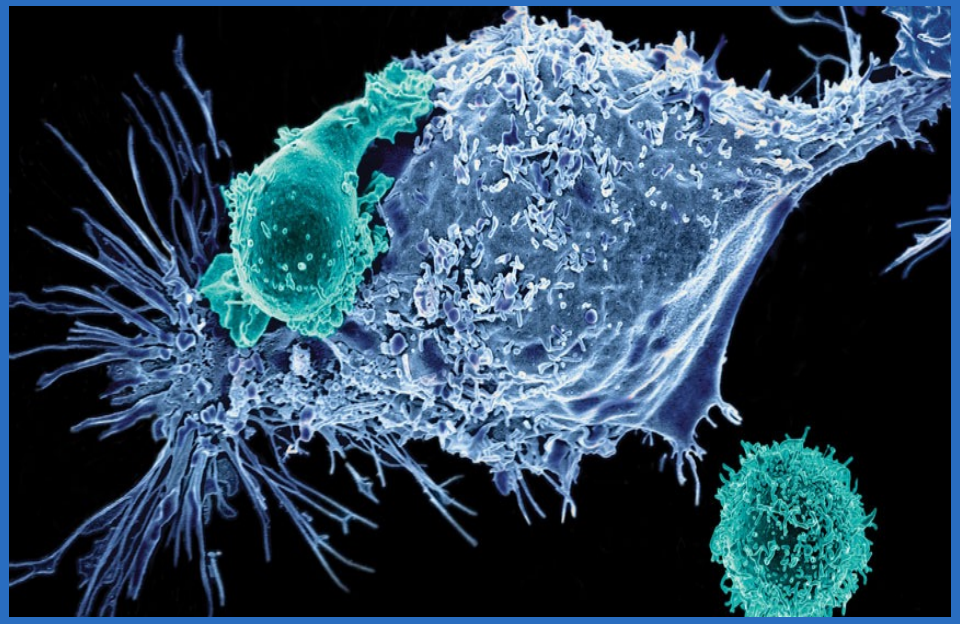
City of Hope®

Advances in CAR T Cells and Other Cellular based Therapies



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Presentation Objectives

- Overview of CAR T cell therapy (what and how)
- Current status of CAR T cell therapy (What's available in the clinic)
- Management of CAR T treatment related side effects
- What's on the horizon? (new therapies)

CHAPTER 1

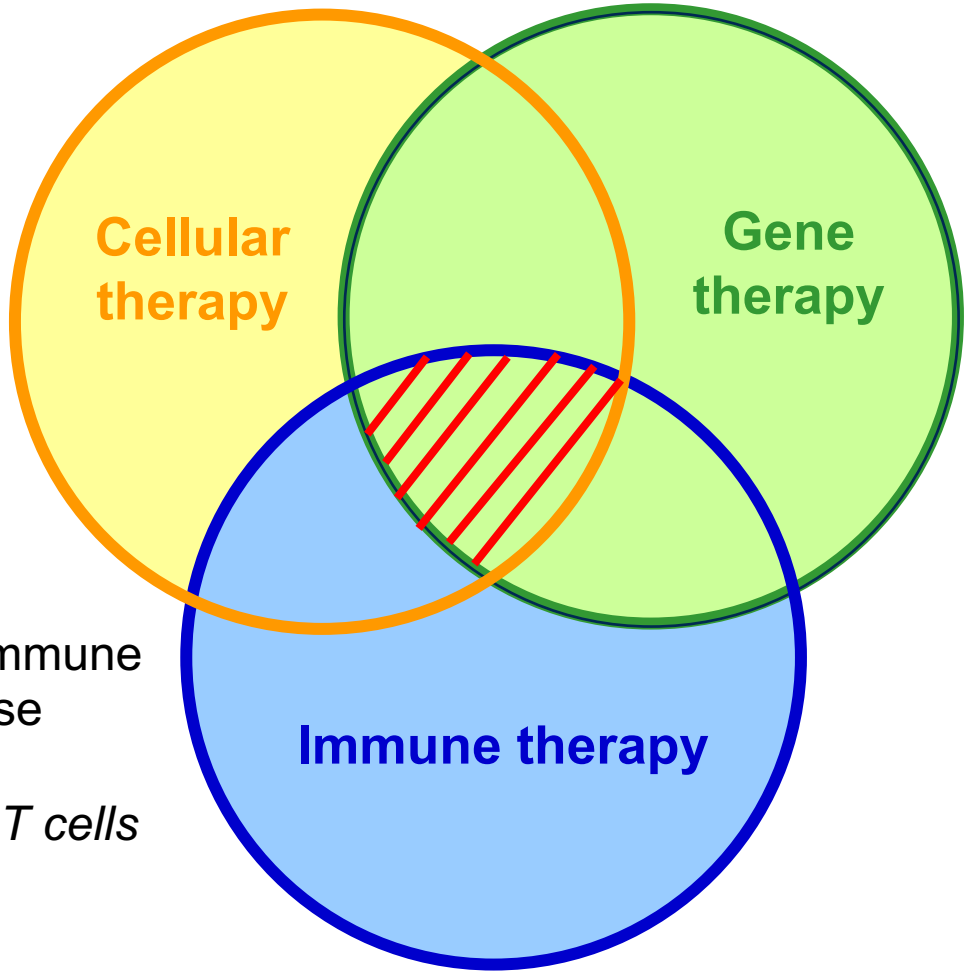
Overview of CAR T Cell Therapy

What's CAR T Cell Therapy

Cellular therapy

Using autologous(self)or allo(others) cells as therapy

cells = T cells



Gene therapy

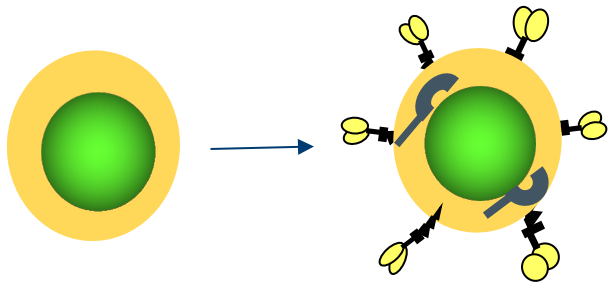
Insertion of genes into cells, causing these cells to produce a new therapeutic protein

new therapeutic protein = CAR

Immune therapy

Harnessing the power of the immune system to treat patient's disease

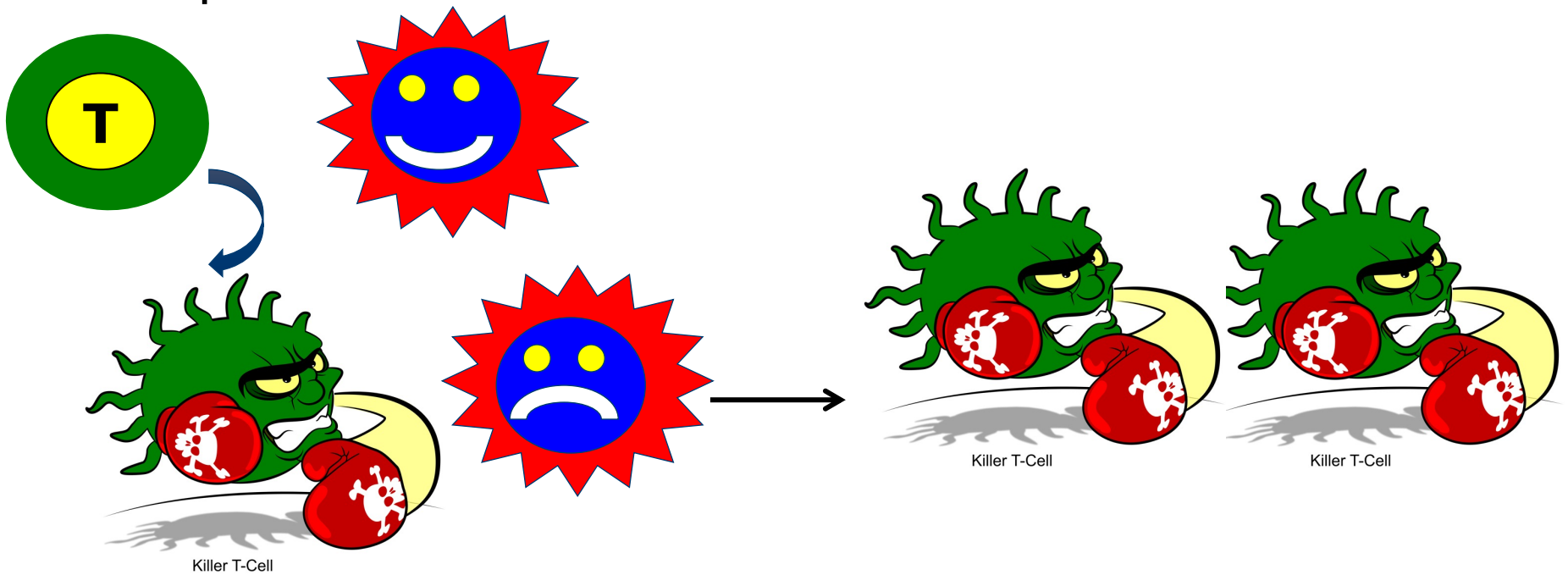
immune system component = T cells



The Goal of CAR T Cell Therapy

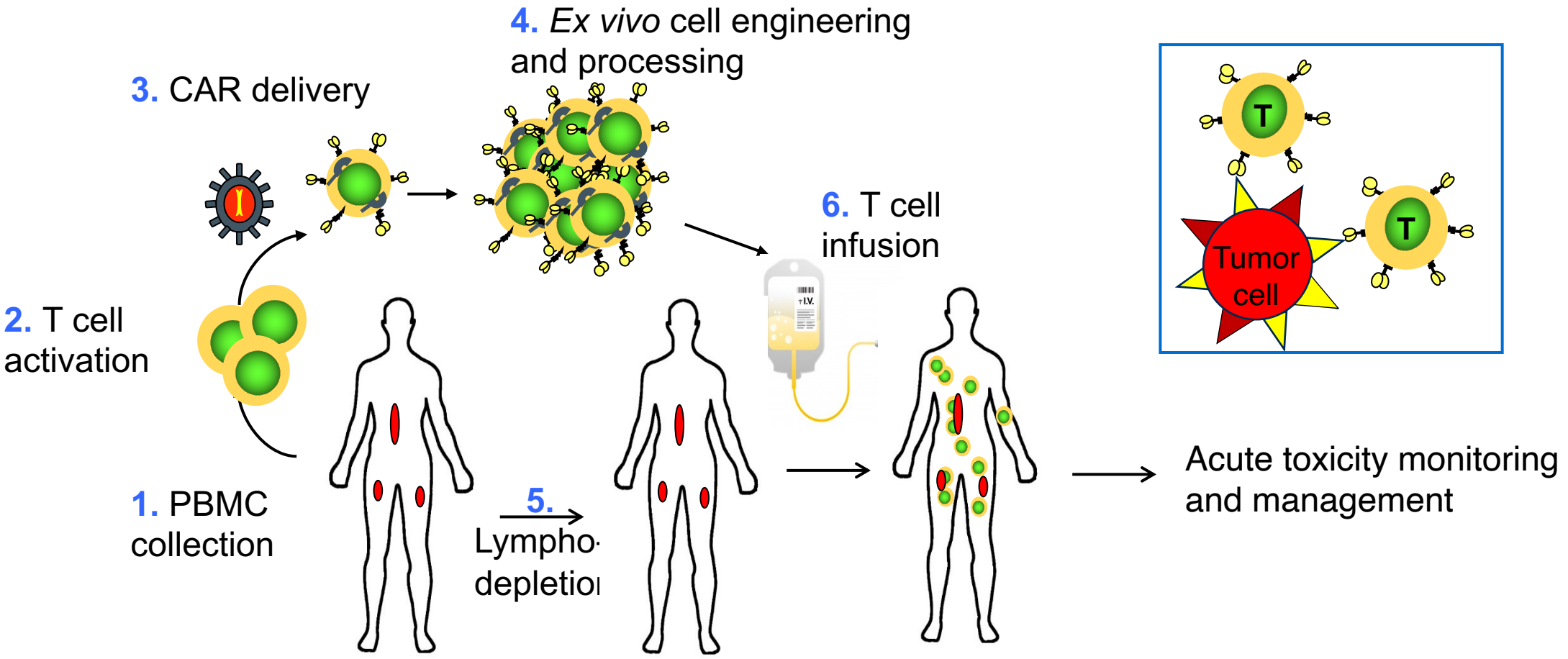
- Harness the power of immune system to recognize and eliminate cancer cells

- Genetic modification of T cells to redirect them to transform to robust tumor specific T cells.



CAR: Chimeric antigen receptor

The Common Process of CAR T Cell Therapy

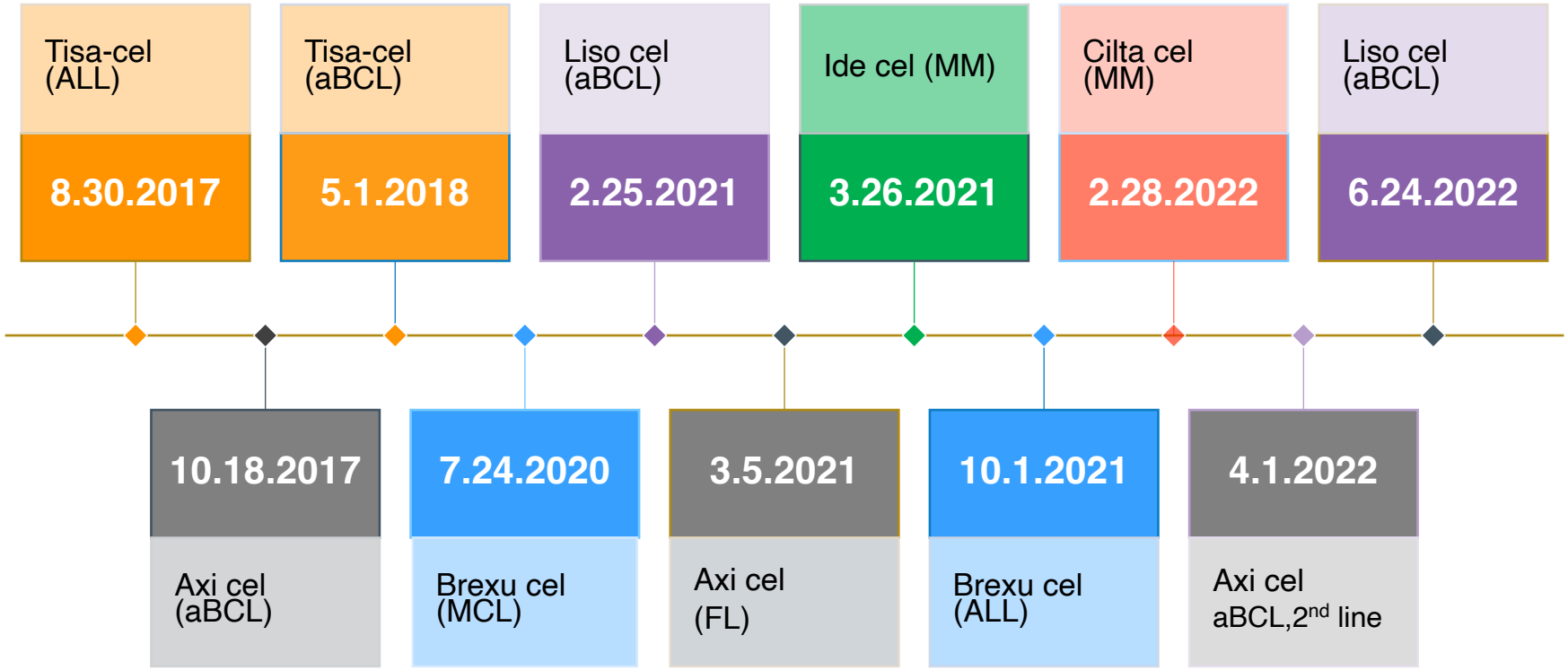


Variables:
- the starting population: VST, subset enrichment/depletion, …
- manufacturing process activation method, cytokines, expansion time,…
- infused products: bulk or defined population, …

CHAPTER 2

The Current Status of CAR T Cell Therapy

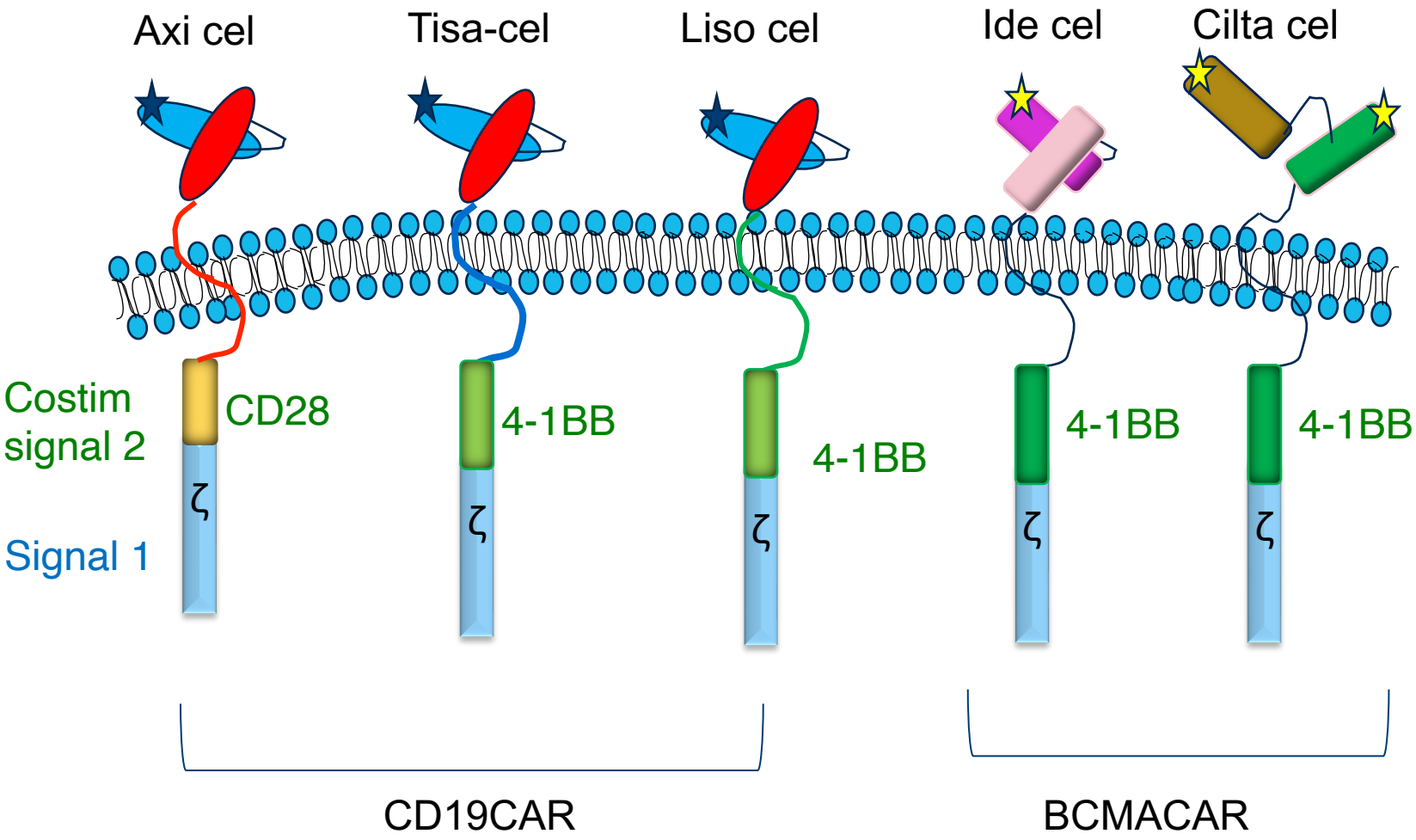
FDA Approved CAR T Cell Therapy



- ALL
  - Tisa-cel
  - Brexu cel
- B cell lymphoma
  - aBCL
    - Axi cel
    - Tisa-cel
    - Liso cel
  - FL
    - Axi cel,
    - Tisa cel
  - MCL
    - Brexu cel
- Multiple Myeloma
  - Ide cel
  - Cilta cel

Axi cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu cel: brexucabtagen autoleucel;
Liso cel: lisocabtagene maraleucel; Ide cel: idecabtagene vicleucel; Cilta cel: ciltacabtagene autoleucel

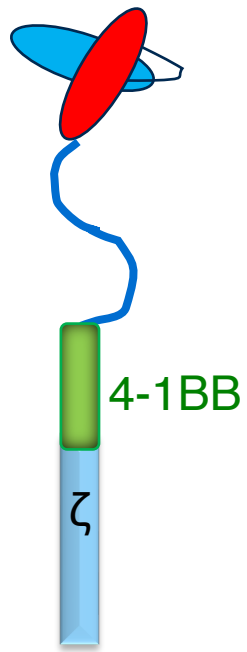
Not all CARs are created the same



Acute Lymphoblastic Leukemia: Tisagenlecleucel (CD19CAR)

Indication: < 26 y.o with B cell ALL refractory or in second or later relapse, *approved 8.30.2017*

Tisa-cel



Real World Experience (CIMBTR registry)

	ELIANA	Real World
Patients infused	N =75	N = 159 (103 ≧ 3 mo)
Best CR rate at 3 mo	81% (100% MRD-)	88% (100% MRD-)
6 month DOR	NR	77%
EFS	50% (13.6 mo)	68% (6 months)
OS	76% (13.6 mo)	94% (6 months)
Grade ≧ 3 CRS	49% (Penn scale)	13.3%(ASTCT)
Grade ≧ 3 NT	13% (Penn scale)	8.6% (ASTCT)

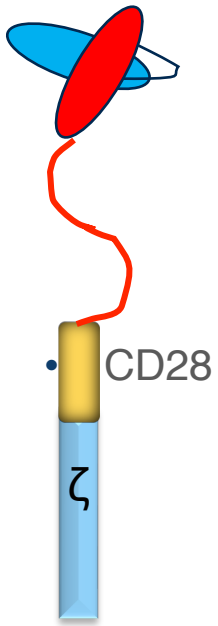
SL Maude et al. N Engl J Med 2018;378:439-448.

Grupp et. al. ASH 2019

Acute Lymphoblastic Leukemia: Brexucabatagene autoleucel (CD19CAR)

Indication: ≥ 18 y.o, with B cell ALL refractory or in second or later relapse, *approved 10.1.2021*

ZUMA-3: N =71, 92% (N=65) successful production; 55 patients received CAR T infusion.



	ZUMA-3
Median age (years)	40 (19-84)
Median No. of prior therapies	2 (1-8)
Prior AlloSCT	42% (n=23)
Median BM blast% preLD	59% (0-98%)
Median time from leuk to CAR T delivery	13 days in US 14-15 days in Europe

CR/CRi	70.9% (97% MRD-ve)
Median OS	18.2 Months (15.9 –NE)
Median RFS	11.6 months (2.7-15.5)
AlloSCT	10 (18%) at median 98 days
Grade≧ 3 CRS	24% (89% all grade)
Grade ≧ 3 NT	25% (60% all grade)
Grade 5	18% (N =10, 4-PD, 1NT, 1 PNA, 1 septic shock)

Shah et al. Lancet 2021

FDA approved CAR T Cell Products for B-cell lymphoma

Axicabtagene ciloleucel

- aBCL

Indication
Adult pts with
rel/ref BCL after ≥ 2 lines,
tFL, High grade B cell lymphoma
primary mediastinal B cell lymphoma

- FL

Indication
Adult pts with
rel/ref FL after ≥ 2 lines

Tisagenlecleucel

- aBCL

Indication
Adult pts
with rel/ref LBCL after ≥ 2 lines,
tFL, High grade B cell lymphoma

- FL

Indication
Adult pts with
rel/ref FL after ≥ 2 lines

Lisocabtagene maraleucel

- aBCL

Indication
Adult pts with
rel/ref BCL after ≥ 2 lines,
tFL, High grade B cell lymphoma
primary mediastinal B cell lymphoma

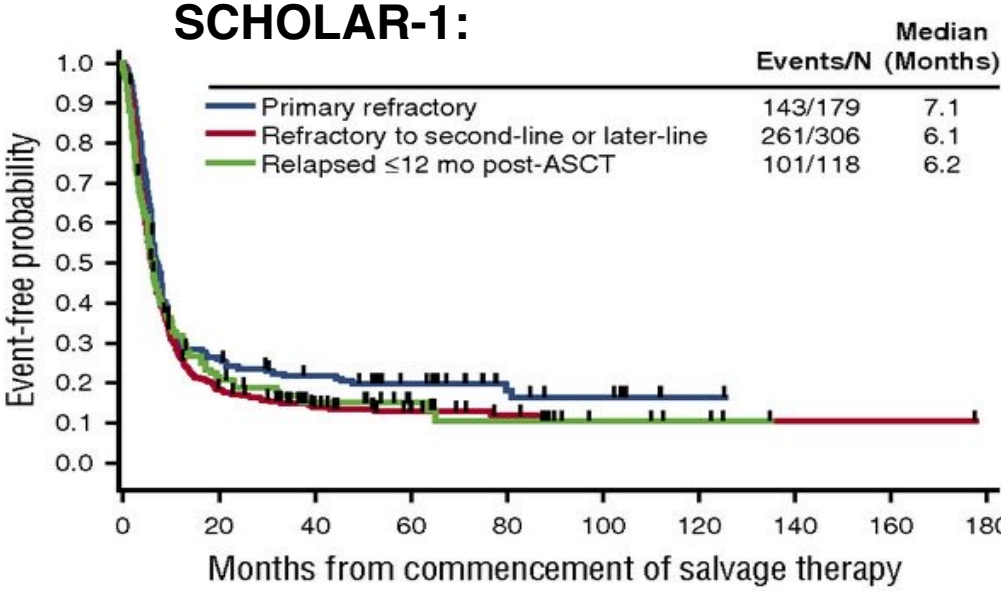
Brexucabtagene autoleucel

- MCL

Indication
Adult pts with rel/ref MCL after ≥1 lines

CAR T unequivocally led to significant improvement in OS

SCHOLAR-1:

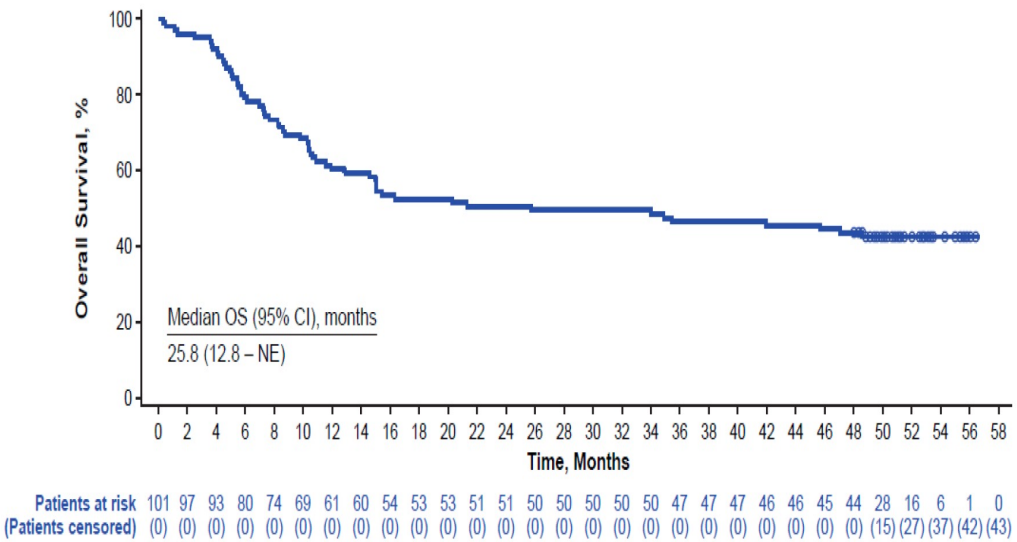


The pooled CR: 7% (95% CI, 2-15)

Median OS: 6.3 Months (95% CI, 5.9 -7.0)
1-year OS: 28%

Crump et al. JCO 2016

ZUMA-1 : OS 44% with f/u > 4 years



- OS 44% at 4 years
- Primary cause of death (n=58): PD (46)
- No new safety concern

Tx related secondary malignancy, or RCR cases

- Detectable B cells in blood (21/21)

Jacobson et. al. ASH 2020 & 2021

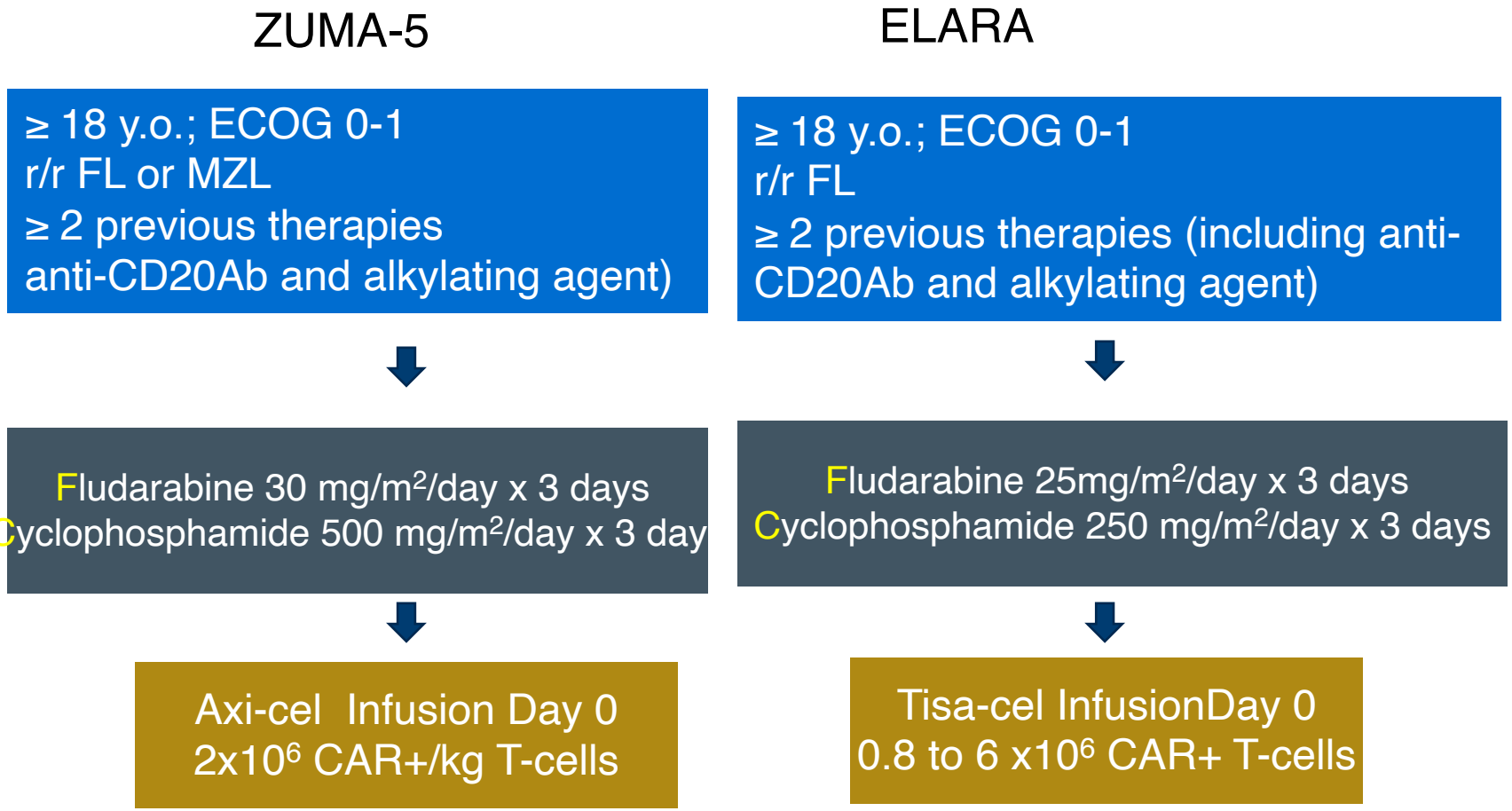
Real World experience with Axi-cel: similar to trial experience

	6 center experience (N = 136)	17 center experience (N = 295)	ZUMA-1 (N = 111)
Median age, yrs	61 (21-79)	58 (64-77)	58 (23-76)
Prior ASCT %	30	31	25
Bridging therapy %	57	55	0
T cell not infused	13 (9.6%) 6 PD 1 CR 3 product failure 2 infection; 1 others	21 (7.1%) 12 PD 1CR 7 product failure 1 infection	10 (9%) 1 PD 2 CR 1 product failure 6 AEs (1 death)
Not Meet ZUMA-1 Criteria%	62%	43%	0%
Best ORR % day 30	74	80	78
Best CR %	49 (ITT 44)	47 (ITT 44)	52 (ITT 47)
CR % at day 90	n/a (53 at month 6)	57	58

CART for iNHL: ZUMA-5 and ELARA Phase II Studies

Primary endpoints:
ORR

Key secondary endpoints
CR, ORR, DoR, PFS, OS, AE, CAR and cytokine levels.



Jacobson et al. Abstr 700. ASH 2020; *Fowler et al. Nature Medicine* **28**, 325–332 (2022)

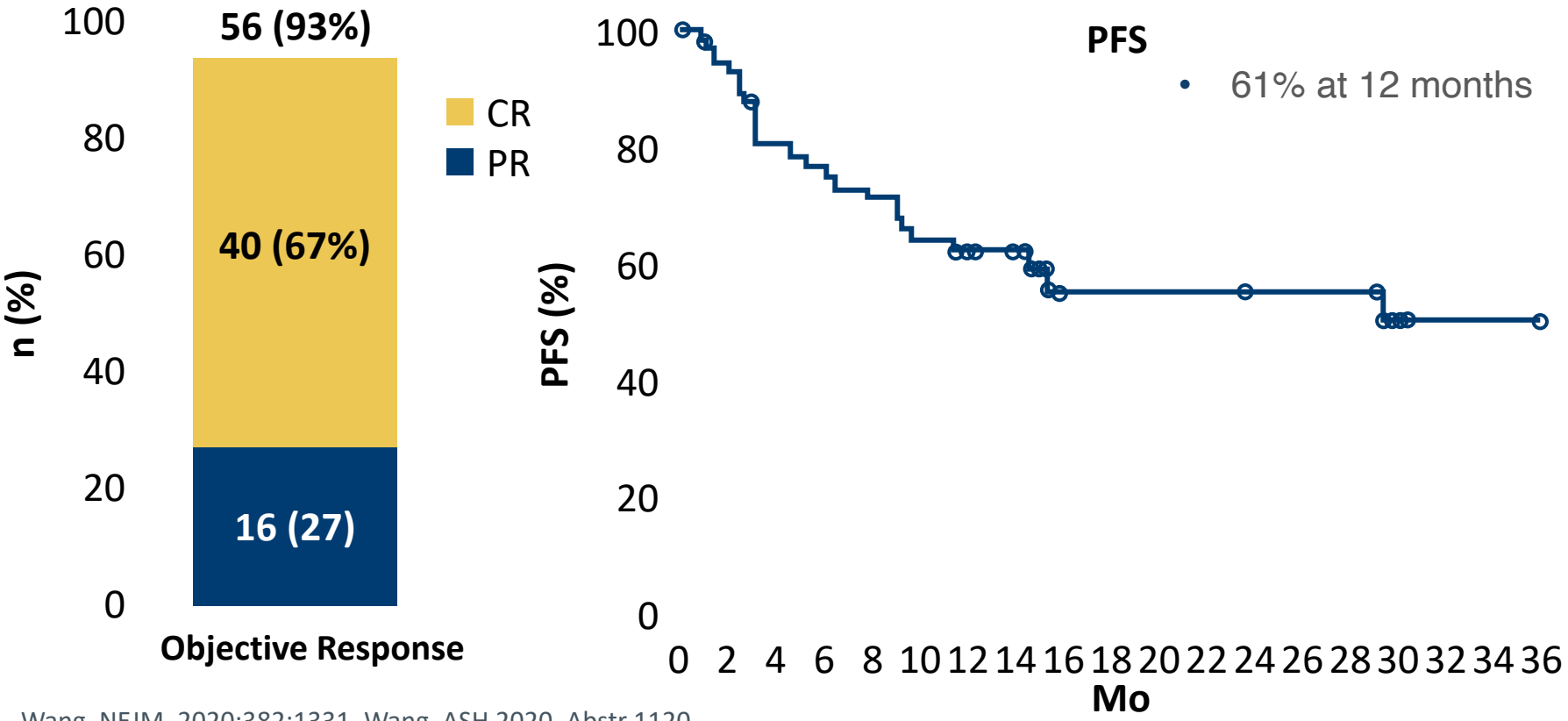
CART for iNHL: ZUMA-5 and ELARA Studies

	ELARA	ZUMA-5	ZUMA-5
iNHL	**r/rFL, N =97** 94 (evaluable)	**r/r/FL,N=124** 85 (evaluable)	*MZL N=22* 20 (evaluable)
Median age	57 (29-73)	60 (52-67)	66 (53-68)
Median prior Tx	4 (2-13)	3(2-4)	3(2-5)
POD24	60%	55%	57%
Prior ASCT	36%	24%	13%
ORR/CR	86%/69%	94%/79%	83%/65%
CRS, ≥ gr3	0	6%	9%
NT, ≥ gr3	3%	15%	41%
Grade 5	3 due to lymphoma	3 (CRS, aortic dissection, infection)	0
PFS (12 mo)	67%	77.5%	45.1%

Shuster et al. ASCO 2021
Thieblemont. et al ASH 2021
Jacobson et al. ASH 2020

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Relapsed/Refractory MCL

- Multicenter, single-arm, open-label phase II trial of brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma (N = 74 enrolled, 68 received agent)
  - After failure of BTKi and up to 5 prior therapies; bridging steroid ± BTKi permitted (37%)



- CRS grade ≥ 3: 15%
- Neurotoxicity grade ≥ 3: 31%
- Tocilizumab: 59%
- 1 gr 4 cerebral edema
- 2 gr 5 events (PNA and infection)

Wang. NEJM. 2020;382:1331. Wang. ASH 2020. Abstr 1120.

Slide credit: clinicaloptions.com

Conclusions- lymphoma

- Significant clinical benefit has been seen in variety of lymphomas using anti-CD19 CAR T-cells
- There is an increasing understanding of the factors and mechanisms affecting initial and subsequent loss of response to CAR T cell therapy
- More efforts are needed to make CAR T cell therapy available to more NHL patients.

Slide credit: clinicaloptions.com

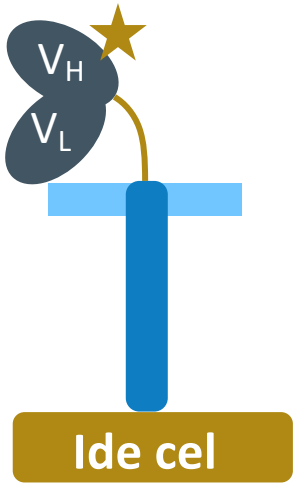
FDA Approved CAR T Cell Therapy for Multiple Myeloma

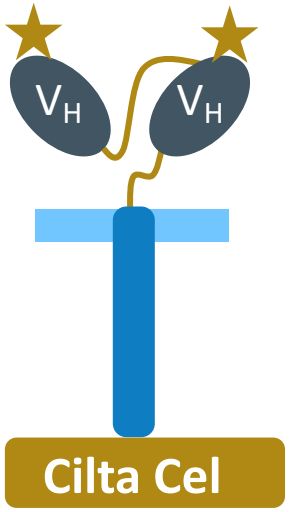
Idecabtagene

Ciltacabtagene autoleucel

Indication

Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.





FDA Approved CAR T Cell Therapy for Multiple Myeloma

	KarMMa	CARTITUDE-1
CAR	Ide cel	Cilta cel
Pt No.	N =140 128 (evaluable)	N=113 97 (evaluable)
Median age	61 (33-78)	61 (43-78)
Median prior Tx	6 (3-16)	6(3-18)
Prior Allo	-	8%
Prior ASCT	94%	90%
ORR/CR	73%/33%	97%/67%
CRS, ≥ gr3	6%	4%
NT, ≥ gr3	3%	9%
PFS	Median 8.6 mo	76.6% (12 mo)
PFS	-	60.5% (24 mo)

Anderson ASCO 2021
Martin et al. ASH 2021

Conclusion – multiple myeloma

- CAR T-cell therapy is now FDA approved for R/R MM
- Much work needed to understand how best to use this therapy
  - Single agent vs combination
  - Maintenance vs no maintenance
- Understanding rational sequencing of available BCMA-directed therapy will be important
  - ADCs, bispecific antibodies, CAR T-cell therapy

CHAPTER 3

Management of CAR T treatment related side effects

CAR T Cell Therapy: Complications

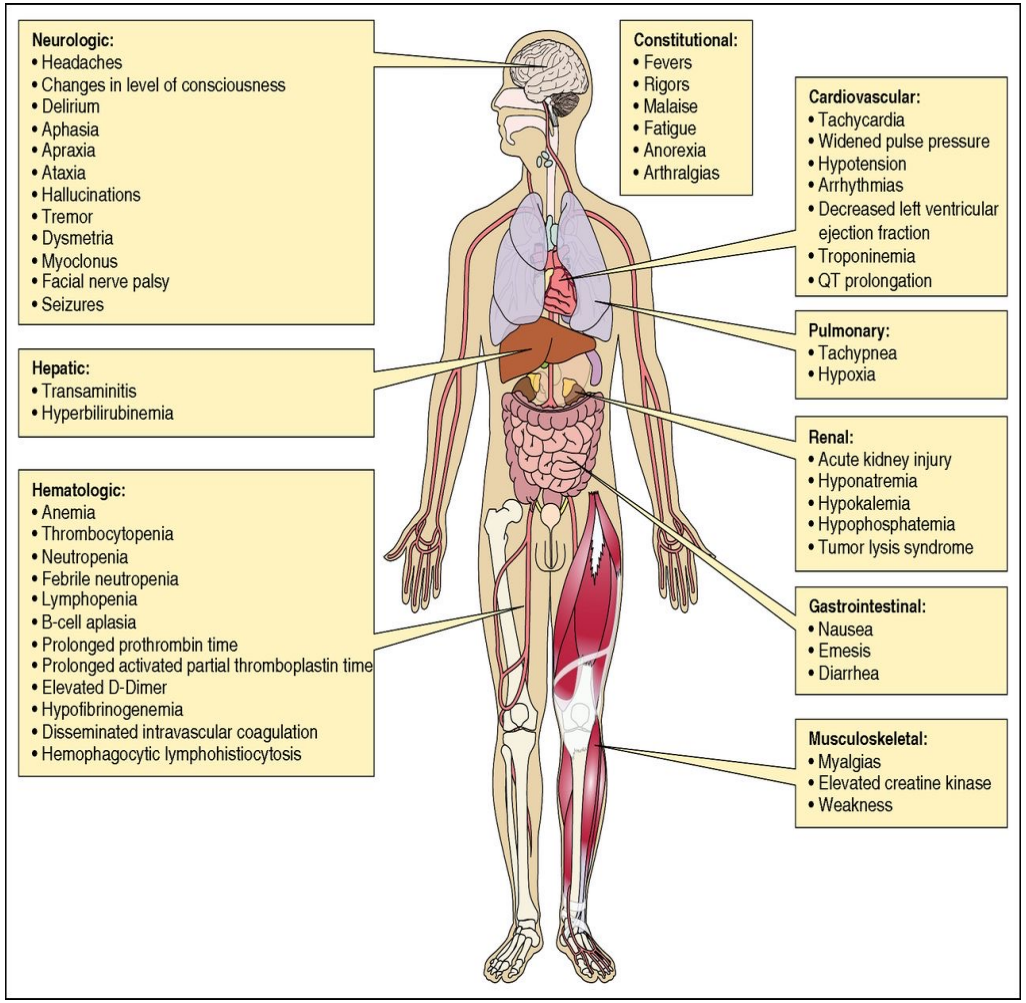
Commonly reported important adverse events

- On target off tumor effects, i.e. B cell aplasia (CD19CAR)
- Lymphodepletion chemo-related toxicity
- Tumor lysis syndrome
- Macrophage activation syndrome (HLH/MAS)
- Coagulopathy
- Cytokine release syndrome
- Neurotoxicity
- Infection

Cytokine Release Syndrome

- A constellation of inflammatory symptoms from cytokine elevations.
- Association with T cell activation and proliferation
- Association with clinical benefit in some CAR T treatment and toxicity

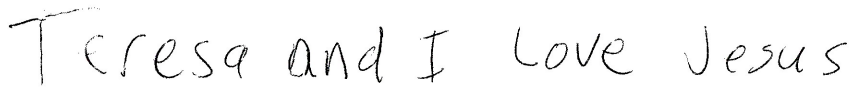
- Trio: Fever, low blood pressure, low oxygen



Jennifer N. Brudno, and James N. Kochenderfer Blood 2016;127:3321-3330

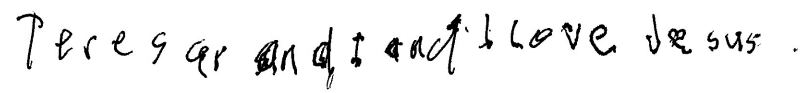
Neurologic Toxicity

D0



D3

D6



D14

D21

D28

SOC CAR T Emergent CRS and Neurotoxicity

	CRS incidence	Median onset	Median duration	Neurotoxicity incidence	Median onset	Median duration
Axi cel	94%, G3, 13%	2 (1-12)	7 (2-58)	87%; G3, 31%	4 (1-43)	17 (2-58)
Early steroids/toci	G3, 2%	2	7	G3, 20%	6	8
Tisagenlecleucel ALL	74%, G3 49%	3 (1-51)	8 (1-36)	72%, G3 21%	6 (1-359)	6
aNHL	79%. G3 23%			58%, G3 18%	6 (1-359)	14
Liso cel	46%, G3, 4%	5(1-15)	5 (1-17)	35%, G3, 12%	8 (1-46)	12 (1-87)
Brecu cel	91%, G3 18%	3 (1-13)	10 (1-50)	81%, G3 37%	6 (1-32)	21 (2-454)
Abecma	85%, G3 9%	1 (1-23)	7 (1-63)	28%, G3 4%	2 (1-42)	5 (1-578)

* Penn grading criteria. All others use Lee's criteria

Other AEs: cytopenia, infection, HLH/MAS, etc.

Infection

FHCRC cohort, N=133

Incidence: **23%**
Median Time to onset: 6

Bacterial 17% (N =22)
Viral 11% (N = 11)
Fungal 5% (N = 6)
Fatal infection 4% (n=5)

Other risk factors
- ALL patients
- >= 4 lines of prior therapies
- Higher CAR dose
- Severe CRS

ZUMA-1 cohort, N=108

Incidence: **38%**
Median Time to onset: 6

Bacterial 9%
Viral 4%
Unspecified 16%
Severe infection 23%

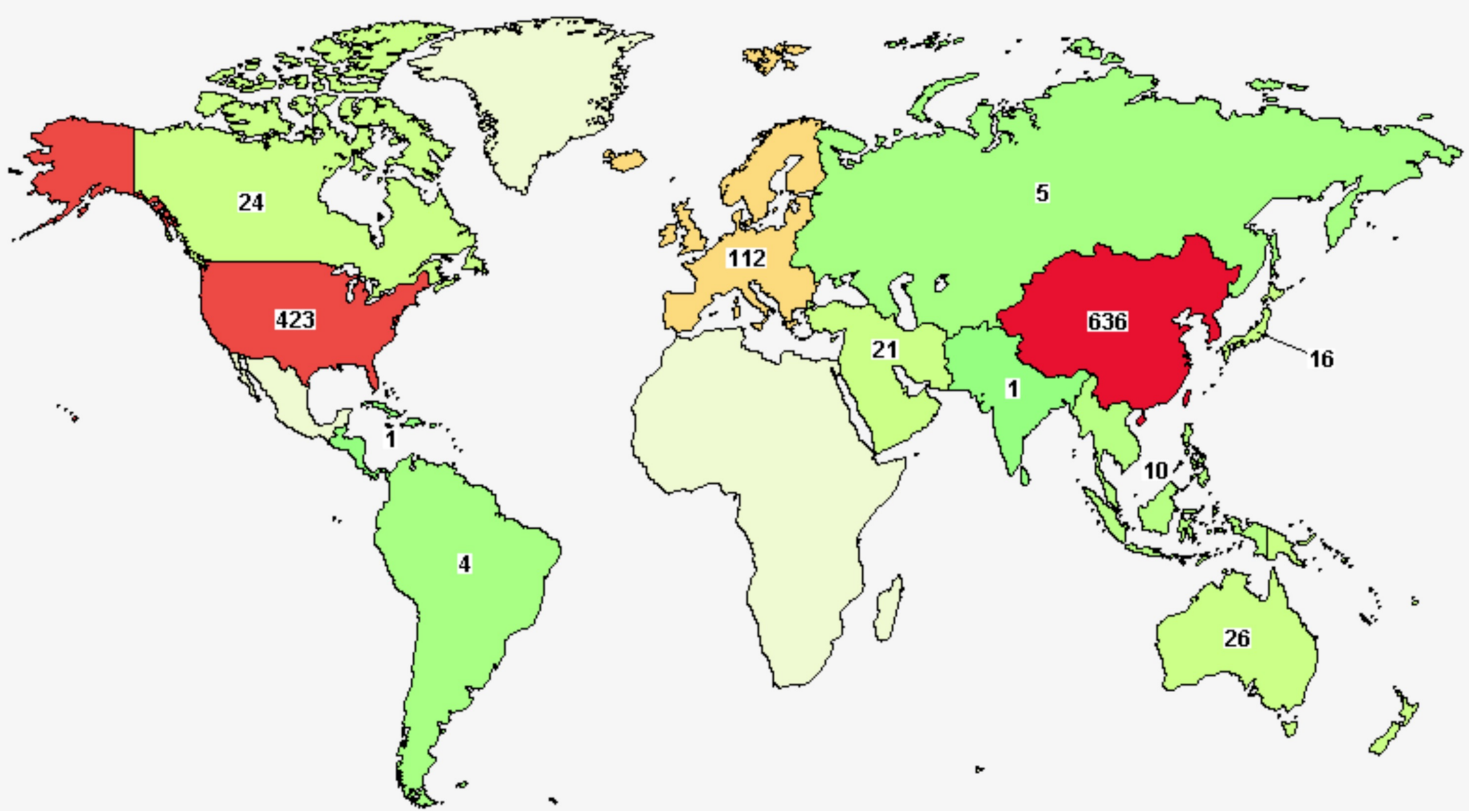
ID prophylaxis is recommended
- AutoHCT guideline
- Anti-fungal prophylaxis in pts with prior HCT

Hill et al.Blood 2017; Budde and Zaia. Blood 2019
Yescarta.com

CHAPTER 4

What's on the horizon? (new therapies)

Landscape of CAR T Cell Trials



Worldwide
CAR trials = 2241
CAR T trials = 1212

Clinicaltrials.gov accessed 8/18/2022

Clinical trials provide new treatment options

Access to novel CAR T cell therapy

- CARs for new targets (i.e. bispecific CARs, CARs for T cell lymphoma, AML, solid tumors)
- Test ”old” CAR earlier in disease course
- Test CARs in combination with other agents to further enhance response rate (+ immune booster)
- Test new manufacturing platform to make CARs with higher potency and shorter production time
- Improve safety by incorporating novel agents to prevent or mitigate CRS/NT complications;
- Novel vaccine or anti-microbials trials to decrease infection risk post CAR T cell therapy

COH CAR T Clinical trial Portfolio

COH Clinical Trial
COH Manufacture/IIT

N =15

- CD19CAR
- CD123CAR
- CD19-CMV CAR
- CD33CAR
- BAFFR
- FLT3
- HIV-CMVCAR
- IL13Ra2
- Her2CAR
- PSCACAR
- TAG72CAR

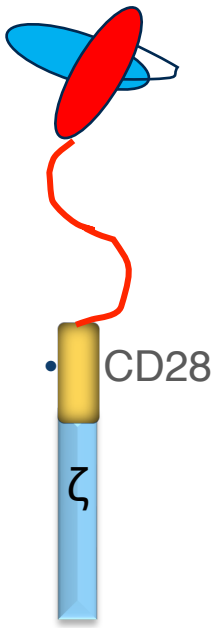
COH Clinical Trial
Sponsored

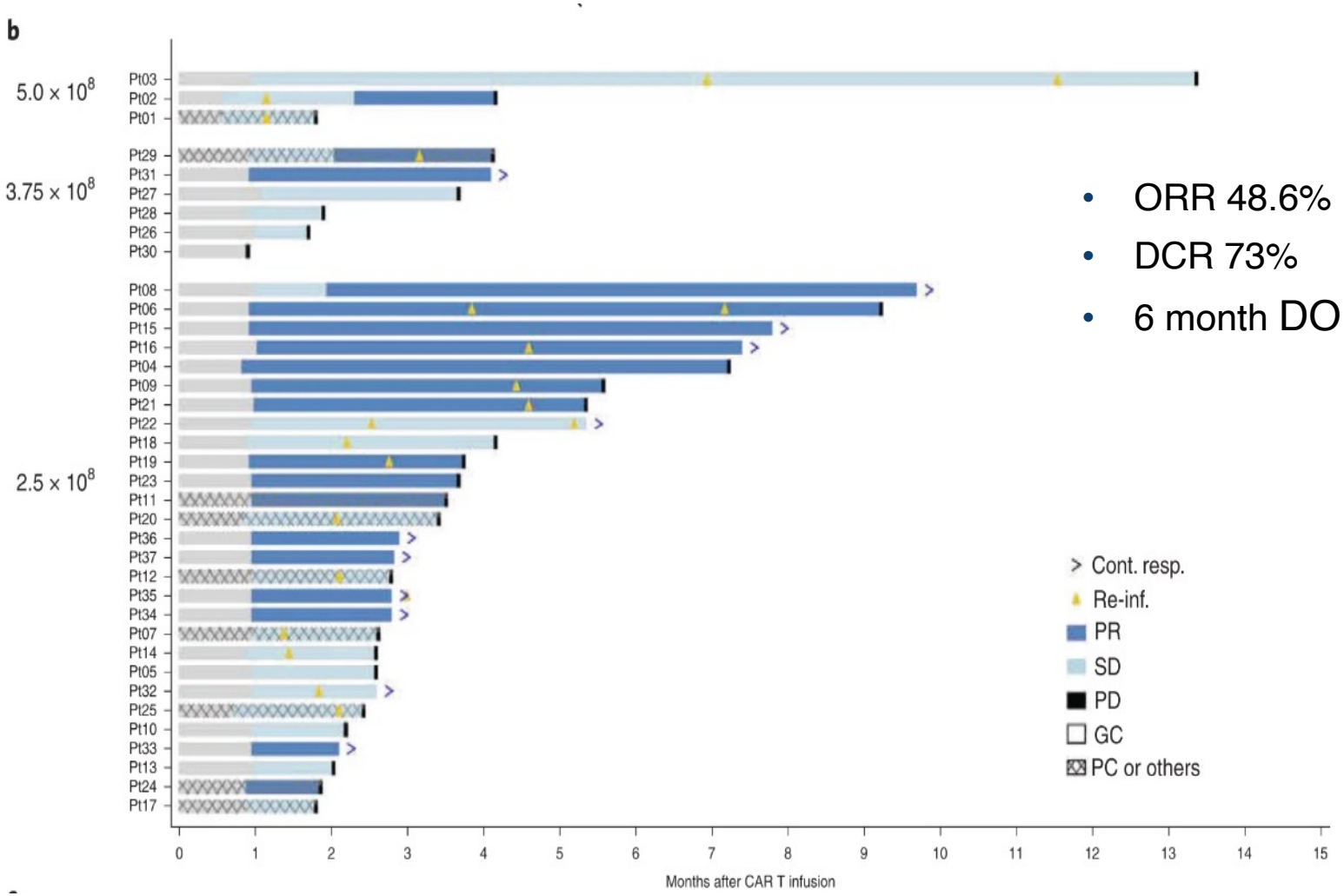
N = 43

- BCMA
- CD5
- CD7
- CD19
- CD19/20
- CD30
- CS1
- ROR1
- More coming

- CD70 ---------- TCL, RCC
- Claudin18.2-----Gastric
- GPC3----------HCC
- MUC1----------Breast
- HPV----------H&N
- ICAM-1----------Thyroid
- KLK2----------Prostate
- PSMA----------Prostate
- Her2----------Breast
- More coming

Claudin18.2 CAR T cells in GI cancers: phase 1 trial interim results





- ORR 48.6%
- DCR 73%
- 6 month DOR: 44.6%

Nature Medicine **volume 28**, pages1189–1198 (2022)

~~CAR T~~ therapy earlier in the disease course: CAR is better than ASCT

CAR T cell therapy in 2nd line setting vs chemo followed by autologous stem cell transplant (ASCT)

- Three phase 3 clinical trials: ZUMA-7, TRANSFORM, BELINDA
- Randomized LBCL pts with no response or relapse within 12 months from the first line treatment) to either CD19CAR T or standard of care chemo followed auto transplant

Locke et al. ASH 2021; Bishop et al. ASH 2021

ZUMA-7: ORR and OS (Key Secondary Endpoints)

Response, %	Axi-cel (n = 180)	SoC (n = 179)	OR (95% CI)	*P* Value
ORR	**83**	**50**	5.31 (3.1-8.9)	<.0001
▪ CR	65	32		
▪ PR	18	18		
Median OS, mo (95% CI)	NR (28.3-NR)	35.1 (18.5-NE)	0.730 (0.530-1.007)	.0270 (NS)

- With 24.9 mo of median follow-up, Axi-cel showed improved EFS and response rates vs SoC
  >4-fold greater median EFS, with EFS improvements across key subgroups
- Axi-cel had a manageable safety profile

- the ZUMA-7 results mark a paradigm shift whereby axi-cel should be considered the new SoC for patients with 2L R/R LBCL

Locke. ASH 2021. Abstr 2.

Slide credit: clinicaloptions.com

Clinical trials provide new treatment options

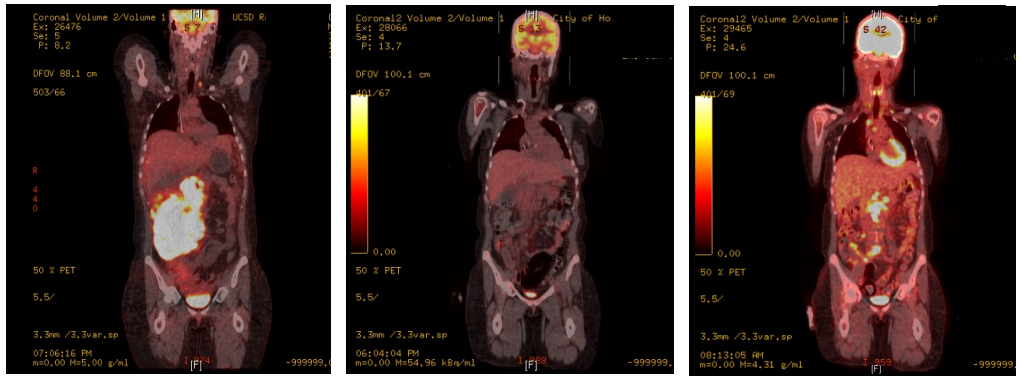
Access to novel CAR T cell therapy

- CARs for new targets (i.e. bispecific CARs, CARs for T cell lymphoma, AML, solid tumors)
- Test ”old” CAR earlier in disease course
- Test CARs in combination with other agents to further enhance response rate (i.e. immune booster)
- Test new manufacturing platform to make CARs with higher potency and shorter production time
- Improve safety by incorporating novel agents to prevent or mitigate CRS/NT complications
- Novel vaccine or anti-microbials trials to decrease infection risk post CAR T cell therapy

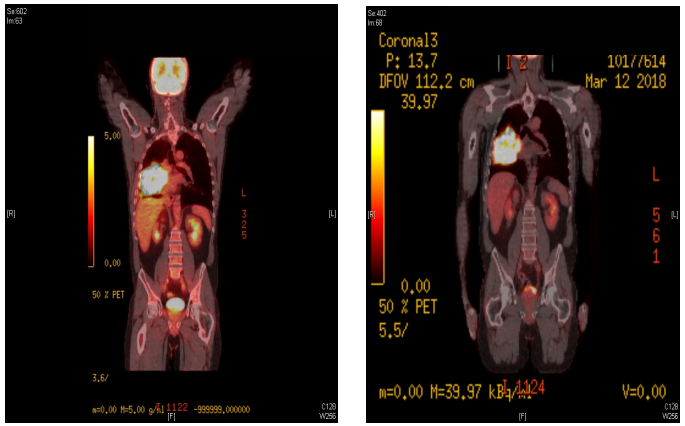
CAR T-cell Therapy: Overcoming Challenges

- Post CAR T relapse or non-responders

Pre | Day 40 | Day 167



Pre | Day 28



Potential resistance mechanism

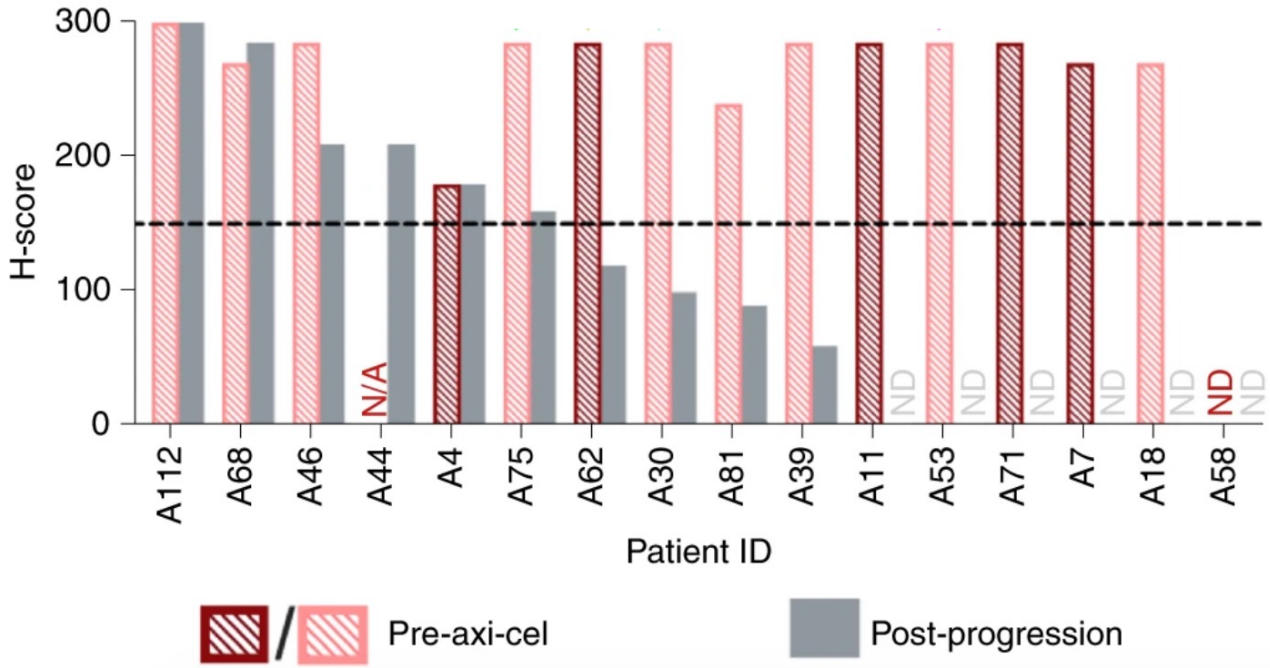
- Unfit CAR T products
  - Armored CARs (CD19CAR-IL18)
  - ibrutinib (CLL pt)
  - PI3Ki (BB21217)
  - iMiDs (PLATFORM)
  - 4-1 BB agonists (ZUMA-11)
  - CAR+cytokines (i.e. IL-7) (COH)
- tumor cell/environment
  - Add PD-1/PD-L1 blockade (PLATFORM)
  - Eliminate Treg cells
    - Tisa-cel + antiCD25ADC (E7777)
- Antigen/epitope escape

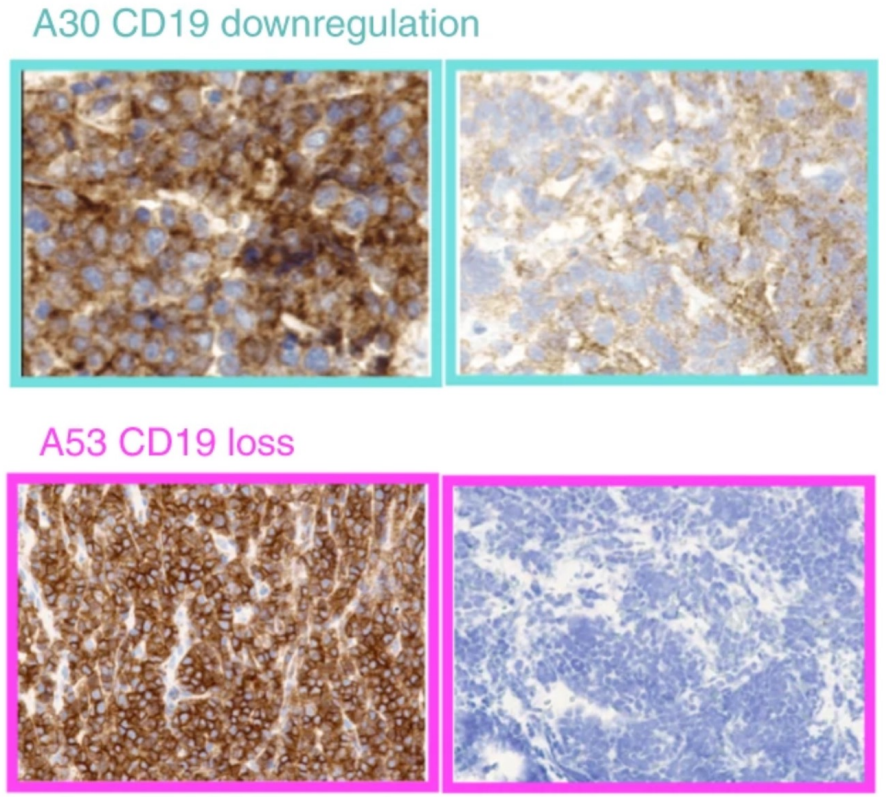
~50% ALL; ~25% NHL relapse

Ag loss; epitope loss; ↓expression

  - Dual targeting
  - (i.e.CD19/20, CD19/CD22, CD19/BAFFR)
  - CAR with a different target (CD22, BAFFR, ROR1)

CD19 loss or down regulation correlated with progression post Axi cel

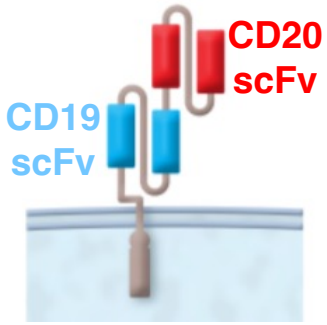


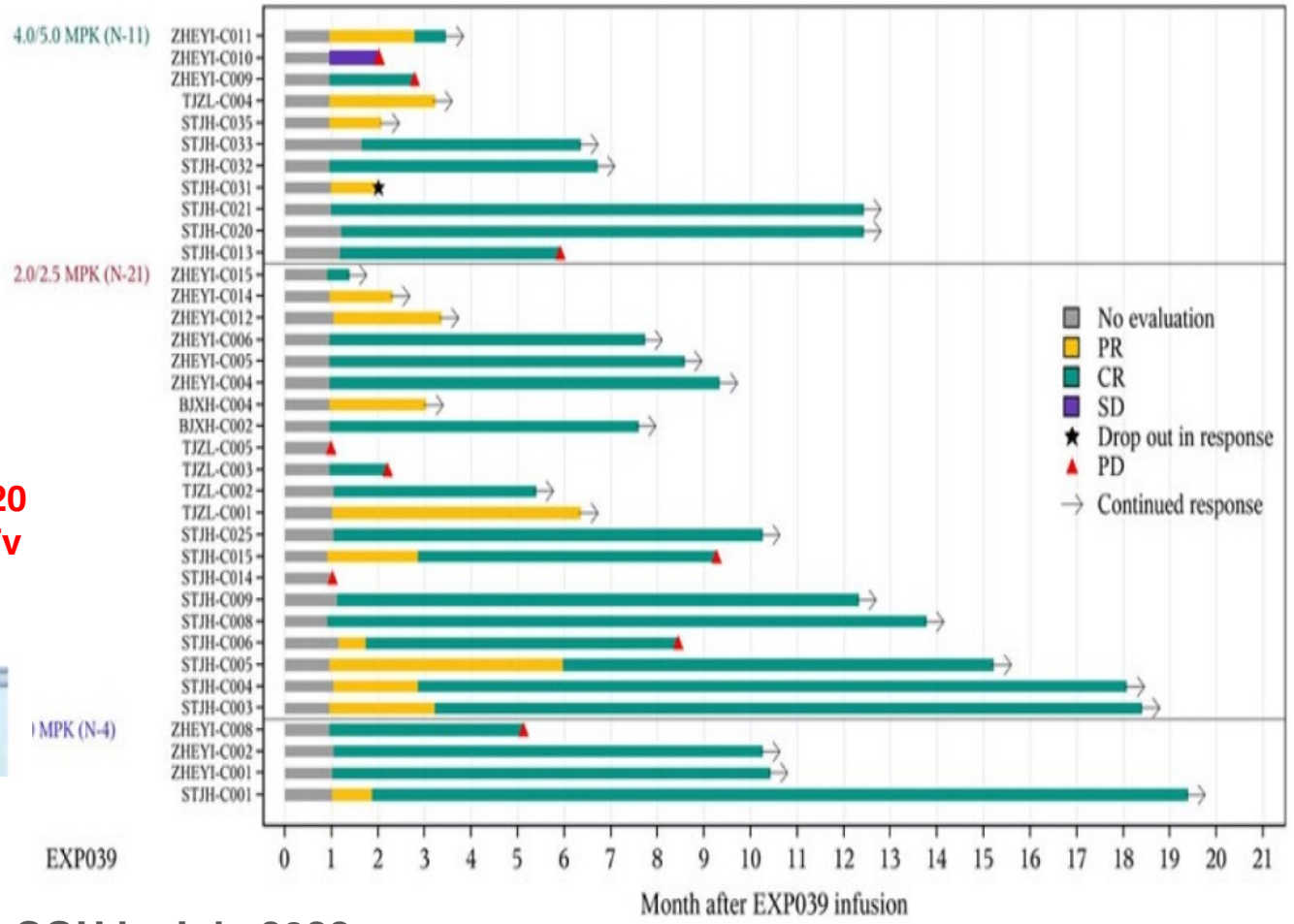


C-CAR039 (CD19CAR/CD20CAR)

- At data cut-off of 06/30/2021:
  - 36 patients had ≥28 days of follow up
  - Median time to CR was 1.1 months (0.9)-6)
  - Median DOR was NR (95% CI 8.4-NE)
  - **M6 PFS rate 83.2% (95% CI 69.1-100)**

Best Response	Total
ORR, n (%)	**33 (91.7)**
CR, n (%)	**26 (72.2)**
PR, n (%)	7 (19.4)
SD, n (%)	1 (2.8)
PD, n (%)	2 (5.6)





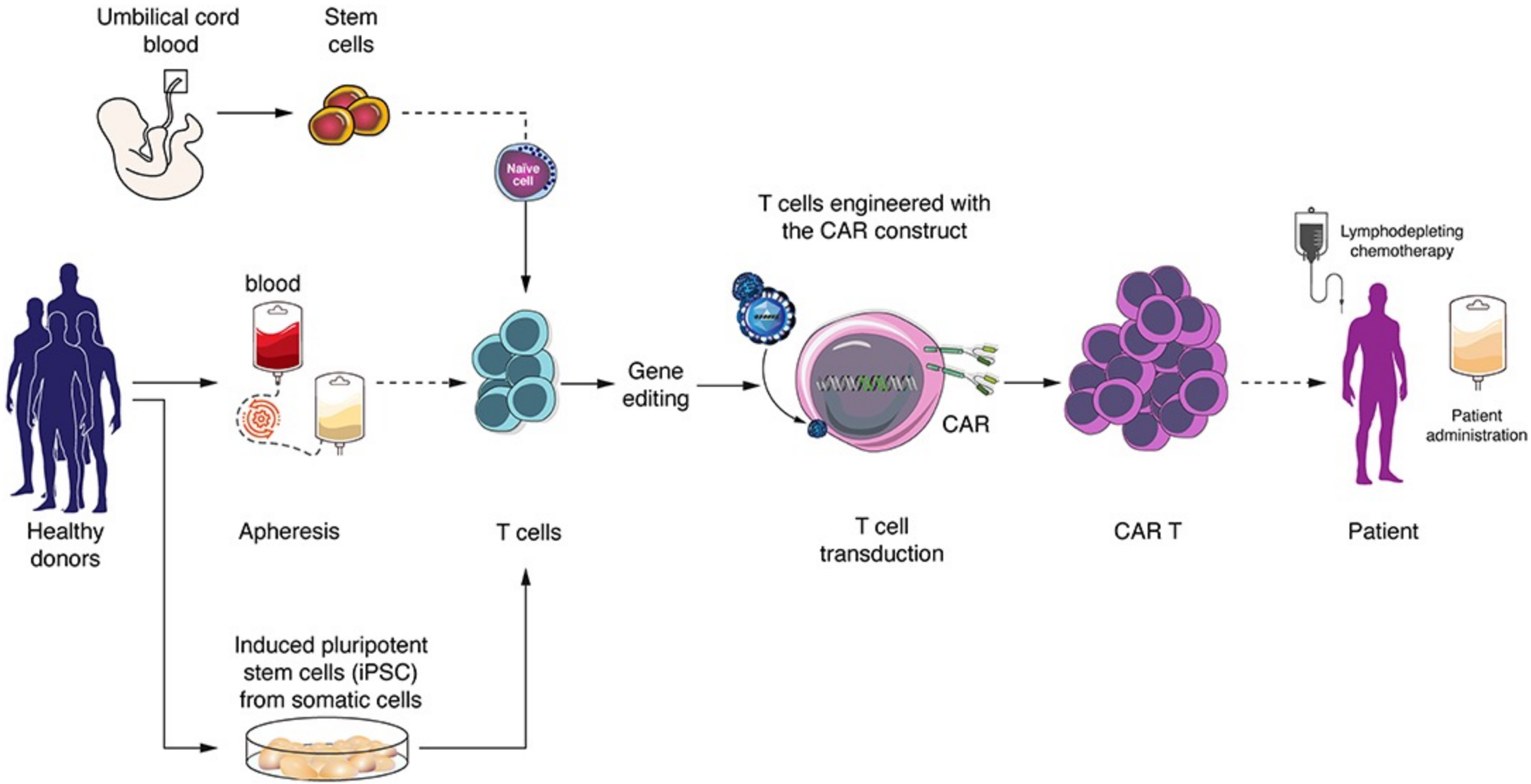
- ASCO 2021
- **Opened at COH in July 2022**

ASCO, 2021

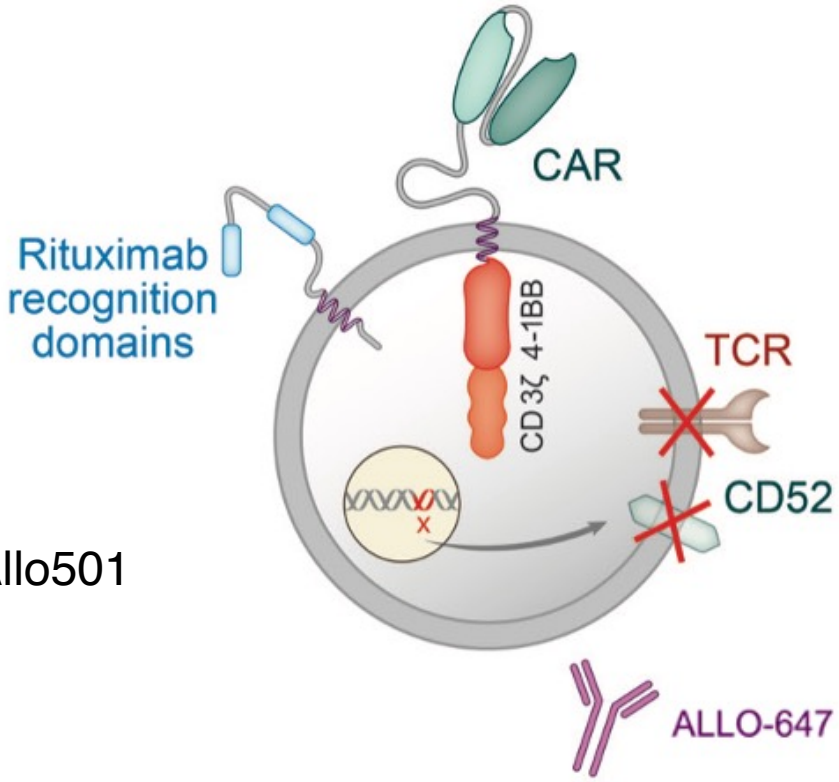
CAR T-cell Therapy: Challenges

- **Highly aggressive disease**

  bridging therapy to stabilize disease and debulk (which regimen?)
  - products with short manufacturing time
  - off the shelf products (CAR T, CAR NK).


Umbilical cord blood
Stem cells
Naive cell
T cells engineered with the CAR construct
Lymphodepleting chemotherapy
blood
Gene editing
CAR
Patient administration
Healthy donors
Apheresis
T cells
T cell transduction
CAR T
Patient
Induced pluripotent stem cells (iPSC) from somatic cells

ALPHA study (NCT03939026), ALLO-501 and ALLO-647



Allo501

Patient Population
- r/r DLBCL, FL, (4 had autoCART); N = 22

Dose levels
- 40M, 120M, 360M Allo501

Lymphodepletion Regimens
- LD1: Flu/Cy and ALLO-647 13 mg/d x 3 days
- LD2/LD3: Flu/Cy and ALLO-647 30 mg/d x 3 days (concomitant/staggered)

Median/Mean Time from Enrollment to Start of Lymphodepletion: 5 Days

ASCO 2020 Abstract 8002: Neelapu SS *et. al.*

Allogeneic CARs Racing in The Clinic

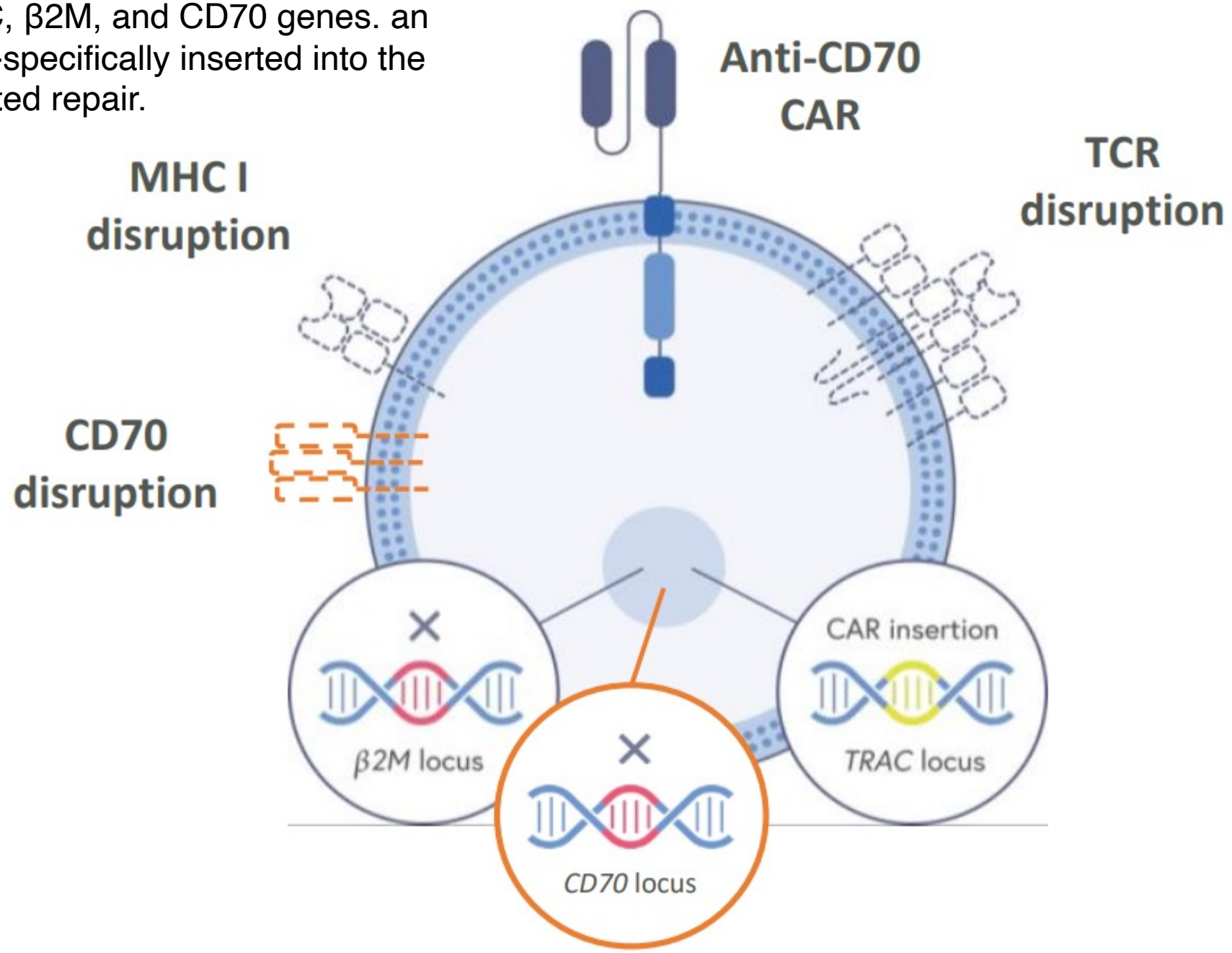
	CRS	ICANS	GVHD	ORR	CR
Allo501+647 N =22	5% ≥ grade 3	0	0	63% (12/19)	37% (7/19)
CD19CAR NK N= 11	0	0	0	73% (8/11)	64% (7/11)
PBCAR19 N =6	0	0	0	66% (4/6)	17% (1/6)

- AlloCARs appear to be safe with encouraging activity
- The immediate availability is clinically attractive
- Further study to optimize effective prevention of host versus graft rejection is necessary.

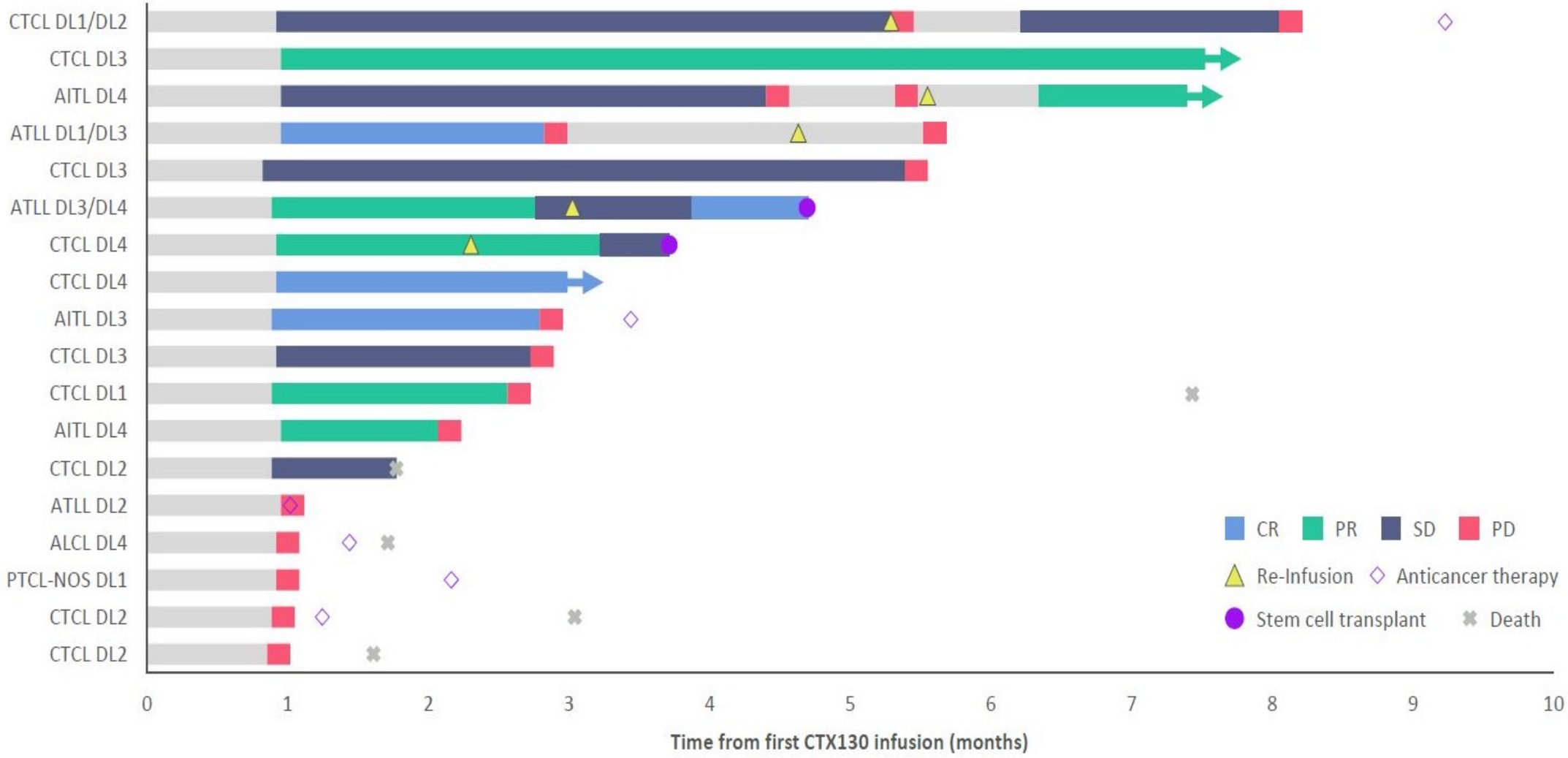
The winner in the allogeneic CARs is yet to be determined.

Neelapu SS *et. al*. ASCO 2020: Abstract 8002; Liu et al. NEJM 2020, 382:545-553; Shah et al. ASH 2019

CTX130 cell design.
genetic disruptions of the TRAC, β2M, and CD70 genes. an anti-CD70 CAR cassette is site-specifically inserted into the TRAC locus by homology-directed repair.



Off the shelf CD70CAR T cells: Encouraging response in T cell lymphoma



Swaminathan P Lyer EHA 2022

What have we learned?

- CAR T therapy has changed the outcome of patients with hematologic malignancies.
- Different CAR T design and products are associated with distinct safety profiles.
- Clinical expertise and infrastructure are needed to deliver CAR T safely, effectively, and to regulatory standard
- Ongoing effects (clinical trials, preclinical studies) aim to further improve efficacy, reduce toxicities, reduce cost, and expand disease types and indications.
- Cost effectiveness will be assessed in long term follow up of treated patients.

Thank you!

. Total CAR T patients treated: N > 900 from 2000 to July 2022 at COH
. Trials available for both heme and solid tumor patients

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