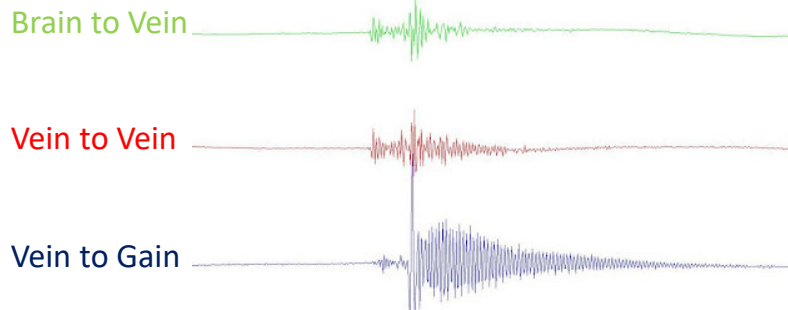


Immunotherapy and CAR-T Cell Therapy: A Survivors Journey



Matthew Lunning D.O. FACP
Associate Professor
6/7/2024

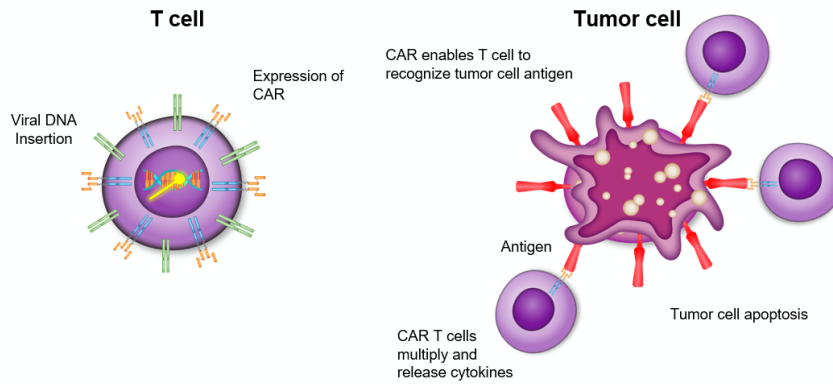


Disclosures

Updated 6/2024	
Research Support	Fate Therapeutics
Consultancy	AbbVie, BMS, FATE, Genentech, Genmab, Ipsen, J&J, Kite, LOXO, Recordati, Regeneron, SeaGen, ViTToria,
Employment	NONE
Stock/Equity	NONE
Speakers Bureau	NONE

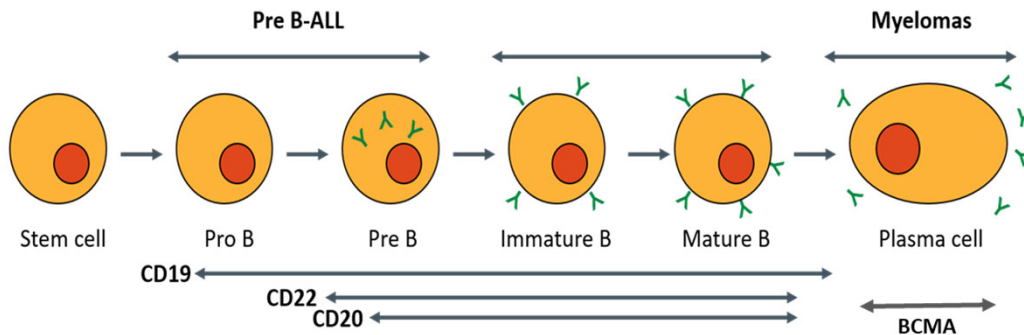


What is



3

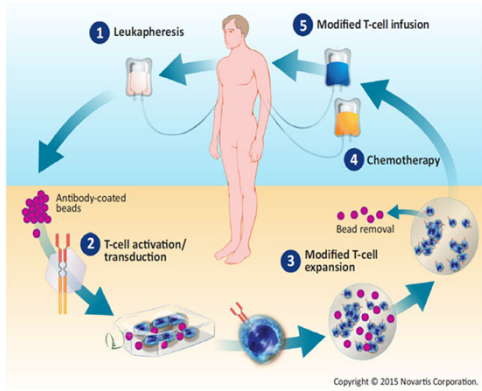
CAR T-Cell Antigen Selection



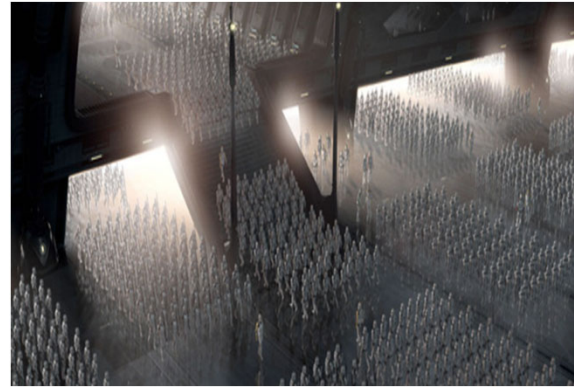
4

CAR-T on Demand

Autologous

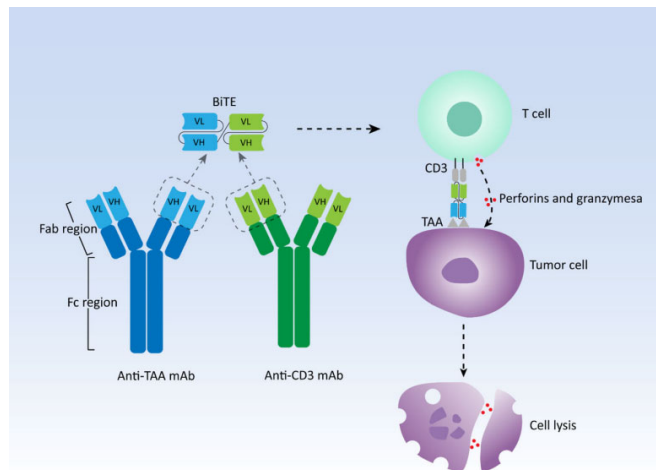


Allogeneic



5

Bispecific T-cell Engagers



Zhou et al. Biomarker Research 2021

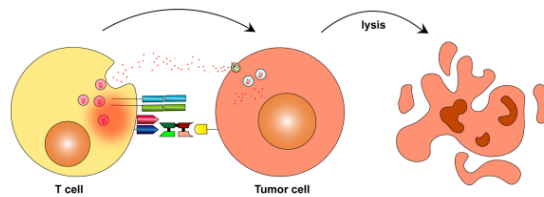
6

Bispecifics As Pasta



7

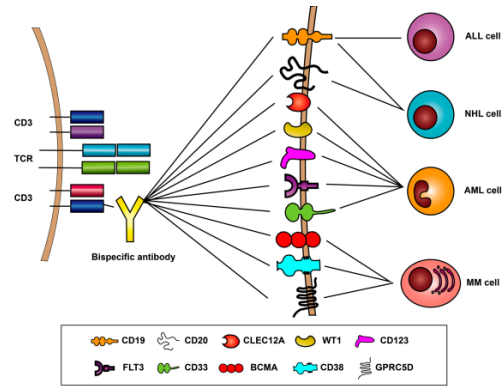
The Kiss of Death



Tian et al. Journal of Hematology & Oncology 2021

8

Many Types



Tian et al. Journal of Hematology & Oncology 2021

9



FDA APPROVED INDICATIONS

1. DLBCL (Axi-cel, Liso-cel, and Tisa-cel)
2. FL (Axi-cel, Liso-cel and Tisa-cel)
3. MCL (Liso-cel and Brexu-cel)
4. ALL (Tisa-cel & Brexu-cel)
5. MM (Ida-cel and Cilta-cel)
6. Chronic Lymphocytic Leukemia (Liso-cel)



10



FDA APPROVED INDICATIONS

1. DLBCL (Glofit & Epcor)
2. FL (Mosun)
3. MCL (None)
4. ALL (Blin)
5. MM (Tec)
6. CLL (None)



11

A Survivors Journey

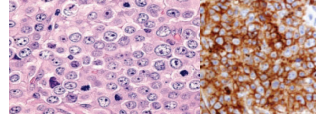
- EF is a 64 y.o. man who noted fatigue and unintentional weight loss of 10 kgs in 2 months.
- Wife notes he has been “sweating the bed” and she now chooses to sleep in the guest room.
- On exam he has multiple lymph nodes palpable in his cervical region.
- No reported fevers (doesn’t own a thermometer)
- He continues to work but is tired by end of the day and does not feel refreshed in the morning



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Initial Evaluation

- Seen by PCP with abnormal exam noting diffuse adenopathy
- He undergoes an excisional biopsy of a right cervical lymph node.
- Pathology notes partial effacement of nodal architecture by large cleaved cells
- IHC: CD20+, CD10-, BCL-2-MYC 40%,
- FISH: Negative for MYC and BCL-2/BCL-6
- **Dx: DLBCL-NOS; non-GCB**



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Oncology Consult

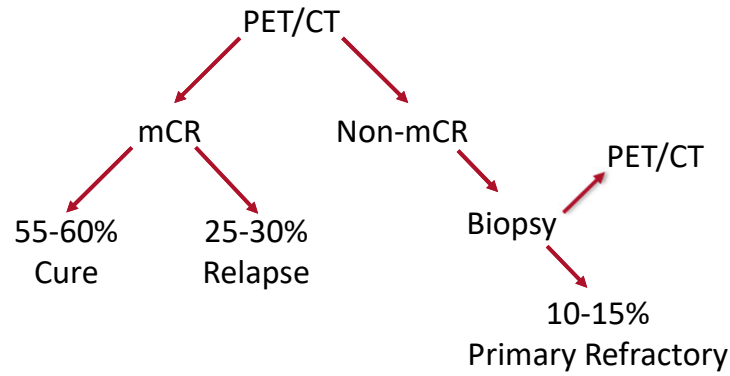
- PET/CT demonstrates avid adenopathy above and below the diaphragm with avid lytic bone lesions noted.
- CBC, CMP, and LVEF normal
- LDH elevated
- Bone marrow: Deferred
- Stage: IVB
- IPI score 3 (Stage, Age, and LDH)
- Curative intent therapy discussed



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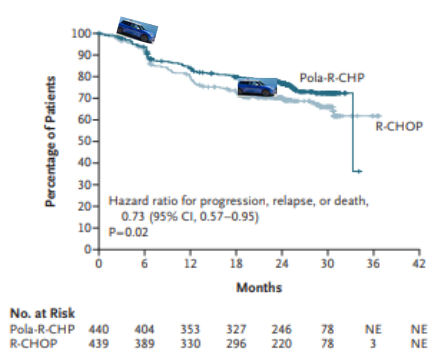
Expected Journey

Induction Therapy
(Pola-R-CHP, R-CHOP or DA-EPOCH-R)



15

A New Day For DLBCL



Adverse Event	Pola-R-CHP (N = 435)		R-CHOP (N = 438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0



Tilly H et al. NEJM 2022

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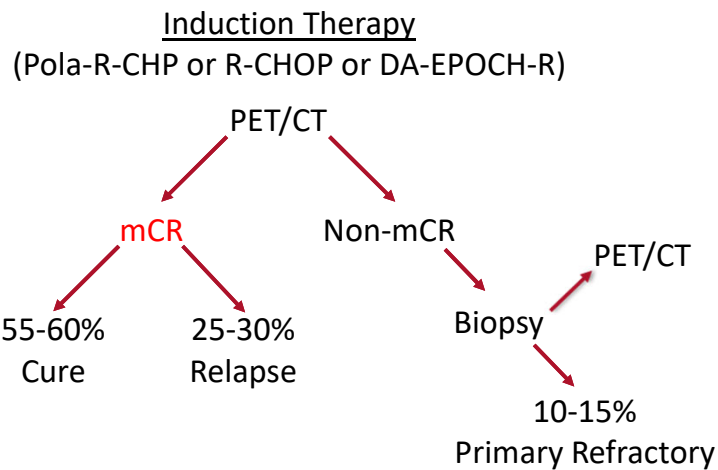
Journey Completed?

- Interim PET/CT after 4 cycles of Pola-R-CHP demonstrates improvement in nodal with diffuse skeletal uptake (growth factor effect). Sequences for minimal residual disease (MRD) identified.
- End of treatment PET/CT, 2 months after 6 cycles of Pola-R-CHP demonstrated resolved nodal disease and bone avidity assessed as Deauville 3 (below liver background). Sequences for MRD present on peripheral blood.



17

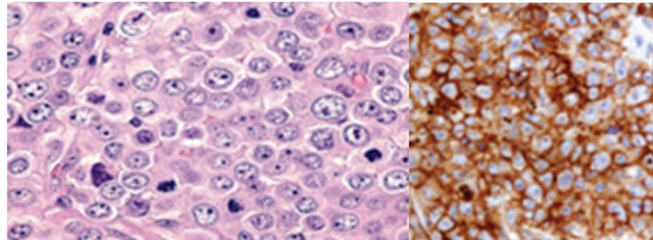
Expected Journey



18

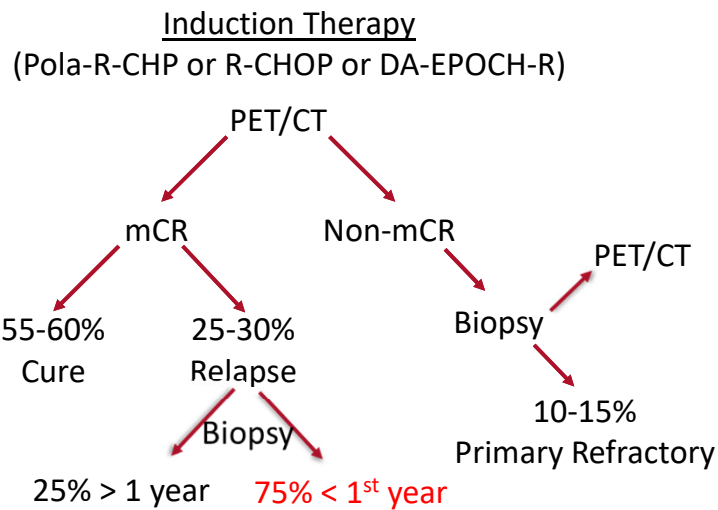
Survivorship Visit

- All LBCL patients are referred to NM Survivorship
- Complains of return of night sweats (6 weeks post last PET/CT)
- Earlier PET/CT (was scheduled at 5 months post txt)
- PET/CT notes diffuse adenopathy and a new liver lesion
- Pathology notes large cleaved cells
- IHC: CD20+, CD10-, CD30+ (30%), Ki-67 90%
- DLBCL-NOS



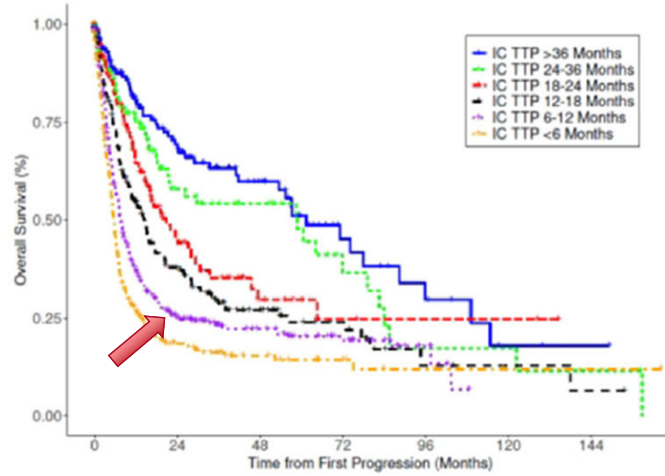
19

Journey Interrupted



20

Journey Interrupted



Maurer et al. AJ Heme 2021



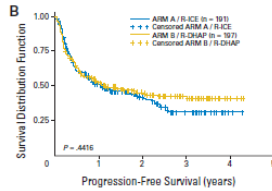
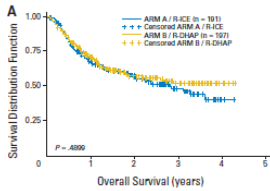
Prior to 4/2022 Are they a transplant candidate?

Yes Maybe No

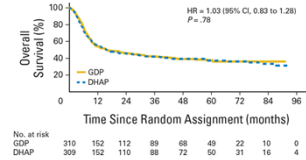
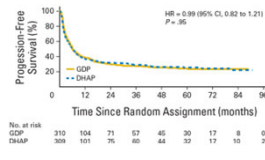


All Comers 2nd Line Outcomes

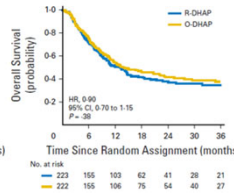
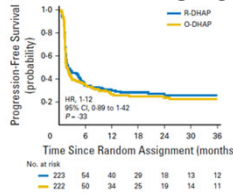
Coral (R-ICE vs R-DHAP)



LY12 (GDP vs DHAP)



ORCHARDDD



Gissebrecht et al. JCO. 2010; van Imhoff et al. JCO 2017 Crump M, et al. J Clin Oncol, 2014.



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After to 4/2022 Are they a CAR-T candidate?

Yes

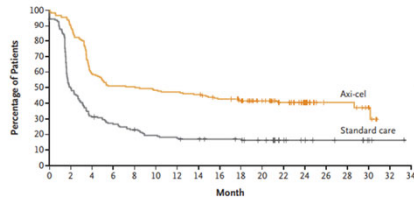
Maybe

No

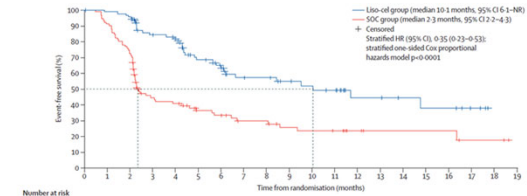


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His Next Journey ZUMA-7 & TRANSFORM



No. at Risk	Month	Axi-cel	Standard care
180	0	180	179
163	2	163	163
106	4	106	106
92	6	92	92
87	8	87	87
85	10	85	85
82	12	82	82
74	14	74	74
67	16	67	67
52	18	52	52
40	20	40	40
26	22	26	26
12	24	12	12
6	26	6	6
3	28	3	3
1	30	1	1
0	32	0	0



Number at risk (number censored)	Time from randomisation (months)	Liso-cel group	SOC group
92	0	92	92
89	2	89	89
86	4	86	86
62	6	62	62
43	8	43	43
35	10	35	35
29	12	29	29
27	14	27	27
26	16	26	26
21	18	21	21
19	20	19	19
14	22	14	14
12	24	12	12
11	26	11	11
10	28	10	10
6	30	6	6
4	32	4	4
3	34	3	3
2	36	2	2
1	38	1	1
0	40	0	0

	ASCT (n=179)	Axi-cel (n=180)
mEFS; months (95% CI)	2.0 (1.6-2.8)	8.3 (4.5-15.8)
mPFS; months (95% CI)	3.7 (18.5-NE)	14.7 (2.9-3.9)
mOS; months (95% CI)	35.1 (18.5-NE)	NR (28.3-NE)

	ASCT (n=92)	Liso-cel (n=92)
mEFS; months (95% CI)	2.3 (2.2-4.3)	10.1 (6.1-NR)
mPFS; months (95% CI)	5.7 (3.9-9.4)	14.8 (6.6-NR)
mOS; months (95% CI)	16.4 (11.0-NR)	NR (15.8-NR)

Survival Advantage

Immature for Survival



Locke FL, et al. *N Engl J Med.* 2022;386(7):640-654; Kamdar M, et al. *Lancet.* 2022;399(10343):2294-2308.

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CAR-T ASAP?



Clinical Trials



Commercial World

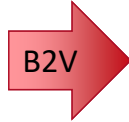


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CAR-T ASAP

Commercial World

Clinical Trials



We Want to Do CAR-T

Apheresis

Infusion



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Cell Therapy Impact Quotient (CTIQ)



B2V

Patients infused

Patients intended for CAR-T (iCAR-T)



V2V

Patients infused

Patients apheresed for CAR-T (aCAR-T)



V2G

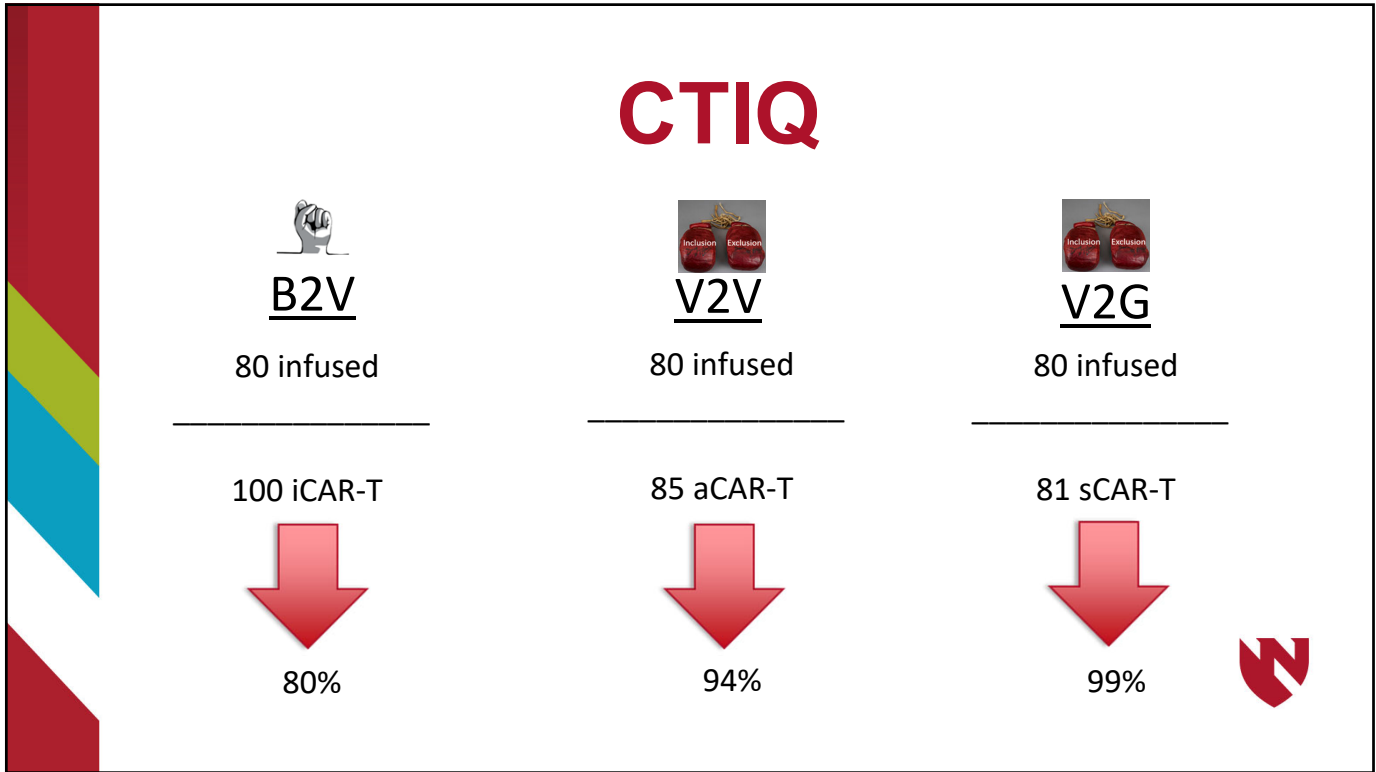
Patients infused

Patients in Spec for CAR-T (sCAR-T)

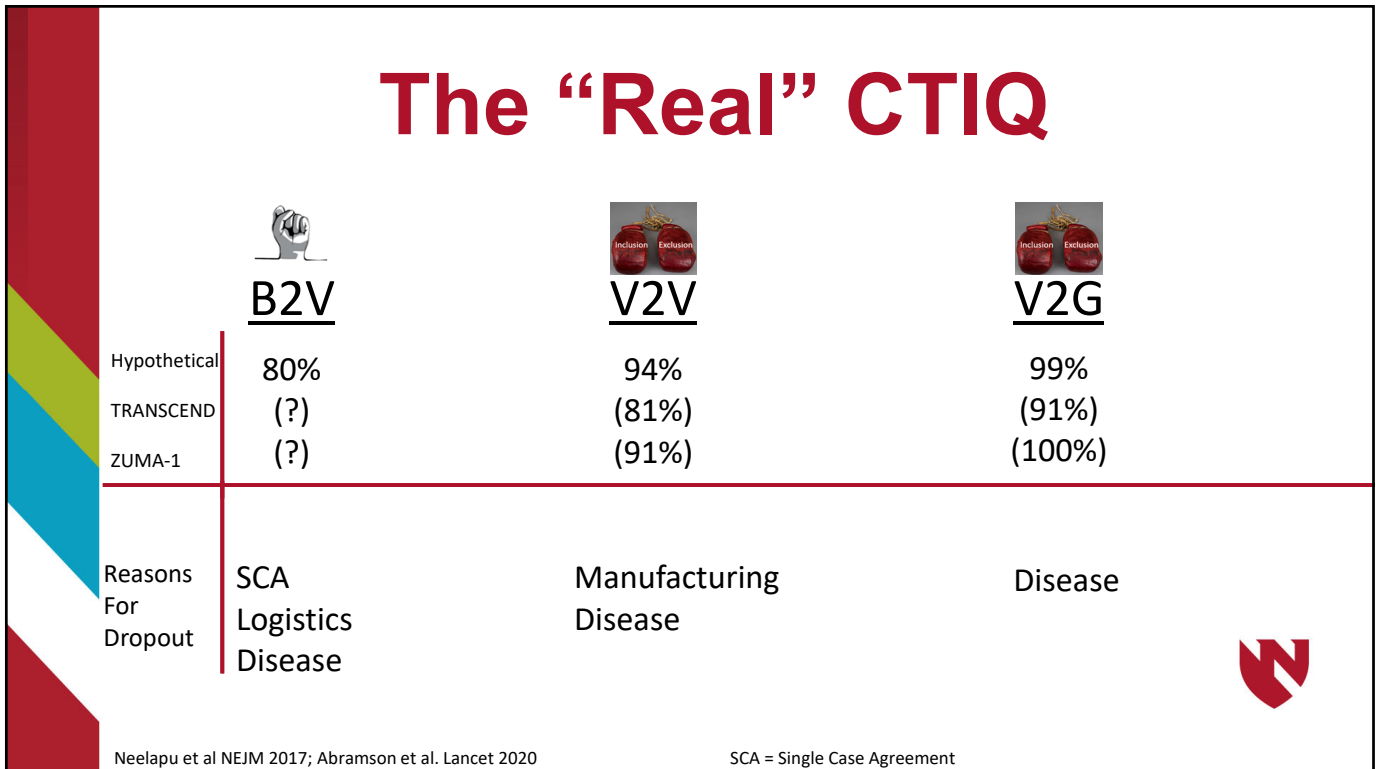


B2V = Brain to Vein; V2V = Vein to Vein; V2G = Vein to Gain

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29



30

The “Real” CTIQ

B2V

80%

Single Center Data

V2V

94%

Real World
Experience

Safety Data Sets
mITT

V2G

99%

Clinical Trials

Efficacy Data Sets



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

Addressing The B2V: Before the Door

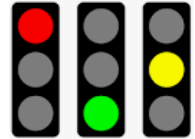
- Insurance Type
 -
 -
 -
- Prior lines of treatment
 - 1st vs 2nd line +
- Disease State
 - Refractory
 - **Very early relapse (2-6 months)**
 - Early relapse (7-11 months)
 - Relapse (12 months+)
- Slot availability trend
 - Quarterly
- Out of specification trend
 - Quarterly



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B2V Insurance Type History

- Private insurance (weeks to months); 
 - How long did it take for prior single case agreement (SCA)
 - Extra inclusion criterion
 - TTE, PFTs, HCSCT markers
- Medicare (days to months)
 - Managed plan may be treated as Private (required SCA)— 
 - If supplement, then move quickly to apheresis— 
- Medicaid (weeks to months)
 - Managed plan may be treated as Private (required SCA) 
 - Need to discuss with the State (Nebraska/Iowa/etc) regarding payment/approval 
- Tricare (Unknown)
 - Referred to VA center (Nashville, TN) 



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B2V: The Disease Doesn't Care

- Insurance
 - **Private**, Medicare, Medicaid (State), TriCare
- Need to bridge at all
 - **Yes** or No
- Early bridging (Brain to Vein)
 - **Yes** or No
- Late bridging (Vein to Vein)
 - Yes or No or **Unknown**
- Lymphodepleting chemo to infusion of CAR-T
 - Do we have fludarabine—Yes or No



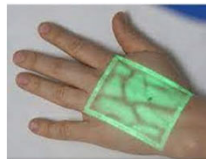
34

Getting There Is Half The Battle

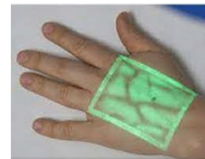
- He received B2V bridging with Gem-Ox
 - Disease stabilization without ECOG migration
- Liver function normalized and bilirubin remained normal
- CBC with persistent anemia (hgb 10.5) and transient thrombocytopenia
- No neuropathy seen
- Goes on to apheresis



35



to

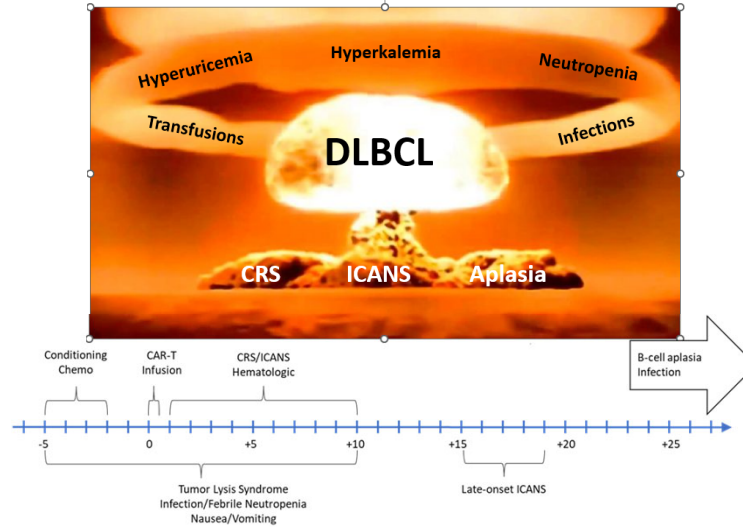


- Need to bridge AGAIN....
 - Maybe, know the V2V time of product
 - 17-30+ days depending on construct
- Early bridging (Brain to Vein)
 - Yes; completed Gem-Ox (no AEs)
- Late bridging (Vein to Vein)
 - Consider active surveillance
 - Consider steroids
 - Consider radiation (BOOM-BOOM)
 - Consider cycle 2 of Gem-Ox



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Vein To Gain: Curative Intent Again

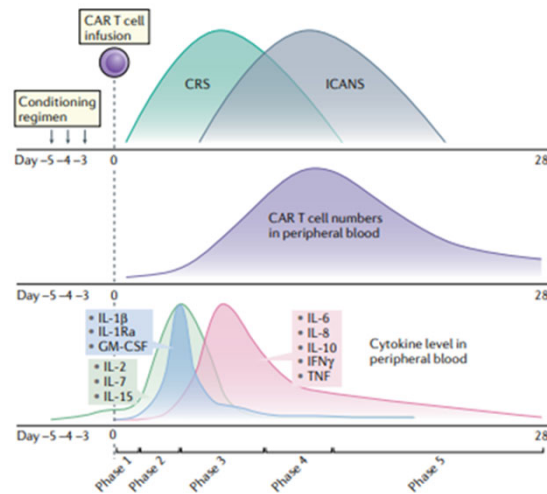


CRS = Cytokine Release Syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome



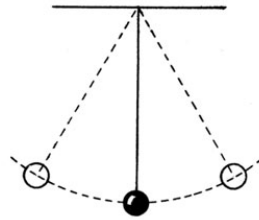
37

Close Monitoring



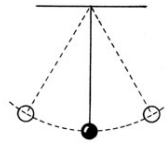
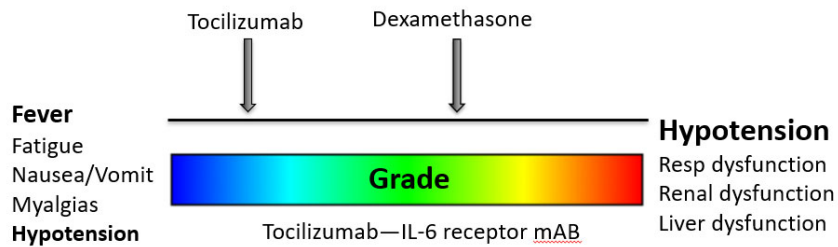
38

Team Management Evolves



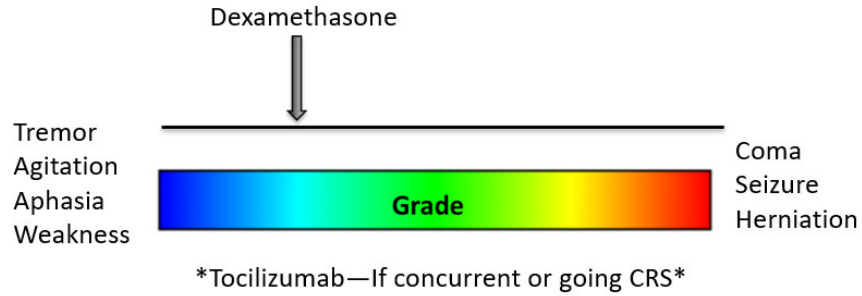
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Management of CRS



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Management of ICANS

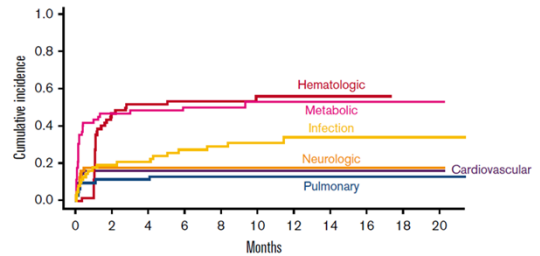


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Day 29 and Beyond

3rd Line+ DLBCL

Product	Delayed G ≥ 3 hematologic toxicity	G ≥ 3 infections	IVIg Use
Tisagenlecleucel	32%	20%	30%
Axicabtagene ciloleucel	17%	28%	33%
Lisocabtagene maraleucel	37%	12%	21%



Schuster SJ, et al. *N Engl J Med.* 2019; Locke FL, et al. *Lancet Oncol.* 2019; Abramson JS, et al. *Lancet.* 2020 G = Grade

42

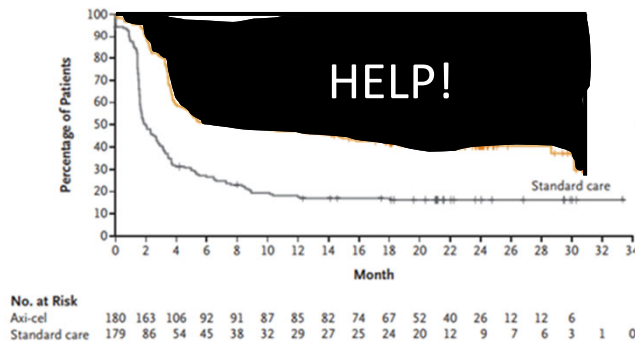
Journey Back To Survivor

- Able to manufacture CAR-T post-Gem-Ox
- Received commercial CAR-T after Cy/Flu lymphodepleting chemotherapy
- Grade 2 CRS and Grade 1 ICANS
- Metabolic complete response at 3- and 6-months post CAR-T via PET/CT
- Periodic GCSF for ANC < 500
- IVIG is started given recurrent sinopulmonary infections and IgG < 200
- Started re-vaccination per post-CAR-T protocol
- Bactrim/Acyclovir until CD4+ > 200 assess when ALC > 500



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Relapses Do Occur

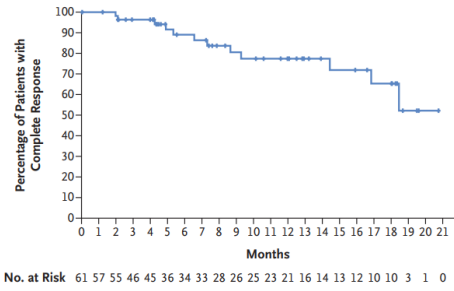
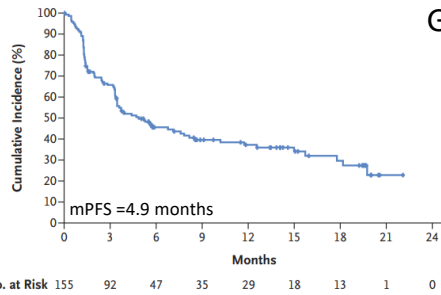


Locke FL, et al. *N Engl J Med.* 2022



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Rigatoni to the Rescue



Subgroup	No. of Patients	Complete Response (95% CI) percent
Previous CAR T-cell therapy		
Yes	52	35 (22–49)
No	103	42 (32–52)

Dickinson et al. NEJM 2022

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The Next Shift



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University of Nebraska
Medical Center



Nebraska
Medicine