ADVANTIG-105: Phase 1 dose-escalation study of anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) in combination with tislelizumab in patients with advanced solid tumors

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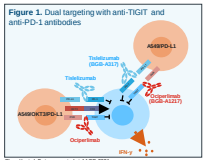
Introduction

- Targeting programmed cell death protein-1 (PD-1)/ programmed death-ligand 1 (PD-L1) and additional immune inhibitory receptors expressed on T cells may overcome tumor immune escape and enhance antitumor response[1–3]
- 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[4,5]
- Ociperlimab (BGB-A1217) is a novel, humanized monoclonal antibody that binds to TIGIT with high affinity and specificity, and has demonstrated competent binding with C1q and all Fcγ receptors while inducing antibody-dependent cellular cytotoxicity[6]
- Tislelizumab is an anti-PD-1 monoclonal antibody (mAb) engineered to minimize binding to FcγR on macrophages and abrogate antibody-dependent phagocytosis. This is a potential mechanism for resistance to anti-PD-1 therapy[7,8]
- 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[9,10]
- Pre-clinical data indicate that the safety profile of ociperlimab is adequate to support first-in-human (FIH) dosing[6]
- We report the results of a Phase 1, FIH study that evaluated the pharmacokinetics (PK), safety, and preliminary antitumor activity of ociperlimab plus tislelizumab in patients with advanced, metastatic, unresectable solid tumors

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



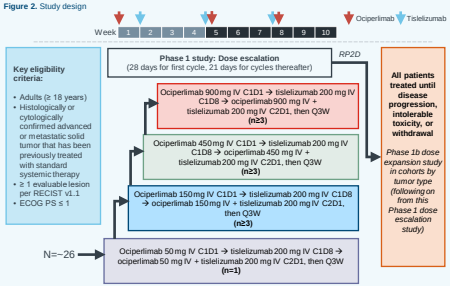
Chen X, et al. Data presented at AACR 2021.
*PVR positive A549 cells; †anti-CD3 antibody clone; PBMC, human peripheral blood mononuclear cells; PVR, poliovirus receptor

Methods

Study design and treatment

- A Phase 1 dose escalation study was conducted in 3 centers between August 2019 and October 2020 across Australia in 26 patients with advanced, metastatic, unresectable solid tumors, for which standard therapy was ineffective, intolerable or unavailable (clinicaltrials.gov NCT04047862) (**Figure 2**)
- Data cut-off (DCO) was February 21, 2021
- Eligible patients received an escalating dose of ociperlimab intravenously (IV) as a single agent on Cycle 1 Day 1 and tislelizumab 200 mg IV on Cycle 1 Day 8
- If tolerated, patients received four escalating doses of ociperlimab (50–900 mg) plus tislelizumab 200 mg sequentially on Day 29 and every three weeks (Q3W) thereafter until discontinuation

Figure 2. Study design



Primary endpoints:
- AEs, serious AEs, MTD or MAD

Secondary endpoints:
- ORR*, DoR*, DCR*, serum concentrations and other PK parameters of ociperlimab and tislelizumab at specified timepoints, immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs

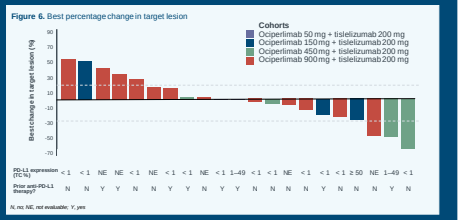
Exploratory endpoints:
- TIGIT receptor occupancy in peripheral blood and PD-L1 expression in tumor tissues

*Assessed per RECIST v1.1. ADA, antidrug antibodies; AE, adverse event; C, cycle; D, day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenously; Q3W, every 3 weeks; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; v, version

Conclusions

- In this **Phase 1 dose escalation** study, ociperlimab plus tislelizumab was **well tolerated** in patients with advanced solid tumors
- The **types and severity** of **adverse events** observed were **consistent** with **tislelizumab monotherapy**. **No DLTs** were observed
- **Preliminary anti-tumor activity** was observed
- Recommended Phase 2 dose is **ociperlimab 900 mg IV** plus tislelizumab 200 mg IV Q3W

Figure 6. Best percentage change in target lesion



Endpoints and assessments

- Primary, secondary, and exploratory endpoints are listed in **Figure 2**
- For initial dose-finding recommendations, adverse events (AEs) were assessed according to a 28-day dose-limiting toxicity (DLT) assessment window, which started on the first day of study drug administration
- Dose escalation occurred according to a 3 + 3 design
- PD-L1 expression was assessed on archival tumor tissue using the investigational VENTANA PD-L1 (SP263) assay

Statistical analysis

- The safety (SAS), efficacy evaluable, and PK analysis sets included all patients who received ≥ 1 dose of study drugs
- Primary and secondary endpoints were based upon investigators' assessments per RECIST v1.1

Results

Patients

- In total, 26 patients with localized unresectable or metastatic solid tumors were enrolled into this Phase 1, dose escalation study to receive doses of ociperlimab ranging from 50–900 mg (**Table 1**)
- Median age of patients was 55.5 years and 11 (42.3%) patients were male
- At the data cut-off (February 21, 2021) 22 patients discontinued treatment, and 14 patients were discontinued from the study (**Table 2**)
- Patient tumor types included squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, head and neck cancer, gastric/gastroesophageal junction cancer, esophageal cancer, pancreatic cancer, colorectal cancer, uterine cancer, and melanoma

Table 1. Baseline characteristics

	OCI 50 mg plus TIS 200 mg (n=1)	OCI 150 mg plus TIS 200 mg (n=3)	OCI 450 mg plus TIS 200 mg (n=6)	OCI 900 mg plus TIS 200 mg (n=16)	Total (N=26)
Sex, n (%)					
Male	1 (100.0)	2 (66.7)	2 (33.3)	6 (37.5)	11 (42.3)
Female	0 (0.0)	1 (33.3)	4 (66.7)	10 (62.5)	15 (57.7)
Race, n (%)					
Asian	0 (0.0)	0 (0.0)	2 (33.3)	3 (18.8)	5 (19.2)
White	1 (100.0)	2 (66.7)	3 (50.0)	12 (75.0)	18 (69.2)
Other	0 (0.0)	1 (33.3)	1 (16.7)	1 (6.3)	3 (11.5)
Age, (years)					
Median	50.0	42.0	60.0	54.0	55.5

OCI, ociperlimab; TIS, tislelizumab

Table 2. Patient disposition and reasons for discontinuation

	OCI 50 mg plus TIS 200 mg (n=1)	OCI 150 mg plus TIS 200 mg (n=3)	OCI 450 mg plus TIS 200 mg (n=6)	OCI 900 mg plus TIS 200 mg (n=16)	Total (N=26)
Number of patients treated with any study drug, n (%)	1 (100.0)	3 (100.0)	6 (100.0)	16 (100.0)	26 (100.0)
Patients discontinued from ociperlimab, n (%)	1 (100.0)	2 (66.7)	5 (83.3)	14 (87.5)	22 (84.6)
Patients discontinued from tislelizumab, n (%)	1 (100.0)	2 (66.7)	5 (83.3)	14 (87.5)	22 (84.6)
Reasons for discontinuation from study drugs, n (%)					
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (3.8)
Withdrawal by patient	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	2 (7.7)
Progressive disease	1 (100.0)	2 (66.7)	5 (83.3)	11 (68.8)	19 (73.1)
Patients discontinued from study, n (%)	1 (100.0)	2 (66.7)	3 (50.0)	8 (50.0)	14 (53.8)

TEAEs

- In total, 25 (96.2%) of 26 patients had ≥ 1 treatment-emergent adverse event (TEAE) (**Table 3**). Fifteen (57.7%) patients experienced at least one immune-related TEAE. There were three Grade ≥ 3 immune-related AEs (colitis, cortisol decrease, and diabetic ketoacidosis), which occurred in the ociperlimab 900 mg group
- No DLTs were observed

Table 3. AEs and SAEs in the safety analysis set

	OCI 50 mg plus TIS 200 mg, n (%) (n=1)	OCI 150 mg plus TIS 200 mg, n (%) (n=3)	OCI 450 mg plus TIS 200 mg, n (%) (n=6)	OCI 900 mg plus TIS 200 mg, n (%) (n=16)	Total, n (%) (N=26)
Patients with ≥1 TEAE	1 (100.0)	3 (100.0)	6 (100.0)	15 (93.8)	25 (96.2)
Any treatment-related TEAE	1 (100.0)	1 (33.3)	5 (83.3)	10 (62.5)	17 (65.4)
Serious TEAE	1 (100.0)	1 (33.3)	2 (33.3)	9 (56.3)	13 (50.0)
Serious treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	4 (15.4)
Grade ≥ 3 TEAE	1 (100.0)	1 (33.3)	3 (50.0)	11 (68.8)	16 (61.5)
Grade ≥ 3 treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	4 (15.4)
Immune-related TEAEs	1 (100.0)	1 (33.3)	5 (83.3)	8 (50.0)	15 (57.7)
Serious immune-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	3 (11.5)
Grade ≥ 3 immune-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	3 (11.5)

SAE, serious adverse event

Efficacy and PK/PD data

- At DCO, partial response was observed in two patients (one patient at 450 mg ociperlimab, and one patient at 900 mg ociperlimab). Stable disease was observed in ten patients (one at 150 mg, two at 450 mg, and seven at 900 mg ociperlimab). The longest duration of stable disease was 54 weeks (one patient at 150 mg ociperlimab) (**Figure 3**)
- After IV administration, serum concentration of ociperlimab decreased in a biphasic manner. Exposure of ociperlimab increased approximately dose proportionally from 50–900 mg (**Figure 4**)
- Complete and sustained receptor occupancy of CD8 T cells (**Figure 5**), CD4, Treg, and NK cells in PBMCs was observed at ≥ 50 mg doses of ociperlimab and at all timepoints
- Three patients had a > 30% reduction in target lesions (**Figure 6**)

Figure 3. Duration of treatment response

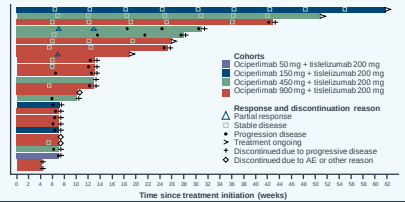


Figure 4. Mean (± SD) serum concentration-time profiles of ociperlimab

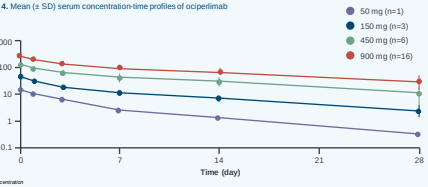
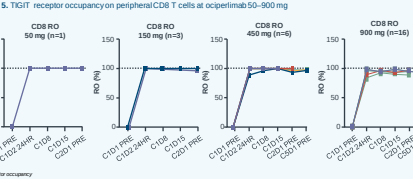


Figure 5. TIGIT receptor occupancy on peripheral CD8 T cells at ociperlimab 50–900 mg



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