AdvanTIG-302: Anti-TIGIT monoclonal antibody ociperlimab plus tislelizumab vs pembrolizumab in programmed death ligand 1-selected, previously untreated, locally advanced, unresectable or metastatic non-small cell lung cancer

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Introduction

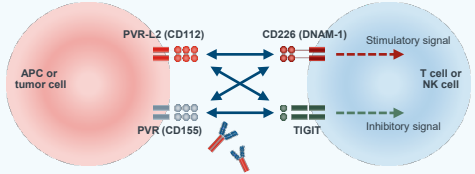
Unmet need in lung cancer

- Lung cancer is the most common cancer worldwide (2.2 million cases in 2020) and the leading cause of cancer mortality worldwide (1.8 million deaths in 2020)[1]
- Non-small cell lung cancers (NSCLC) represent ~85% of lung cancer cases, and long-term prognosis with conventional treatment is poor for patients with locally advanced or metastatic disease[2,3]
- Monotherapy with programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) monoclonal antibodies (mAbs) has improved clinical outcomes for patients with non-oncogenic driven NSCLC, but clinical efficacy is limited by primary and secondary resistance, and improvements in overall survival (OS) are required[4,5]

Introduction to ociperlimab, tislelizumab and the AdvanTIG-302 study

- T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is a co-inhibitory, immune checkpoint receptor that is upregulated on T cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses[6,7]
- Ociperlimab (BGB-A1217) is a novel, humanized mAb that binds to TIGIT with high affinity and specificity, blocking the interaction with its ligands on tumor cells, and has competent Fc effector function[8] (Figure 1)[8]
- Tislelizumab is an anti-PD-1 mAb that has been engineered to minimize binding to FcγR on macrophages and abrogate antibody-dependent phagocytosis, which has been proposed as a potential mechanism of resistance to established anti-PD-1 mAbs[10,11]
- Dual targeting of tumors with anti-TIGIT and anti-PD-1 mAbs produces synergistic immune cell activation and enhanced antitumor activity in preclinical and clinical studies[6,12]
- We report the design of the ongoing Phase 3 AdvanTIG-302 study, which is investigating the efficacy and safety of ociperlimab plus tislelizumab vs the anti-PD-1 mAb pembrolizumab as a single agent, in patients with PD-L1-selected, previously untreated, locally advanced, unresectable or metastatic NSCLC

Figure 1. Ociperlimab activates T/NK cells by blocking TIGIT and ligand interaction



Methods

Study design

- AdvanTIG-302 is a Phase 3, multicenter, international, randomized, double-blind study currently being conducted in 170 centers (clinicaltrials.gov NCT04746924) (**Figure 2**)
- Approximately 605 adults with PD-L1-selected, locally advanced or recurrent NSCLC that is unresectable or not amenable to radiotherapy, with or without chemoradiotherapy, or previously untreated metastatic disease, whose tumors do not harbor epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations will be enrolled (**Figure 3**)
- Study enrollment has begun and is ongoing
- Eligible patients will be randomized 5:5:1 to:
  - **Arm A:** Ociperlimab 900 mg plus tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W)
  - **Arm B:** Pembrolizumab 200 mg plus placebo IV Q3W
  - **Arm C:** Tislelizumab 200 mg plus placebo IV Q3W
- Stratification factors include histology (squamous vs non-squamous) and region (Asia vs non-Asia)
- Study treatments will be continued until disease progression by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), unacceptable toxicity, withdrawal, or the timepoint at which the investigator considers that the patient is no longer benefiting from study treatment. Treatment beyond investigator-assessed, RECIST v1.1-defined disease progression is permitted. Crossover between treatments is not permitted
- Tislelizumab monotherapy has demonstrated activity in pre-treated NSCLC and is expected to be active in patients with previously untreated NSCLC. Arm C was implemented with the intent to generate tislelizumab monotherapy data in this specific NSCLC population so that the relative contributions of tislelizumab and ociperlimab in Arm A can be understood

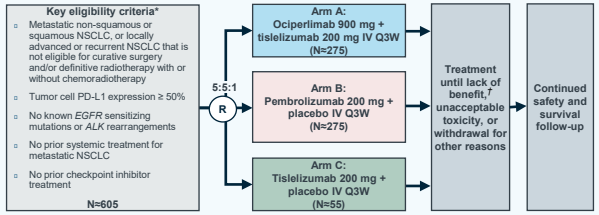
Conclusions

AdvanTIG-302 is an **ongoing Phase 3 study investigating whether ociperlimab + tislelizumab** combination therapy **prolongs PFS and OS** vs **pembrolizumab monotherapy** in adults with **PD-L1 high, locally advanced/recurrent or untreated metastatic NSCLC**

This study will provide insight into the effect of **dual targeting** with **anti-TIGIT** and **anti-PD-1 antibodies** (ociperlimab and tislelizumab) vs **anti-PD-1 monotherapy** (pembrolizumab) in first-line NSCLC

Figure 2. Enrollment sites

Figure 3. Study design



Randomization stratified by histology (squamous vs non-squamous) and region (Asia vs non-Asia);†Patients were ineligible if they had active leptomeningeal disease, an autoimmune disease or infection, a history of interstitial lung disease or diabetes, an active malignancy ≤ 2 years previous, a condition that required systemic treatment with steroids, hepatitis B or C, HIV, cardiovascular risk factors, a surgical procedure or live vaccine ≤ 28 days before randomization, concurrent participation in clinical trial, or a pregnant woman. †The timepoint at which the investigator considers that the patient is no longer benefiting from study treatment

R, randomization

Study population

- Key eligibility criteria included:
  - Aged ≥ 18 years
  - Histologically or cytologically documented locally advanced or recurrent NSCLC ineligible for curative surgery or definitive radiotherapy (with or without chemoradiotherapy), or metastatic NSCLC (non-squamous or squamous)
  - No prior systemic treatment for metastatic NSCLC
  - Provision of fresh or archival tumor tissue for central evaluation of levels of PD-L1 and other biomarkers
  - Tumor cell PD-L1 expression ≥ 50% (centrally determined by VENTANA PD-L1 [SP263] assay)
  - ≥ 1 measurable lesion, as per RECIST v1.1
  - ECOG PS (Eastern Cooperative Oncology Group performance status) ≤ 1
  - Adequate organ function
  - No known sensitizing mutation in the *EGFR* gene or *ALK* fusion oncogene
  - No prior treatment with anti-PD-1/L1 antibodies or any other checkpoint inhibitors

Endpoints and assessments

- Dual primary endpoints are:
  - Investigator-assessed progression-free survival (PFS) according to RECIST v1.1 for Arm A vs B
  - OS for Arm A vs B
- Secondary endpoints and exploratory endpoints are listed in **Table 1**
- All efficacy-related endpoints will be assessed in the intent-to-treat analysis set (all randomized patients)
- Radiological imaging will be performed every 9 weeks for the first year of the study and every 12 weeks thereafter
- Tumor responses will be assessed by investigators and a blinded independent review committee (BIRC) using RECIST v1.1
- Patient-reported health-related quality of life assessments will be performed at baseline, every other cycle through Cycle 13, every 4 cycles thereafter, and at the end-of-treatment visit
- Safety will be assessed through monitoring of the incidence and severity of adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0), laboratory results, vital signs, ECOG PS, and other examinations
- Safety analyses will be performed using the safety analysis set (all randomized patients receiving ≥ 1 dose of study drug)

Statistical analysis

- The dual primary endpoints of PFS and OS will be estimated using the Kaplan-Meier method, with a stratified log-rank test used to compare Arm A vs B and treatment effect estimated using a Cox regression model
- Two interim analyses are planned:
  - An interim analysis will be performed for PFS when ~65% of the targeted number of anticipated events have occurred;
  - An interim analysis will be performed for OS at the time of final PFS analysis

Table 1. Secondary and exploratory endpoints

Secondary endpoints	Exploratory endpoints
• PFS by BIRC* in Arm A and Arm B	• ORR and DoR by BIRC* in Arm A and Arm B
• ORR by investigators* in Arm A and Arm B	• DCR, CBR and TTR by BIRC and investigators* in Arm A and Arm B
• DoR by investigators* in Arm A and Arm B	• PFS after next line of treatment (PFS2)
• Health-related quality of life	• OS, PFS, ORR, DoR, by BIRC and investigators* in Arm C
◦ EORTC QLQ-C30†	• Incidence and severity of AEs in Arm C
◦ EORTC QLQ-LC-13	• Association between biomarkers and response or resistance
◦ EQ-5D-5L questionnaire	• Pharmacokinetics
• Time to deterioration	• Host immunogenicity
• Incidence and severity of AEs	

**According to RECIST v1.1; †Analyzed using the global health status scale of the QLQ-C30 tool*

AE, adverse events; BIRC, blinded independent review committee; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; EORTC QLQ-LC-13, EORTC Quality of Life Questionnaire Lung Cancer 13; EQ-5D-5L, 5 Level EuroQol 5 Dimension; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization to objective disease progression after next line of treatment or death from any cause, whichever occurs first; TTR, time to response

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