What is CAR-T Therapy?

Will it replace BMT?

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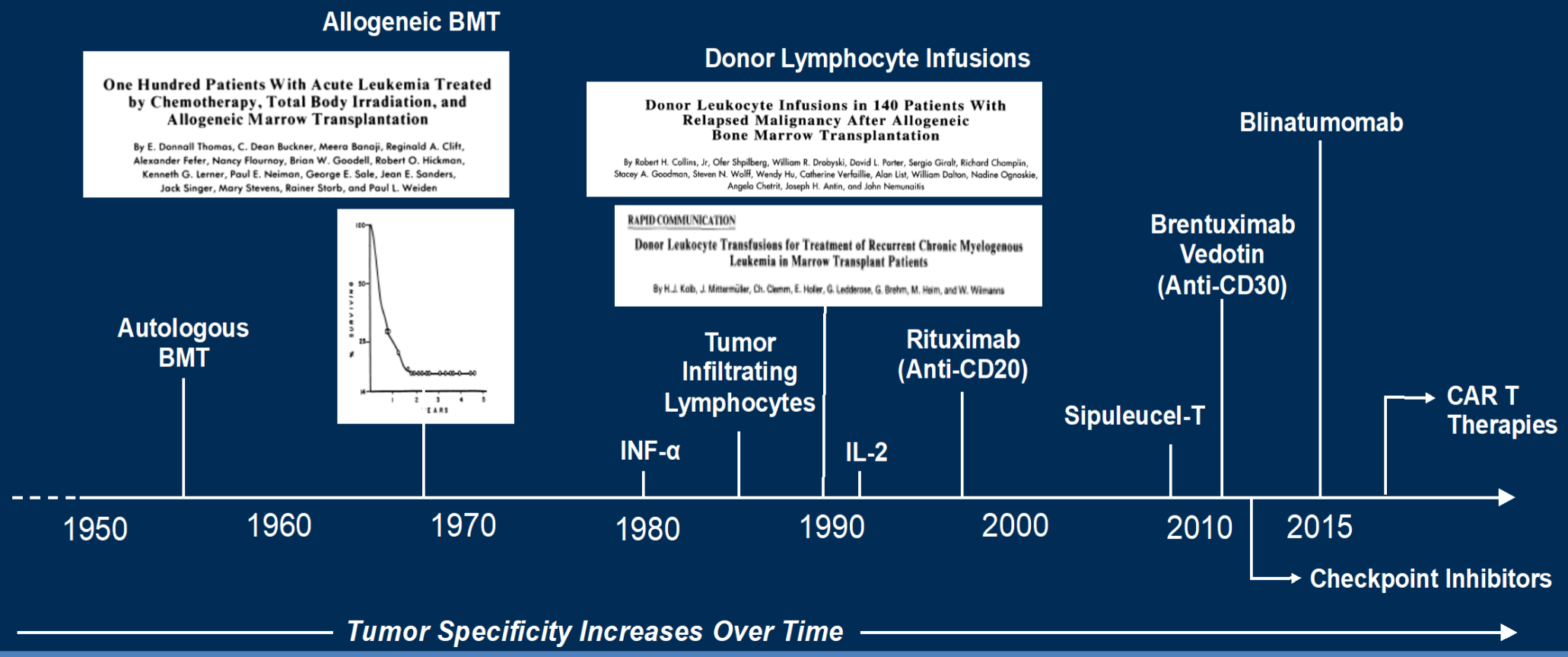
CancerCare Manitoba

University of Manitoba

Timeline of Advances in Immunotherapy



N.S. man's Stage 4 cancer is in remission after $900K treatment in Boston

Stephen Saunders is the first Nova Scotian to be publicly covered for CAR-T therapy in Boston

Laura Fraser · CBC News · Posted: May 03, 2019 6:00 AM AT | Last Updated: May 3

Objectives

1. To explain the rationale behind CAR-T therapy
2. To update clinical outcomes after CAR-T therapy
3. To discuss if CAR-T will replace BMT

Disclosures & Acknowledgments: M Seftel

Research support	Teva
Employee	-
Consultant	Abbvie,
Stockholder	-
Speaker	-
Scientific advisory board	Teva, Amgen, Pfizer

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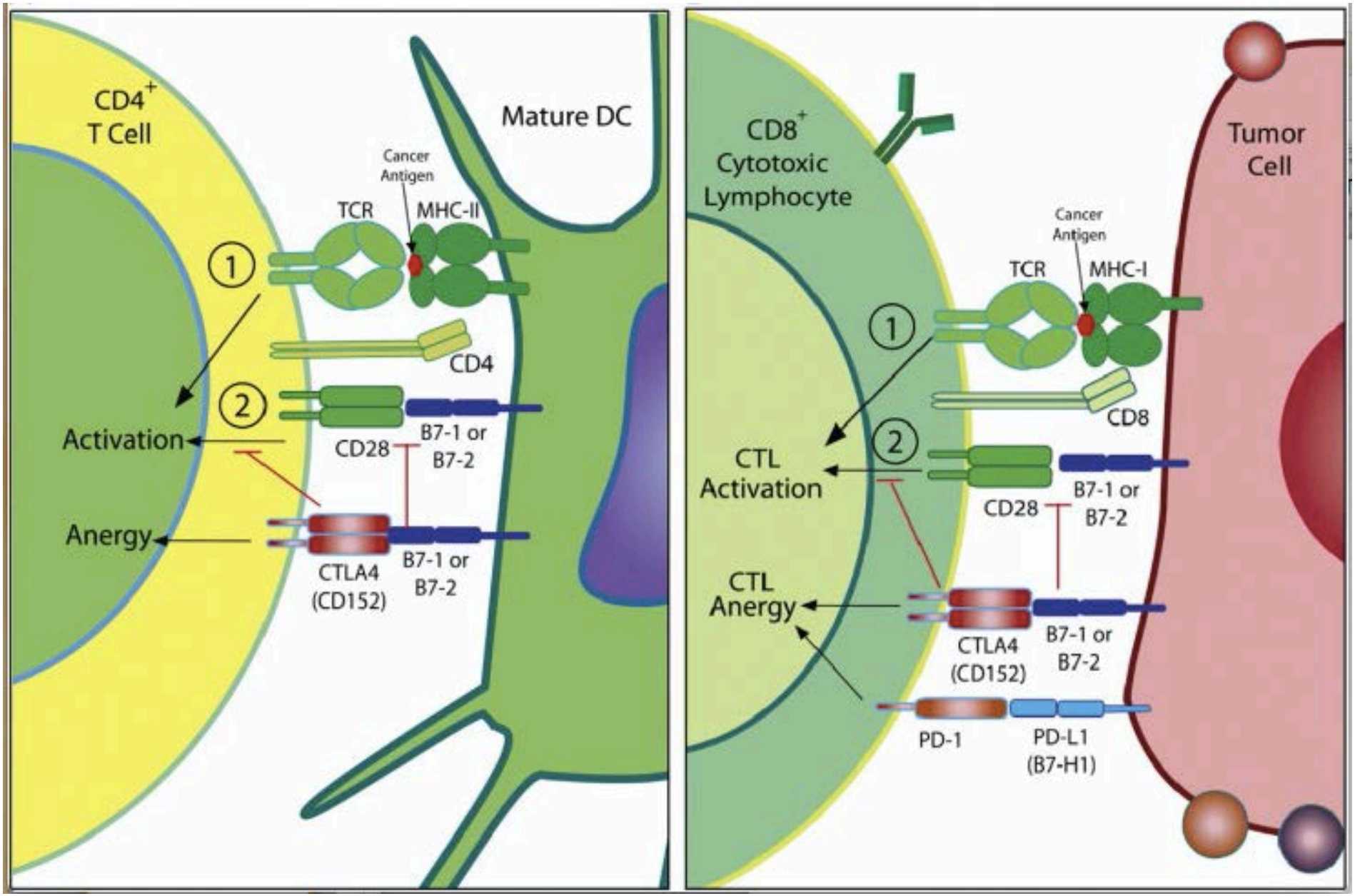
T-cell signaling in malignancy



Berkholder B et al. Biochimica et Biophysica Acta 2014.

CART - Rationale

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)

CAR-T - Rationale

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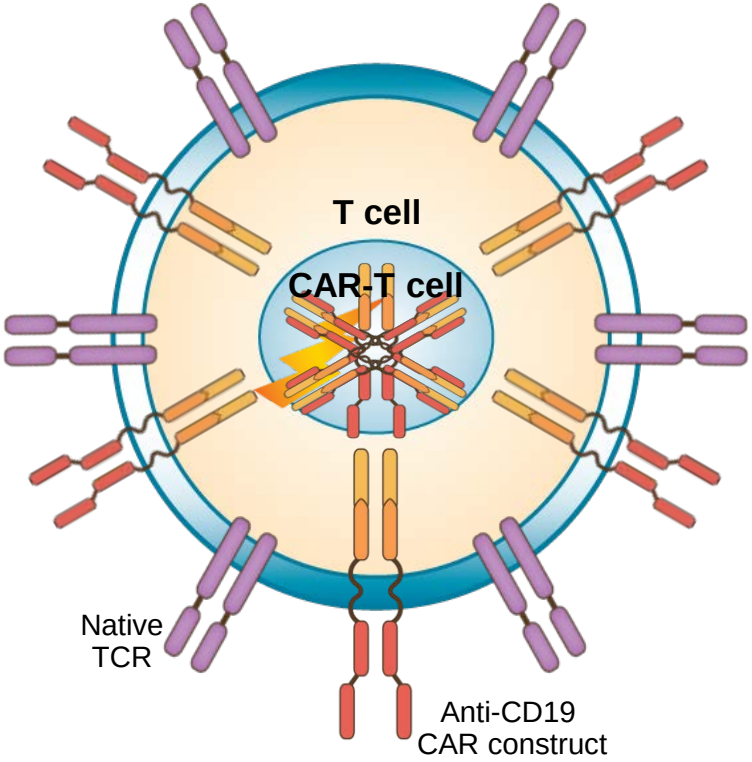
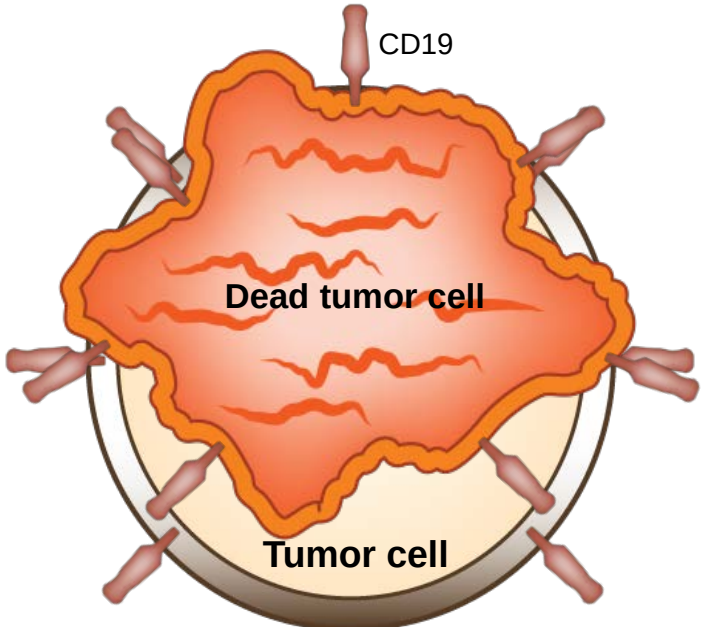
"These chimeric genes…are non-MHC-restricted and universal. This approach can be exploited to direct cytotoxic T lymphocytes to kill tumor…"

Chimeric Antigen Receptor T cells (CARTs)

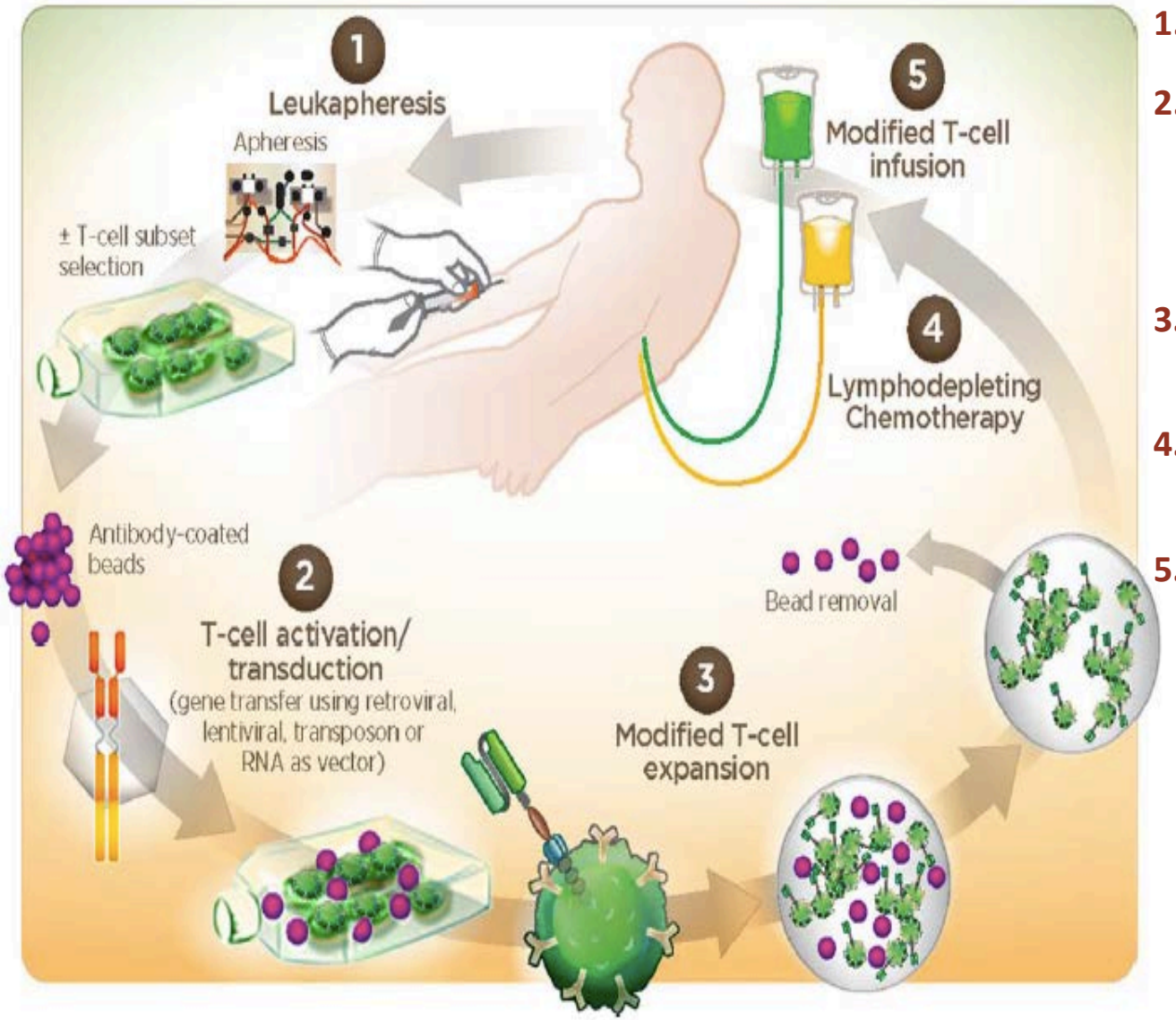


Retroviral
or
Lentiviral
vector



Milone MC, et al. *Mol Ther. 2009*
Porter DL et al. *NEJM 2011*
Kalos M, et al. *Sci Transl Med.* 2011
Maude et al. *NEJM 2014.*

CAR Manufacturing and Administration



Frey N et al. Am J Hematology. 2016

1. **Leukapheresis:** T cells harvested
2. **T cells activated** on antibody-coated beads **and genetically transduced ex vivo** with construct encoding anti-CD19 CAR
3. **Ex vivo expansion** on antibody-coated beads
4. **Chemotherapy:** Lymphodepletion before T-cell infusion
5. **Cells reinfused**

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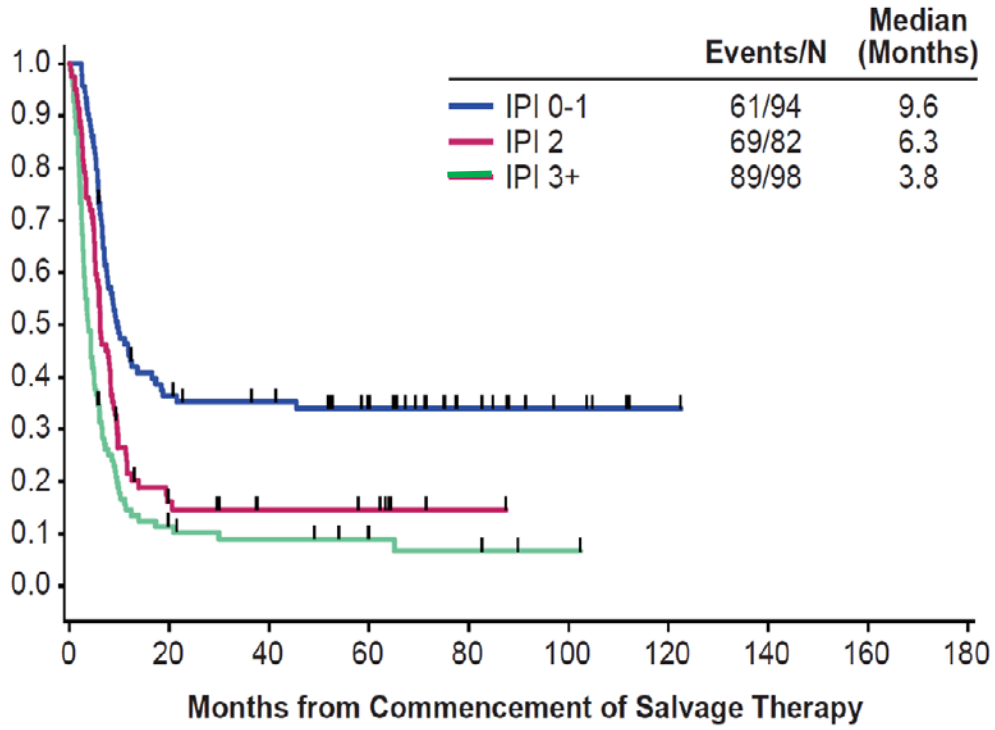
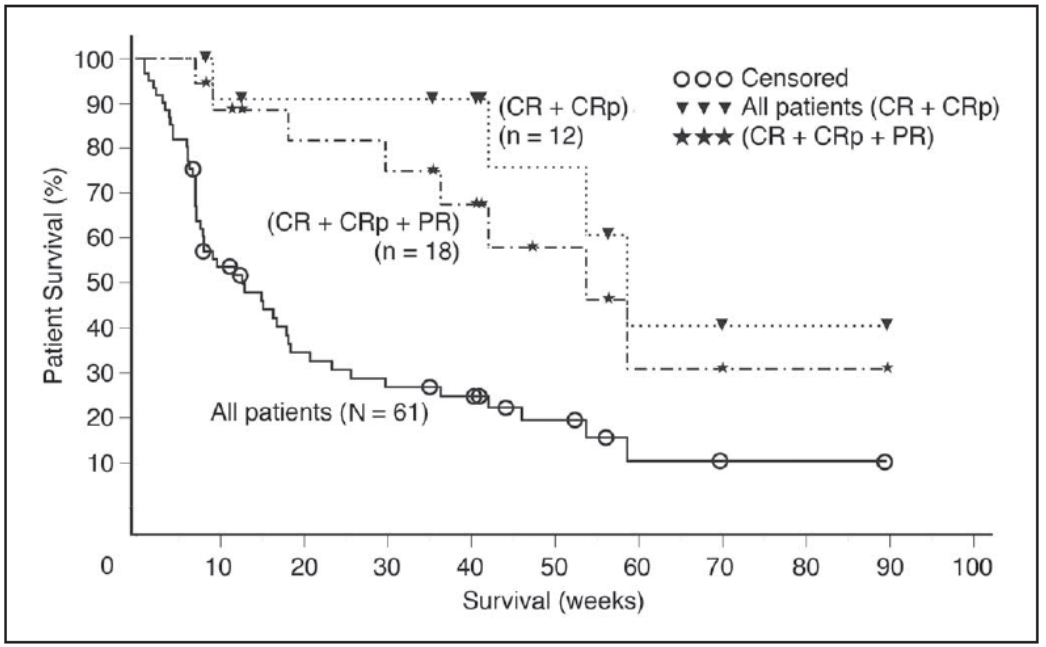
Patients with Rel/ref ALL or NHL with available therapy

Non-Hodgkin Lymphoma



Crump M et al. Blood 2017

Pediatric ALL



Jeha S et al. J Clin Oncol 2006

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

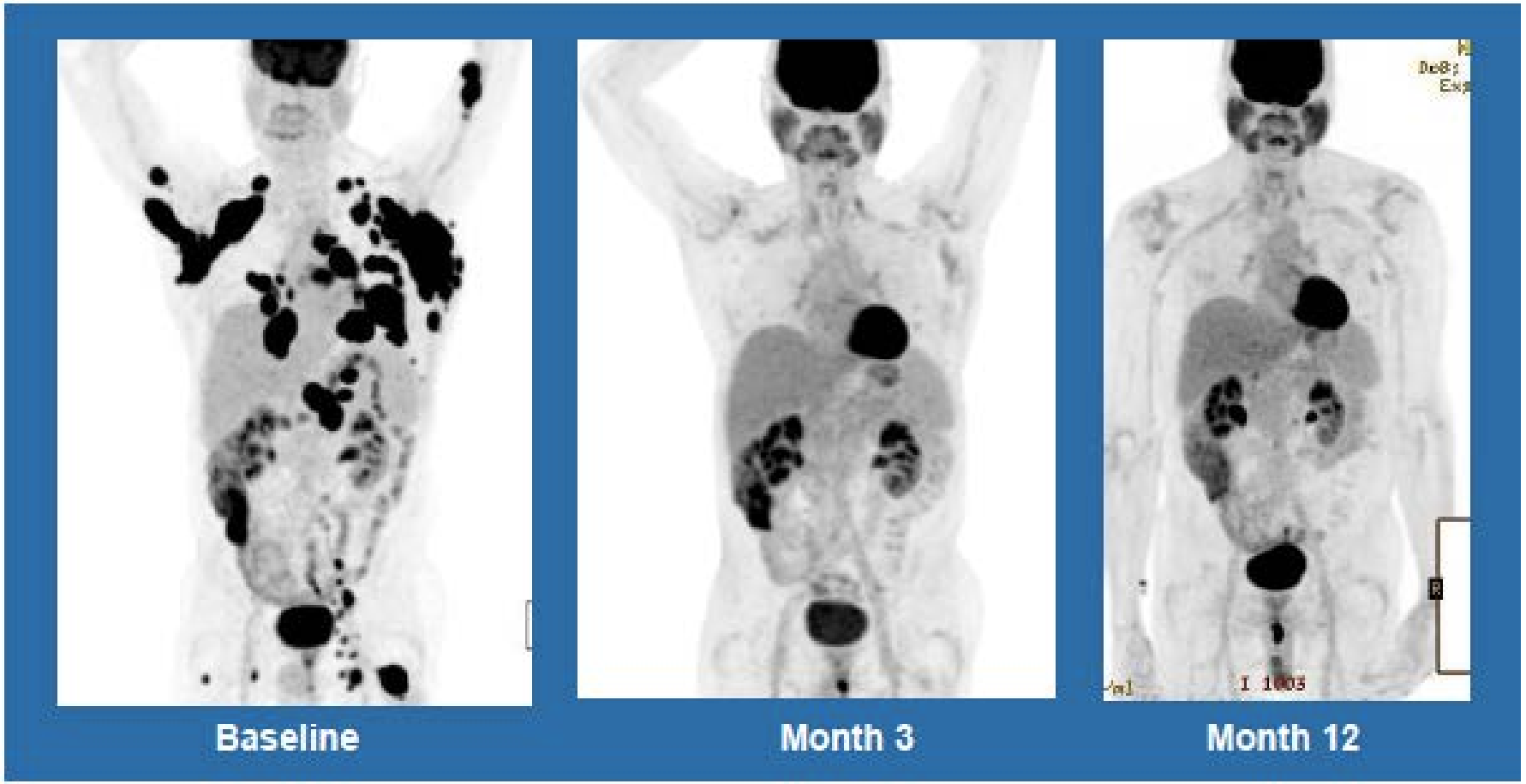
For Immediate Release August 30, 2017

Oncology Drug Advisory Committee (ODAC) members:

"Paradigm changing…"; "Most exciting thing I've seen in my life…"; "Major advance…"; "Impressive clinical efficacy… in a disease with strong unmet need"

CD19 CART active against Bulky Lymphoma

62M with DLBCL refractory to R-CHOP, R-GDP, R-ICE, R-Lenalidomide.

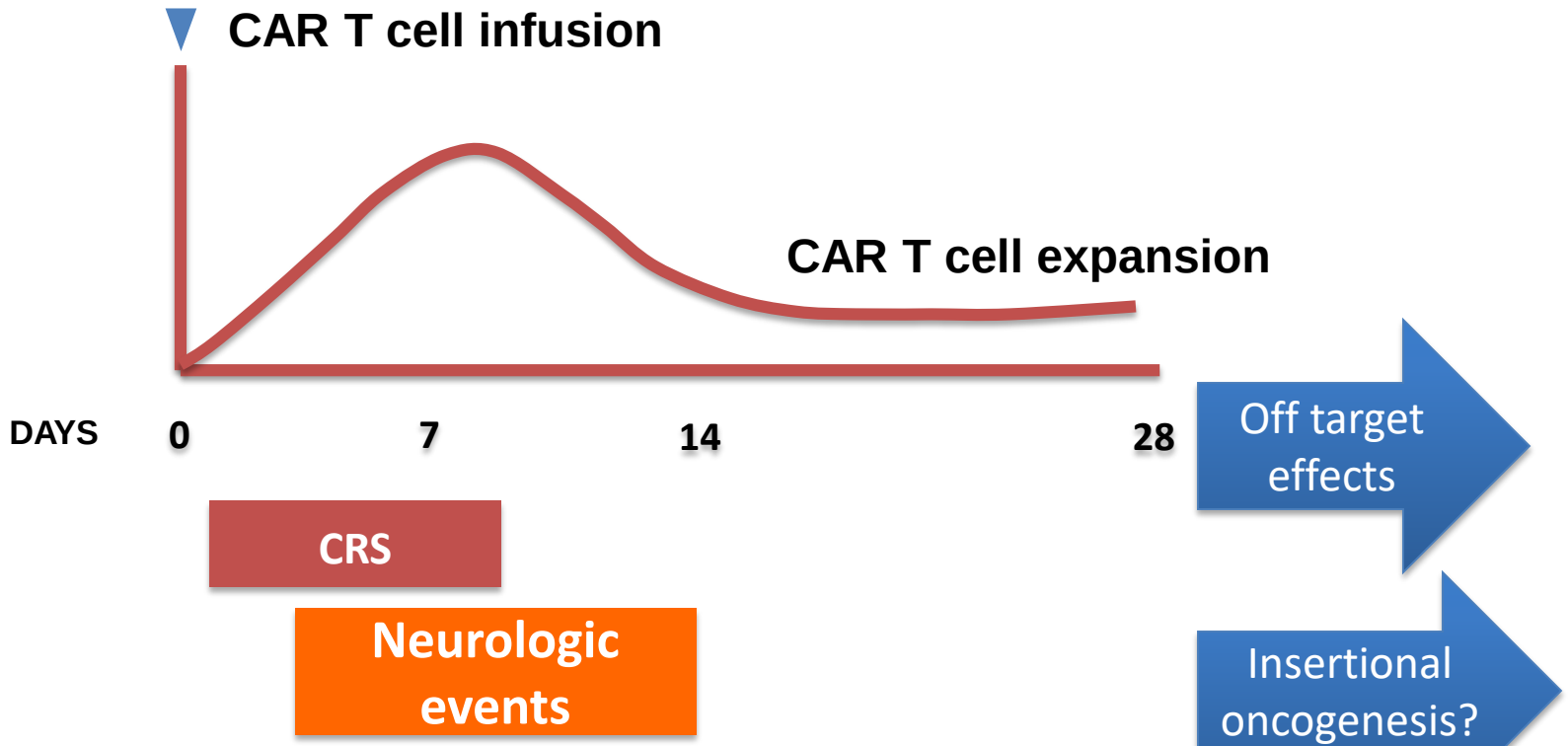


1. Crump et al. ASCO 2016. 2. Locke & Neelapu et al. AACR 2017.

Anti-CD19 CAR T Products in Late Clinical Development

	Axicabtagene Ciloleucel (Yescarta; KTE-C19)	Tisagenlecleucel (Kymriah; CTL019)	Liso-Cel (JCAR017)
Company	KITE/Gilead	Novartis	Juno
Indications **(HC Approved in red)**	**DLBCL, high grade B-NHL, TFL PMBCL**,MCL, ALL, CLL	**DLBCL, TFL, ALL,** CLL	Adult NHL, Pediatric ALL, CLL
Stimulatory Domain	CD28-CD3ζ	4-1BB-CD3ζ	4-1BB-CD3ζ
Viral Vector	Gamma retrovirus	Lentivirus	Lentivirus

Adverse events after CART



May occur within minutes or hours but generally appears within days or weeks

Coincides with maximal T-cell expansion

Lee DW et al. Blood. 2014;124(2):188-195.

Pivotal Trials FDA for Anti-CD19 CART

	ELIANA (N= 75)	ZUMA (N=101)
Patients	• 92 Pediatric/young adult pts with rel/ref CD19+ ALL • Median age 12 years (3-23) • Median follow-up 13 months	• 111 adults with DLBCL, PMBCL or transformed FL • Median age 58 years (23-76) • Median follow-up 15 months
Product	Tisagenlecleucel Lentivirus; 4-1BB co-stim domain	Axicabtagene Ciloleucel Gamma-retrovirus; CD28 co-stim domain
Efficacy	• ORR 81% at 3 months • OS 76% at 1 year	• ORR: 82% at 6 months • OS: 59% at 12 months
Toxicity	• Grade 3/4 AEs: 73% • CRS: 77% • Neurotoxicity: 40% • 47% ICU admissions • TRM: 3 pts	• Grade 3/4 AEs: 95% • CRS: 93% (13% grade 3/4, all resolved except one) • Neurotoxicity: 64% (28% grade 3 or 4, all resolved except one) • TRM: 2 pts

Maude S et al. NEJM 2018

Neelapu S et al. NEJM 2017

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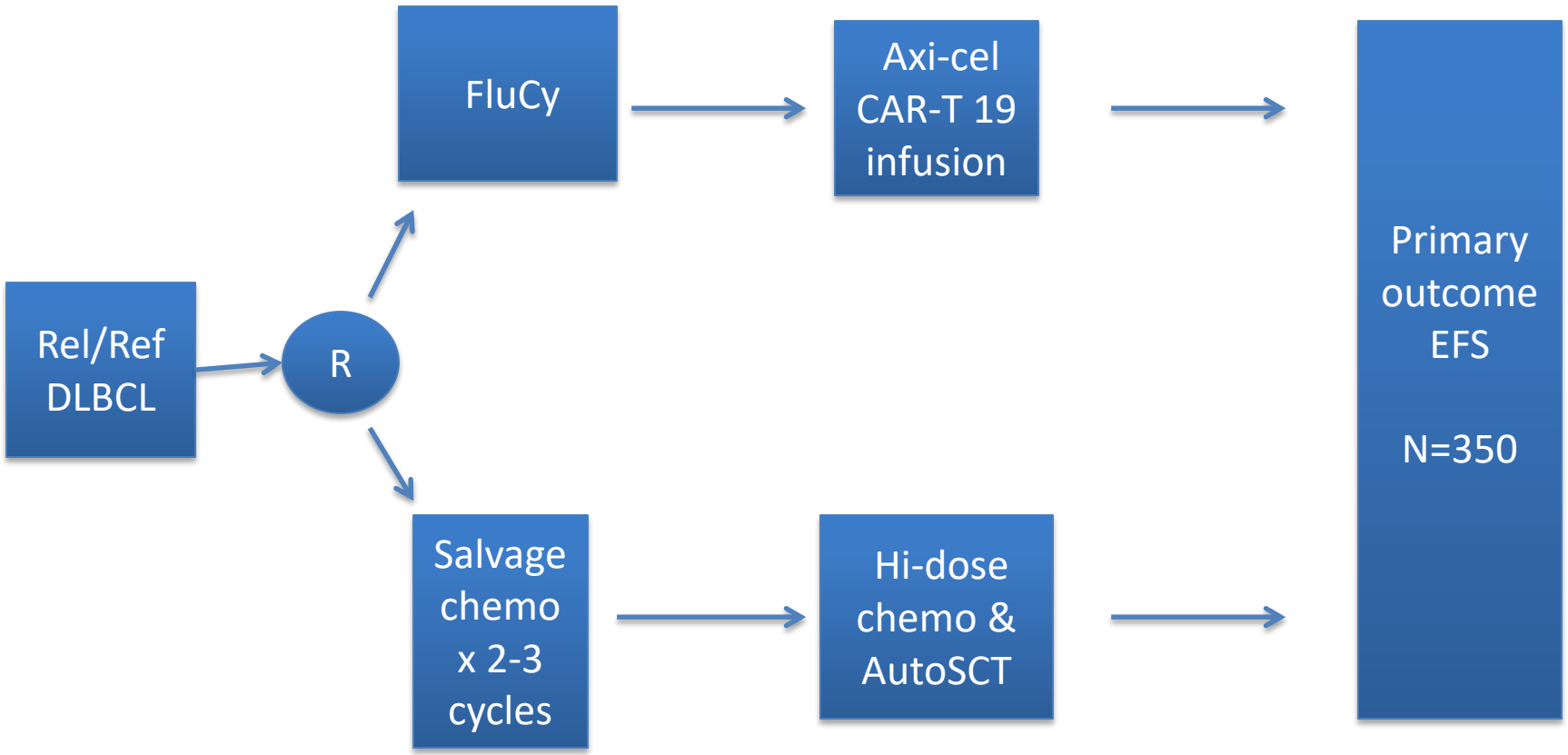
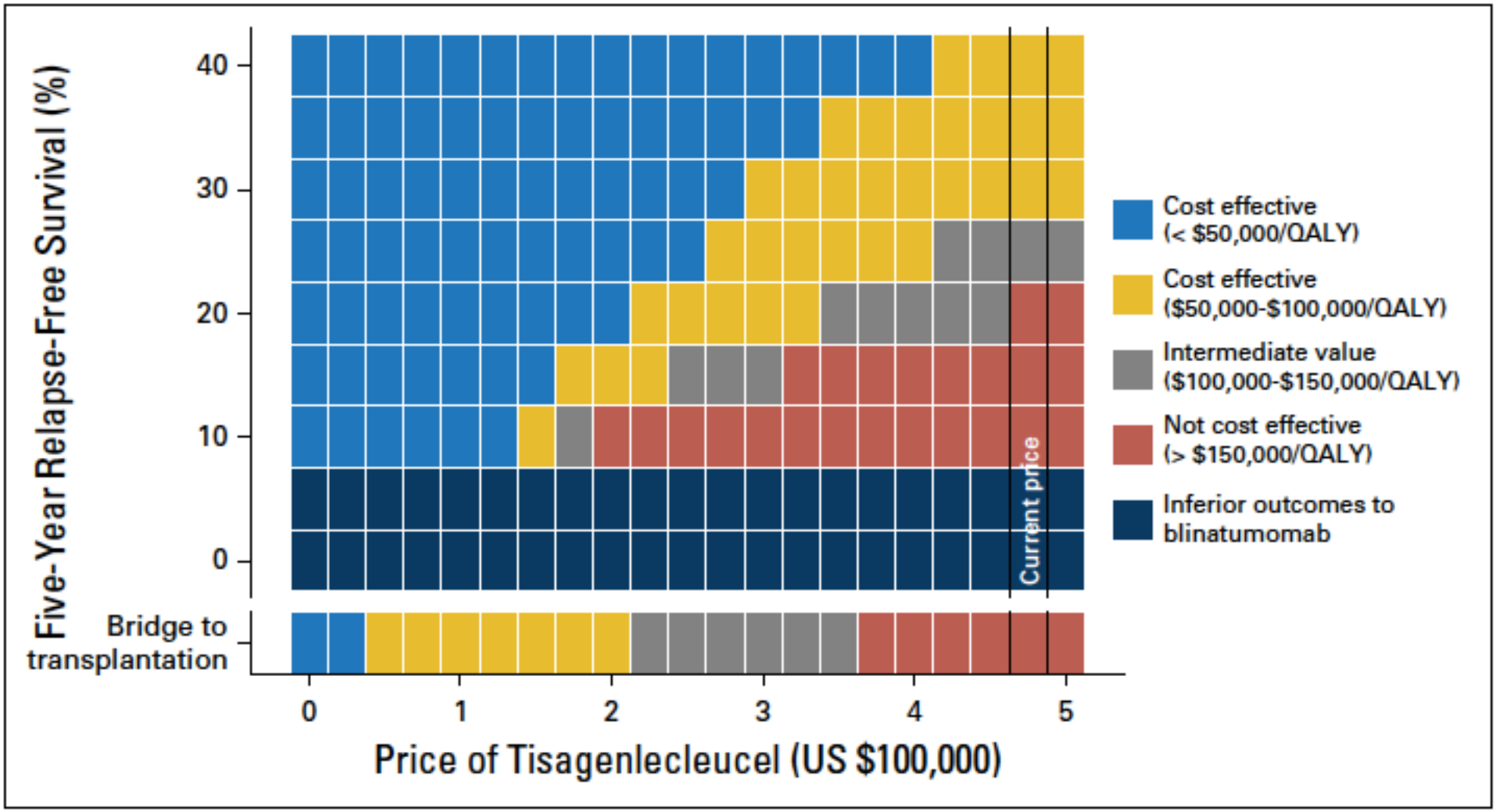
“ZUMA 7” Multicentre RCT



Open at CCMB
Sponsor: Kite/Gilead

Cost-effectiveness considerations (B-ALL)



Lin et al, JCO 2018

CADTH Evidence Driven.

INBRIEF | Summarizing the Evidence

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma

"Appears Promising, but there are many uncertainties"

For r/r ALL, tisagenlecleucel, compared with end-of-life chemotherapy, was associated with an incremental cost per quality-adjusted life-year (QALY — a measure of the quantity and quality of life for a patient, as well as value for money for medical interventions) of $53,269. Tisagenlecleucel is likely to be cost-effective for r/r ALL if the willingness-to-pay threshold is $100,000 per QALY. It was estimated from the budget impact

For r/r DLBCL, tisagenlecleucel, compared with palliative chemotherapy, was associated with an incremental cost per QALY of $211,870. Tisagenlecleucel is not likely to be cost-effective if the willingness-to-pay threshold is $100,000

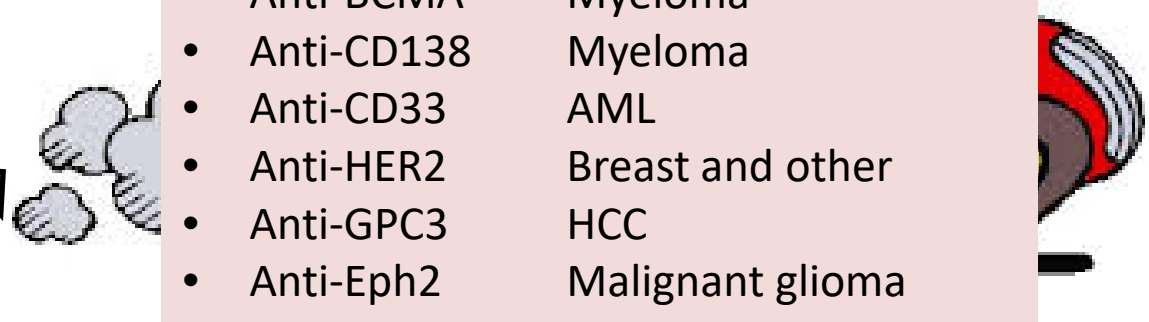
The CARS are in the showroom*

Change the DRIVER:
- New vectors

Add BRAKES:
- Suicide gene inserts

Current CAR-T trials:

• Anti-CD22	ALL and Lymphoma
• Anti-CD30	Lymphoma
• Anti-BCMA	Myeloma
• Anti-CD138	Myeloma
• Anti-CD33	AML
• Anti-HER2	Breast and other
• Anti-GPC3	HCC
• Anti-Eph2	Malignant glioma



Improve TOXICITY:
- Treatment of CRS/neurotox
- Predictors of CRS

Improve the EVIDENCE
- Clinical trials
- Economic analyses

Change the ROAD:
- New antigens
- New tumours

*Perales M et al. Biol Blood Marrow Transpl 2018

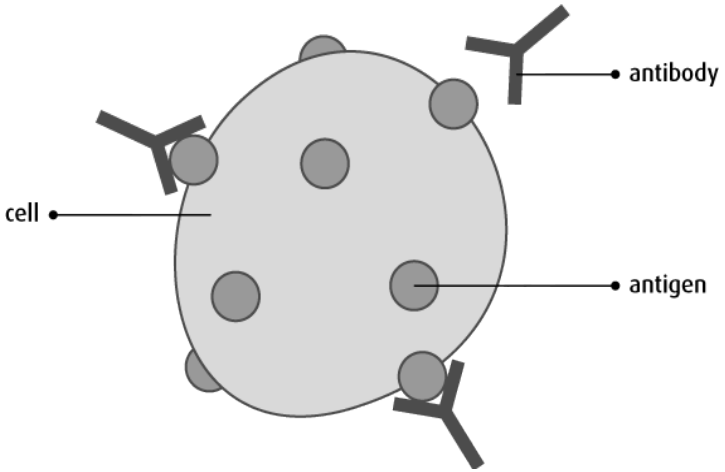
Conclusions- CAR-T therapy

- Commercialized
- Haem malignancy at forefront
- Toxicity: Restricted use to BMT centres with ready access to ICU care
- RCTs and long-term follow-up needed
- NOT ready to replace conventional use of BMT

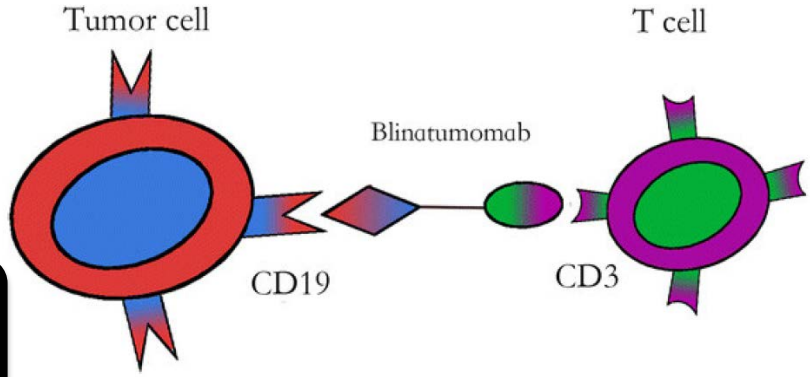
Extra slides

Immunotherapy in Cancer: 2019

Antibodies



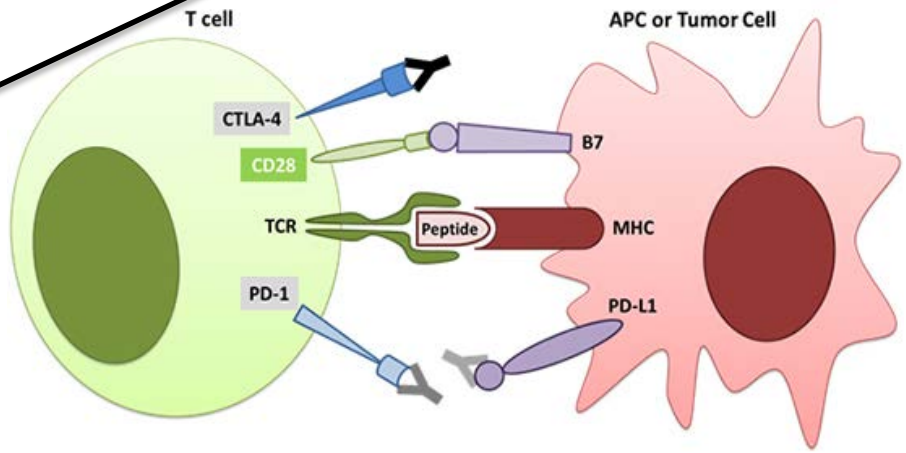
Bispecific T-cell engagers (BiTEs)



Immunotherapy

CAR-T cells

Checkpoint inhibitors



ORIGINAL ARTICLE FREE PREVIEW

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

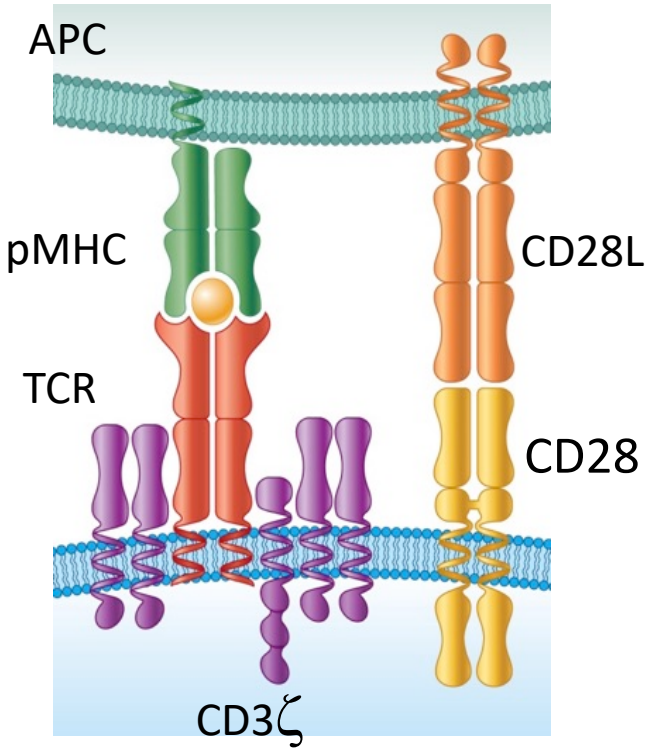
Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., et al.

May 2, 2019

Raje N et al, NEJM 2019

CAR Design

Native T-Cell Receptor



Chimeric Antigen Receptor

scFv (eg. CD19)

Costimulatory Signal 2: eg. CD28, 41BB

Essential Signal 1: CD3ζ

CAR-T cells

- Permanently genetically altered to express CAR receptors on the cell surface
- Recognize cell surface antigen without MHC presentation
- Become activated upon antigen recognition