State of the art: CAR-T cell therapy in lymphoma

14th annual California Cancer Consortium conference

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8/11/18

Financial disclosures

- Consultant for Juno therapeutics
- Speaker for ibrutinib (Pharmacyclics/Jannsen)
- Speaker for brentuximab vedotin (Seattle Genetics)
- Off label products I will discuss: JCAR017 (Juno CAR-T cells); COH CAR-T cells; KTE-C19 (Kite pharma CAR-T cells in mantle cell lymphoma)

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B-cell non-Hodgkin lymphomas

- Small B-cell lymphoid neoplasms
  - CLL/SLL/B-PLL/MBL
  - Follicular lymphoma
  - Marginal zone lymphoma
  - Hairy cell lymphoma
  - Waldenstrom's macroglobulinemia/LPL
  - Mantle cell lymphoma
- Diffuse large B-cell lymphoma
  - and all it's subtypes like EBV+, PCNSL
- High grade B-cell lymphomas
  - NOS
  - Double/triple hit

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CD19 CAR T products in pivotal trials in B-NHL

	NCI	U Penn	FHCRC / SCH
CD19 Ab	FMC63	FMC63	FMC63
Hinge	CD28	CD8a	CD28
Transmembrane	CD28	4-1BB	4-1BB
Signal 2	CD3ζ	CD3ζ	CD3ζ
Signal 1			
Gene transfer	Retrovirus	Lentivirus	Lentivirus
	Kite Pharma	**Novartis**	**Juno Therapeutics**
	KTE-C19	**CTL-019**	**JCAR017 (CD4:CD8 = 1:1)**
	Axicabtagene ciloleucel	**Tisagenlecleucel**	**Lisocabtagene maraleucel**
	Axi-cel		**Liso-cel**

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

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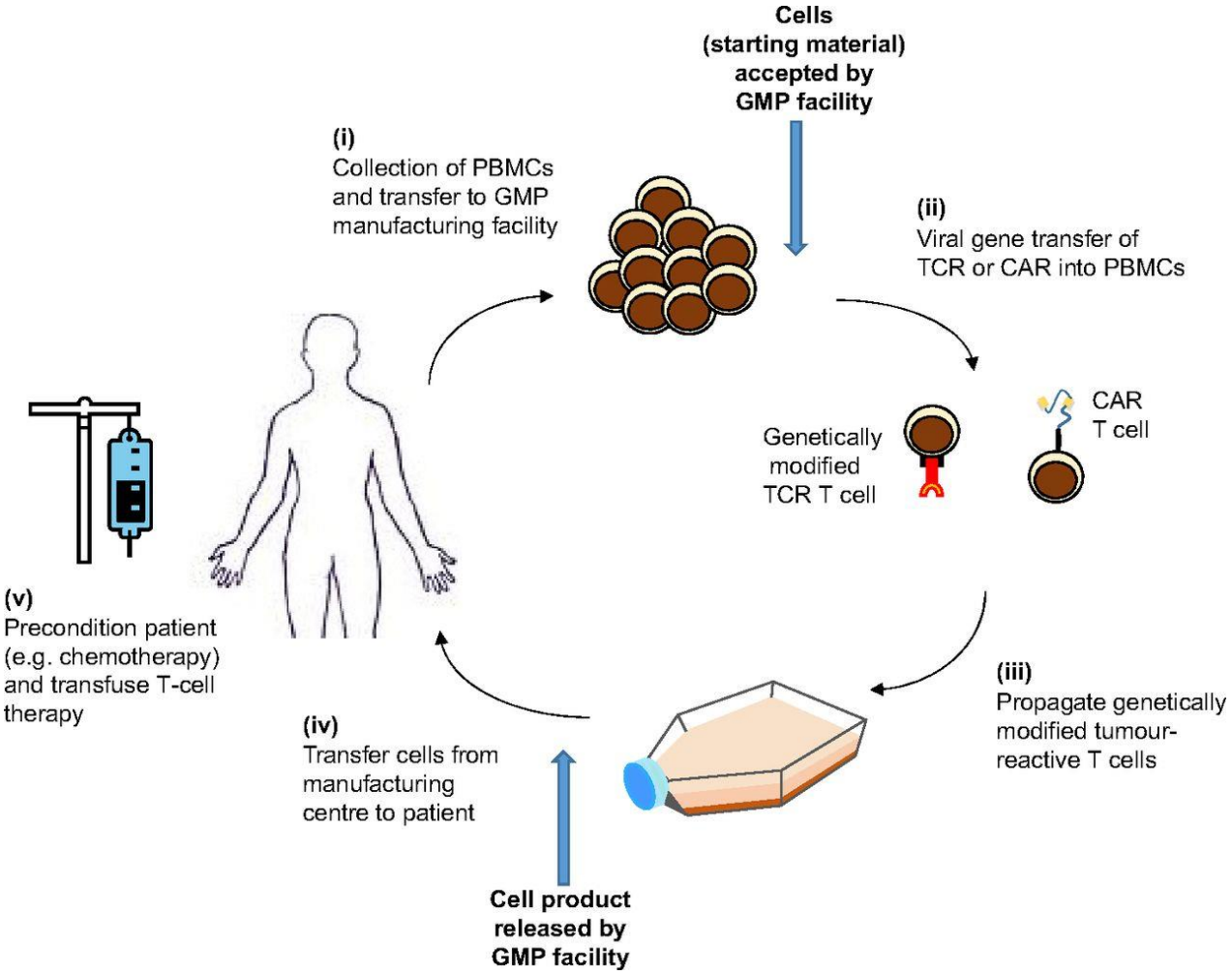
CAR-T cell manufacturing



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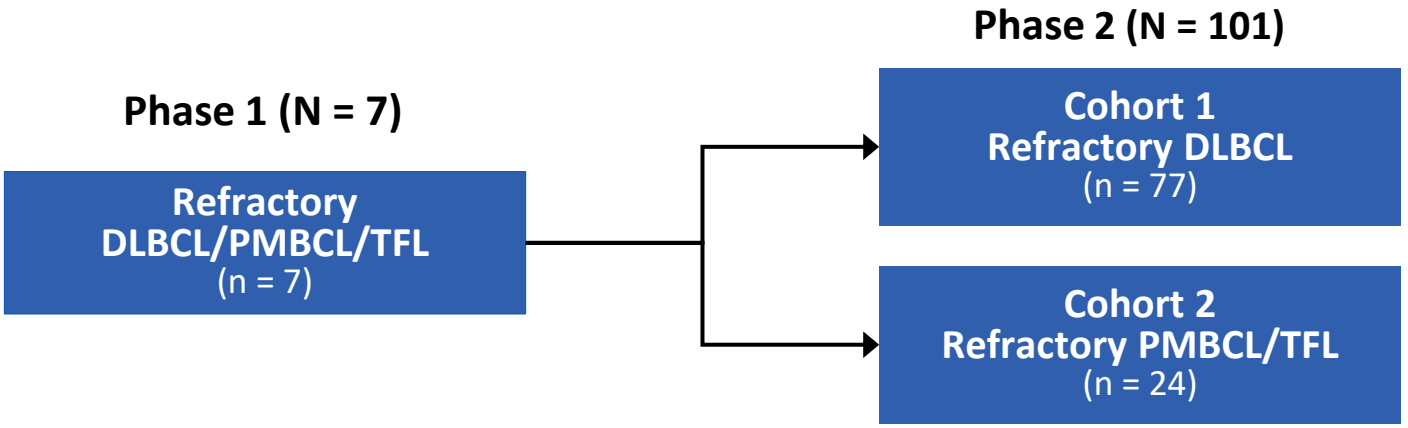
ZUMA1: 1st multicenter trial of CD19 CAR T cell therapy in refractory aggressive B-cell NHL



Key eligibility criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline
- No bridging therapy allowed

- **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
- 17-day average turnaround time from apheresis to delivery to clinical site

Neelapu S, Locke F, et al. N Eng J Med 2017

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ZUMA1: Efficacy

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	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
- Study met primary endpoint for ORR ($p < 0.0001$) at primary analysis

Neelapu S, Locke F, et al. N Eng J Med 2017

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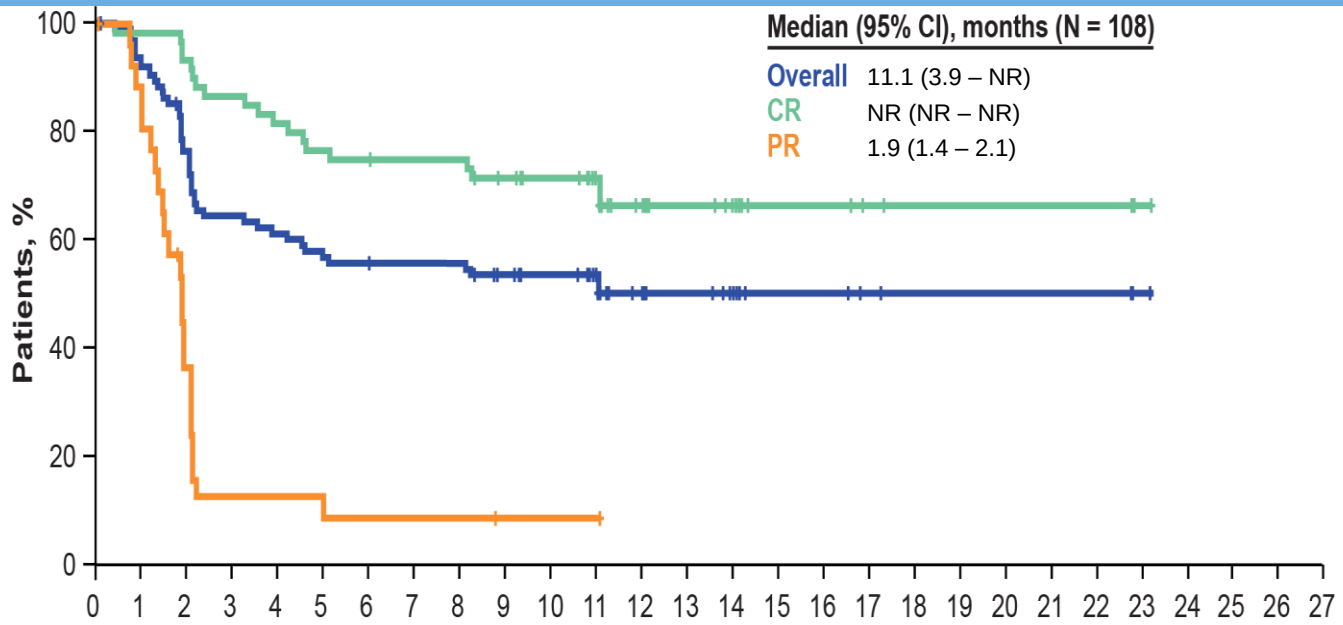
ZUMA-1: Duration of Response by Best Objective Response



Patients at Risk

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

- Median duration of CR has not been reached
- 3 of 7 (43%) Phase 1 patients have ongoing CR at 24 months

NR, not reached.

Neelapu S, Locke F, et al. N Eng J Med 2017

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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
- 43% use of tocilizumab and 27% use of corticosteroids

[a]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

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FDA approvals

- Axicabtagene ciloleucel/axi-cel (Kite Pharma) was FDA-approved in 10/2017 for patients with rel/ref DLBCL after 2 or more lines of therapy

- Tisagenlecleucel (Novartis) was also FDA-approved in 5/2018 for rel/ref DLBCL after 2 or more lines of therapy

JULIET trial: Ph2 study of tisagenlecleucel in DLBCL

- single-arm, open-label phase II trial, global study
- Autologous T cells that express a CD19-directed CAR (CTL019)
- Rel/ref DLBCL or FL pts
- N = 28, ages 22 to 76 years
- ORR 64% (18/28), CR in 6/14 with DLBCL (43%) and 10/14 with FL (71%)
- At a median follow-up of 28.6 months, 86% of DLBCL pts who had a response and 89% of FL pts who had a response maintained their response
- Severe CRS occurred in 5 patients (18%); serious encephalopathy occurred in 3 (11%)
- All patients in CR by 6 months remained in remission at 7.7-37.9 months (median 29.3 months)

Schuster SJ, et al. N Engl J Med 2017; 377:2545-54

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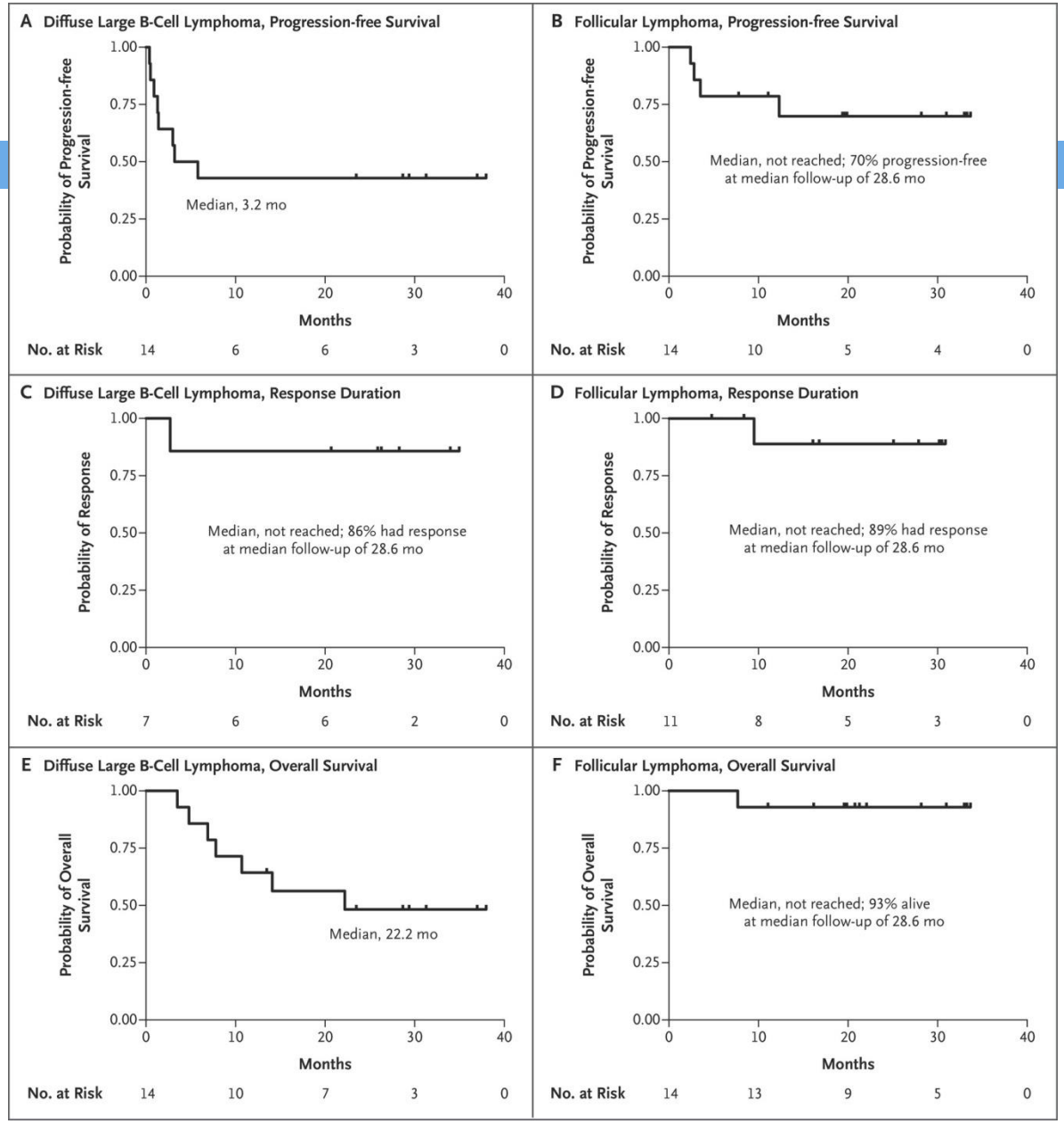

The therapy was done on an outpatient basis for many patients (26%) and the manufacturing process allowed investigators to generate CAR T cells from previously collected and frozen blood cells, permitting successful shipment around the world

Schuster SJ, et al. N Engl J Med 2017; 377:2545-54

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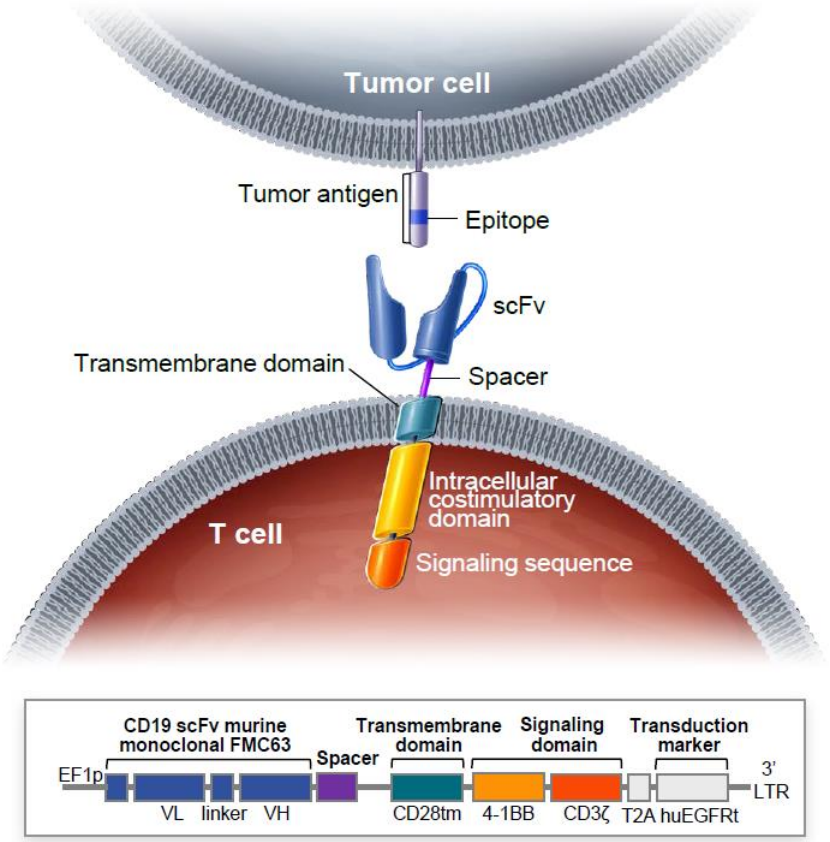
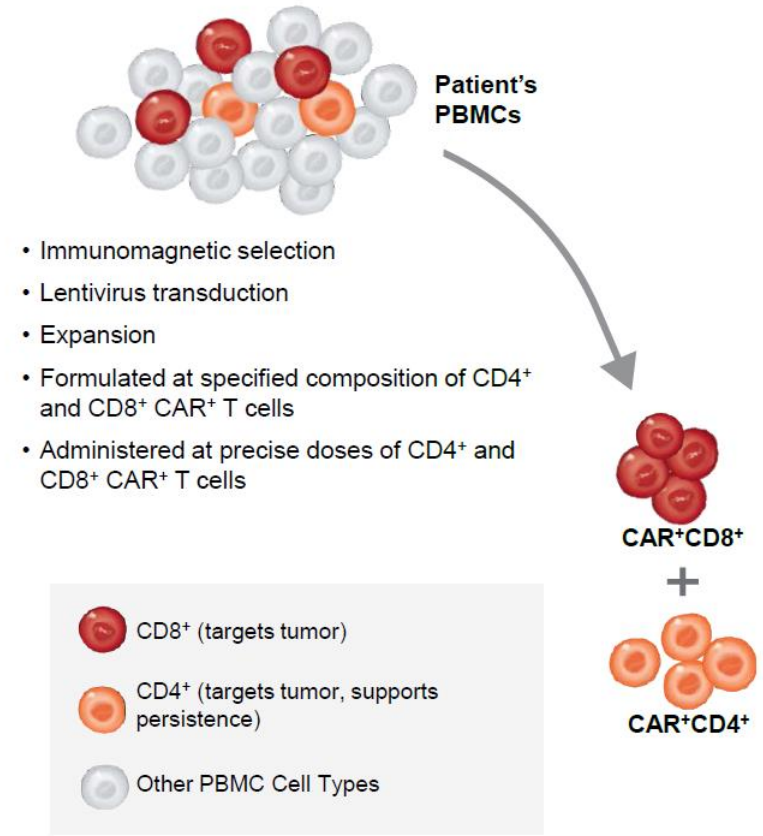
TRANSCEND-NHL001: multicenter Ph1 trial of CD19-CAR for rel/ref aggressive B-NHL

Lisocabtagene Maraleucel (Liso-cel; JCAR017)

CD19-Directed Defined Cell Product





Abramson J, et al. ASCO and EHA 2018

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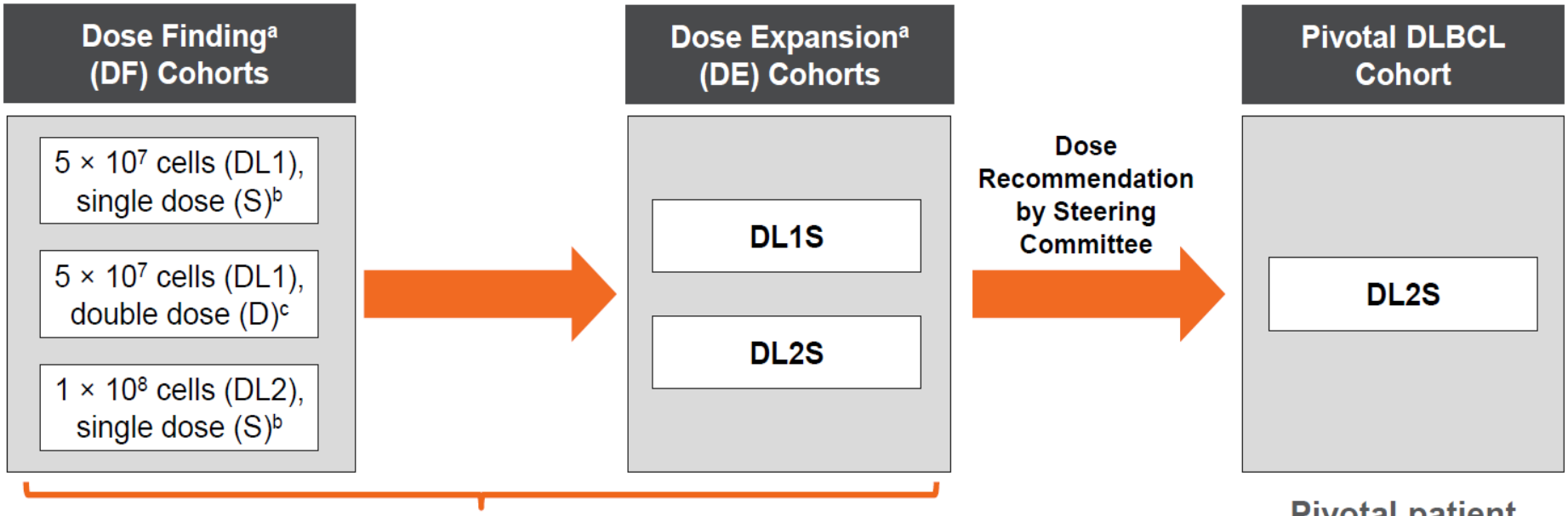
Multicenter, Seamless Design Pivotal Trial
(TRANSCEND NHL 001; NCT02631044)



Data will be presented from DF and DE DLBCL cohorts

- 102 patients treated (**FULL**)[d]
- 73 patients treated in analysis set matching pivotal patient population (**CORE**)[e]

[a] Disease-specific Dose Finding and Dose Expansion cohorts enrolled [DLBCL and MCL].
[b] Administered on Day 1.
[c] Administered on Day 1 and Day 14.
[d] DLBCL FULL cohort: DLBCL, NOS de novo and transformed from any indolent lymphoma, ECOG 0-2.
[e] DLBCL CORE cohort: DLBCL, NOS de novo and transformed from FL, ECOG 0-1, high grade B-cell lymphoma.

Abramson J, et al. ASCO and EHA 2018

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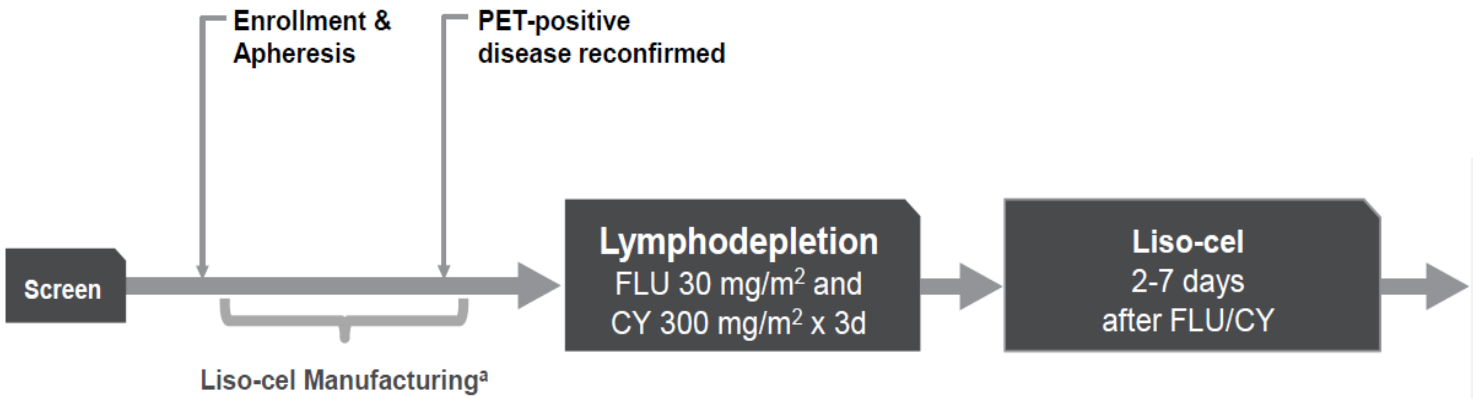
TRANSCEND NHL 001 (NCT02631044)



FOLLOW-UP

Initial: 12 months

On-study: 24 months

Long-term: up to 15 years after last liso-cel treatment

ENROLLMENT COHORTS

- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed FL)
  - High grade B-cell lymphoma (double/triple hit)
  - DLBCL transformed from CLL or MZL
  - PMBCL
  - FL3B

  } CORE

  } FULL
- MCL after 1 line of therapy

PATIENT ELIGIBILITY

- Prior SCT allowed[b]
- Secondary CNS involvement allowed
- ECOG 0-2[b]
- No minimum absolute lymphocyte count requirement for apheresis

FLU, fludarabine; CY, cyclophosphamide.
[a] Therapy for disease control allowed.
[b] ECOG 2 and prior allogeneic HSCT excluded from pivotal cohort.

Abramson J, et al. ASCO and EHA 2018

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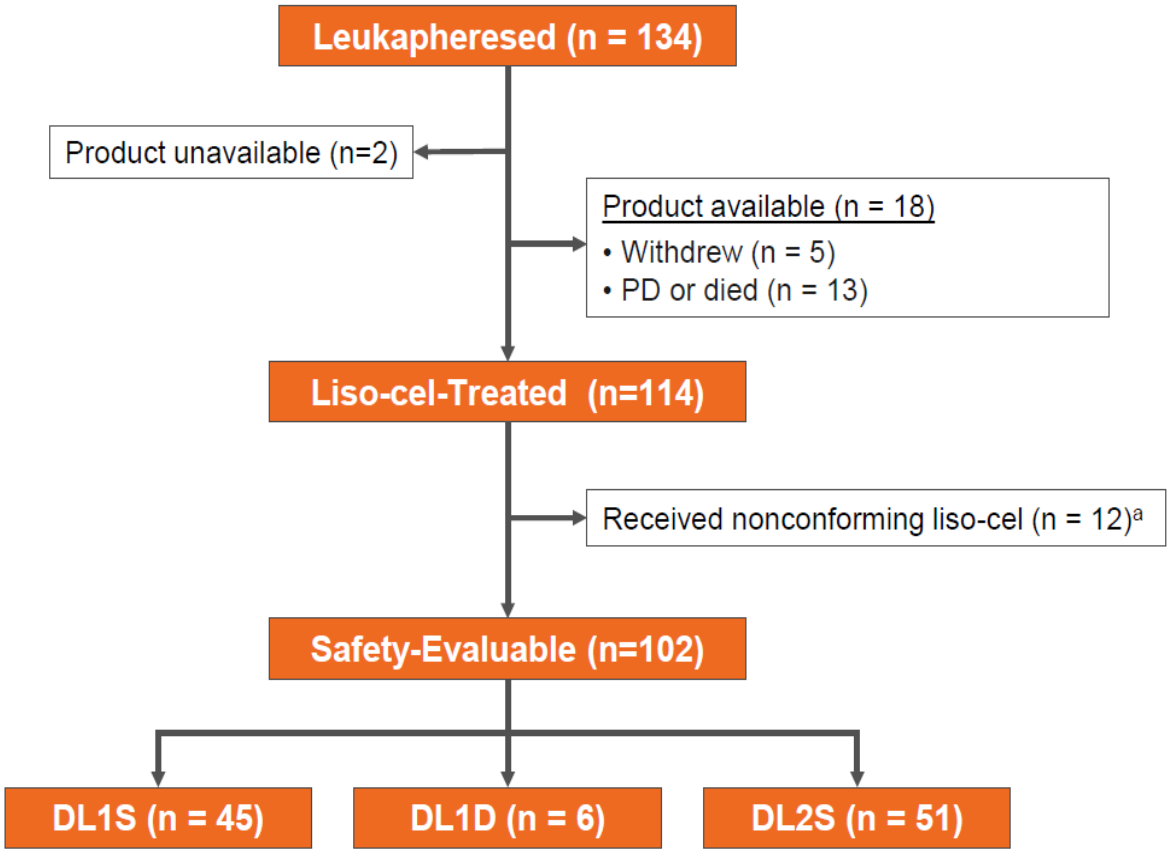
CONSORT Diagram: DLBCL Cohort



- **Product available for 99% (132/134) of patients apheresed in DLBCL cohort**
- **Seven MCL subjects treated thus far with liso-cel at DL1S**
- **Eight patients treated in outpatient setting as of April 3**

Abramson J, et al. ASCO and EHA 2018

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Results – TRANSCEND NHL 001

- No increase in CRS or neurotoxicity (NT) at DL2 in the CORE set of patients
- No deaths from CRS or NT
- In the FULL set of pts, time to onset of CRS was 5 days and to NT was 10 days
- In the FULL set of pts, 5% received tocilizumab for CRS and 8% received steroids
- High responses seen: best overall response in the FULL subset was 75% with 54% CR (n=102); 40 and 34% respectively at 6 month followup [best for tFL subset]

Abramson J, et al. ASCO and EHA 2018

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High Response Rates in R/R DLBCL

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

	All Dose Levels[a]	DL1S	DL2S
BOR, n[b]	73	33	37
ORR, % (95% CI)	80 (68, 88)	79 (61, 91)	78 (62, 90)
CR, % (95% CI)	59 (47, 70)	55 (36, 72)	62 (45, 78)
≥ 3-mo f/u, n[c]	73	33	37
3-mo ORR, % (95% CI)	59 (47, 70)	52 (34, 69)	65 (48, 80)
3-mo CR, % (95% CI)	45 (34, 57)	36 (20, 55)	51 (34, 68)
≥ 6-mo f/u, n[d]	73	33	37
6-mo ORR, % (95% CI)	47 (35, 59)	42 (26, 61)	49 (32, 66)
6-mo CR, % (95% CI)	41 (30, 53)	33 (18, 52)	46 (30, 63)

BOR, best overall response.

Baseline high tumor burden[e] well balanced between DL1 and DL2 (~1/3)

[a] Three patients treated on DL1D with similar outcomes.
[b] Includes patients with event of PD, death, or 28-day restaging scans. Two patients did not have restaging scans available.
[c] The denominator is number of patients who received JCAR017 ≥ 3 months ago, prior to data snapshot date, with an efficacy assessment at month 3 or prior assessment of PD or death.
[d] The denominator is number of patients who received JCAR017 ≥ 6 months ago, prior to data snapshot date, with an efficacy assessment at month 6 or prior assessment of PD or death.
[e] Defined as sum of the products of diameters (SPD) > 50 cm^2.

Data as of May 4, 2018

Abramson J, et al. ASCO and EHA 2018

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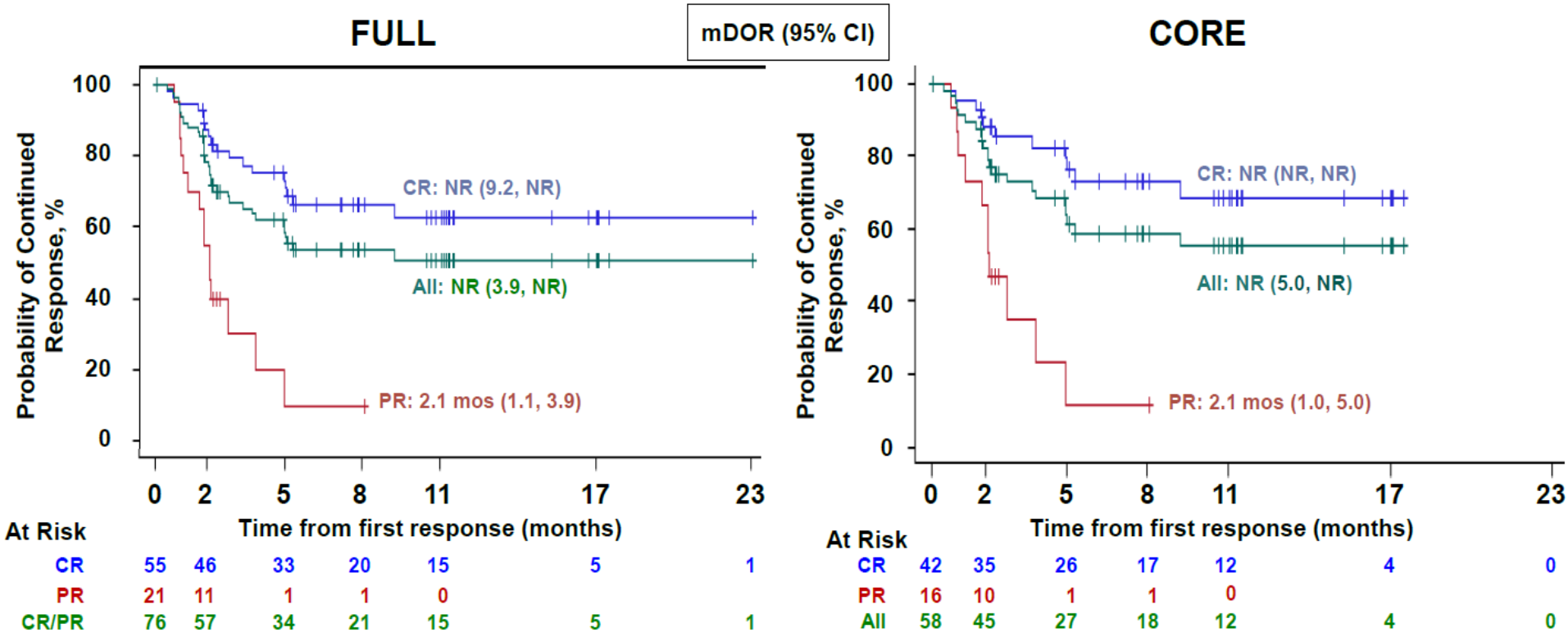
Durability of Response (DOR)

DOR Encouraging in High-Risk DLBCL Patient Population



In CORE population, 88% of patients with CR at 3 months stay in CR at 6 months; 97% of patients in response at 6 months stay in response for a longer-term

Median F/U=8 months (mos)

Data as of April 4, 2018

Abramson J, et al. ASCO and EHA 2018

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Ongoing CAR-T cell trials for DLBCL at COH

- Phase I study to evaluate cellular immunotherapy using memory-enriched T cells lentivirally transduced to express a CD19-specific, hinge-optimized, CD28-costimulatory chimeric receptor and a truncated EGFR following lymphodepleting chemotherapy in adult patients with CD19+ B-cell lymphoproliferative neoplasms [NHL and CLL strata]

- Celgene PLATFORM trial
  - JCAR017 + [durvalumab]/[CC-122]/etc
  - Various dose levels
  - Rel/ref DLBCL
  - No CNS involvement allowed

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B-cell non-Hodgkin lymphomas

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CD19 specific CAR-T cells in CLL

- N = 14 (heavily pretreated); median cell dose = 1.6x10^8 CTL019 cells
- 4 CRs (29%), all MRD neg and with no relapses; 4 (29%) PRs; ORR 57%
- CAR-T cells detectable 3 yrs later in some
- Expected toxicities: B cell aplasia, delayed TLS and cytokine release syndrome in all responding patients

Porter D, et al. Science Translational Medicine 2015; 7 (303): 303ra139

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CD19 CAR-T cells in ibrutinib-refractory CLL

- N = 24, median age 60 yrs
- MTD 2x10^6 CAR-T cells/kg; CD8+:CD4+ CAR-T cells 1:1
- 19 ibrutinib ref, 3 ibrutinib intolerant, 2 had not progressed on ibrutinib; 6 were ref to venetoclax; 23 had complex karyotype and/or del17p
- 20 pts (83%) had CRS and 8 pts (33%) had neurotoxicity
- ORR at 1 month in 19 of 20 restaged pts who had received Flu/Cy and CAR-T cells at or below MTD was 74% (4/19 CR, 10/19 PR)
- 15/17 patients (88%) with marrow disease before CAR-T cells had no disease by flow cytometry after CAR-T cells; 12 underwent deep IGH sequencing and 7 had no malignant IGH sequences detected
- Absence of the malignant IGH clone in marrow of patients with CLL who responded by IWCLL criteria was associated with 100% progression-free survival and overall survival (median 6.6 months follow-up) after CAR-T cell immunotherapy

Turtle C, et al. J Clin Oncol 2017; 35 (26): 3010-20

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TRANSCEND-CLL (017004) - ongoing

- Main inclusion criteria:
  - CLL/SLL with indication to treat
  - Relapsed/refractory after 2 (if with high risk features) or 3 (if no high risk features) lines of therapy including ibrutinib (or intolerant to ibrutinib)
  - Monotherapy as well as combination (ibrutinib) cohorts

Zuma 2 : Ph2 study of KTE-C19 in MCL (ongoing)

- Rel/ref MCL
- Upto 5 prior lines of therapy including ibrutinib


?s