Exploration of Potential Biomarkers Correlated With Efficacy of Ociperlimab (Anti-TIGIT) Plus Tislelizumab (Anti–PD-1) in 1L PD-L1+ Non–Small Cell Lung Cancer (NSCLC)

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Conclusions

Expression of anti-TIGIT MOA-related genes and signatures correlated with efficacy in ociperlimab + tislelizumab–treated 1L PD-L1+ NSCLC.

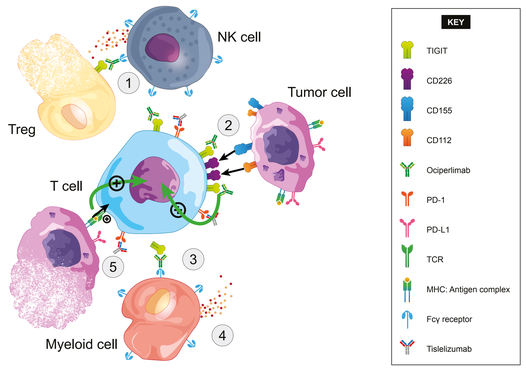
Combining mRNA expression of anti-TIGIT MOA-related genes with PD-L1 protein expression identified subgroups of patients with NSCLC with improved efficacy.

Further validation of these results is required in a larger population.

Background

- Studies have shown promising antitumor activity of anti–T-cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) therapy in combination with anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy in patients with NSCLC[1-3]
- Ociperlimab is an anti-TIGIT monoclonal antibody (mAb) that has multiple mechanisms of action (MOAs) in modulating the tumor environment; tislelizumab is an anti-PD-1 mAb that blocks the PD-1/PD-L1 immune checkpoint, resulting in T-cell activation (**Figure 1**)[4-8]

Figure 1. Mechanism of Action of Ociperlimab and Tislelizumab Combination Therapy



1. In the tumor microenvironment, binding of ociperlimab to TIGIT leads to a reduction of Tregs by inducing potential antibody-dependent cellular cytotoxicity, but not cytotoxic T cells
2. By binding TIGIT, ociperlimab increases availability of CD155 (PVR) and CD112 (PVRL2; Nectin-2) to bind to co-stimulatory receptor CD226, leading to immune cell activation
3. TIGIT expression is reduced on T-cell surfaces through Fc-dependent trogocytosis, while CD226 is upregulated in a Fc-dependent manner
4. Fc/FcγR engagement results in a proinflammatory tumor microenvironment through myeloid cell and NK cell activation
5. Tislelizumab is a next-generation anti–PD-1 antibody, designed to minimize FcγR binding on macrophages in order to abrogate antibody-dependent cellular phagocytosis, a potential mechanism of resistance to anti–PD-1 therapy

MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PVR, poliovirus receptor; PVRL2, poliovirus ecotpr-related 2; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; Tregs, regulatory T cells.

- In the ongoing phase 1/1b, open-label AdvanTIG-105 dose-escalation/expansion trial (NCT04047862), ociperlimab + tislelizumab showed preliminary antitumor activity and was well tolerated in patients with advanced solid tumors, including NSCLC[9]
- We investigated whether expression of the following anti-TIGIT MOA-related markers was associated with the efficacy of ociperlimab + tislelizumab in Cohort 3 (Stage IV PD-L1+ NSCLC) of the AdvanTIG-105 study:
  - **Components of the TIGIT pathway**
  - **Regulatory T cell (Treg)–related genes**
  - **Macrophage-related genes**

Methods

Trial Design

- AdvanTIG-105 is an open-label, multicenter, phase 1/1b trial
- Cohort 3 inclusion criteria, treatments, and endpoints have been presented previously[10]

Biomarker Testing

- Biomarker testing was performed on tumor tissue samples obtained from patients in Cohort 3
- Immunohistochemistry (IHC) was performed to evaluate PD-L1 protein expression on tumor cells (TCs) for all available patient samples using the Ventana SP263 IHC assay at a central laboratory
- IHC was performed to evaluate TIGIT protein expression on immune cells for all available patient samples using a formulation locked assay with the Roche SP410 antibody
- mRNA expression levels of TIGIT, CCR8, and a tumor-associated macrophage (TAM) signature were evaluated using TruSeq RNA Access technology (Illumina®) for all available patient samples in Sequanta
  - Hematoxylin and eosin images were marked for macro dissection by a pathologist prior to RNA extraction

Analysis and Statistical Methods

- The data cutoff for efficacy analyses was February 2, 2023
- Analyses were performed for patients from Cohort 3 (intention-to-treat PD-L1 IHC evaluable; N=45) with available gene expression profiles (GEP evaluable; N=24)
- Overall response rate (ORR) analysis was based on confirmed best overall response data
  - Correlation of GEP and ORR in volcano plots used *P* values calculated with limma moderated t-statistics
  - Responders were defined as patients with complete or partial responses; non-responders were defined as patients with stable or progressive disease
- Progression-free survival (PFS) by investigator was used for survival analyses
  - For forest plots, a Cox regression model was used to calculate *P* values of PFS hazard ratio (HR; high vs. low) by median cutoff for gene expression
  - For Kaplan-Meier (KM) curves, a log-rank test was used to compare subgroup survival. *P* values from KM curves were calculated with a two-sided unstratified KM log-rank test model
  - The 95% confidence interval for median PFS (mPFS) was generated using the Brookmeyer method

Results

Baseline Characteristics and Efficacy for Cohort 3

- Baseline characteristics were similar for PD-L1–evaluable (all patients in Cohort 3; N=45), TIGIT-evaluable (N=43), and GEP-evaluable (N=24) patient populations (**Supplementary Table 1**, available for download by scanning the Quick Response [QR] code to the right)
- PFS was similar for PD-L1–evaluable and GEP-evaluable patients (**Supplementary Figure 1**, available for download by scanning the QR code to the right)

Correlation of TIGIT Pathway GEP and Response to Ociperlimab + Tislelizumab

- Treatment response to ociperlimab + tislelizumab was positively correlated with mRNA expression of TIGIT pathway components and related genes (**Figure 2A**)
- Patients with high expression of TIGIT had significantly improved mPFS versus those with low expression of TIGIT at a top one-third cutoff (**Figure 2B**)
- Patients with high expression of CD226, a TIGIT pathway component, also had significantly improved mPFS versus CD226-low patients at a median cutoff (**Figure 2C**)

Correlation of Treg-Related GEP and Response to Ociperlimab + Tislelizumab

- Treatment response was positively correlated with mRNA expression of Treg-related genes (**Figure 3A**)
- High expression of several Treg-related genes was associated with decreased risk of progression/death, compared with low expression, at a median cutoff (**Figure 3B**)
- Patients with high CCR8 expression, representative of tumor-infiltrating Treg cells with highly immune suppressive functions, had significantly longer mPFS versus CCR8 low patients at a median cutoff (**Figure 3C**)

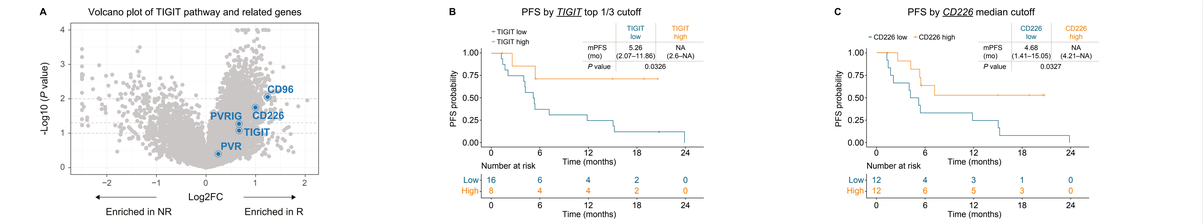
Correlation of Macrophage-Related GEP and Response to Ociperlimab + Tislelizumab

- Treatment response was positively correlated with mRNA expression of macrophage-related genes (**Figure 4A**)
- High expression of several macrophage-related genes was associated with decreased risk of progression/death, compared with low expression, at a median cutoff (**Figure 4B**)
- Patients with high expression of a TAM signature, representative of tumor inflammatory suppressive macrophages, had significantly longer mPFS versus TAM low patients at a median cutoff (**Figure 4C**)

Dual Biomarker Segmentation by PD-L1 IHC and GEP

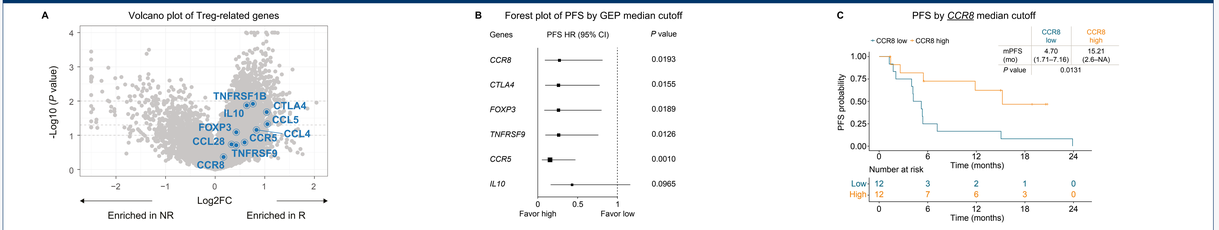
- Significantly improved mPFS was observed in PD-L1 high (TC ≥25%) + TIGIT high (**Figure 5A**), PD-L1 high + CCR8 high (**Figure 5B**), and PD-L1 high + TAM signature high (**Figure 5C**) patient subgroups, compared with all other dual biomarker combinations
  - Median cutoffs were used for TIGIT, CCR8, and TAM signature expression
- A highly overlapped PD-L1 high + TIGIT high + CCR8 high + TAM signature high patient population was observed in dual biomarker analyses (**Figure 5D**)

Figure 2. Response to Ociperlimab + Tislelizumab by Expression of the TIGIT Pathway and Related Genes



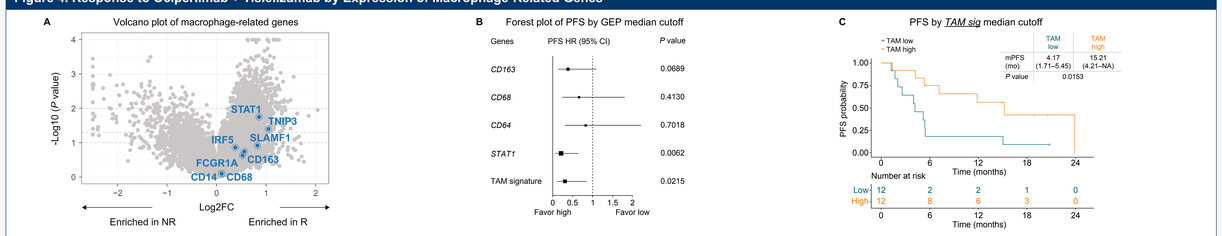
mPFS, median progression-free survival; NA, not applicable; NR, non-responders; PFS, progression-free survival; R, responders; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

Figure 3. Response to Ociperlimab + Tislelizumab by Expression of Treg-Related Genes



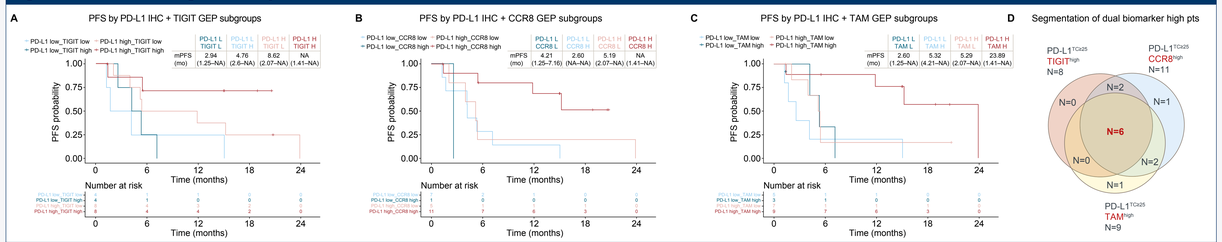
CI, confidence interval; GEP, gene expression profile; HR, hazard ratio; mPFS, median progression-free survival; NA, not applicable; NR, non-responders; PFS, progression-free survival; R, responders; Treg, regulatory T cell.

Figure 4. Response to Ociperlimab + Tislelizumab by Expression of Macrophage-Related Genes



CI, confidence interval; GEP, gene expression profile; HR, hazard ratio; mPFS, median progression-free survival; NA, not applicable; NR, non-responders; PFS, progression-free survival; R, responders; TAM, tumor-associated macrophage.

Figure 5. Dual Biomarker Segmentation by PD-L1 IHC and GEP



GEP, gene expression profile; IHC, immunohistochemistry; mPFS, median progression-free survival; NA, not applicable; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; TAM, tumor-associated macrophage; TC, tumor cell; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

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Presenter disclosures

Hengrui Zhu is an employee of BeiGene and may own company stock/stock options.

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