Updates in CAR-T Therapy

Ochsner Cancer Updates

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10/28/2022

Ochsner™ Health System

Disclosures

- Speaker Bureau: Jazz Pharmaceuticals, BMS, Lilly, Beigene
- Advisory Board: Celgene, Daiichi Sankyo, Janssen Biotech

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Agenda

- CAR-T Updates in Lymphoma
- CAR-T Updates in Myeloma
- Challenges in CAR-T Therapy
- Future Directions

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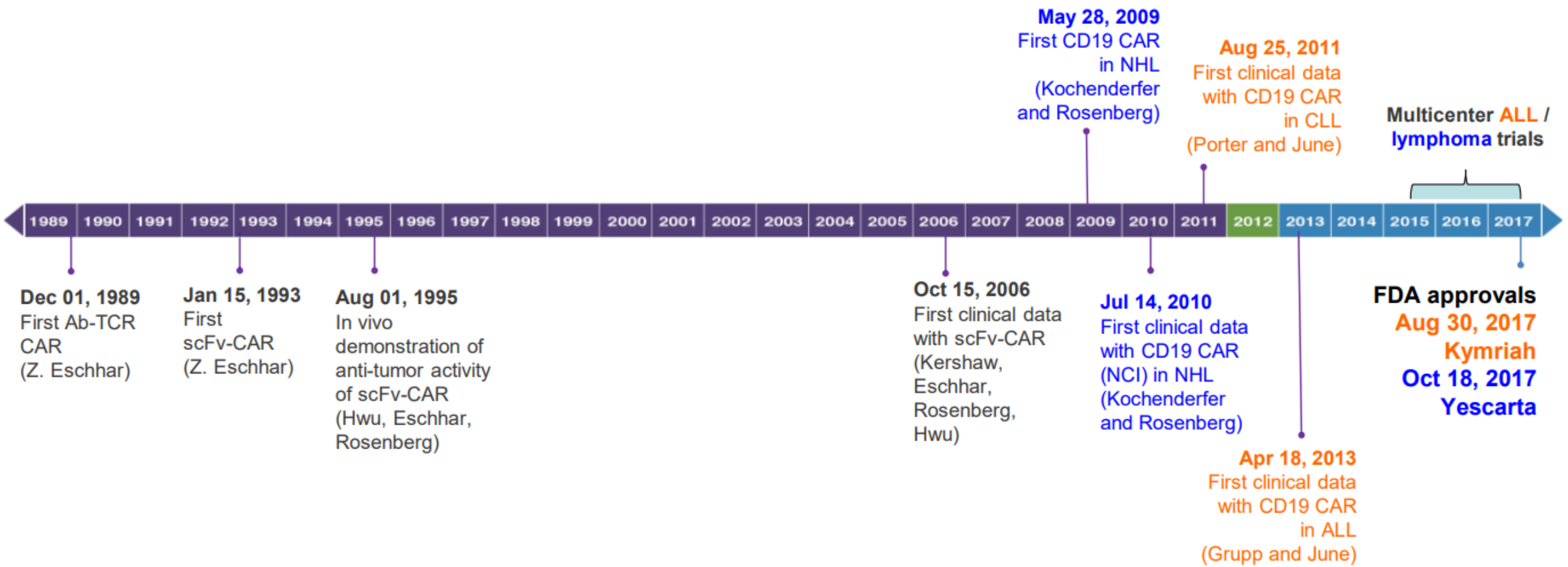
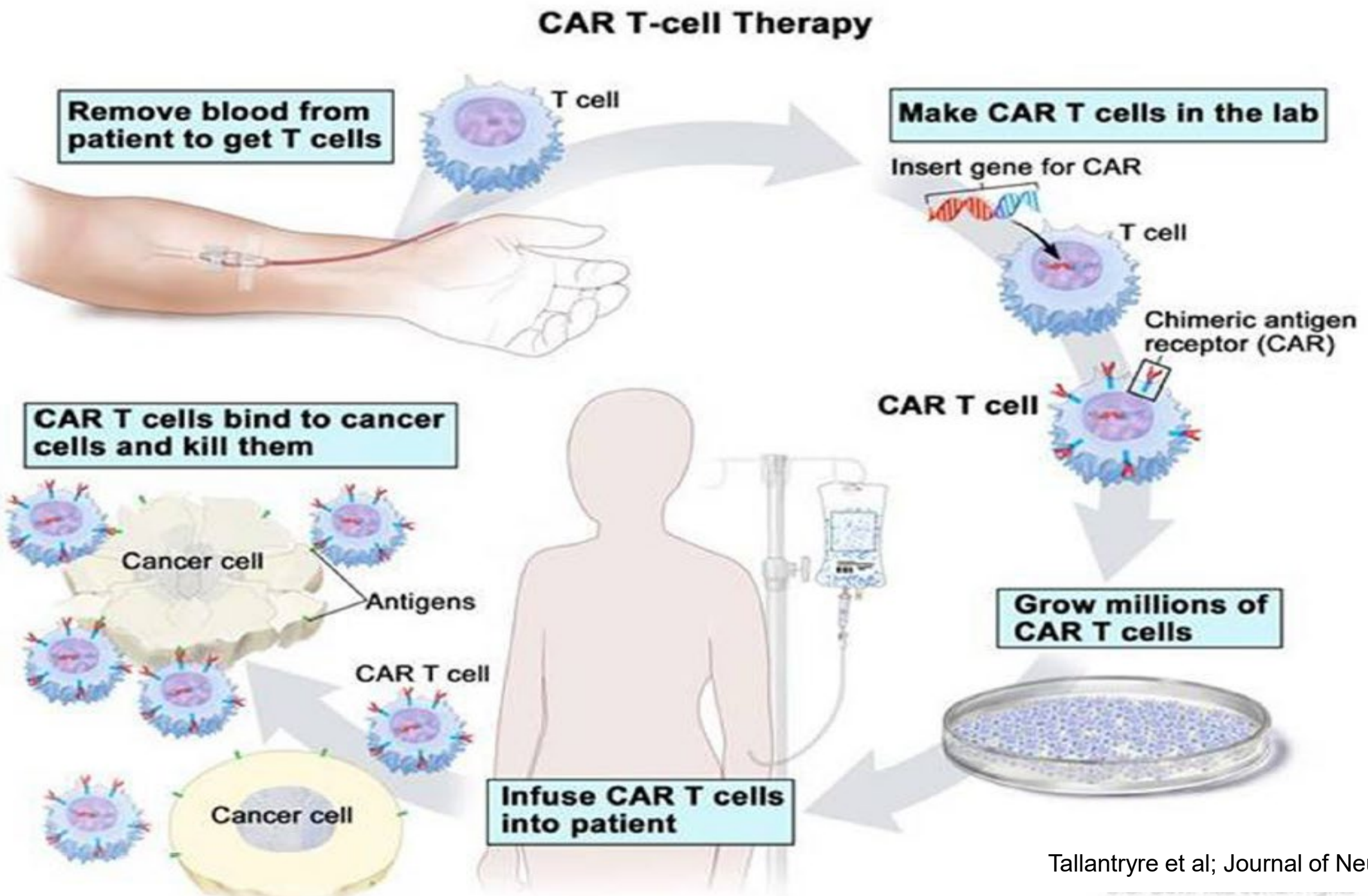
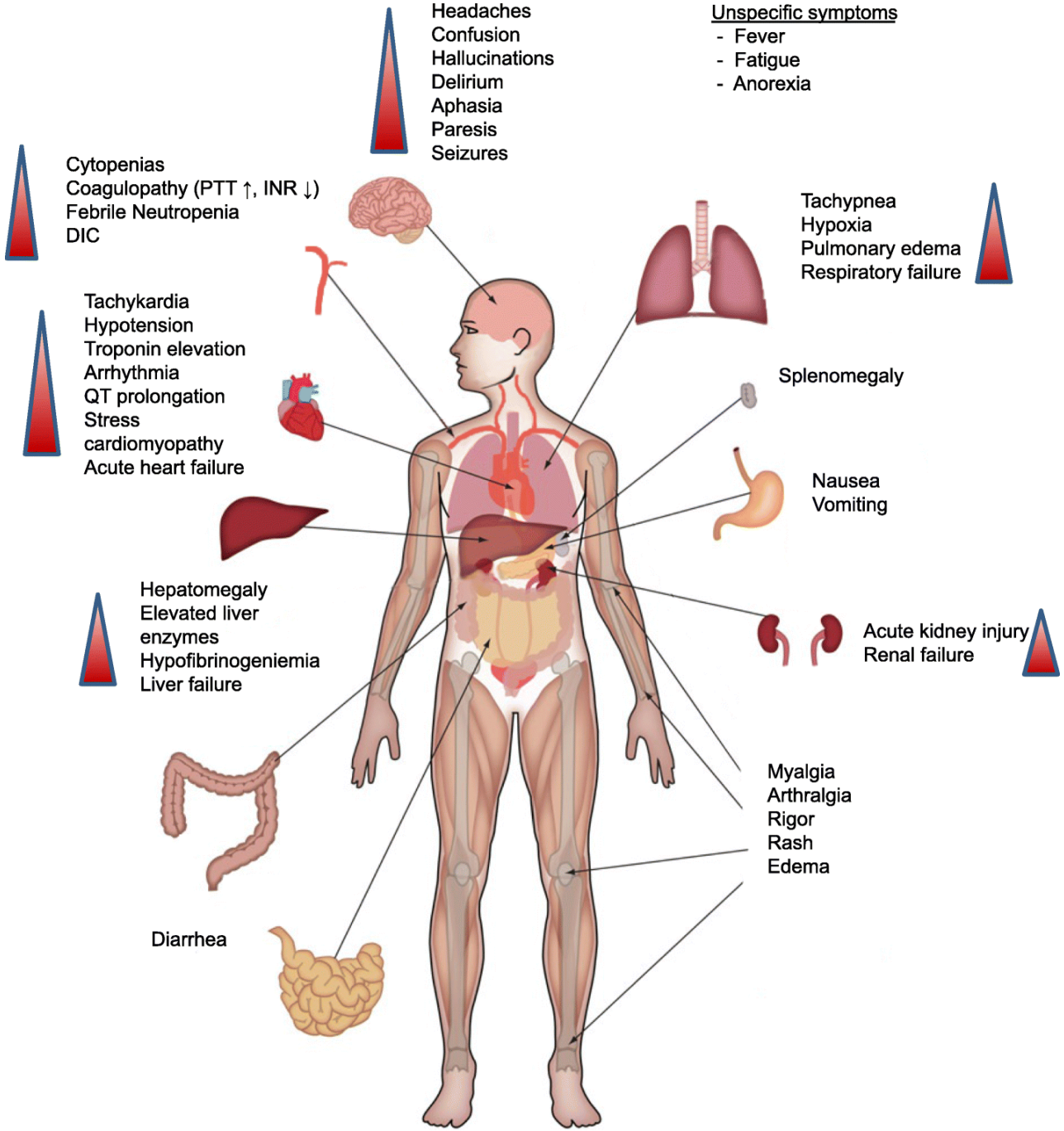
CAR T-cell Development: From Discovery to FDA Approval

Discovery to FDA approval ~25 years





Tallantryre et al; Journal of Neurology 2021



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CAR T Cell Therapy in Lymphoma

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

ZUMA-1

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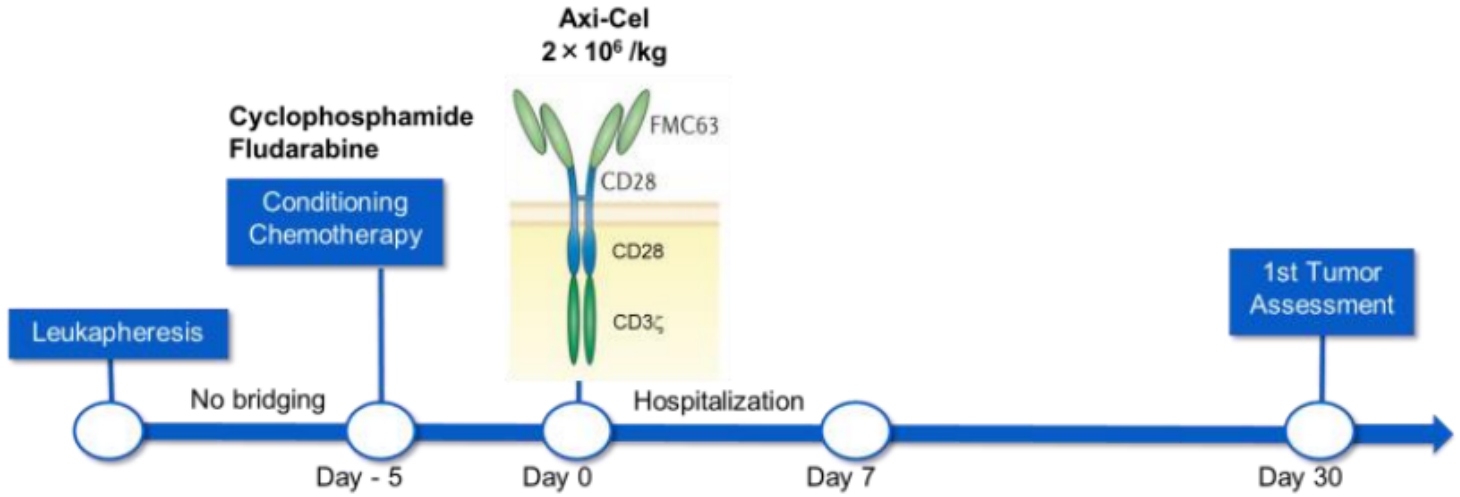
ZUMA1: Phase I/II Study Design



Phase 1 (N = 7)

Refractory DLBCL/PMBCL/TFL (n = 7)

Phase 2 (N = 101)

- Cohort 1 Refractory DLBCL (n = 77)
- Cohort 2 Refractory PMBCL/TFL (n = 24)

1 unsuccessful manufacture
4 adverse events
1 death from disease
2 non-measurable disease

Key eligibility criteria

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

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

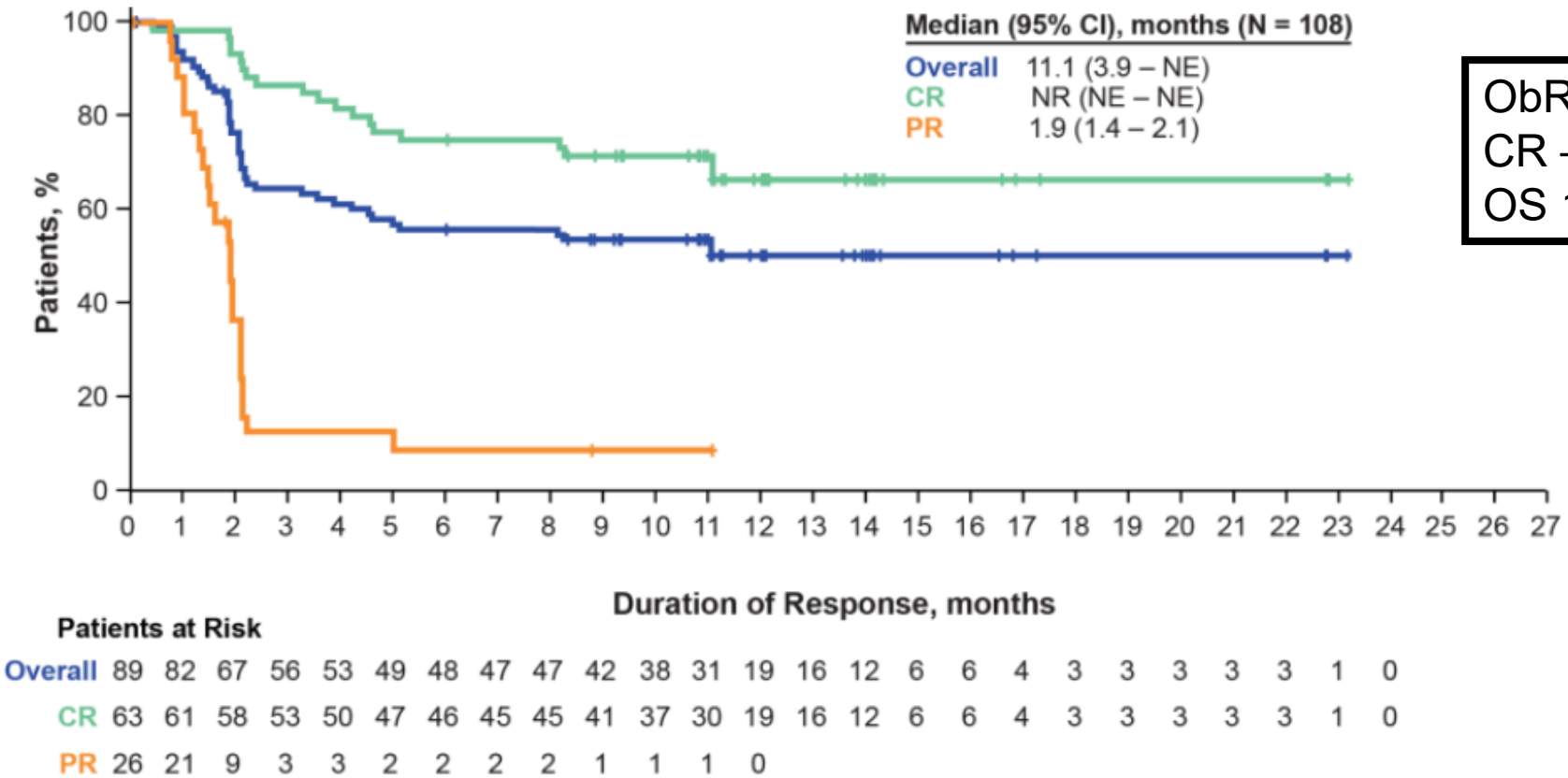
Conditioning regimen

- Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² 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

ZUMA1: Duration of Response by Best Objective Response

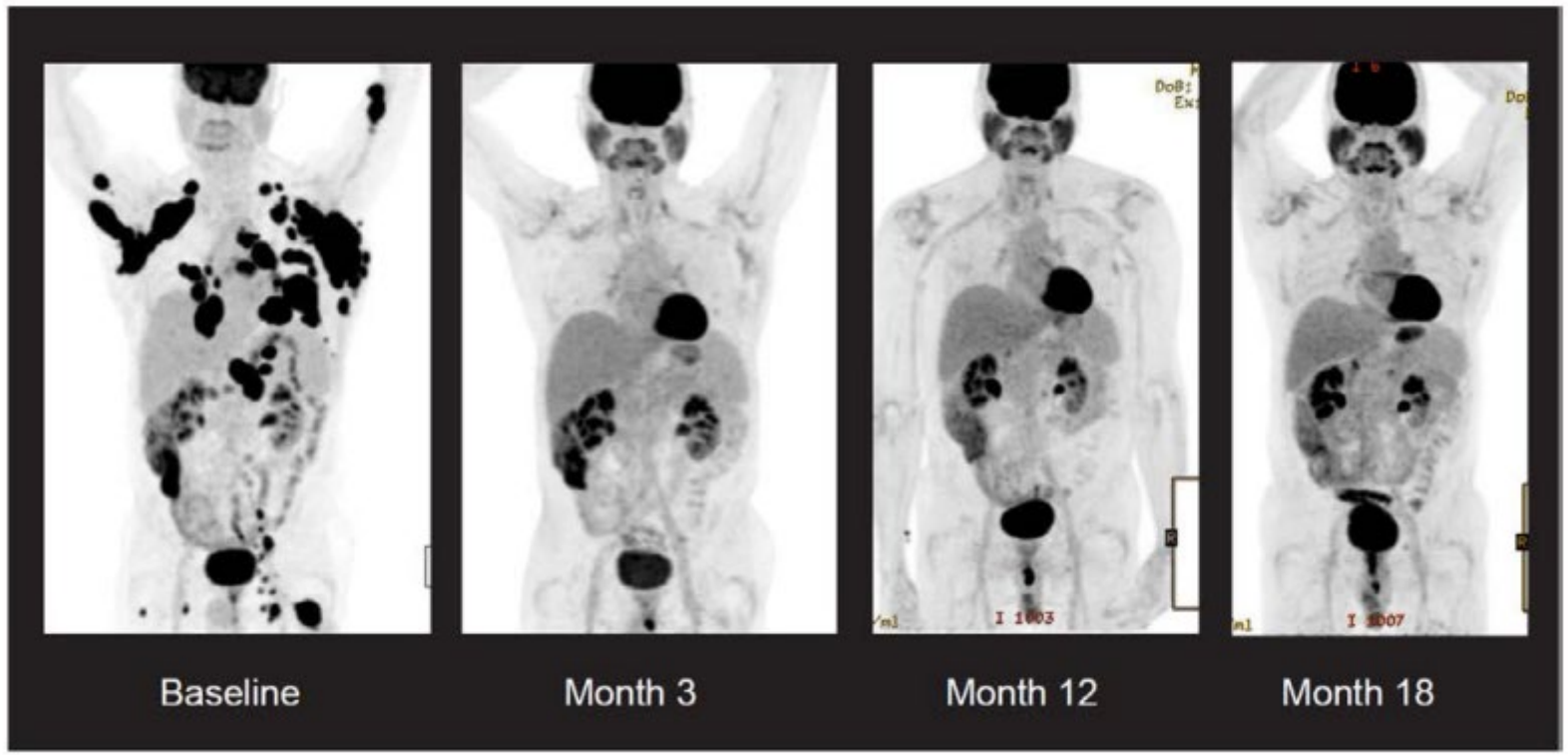


ObRR – 82%
CR – 54%
OS 18m – 52%

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

CR, complete response; NR, not reached; PR, partial response.

Neelapu et al. N Eng J Med 2017



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ZUMA1: Safety

	Pivotal cohort (N=101)	
	CRS	**NE**
All grades	93%	64%
Grade ≥3	13%	28%
Time to onset [Median (Range)]	2 (1-12) days	5 (1-17) days
Time to resolution (Median)	8 days	17 days
Tocilizumab usage	43%	
Corticosteroids usage	27%	

- 3 deaths due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism
- Lee criteria used for CRS grading
- CTCAE criteria used for neurological event (NE) grading

Neelapu et al. N Eng J Med 2017

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

JULIET

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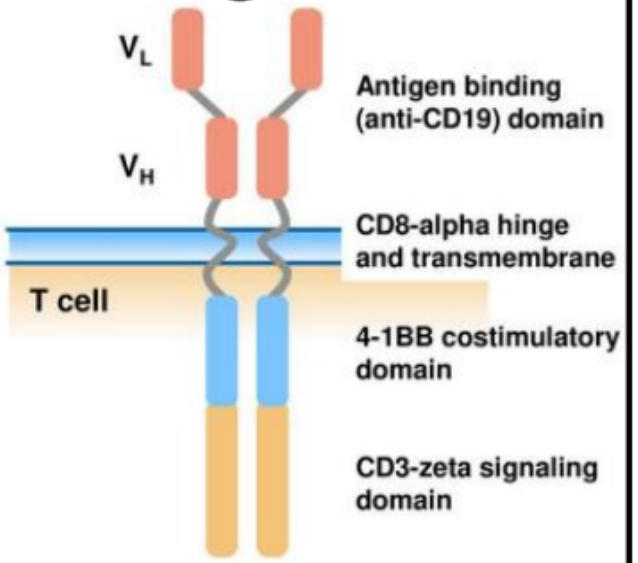
JULIET: Tisagenlecleucel Study Design

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



Screening

Apheresis and Cryopreservation

Bridging Chemotherapy[b]

Enrollment[a]

CTL019 Manufacturing

Restaging

Lymphodepletion[c]

CTL019 Infusion[d]

Safety and Efficacy Follow-Up[e]

Imaging at months 1, 3, 6, 9, 12...

Time to infusion 54 days

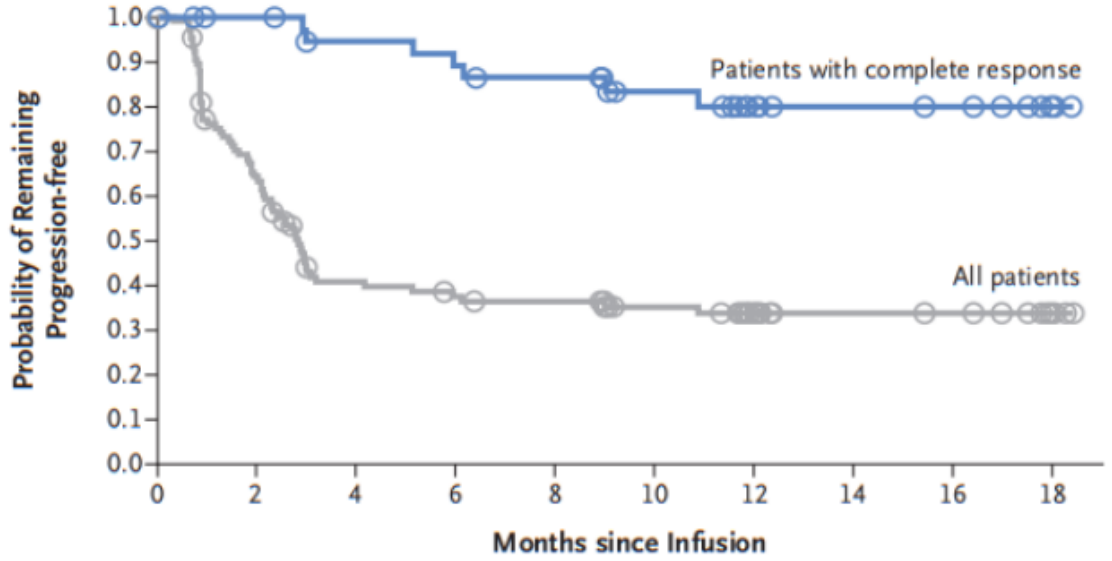
[a] Eligibility criteria confirmed.
[b] To prevent rapid disease progression during CTL019 manufacturing.
[c] To be completed 2 to 14 days prior to CTL019 infusion.
[d] Infusion conducted in- or out-patient at investigator discretion.
[e] Long-term follow-up for 15 years (NCT02445222).

RRDLBCL
Ineligible for or progressed after ASCT

JULIET: Survival

Primary End Point
ORR- 52%
CR- 40%
PFS 12m – 65%

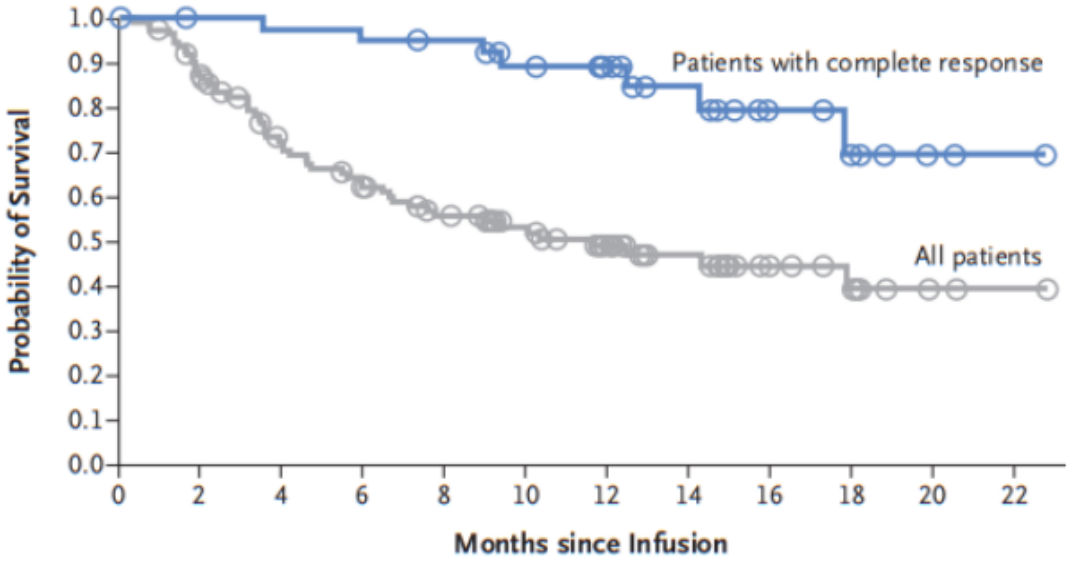
B Progression-free Survival



No. at Risk

Patients with complete response	40	39	39	36	35	35	33	31	31	29	24	23	15	9	9	9	8	7	2
All patients	111		65		38		34		32		25		16		10		9		3

D Overall Survival



No. at Risk

Patients with complete response	40	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111		94		71		60		50		40		28		19		11		8		2		1

Schuster et. al. *NEJM.* 2018

Juliet: Safety

	CRS	NE
All Grades	58%	21%
Grade ≥ 3	22%	12%
Time to Onset (median range)	3 (3-9) days	6 (1-17) days
Time to Resolution (Median)	7 days	14 days
Tocilizumab Usage	14%	
Corticosteroid Usage	10%	

- 3 deaths within 30 days of infusion, all from lymphoma progression
- University of Pennsylvania Grading System for CRS
- CTCAE v4.03 used for neurologic event (NE) grading

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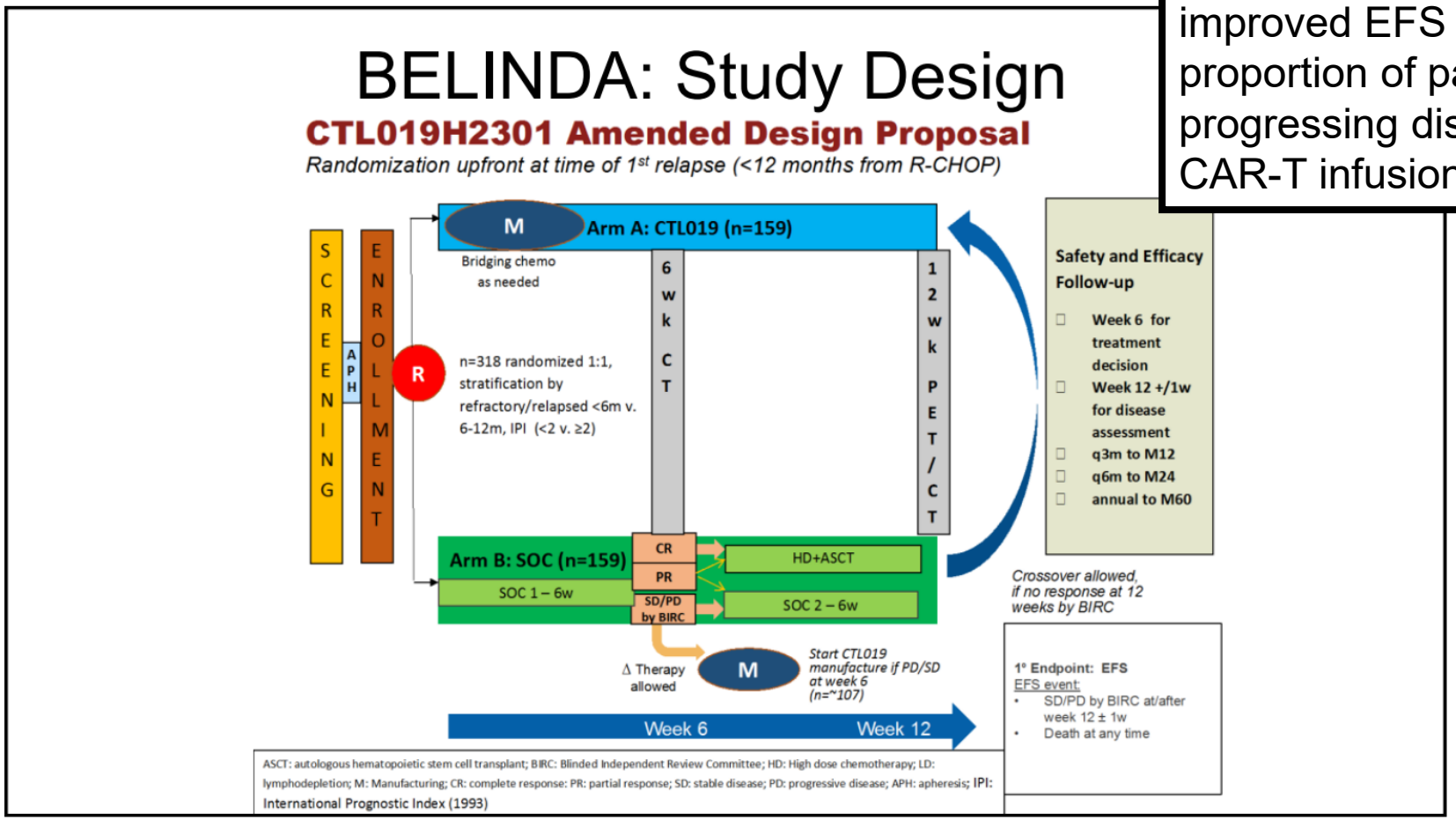
Schuster et al. NEJM 2018

Late Breaking Abstract ASH 2021

Did not meet endpoint of improved EFS due to high proportion of patients with progressing disease prior to CAR-T infusion



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Axicabtagene Ciloleucel as Second-Line Therapy for Large Cell Lymphoma

ZUMA-7

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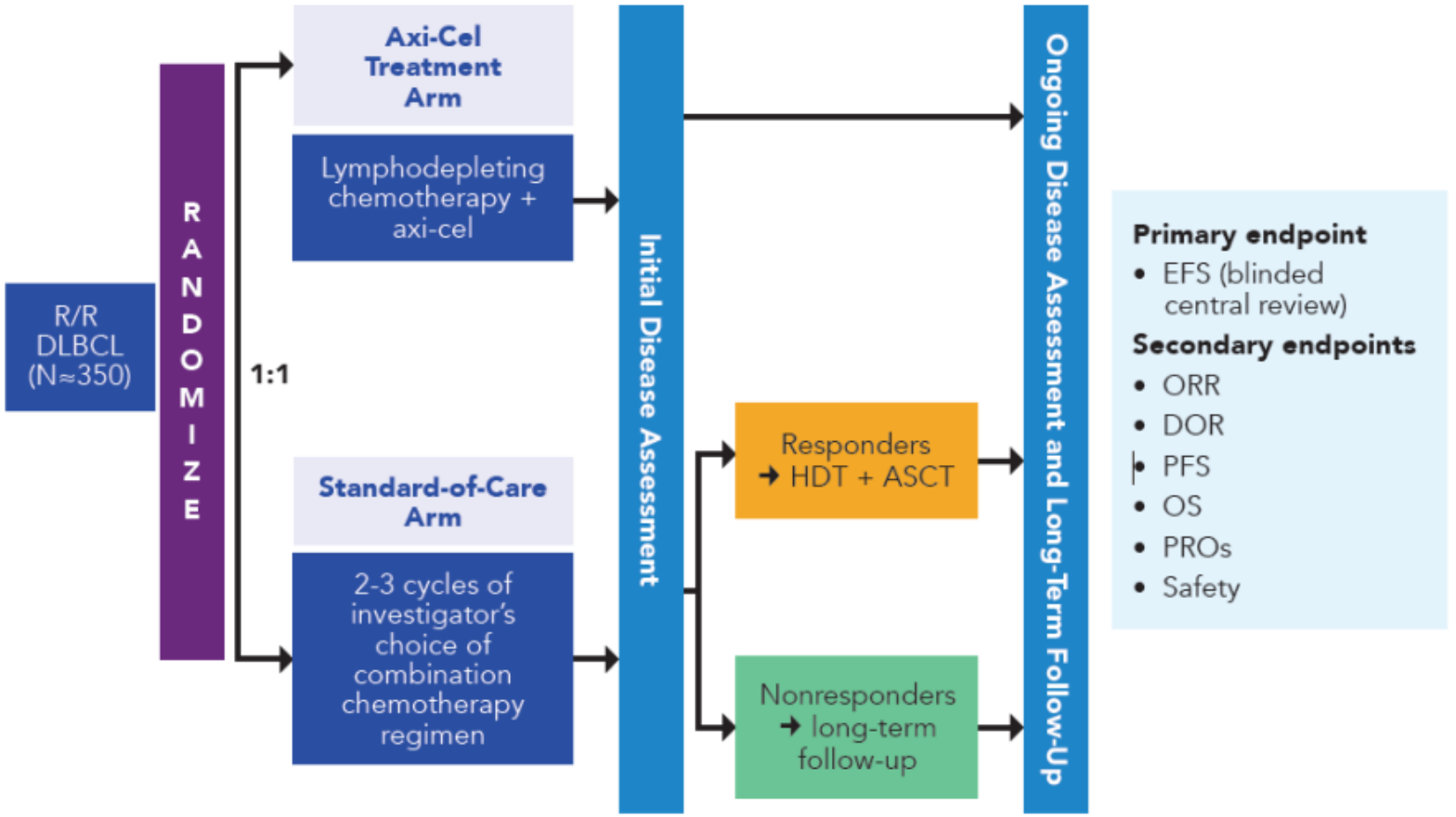
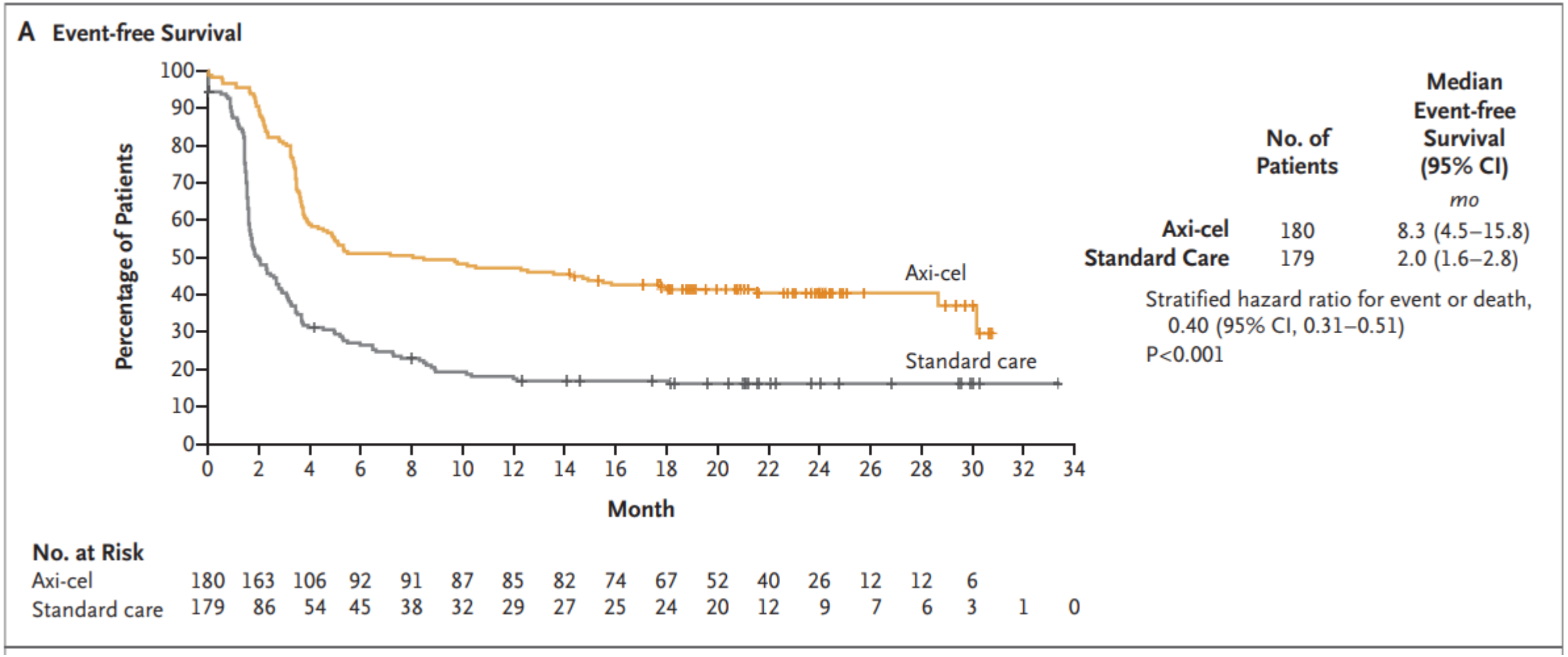
ZUMA 7: Axicabtagene Ciloleucel vs. Standard of Care in Subjects with R/R DLBCL

Eligible patients:
First relapse of DLBCL including tFL
- primary refractory
- SD
- PR with relapsed ≤ 12 months

Candidate for HDT/ASCT



No chemotherapy bridging is allowed.
ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; DOR, duration of response; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; HDT, high-dose therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.



- Median follow-up of 24.9 months
- ORR 83% vs 50%
- CR 65% and 32%
- OS 2 years 61% and 52%

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Locke et al. NEJM 2022

Zuma 7: Safety

	CRS	NE
All Grades	92%	60%
Grade ≥ 3	6%	21%
Time to Onset (median range)	3 (1-10) days	7 days
Time to Resolution (Median)	7 days	9 days
Tocilizumab Usage	65%	
Corticosteroid Usage	24%	

- 7 deaths: HBV reactivation, COVID19, Lung cancer, MI, PML, Sepsis
- CTCAE v4.03 used for CRS and neurologic event (NE) grading

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Locke et al, NEJM 2022

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

TRANSFORM

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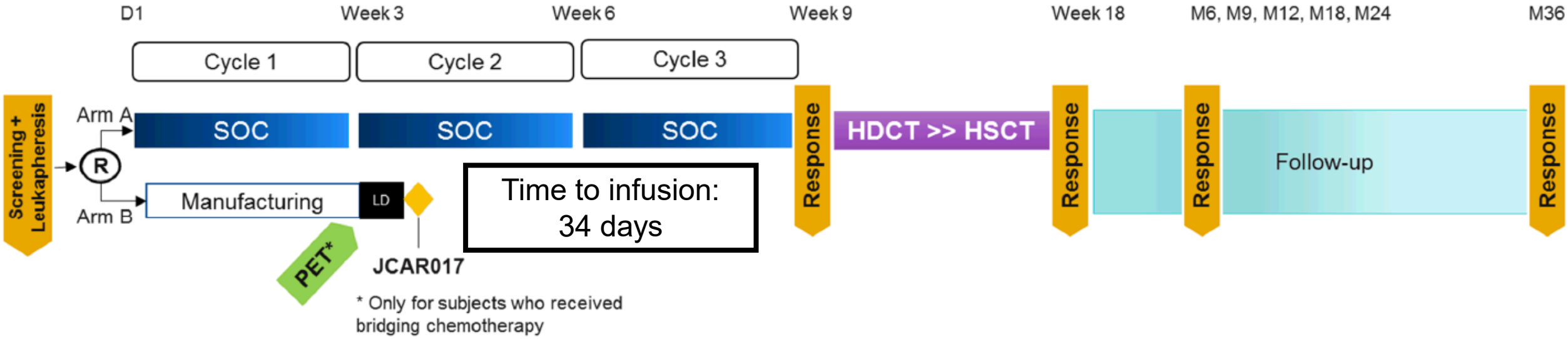
- RR DLBCL
- Candidates for ASCT

Transform: Study Design



Abbreviations: D = day; HDCT = high dose chemotherapy; HSCT = hematopoietic stem cell transplant; LD = lymphodepleting chemotherapy; M = month; PET = positron emission tomography; R = randomization; SOC = standard of care.

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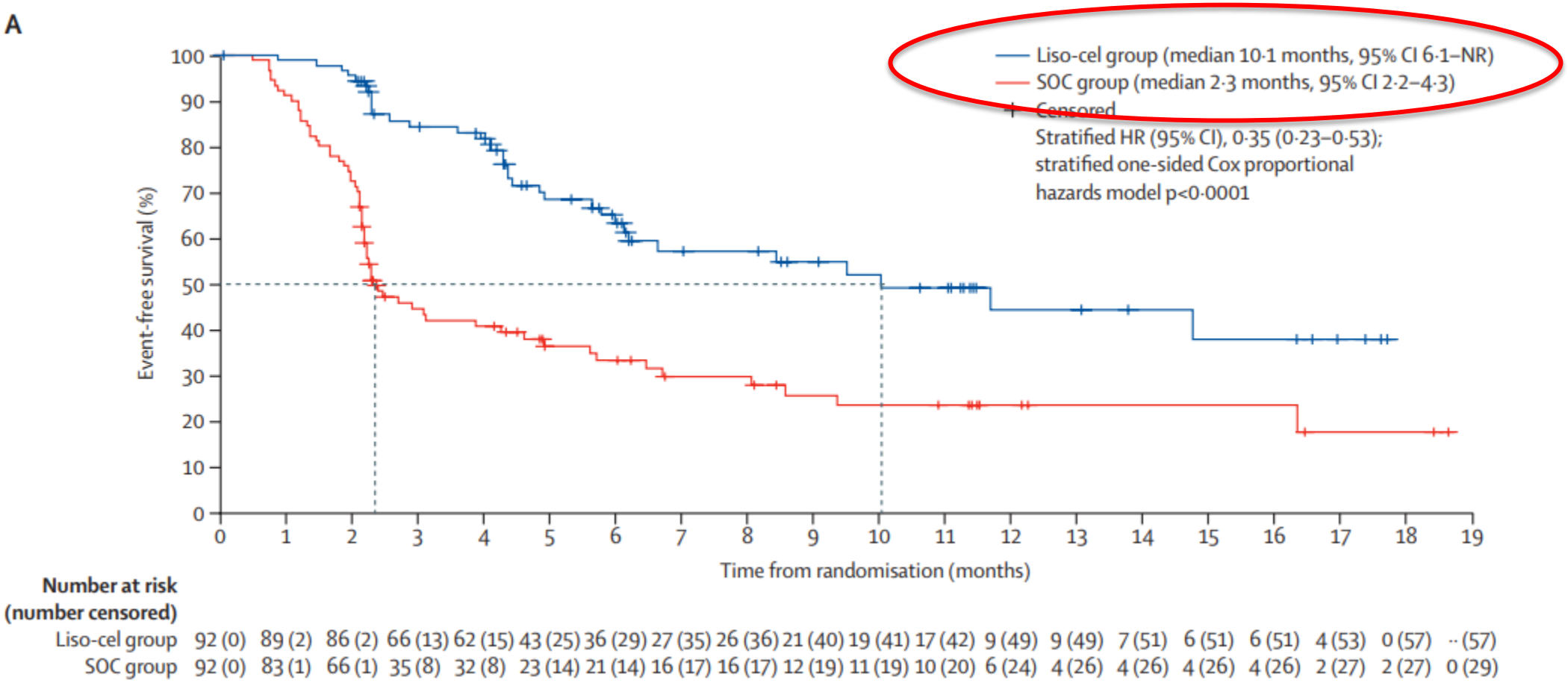

- Primary Endpoint Event Free Survival
- Median follow-up 6.2 months
- ORR 86% vs 48%
- CR 66% VS 39%

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Kamdar et al, Lancet 2022

Transform: Safety

	CRS	NE
All Grades	49%	12%
Grade ≥ 3	1%	4%
Time to Onset (median range)	5 (3-8) days	11(10-17) days
Time to Resolution (Median)	4 days	6 days
Tocilizumab Usage	9%	
Corticosteroid Usage	7%	

- 13 deaths lymphoma progression, COVID19, FTT, unknown
- Lee Criteria for CRS grading
- CTCAE v4.03 used for neurologic event (NE) grading

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Kamdar et al, Lancet 2022

	Axicabtagene ciloleucel		Tisagenleclecuel	Lisocabtagene maraleucel
Patients	111	180	111	92
Bridging Therapy	Glucocorticoids		Physicians Choice	RDHAP RGDP RICE
Lymphodepleting Chemotherapy	500 mg/m2 Cyclophosphamide 30mg/m2 Fludarabine		250 mg/m2 Cyclophosphamide 25mg/m2 Fludarabine	300 mg/m2 Cyclophosphamide 30mg/m2 Fludarabine
CAR-T Dose	2 x 10^6/kg		0.75 x 10^6/ kg	100 x 10^6/kg
Efficacy ORR CR	82% 54%	83% 65%	52% 40%	86% 66%
Toxicity CRS ICANS	13% 28%	6% 21%	22% 12%	1% 4%
Cost	373,000		475,000	432,000

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Large Cell Lymphoma

- Aggressive B-cell cancers with genetic/ clinical heterogeneity
- Autologous stem cell transplant – 30-40% durable PFS
- CAR-T therapy – 40% durable PFS

- Axicabtagene ciloleucel
- Tisagenlecleucel
- Lisocabtagene maraleucel

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B-cell non-Hodgkin Lymphomas

- Lisocabtagene maraleucel
  - High grade B cell lymphoma
  - Primary mediastinal large B-cell
  - Follicular lymphoma grade 3
- Brexucabtagene autoleucel
  - Mantle Cell Lymphoma
- Axicabtagene Ciloleucel
  - High grade B cell lymphoma
  - Primary mediastinal B-cell
  - Follicular lymphoma

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CAR T Cell Therapy in Multiple Myeloma

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FDA Approved Agents

- Idecabtagene vicleucel
  - March 2021
  - ≥ 4 lines of prior therapy including IMID, PI, CD38ab
- Ciltacabtagene autoleucel
  - February 2022
  - ≥ 4 lines of prior therapy including IMID, PI, CD38ab

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Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study

CARTITUDE -1

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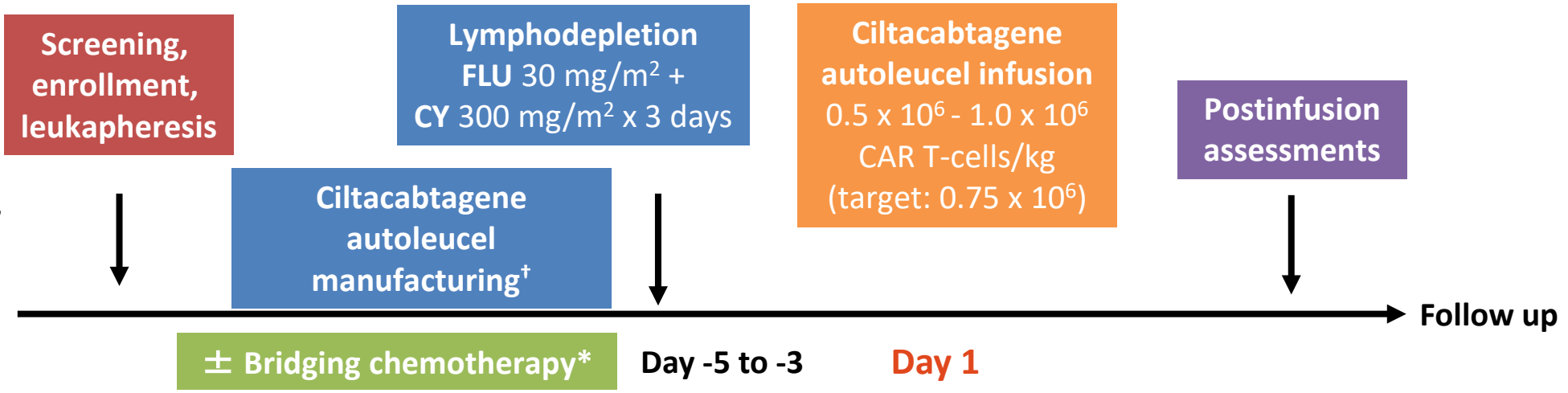
CARTITUDE-1: Study Design

Median turnaround time for CAR-T cells = 29 days

- Phase Ib/II trial conducted in the United States

Patients with R/R MM with measurable disease, ECOG PS ≤ 1; ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD (N = 113)



*73 patients received bridging therapy with previously used agents to maintain at least SD.
0 patients d/c due to manufacturing failure.

- Of 113 patients, 97 received ciltacabtagene autoleucel; phase Ib (n = 29); phase II (n = 68); median dose: 0.71 x 106 (0.51–0.95 x 106) CAR+ viable T-cells/kg

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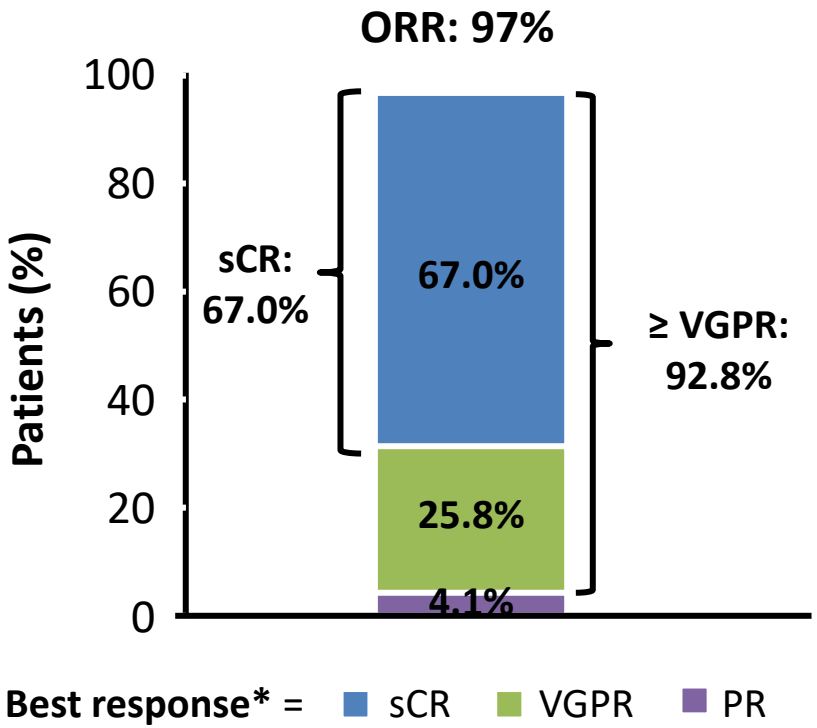
Madduri. ASH 2019. Abstr 577. Madduri. ASH 2020. Abstr 177.

CARTITUDE-1: ORR and MRD Assessment



- Time to response 1 month
- PFS 12 m: 77%

MRD Status	N	Evaluable Patients* (%) (n = 57)	All treated Patients (%) (N = 97)
Overall MRD neg	53	93.0	54.6
MRD neg and sCR	33	57.9	34.0
MRD neg and ≥ VGPR	49	86.0	50.5

- Median time to first response: 1 mo (range: 0.9-8.5 mos)
  - 70 (72.2%) patients have ongoing responses
- MRD 10^{-5} negativity achieved by 93.0% of evaluable patients
  - Median time to MRD 10^{-5} negativity: 1 mo (range: 0.8-7.7)

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Madduri. ASH 2020. Abstr 177. Berdeja et al, Lancet 2021.

CARTITUDE 1: Safety

	CRS	NE
All Grades	95%	21%
Grade ≥ 3	4%	9%
Time to Onset (median range)	7 (5-8 days)	8 (6-8 days)
Time to Resolution (Median)	4 days	4 days
Tocilizumab Usage	69%	4%
Corticosteroid Usage	22%	9%

- 14 deaths Sepsis, CRS, HLH, Lung Abscess, Respiratory Failure, Neurotoxicity, Progressive Disease, Pneumonia, AML
- Lee Criteria for CRS grading
- CTCAE v5 used for neurologic event (NE) grading

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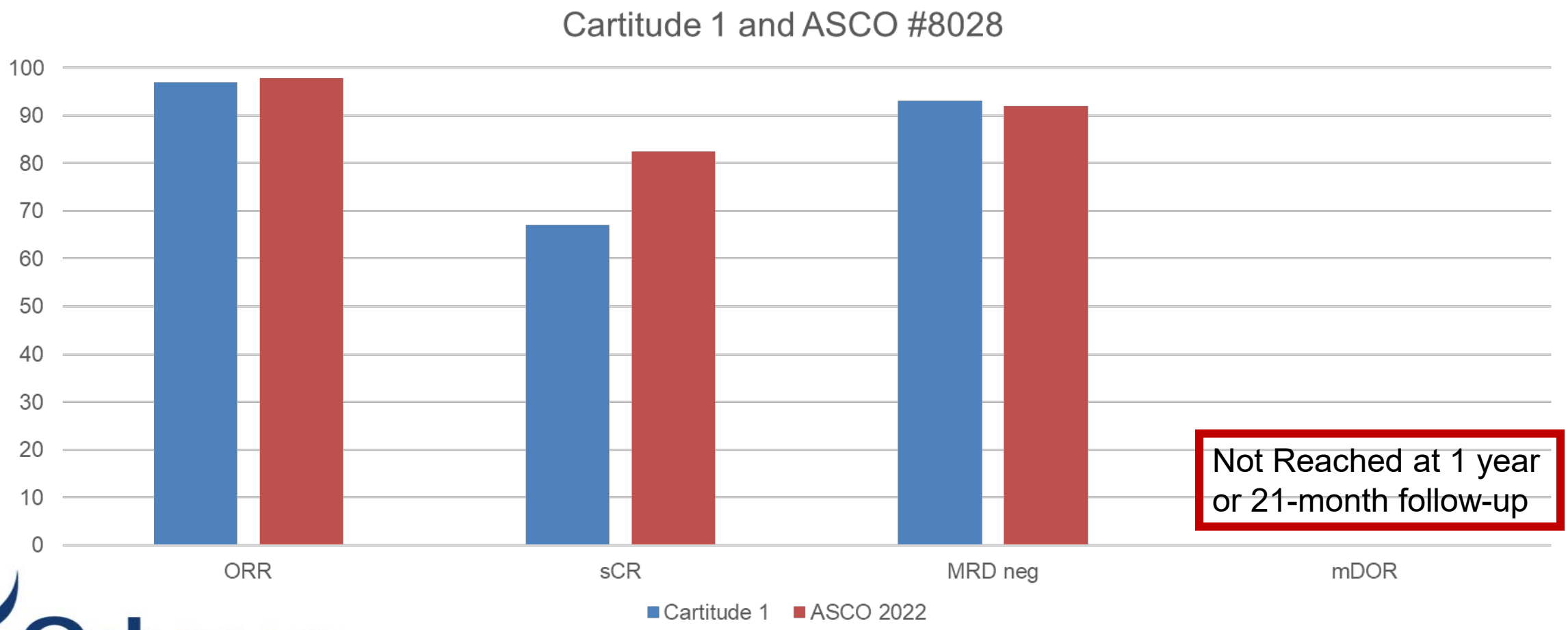
Berdeja et al, Lancet 2021

ASCO 2022 Update



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Efficacy and safety of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR T-cell therapy, in patients with progressive multiple myeloma (MM) after one to three prior lines of therapy.

CARTITUDE-2

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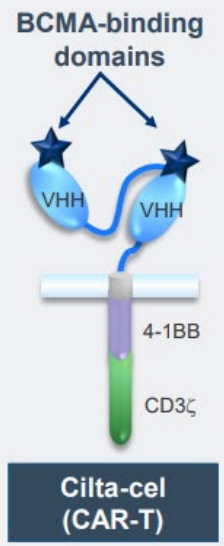
CARTITUDE-2

Cohort A: 1 – 3 prior lines, lenalidomide refractory RRMM

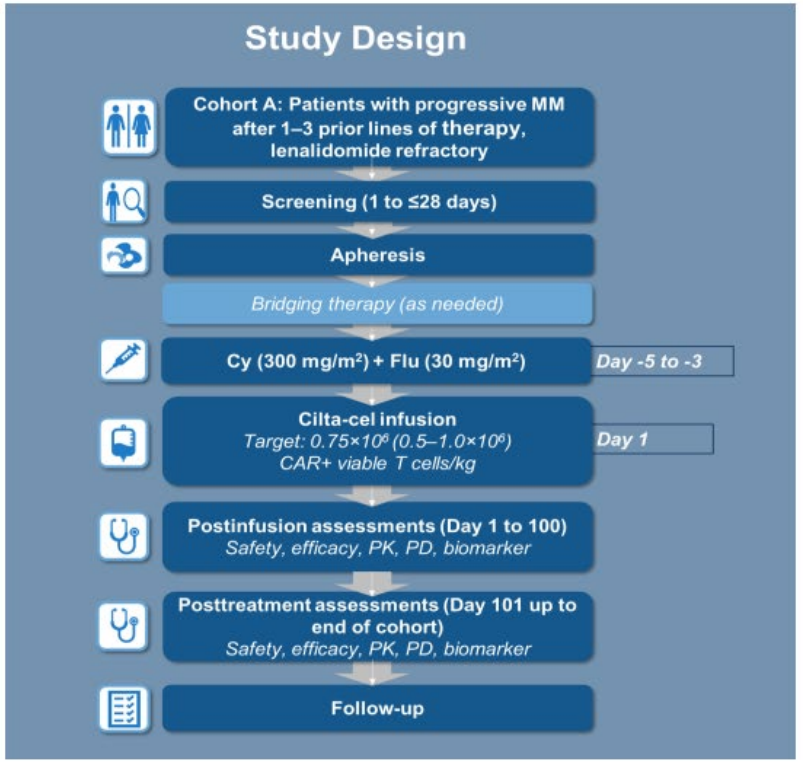
- **CARTITUDE-2 is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel in patients with multiple myeloma in various clinical settings**



Cohort A:
- Cohort A patients had progressive MM after 1–3 prior lines of therapy, and were refractory to lenalidomide
- Despite advances continued unmet need with mPFS of 9.9 months (DPd)[1]

Primary objectives
- Minimal residual disease (MRD) 10^{-5} negativity

Secondary objectives
- ORR, duration of response, time and duration of MRD negativity, and incidence and severity of adverse events



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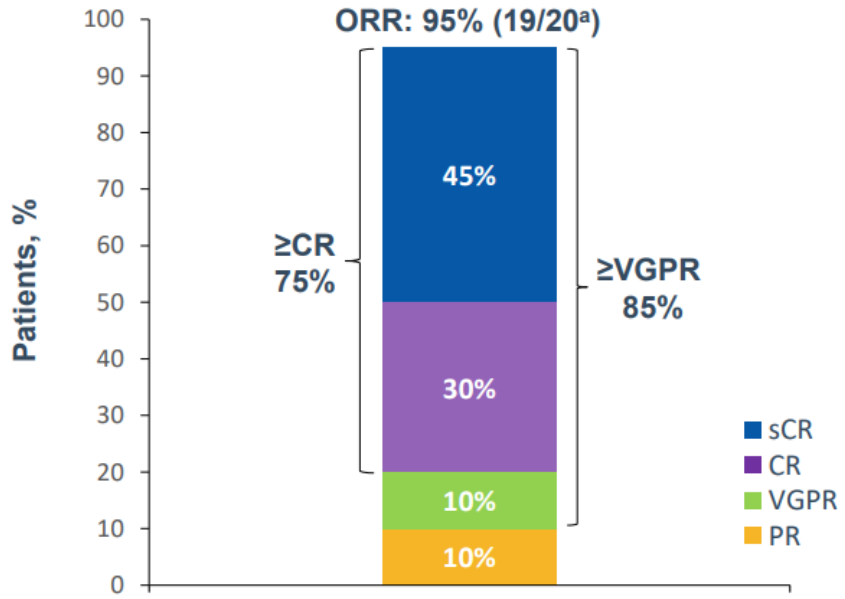
JCO 2021; 39(15): 8013

CARTITUDE-2

- Cohort A included 20 patients who had progressive MM after 1–3 prior lines of therapy and were refractory to lenalidomide
- Median prior lines of therapy: 2 (range, 1-3); 1 patient treated in an outpatient setting



- No progression of disease at median follow-up of 5.8 months (range 2.5-9.8)
- All patients (n=4) with MRD-evaluable[b] samples at the 10^{-5} threshold were MRD negative at data cut-off
- The safety profile was manageable
  - CRS occurred in 85% (n=17); mostly grades 1/2; median time to CRS onset was 7 days (range, 5–9)
  - Neurotoxicities occurred in 20% (n=4) of patients; no grade ≥3; no incidence of movement and neurocognitive TEAEs
  - 1 death occurred 100 days after infusion due to COVID-19 (assessed as tx related by the investigator)

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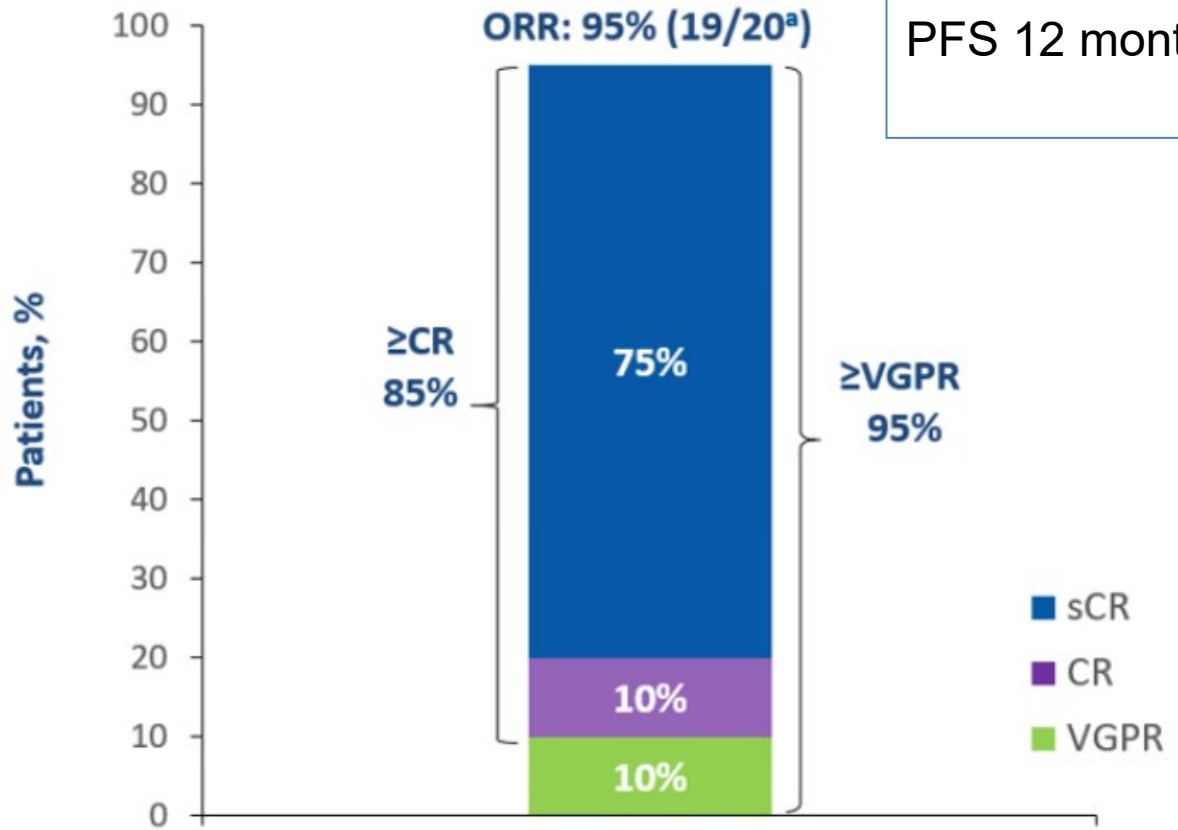
JCO 2021; 39(15): 8013

CARTITUDE-2 #3866

ASCO 2022 #8020

<u>17.1 months follow-up</u>
ORR – 95%
CR – 90%
PFS 12 months – 75%



2021 ASH Annual Meeting abstract #3866

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

KARMMA

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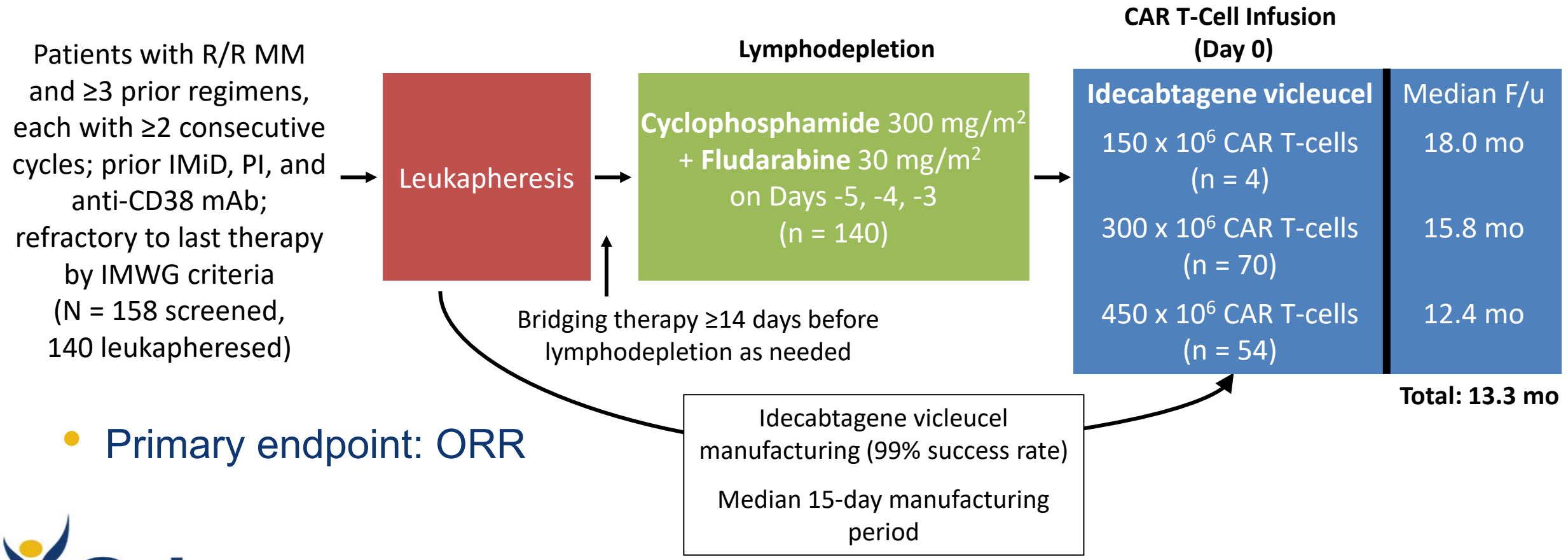
Phase II KarMMa Update: Idecabtagene Vicleucel in R/R MM, Study Design

- Multicenter, single-arm phase II trial



- Primary endpoint: ORR

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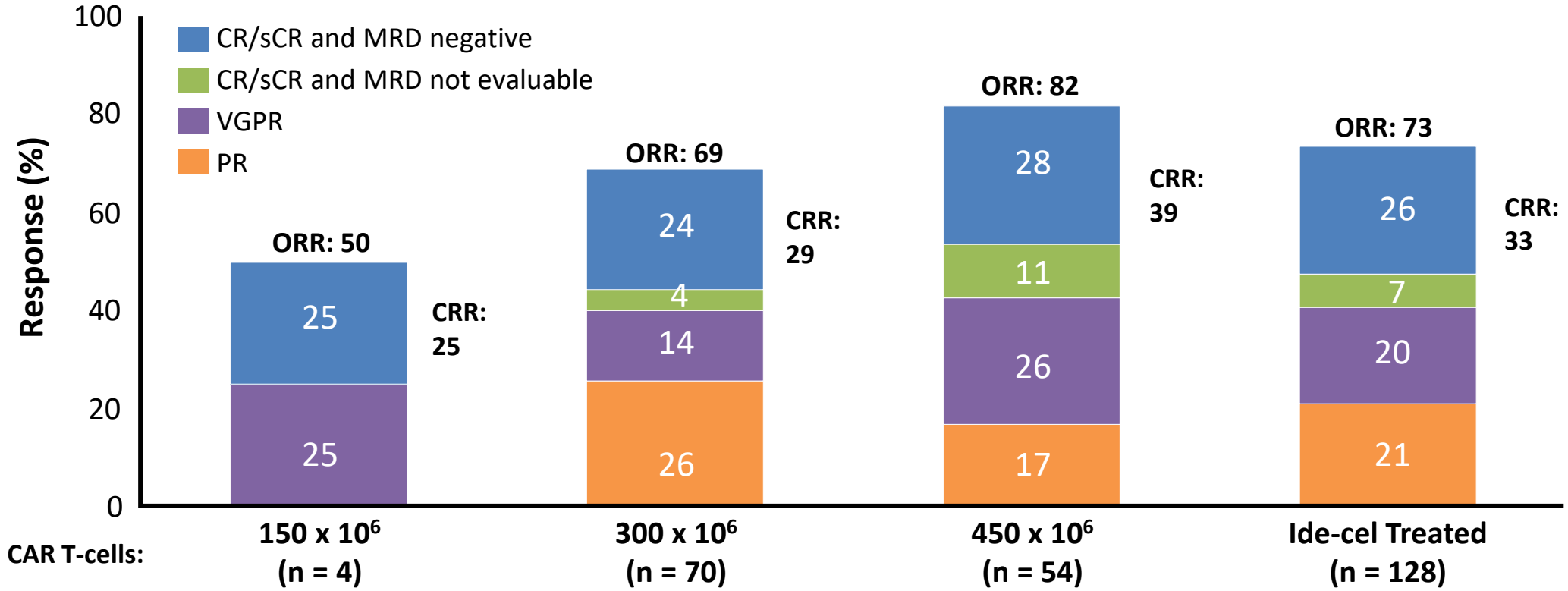
Anderson. ASCO 2021. Abstr 8016. Munshi. NEJM. 2021;384:705.

Phase II KarMMa Update: Clinical Response of Idecabtagene Vicleucel in R/R MM



- ORR: 73% ; CR (CR/sCR): 33%
- Median time to first response: 1.0 mo (range: 0.5-8.8); median time to CR: 2.8 mo (range: 1.0-11.8)
- Median follow-up of 13.3 mo across target dose levels

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Anderson. ASCO 2021. Abstr 8016. Munshi. NEJM. 2021;384:705.

ASH 2021 Update

Outcomes for patients receiving sAMT and anti-BCMA therapy

Parameter	sAMT (n = 68)	anti-BCMA (n = 11)
ORR to ide-cel, % (95% CI)	76 (66–87)	91 (74–100)
CR rate to ide-cel, % (95% CI)	26 (16–37)	55 (25–84)
PFS with ide-cel, median (95% CI), months	6.1 (4.9–10.9)	12.1 (7.5–12.3)
Duration of first sAMT, median (range),[a] days	44 (1–533)[b]	48 (20–305)
Duration of all sAMT, median (range),[a] days	215 (1–757)[b]	305 (113–486)
PFS2, median (95% CI), months	13.6 (10.1–16.0)	15.5 (14.3–19.0)
OS, median (95% CI), months	24.8 (19.4–31.2)	31.0 (24.0–NE)

[a]Duration of sAMT is date of last dose of last AMT minus date of first dose of first sAMT. If last date not known then last alive date or death date was used; [b]For this group, n = 67.
CR, complete response; NE, not estimable; ORR, overall response rate.

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2021 ASH Annual Meeting abstract #2743

		Idecabtagene	Ciltacabtagene
Patients		124	97
Bridging Therapy		Physicians Choice (88%)	Physicians Choice
Lymphodepleting Chemotherapy		300mg/m2 Cyclophosphamide 30mg/m2 Fludarabine	300mg/m2 Cyclophosphamide 30mg/m2 Fludarabine
CAR-T Dose		450 x 10^6/kg	0.75 x 10^6/ kg
Efficacy	ORR CR MRD-	73% 33% 28%	97% 78% 58%
Toxicity	CRS ICANS	6% 3%	5% 2%*
Cost		419,000	465,000

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CAR-T in Multiple Myeloma

- Very high overall response rates in heavily pretreated populations
- Responses deepen over-time, updates in longer follow-up of CARTITUDE and KARRMA studies will be important
- Rates of severe CRS and neurotoxicity have been low suggesting outpatient administration will become feasible

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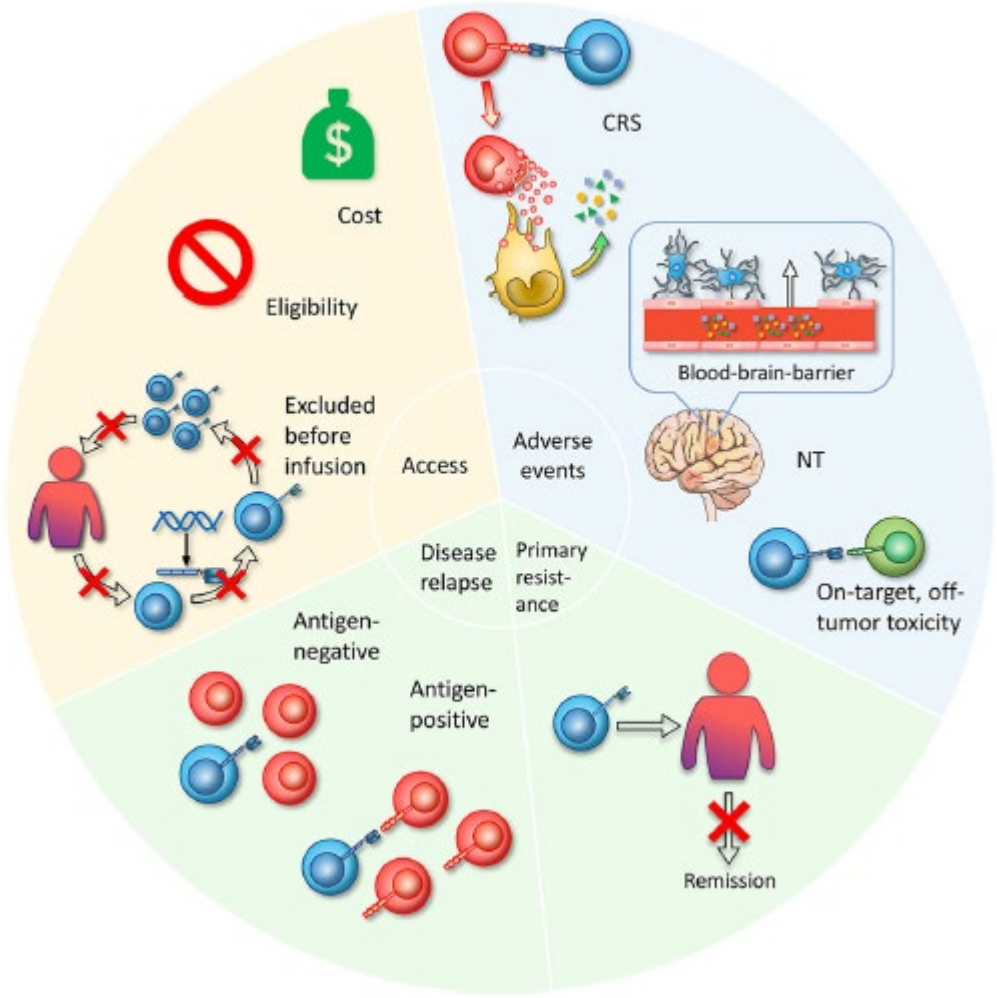
CHALLENGES AND FUTURE DIRECTIONS



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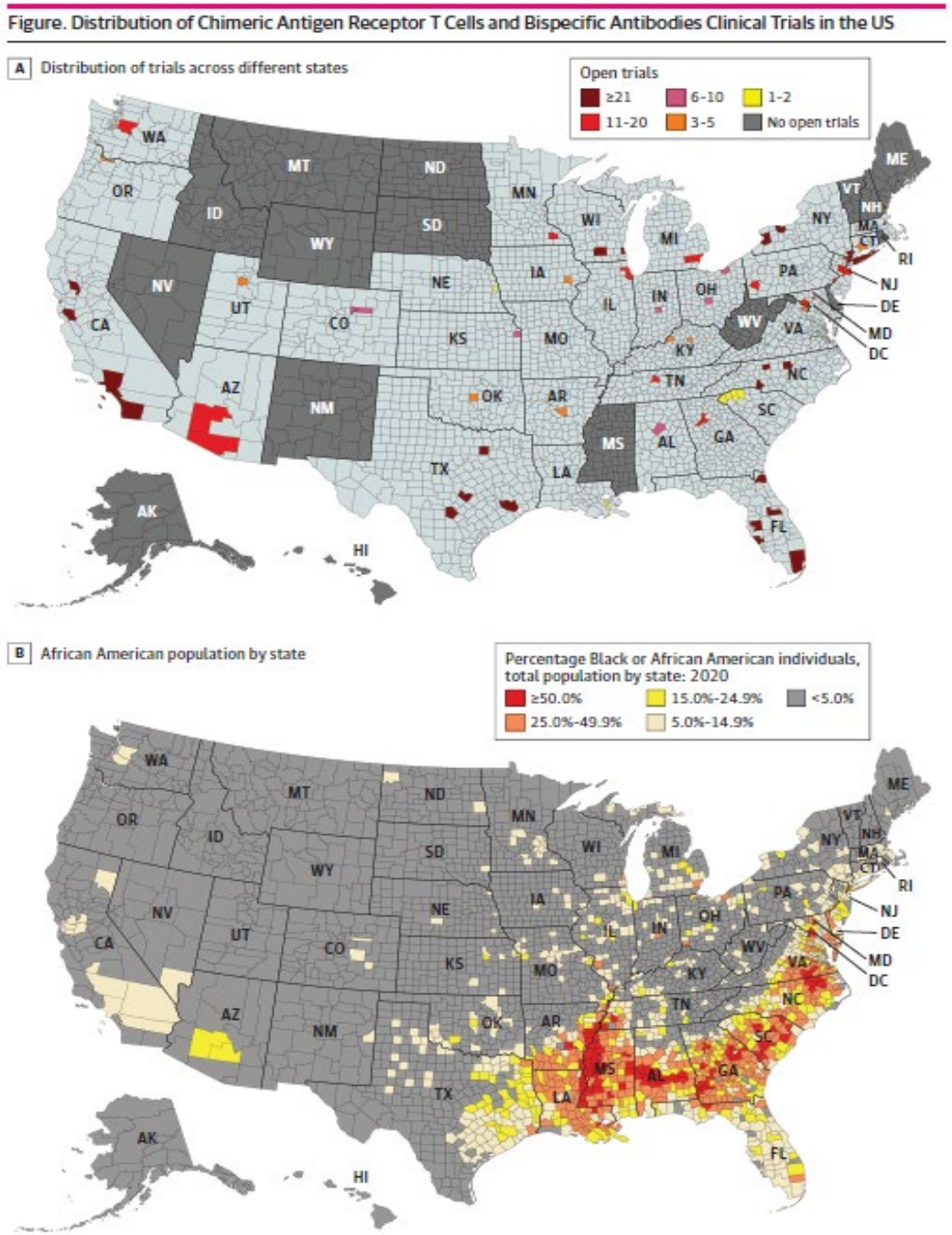
CAR-T Access in Myeloma

- The South has the most clinical trial sites for CAR-T and BiTE therapies
- According to Census Bureau data only 35% of the country's Black population live in a county/parish with a CAR-T trial.



JAMA Network Open. 2022;5(8):e2228877.

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Current Challenges in CAR-T Programs

- Availability

News > Medscape Medical News > Features

Patients Waiting Months for 'Last Chance' CAR T-Cell Therapy

Roxanne Nelson, RN, BSN

July 14, 2022

- Fludarabine Shortage

Transplant Cell Ther. 2022 Aug 6;S2666-6367(22)01518-4. doi: 10.1016/j.jtct.2022.08.002. Online ahead of print.

Perspective: An International Fludarabine Shortage: Supply Chain Issues Impacting Transplantation and Immune Effector Cell Therapy Delivery

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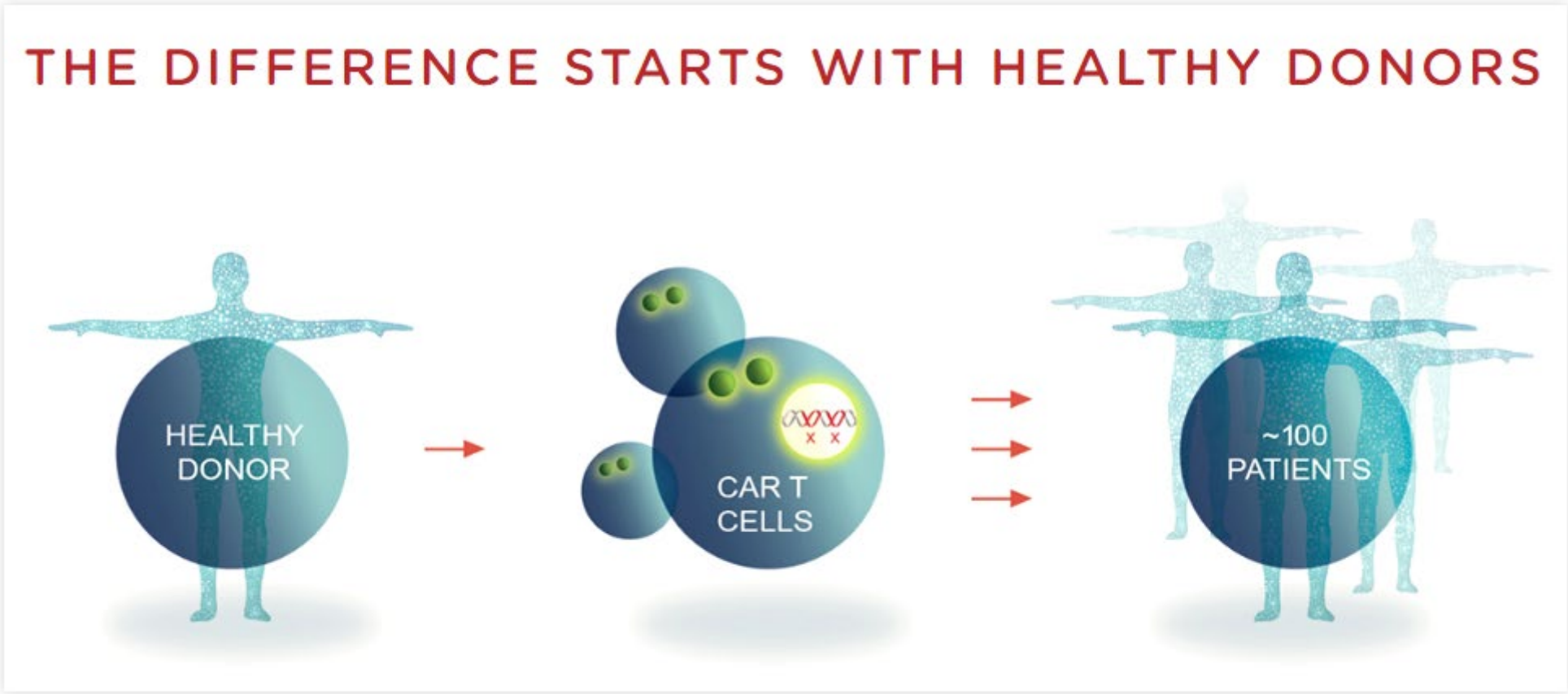
Future Directions



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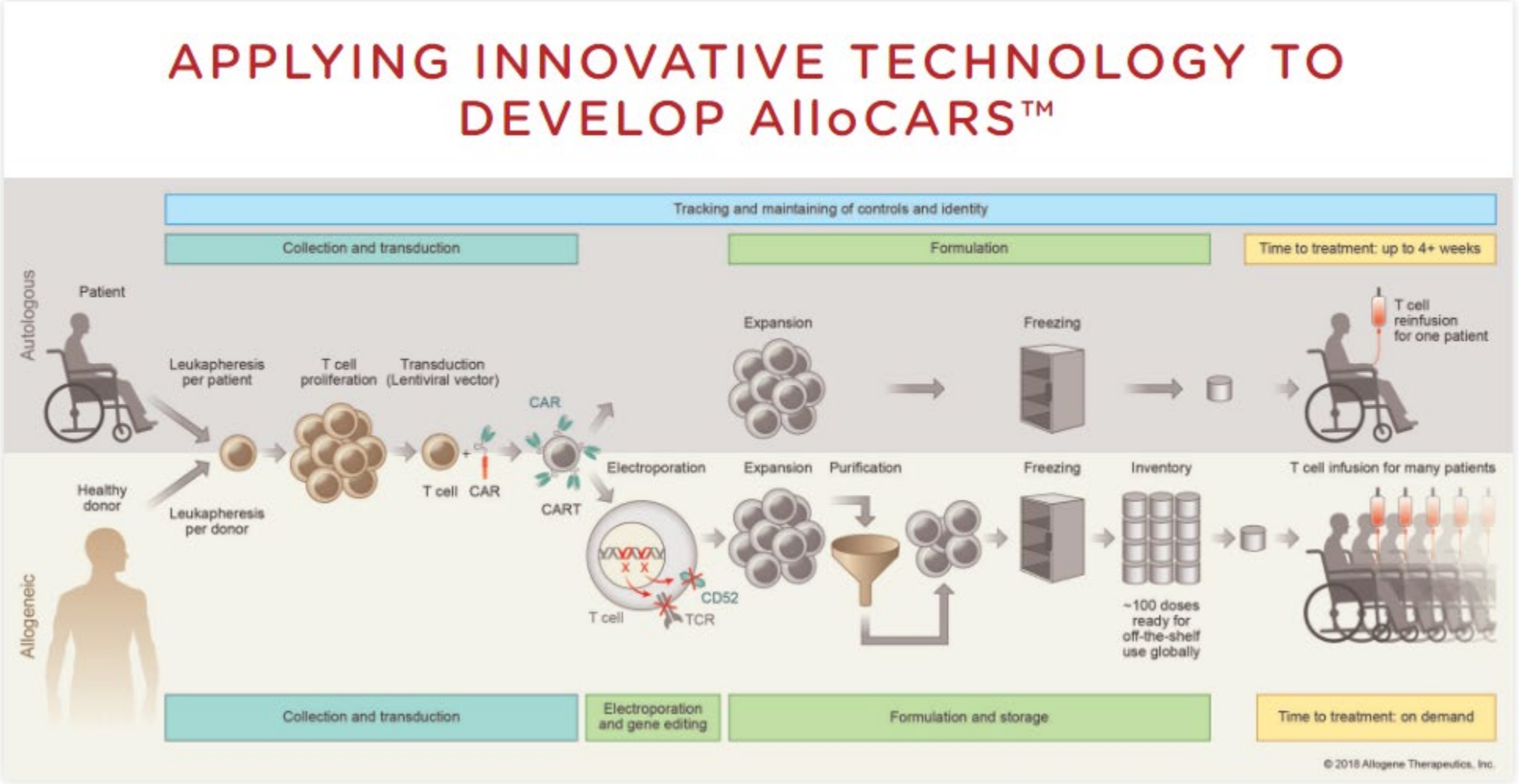
Future Directions



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Thank you and Questions.

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