (acetaminophen) and Benadryl® (diphenhydramine)
- Infusion of cells
- Postinfusion NS
- Monitored V/S q15 minutes throughout the infusions and for 1 hour post
- Then monitor V/S q3 hours post transfusion

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Patient Y: Day +2

- Develops grade 1 CRS
  - Fevers up to 104, tachycardia
  - Grade 1-2 treated with supportive care including Tylenol® (acetaminophen), NSAIDs, and fluids
  - Grade 3-4 treated with tocilizumab, an IL-6 inhibitor
    - May also require pressors and transfer to the ICU

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Neurological Toxicities

- Patients are at risk for neurotoxicities associated with CAR-T infusion/Cytokine Release Syndrome

Prophylaxis/Monitoring includes:

- Keppra® (levetiracetam) 750 mg BID started the night before the infusion for seizure prophylaxis
- Neuro checks q4 hours & PRN
- Consult to neurology with baseline MRI
- CARTOX score
  - A 10/10 scoring system composed of orientation, object recognition, and handwriting
  - Performed daily from day 0 through day 30
  - CRES score takes into account LOC, opening pressure on LP, MRI, and EEG findings

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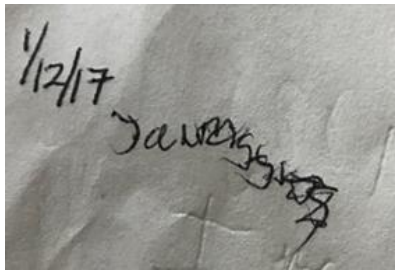
Patient Y: Day 10

- On routine neurologic evaluation, CARTOX score was 2/10
- Complained of headaches, blurred vision
- Handwriting was illegible, speech slurred



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Patient Y: Day 10

- **MRI**: **autoimmune encephalitis**
- EEG: Diffuse slowing consistent with metabolic encephalitis
- LP: Opening pressure 21. No infection

- Consulted neuro-oncology
  - Dexamethasone 10 mg IV q6 hours
  - IVIG x 2 days

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Patient Y
Day +16: Discharge

- WBC 0.85, ANC 500; Hgb 7.2; plt ct 49K
- Neurologic toxicities improved, but with persistent tremor. Steroids gradually tapered
- Still with significant weakness, requiring home PT and daily visits
- Growth factor use is controversial, used after Day 21 to keep ANC greater than 750

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Patient Y: Day +30

- Day 30 scans show CR
- Continues with tremor: treated with propranolol 12.5 mg BID
- Can stop Keppra® (levetiracetam) PPx at day +30
- Start Bactrim® (sulfamethoxazole and trimethoprim) /pentamidine for PCP PPx

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Patient Y: Day +52

- Presented with fevers, cough, and headaches
- Respiratory PCR + for rhinovirus
- IgG <300
- Started monthly IVIG for treatment of hypogammaglobulinemia associated with CAR-T therapy

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Hypogammaglobulinemia

- B cells have CD19 antigens, which CAR-T cells destroy
- Patients with decreased immune function are more susceptible to illness
- Consider supplementing with IVIG to keep IgG levels >400

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Patient Y: Day +90

- Day +90 scans show complete remission
- His tremor has resolved, d/c propranolol
- Energy level is improving, back to working part time
- Return for repeat scans q3 months
- Acyclovir for 1 year post treatment, PCP PPx for 6 months

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Future Questions and Directions

- When is the ideal timing for CAR T?
  - ZUMA-7: CAR T Versus SOC salvage therapy followed by auto transplant
- Can any drugs enhance CAR-T cell function?
  - ZUMA-6: CAR T cells in conjunction with atezolizumab (PD-L1 inhibitor)
  - CTL019 + ibrutinib
- Should we use CAR T in more indolent forms of lymphoma?
  - ZUMA-5: Follicular lymphoma
- Can we build CARs for other cancers?
  - Myeloma (BCMA), AML (CD33), ovarian

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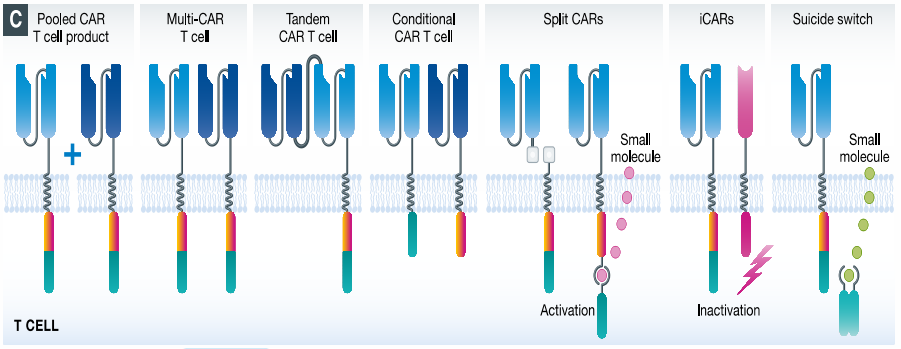
New CAR T Constructs



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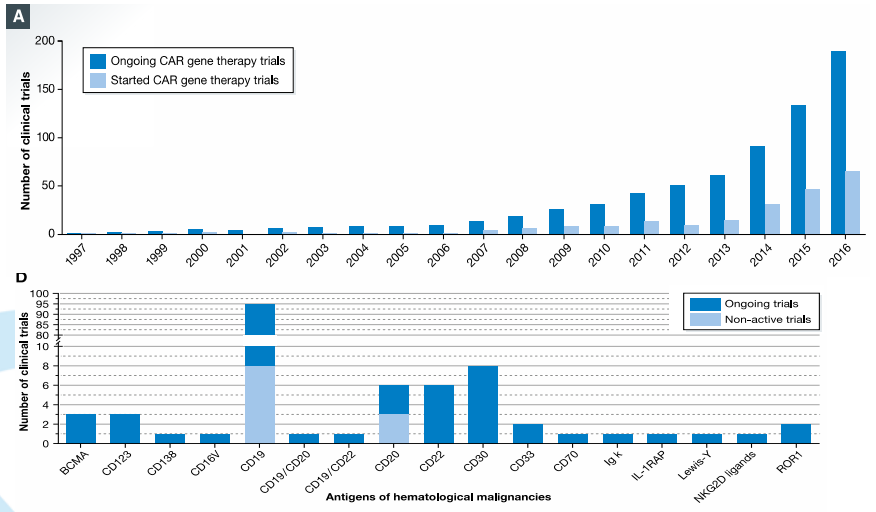
CAR T-cell Clinical Trials Over Time and Current Targets



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THANK YOU

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CAR T-CELL THERAPY FOR HEMATOLOGIC MALIGNANCIES: FOCUS ON DIFFUSE LARGE B-CELL LYMPHOMA

Resources for HCPs

Online & In-person free CME & CE courses: www.LLS.org/CE

Clinical Trials and Research

- Clinical Trials: Learn more about clinical trials: www.LLS.org/ClinicalTrials
- Research: Focused on finding cures, driving research in areas of unmet medical need, and bridging the gap between academic discovery & drug development: www.LLS.org/Research

Advocacy dedicated to removing barriers to care: www.LLS.org/Advocacy

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Resources for Patients

- CART specific resources: www.LLS.org/CART
- Free Information Booklets: www.LLS.org/Booklets
- Telephone/Web Education Programs: www.LLS.org/Programs and www.LLS.org/Educationvideos
- Support Resources: www.LLS.org/Support
  - Financial Assistance
    - Co-Pay
    - Travel Assistance
    - Referral to Medication Access programs
  - Information Resource Center
  - LLS Chapters
  - LLS Community (social media platform)
  - Patti Robinson Kaufman First Connection Program (peer-to-peer)
  - One-On-One Nutrition Consultations (PearlPoint)

Additional support resources: www.LLS.org/support

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Resources for Patients

Information Resource Specialists: www.LLS.org/IRC

Assist through treatment, financial & social challenges, and give accurate treatment and support information. HCPs can also order free materials to distribute to patients.

Clinical Trial Support Center: www.LLS.org/CTSC

Patients & caregivers work one-on-one with clinical trial specialists who are registered nurses with expertise in blood cancers. RNs will personally assist through the clinical trial process, providing an additional resource to your HCP team.

- Phone: (800) 955-4572, M-F, 9 am to 9 pm ET
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists

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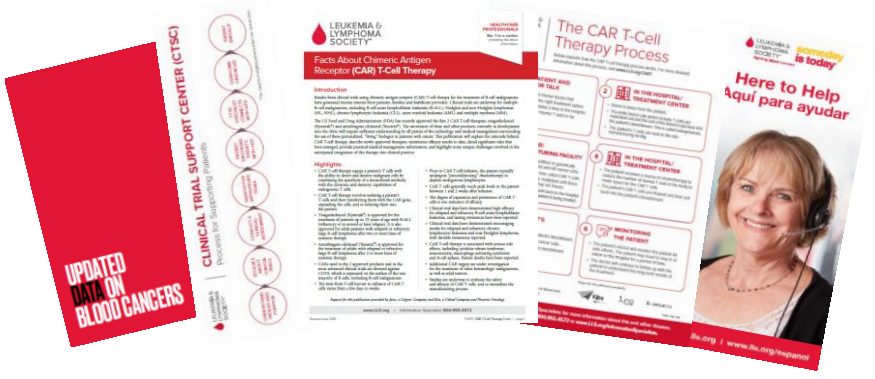
GUIDES, BOOKLETS, AND FACT SHEETS

Supporting Patients, Caregivers and Professionals



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