Primary and Secondary Mechanisms of Resistance to Autologous Anti-CD19 CAR T cell Therapy in Refractory Non-Hodgkin's Lymphoma (rNHL)

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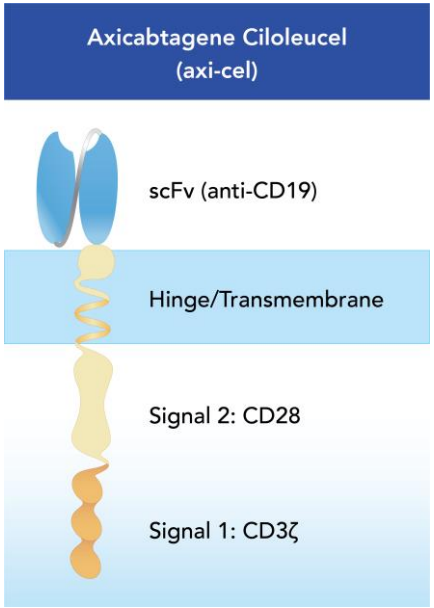
Kite, a Gilead Company

Disclosures

John Rossi: Employment, Kite, a Gilead Company; Equity ownership, Gilead Sciences, Inc.

ZUMA-1: Background

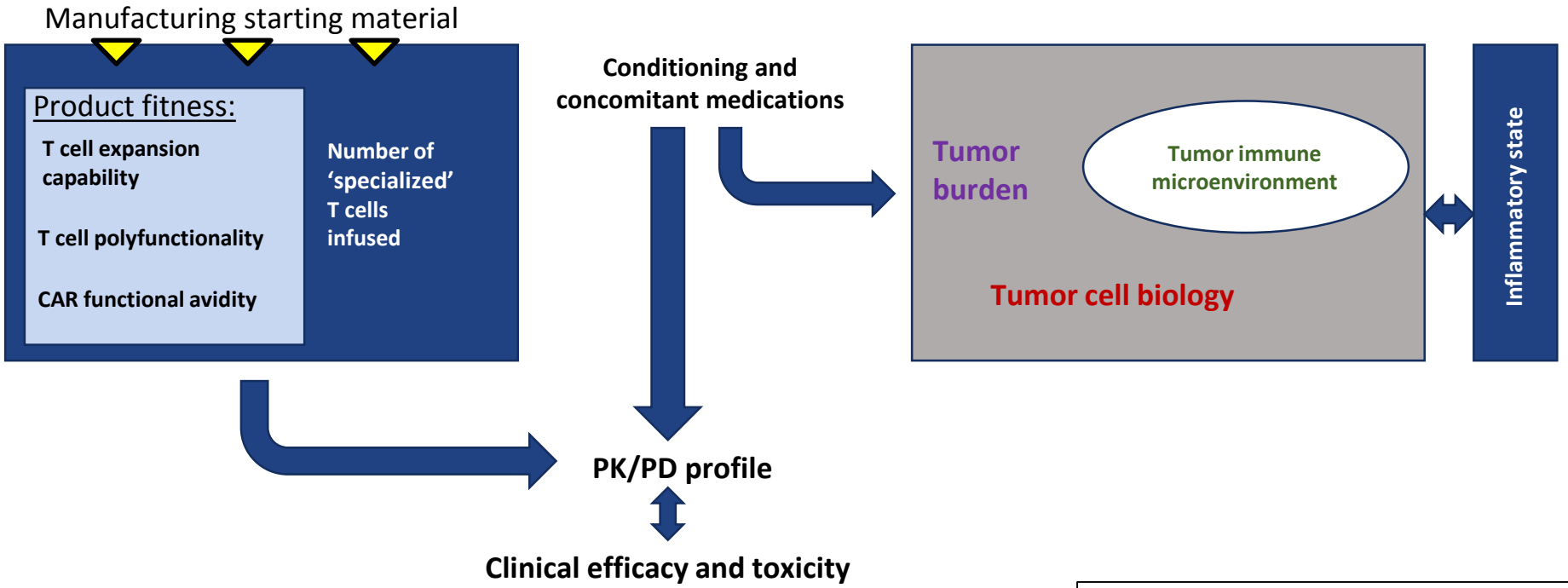
- Unmet need in refractory large B cell lymphoma (SCHOLAR-1, N = 636)[1]
  - ORR = 26%; CR rate = 7%
  - Median OS = 6.3 mo
- Axi-cel is an autologous anti-CD19 CAR T therapy
- Axi-cel (YESCARTA®) was approved on October 18, 2017 by the US FDA for the treatment of adult patients with relapsed or refractory large B cell lymphoma[2]
- ZUMA-1 primary analysis (N = 101) demonstrated[3]:
  - **ORR = 82%; CR rate = 54%**
  - **44% of patients with ongoing response (8.7 mo median follow-up)**
  - 13% and 28% of patients experienced Grade ≥ 3 CRS and NE, respectively



CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NE, neurologic event; ORR, objective response rate; OS, overall survival.

1. Crump M, et al. *Blood*. 2017;130:1800-1808. 2. YESCARTA (axicabtagene ciloleucel) [package insert]. Santa Monica, CA: Kite Pharma. 2017. 3. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544.

Factors That Influence Treatment Success and Failure to CAR T Cell Therapy: A Hypothesized Model

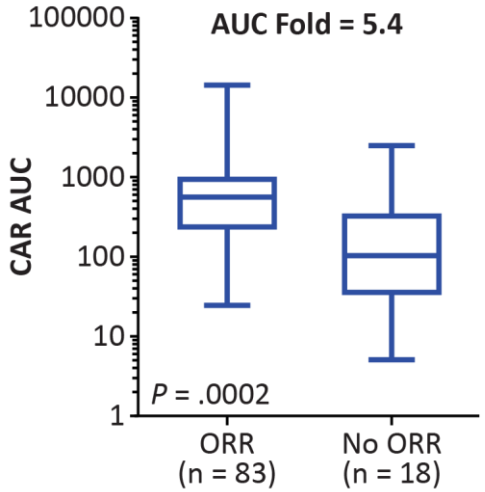


Adapted from Locke et al SITC 2018 #P212

CAR, chimeric antigen receptor; PD, pharmacodynamics; PK, pharmacokinetics.

In ZUMA-1 CAR T Cell Expansion Associated With Response

Objective Response Rate (ORR)



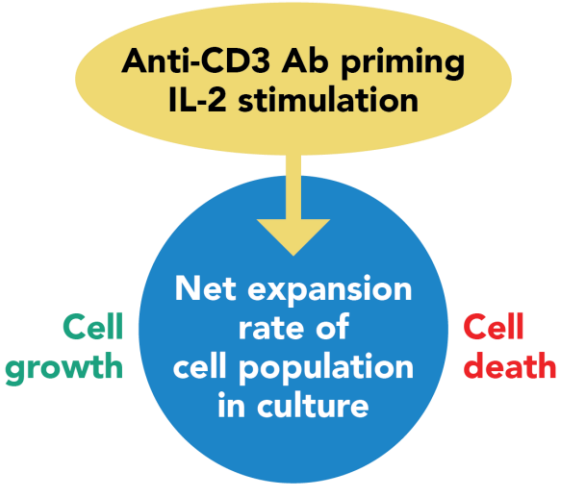
- CAR expansion was significantly associated with response ($P < .001$), with an $AUC_{Day0\text{-}28}$ that was 5.4 times as high among patients with a response as among those who did not have a response

- CAR $AUC_{Day0\text{-}28}$ is defined as cumulative levels of CAR+ cells/µL of blood over the first 28 days post axi-cel
- AUC fold change is shown for patients with vs. without response

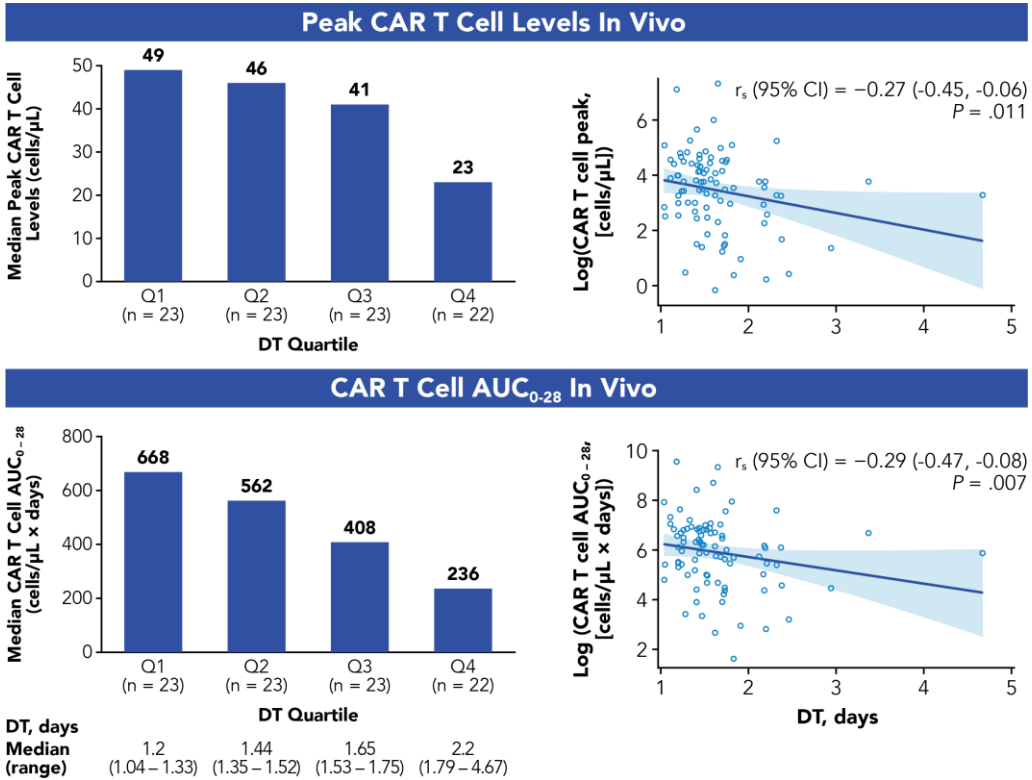
Locke et al ASCO 2017 #3023

Measurement of Pre-Treatment Kinetics of Expansion of Product T Cells and Association With Expansion

T cell expansion rate, a component of product "fitness", measured pretreatment



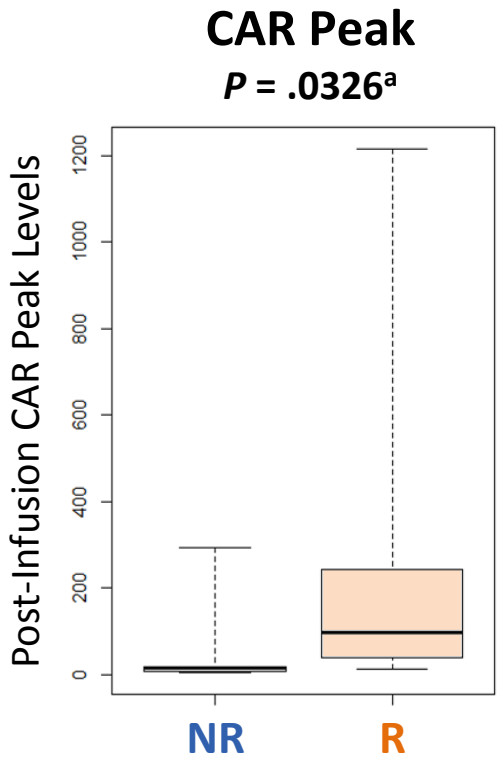
$$\text{Doubling time} = \frac{\ln(2) \times \text{duration}}{\ln\left(\frac{\text{Total viable cells at harvest}}{\text{Total viable cells at Day 3}}\right)}$$

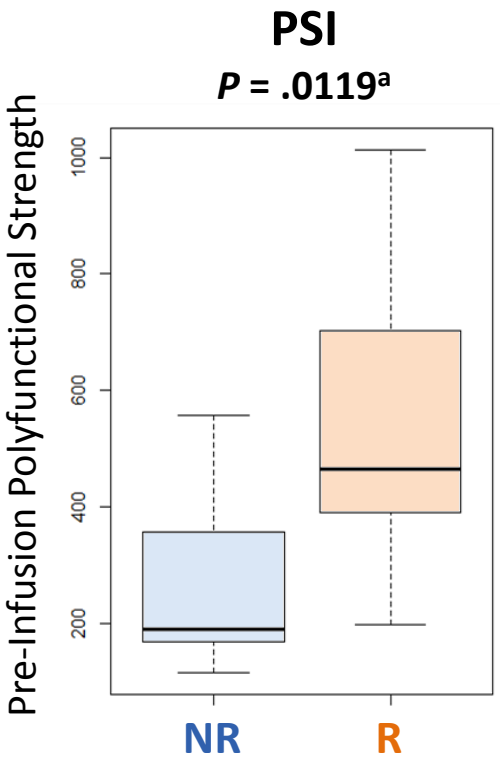


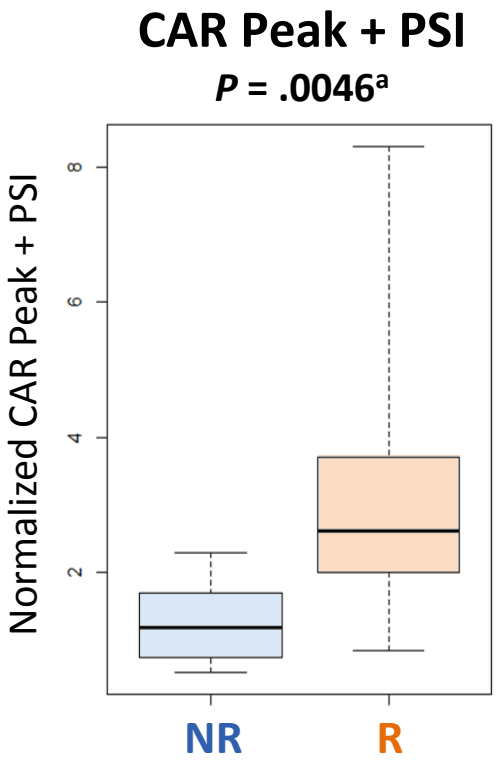
CAR, chimeric antigen receptor; DT, doubling time; Q, quartile.

Adapted from Locke et al SITC 2018 #P212

CAR Peak Levels *In Vivo* and Polyfunctional Strength Associated With Objective Response



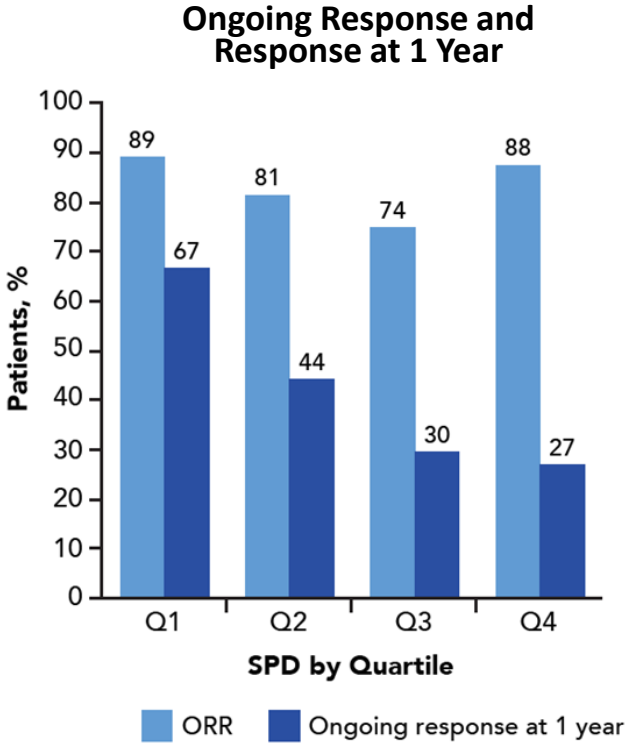


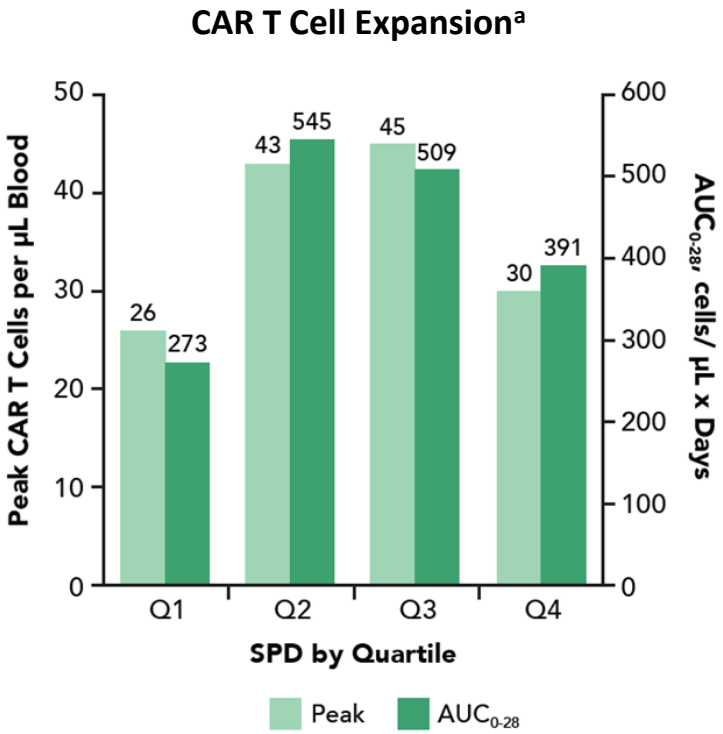


[a]Mann-Whitney U Test.
CAR, chimeric antigen receptor; NR, nonresponder; PSI, polyfunctional strength index; R, responder.

Rossi et al AACR 2017 #2990

Outcomes by Quartiles of SPD in ZUMA-1



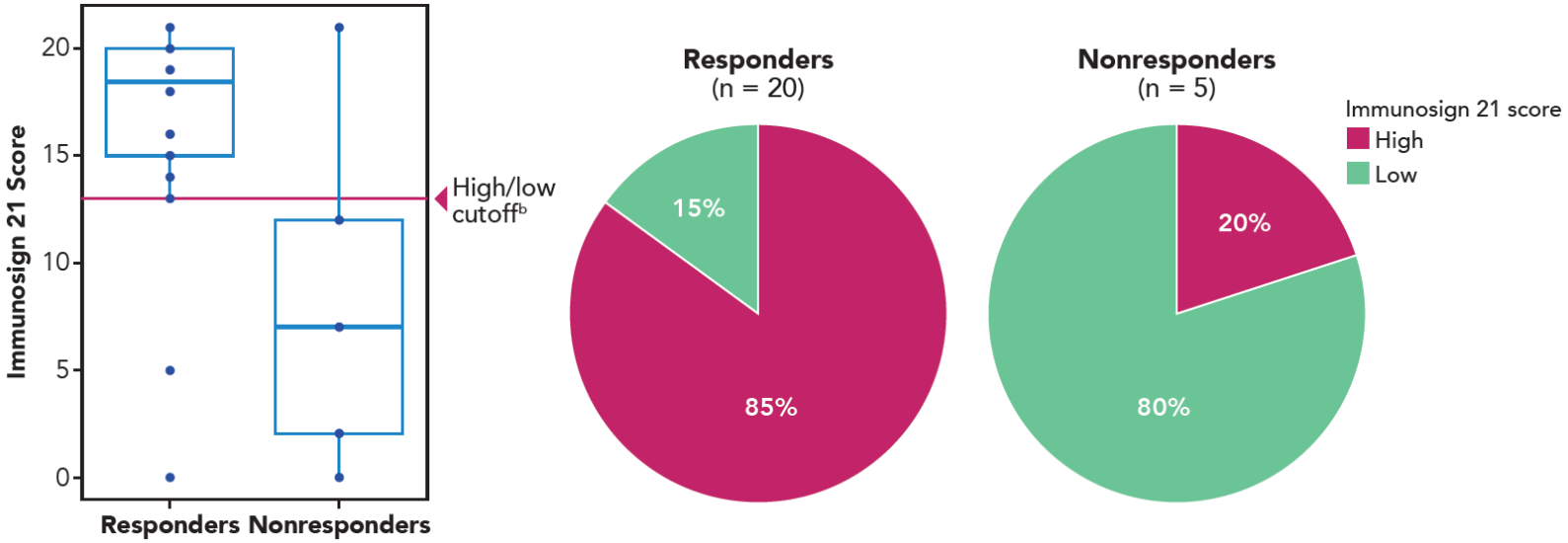


[a]Median values.

AUC_{0-28}, area under the curve from Day 0 to Day 28; ORR, objective response rate; Q, quartile.

Locke et al ASCO 2018 #3039

Association Between Immunosign® 21 Score Measured Before CAR T Cell Treatment and Clinical Outcome[a]

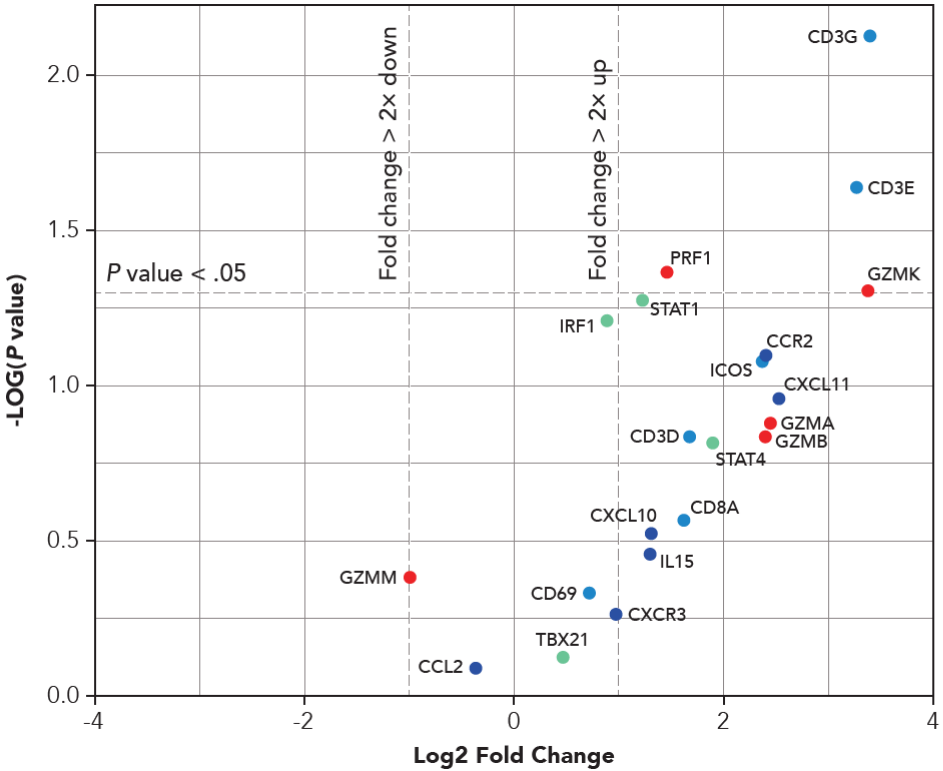


- A high Immunosign 21 score was associated with objective response at a minimum follow-up of 9 months (P = .012)
- In a sensitivity analysis, which included the delayed responder, the association between a high Immunosign 21 score and objective response had a P = .053

[a]This analysis was performed on samples from 25 patients treated with axi-cel with a minimum follow-up of 9 months. One patient subsequently converted from a "nonresponder" to a "responder" at 12-month follow-up.
[b]Cutoff was arbitrarily defined as the 25th percentile of the observed scores among samples.

Rossi et al AACR 2018 #LB-016

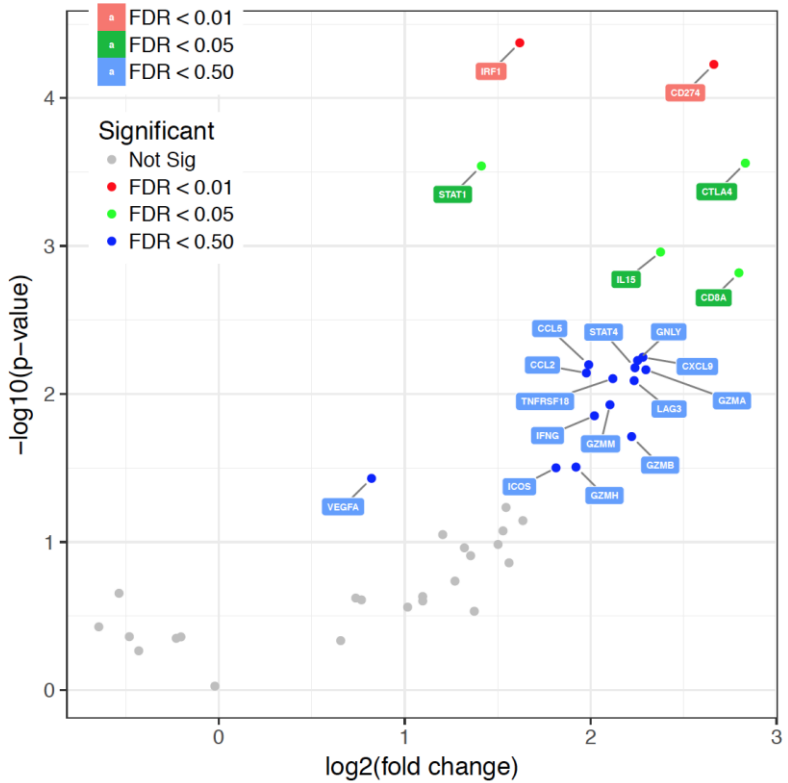
Differences in Expression of Immunosign 21 Genes Measured Before CAR T Cell Treatment in Responders vs Nonresponders[a]

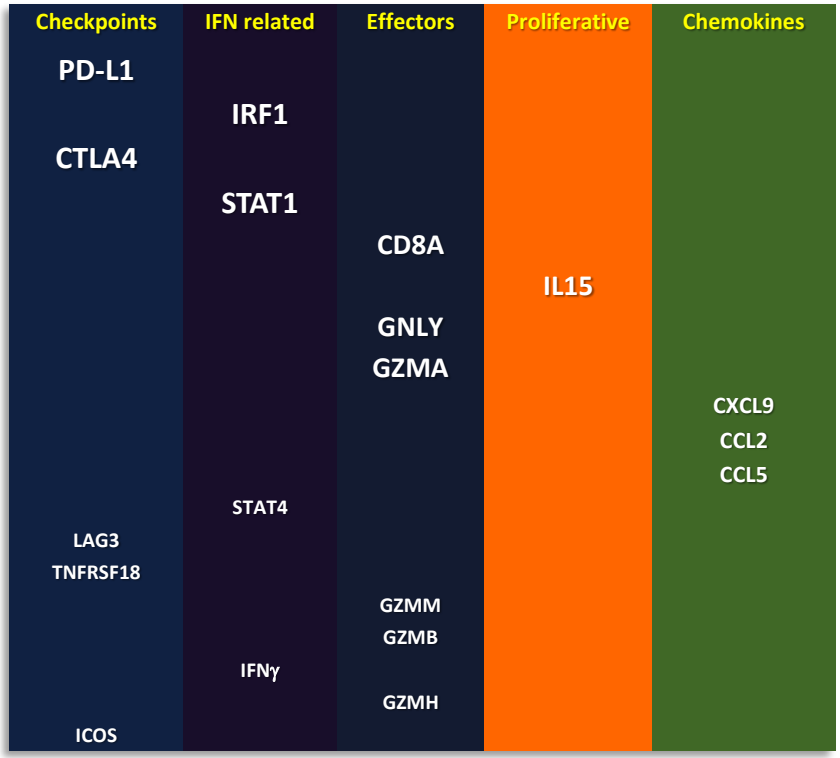


[a]This analysis was performed on samples from 25 patients treated with axi-cel with a minimum follow-up of 9 months. One patient subsequently converted from a "nonresponder" to a "responder" at 12-month follow-up.

Rossi et al AACR 2018 #LB-016

Treatment with Axi-Cel Results in Rapid and Dramatic Changes in the Tumor Immune Microenvironment

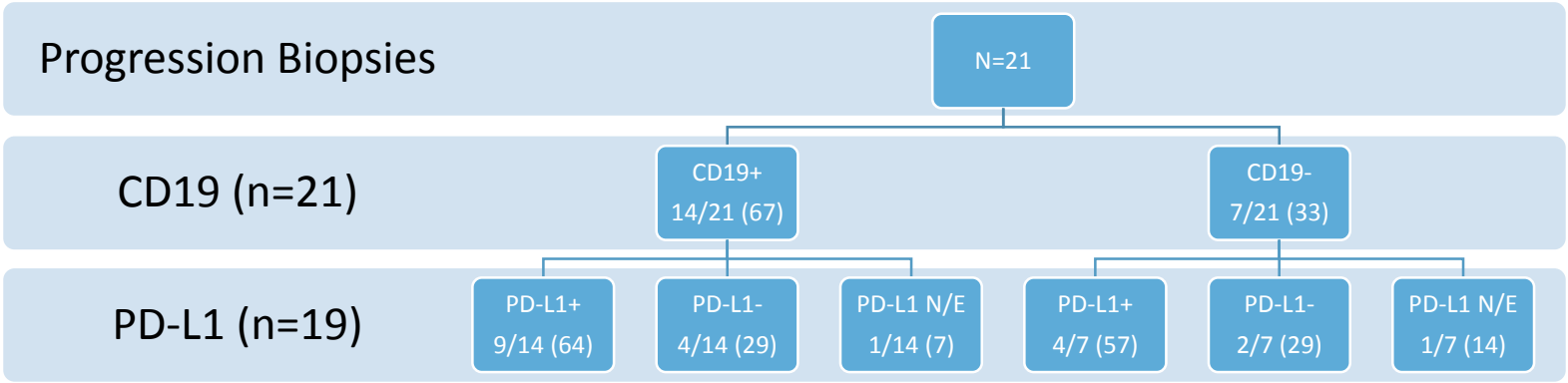




Top transcripts from a pre-specified 43 immune gene panel upregulated in tumor 7-21 days after treatment. IDO1 and other genes not in the 43 panel are pending.

Galon et al ASCO 2017 #3025

Analysis of B Cell and Immune-Related Molecules at Progression Identifies Relapse with CD19+ or CD19- Tumor cells



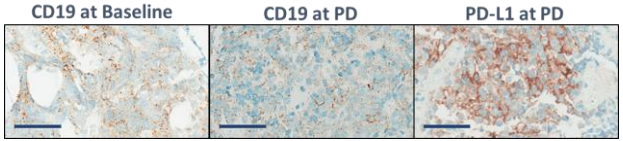
Post-progression tumor biopsies (21 evaluable patients)

- 33% were CD19-
- 62% were PD-L1+

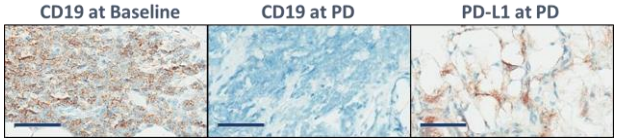
At Baseline, 94% (16/17) of evaluable patients were CD19+

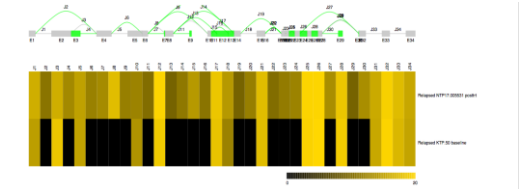
Baseline and post-progression samples not obtained from the same lesions.
PD-L1, programmed death ligand 1.

Example CD19+ relapse



Example CD19- relapse





CD19 RNA splice variants identified
In DLBCL relapse biopsies

Adapted from Neelapu et al ASH 2018 #578

CAR T can be Effective in Adult B-ALL Subjects who Have Failed Prior Blinatumomab Immunotherapy

	Prior Blin (n = 8)	Blin-Naive (n = 10)	Overall (N = 18)
CR Rate (CR + CRi), n (%)	5 (63)	8 (80)	13 (72)
CR	5 (63)	8 (80)	13 (72)
CRi	0	0	0
Blast-free hypoplastic/aplastic BM, n (%)	1 (13)	1 (10)	2 (11)
Undetectable MRD, n (%)	7 (88)	10 (100)	17 (94)

- 94% of patients achieved a response with undetectable MRD (8 week follow-up)
  - 7/8 with prior blinatumomab and 10/10 who were blinatumomab-naive
- **Among 6 evaluable patients who did not respond to prior blinatumomab: 5 had undetectable MRD response to KTE-C19**

Shah et al ASCO 2018 #7006

CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission.

Conclusions

- In ZUMA-1 ~20% of treated patients were primary refractory to anti-CD19 CAR T cell therapy
  - Mechanisms of primary treatment related failure ascribable to:
    - Product T cell fitness
    - CAR T cell function in product
    - Immune exclusionary tumor microenvironment

- In ZUMA-1 ~35% of treated patients experienced a secondary treatment-related failure
  - Mechanisms of secondary treatment-related failure ascribable to:
    - High tumor burden
    - Rapid upregulation of immune checkpoints
    - CD19 target antigen loss

- In adult B-ALL, CAR T therapy might be an effective treatment option for patients who have failed a prior immunotherapy regimen

Acknowledgments

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