Overview of CAR-T Cells and Toxicities

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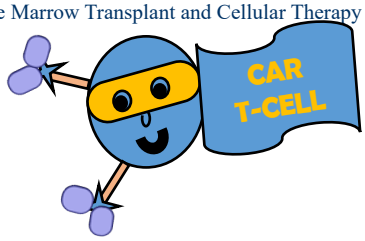

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Overview

- CAR-T Cell Therapy Overview
- Clinical Trial Results and Initial FDA Approvals
- New Indications and 2021 Approvals
- Toxicities and Current Management
- UNC Clinical Trials

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CAR-T Cell Therapy Overview

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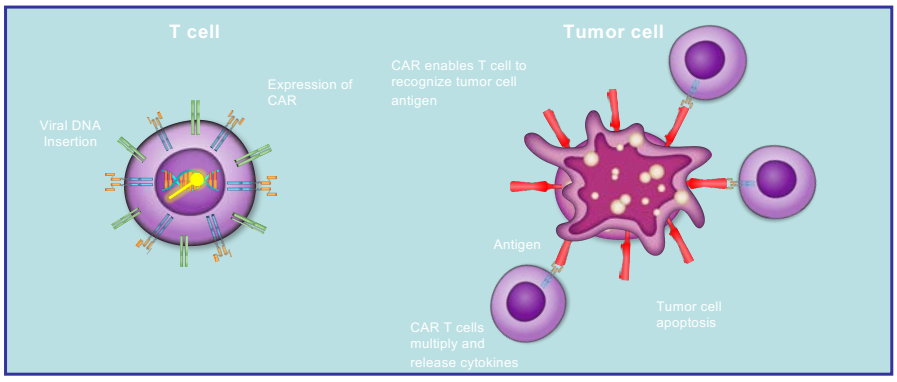
Chimeric Antigen Receptor T cells



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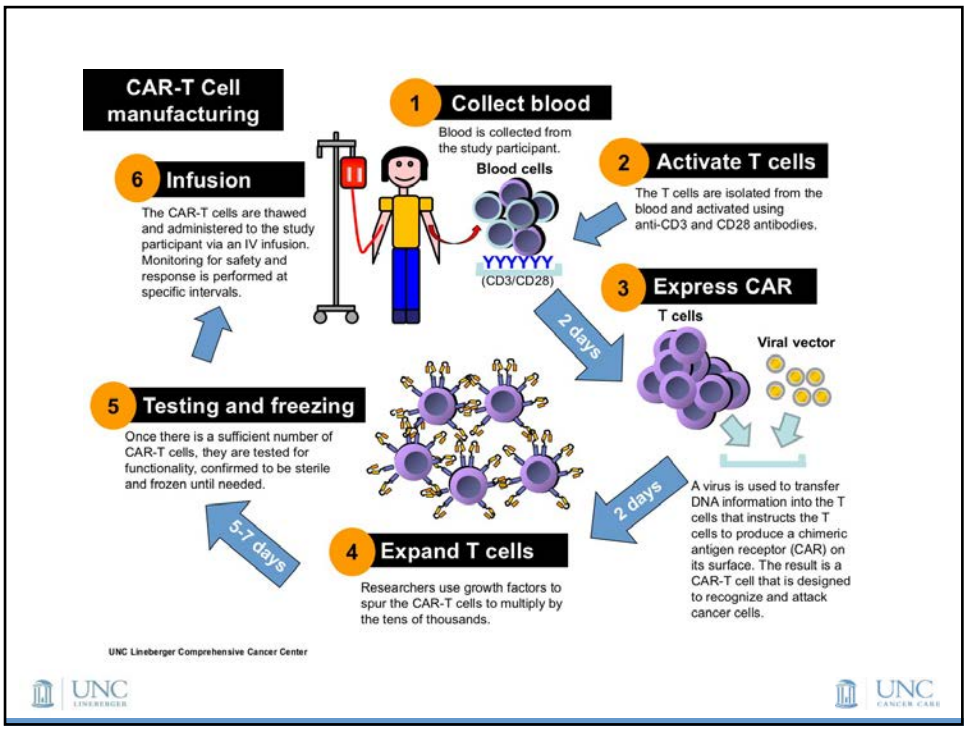

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Characteristics of Ideal Target

- Expression on malignant cells
- Limited off target expression/toxicity
- CD19 – cell surface marker present on B cells -> potential target in B-cell malignancies such as B-ALL and B-cell lymphoma

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Clinical Activity of CAR-T Cells

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Case Example

- 18 yo F initially diagnosed with ALL in 2010 at age 11
- Treated with aggressive pediatric regimen and achieved remission
- However, relapsed 1 year post therapy – underwent transplant
- 5 years later, found to have relapsed on routine blood work

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CTL019 (Tisagenlecleucel, KYMRIAH®)

KYMRIAH™

- Pivotal phase 2 study:
  - ELIANA (NCT02435849)
- Evaluable patients: N = 63
  - 10% primary refractory disease
  - 48% one prior stem cell transplantation
  - 8% two prior stem cell transplantations
- 18 month follow up at ASH 2019 – 66% PFS and 70% OS

Results	N = 63
CR/Cri[a,b] (95% CI)	52 (83%) (71%, 91%) *P*<0.0001
CR[c]	40 (63%)
CRi[d]	12 (19%)
CR or CRi with MRD-negative bone marrow[e,f] (95% CI)	52 (83%) (71%, 91%) *P*<0.0001
Duration of Remission[g]	N = 52
Median (months) (95% CI)	Not reached (7.5, NE[h])

[a]CR/CRi was calculated based on all patients who received KYMRIAH and completed at least 3 months follow-up, or discontinued earlier prior to the data cutoff. Requires remission status to be maintained for at least 28 days without clinical evidence of relapse. [b]The null hypothesis of CR/CRi less than or equal to 20% was rejected. [c]CR was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and ANC >1,000/microliter) without blood transfusion. [d]CRi (complete remission with incomplete blood count recovery) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion. [e]MRD negative was defined as MRD by flow cytometry less than 0.01%. [f]The null hypothesis of MRD-negative remission rate less than or equal to 15% was rejected. [g]Duration of remission was defined as time since onset of CR or CRi to relapse or death due to underlying cancer, whichever is earlier, censoring for new cancer therapy including stem cell transplantation (N = 52). [h]Not Estimable.

1. KYMRIAH [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2017.
2. Buechner J, et al. *Haematologica.* 2017:102(s2): Abstract S476.

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FDA Approval

- August 30, 2017 – FDA approved first anti-CD19 CAR-T cell product, tisagenlecleucel (Kymriah), for the treatment of pediatric and young adult patients (under 25) with relapsed/refractory B-cell precursor acute lymphoblastic leukemia

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Case Example

- 56 yo F with stage IV double hit DLBCL
- Treated with 6 cycles of DA-R-EPOCH with progressive disease at end of therapy
- Treated with R-ICE salvage with no response
- What would be your recommendation for therapy?

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FDA Approval

- October 18, 2017 – FDA approves CD19+ CAR-T cell therapy Yescarta (Axicabtagene ciloleucel) to treat adults with certain types of large B-cell lymphoma
- On May 1, 2018 – FDA expanded approval of Kymriah (tisagenlecleucel) to treat adults with relapsed/refractory large B cell lymphoma

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2021 Update: New CD19+ Product for DLBCL

- February 5, 2021: FDA approves Breyanzi (Lisocabtagene maraleucel) for treatment of R/R DLBCL after 2 or more lines of therapy

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	Axicabtagene ciloleucel ZUMA-1 trial[3,4]			Tisagenlecleucel JULIET trial[5,6]		Lisocabtagene maraleucel TRANSCEND NHL 001 trial[10]				
US FDA approved	Yes			Yes		No				
CAR construct	Anti-CD19, CD28, CD3z			Anti-CD19, 4-1BB, CD3z		Anti-CD19, 4-1BB, CD3z (tEGFR)				
Costimulatory domain	CD28			4-1BB		4-1BB				
Vector	Retrovirus			Lentivirus		Lentivirus				
CAR T-cell manufacturing	Bulk, fresh			Bulk, cryopreserved		CD8+ and CD4+ T cells: separate, fresh				
CAR T-cell dose	2.0 × 10^6 cells/kg, max 2.0 × 10^8 cells			0.6-6 × 10^8 cells		1.0 × 10^8 CD8+ and CD4+ cells				
Bridging therapy	No			Yes: 92%		Yes: 59%				
Lymphodepletion	Flu/Cy (30 mg/m², 500 mg/m²) × 3 d			Flu/Cy (25 mg/m², 250 mg/m²) × 3 d or bendamustine (90 mg/m²) × 2 d		Flu/Cy (30 mg/m², 300 mg/m²) × 3 d				
Secondary CNS lymphoma	No			No		Yes: small number				
ALC cutoff for manufacturing, per µL	ALC ≥100			ALC ≥300		None				
Lymphoma subtypes enrolled	DLBCL/ HGBCL	PMBL	tFL	DLBCL/ HGBCL	tFL	DLBCL	HGBCL	t-iNHL	PMBL	FL3B
Evaluable patients, n	77	8	16	89	22	137	36	78	15	3
Follow-up time, mo	15.4			14		12.3				
Efficacy, n	101			93		256				
Best ORR, % (CR%)	82 (54)			52 (40)		73 (53)				
DOR at 12 mo	11.1 mo/NR*			NR		NR (all patients)				
						5.6 mo	10.8 mo	NR (tFL)	NR	—
DOR for CR at 12 mo	NR			NR		NR				
OS at 12 mo, %	59			49		58				
Median follow-up for trial, mo	27			24		12				
Safety, n	101			111		269				
CRS ≥grade 3, %	13†			22‡		2‡				
CRS time to onset median duration (range)	2 d (range, 1-12)			3 d (range, 1-9)		5 d (range, 1-14)				
	8 d (not reported)			7 d (range, 2-30)		5 d (1-17)				
Neurotoxicity ≥grade 3, %	28			12		10				
Neurotoxicity time to onset median duration (range)	5 d (range, 1-17)			6 d (range, 1-17)		9 d (range 1-66)				
	not reported			14 d (not reported)		11 d (range, 1-86)				

Chong and Porter, ASH education book, 2020

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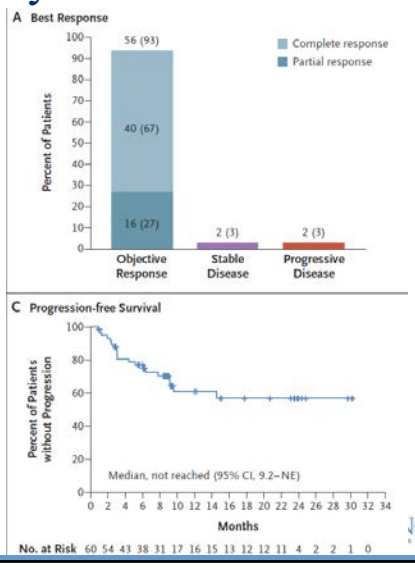
2020 Approval: Brexucabtagene autolecel (Tecartus) for Relapsed/Refractory Mantle Cell

- Manufacturing process removes circulating CD19 expressing malignant cells, reducing possible activation and exhaustion of CAR-T cells
- ORR 93%, CR 67%; 12 month PFS 61%
- Similar toxicities to axi-cel



Wang et al., NEJM 2020

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New Indications and 2021 Approvals

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Axi-Cel for Follicular Lymphoma

- March 5, 2021– FDA approved Yescarta (Axi-cel) CD19+ CAR-T therapy for relapsed/refractory Follicular Lymphoma after 2 or more lines of therapy

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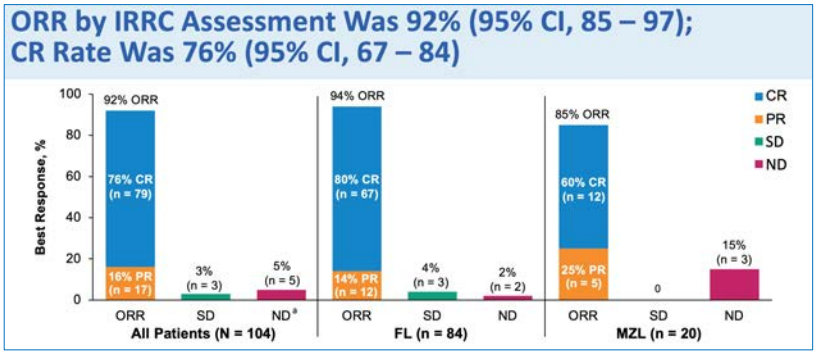
Zuma-5: Axi-cel for Follicular Lymphoma: Efficacy



12 month PFS 78% for Follicular Lymphoma

Jacobson et al., ASH 2020

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Zuma-5: Axi-cel for Follicular Lymphoma: Safety

Parameter	FL (n = 124)	MZL (n = 22)
CRS, n (%)[a]		
Any grade	97 (78)	22 (100)
Grade ≥ 3	8 (6)	2 (9)
Most common symptoms of any grade, n/n (%)		
Pyrexia	94/97 (97)	20/22 (91)
Hypotension	39/97 (40)	10/22 (45)
AE management, n (%)		
Tocilizumab	56 (45)	15 (68)
Corticosteroids	19 (15)	6 (27)
Median time to onset (range), days	4 (1 – 15)	4 (1 – 9)
Median duration of events (range), days	6 (1 – 27)	6 (2 – 14)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)

- Grade 4 and Grade 5 CRS occurred in 1 patient each

Parameter	FL (n = 124)	MZL (n = 22)
Neurologic events, n (%)[a]		
Any grade	70 (56)	17 (77)
Grade ≥ 3	19 (15)	9 (41)
Most common events of any grade, n/n (%)		
Tremor	36/70 (51)	9/17 (53)
Confusional state	28/70 (40)	7/17 (41)
AE management, n (%)		
Corticosteroids	38 (31)	14 (64)
Tocilizumab	7 (6)	2 (9)
Median time to onset (range), days	7 (1 – 177)	7 (3 – 19)
Median duration of events (range), days	14 (1 – 452)	10 (2 – 81)
Patients with resolved events, n/n (%)	67/70 (96)	14/17 (82)

- Grade 4 neurologic events were reported for 3 patients; no Grade 5 events were reported

Jacobson et al., ASH 2020

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First BCMA CAR Approved for Multiple Myeloma

- March 26, 2021: FDA approves Abecma (Idecabtagene vicleucel) for treatment of Multiple Myeloma after four or more lines of therapy
- Including: Immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

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Abecma

- BCMA expressed by mature B cells -> overexpression and activation associated with MM
- Data based on KarMMa Trial
- Median follow up 11.3 months
- 128 patients treated at target dose -> ORR 73.4%, 31.3% CR
- Median PFS 8.6 months

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Toxicities and Management

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Case Example

- 51 yo F with relapsed/refractory DLBCL
- Initially treated with R-CHOP x 5 cycles with progressive disease and received 4 cycles of R-GDP with progressive disease
- Initially evaluated for autoSCT but given refractory disease to salvage, decision made to proceed with CAR-T
- Decision made to treat with axi-cel (Yescarta)
- PET/CT prior to treatment showed bulky RP adenopathy

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Case Example

- 48 hours after infusion developed fevers.
- Treated with Tylenol and started on IV cefepime for empiric coverage
- Fevers persisted for 3 days through day 5 and subsequently developed hypotension with BP in the 90's systolic. Did not require pressors.
- How would you treat this patient?

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Case Example

- Received dose of tocilizumab with response of hypotension and fevers
- On day 7, she developed altered mental status, agitation, and aphasia with ICE score decreasing from 10/10 to 4/10 to 0/10 and requiring transfer to MICU for closer monitoring
- CT head and MRI brain unremarkable, EEG with diffuse slowing consistent with encephalopathy

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Case Example

- Patient received dexamethasone 10 mg q6h with improvement over the next 24-48 hours with improvement close to baseline by day 10 post CAR-T cell infusion

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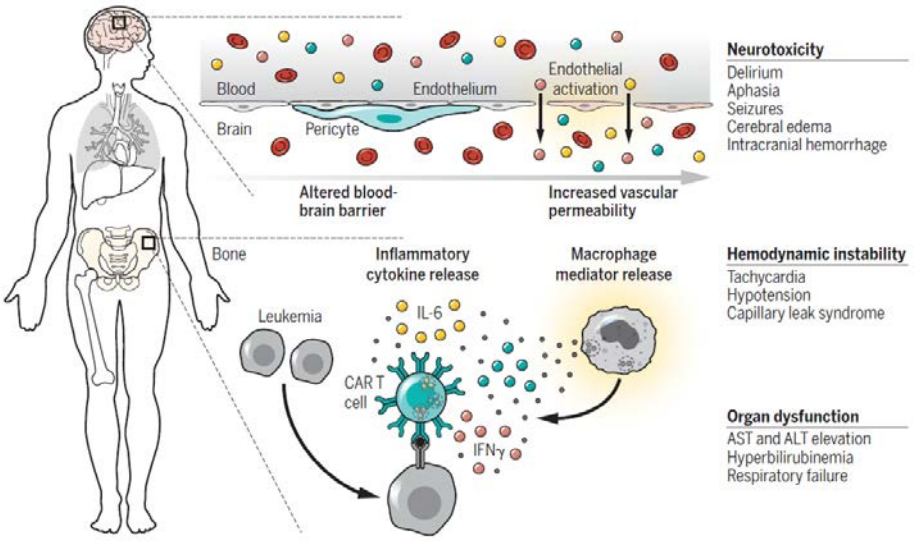
Cytokine Release Syndrome



June et al., Science 2018

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FDA Approval of Tocilizumab

- August 30, 2017: At the same time FDA approved tisagenlecleucel, FDA also approved tocilizumab (anti-IL6 receptor antibody) for treatment of cytokine release syndrome

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HLH/MAS-like Toxicity

- Generally overlap with CRS
- High fevers, pancytopenia, high ferritin, LFT abnormalities, delayed coagulopathy
- Can be later onset than CRS
- Generally treat with tocilizumab
- Consider anakinra

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Neurotoxicity/ICANS

- Typically present with toxic encephalopathy -> diminished attention, language disturbance, impaired handwriting
- Confusion, disorientation, agitation, aphasia, somnolence, tremors
- Severe symptoms: seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, cerebral edema

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ICE Score

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point

Lee et al., BBMT 2019

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Example of Dysgraphia

b

Day 4, MMSE 29/30

I love Shawnee, KS.

Day 5, MMSE 27/30

Day 6, MMSE 29/30

I miss my kids.

Neelapu et al., Nature Reviews Clinical Oncology 2017

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Management of Neurologic Toxicity of CAR-T cells

- Work up depends on presentation: MRI, lumbar puncture, EEG
- Treat with tocilizumab if concurrent CRS
- First line agent: systemic corticosteroids (dexamethasone) – usually give for grade 2 or higher and no concurrent CRS or if tocilizumab doesn't work in patients with concurrent CRS
- Treat seizures with standard anti-epileptic therapy

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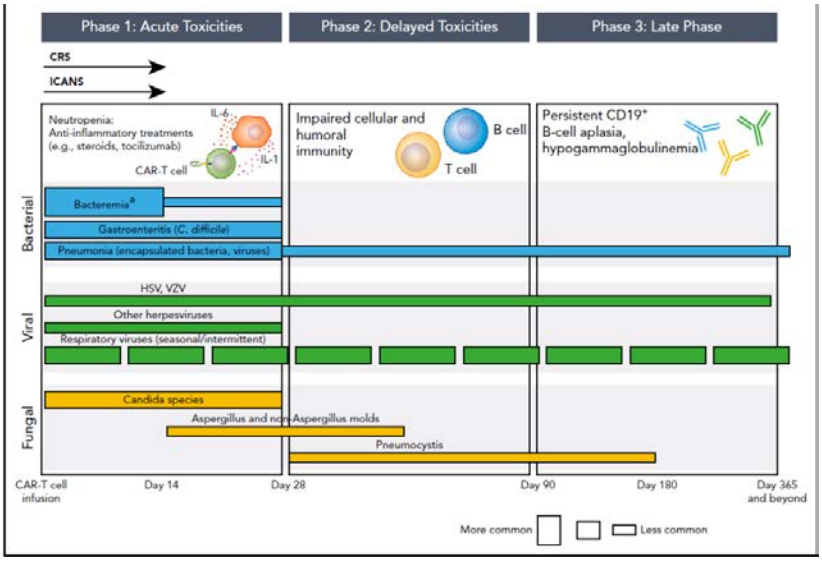
Infection Risk



Hill and Seo, Blood 2020

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Cytopenias

- Cytopenias persist > 1 month in ~1/3 of patients who get CD19-directed CAR-T cells
- Biphasic pattern
- Consider GCSF for persistent neutropenia after day 28

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Future Directions and UNC Trials

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Anticipated Upcoming Approvals

- JNJ-428 is a BCMA CAR developed by Janssen
- Trial: CARTITUDE-1
- Phase 1b/2 data: (n=29)
  - ORR: 100%
  - CR: 69% (66% stringent CR)
  - VGPR: 86% or better
  - PR: 14%
  - 27/29 pts were progression free at 6mon

Madduri et al., ASH 2020

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Anticipated Upcoming Approval

- Tisa-cel for follicular lymphoma
- ORR/CR of 82.7% and 65.4%
- 6 month PFS 73.2%
- No grade $\geq$ 3 CRS
- Low < 10% any grade and 1% grade $\geq$ 3 ICANS

Fowler et al., ASCO 2020

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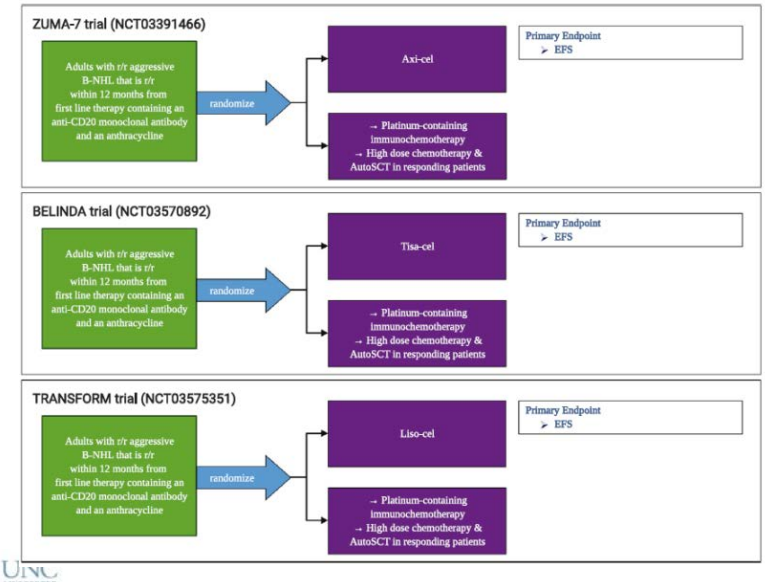
Comparing CAR-T to Transplant in DLBCL



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CD30 CAR-T Cell Trials

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

original reports

Carlos A. Ramos, MD[1,2]; Natalie S. Grover, MD[3,4]; Anne W. Beaven, MD[3,4]; Premal D. Lulla, MD[1,2]; Meng-Fen Wu, MS[1,5]; Anastasia Ivanova, PhD[1,6]; Tao Wang, PhD[1,5]; Thomas C. Shea, MD[3,4]; Cliona M. Rooney, PhD[1,2,3]; Christopher Dittus, DO[3,4]; Steven I. Park, MD[3]; Adrian P. Gee, PhD[1,7]; Paul W. Eldridge, PhD[3]; Kathryn L. McKay, MS[3]; Biju Mehta, MS[1]; Catherine J. Cheng, MS[3]; Faith B. Buchanan, PA[3]; Bambi J. Grilley, RPh[1]; Kaitlin Morrison, PhD[3]; Malcolm K. Brenner, MD, PhD[1,2,3,7]; Jonathan S. Serody, MD[3,4,8]; Giampietro Dotti, MD[3,9]; Helen E. Heslop, MD[1,2,3,7]; and Barbara Savoldo, MD, PhD[3,9,10]

Journal of Clinical Oncology®

July 2020

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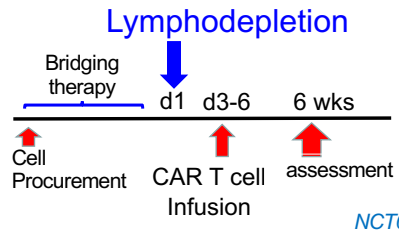
CD30.CAR-T Cells



Bendamustine (90 mg/m²/day) x 2 days
or
Bendamustine (70 mg/m²/day) x 3 days
Fludarabine (30 mg/m²/day) x 3 days

Cyclophosphamide (500 mg/m²/day) x 3 days
Fludarabine (30 mg/m²/day) x 3 days

NCT02690545
Feb 2016

UNC LINEBERGER

Baylor College of Medicine

NCT02917083
Sept 2016

- Phase 1/2 trials run in parallel at BCM and UNC
- CD30⁺ lymphomas
  - Progressed after 2 lines of tx
  - Any level of CD30 expression
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

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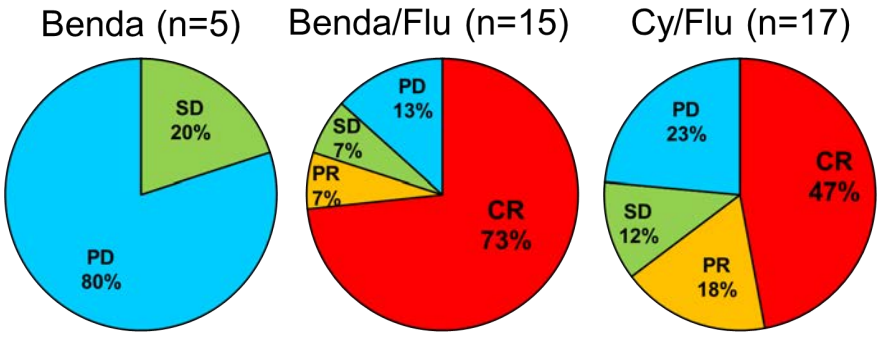
Clinical Responses



Patients with active disease at time of treatment

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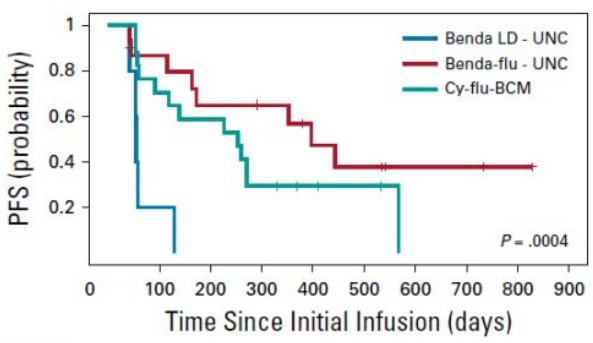
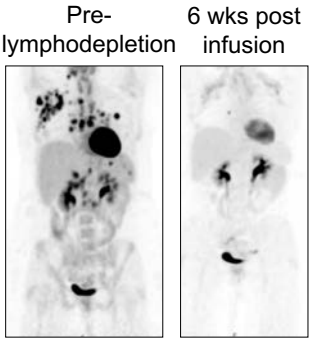
Clinical Responses





Patients had active disease and complete response
N=19, Median PFS: 444 days, 95% CI: 260 - NA

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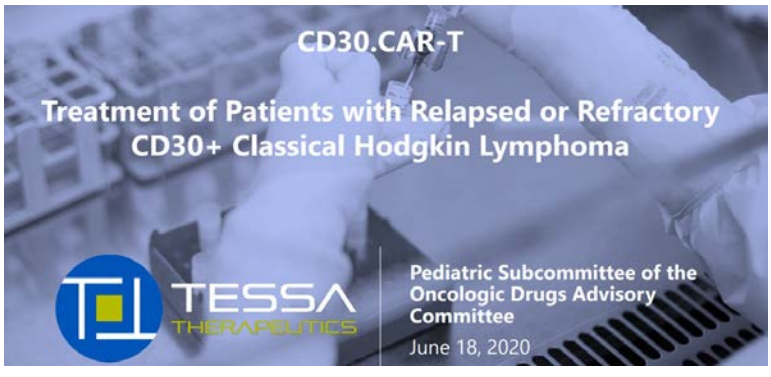
FDA granted RMAT designation to CAR T-cell therapy for HL



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Can we be effective without causing toxicities?

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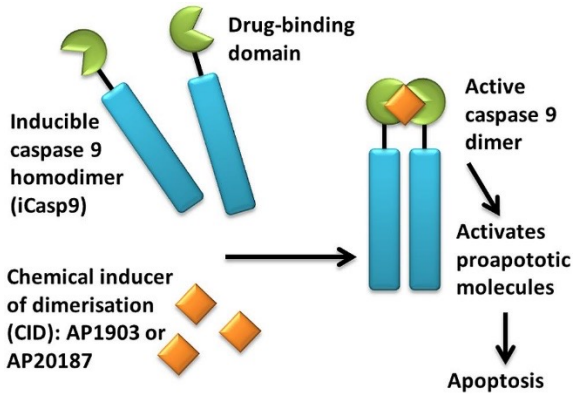
CARs with a Safety Switch

- CAR-T cells with inducible caspase 9 safety switch



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CD19.CAR-T with iC9 Safety Switch

- 26 yo F with refractory B-ALL received CD19 CAR-T cells with iC9 safety switch
- Developed severe neurotoxicity (ICANS) with non-convulsive status epilepticus with stupor persisting for 72 hours despite standard of care steroids

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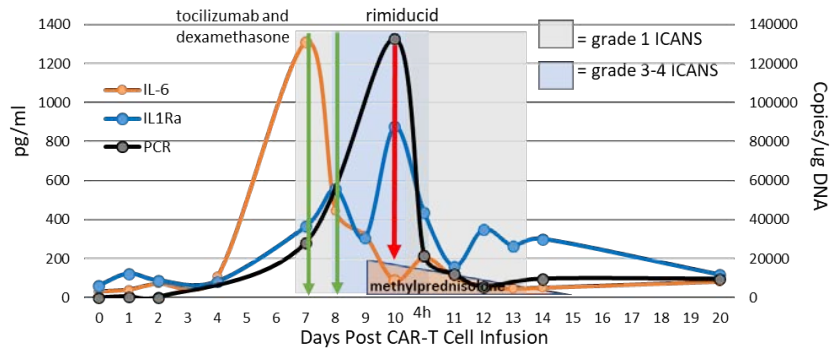
Neurotoxicity Resolved with Rimiducid (Dimerizing Agent)



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Other Open CAR-T Trials

- CD30 CAR with CCR4 – Hodgkin Lymphoma and Cutaneous T cell Lymphoma
- C30 CAR- T cell Lymphoma
- CD138.CAR – Multiple myeloma
- Kappa.CAR – Lymphoma
- GD2.CAR- neuroblastoma and osteosarcoma
- B7H3 CAR – ovarian cancer
- HER2 CAR Macrophage – Solid Tumors

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Challenges of CAR-T Cells in Solid Tumors

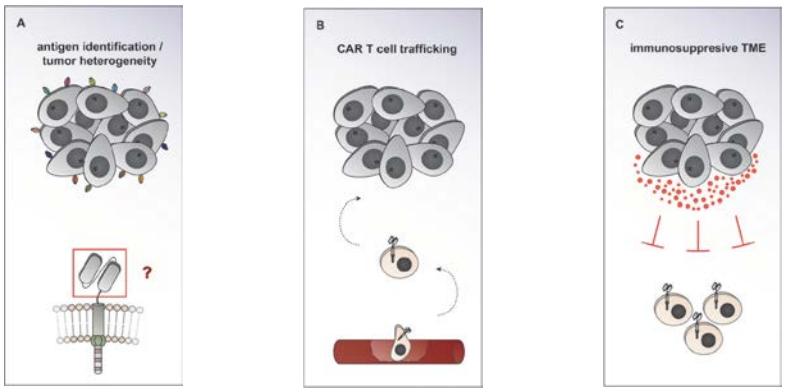

Figure adapted from: Schmidt A, et al. Frontiers in Immunology. 2018. and Carisma Therapeutics

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Summary

- CD19 directed CAR-T cells have shown promising efficacy in the treatment of ALL and B-cell lymphomas
- Many new FDA approved products including new indications for Mantle Cell lymphoma, Follicular Lymphoma, and Multiple Myeloma
- Major toxicities of therapy include cytokine release syndrome and neurotoxicity
- Future directions of CAR-T cells include identifying novel targets and overcoming barriers to efficacy and safety

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