Chimeric Antigen Receptor T Cells Charting the Course from Clinical Trials to Commercialization

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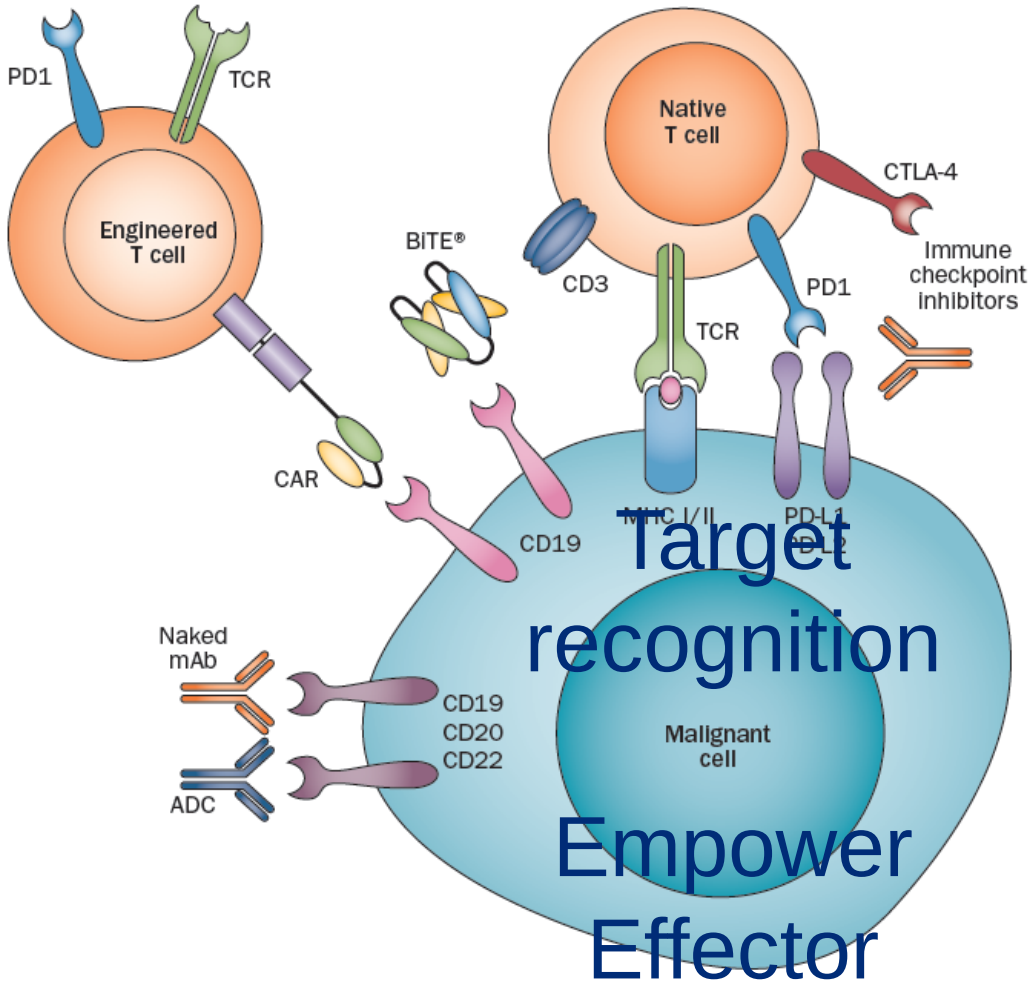
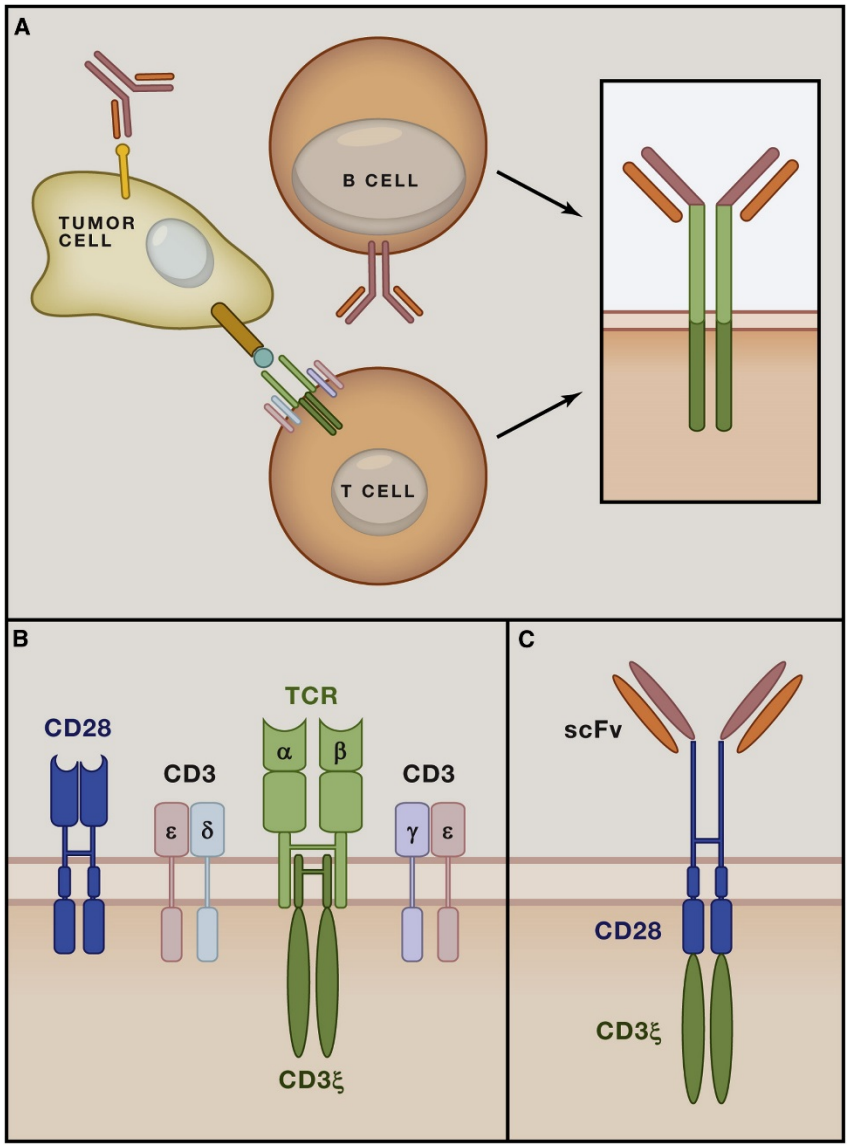
Anti-Tumor Biological-Immunotherapy Arsenal



- Checkpoint blockade (PD-1, CTLA-4, LAG-3)
- Agonist antibodies (CD137, GITR, CD40)
- T cell engagers: antibodies (blinatumomab) or TCR X anti-CD3 (scFv)
- Naked and ADC antibodies (Rituximab, Herceptin)
- Engineered T cells (CAR-T)
- TCR-transduced T cells

Batlevi, Nat Rev Clin Onc 2015

Principles of T Cell Engineering and CAR Design

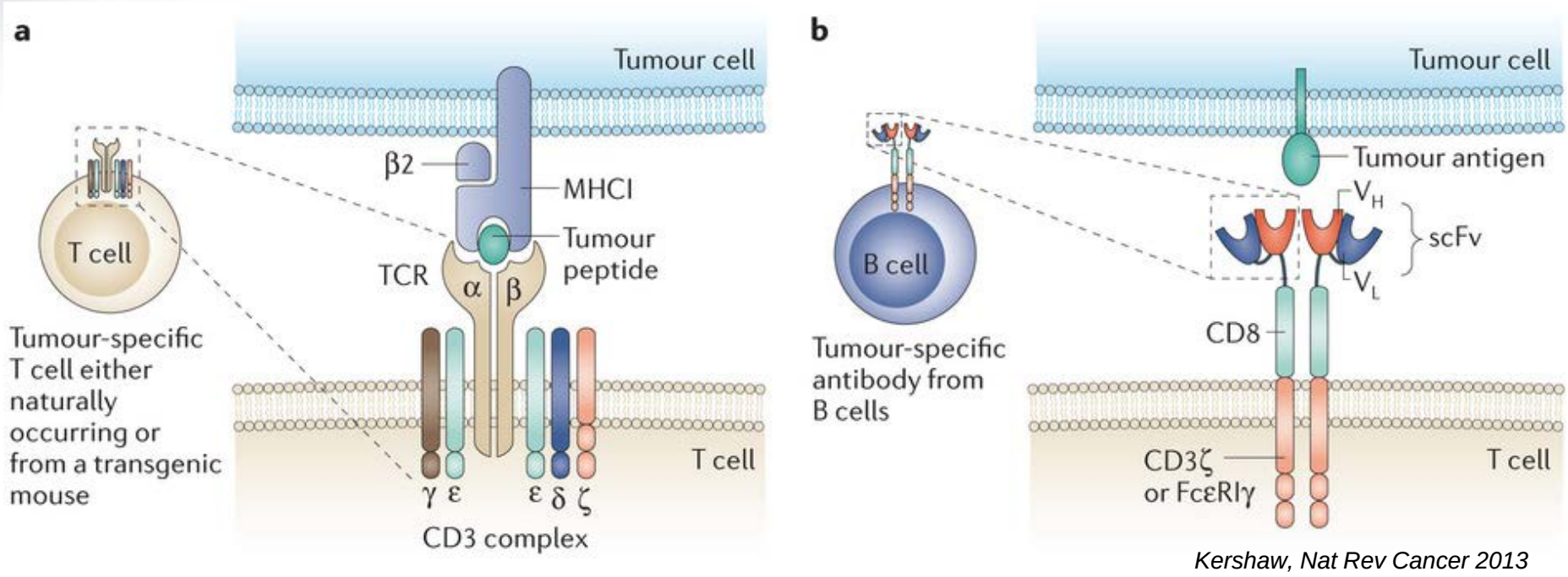


Specificity

Activity

Jacques F.A.P. Miller, Michel Sadelain (2015) Cancer Cell 27(4):439-449

Chimeric Antigen Receptor (CAR) T-Cell Structure and Mechanisms

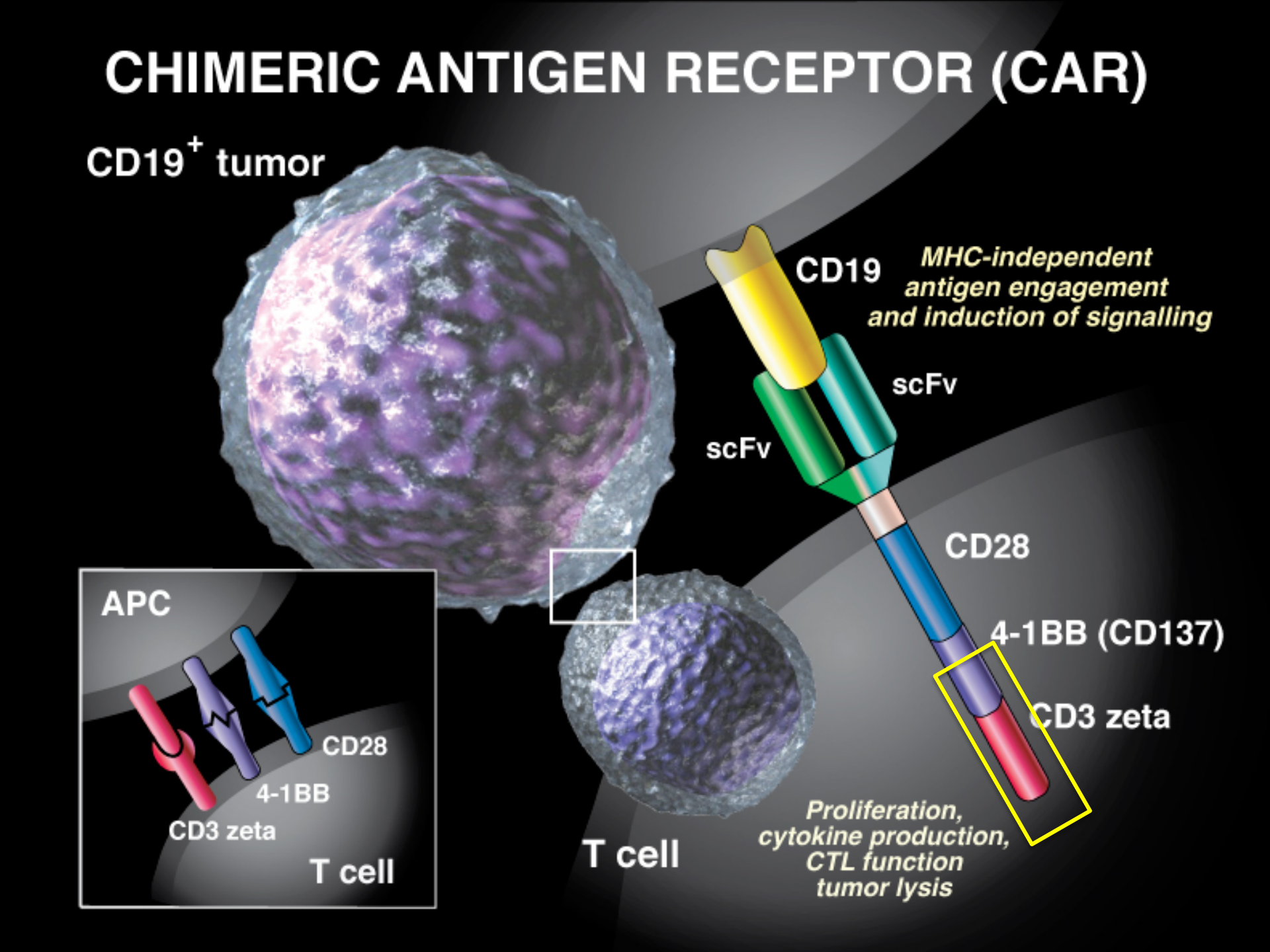


Kershaw, Nat Rev Cancer 2013

- Recognition of tumor Ag in its native state – affinity of CAR-T can be optimized.
- Intracellular domain can be modified to increase efficacy and durability of CAR-T
- CAR-T are still subject to the same regulatory and tolerigenic constraints of natural T cells,including checkpoints, Treg, MDSC
- CAR-T can be engineered to express cytokines and chemokines that further enhance function and migration
- Can be modified to express suicide genes that limit CAR-T population if toxicity occurs

Cellular and Recombinant Immunotherapeutics

	Intra-cellular Targets	Cell surface targets
Cellular	**TCR T Cells**	**CAR T Cells (autologous/allogeneic)**
Recombinant	**Bispecific TCR-anti-CD3 (e.g. ImmTACs)**	**Bispecific antibodies (incl. anti-CD3)**

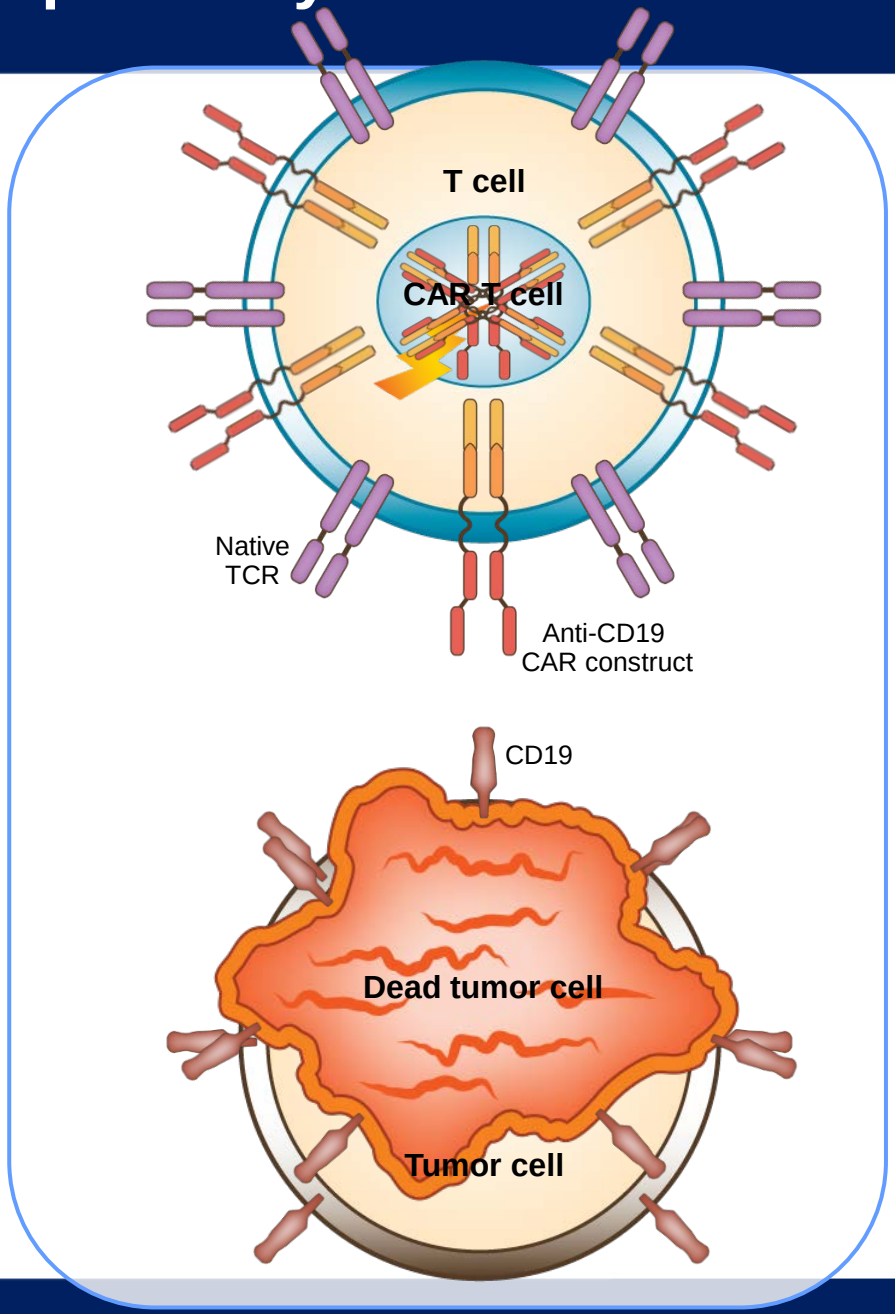

CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent antigen engagement and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation, cytokine production, CTL function tumor lysis

Redirecting T cell Specificity in CAR T cells

Goals for modern, highly active cell therapy:

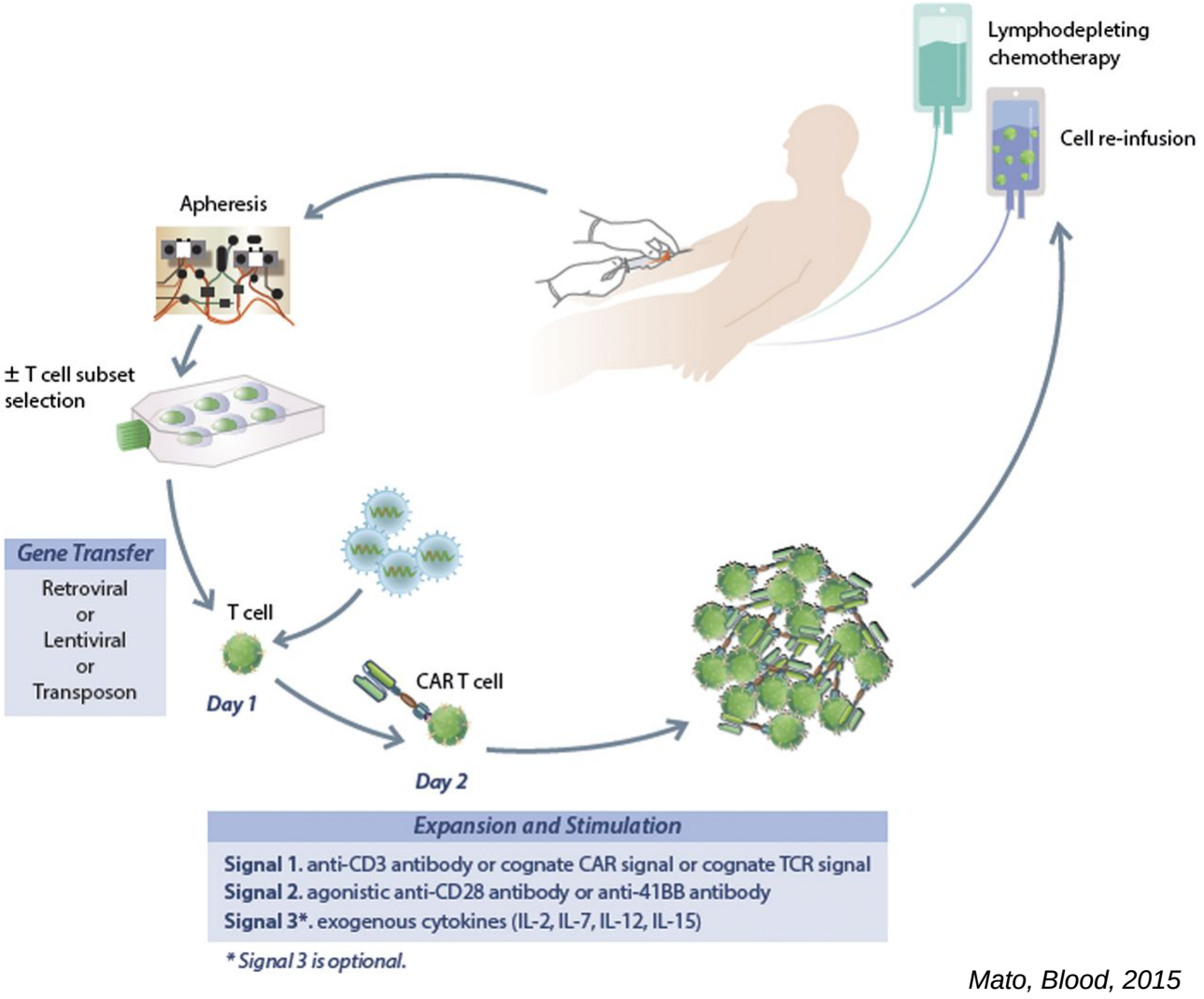
- Proliferation – high level of in vivo proliferation correlates with high response rates (and toxicity?)
- Persistence – longer term persistence may allow longer term disease control.

  Length of persistence needed for long-term disease control is unknown



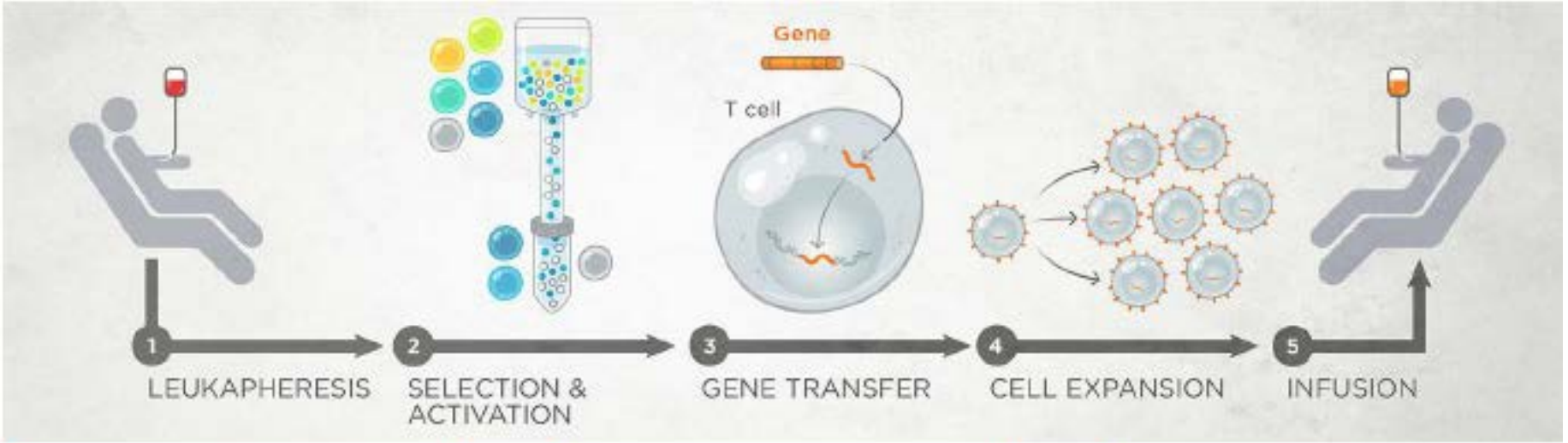
Generation of CAR-T cells: Patient to Lab to Patient

CAR-T cell generation is a multi-step complex process that involves manipulation of T cells ex vivo, conditioning the patient with cytoreductive therapies, and reinfusing CAR-T cells



Mato, Blood, 2015

Engineer T Cells To Recognize And Kill Cancer Cells



Clinical Activity	Cost Structure	Patient Convenience
▪ Expansion	▪ Automation	▪ Turnaround time
▪ Potency	▪ Closed platform	▪ Cryopreservation
▪ Persistence	▪ Scalable process	▪ Industrialization

CD19 CAR T Cell Status 2016

- CAR T cells offer potential to cure patients
- CD19 targeted CAR T cells have proven to be highly active in B cell malignancies: Acute Lymphoblastic Leukemia, Chronic Lymphocytic Leukemia, Non-Hodgkin's Lymphoma, ? Multiple Myeloma
- While potentially curative, there is very real toxicity
  - Fever, cytokine release syndrome, transient neurologic changes
- Multiple investigational products are in clinical development directed against CD19
  - Multicenter trials with central manufacturing
  - International trials

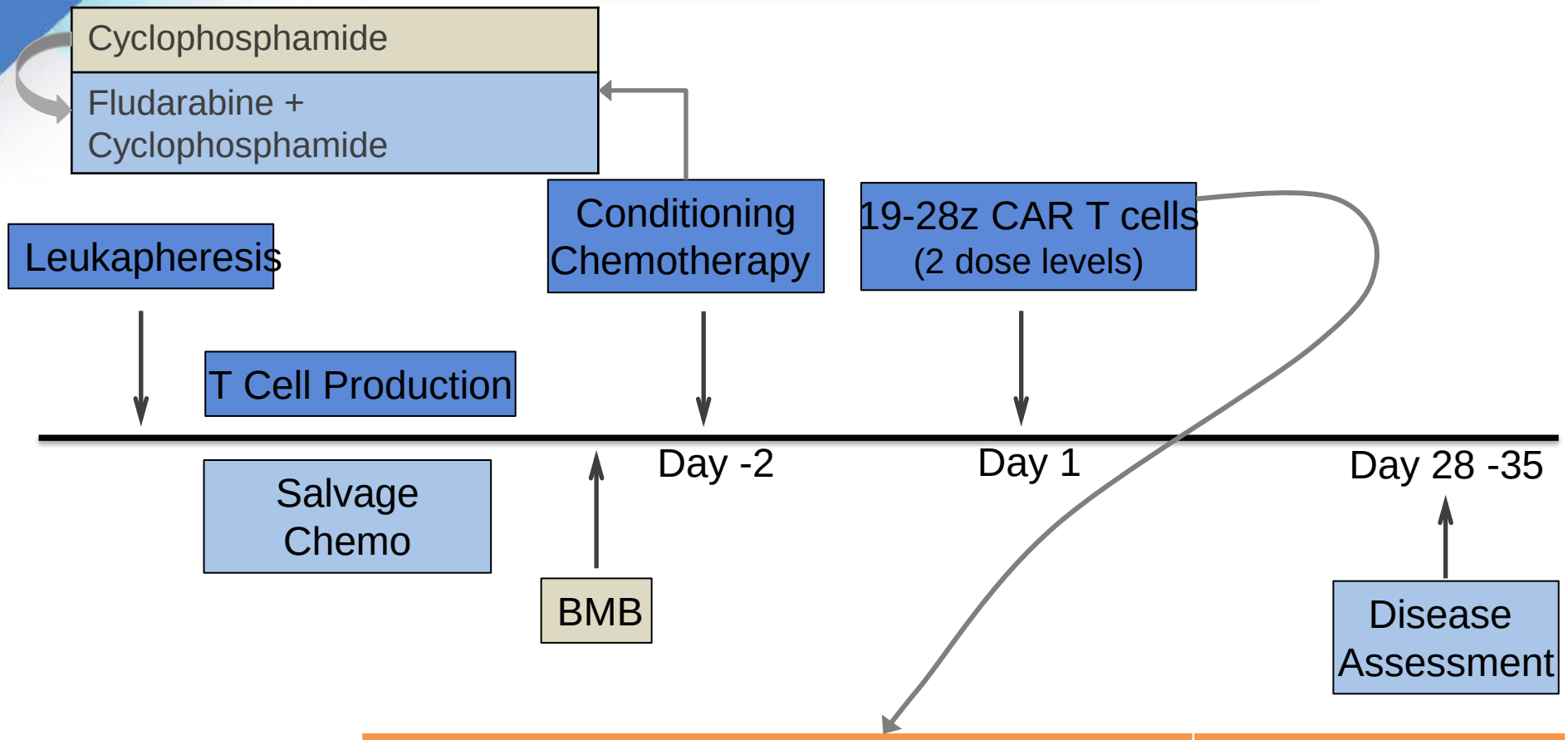
Selected CD19-directed Product Candidates in Clinical Trials Design Elements

Select Key Elements	JUNO JCAR014	JUNO JCAR015	JUNO JCAR017	Novartis CTL019	Kite KTE-C19
Costim domain	4-1BB	CD28	4-1BB	4-1BB	CD28
Binding domain	FMC63 (murine)	SJ25C1 (murine)	FMC63 (murine)	FMC63 (murine)	FMC63 (murine)
Starting cell population	CD4 + $CD8_{cm}$	CD4 + CD8 co-culture	CD4 + CD8	PBMC	PBMC
Ablation technology	EGFRt	None	EGFRt	None	None
Vector	Lentivirus	Retrovirus	Lentivirus	Lentivirus	Retrovirus

Summary of Select CD19-directed ALL Clinical Trials

Study No./Phase [Reference]	Product Name / Sponsor	Study Population	Sponsor [ClinicalTrials.gov Identifier]	CR Rate	Safety *CRS= Cytokine release syndrome*
2639/Phase 1/2 [Turtle, ASH 2015, Abstract 184, Abstract 3773]	JCAR014 / JUNO	R/R CD19+ adult ALL, NHL, CLL	FHCRC [NCT01865617]	CR: 27/29 (93%) in ALL ORR: 7/11 (64%) in NHL; 8/9 (89%) in CLL	sCRS: 7/30 (23%) in ALL; 4/32 (13% in NHL; 1/9 (11%) in CLL Grade ≥3 Neurotoxicity: 15/30 (50%) in ALL; 9/32 (28%) in NHL; 3/9 (33%) in CLL
09-114/Phase 1 [Park, ASH 2015, Abstract 682]	JCAR015 / JUNO	R/R or MRD+ CD19+ adult B-cell ALL	MSKCC [NCT01044069]	CR: 37/45 (82%)	sCRS: 11/46 (24%) Grade ≥3 Neurotoxicity: 13/46 (28%)
13-052/Phase 1 [Curran, ASH 2015, Abstract 2533]	JCAR015 / JUNO	R/R or MRD+ CD19+ pediatric/young adult B-cell ALL	MSKCC [NCT01860937]	CR: 7/11 (64%)	sCRS: 2/7 (29%)
PLAT-02/Phase 1 [Jensen, CIPO 2015]	JCAR017 / JUNO	R/R CD19+ pediatric/young adult B-cell ALL	SCRI [NCT02028455]	MRD-negative CR: 29/32 (91%)	sCRS: 6/22 (27%) Grade ≥3 Neurotoxicity: 4/22 (18%)
10-007706/ Phase 1 [Grupp, ASH 2015, Abstract 681]	CTL019 / Novartis	R/R CD19+ pediatric/ young adult B-cell ALL	U Penn [NCT01626495]	CR: 55/59 (93%)	Any Grade CRS: 52/59 (88%)
120112/Phase 1 [Lee, ASH 2015, Abstract 684]	KTE-C19 / Kite	R/R CD19+ B-cell ALL	NCI [NCT01593696]	CR: 27/46 (59%) in ALL	sCRS: 7/46 (15%) Grade ≥3 Neurotoxicity: n=3 patients

MSKCC 09-114 Ph1 Study Design
JCAR 15 Academic Version



Disease Status	CAR T Cell Dose
Morphologic disease (≥5% blasts in BM or EM disease)	1 x 10^6 CAR T cells/kg
Minimal disease (<5% blasts in BM)	3 x 10^6 CAR T cells/kg

MSKCC 09-114 Study Progress

- 46 adult patients with relapsed/refractory ALL treated with 19-28z CAR T cells at MSKCC
  - 46 patients evaluable for toxicity assessment
  - 45 patients evaluable for response assessment with >1 month follow up
- Median follow-up: 6 months (1-45 months)
  - Data cutoff date: Nov 2, 2015
- Cumulative follow-up
  - 20/45 (44%) patients with ≥ 6 months of follow up
  - 9/45 (20%) patients with ≥ 1 year of follow up

Baseline Patient Characteristics

Characteristic	Number of Patients N=46 (%)
Sex	
Male	34 (74)
Female	12 (26)
Age at infusion (years)	
18-29	11 (24)
30-59	25 (54)
≥60	10 (22)
Median (range)	45 (22-74)
Prior allogeneic HSCT	
Yes	18 (39)
No	28 (61)

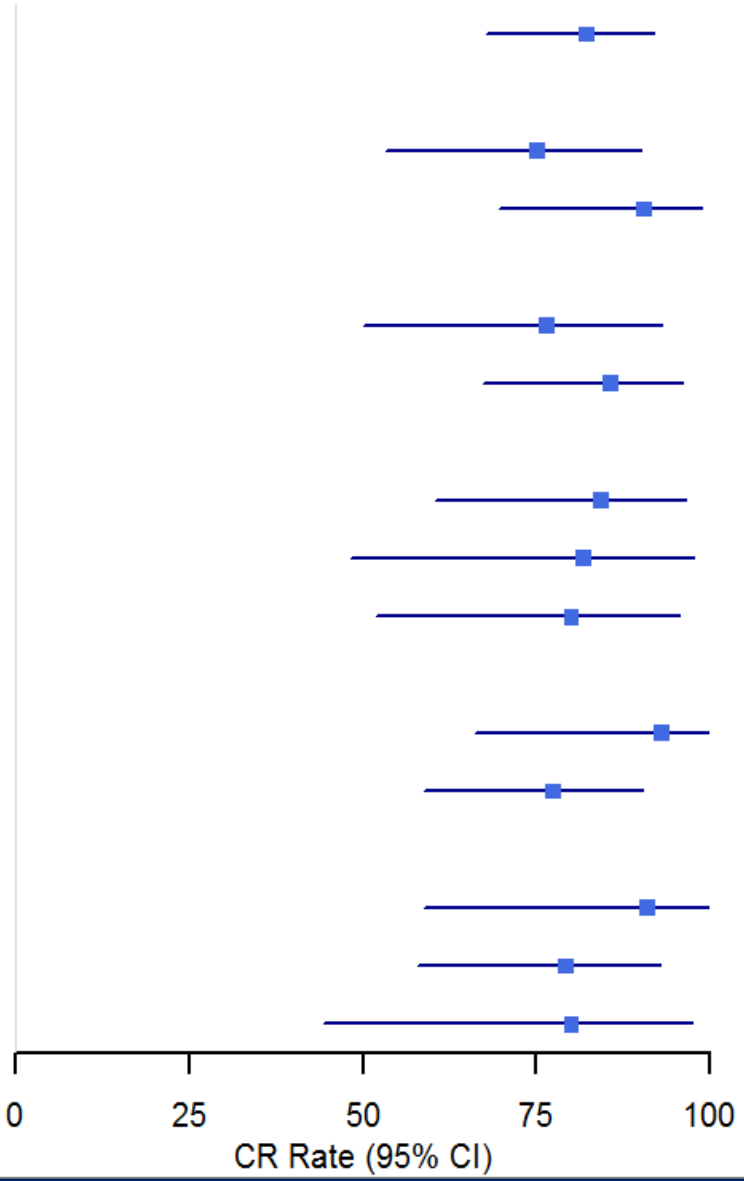
Summary of Clinical Outcomes

	Number of Patients N=45 (%) [95% CI]
Overall CR Rate	37/45 (82%) [68 – 92]
Morphologic disease (≥5% blasts)	18/24 (75%) [53 – 90]
Minimal disease (<5% blasts)	19/21 (90%) [70 – 99]
Overall MRD Negative CR Rate*	30/36 (83%)
Median Time to CR (range)	21 days (8 – 46)

*Assessed among those patients who achieved CR and evaluable for MRD analysis (n=36)

CR Rates by Subgroups

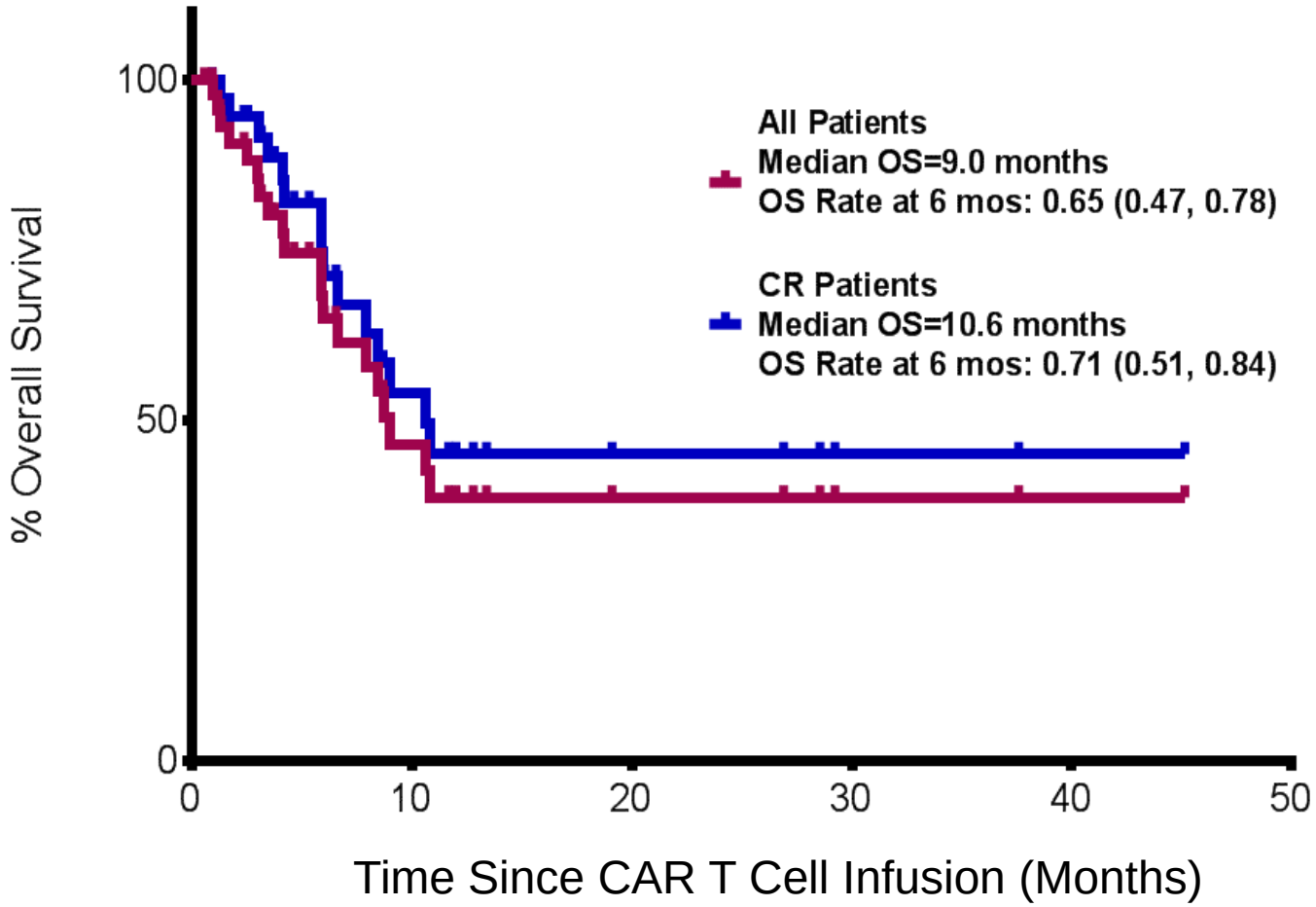
Subgroups	N	CR Rate
Overall	45	82.2
Disease Burden		
Morphological	24	75.0
Molecular	21	90.5
Pre-CAR HSCT		
Yes	17	76.5
No	28	85.7
# of Prior Therapies		
2	19	84.2
3	11	81.8
>=4	15	80.0
Ph+ Status		
Ph+	14	92.9
Ph-	31	77.4
Age Group (Years)		
18-29	11	90.9
30-59	24	79.2
>=60	10	80.0



Post-CAR T Cell Infusion: Subsequent Treatments & Relapses

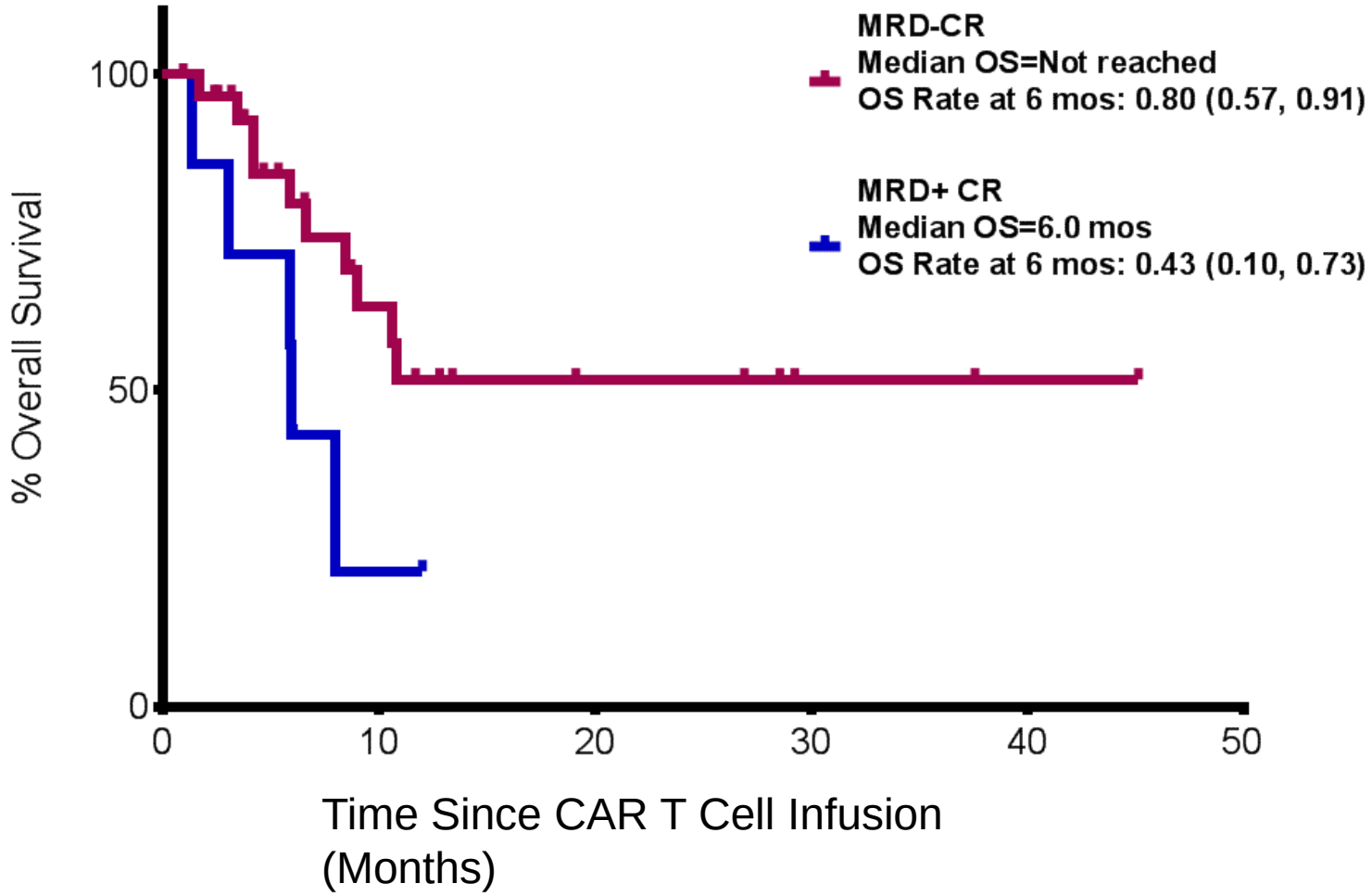
- 13 of 37 CR (35%) patients proceed to allogeneic HSCT after achieving CR to CAR T cells
  - 11 patients had *no* prior HSCT and 2 patients had prior HSCT
- 18 patients relapsed during follow-up
  - 4/18 relapses in patients after post-CAR T allo-HSCT
  - 3/18 relapses were with CD19-undetectable blasts

Overall Survival:
All Patients & CR Patients

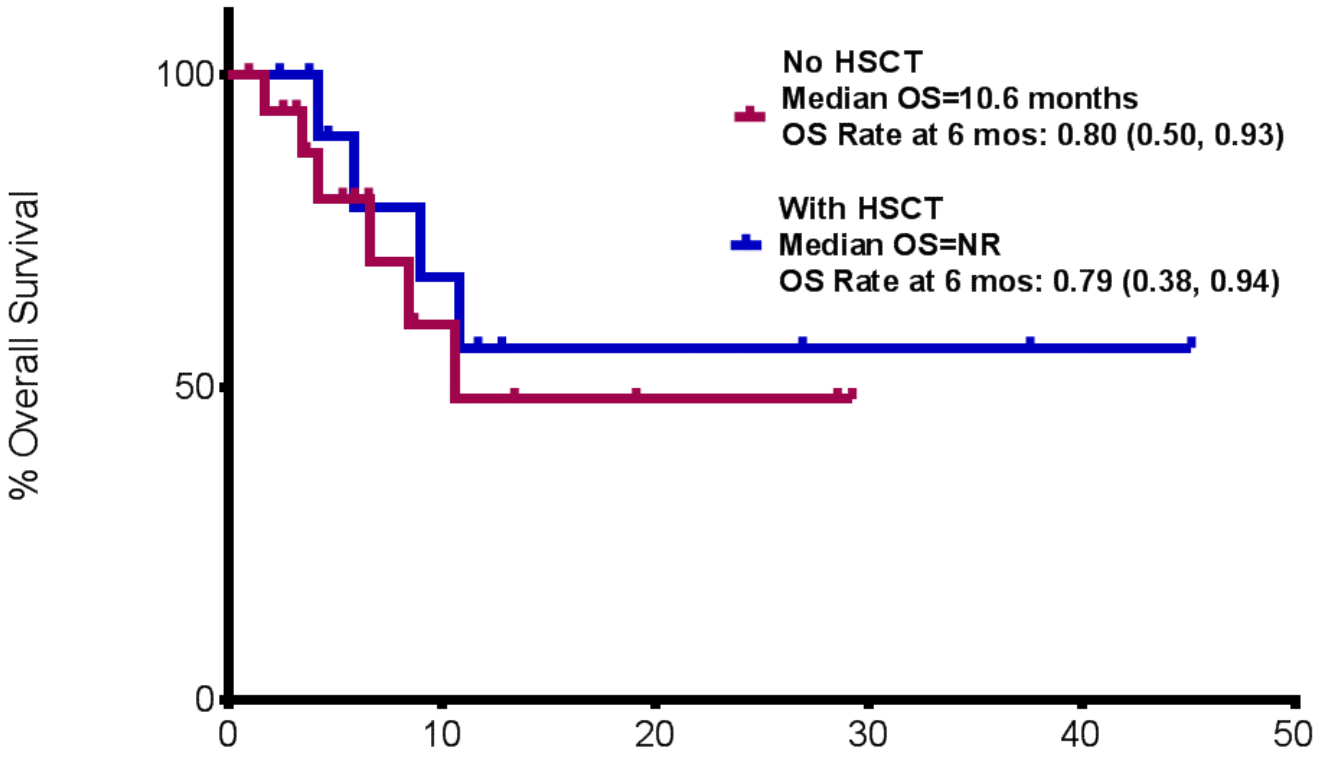


Historical SOC median survival ~3 months (O'Brien, et al, 2008)

Overall Survival:
By MRD Status After CAR T Cell Treatment



Overall Survival:
By HSCT Status Post CAR T Cells – MRD-CR Patients



CRS & Neurological Toxicities

Subgroups	Severe CRS*	Grade 3/4 Neurotoxicity	Grade 5 Toxicity
Overall	11 (24%)	13 (28%)	3 (6%)¶
Pre-T cell Disease Burden			
Morphologic disease (n=25)	11 (44%)	10 (40%)	
MRD (n=21)	0 (0%)	3 (14%)	

***Requiring vasopressors and/or mechanical ventilation for hypoxia**

¶All pts received a higher dose ($3x10^6$ CAR T cells/kg): 2 pts with sepsis/multi-organ failure; 1 pt had seizure, but unknown cause of death

- CRS managed with IL-6R inhibitor (14 pts) and/or steroid (15 pts)
- Neurological symptoms are reversible, and can occur independent of CRS

CD 19 CAR T Cells Clinical Status

- CD 19 directed CAR T Cells are highly active in the treatment of B-cell ALL
- High Complete remission rates are observed but this is balanced by significant adverse events that can be mitigated by intensive monitoring and intervention
- Multiple products are in registration trials in ALL and NHL
- Multiple Orphan Drug Designations granted
- Resistance due to splice variants in target antigen may be addressed by use of additional targets
- Opportunity to quickly improve the construct design and manufacturing for clinical trials

Discussion

Clinical and Regulatory Challenges for Development of CAR T Cells

- Large CMC investment (dedicated manufacturing facilities in multiple regions, ie, US, EU, Japan)
- Complex logistics to manufacture and deliver personalized cellular product (transport, import/export permits, QP release)
- Rapid innovation and short cycle time to engineer improvements in design and manufacturing for successor product directed against the same tumor target
  - Are refined products considered different?
  - Is a clinical trial needed for each successor product?
  - How is comparability for next generation improvements established?
- Onerous, complicated, and confusing comparability requirements can differ by region/HA)
- Need defined endpoints for rapid assessment of clinical benefit that will shorten time to market access for patients
- Impact of stem cell transplant censoring on defining risk benefit profile
- Overlapping scope of regulations for both gene therapy and cellular therapy
- National/local hospital exemptions

Key Regulatory Challenges Associated with CAR-T development

- Can a single arm Phase 1 / 2 trial with compelling clinical outcome and reasonable safety data in a high unmet medical population constitute grounds for full approval in this population without adequate treatment options?
- If randomized confirmatory trials are required, what is an acceptable design?
  - Randomisation against previous SOC may not be practicable any longer
  - Alternative ways to provide more data post approval (eg control against RWD)?
  - How can clinical superiority be demonstrated against other CAR-T cell products, given that a comparative trial may not be possible?
- How can the Regulatory framework account for iterative improvements in design and manufacturing, from original CAR T cell product to successor constructs, occurring in a relatively short timeframe?
- How are expected changes to manufacturing processes (and sites) during clinical development qualified?
- How to determine impact of process changes with one-patient one-batch? Critical quality attributes for comparability?
- What “genetic engineering” regulations are fit for purpose for these products?