Real-World Analyses to Evaluate the Role of TIGIT as a Target in First-Line Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinomas

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Conclusions

- This real-world study used RNA sequencing (RNA-seq) and clinical outcome data from patients with previously untreated, advanced, or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinomas (GC/GEJC/EAC) to highlight the role of T-cell immunoreceptor with Ig and ITIM domains (TIGIT) as an anti-cancer target
- *TIGIT* expression was highly correlated with expression of an effector T cell (Teff) gene set and *FOXP3* in GC/GEJC/EAC tumors
- High Teff or TIGIT expression (vs lower expression) was associated with numerically longer real-world time to next treatment or death (TTNTD) in patients who received first-line treatment with an immune checkpoint inhibitor (ICI) + chemotherapy (chemo)
  - The longer TTNTD seen in patients whose tumors had high *TIGIT* expression may be driven by these patients also having tumors with high Teff expression
- When *TIGIT* was normalized for Teff infiltration, there was no longer a benefit observed with ICI + chemo for patients whose tumors had high *TIGIT* expression
- Preclinical studies using colon or gastric cancer cells have shown that combining anti-TIGIT and anti–programmed cell death protein-1 (PD-1) leads to enhanced T cell activation.[1,2] Results from this real-world analysis suggest that this strategy may benefit patients with TIGIT-high GC/GEJC/EAC receiving first-line treatment. Larger studies may help confirm these findings

Plain Language Summary

- “Checkpoint” proteins are sometimes used by cancer cells to avoid the immune system. “PD-1” and “TIGIT” are two types of checkpoint proteins
- Some cancer drugs work by helping the immune system find and attack cancer cells. These drugs are called “immune checkpoint inhibitors,” or ICIs
- ICIs that target PD-1 are used with chemo to treat certain cancers of the stomach or esophagus that have spread throughout the body
- But these drugs do not work for all types of these cancers. Researchers are looking at whether drugs that target TIGIT could help additional patients
- In this study, we measured the amount of genes that make TIGIT and other related proteins in samples of stomach or esophageal cancers. We compared these measurements with how long patients stayed on their first treatment or how long these patients lived
- After adjusting the gene measurements to make them comparable, we found that patients who took an ICI + chemo and whose cancers had a high level of TIGIT stayed on treatment and were alive for about the same amount of time as patients whose cancers had a low level of TIGIT
- Our results suggest that patients who have not had treatment for stomach or esophageal cancers that have spread throughout the body may benefit from cancer treatment that combines a drug that targets TIGIT with a drug that targets PD-1

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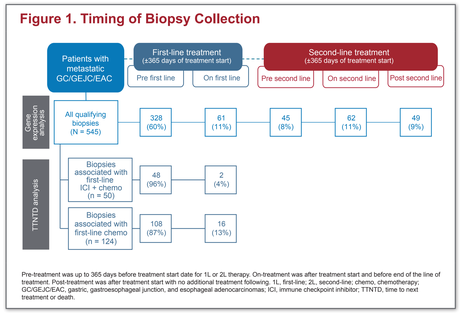
Introduction

- Anti–PD-1 ICIs in combination with chemo are approved for the treatment of GC/GEJC/EAC[3–5]
  - However, new treatment strategies are needed, as the currently available therapies are more effective in specific tumor subtypes, and many patients do not benefit from treatment[6,7]
- TIGIT is a potential anti-tumor ICI target in GC/GEJC/EAC[1,2,7–12]
  - TIGIT is overexpressed in GC/GEJC/EAC, and preclinical studies in GC/GEJC/EAC have shown that TIGIT blockade enhanced anti-tumor immunity[2,7,9–11]
- Preclinical studies have also shown that combining anti-TIGIT and anti–PD-1 or anti–programmed death ligand 1 (PD-L1) enhanced Teff expansion and function, and ongoing clinical studies have shown encouraging activity for this strategy in GC/GEJC/EAC[1,2,8,12–14]
- Previous research has shown associations between response to ICIs and Teff infiltration, immune gene signatures, and additional markers such as PD-L1 and tumor mutational burden[6,15]
- Understanding how *CD274* (PD-L1), Teff, and *TIGIT* RNA expression levels correlate with real-world outcomes of first-line treatment can inform the potential for TIGIT as a target in GC/GEJC/EAC

Methods

- Deidentified real-world data for patients with metastatic GC/GEJC/EAC were included from the Tempus AI, Inc., clinicogenomic database
- Biopsies were taken within 365 days of start of a line of therapy, had collection site annotated, and were to include whole transcriptome RNA-seq, 648 gene panel DNA-seq, and PD-L1 immunohistochemistry from the same biopsy sample **(Figure 1)**; biopsies could have been pre-treatment, on-treatment, or post-treatment
  - Data were acquired and analyzed in the Tempus Lens platform from Tempus AI, Inc.
- Gene expression analyses used all qualifying biopsies. Analyses of TTNTD by gene expression levels used biopsies from before (pre-treatment) and on (on-treatment) first-line treatment
  - For patients with multiple biopsies, the most recent biopsy was used
- Genes evaluated in this study included:
  - Genes in the *TIGIT* axis: *TIGIT*, *CD226*, and *CD155* (*PVR*; encodes the ligand for TIGIT)
  - Genes associated with T regulatory cells: *CD274*, *FOXP3*, *CCR8*, *CD8A*, *NT5E*, *IKZF1*, and *IKZF2*
  - Natural killer cell gene set (geometric mean of *GNLY*, *KLRD1*, *KLRB1*, *KLRF1*)
  - Teff gene set (geometric mean of *CD8A*, *EOMES*, *GZMA*, *GZMB*, *IFNG*, *PRF1*)
- Gene expression comparisons used the Wilcoxon test, Kruskal-Wallis test, and Spearman correlation. Gene signature analyses were performed using single-sample gene set enrichment analysis (ssGSEA)
- TTNTD (maximum follow-up 24 months) was assessed for first-line ICI + chemo or chemo using the Kaplan-Meier method and compared by expression level (high [≥ median] vs low [< median]) of *TIGIT*, Teff gene set, and TIGIT normalized by Teff gene set

Figure 1. Timing of Biopsy Collection



Pre-treatment was up to 365 days before treatment start date for 1L or 2L therapy. On-treatment was after treatment start and before end of the line of treatment. Post-treatment was after treatment start with no additional treatment following. 1L, first-line; 2L, second-line; chemo, chemotherapy; GC/GEJC/EAC, gastric, gastroesophageal junction, and esophageal adenocarcinomas; ICI, immune checkpoint inhibitor; TTNTD, time to next treatment or death.

Results

- The gene expression analysis was based on a population of 545 patients. Of these, 50 patients received first-line ICI + chemo and 124 patients received first-line chemo and were included in the analysis of TTNTD
- Patients had a median age of 63 years with a primary cancer site of esophagus (38%), stomach (38%) or cardia (24%) **(Table 1)**

Table 1. Patient Baseline Characteristics

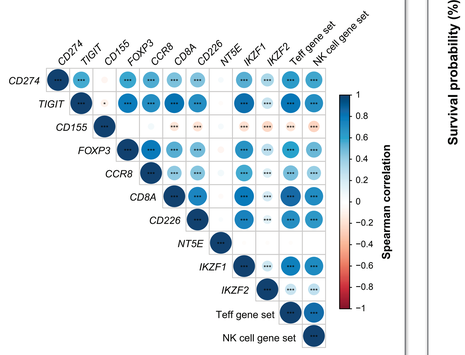
Characteristic	Patients (N = 545)
Median age, years (IQR)	63 (54–70)
Male sex, n (%)	398 (73)
Race, n (%)[a]	
White	289 (82)
Black	24 (7)
Asian	15 (4)
Primary cancer site, n (%)[b]	
Esophagus	205 (38)
Stomach	205 (38)
Cardia	133 (24)

[a]Race of “other” reported for 23 (7%) patients; race was unknown for 194 patients. [b]Primary site was unknown for 2 patients. IQR, interquartile range.

Immune Gene Expression in GC/GEJC/EAC

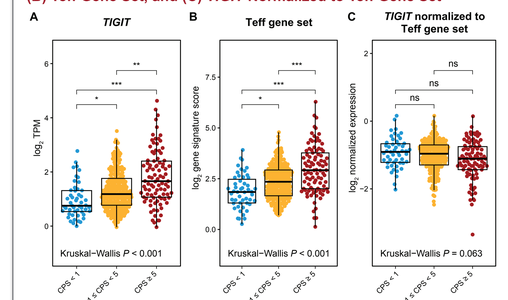
- *TIGIT* expression was most highly correlated with Teff (R = 0.80, P < 0.001) and *FOXP3* expression (R = 0.78, P < 0.001), followed by *CD274* expression (R = 0.57, P < 0.001) **(Figure 2)**
- Positive correlations with PD-L1 combined positive score were observed for *TIGIT* and Teff expression (P < 0.001 for both) but not *TIGIT* normalized to Teff levels (P > 0.05) **(Figure 3)**
- Biopsies from liver metastases, which tend to show a poor response to ICIs,[16] had lower immune signature scores (B-cell and inflammatory signature scores) vs stomach tumor biopsies (P < 0.001) **(Figure 4)**

Figure 2. Gene Expression Correlations



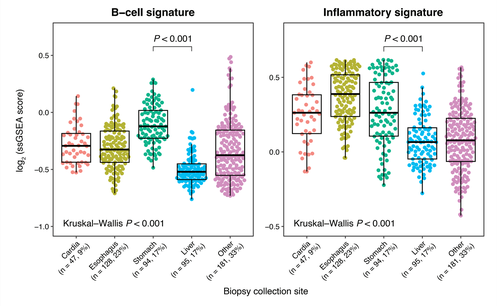
Heatmap of Spearman correlations. ***P < 0.001. **P < 0.01. *P < 0.05. NK, natural killer; Teff, effector T cell.

Figure 3. Correlations Between PD-L1 CPS and (A) *TIGIT*, (B) Teff Gene Set, and (C) *TIGIT* Normalized to Teff Gene Set



Analysis based on 51 biopsies with CPS < 1, 227 with CPS ≥ 1 and < 5, and 93 with CPS ≥ 5. Pairwise comparisons are based on the Bonferroni-corrected Wilcoxon test. ***P < 0.001. **P < 0.01. *P < 0.05. CPS, combined positive score; ns, not significant; PD-L1, programmed death ligand 1; Teff, effector T cell; TPM, transcripts per million.

Figure 4. Immune Gene Signature Scores by Biopsy Tumor Site

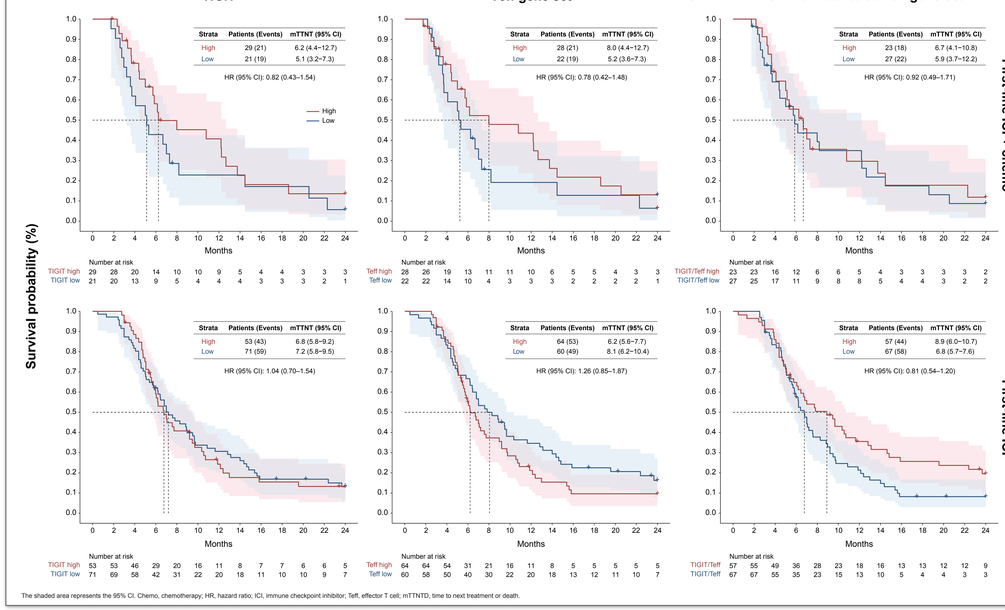


Analysis based on 47 (9%) cardia biopsies, 128 (23%) esophageal biopsies, 94 (17%) stomach biopsies, 95 (17%) liver biopsies, and 181 (33%) biopsies from other sites. ssGSEA enrichment scores are reported for the B-cell signature (*CD79A*, *MS4A1*, *CD19*, *STAP1*, *FAM30A*, *POU2AF1*, and *FCRL5*) and the inflammatory signature (*CCL2*, *IL1B*, *CXCL8*, *IL6*, and *PTGS2*). Pairwise comparisons are based on the Bonferroni-corrected Wilcoxon test. ssGSEA, single-sample gene set enrichment analysis.

Real-World Clinical GC/GEJC/EAC Outcomes in Gene Expression Subgroups

- High vs low expression of *TIGIT* and Teff were associated with numerically longer TTNTD for ICI + chemo, which was not observed in the ICI cohort **(Figure 5A and 5B)**
- When *TIGIT* expression was normalized to Teff levels there was no longer a difference in TTNTD between patients with high vs low *TIGIT* expression in the ICI + chemo group **(Figure 5C)**

Figure 5. TTNTD in Patients With High vs Low *TIGIT* and Teff Gene Set Expression



The shaded area represents the 95% CI. Chemo, chemotherapy; HR, hazard ratio; ICI, immune checkpoint inhibitor; Teff, effector T cell; mTTNTD, time to next treatment or death.