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

- 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

No. of Patients

| 106 | 98 | 99 | 99 |

Time Post-Axi-cel Infusion, months

| 1 | 2 | 3 | 6 | 12 | 18 | 24 |

Durable Response

Durable Response by Peak CAR T Cells

$P = 0.0159$

Durable Response by Peak CAR T Cells / Tumor Burden

$P = 0.0017$

BL, baseline; LLOQ, lower level of quantification.

Solid line indicates median. Dashed lines indicate Q1 and Q3.

Locke FL, et al. submitted for publication.
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

**Immune system pre-Tx**
- ↑ CD27+ CD28+ CD4+ Tn cells
- ↑ CD14+ CD16+ myeloid cells
- ↑ Inflammation

**Product attributes**
- ↑ CD45RA+ CCR7+ T cells

**Tumor characteristics**
- ↑ CD8+ PD-1+ TIM-3- T cells
- ↑ Tumor burden ↑ Myeloid signature

**Tumor antigen biology**
- ↑ Target-negative tumor cells

**CAR T cell expansion in vivo**
- ↑ Peak CAR / Tumor burden

≈ 40% ongoing response
≈ 45% relapse
≈ 15% no response

**Durable clinical response**

Neelapu et al NEJM 2017
Locke et al Lancet Oncology 2018
Locke et al Blood Advances 2020
Plaks et al submitted
Scholler et al submitted
Pre-Treatment Tumor Burden and Durable Response Following Axi-Cel

Probability of Durable Response by Baseline Tumor Burden

- Probability of durable response
- Baseline tumor burden, mm$^2$
- $P = 0.0259$

Probability of Durable Response by Product T Cell Fitness

- Probability of durable response
- CD8$^+$ $T_N$ Cells/Tumor Burden (10$^6$ cells/mm$^2$)
- $P = 0.0162$
- $N = 43$

TN defined as CD45RA$^+$ CCR7$^+$

Tumor Immune Contexture Associates with Axi-Cel Outcomes in DLBCL

TME density of CD3+ CD8+ T cells

Immune gene expression in TME
CD19-Related Axi-Cel Treatment Evasion in a Subset of Axi-Cel Patients

Differential change in CD19 and CD20 expression at relapse

IHC, immunohistochemistry

Neelapu SS, et al. ASH 2019 #203
Plaks et al, submitted
Mechanisms of Axi-Cel Treatment Resistance in LBCL: Summary

~ 40%

Durable response

~ 15%

Target related secondary Tx resistance

- Optimal product attributes
- Favorable TME
- Robust CAR T cell expansion
- Complete tumor elimination

~ 30%

Product & tumor-related secondary Tx resistance

- Large tumor burden & detrimental TME (myeloid cells)
- Suboptimal product attributes (↓dose of juvenile T cells)
- Low CAR T cell expansion / tumor burden
- Partial tumor reduction
- Relapse with target-positive tumor

~ 15%

Primary Tx resistance (PD or SD)

- Detrimental TME (immune desert or exclusionary)
- Low product T cell fitness
- Suboptimal CAR T cell expansion
- Lack of tumor reduction

- Optimal product attributes
- Favorable TME
- Robust CAR T cell expansion
- Complete tumor elimination

- Large tumor burden & detrimental TME (myeloid cells)
- Suboptimal product attributes (↓dose of juvenile T cells)
- Low CAR T cell expansion / tumor burden
- Partial tumor reduction
- Relapse with target-positive tumor

- Detrimental TME (immune desert or exclusionary)
- Low product T cell fitness
- Suboptimal CAR T cell expansion
- Lack of tumor reduction
Potential optimizations to enhance clinical efficacy of anti-CD19 CAR treatment in lymphoma

Primary Tx resistance
- Low product T cell fitness
  - “Cold” TME

Secondary Tx resistance
- Large tumor burden & detrimental TME
  - Low CAR T cell expansion / tumor burden
- CD19 related evasion

- Manufacturing and product attributes optimization; off the shelf products
- Combinations or sequencing with checkpoints; CAR armoring
- Re-dosing with CAR T cells (consolidative)
- Combination / consolidation with anti-CD20/CD22 agents (R², Bites, ADC)
- Dual targeted CAR T cell products
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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