SITC 2017

A Phase 1 Study of TSR-022, an Anti–TIM-3 Monoclonal Antibody, in Patients with Advanced Solid Tumors

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NCT02817633 CLINICAL TRIAL

Presenter Disclosure Information

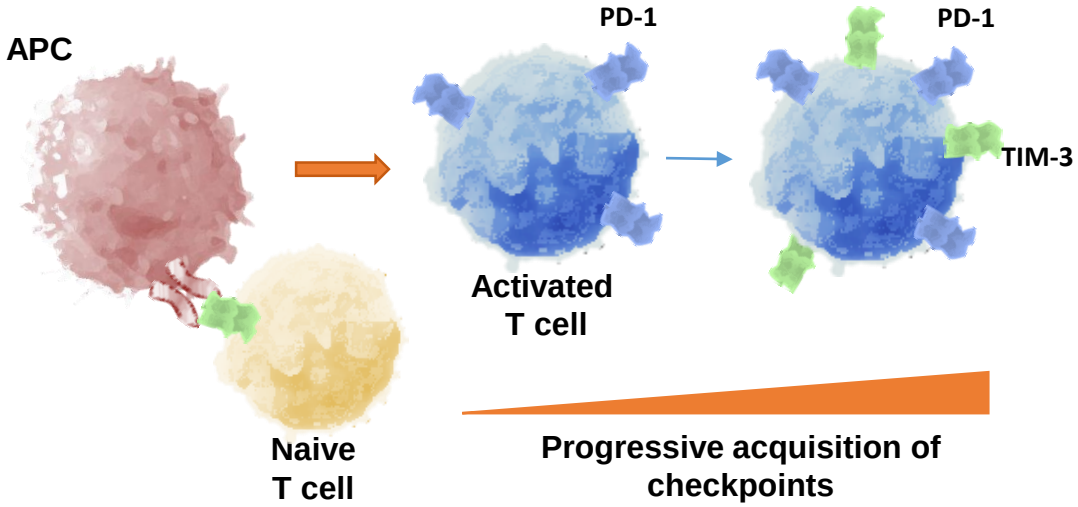
Glen J. Weiss

The following relationships exist related to this presentation:

TESARO – travel reimbursement

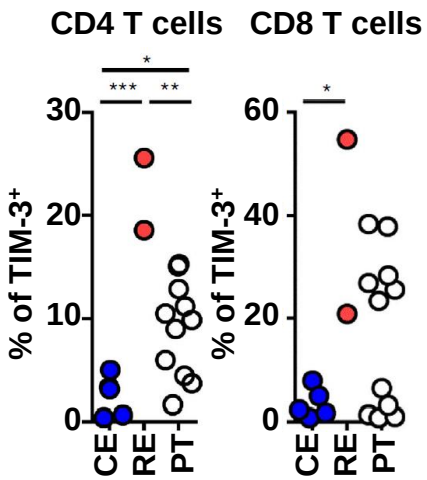
TIM-3 is a key immune checkpoint and a next-generation cancer immunotherapy target

TIM-3 negatively regulates T-cell activation and is a marker of exhausted T cells



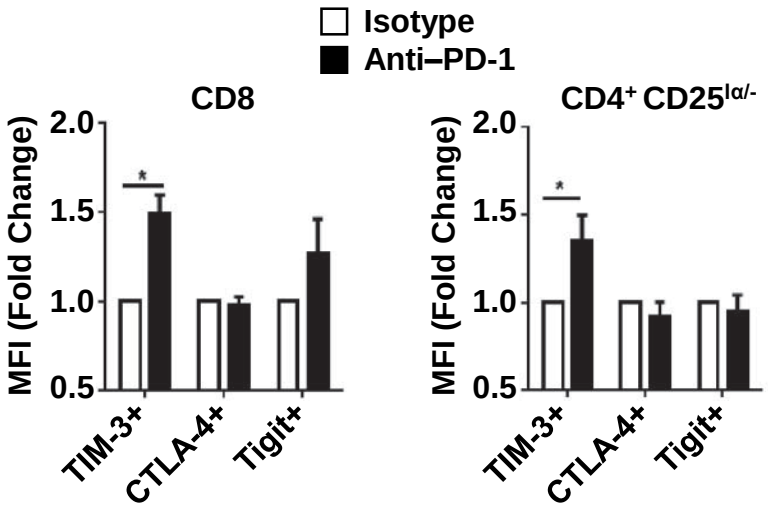
PD-1 resistance is associated with increased TIM-3 expression in patient TILs

NSCLC



Koyama et al. Nature Comm. 2016.

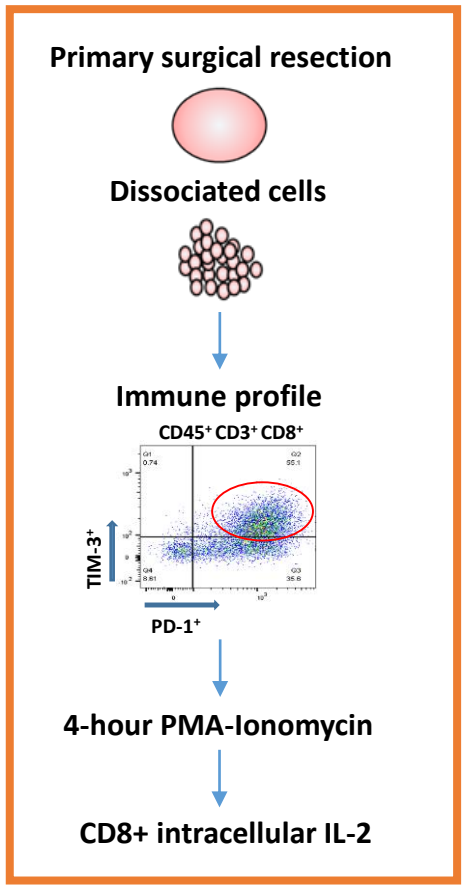
HNSCC



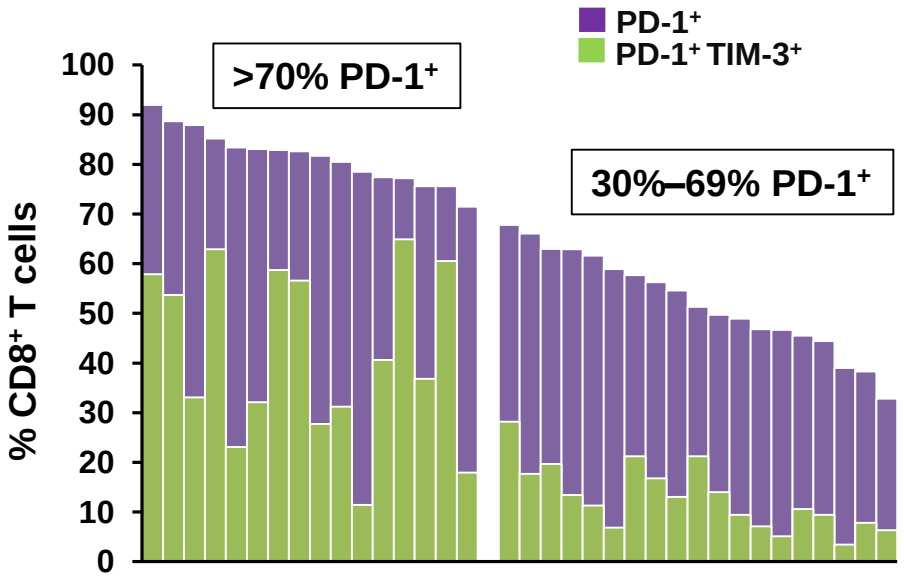
Shayan et al. OncoImmunology. 2016.

HNSCC=head and neck squamous cell carcinoma; NSCLC=non–small cell lung cancer; PD-1=programmed death 1; TIL=tumor-infiltrating lymphocyte; TIM-3=T-cell immunoglobulin and mucin-domain–containing-3; CE=control effusion; RE=resistant effusion; PT=primary tumor.

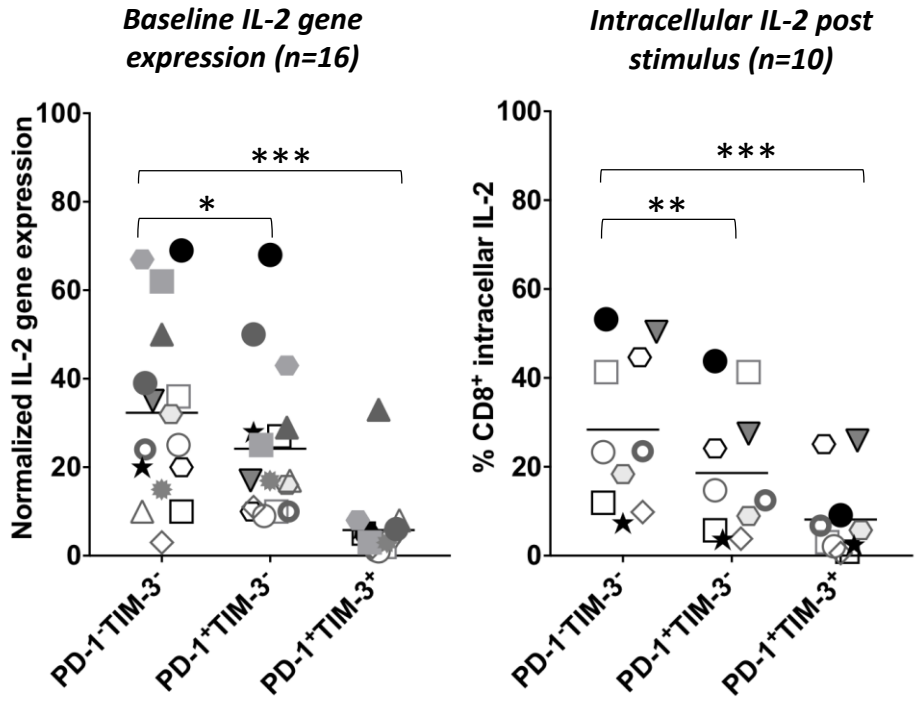
TIM-3 is co-expressed with PD-1 on primary NSCLC TILs and is associated with T-cell dysfunction



TIM-3 is expressed on NSCLC CD8+ T cells with high PD-1



PD-1+ TIM-3+ CD8+ T cells are more dysfunctional



*p≤0.05; **p≤0.001; ***p≤0.0001.

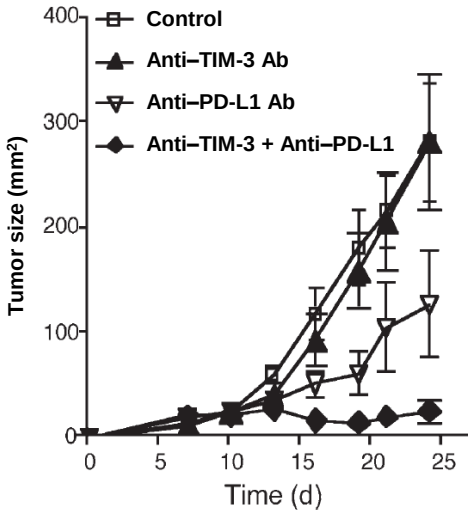
For additional analyses see Travers et al. Abstract #P307.

IL-2=interleukin-2; NSCLC=non–small cell lung cancer; PMA=phorbol myristate acetate; TIL=tumor-infiltrating lymphocyte.

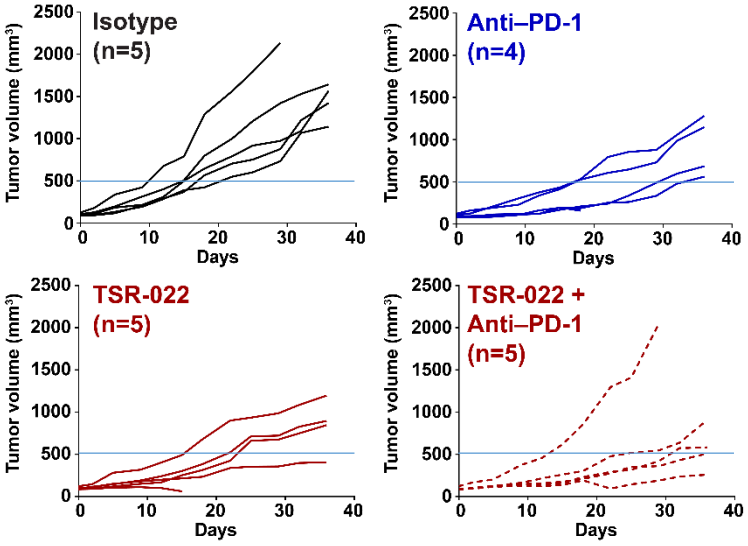
TSR-022 is a novel anti–TIM-3 antibody that increases T-cell activation

TIM-3 blockade enhanced antitumor activity of anti–PD-1 *in vivo*

CT26 syngeneic model



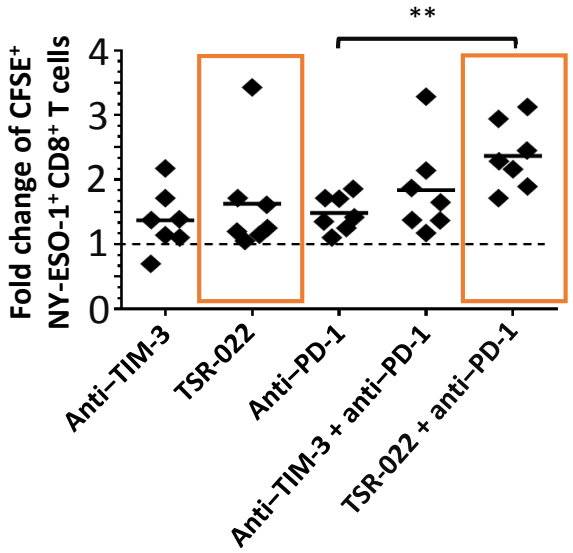
HuNOG-EXL-A549 humanized mouse model



Sakuishi et al. J Exp Med. 2010.

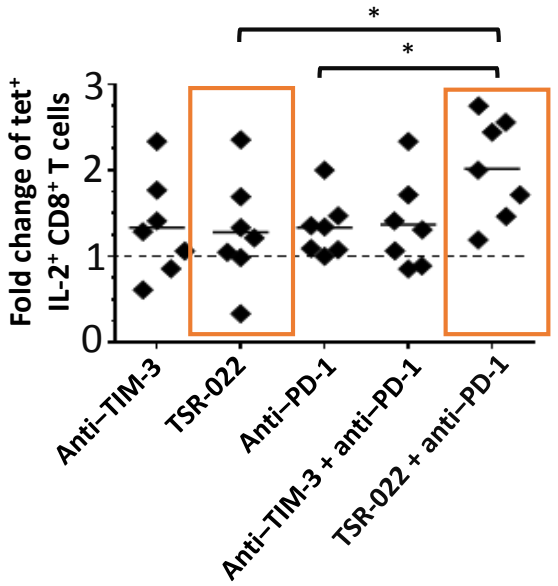
TSR-022, with PD-1 blockade, increased the activity of antigen-specific T cells from melanoma patients

Proliferative capacity



* p≤0.05; **p≤0.001

IL-2 production



Hassane Zarour & John Kirkwood
Unpublished data

Ab=antibody; IL-2=interleukin-2.

TSR-022 Study Schema, NCT02817633

Part 1: Dose Escalation

- **Part 1a:** Dose escalation TSR-022 monotherapy

Dose Q2W, mg/kg	n
0.03	3
0.1	3
0.3	3
1	9*
3	8*
10	12*

- **As of October 2017, a total of 38 patients had been enrolled in Part 1a**

* Additional patients are included for PK/PD analysis.

- **Part 1b:** Dose escalation TSR-022 in combination with an anti–PD-1 antibody

Part 2: Expansion Cohort

- **Part 2:** TSR-022 in specific tumor types (monotherapy and combination with an anti–PD-1 antibody)
  - **Melanoma**
  - **NSCLC**
  - **and other**

Key Inclusion Criteria

- Adult patients with advanced or metastatic solid tumors who have disease progression or treatment intolerance after treatment with available therapies
- Adequate organ function and ECOG performance status
- Prior treatment with immune checkpoint inhibitors is allowed

Endpoints

Primary endpoints

- Safety and tolerability of TSR-022 by CTCAE v4
- Determine recommended phase 2 dose (RP2D) and schedule (monotherapy and combination with an anti–PD-1 antibody)

Secondary endpoints

- Pharmacokinetics (PK)
- Overall response rate, duration of response
- disease control rate, progression-free survival, overall survival, immunogenicity

Exploratory endpoints

- Pharmacodynamics (PD)

CTCAE=Common Terminology Criteria for Adverse Events;
ECOG=Eastern Cooperative Oncology Group.

Part 1a: Patient demographics and baseline characteristics

Characteristic	All patients enrolled (N=38)
Age, y	
Mean (SD)	60.1 (13.5)
Median (min, max)	61.0 (25, 85)
Sex, n (%)	
Male	21 (55.3)
Female	17 (44.7)
ECOG performance status score, n (%)	
0	10 (26.3)
1	28 (73.7)
Number of prior treatment lines, n (%)	
Mean (SD)	3.2 (2.3)
Median (min, max)	2.0 (1, 10)
Prior immunotherapy, n (%)	
yes	14 (36.8)

Tumor site, N=38

- Colon (n=5)
- Skin (n=4)
- Ovary (n=1)
- Breast (n=2)
- Brain (n=2)
- Head and neck (n=2)
- Testis (n=1)
- Pleura (n=1)
- Lung (n=2)
- Rectum (n=3)
- Thyroid (n=2)
- Liver (n=2)
- Esophagus (n=1)
- Other (n=10)

ECOG=Eastern Cooperative Oncology Group; SD=standard deviation.
As of October 2017, database cutoff.

Safety

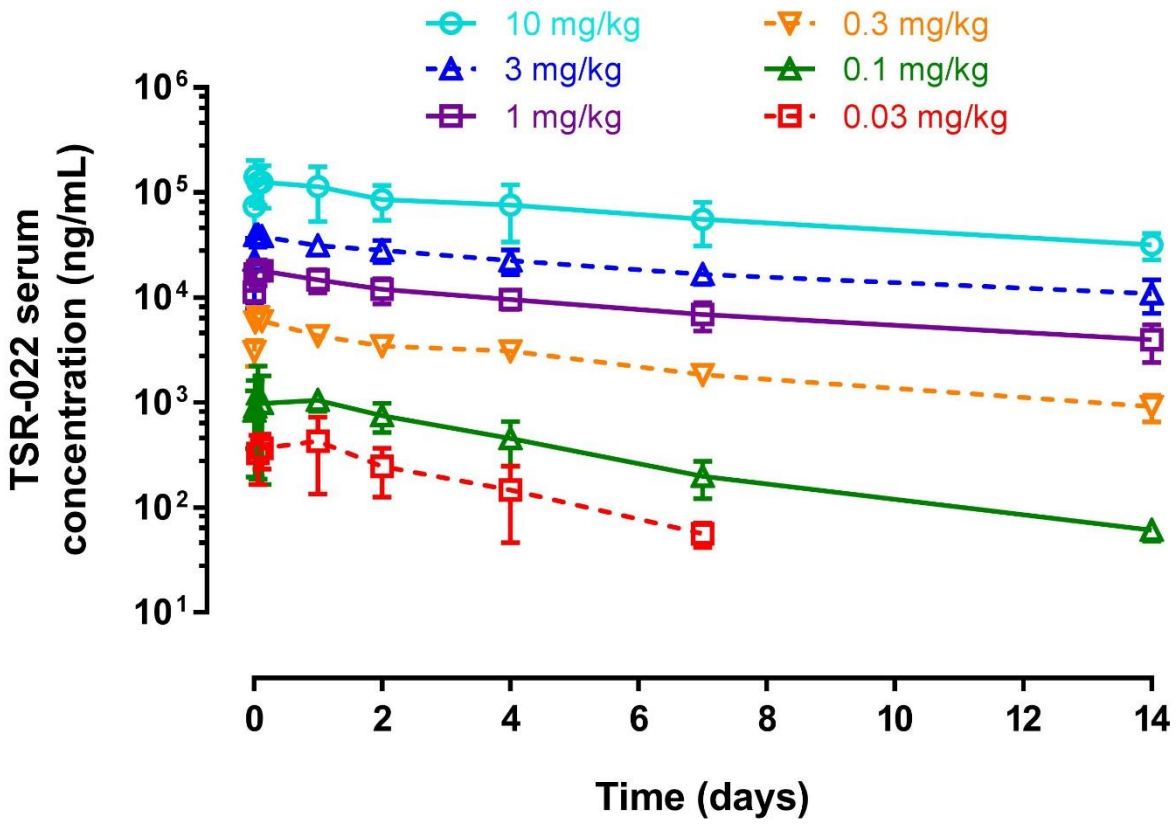
Treatment-related TEAEs in >5% patients (N=38)		
	Total	**Grade ≥3**
Patients with any treatment-related AE, n (%)	**27 (71.1)**	**2 (5.3)**
Fatigue	6 (15.8)	0
ALT increased	3 (7.9)	0
AST increased	3 (7.9)	0
Back pain	3 (7.9)	0
Lymphocyte count decreased	3 (7.9)	0
Nausea	3 (7.9)	0
Anemia	2 (5.3)	0
Chills	2 (5.3)	0
Decreased appetite	2 (5.3)	0
Dyspnea	2 (5.3)	1 (2.6)
Lipase Increased	2 (5.3)	1 (2.6)
Neutrophil count decreased	2 (5.3)	0
Pain	2 (5.3)	0
Peripheral sensory neuropathy	2 (5.3)	0
Rash maculopapular	2 (5.3)	0
Vomiting	2 (5.3)	0

- Drug-related SAEs
  - Grade 3 dyspnea and Grade 2 Pneumonitis, reported in a patient with extensive mediastinal disease and superior vena cava syndrome (1 mg/kg)
- DLTs:
  - Grade 3 immune-related lipase elevation without symptoms (10 mg/kg)
- No grade 4 or 5 related AEs

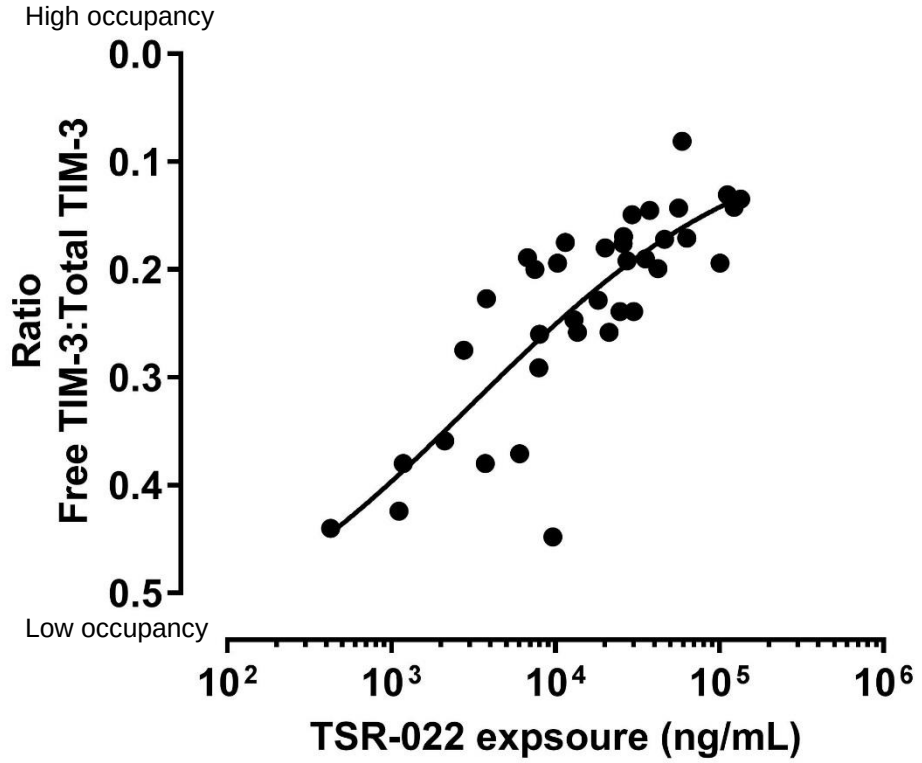
AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; DLT=dose-limiting toxicity; SAE=serious adverse event.

TSR-022 exposure is dose proportional and receptor occupancy correlates with TSR-022 exposure

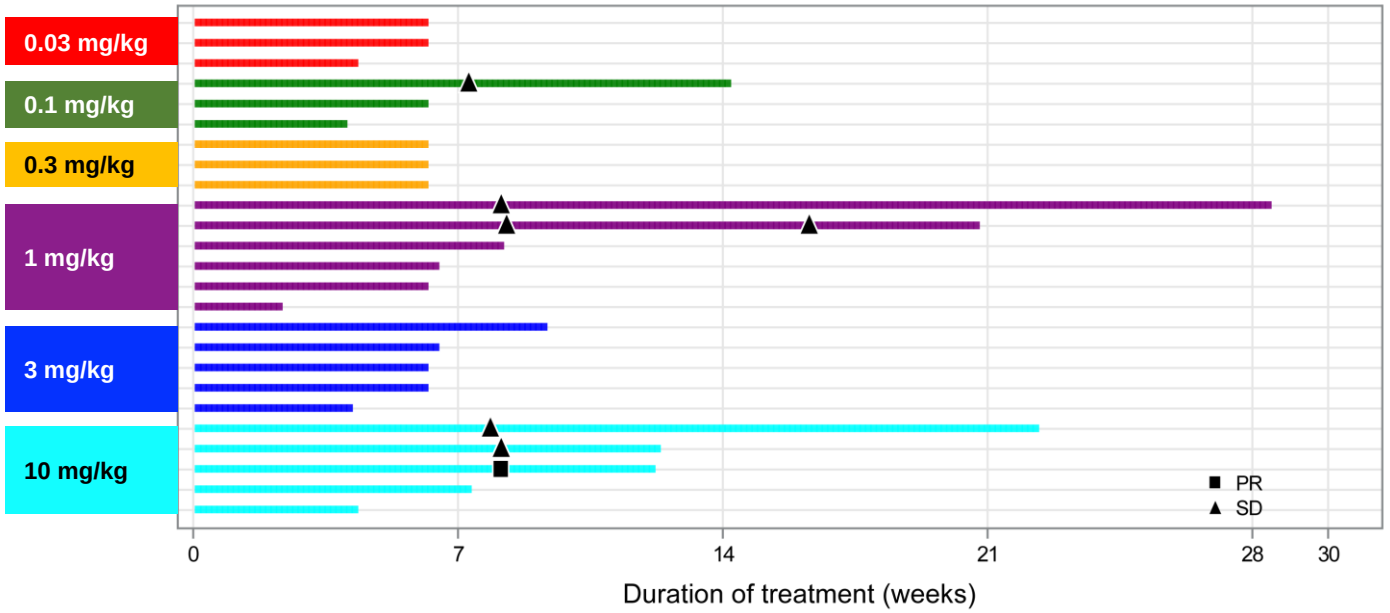
Pharmacokinetic profile

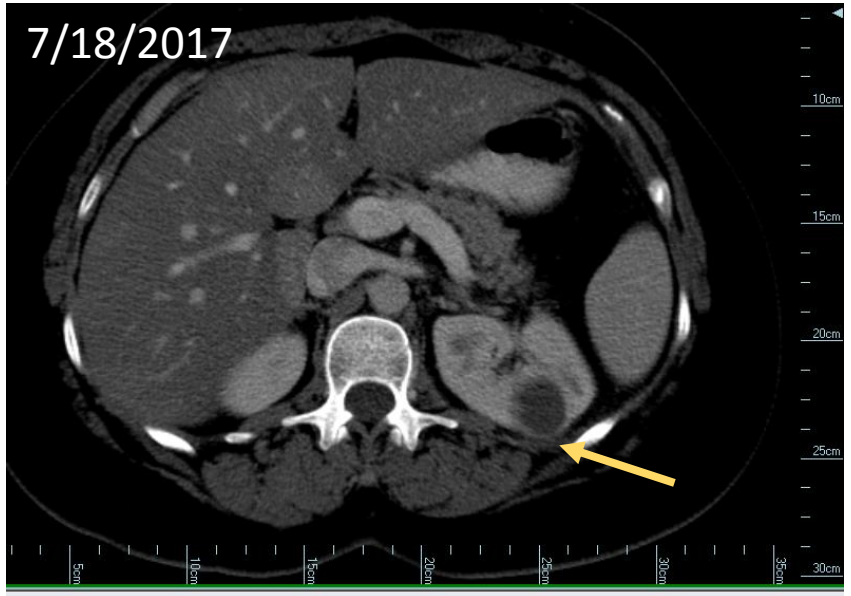


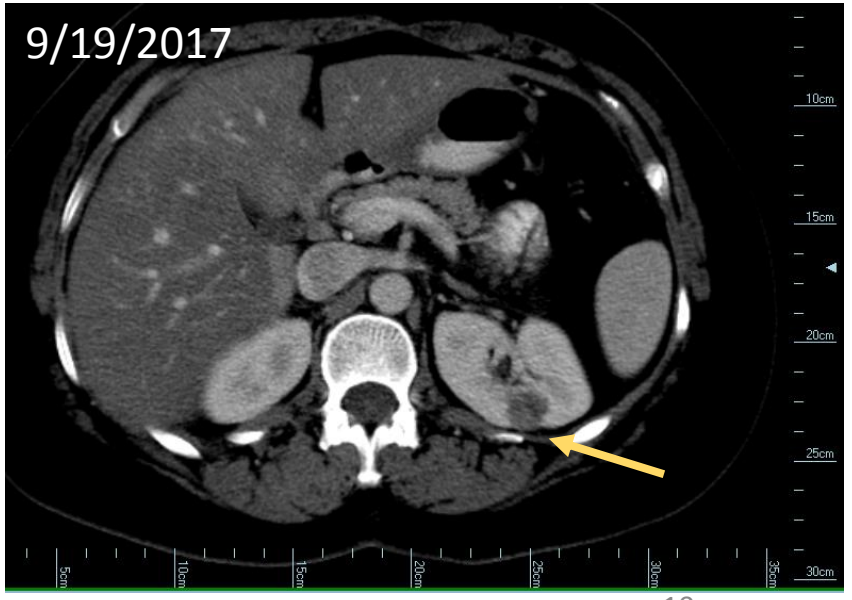
Receptor occupancy on peripheral monocytes



Clinical Activity







- As of Oct 2017, 38 pts have been treated with monotherapy in part 1a (including additional PK/PD patients)
- Best response observed in patients evaluable for efficacy*
  - Stable Disease (5/25* pts) and Partial Response (1/25 pts* at 10mg/kg) as best response were observed in pts with rectal, thyroid, neuroendocrine, H&N cancer, and soft tissue sarcoma

*Efficacy Evaluable Population: patients who received at least 2 doses and either had at least one post-baseline assessment or had discontinued treatment due to clinical progression prior to post-baseline tumor assessment.

Summary and conclusions

- TIM-3 is a checkpoint receptor that negatively regulates T-cell activity, is implicated in resistance to PD-1 blockade, and can be targeted by TSR-022.
- TSR-022 monotherapy is well tolerated across multiple dose levels, consistent with the safety profiles of other checkpoint inhibitors.
- PK findings were linear, and receptor occupancy correlated with TSR-022 exposure.
- Dose-escalation of TSR-022 in combination with TSR-042, an anti–PD-1 antibody, is currently ongoing (NCT02817633).

Acknowledgments

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AMBER NCT02817633 CLINICAL TRIAL

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UPMC LIFE CHANGING MEDICINE

Hassane Zarour

John Kirkwood

Study Sponsor

TESARO

Clinical Study Team