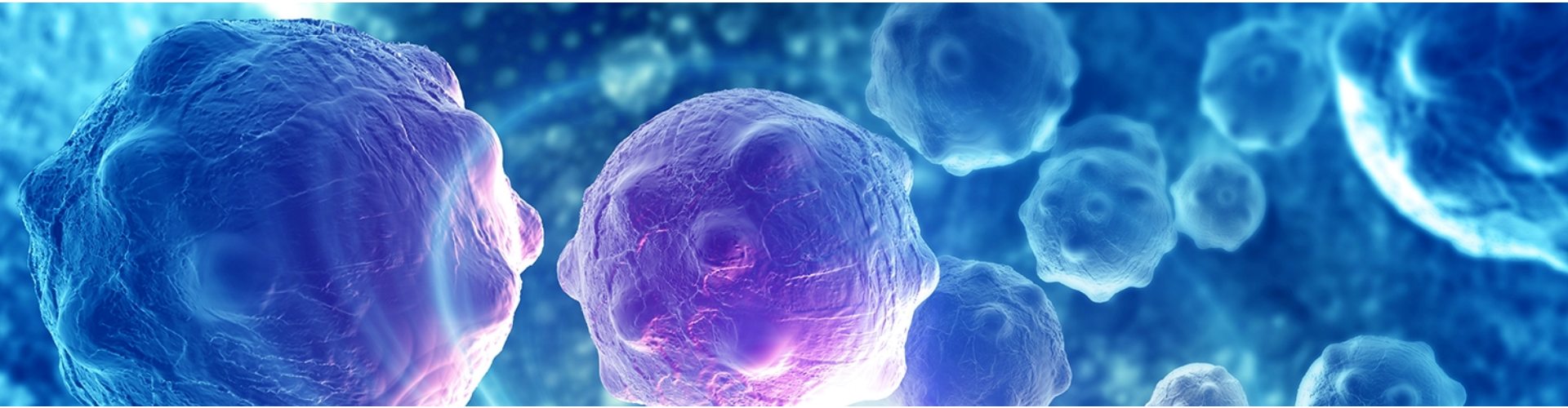

# Scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products

EMA Workshop
Nov 15-16 2016

Kite Pharma
FOCUSED ON THE CURE

# Margo Roberts: Biomarkers of Response/Safety for anti-CD19 CAR T cell Therapy



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To the extent statements contained in this presentation are not descriptions of historical facts regarding Kite Pharma, Inc. (“Kite,” “we,” “us,” or “our”), they are forward-looking statements reflecting management’s current beliefs and expectations. Forward-looking statements are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry’s actual results, levels or activity, performance, or achievements to be materially different from those anticipated by such statements. You can identify forward-looking statements by words such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes. Forward-looking statements contained in this presentation include, but are not limited to, statements regarding: (i) the success and timing of our product development activities and clinical trials; (ii) the ability and willingness of the National Cancer Institute (NCI) to continue research and development activities relating to our product candidates; (iii) our ability to obtain and maintain regulatory approval of KTE-C19 and any other product candidates; (iv) our ability to further develop and commercialize our product candidates; (v) our plans to research, discover and develop additional product candidates, including through our subsidiary Kite Pharma EU, and next generation product candidates, including a next-generation CAR with an “on/off” or “control” switch; (vi) our and our partners’ ability to develop, manufacture and commercialize our product candidates and to improve the manufacturing process; (vii) the size and growth potential of the markets for our product candidates, and our ability to serve those markets; (viii) the rate and degree of market acceptance of our product candidates; (ix) our ability to attract and retain key scientific or management personnel; (x) the anticipated timing of clinical data availability; (xi) the anticipated timing of submitting a Biologics License Application for KTE-C19 and commercially launching KTE-C19; (xii) our plans to expand geographically; (xiii) our ability to meet the milestones set forth herein; and (xiv) our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates.

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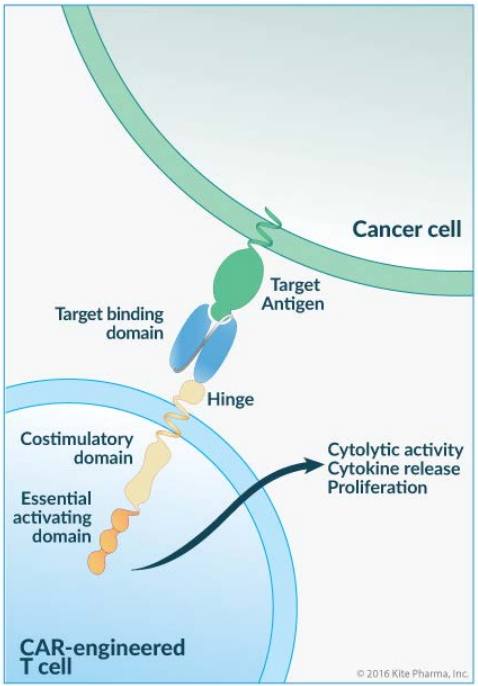
# Dual Platform Targets Both Hematological and Solid Cancers

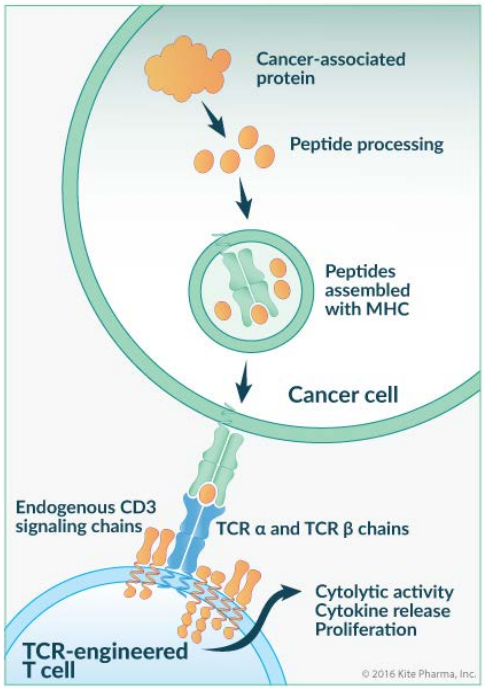
## Chimeric Antigen Receptor (CAR)

Cell surface targets




## T Cell Receptor (TCR)

Intracellular Targets

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# Refractory DLBCL Has Consistently Poor Outcomes

- DLBCL is the most common subtype of NHL
  - 26,000 new cases and 10,000 deaths in the US/year
- Outcomes in relapsed DLBCL are heterogeneous
  - ORR up to 63% (CORAL)[1]
- Outcomes in refractory DLBCL are homogenous and poor (SCHOLAR-1)
  - ORR 26% (CR 8% and PR 16%)[2]
  - mOS is 6.6 months[2]
- NCI study of anti-CD19 CAR T cells showed promising results
  - ORR: 73%, CR 55% in DLBCL, MCL, and TFL; most had refractory disease[3]



Abbreviations: CR, complete response; DLBCL, diffuse large B cell lymphoma; mOS, median overall survival; NCI, National Cancer Institute; ORR, overall response rate; MCL, mantle cell lymphoma; TFL, transformed follicular lymphoma.

1. Gisselbrecht C, et al. J Clin Oncol. 2010;28:4184-4190. 2. Crump M, et al. ASCO 2016. Abstr 7516.
3. Kochenderfer J, et al. ASCO 2016. Abstr LBA3010.

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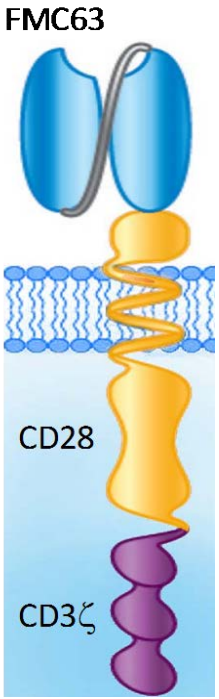
# Low-Dose Conditioning Chemotherapy and anti-CD19 CAR T Cells May Elicit Distinct Immune Programs Associated With Clinical Responses

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**Acknowledgements: This study was conducted under a cooperative research and development agreement (CRADA) between NCI and Kite Pharma**

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# Treated Patients

- The protocol enrolled patients with advanced lymphoma, but essentially normal organ function and ECOG 0 or 1 performance status
- A total of 22 patients were treated
- 19 patients had diffuse large B-cell lymphoma (DLBCL)
- 11 of the 19 DLBCL patients had chemotherapy-refractory lymphoma
- We also treated 2 patients with follicular lymphoma and 1 patient with mantle cell lymphoma

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# Anti-CD19 CAR T cell Clinical Protocol

- Conditioning chemotherapy on days -5 to -3
  - Fludarabine: 30 mg/$m^2$ daily for 3 days
  - Cyclophosphamide: 300 or 500 mg/$m^2$ daily for 3 days

- Infusion of anti-CD19 CAR T cells on day 0
  - 7 patients: 1x$10^6$ CAR T cells/kg
  - 14 patients: 2x$10^6$ CAR+ T cells/kg
  - 1 patient: 6x$10^6$ CAR+ T cells/kg

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# Summary of Adverse Events

- All patients had fevers
- 12 of 22 patients (55%) had Grade 3 or 4 neurologic AEs including confusion, dysphasia, encephalopathy, and gait disturbances
- Only 4 of 22 (18%) had Grade 3 or 4 hypotension
- All AEs in these patients completely resolved, usually in less than 2 weeks

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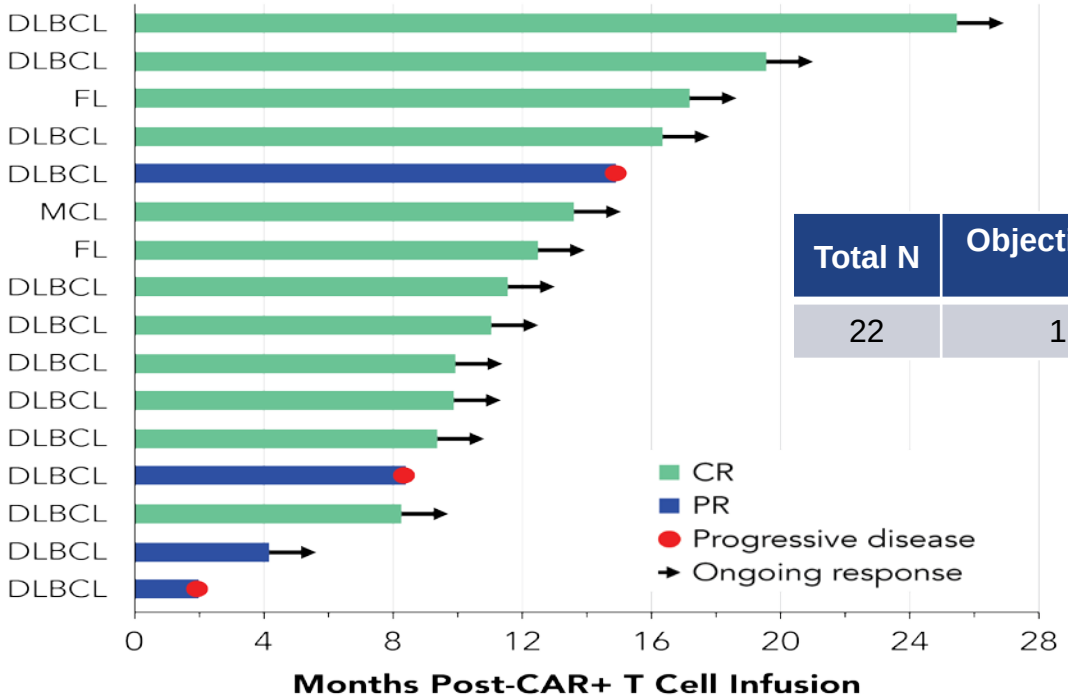
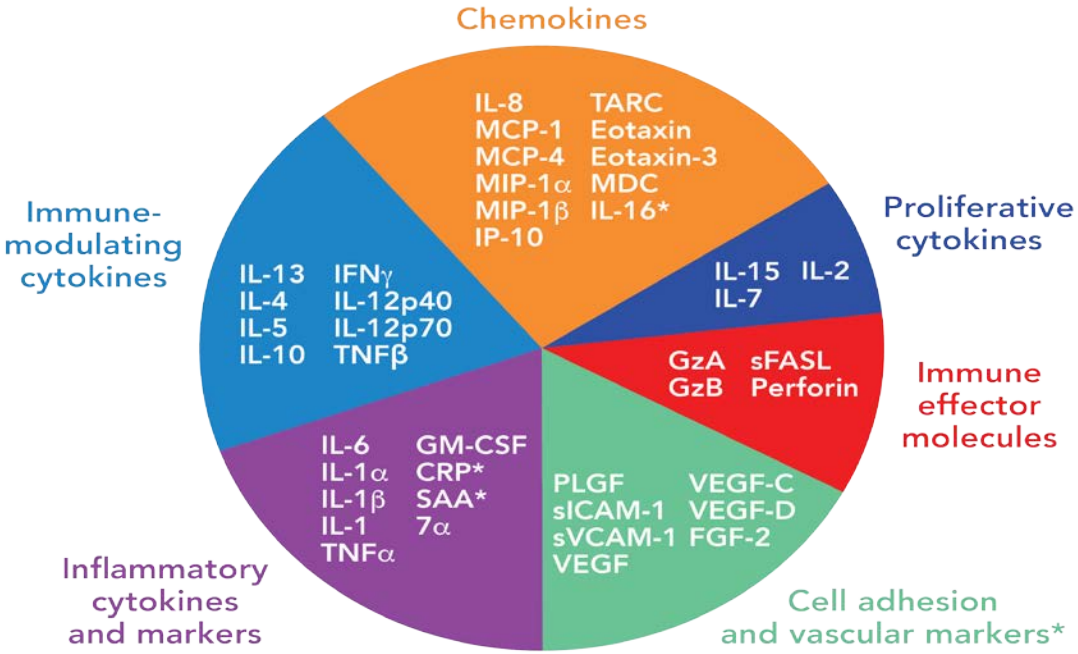
# Durability of Response in Patients who Achieved CR or PR After Low-Dose Conditioning Followed by anti-CD19 CAR T cells



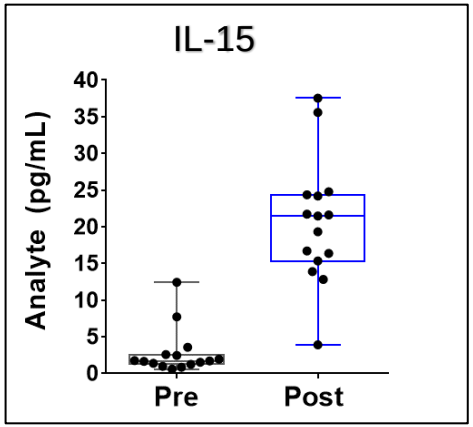

| Total N | Objective response N (%) | Complete response N (%) |
|---|---|---|
| 22 | 16 (73%) | 12 (55%) |

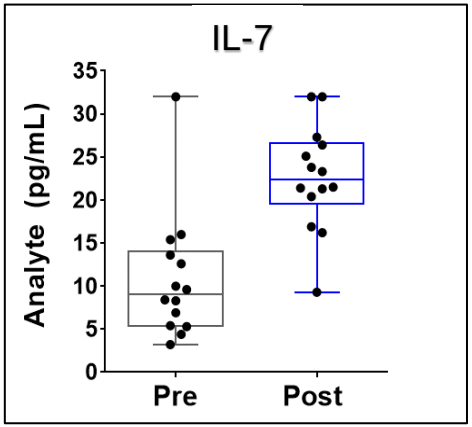
# Immune Markers Measured
# - Co-Culture of anti-CD19 CAR T cell Products with Target Cells
# - Patient Serum Samples Following Treatment

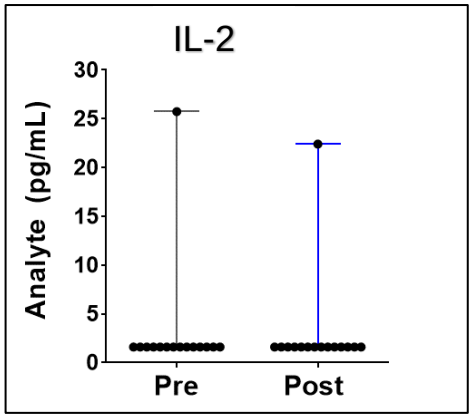


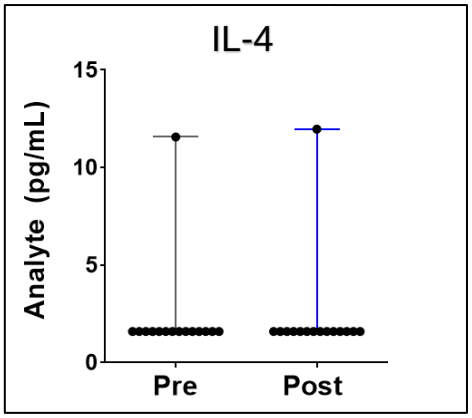

*Not included in analysis of co-culture
Gz, Granzyme.

# Selective Induction of T-cell Homeostatic Cytokines IL-15 and IL-7 in Response to Conditioning




- In mouse models, lymphodepletion prior to adoptive transfer markedly enhances anti-tumor activity of transferred T cells
  - Various mechanisms including IL-15 and IL-7
- Lymphodepletion associated with higher response rate/durability of response in TIL-treated metastatic melanoma patients, relative to minimal/no lymphodepletion*
  - Correlated with increased levels of IL-7 and IL-15

*Refs: Dudley et al., (2008) J Clin Oncol; Rosenberg et al., (2011)

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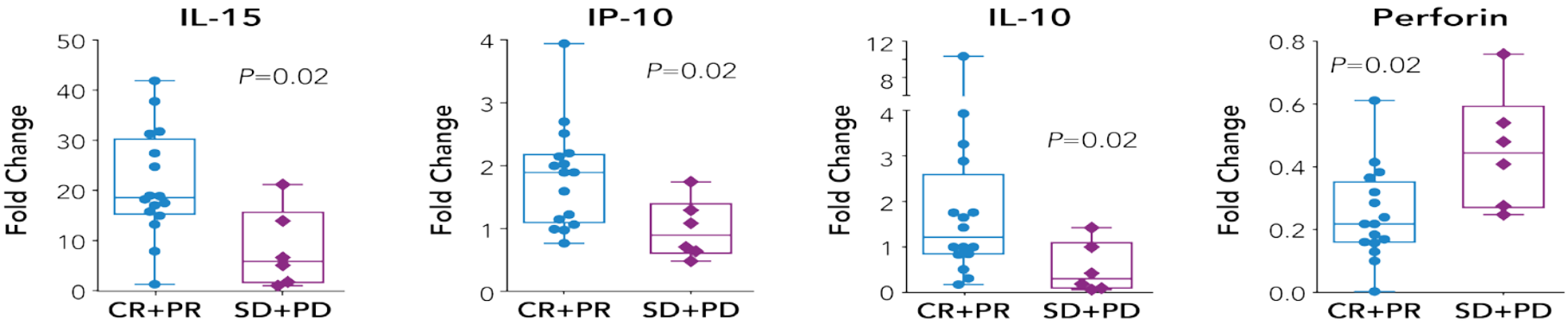
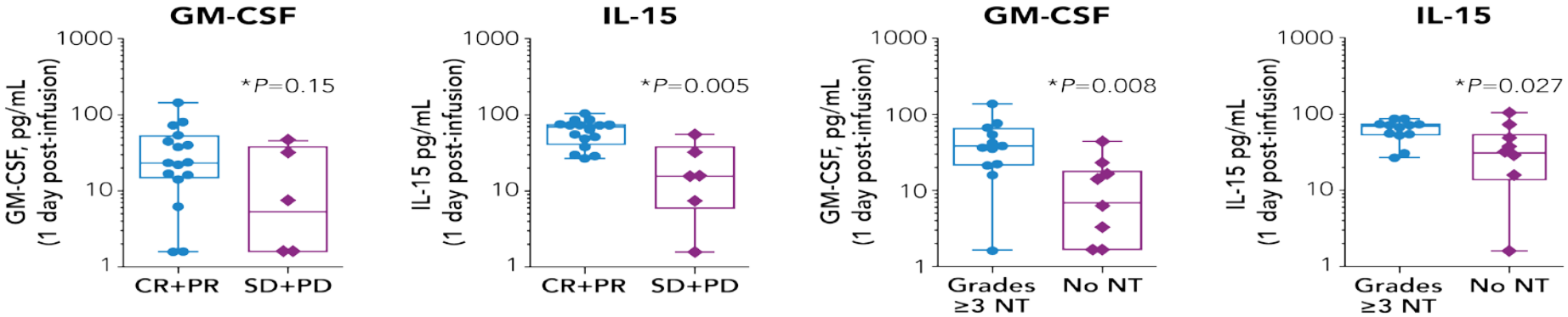
# Low-Dose Conditioning Chemotherapy with Cyclophosphamide and Fludarabine Modulates the Serum Levels of IL-15, IP-10, IL-10, and Perforin*: Correlation with Clinical Response




*Exact Wilcoxon two-sample test was used to compare the fold change values (post- vs pre-conditioning) across responder vs non-responder groups. All *P* values are unadjusted.

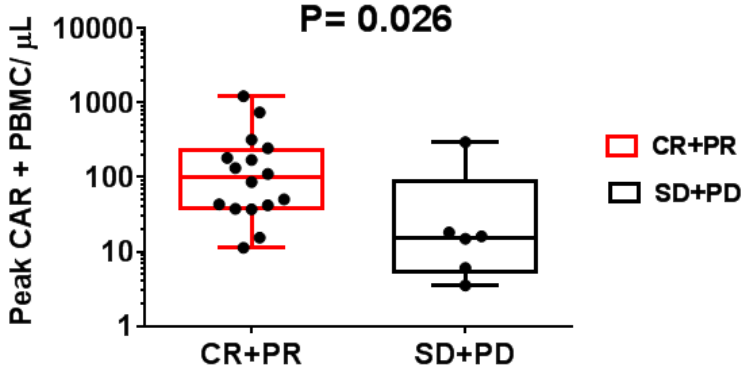
# Levels of IL-15 and GM-CSF are Elevated One Day After anti-CD19 CAR T cell Infusion in Patients who had an Objective Response or Experienced a Grade ≥3 Neurologic AE



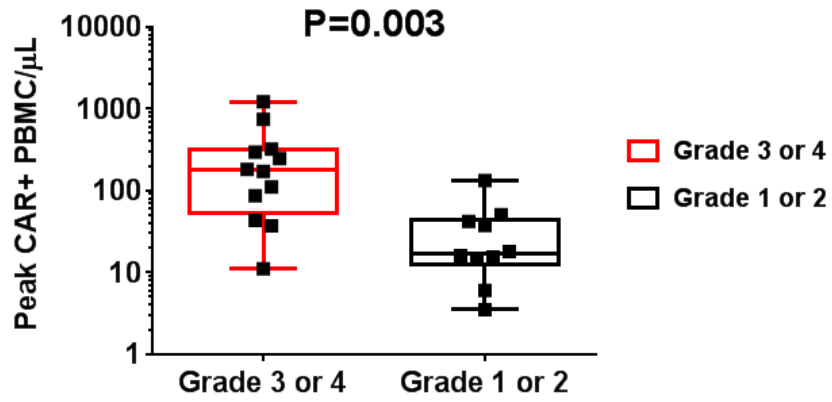

*Exact Wilcoxon two-sample test; *P* value is uncorrected for multiple comparisons.
NT, neurotoxicity.

# High Peak Levels of Blood anti-CD19 CAR+ Cells are Associated With Objective Response and Neurologic AEs

**Association of peak CAR+ cell level with response**




**Association of peak CAR+ cell level with neurological AEs**

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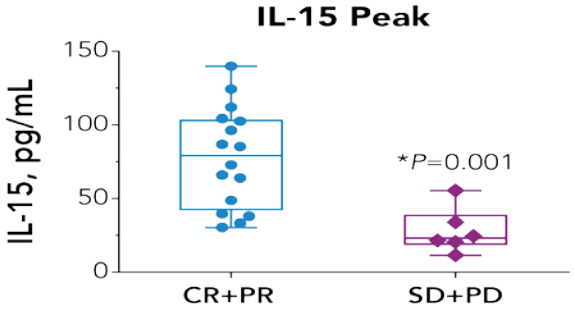
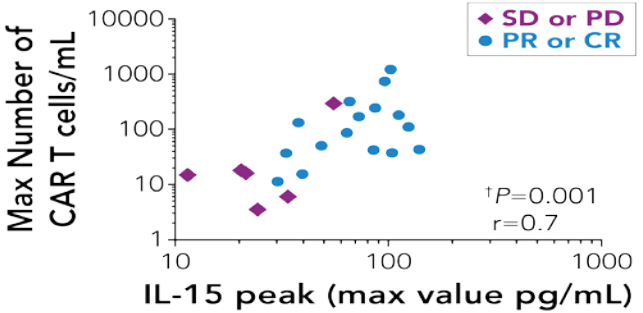
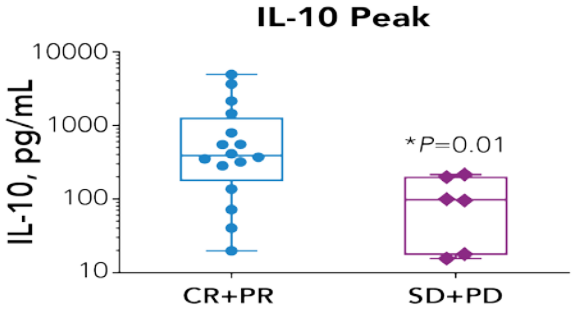
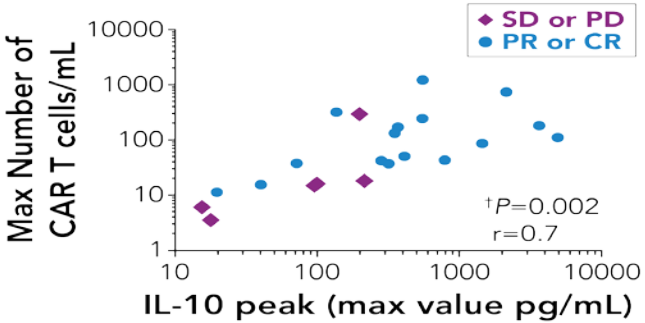
# Peak Serum Biomarkers (IL-15, IL-10) and anti-CD19 CAR T cell Levels in Blood are Elevated in Patients with Objective Response*



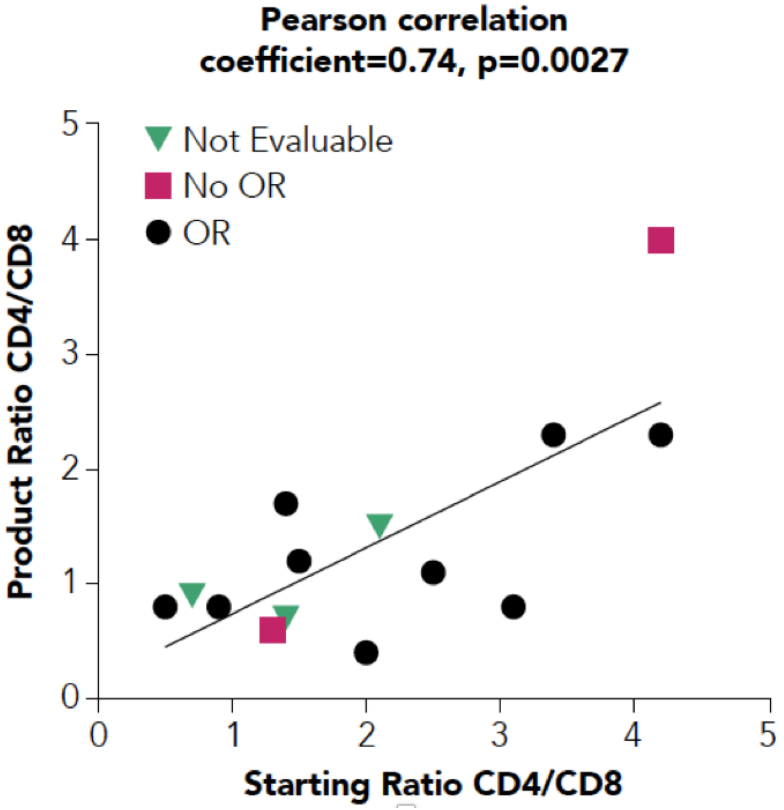



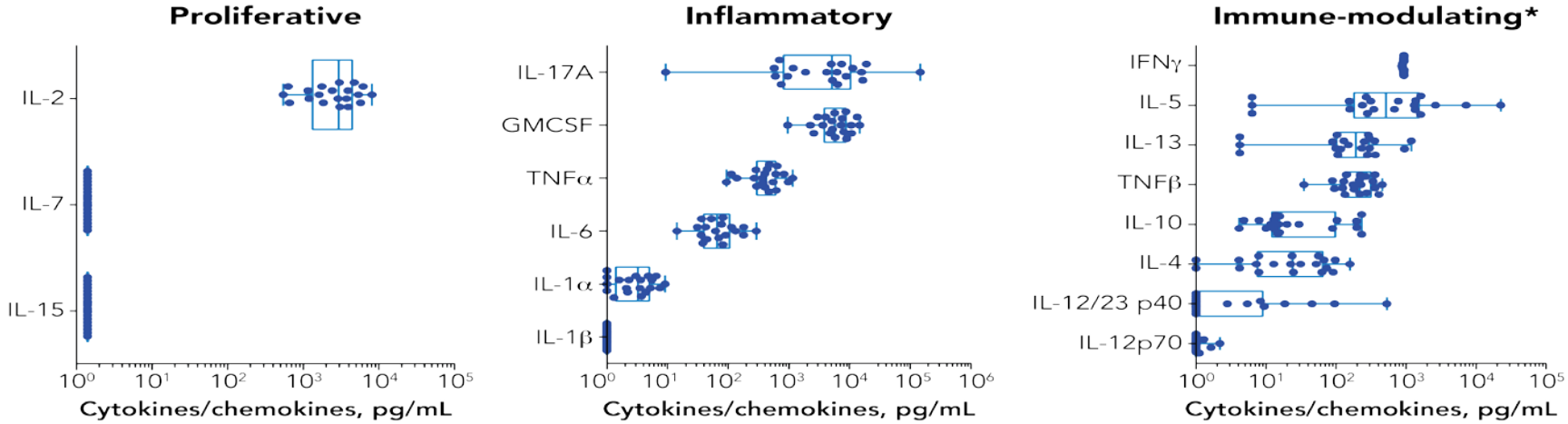

*Exact Wilcoxon two-sample test; †Spearman correlation coefficient and *P* value.
*P* value is uncorrected for multiple comparisons.

# Clinical Responses Observed Across a Broad Range of CD4:CD8 Ratios in the anti-CD19 CAR T cell Product




*2 CE patients were not evaluable for clinical response; 1 patient was not evaluable at the time of this analysis

# Cytokine and Chemokine Production in Co-Cultures of anti-CD19 CAR T cells and CD19+ Target Cells in vitro




*All samples above ULOQ at 1:20 dilution for IFNγ

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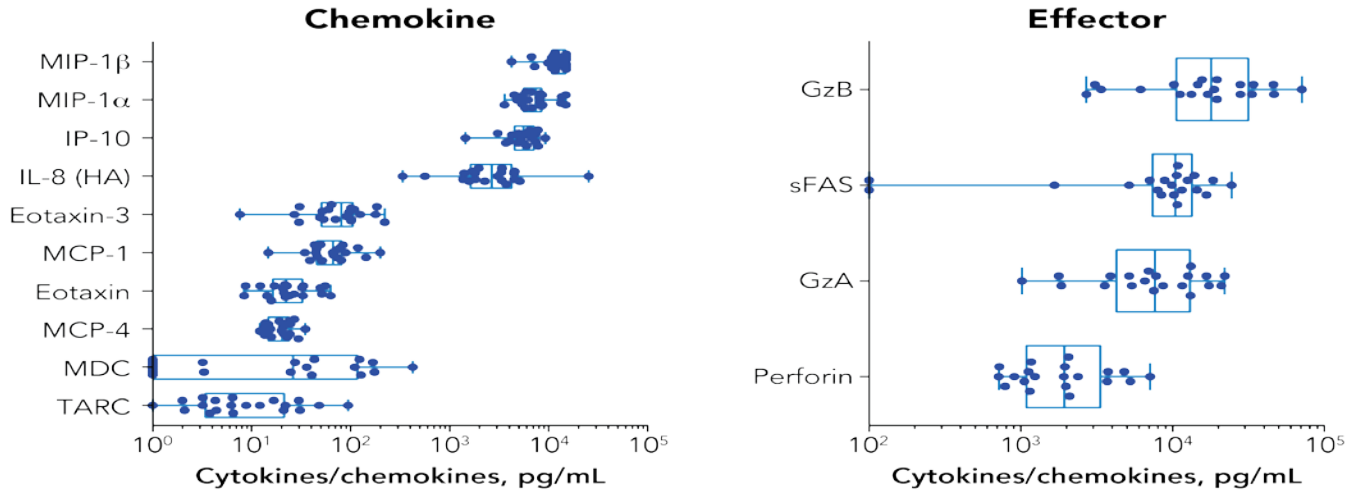
# Cytokine and Chemokine Production in Co-Cultures of anti-CD19 CAR T cells and CD19+ Target cells in vitro (cont.)




Gz, Granzyme.

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# Summary and Conclusions

- Anti-CD19 CAR T cells preceded by low-dose chemotherapy have significant activity against advanced lymphoma
- The dominant toxicities in these patients were neurologic. The toxicities resolved
- Both anti-lymphoma responses and neurologic AEs were associated with higher blood levels of anti-CD19 CAR T cells and select cytokines
- Polyfunctional anti-CD19 CAR T cells and cytokines may associate with outcome
- Anti-CD19 CAR T cells have entered multicenter clinical trials

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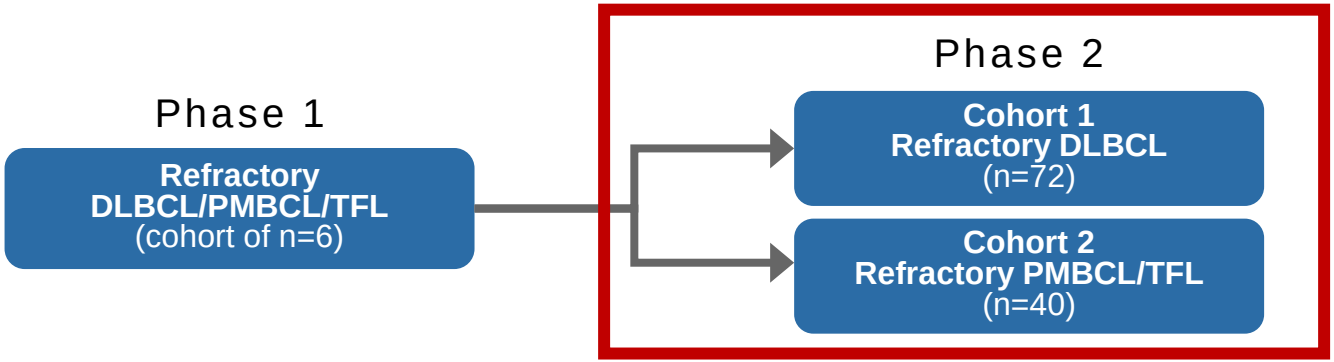
# ZUMA-1 Is a Multicenter Trial of KTE-C19 in Chemorefractory Aggressive NHL (NCT02348216)




**Eligibility criteria**

- Chemotherapy-refractory disease: PD or SD as best response to most recent chemotherapy or relapse ≤12 months of prior ASCT
- Adequate prior therapy: anti-CD20 mAb and an anthracycline-containing chemotherapy
- ECOG PS 0-1

**Primary endpoint**

- Phase 1: incidence of DLTs
- Phase 2: ORR

**Key secondary endpoints**

- DOR
- PFS/OS
- Safety
- Levels of CAR and cytokines

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# Summary of ZUMA-1 Interim Analysis

| | ZUMA-1 Phase 2 | | | | | |
|---|---|---|---|---|---|---|
| | DLBCL (n=51) | | TFL/PMBCL (n=11) | | Combined (n=62) | |
| | ORR (%) | CR (%) | ORR (%) | CR (%) | ORR (%) | CR (%) |
| Best ORR | 76* | 47 | 91 | 73 | 79 | 52 |
| Month 3 | 39 | 33 | 64 | 64 | 44 | 39 |

* P<0.0001

- Grade 3+ CRS 18%; Neurologic AE: 34%
- Grade 5 KTE-C19 related AE: 3%

Full Data at Upcoming Scientific Meeting

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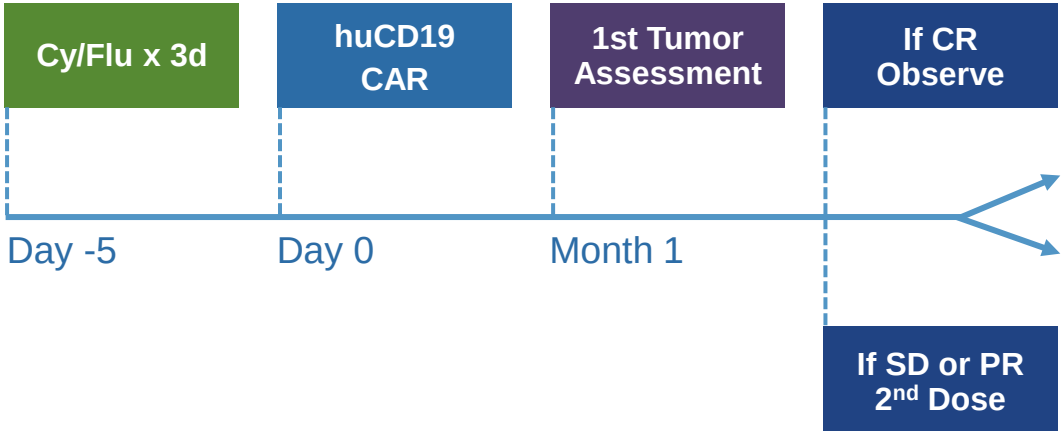
# Human anti-CD19 CAR Trial to Explore Potential of Re-dosing

## Rationale

- Utilizes new human CD19 construct
- Potentially less T-cell immune responses

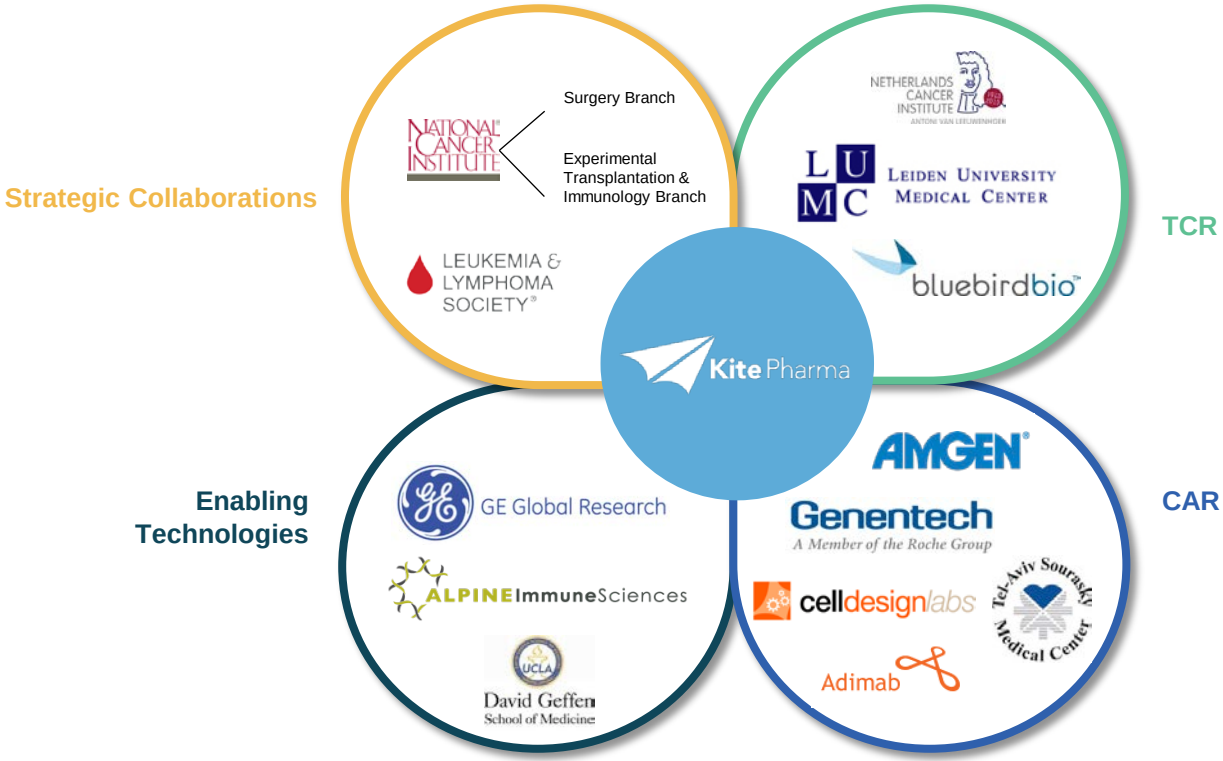
## Key Eligibility Criteria

- B-NHL and CLL
- Relapsed/refractory disease
- ECOG 0 or 1




Preliminary Data in 2016

# Leveraging Academic and Industry Collaborations for Next Generation Technologies

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