Directions and Challenges as the Immune Effector Cell Field Explodes – From Bench to Clinic and From Collection to Manufacturing to Patient

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MABB Spring Seminar

April 4th, 2023

Dana-Farber Cancer Institute

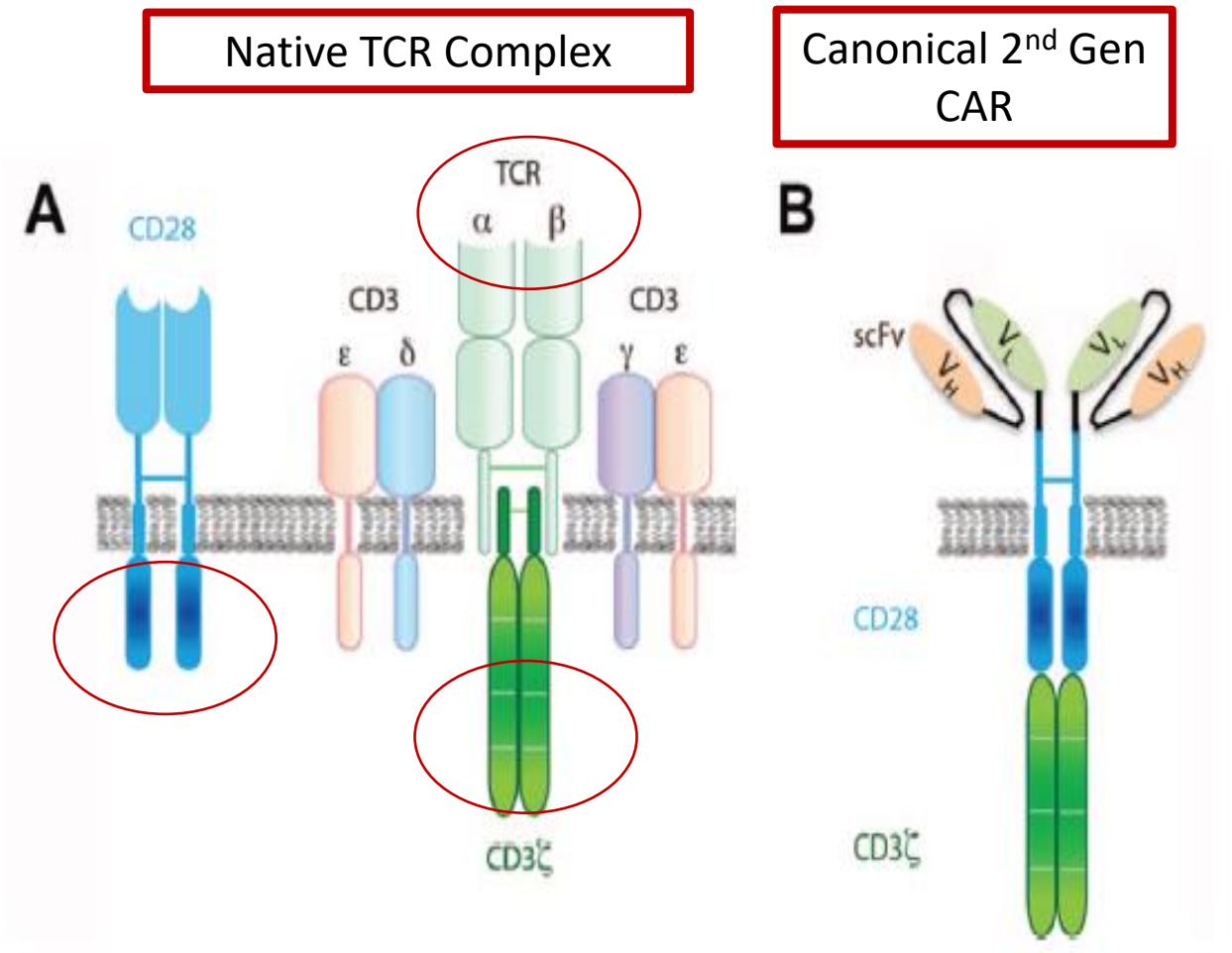
Disclosures

Ad Hoc Advisory Boards for Glaxo Smith Kline, Iovance, Kite/Gilead, SmartImmune, and Sobi

Overview

- Chimeric Antigen Receptor T Cells – the base model
- Future CAR directions and other makes and models
- It Takes a Village
- Standardization will be key to sustainability

Chimeric Antigen Receptor Design and Rationale



Sadelain, Park ASH Educ Program, 2015

CAR T Cells

- These T cells exploit native antibody or T cell recognition and signaling pathways
- Genetic engineering and introduction of unique combinations of proteins through viral vectors allows generation of T cells recognizing a particular tumor protein
- These cells are a "living drug", expanding dramatically after infusion, and effectively killing tumor cells

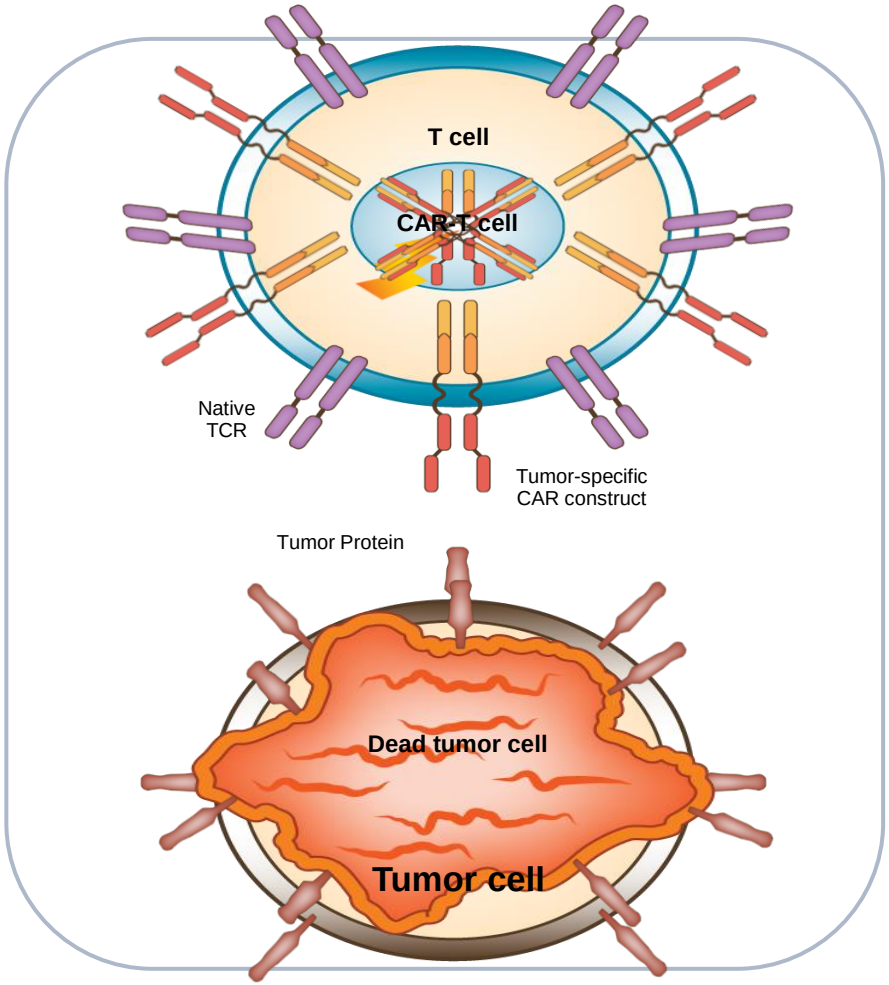
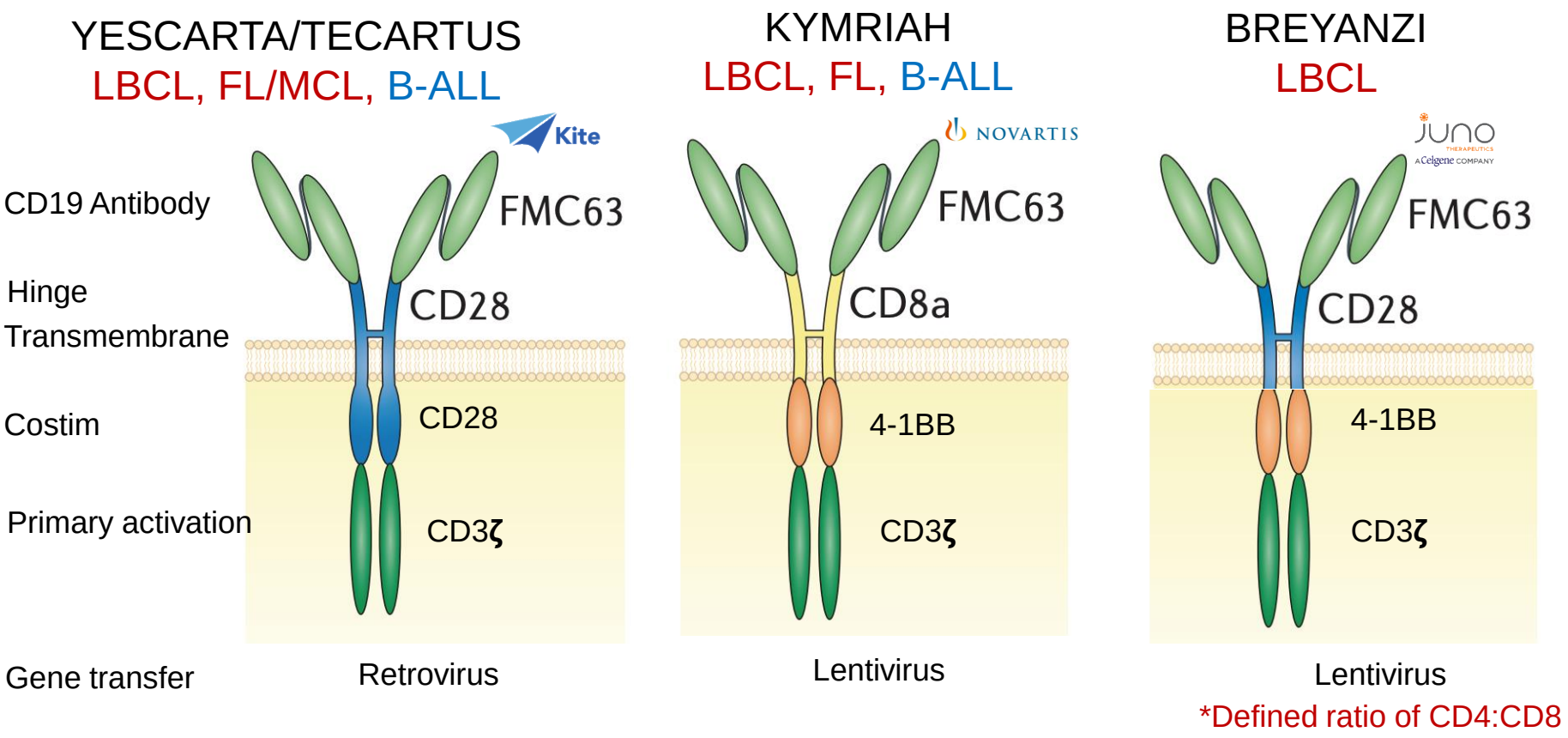


Image courtesy of Stephan Grupp, UPenn

CD19 Chimeric antigen receptor-T cells available commerically:
LBCL + MCL + B-ALL Late line and 2nd line



Adapted from Nat Rev Drug Discov. 2015 Jul; 14(7): 499–509.

CD19 CAR T-cells for DLBCL: 40% Durable Remission Rate

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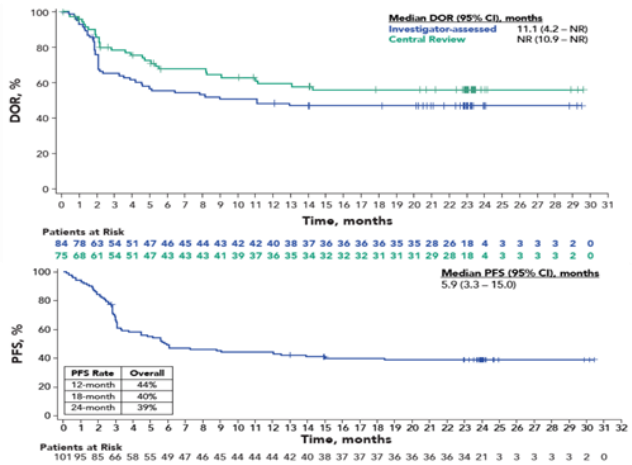
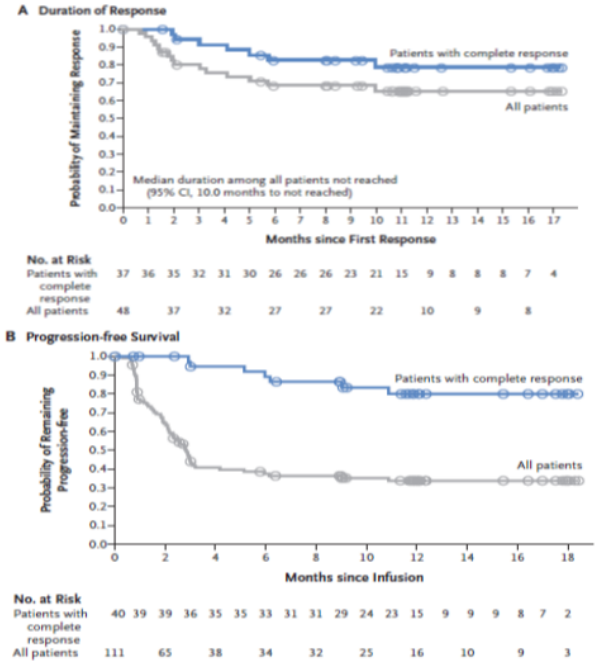
Yescarta
ZUMA-1

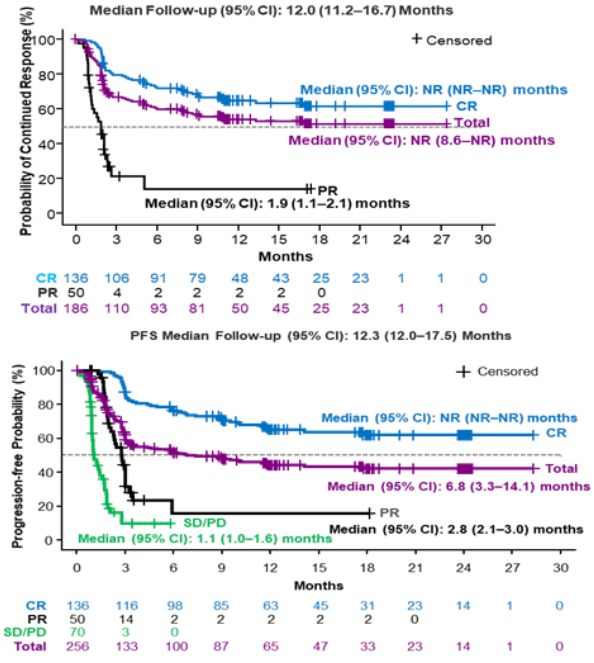


Locke et al Lancet Oncology 2019;20:31
Schuster et al NEJM 2018
Abramson et al ASH 2019

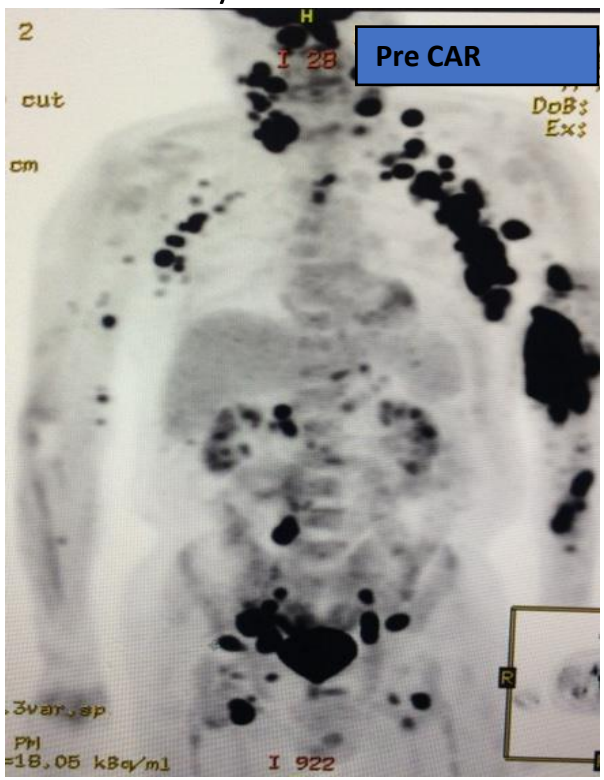
Kymriah
JULIET

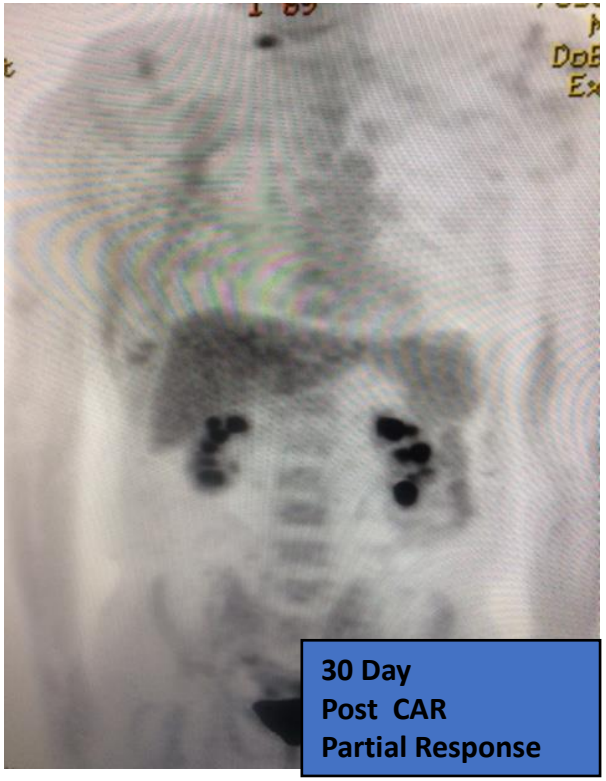


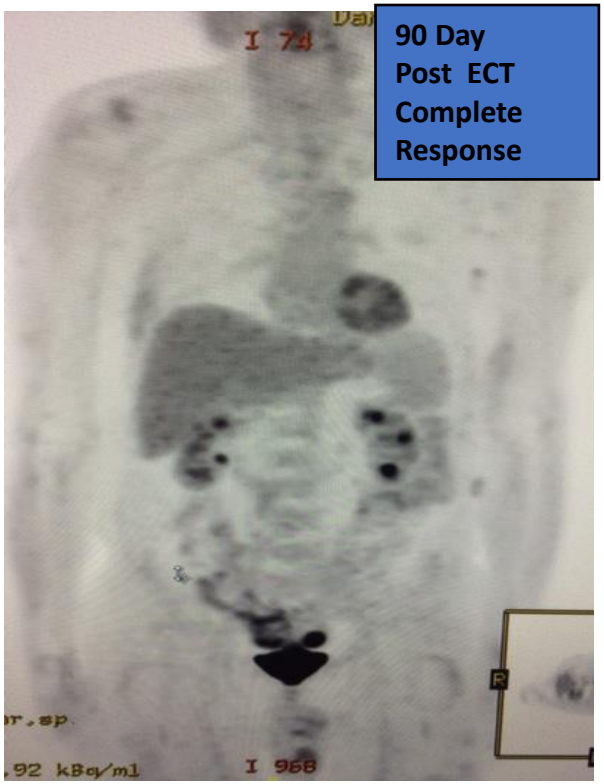
Breyanzi
TRANSCEND-001



Case Study - DLBCL

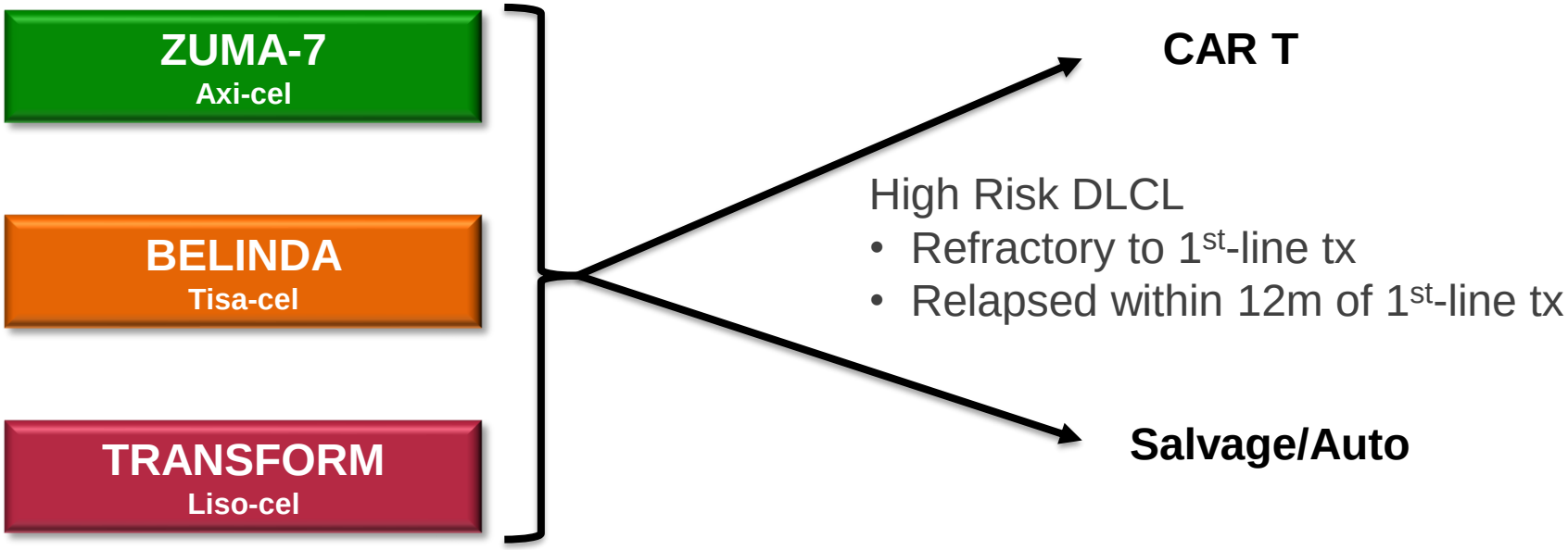






Moving to earlier lines of therapy…

Will CAR T-cells Replace Auto-transplant?



ZUMA7, TRANSFORM, BELINDA EFS and OS => Approval of Yescarta and Breyanzi in 2nd Line

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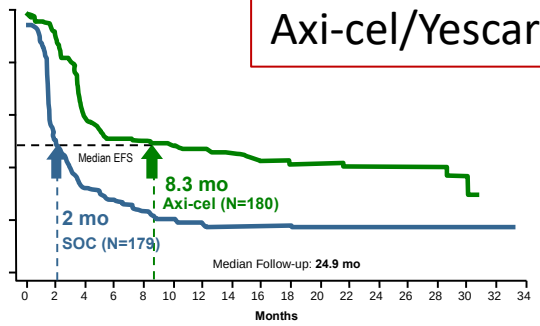
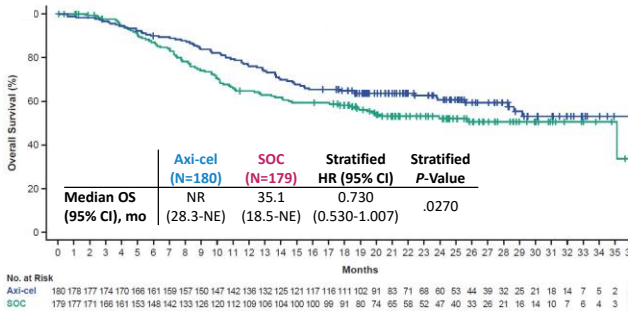
ZUMA-7[1]

HR 0.398 (95% CI, 0.308–0.514); *P* < 0.0001

Axi-cel/Yescarta



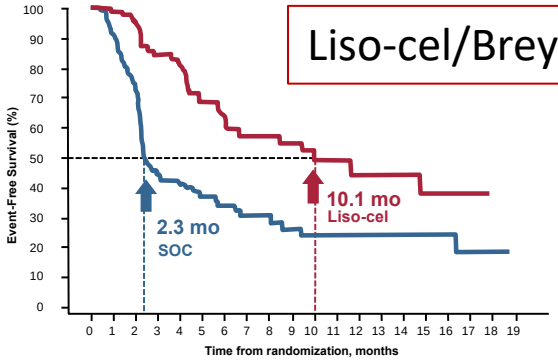


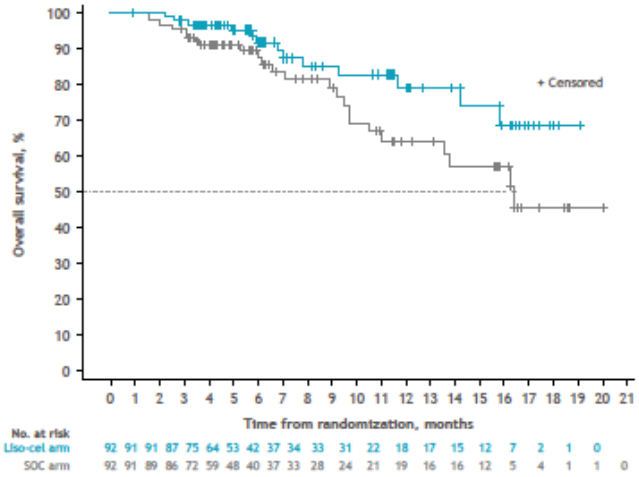
	Axi-cel (N=180)	SOC (N=179)	Stratified HR (95% CI)	Stratified *P*-Value
Median OS (95% CI), mo	NR (28.3-NE)	35.1 (18.5-NE)	0.730 (0.530-1.007)	.0270

TRANSFORM[2]

HR 0.349 (95% CI, 0.229-0.530); *P* < 0.0001

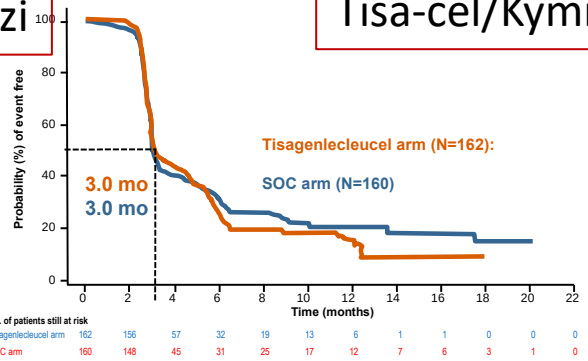
Liso-cel/Breyanzi



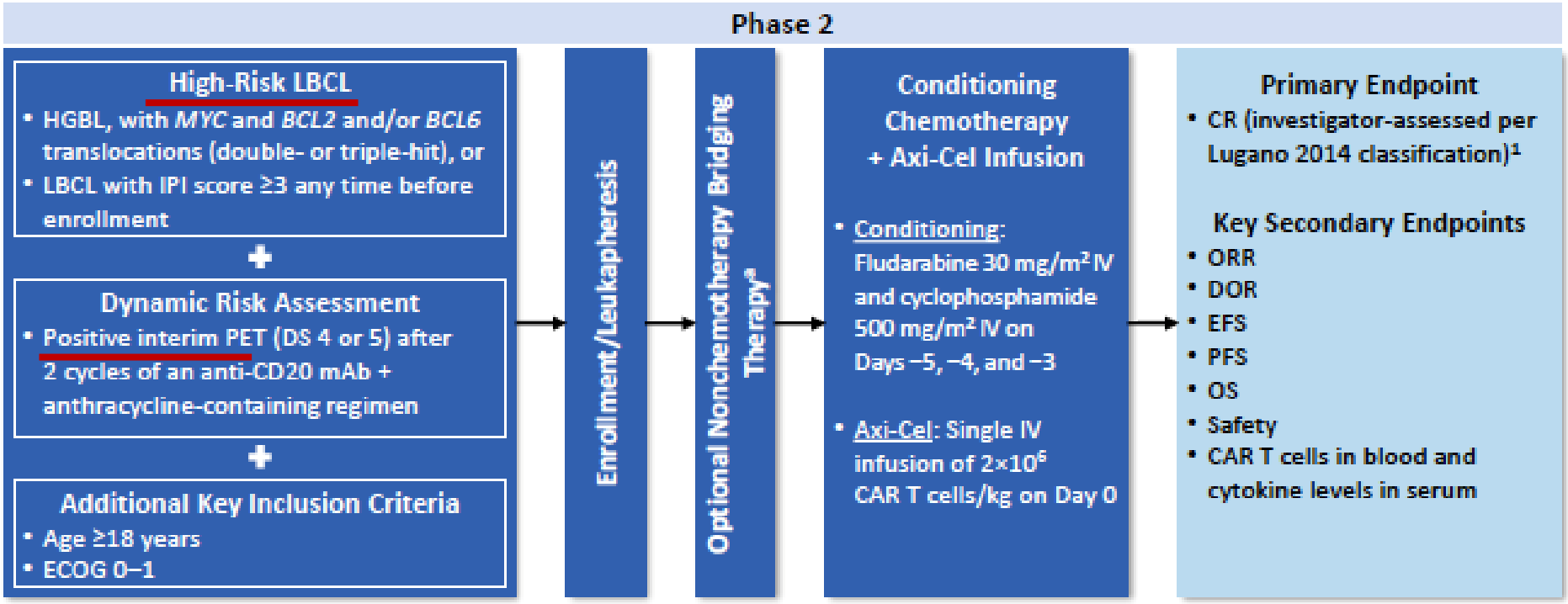


BELINDA[3]

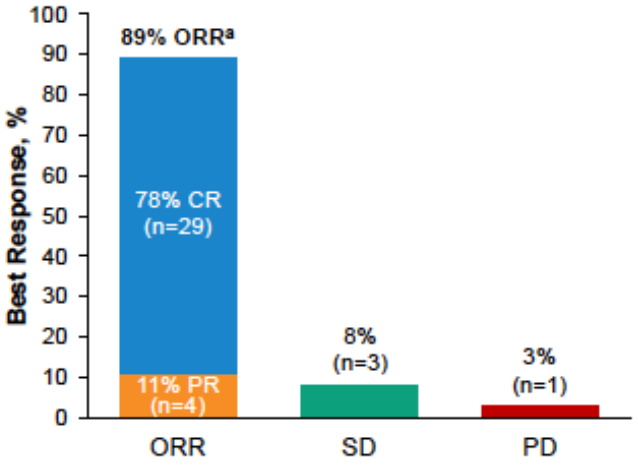
Tisa-cel/Kymriah



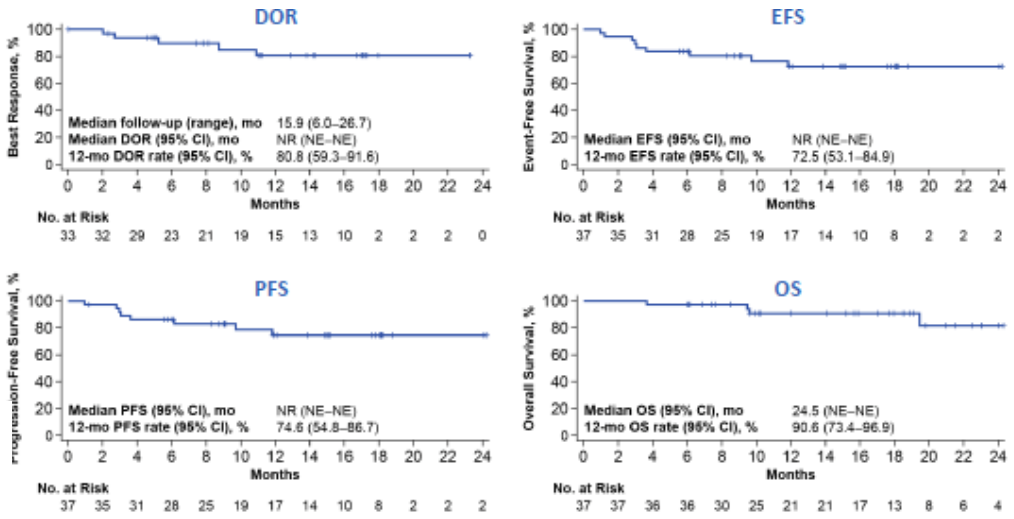
ZUMA 12: Axi-cel in Frontline High-risk LBCL



ZUMA12 RESULTS => Frontline Randomized Study



Parameter, Median (Range)	ZUMA-12[a] (N=40)	ZUMA-1 Cohort 1[b] (N=77)
Total no. of T cells infused×10[6]	304 (165 –603)	295 (149–760)
Total no. of CAR T cells infused×10[6]	165 (95–200)	160 (96–200)
Total no. of CCR7+CD45RA+ T cells[c] infused×10[6]	105 (33–254)	40 (2–215)
CCR7+CD45RA+ T cells[c], %	35 (7–80)	14 (1–76)
Doubling time, days	1.6 (1.3–3.4)	1.5 (1.0–3.8)
IFN-γ, pg/mL	4013 (529–14,700)	5826 (858–17,800)



Combinations for safety and efficacy

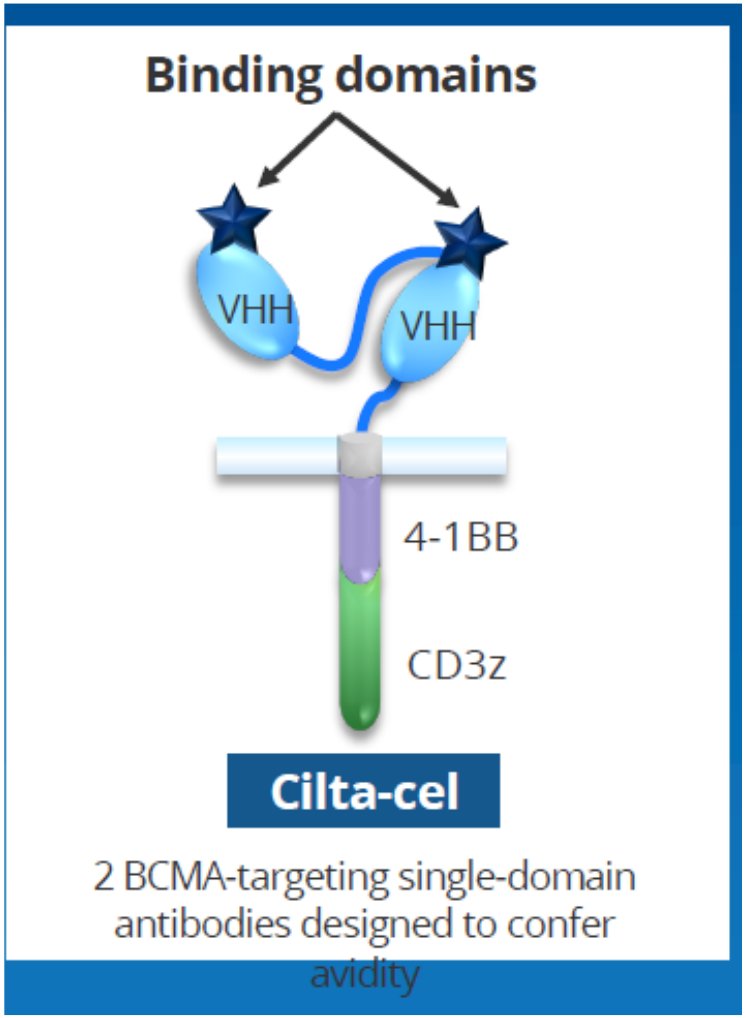
12

Central Nervous System Dz

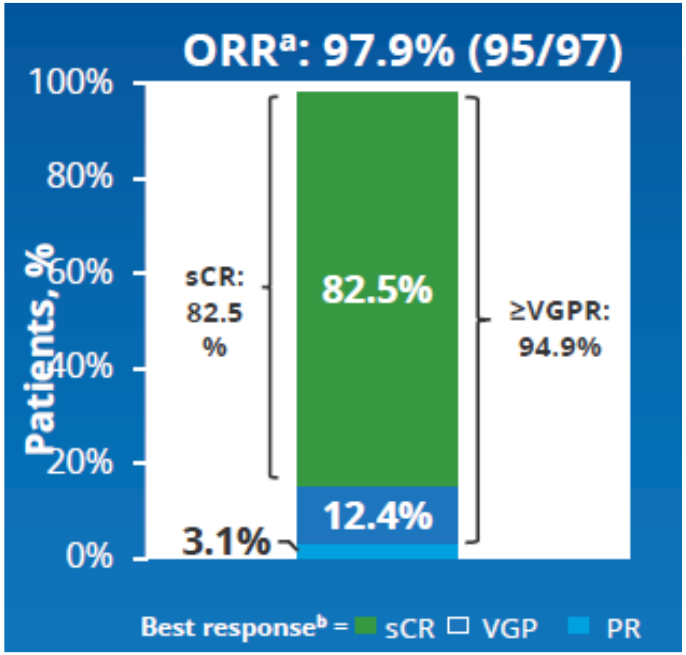
Commercial CAR T cells in Multiple Myeloma

- These CAR T cells are second generation CAR T cells, each using a costimulatory domain (41BB) and a CD3 -ζ Activation Domain
- CAR-T cells are **"anti-BCMA"** (B-cell maturing antigen); BCMA is uniquely expressed on plasma cells and a small subset of B-cells
- *Generally* fewer/lower grade side effects as compared to CAR-T cells in lymphoma.
- Construct of an Anti-BCMA CAR T Cell
  1. **Abecma/Ide-cel** (BMS): costimulatory domain is 41BB→ slower onset/lower peak of cell expansion (MM)
  2. **Carvykti/Cilta-cel** (Janssen): costimulatory domain is 41BB. Less frequent and highly predictable kinetics.

>80% responses rates in both.
Durability different.
Manufacturing issues…

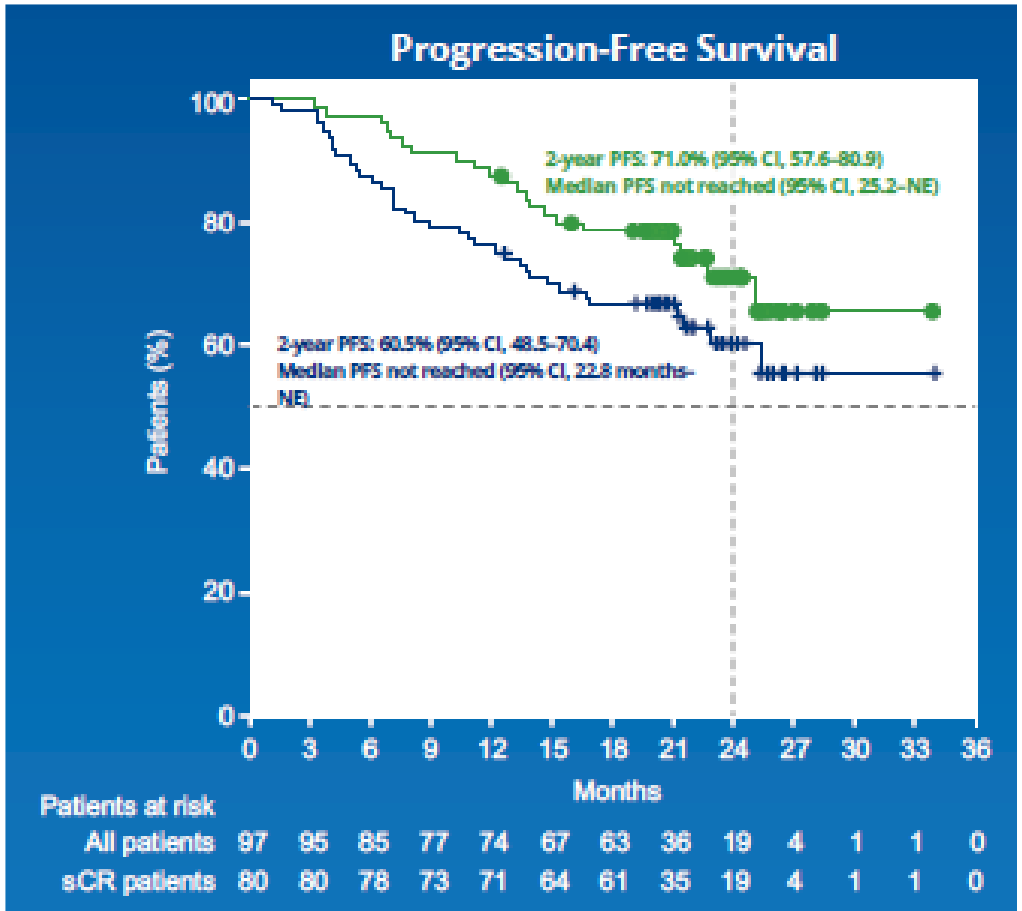


CARTITUDE-1: Efficacy Response



Responses deepened over time from the 1-year follow-up

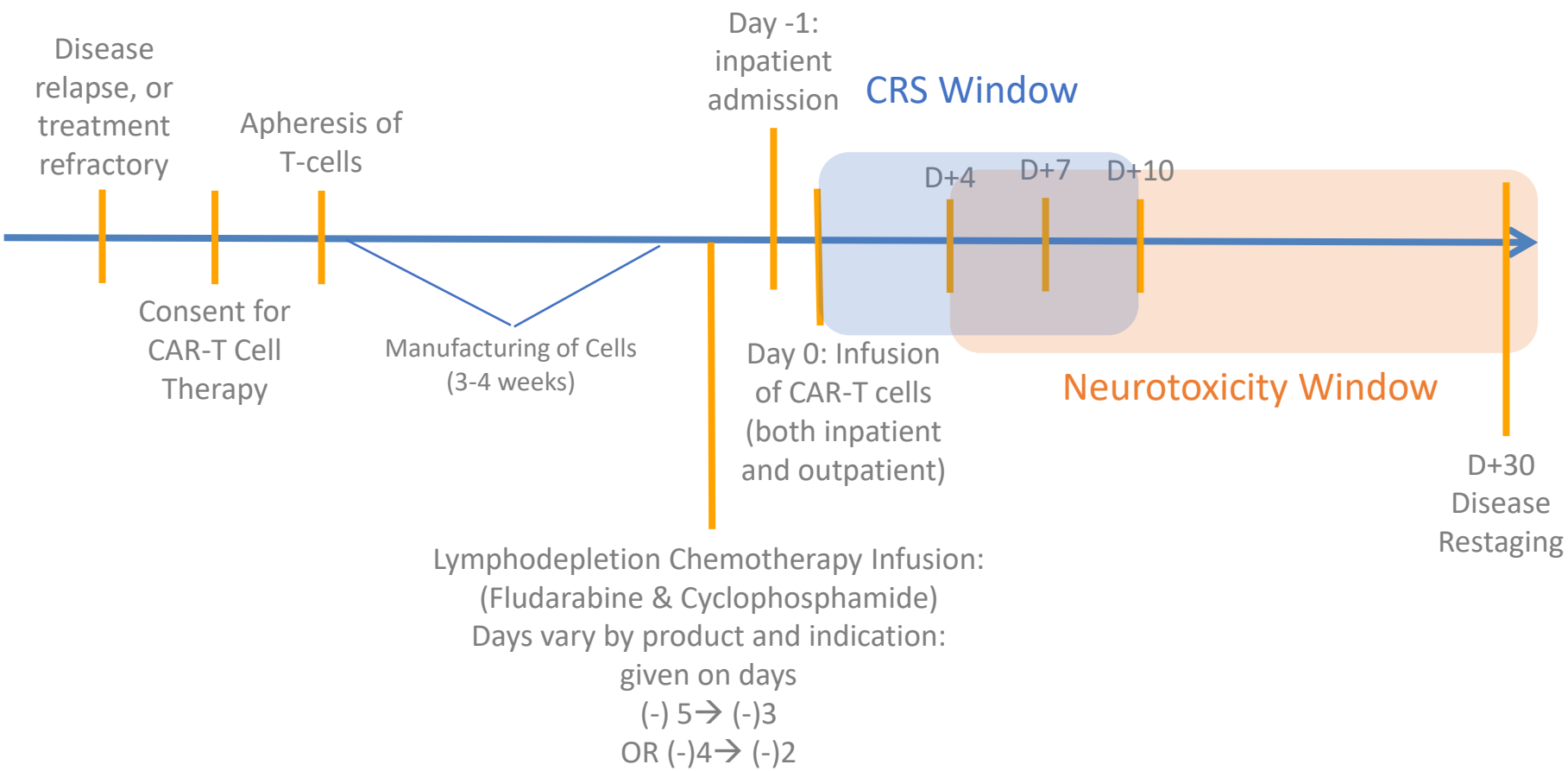
Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83



Ide-cel vs. Cilta-cel

	Cilta-Cel	Ide-Cel
	SAFETY	
CRS (all; grade 3 or 4)	95% (5%)	84% (5%)
Median Onset CRS	**7 days**	**1 day**
ICANS (all, gr 3 or 4)	17% (2%)	18% (3%)
Infections (all, gr 3 or 4)	58% (20%)	69% (22%)
Grade 3 or 4 neutropenia > 1 mo	10%	41%
Grade 3 or 4 thrombocytopenia > 1 mo	25%	48%
Delayed neurotoxicity (all, gr 3 or 4)	**12% (9%)**	None
	EFFICACY	
ORR: CR rate	**98%; 82.5%**	**73%; 33%**
MRD negativity	92% (evaluable)	26%
PFS	NR; 24 mo 60.5%	Median 8.8 months
OS	NR; 24 mo: 74%	Median 19 mo

Treatment Trajectory



Toxicities can be SIGNIFICANT!!
ASTCT Cytokine Release Syndrome Grading

Lee DW et al. *Biol Blood Marrow Transplant*. 2019; 625-638.

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with/without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask or venturi mask	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

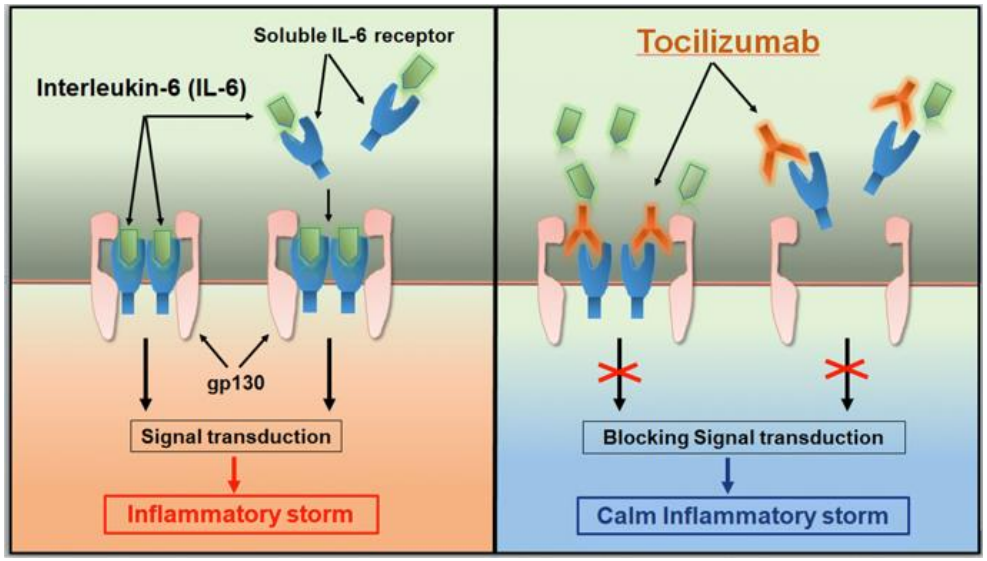
All commercial CARs to date have been issued with a RISK EVALUATION and MITIGATION STRATEGY

CRS Management

Tocilizumab: antagonist of IL-6 receptor

- Blocks the receptor of a cytokine released/upregulated in CRS; decreases fever curve, etc.
- Does NOT decrease efficacy of CAR T cells
- Does NOT cross blood brain barrier
- Dose: 8mg/kg IV can be given every 8 hours x4 total doses, not to exceed 3 doses in a 24 hour period

Dexamethasone: steroid; dampens immune response; crosses blood-brain barrier



Fu, B. J Transl Med. 2020.

ASTCT Immune Effector Cell-Associated Neurotoxicity Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE* score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A		Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

***ICE Encephalopathy Assessment Tool**

Orientation: Orientation to year, month, city, hospital; *4 points*

Naming: Ability to name 3 objects; *3 points*

Following commands: Ability to follow commands; *1 point*

Writing: Ability to write a standard sentence; *1 point*

Attention: Ability to count backwards from 100 by 10; *1 point*

Lee DW et al. *Biol Blood Marrow Transplant*. 2019; 625-638.

CD19 CAR T-cells for DLBCL: Outcomes in the Real World

TOTALLY Match Trial Data….and toxicities improving with time

	Jacobson et al, JCO 2020	Nastoupil et al, JCO 2020	Axi-cel CIBMTR	Tisa-cel CIBMTR	CAR T-cell Consortium		UK Experience	
Product	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
# treated	122	275	533	155	158	86	62	29
ORR/CR	70/50	82/64	74/54	62/40	75/53	59/42	37/21	17/29
6m ORR	41	NR	NR	34	~51	~35-40	~35-40	
CRS (%)	93	91	83	45	85	41	NR	
Gr 3+ CRS (%)	16	7	9	5	8	1	11	
NT (%)	70	69	53	18	53	14	NR	
Gr 3+ NT (%)	35	31	17	5	33	0	13	

Jacobson et al JCO 2020
Nastoupil et al JCO 2020
Pasquini et al ASH 2020
Pasquini et al Blood Adv 2020
Riedell et al TCT 2020
Kuhl et al ASH 2019

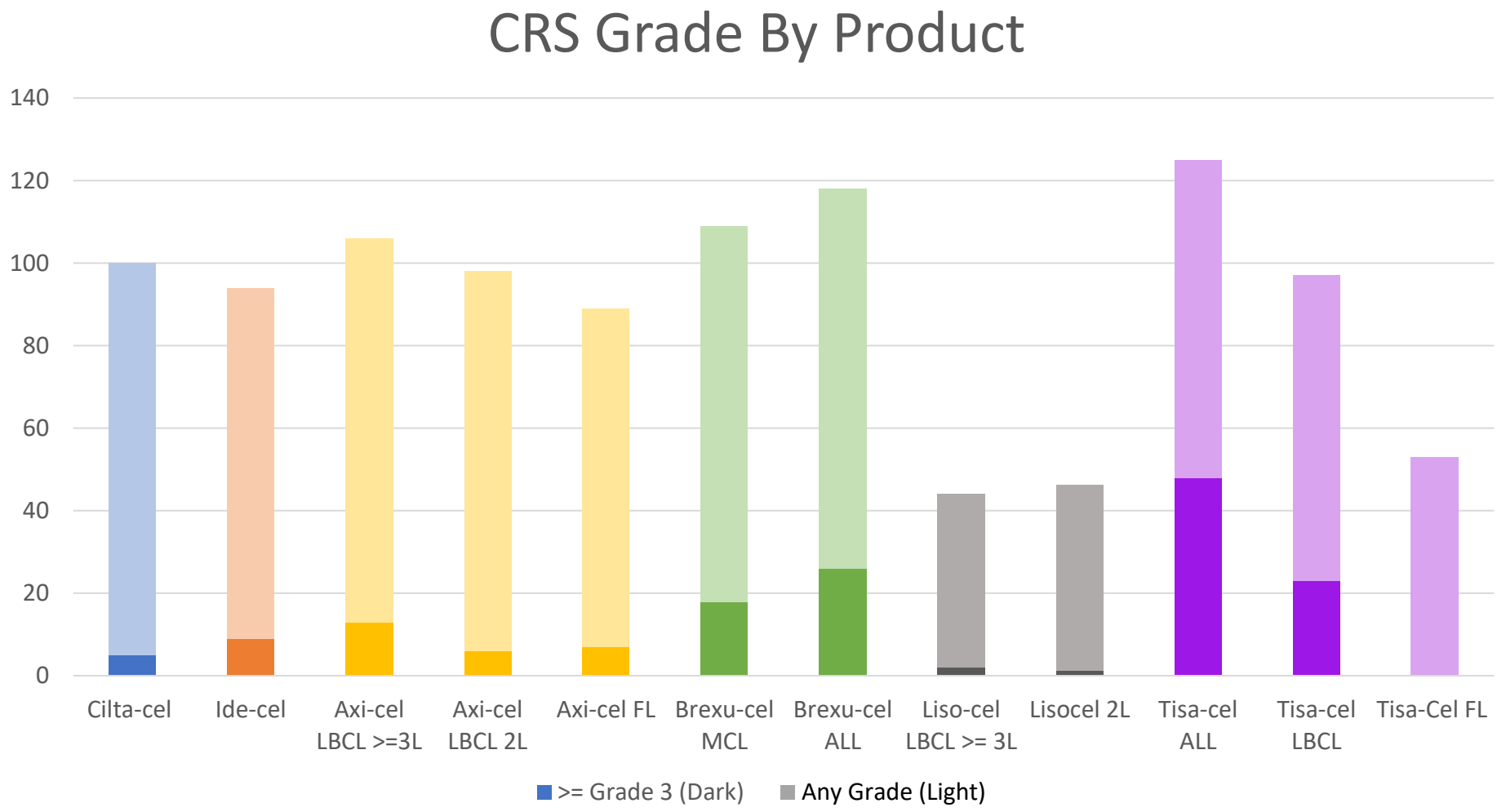
	2017-2018	2019	2020	2021
CRS Grade 3 or higher	15%	4%	1%	2%
Neurotox Grade 3 or higher	40%	30%	26%	15%
ICU Transfer	**21%**	**9.7%**	25%	8%

- Risk Factors for Development of CRS and ICANS

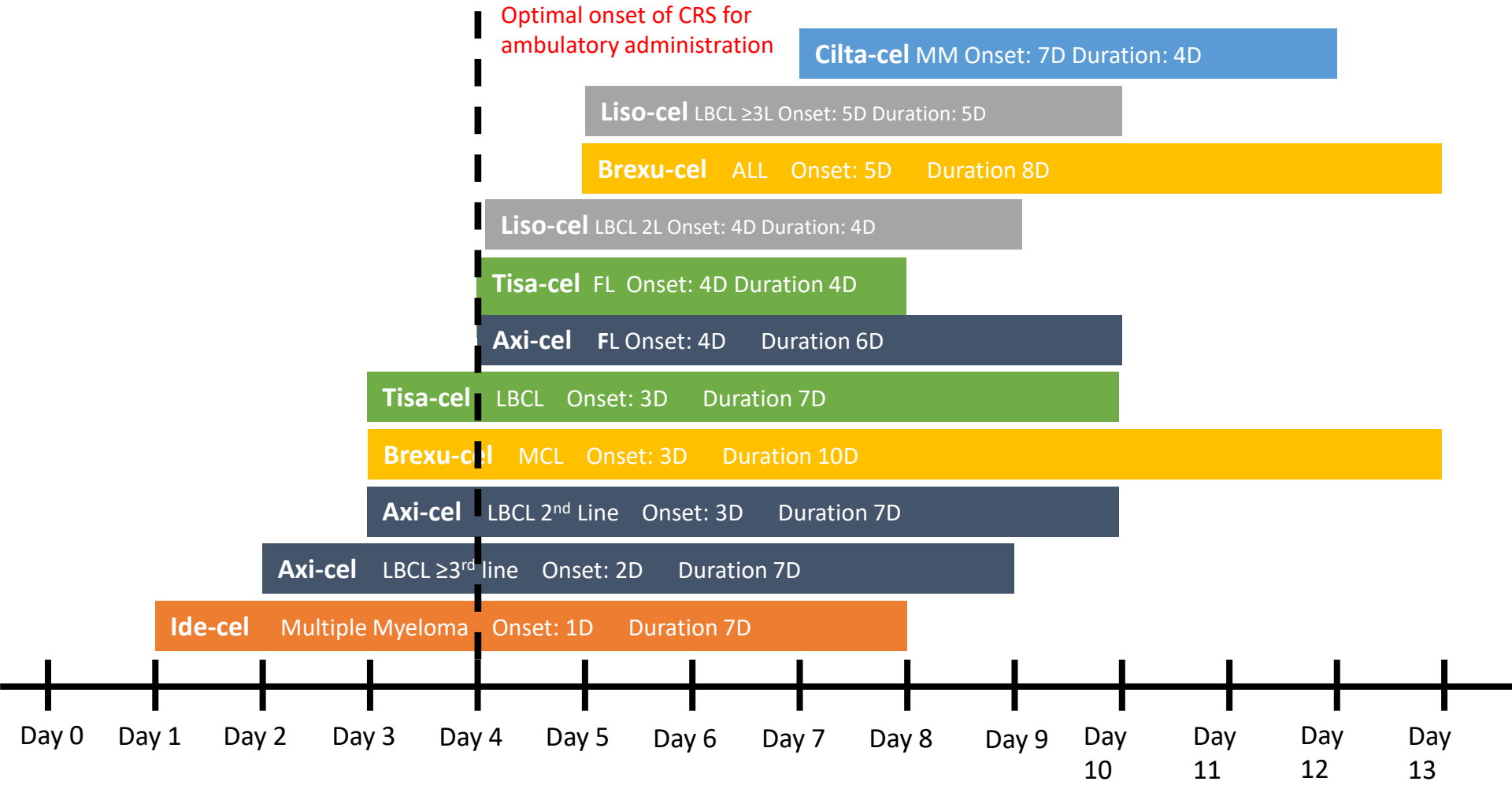
Risk factors for CRS	Risk factors for ICANS
• Disease burden • Higher CAR T-cell doses • CARs containing CD28 costimulatory domains	• Disease burden • Peak CAR T-cell expansion • Extramedullary disease • Younger age • Pre-existing neurological comorbidities • Higher CAR T-cell doses • High-grade CRS • CD19 targeting CAR T-cell therapies

Maus WV et al. *J Immunother Cancer*. 2020;8:1-25.

- Earlier use of tocilizumab and steroids for early and lower grade toxicities is common


CRS Grade By Product
140
120
100
80
60
40
20
0
Cilta-cel
Ide-cel
Axi-cel LBCL >=3L
Axi-cel LBCL 2L
Axi-cel FL
Brexu-cel MCL
Brexu-cel ALL
Liso-cel LBCL >= 3L
Lisocel 2L
Tisa-cel ALL
Tisa-cel LBCL
Tisa-Cel FL
>= Grade 3 (Dark)
Any Grade (Light)

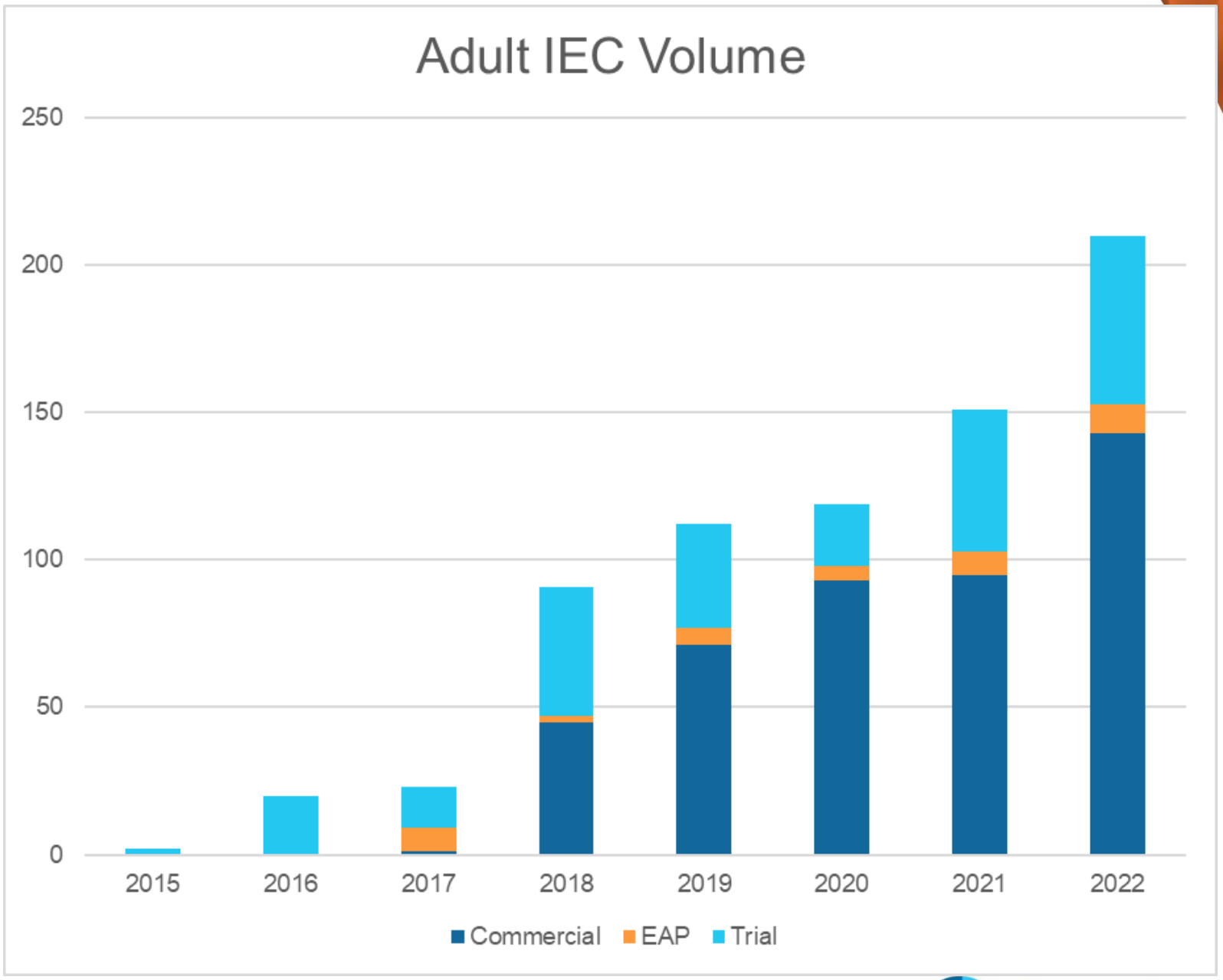
CRS: Median Onset and Duration by Product



Increased demand has put strain on inpatient bed resources => Migration to outpatient administration

Other Possible Side Effects – always learning

- **Prolonged Cytopenias**
  - For NHL typically give Neulasta on day -2 to prevent this
- **Hypogammaglobinemia**
  - The CAR T cells target CD 19+ B Cells, which can also result in the destruction of normal B cells….. Causing B cell aplasia and thus, hypogammaglobinemia
- **Infection**
- **HLH/MAS**
  - severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T cells
  - Many features overlap with CRS
    - fever, splenomegaly, cytopenias, liver dysfunction, sepsis like picture, hypertriglycemia, increased serum ferritin, soluble CD25, and can lead to multiorgan failure
  - BMBx for diagnosis→ Hemophagocytosis in bone marrow or spleen or lymph nodes.
- **Parkinsonian side effects – esp Carvykti**



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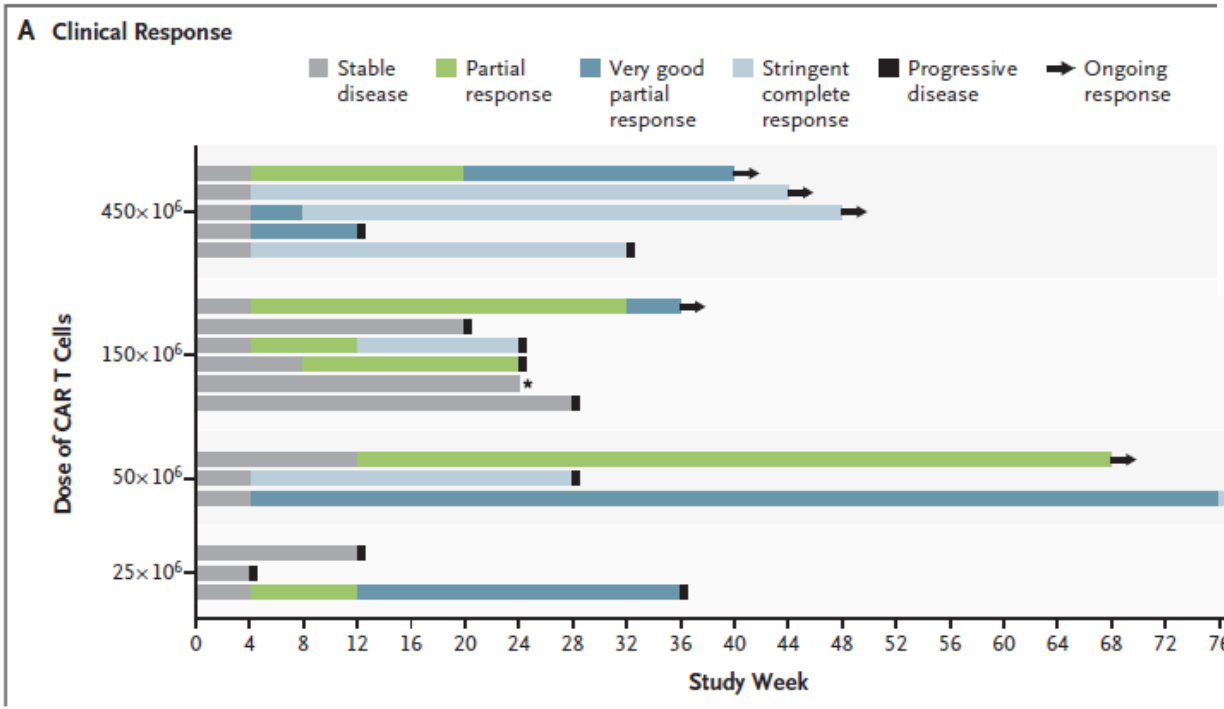
New CAR Targets/Allogeneic CARs

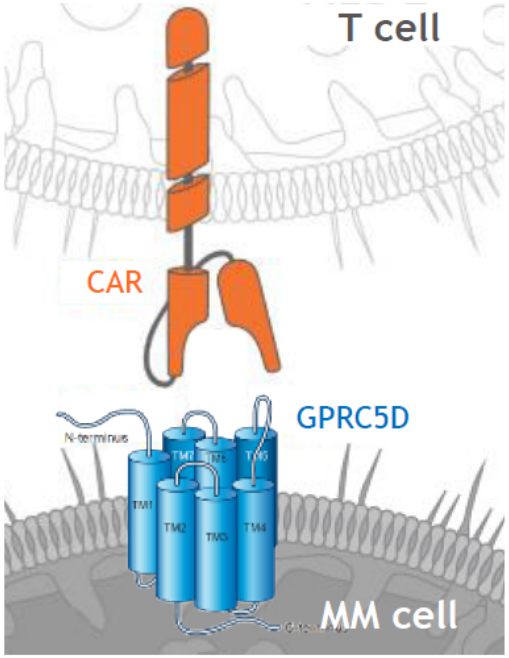
New Antigen Targets in Myeloma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

GPRC5D-Targeted CAR T Cells for Myeloma



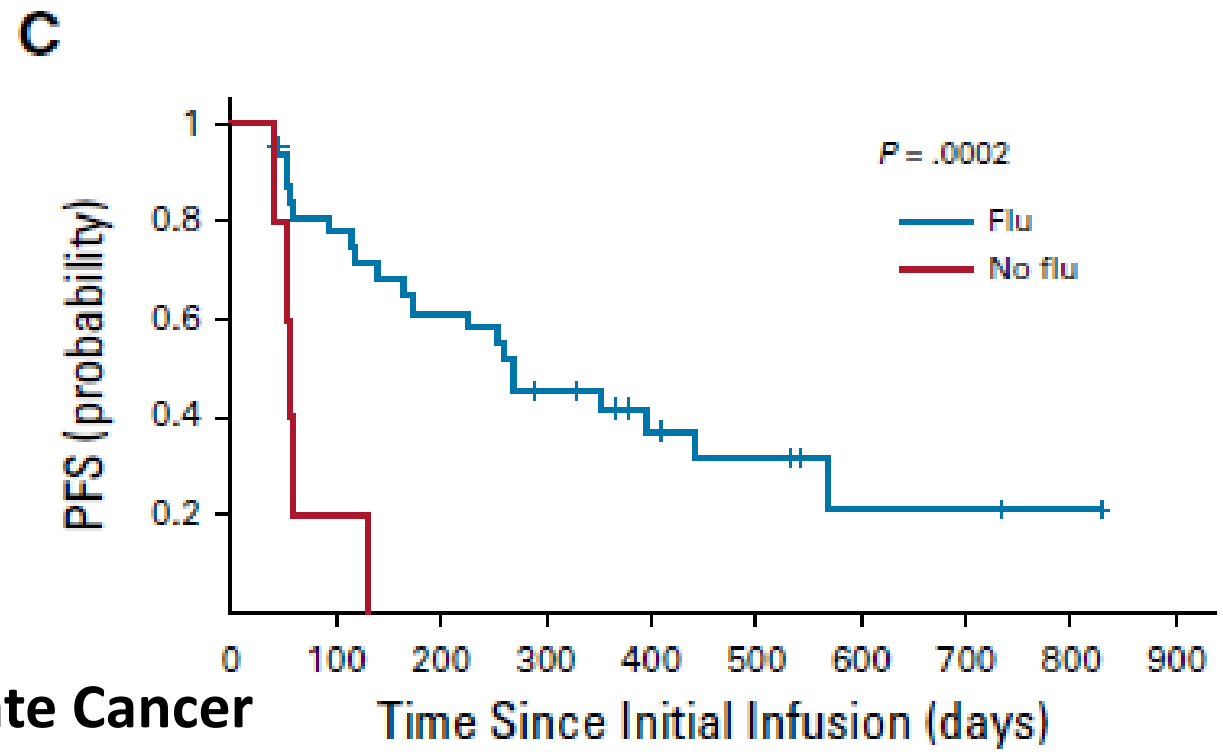


58% Response Rate

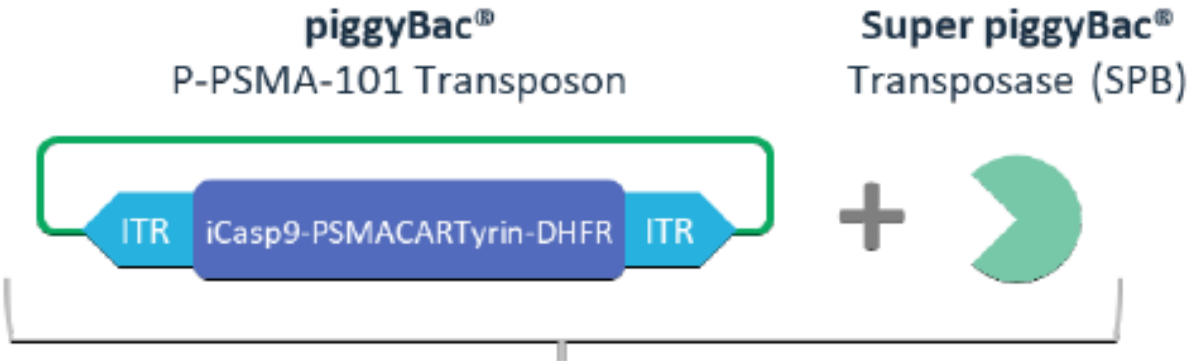
CD30 CARs in Hodgkins

- 41 patients
- OR in 32 with active disease 72%, CR 59%
- 1yr PFS 36%

Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma



PSMA CARs in Prostate Cancer

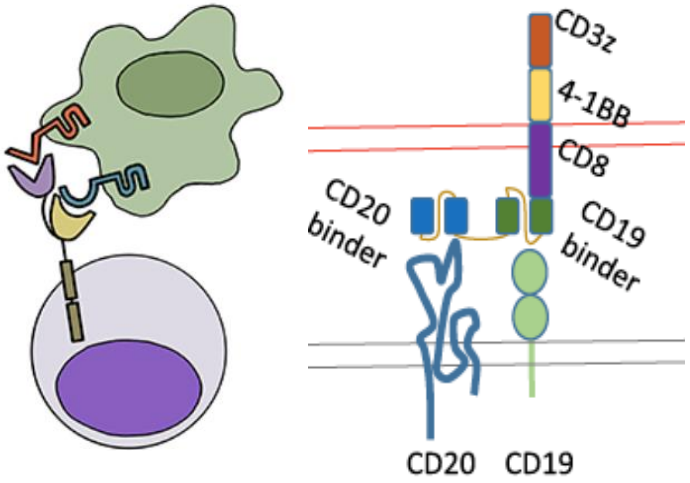


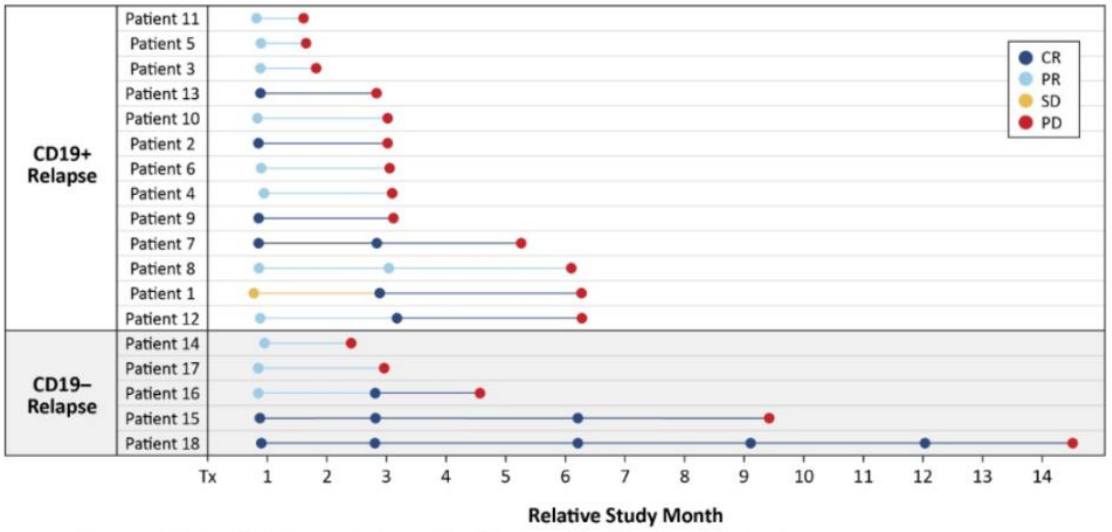
Two trials (Poseida & Tmunity) on hold by FDA/closed for toxicities

Targeting Relapse and Persistence in Multiple Ways

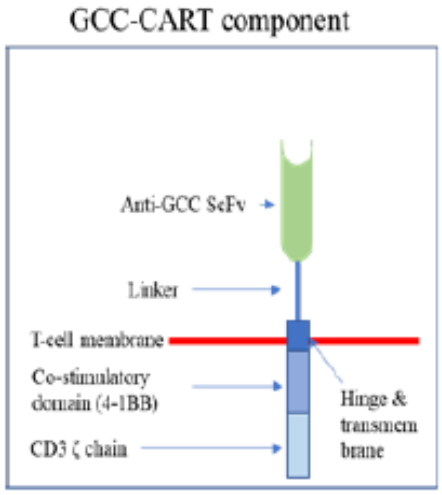
Dual Targeting

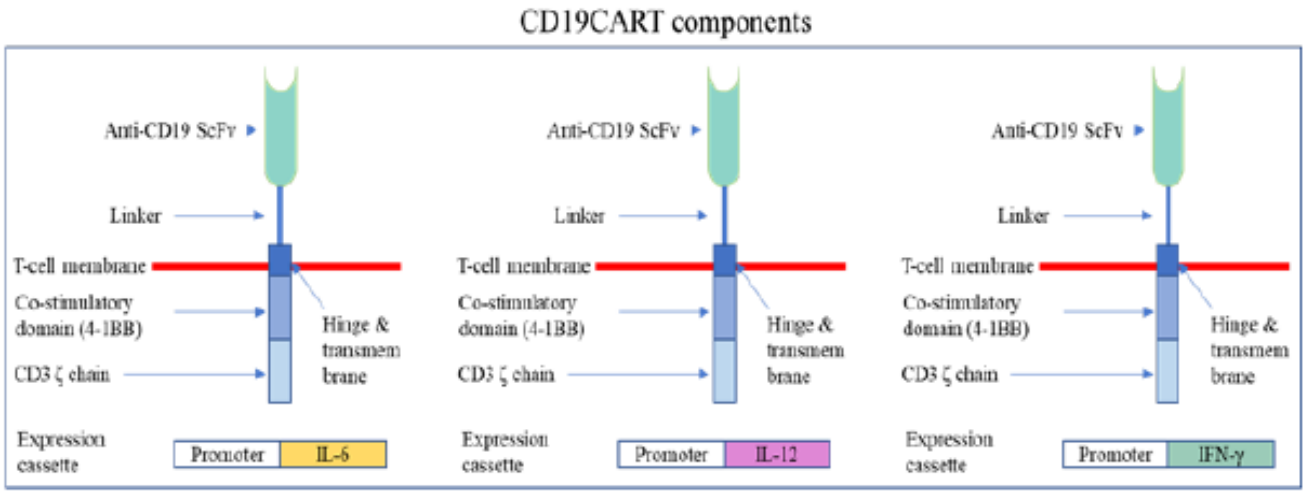
- CD19+CD20 CAR





Extra stimulation





Allogeneic/Off-the-Shelf Options
Ready Availability vs Persistence vs Toxicity

Allogeneic:

- **CD19 CAR in NHL and ALL**

CAR – Adeno-associated viral vector
TCR knock out thru ARCUS nuclease
mRNA electroporation

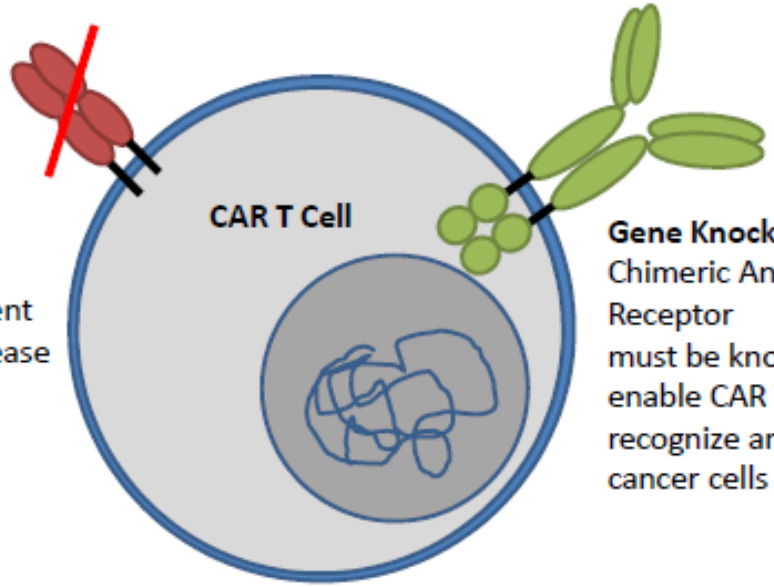
CAR T: Gene Modifications

PRECISION BIOSCIENCES

"Universal" (allogeneic) CAR T Products from Gene Editing – 2 essential features:

Make allogeneic (donor-derived) product

Gene Knock Out:
T cell receptor expression must be knocked out to prevent graft versus host disease



Gene Knock In:
Chimeric Antigen Receptor
must be knocked in to enable CAR T cells to recognize and kill cancer cells

These two essential features can be produced at the same time by using HDR to achieve targeted knock-in of a CAR gene into the TCR alpha chain locus

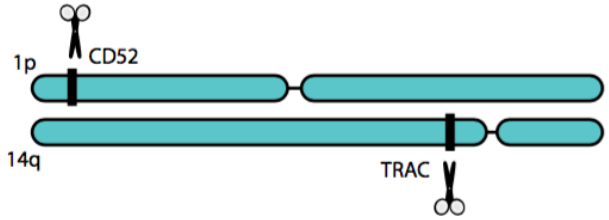
Additional Approaches

ALL

- **Low affinity** CD19 CAR – **faster dissociation kinetics**
- **Allogeneic** CD22 CAR

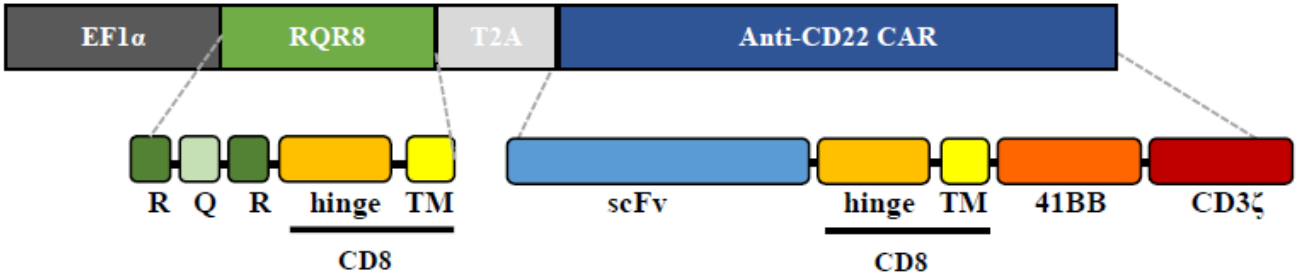
AML

- **Allogeneic** CD123 CAR
- **NKG2D NK cell CAR**



R= CD20 mimetope (rituximab)

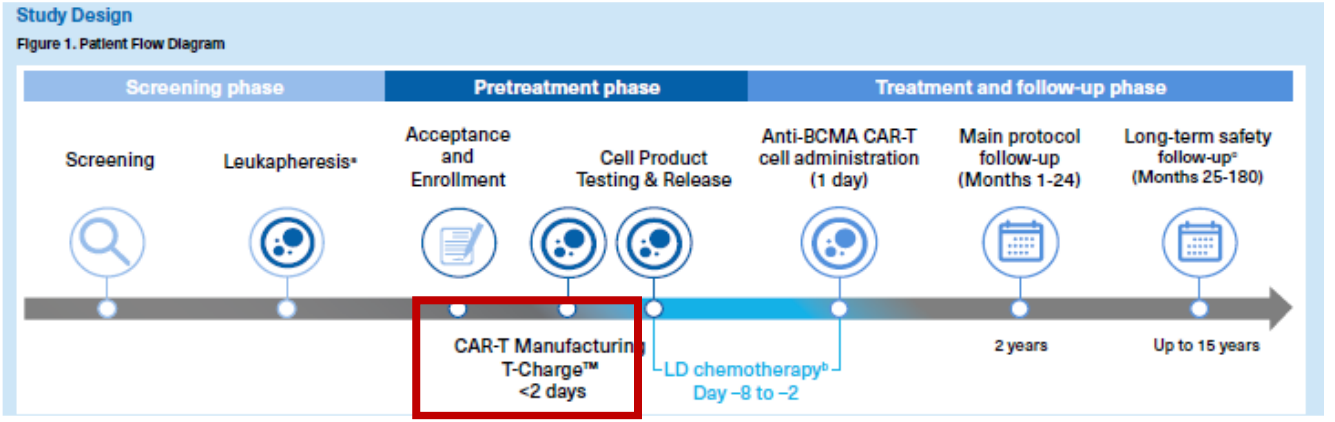
Q= CD34 epitope (QBEnd10)

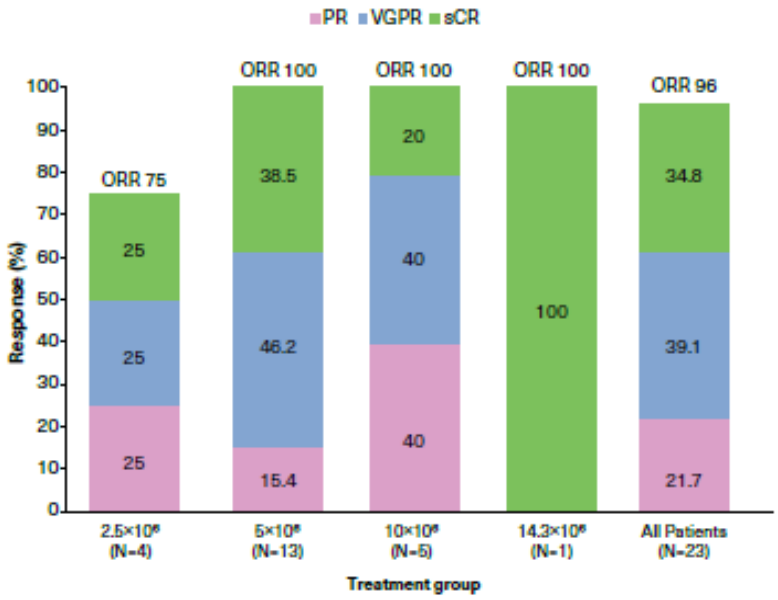


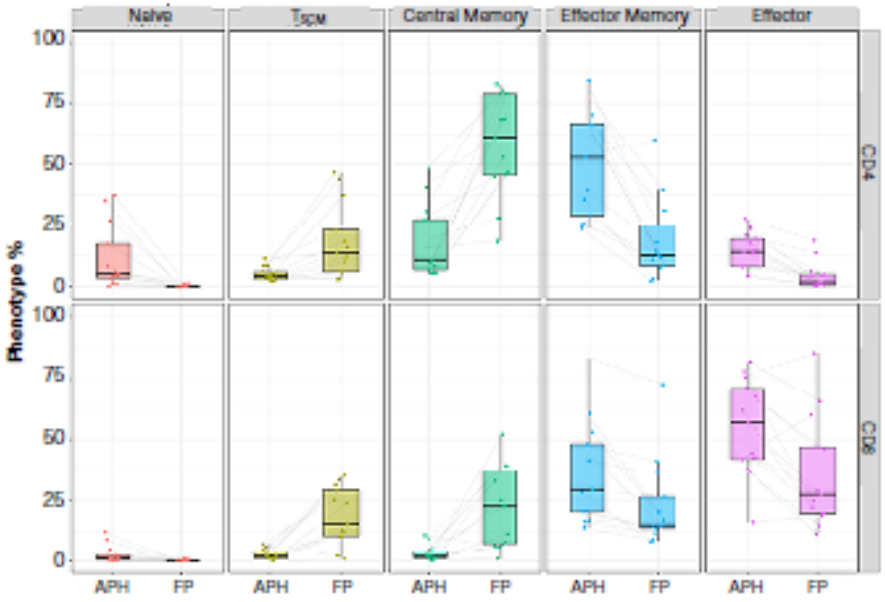
CAR – Lentiviral Vector
CD20-based “suicide” tag
TCR + CD52 knock out thru TALEN nucleases via mRNA electroporation

Shorter Manufacturing Time – More Memory Phenotype

Phase I Study Data Update of PHE885, a Fully Human BCMA-Directed CAR-T Cell Therapy Manufactured Using the T-Charge™ Platform for Patients With Relapsed/Refractory Multiple Myeloma





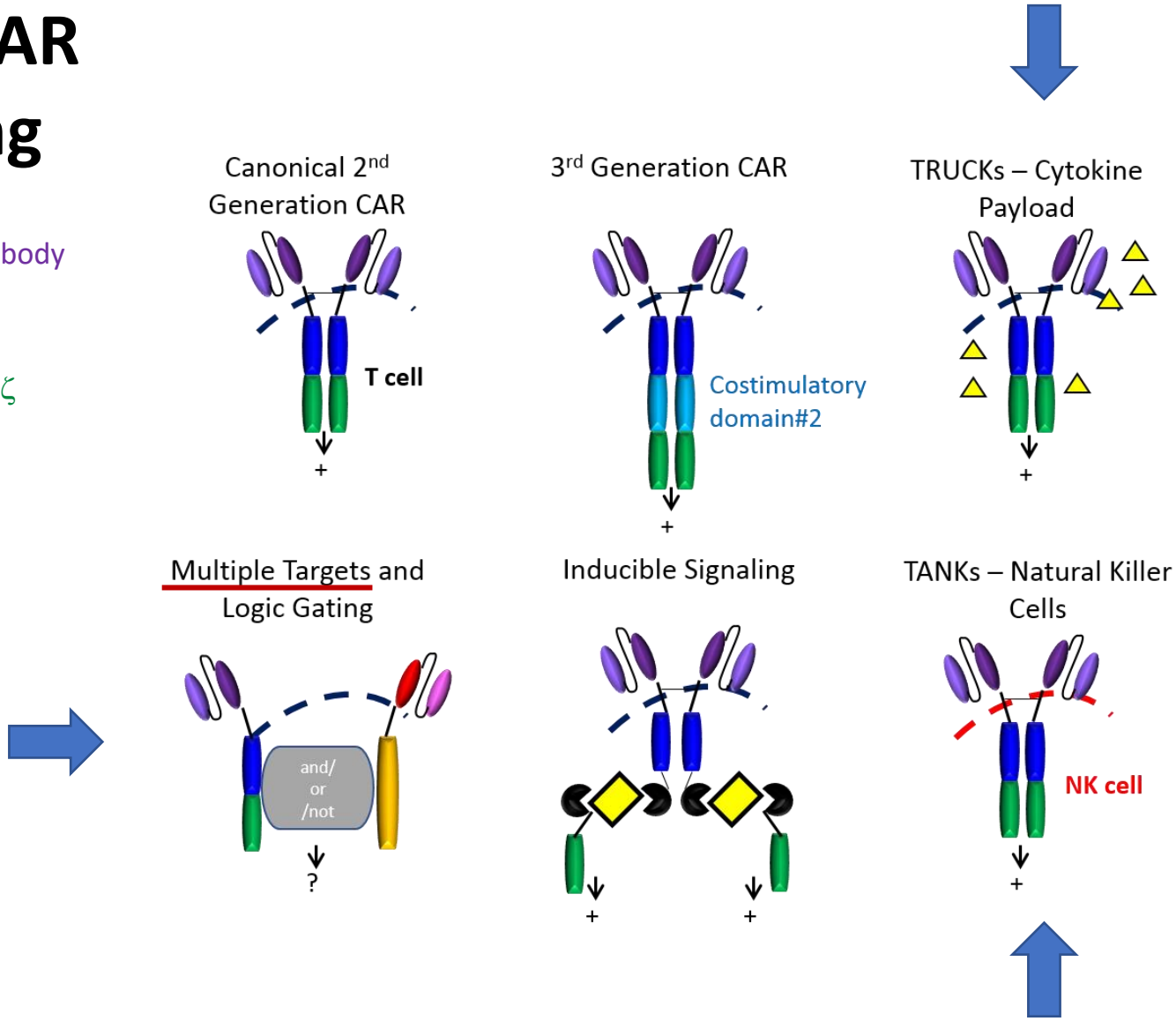


Ongoing CAR Engineering

Antigen recognition- Antibody scFv moieties

Costimulatory domain#1

Activation domain – CD3ζ

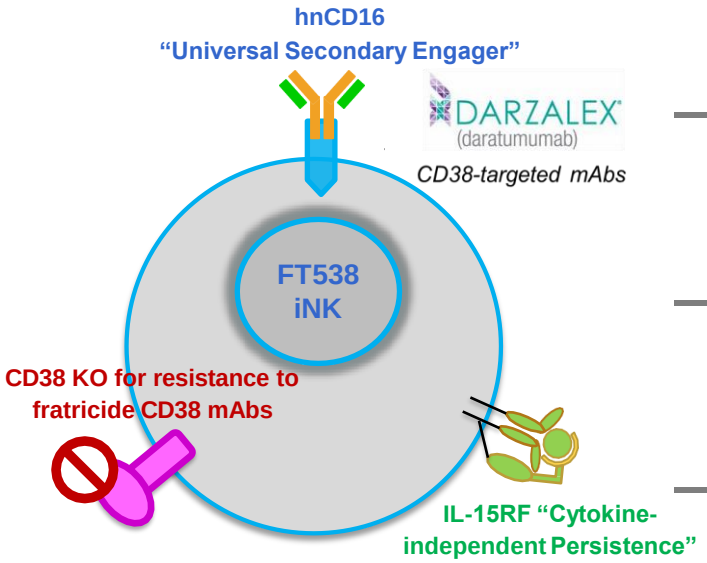


Induced Pluripotent Stem Cell-Based Cell Therapies

FT538: hnCD16 + IL-15RF + CD38KO NK Cell Product Candidate

First-ever CRISPR-edited iPSC-derived Cell Therapy

Engineered with Three Components to Enhance Multiple Mechanisms of Innate Immunity



hnCD16: High-affinity 158V, non-cleavable CD16 Fc receptor that has been modified to augment antibody-dependent cellular cytotoxicity by preventing CD16 down-regulation and enhancing CD16 binding to tumor-targeting antibodies

---

CD38KO: Deletion of CD38 to eliminate anti-CD38 antibody mediated NK cell fratricide. Also shown to improve NK cell biology and potency through optimization of metabolic signaling

---

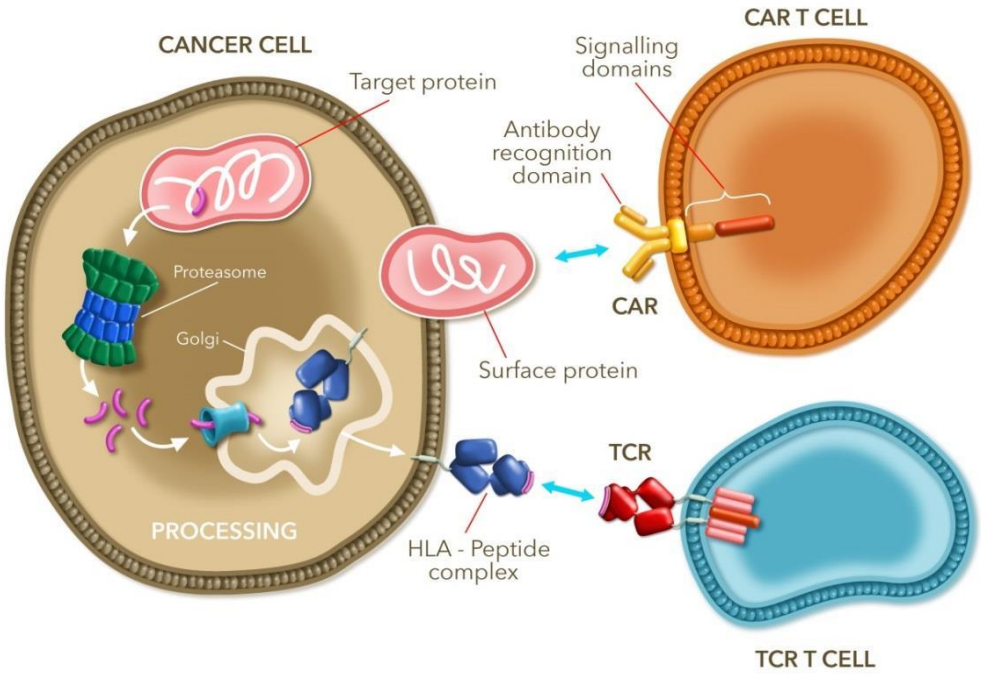
IL-15RF: Interleukin-15 receptor fusion, a potent cytokine complex that promotes survival, proliferation and trans-activation of NK cells and CD8 T cells

Beyond CARs

Different Types of Antigen-Detection

- Genetically Engineered – CARs vs Engineered TCRs

  CARs are not MHC restricted but only see see surface proteins



HLA-A02
NY-ESO-1 peptide and
MAGE-A4 peptide
Sarcoma

HLA-A02
E16 HPV peptide
H&N cancer

SPEARHEAD-1: Phase 2 Study of MAGE-A4 eTCR in Synovial Sarcoma

- **Only HLA-A02+ patients** with synovial or myxoid round-cell sarcoma + others
- All with progression after at least 1 prior therapy
- **38** infused with **Afami-cel**

- Cohorts based on dosing of Flu/cy and expression levels of MAGE-A4

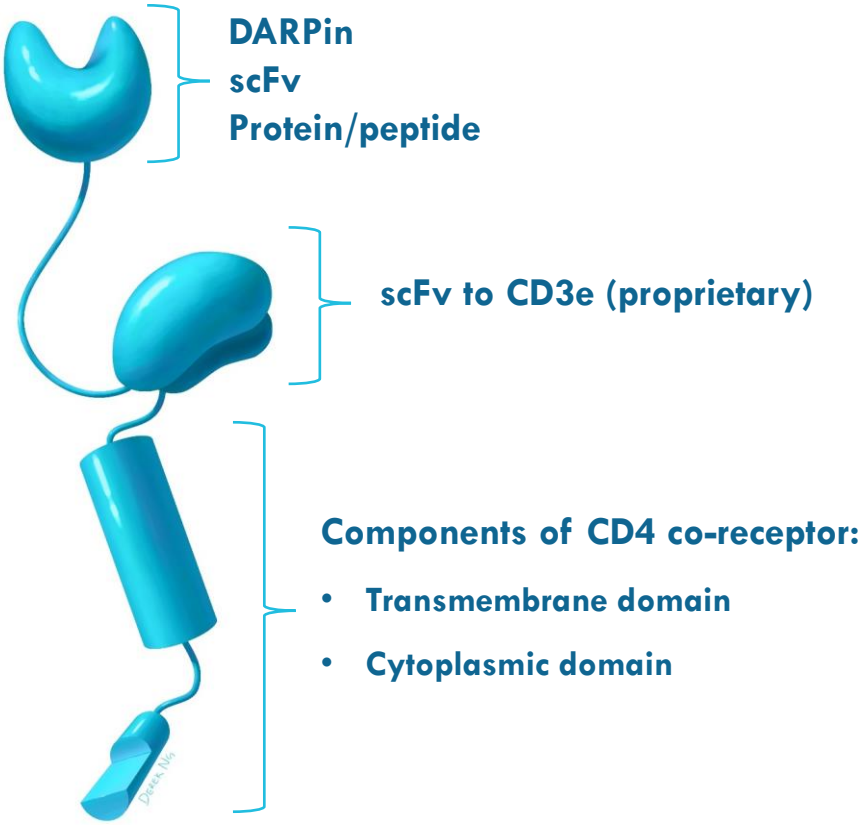
- ORR 24% (**44% in synovial sarcoma**)
- Persistence of cells detected to 18 months

- Complications of “low-grade, reversible” CRS in 55%, no ICANS in synovial sarcoma pts
- 45% incidence of >/= Grade 3 cytopenias but “low” clinical sequelae

- **BLA registration initiated**

The T Cell Antigen Coupler (TAC) Receptor

- A novel chimeric receptor
- Composed of 3 domains:
    1. **Ligand binding domain**
    2. **T-Cell Receptor recruiting domain = CD3 binding domain**
    3. **Co-receptor domain**
- No activation nor co-stimulatory domains
- COM Patent granted in US, JP, CN, AU, MX

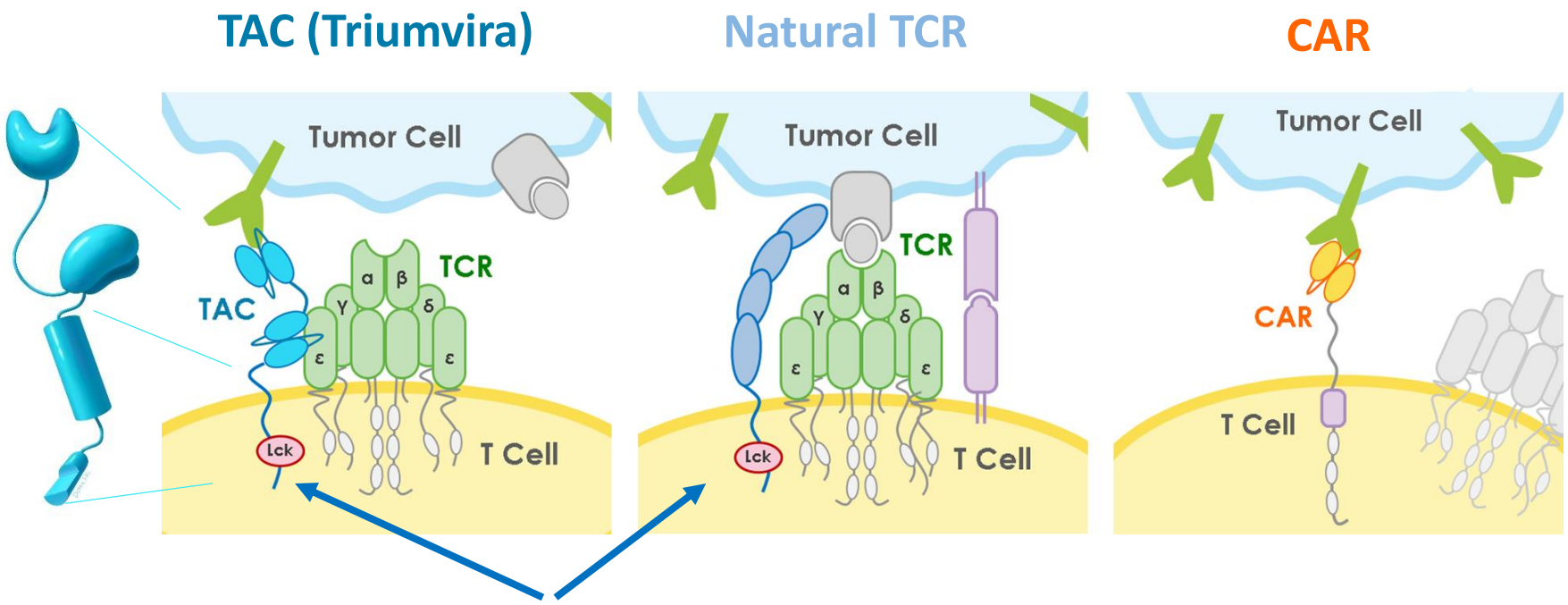


nature COMMUNICATIONS

Helsen et al., 2018

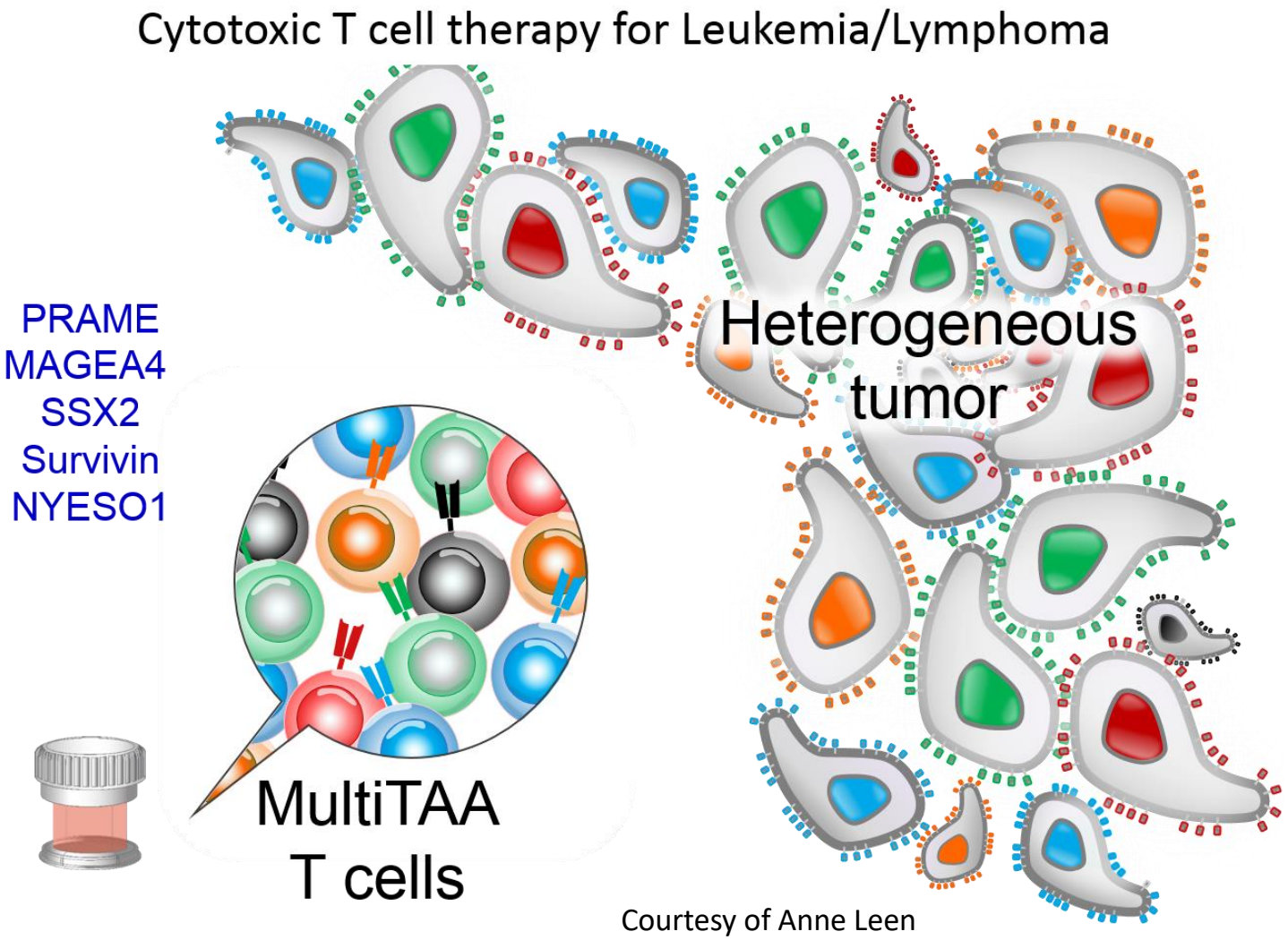
The chimeric TAC receptor co-opts the T cell receptor yielding robust anti-tumor activity without toxicity

TAC vs TCR vs CAR

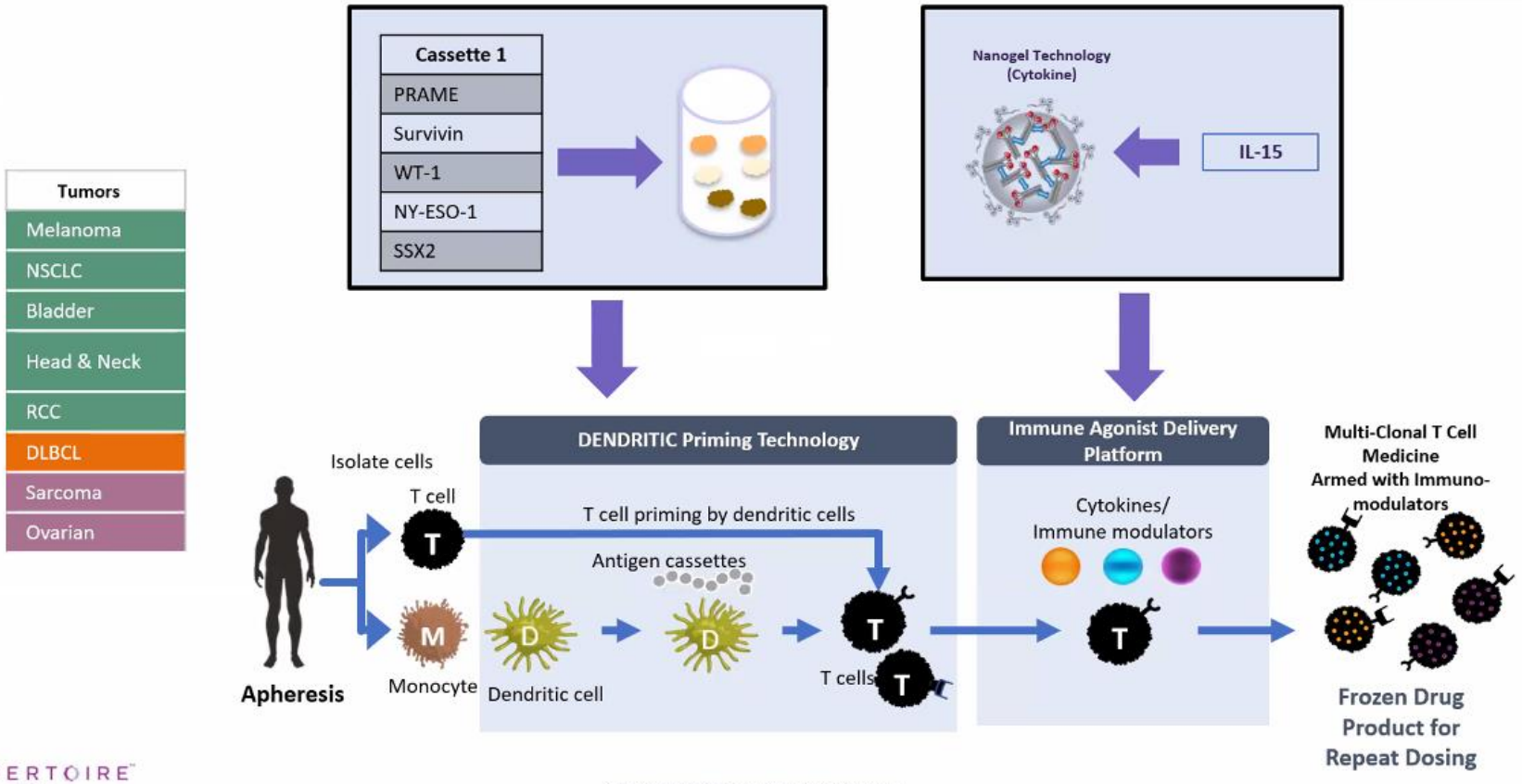


TAC provides the intracellular Co-Receptor function and co-opts the natural TCR, designed to mimic normal TCR activation

No Genetic Engineering – Selection for Specific Antigens/Attributes



A Phase 1/2 Study of PRIME IL-15 Loaded T Cells Alone and in Combinatic
Pembrolizumab in Patients with Select Solid Tumors and Lymphomas

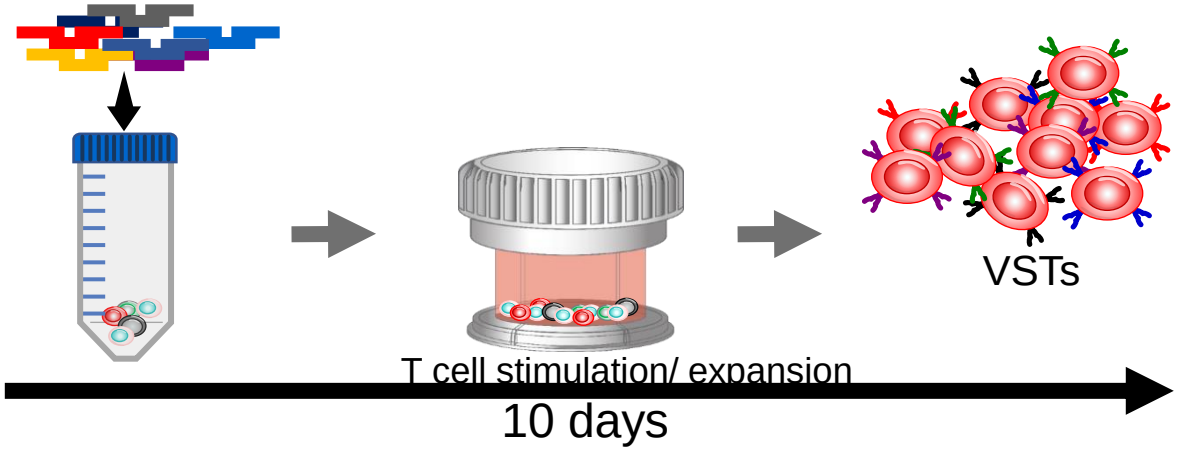


Applications in Infectious Diseases as well as Cancers

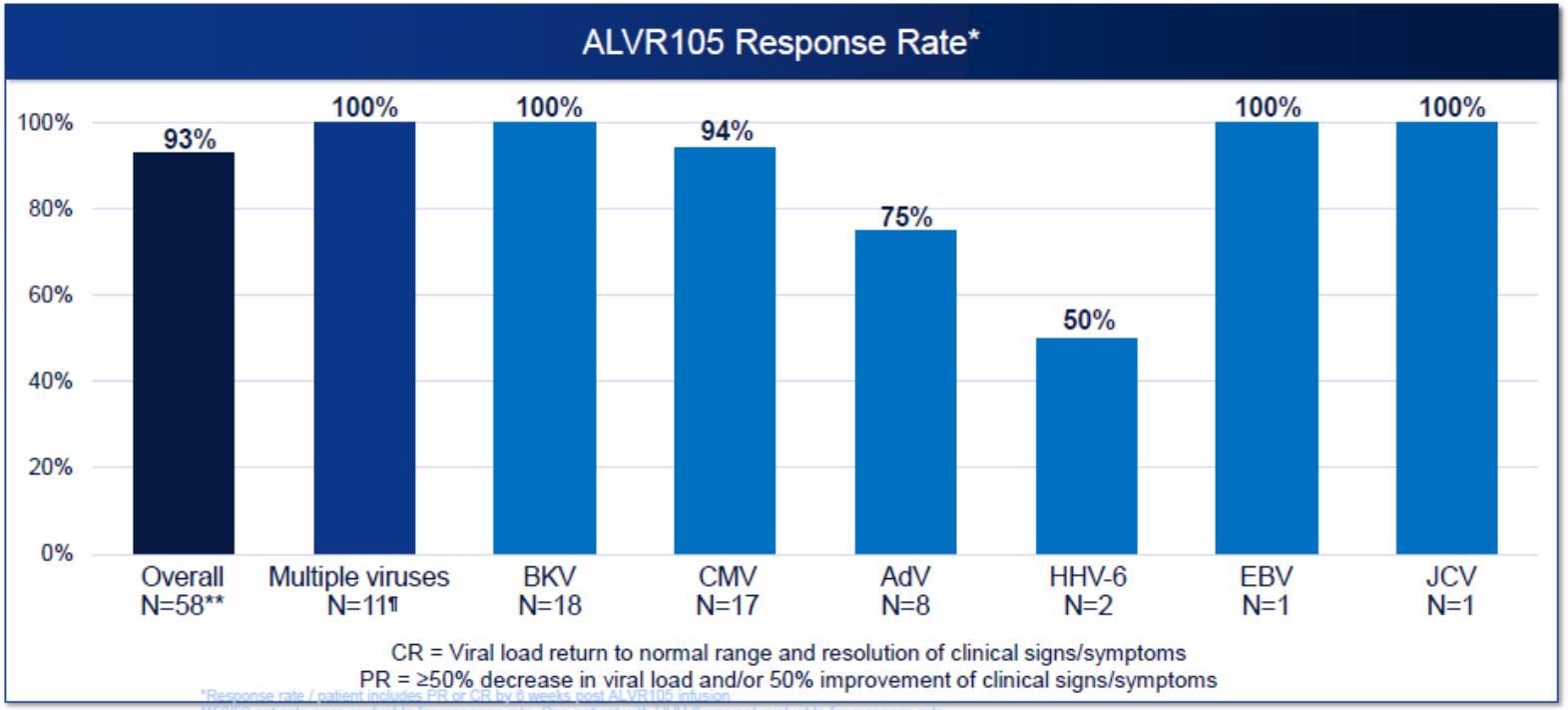
Donor-derived VSTs

Gerdemann et al, Mol Ther; 2013,

AdV– Hexon, Penton
EBV– EBNA1, LMP2, BZLF1
CMV– IE1, pp65
BKV– LT, VP1
HHV6– U11, U14, U90



93% of Patients Achieved a Clinical Response by 6 Weeks Post ALVR105 Treatment[1,2]



*Response rate / patient includes PR or CR by 6 weeks post ALVR105 infusion
**58/59 patients were evaluable for response rate. One patient with HHV-6 was not evaluable for response rate.
¶ 11/11 patients had a response to ≥1 virus(es) and 19 of 23 viruses across the 11 patients responded to ALVR105.
1. Tzannou, JCO 2017; 2. Type B Meeting Briefing Package.

allo Vir

re•act Ph1/2 RTI Trial

CHARMS Trial post Allogeneic HSCT, Tzannou et al, JCO, 2017

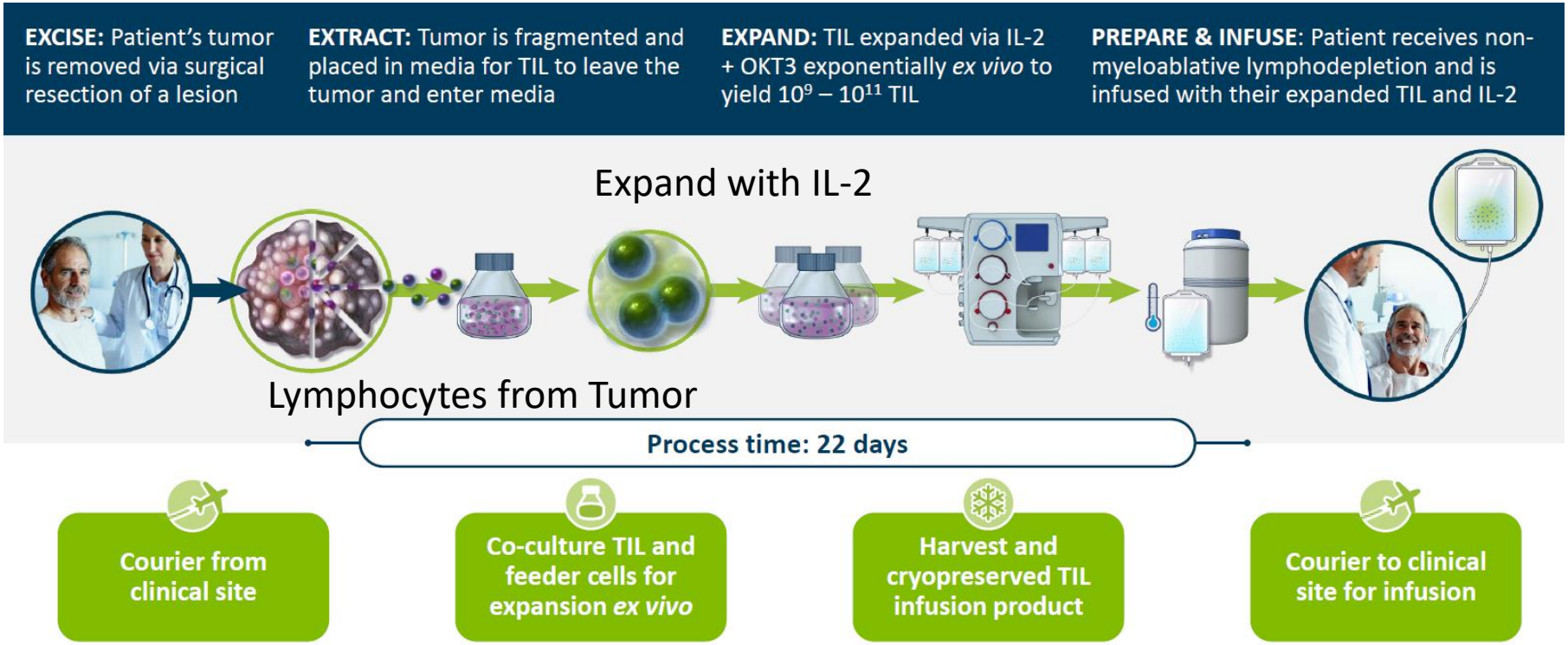
Trials for treatment, prophylaxis….and against respiratory viruses

Dana-Farber Cancer Institute

Tumor Infiltrating Lymphocytes

Different Types of Cells

- Non-Genetically Engineered
  - Simple Numerical Expansion but of Cells INSIDE Tumors



- Initial Iovance Trial Outcomes Data

IOVANCE BIOTHERAPEUTICS	Cohort Size	Mean # Prior Therapies	Objective Response Rate (ORR)	Disease Control Rate (DCR)	Median Duration of Response (DOR)
Melanoma	66	3.3	36.4%	80.3%	Not reached as of 18.7 months of follow-up
Cervical Cancer	24	2.4	44%	85%	Not reached as of 7.4 months of follow-up
Non-Small Cell Lung Cancer	12	n/a	25%	n/a	Not reached

Source: https://ir.iovance.com/static-files/dd026048-1c0a-42ff-bf4d-bec7f9acbd98

- BLA filed with FDA in Metastatic Melanoma

Cell Pharmacy by CMCF SCT to support over 35 Cell Therapy clinical trials under DF/HCC

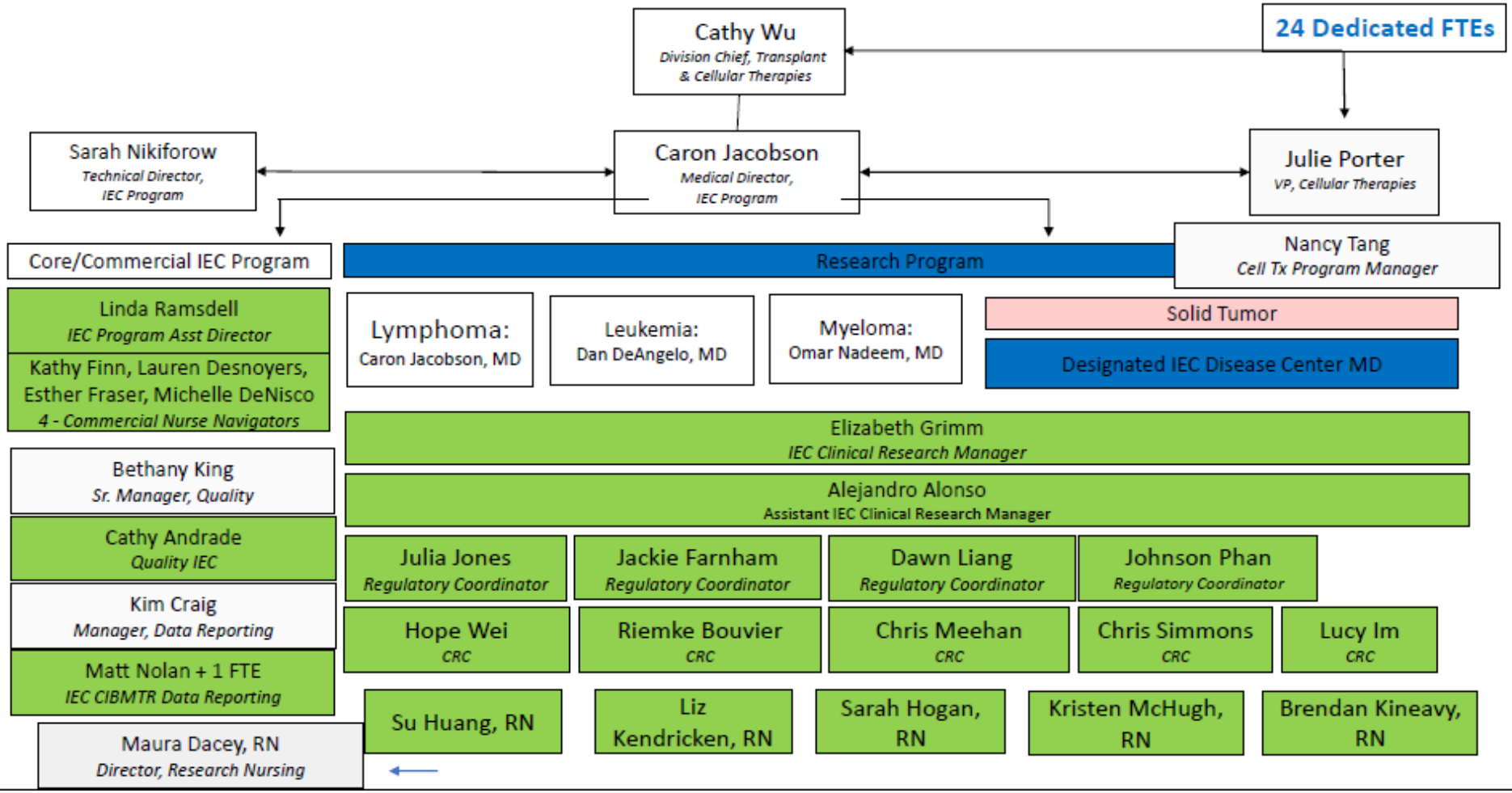
Manufactured-Off-Site (MOS)

- **35 IEC Clinical Trials, 6 Licensed IEC products, 2 licensed gene therapy stem-cell products** where products are manufactured off site (MOS)
- CMCF serves as the intermediary to maintain chain-of-identity (COI) and chain-of-custody (COC)
- Responsible for shipping, inventory, thaw and release for infusion
- **Diseases treated** include:
  - Licensed CARs - B-ALL, B-NHL, Myeloma – DFCI; B-ALL - BCH
  - Licensed Stem Cell Gene Therapy - beta-Thalassemia, ALD – BCH
  - Trials – **B-ALL, AML, Myeloma, Breast, GI (Gastric, Colon, Anal), Head&Neck, Liver Lung, Prostate, Sarcoma, Viral Diseases** – DFCI, BCH
- **Types of Cells Delivered:** - **Autologous and Allogeneic T-cell CAR, T-cell Activating Complex T cells, Anti-tumor antigen CTLs, Anti-viral CTLs, iPSC-derived NK-cell CARs**

Overview

- Chimeric Antigen Receptor T Cells – the base model
  - **Here to stay!!**
- Future CAR directions and other makes and models
  - **Allogeneic/off-the-shelf options**
  - **Suicide switches and other alterations for safety**
  - **Engineered TCRs and other linkers, esp. in solid tumors**
  - **Non-genetically engineered cells – antigen-specific or TILS**
- It Takes a Village
- Standardization will be key to sustainability

DFCI IEC Program (updated Feb 2023)



Current IEC Program Meetings:

IEC Portfolio Review* (Monthly)	Inpatient/Outpatient Clinical Workgroup* (Weekly)	Cell Processing & Manipulation Workgroup (Monthly)	IEC QA Review Meeting (Monthly) FACT Review (3 months)
Centralized and streamlined review process of: • Clinical volume • Research portfolio • Safety and efficacy outcomes • Financial updates and concerns • Upcoming trials with safety and/or capacity concerns	• Discussion of clinical communication workflows and tools • Review of current inpatients, upcoming patients, recently treated patients with clinical issue • MDs, Nursing, Pharmacy, Specialists, Social Work, Financial Clearance	• Optimizing general workflows between apheresis, cell processing and nursing • Design of interfaces within DFHCC and with sponsor • Analysis of chain of custody, identity of products • Training re: upcoming trials *	• Review and appraisal of SOPs and data management and reporting issues • Assessment of REMS & FACT compliance • Preparation for commercial and accrediting agency audits • Data reporting to CIBMTR

Disease Group Evaluation | **+/- Upstream Huddle** | **Regular Dz Group/IEC core mtgs**

IEC Inpatient Service *

- PA-run service = PALS
- All PAs and attendings are IEC and REMS trained
- Patients all admitted to IEC and REMS trained pods
- Ongoing involvement by specific IEC-trained neurologists, intensivist, and cardiologists in patient care

Streamlining Apheresis Resources

Before Feb. 2018, autologous MM **collection target for patients under 65 years old was 8x10e6 CD34+cells/kg,** allowing for two potential transplants.

Data reviewed for 2012, 2014, and 2016 (n=165 MM patients collected):

- Overall 70.9% of patients (range/year, 63 - 80%) received a first transplant/reinfusion
- **Only 1.2%** of those initially transplanted received a second transplant
- **Over 50%** of cells collected remained in storage

MM patients under 65	2012	2014	2016
Patients collected:	55	62	48
# getting 1st transplant	44	43	30
# getting 2nd transplant:	**2**	**0**	**0**
# of bags collected:	264	324	164
# of bags stored:	**146 (55.3%)**	**178 (54.9%)**	**83 (50.6%)**

Apheresis

Pre: Prior to the change, (Jul. to Dec. 2017), MM patients under 65 (n=65):

- **Utilized mean bed-days per collection of 2.13** (range 1-4 days, SE 0.13)
- **31% completed collection in 1 day**

Post: After targets changed**, (**Feb. – Jul. 2018), MM patients under 65 (n=44):

- **Utilized mean bed-days per collection of 1.45** (range 1-4, SE 0.11, **p < 0.01)**
- **66% completed collection in 1 day (p < 0.0001) (Fig. 3)**
- **Allogeneic stem cell collections increased by 43% (p < 0.0001)**
- **MNC collections increased by 146% (p < 0.0001)**

Continued reevaluation required
Clinical practice patterns impact this

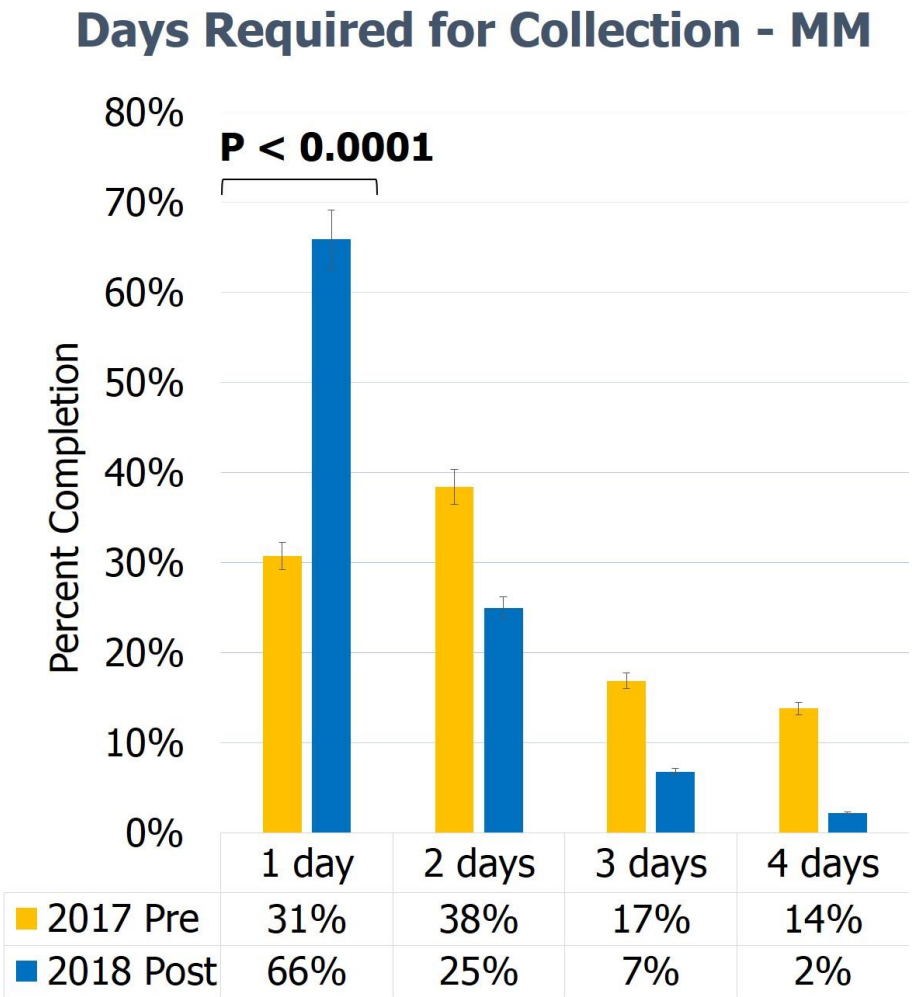


Fig. 3

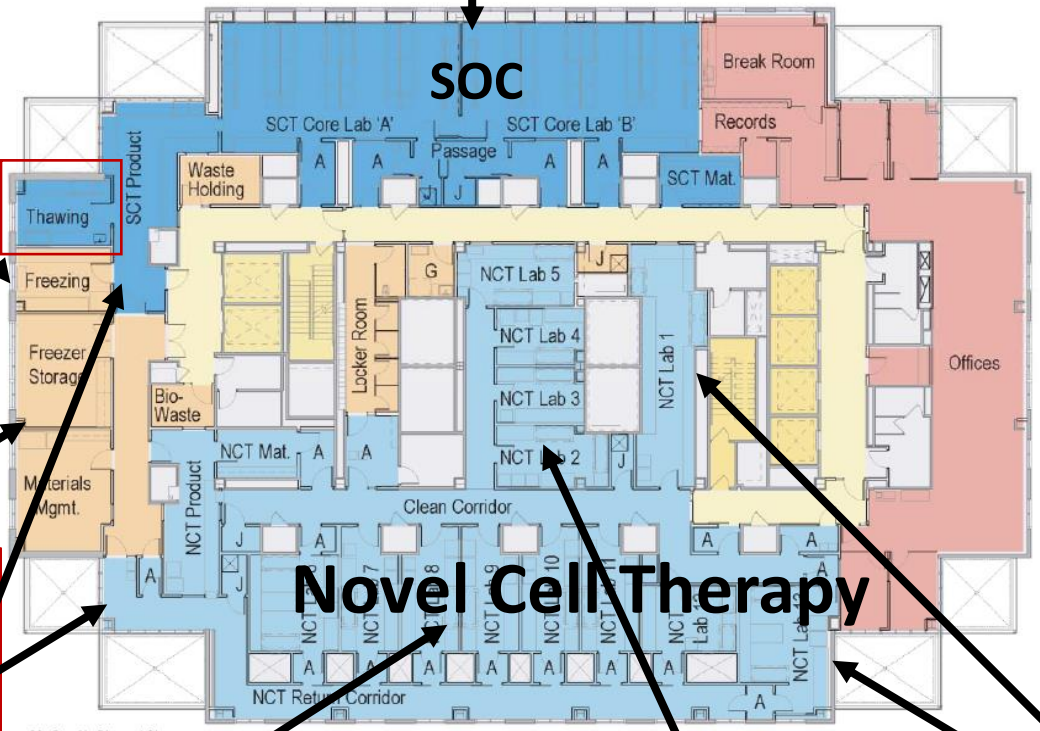
CMCF- Smith 12th Floor
Cell Pharmacy AND Complex Manufacturing

Doubled SOC manufacturing space – 6-> 12 clean room workstations
3200 sq ft

Immediate access to controlled rate freezing

Larger on-site materials and tank spaces

Dedicated Shipping & Receipt Areas



- **Creation of "Manufactured Off Site" group, aka Cell Pharmacy**
- **4 FTEs**
- **Dedicated Shipping and Receiving Area**

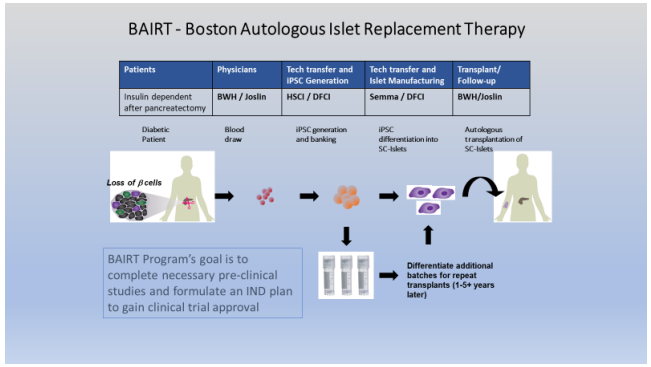
- **70 FTE**
- **65 Clinical Trial Supported**
- **25 INDs with complex manufacturing**

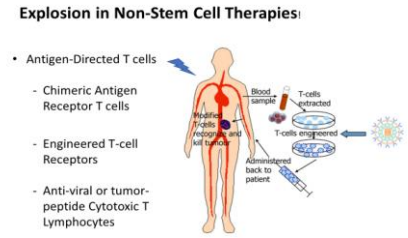
Genetic Engineering Negative Pressure

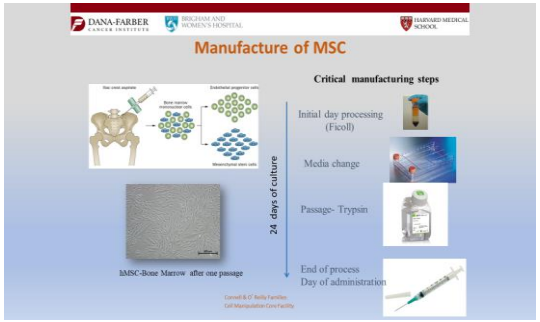
Vaccine Development

Regenerative Medicine

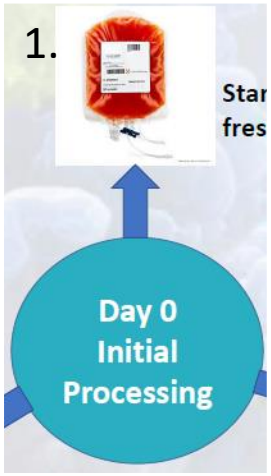
CMCF's NCT – Novel Cell Therapy Lab

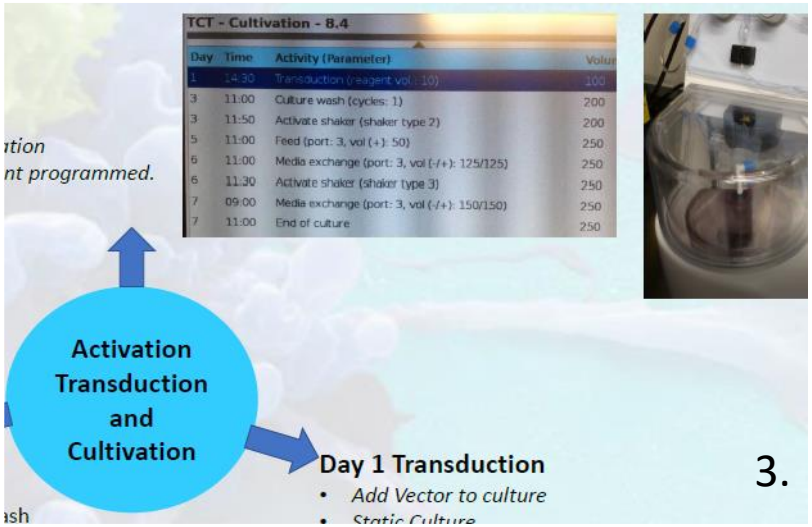


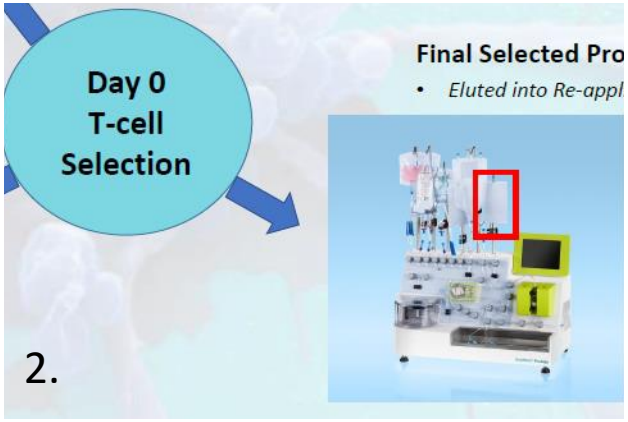




Closed Automated Processing
Enabling Point-of-Care CAR Manufacturing







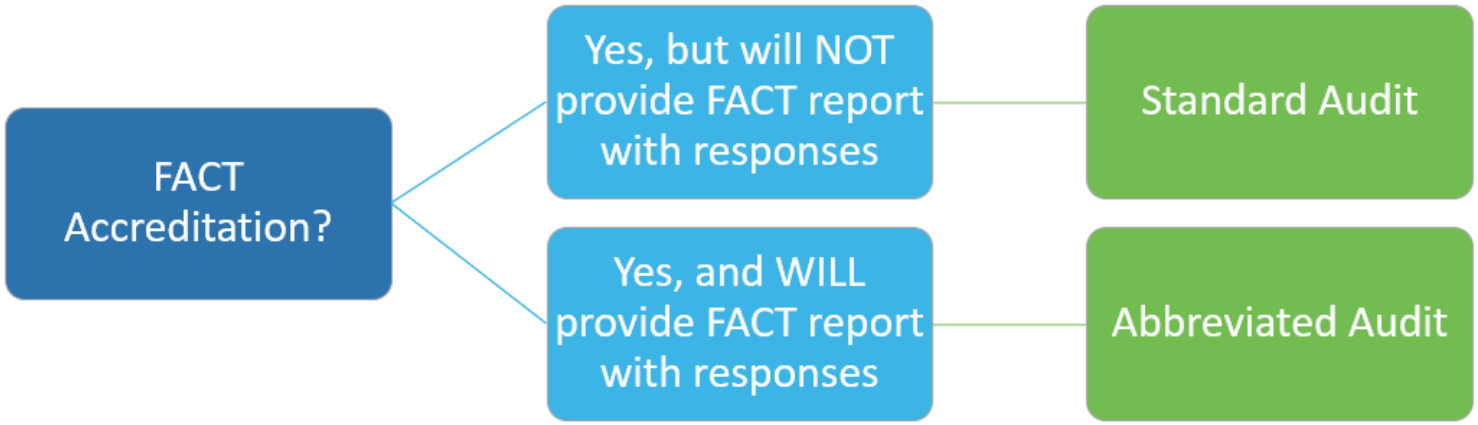
>140 runs on
Miltenyi Prodigy

ASTCT 80/20 Updates over last year +

- **Tailor accreditation** approach — **FACT Audit Modularization**
- **Centralize REMS** and eventually **transition to SOC** processes/audit
- **Streamline REMS reporting** — **Engagement with CTLM**
- **Centralize education** for treatment center staff — **Engagement with SITC, Webinars**
- Create **common IT platform(s)** — **Clinician Engagement w/Deloitte, Accenture**
- Use **universal language** and labelling — **Standards Coordinating Body/ICBBA**
- Improve **communication** between centers and manufacturers — **Workshop Q2 2023**
- Maintain **communication with FDA** — **Engagement with CTLM**

White Paper Published in TCT Journal

Standard Audit vs. Abbreviated Audit

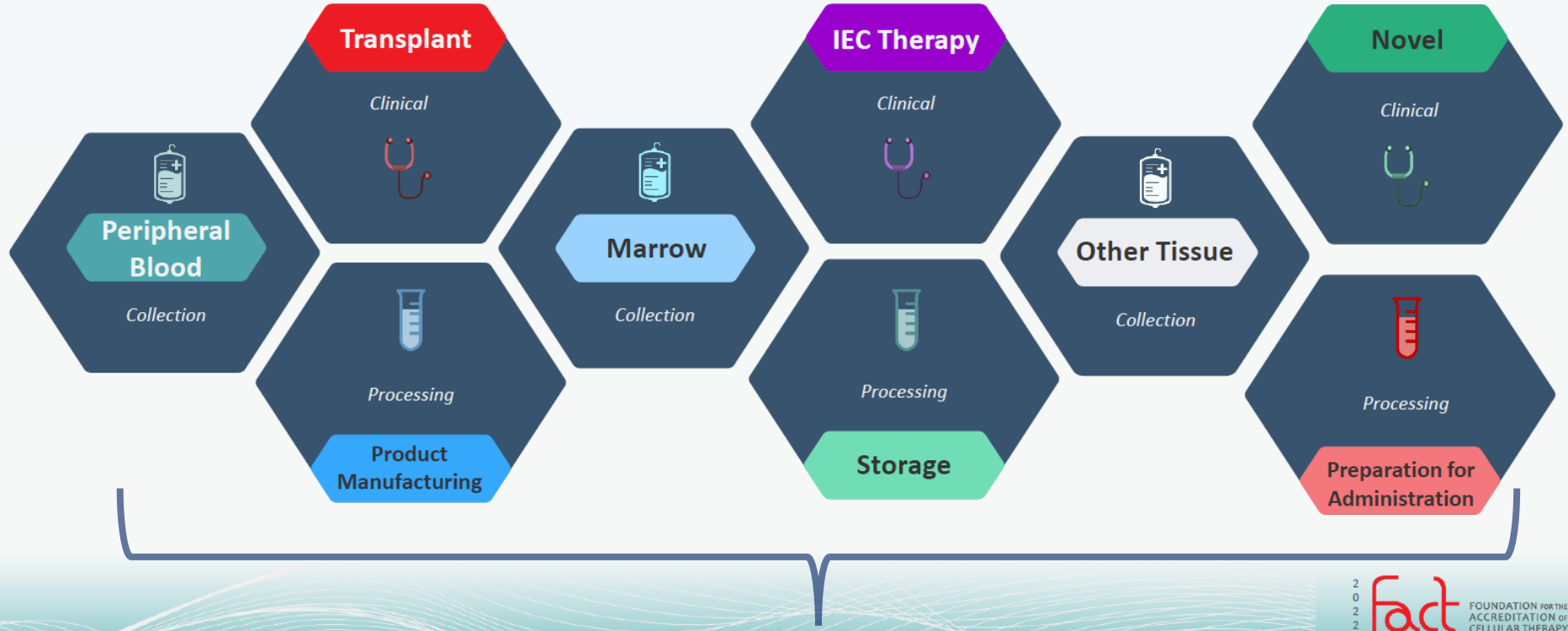


ASTCT

Slide courtesy of Tracey Hlucky, Kite/Gilead
As presented at public AcCELLerate Forum Nov 2021

Modular Accreditation to Match an Organization's Activities

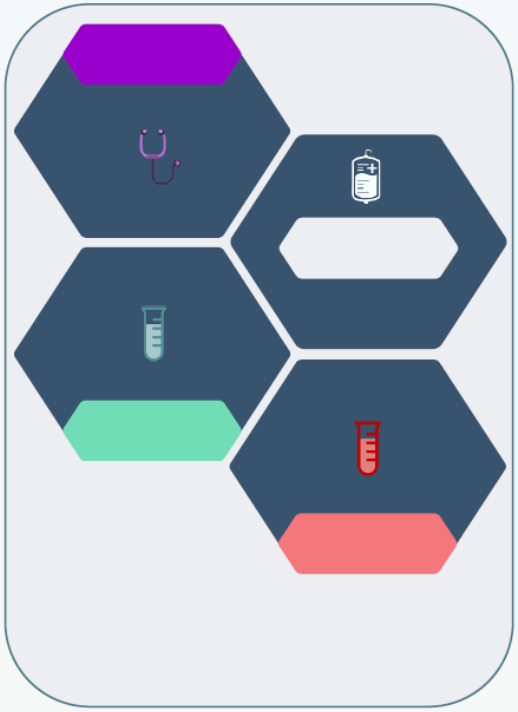
Enabled by Customized Inspection Checklists



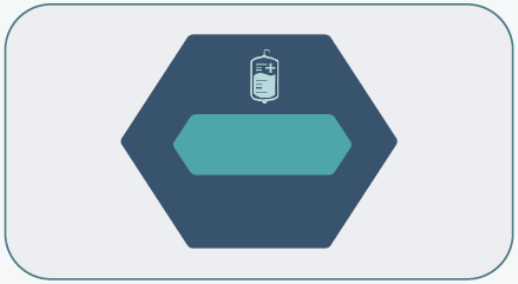
Examples of Accredited Services at a Single Program

Transparently displayed on FACT Website

Transplant, peripheral blood, manufacturing, storage, and preparation for administration



IEC therapy, other tissue, storage, and preparation for administration



Stand-alone peripheral blood collection site. *As of September 19, 2022, 26 such sites are FACT accredited.*

Stand-alone collection site for other tissues, such as tumor resection

Cell Therapy

A team effort!!

Cell Manipulation Core Facility

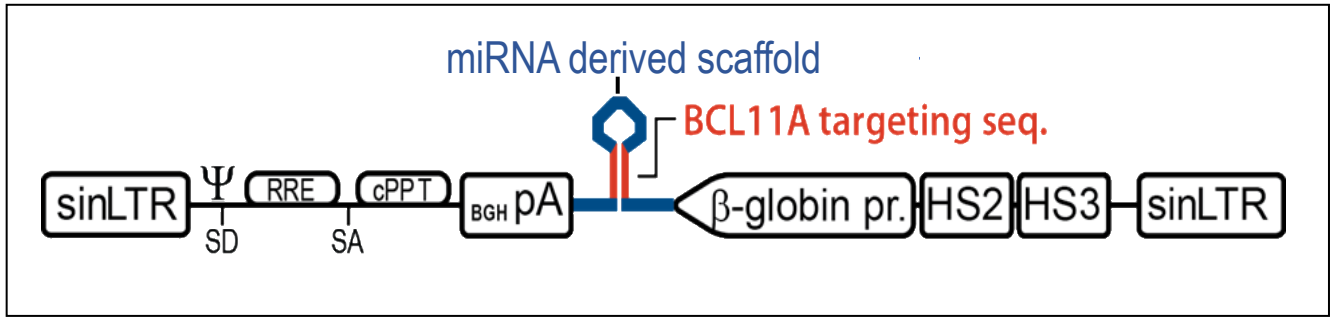
Dana-Farber Cancer Institute

Dana-Farber
Cancer Institute

Questions?

Development of lentiviral vector targeting BCL11A

Background	BCL11A is a validated repressor of HbF
Approach	Knock down BCL11A via short hairpin RNAi to allow erythroid-lineage-specific knockdown and thus induce γ-globin expression
Advantage	Harness the physiologic switch machinery → Simultaneously increase HbF and decrease HbS



* GMP vector produced and supplied to BCH by bluebird bio

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 21, 2021 VOL. 384 NO. 3

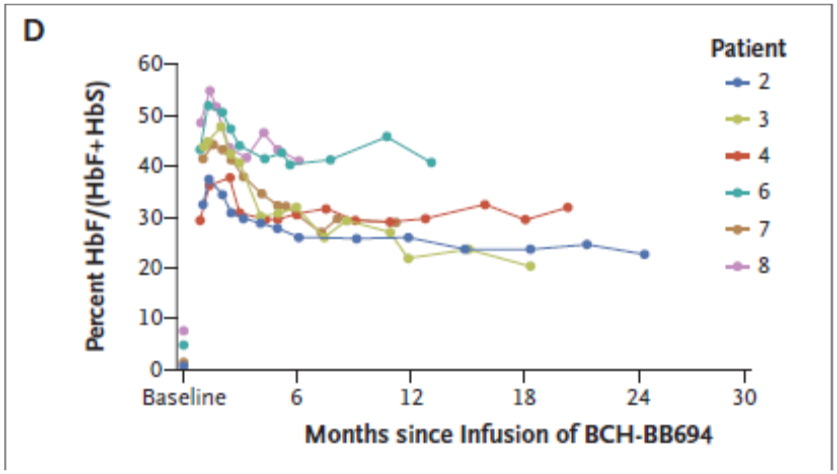
Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease

- 6 patients with median follow-up 18 months (range, 7-29)
- All patients engrafted
- Robust and stable HbF induction (20.4-41.3%)
- Clinical manifestations of sickle cell disease reduced or absent

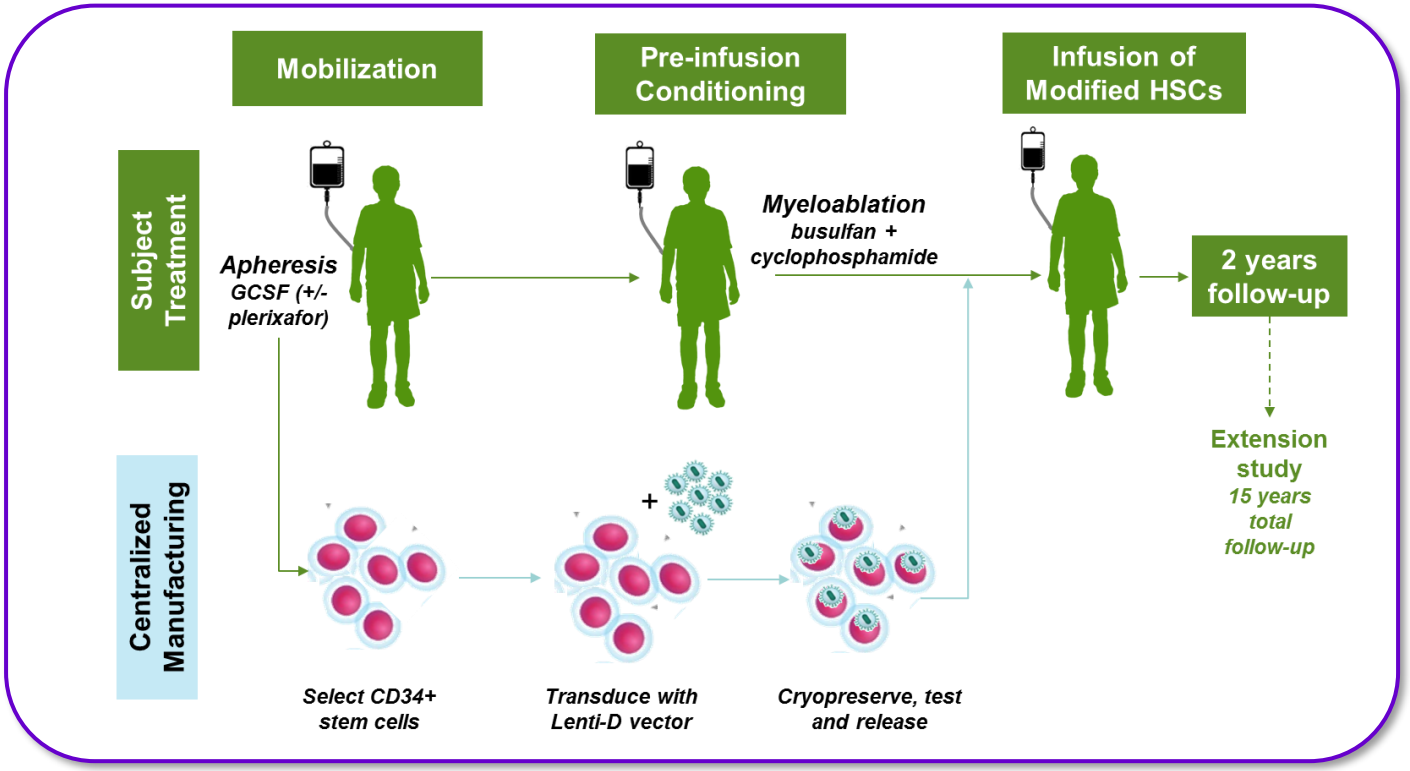
- Academic/Industry collaboration
- Transfusion medicine partnering invaluable
- Scaling and new analytics a challenge
- *** Caution re . Genetic engineering and 2ndary malignancies!!

Table 4. Clinical Events before and after Infusion.*

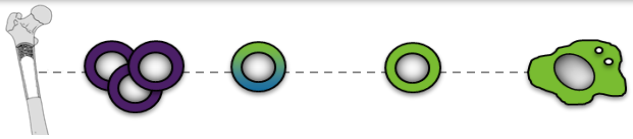
Patient Number	Months since Infusion	No. of Transfusions (Annualized)		No. of Severe Sickle Cell Clinical Events†		
		Prestudy	After Engraftment	Prestudy	After Gene Therapy (<5 mo)	After Gene Therapy (≥5 mo)
2	29	12.5	0	0	0	0
3	19	10.5	5.7	0	0	0
4	20	2	0	13	5	1‡
6	16	3	0	6	0	0
7	12	11	0	0	0	0
8	7	1	0	3	0	0



Starbeam Study: Treatment Protocol



Lenti-D Drug Product (DP) consists of an autologous CD34+ cell-enriched population that contains cells transduced with lentiviral vector that encodes an *ABCD1* cDNA for human ALDP



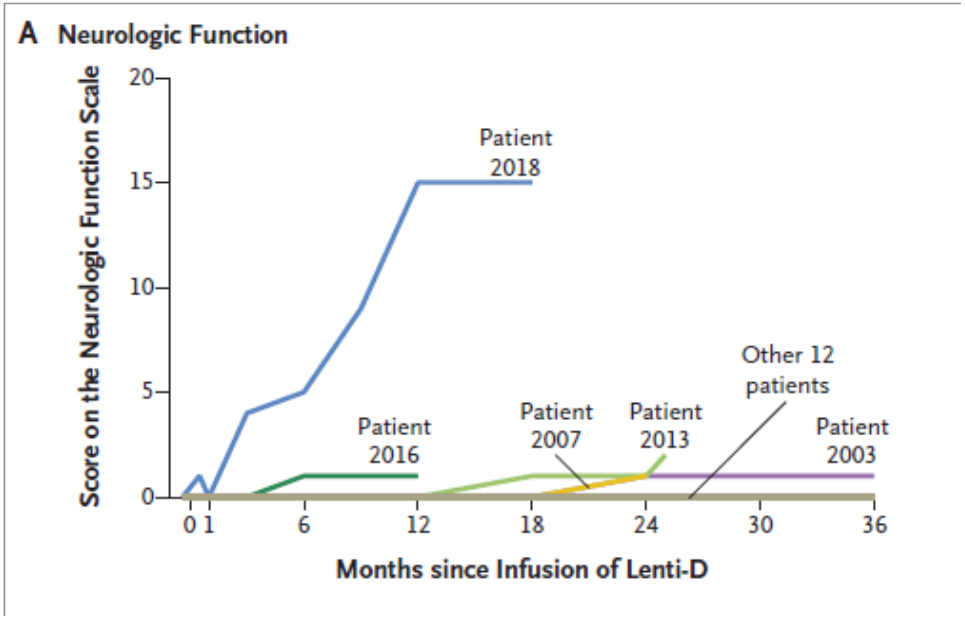
Monocytes (CD14+) differentiate into microglia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D.,



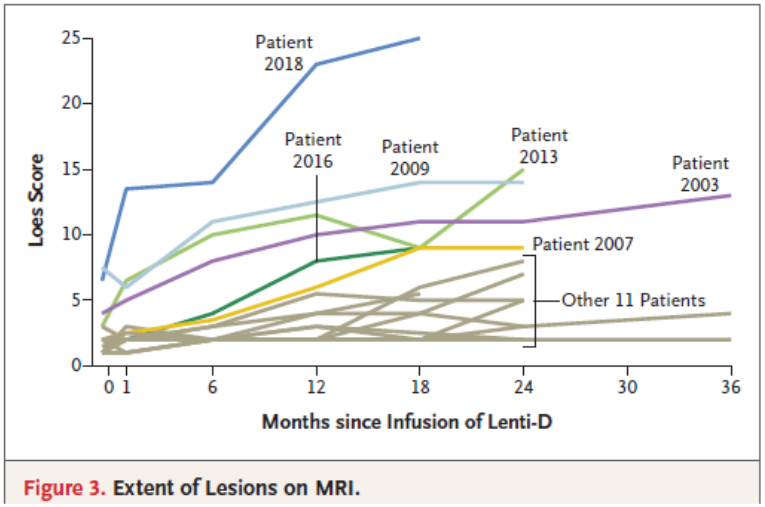


Figure 3. Extent of Lesions on MRI.

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(elivaldogene autotemcel)
suspension for IV infusion

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