Follow the Yellow Brick Road for Cellular Therapies and Immune Modulators: CARs, TILs and BiTEs Oh My!

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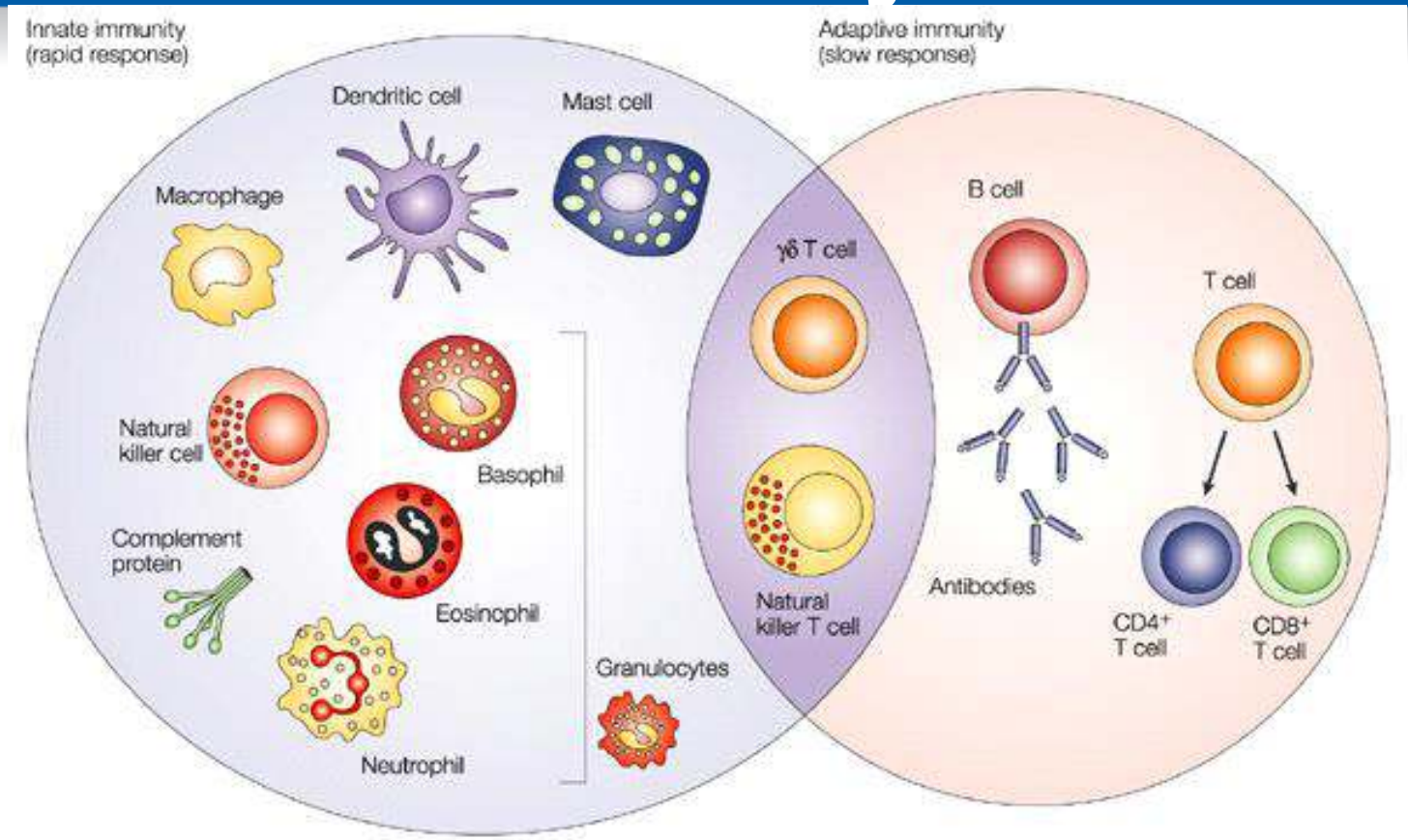
Conflict of Interest

- We have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation
- As part of this presentation, we will be discussing investigational drugs as well as off-label uses

Objectives

- Discuss mechanisms of action behind chimeric antigen receptor T-cell (CAR-T), Tumor Infiltration Lymphocytes (TILs) and Bispecific T-cell Engagers (BiTEs) therapies
- Compare and contrast efficacy and safety of CAR-T, TILs and BiTEs for the treatment of hematologic and solid tumor malignancies
- Review monitoring strategies for the management of adverse events associated with CAR-T, TILs and BiTEs

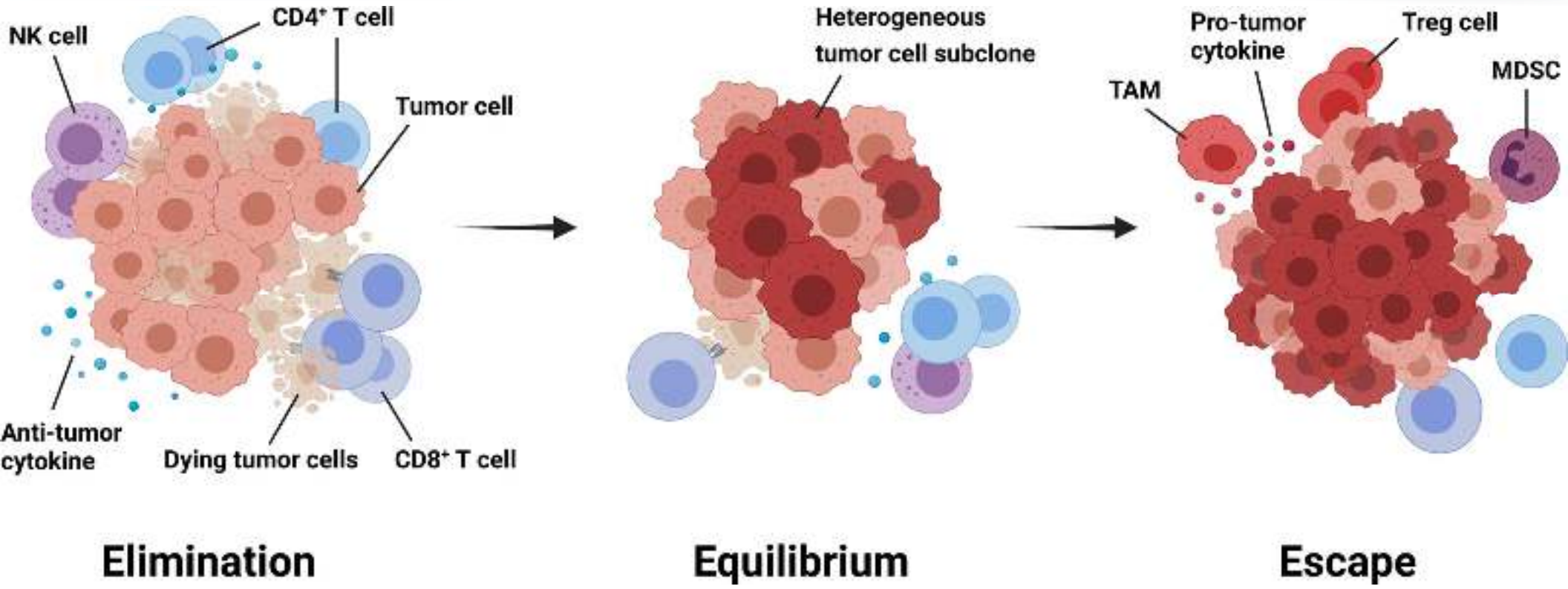
The Immune System



Nature Reviews | Cancer

Dranoff G. *Nat Rev Cancer*. 2004;4(1):11-22.

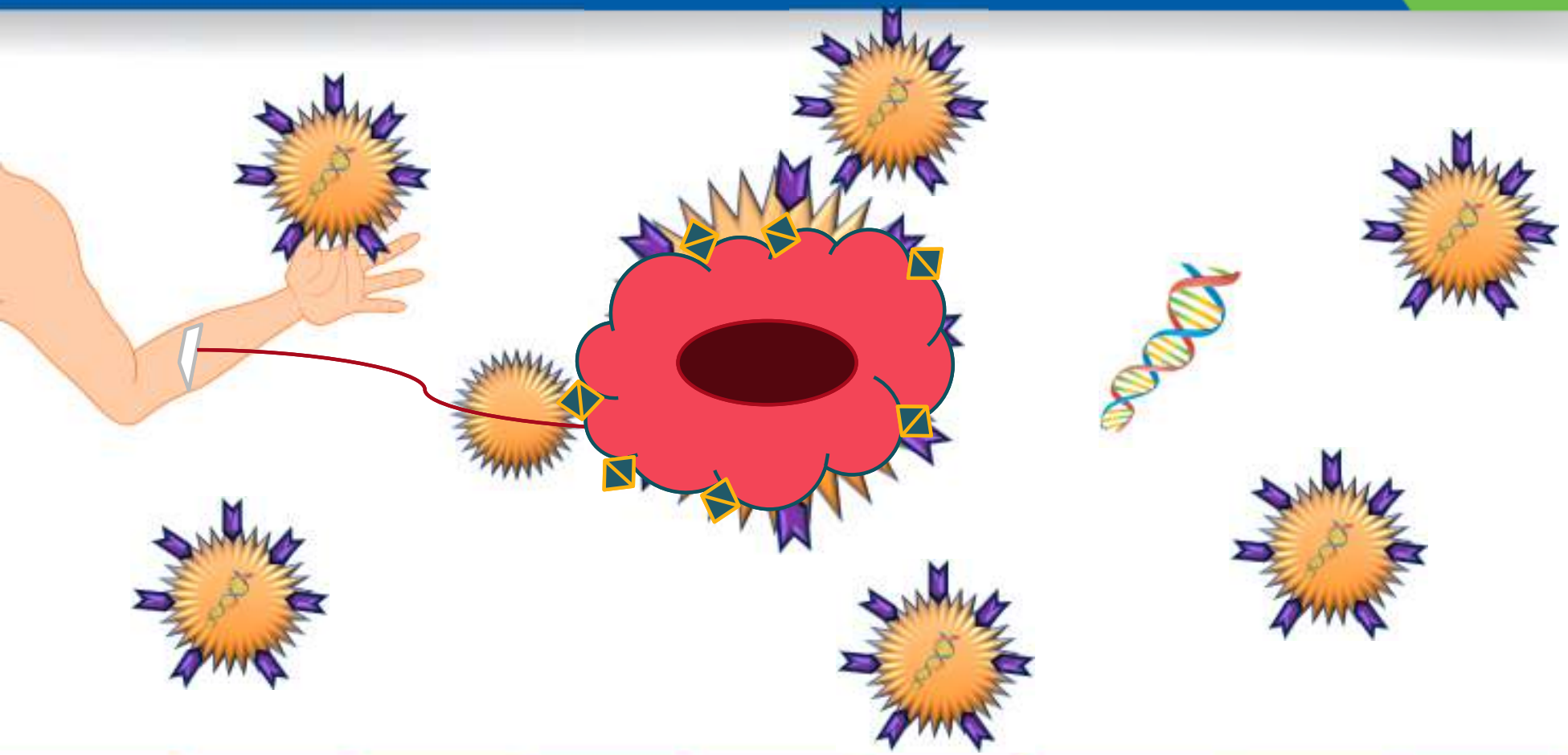
The Three E's of Immunoediting



Dunn GP, Old LJ, Schreiber RD. *Annu Rev Immunol*. 2004;22:329-360.

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPIES (CAR-T)

CAR-T Mechanism of Action



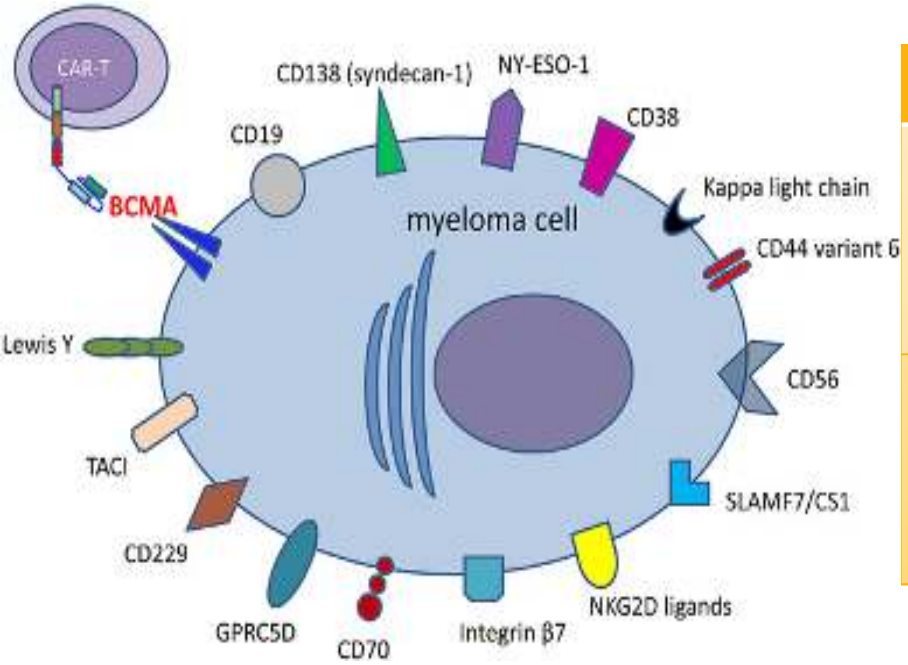
Winslow, T. *National Cancer Institute. 2017*

CD-19 based CAR-T FDA Approved Products

CAR-T Product	Construct	FDA Indication	Objective Response Rates (ORR)	Overall Survival	Incidence of Cytokine Release Syndrome (CRS)	Incidence of Neurotoxicity
Tisagenlecleucel (Kymriah®) – Tisa-cel	• CD-19 • CD3ζ T-cell activation domain • 4-1BB costimulatory domain	B-Acute Lymphoblastic Leukemia (B-ALL) that is refractory or in 2nd or later relapse in patients up to 25 years of age	81%	• 90% @ 6 months • 76% @ 12 months	All Grades: 77% Grade III-IV: 46%	All Grades: 40% Grade III-IV: 13%
		Relapsed/refractory (R/R) DLBCL	52%	49% @ 12 months	All Grades: 58% Grade III-IV: 22%	Grade III-IV: 12%
		R/R Follicular Lymphoma (FL) after 2 or more lines of therapy	86.2%	PFS: 67% @ 12 months	All Grades: 48.5% Grade III-IV: 0%	All Grade: 4.1% Grade III-IV: 1%
Axicabtagene ciloleucel (Yescarta®) – Axi-cel	• CD-19 • CD3ζ T-cell activation domain • CD28 costimulatory domain	R/R DLBCL, including refractory to 1st line therapy or relapse within 12 months of 1st line therapy	83%	50.5% @ 24 months 44% @ 4 years	All Grades: 92% Grade III-IV: 11%	All Grades: 67% Grade III-IV: 32%
		R/R FL after 2 or more lines of therapy	92%	87.4%	All Grades: 82% Grade III-IV: 7%	All Grades: 59% Grade III-IV: 19%
Brexucabtagene autoleucel (Tecartus®) – Brexu-cel	• CD-19 • CD3ζ T-cell activation domain • CD28 costimulatory domain	R/R B-ALL in adults	71%	71% @ 12 months	All Grades: 89% Grade III-IV: 24%	All Grades: 60% Grade III-IV: 25%
		R/R Mantle Cell Lymphoma (MCL) in adults	93%	83% @ 12 months	All Grades: 91% Grade III-IV: 15%	All Grades: 63% Grade III-IV: 31%
Lisocabtagene maraleucel (Breyanzi®) – Liso-cel	• CD-19 • CD3ζ T-cell activation domain • 4-1BB costimulatory domain	R/R Large B-cell Lymphoma	73%	74.7% @ 6 months 57.9% @ 12 months	All Grades: 42% Grade III-IV: 2%	All Grades: 30% Grade III-IV: 10%

Maude SL, Laetsch TW, Buechner J, et al. *N Engl J Med*. 2018;378(5):439-448. Schuster SJ, Bishop MR, Tam CS, et al. *N Engl J Med*. *2019;380(1):45-56*. Fowler NH, Dickinson M, Dreyling M, et al. *Nat Med*. 2022;28(2):325-33
Locke FL, Ghobadi A, Jacobson CA, et al. *Lancet Oncol*. 2019;20(1):31-42. Jacobson CA, Chavez JC, Sehgal AR, et al. *Lancet Oncol*. 2022;23(1):91-10
Abramson JS, Palomba ML, Gordon LI, et al. *Lancet*. 2020;396(10254):839-852. Wang M, Munoz J, Goy A, et al. *N Engl J Med*. 2020;382(14):1331-134
Kymriah (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2022. Yescarta (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma Inc; April 202
Tecartus (brexucabtagene autoleucel) [prescribing information]. Santa Monica, CA: Kite Pharma Inc; October 2021. Breyanzi (lisocabtagene maraleucel) [prescribing information]. Bothell, WA: Juno Therapeutics Inc; July 202

BCMA based CAR-T FDA Approved Products



CAR-T Product	Construct	FDA Indication	ORR	OS	Incidence of (CRS)	Incidence of Neurotoxicity
Idecabtagene vicleucel (Abecma®) – Ide-cel	• B-cell maturation antigen (BCMA) • CD3ζ T-cell activation domain • 4-1BB costimulatory domain	R/R Multiple Myeloma after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor & and anti-CD38 monoclonal antibody	73%	78% @ 12 months	All Grades: 84% Grade III-IV: 5%	All Grades: 18% Grade III-IV: 0%
Ciltacabtagene autoleucel (Carvykti®) – Cilta-cel	• B-cell maturation antigen (BCMA) • CD3ζ T-cell activation domain • 4-1BB costimulatory domain	R/R Multiple Myeloma after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor & and anti-CD38 monoclonal antibody	97%	89% @ 12 months	All Grades: 95% Grade III-IV: 4%	All Grades: 21% Grade III-IV: 9%

Munshi NC, Anderson LD Jr, Shah N, et al. *N Engl J Med*. 2021;384(8):705-716
Berdeja JG, Madduri D, Usmani SZ, et al. *Lancet*. 2021;398(10297):314-324
W, Xiangmin P, Bin, H, He, X, Kailin. *ImmunoMedicine*. 2021; 1:e1030
Abecma (idecabtagene vicleucel) [prescribing information]. Summit, NJ: Celgene Corporation; March 2021
Carvykti (ciltacabtagene autoleucel) [prescribing information]. Horsham, PA: Janssen Biotech Inc; February 2023

Collection Considerations: Leukapheresis

LABORATORY EXCLUSION CRITERIA FOR LEUKAPHERESIS						
	Lisocabtagene Maraleucel (Breyanzi)	Idecabtagene Vicleucel (Abecma)	Tisgenlecleucel (Kymriah)	Axicabtagene Ciloleucel (Yescarta)	Brexucabtagene Autoleucel (Tecartus)	Ciltacabtagene Autoleucel (Carvykti)
Platelets ($x10^9$ cells/L)	< 50	< 50	< 50	< 75	< 75	< 50
Absolute Neutrophil Count ($x10^9$ cells/L)	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0	< 0.75
Absolute Lymphocyte Count ($x10^9$ cells/L)			< 300	< 100	< 100	< 300
Creatinine Clearance (mL/min)	< 45	≤ 45	< 60	< 60	< 60	< 40

Collection Considerations: Apheresis

DISCONTINUATION PRIOR TO LEUKAPHERESIS	Lisocabtagene Maraleucel (Breyanzi)	Idecabtagene Vicleucel (Abecma)	Tegvavicleucel (Kymriah)	Axicabtagene Ciloleucel (Yescarta)	Brexucabtagene Autoleucel (Tecartus [MCL])	Brexucabtagene Autoleucel (Tecartus [ALL])	Ciltacabtagene Autoleucel (Carvykti)
Alemtuzumab			6 months			6 months	
Anti-Thymocyte Globulin			6 months				
Blinatumomab			14 days			7 days	
Checkpoint Inhibitors:							
Atezolizumab				81 days	81 days	81 days	
Avelumab				19 days	19 days	19 days	
Cemiplimab				60 days	60 days	60 days	
Dostarlimab				71 days	71 days	71 days	
Durvalumab				54 days	54 days	54 days	
Ipilimumab				47 days	47 days	47 days	
Nivolumab				75 days	75 days	75 days	
Nivolumab & Relatlimab				81 days	81 days	81 days	
Pembrolizumab				66 days	66 days	66 days	
Cytotoxic Chemotherapy	2 weeks	2 weeks	2 weeks, except for: Bendamustine: 12W Fludarabine: 12W Cladribine: 8W	2 weeks or 5 half-lives*	2 weeks or 5 half-lives*	7 days or 5 half-lives*, except for: Cladribine: 12W Clofarabine: 12W	2 weeks
Donor Lymphocytes			4 weeks			4 weeks	
Experimental Agents	4 weeks	2 weeks	30 days	2 weeks or 5 half-lives*	2 weeks or 5 half-lives*	7 days or 5 half-lives*	2 weeks or 5 half-lives*
Growth Factors:							
Long Acting			2 weeks				
Short Acting			5 days				
GVHD/Immunosuppressive Antibodies (Ex: Calcineurin inhibitors, methotrexate, mycophenolate, rapamycin, anti-TNF, IL6, anti IL6R)	4 weeks		2 weeks	7 days	7 days	4 weeks	6 weeks
Hematopoietic Stem Cell Transplant							
Allogeneic	90 days		12 weeks				6 months
Autologous	---		---				12 weeks
Intrathecal CSF Prophylaxis			7 days				
Monoclonal Antibodies for MM (Daratumumab, Elotuzumab, Isatuximab)		2 weeks					3 weeks
PEG-asparaginase			4 weeks			3 weeks	
Proteasome Inhibitors (Bortezomib, Carfilzomib, Ixazomib)		2 weeks					2 weeks
Radiation	5 weeks			2 weeks	2 weeks		2 weeks
Steroids:	7 days	2 weeks	7 days	7 days	7 days	7 days	7 days
Cut off in Prednisone Equivalents	>20 mg/day	>20 mg/day	>1 mg/m2/day	≥ 5 mg/day	>5 mg/day	>5 mg/day	≥ 20 mg/week
Targeted Therapies	2 weeks	2 weeks	3 days, except for: Imatinib, Dasatinib, or Ponatinib: 2 weeks Nilotinib: 5 days	2 weeks or 5 half-lives*	BTKi: 2 weeks or 5 half-lives*	TKIs: 7 days or 5 half-lives*	2 weeks or 5 half-lives* (IMIDs: 7 days)

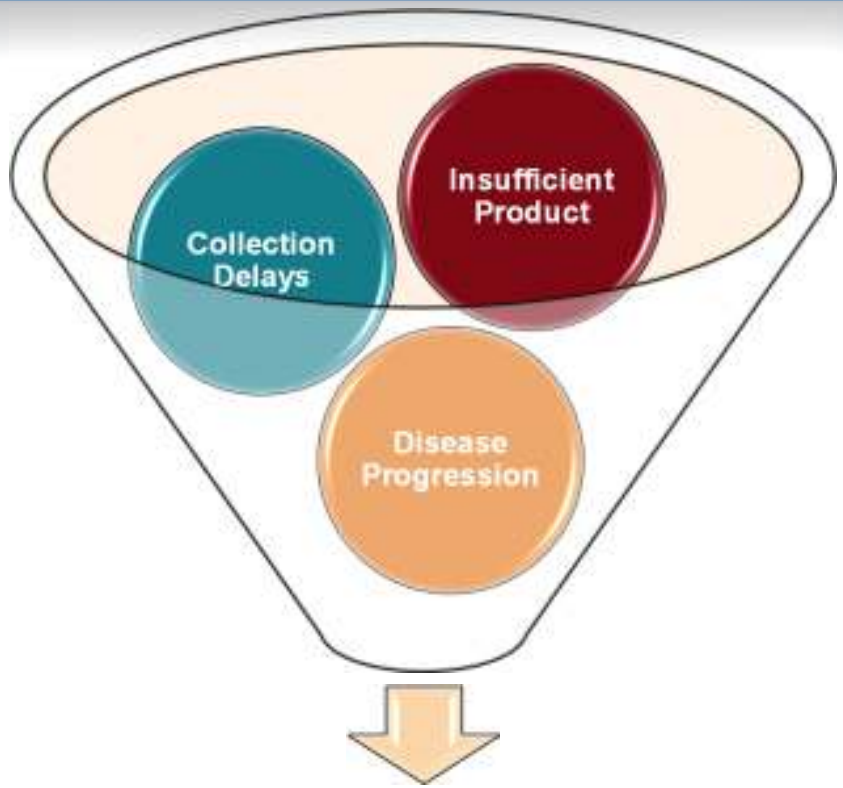
RPCCC: Standards of Practice Discontinuation Prior to Leukapheresis and CAR-T. 2022

Collection Considerations: Bridging Therapy

DISCONTINUATION PRIOR TO LYMPHODEPLETING CHEMOTHERAPY/PRODUCT ADMINISTRATION							
	Lisocabtagene Maraleucel (Breyanzi)	**Idecabtagene Vicleucel (Abecma)**	**Tisgenlecleucel (Kymriah)**	**Axicabtagene Ciloleucel (Yescarta)**	**Brexucabtagene Autoleucel (Tecartus [MCL])**	**Brexucabtagene Autoleucel (Tecartus [ALL])**	**Ciltacabtagene Autoleucel (Carvykti)**
Cytotoxic Chemotherapy	7 days	2 weeks	2 weeks	5 days, **except for:** If BR = 14 days If HDMP + R = 7 days		7 days or 5 half-lives*	2 weeks
Donor Lymphocytes	6 weeks						
Experimental Agents		2 weeks		5 days			2 weeks or 5 half-lives*
Growth Factors: **Long Acting** **Short Acting**						Not Allowed 1 day	Not Allowed 1 day
GVHD/Immunosuppressive Antibodies			2 weeks		5 days	7 days	
Intrathecal CSF Prophylaxis			7 days			7 days	
Monoclonal Antibodies for MM (Daratumumab, Elotuzumab, Isatuximab)		2 weeks					3 weeks
Proteosome Inhibitors (Bortezomib, Carfilzomib, Ixazomib)		2 weeks					2 weeks
Radiation			2 weeks				2 weeks
Steroids: **Cut off in Prednisone Equivalents**	3 days >20 mg/day	2 weeks >20 mg/day	3 days >3 mg/m²/day	5 days	5 days >5 mg/day	7 days >5 mg/day	7 days ≥ 70 mg/week
Targeted Therapies		2 weeks	3 days, **except for:** Hydrea: 2 weeks	5 days	BTKi: 5 days	TKIs: 7 days	2 weeks or 5 half-lives* (IMIDs: 7 days)

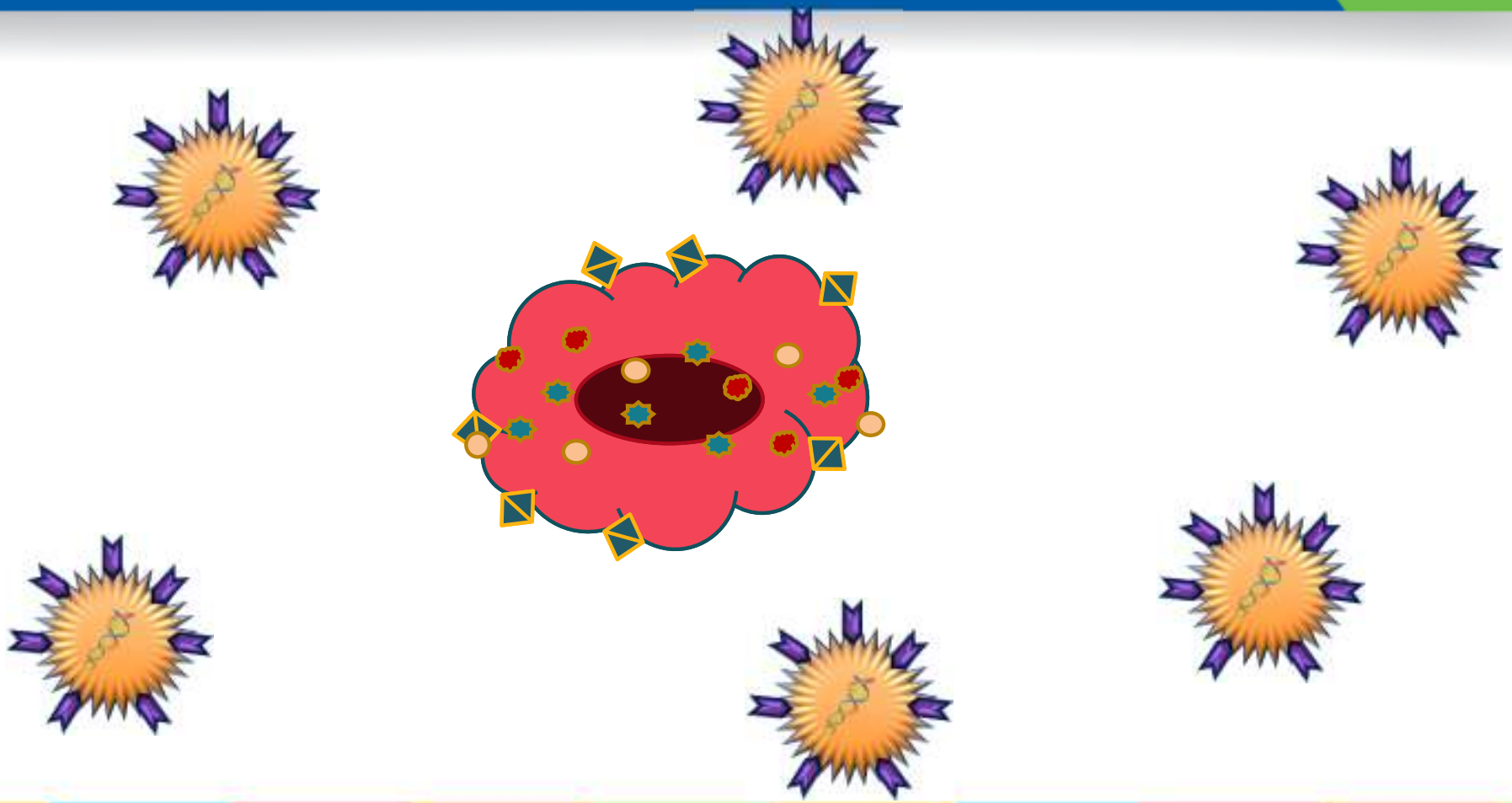
RPCCC: Standards of Practice Discontinuation Prior to Leukapheresis and CAR-T. 2022

CAR-T Considerations



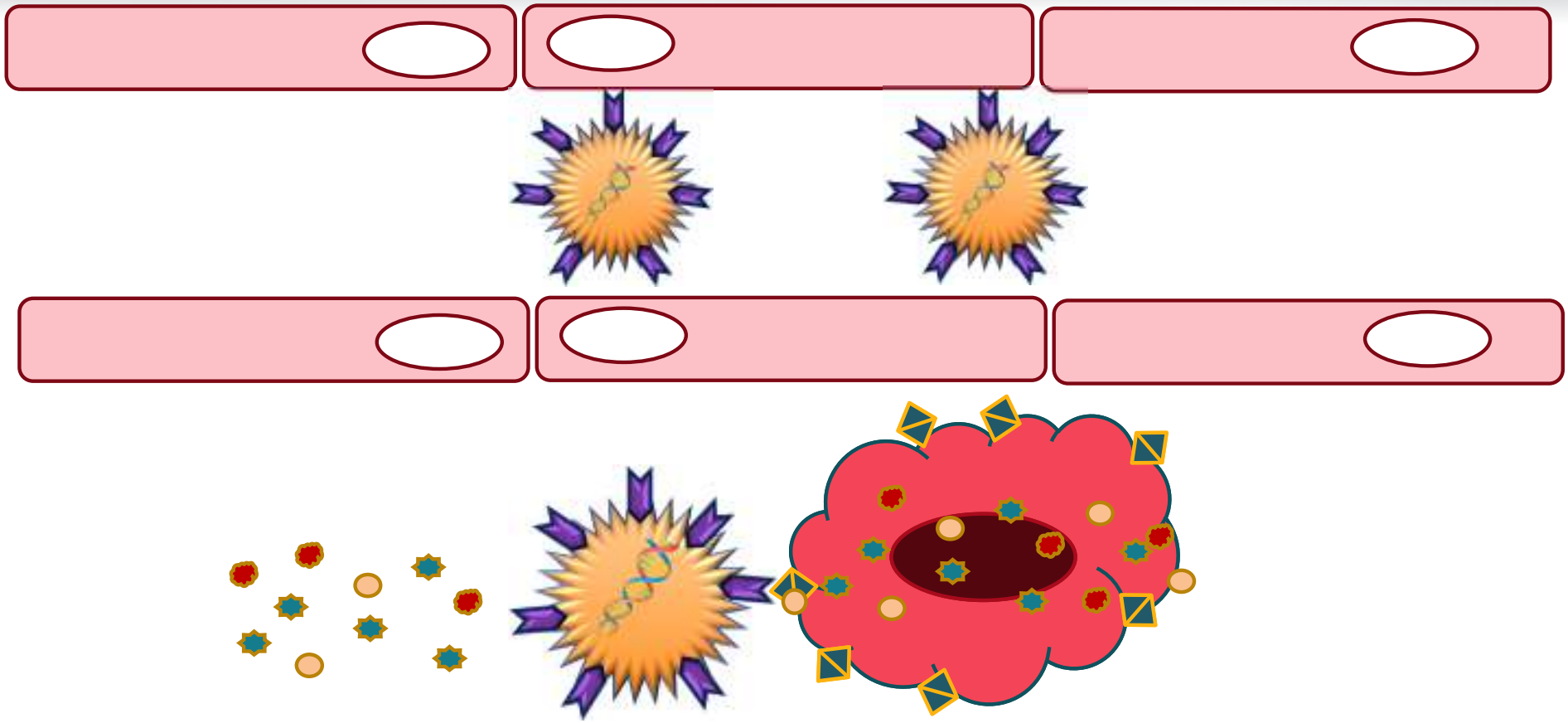
Delayed Therapy

Cytokine Release Syndrome (CRS)/ Neurotoxicity



Xiao X, Huang S, Chen S, et al. *J Exp Clin Cancer Res*. 2021;40(1):367.

Cytokine Release/ Neurotoxicity



Xiao X, Huang S, Chen S, et al. *J Exp Clin Cancer Res*. 2021;40(1):367.

ASTCT CRS Consensus Grading

ASTCT CRS Consensus Grading

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 or 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 (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

CRS Treatment Guidance

Grade 1

- Symptomatic Management

Grade 2

- Clinically Stable- Symptomatic Management
- Unstable- Consider Tocilizumab 8 mg/kg x 1 dose +/- Dexamethasone 10 mg PO BID x 2 doses

Grade 3

- Tocilizumab 8 mg/kg + Dexamethasone 10 mg BID to QID

Grade 4

- Tocilizumab 8 mg/kg + Dexamethasone 10 gm QID;
- Methylprednisolone 1 g IV daily x 3 doses can be considered

Chou CK, Turtle CJ. *Expert Opin Biol Ther.* 2020;20(6):653-664.

ASTCT ICANs Consensus Grading

ASTCT ICANS Consensus Grading for Adults

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	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

* ICANS- Immune Effector Cell-Associated Neurotoxicity Syndrome

Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

ICANs Treatment Guidance

Grade 1

- Symptomatic Management
- Addition of Levetiracetam

Grade 2

- Consider Dexamethasone 10 mg PO BID x 2 doses

Grade 3

- Dexamethasone 10 mg BID to QID

Grade 4

- Dexamethasone 10 gm QID
- Methylprednisolone 1 g IV daily x 3 doses can be considered

Chou CK, Turtle CJ. *Expert Opin Biol Ther.* 2020;20(6):653-664.

Alternative CRS/ICANs Treatment(s)

Anakinra

- Interleukin-1 Receptor Antagonist (IL-1)
- High Dose (> 200 gm/day; n=20) vs. Low-Dose (≤ 200 mg/day; n=21)
- CRS and/or ICANS Resolution (HR, 2.19; 95% CI, 0.94 to 5.12; P=.069)
- Lower ICANS grade over time (β= -0.89; 95%CI, -1.5 to -0.3 ;P=.002)
- Safe to treat with up 12 mg/kg/day (Continuous Infusion vs. Subcutaneous)

Dasatinib

- Blocks adenosine triphosphate (ATP) binding of sites of lymphocyte-specific protein tyrosine kinase (LCK)
- Case Report (ICANs Grade 4)- 100 mg/day
- Drug Interactions/Off-Label

Ruxoltinib

- Downregulation of IL-1, IL-6, tumor necrosis factor-α (TNF-α), and interferon-ϒ (INF-ϒ)
- Count Recovery/Aplasia

Siltuximab

- Anti-IL-6 Therapy
- Siltuximab First (n=40) vs Tocilizumab First (n=93)
- CRS-All Grades (67.5%; n=27 vs. 71.6%; n=68)
- Neurotoxicity- All Grades (32.5%; n=13 vs. 40%; n=38)

Gazeau N, Liang EC, Wu QV, et al. *Transplant Cell Ther.* 2023;S2666-6367(23)01233-2.
Baur K, Heim D, Beerlage A, et al. *J Immunother Cancer.* 2022;10(12):e005956.
Weber EW, Lynn RC, Sotillo E, et al. *Blood Adv.* 2019;3(5):711-717.
Pan J, Deng B, Ling Z, et al. *J Cell Mol Med.* 2021;25(2):1089-1099.
Patel S, Cenin D, Corrigan D, et al. *Blood 2022*; 140 (Supplement 1): 5073–5074.

CRS Prophylaxis/High Risk Patients

Dexamethasone Prophylaxis (axicabtagene ciloleucel)

- Zuma 1- Cohort 6 (N=40) - Dexamethasone 10 mg (Day 0, 1, and 2)
- CRS (Median onset 5 days (Range:1-15 days), Median duration 4 days (Range:1-11 days))
  - Any Grade (N=32; 80%); Grade 1 (N=14; 35%), Grade 2 (N=18; 45%)
- Neurotoxicity (**Median onset 6 days (Range- 2-162 days), Median duration 18.5 days (Range:1-103 days))**
  - Any Grade (N=23; 58%); Grade 3 (N=3; 8%), Grade 4(N=2; 5%)

High Risk Patients

- M-EASIX Score (LDH (U/L) x Creatinine (mg/dL) / Platelets(10^9 cells/L))
- Cut-point of 6.2- 96.43% negative predictive value for severe CRS
- RULE of 4 (Ferritin > 400, CRP > 4)
- Tumor Lysis Prophylaxis??

Oluwole OO, Bouabdallah K, Muñoz J, et al. *Br J Haematol.* 2021;194(4):690-700.
Greenbaum U, Strati P, Saliba RM, et al. *Blood Adv*. 2021;5(14):2799-2806.

CAR-T Future Directions

AlloCAR-T – "Off the shelf" using healthy donors

- Immediate availability for treatment
- Standardization of CAR-T cell product
- Can re-dose & combine CAR-T cells directed against different targets
- Decreased costs

Expansion into other malignancies

- AML – Target Antigens: CD33, CD123, CLL1, FLT3
- CLL – Target Antigens: CD19, IgG Kappa

Alteration of CAR-T constructs – leads to enhanced T-cell activity, potency & persistence

- 3rd Generation: Use of 2 separate co-stimulatory domains
- 4th Generation [T-cell redirected for universal cytokine-mediated killing (TRUCKs)]: Activate downstream transcription factor to induce cytokine production (constitutively or inducible expressing inflammatory cytokines, IL-12 or IL-18)
- 5th Generation: Gene editing with CRISPR leading to TRAC gene inactivation

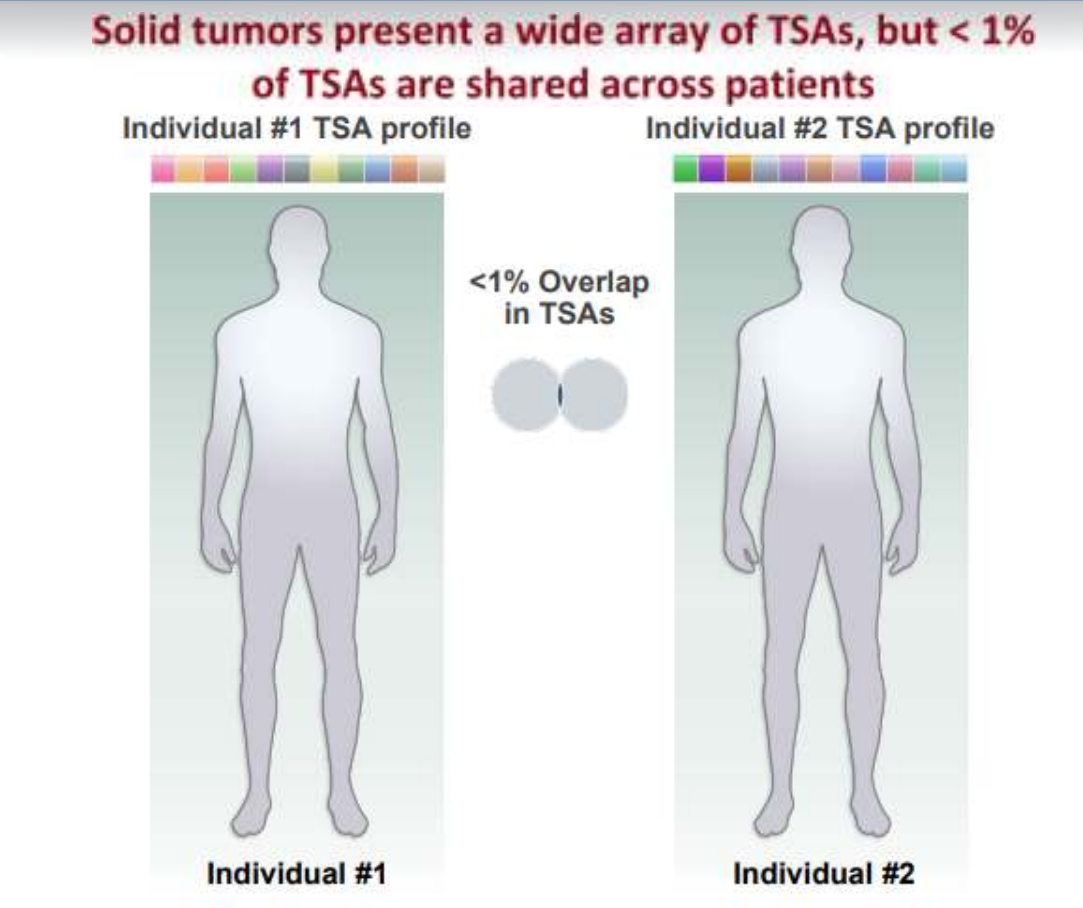
NK Cells as an immunologic target

- Does not require HLA matching
- Does not induce a GvHD response as compared to T-cells
- Immediate availability – "allo product"

Depil S, Duchateau P, Grupp SA, et al. *Nat Rev Drug Discov*. 2020;19(3):185-199.
Vishwasrao P, Li G, Boucher JC, et al. *Cancers (Basel)*. 2022;14(5):1241.
Goldenson BH, Hor P, Kaufman DS. *Front Immunol*. 2022;13:841107.

TUMOR INFILTRATING LYMPHOCYTES (TILS)

Rationale for TIL Use in Solid Tumors



AE, adverse event; TCR, T-cell receptor; TME, tumor microenvironment; TSA, tumor-specific antigen

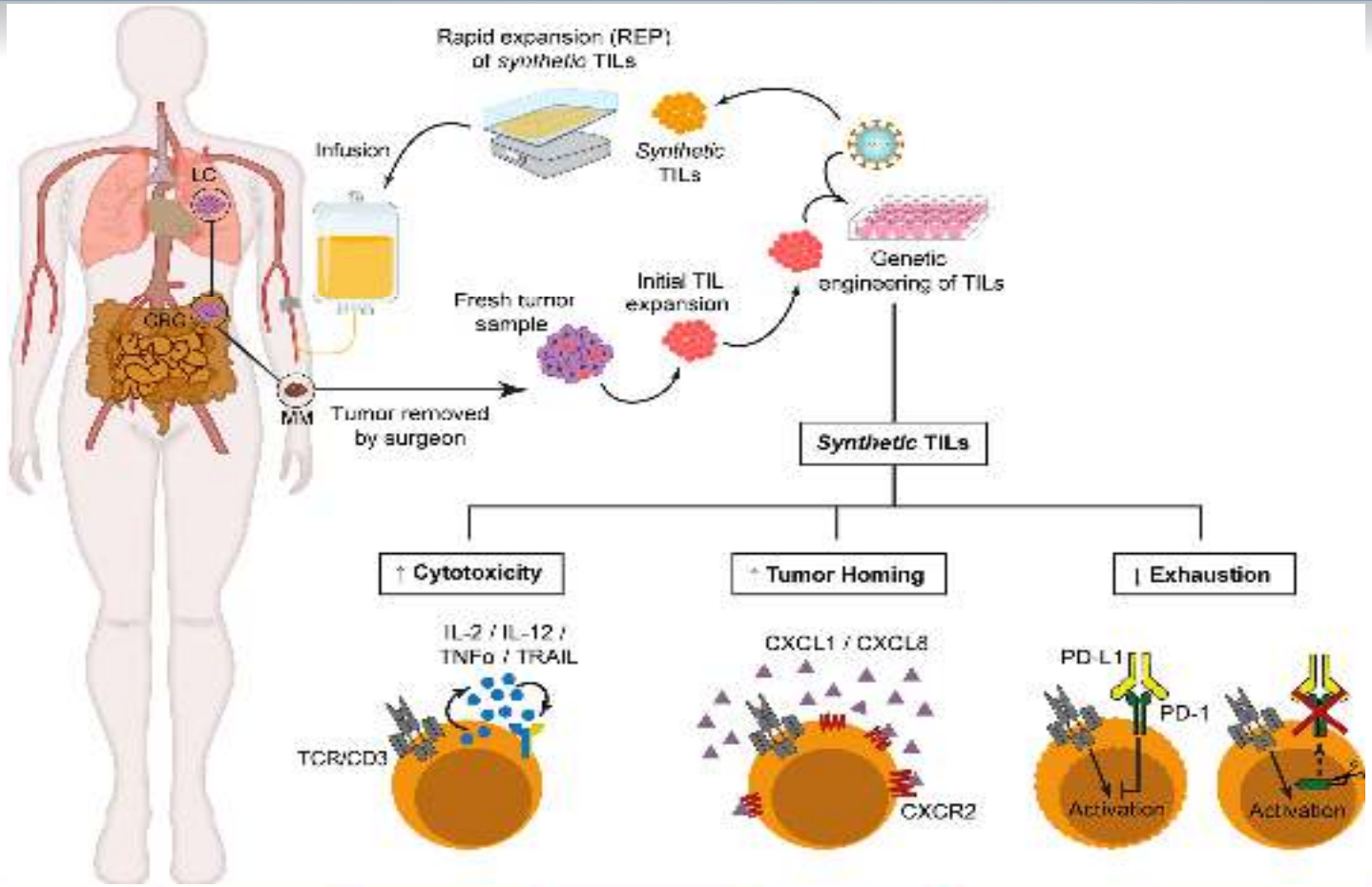
TILs are polyclonal & recognize a multitude of an individual's TSAs

TIL therapy has the potential to overcome challenges that make CAR-T therapy impractical in solid tumors, including:

1. Delivery of CAR-T cells or TCR-modified T-cells into TME
2. Immunosuppression of CAR-T cells or TCR-modified T-cells in TME
3. Lack of heterogeneous TSA expression in all tumor cells
4. Incidence of CRS and other autoimmune AEs with CAR-T cells and TCR-modified T-cells

Tran E, Robbins PF, Rosenberg SA. *Nat Immunol.* 2017;18(3):255-262.
Fardis M, DiTrapani K, Finckenstein FG, et al. *Cell & Gene Therapy Insights.* 2020; 6(6), 855–863.
TIL cell therapy Working Group. https://tilworkinggroup.com/

TILs Mechanism of Action



Jiménez-Reinoso A, Nehme-Álvarez D, Domínguez-Alonso C, et al. *Front Oncol.* 2021;10:593848
TIL cell therapy Working Group. https://tilworkinggroup.com/

TIL Literature

TIL Product	Sponsor	Number of Patients Treated	Number of Prior Therapies Allowed	Objective Response Rates	Median Overall Survival
Intramural TIL program	NCI	93	3†	56%	36% @ 3 yrs 29% @ 5 yrs
Intramural TIL program††	Netherlands Cancer Institute	168	1‡	49%	25.8 months
Lifileucel (LN-144)*	Iovance Biotherapeutics	66	Median 3 (1-9)	31.4%	13.9 months

†Heavily pretreated population: 95% had received at least 1 line of therapy; 40% had received at least 2 lines. Majority had not received Anti-CTL4A

††Compared TIL vs. ipilimumab, majority of patients had lower-risk disease

‡Prior Anti-CTLA4 was excluded. Majority received prior Anti-PD1 (86% dx refractory to this)

*Prior immune checkpoint inhibitors were required

All adverse events were related to lymphodepleting chemotherapy or IL-2

Rosenberg SA, Yang JC, Sherry RM, et al. *Clin Cancer Res*. 2011;17(13):4550-4557
Yang JC, Rosenberg SA. *Adv Immunol*. 2016;130:279-294
Sarnaik AA, Hamid O, Khushalani NI, et al. *J Clin Oncol*. 2021;39(24):2656-2666
Chesney J, Lewis KD, Kluger H, et al. *J Immunother Cancer*. 2022;10(12):e005755
Rohaan MW, Borch TH, van den Berg JH, et al. *N Engl J Med*. 2022;387(23):2113-2125

TIL Toxicities

Common AEs from IL-2

- Hypotension
- Nausea/Vomiting
- Diarrhea
- Confusion
- SOB
- Pulmonary edema
- Abnormal LFTs
- Renal failure
- Pancytopenia
- Rash
- Fever, chills/rigors
- Malaise
- Infections

Education, Careful Monitoring & Early Management is Critical!!

- Counsel patients & caregivers
- Ensure proper fluid status, vitals & utilize pressor support PRN
  - Minimize IV fluids when tolerating diet & not clinically vasodilated
- Monitor cognitive function
- Monitor at baseline & during treatment as clinically indicated:
  - CBC with differential & CMP prior to each dose; monitor for rising SCr
  - Vitals Q4H, unless on pressors then Q2H
  - Pulse oximetry Q8H or Q4H if on pressors (start O_2 if oximeter is < 90%) & check CXR
  - Neuro-assessment/mental status Q8H
  - Strict I&Os Q8H & daily weights
  - Telemetry monitoring
  - EG if persistent tachycardia for over 2 hrs

Proleukin (aldesleukin) [prescribing information]. Yardley, PA: Clinigen, Inc; September 2019.
TIL cell therapy Working Group. https://tilworkinggroup.com/

IL-2 Management

- Institutional-based guidelines are necessary
- Pretherapy interventions:
  - Discontinue antihypertensive medications 24 hrs prior to IL-2
  - Start scheduled APAP, indomethacin/naproxen (avoid if any baseline renal dysfunction), anti-emetics & H2 blocker before administration
  - Minimize unnecessary IV fluids before beginning IL-2
- General principles of IL-2 administration:
  - Blood pressure (BP) target assigned based on baseline BP and assessed prior to each dose
  - Urine output assessed prior to each dose (150 mL/8 hrs)
  - Chills/rigors occur within 1-2 hrs of each dose, fever occurs 1-2 hrs after chills/rigors
  - **NOTE: IL-2 management should not be confused with CAR-T AE management; DO NOT GIVE Tocilizumab and steroids.**
    - Steroids should be avoided unless adrenal insufficiency is suspected
    - For those with known adrenal insufficiency/hypophysis, keep physiologic replacement & boost if there is clinical sign of adrenal insufficiency

Normal BP for patient	Target BP on therapy
< 100 mm Hg	> 80 mm Hg
100-120 mm Hg	> 85 mm Hg
> 120 mm Hg	> 90 mm Hg

Schwartzentruber DJ. *J Immunother*. 2001;24(4):287-293.

General IL-2 Management Guidelines

Toxicity	Management
Cardiovascular	Sinus tachycardia > 120 bpm sustained for 1 hr • Assess fluid status & may administer NS or LR 500 mL IV fluid bolus • Assess telemetry/EKG for arrhythmias • Replace electrolytes • If arrhythmia or sustained tachycardia despite correction of reversible factors (hypotension, fever, dopamine) then may need to hold dose of stop IL-2 therapy
Gastrointestinal	• N/V: scheduled ondansetron 8 mg IV Q8H 30 minutes prior to each dose • Prochlorperazine or lorazepam as PRN options • Diarrhea: loperamide 2 mg Q2H PRN, Diphenoxylate/atropine PRN for refractory to loperamide • GI ppx: PPI or H2 blocker per institutional standard • Transient cholestasis is reversible after discontinuation of IL-2
Dermatologic	• Macular erythema, pruritus, desquamation • Diphenhydramine or hydroxyzine PRN itching per institutional standard • Aveeno & Lubriderm lotion TID
Endocrine	• If hypothyroidism persistent after therapy is completed, supplement with levothyroxine • Keep patients on physiologic replacement & boost if there is clinical sign of adrenal insufficiency; consider treating at 2x or 3x baseline during IL-2 induced hypotension
Hematologic	• PRBC transfusion for Hgb < 7 gm/dL • Platelet transfusion if < 10k/mcL if no prior history of CNS mets or < 20k/mcL if history of CNS mets • Neutropenia: G-CSF, can be stopped with ANC > 1000/mcL for 2-3 consecutive days
Infectious	• 10-30% incidence of staphylococcus bacterial infections • Neutropenic Fever • Antibiotics per institutional standards

TIL cell therapy Working Group. https://tilworkinggroup.com/

General IL-2 Management Guidelines

Toxicity	Management
Fevers/chills/rigors	Fever above 100.5°C • Acetaminophen 650 mg PO Q4H scheduled • Indomethacin/naproxen (avoid if any baseline renal dysfunction) PO BID scheduled. Stop if SCr > 2 mg/dL, decreased urine output or platelets < 50k/mcL • Hydromorphone 0.5 mg IV Q15min PRN for rigors, may repeat x 3 total doses • Meperidine 25 mg IV once PRN for rigors refractor to hydromorphone (if SCr < 1.7 mg/dL)
Blood pressure	Target BP set on admission and assessed prior to each dose – Assess about 2 hrs prior to dose • If not meeting target, administer NS or LR 250-500 mL IV bolus over 30 mins • Repeat BP 30 mins post bolus; if not meeting target, then may repeat additional 250-500 mL IV bolus • If not on oxygen, more fluid can typically be given & pressors/stopping IL-2 are typically not needed • If unresponsive to IV fluids, pressor support indicated
Urine output	SCr monitored daily Urine output 150 mL/8 hrs – Assessed 2x daily, including about 2 hrs prior to dose • If not meeting target, administer NS or LR 250-500 mL IV bolus over 30 mins • Check urine output 1 hr post IV bolus, if < 150 mL/8 hrs then may repeat another 250-500 mL IV bolus • Persistent low urine output despite IV fluid bolus, then initiate dopamine at renal perfusion dose (i.e. 2 mcg/kg/min). Urine output of 150 mL/8 hrs must be established before additional IL-2 doses may be given
Pulmonary	• O_2 saturation should be maintained above ≥ 92%, initiate oxygen therapy if O_2 < 95% (study 90-92%) • Physical exam with auscultation of rales in lung bases • CXR should be obtained to assess for pleural effusions or pulmonary edema

Guidelines for IL-2 Dose Skipping or Discontinuation

System	Relative Criteria	Absolute Criteria
Cardiac	• Sinus tachycardia (> 120 bpm)	• Sustained sinus tachycardia > 2 hr while afebrile after correcting hypotension, fever, and tachycardia and stopping dopamine • Atrial fibrillation, supraventricular tachycardia, or ventricular arrhythmias • Elevated CK, troponin (cardiac/renal source), or EKG changes of ischemia
Gastrointestinal	• Diarrhea 1000 mL/shift	• Diarrhea 1000 mL/shift x 2 • AST/ALT LFTs > 500 IU/L or bilirubin > 8 mg/dL
Hemodynamic	• Any requirement for pressors	• Fluid requirement results in pulmonary edema requiring supplemental O_2 that cannot be weaned off before next dose is due • Maximum phenylephrine 1.5-2 mcg/kg/min
Hemorrhagic	• Guaiac + sputum, emesis, stool • Platelets 30k-50k/mcL	• Frank blood sputum, emesis, stool
Musculoskeletal	• Extremity tightness	• Extremity paresthesias
Neurologic	• Vivid dreams • Emotional lability	• Hallucination, disorientation, or mental status changes not reversible • Persistent crying
Pulmonary	• Resting SOB • Rales 1/3 up chest on physical exam	• > 2L O_2 by nasal cannula for saturation ≥ 95% or 40% O_2 mask • Endotracheal intubation • Moist rales 1/2 up chest on physical exam • Pleural effusion requiring tap or chest tube
Renal	• Urine output < 150 mL/8 hrs • SCr increased of 2-3x baseline • Bicarbonate < 18 mEq/L	• Urine output < 80 mL/8 hrs • SCr ≥ 3 mg/dL • Persistent acidosis despite replacement

TIL cell therapy Working Group. https://tilworkinggroup.com/

When to Skip a Dose or Discontinue IL-2

- Assess IL-2 criteria prior to each dose of IL-2 to determine if dosing is appropriate

Observation Criteria	Action
≤ 3 relative criteria	Initiate correction measure ± skip IL-2
≥ 3 relative criteria	Initiate correction measure, skip IL-2 Stop IL-2 if not reversible
Any absolute criteria	Initiate correction measure, skip IL-2 Stop IL-2 if not reversible

- Allow dosing delay of up to 2 hours if patient can get within parameters, but do not delay the next dosing
- Administer IL-2 doses at least 6 hrs apart
- If dosing skipped > 24 hrs → Stop IL-2
- If two consecutive doses are skipped → Stop IL-2

Schwartzentruber DJ. *J Immunother*. 2001;24(4):287-293.

"TILS 2023 & Beyond"

Lifileucel

- Regenerative medicine advanced therapy (RMAT) designation per FDA
- Biologics license application (BLA) accepted by FDA 5/2023
- PDUFA date – 11/25/2023

Adoption into upfront therapy

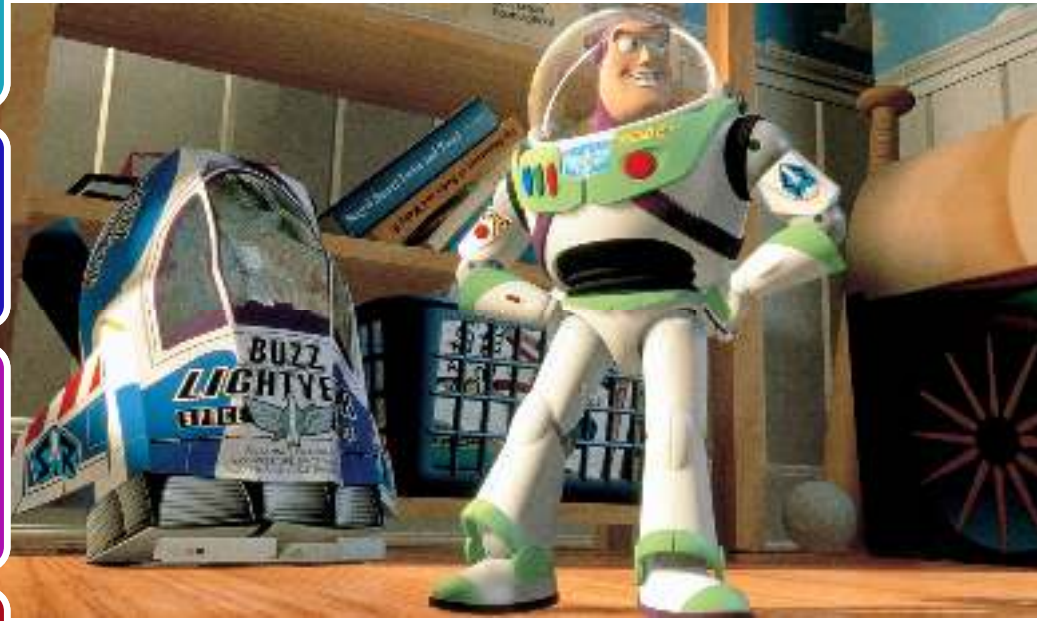
- TILs + Immune checkpoint inhibitors

Utilization in other malignancies

- Cervical Cancer
- Lung Cancer
- Head & Neck Cancer
- GI malignancies & Breast Cancer

Third Generation TIL & New TIL targets

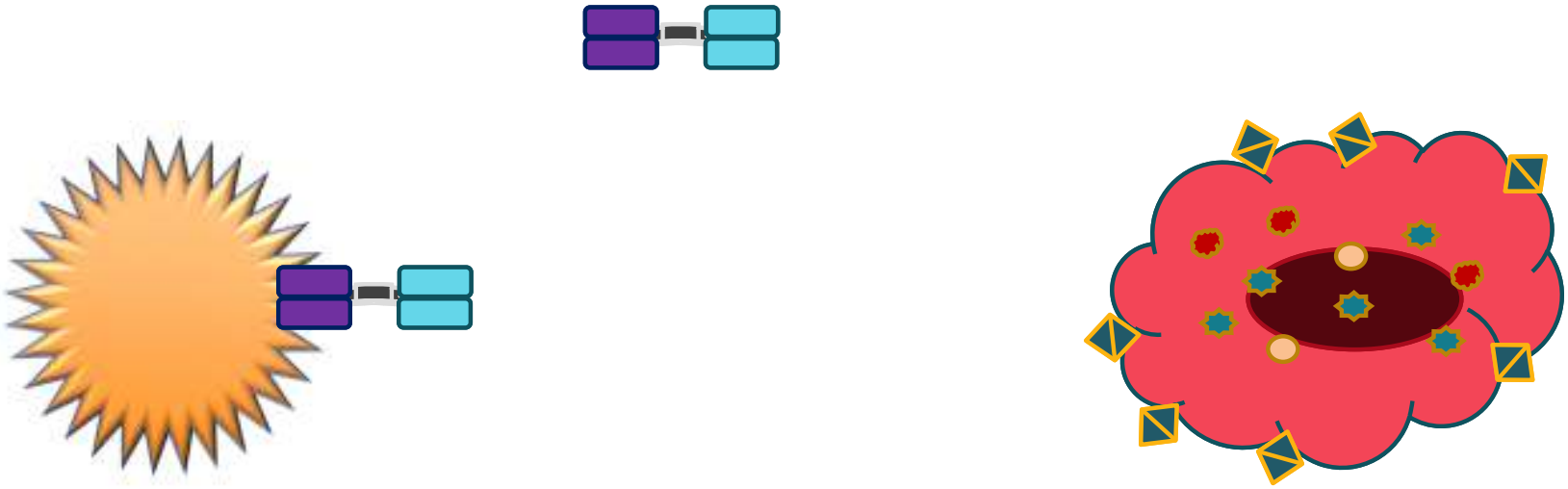
- Gene-edited TILs – TALEN, CRISPR technology
- PD-1 selected TIL - LN-145-S1
- PD-1 inactivated TIL: IOV-4001
- IL-2 analog – improved toxicity profile



Rosenberg SA, Parkhurst MR, Robbins PF. *Cancer Cell*. 2023;41(4):646-648.
https://www.iovance.com/clinical-pipeline/
https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
TIL Therapy in Combination With Checkpoint Inhibitors for Metastatic Ovarian Cancer - Full Text View - ClinicalTrials.gov

BI-SPECIFIC T-CELL ENGAGERS (BITES)

BiTEs Mechanism of Action



Cho et al. Frontiers in Onc. 2022.

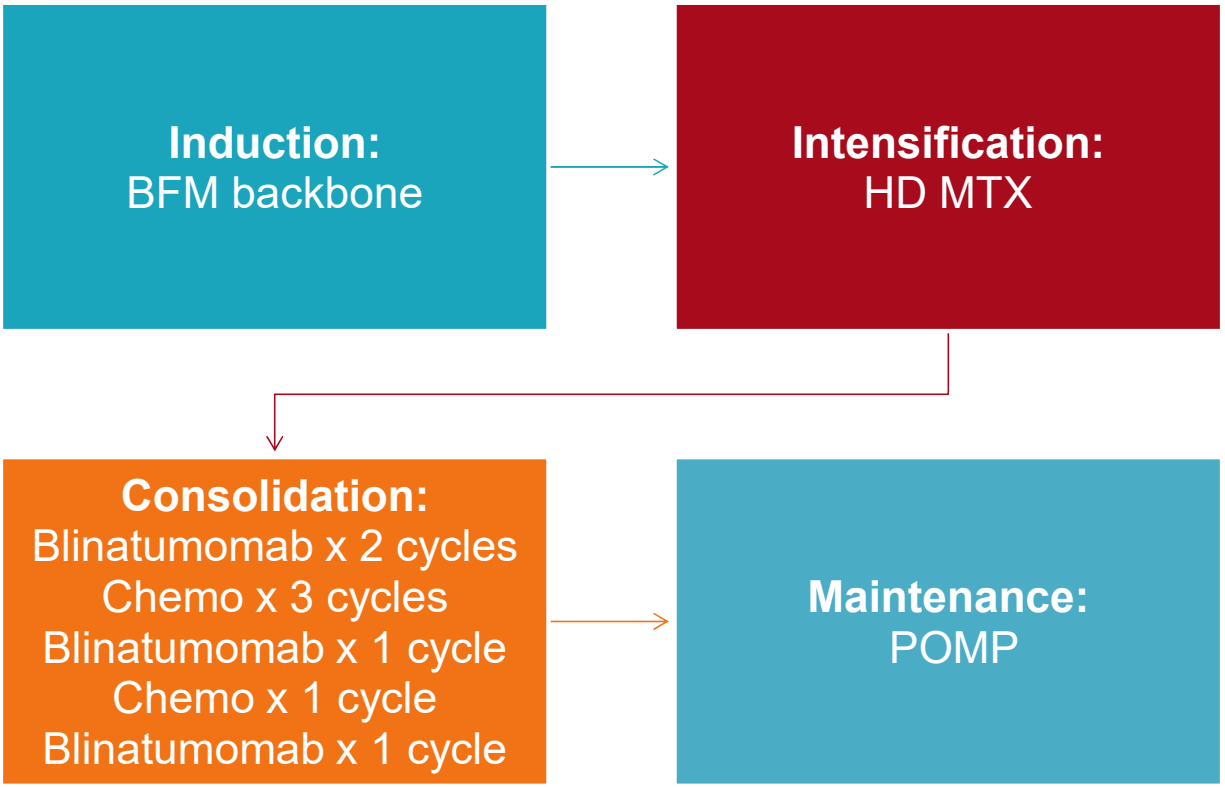
Currently Available BiTE Products

BiTE Product	Construct	FDA Indication	Objective Response Rates	Overall Survival	Incidence of CRS	Incidence of Neurotoxicity
Blinatumomab (Blincyto®) – administered as continuous infusion (CIVI), 28 days on/14 days off	• CD-19 • CD3	R/R Ph- ALL in adults & children	86.4%	54% @ 6 months	All Grades: 14.2% Grades III-IV: 4.9%	Grades III-IV: 9.4%
		R/R Ph+ ALL in adults & children, given in combination with BCR-ABL inhibitor	36%	7.1 months	All Grades: 7% Grades III-IV: 0%	All Grades: 47% Grades III-IV: 7%
		ALL, minimal residual disease (MRD) positive in adults & children	78%*	36.5 months	All Grades: 3% Grade III-IV: 2%	All Grades: 53% Grades III-IV: 13%
Teclistamab (Tecvayli®) – administered as subcutaneous (SubQ) injection Days 1, 4 & 7 followed by weekly	• BCMA • CD3	R/R Multiple Myeloma after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor & and anti-CD38 monoclonal antibody	63%	18.3 months	All Grades: 72.1% Grades III-IV: 0.6%	All Grades: 14.5% Grades III-IV: 0.6%
Tebentafusp (Kimmtrak®) – administered as an IV infusion weekly	• Glycoprotein 100(gp100) • CD3	Unresectable or metastatic uveal melanoma, HLA-A*02:01-positive	9%	73% @ 12 months 21.7 months	All Grades: 89% Grades III-IV: 1%	0%
Mosunetuzumab (Lunsumio®) – administered as an IV infusion weekly on Days 1, 8 & 15 of a 21-day cycle	• CD20 • CD3	R/R FL after 2 or more lines of therapy	80%	Not reached	All Grades: 44% Grades III-IV: 2%	All Grades: 5% Grades III-IV: 0%
Epcoritamab (Epkinly®) – administered SubQ weekly for Cycles 1-3, biweekly Cycles 3-9, then monthly	• CD20 • CD3	RR DLBCL, including arising from indolent lymphoma, after 2 or more lines of therapy	63.1%	Not reached	All Grades: 49.7% Grades III-IV: 2.5%	All Grades: 6.4% Grades III-IV: 0.6%

*MRD negativity rate

Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; February 2022.
Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.
Kimmtrak (tebentafusp) [prescribing information]. Conshohocken, PA: Immunocore Commercial LLC; November 2022.
Lunsumio (mosunetuzumab) [prescribing information]. South San Francisco, CA: Genentech, Inc; December 2022.
Kantarjian H, Stein A, Gökbuget N, et al. *N Engl J Med*. 2017;376(9):836-847. Gökbuget N, Dombret H, Bonifacio M, et al. *Blood*. 2018;131(14):1522-1531. Topp MS, Kufer P, Gökbuget N, et al. *J Clin Oncol*. 2011;29(18):2493-2498.
Topp MS, Gökbuget N, Zugmaier G, et al. *Blood*. 2012;120(26):5185-5187. Martinelli G, Boissel N, Chevallier P, et al. *J Clin Oncol*. 2017;35(16):1795-1802. Moreau P, Garfall AL, van de Donk NWCJ, et al. *N Engl J Med*. 2022; 387:495-505.
Nathan P, Hassel JC, Rutkowski P, et al. *N Engl J Med*. 2021;385(13):1196-1206. Budde LE, Sehn LH, Matasar M, et al. Lancet Oncol. 2022;23(8):1055-1065. Thieblemont C, Phillips T, Ghesquieres H, et al. *J Clin Oncol*. 2023;41(12):2238-2247.

Blinatumomab Consolidation – Up-Front ALL



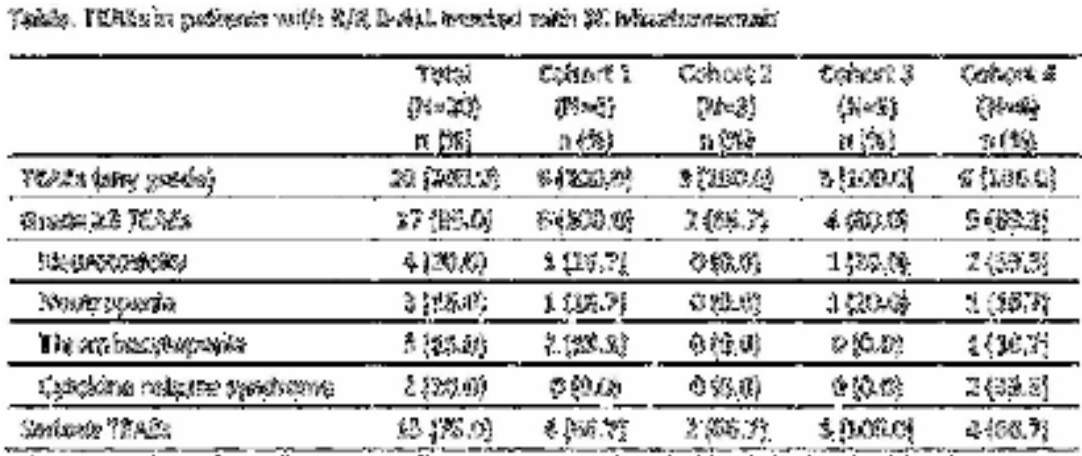
- Late breaking abstract from ASH 2022
- Improved OS: median OS – not reached vs. 71.4 months (Hazard ratio 0.42, 95% CI: 0.24 – 0.75; two-sided p=0.003)
  - Irrespective of MRD status
- Represents a new standard of care for Ph- ALL
  - Cooperative group trials are now being amended to incorporate blina up-front in consolidation

BFM: Berlin-Frankfurt-Münster backbone; HD MTX: High-Dose Methotrexate; POMP: Prednisone, Vincristine, Methotrexate, Mercaptopurine

Litzow MR, Sun Z, Paietta E, et al. *Blood*. 2022; 140 (Supplement 2): LBA–1.

Blinatumomab – Future Directions

- CIVI administration is a HUGE patient inconvenience
  - SubQ administration can improve quality of life (QoL)as reduce overall costs by giving less drug
- SubQ dosing was daily on Days 1-7, followed by three times a week on Days 8-26 for Cycle 1
  - Subsequent cycles, dosed at three times a week on Days 1-26
- No dose-limiting toxicities
- Pharmacokinetics/Pharmacodynamics profile is equivalent to that of CIVI
- 64.3% achieved a complete response with full or partial hematologic recovery & MRD negativity within 2 cycles



Sánchez PM, Zugmaier G, Gordon P, et al. *Blood.* 2022; 140 (Supplement 1): 6122–6124.

Teclistamab – Future Directions

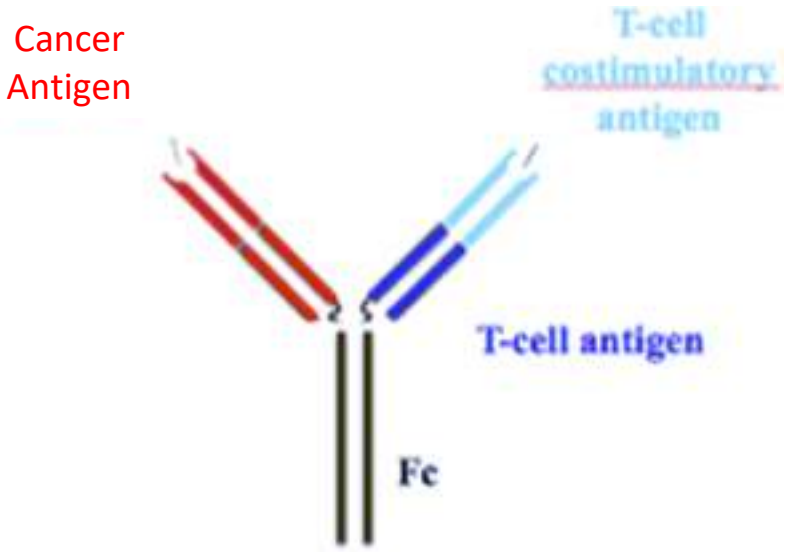
Currently no comparative data to compare to other regimens in multiple myeloma & no insight on sequencing

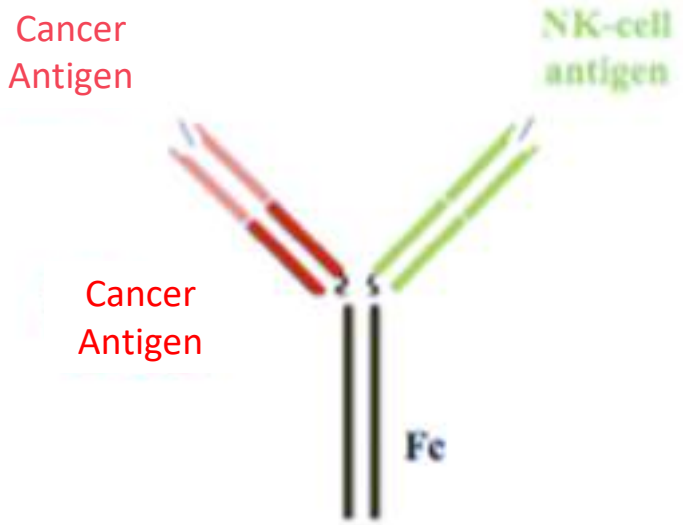
Blantamab mafodotin withdrawn → Teclistamab provides same target with improved safety profile & similar/improve efficacy data

Teclistamab is the preferred BCMA therapy for transplant/CAR-T ineligible patients

Zamagni E, Boccadoro M, Spencer A, et al. *Blood* 2022; 140 (Supplement 1): 7289–7291
Searle E, Quach H, Wong SW, et al. Blood 2022; 140 (Supplement 1): 394–396.

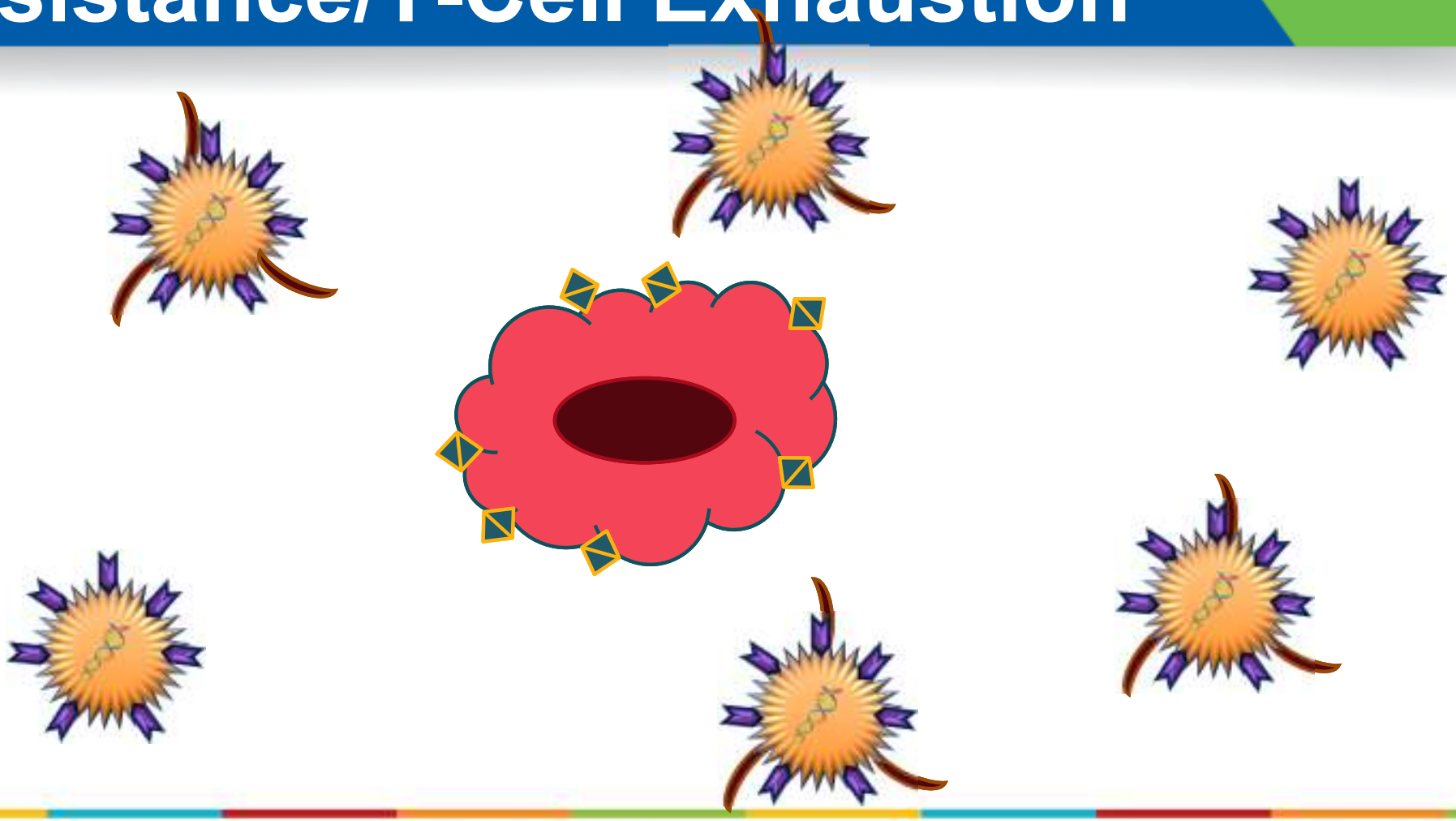
Tri-specfic T-cell Engagers (TriTE)





Lancman G, Richter J, Chari A. *Hematology Am Soc Hematol Educ Program.* 2020;2020(1):264-271
Goebeler ME, Bargou RC. *Nat Rev Clin Oncol.* 2020;17(7):418-434

Resistance/T-Cell Exhaustion



Brown CE, Mackall CL. *Nat Rev Immunol.* 2019;19(2):73-74.
Shah NN, Fry TJ. *Nat Rev Clin Oncol*. 2019;16(6):372-385.

Future Therapies

MajesTEC-2 – Phase 1b

- Teclistimab w/ Daratumumab + Lenalidomide
- ORR 100% (13/13) at 0.72 mg/kg dosing
- ORR 81.3% (13/16) at 1.5 mg/kg dose
- VGPR or better in 12 patients

Future Progress

- Teclistamb maintenance therapy following auto transplant (MajesTEC-4)
- BiTE bridging to CAR-T
- Post CAR-T Maintenance
- CAR-T and BiTE Therapy in Solid Tumor
- Combination Therapies

Searle E, Quach H, Wong SW, et al. Blood 2022; 140 (Supplement 1): 394–396.
Zamagni E, Boccadoro M, Spencer A, et al. *Blood* 2022; 140 (Supplement 1): 7289–7291.

WHERE DO WE COME IN AS PHARMACISTS?

Pharmacist Involvement

- Education: patients, caregivers & clinical team
- Clinical responsibilities
  - Medication history
  - Determine eligibility for therapy modality
  - Profile review: drug-drug interactions, con-meds
  - Supportive care & AE management
- Generation of standard operating procedures, guidelines & ordersets
- Operations
- Pharmacy-led research

Booth JP, Kusoski CL, Kennerly-Shah JM. *J Oncol Pharm Pract*. 2020;26(7):1725-1731
Marzal-Alfaro MB, Escudero-Vilaplana V, Revuelta-Herrero JL, et al. *Front Oncol*. 2021;11:636068

Conclusions

Immune modulators & cellular therapies have been shown to be safe & effective for a variety of malignancies

The future is bright for these modalities looking at altering constructs to improve toxicity profiles & immune function, as well as use in other malignancies

Oncology pharmacists play a critical role in managing patients who receive these modalities


QUESTIONS?