Pharmacodynamic and Predictive Biomarkers Supporting Development of CAR T Cells for the Treatment of B-Cell Malignancies

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Kite, A Gilead Company

Disclosures

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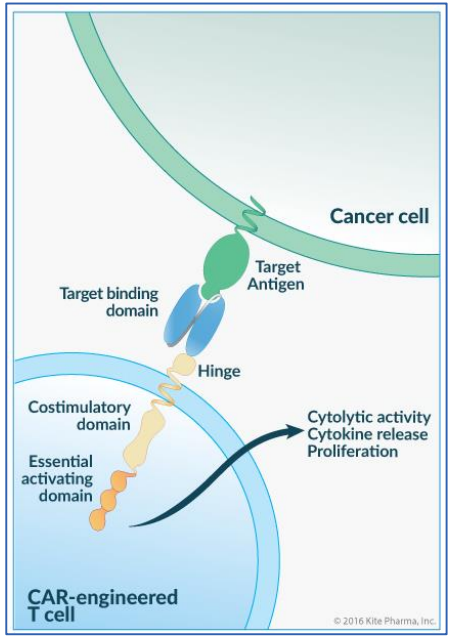
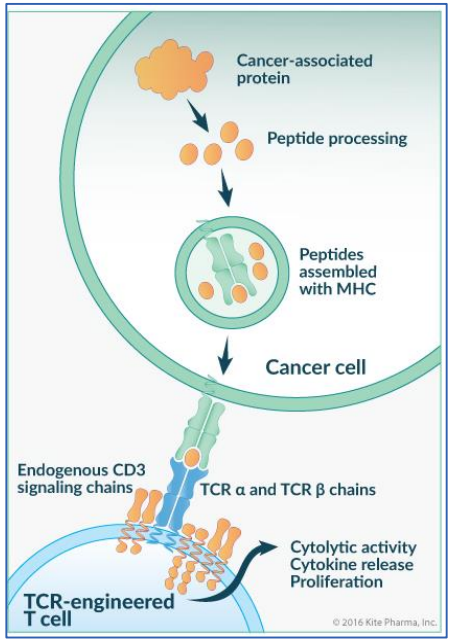
Employment at Kite, a Gilead Company, and equity ownership in Gilead Sciences, Inc.

Immune Repertoire Engineering

Chimeric Antigen Receptor (CAR)



Engineered T Cell Receptor (TCR)

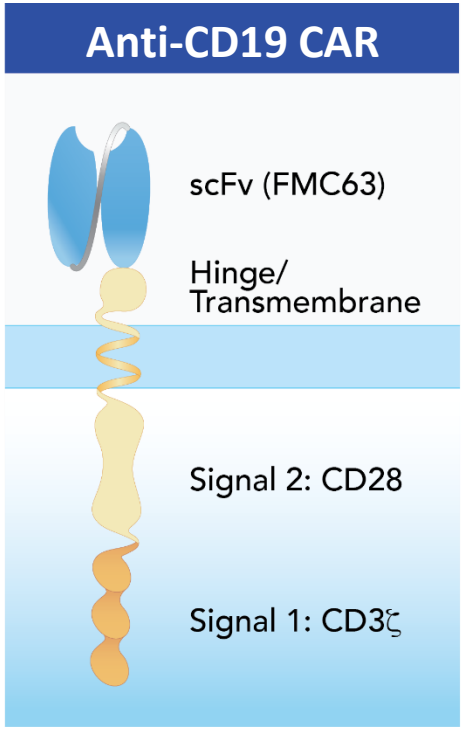


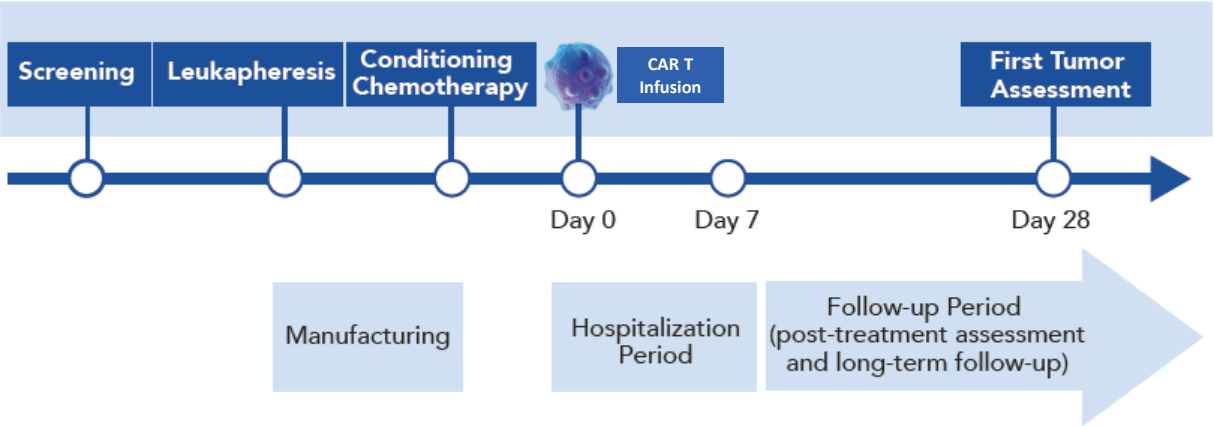
A Milestone for Cellular Based Therapy in Cancer

On 18 October 2017, YESCARTA received regular (full) approval by the FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Update to latest

Anti-CD19 CAR Design and Treatment Schema





- **Cyclophosphamide (300 or 500 mg/m^2) and Fludarabine (30 mg/m^2) daily for 3 days**
- **2 day rest followed by anit-CD19 CAR T at target dose of 2e6/ kg**

ZUMA-1: NCT02348216
NCI: NCT00924326 (murine)
NCI: NCT02659943 (human scFv)

ZUMA-1: Multicenter Trial of Axicabtagene Ciloleucel (axi-cel) in Refractory Aggressive NHL

Phase 1

Refractory DLBCL/PMBCL/TFL
(n = 7)

Phase 2 (N = 101)

Cohort 1
Refractory DLBCL
(n = 84)

Cohort 2
Refractory PMBCL/TFL
(n = 24)

Key Eligibility Criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline
- ECOG 0-1

Primary end point

- Phase 2: Objective Response Rate (ORR) tested in the first 92 patients dosed[a]

Key secondary end points

- DOR, OS, safety, levels of CAR T and cytokines

99% successfully manufactured (90% dosed)

[a]Type 1 error was controlled at the 1-sided 0.025 level and split between the testing of cohort 1 and cohorts 1 and 2 combined with the exact binomial test comparing observed ORR to a hypothesized rate of 20%. ORR was also assessed in all patients dosed (mITT) and in all patients enrolled (ITT)

ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; mAB, monoclonal antibody; NHL, non-Hodgkin lymphoma; OS, overall survival; PMBCL; primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

Ongoing Response in Pivotal ZUMA-1 Trial Highlights the Promise of Engineered Cellular Based Therapy in Cancer

<2 Years + **22 Clinical Trial Sites** + **101 Patients with Aggressive NHL** = **82% ORR**
54% CR
44% in ongoing response
39% in ongoing CR

Axi-Cel Maintained Ongoing Responses at Median Follow-up of 8.7 Months (Locke AACR 2017)

Reduction in CRS and Neurologic Toxicity Rates at the Primary Analysis Compared to Interim Analysis

Interim Analysis

- Grade 3+ CRS = 18%
- Grade 3+ Neurologic Events = 34%
- 3 Grade 5 AEs
  - Reported at ASH 2016
    - 2 related to axi-cel (one hemophagocytic lymphohistiocytosis and one cardiac arrest in the setting of CRS)
    - 1 deemed unrelated by investigator

Primary Analysis

- Grade 3+ CRS = 13%
- Grade 3+ Neurologic Toxicity = 28%
- Grade 5 = No additional events

Reduction in Grade 3+ AEs May Reflect Improved Management Strategies & Increased Investigator Experience with Axi-Cel

Comprehensive Translational Strategy

Conditioning
FACS, Multiparametric ELISA

Tumor (TME)
NanoString, RNAseq, Imaging (HalioDx)

Product
FACS, Multiparametric ELISA
Single Cell Analysis (IsoPlexis)

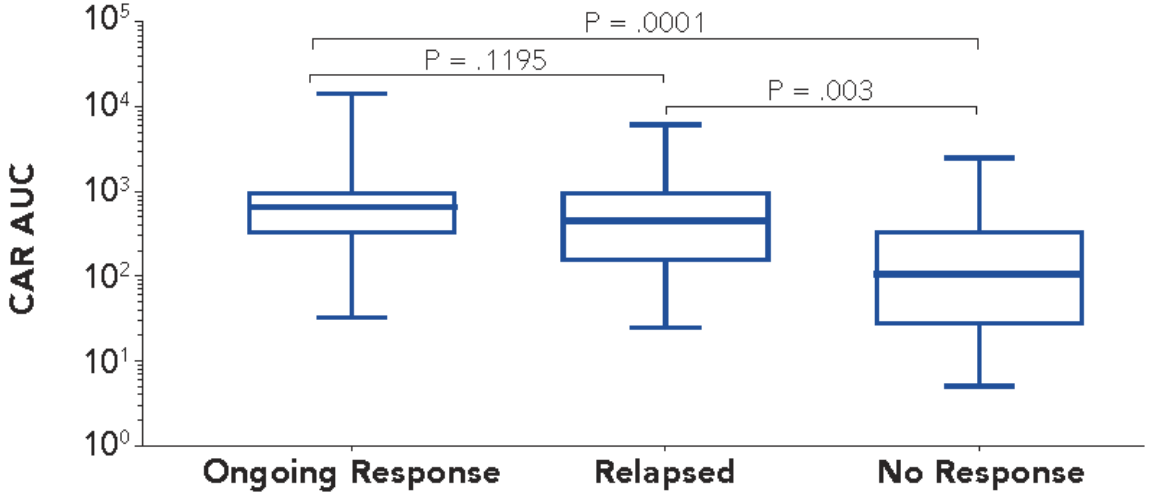
PK profile
FACS, qPCR

PD profile
Multiparametric
ELISA, TME
RNA Expression

Efficacy
↓
Correlative Analysis
↑
Toxicities

Immunogenicity (ELISA, Cell Based FACS)
B cell aplasia (FACS)
RCR (qPCR)

CAR T Cell Exposure is Associated With Clinical Response



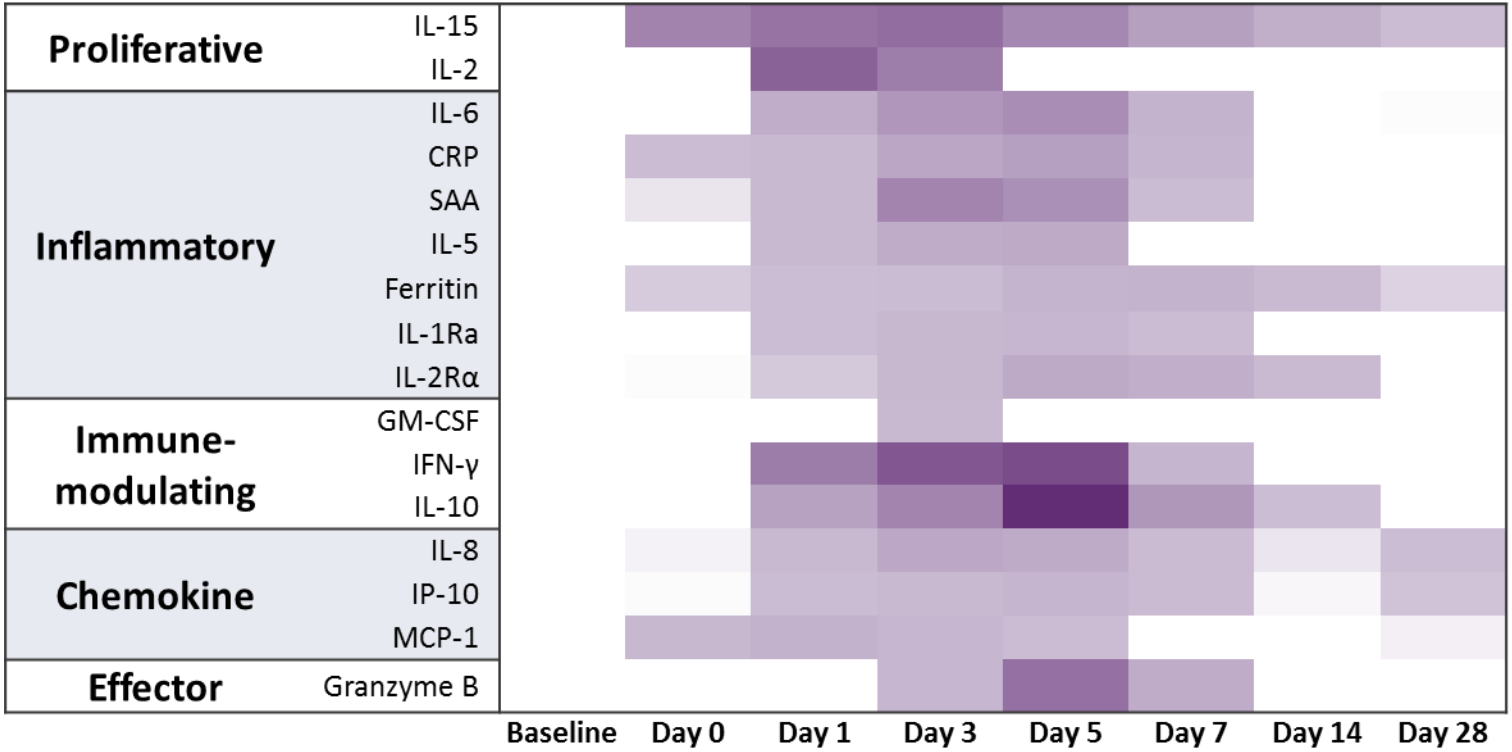
	Ongoing Response	Relapsed	No Response
N	49	34	17
Median (Q1, Q3)	656.2 (326.2, 981.2)	460.5 (166.6, 981.7)	103.3 (49.5, 321.2)
Fold Change vs No Response	6.4	4.5	N/A

Following a significant Kruskal-Wallis test (P = 0.0004), a post-hoc pairwise comparisons through Dunn's test were conducted. The pairwise comparisons' P values were adjusted using the Holm method.

- CAR T cell AUC for patients with responses was significantly greater than that of patients with no responses
- While the AUC value is numerically higher, no significant difference in CAR T cell AUC was observed between patients with ongoing response and patients with relapse

Locke et al ASCO 2017

Axi-cel Related Biomarker Signature in Blood



- Analytes shown were elevated in ≥50% of patients with ≥2-fold induction above baseline out of a panel of 44 measured

Serum analytes measured MSD®, Luminex®, and Quantikine™ ELISA.
CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; SAA, serum amyloid A

Key Findings: Factors that Influence Clinical Outcomes

Product
Proliferative capability
Polyfunctionality*

Conditioning
IL-15 Levels
Lymphodepletion

Tumor environment*
Immune programs
Checkpoints
Target expression

Efficacy and Toxicities

CAR T cell activation and expansion
Cytokine profile related to activated T cell and myeloid cells

*Subsequent speakers will present in more detail novel analysis approaches

Acknowledgements

Kite

Translational Sciences
Clinical Operations and Development
Biometrics

National Cancer Institute

James N. Kochenderfer
Stephen A. Rosenberg

ZUMA-1 Clinical Trial

Sattva Neelapu (MDACC)
Frederick Locke (Moffitt)

Translational Platform Support

Sean Mackay (IsoPlexis)
Patrick Paczkowski (IsoPlexis)
James Heath (Cal Tech)

Jérôme Galon (INSERM/ HalioDx)
Corinne Danan (HalioDx)
Sarah Turcan (HalioDx)

Patients, families, investigators

Some activities supported under 2 CRADAs between and NCI
PIs Drs. Steven Rosenberg and James Kochenderfer