Mechanisms of Treatment Resistance in Context of Axicabtagene Ciloleucel for Lymphoma

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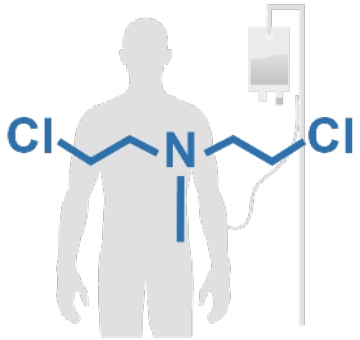
Disclosure

Employment at Kite, a Gilead Company, and equity ownership in Gilead Sciences, Inc.
Scientific Advisory Board, Elicio Therapeutics

Historical Evolution of Cancer Therapies

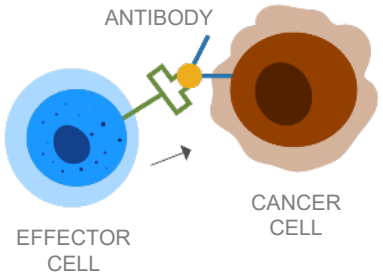
1940s



First chemotherapy approved

Chemotherapy
Indiscriminate – kills healthy and cancer cells

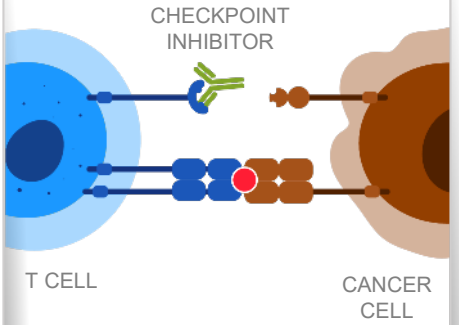
1990s



First targeted antibody therapy approved

Targeted Therapies
Target receptor/molecular oncogenic drivers

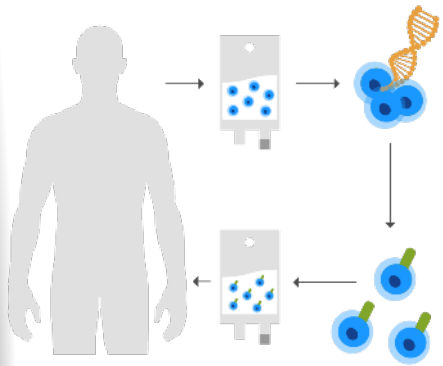
2010s



Checkpoint inhibitors approved

Immuno-Oncology
Checkpoint and innate immunity modulators

2017



CD19 CAR T cell therapy introduced

T Cell Therapy
Re-engineered T cells

CAR: Chimeric Antigen Receptor

Sudhakar A. J Cancer Sci Ther 2009;1:1-4; Chen DS, Mellman I. Immunity 2013;39:1-10.

Five T Cell Therapy Products Approved to Date
All in B-Cell Malignancies including Myeloma, and Target CD19 and BCMA

August 30, 2017 – Kymriah® (tisagenlecleucel) for the treatment of patients up to 25 years of age with **B-cell precursor acute lymphoblastic leukemia (ALL)** that is refractory or in second or later relapse

October 18, 2017 – Yescarta® (axicabtagene ciloleucel) for the treatment of adults with certain types of **relapsed or refractory large B-cell lymphoma** after receiving 2 or more lines of systemic therapy

May 1, 2018 – Kymriah® (tisagenlecleucel) the treatment of adult patients with **relapsed or refractory (r/r) large B-cell lymphoma** after two or more lines of systemic therapy

July 24, 2020 – Tecartus® (brexucabtagene autoleucel) for **relapsed or refractory Mantle Cell Lymphoma**

February 5, 2021 – Breyanzi® (lisocabtagene maraleucel) **for adults with relapsed or refractory (r/r/) large B-Cell lymphoma** after two or more lines of systemic therapy and **follicular lymphoma grade 3B.**

March 5, 2021 – Yescarta® (axicabtagene ciloleucel) for treatment of adult patients with **relapsed or refractory Follicular Lymphoma** after two or more lines of systemic therapy.

March 5, 2021 – Abecma® (idecabtagene vicleucel), for patients with **relapsed or refractory multiple myeloma** who have previously received at least four lines of treatment,

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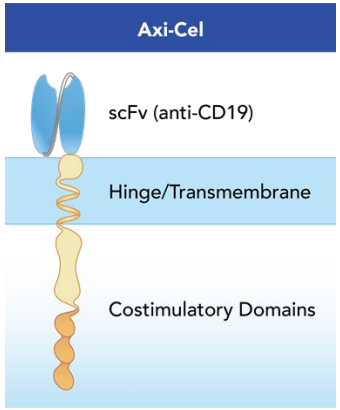
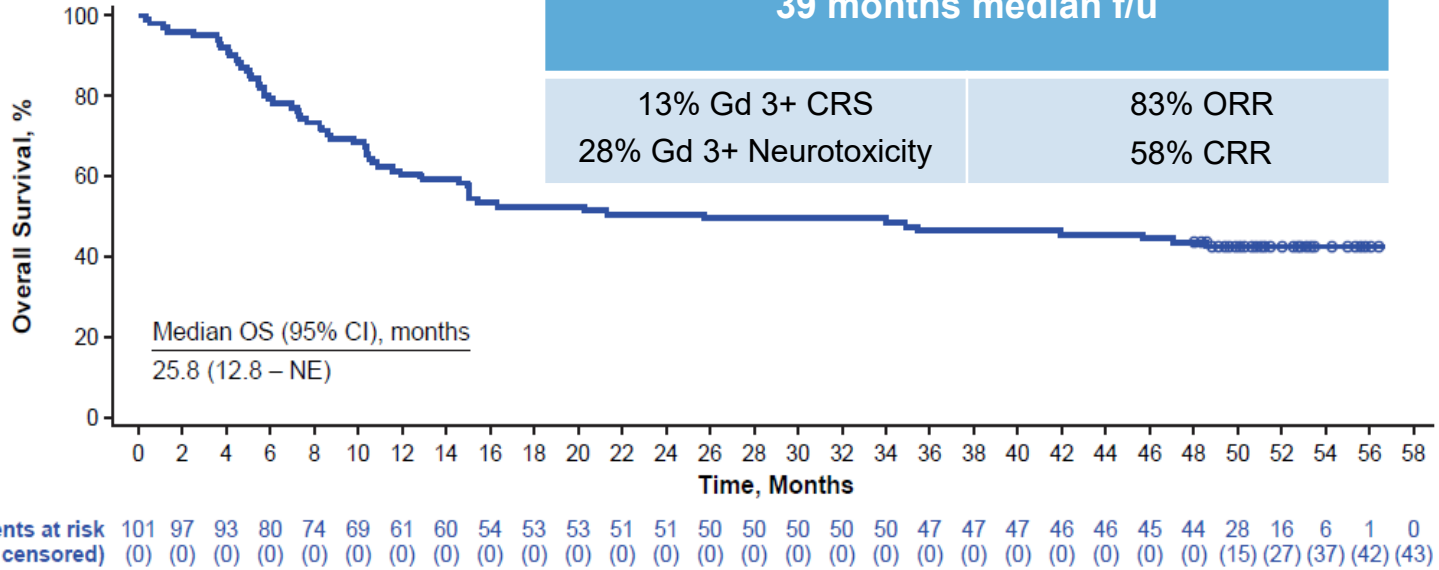
ZUMA-1 Axi-Cel Trial in DLBCL: Updated Overall Survival (mITT, n = 101)



39 months median f/u

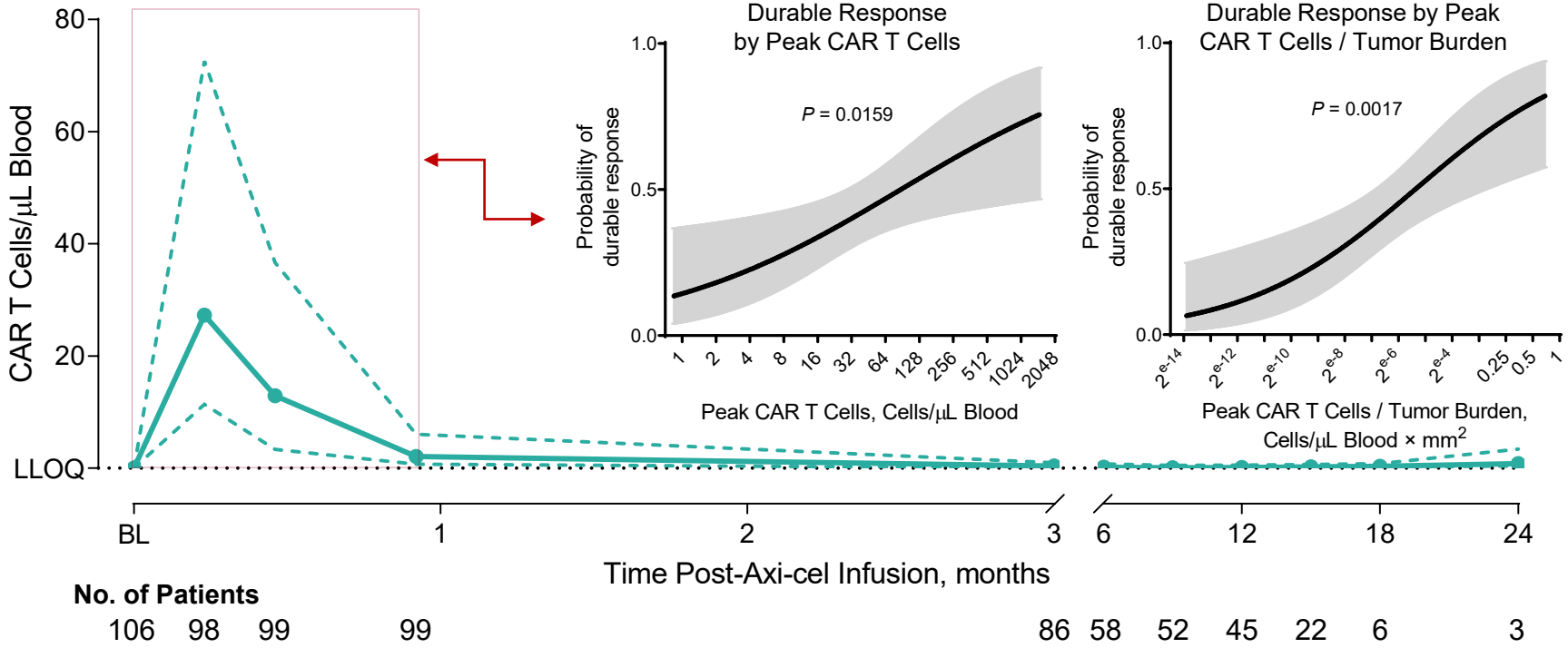
13% Gd 3+ CRS	83% ORR
28% Gd 3+ Neurotoxicity	58% CRR



- Among axi-cel–treated patients (mITT, n = 101), with ≥ 4 years of follow-up (median, 51.1 months), median OS was 25.8 months, and the KM estimate of the 4-year OS rate was 44%
- Among the entire enrolled population (ITT, n = 111), median OS was 17.4 months, and the KM estimate of the 4-year OS rate was 41%

Axi-cel, axicabtagene ciloleucel; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; OS, overall survival.

CAR T Cell Expansion and Durable Response Following Axi-Cel



BL, baseline; LLOQ, lower level of quantification.
Solid line indicates median. Dashed lines indicate Q1 and Q3.

Neelapu SS, et al. *NEJM* 2018.
Locke FL, et al. AACR 2017.
Locke FL, et al. *Lancet Oncol*, 2018.
Locke FL, et al. submitted for publication.

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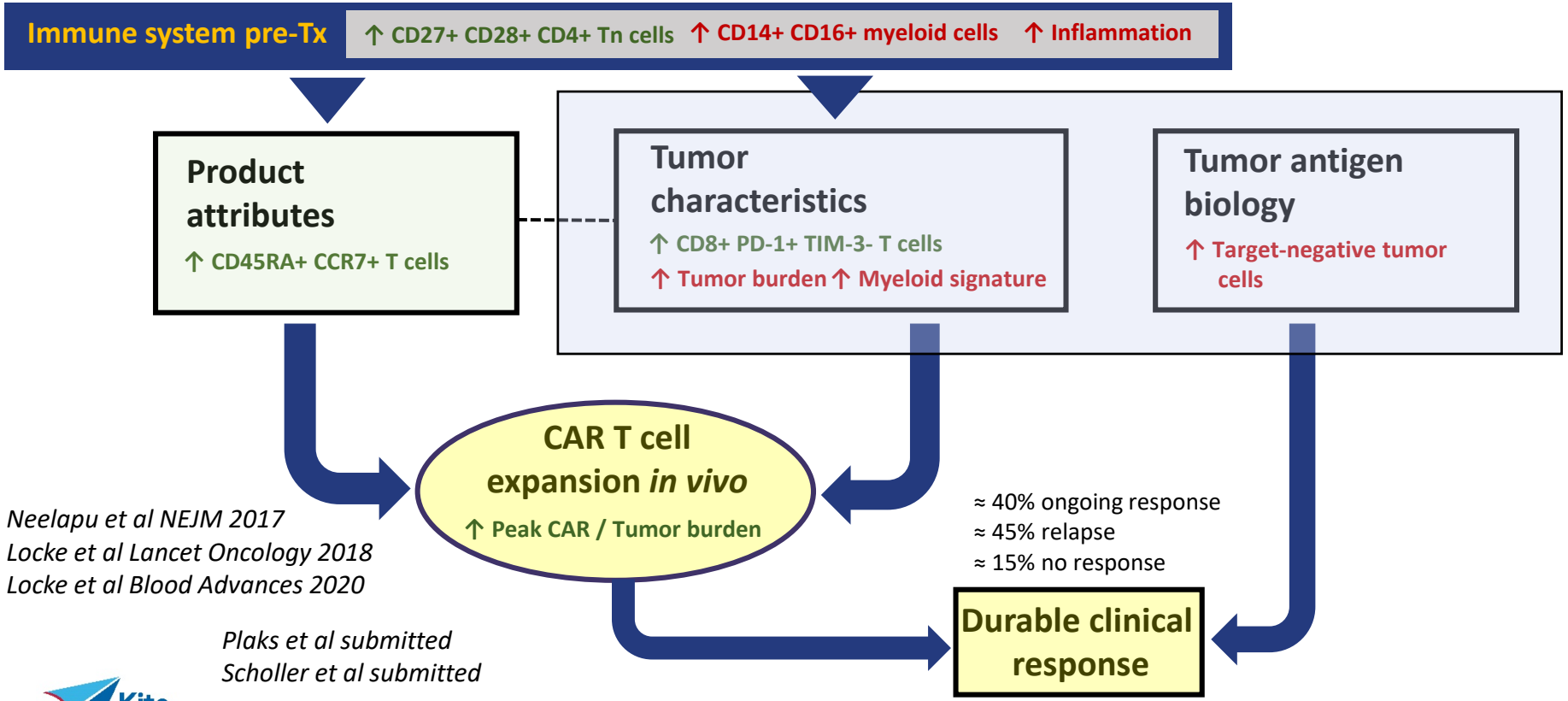
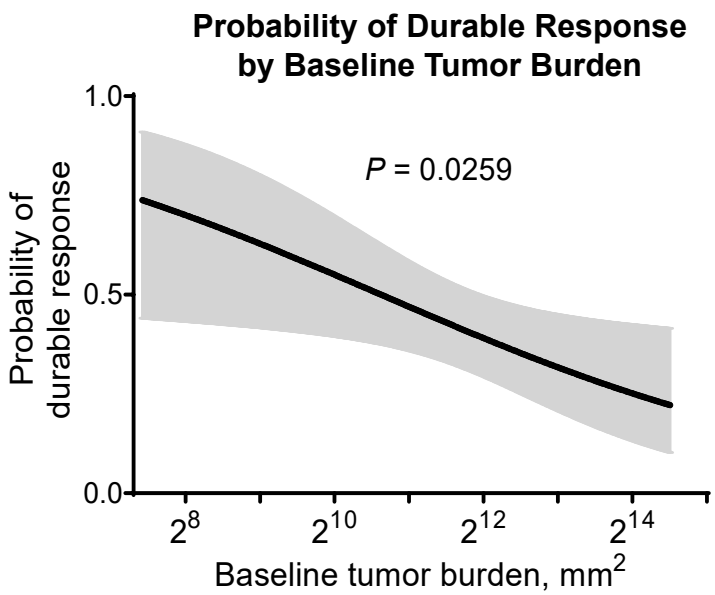
Key Questions

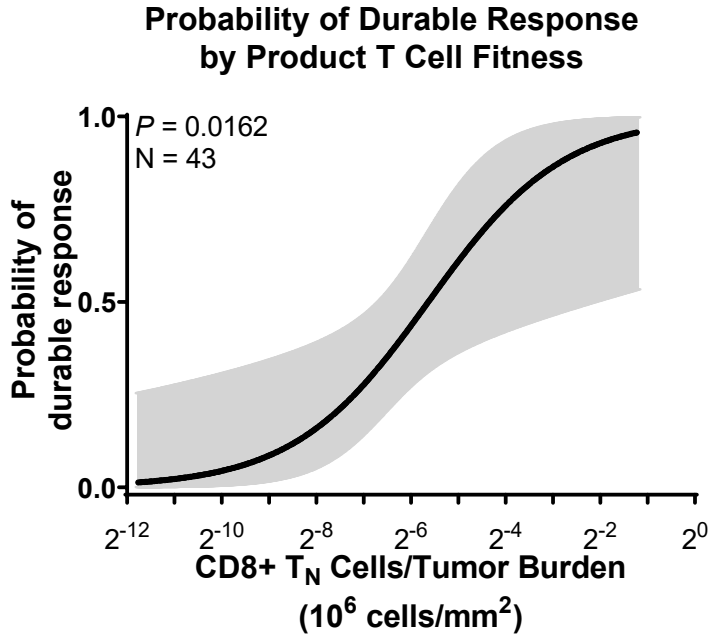
- What are categories of factors that influence clinical outcomes to Axi-cel ?
- Which are the most influential parameters within each category ?
- What are potential treatment optimizations based on mechanisms of treatment resistance ?

Product Attributes and Tumor Characteristics that May Influence Clinical Efficacy of Axi-cel in LBCL



Pre-Treatment Tumor Burden and Durable Response Following Axi-Cel



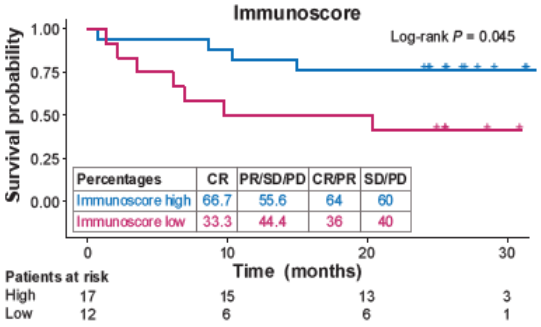


T_N defined as CD45RA+ CCR7+

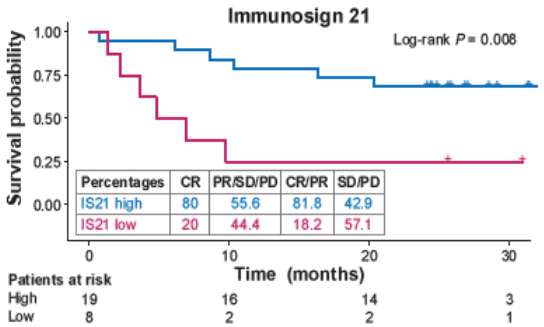
Locke FL, et al. ASCO 2018. #3039.
Locke FL, et al. Blood Advances 2020

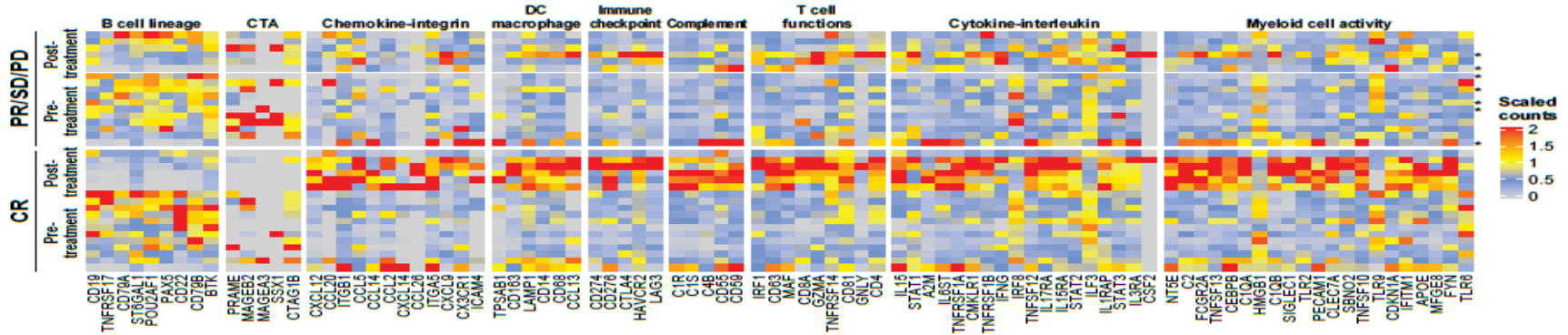
Tumor Immune Contexture Associates with Axi-Cel Outcomes in DLBCL

TME density of CD3+ CD8+ T cells



Immune gene expression in TME

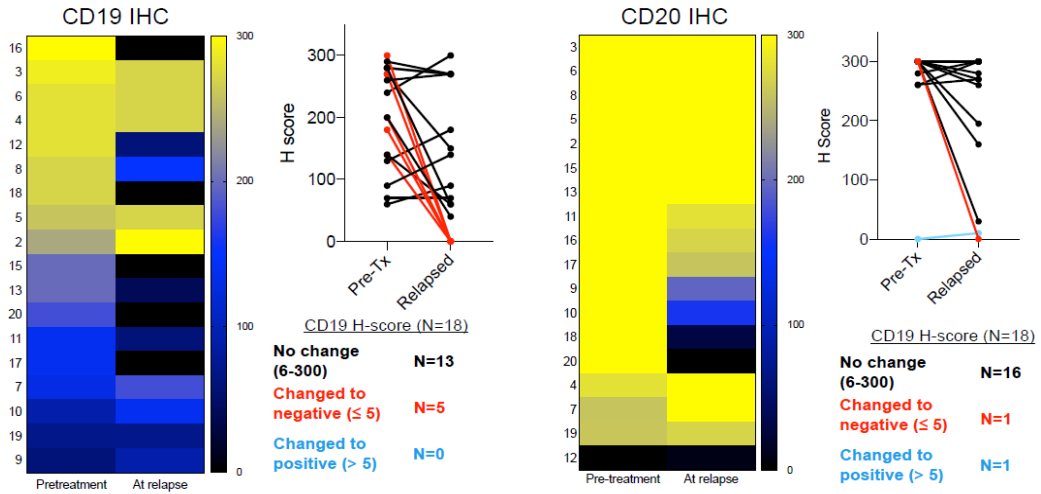




Scholler et al, submitted

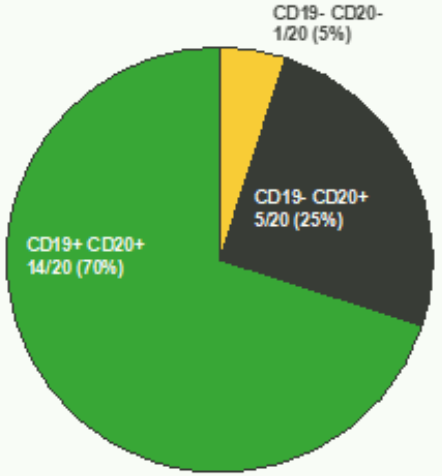
CD19-Related Axi-Cel Treatment Evasion in a Subset of Axi-Cel Patients

Differential change in CD19 and CD20 expression at relapse



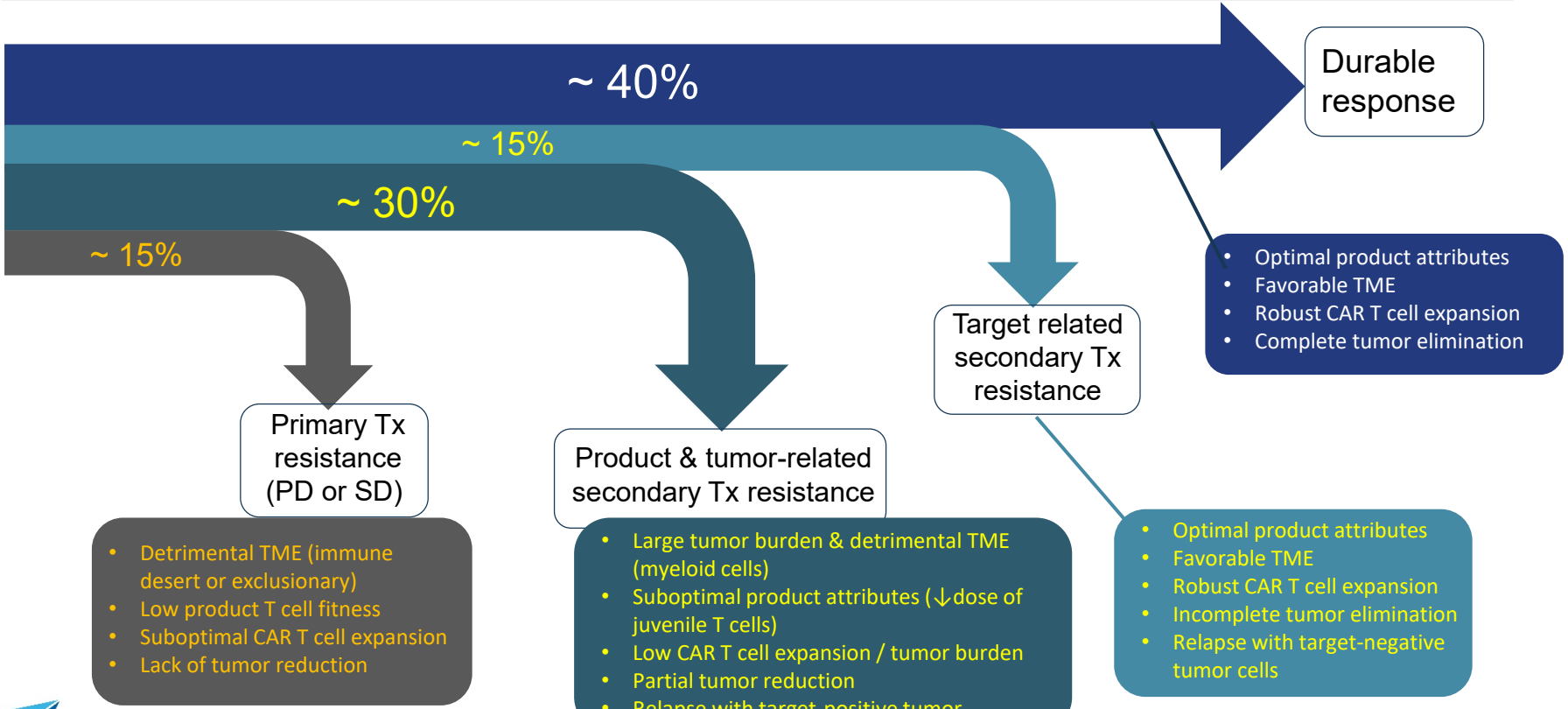
IHC, immunohistochemistry

CD19 and CD20 expression at relapse



Neelapu SS, et al. ASH 2019 #203
Plaks et al, submitted

Mechanisms of Axi-Cel Treatment Resistance in LBCL: Summary



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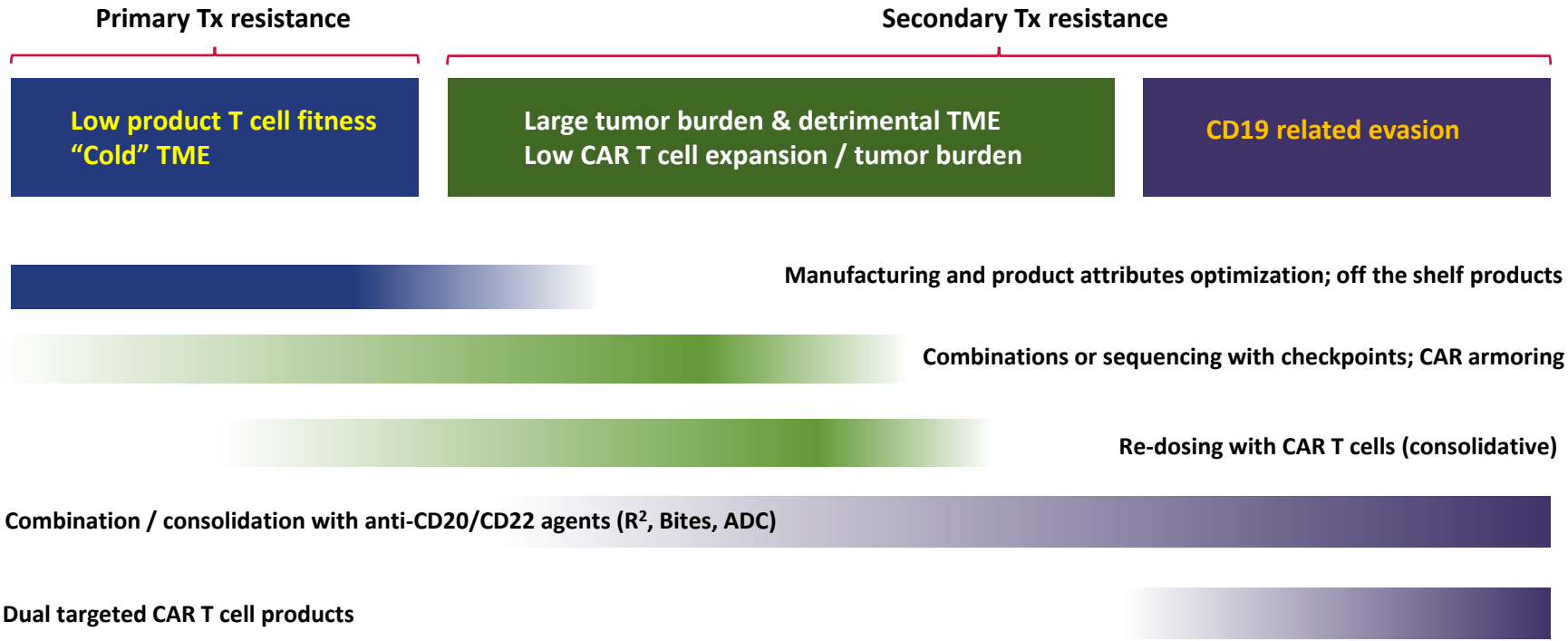
Potential optimizations to enhance clinical efficacy of anti-CD19 CAR treatment in lymphoma



Conclusions

- Durable response to Axi-cel occurs in a subset of DLBCL patients with optimal product attributes and tumor characteristics
- Major mechanisms of treatment resistance to Axi-cel in DLBCL include
  - Limited product T cell fitness or dose of specialized T cells / tumor burden
  - An immune detrimental tumor microenvironment
  - Target related evasion

Major directions / questions

- Product and treatment optimizations that enhance efficacy and lower toxicities
- Role of endogenous T cell repertoire and immune cells
- Off the shelf cell therapies with improved clinical performance over autologous

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