Vehicles in the Cell Therapy Garage within the ImmunoOncology City

Sarah Nikiforow, MD, PhD-

Technical Director, Immune Effector Cell Program

Medical Director, Cell Manipulation Core Facility

BWH Medicine Residency
Noon Conference 7/26/2024

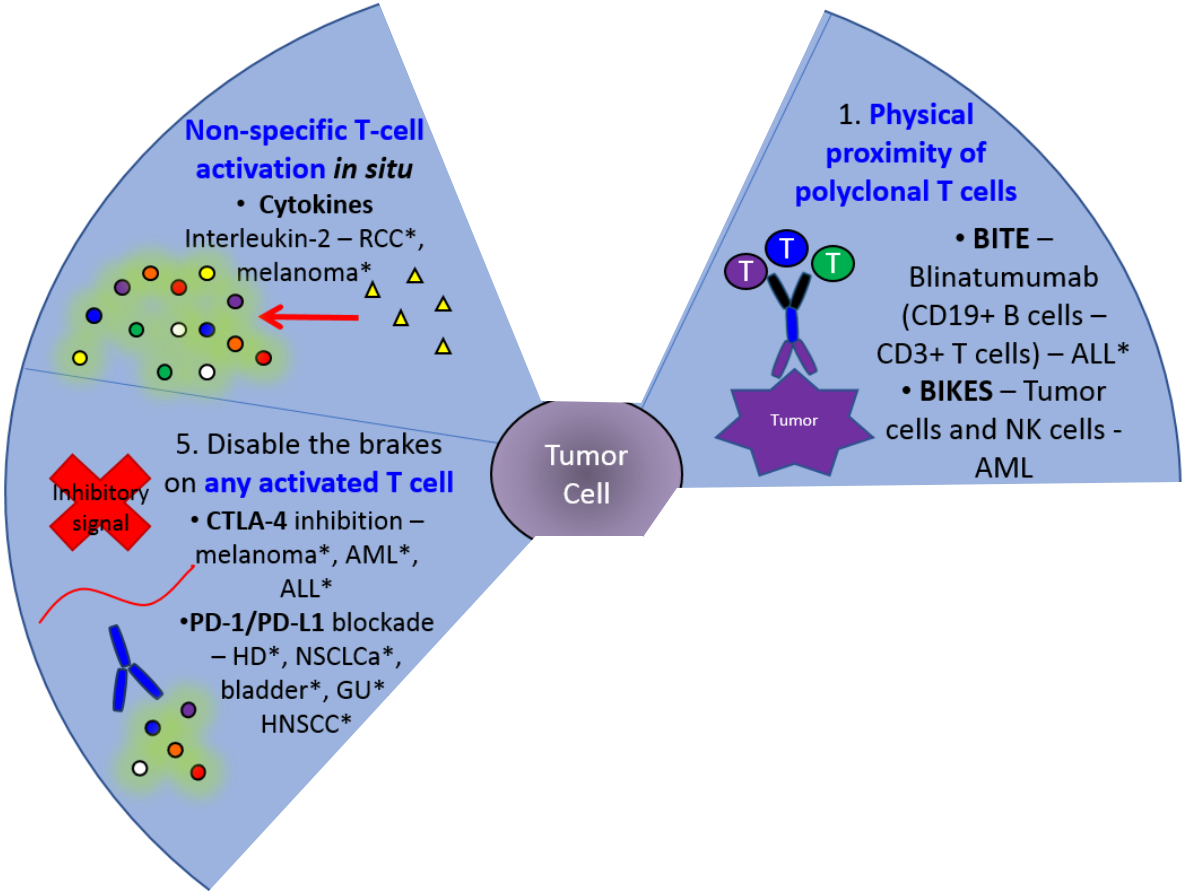
Dana-Farber Cancer Institute

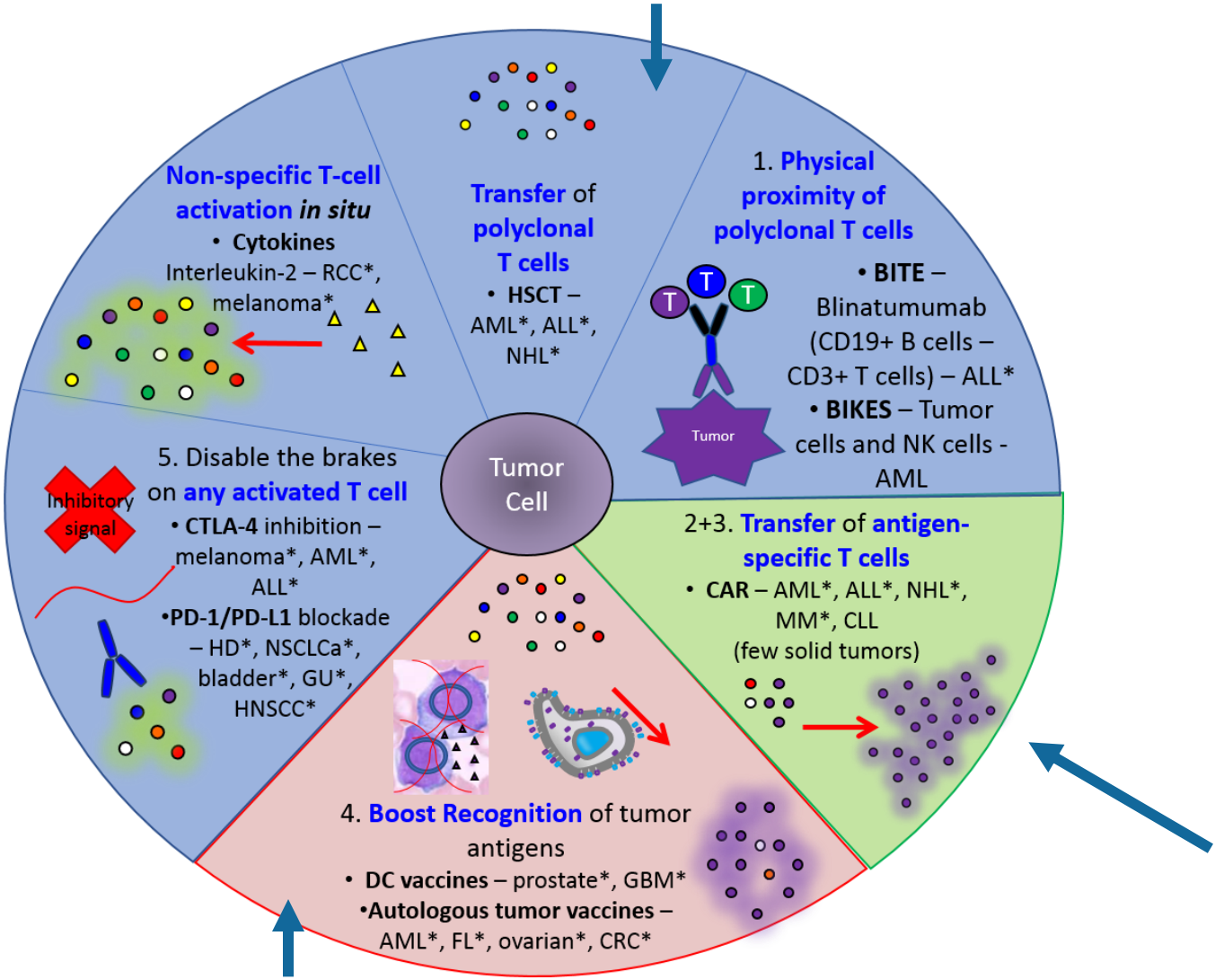
Disclosure

- Ad Hoc Advisory Boards for A2 Bio, Iovance, Legend Biotech, Kite/Gilead, SmartImmune, Sobi

Overview

- Wheel of ImmunoOncology
- Delving into Cell Therapy Approaches
- Applications for “typical” Chimeric Antigen Receptor Cells
- Peek into current IEC trial offerings
- Tumor Infiltrating Lymphocytes – they are HERE!!


Non-specific T-cell activation *in situ*
• **Cytokines**
Interleukin-2 – RCC*, melanoma*
1. **Physical proximity of polyclonal T cells**
T
T
T
Tumor
• **BITE** – Blinatumumab (CD19+ B cells – CD3+ T cells) – ALL*
• **BIKES** – Tumor cells and NK cells - AML
Tumor Cell
Inhibitory signal
5. Disable the brakes on **any activated T cell**
• **CTLA-4** inhibition – melanoma*, AML*, ALL*
•**PD-1/PD-L1** blockade – HD*, NSCLCa*, bladder*, GU* HNSCC*


Non-specific T-cell activation *in situ*
• Cytokines
Interleukin-2 – RCC*, melanoma*
Transfer of polyclonal T cells
• HSCT – AML*, ALL*, NHL*
1. Physical proximity of polyclonal T cells
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Tumor Cell
Inhibitory signal
5. Disable the brakes on any activated T cell
• CTLA-4 inhibition – melanoma*, AML*, ALL*
•PD-1/PD-L1 blockade – HD*, NSCLCa*, bladder*, GU*, HNSCC*
2+3. Transfer of antigen-specific T cells
• CAR – AML*, ALL*, NHL*, MM*, CLL
(few solid tumors)
4. Boost Recognition of tumor antigens
• DC vaccines – prostate*, GBM*
•Autologous tumor vaccines – AML*, FL*, ovarian*, CRC*

New Aspects with “Standard” Stem Cell Transplant

- Autologous Collection, High Dose Chemotherapy, Auto Stem Cell Rescue
  - No graft manipulation
  - Lymphoma in relapse and myeloma after initial therapy

  *** Stay tuned as CARs moving up in therapy

- Allogenic stem cell therapy (Donor collection, Chemotherapy, infusion, GvHD prophylaxis)
  - Graft “sculpting” is now a reality

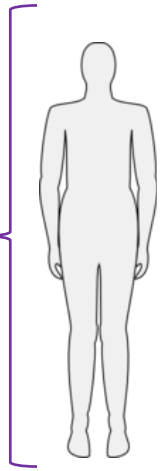
Issues Affecting Flow of Allo HSCT

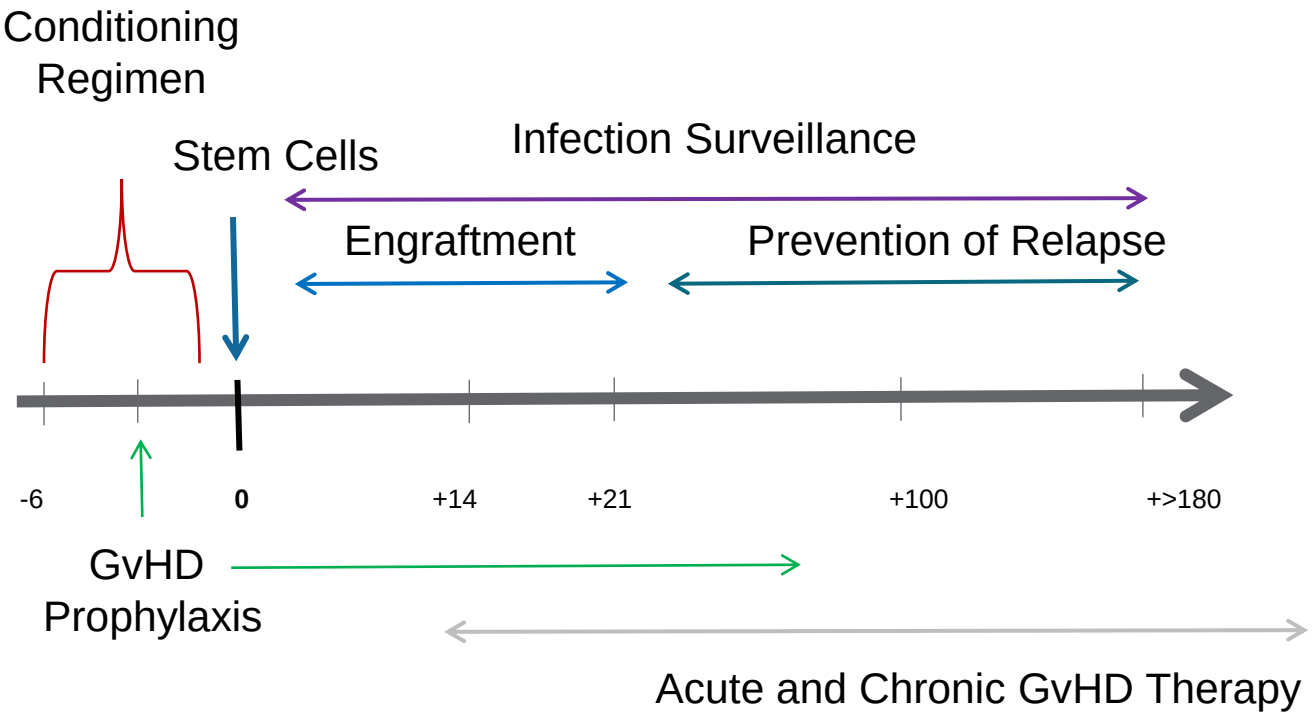
1. Is transplant indicated?
2. What donor is suitable?

Patient Related
-Age
-Gender
-Comorbidities

Prior Therapy
-Type of chemo
-Prior transplant

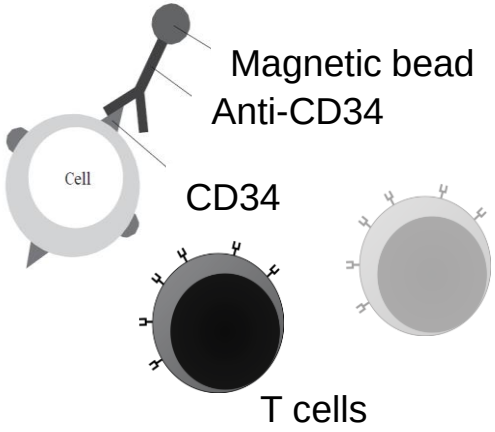
Disease Related
-Myeloid vs. Lymphoid
-Stage
-Disease status





"What's in the bag"

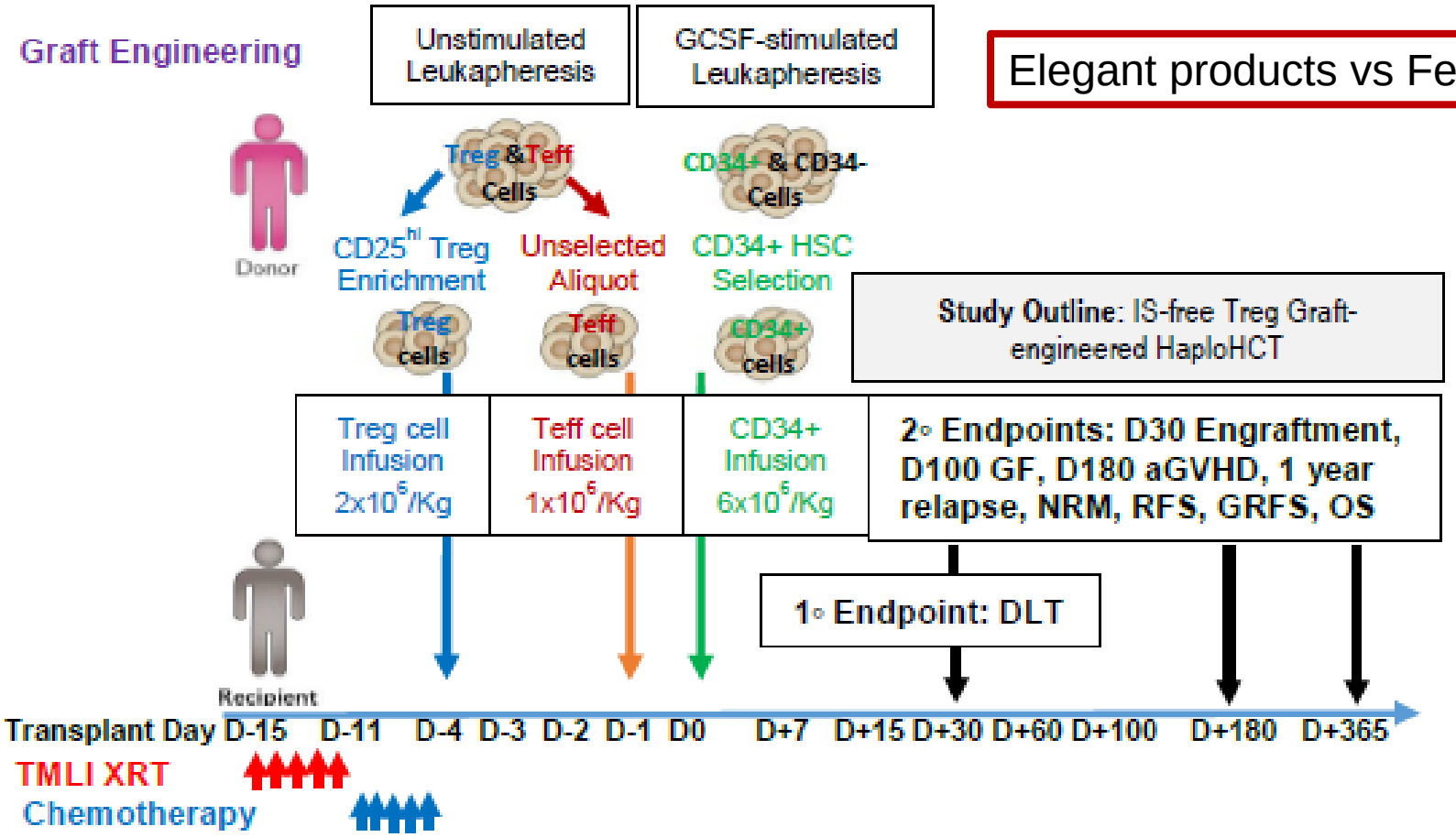
- **Graft Source** – CD34-selected peripheral blood stem cells versus 2 more standard versions of bone marrow transplantation regimens



NK cells

Graft Sculpting – Protocol 20-336 John Koreth

TITLE: A Pilot/Phase 1 Study of Immunosuppression-free Regulatory T-cell Graft-engineered Haploidentical Hematopoietic Cell Transplantation in Relapsed/Refractory AML/MDS



Elegant products vs Feasibility??

New Aspects with “Standard” Stem Cell Transplant

- Autologous Collection, High Dose Chemotherapy, Auto Stem Cell Rescue
  - No graft manipulation
  - Lymphoma in relapse and myeloma after initial therapy

  *** Stay tuned as CARs moving up in therapy

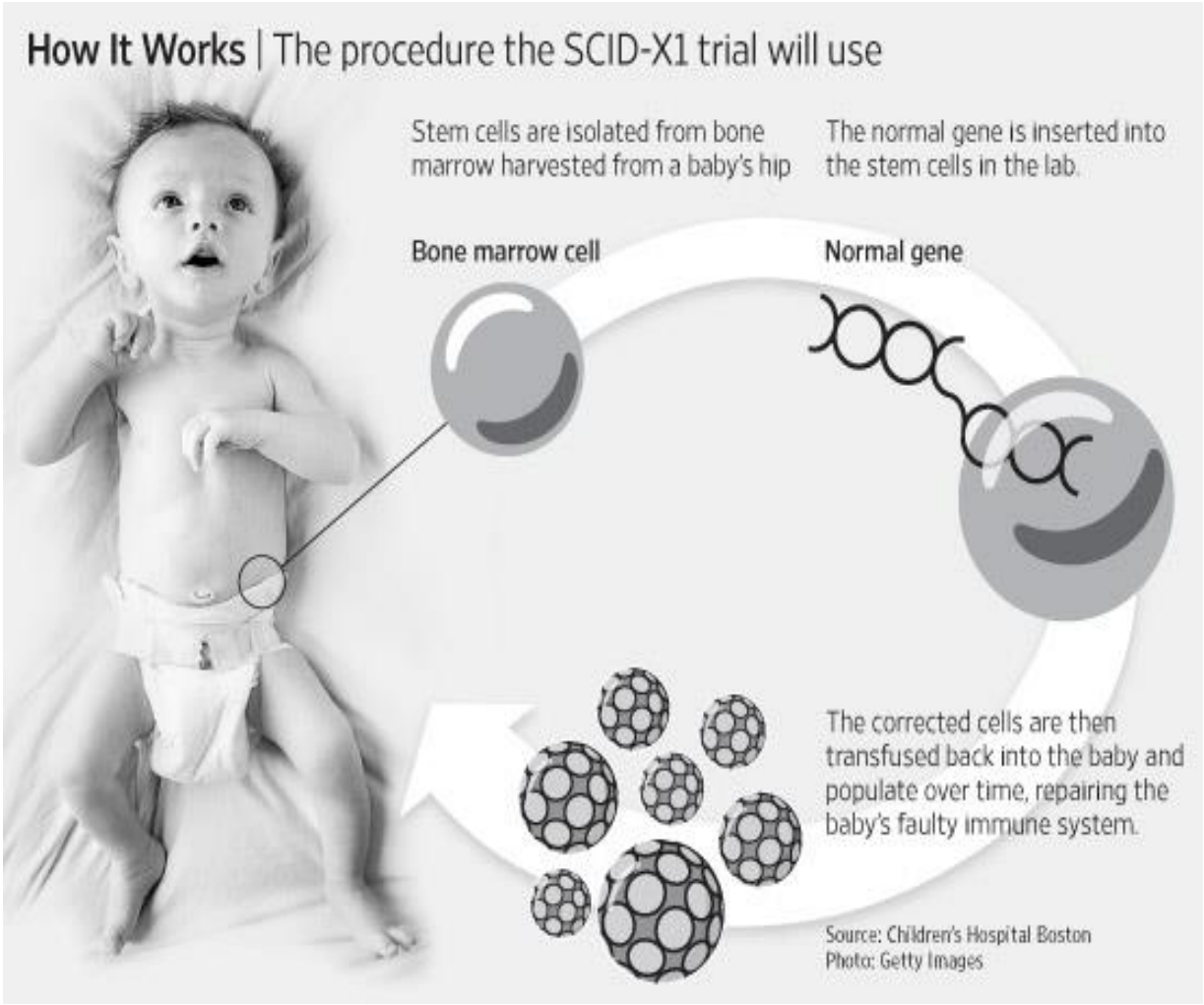
- Allogenic stem cell therapy (Donor collection, Chemotherapy, infusion, GvHD prophylaxis)
  - Graft “sculpting” is now a reality

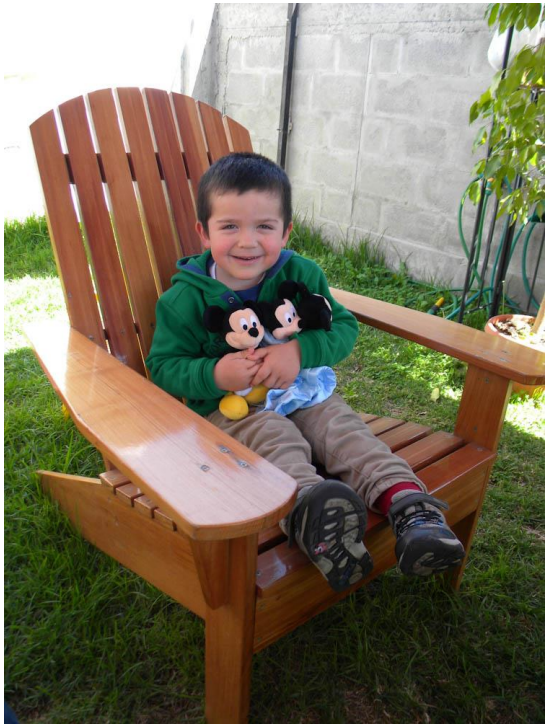
- Genetic modification of stem cells – typically in autologous setting
  - Pediatric Immunodeficiencies and sickle cell disease

  *** Now commercially available!!

Genetic Engineering of Autologous Stem Cells - what's missing? (X-Linked SCID, WAS, ALD, CGD)

Self inactivating gammaretroviral vector encoding the human common cytokine receptor gamma chain (γc).



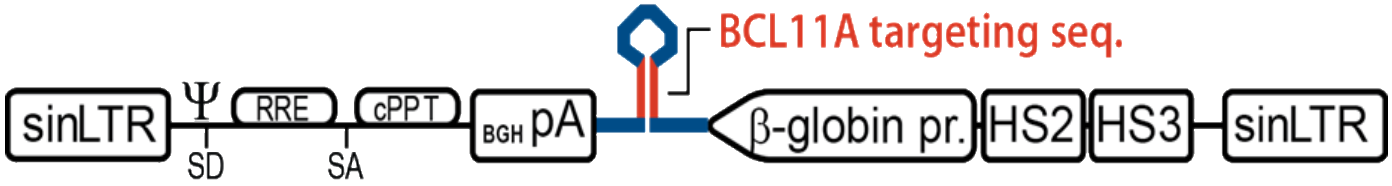


INTERNATIONAL GENE THERAPY SCID-X1 TRIAL

Fetal hemoglobin (HbF), flipping the switch

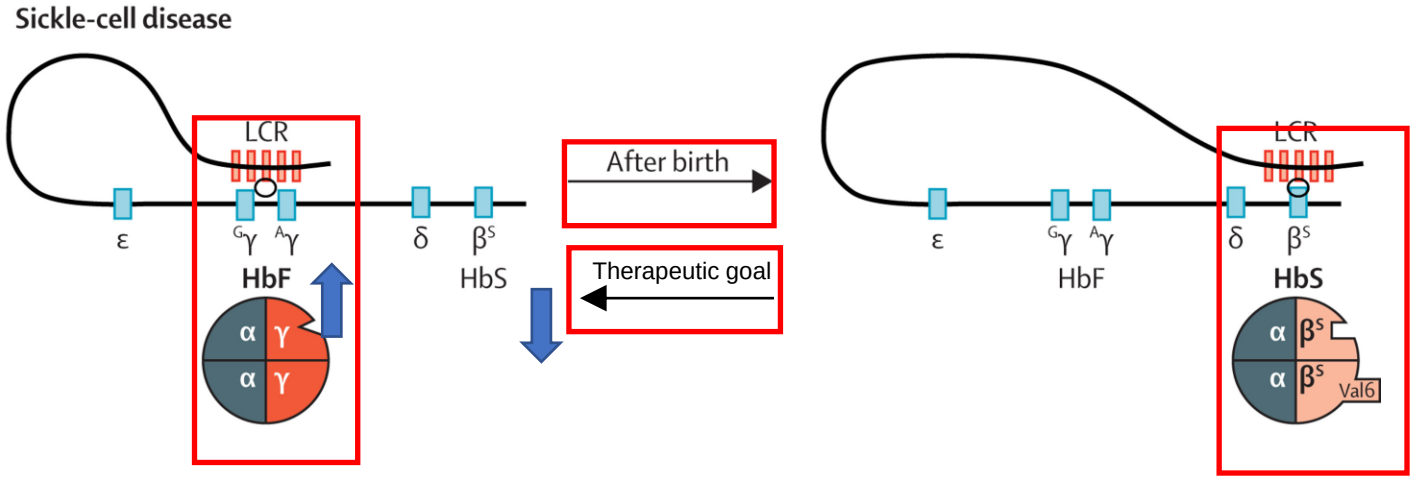
Down regulation of bcl11A – leading to upreg of HgbF

GRASP Trial – lentivirus carrying short hairpin RNA (other trials CRISPR/CAS9)



Our approach:
Knockdown of BCL11A via RNAi using lentiviral vectors to induce γ-globin expression

Advantage:
Harnesses the physiologic switch machinery → simultaneously induce HbF and silence HbS
- α to β chains expression remains balanced



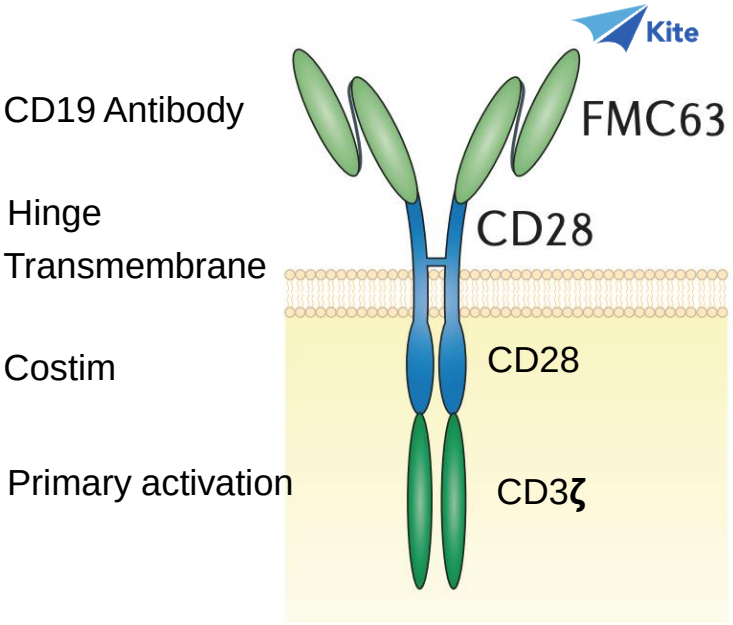
Lettre and Bauer. Lancet 2016

DFCI - Cell Manipulation Core Facility

Vs Commercial Manufacturing/Sponsor Facilities

“Typical” CARs

- Multiple cell types are now being genetically manipulated.
- T cells or NK cells can have CARs introduced. Typically using Retrovirus or Lentiviral vectors



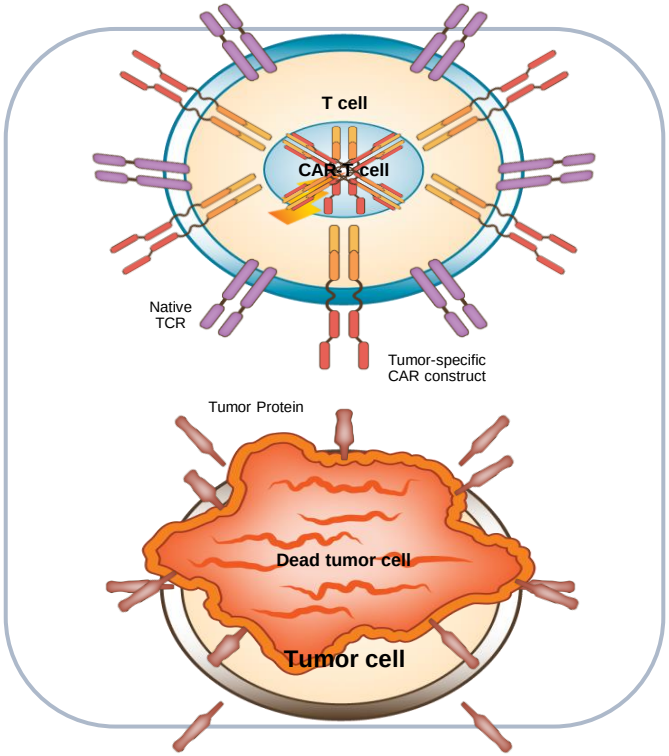


Image courtesy of Stephan Grupp, UPenn

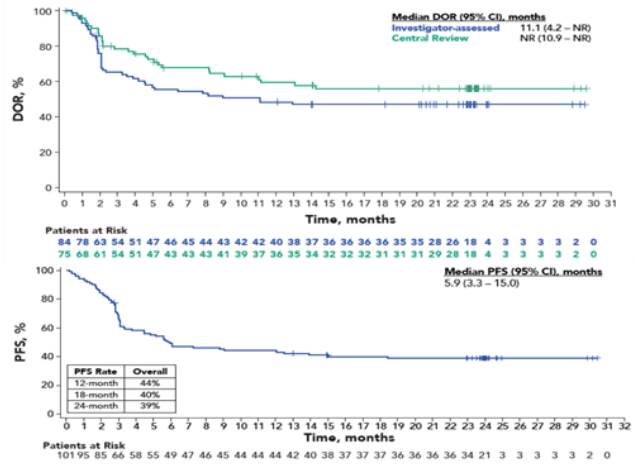
Current State of "Standard" CAR Therapy

- Commercial Approval of CD19 and BCMA CARs
  - Slightly different safety and efficacy profiles
  - Different logistical considerations – manufacturing success and turnaround time.
  - Different duration of response

CD19 CAR T-cells for >/= 2nd line therapy
DLBCL: 40% Durable Remission Rate

YESCARTA/TECARTUS
LBCL, FL/MCL, B-ALL

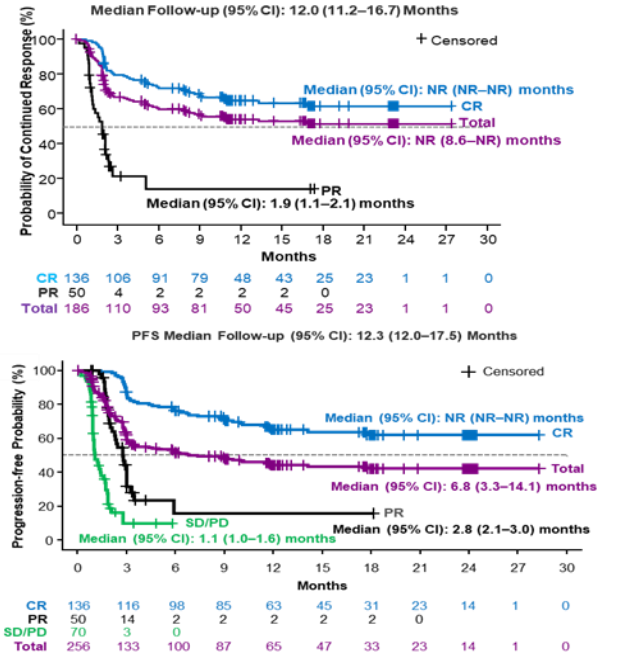
ZUMA-1



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

BREYANZI
LBCL, FL, CLL

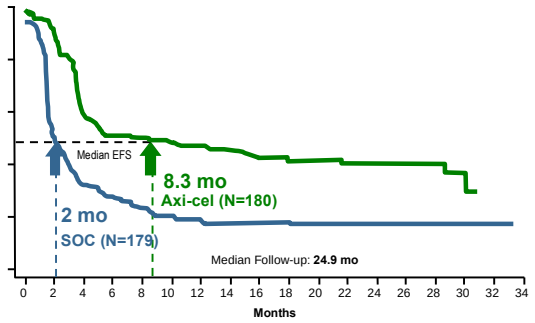
TRANSCEND-001

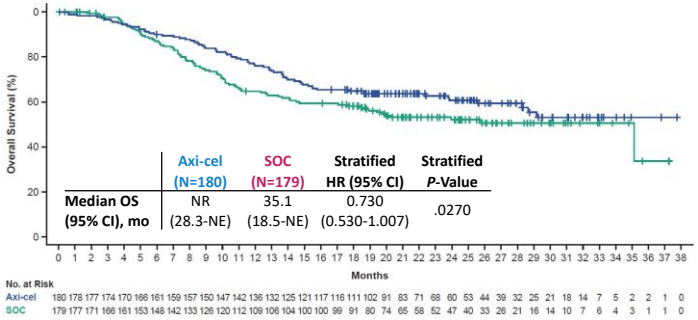


Randomized trials vs auto SCT in DLBDL – CARs win!!

YESCARTA ZUMA-7[1]

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

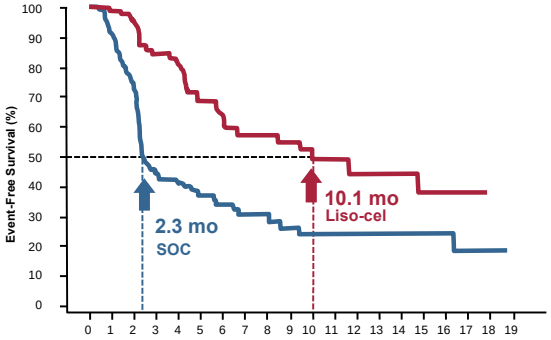


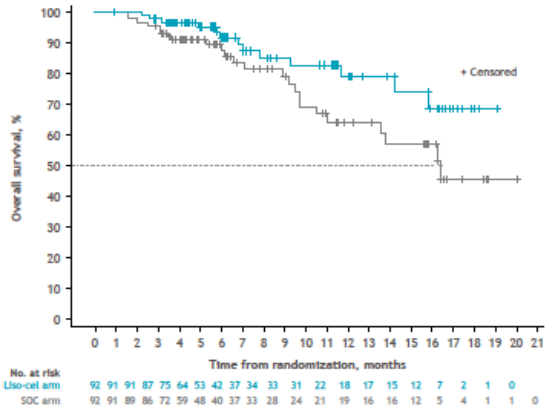


	Axi-cel (N=180)	SOC (N=179)	Stratified HR (95% CI)	Stratified *P*-Value
Median OS (95% CI), mo	NR (28.3-NE)	35.1 (18.5-NE)	0.730 (0.530-1.007)	.0270

TRANSFORM[2] Breyanzi

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





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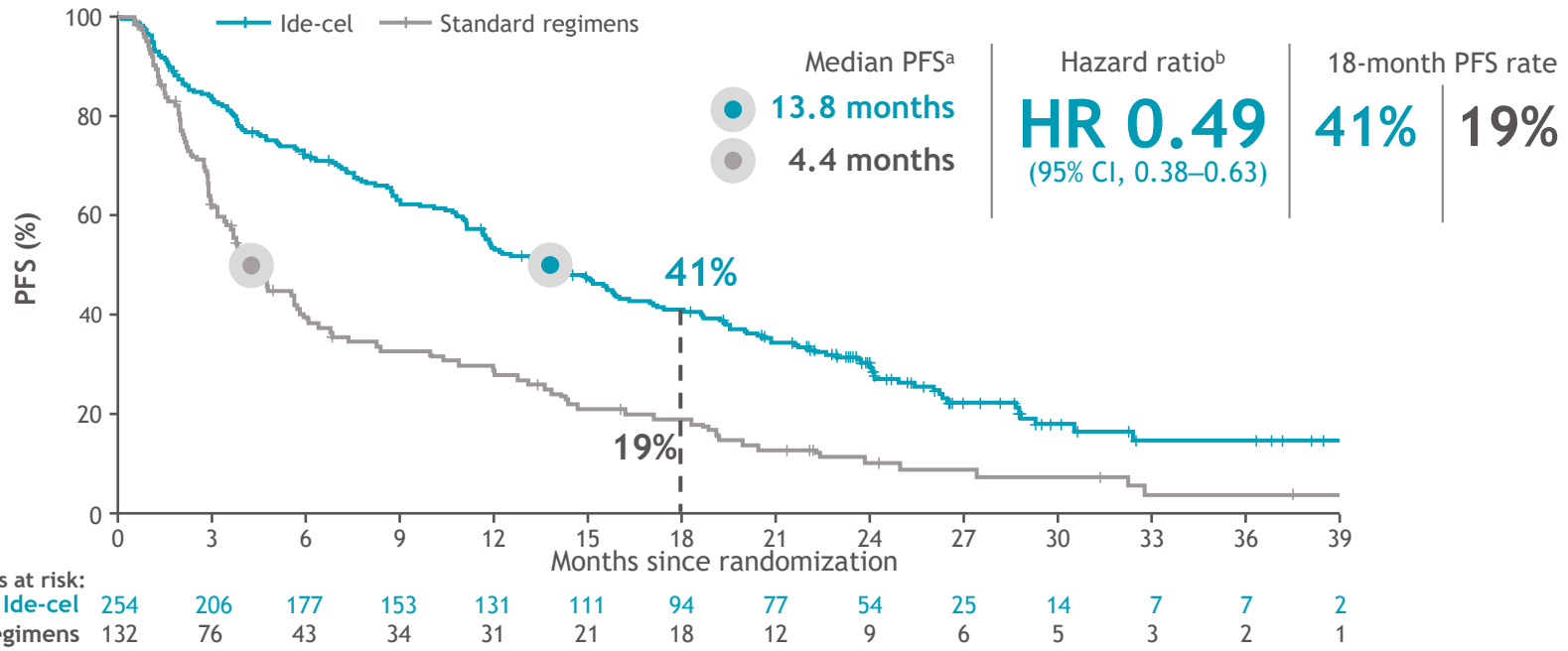
Significant benefit with ide-cel at final PFS analysis (ITT population)

KarMMa-3 updated analysis

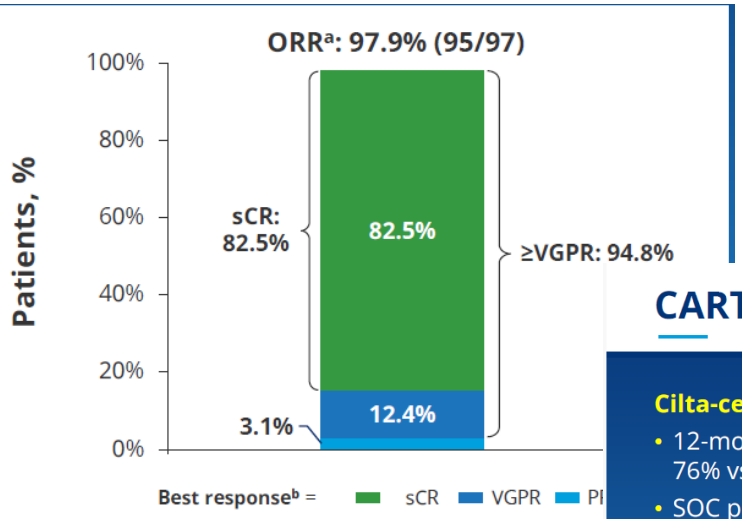
Abecma vs Standard Regimens



PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC. [a]Based on Kaplan-Meier approach; [b]Stratified HR based on univariate Cox proportional hazard model. CI is two-sided. IMWG, International Myeloma Working Group.

Rodríguez-Otero P, et al. ASH 2023 Abstract 1028

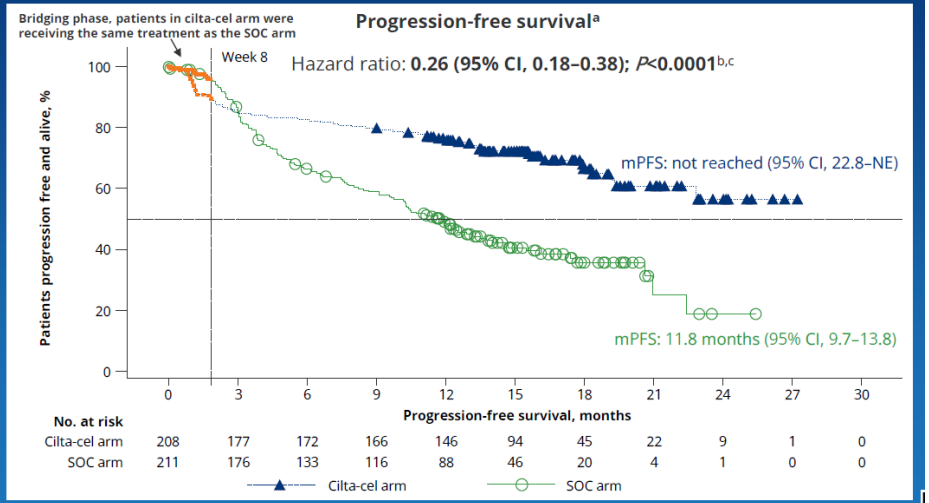
Cartitute-1: CARVYKTI (Cilta-cel) in >/= 4 L therapy for multiple myeloma



CARTITUDE-4: Primary Endpoint – PFS (ITT Population)

Cilta-cel vs SOC

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected

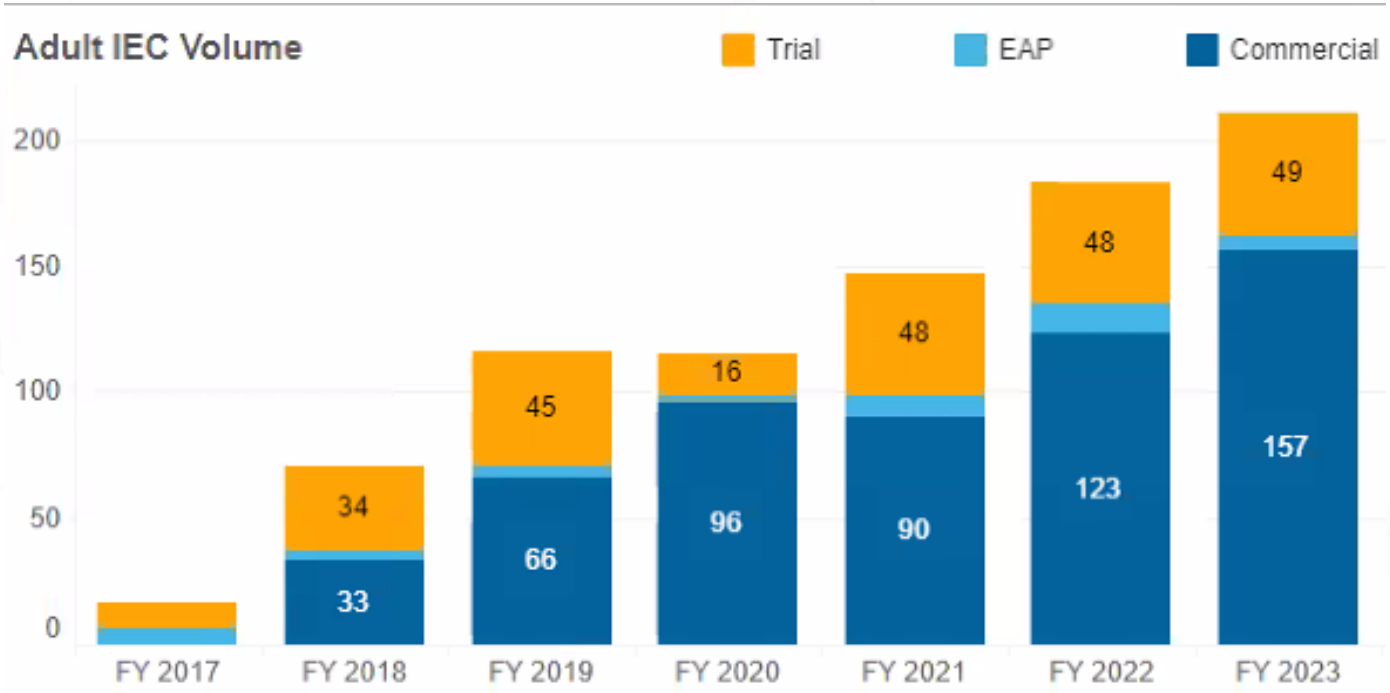


Current State of "Standard" CAR Therapy

- Commercial Approval of CD19 and BCMA CARs
  - Slightly different safety and efficacy profiles
  - Different logistical considerations – manufacturing success and turnaround time.
  - Different duration of response

- Ongoing improvements
  - Moving up in lines of therapy (?even first line for high risk?)
  - Reduce time from identified need to infusion (allogeneic or off-the shelf?)
  - Different editing approaches (reduce risk of 2ndary malignancies)

  - Understanding optimal timing and prior therapies for the patients (choices chemo, sequencing vs BITEs)



- 11 major clinical audits in past 12 mos (REMS, FACT, NMDP, CIBMTR)
- Currently onboarding 5 new products (Autolus, Adaptimmune, Iovance, bbb, Vertex)
- Expecting 3 new label changes

Dana-Farber Cancer Institute

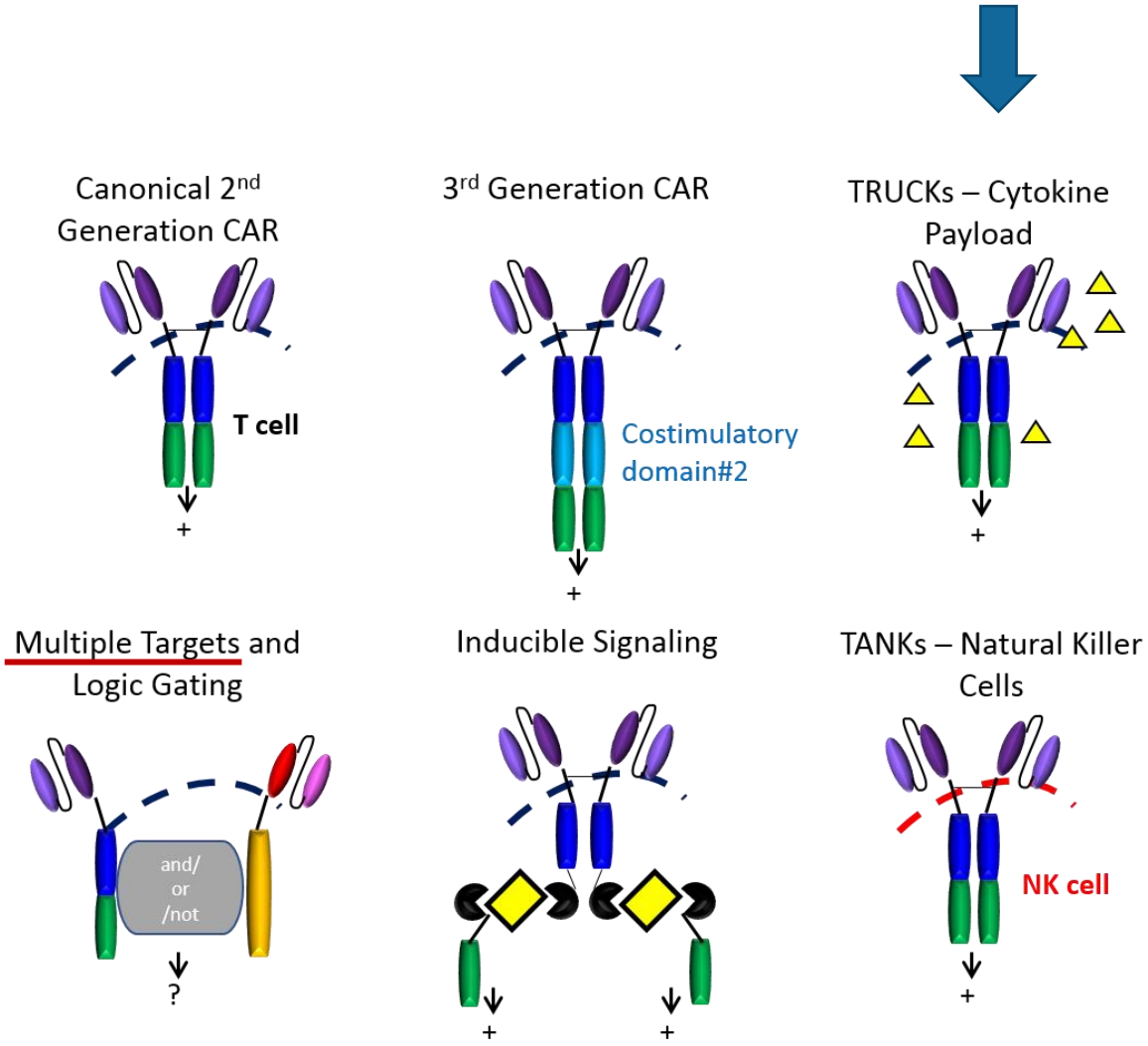
DIA

Ongoing CAR Engineering

Antigen recognition- Antibody scFv moieties

Costimulatory domain#1

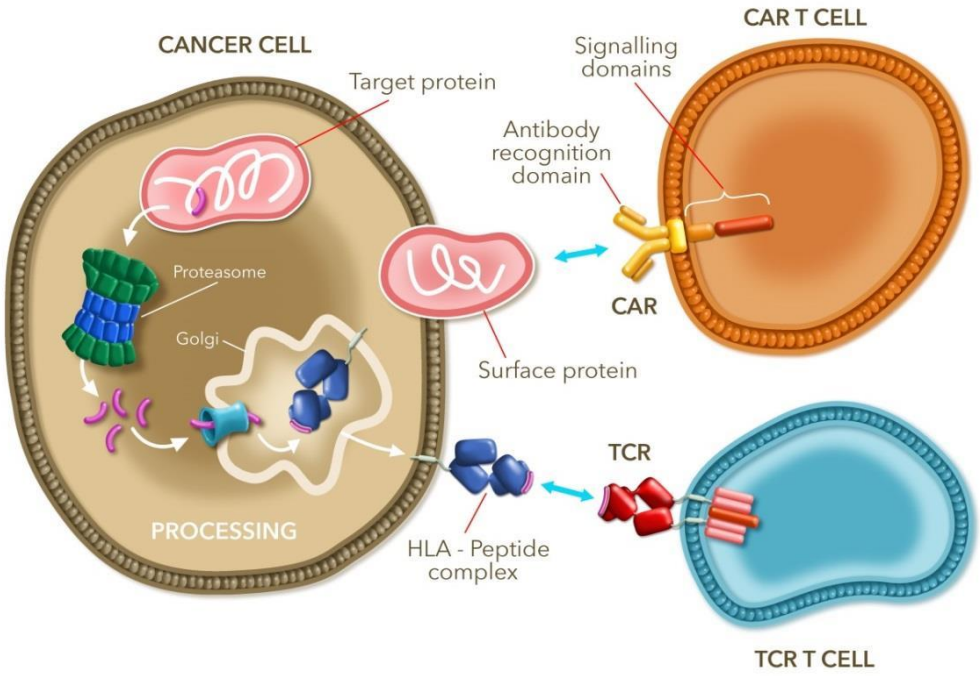
Activation domain – CD3ζ



Different Types of Cells

- Genetically Engineered – CARs vs Engineered TCRs

  CARs are not MHC restricted but only see see surface proteins



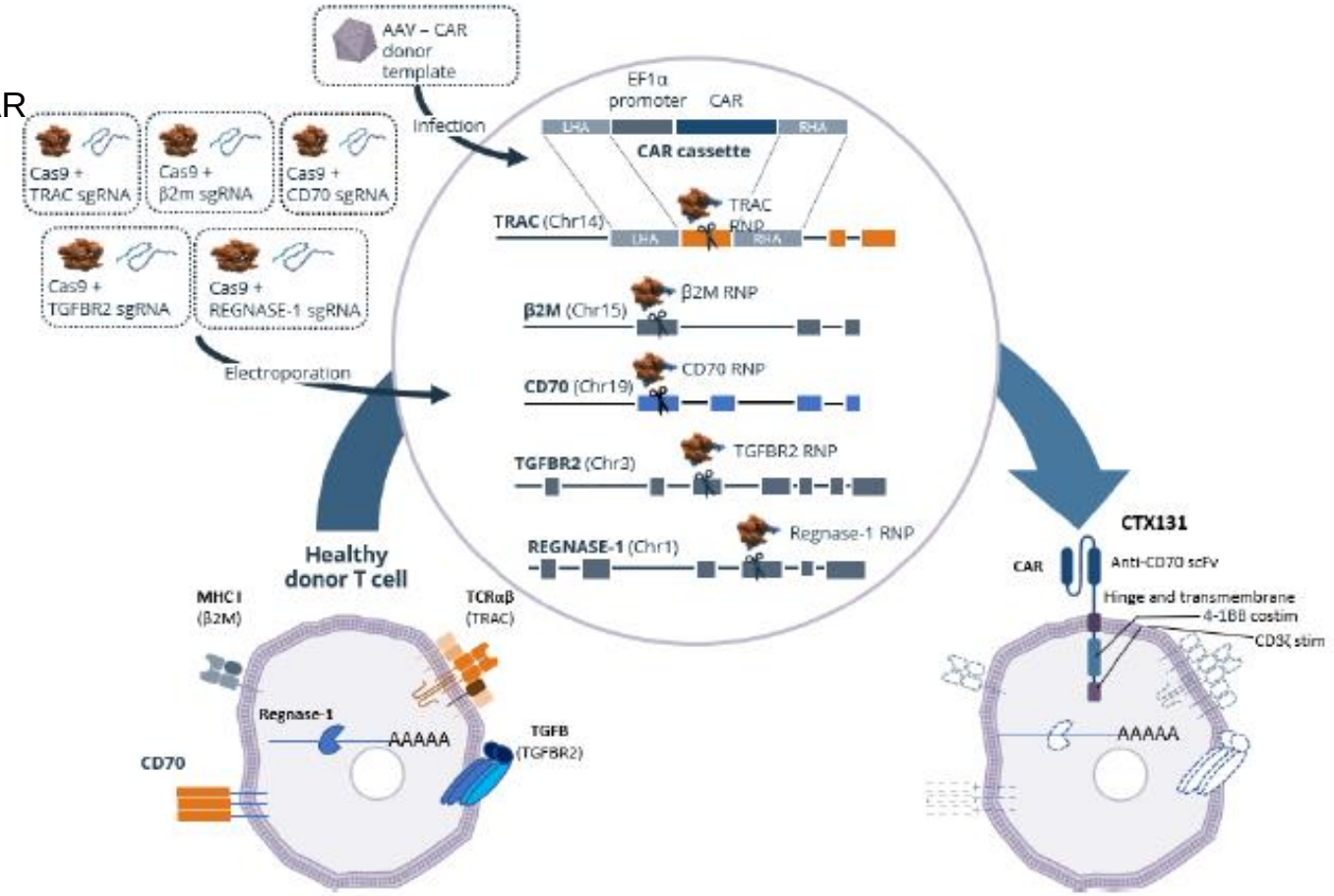
HLA-A02
- NY-ESO-1 or MAGE-A4

Sarcoma
- Mesothelin – multiple dzs
- TP52 R175K – multiple dzs

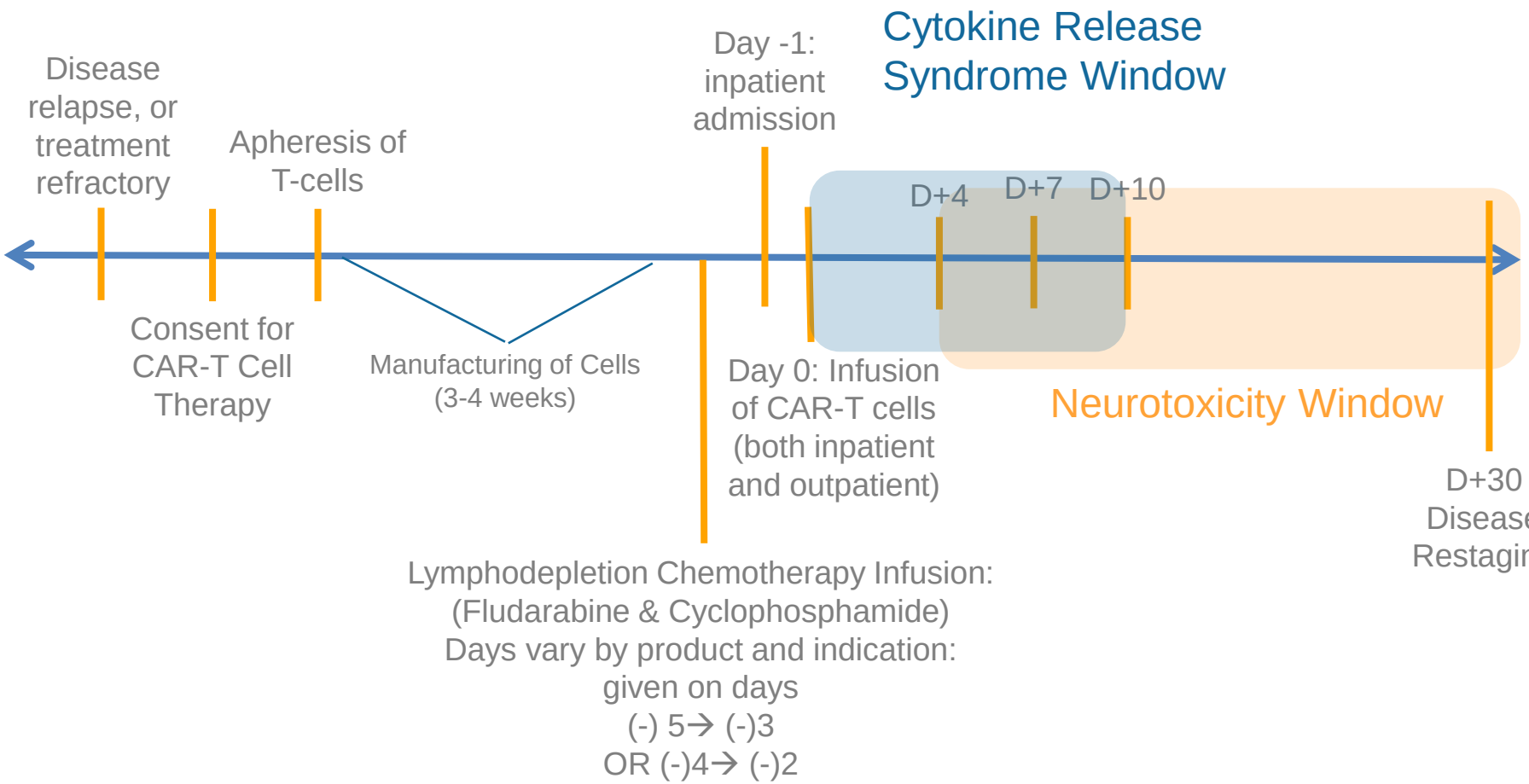
HLA-A02
E16 HPV peptide
H&N cancer

Hold on to your seats !!!!

Solid Tumors:
GU:
CRISPR Allo antiCD70 CAR



Treatment Trajectory



ASTCT Consensus for CRS Grading

Consensus therapy tocilizumab (anti IL-6 Receptor Ab) and dexamethasone

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)

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

Neurotoxicity Grading – ASTCT ICANS

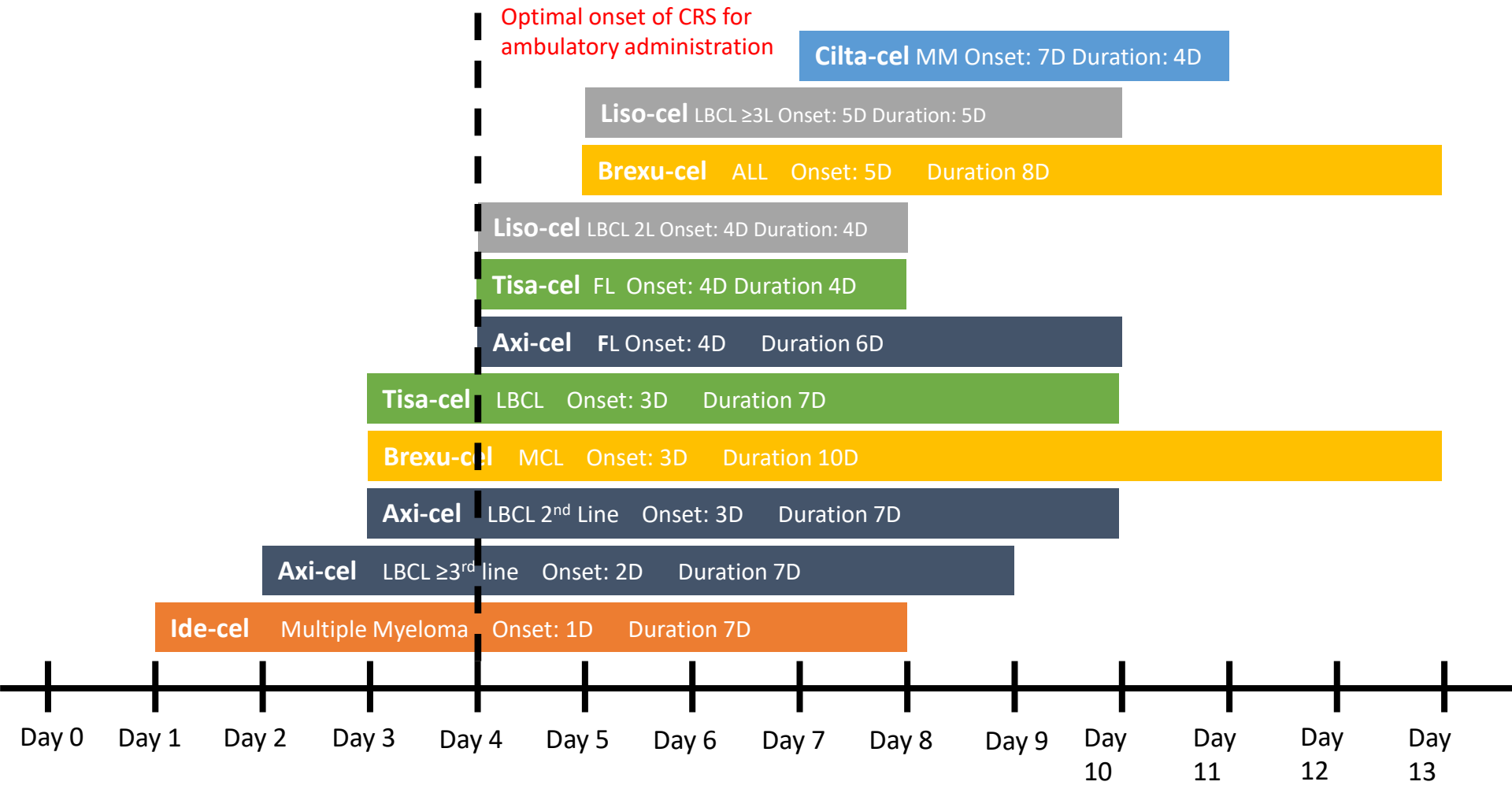
Consensus Therapy High dose steroids, anti-epileptics

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.

CRS: Median Onset and Duration by Product
We know expected toxicities, timing, severity



CAN VARY GREATLY between different products and types of cell therapies – guidance by oncologist/cell therapist is key!!

Other Possible Side Effects

- **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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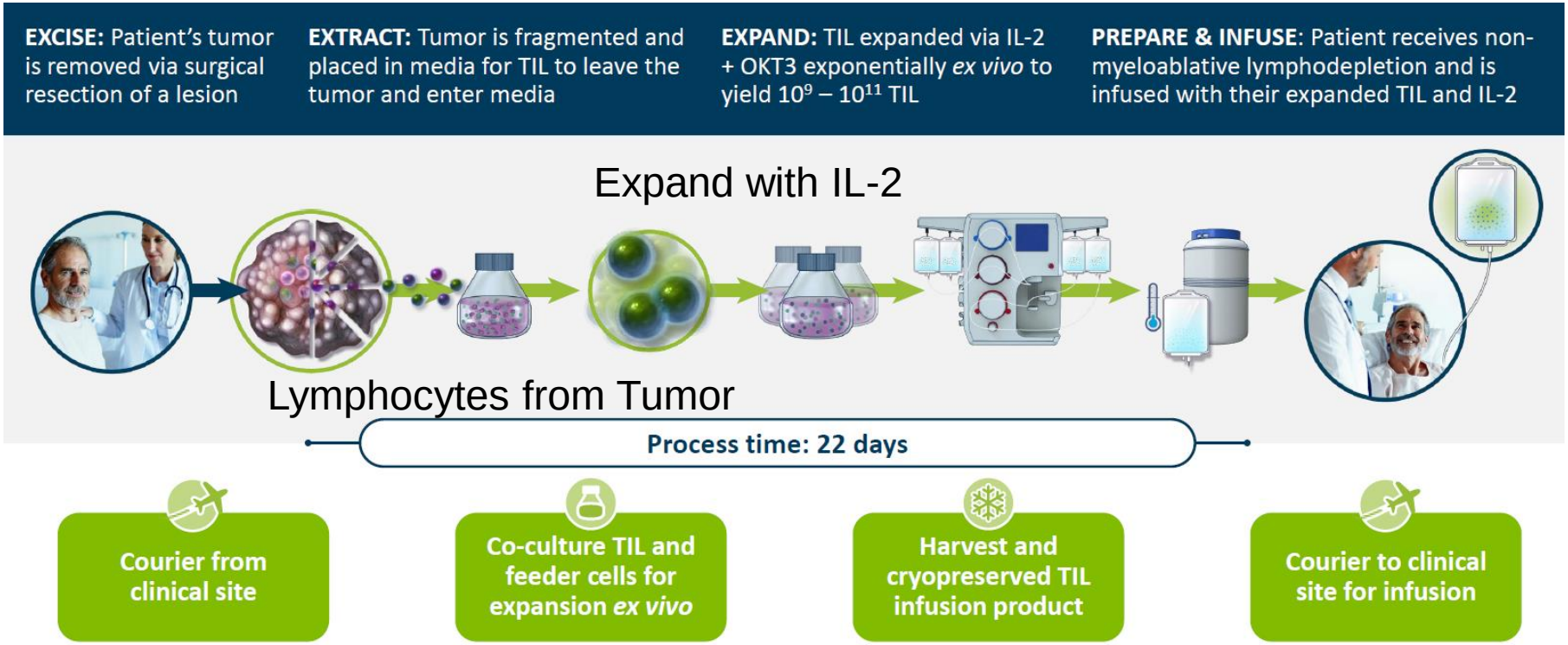
- Delving into Cell Therapy Approaches
- Applications for “typical” Chimeric Antigen Receptor Cells
- Peek into current IEC trial offerings
- Tumor Infiltrating Lymphocytes – they are HERE!!

Dana-Farber Cancer Institute

Tumor Infiltrating Lymphocytes

Different Types of Cells

- Non-Genetically Engineered
  - Simple Numerical Expansion

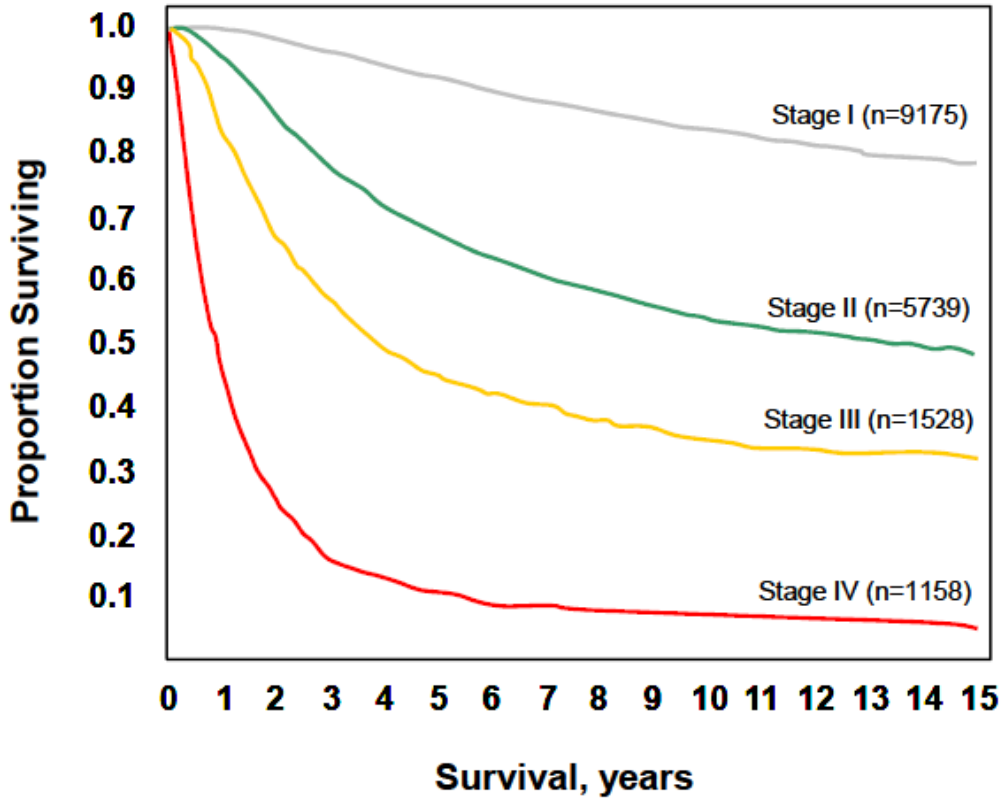


Initial Iovance Trial Outcomes Data

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

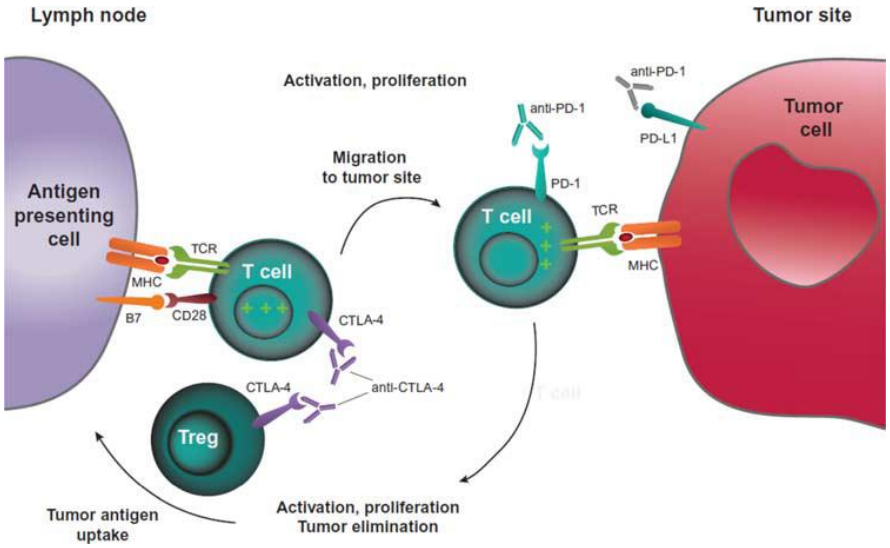
Source: https://ir.iovance.com/static-files/dd026048-1c0a-42ff-bf4d-bec7f9acbd98

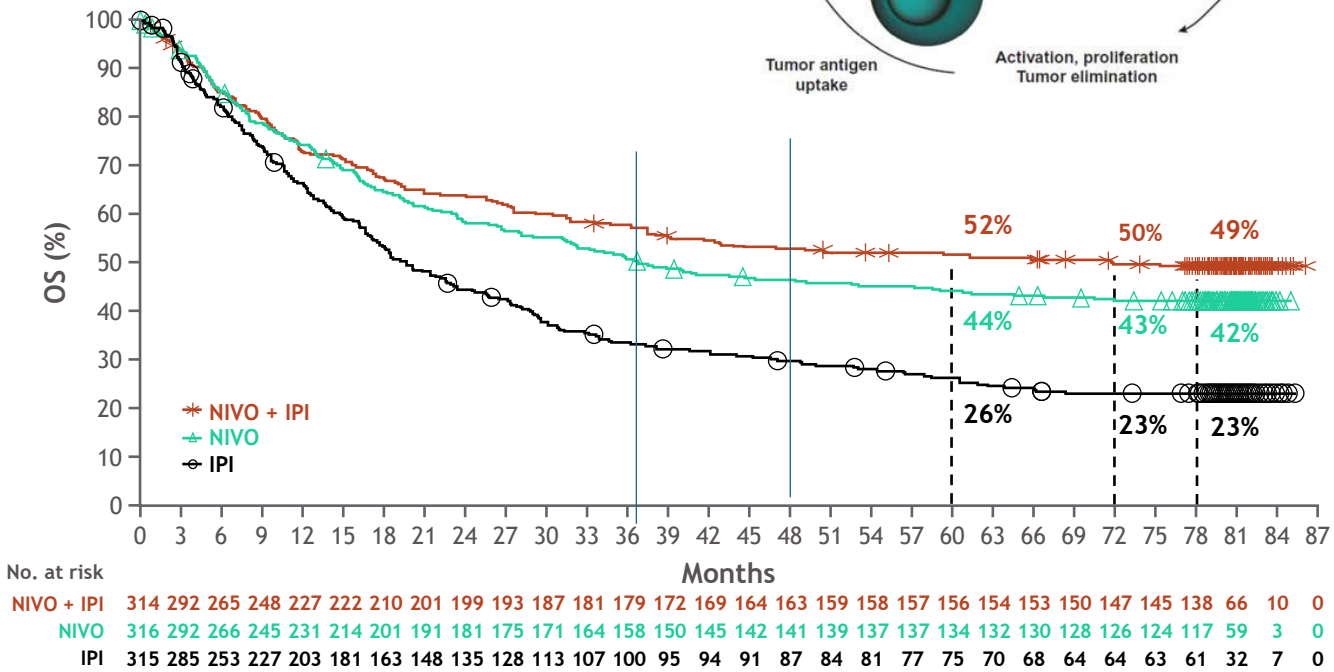
Survival by melanoma stage



Balch CM et al. J Clin Oncol 2001

Checkmate 067: Ipilimumab and nivolumab in advanced melanoma – Overall Survival





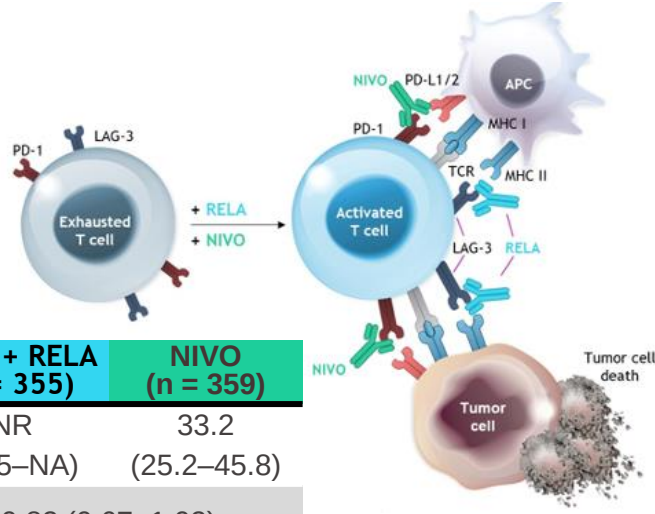
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.43–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.84 (0.67–1.04)	–	–

[a]Descriptive analysis.

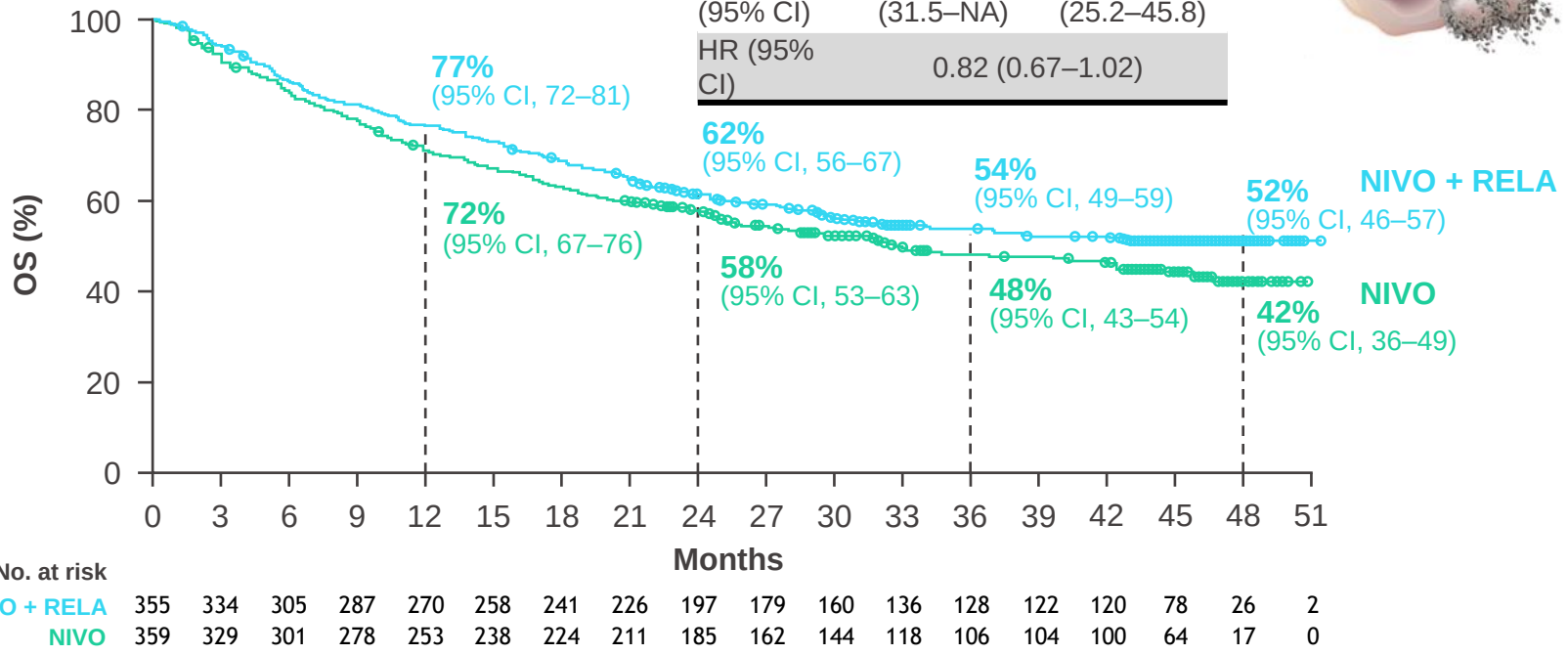
Wolchok et al. ASCO 2023

RELATIVITY-047: Overall Survival (Targeting Lag-3)

Updated secondary endpoint

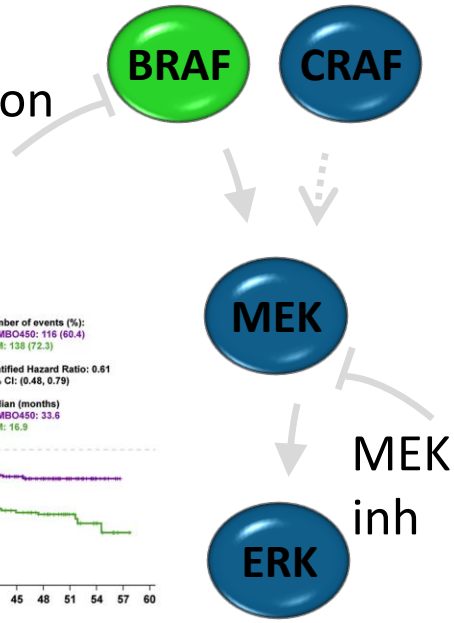


	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo	NR	33.2
(95% CI)	(31.5–NA)	(25.2–45.8)
HR (95% CI)	0.82 (0.67–1.02)	

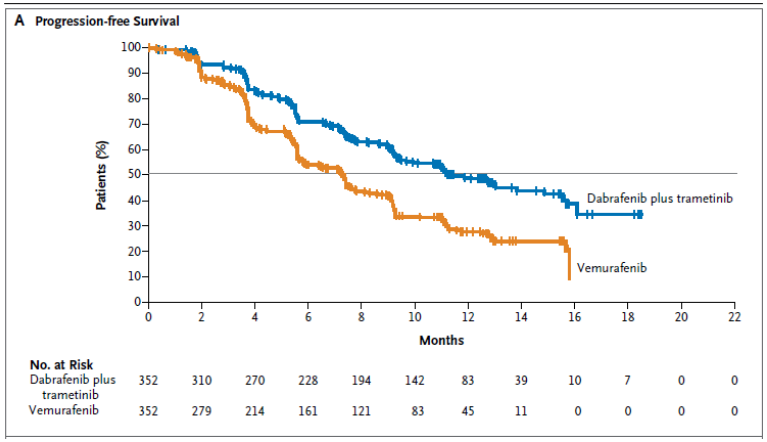


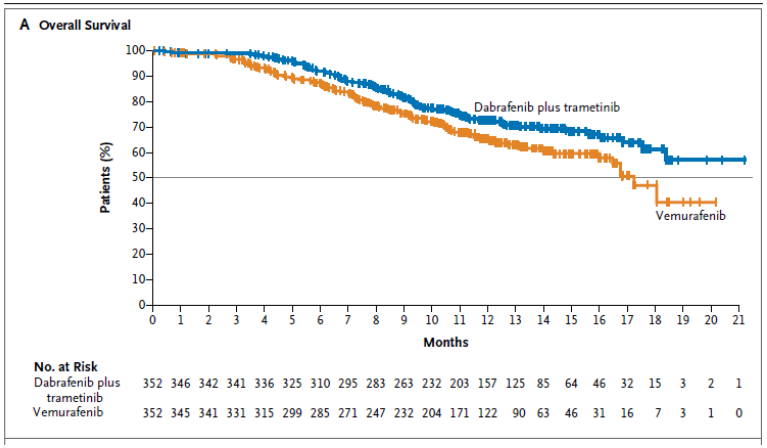
RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

BRAF/MEK targeted therapies



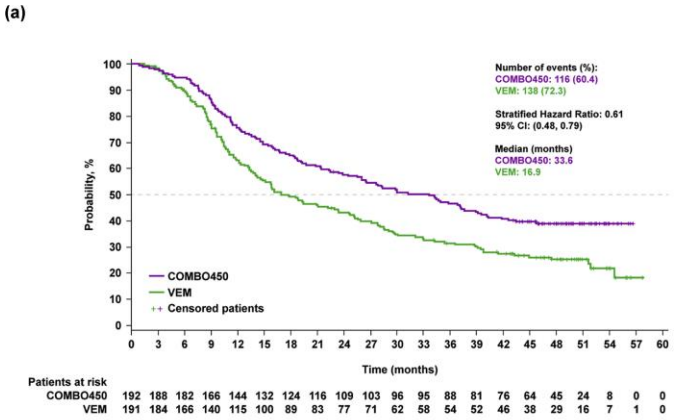
Dabrafenib/Trametinib

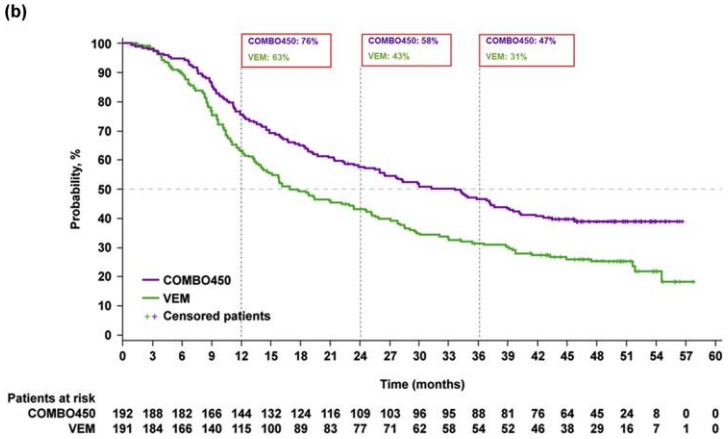




Robert et al. NEJM 2015

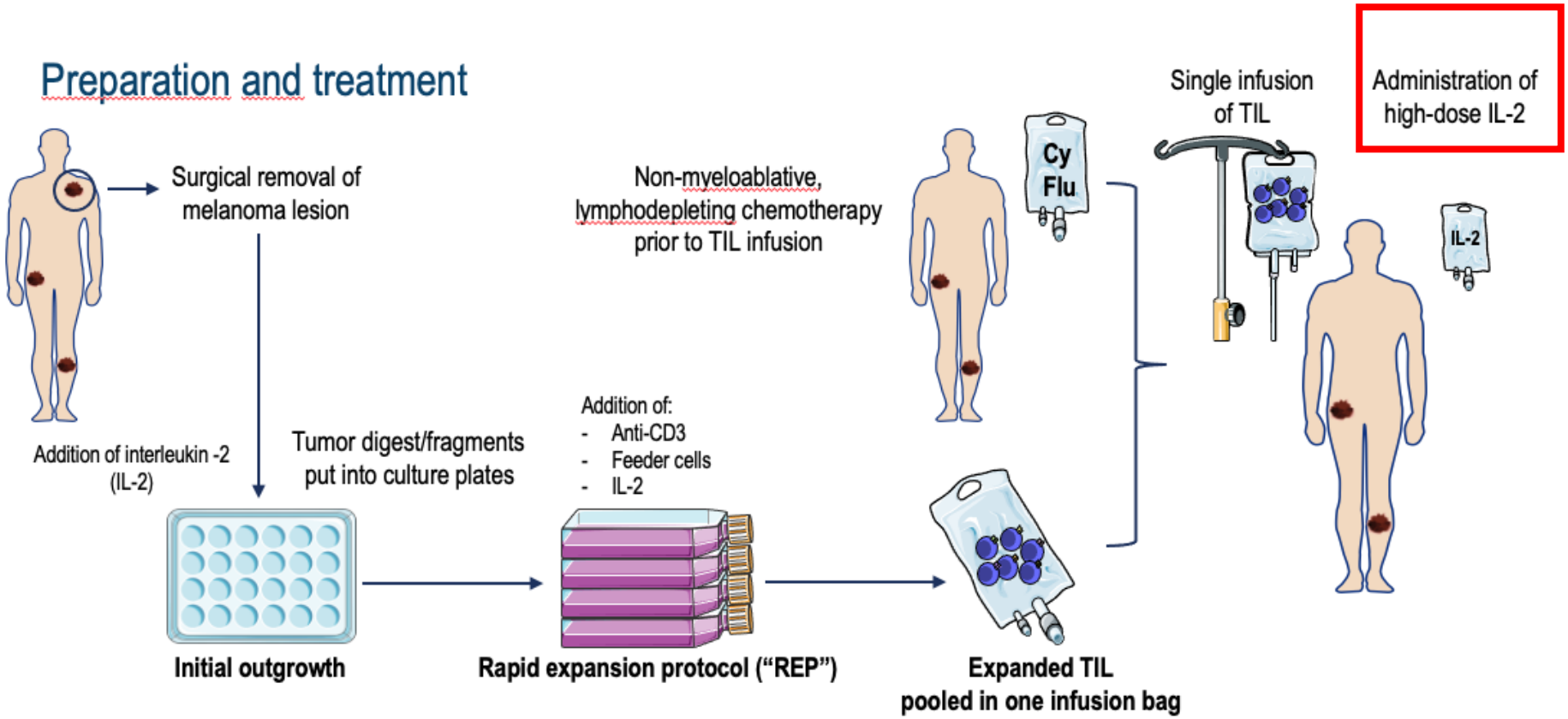
Encorafenib/Binimetinib





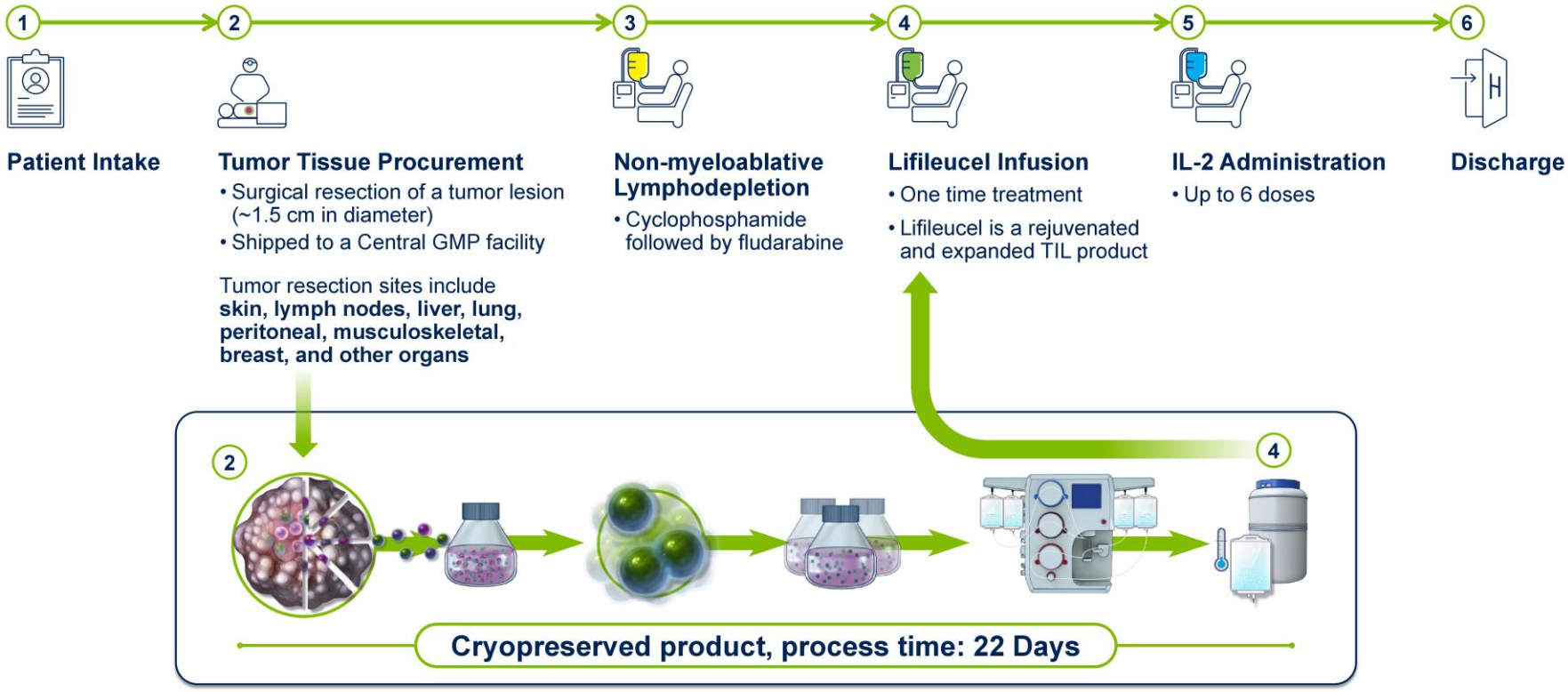
Ascierto et al EJC 2020

TIL therapy in melanoma



Haanen et al ESMO 2022, Larkin et al. ASCO 2021

Patient Journey and TIL Manufacturing



GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

4

Presented By: **James M. G. Larkin, MD, FRCP, PhD**

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2021 ASCO ANNUAL MEETING

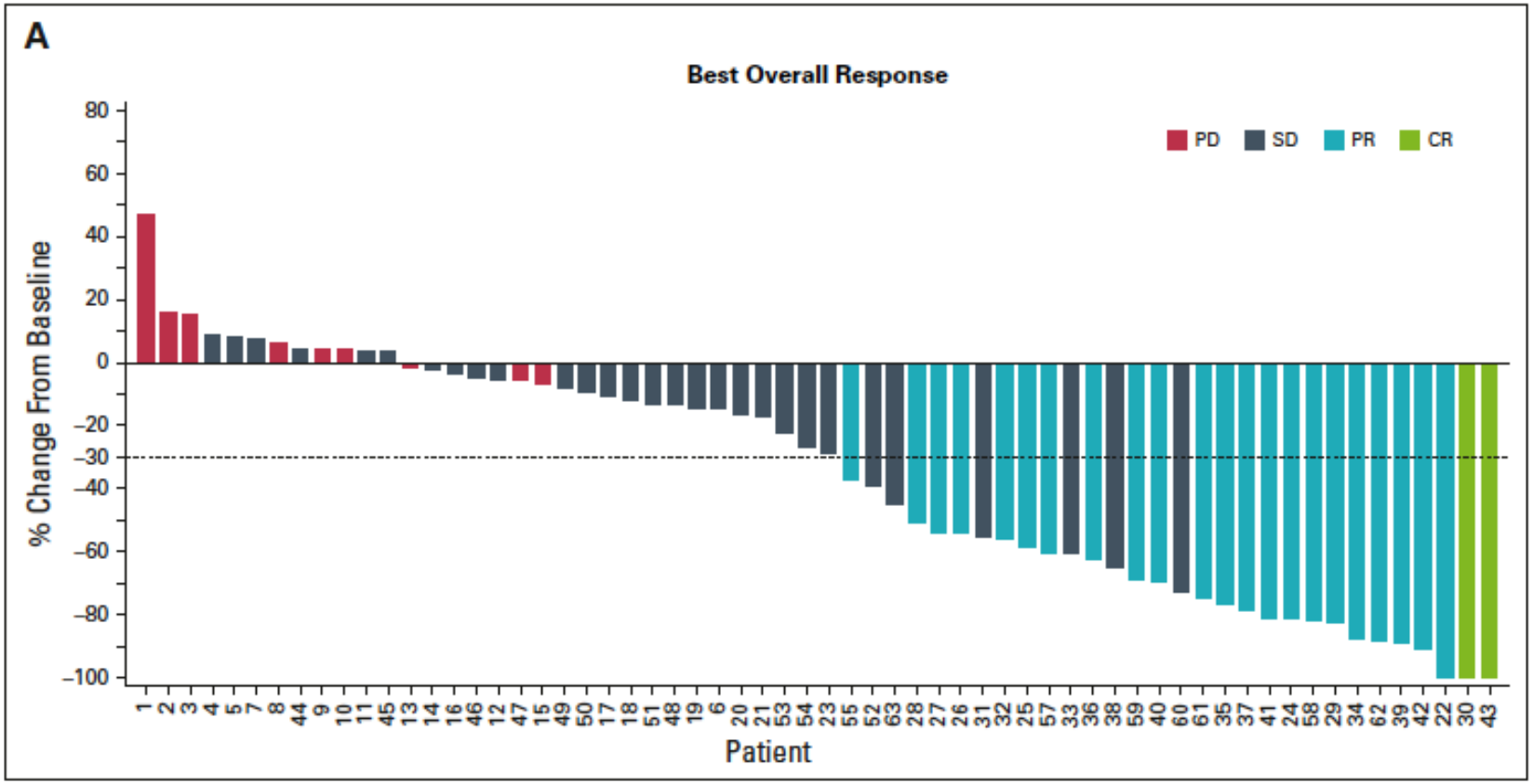


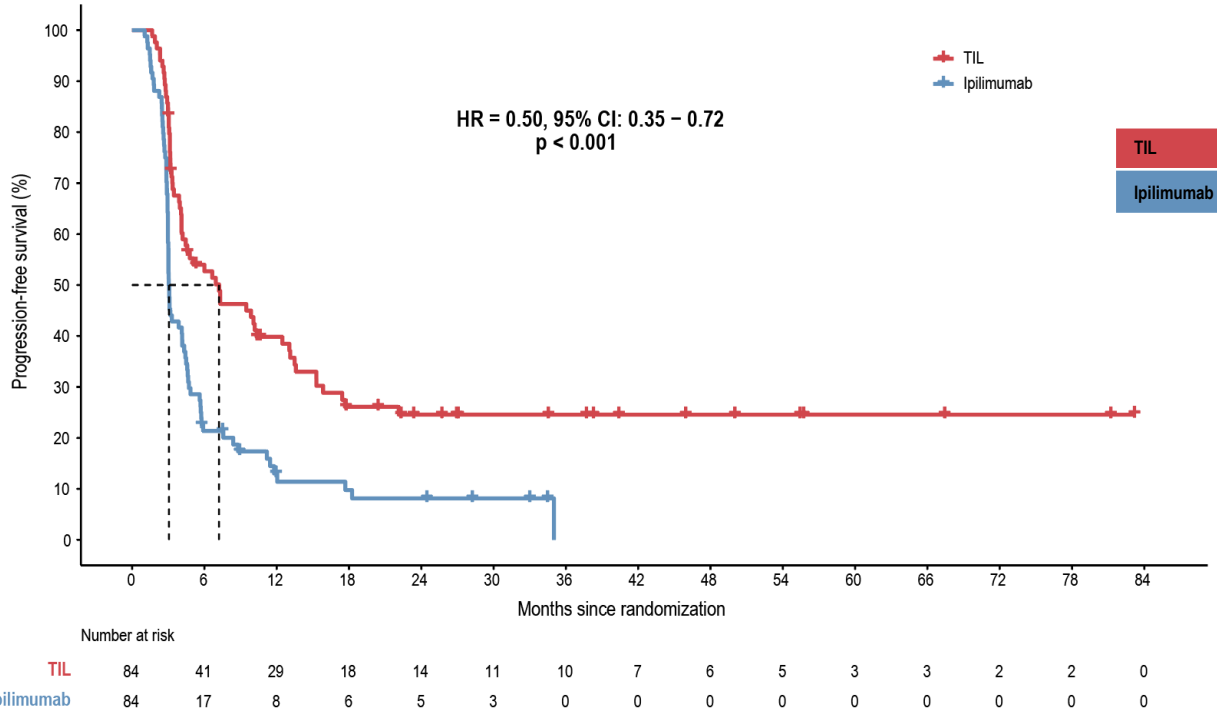
FIG 1. Change in tumor burden of target lesions, response by subgroup, and response assessment in individual patients. (A) Waterfall plot depicting BOR as assessed by investigator and the best change from baseline in the SOD of the target lesions (per RECIST v1.1 criteria) in the FAS. A change of −100% from baseline is presented for CR assessment that includes lymph node lesions that resolved to < 10 mm. The horizontal dashed line indicates a 30% reduction in the tumor burden in the target lesions. Twelve patients had an increase in the SOD of the target lesions, whereas 50 patients had a decrease in the SOD of the target lesions. Thirty patients (two CR, 22 PR, and six SD) had > 30% reduction in the SOD of the target lesions. Three patients had no post-TIL assessments because of early death. One patient had no post-TIL assessment because of start of new anticancer therapy before day 42. (continued on next page)

Lifileucel, 36% response rate

Sarniak et al. JCO 2021

Results (1)

Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

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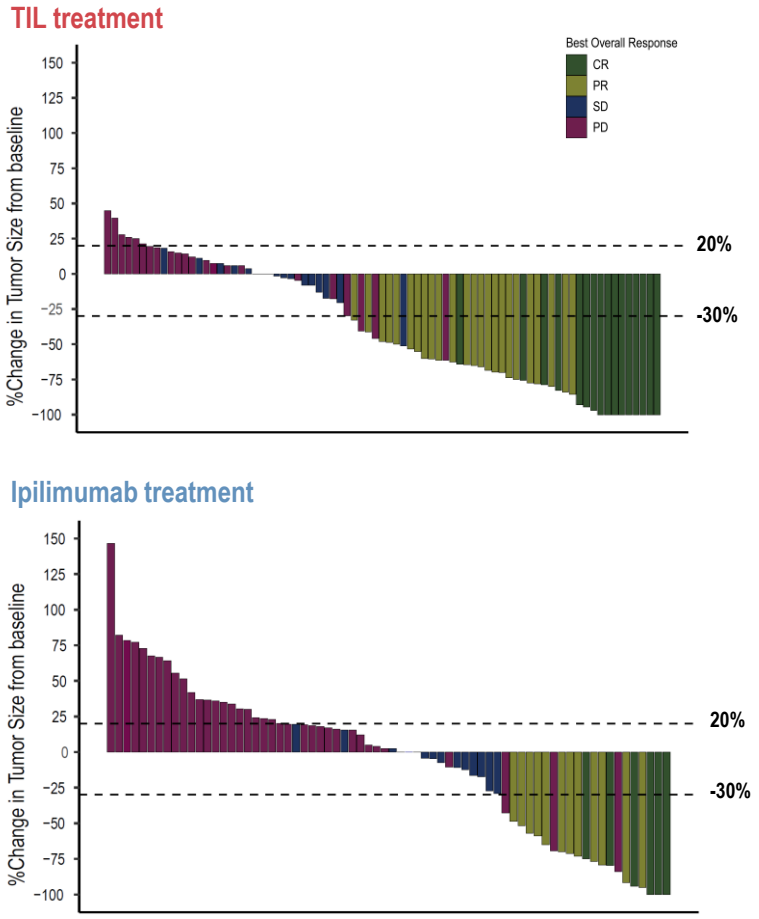
Results (3)

Best overall response according to RECIST 1.1*

	TIL (n=84)	Ipilimumab (n=84)
Best overall response	**n (%)**	**n (%)**
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done#	3 (3.6)	11 (13.1)
Overall response†	41 (48.8)	18 (21.4)
Clinical benefit‡	57 (67.9)	33 (39.3)

*In the intention-to-treat population. #In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. †Defined as CR plus PR and ‡CR, PR plus SD according to RECIST 1.1.



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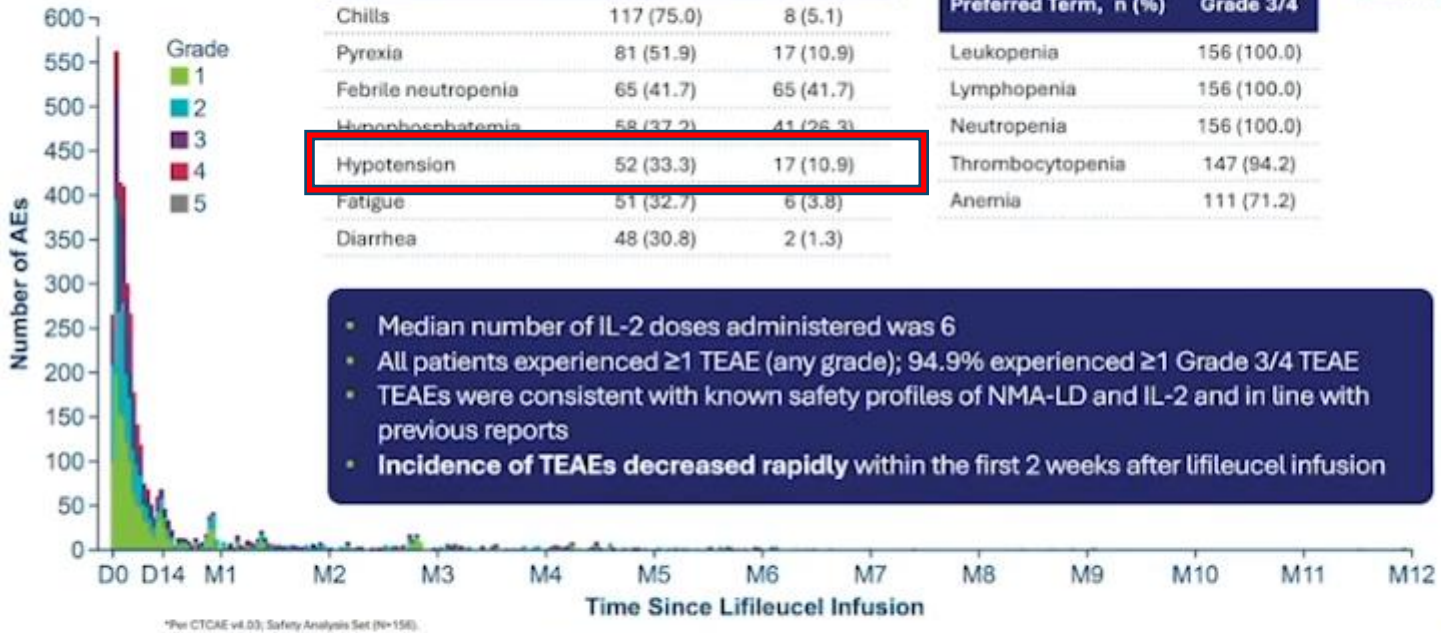
Safety

Non-Hematologic TEAEs in ≥30% of Patients*†

Preferred Term, n (%)	Any Grade	Grade 3/4
Chills	117 (75.0)	8 (5.1)
Pyrexia	81 (51.9)	17 (10.9)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Diarrhea	48 (30.8)	2 (1.3)

Grade 3/4 Hematologic Lab Abnormalities*

Preferred Term, n (%)	Grade 3/4
Leukopenia	156 (100.0)
Lymphopenia	156 (100.0)
Neutropenia	156 (100.0)
Thrombocytopenia	147 (94.2)
Anemia	111 (71.2)



- Median number of IL-2 doses administered was 6
- All patients experienced ≥1 TEAE (any grade); 94.9% experienced ≥1 Grade 3/4 TEAE
- TEAEs were consistent with known safety profiles of NMA-LD and IL-2 and in line with previous reports
- **Incidence of TEAEs decreased rapidly** within the first 2 weeks after lifileucel infusion

*Per CTCAE v4.03; Safety Analysis Set (N=156).
†Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1).
All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported.
15 events were reported after Month 12 (Grade 1, n=7; Grade 2, n=6; Grade 3, n=1; Grade 5, n=1).
AE, adverse event; D, day; IL-2, interleukin 2; M, month; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

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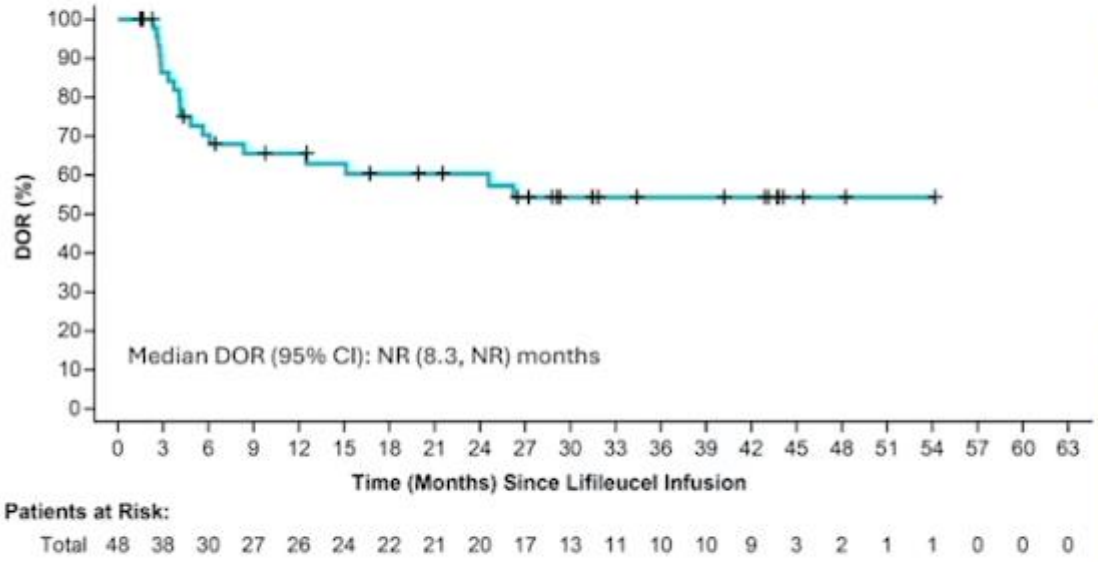
Objective Response Rate (IRC-assessed)

	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
ORR, n (%)	**23 (34.8)**	**25 (28.7)**	**48 (31.4)**
(95% CI)	(23.5, 47.6)	(19.5, 39.4)	**(24.1, 39.4)**
Best overall response, n (%)			
CR	5 (7.6)	4 (4.6)	**9 (5.9)**
PR	18 (27.3)	21 (24.1)	**39 (25.5)**
SD	24 (36.4)	47 (54.0)	**71 (46.4)**
Non-CR/Non-PD*	1 (1.5)	0	**1 (0.7)**
PD	15 (22.7)	12 (13.8)	**27 (17.6)**
Nonevaluable†	3 (4.5)	3 (3.4)	**6 (3.9)**

- **IRC-assessed ORR** was **31.4%**
- The concordance rate between IRC- and investigator-assessed ORR was 91%
- Median number of TIL cells infused was 21.1×10^9 (range, 1.2×10^9 to 99.5×10^9)
- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days

*Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.
†Six patients were nonevaluable for response (5 due to early death; 1 due to new anticancer therapy).
CR, complete response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response

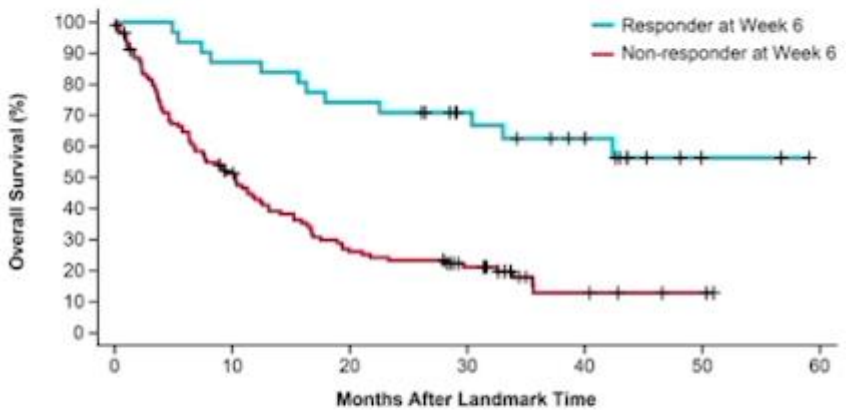


	Cohort 2 (n=23)	Cohort 4 (n=25)	Cohort 2+4 (N=48)
Median DOR*, months	NR	10.4	NR
95% CI	(NR, NR)	(4.1, NR)	(8.3, NR)
Min, max (months)	1.4+, 54.1+	1.4+, 34.3+	1.4+, 54.1+

- At a median study follow up of 36.5 months, **median DOR** was **not reached**
- 41.7% of responses were maintained ≥24 months

*Based on Kaplan-Meier estimate.
DOR, duration of response; NR, not reached.

Overall Survival by Response at 6 Weeks After Lifileucel Infusion



Patients at Risk							
Responders	31	27	23	17	11	2	0
Non-responders	116	56	28	18	5	2	0

	Median OS* (months), by response at 6 weeks[1]	95% CI
Responders	NR	(30.4, NR)
Non-responders	10.3	(6.8, 13.1)
Log-rank *p*-value	<0.0001	

- In a landmark analysis in patients who achieved response at first assessment (6 weeks [~1.5 mo] post-lifileucel infusion), **median OS was not reached**

1. Buyse M, Piedbois P. On the relationship between response to treatment and survival. *Stat Med*. 1996;15:2797-2812.
*Based on Kaplan-Meier estimate.
NR, not reached; OS, overall survival.

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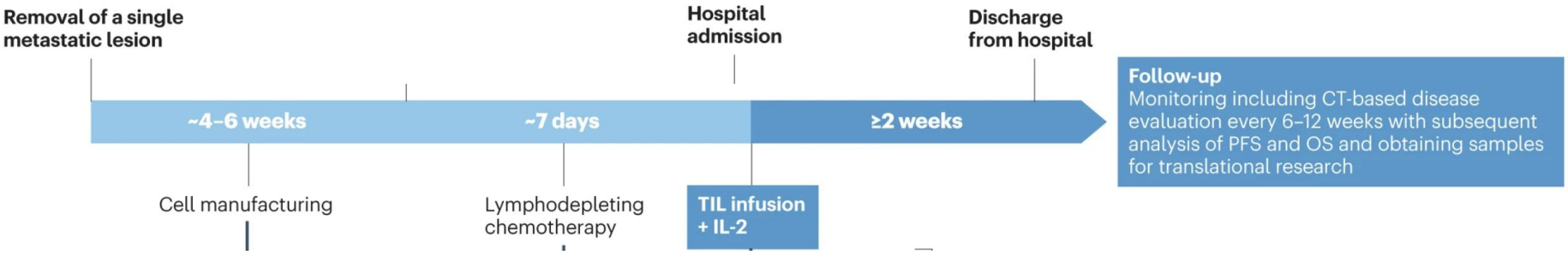
Why are we preparing for TILS and trials utilizing HD IL-2?

- Currently we have one trial open in Melanoma Oncology using TILS and HD Interleukin-2 - Lyell
    - We expect to treat a melanoma TILs patient in August.
- **Commercial approval of Iovance TILS for Melanoma in February 2024 with plans to admit our first patient for this 8/12,**
    - **Anticipated volume could be up to four patients per month**
- Seeing more IEC trials utilizing HD IL-2 post cell infusion
- Patients receiving TILS/HD IL-2 will all be admitted to PALS, localized to the 9A pod

Screening testing

- Labs
- Disease restaging unless very recently done including brain MRI
- ECHO (or MUGA) within 6 months with EF >35%
- PFTs in pts with prior lung surgery, respiratory symptoms, active or prior smoking within 2 years, history of pneumonitis, COPD or asthma. FEV must be > 50% of predicted and DLCO must be > 50%

Patient course



- 7 days of flu/cy chemotherapy given on Yawkey 6 (doesn't start until product received)
- Admission for TIL infusion
- Up to 6 doses high dose IL-2 given every 12 hours

Current General Resources:

1. Dedicated IEC team, on both research and commercial side
2. All patients on PALS team

Common Side Effects

TILS Cells	HD IL-2
Infusion Reaction	Constitutional symptoms, Capillary Leak Syndrome
	Cardiac: **Hypotension**, Tachycardia
	Pulm: hypoxia, pulmonary edema
	GI: N/V/D
	Derm: macular erythema, pruritis, moist desqamation
	Renal: AKI, anuria, metabolic disarray
	Heme: Anemia, thrombocytopenia, neutropenia

Safety Mitigation Strategies for IL-2

- IL-2 dosing decisions will decided after discussion between the nurse and PI. These decisions will be made at: prior to the dose being administered
  - Timing will depending on dosing frequency (BID VS TID)
  - labs will be drawn 1 hour prior to appointed decision time to accommodate IL-2 dosing decision making
- Once labs are resulted, the RN will page the PI to discuss the checklist (see following slides) and determine if dose to be given.
  - RN will notify **RC** of discussion, so **RC** can also discuss concerns w/ the PI as well.
- The Melanoma TILs PI Elizabeth Buchbinder available 24/7 to provide additional clinical support for the first few patients treated while the patient is receiving IL-2
- Planning to admit all patients on Sunday to enable TIL infusion Monday. Thus high-dose IL-2 administrative spanning Tues, Wed, Thurs, Fri….with most indications not proceeding with dosing beyond that point.
- Patients will be localized to 1 pod to start (9A) so we can gain experience with one group of nursing first
- All IL-2 will be administered on weekdays
  - patient will be admitted Sunday for Monday administration of cells

Guidelines for IL-2 Dose Skipping or Discontinuation

ALL dose skipping or discontinuation will be made by the PI

Skip a dose of IL-2 OR Discontinue IL-2 if:

< 3 relative criteria → initiate corrective measure +/- skip dose of IL-2

>= 3 relative criteria → initiate corrective measures, skip dose of IL-2 or Discontinue IL-2 if not reversible

>=1 absolute criteria → Initiate corrective measures, skip dose of IL-2 or Discontinue IL-2 if not reversible

If doses are skipped for >24 hours (ie two consecutive doses) → Discontinue IL-2

- Skipped doses will not be made up
- Administer IL-2 at least 8 hours apart

System	Relative Criteria	Absolute Criteria
Cardiac	Sinus tachycardia (120-130 beats per min)	Sustained sinus tachycardia after correcting hypotension, fever, and tachycardia and stopping dopamine Atrial fibrillation, supraventricular tachycardia, or ventricular arrhythmias Elevated CK, troponin, or EKG changes of ischemia Sinus tachycardia > 130 bpm Ventricular arrhythmias
Gastrointestinal	Diarrhea, 1000 mL/shift Ileus/abdominal distention Bilirubin >7mg/dL	Diarrhea 1000 mL/shift x 2 Vomiting not responsive to medication Severe, unrelenting abdominal pain Severe abdominal distention affecting breathing
Hemodynamic	Patients BP is soft, but not hypotensive	Patient receiving IV fluid boluses or any dose of Pressors
Hemorrhagic	Sputum, emesis, or stool hemepositive Platelets 30,000 to 50,000/mm	Frank blood in sputum, emesis, or stool Platelets < 30,000/mm
Musculoskeletal	Extremity tightness	Extremity paresthesias

TILS communication and Escalation Plan for Critical Care

1. Target blood pressure is set on admission by the PI by either protocol specific criteria OR standards set for patients receiving IL-2 if not dictated by protocol (BP MAP < 65 (SBP <90) AND the patient is symptomatic).
2. If the patient's BP is not meeting goal, the nurse will page the **responding clinician (RC).** At that time **RC** will put in orders for 1x 250cc NS fluid bolus. The nurse will admin the bolus and recheck VS at bolus completion, or sooner if clinically indicated. **RC** will notify PI that boluses are initiated.
3. If continued or recurrent hypotension, the **RC** can repeat 250cc NS bolus two more times, for a total of 750cc NS. When placing orders for the last bolus, the **RC** will also make Phys aware. Nurse Director to call ICU bed flow nurse so an ICU bed can be identified. Nurse will administer and will recheck BP, and if needed call a **RAPID RESPONSE** for continued SBP <90.
4. If Pressor support is needed Phys/RC will order Neo (Phenylephrine) IV
    - Stat nurse will administer the Neo
    - Patient can stay on the floor with stat nurse managing and ICU consulting/managing pressors for short amount of time if no bed immediately available
        - If patient is able to come off pressors at that time, transfer can be cancelled if appropriate

TILS communication and Escalation Plan for Critical Care

Once transfer is initiated, the ICU attending cannot co-manage the patient until the patient is in an ICU bed. They can provide remote expert support to the **RC**.

Once the decision is made to transfer, the Phys and the Nurse Admin will be able to look for beds, our preference for TILS patients are 1) MICU or MED/SURG ICU 2) CCU 3) Surgical ICU 4) Neuro ICU.

Looking for more details

Open access **Position article and guidelines**

Journal for ImmunoTherapy of Cancer

Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy

Allison Betof Warner ,[1] Omid Hamid,[2] Krishna Komanduri,[3] Rodabe Amaria,[4] Marcus O Butler,[5] John Haanen ,[6] Sarah Nikiforow,[7] Igor Puzanov ,[8,9] Amod Sarnaik ,[10] Michael R Bishop,[11] Adam J Schoenfeld [12]

Cell Therapy
A team effort!!

Dana-Farber
Cancer Institute

Questions?