CAR T-Cell and Cellular Therapy Update

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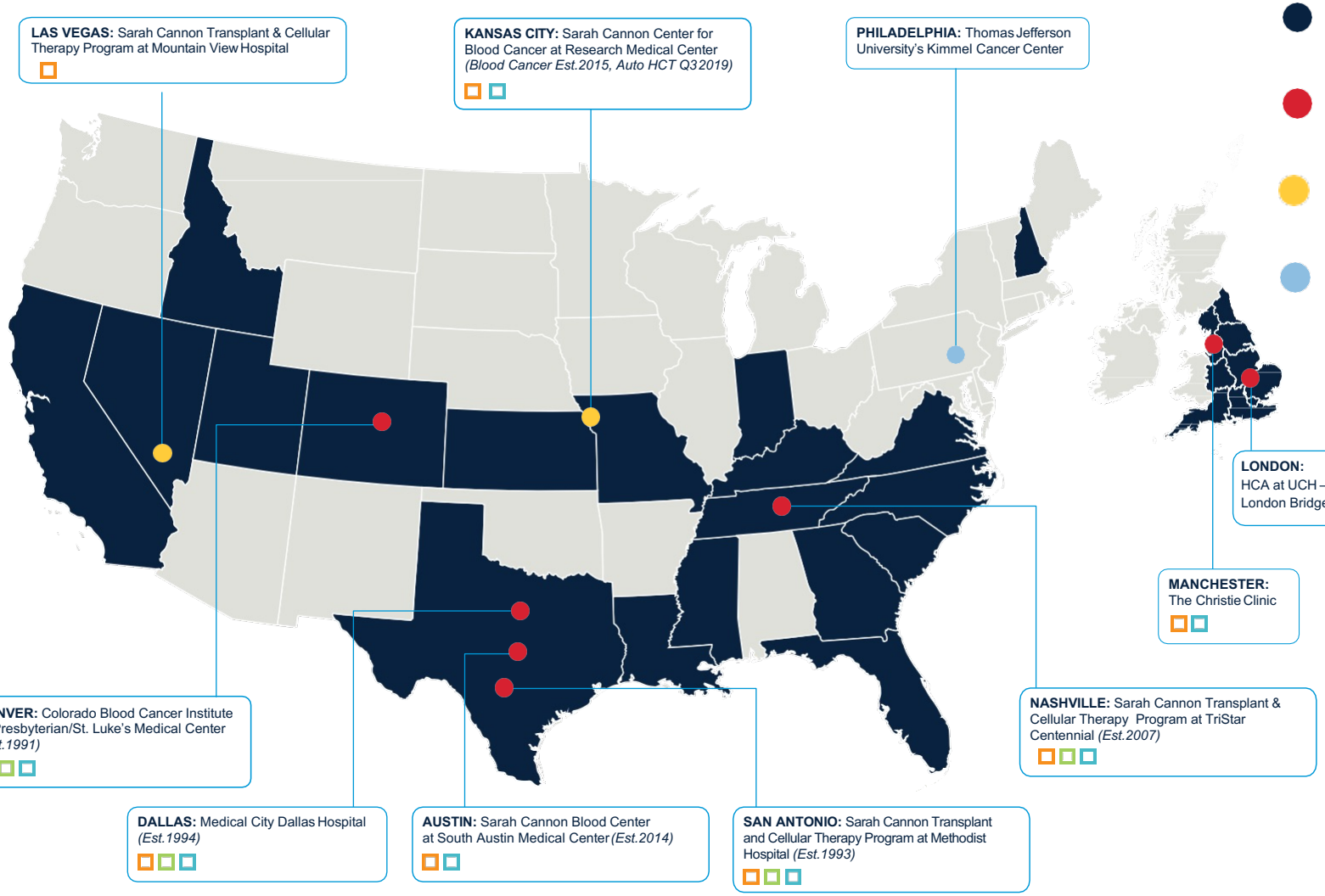
Transplant & Cellular Therapy Network

Sarah Cannon Transplant & Cellular Therapy Network



1,400+

HCTs & cellular therapies performed in 2021

16K+

HCTs & cellular therapies performed since 2011

1

Comprehensive network approach to patient care

Sarah Cannon Transplant & Cellular Therapy Network 10 YEARS 2011-2021

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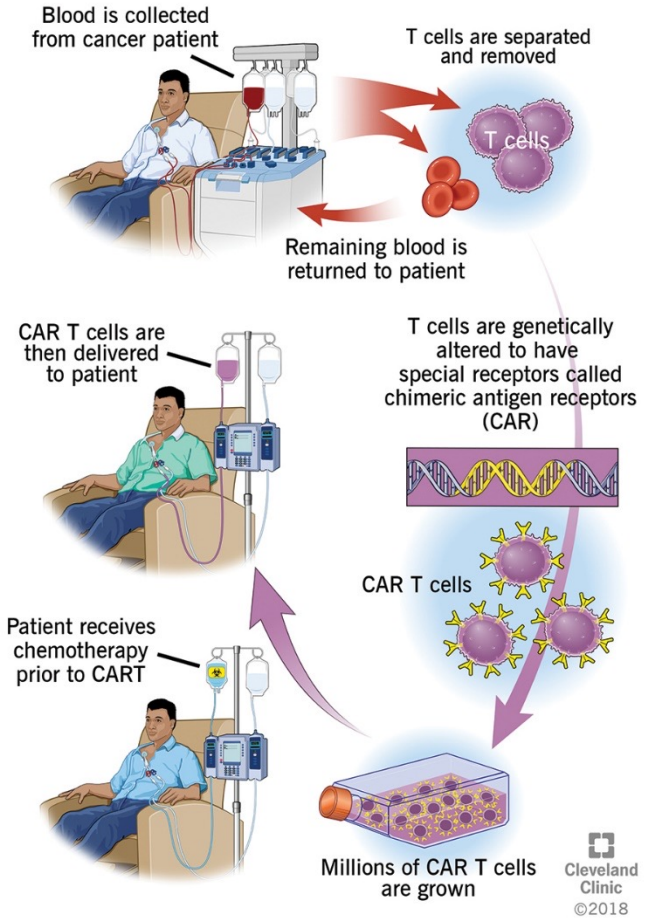
Adult Pediatric FACT/JACIE Accreditation

CAR T-Cell Therapy

- T-cells isolated → genetically engineered to recognize tumor specific antigens on cancer cells → cultured & expanded → infused back to patient
  - Autologous – cells derived from patient
  - Allogeneic “Off-the-shelf” – cells derived from donor(s)



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The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

SA Grupp et al. New Engl J Med, 2013

The New York Times

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia. Jeff Swensen for The New York Times

By Denise Grady
Dec. 9, 2012

emilywhiteheadfoundation.org

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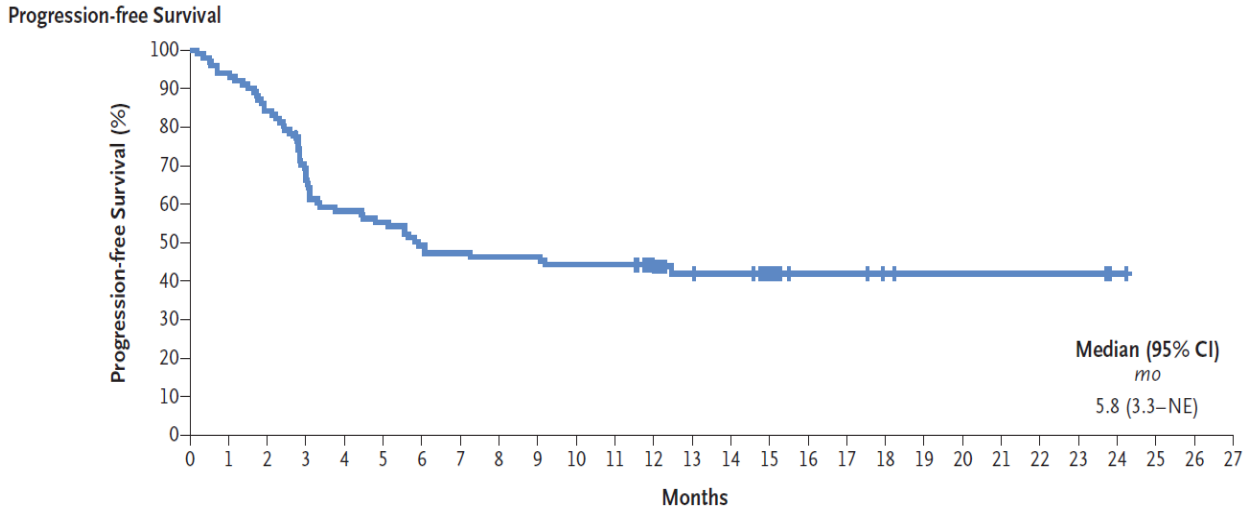
ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

SS Neelapu et al. New Engl J Med, 2017



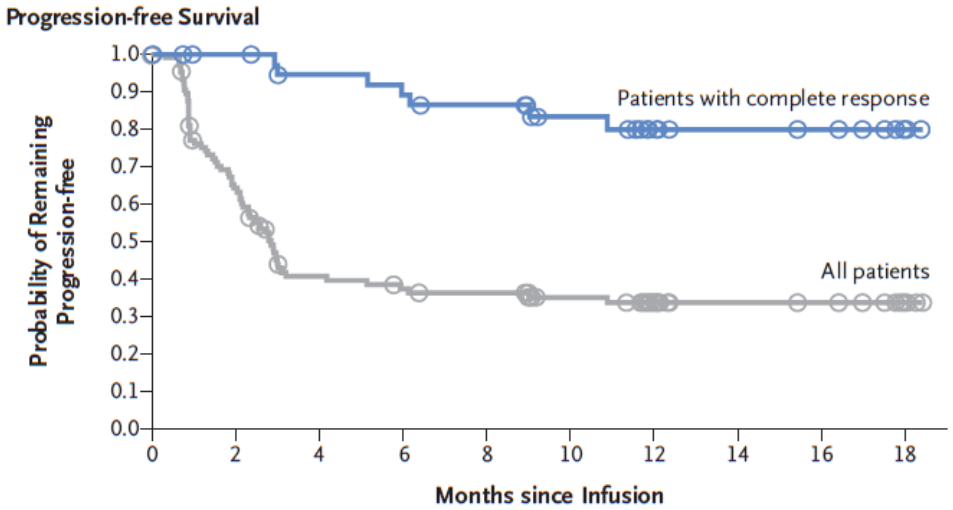
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

SJ Schuster et al. New Engl J Med, 2019



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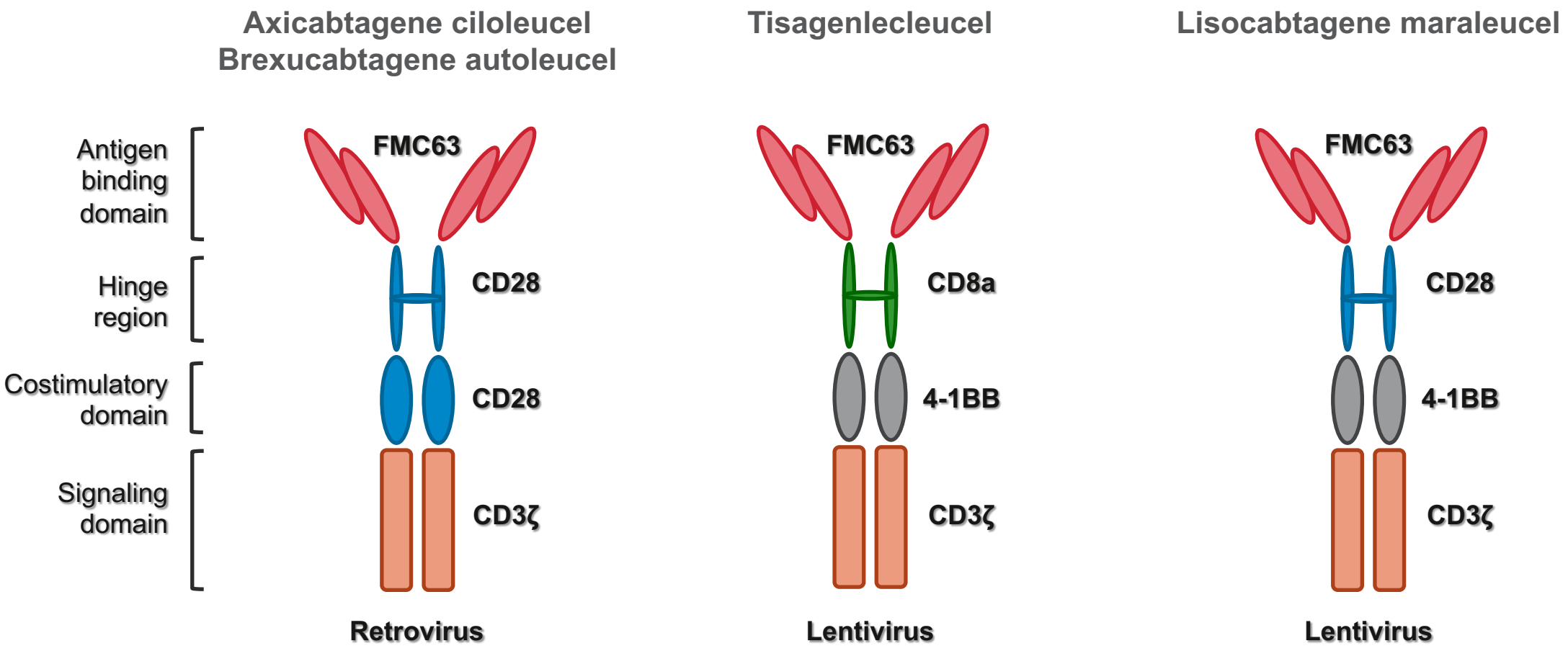
FDA Approved CAR T-cell Products



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FDA Approved CAR T-cell Products

- **Axicabtagene ciloleucel**
  - Adults with LBCL refractory to 1st line therapy or relapse within 12 mos of 1st line therapy
  - Adults with relapsed/refractory LBCL after ≥2 lines of therapy
  - Adults with relapsed/refractory follicular lymphoma after ≥2 lines of therapy
- **Brexucabtagene autoleucel**
  - Adults with relapsed/refractory MCL
  - Adults with relapsed/refractory B-cell ALL
- **Lisocabtagene maraleucel**
  - Adults with LBCL refractory to 1st line therapy or relapse within 12 mos of 1st line therapy; relapsed/refractory after ≥2 lines of therapy
- **Tisagenlecleucel**
  - Up to 25 yrs of age with B-cell ALL that is refractory or in 2nd or late relapse
  - Adults with relapsed/refractory LBCL after ≥2 lines of therapy
  - Adults with relapsed/refractory follicular lymphoma after ≥2 lines of therapy
- **Idecabtagene vicleucel**
  - Adults with relapsed/refractory myeloma after ≥4 lines of therapy
- **Ciltacabtagene autoleucel**
  - Adults with relapsed/refractory myeloma after ≥4 lines of therapy

CAR T-cell Therapy For Lymphoma

CAR T-cells Vs. Autologous HCT In 2L DLBCL

- 2-year EFS for refractory/relapsed disease after 1L therapy is ~20%
  - ~50% are transplant eligible → ~50% respond to salvage therapy and proceed to HCT
- Three randomized trials:
  - **ZUMA 7: Axi-cel vs. SOC**
    - CRR 65% vs. 32% (p<0.001); EFS HR 0.40 (p<0.001)
  - **TRANSFORM: Liso-cel vs. SOC**
    - CRR 66% vs. 39% (p<0.001), EFS HR 0.35 (p<0.001)
  - **BELINDA: Tisa-cel vs. SOC**
    - CRR 28.4% vs. 27.5% (p=0.83); EFS HR 1.07 (p=0.69)

ZUMA 7 vs. TRANSFORM vs. BELINDA trials

- Treatment assignment
  - ZUMA 7: no bridging chemo for axi-cel arm, no crossover allowed to CAR T-cell arm
  - BELINDA & TRANSFORM: Chemo allowed on both arms, crossover allowed if progressive disease after SOC chemo (EFS event in TRANSFORM; no response to 2nd salvage in BELINDA)
  - BELINDA: second salvage allowed prior to proceeding with CAR T-cell vs. auto HCT
- Cell manufacturing
  - Medan time from apheresis to CART infusion: ZUMA 7 29 days, BELINDA 52 days
- EFS endpoint
  - Earlier assessment of endpoint (e.g., stable disease) on BELINDA (wk 12) and TRANSFORM (wk 9) vs ZUMA 7 (wk 21)

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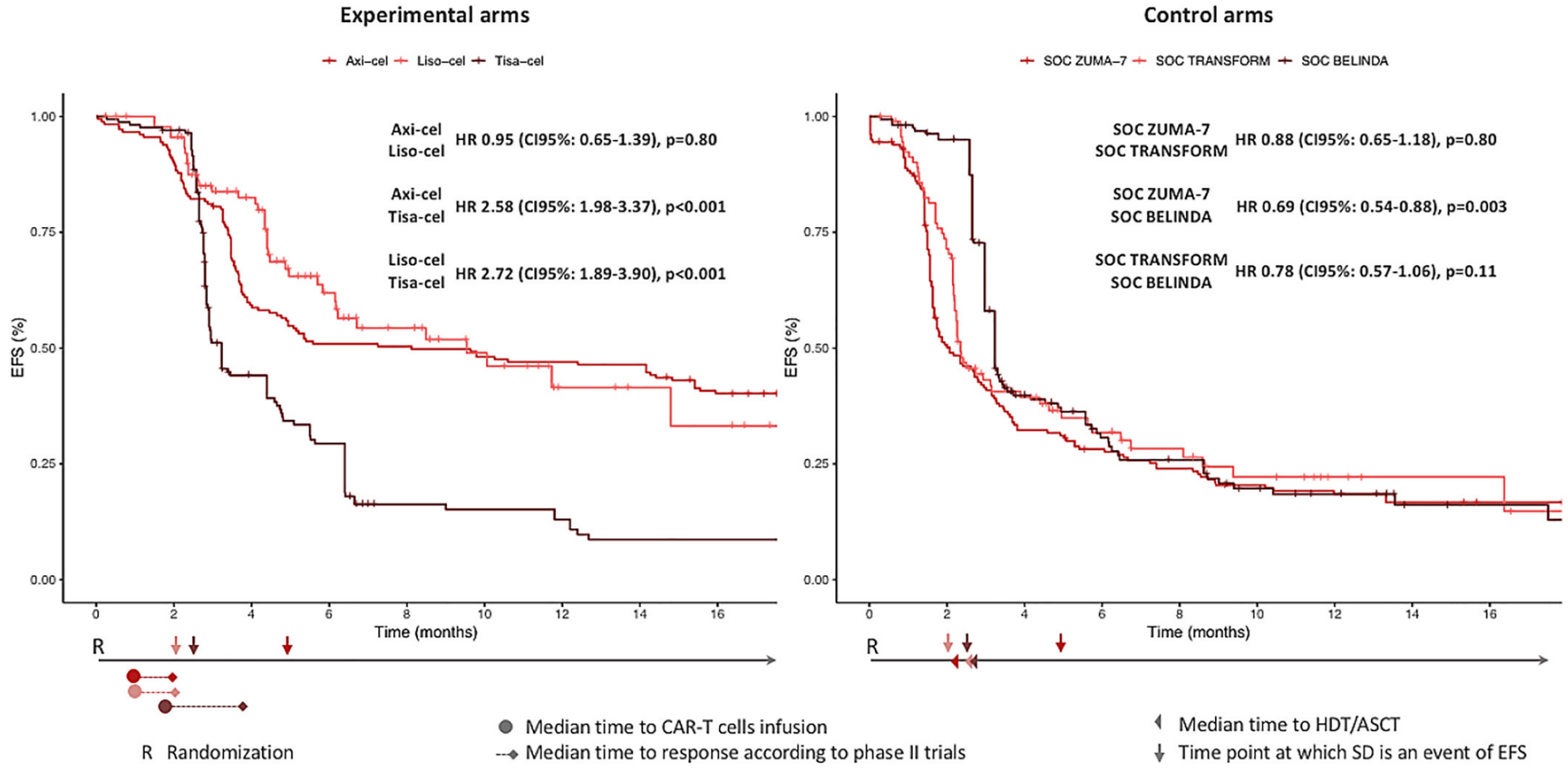
ZUMA 7 vs. TRANSFORM vs. BELINDA trials



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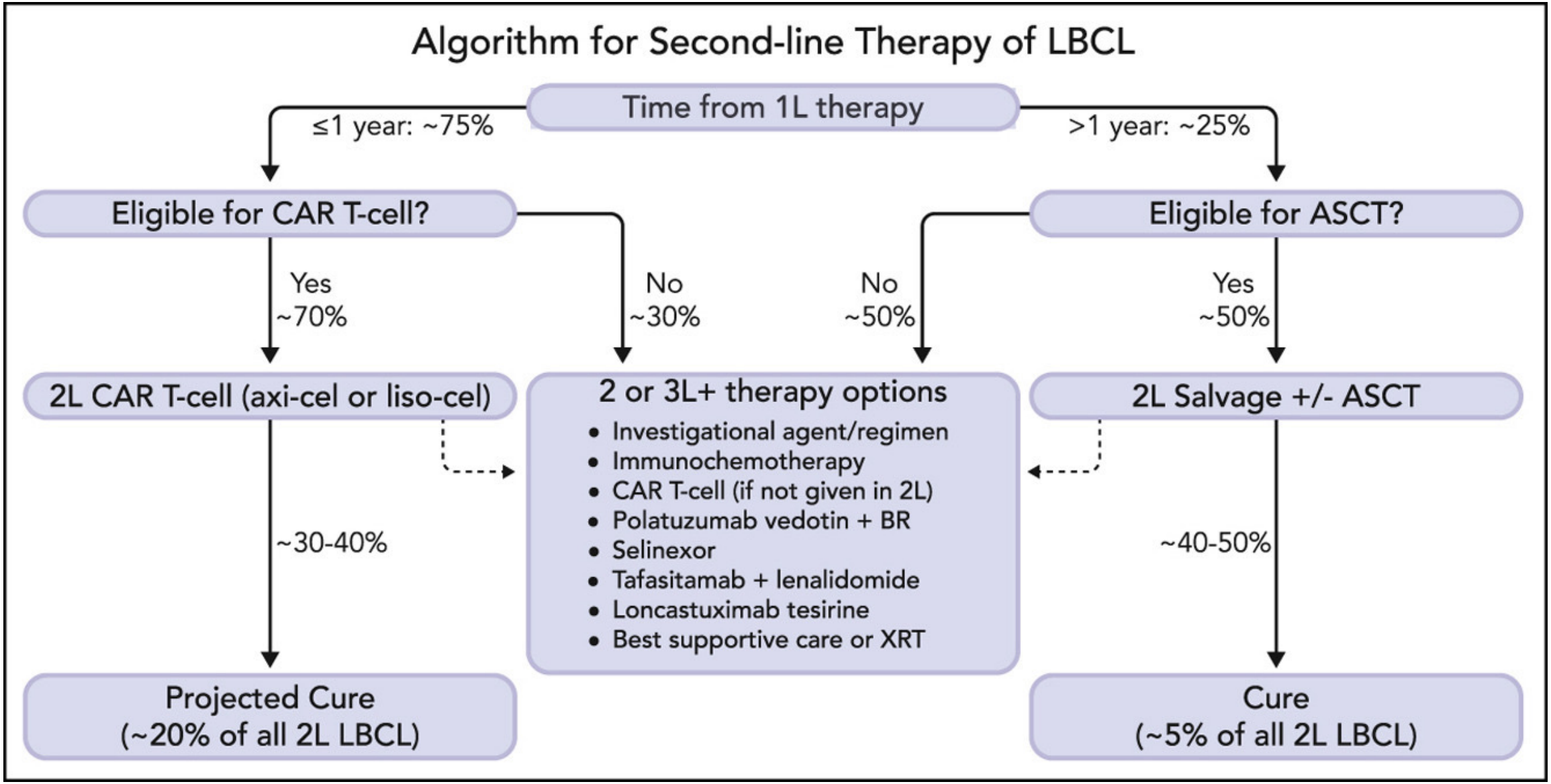

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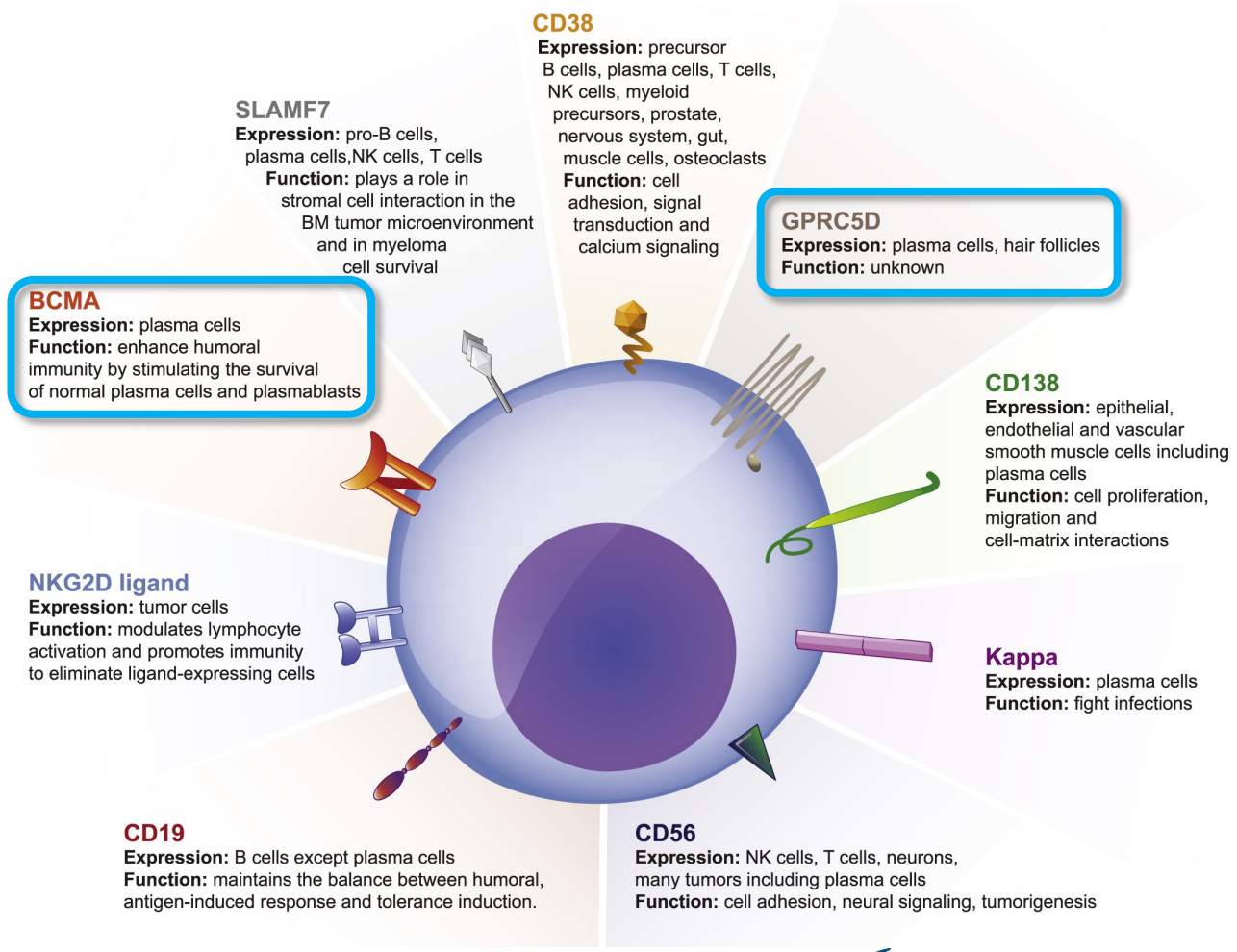
CAR T-cell Therapy For Multiple Myeloma

Immunotherapy Targets In Myeloma

- BCMA
  - Member of TNF receptor family
  - Expressed on cell surface
  - Expressed exclusively on plasma cells
  - Higher expression on myeloma cells
  - Expression increases MGUS → myeloma
- CAR T-cell constructs
  - Ide-cel: murine scFv single binding domain
  - Cilta-cel: two camelid VH binding domains
    - Higher activity and less immunogenicity



 Shah et al, Best Prac Res Clin Hematol, 2020

Clinical Trials: Ide-cel Vs. Cilta-cel

Patient Characteristics	KarMMA (Ide-cel, N=128)	CARTITUDE-1 (Cilta-cel, N=97)
Median age	61 years	61 years
Median prior lines of Rx	6	6
Bridging therapy	87%	75%
Triple-refractory disease	84%	88%
Penta-refractory disease	26%	42%
High risk cytogenetics	35%	24%

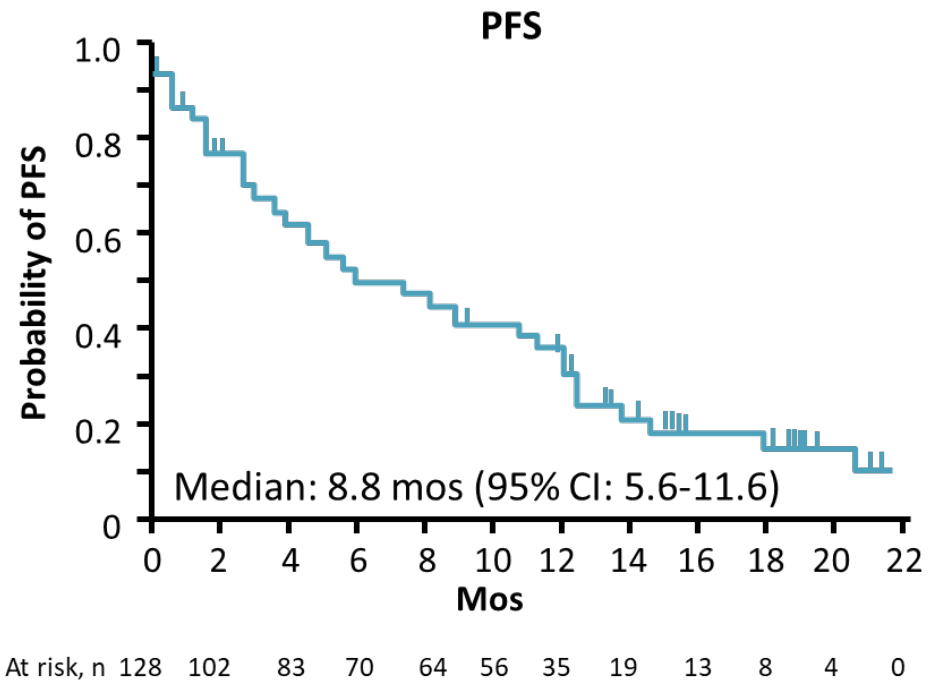
Outcomes	KarMMA (Ide-cel, N=128)	CARTITUDE-1 (Cilta-cel, N=97)
ORR/CR	73%/33%	97%/78%
MRD negativity	28%	58%
Median PFS	9.2 mos	24 mos
CRS all/grade 3-4	85%/6%	95%/5%
ICANS all/grade 3-4	19%/3%	17%/2%
Grade 3-4 neutropenia	40%	30%

FDA Approval: Relapsed/refractory to ≥4 lines of therapy, including IMID, proteasome inhibitor, and anti-CD38 monoclonal antibody

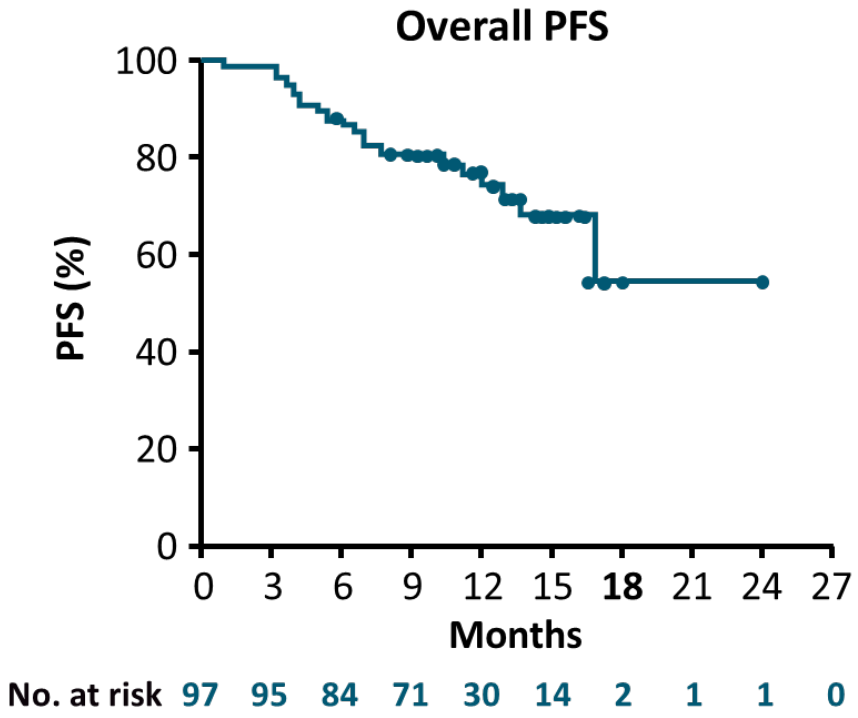
Munshi et al, New Engl J Med, 2021
Berdeja et al, Lancet, 2021

Clinical Trials: Ide-cel Vs. Cilta-cel

KarMMA Trial



CARTITUDE-1 Trial



 Munshi et al, New Engl J Med, 2021
Berdeja et al, Lancet, 2021

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Preliminary Results of KarMMA-3 Trial

- Phase 3 RCT focusing on patients who have received at least 2 but no more than 4 prior lines of therapy (including IMID, proteasome inhibitor, and daratumumab)
- Patients randomized to ide-cel vs. standard regimens (daratumumab, pomalidomide, dexamethasone, bortezomib, ixazomib, lenalidomide, carfilzomib, or elotuzumab
- Prespecified interim analysis showed improvement in ORR and PFS

https://news.bms.com/news/details/2022/Bristol-Myers-Squibb-and-2seventy-bio-Announce-Topline-Results-from-KarMMa-3-Trial-Showing-Abecma-idecabtagene-vicleucel-Significantly-Improves-Progression-Free-Survival-Versus-Standard-Regimens-in-Relapsed-and-Refractory-Multiple-Myeloma/default.aspx

Future Directions In CAR T-cell Therapy

Late Complications Of CAR T-cell Therapy

Late Effects	Screening and Preventative Care at Specific Time-points
Prolonged Cytopenia	CBC with diff every 30 days until normalization of blood counts
Hypogammaglobulinemia	Immunoglobulin levels monthly beyond day 30, until IgG>400 mg/dl
Neuropsychiatric Late Effects	Clinical evaluation for neuropsychiatric dysfunction at least monthly, with diagnostic tests [e.g. neuropsychological testing, MRI] as indicated
Immune-related Adverse Events	Clinical evaluation for immune-relate adverse events such as pneumonitis or colitis at least every month until one year and every six months
Second Cancer	Age and sex-appropriate screening for solid cancers; Periodic monitoring of CBC to screen for therapy-related myeloid neoplasms
Late Infections	CD4+ T-cell count monthly beyond day 30 until CD4 count > 200 cells/µL

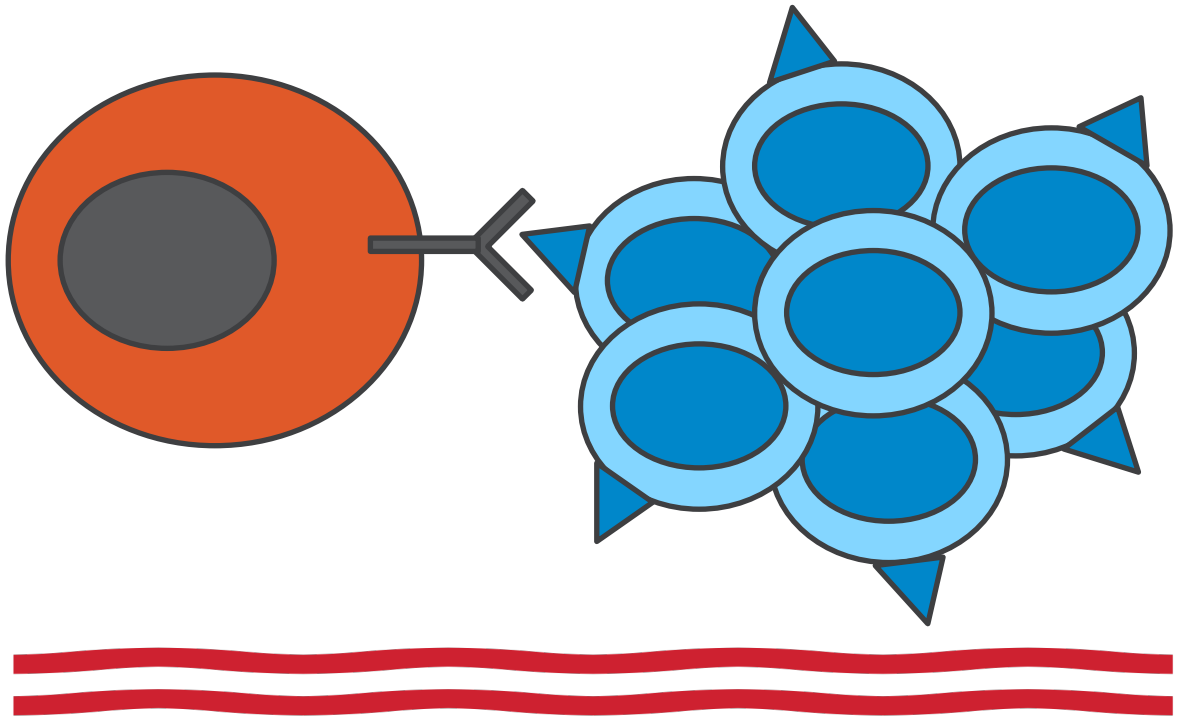
Overcoming Resistance To CAR T-cell Therapy

CAR T-cell

Baseline defects
- Allogeneic T-cells
- CAR-NK cells

T-cell exhaustion
- Combine checkpoint blockade with CART
- Genetic modification (↑PD1 expression)

T-cell subsets
- PI3K inhibitors during ex vivo CART generation



Tumor

Antigen escape
- Target alternate tumor antigen
- Target multiple antigens

Antigen masking
- T-cell selection prior to expansion

TME

Cancer associated fibroblasts
- Combine CART + CAF directed Abs

Regulatory T-cells
- Combine CART + CTLA4 Abs

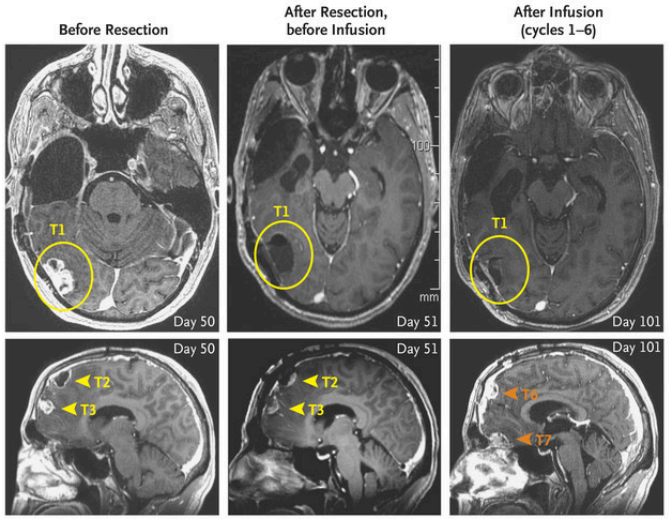
CAR T-cell Therapy For Solid Tumors

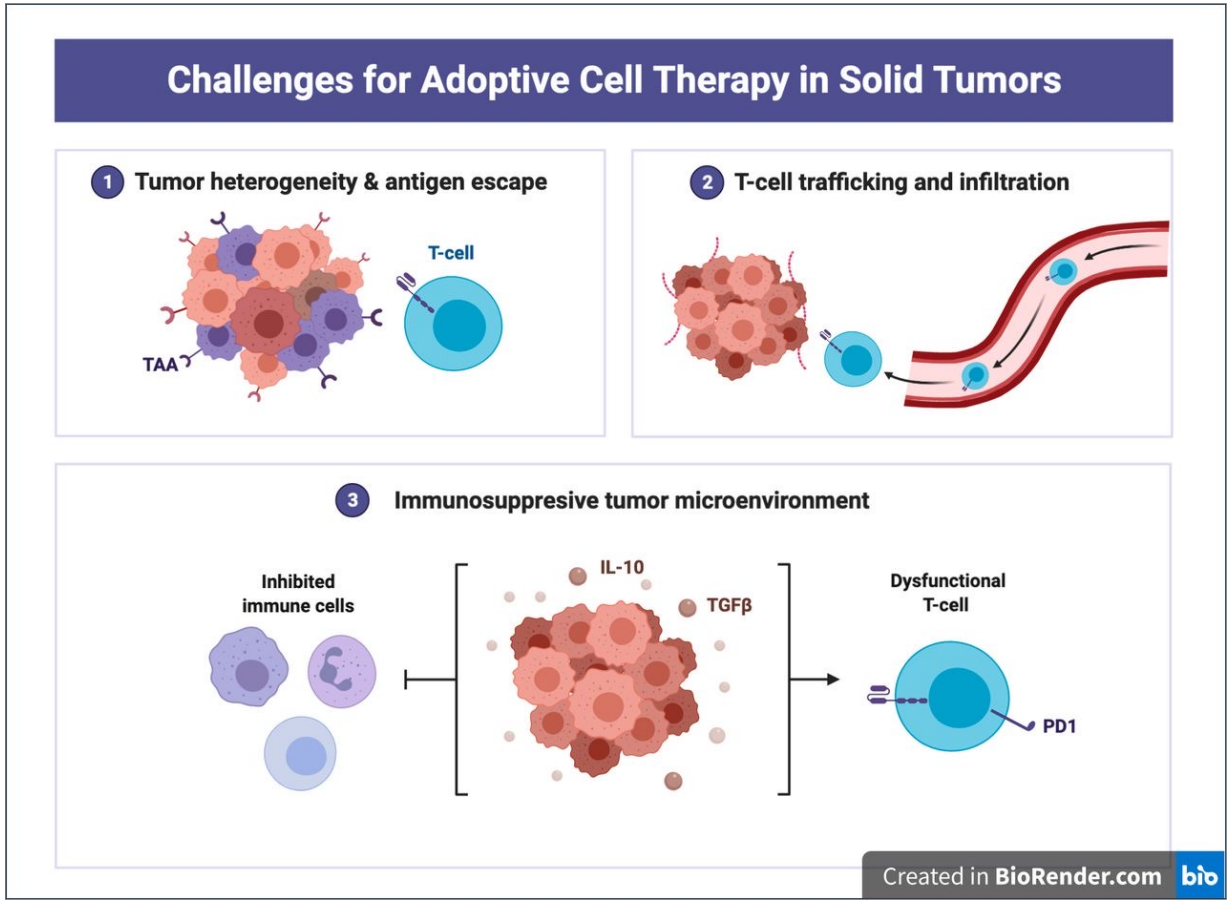
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., Julie A. Ressler, M.D., Michael C. Jensen, M.D., Michael E. Barish, Ph.D., Mike Chen, M.D., Ph.D., Jana Portnow, M.D., Stephen J. Forman, M.D., and Behnam Badie, M.D.





Brown et al, New Engl J Med, 2016
Kirtane et al, J Immunotherapy Cancer,

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Optimizing Access To CAR T-cell Therapy

Healthcare Delivery Infrastructure	+	Individualized Patient Approvals	+	Therapy Delivery Economics	+	Supply Chain Orchestration	=	Access to Care
• Outpatient structure • Standard site certification • Standard accreditation (e.g., FACT) • Standard data reporting (e.g., CIBMTR)		• Pre-negotiate case rates • Improve time to approval		• CMS reform • Classification as cells, not drug • Reimbursement agnostic to site of care • Decrease cost of cells • Financial toxicity		• Streamline ordering • Standardize collection		• Facilitate timely referral • Increase clinical capacity • Clinical trials

Future of CAR T-cell/Other Cell Therapies

- Increasing demand
  - New approvals
  - New indications for existing products
  - Clinical trials (including solid tumors)
- Safer products
- Off-the-shelf products
- Outpatient administration

- Access issues
- Drug price
- Reimbursement
- Production issues
- Quality and regulatory oversight

Thank You

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