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Integration of CD19-Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy into the Management of Lymphomas

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Disclosures

- Research support: Celgene, Genentech, Janssen, Karus, Lam Therapeutics, Merck, TG Therapeutics
- Honorarium: Bayer, Celgene, Gamida, Genentech, Gilead/KITE, Janssen, Novartis, Spectrum

Questions regarding CAR T-cell therapy

Dr Peswani

Dr Morganstein

Dr Brenner

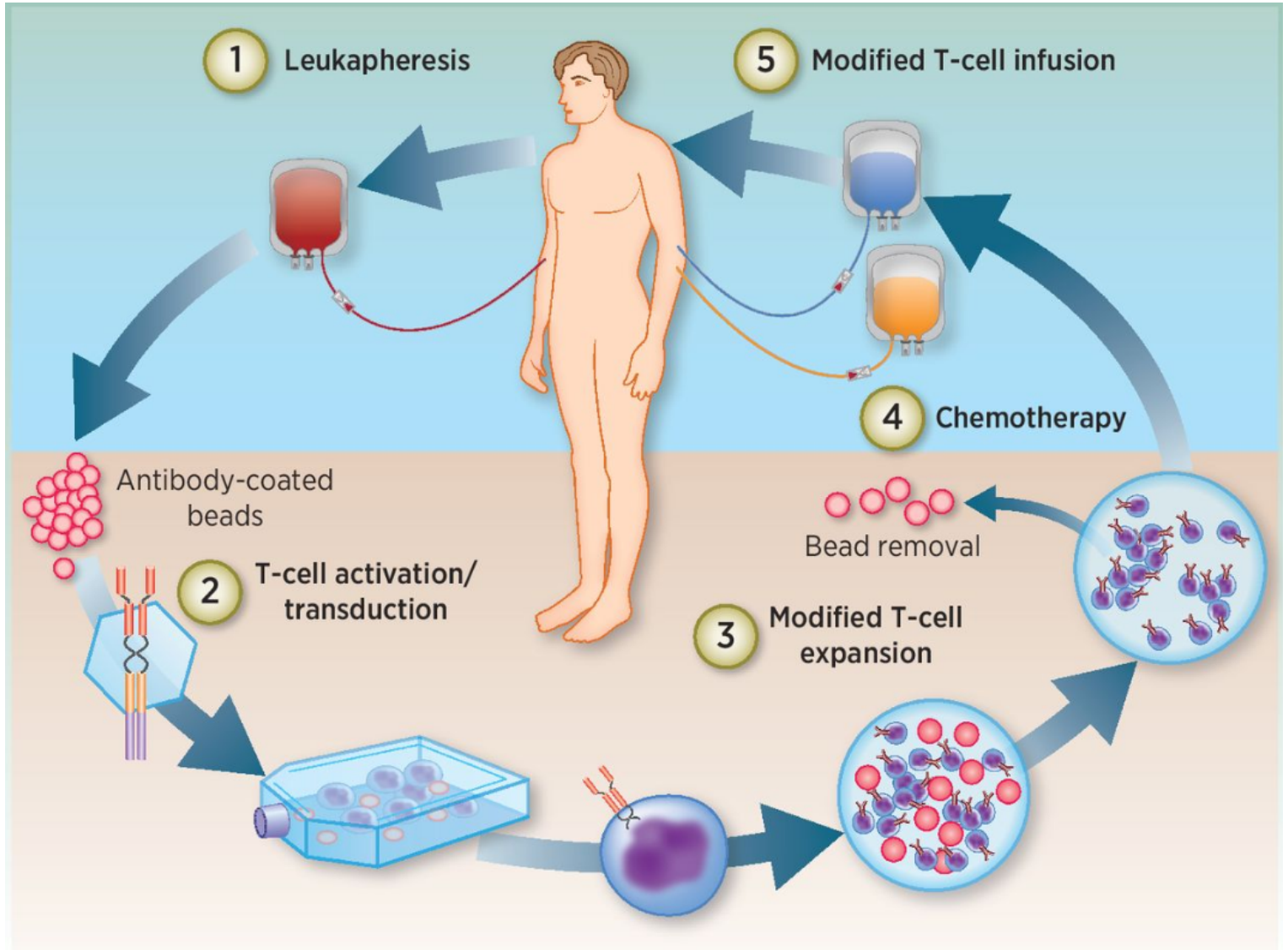
Dr Khan

Case Presentation: Dr Morganstein

41-year-old man with a 2-month-old baby

- Presented with significant abdominal pain and retroperitoneal lymphadenopathy
- Diagnosis: DLBCL (germinal center subtype)
- R-CHOP x 2, with no response
- MSKCC: Salvage R-ICE (CR) → ASCT
  - Relapse after 6 months
- CAR-T therapy

Chimeric Antigen Receptors (CAR) for Adoptive T-cell Therapy



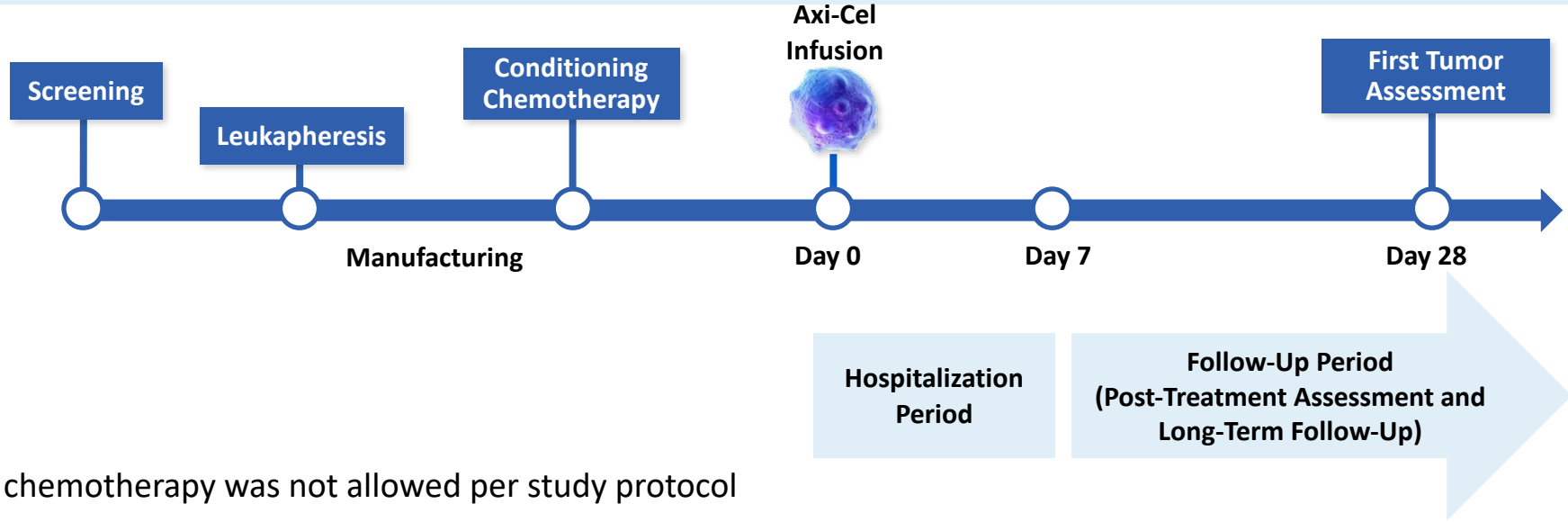
Maus & June. CCR Focus. April 2016

CD19 CAR T-cell Products in Pivotal Trials in NHL

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

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

ZUMA-1 Study Design



- Bridging chemotherapy was not allowed per study protocol

Key eligibility criteria

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

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

- **Data cutoff: August 11, 2018**
- **Median follow-up for Phase 2: 27.1 months**

Patient populations

- **Safety: N = 108 (Phase 1 + 2)**
- **Efficacy: n = 101, assessed by investigator and central review**

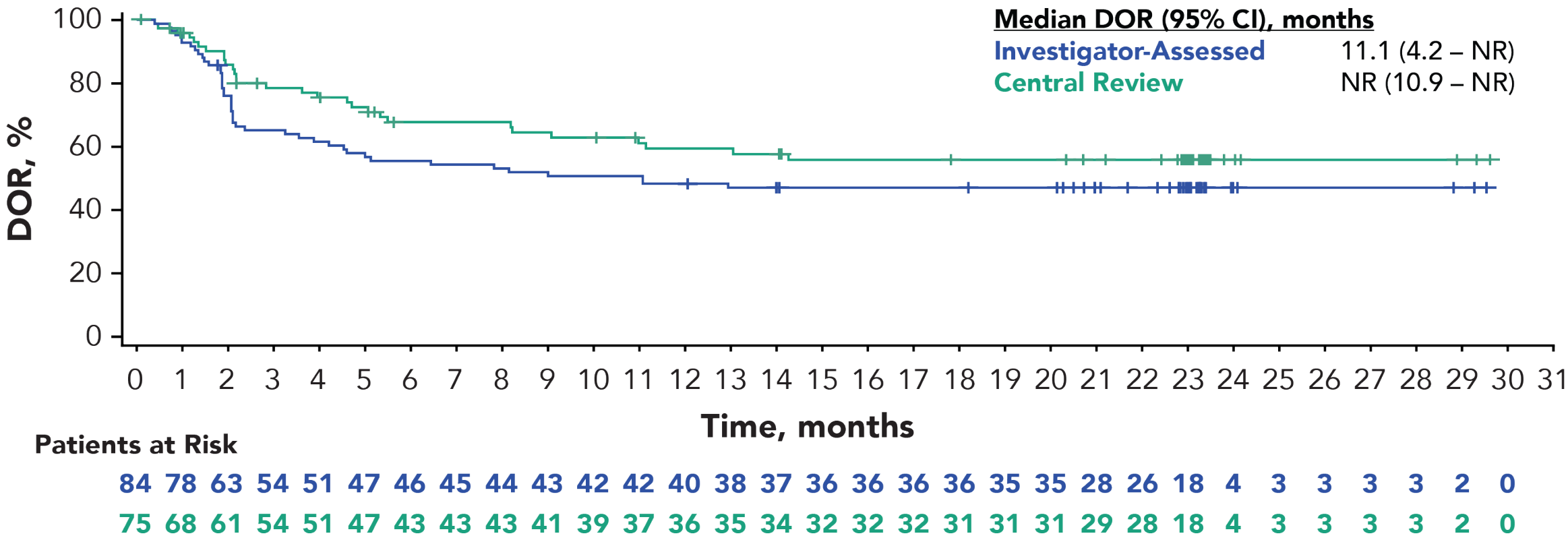
ASCT, autologous stem cell transplantation; DLBCL, diffuse large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

ZUMA-1: Baseline Characteristics

Characteristic	DE/HGBCL (n = 37)	Overall (N = 108)
Median age (range), y	60 (28 – 76)	58 (23 – 76)
≥ 65, n (%)	9 (24)	27 (25)
Male, n (%)	25 (68)	73 (68)
ECOG 1, n (%)	22 (59)	62 (57)
Disease stage III/IV, n (%)	29 (78)	90 (83)
IPI score 3 – 4, n (%)	15 (41)	48 (44)
≥ 3 Prior therapies, n (%)	28 (76)	76 (70)
Refractory Subgroup Before Enrollment	**(n = 37)**	**(N = 108)**
Refractory to second- or later-line therapy, n (%)	29 (78)	80 (74)
Best response as PD to last prior therapy	22 (59)	70 (65)
Relapse post-ASCT, n (%)	8 (22)	25 (23)

ASCT, autologous stem cell transplantation; DE/HBGCL, double-expressor or high-grade B cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PD, progressive disease.

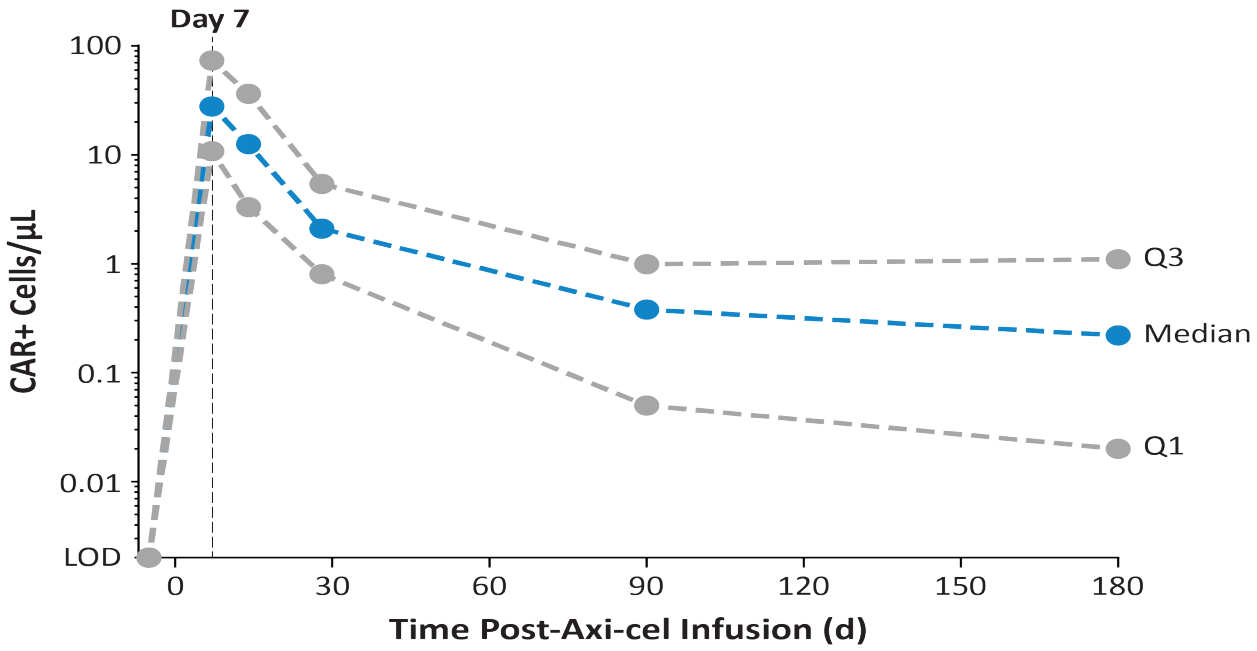
ZUMA-1 Duration of Response by Investigator Assessment and Central Review, 2 Year Follow-Up

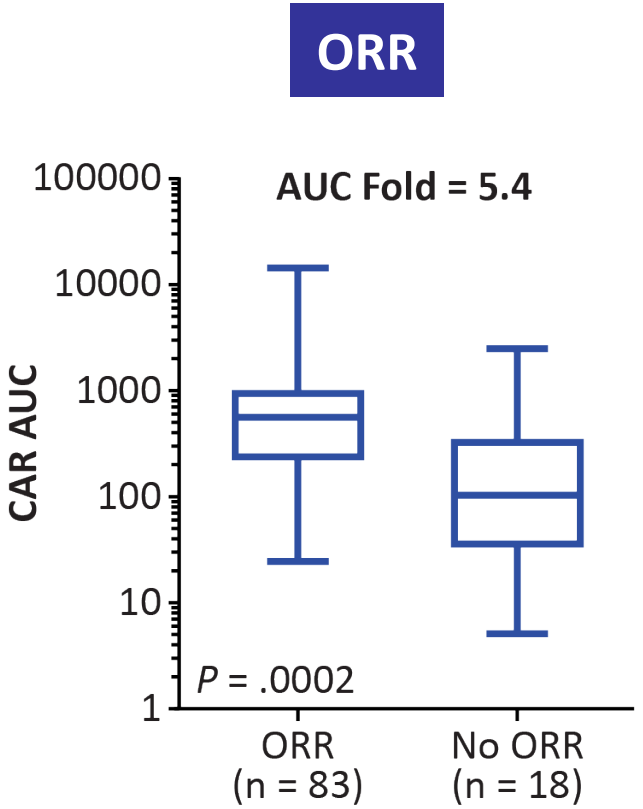


- Median DOR for complete responders has not been reached

Median duration of response was NR (95% CI, 10.9 months – NR) by central review because of several patients with early progressive disease who were assessed as in response by central review and had to be censored for receiving next anticancer therapy.
DOR, duration of response; NR, not reached.

ZUMA-1: CAR T-cell expansion after axi-cel infusion is associated with response





- Peak expansion observed within 2 weeks
- CAR T cells detectable beyond two years after infusion

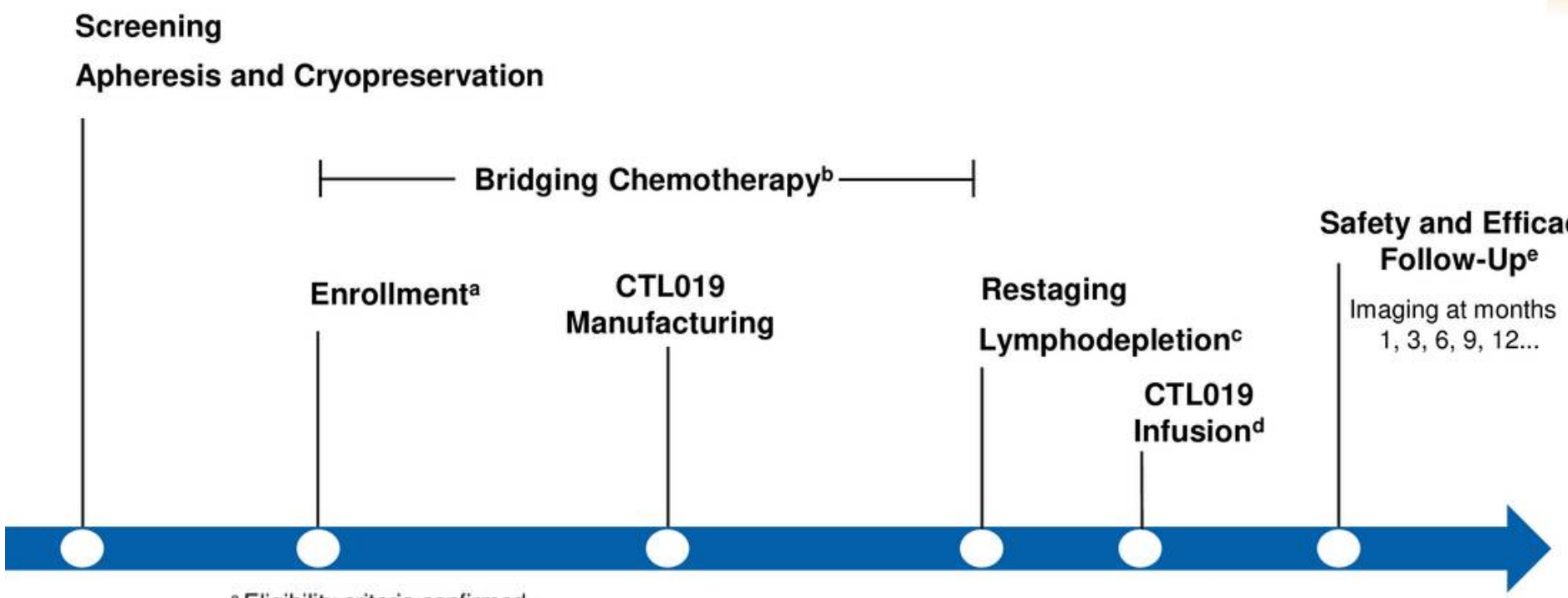
Neelapu et al. N Eng J Med 2017

Biomarkers of Response after Axi-cel: Summary

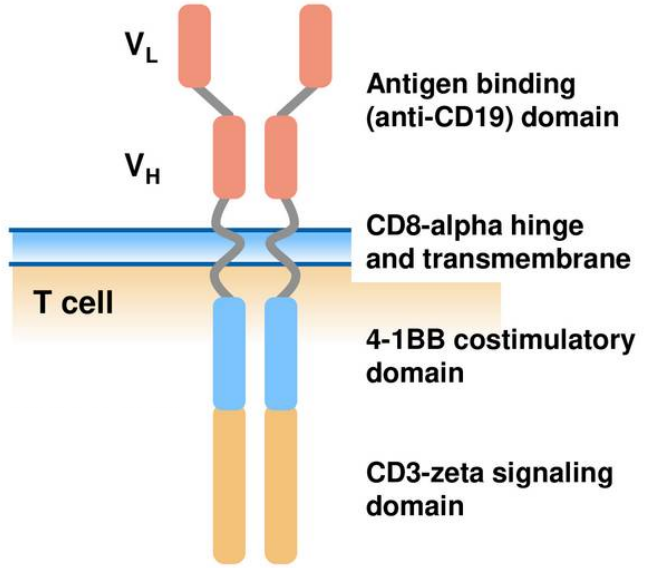
Covariate	Impact on efficacy
Clinical prognostic markers	
Age, stage, IPI, bulky, extranodal, refractory subgroup, primary refractory, prior ASCT	No
Product characteristics	
CD4:CD8 ratio	No
Phenotype	No
T-cell doubling time	No
Polyfunctionality	Yes
Tumor characteristics	
Cell or origin (ABC vs. GCB)	No
DLBCL vs. PMBCL vs. TFL	No
CD19 H score	No
Post-infusion	
Peak CAR and CAR-AUC	Yes
Tocilizumab and steroid use	No
CD19 expression at progression	Yes

JULIET: Tisagenlecleucel Study Design

JULIET is a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in adult patients with r/r DLBCL (NCT02445248)



[a] Eligibility criteria confirmed.
[b] To prevent rapid disease progression during CTL019 manufacturing.
[c] To be completed 2 to 14 days prior to CTL019 infusion.
[d] Infusion conducted in- or out-patient at investigator discretion.
[e] Long-term follow-up for 15 years (NCT02445222).



JULIET: Baseline Characteristics

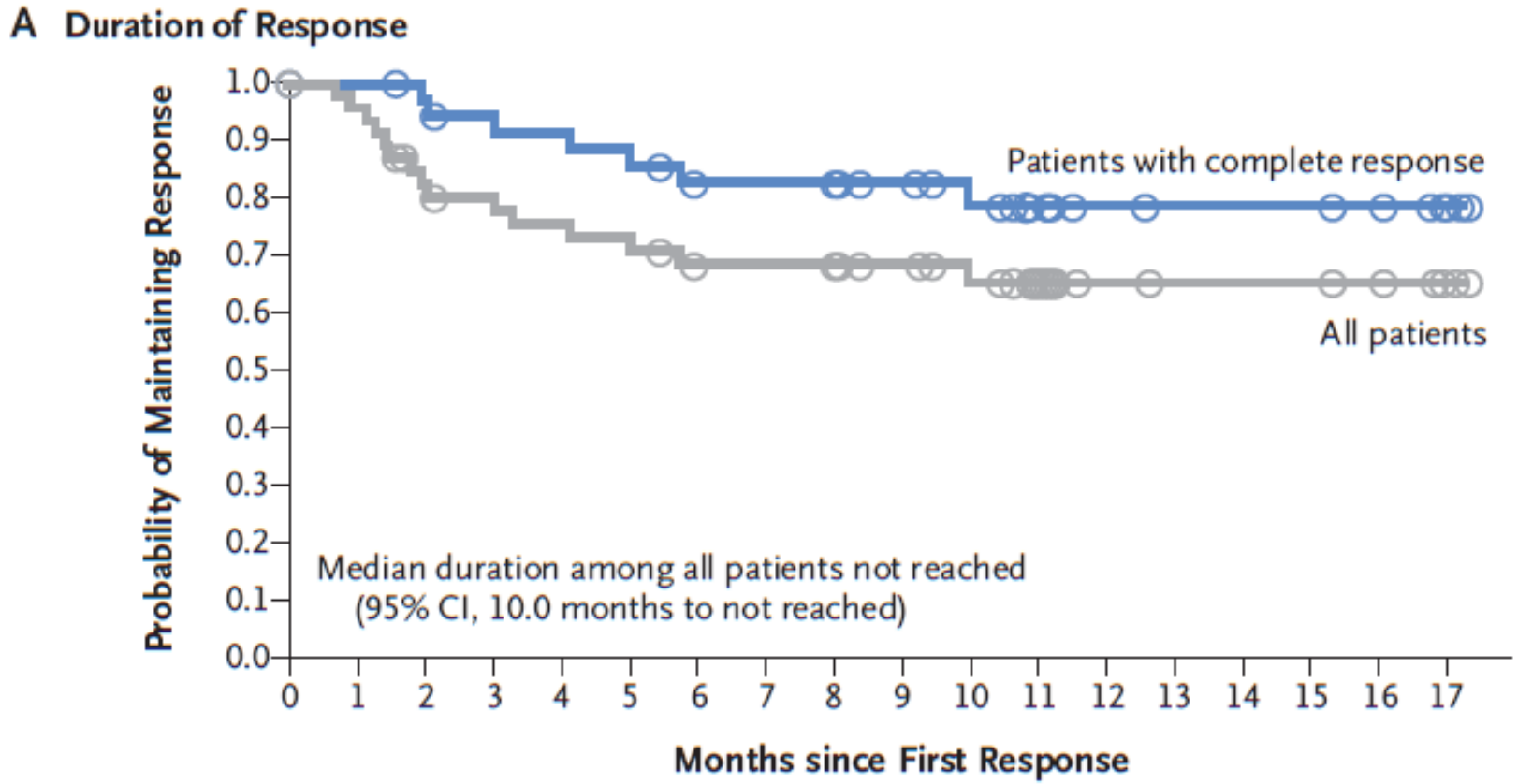
	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	79
Transformed follicular lymphoma, %	19
Double/triple hits in *CMYC/BCL2/BCL6* genes, %	17[a]
Cell of origin[b]	
Germinal/Nongerminal 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.

Schuster, Bishop, Tam *et al*, N Engl J Med. 2019 Jan 3;380(1):45-56.

auto-SCT, autologous stem cell transplant;
ECOG, Eastern Cooperative Oncology Group.

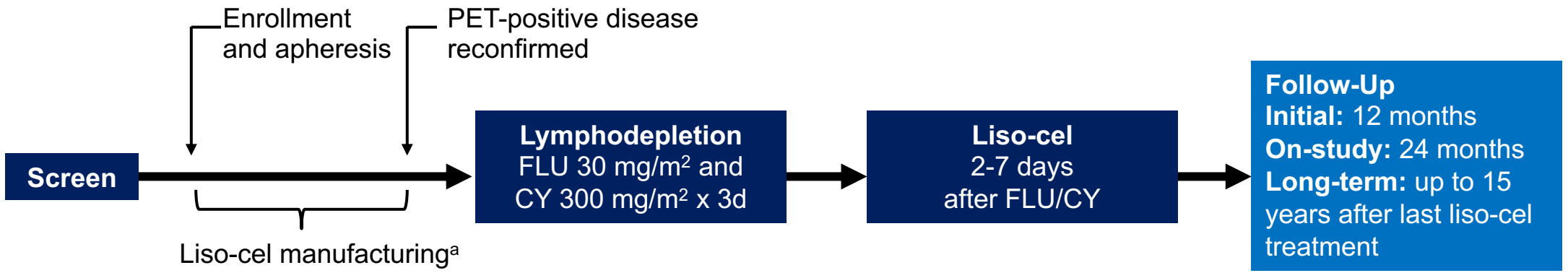
JULIET Duration of Response



No. at Risk																	
Patients with complete response	37	36	35	32	31	30	26	26	26	23	21	15	9	8	8	8	7	4
All patients	48		37		32		27		27		22		10		9		8	

Schuster et. al. *NEJM.* 2018

TRANSCEND NHL 001 Study Design



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 PS 0-2[b]
- No minimum absolute lymphocyte count requirement for apheresis

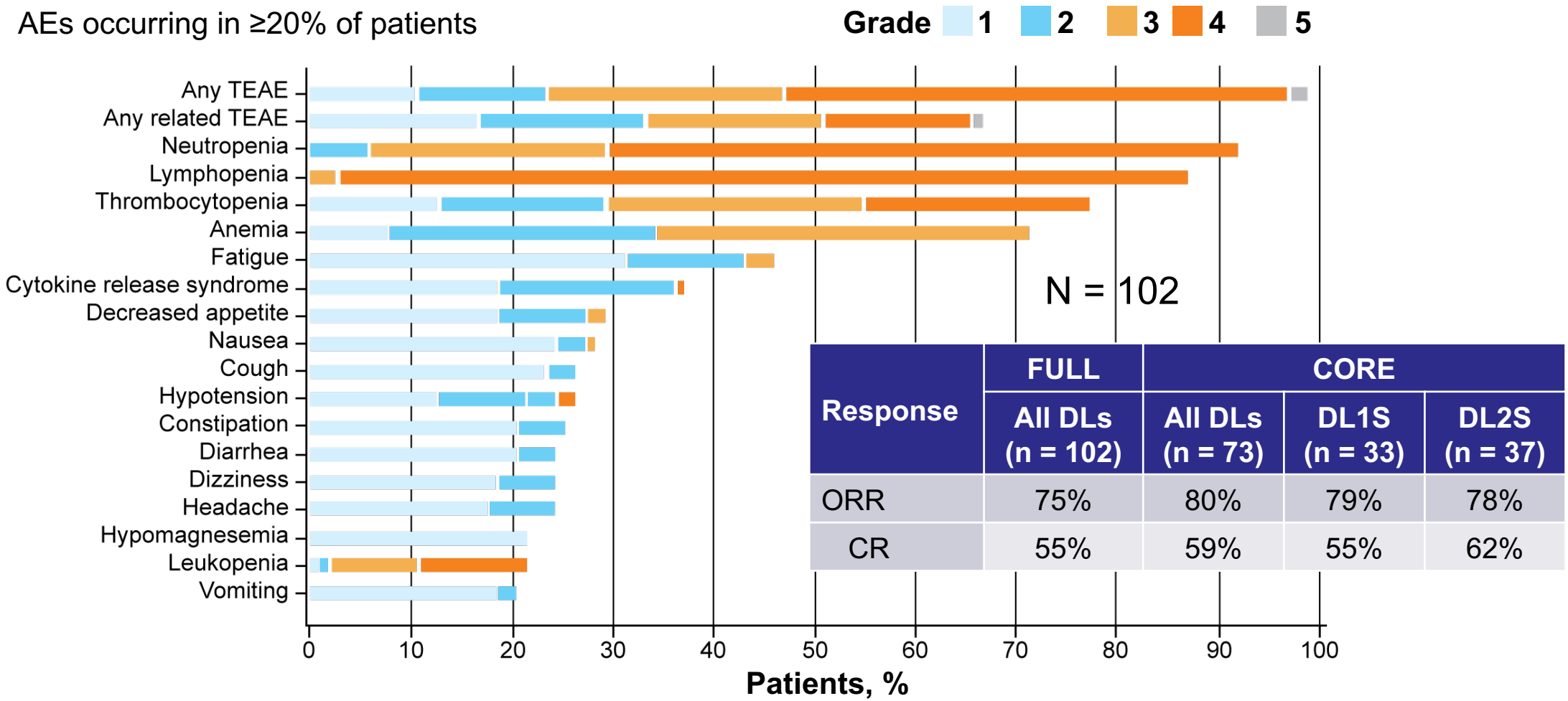
CLL, chronic lymphocytic lymphoma; CNS, central nervous system; CY, cyclophosphamide; FLU, fludarabine; MZL, marginal zone lymphoma; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma.

[a] Therapy for disease control allowed.

[b] ECOG 2 and prior allogeneic HSCT excluded from pivotal cohort.

Abramson J et al. Proc ASCO 2018;Abstract 7505.

TRANSCEND NHL 001: Safety and Efficacy in the DLBCL Cohort



Response	FULL	CORE		
	All DLs (n = 102)	All DLs (n = 73)	DL1S (n = 33)	DL2S (n = 37)
ORR	75%	80%	79%	78%
CR	55%	59%	55%	62%

DLs = dose levels; DL1S = DL 1, single dose; FULL data set includes all patients in the DLBCL cohort treated with liso-cel at all DLs; CORE data set includes only patients meeting the inclusion criteria for the pivotal cohort, including DLBCL NOS (de novo or transformed from FL) and high-grade lymphoma

Abramson JS et al. *Proc ASCO* 2018;Abstract 7505.

Multicenter CD19 CAR T-Cell Trials in Aggressive NHL

Study / Sponsor	ZUMA-1	JULIET	TRANSCEND
Reference	Neelapu et al, NEJM 2017	Schuster et al, NEJM 2018	Abramson et al, ASH 2019
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	0.6-6 x 10^8	0.5-1.5 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL/PMBCL/TFL/FL Gr 3B
Treated/Enrolled	101/111 (91%)	111/165 (67%)	268/342 (78%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	49%	34%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	93%	99%
ORR / CR (%)	82 / 54	52 / 40	73 / 53

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Cytokine Release Syndrome and Neurotoxicity: Multicenter CD19 CAR T trials in adult NHL

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Ref
ZUMA-1	CD19/CD3ζ/ CD28	101	93%	13%	64%	28%	Neelapu et al, NEJM 2017
JULIET	CD19/CD3ζ/ 4-1BB	111	58%	22%	21%	12%	Schuster et al, NEJM 2018
TRANSCEND	CD19/CD3ζ/ 4-1BB	268	42%	2%	30%	10%	Abramson et al, ASH 2019

- Lee criteria used for CRS grading on ZUMA-1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading

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Integration of CD19-directed CAR T cell therapy in standard of care practice

Characteristics Differentiating Patients in the Real World from ZUMA-1

- 129 of 175 (43%) patients would not have met eligibility for ZUMA-1 at the time of leukapheresis.
  - 59% would have not met 1 criterion
  - 41% would have not met ≥ 2 criteria

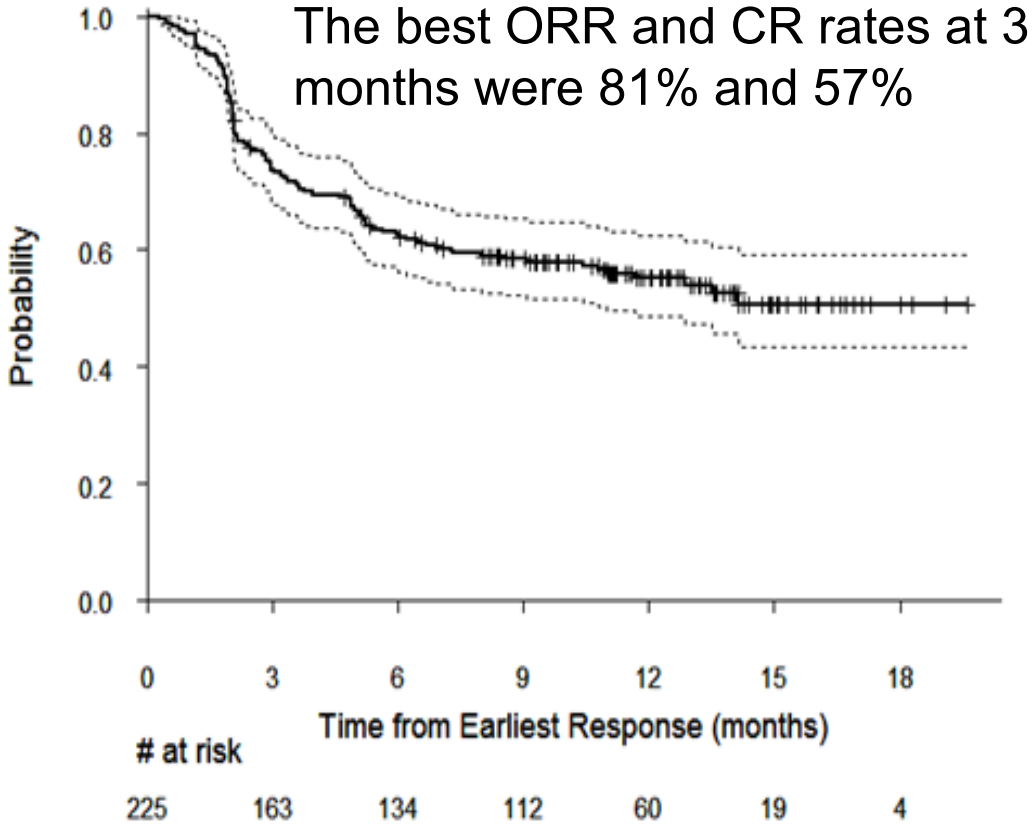
Criteria Excluded from ZUMA-1	N (%)
ECOG PS > 1	58 (19)
Platelets < 75	34 (11)
Active DVT/PE	31 (10)
GFR < 60	21 (7)
History of CNS lymphoma	21 (7)
Prior checkpoint inhibitor	17 (6)
LVEF < 50%	10 (3)
Symptomatic pleural effusion	10 (3)
Bilirubin > 1.5 g/dL	7 (2)
Prior CD19 directed therapy	5 (2)

Nastoupil, ASH 2018, in press

Efficacy of Axi-Cel in Clinical Practice

Duration of Response

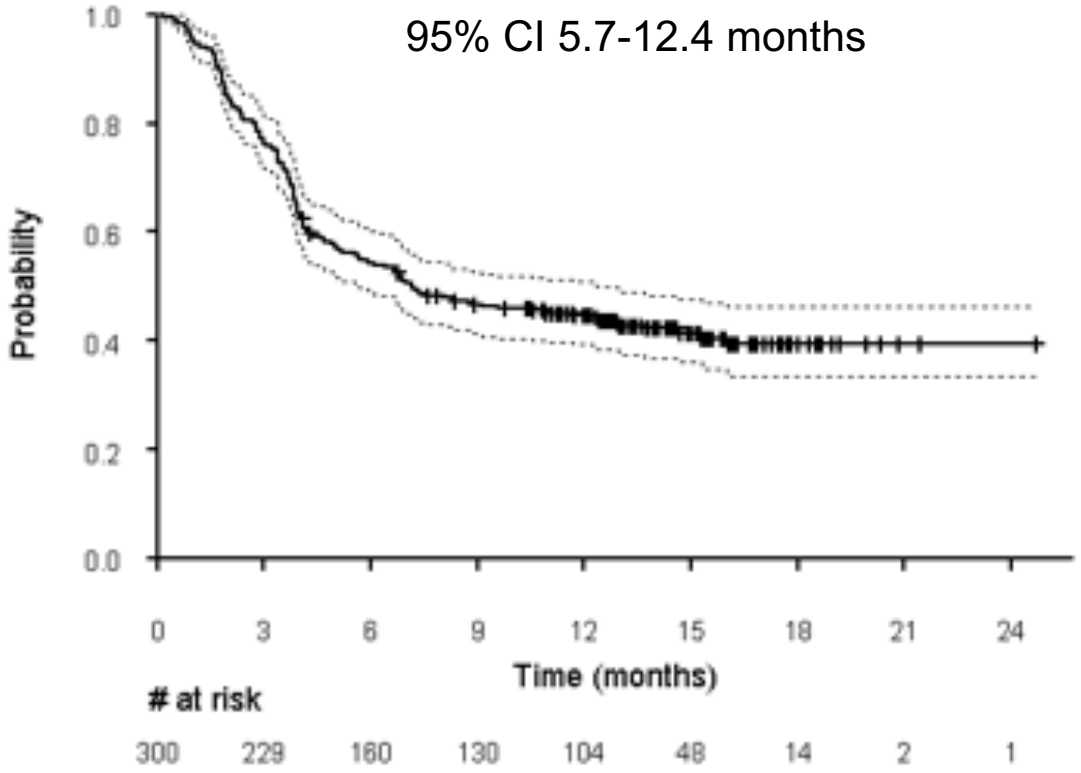
The best ORR and CR rates at 3 months were 81% and 57%



Progression Free Survival

Median 7.2 months

95% CI 5.7-12.4 months



Nastoupil, ASH 2018, in press

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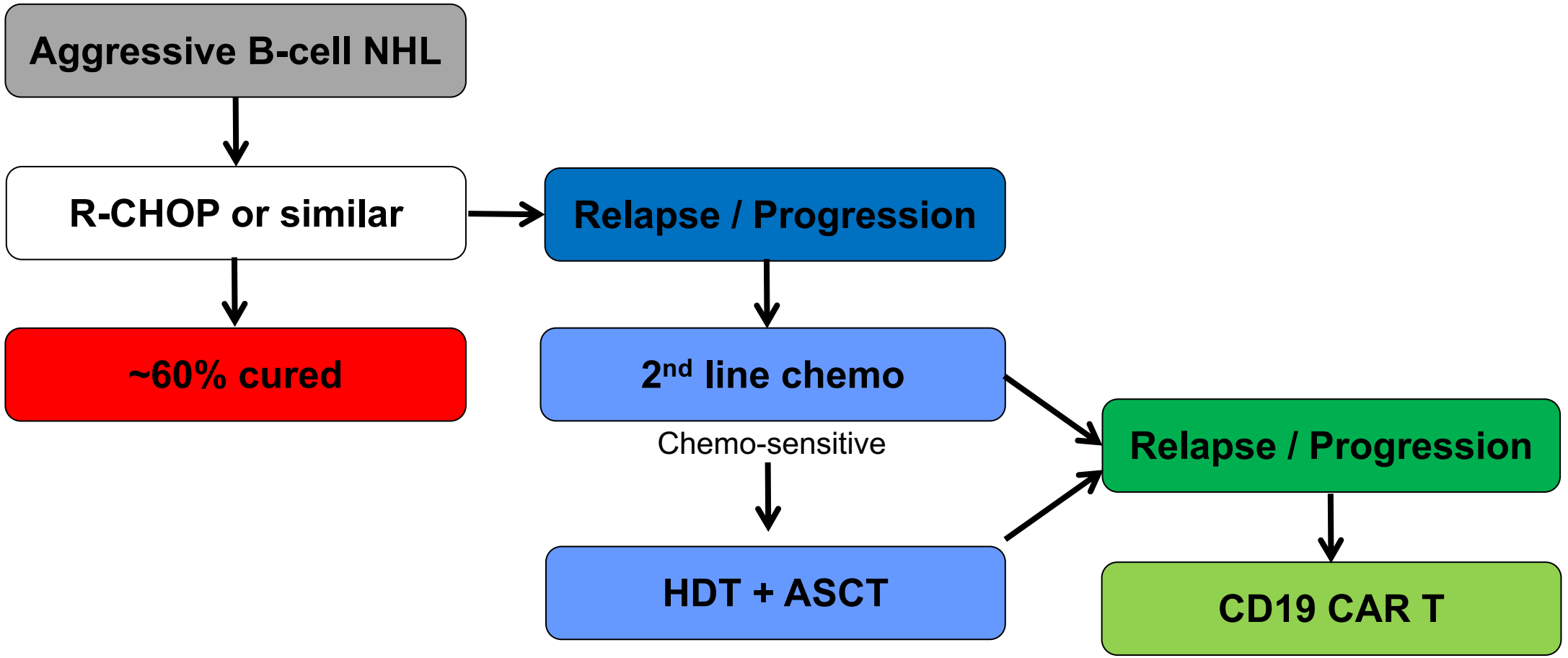
CD19 CAR T in NHL: Current Management of DLBCL



Future Directions:

CD19 CAR T in high-risk aggressive B-cell NHL

Randomized trials of CD19 CAR T vs. ASCT

CD19 CAR T in high-risk iNHL, MCL;
Off the shelf CAR Ts
Exploiting Mechanisms of Resistance