Weill Cornell Medicine

Challenges of Trial Design Incorporating Pharmacodynamics

The Importance of Mechanism-Driven Drug Development

Jedd D. Wolchok, MD, PhD, FASCO
Director, Meyer Cancer Center

Weill Cornell Medicine

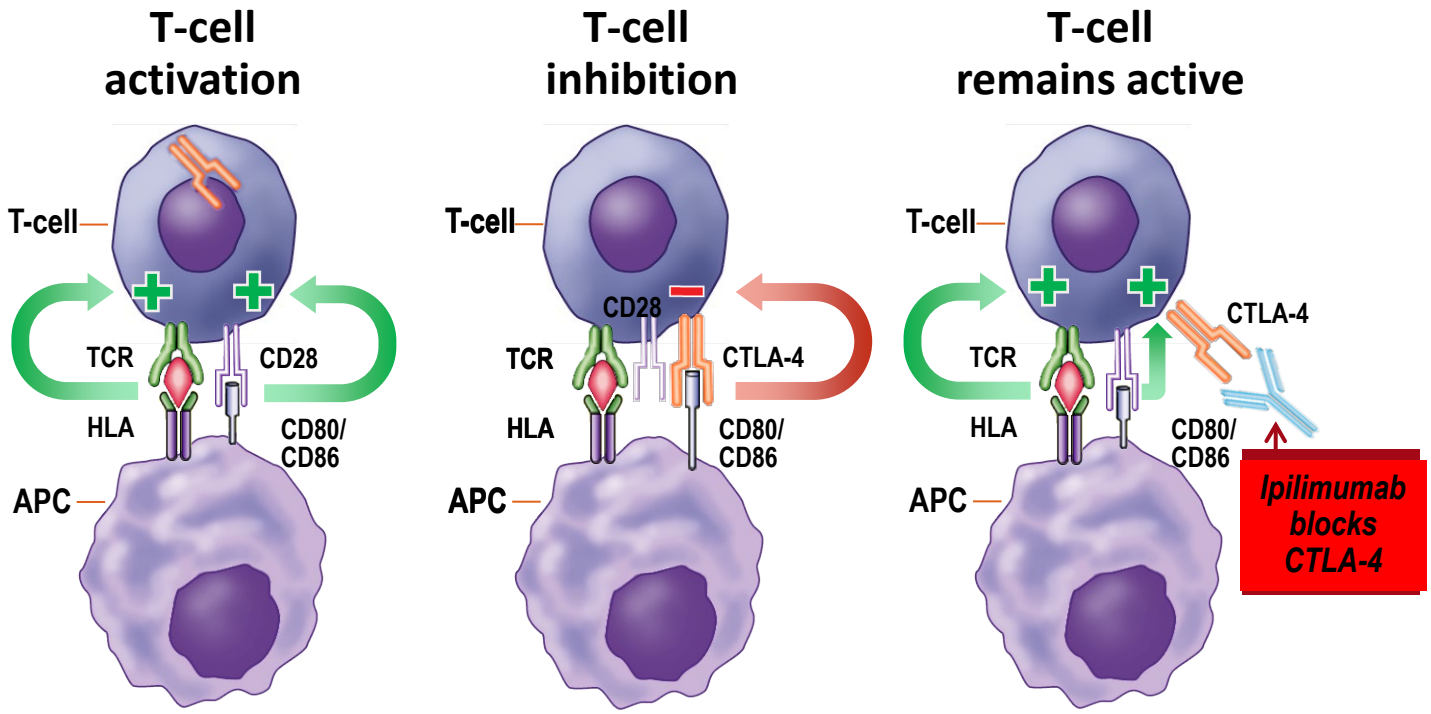
Disclosure Information
Jedd Wolchok, MD, PhD, FASCO

Consultant for:
Apricity; Arsenal IO; Ascentage Pharma; AstraZeneca; Bicara Therapeutics; Boehringer Ingelheim; Bristol Myers Squibb; Daiichi Sankyo; Dragonfly; Georgiamune; Imvaq; Maverick Therapeutics; Psioxus, Recepta; Tizona; Trieza; Sellas; Werewolf Therapeutics.

Grant/Research Support from:
Bristol Myers Squibb

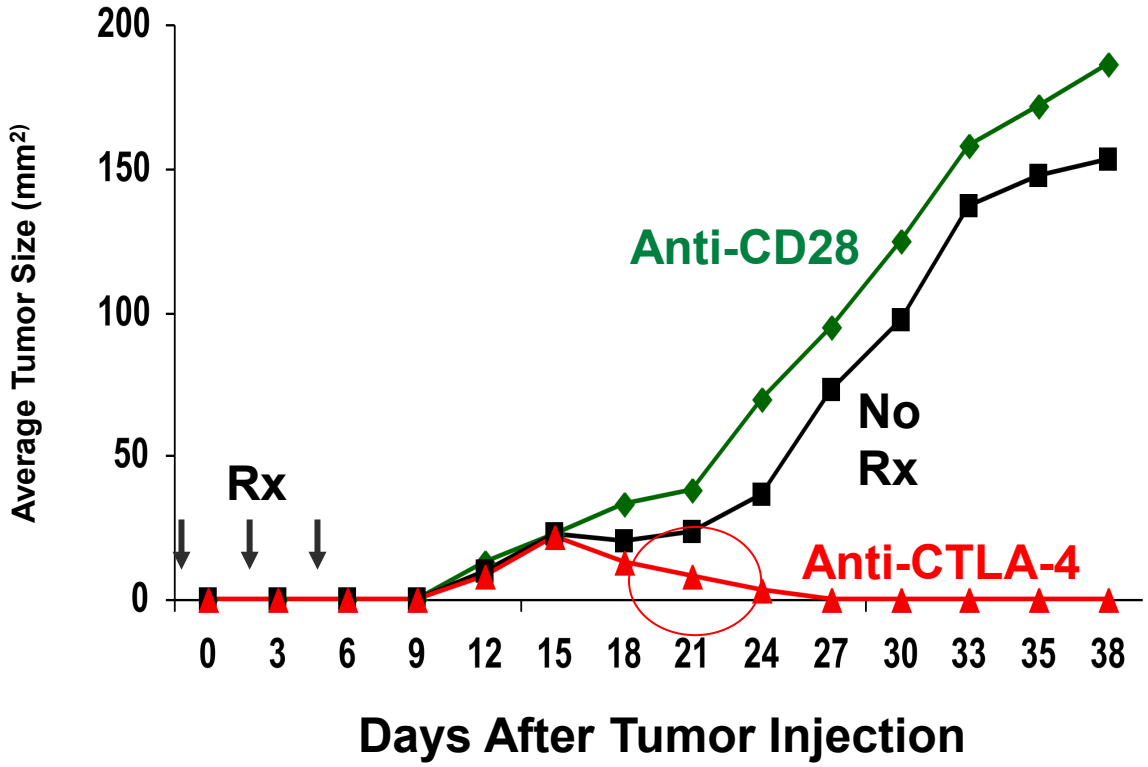
Equity in:
Tizona; Imvaq; Linneaus; Apricity; Arsenal IO; Georgiamune; Trieza; Ascentage

Ipilimumab Augments T-Cell Activation and Proliferation



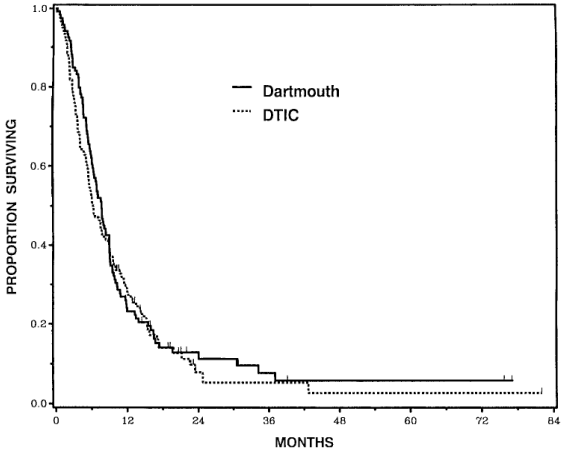
Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.

Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

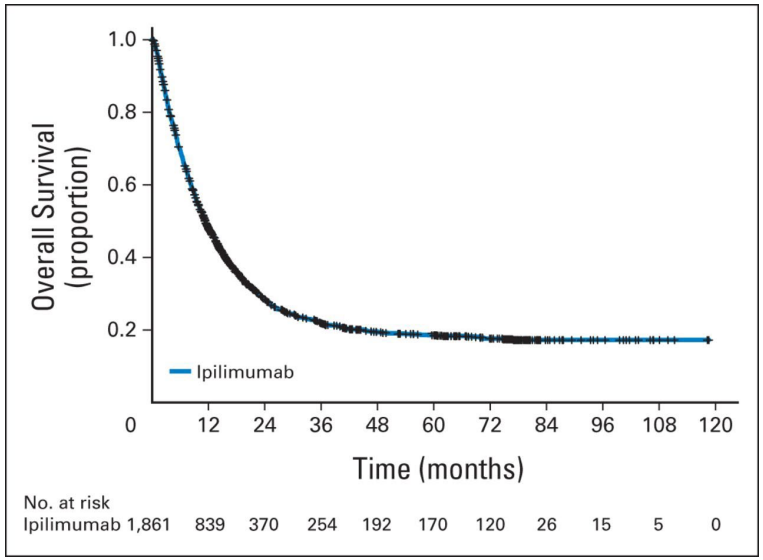


Leach et al., Science, 1996

Ipilimumab Phase II and III data :
Primary analysis of pooled overall survival (OS) data in context of prior standard care



Chapman et al. J Clin Oncol, 1999



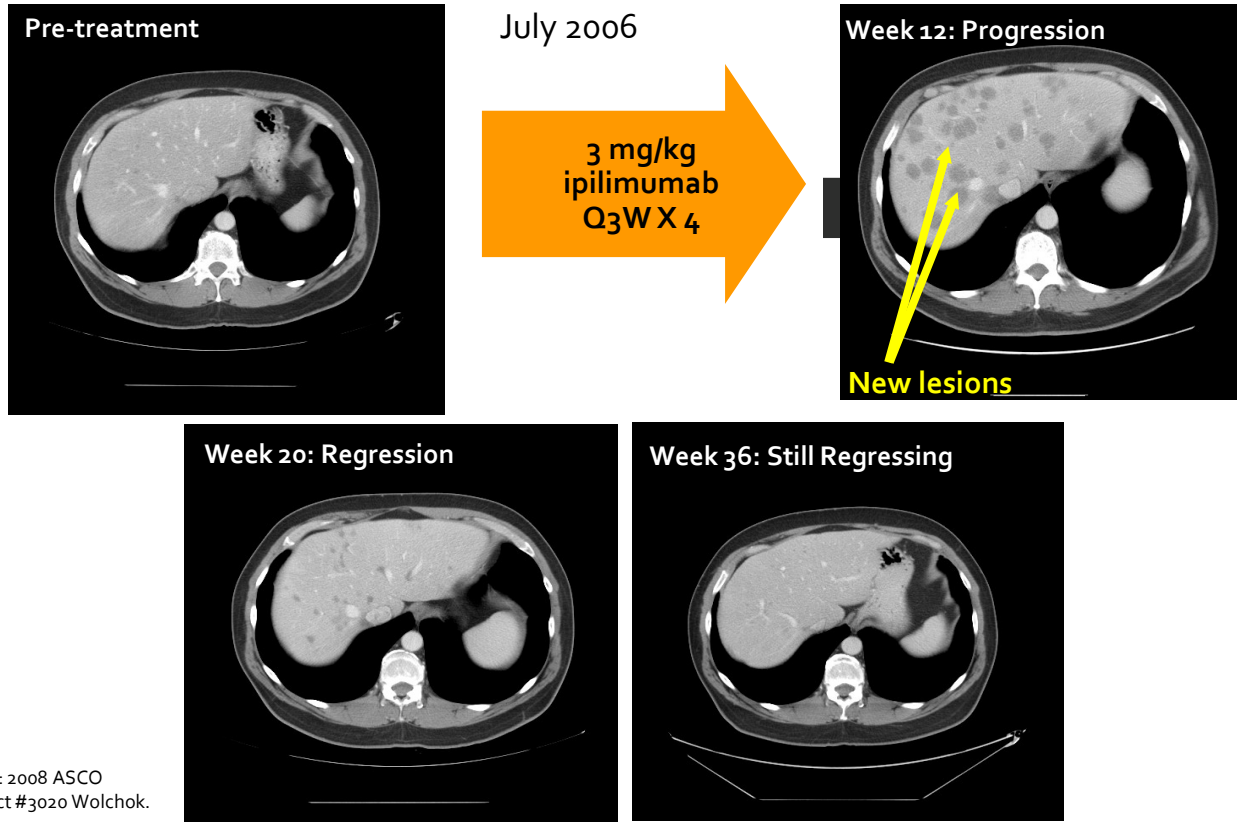
Dirk Schadendorf et al. JCO 2015;33:1889-1894

JOURNAL OF CLINICAL ONCOLOGY ASCO

Four Patterns of Response to Ipilimumab Therapy Observed

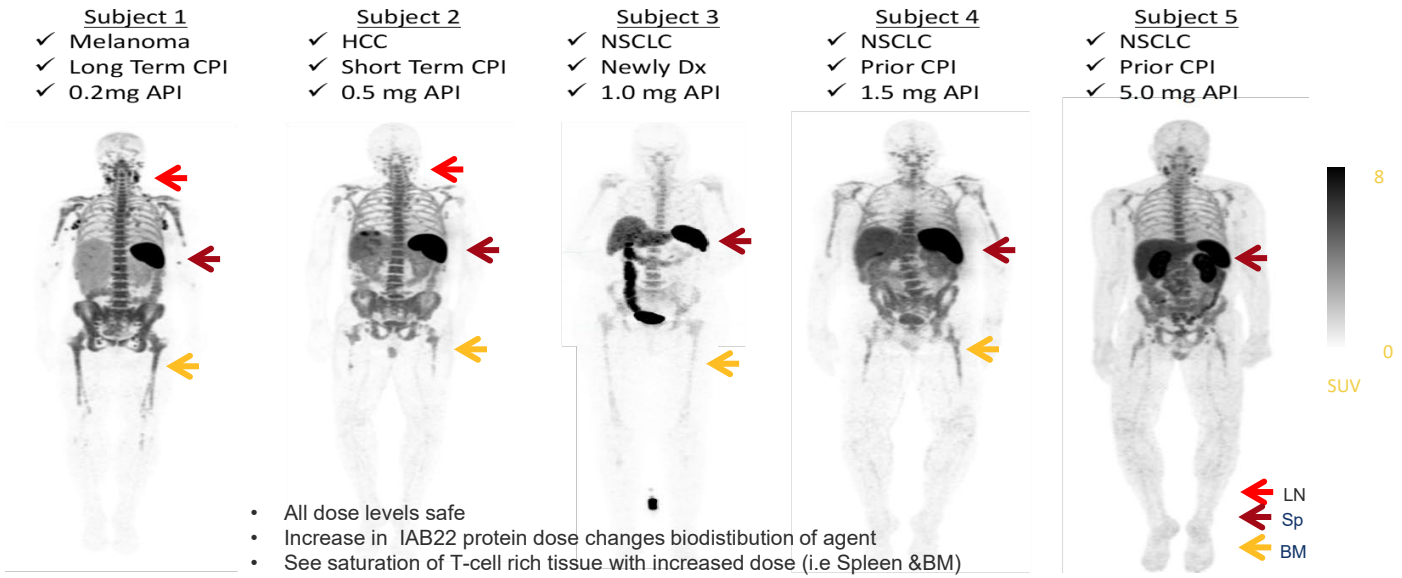
- 2 conventional:
  - **Response in baseline lesions**
  - **'Stable disease' with slow, steady decline in total tumor volume**
- 2 novel:
  - **Response after initial increase in total tumor volume**
  - **Response in index plus new lesions at or after the appearance of new lesions**

Ipilimumab Pattern of Response: Atypical



Source: 2008 ASCO
Abstract #3020 Wolchok.

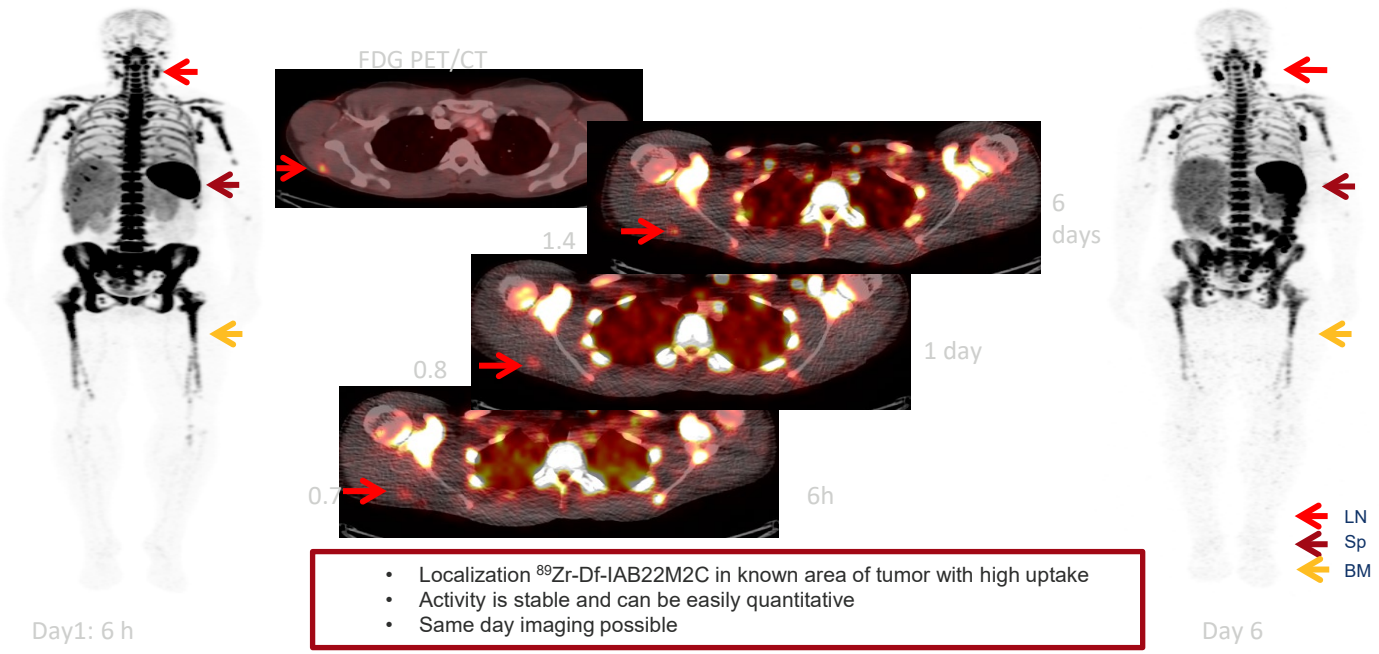
Summary of First-in-Human 89Zr IAB22M2C PET/CT



- All dose levels safe
- Increase in IAB22 protein dose changes biodistibution of agent
- See saturation of T-cell rich tissue with increased dose (i.e Spleen &BM)

Pandit-Taskar et al., *J Nucl Med*, 2019

Is a drug hitting its target?
Pharmacodynamic imaging of T cells: Melanoma

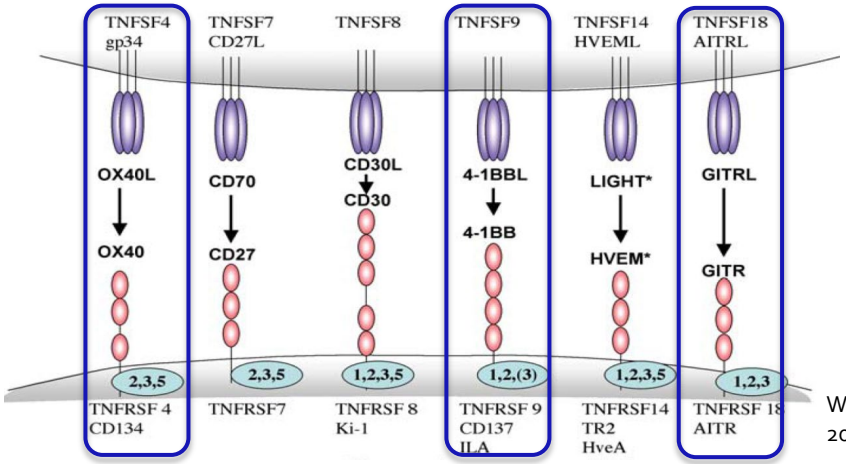


- Localization ^{89}Zr-Df-IAB22M2C in known area of tumor with high uptake
- Activity is stable and can be easily quantitative
- Same day imaging possible

Pandit-Taskar et al., *J Nucl Med*, 2019

GITR Agonism as a means to overcome suppressive cells in the microenvironment

TNF family members: targets for agonist immunotherapy

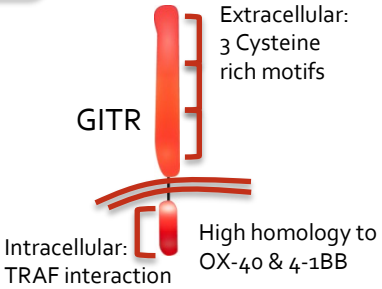


Watts TH. Ann Rev Immunol. 2005;23

GITR

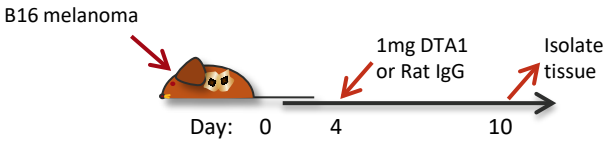
(Glucocorticoid Induced Tumor necrosis factor Related gene)

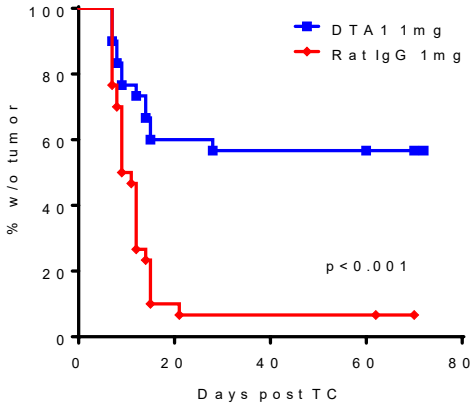
- Constitutively expressed at high levels on regulatory T cells
- Expressed at low levels on resting CD4 and CD8 T cells
- Upregulated following T cell activation (24-48hrs)
- GITR-L is expressed mainly on macrophages, DC's, B cells



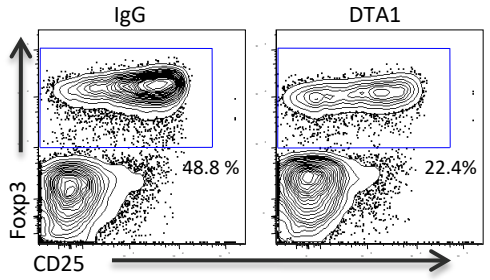
Agonist antibodies to GITR (DTA-1) have been demonstrated to break self tolerance

Anti-GITR (DTA-1): B16 murine transplantable melanoma model

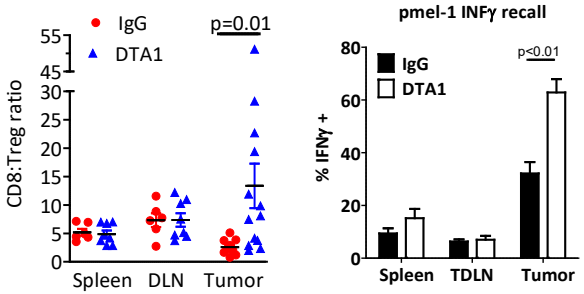




DTA-1 causes 50% reduction of intra tumor Tregs:



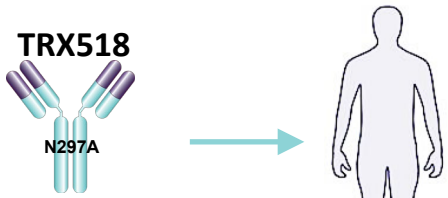
Reduced Tregs alters CD8:Treg ratio and correlates with enhanced Teff function



Cohen & Schaer et al. PLoS ONE 2010 May 3;5(5)

First in-human Phase 1 trial with the fully humanized agonist anti-GITR antibody TRX518

Phase 1, open-label, non-randomized, single ascending dose trial



Aglycosyl humanized agonist anti-human GITR mAb (dose range: 0.0001-8.0 mg/kg)

Patients with advanced refractory solid tumors

Safety and tolerability
Pharmacokinetics

Immune activity/ Pharmacodynamics

ClinicalTrials.gov Identifier: NCT01239134.

Roberta Zappasodi

Zappasodi et al., *Nature Medicine*, 2019

First in-human Phase I trial with fully humanized agonist anti-GITR antibody TRX518

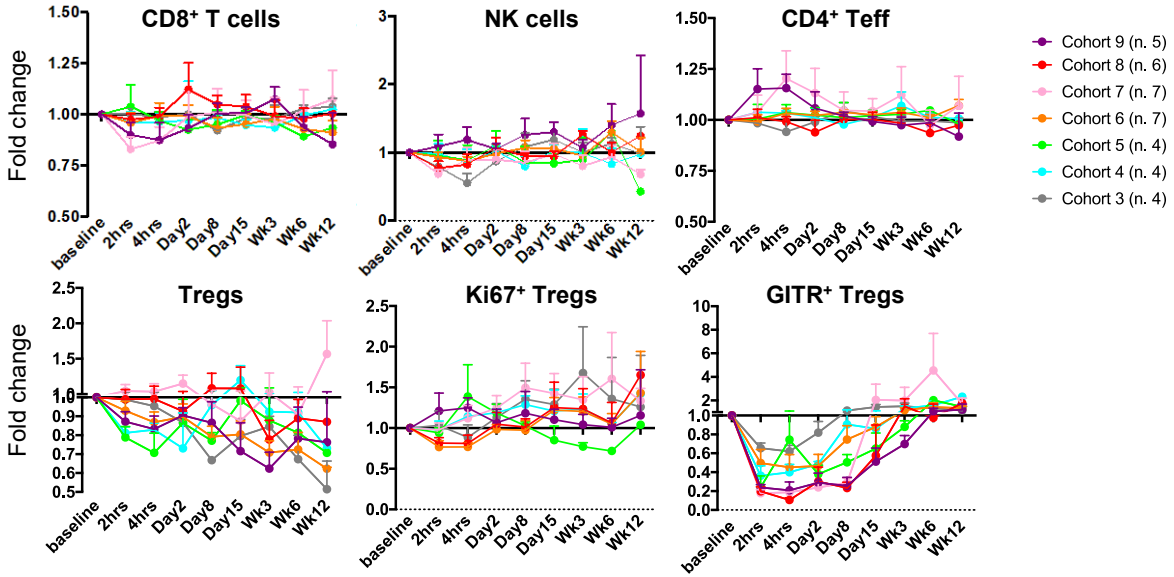
Patients & Samples

TRX518 Dose (mg/kg)						
0.005	0.05	0.5	1	2	4	8
Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9
LUNG	COLON	COLON	COLON	COLON*	COLON*	MELANOMA*
MELANOMA	FIBROMELLAR HEPATOCA	COLON	LUNG	COLON	LUNG	BLADDER*
THYMIC CARCINOMA	GASTRIC ADENOCA	MELANOMA	LUNG	LUNG*	ADENOID CYSTIC	GIST
THYMOMA	UROTHELIAL	OVARIAN	MELANOMA*	LUNG*	ENDOMETRIAL	PANCREAS HEAD ADENOCA
			MELANOMA	LUNG	HEPATOCELLULAR	PNACREATIC
			UROTHELIAL	MELANOMA*	LARYNGEAL	
			LEIOMYOSARCOMA	NEUROENDOCRINE		

- 37 patients with available pre- and post-therapy (up to 8 time points) PBMC samples for FACS analyses;
- 8 patients with available pre- and post-therapy tumor biopsies for analyses of immune infiltrate (*).

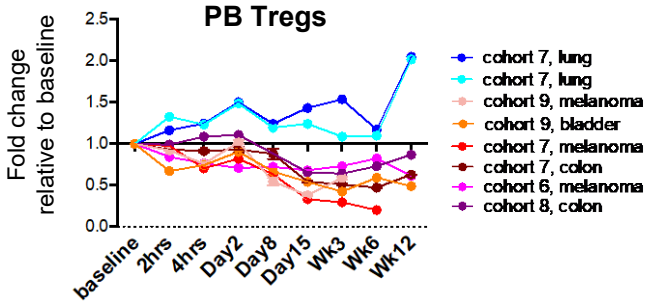
Zappasodi et al., *Nature Medicine*, 2019

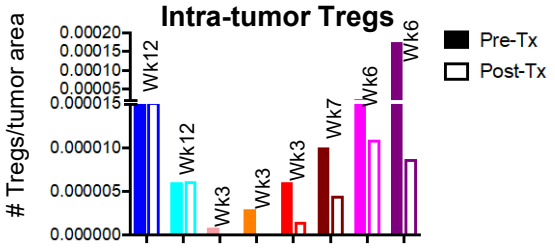
TRX518 preferentially affects Tregs and GITR$^+$ Tregs in peripheral blood



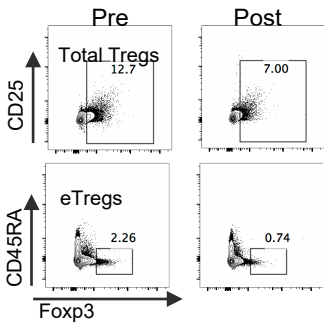
Zappasodi et al., *Nature Medicine*, 2019

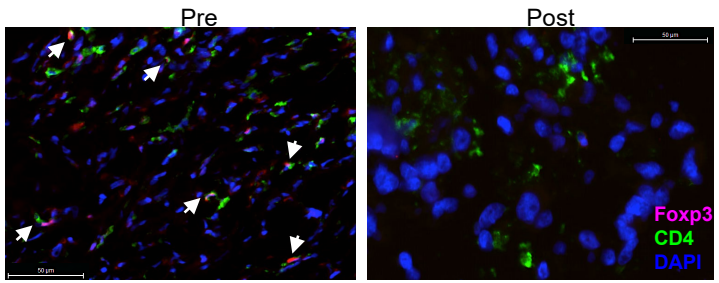
Tregs are similarly modulated in PBMC and tumor after TRX518





Cohort 9, melanoma



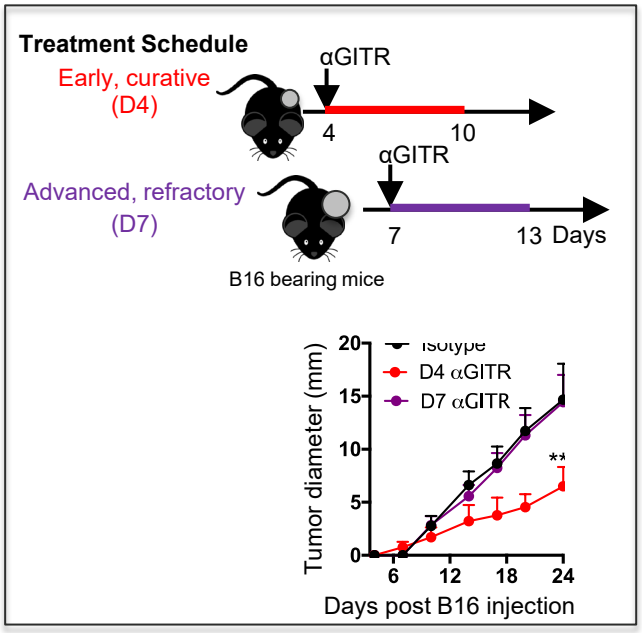


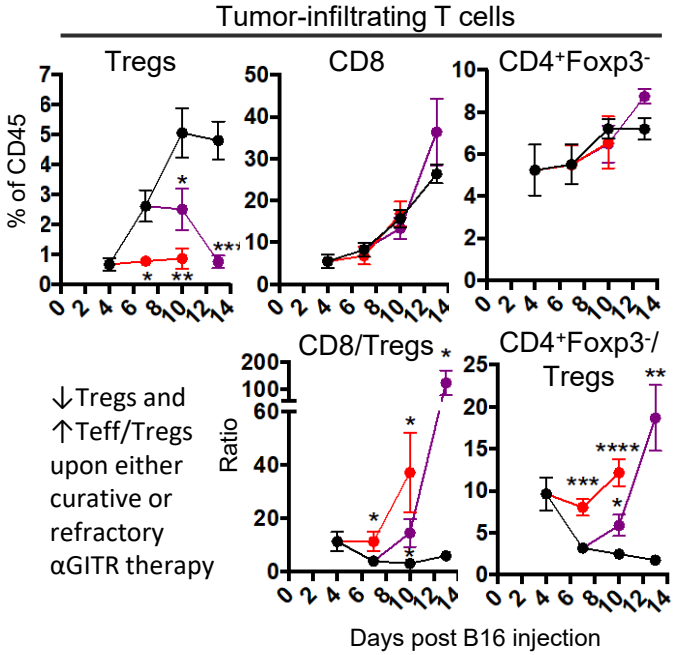
Question

Concordant down-regulation of Tregs in peripheral blood and tumor upon TRX518 was not sufficient to achieve substantial clinical responses in this patient population

Model in mice the determinants of anti-tumor activity of anti-GITR

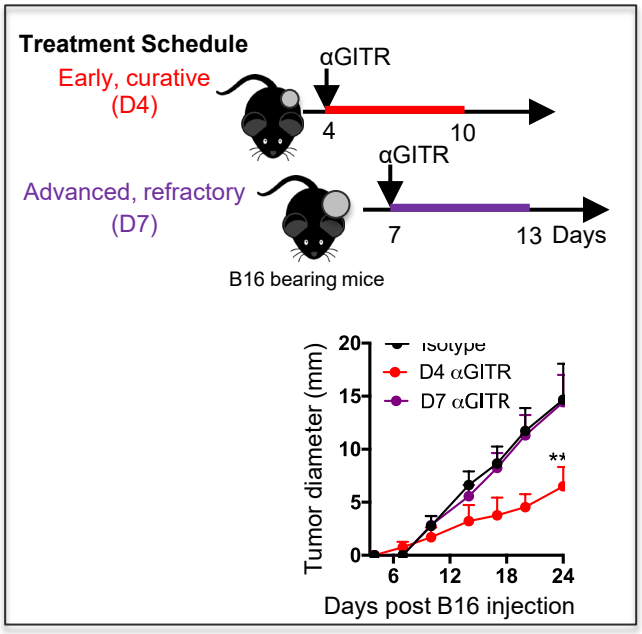
Model of response and refractoriness to αGITR – Role of Tregs

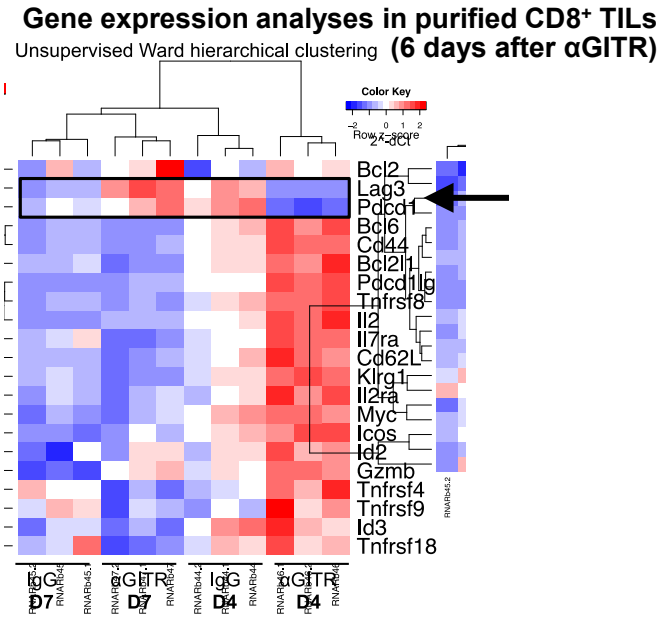




Zappasodi et al., *Nature Medicine*, 2019

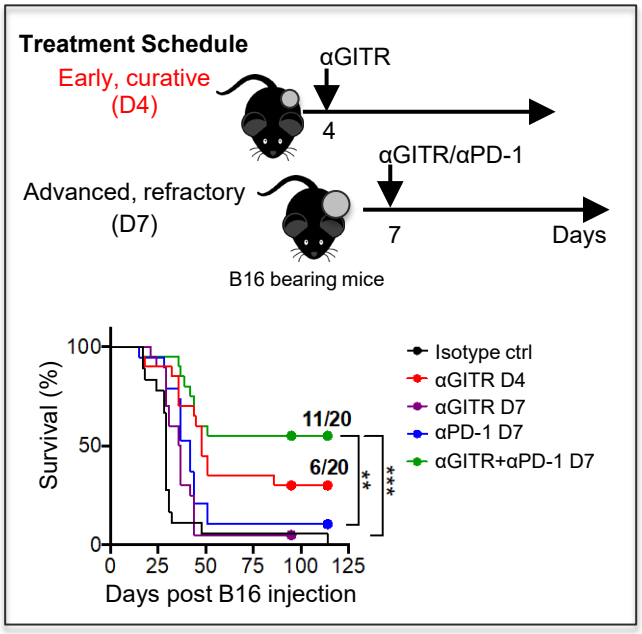
Model of response and refractoriness to αGITR – Role of T-cell exhaustion

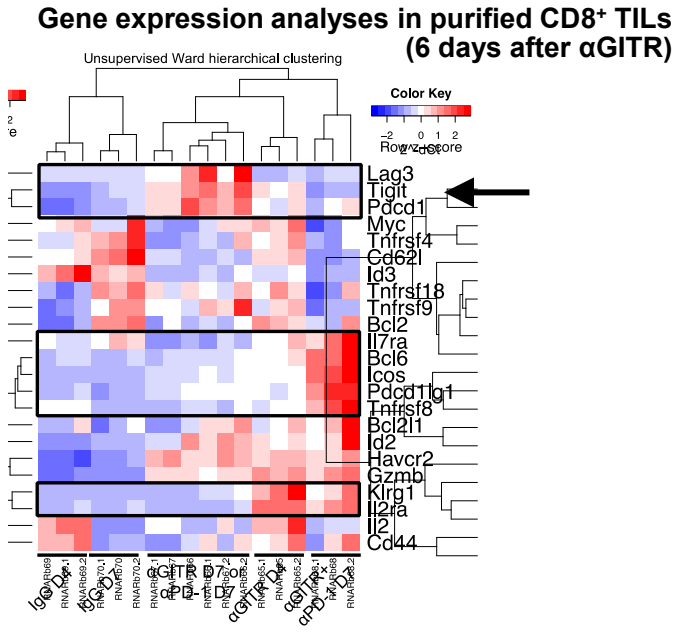




Zappasodi et al., *Nature Medicine*, 2019

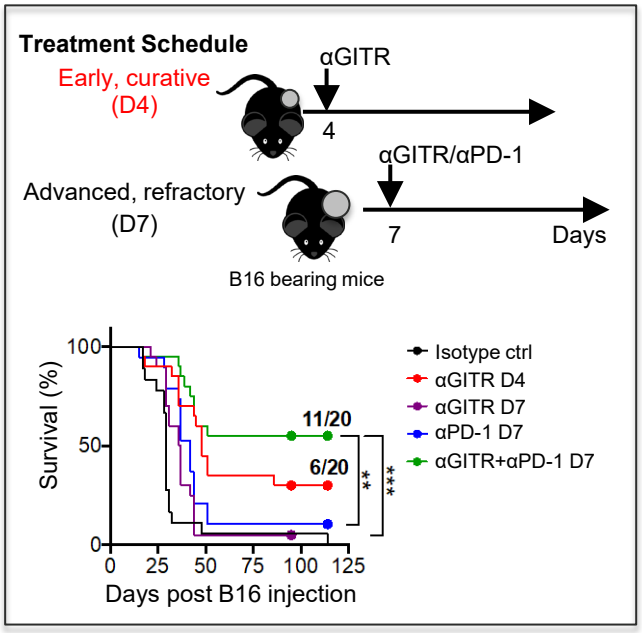
Overcoming refractoriness to αGITR with PD-1 blockade

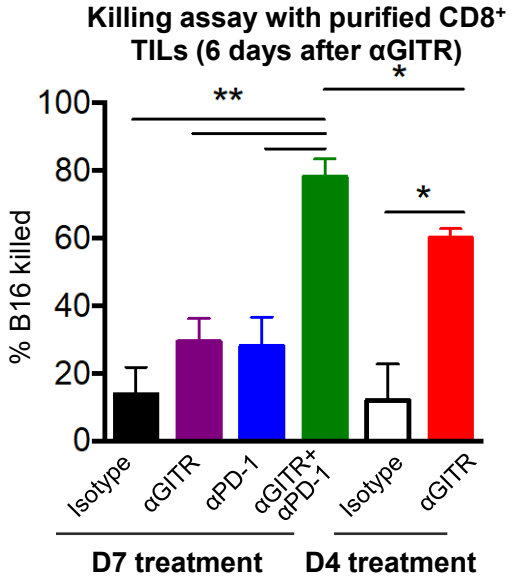




Zappasodi et al., *Nature Medicine*, 2019

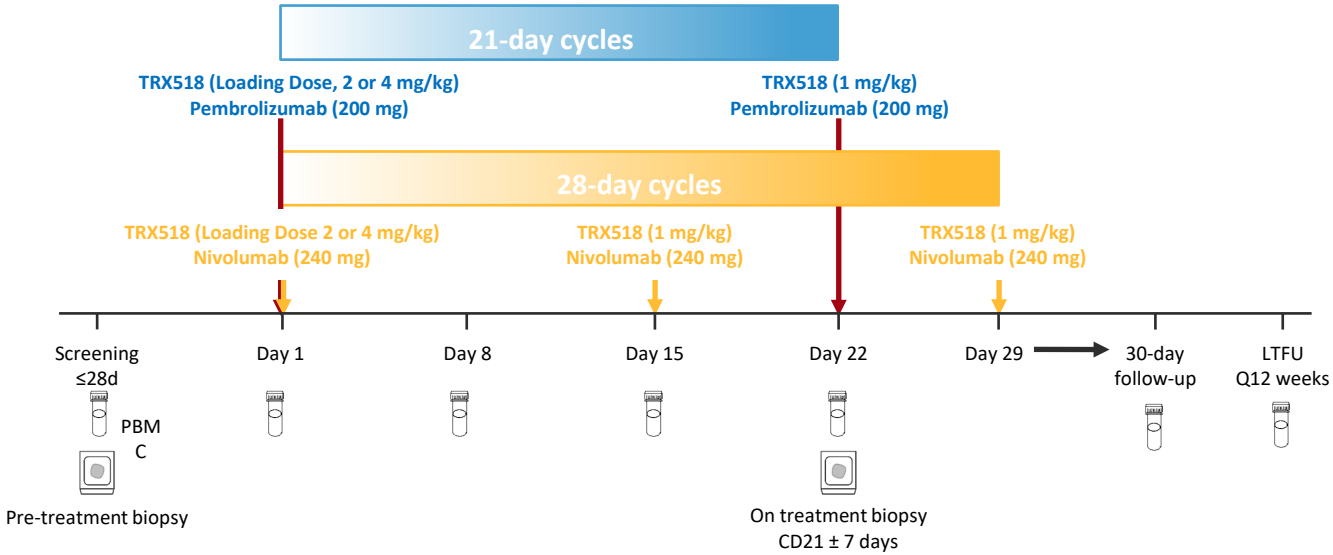
Overcoming refractoriness to αGITR with PD-1 blockade





Zappasodi et al., *Nature Medicine*, 2019

A multi-part Phase 1 multicenter open-label study of TRX518 in combination with pembrolizumab or nivolumab in adults with advanced solid tumors



ClinicalTrials.gov Identifier: NCT02628574.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Phase IB Study of GITR Agonist Antibody TRX518 Singly and in Combination with Gemcitabine, Pembrolizumab, or Nivolumab in Patients with Advanced Solid Tumors

Diwakar Davar[1], Roberta Zappasodi[2,3,4,5], Hong Wang[6], Girish S. Naik[7], Takami Sato[8], Todd Bauer[9], David Bajor[10], Olivier Rixe[11], Walter Newman[7], Jingjing Qi[12], Aliya Holland[12], Phillip Wong[12], Lianna Sifferlen[7], Diane Piper[7], Cynthia A. Sirard[7], Taha Merghoub[3,4,13,14,15], Jedd D. Wolchok[3,4,13,14,15], and Jason J. Luke[1]

ABSTRACT

Purpose: TRX518 is a mAb engaging the glucocorticoid-induced TNF receptor–related protein (GITR). This open-label, phase I study (TRX518-003) evaluated the safety and efficacy of repeated dose TRX518 monotherapy and in combination with gemcitabine, pembrolizumab, or nivolumab in advanced solid tumors.

Patients and Methods: TRX518 monotherapy was dose escalated (Part A) and expanded (Part B) up to 4 mg/kg loading, 1 mg/kg every 3 weeks. Parts C–E included dose-escalation (2 and 4 mg/kg loading followed by 1 mg/kg) and dose-expansion (4 mg/kg loading) phases with gemcitabine (Part C), pembrolizumab (Part D), or nivolumab (Part E). Primary endpoints included incidence of dose-limiting toxicities (DLT), serious adverse events (SAE), and pharmacokinetics. Secondary endpoints were efficacy and pharmacodynamics.

Results: A total of 109 patients received TRX518: 43 (Parts A+B), 30 (Part C), 26 (Part D), and 10 (Part E), respectively. A total of 67% of patients in Parts D+E had received prior anti–PD(L)1 or anti–CTLA-4. No DLTs, treatment-related SAEs, and/or grade 4 or 5 AEs were observed with TRX518 monotherapy. In Parts C–E, no DLTs were observed, although TRX518-related SAEs were reported in 3.3% (Part C) and 10.0% (Part E), respectively. Objective response rate was 3.2%, 3.8%, 4%, and 12.5% in Parts A+B, C, D, and E, respectively. TRX518 affected peripheral and intratumoral regulatory T cells (Treg) with different kinetics depending on the combination regimen. Responses with TRX518 monotherapy+anti–PD1 combination were associated with intratumoral Treg reductions and CD8 increases and activation after treatment.

Conclusions: TRX518 showed an acceptable safety profile with pharmacodynamic activity. Repeated dose TRX518 monotherapy and in combination resulted in limited clinical responses associated with immune activation.

Concluding Thoughts

- Consider: did the drug fail or did the trial fail to evaluate it intelligently?
- Translational research is a team sport; collaborate with all colleagues to reach best conclusions.
- Never stop asking “why?”

Thanks for the support!

Ludwig Cancer Research, Parker Institute, NIH, Swim Across America, Mark Foundation, Melanoma Research Alliance, Dept of Defense, SU2C, Breast Cancer Research Fdn, Damon Runyon Fdn, ASCO Conquer Cancer Fdn, Sephora

Special Thanks: Patients & their Families