Poster Display
80 P (#388)

GITR Agonist Antibody TRX518 in Combination with Gemcitabine, Pembrolizumab or Nivolumab in Advanced Solid Cancers: Preliminary Safety and Efficacy from a Phase 1b Trial

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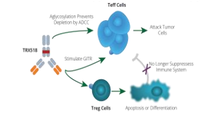
Introduction

- TRX518 is an aglycosylated, humanized non-depleting IgG1 glucocorticoid-induced TNFR-related protein (GITR)agonist antibody, engineered to maximize GITR activation of immune response to tumors
- TRX518 does not engage in antibody dependent cellular cytotoxicity (ADCC)
- TRX518 does not deplete GITR expressing Teff cells
- TRX518 activates GITR on Treg cells and reduces suppressor function
- TRX518 modulates infiltrating immune cells through upregulation of Granzyme B (GmzB) and CD8+ Teff cells and downregulation of Tregs
- TRX518 is safe and well tolerated as a monotherapy in an ongoing study with preliminary clinical benefit in ~55% of patients with ~24% had more than 4 cycles in heavily pretreated solid cancers (NCT02628574)
- TRX518 monotherapy, at the highest dose tested resulted in 4 patients had stable disease with tumor volume reductions (appendiceal, hepatocellular, renal and ovarian cancer)
- TRX518 monotherapy resulted in durable disease stability in a patient with hepatocellular carcinoma (non-virally mediated and resistant to anti-PD-1/CTLA4 combination) who continues on therapy after 18 months with stable disease and overall tumor burden reduction
- Pre-clinical data provide the mechanistic rationale for TRX518 in combination with immunotherapy[1,2,3]



Study Design

TRX518 + Gemcitabine
Part C
TRX518: day 2
Gemcitabine: days 1 & 8
21 day Cycle

Cohort 1: 3+3 design (up to 6 patients)
TRX518: 2 mg/kg load, 1 mg/kg maintenance
Gemcitabine 1000 mg/m2

Cohort 2: 3+3 design (up to 6 patients)
TRX518: 4 mg/kg load, 1 mg/kg maintenance
Gemcitabine 1000 mg/m2

Expansion cohort: (n=20)
TRX518: MTD or highest dose tested
Gemcitabine 1000 mg/m2

TRX518 + Anti-PD-1
Part D
TRX518: day 1
Pembrolizumab: day 1
21 day Cycle

Cohort 1: 3+3 design (up to 6 patients each for Parts D and E)
TRX518 2 mg/kg load, 1 mg/kg maintenance
Part D: pembrolizumab 200 mg
Part E: nivolumab 240 mg

Cohort 2: 3+3 design (up to 6 patients each for Parts D and E)
TRX518 4 mg/kg load, 1 mg/kg maintenance
Part D: pembrolizumab 200 mg
Part E: nivolumab 240 mg

Expansion cohorts: [Part D- n=20, Part E- n=20]
TRX518: MTD or highest dose tested
Part D: pembrolizumab 200 mg
Part E: nivolumab 240 mg

Part E
TRX518: days 1 & 15
Nivolumab: days 1 & 15
28 day Cycle

Objectives: Safety (DLT, MTD), ORR, ODCR, PFS, DoR, OS, PK, ADA
Exploratory: Peripheral changes in Tregs and intra-tumoral changes in Treg and CD8 infiltrates

Key Inclusion Criteria

- Advanced/metastatic solid cancers (adult patients)
- ≥ 1 prior therapy for advanced/metastatic disease
- ECOG PS of 0 or 1 and acceptable organ function
- Measurable disease per RECIST v1.1
- Parts C/D/E: Advanced cancers for which gemcitabine (Part C), pembrolizumab (Part D) or nivolumab is clinically appropriate (Part E)

Key Exclusion Criteria

- Prior anti-GITR therapy
- Treatment with surgery or chemotherapy within 21 days; radiation therapy within 14 days; investigational agent within 30 days
- Active infection requiring systemic therapy or recent live vaccine
- Pharmacologic doses of steroids (>10 mg prednisolone or equivalent) at baseline

Baseline Characteristics – Heterogenous, heavily pre-treated patients

Part	TRX518 + Gemcitabine		TRX518 + Pembrolizumab		TRX518 + Nivolumab	
Dose	2 mg/kg	4 mg/kg	2 mg/kg	4 mg/kg	2 mg/kg	4 mg/kg
n	4	26	3	2	7	2
Median Age (Range)	60 (56 - 76)	67.5 (36 - 80)	66 (62 - 77)	65.5 (45 - 86)	60 (28 - 75)	60.5 (47 - 74)
Gender (F)	1	16	2	1	4	2
ECOG PS						
0	2	7	3	1	3	1
1	2	17	0	1	4	1
Tumor Type						
Pancreatic	2	12	-	-	-	-
Biliary Tract	-	5	-	-	-	-
Esophageal SCC	-	-	-	1	-	-
Urothelial	-	-	2	-	2	-
Melanoma	-	-	1	1*	-	-
Ovarian	-	2	-	-	-	-
Mesothelioma	1	2	-	-	-	-
Other Cancers	1	5	-	-	5	2
Prior Systemic Therapies						
Median (Range)	2.5 (1-3)	2 (1-9)	3 (1-5)	0.5 (0-1)	1 (0-2)	3.5 (3-4)
Gemcitabine (n, %)	2 (50%)	15 (58%)	-	-	-	-
Anti-PD-1/PD-L1 (n, %)	1 (25%)	9 (35%)	3 (100%)	0 (0%)	3 (43%)	1 (50%)

*Ocular Melanoma

Safety

Drug Exposure

Median Number of TRX518 Cycles (Range)

- TRX518 + gemcitabine: 2 mg/kg load: 1.5 (1-2); 4 mg/kg load: 3 (1-9)
- TRX518 + pembrolizumab: 2 mg/kg load: 4 (2-4); 4 mg/kg load: 8.5 (8-9)
- TRX518 + nivolumab: 2 mg/kg load: 2 (1-6); 4 mg/kg load: 1.5 (1-2)

TRX518 is safe and well-tolerated in combination studies with no DLTs or TEAE leading to study drug discontinuation

Adverse Events Reported in ≥ 15% patients: Overall and Related

TRX518 + Gemcitabine

Majority of patients (89%) had treatment emergent adverse events (TEAE) of which 57% of patients experienced ≥ Grade 3 and 32% of patients had related ≥ Grade 3 events
39% of patients had SAEs, 7% were reported to be related
Related ≥ Grade 3 events included neutropenia, lymphopenia, anemia and thrombocytopenia; consistent with safety profile of gemcitabine monotherapy

Part C (N=28)	Regardless of Causality		Related to Study Treatments	
TEAEs	Any Grade	Grade>=3	Any Grade	Grade>=3
Any	25(89.3)	16(57.1)	21(75.0)	8(28.6)
Serious	11(39.3)	11(39.3)	2(7.1)	2(7.1)
DLT	-	-	-	-
Preferred Term	n (%)	n (%)	n (%)	n (%)
Fatigue	11(39.3)	3(10.7)	6(21.4)	0
Nausea	10(35.7)	0	6(21.4)	0
Anaemia	9(32.1)	4(14.3)	5(17.9)	3(10.7)
Decreased Appetite	8(28.6)	0	2(7.1)	0
Platelet Count Decreased	8(28.6)	1(3.6)	7(25.0)	1(3.6)
Aspartate Aminotransferase Increased	7(25.0)	0	2(7.1)	0
Constipation	7(25.0)	0	1(3.6)	0
Hypoalbuminaemia	7(25.0)	2(7.1)	2(7.1)	0
Hyponatraemia	6(21.4)	4(14.3)	2(7.1)	0
Lymphocyte Count Decreased	6(21.4)	3(10.7)	6(21.4)	2(7.1)
Neutrophil Count Decreased	6(21.4)	4(14.3)	6(21.4)	4(14.3)
Unspoken	6(21.4)	5(17.9)	3(10.7)	1(3.6)
Vomiting	6(21.4)	0	3(10.7)	0
Abdominal Pain	5(17.9)	1(3.6)	0	0
Alanine Aminotransferase Increased	5(17.9)	0	2(7.1)	0
Blood Alkaline Phosphatase Increased	5(17.9)	1(3.6)	1(3.6)	0
Hypertension	5(17.9)	0	0	0

TRX518 + Anti-PD1 inhibitors

All patients (100%) had TEAEs of which 29% of patients experienced ≥ Grade 3 and 0% of patients had related ≥ Grade 3 events
21% of patients had SAEs, 7% were reported to be related
One related TESAE – Grade 2 atrial fibrillation
No reported related ≥ Grade 3
No apparent increased incidence of immune related AEs

Part D and E (N=14)	Regardless of Causality		Related to Study Treatments	
TEAEs	Any Grade	Grade>=3	Any Grade	Grade>=3
Any	14(100.0)	4(28.6)	9(64.3)	-
Serious	3(21.4)	2(14.3)	1(7.1)	-
DLT	-	-	-	-
Preferred Term	n (%)	n (%)	n (%)	n (%)
Anaemia	5(35.7)	2(14.3)	0	0
Back Pain	4(28.6)	0	0	0
Weight Decreased	4(28.6)	0	0	0
Aspartate Aminotransferase Increased	3(21.4)	0	1(7.1)	0
Dyspnoea	3(21.4)	1(7.1)	0	0
Hypertension	3(21.4)	0	0	0
Hyponatraemia	3(21.4)	1(7.1)	0	0

Events which occurred in 2 patients include: ALT increased*, bilirubin increased, LDH increased*, arthralgia*, constipation, fatigue*, haematuria*, hypoalbuminaemia, hypophosphataemia, nausea, oedema peripheral, pain in extremity, skin infection, lymphocyte count decreased*
* Study medication related events ≤ Grade 2

Data as of November 15, 2018

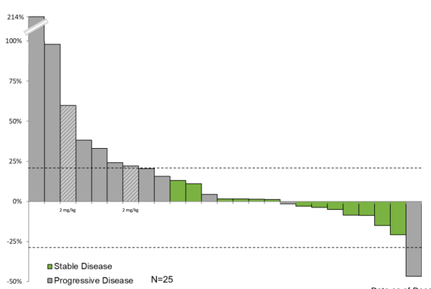
Efficacy - TRX518 + Gemcitabine

Overall Evaluable Population

Clinical benefit with tumor reduction noted in pancreatic, biliary tract and immune resistant tumors

- 25 evaluable patients: Best response: SD: n=13 (52%), PD: n=12 (48%)
- 5 non-evaluable patients: 2 patients pending post-baseline imaging, 3 patients with unrelated early discontinuations/deaths
- Clinical benefit observed in higher dose cohort (4 mg/kg load, 1 mg/kg maintenance)
- 19 subjects had pancreatic or biliary tract cancer, 15 are evaluable, 9 remain on study
  - Pancreatic cancer: 5/10 (50%) had SD, 2 with tumor reductions (-9%, -21%), 4 still on study
  - Biliary tract cancer: 4/5 (80%) with SD; 1 with tumor reduction (-3%), 3 still on study
  - 9/19 (47.4%) of pancreatic and biliary tract cancer patients have received ≥4 cycles (7 remain on therapy)
- Additional reductions in tumor burden and durable clinical benefit noted in appendiceal cancer (-4% in Cycle 7), mesothelioma (-5% in Cycle 6), and two in ovarian cancer (-15% in Cycle 5, -9% off after 4 cycles)

TRX518 + Gemcitabine: Evaluable Population by Response & Dose



Data as of December 5, 2018

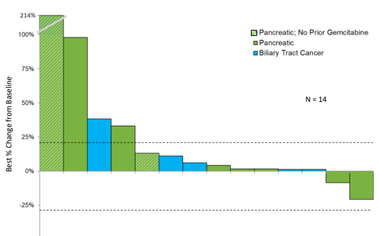
Efficacy - TRX518 + Gemcitabine

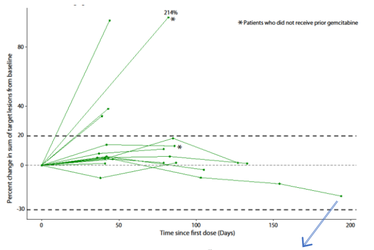
Subgroup Analysis for Pancreaticobiliary Tumors at Target Dose:

TRX518 + gemcitabine Part C	n	RE	SD	PD	ODCR (RE)
Overall	30	25	13	12	52%
2 mg/kg load; 1 mg/kg maintenance	4	2	0	2	0%
4 mg/kg load; 1 mg/kg maintenance	26	23	13	10	56.5%
Pancreatic Cancer	14	10	5	5	50%
Biliary Tract Cancer	5	5	4	1	80%
Other Cancers	11	10	4	6	40%
Pancreatic + Biliary Tract Cancer 4 mg/kg load; 1 mg/kg maintenance	17	14	9	5	64.3%
Prior gemcitabine	17	13	8	5	61.5%
Pancreatic + Biliary Tract Cancer 4 mg/kg load; 1 mg/kg maintenance Prior gemcitabine	15	12	8	4	66.7%

67% ODCR (8/12) in PBC TRX518 higher dose patients who have received prior gemcitabine

Pancreatic and Biliary Tract Cancer Patients, TRX518 (4 mg/kg Load) + Gemcitabine





Patient Case Study: Durable Stable Disease in Pancreatic Cancer Patient Previously Treated with Gemcitabine

48 year old female diagnosed one year prior to study entry, previously treated with three prior therapies (FOLFIRINOX, gemcitabine/nab-paclitaxel and capecitabine). Initial post-therapy scans revealed mild growth followed by a deepening reduction of disease burden over time (>180 days). Patient continues on study dosing in Cycle 9.

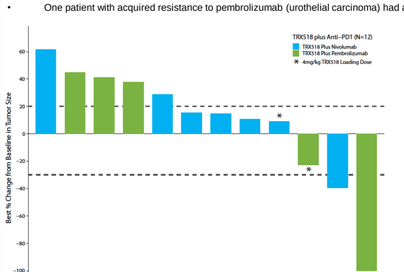
Efficacy - TRX518 + Anti-PD-1 Therapies

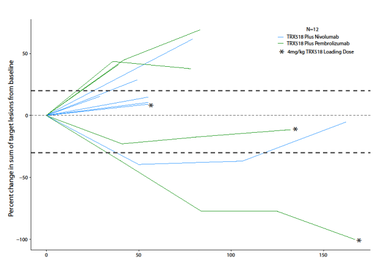
TRX518 + pembrolizumab

- ORR of 20% (1 CR of 5 evaluable); DCR of 40% (1 CR and 1 SD)
- Esophageal SCC patient has had confirmed CR (cCR); active on study in Cycle 11
- Ocular melanoma patient had a best response of stable disease with -23% tumor volume reduction, active on study in Cycle 9
- Clinical benefit demonstrated at higher dose of TRX518 (4mg/kg load)

TRX518 + nivolumab

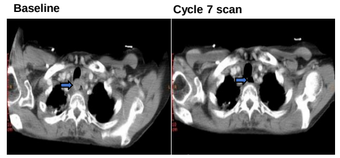
- ORR of 14.3% (1 PR of 7 evaluable); 2 NE (due to clinical progression)
- One patient with acquired resistance to pembrolizumab (urothelial carcinoma) had a confirmed PR (cPR), off study after 6 cycles



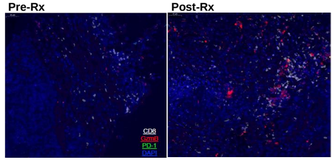


Pharmacodynamic Changes - TRX518 + Anti-PD-1 Therapies

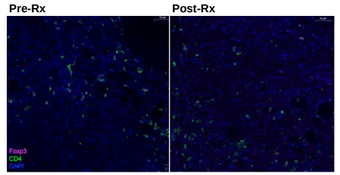
Complete Response:TRX518 (4 mg/kg load) + pembrolizumab
Esophageal Squamous Cell Carcinoma: 86 year old female
previously treated with concurrent carboplatin/paclitaxel/XRT



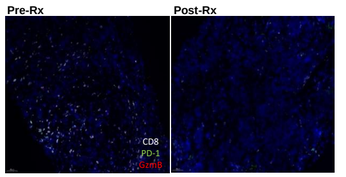
Complete response after six cycles of treatment; patient continues on study in Cycle 11



Increased infiltration of CD8+ cells and increased Gzmb staining post TRX518 + pembrolizumab

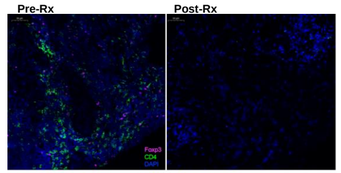


Decreased staining of FOXP3/CD4 cells post TRX518 + pembrolizumab treatment

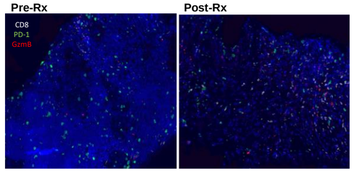


Non-responder: No increase in CD8 cells post TRX + pembrolizumab in a patient with urothelial carcinoma with prior pembrolizumab progression

Partial Response: TRX518 (2 mg/kg load) + nivolumab
Urothelial cancer: 75 year old male with acquired resistance to pembrolizumab



Decreased staining of FOXP3/CD4 cells post TRX518 + nivolumab treatment



Increased infiltration of CD8+ cells and increased Gzmb staining post TRX518 + nivolumab

Conclusions

- TRX518 is safe and well-tolerated in combination with gemcitabine or anti-PD-1 therapy with no dose-limiting or additive toxicity; no new safety signals
- TRX518 in combination with gemcitabine demonstrated meaningful clinical benefit in heavily pre-treated patients (2 median priors, range 1-5, 89.5% with prior gemcitabine) with pancreaticobiliary cancer; 47% have received 4+ cycles of therapy, 37% remain active on study. Additionally, patients with other immuno-resistant tumors (mesothelioma, appendiceal and ovarian cancer) have had durable clinical benefit and objective reduction in tumor volume
- TRX518 in combination with anti-PD-1 therapy achieved objective responses including a durable cCR in esophageal SCC and cPR in pembrolizumab resistant urothelial cancer. Additionally, a patient with ocular melanoma has had stable disease with an overall tumor volume reduction of 23%
- Greater clinical benefit observed with higher tested TRX518 loading dose
- Pharmacodynamic evidence of increased intra-tumoral Granzyme B and infiltration of CD8+ T cells and Treg reduction suggests pharmacologic activity in responders
- Results support further clinical investigation of TRX518
- Additional combination studies with TRX518 are planned for 2019

References

1. Wang et al., *Sci. Immunol.* 2018 Nov.
2. Zappasodi et al., *SITC 2018 Annual Meeting.*
3. Ponte et al., *Immunology.* 2010 Jun.

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