FLASCO Fall 2023 Session

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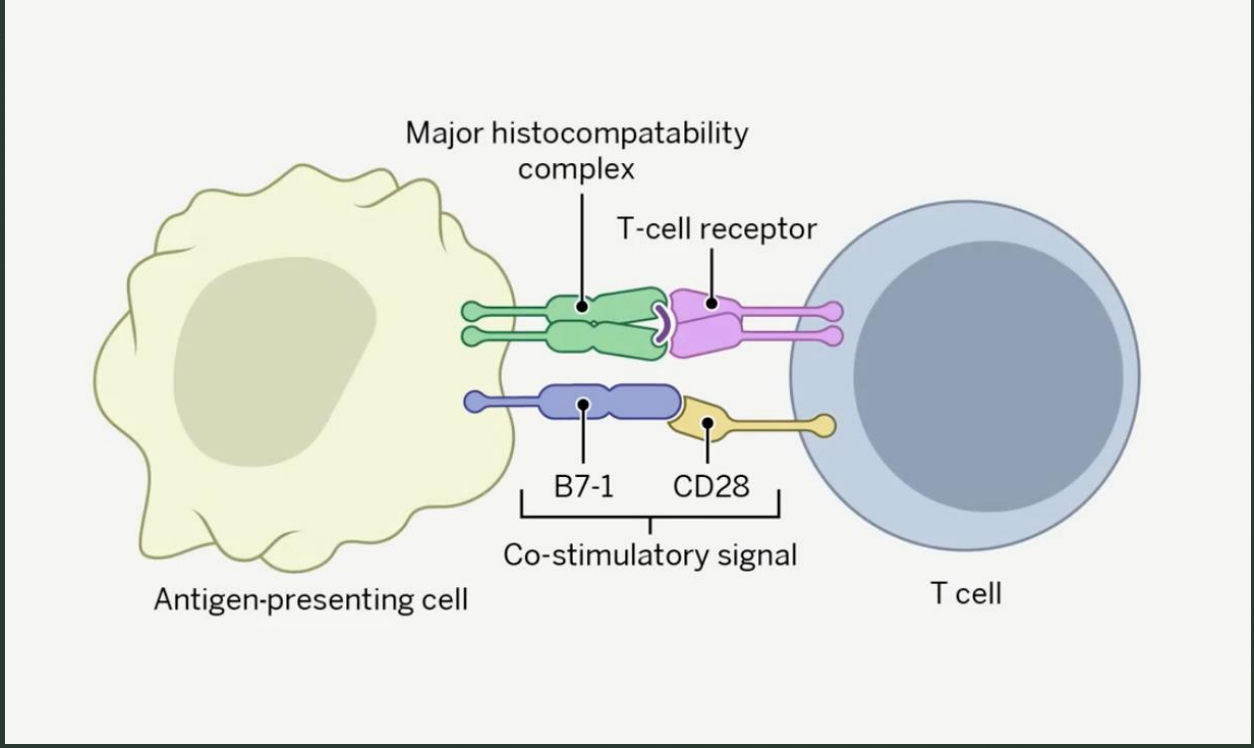
Saturday October 21, 2023

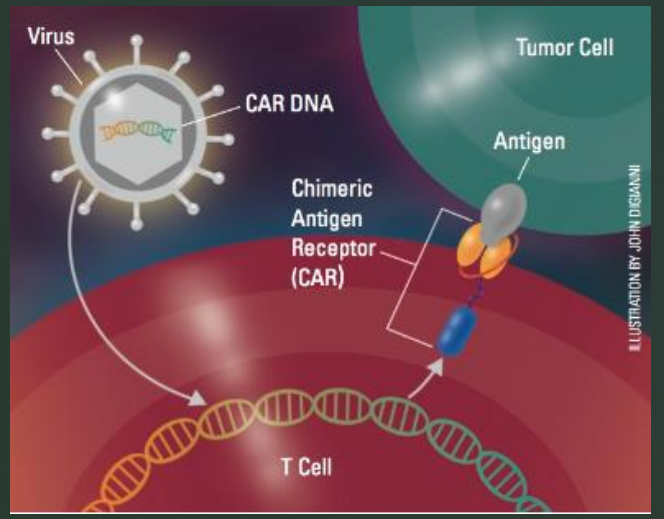
CAR T Innovations

Practice Changing Updates

Cytotoxic T Cells



Chimeric Antigen Receptor (CAR) T-Cell



- The Chimera (Greek mythology) – a fire-breathing hybrid creature merged from a lion, a goat, and a snake.
- The CAR T-Cell is the merged form of cytotoxic T cell and antibodies

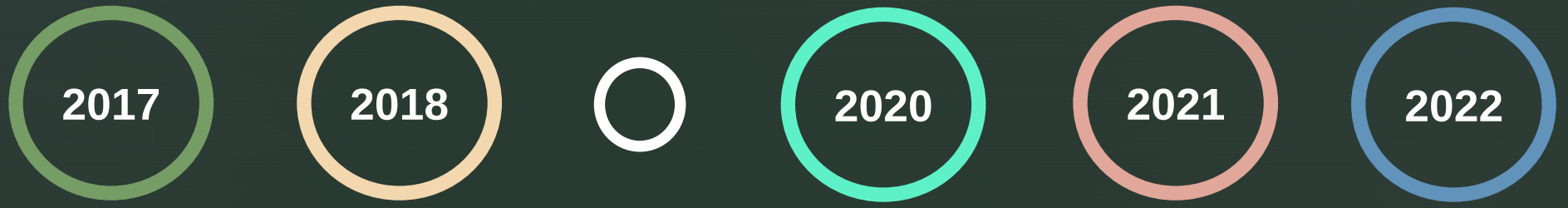
Pivotal Anti-CD19 CAR T-cell Trials

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND NHL 001[4]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Study phase	II	II	I/II
Patient population	DLBCL NOS, TFL, PMBCL	DLBCL NOS, TFL	DLBCL, Transformed iNHL, PMBCL
Patients apheresed/ treated, n	111/101	165/111	344/269*
Bridging therapy	None allowed	92%	59%
ORR, % CR, %	82% 54%	52% 40%	73% 53%

*256 included in the efficacy-evaluable set.

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

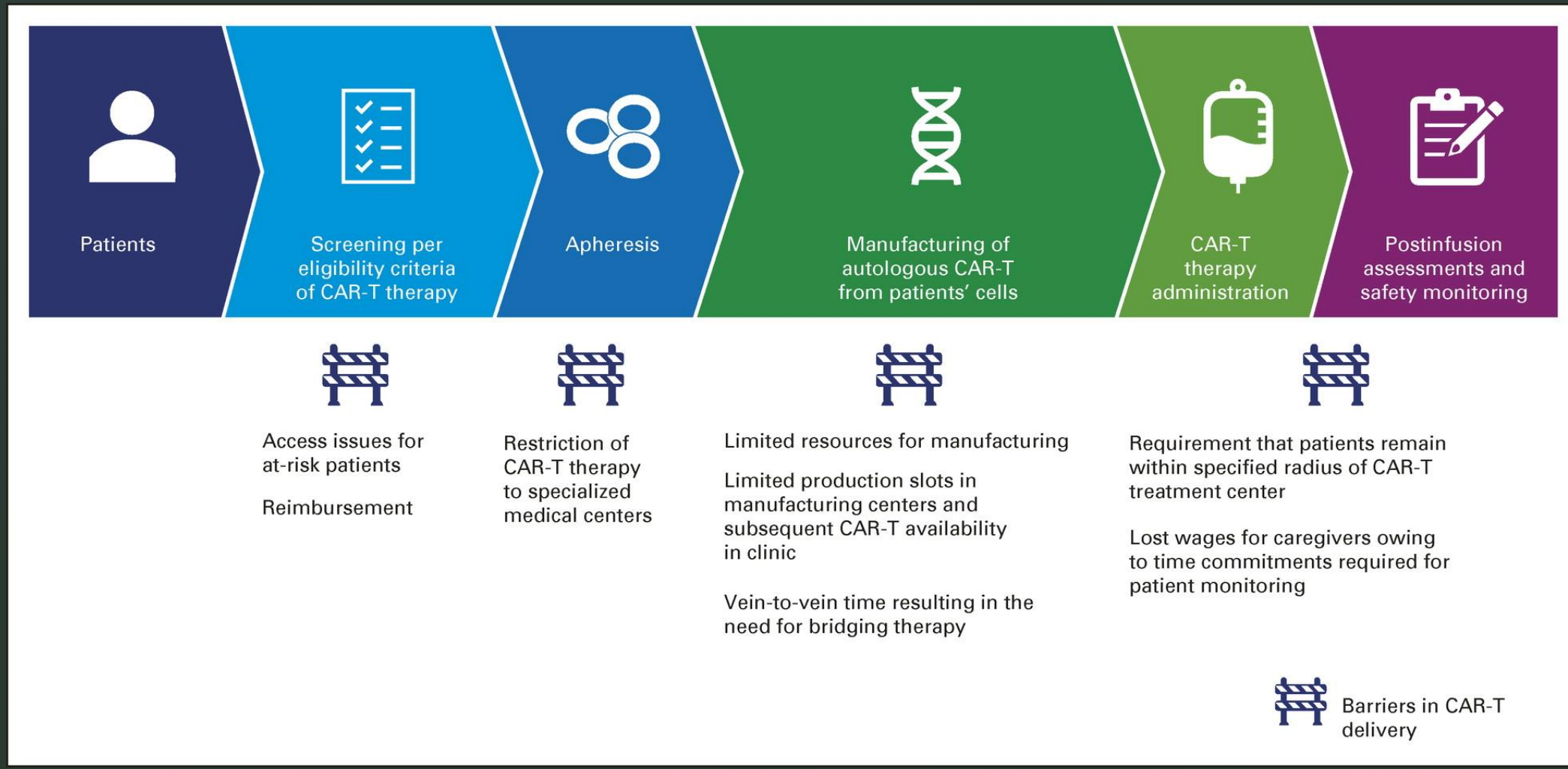
Timeline of CAR T Therapy FDA Approvals



	2017	2018	2020	2021	2022
ALL	Tisagenlecleucel 08/2017				
LBCL	Axicabtagene ciloleucel 10/2017	Tisagenlecleucel 05/2018		Lisocabtagene maraleucel 02/2021	
MCL			Brexucabtagene autoleucel 07/2020		
FL				Axicabtagene ciloleucel 03/2021	Tisagenlecleucel 05/2022
MM				Idecabtagene vicleucel 03/2021	Ciltacabtagene autoleucel 02/2022

Adapted from Pan, K., et al. *J Exp Clin Cancer Res* **41**, 2022) https://doi.org/10.1186/s13046-022-02327-z

Barriers to CAR T

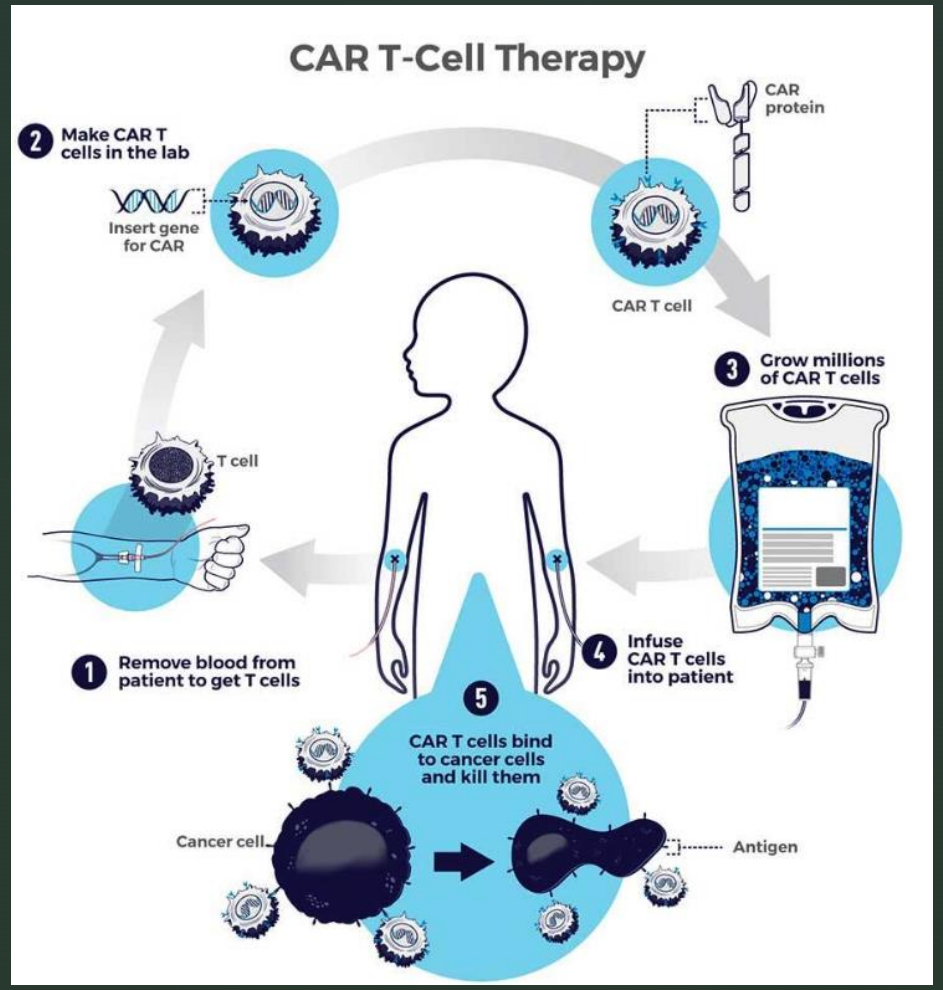


DOI: 10.1200/OP.22.00315 *JCO Oncology Practice* 18, no. 12 (December 01, 2022) 800-807.

CAR T Challenges

- Manufacturing time, costs, and complex logistics
- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)
- Toxicity and safety

The CAR T-Cell Process



Cancer.gov

Time, Money, Logistics

- In the JULIET, TRASCEND-NHL-001, and ZUMA-1 trials, 31%, 15%, and 9% of patients, respectively, had leukapheresis but did not receive CAR-T therapy.
- "Financial toxicity" – cost can go upwards of $500k per dose
- Manufacturing failures
- Solutions: Reduced manufacturing times and cost, off the shelf CAR T or NK cells, decentralized manufacturing

Mikhael, et al. JCO Onc Clin Practice 2022

“Off the shelf” Engineered Cellular Products: Allogeneic Therapies

Advantages

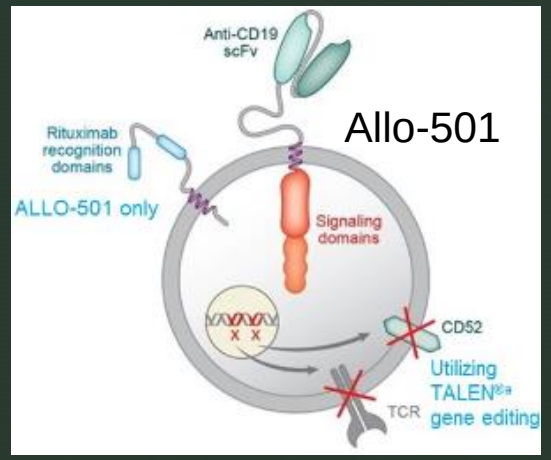
- “Off-the-shelf”, readily available
- More cost-effective
- Scale to larger numbers
- Expand access to therapy (ie, leukopenic patients)
- Healthy donor cells = more T cell fitness

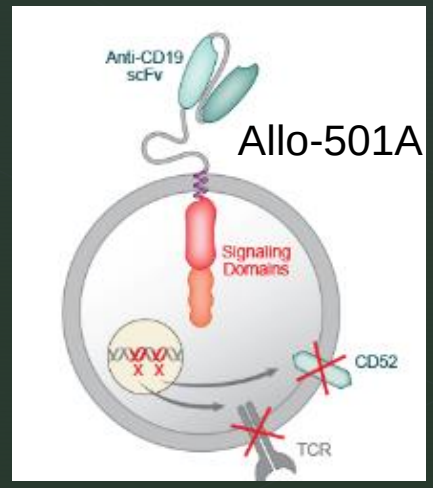
Disadvantages

- Risk of graft vs host disease (GvHD)
- Host allorejection
- Limited data available

Allogeneic CAR T Cells: Current Trials of Interest

- Phase 1 ALPHA/ALPHA 2 for ALLO-501 and ALLO-501A
- An off-the-shelf, anti-CD19 allogeneic CAR T cell product.
  - ALLO-501 is similar to ALLO-501A except for the inclusion of a rituximab off switch.
- Manageable safety profile, tolerability with no DLTs and preliminary efficacy in CAR T naïve pts.





ALPHA/ALPHA 2 Phase I Updates

- Update on 12 of 33 CAR T naïve pts with r/r LBCL received a 3 day Flu/Cy lymphodepletion + 90 mg of Allo-647 + single dose of ALLO-501 or ALLO-501A

Baseline Characteristics for Patients Treated With Selected Phase 2 Regimen (N=12)	
Age, median	60 years
Stage IV disease	67%
ECOG PS of 1	92 %
Baseline LDH > ULN	67 %
IPI score >2	50 %
Germinal center subtype	50 %
Double or triple hit	33 %
Median # prior regimens	3
Prior transplant	50%
Extranodal disease	58%

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; IRR = infusion-related reactions; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Adverse Events of Interest	All r/r CAR T-naïve LBCL[a] (N=33)		Patients Treated With Phase 2 Selected Regimen (N=12)	
	All Gr n (%)	Gr≥3 n (%)	All Gr n (%)	Gr≥3 n (%)
CRS	8 (24)	0	4 (33)	0
ICANS	0	0	0	0
Neurotoxicity	13 (39)	2 (6)	4 (33)	0
GvHD	0	0	0	0
IRR	16 (49)	3 (9)	8 (67)	0
Infection[b]	19 (58)	5 (15)	8 (67)	1 (8)
Prolonged Gr≥3 Cytopenia	-	4 (12)	-	2 (17)

CRS = cytokine release syndrome; GvHD = graft-versus-host disease; ICANS = immune effector cell-associated neurotoxicity syndrome; IRR = infusion-related reactions.
[a] All patients received product manufactured in the same way as the selected Phase 2 process. [b] Infections include low grade viral infections, some of which are detected on weekly surveillance. No fatal infections or PJP/MAC/TB were seen.

Locke, et al. Phase 1 Results with Anti-CD19 Allogeneic CAR T ALLO-501/501A in Relapsed/Refractory Large B-Cell Lymphoma (r/r LBCL). *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 2517-2517.

ALPHA/ALPHA 2 Phase I Updates

- Efficacy results (ASCO 2023: Locke, et al) of Phase 2 regimen:
  - ORR 67% (8/12), CR 58% (7/12)
  - All patients followed through month 6:
    - 5 patients sustained CR
    - 4 of 5 remain in CR at data cut off April 20,2023
    - Median duration of response of 23.1 months, 3 remain in remission at 24+ months with the longest at 31+ months
- Phase 2 ALPHA2 trial enrolling
- ALPHA 3 ongoing to study ALLO-501/501A in earlier line DLBCL

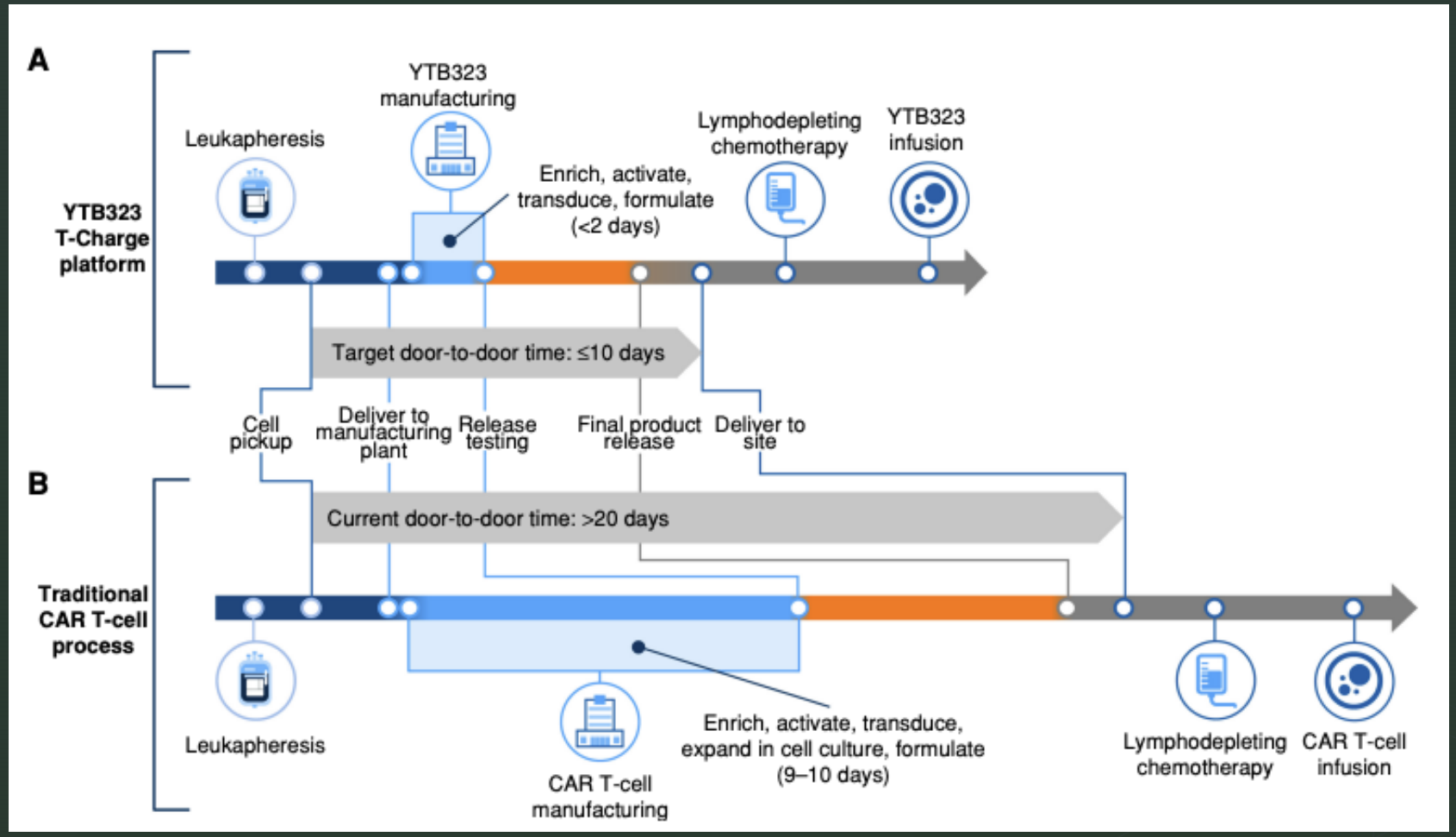
Locke, et al. Phase 1 Results with Anti-CD19 Allogeneic CAR T ALLO-501/501A in Relapsed/Refractory Large B-Cell Lymphoma (r/r LBCL). *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 2517-2517.

Rapid CAR T manufacturing

- YTB323 - A novel autologous CD19- directed CAR T-cell therapy expressing the same validated CAR as tisa-cel, manufactured using a next generation platform (“T-Charge”) in <2 days
- Pre-clinical data in mice showed enhanced expansion ant anti-tumor activity at doses 25-fold lower than tisa-cel.
- Preliminary phase I data reported Sept 2023 (AACR): YTB323 showed promising overall safety,

Dickinson, et al. A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. *Cancer Discov* 1 September 2023; 13 (9): 1982–1997. https://doi.org/10.1158/2159-8290.CD-22-1276

Rapid CAR T manufacturing



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YTB323 Safety & Efficacy

- Phase I trial
  - 20 pts with r/r DLBCL received YTB323 at DL1 (n=4) or DL2 (n=16)
    - Doses 10 to 50 times lower than the typical tisa-cel dose
- Results:
  - CRS: any grade, 35%; grade ≥ 3, 6%
  - Neurotoxicity: any grade 25%; grade ≥ 3, 6%
  - Low/comparable rates of infection and cytopenias
  - 2 deaths at DL1, 3 deaths at DL2 – none treatment related
  - ORR: 75% for DL1, 80% for DL2
  - At month 3, one (25%) patient at DL1 and 11 (73%) at DL2 achieved a complete response (CR).

Dickinson, et al. A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. *Cancer Discov* 1 September 2023; 13 (9): 1982–1997. https://doi.org/10.1158/2159-8290.CD-22-1276

CAR T Challenges

- Manufacturing time, costs, and complex logistics
- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)
- Toxicity and safety

Patient and Disease Factors

- Progression of disease
- Poor harvesting
- T-cell fitness
  - Quality of cells impacted from disease or prior therapies
- Antigen loss/escape
- Tumor microenvironment

T-Cell Fitness

- Impacted by age, chronic infection, disease burden, and prior treatments
- Lower proportion of naive memory T-cells in the CAR product have been associated with lack of durable response
- Approaches:
  - CAR T in earlier lines of therapy, early lymphopheresis

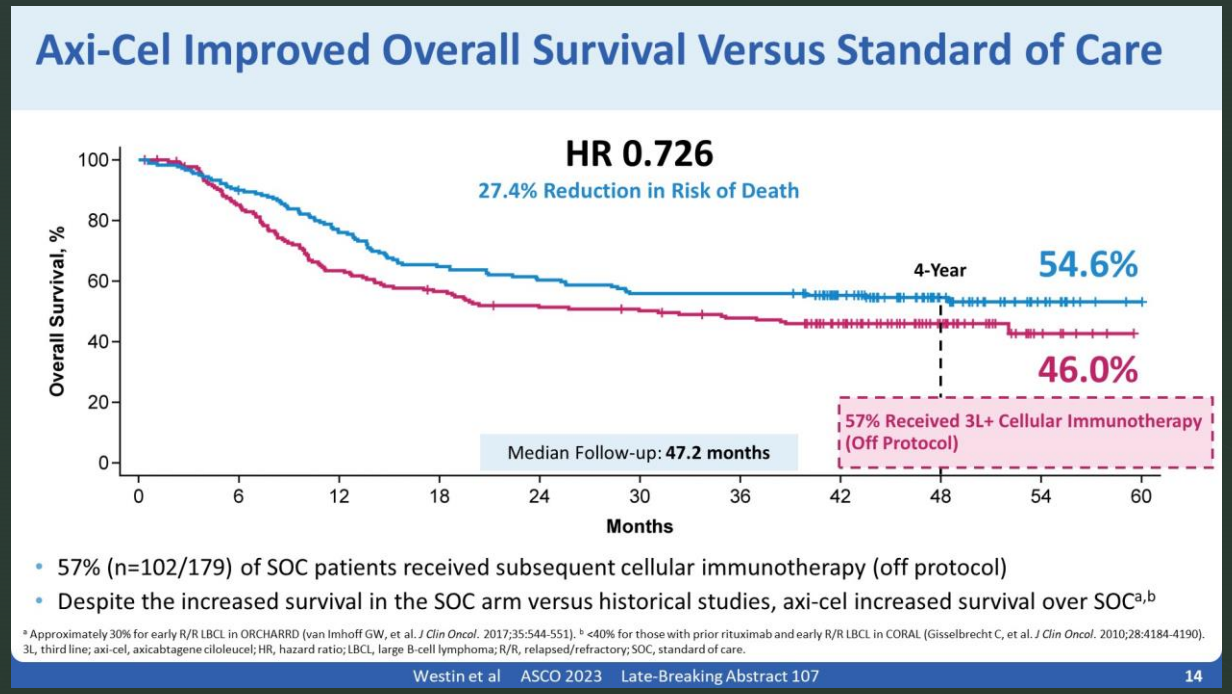
Nature.com

CAR T-cells in 2nd line r/r LBCL

	ZUMA-7	TRANSFORM	BELINDA
Product	Axi-cel	Liso-cel	Tisa-cel
ORR (%)	83 v 50	165	46 v 43
CR (%)	65 v 32	74 v 43	28 v 28
mEFS (months)	8.3 v 2.0	NR v 2.4	3.0 v 3.0
EFS (%)	24m: 41 v 16	18m est: 51 v 19	10m: 19 vs 20
mPFS (months)	14.7 v 3.7	NR v 6.2	NR
mOS	NR v 35.1	NR v 29.9	NR

Locke et al NEJM 2022; 386:641, Abramson et al Blood 2023; 141:1675, Bishop et al NEJM 2022; 386:637
Slide adapted from Caron Jacobson, MD ASCO 2023 presentation

ZUMA-7 Updates



Westin J, et al. Abstract LBA107. Presented at: ASCO Annual Meeting; June 2-6, 2023; Chicago.

- High-risk population of 352 pts randomized to treatment
  - 94% received axi-cel
  - 36% SOC (HDC +ASCT)
- OS benefit of 54.6% v 46%
  - 57% in SOC arm still went on to receive 3L + CAR T

Taking it another step further…

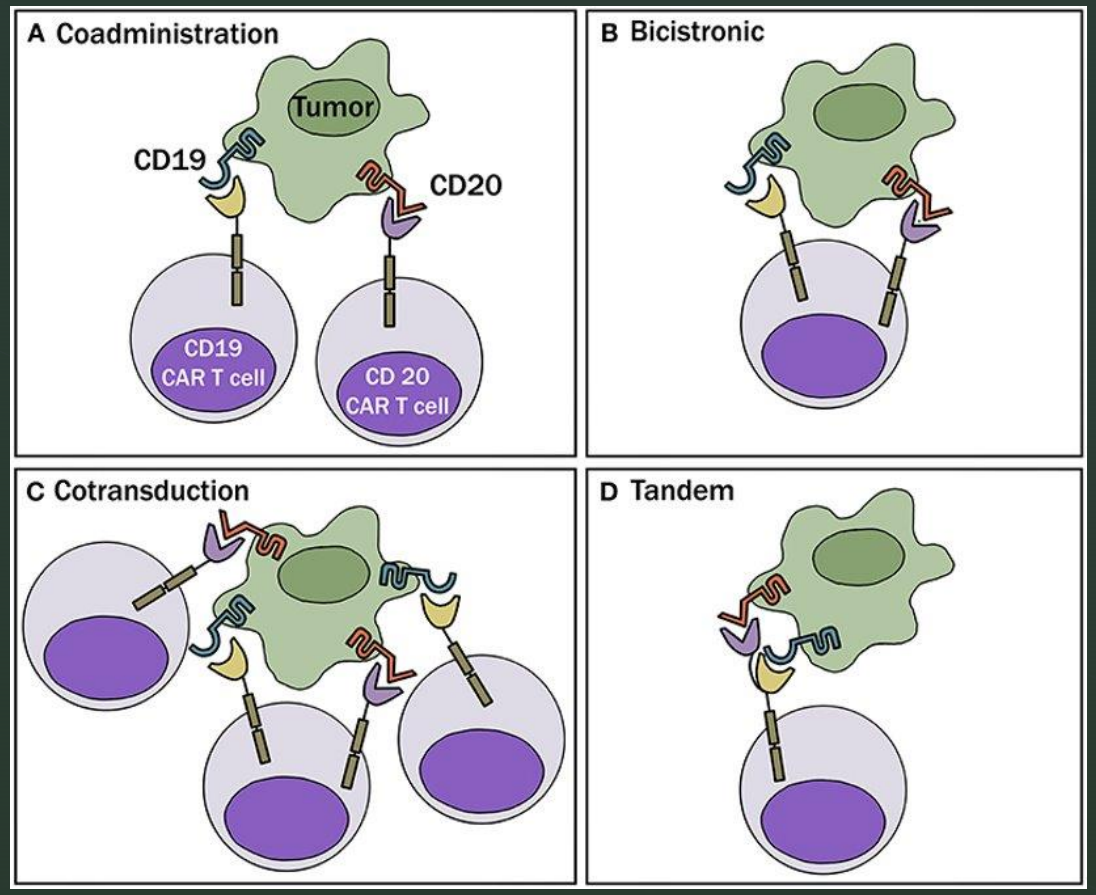
- ALYCANTE – phase 2 trial looking at axi-cel in r/r DLBCL as 2nd line in transplant- ineligible pts
  - 62 patients
  - CMR of 71% at 3 months
  - mPFS 11.8 months (median f/u 12 months)
- Results support axi-cel as 2nd line in ASCT-ineligible pts with r/r DLBCL

Houte, et al. *Nature Medicine*. 14 Sept 2023

Tumor Immune Escape

- 2/3 of pts relapse after CD19-directed CAR T cell therapy
  - Antigen loss is a common mechanism
  - Downregulation of CD19 receptor
- Proposed solutions
  - Single targeted CAR construct against other B-cell lymphoma antigens
  - Multi-targeted CARs

Multi-targeted CAR T-cell Approaches



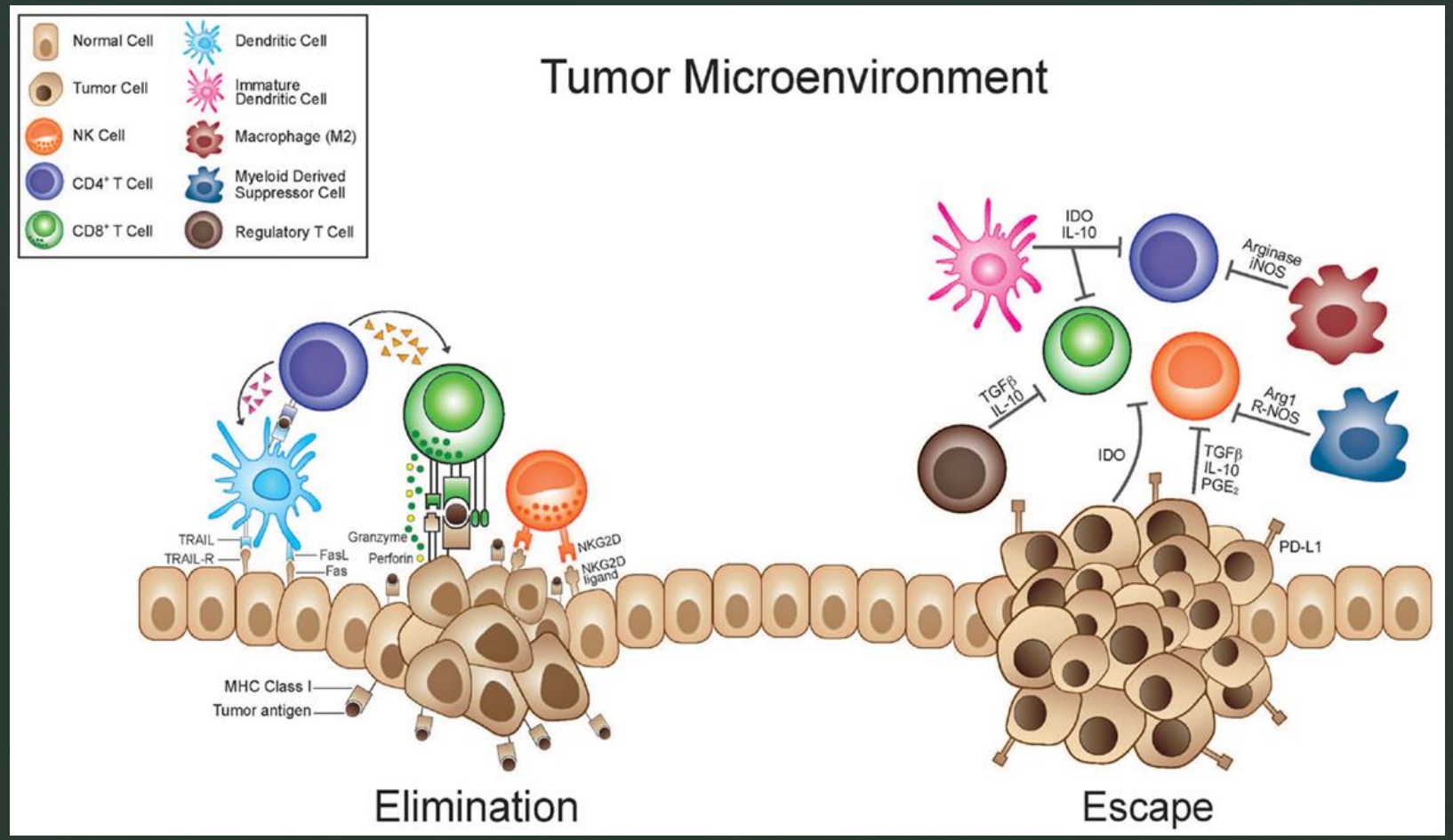
Shah, N. et al. Front. Onc. 9:146, 2019

Bispecific CAR T Therapy

- DALY2-US Trial - Phase 2 randomized trial of bispecific ANTI-CD20/19 CAR T (Zamtocabtagene autoleucel)
  - 22 pts with r/r DLBCL after ≥2L, ineligible for HDC +ASCT
    - 28% previously treated with anti-CD19 or anti-CD79 agents
  - No bridging chemo allowed
  - Manufactured in 12 day process (vein-to-vein 14 days), infused fresh
- Results: 18 of 22 (82%) with response
  - 46% with CR, 36% with PR
  - Post-progression biopsy available in 5 pts – no isolated CD19 loss, 1 dual target loss

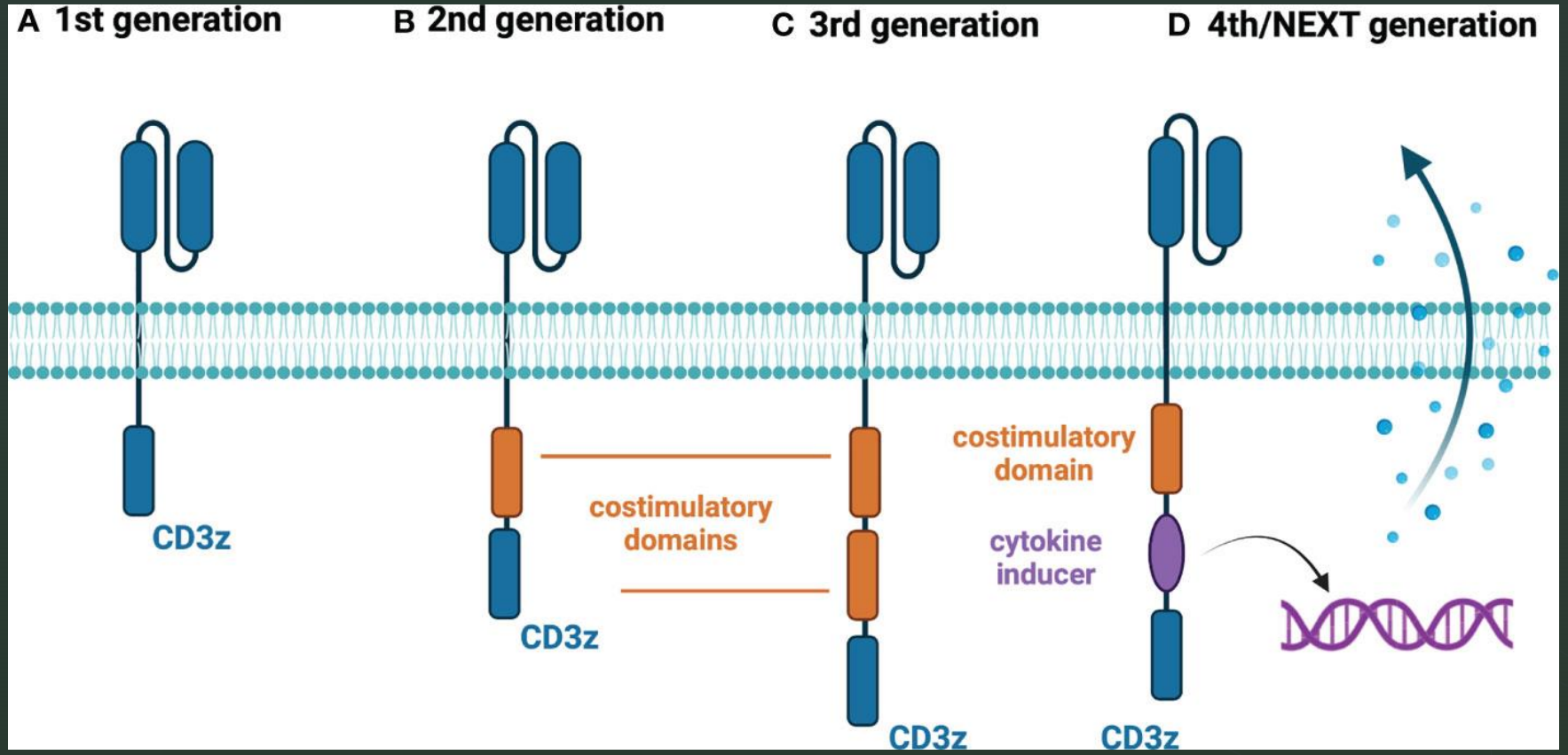
Shah N, et al. *Hemasphere*. 2023;7(Suppl):e07109dc. Published 2023 Aug 8.

Tumor Microenvironment



Frontiers in Oncology

Generations of CAR T Cells



Front. Immunol., 28 October 2022. Sec. Cancer Immunity and Immunotherapy. Volume 13 - 2022 |

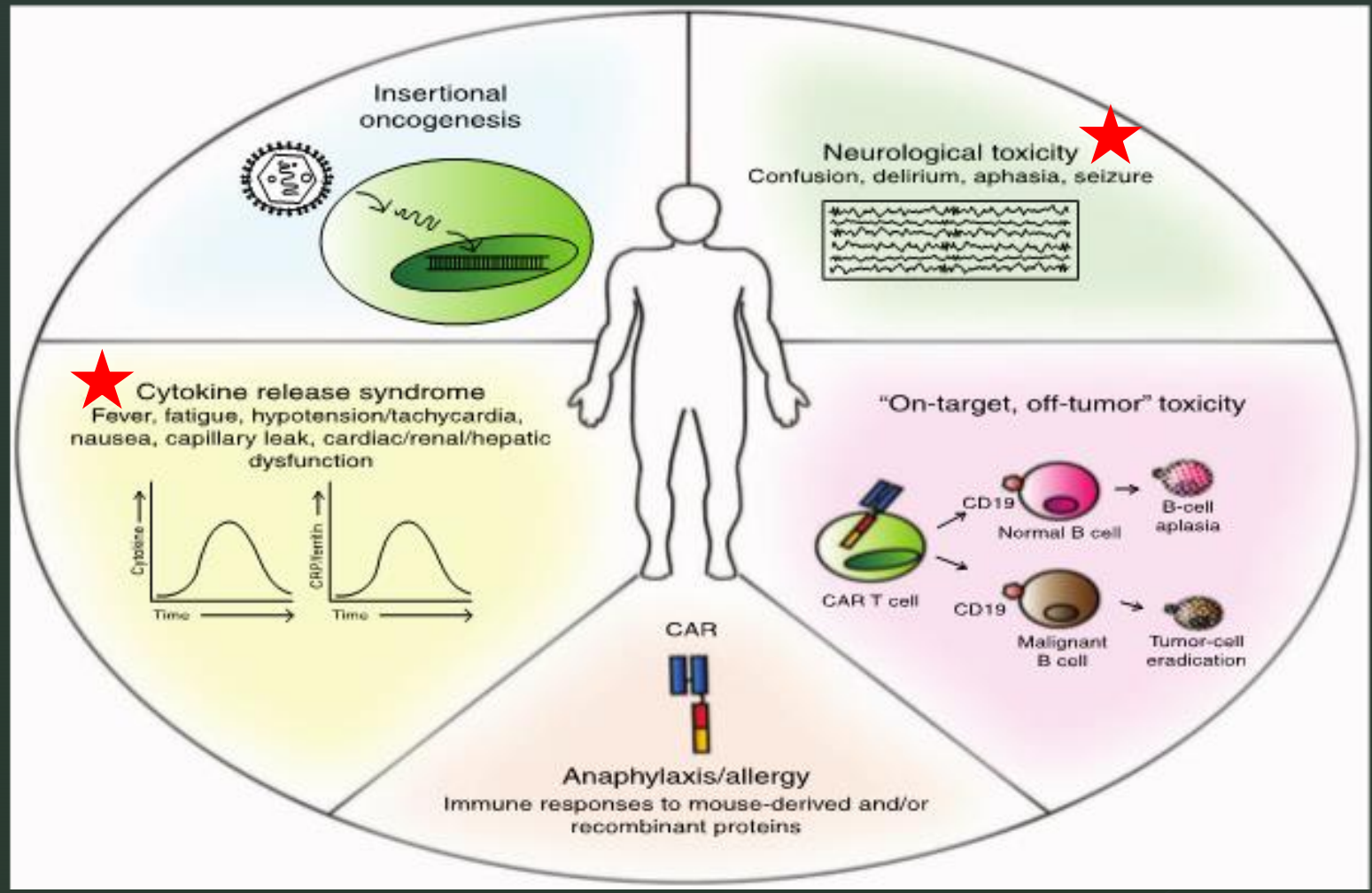
Next Generation CAR T-cells

- 4th / next generation
  - Cytokine secreting CARs deposit interleukins into the target, in turn attracting an innate cell response and remodeling the TME
  - “Armored” CARs
    - via PD1 pathway in hematology: MC-19PD1 CAR-T in r/r B Cell Lymphoma (NCT03932955) -no results available
  - Switchable CAR T- cells
  - Universal CAR T-cells

CAR T Challenges

- Manufacturing time, costs, and complex logistics
- Patient/disease factors:
  - T cell fitness and persistence
  - Tumor immune escape (CD19 antigen loss)
- Toxicity and safety

CAR T-related toxicities



Bonifant et al. Molecular Therapy 2016;(3):16011

CRS & ICANS

Cytokine Release Syndrome (CRS)

- Most common toxicity resulting from the release of cytokines from activated CAR T cells, as well as bystander immune cells.
- Usually within the first 7 days
- Hallmark = fever
- Key manifestations: fever, chills, hypotension, tachycardia, hypoxia

IEC-Associated Neurotoxicity syndrome (ICANS)

- Second most common toxicity
- Pathophysiology not well understood
- Can occur with or without CRS
- Common: confusion/delirium, aphasia, weakness, headaches, tremor, altered level of consciousness
- Rare: motor weakness, seizures, cerebral edema

Graded using ASTCT Consensus grading scale (Lee, et al 2018)

Toxicity Management

Cytokine Release Syndrome (CRS)

- Supportive care, rule out infection
- Tocilizumab (IL-6 receptor antagonist)
  - FDA approved
  - Effective, not directly cytotoxic
  - Most respond to 1 or 2 doses
- Steroids are used for severe CRS

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- Mainstay of treatment is corticosteroids at escalating doses
- Grade 3 ICANS remains high in real world experiences
- Need for more effective strategies

ICANS Pathophysiology

- Not well understood
- Optimal management of severe or refractory ICANS remains ill-defined
- Anti-cytokine therapy as therapeutic option
  - Tocilizumab has limited CNS penetration
    - Not effective for ICANS with potential negative influence
  - Alterative agents:
    - IL-1 (Anakinra), IL-6 (Siltuximab)

Anakinra

- Recombinant IL-1 receptor antagonist competitively inhibits IL-1 receptor signaling and therefore blocks downstream production of inflammatory cytokines including IL-6.
- Higher levels of IL-1a are seen in serum and CSF of severe ICANS
- In murine models, anakinra effectively treated both CRS and ICANS

Phase II Trials

Authors	Park, et al 2021	Frigault, et al 2021
Disease	LBCL or MCL	r/r LBCL
Anakinra indication	Prophylaxis	Prophylaxis
Dosing via SQ inj	100 mg q12h on Day 2 to Day 10+ or earlier if 2 fevers	200 mg 4 hours prior to infusion and qd x 7 days
n	n=31	n= 6
Adjunctive therapies	yes	--
Grading criteria	ASTCT	Lee 2013
Rate of ICANS	D30, 2/31 (6%)	D28, 2/6 grade 3
Severe CRS	2 (6%)	0

Anakinra prophylaxis

- Phase 2 trial in r/r LBCL and MCL patients treated with commercial anti-CD19 directed CAR T
- Cohort 1: SubQ injection of anakinra from day 2 until at least day 10 post-CAR T-cell infusion
  - n=31, 74% received axi-cel, 13% received brexi-cel, 4% tisa-cel
  - ICANS, all grade = 19%
    - Severe (grade ≥ 3) ICANS = 9.7%. No grade 4 or 5.
  - CRS, all grade = 74% (19 pts)
    - Severe CRS = 6.4%
- ORR 77%, CR 65%

Park, et al. Nature Medicine 03 July 2023

Anakinra for refractory toxicities

- Retrospective review by Gazeau, et al (2023)
  - 43 pts - 37 with NHL, 5 with ALL, and 1 with MM
  - Commercial product (n=7) or investigational (n=6)
  - Grade 2 refractory CRS (n=3) or ICANS (n=40)
  - Two anakinra dosage groups were retrospectively defined as:
    - “high dose” (>200mg/day IV) and “low dose” (100-200mg/day SC or IV)
- Conclusions:
  - High-dose anakinra (up to 12 mg/kg/day) for refractory CRS or ICANS was safe.
  - Higher dose may be associated with faster CRS/ICANS resolution and was independently associated with lower TRM

- TRM at day 28 and day 60 was 7% and 23%, respectively
- Day 28 TRM was 47% in the low dose cohort (n=15) and 0% in the high dose cohort (n=23)

Take Home Points

- Novel manufacturing processes are being evaluated to decrease vein-to-vein time and increase CAR efficacy & persistence
- Favorable results showing benefit for use of CAR T as earlier therapy, especially in high risk patients
- CAR T-cell therapy viable option for ASCT-ineligible patients
- Anakinra for prophylaxis or refractory toxicity management without reducing treatment efficacy

What's on the CAR T horizon?

- Allogeneic CARs – NK, iPSCs
- Earlier lines – Zuma-23: phase 3 axi-cel in 1st line
- Novel CAR T targets
- Dual binding CARs
- Universal CARs
- New CAR constructs for solid tumors
- On/Off Switches

Chimera vs CAR T-cell

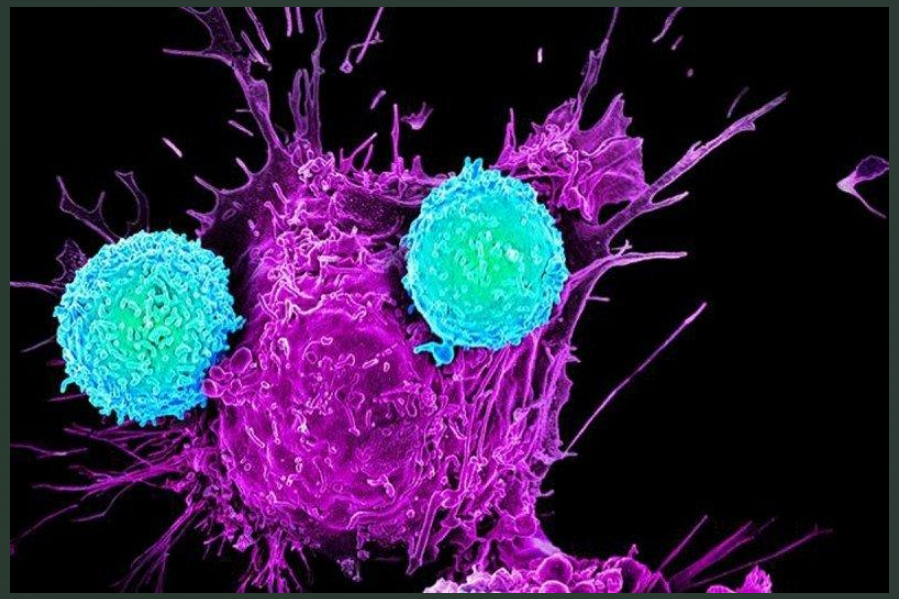


Image from J Clin Invest Aug12016. Cherkassy L, et al. Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor mediated inhibition.

Thank You!

Questions?