AdvanTIG-203: A randomized Phase 2 study comparing anti-TIGIT monoclonal antibody ociperlimab plus tislelizumab vs tislelizumab plus placebo as second-line treatment in patients with advanced or recurrent esophageal squamous cell carcinoma expressing programmed death-ligand 1 (PD-L1)

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Introduction

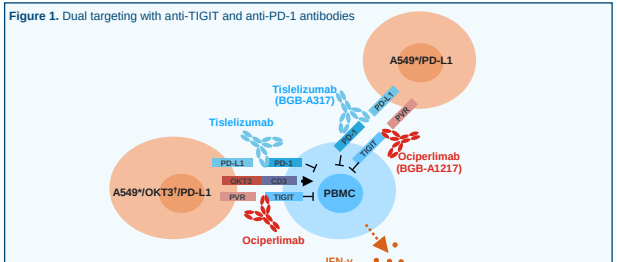
Unmet need in ESCC

- Esophageal cancer is the eighth most common cancer globally, with approximately 544,000 deaths in 2020, and is the sixth most common cause of cancer-related deaths.[1] Esophageal squamous cell carcinoma (ESCC) represents over 90% of esophageal cancer cases in Asia, South America, and the Middle East[2]
- First-line treatment with programmed cell death protein-1 (PD-1) antibodies in combination with chemotherapy has been shown to provide improvements in objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) vs chemotherapy alone, in patients with advanced ESCC[3]
- PD-1 antibodies have also demonstrated improvements in ORR and OS vs second-line chemotherapy in patients with recurrent locally advanced or metastatic ESCC, who progressed on or after one prior line of systemic treatment.[4,5] PD-L1 may be a predictive biomarker for clinical benefit[6]
- However, for patients who are anti-PD-1 naïve, there is still an unmet need for second-line treatment options. Few patients with ESCC receive treatment beyond second-line therapy, often due to a significant decline in performance status and lack of clinical benefit. In general, fewer than 5% of patients with ESCC survive beyond 5 years[2]

Introduction to ociperlimab, tislelizumab, and the AdvanTIG-203 study

- T-cell immunoreceptor with immunoglobulin (Ig) and tyrosine-based inhibition motif domain (TIGIT) is a co-inhibitory immune checkpoint receptor expressed on immune cells, including T cells and natural killer (NK) cells in multiple solid tumors, which can inhibit anticancer immune responses[7,8]
- Ociperlimab (BGB-A1217) is a humanized IgG1 monoclonal antibody designed to bind to TIGIT with high specificity and affinity. Ociperlimab binds to TIGIT, blocking interaction with CD155 (poliovirus receptor; PVR) and CD112 (PVR-L2; nectin-2) ligands on tumor cells, resulting in reactivation of T cell-mediated and NK cell antitumor immune responses[9]
- Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[10,11]
- Tislelizumab demonstrated statistically significant and clinically meaningful improvement in OS in patients with advanced or metastatic ESCC, compared with second-line chemotherapy[12]
- Dual targeting of tumors with anti-TIGIT and anti-PD-1 monoclonal antibodies (**Figure 1**) produces synergistic immune cell activation and enhanced antitumor activity in preclinical and clinical studies[8,13]
- We report the design of an ongoing Phase 2, AdvanTIG-203 study, which is investigating the efficacy and safety of ociperlimab plus tislelizumab in patients with previously treated, unresectable, locally advanced, recurrent or metastatic ESCC

Figure 1. Dual targeting with anti-TIGIT and anti-PD-1 antibodies



*Chen X, et al. Data presented at AACR 2021 (Abstract 1854). *PVR positive A549 cells; †anti-CD3 antibody clone; CD3, cluster of differentiation 3; IFN-γ, interferon-gamma; OCI, ociperlimab; OKT3, muromonab-CD3; PBMC, human peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PMBC, peripheral blood mononuclear cell; PVR, poliovirus receptor; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain*

Conclusions

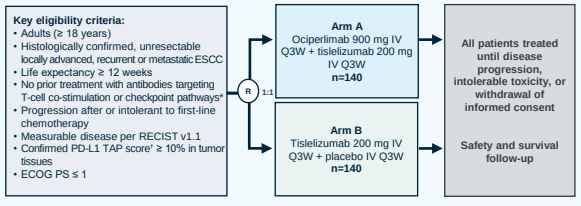
AdvanTIG-203 is an **ongoing Phase 2 study** investigating whether **ociperlimab + tislelizumab** combination therapy **improves ORR and OS** vs **tislelizumab + placebo** in adults with **unresectable, locally advanced, recurrent or metastatic ESCC**

Methods

Study design and treatment

- AdvanTIG-203 is a randomized, Phase 2, double-blind study (NCT04732494) being conducted in approximately 100 centers globally in ~280 patients with unresectable, locally advanced, recurrent or metastatic ESCC, whose tumors express PD-L1 (tumor area positivity [TAP]) score ≥ 10%) (**Figure 2**)
- Study enrolment has begun, and recruitment is ongoing
- Eligible patients will be randomized 1:1 to:
  - **Arm A:** Ociperlimab 900 mg plus tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W)
  - **Arm B:** Tislelizumab 200 mg plus placebo IV Q3W
- Stratification factors include Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 vs 1), number of organs with metastases (≤ 1 vs ≥ 2), and region (Asia vs non-Asia)
- Study drugs (including placebo) will be administered until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), unacceptable toxicity, or withdrawal of informed consent, whichever occurs first

Figure 2. Study design



Anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT, or any other antibodies; †PD-L1 expression is determined by PD-L1 score assessed by tumor area positive score (TAP) (previously referred to visually-estimated Combined Positive Score [vCPS] in protocol), which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background and tumor-associated immune cells with any staining above background using Ventana PD-L1 (SP263) assay; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain

Endpoints and assessments

- Co-primary endpoints are:
  - Investigator-assessed ORR in the intent-to-treat (ITT) analysis set, according to RECIST v1.1
  - OS in the ITT analysis set
- Secondary endpoints are listed in **Table 1**
- Tumor imaging will be performed at baseline (≤ 28 days before randomization). During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks and every 12 weeks (± 7 days) thereafter
- Responses will be assessed using RECIST v1.1. If a patient continues to benefit from study drugs after disease progression per RECIST v1.1, the patient may continue the study treatment at the investigator's discretion
- Patients will be evaluated for adverse events (AEs) and serious AEs (SAEs), and immune-mediated AEs. Vital signs, physical examinations, ECOG PS change, electrocardiogram results, and other examinations will be used for safety assessments (**Table 1**)

Table 1. Secondary and exploratory endpoints

Secondary endpoints	Exploratory Endpoints
• ORR by IRC*	• Association between exploratory biomarkers and clinical efficacy, disease status, and resistance
• PFS by IRC and investigators*	– Biomarkers include, but are not limited to, TIGIT, CD226, CD155, CD112 and PD-L1, GEP, and TMB/gene mutation/MSI
• DoR by IRC and investigators*	• Serum ociperlimab and tislelizumab concentrations at specified timepoints
• DCR by IRC and investigators*	• Immunogenic responses to ociperlimab and tislelizumab‡
• CBR by IRC and investigators*	• QoL, measured by EQ-5D-5L assessment
• HRQoL	
– EORTC, QLQ-C30, and QLQ-OES18	
• Type, frequency, and severity of AEs and SAEs†	

**According to RECIST v1.1; †Graded by NCI-CTCAE version 5.0; ‡Assessed through detection of antidrug antibodies*
AE, adverse event; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, European Quality of Life 5 Dimensional 5-Level; GEP, gene expression profiling; HRQoL, health related quality of life; IRC, independent review committee; MSI, microsatellite instability; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QLQ-C30, EORTC Quality of Life Questionnaire Core 30; QLQ-OES18, EORTC Quality of Life Oesophageal Cancer Questionnaires 18; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; TMB, tumor mutation burden

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