Results from Ph1a/1b Analyses of TTX-080, a First-in-Class HLA-G Antagonist, in Combination with Cetuximab in Patients with Metastatic Colorectal Cancer and Head and Neck Squamous Cell Carcinoma

Susanna Ulahannan[1], Thomas U Marron[2], Haeseong Park[3], John Kaczmar[4], Ryan Stephenson[5], Nehal Lakhani[6], Greg Durm[7], Jaspreet Grewal[8], Anthony El-Khoueiry[9], Jason Luke[10], Courtney Beers[11], Swaminathan Murugappan[11], Patricia LoRusso[12], Douglas Adkins[13], J. Randolph Hecht[14]

[1]University of Oklahoma Medical Center, [2]Icahn School of Medicine Mount Sinai, [3]Dana Farber Cancer Institute, [4]Medical University of South Carolina, [5]Robert Wood Johnson Medical School, Rutgers University, [6]START Midwest, [7]Indiana University, [8]Norton Cancer Institute, [9]USC Norris Comprehensive Cancer Center, [10]UPMC Hillman Cancer Center, [11]Tizona Therapeutics, [12]Smilow Cancer Hospital at Yale, [13]Washington University School of Medicine, [14]University of California Los Angeles (UCLA) Jonsson Comprehensive Cancer Center

TIZONA THERAPEUTICS

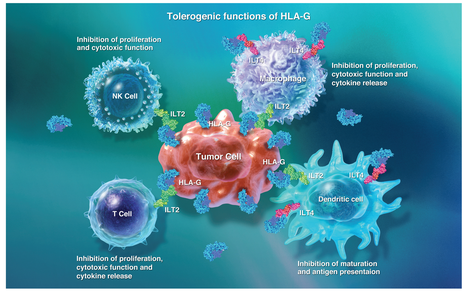
Abstract 2524

Background

TARGET: Human leukocyte antigen G (HLA-G), a non-classical MHC class I molecule expressed on solid tumors, is known to drive immune suppression, promote cancer cell immune escape and lead to tumor development and growth. HLA-G mediates suppression through ILT2 and ILT4 on lymphoid (ILT2) and myeloid (ILT2 & ILT4) cell subpopulations. Blocking HLA-G has the potential to reverse immune tolerance and activate anti-tumor immune responses.

PRODUCT CANDIDATE: TTX-080 is a novel, first-in-class, fully human monoclonal antagonistic antibody that is designed to bind to HLA-G and block interactions with its known receptors, ILT2 and ILT4, to prevent immune suppression and enable active anti-tumor responses.

CETUXIMAB: Patients with mCRC and locally advanced/metastatic HNSCC have high umet clinical need. Cetuximab as a monotherapy is approved for treatment in both tumor types. In previously reported studies, cetuximab used as monotherapy in WT RAS mCRC achieved 10%-19% ORR (best response)[1,2] and in mHNSCC achieved 13% ORR (best response) in all comers[3] and 25% ORR in HPV-negative patients.[4] Cetuximab monotherapy previously showed 3.5-5.2-months PFS estimates in similar WT RAS populations.[1,2]



CLINICAL STUDY DESIGN:

- The Phase 1a dose-escalation portion of the trial determined safety and the recommended Phase 2 dose of TTX-080.
- Phase 1b part of the evaluated safety and preliminary efficacy of TTX-080 as monotherapy and in combination with either cetuximab (EGFR inhibitor) or pembrolizumab (PD-1 inhibitor) in patients with advanced refractory/resistant solid tumors (n=240). (NCT04485013)
- mCRC patients were enrolled in three separate arms - TTX-080 monotherapy, TTX-080 + cetuximab in Anti-EGFR treated WT KRAS mCRC, and in Anti-EGFR naïve WT KRAS mCRC
- mHNSCC patients were enrolled in two separate arms (TTX-080 + cetuximab and TTX-080 + Pembrolizumab).
- Herein, we report safety and efficacy of TTX-080 + cetuximab primarily from Anti-EGFR naïve WT KRAS mCRC arm and mHNSCC arm. Data cutoff: April 15, 2024.

Results

Phase 1a: Safety of TTX-080 Monotherapy in Advanced Solid Tumors

- No DLTs were reported and the MTD was not reached (0.2-20 mg/kg Q3W).
- Decreased appetite, arthralgia, and fatigue were the most common TTX-080-related adverse events (TRAE) across all dose cohorts.
- A dose of 20 mg/kg Q3W was selected as the recommended Phase 1b dose for TTX-080. It was selected based upon the optimal biological dose of a PK trough value of 50ug/mL.

Phase 1b: Safety and Efficacy of TTX-080 + Cetuximab in Anti-EGFR Naive mCRC and mHNSCC

Anti-EGFR Naïve WT KRAS mCRC Arm:

- 25 patients with Anti-EGFR naive, WT KRAS mCRC were enrolled. WT KRAS results are as reported by site and did not require confirmation.
  - 16 out of 25 were determined to be patients with WT RAS, WT BRAF and HER2-negative tumors (biopsy and ctDNA samples).
  - 22 out of 25 WT KRAS patients and 14 out of 16 WT RAS, BRAF, HER2-negative patients were tumor response evaluable (had at least one post treatment scans).
  - The median age of patients in the WT KRAS group was 63 (21, 80). 48% of patients were female and 52% of patients were male.

mHNSCC Arm:

- 23 patients with advanced/metastatic mHNSCC were enrolled.
  - 18 out of 23 patients had HPV status determined.
  - 7 out of 18 were HPV-negative and 11 out of 18 were HPV-positive.
  - Median age of patients was 64 (45, 83). 17% of patients were female and 83% of patients were male.

mCRC Results

Table 1. Key Characteristics of Anti-EGFR Naïve mCRC Patients

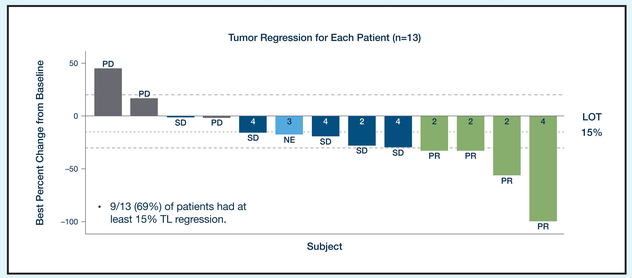
Anti-EGFR Naïve mCRC Tumor Response Evaluable (N=22)	WT KRAS (N=22)	WT RAS, WT BRAF, HER2-Negative (N=14)
Primary location: Left Right	14/22 (64%) 8/22 (36%)	12/14 (85%) 2/14 (15%)
Site of metastases: Lung Only Liver	1/22 (4.5%) 14/22 (64%)	1/14 (7%) 6/14 (43%)
Number of prior lines of treatment: 1 2 ≥3	1/22 (4.5%) 7/22 (31.5%) 14/22 (64%)	1/14 (7%) 6/14 (43%) 7/14 (50%)
Previous treatments received: 5 Fluoropyridine Oxaliplatin Irinotecan Anti-VEGF	22/22 (100%) 20/22 (90%) 18/22 (82%) 16/22 (73%)	14/14 (100%) 12/14 (85%) 11/14 (78%) 11/14 (78%)

Table 2. Response Rates by Central Review of TTX-080 + Cetuximab in Anti-EGFR Naïve mCRC Patients

Anti-EGFR Naïve mCRC Arm	WT KRAS	WT RAS, WT BRAF, HER2-Negative
Response Evaluable Patients	22	14
ORR (Best Response)*	5/22 (23%)	4/14 (29%)
PR	5/22 (23%)	4/14 (29%)
SD	10/22 (45%)	6/14 (43%)
DCR (SD, PR and CR)	15/22 (68%)	10/14 (71%)
CBR (CR, PR or SD >90 days)	15/22 (68%)	10/14 (71%)
PD	6/22 (27%)	3/14 (21%)

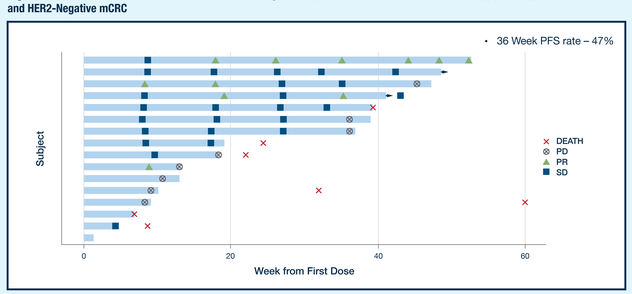
*Best Response is PR or CR reported by Central Reading Center from start of treatment until discontinuation. All 5 responders received prior 5FU. 80% received prior oxaliplatin and bevacizumab. Response evaluable were patients who had a post baseline assessment. ORR determined by central review.

Figure 1. TTX-080 + Cetuximab Drives Anti-Tumor Activity in Patients with WT RAS, WT BRAF and HER2-Negative mCRC



Numbers on the bars indicate number of prior lines of therapy (LOT). One (1) subject not represented in Figure 1 did not have target lesions per Central Review.

Figure 2. TTX-080 + Cetuximab Drove Anti-Tumor Activity and Disease Control in Patients with WT RAS, WT BRAF, and HER2-Negative mCRC



- Median PFS in the WT RAS, WT BRAF and HER2-negative group treated with TTX-080+Cetuximab was 24.4 (10.7, NA) weeks. PFS event rates–75%. Follow up duration was 21 weeks (range 0-52).

Table 3. Treatment-Related Adverse Events of TTX-080 + Cetuximab in Anti-EGFR Naïve mCRC Patients

TRAE reported in ≥5% of patients	Grade 1	Grade 2	Grade 3	Total (N=25)
Nausea	4	1	0	5 (20%)
Infusion-related reaction	0	5	0	5 (20%)
Fatigue	1	2	1	4 (16%)
Dermatitis acneiform	2	1	1	4 (16%)
Headache	0	3	0	3 (12%)
Chills	2	1	0	3 (12%)
Hypomagnesemia	2	1	0	3 (12%)
AST increase	0	0	3	3 (12%)
ALT increase	0	0	3	3 (12%)
Myalgias	0	1	1	2 (08%)
Stomatitis	2	0	0	2 (08%)

TRAE is any AE related to TTX-080 with or without being related to cetuximab. No patients had investigator reported TTX-080 related SAE. Grade 3 AST/ALT elevation considered to be immune-related in patient with PR. Resolved with steroids. Grade 5 Acute respiratory failure possibly related to TTX-080 or cetuximab. Study SRT adjudicated it to be unlikely related to TTX-080 or cetuximab.

mHNSCC Results

Table 4. Key Characteristics of mHNSCC Patients

	HPV-Negative mHNSCC (n=7)	HPV-Positive mHNSCC (n=11)
Primary location of the tumor Oropharynx Oral Cavity Hypopharynx Nasopharynx Larynx	0/7 (0%) 4/7 (57%) 0/7 (0%) 2/7 (29%) 1/7 (14%)	9/11 (81%) 1/11 (9%) 1/11 (9%) 0/11 (0%) 0/11 (0%)
PDL-1 status: Positive Negative Unknown	4/7 (57%) 1/7 (14%) 2/7 (29%)	7/11 (64%) 3/11 (27%) 1/11 (9%)
Number of prior lines of treatment: 1 2 ≥3	5/7 (71%) 2/7 (29%) 0/7 (0%)	5/11 (46%) 4/11 (36%) 2/11 (18%)
Previous treatments received: Chemotherapy Immunotherapy Cetuximab*	3/7 (43%) 7/7 (100%) 0/7 (0%)	7/11 (64%) 8/11 (73%) 1/11 (9%)

*Cetuximab administered in the non-metastatic setting.

Table 5. Response Rates by Central Review of TTX-080 + Cetuximab in HPV-Negative mHNSCC Patients

Response Evaluable Set	HPV-Negative	HPV-Positive
Response Evaluable Patients	7	10
ORR (Best Response)**	4/7 (57%)	0/10 (0%)
CR	1/7 (14%)	0/10 (0%)
PR	3/7 (43%)	0/10 (0%)
SD	1/7 (14%)	4/10 (40%)
DCR (SD, PR and CR)	5/7 (71%)	4/10 (40%)
CBR (CR, PR or SD >90 days)	5/7 (71%)	4/10 (40%)
PD	2/7 (29%)	6/10 (60%)

**Best Response is PR or CR reported by Central Reading Center from start of treatment until discontinuation. ORR determined by central review.

Figure 3. TTX-080 + Cetuximab Drove Anti-Tumor Activity in HPV-Negative mHNSCC Patients

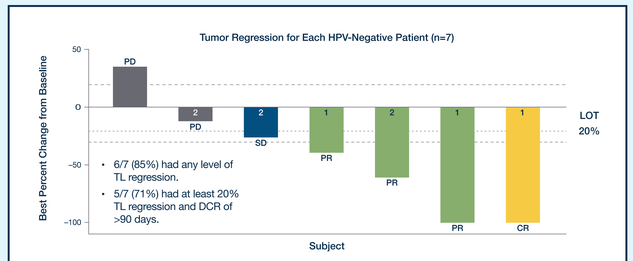
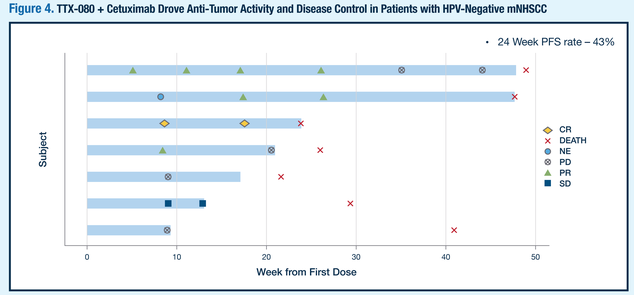


Figure 4. TTX-080 + Cetuximab Drove Anti-Tumor Activity and Disease Control in Patients with HPV-Negative mNHSCC



- Median PFS in the HPV-negative HNSCC group treated with TTX-080 + Cetuximab was 23.9 (9, NA) weeks. PFS event rate–100%. Follow up duration was 24 weeks (range 9-48).

Table 6. Treatment-Related Adverse Events of TTX-080 + Cetuximab in mHNSCC Patients

TRAE reported in ≥5% of patients	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=23)
Fatigue	3	1	0	0	4 (17%)
Pruritis	3	0	0	0	3 (13%)
Anemia	0	2	0	1	3 (13%)
AST Increase	1	1	0	0	2 (8.7%)

No SAE related to TTX-080 was reported in this TTX-080 + cetuximab treated mHNSCC arm.

Additional Clinical and Translational Data

TTX-080 Induces Statistically Significant*** On-Mechanism Immune Cell Activation in the Periphery and in the Tumor

Peripheral changes detected by flow cytometry from patient PBMCs:

- Increased % of activated Ki67$^+$ NK cells (innate - MOA).
- Increased frequency of ILT2$^+$ CD8$^+$ T cells (antigen experienced TEMRA population).
- Increased frequency of activated Ki67$^+$PD-1$^+$HLA-DR$^+$ CD4 T cells (biological activity).

***Cell populations were analyzed via CellEngine® and statistical analysis using R. Statistical significance was determined using Tukey-Kramer HSD test.

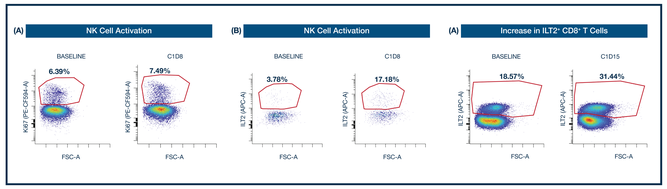
Tumoral Changes detected by RNAseq:

- TTX-080 monotherapy upregulates myeloid activation gene sets known to be associated with anti-tumor activity.

Data from other mCRC Arms (TTX-080 Monotherapy and TTX-080 + Cetuximab in Anti-EGFR Pretreated Arm) Support Potential Contribution of TTX-080 to the Clinical Activity of Combination

- Out of 25 patients enrolled in TTX-080 monotherapy, 30% had CBR >90 days with two patients stayed on treatment for 9 (Figure 5A) and 15 months prior to progression.
- One subject who received TTX-080 only in the TTX-080 cetuximab combo arm achieved PR (Figure 5B) by Central Read.
- Out of 23 patients who were not expected to receive benefit from cetuximab (received anti-EGFR as last line with PD prior to enrollment or who had tumors with mutations in RAS, BRAF or HER2-positivity), 3 patients (1 CR and 2 PR) reported responses (ORR 13%).

Figure 5. Increases in Activated NK Cells and ILT2$^+$ CD8$^+$ T Cells are Detected in Monotherapy Patients



Evidence of NK Cell Activation and Increased Antigen-specific T Cells in the Periphery

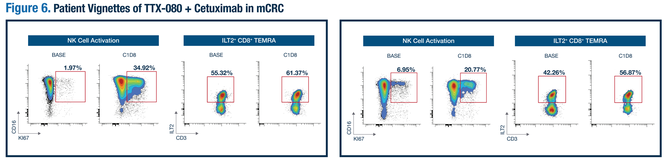
63-Year-Old Caucasian Female with mCRC (Patient #1)

- WT RAS, WT BRAF, HER2-negative.
- Received 2 prior LOT including 5 FU, oxaliplatin, and Avastin®.
- Achieved PR by Central Read with 33% reduction in target lesion; target lesion in liver completely disappeared.
- On treatment for 11 months prior to PD.

53-year-old Caucasian Male with mCRC (Patient #2)

- WT RAS, WT BRAF, HER2-negative.
- Received 4 prior LOT including 5-FU, oxaliplatin, irinotecan, Avastin® and Lonsurf®.
- Achieved PR by Central Read with 100% reduction in target lesion.
- On treatment for 12 months prior to PD.

Figure 6. Patient Vignettes of TTX-080 + Cetuximab in mCRC



Conclusions

- TTX-080 was well tolerated as monotherapy and in combination with cetuximab in patients with mCRC and mHNSCC.
- TTX-080 + cetuximab showed higher response rates in WT RAS mCRC (29%) and HPV-negative mHNSCC (57%) patients, compared to historically published cetuximab monotherapy data.[1,2,3,4]
  - Median PFS was approximately 6 months with TTX-080 + cetuximab in both tumor types.
  - The 36 Week PFS rate in WT RAS mCRC was 47% and the 24 Week PFS rate in HPV-negative HNSCC was 43%.
- TTX-080 demonstrated statistically significant on-mechanism immune cell changes observed in the periphery and myeloid cell activation within the tumor in both combination and monotherapy settings, respectively.
- The combination of TTX-080 + cetuximab in mCRC and mHNSCC warrants further study.

Abbreviations

5FU (fluorouracil); CBR (clinical benefit rate); CR (complete response); ctDNA (circulating tumors DNA); DCR (disease control rate); EGFR (epidermal growth factor receptor); HPV (human papillomavirus); LOT (lines of therapy); mCRC (metastatic colorectal cancer); mHSNCC (metastatic head and neck squamous cell carcinoma); MMS (microsatellite stability); NE (not evaluable); NK (natural killer);ORR (overall response rate); PD (progressive disease); PFS (progression-free survival); PI (principal investigator); PR (partial response); RECIST (Response Evaluation Criteria In Solid Tumors); SAE (serious adverse event); SD (stable disease); SLD (sum of lesion diameter); TL (target lesion); TRAE (treatment-related adverse event); VEG-F (Vascular endothelial growth factor); WT (wild-type)

References

1. Shapiro et al., CCR 2017
2. Loree et al., CCR 2021
3. Vermoken et al., JCO 2007
4. Adkins et al., Oral Biology 2021

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Email: Swaminathan Murugappan, M.D., Ph.D. smurugappan@tizonatx.com