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AdvanTIG-105: a phase I dose escalation study of the anti-TIGIT monoclonal antibody ociperlimab in combination with tislelizumab in patients with advanced solid tumors

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ABSTRACT

Background Ociperlimab, a novel, humanized monoclonal antibody (mAb), binds to T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) with high affinity and specificity. Tislelizumab is an anti-programmed cell death protein 1 mAb. We report results from a phase I, first-in-human, dose escalation study evaluating the safety, pharmacokinetics (PK), and preliminary antitumor activity of ociperlimab plus tislelizumab in patients with advanced solid tumors.

Methods Eligible patients previously treated with standard systemic therapy, or for whom treatment was not available or tolerated, received ociperlimab intravenously on Cycle (C) 1 Day (D) 1 and tislelizumab 200 mg intravenously on C1 D8. If tolerated, patients received ociperlimab plus tislelizumab 200 mg sequentially on D29 and every 3 weeks (Q3W) thereafter until discontinuation. Dose escalation for ociperlimab was planned with four dose levels (50 mg, 150 mg, 450 mg, and 900 mg) according to a 3+3 design. An additional dose level of ociperlimab 1800 mg was also assessed. Primary endpoints were safety, determination of the maximum tolerated (or administered) dose, and the recommended phase II dose (RP2D). Secondary endpoints included overall response rate (ORR), duration of response (DoR), disease control rate (DCR) (Response Evaluation Criteria in Solid Tumors version 1.1), PK, and biomarker analysis.

Results At data cut-off (September 29, 2022), 32 patients had received ≥1 dose of ociperlimab plus tislelizumab 200 mg Q3W. The maximum administered dose was ociperlimab 1800 mg plus tislelizumab 200 mg Q3W. The median age of enrolled patients was 59.5 years (range: 31–79). Most patients (96.9%) experienced ≥1 treatment-emergent adverse event (TEAE); 62.5% of patients experienced ≥grade 3 TEAEs and 50.0% of patients experienced serious TEAEs. No dose limiting toxicity events were reported. The maximum tolerated dose was not reached. The RP2D was ociperlimab 900 mg plus tislelizumab 200 mg Q3W. Overall, ORR was 10.0%, median DoR was 3.6 months, and DCR was 50.0%.

Conclusions Ociperlimab plus tislelizumab was well tolerated in patients with advanced solid tumors, and preliminary antitumor activity was observed with 450 mg, 900 mg, and 1800 mg ociperlimab. Phase II/III trials of ociperlimab 900 mg plus tislelizumab 200 mg Q3W are underway in a range of solid tumors.

Trial registration number NCT04047862.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prognosis for most patients with advanced or metastatic solid tumors remains poor. Combining anti-TIGIT (T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain) and anti-PD-(L)1 (programmed cell death protein 1/ligand 1) immunotherapies, such as ociperlimab plus tislelizumab, could represent a novel approach in the treatment of multiple cancers.

WHAT THIS STUDY ADDS

⇒ This study is a first-in-human, phase I study of ociperlimab plus tislelizumab in patients with advanced solid tumors. Ociperlimab plus tislelizumab is generally well tolerated in patients with advanced solid tumors, and the combination shows preliminary antitumor activity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The safety and antitumor efficacy shown in the dose escalation portion of this study support the continued investigation of this combination in a wide variety of solid tumor types as a potential treatment option.

BACKGROUND

Despite recent advances, the prognosis for most patients with advanced or metastatic solid tumors remains poor.[1] Immune surveillance plays an important role in preventing disease progression and metastasis; however, tumors can exploit various pathways to suppress and escape the host immune system, leading to unchecked tumorigenesis.[2 3] Upregulation of immune checkpoint receptors, such as

programmed cell death protein 1 (PD-1), represents a key mechanism through which tumors inhibit antitumor immune responses.[4] Immunotherapy has significantly changed the landscape of treating malignancies; however, response rates are typically low, acquired resistance is problematic, and achieving prolonged remission is challenging.[5–8]

Anti-PD-1/programmed death-ligand 1 (anti-PD-(L)1) antibodies have achieved clinical benefit in the treatment of many tumor types.[9] First-line, second-line, and third-line PD-1/PD-L1 inhibitor therapy has provided superior progression-free survival (PFS), overall survival (OS), and improved safety versus conventional therapy or placebo.[9] However, for many patients, PD-1/PD-L1 inhibitors alone are unable to overcome tumor immune escape mechanisms.[9 10] Data from a retrospective cross-sectional study estimate that only ~13% of patients eligible for immunotherapy respond to single-agent checkpoint inhibitors.[10] Others have reported that this therapeutic strategy typically achieves low overall response rates (ORRs) of less than 30% in a wide range of solid tumors in both treatment-naïve and previously treated patients.[11]

Tislelizumab is a potent PD-1 inhibitor, which was engineered to minimize binding to Fc gamma (Fcγ) receptors on macrophages.[11 12] Tislelizumab has shown promising efficacy for the treatment of solid tumors.[11 13–18] A recent phase III trial demonstrated that tislelizumab prolonged OS versus standard of care, demonstrating durable antitumor efficacy in esophageal squamous cell carcinoma.[18]

Strategies to enhance antitumor responses to PD-1/PD-L1 inhibitor therapy are being investigated.[19] Combining agents that target multiple immune checkpoints represents a promising avenue for enhancing responses to PD-1/PD-L1 inhibitors.[20] T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is a co-inhibitory immune checkpoint receptor expressed on multiple immune cells, including regulatory T cells (Tregs), activated and exhausted $CD8^+$ and $CD4^+$ T cells, and natural killer (NK) cells.[21] The main ligand of TIGIT, CD155 (also known as poliovirus receptor), is expressed by tumor cells and antigen-presenting cells.[22] TIGIT also binds to CD112, which is over-expressed on tumor cells of many human malignancies.[22] Engagement of TIGIT with CD155 and CD112 leads to inhibitory signaling in T cells and NK cells, and inhibition of a wide range of immune cells by promoting a Treg suppressive function.[23–25]

The combination of PD-1/PD-L1 inhibitors with anti-TIGIT therapies has shown synergistic immune cell activation and antitumor effects relative to PD-1/PD-L1 inhibitor monotherapy in both preclinical mouse models and in preliminary phase I and II data.[24 26 27] Data from the phase II CITYSCAPE trial showed that the anti-TIGIT immunotherapy, tiragolumab, in combination with the anti-PD-L1 immunotherapy, atezolizumab, improved ORR and median PFS compared with placebo plus atezolizumab in first-line non-small cell lung cancer (NSCLC).[27] These data suggest that combining anti-TIGIT and anti-PD-(L)1 immunotherapies could represent a novel approach in the treatment of multiple cancers.

Ociperlimab (BGB-A1217) is a novel, humanized monoclonal antibody (mAb) that binds to TIGIT with high affinity (K_D=0.135 nM) and specificity.[24] Ociperlimab has demonstrated competent binding with complement component 1q and all Fcγ receptors, while inducing antibody-dependent cellular cytotoxicity.[24] Ociperlimab was engineered with these characteristics given that the immunoglobulin G1 backbone, competent Fc (crystallizable fragment) effector function, and the ability to induce antibody-dependent cellular cytotoxicity are believed to be important in the activity of anti-TIGIT mAbs.[24 28] Preclinical studies have demonstrated that anti-TIGIT antibodies with intact Fc-binding regions have enhanced antitumor activity compared with anti-TIGIT antibodies with silent Fc effector function.[28 29] Ociperlimab, either alone or in combination with an anti-PD-1 mAb, promotes in vitro and in vivo immune cell activation, supporting its clinical development for the treatment of solid tumors.[24]

Here, in this report, we report the results of a phase I, first-in-human study that evaluated the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of ociperlimab plus tislelizumab in patients with unresectable locally advanced or metastatic solid tumors.

METHODS

Study design

AdvanTIG-105 was an open-label, multicenter, phase I/Ib clinical trial that investigated the safety, tolerability, PK, and preliminary antitumor activity of ociperlimab combined with tislelizumab, and in later parts of the trial with or without chemotherapy, in patients with unresectable locally advanced or metastatic solid tumors. The study comprised three parts: dose escalation, dose verification, and dose expansion. Patients were recruited from three sites across Australia for the dose escalation part of the study. Here, we report the results from the dose escalation portion of the study, which used a modified 3+3 dose escalation approach shown in online supplemental figure 1. The dose verification and dose expansion portions of this study are not reported herein.

The protocol, informed consent forms, any information given to the patients, and relevant supporting information were submitted, reviewed, and approved by the Institutional Review Board and Independent Ethics Committee before this study was initiated. The study protocol is available in the online supplemental file 1. This study was conducted in full conformance with the International Council for Harmonisation E6 guideline for Good Clinical Practice, the International Council for Harmonisation E2A guideline for Clinical Safety Data Management, and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted.

Table 1 Patient demographics and baseline characteristics (safety analysis set)

	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)	OCI 1800 mg plus TIS 200 mg (n=6)	Total (N=32)
Sex, n (%)						
Male	1 (100.0)	2 (66.7)	2 (33.3)	6 (37.5)	4 (66.7)	15 (46.9)
Female	0 (0.0)	1 (33.3)	4 (66.7)	10 (62.5)	2 (33.3)	17 (53.1)
Race, n (%)						
Asian	0 (0.0)	0 (0.0)	2 (33.3)	3 (18.8)	1 (16.7)	6 (18.8)
White	1 (100.0)	2 (66.7)	3 (50.0)	12 (75.0)	4 (66.7)	22 (68.8)
Other	0 (0.0)	1 (33.3)	1 (16.7)	1 (6.3)	0 (0.0)	3 (9.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (3.1)
Age (years)						
Median (range)	50.0 (50–50)	42.0 (34–70)	60.0 (35–65)	54.0 (31–74)	65.5 (59–79)	59.5 (31–79)
Age group, n (%)						
<65 years	1 (100.0)	2 (66.7)	5 (83.3)	11 (68.8)	2 (33.3)	21 (65.6)
≥65 years	0 (0.0)	1 (33.3)	1 (16.7)	5 (31.3)	4 (66.7)	11 (34.4)
ECOG PS, n (%)						
0	0 (0.0)	2 (66.7)	3 (50.0)	7 (43.8)	2 (33.3)	14 (43.8)
1	1 (100.0)	1 (33.3)	3 (50.0)	9 (56.3)	4 (66.7)	18 (56.3)
Median time from initial diagnosis to study entry, years (range)	1.9 (1.9–1.9)	2.1 (1.2–2.8)	3.7 (1.6–6.6)	1.9 (0.2–8.6)	1.3 (0.8–4.3)	2.0 (0.2–8.6)
Cancer type at initial diagnosis, n (%)						
Squamous NSCLC	0 (0.0)	0 (0.0)	1 (16.7)	1 (6.3)	0 (0.0)	2 (6.3)
Non-squamous NSCLC	0 (0.0)	1 (33.3)	0 (0.0)	1 (6.3)	1 (16.7)	3 (9.4)
Head and neck	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (6.3)
Gastric/gastroesophageal junction	0 (0.0)	0 (0.0)	1 (16.7)	1 (6.3)	1 (16.7)	3 (9.4)
Esophageal	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (6.3)
Pancreatic	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.3)
Colorectal	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Uterine	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.1)
Melanoma	0 (0.0)	0 (0.0)	1 (16.7)	1 (6.3)	0 (0.0)	2 (6.3)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.1)
Kidney	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.1)
Nasopharyngeal	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Sarcoma	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.3)
Other*	0 (0.0)	0 (0.0)	0 (0.0)	7 (43.8)	2 (33.3)	9 (28.1)
Patients with any prior anticancer therapy, n (%)	1 (100.0)	3 (100.0)	5 (83.3)	14 (87.5)	6 (100.0)	29 (90.6)
Patients with prior anti-PD-L1 therapy, n (%)†	1 (100.0)	1 (33.3)	4 (66.7)	4 (25.0)	1 (16.7)	11 (34.4)
PD-L1 expression, n (%)‡						
TC≥1%	0 (0.0)	1 (33.3)	3 (50.0)	1 (6.3)	1 (16.7)	6 (18.8)
TC<1%	1 (100.0)	2 (66.7)	3 (50.0)	7 (43.8)	3 (50.0)	16 (50.0)
Non-evaluable§	0 (0.0)	0 (0.0)	0 (0.0)	8 (50.0)	2 (33.3)	10 (31.3)

Data cut-off: September 29, 2022. The safety analysis set included all patients who received ≥1 dose of study drugs.
*Patients included in the other tumor types category had a variety of tumors, including pleural mesothelioma, right side epithelioid pleural mesothelioma, urachal adenocarcinoma, papillary renal cancer, cholangiocarcinoma, and salivary gland adenocarcinoma.
†Prior anti-PD-L1 therapy data was evaluable for 22 patients.
‡PD-L1 expression on TC was determined using the VENTANA PD-L1 (SP263) assay.
§Ten (31.3%) patients were not evaluable for PD-L1 expression.
ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; OCI, ociperlimab; PD-(L)1, programmed cell death protein 1/programmed death-ligand 1; TC, tumor cells; TIS, tislelizumab.

Table 2 Patient disposition and reasons for discontinuation (safety analysis set)

	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)	OCI 1800 mg plus TIS 200 mg (n=6)	Total (N=32)
Number of patients treated, n (%)	1 (100.0)	3 (100.0)	6 (100.0)	16 (100.0)	6 (100.0)	32 (100.0)
Number of patients treated with ociperlimab	1 (100.0)	3 (100.0)	6 (100.0)	16 (100.0)	6 (100.0)	32 (100.0)
Number of patients treated with tislelizumab	1 (100.0)	3 (100.0)	6 (100.0)	16 (100.0)	6 (100.0)	32 (100.0)
Patients remaining on study, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	4 (25.0)	0 (0.0)	5 (15.6)
Patients remaining on treatment, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.1)
Remaining on ociperlimab, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.1)
Patients discontinued from all study drugs, n (%)	1 (100.0)	3 (100.0)	5 (83.3)	16 (100.0)	6 (100.0)	31 (96.9)
Patients discontinued from study, n (%)	1 (100.0)	3 (100.0)	5 (83.3)	12 (75.0)	6 (100.0)	27 (84.4)
Reason for study discontinuation, n (%)						
Withdrawal by patient	0 (0.0)	0 (0.0)	0 (0.0)	5 (31.3)	2 (33.3)	7 (21.9)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.1)
Death	0 (0.0)	0 (0.0)	4 (66.7)	6 (37.5)	2 (33.3)	12 (37.5)
Patients completing all study assessments	1 (100.0)	2 (66.7)	0 (0.0)	0 (0.0)	2 (33.3)	5 (15.6)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.1)
Radiographic disease progression	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Patients discontinued from ociperlimab, n (%)	1 (100.0)	3 (100.0)	5 (83.3)	16 (100.0)	6 (100.0)	31 (96.9)
Reason for discontinuation, n (%)						
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.1)
Withdrawal by patient	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	2 (33.3)	5 (15.6)
Progressive disease	1 (100.0)	2 (66.7)	5 (83.3)	12 (75.0)	4 (66.7)	24 (75.0)
Radiographic disease progression	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Patients discontinued from tislelizumab, n (%)	1 (100.0)	3 (100.0)	5 (83.3)	16 (100.0)	6 (100.0)	31 (96.9)
Reason for discontinuation, n (%)						
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.1)
Withdrawal by patient	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	2 (33.3)	5 (15.6)
Progressive disease	1 (100.0)	2 (66.7)	5 (83.3)	12 (75.0)	4 (66.7)	24 (75.0)
Radiographic disease progression	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)

Data cut-off: September 29, 2022. The safety analysis set included all patients who received ≥1 dose of study drugs.
OCI, ociperlimab; TIS, tislelizumab.

Study population

Eligible patients were adults (≥18 years of age) with histologically or cytologically confirmed unresectable locally advanced or metastatic solid tumors previously treated with standard systemic therapy (prior anti-PD-(L)1 therapy was permitted) or for whom treatment was not available or not tolerated, and who had not received prior anti-TIGIT therapy. Patients were also required to have ≥1 evaluable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) and an Eastern Cooperative Oncology Group performance status of ≤1.

Exclusion criteria included having active leptomeningeal disease or uncontrolled brain metastasis. Full eligibility criteria are provided in the online supplemental file 1.

Treatment administration

Ociperlimab was administered intravenously as a single agent on Day 1 of each cycle. During the first cycle, 200 mg tislelizumab was administered intravenously on Day 8. Patients were monitored for dose limiting toxicities (DLTs) during a 28-day DLT observation period in the first cycle of treatment, following the first administration of ociperlimab. The doses of ociperlimab tested were 50 mg, 150 mg, 450 mg, and 900 mg. An additional dose level of ociperlimab 1800 mg was also assessed. The dose level of tislelizumab was fixed at 200 mg. The modified 3+3 dose escalation approach included evaluation of the starting dose of ociperlimab (50 mg) in a single patient. Escalation to the next dose level would proceed if no DLTs were observed in this patient; if a DLT was observed in this patient, the dose would be further evaluated using the 3+3 rules. All subsequent ociperlimab dose levels (150 mg and greater) were evaluated in a minimum of three evaluable patients, following the 3+3 rules.

Hematologic DLTs included grade 4 neutropenia lasting >7 days, ≥grade 3 febrile neutropenia, grade 3 thrombocytopenia with clinically significant bleeding, grade 4 thrombocytopenia lasting >7 days, and ≥grade 4 anemia. Non-hematologic DLTs were ≥grade 4 toxicities or grade 3 clinically significant toxicities that did not

Table 3 Summary of adverse events (safety analysis set)

	OCI 50 mg plus TIS 200 mg (n=1)	OCI 150mg plus TIS 200 mg (n=3)	OCI 450 mg plus TIS 200 mg (n=6)	OCI 900 mg plus TIS 200 mg (n=16)	OCI 1800 mg plus TIS 200 mg (n=6)	Total (N=32)
Patients with ≥1 TEAE	1 (100.0)	3 (100.0)	6 (100.0)	15 (93.8)	6 (100.0)	31 (96.9)
≥Grade 3	1 (100.0)	2 (66.7)	4 (66.7)	11 (68.8)	2 (33.3)	20 (62.5)
Serious	1 (100.0)	2 (66.7)	3 (50.0)	9 (56.3)	1 (16.7)	16 (50.0)
Leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	3 (9.4)
Leading to discontinuation of ociperlimab	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	3 (9.4)
Leading to discontinuation of tislelizumab	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	3 (9.4)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with ≥1 TRAE	1 (100.0)	1 (33.3)	5 (83.3)	10 (62.5)	5 (83.3)	22 (68.8)
≥Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.3)
Serious	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.3)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with ≥1 potential immune-mediated AE	0 (0.0)	1 (33.3)	1 (16.7)	3 (18.8)	2 (33.3)	7 (21.9)
Leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.1)
Leading to ociperlimab dose modification	0 (0.0)	1 (33.3)	0 (0.0)	2 (12.5)	2 (33.3)	5 (15.6)
Leading to tislelizumab dose modification	0 (0.0)	1 (33.3)	0 (0.0)	2 (12.5)	2 (33.3)	5 (15.6)
≥Grade 3 immune-mediated AEs	0 (0.0)	0 (0.0)	1 (16.7)	2 (12.5)	1 (16.7)	4 (12.5)
Patients with ≥1 DLT event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data cut-off: September 29, 2022. The safety analysis set included all patients who received ≥1 dose of study drugs.
DLT, dose limiting toxicity; OCI, ociperlimab; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

resolve within 7 days of optimal supportive care. If tolerated, patients then received ociperlimab and tislelizumab sequentially on Day 29 and once every 3 weeks (Q3W) thereafter, until they met a discontinuation criterion.

Discontinuation criteria included, but were not limited to, patient decision, adverse events (AEs), and progressive disease. In general, dose delays for reasons other than the management of AEs were prohibited. Apart from during the first cycle of treatment, if a dose delay was required, both ociperlimab and tislelizumab had to be delayed, and if applicable, re-started at the same time. For patients receiving a dose level of ociperlimab determined to be above the maximum tolerated dose, the dose level of ociperlimab was permitted to be reduced following discussion and agreement with the study sponsor. Dose reductions for tislelizumab were not permitted.

Endpoints and assessments

The primary endpoints of the study were safety, the maximum tolerated or maximum administered dose, and the recommended phase II dose (RP2D) of ociperlimab in combination with tislelizumab. AEs and serious AEs (SAEs) were characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0), timing, seriousness, and relationship to study drugs. Physical examinations, electrocardiograms, and laboratory assessments were also used, as needed, to characterize AEs and SAEs, as well as AEs meeting protocol-defined DLT criteria. The maximum tolerated and administered doses were defined as the highest dose at which <33% of patients experienced a DLT, and the highest dose administered, respectively. Determination of the RP2D of ociperlimab in combination with tislelizumab was informed by the maximum tolerated or administered dose, long-term tolerability, PK, and efficacy data, as well as any other relevant data as available. The RP2D was determined after discussion with the Safety Monitoring Committee (composed of investigators and representatives of the study sponsor) before the initiation of the subsequent phase Ib dose expansion study.

The secondary endpoints of the dose escalation part of this study were ORR, duration of response (DoR), disease control rate (DCR), serum concentrations and PK parameters of ociperlimab and tislelizumab, and immunogenic responses to ociperlimab and tislelizumab. Exploratory endpoints included the investigation of potentially predictive, prognostic, or pharmacodynamic (PD) biomarkers from patient-derived tumor tissue(s) and/or blood samples obtained before, during, and/or after treatment with ociperlimab and their association

Table 4 Treatment-emergent adverse events occurring in ≥10% of patients (safety analysis set)

	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)		OCI 1800 mg plus TIS 200 mg (n=6)		Total (N=32)	
n (%)	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Fatigue	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (66.7)	1 (16.7)	3 (18.8)	0 (0.0)	2 (33.3)	0 (0.0)	10 (31.3)	1 (3.1)
Dyspnea	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (16.7)	0 (0.0)	4 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)	7 (21.9)	1 (3.1)
Diarrhea	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	2 (12.5)	1 (6.3)	1 (16.7)	0 (0.0)	6 (18.8)	1 (3.1)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	3 (18.8)	0 (0.0)	2 (33.3)	0 (0.0)	6 (18.8)	1 (3.1)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	2 (33.3)	0 (0.0)	5 (15.6)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (15.6)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	1 (6.3)	1 (16.7)	0 (0.0)	4 (12.5)	1 (3.1)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.5)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	1 (16.7)	0 (0.0)	4 (12.5)	0 (0.0)

Data cut-off: September 29, 2022. The safety analysis set included all patients who received ≥1 dose of study drugs.
OCI, ociperlimab; TIS, tislelizumab.

with clinical efficacy. PD biomarkers of interest included ociperlimab/TIGIT and tislelizumab/PD-1 receptor occupancy, as well as the activities of Tregs, $CD8^+$ and $CD4^+$ T cells.

Tumor response was assessed by the investigator using RECIST V.1.1. All measurable and evaluable lesions were assessed and documented at the screening visit and reassessed at each subsequent tumor evaluation. Tumor imaging was performed ≤28 days before the first dose of study drugs, and then, from Day 1 of Cycle 1, approximately every 6 weeks for the first 52 weeks, then every 12 weeks thereafter. Blood samples for PK analyses of ociperlimab and tislelizumab were collected at specified time points detailed in the protocol (online supplemental file 1).

Statistical analyses

The safety analysis set included all patients who received ≥1 dose of study drugs. The efficacy evaluable analysis set included all patients who received ≥1 dose of the study drugs, had evaluable disease at baseline, and ≥1 evaluable postbaseline tumor response assessment (unless any clinical progressive disease or death occurred before the first postbaseline tumor assessment). The DLT-evaluable analysis set included patients who received at least 80% of the assigned doses of ociperlimab and tislelizumab (according to the treatment schedule), remained on study for the DLT observation period under sufficient safety evaluation, or patients who experienced a DLT within the observation period. The PK analysis set included all patients who received ≥1 dose of study drugs and had ≥1 derivable PK parameter.

For the dose escalation part of this study, 32 patients were estimated to be sufficient to evaluate the safety and tolerability of increasing dose levels of ociperlimab in combination with tislelizumab per the modified 3+3 design rules.

The secondary efficacy endpoints ORR and DCR were summarized by dose, based on the efficacy evaluable analysis set. Two-sided binomial exact 95% CIs of ORR and DCR were constructed for statistical inference of the point estimate. A Kaplan-Meier curve was used to estimate the median DoR and corresponding 95% CIs.[30] Mean serum ociperlimab concentration versus time data were plotted by dose level. Ociperlimab serum concentration data were analyzed using non-compartmental methods of PK analysis; the mean PK parameters are reported by dose level. Immunogenicity data were summarized using descriptive statistics by the number and percentage of patients who developed detectable antidrug antibodies (ADAs). The incidence of positive and neutralizing ADAs was reported for evaluable patients.

Full statistical methods and exploratory analyses are described in the online supplement. All calculations and analyses were conducted using SAS V.9.2 or higher.

Table 5 Analysis of disease response (efficacy-evaluable analysis set)

	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=5)	OCI 900 mg plus TIS 200 mg (n=16)	OCI 1800 mg plus TIS 200 mg (n=5)	Total (N=30)
ORR, n (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (6.3)	1 (20.0)	3 (10.0)
95% CI	(0.0 to 1.0)	(0.0 to 0.7)	(0.0 to 0.7)	(0.0 to 0.3)	(0.0 to 0.7)	(0.0 to 0.3)
BOR, n (%)						
PR	0 (0.0)	0 (0.0)	1 (20.0)	1 (6.3)	1 (20.0)	3 (10.0)
SD	0 (0.0)	2 (66.7)	2 (40.0)	7 (43.8)	1 (20.0)	12 (40.0)
PD	1 (100.0)	1 (33.3)	1 (20.0)	7 (43.8)	3 (60.0)	13 (43.3)
DCR, n (%)	0 (0.0)	2 (66.7)	3 (60.0)	8 (50.0)	2 (40.0)	15 (50.0)
95% CI	(0.0 to 1.0)	(0.1 to 1.0)	(0.1 to 0.9)	(0.2 to 0.8)	(0.1 to 0.9)	(0.3 to 0.7)
Median DoR, months	NE	NE	2.8	3.6	8.4*	3.6
95% CI	NE	NE	(NE, NE)	(NE, NE)	(NE, NE)	(2.8 to NE)

Data cut-off: September 29, 2022. ORR: CR+PR; DCR: CR+PR + SD. The efficacy-evaluable analysis set included all patients who received ≥1 dose of study drugs, had evaluable disease at baseline, and ≥1 evaluable postbaseline tumor response assessment, unless any clinical PD or death occurred before the first postbaseline tumor assessment.
*Only one patient on an 1800 mg dose had a PR, with a duration of response of 8.4 months.
BOR, best overall response; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; OCI, ociperlimab; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TIS, tislelizumab.

RESULTS

Patients and treatment

In the dose escalation part of this study, patients were recruited from August 2019. As of September 29, 2022, 32 patients had received ≥1 dose of ociperlimab (50–1800 mg) in combination with tislelizumab 200 mg Q3W (online supplemental figure 2).

Patient demographics and baseline clinical characteristics are presented in table 1. Sex was well balanced overall (male: 46.9%). The majority of patients were white (68.8%), and median age was 59.5 years (range: 31–79). The median time from initial diagnosis to study entry was 2.0 years (range: 0.2–8.6). In total, 29 patients (90.6%) had received prior anticancer therapy; of these patients, 82.8% had received ≥2 prior treatment regimens. Patients with a wide variety of tumor types were enrolled in the study and are presented in table 1. The most common tumor types were NSCLC, with five patients (15.6%), and gastric/gastroesophageal junction cancer (GC/GEJC), with three patients (9.4%).

Median study follow-up was 26.5 weeks (range: 4.7–134.4), and median treatment follow-up was 12.9 weeks (range: 4.7–134.4). A total of 31 (96.9%) patients had discontinued from both ociperlimab and tislelizumab at the time of analysis, and 1 (3.1%) patient remained on treatment (table 2; online supplemental figure 2). Of the 32 patients who were included in the safety analysis set and PK analysis set, 31 were included in the DLT-evaluable set (1 patient in the 900 mg dose cohort was not DLT-evaluable due to early withdrawal) and 30 patients were included in the efficacy-evaluable set.

Safety

The maximum administered dose was ociperlimab 1800 mg in combination with tislelizumab 200 mg Q3W. Doses of ociperlimab administered ranged from 50 mg to 1800 mg Q3W (50 mg: 1 patient; 150 mg: 3 patients; 450 mg: 6 patients; 900 mg: 16 patients; 1800 mg: 6 patients).

A summary of treatment-emergent adverse events (TEAEs), including ≥grade 1 TEAEs and ≥grade 3 TEAEs in each ociperlimab dose cohort, is presented in table 3. Most patients (31/32) experienced ≥1 TEAE, 62.5% experienced ≥grade 3 TEAEs, and 50.0% experienced serious TEAEs (table 3). The most commonly occurring TEAE was fatigue, reported in 10 patients (table 4). The most common ≥grade 3 TEAEs were ascites, which occurred in one patient in the ociperlimab 450 mg dose cohort and one patient in the ociperlimab 900 mg dose cohort, and carotid sinus syndrome, which occurred in one patient in the ociperlimab 150 mg dose cohort and one patient in the ociperlimab 1800 mg dose cohort. All other ≥grade 3 TEAEs occurred in one patient each. The most common serious TEAEs were dyspnea, occurring in one patient in each of the ociperlimab 150 mg and 900 mg dose cohorts, and the two cases of carotid sinus syndrome. All other serious TEAEs occurred in one patient each. Three patients experienced TEAEs leading to treatment discontinuation of both ociperlimab and tislelizumab, all in the ociperlimab 900 mg dose cohort. Gastrointestinal disorders were the most common TEAEs leading to treatment discontinuation.

Potential immune-mediated AEs (imAEs) were experienced by seven patients; these included colitis, diarrhea, diabetes mellitus, diabetic ketoacidosis, transaminases increased, hypothyroidism, myositis, pneumonitis, and rash maculopapular (each occurring in one patient). A breakdown of imAEs by cohort is presented in online supplemental table 1. Three patients in the ociperlimab

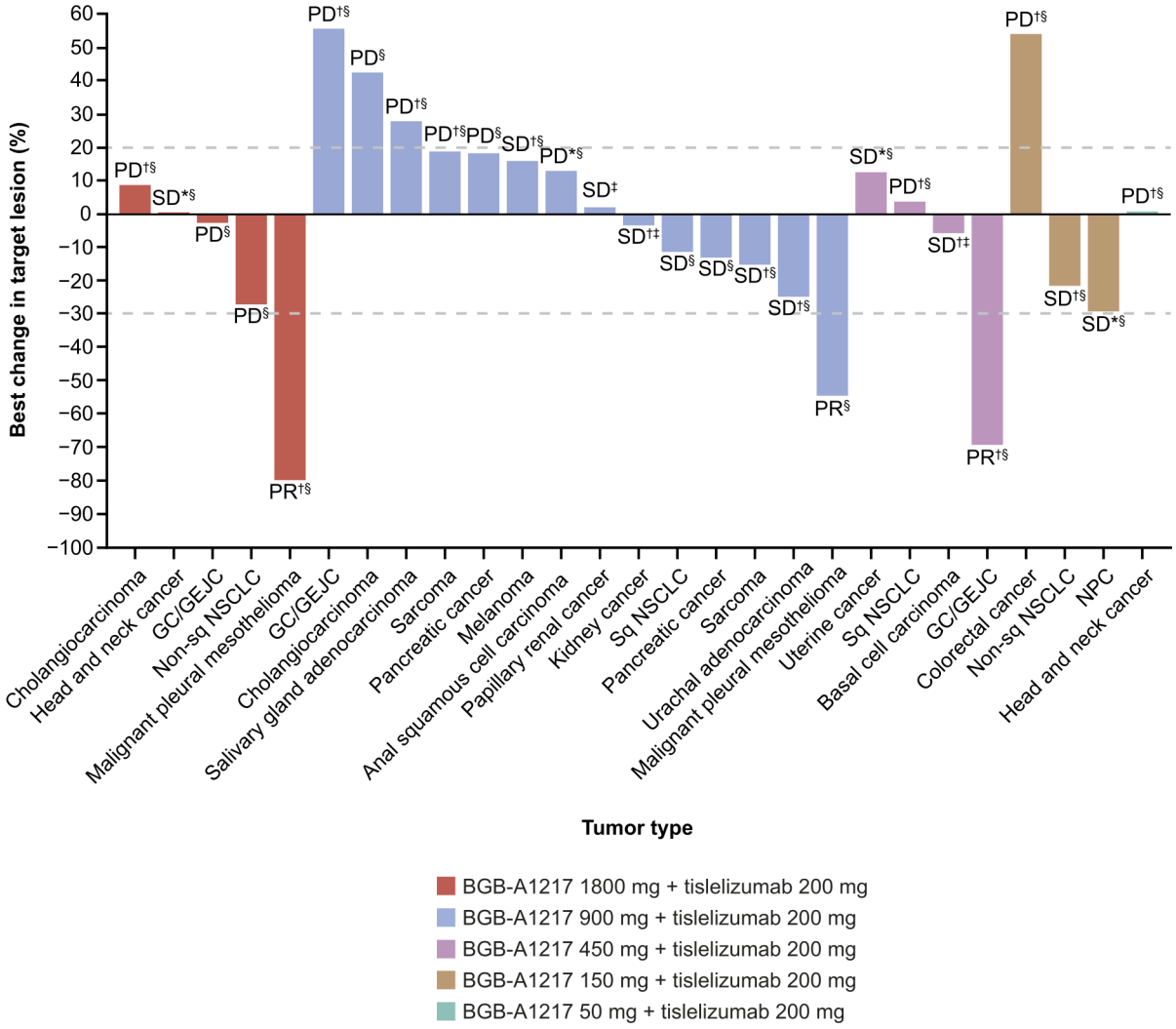

Figure 1 Best change from baseline in target lesion sum of diameters (efficacy evaluable analysis set).
Data cut-off: September 29, 2022. Measured per investigator assessment. Of the 30 patients that were efficacy-evaluable, 27 patients had measurable target lesions pre/post dose. The efficacy-evaluable analysis set included all patients who received ≥1 dose of study drugs, had evaluable disease at baseline, and ≥1 evaluable postbaseline tumor response assessment, unless any clinical PD or death occurred before the first postbaseline tumor assessment. PD, PR, and SD represent best change from baseline.
*PD-L1 TC≥1%; †PD-L1 TC<1%; ‡Did not receive prior anticancer therapy; §Received prior anticancer therapy.
GC/GEJC, gastric/gastroesophageal junction cancer; non-sq, non-squamous; NPC, nasopharyngeal cancer; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; sq, squamous; TC, tumor cells.

900 mg dose cohort had serious imAEs, including colitis (n=1; resolved/recovered after discontinuation of both ociperlimab and tislelizumab); diarrhea (n=1; resolved/recovered); and diabetic ketoacidosis (n=1; resolved/recovered with sequelae after dose delay). There were no serious imAEs reported in the other cohorts.

A summary of treatment-related adverse events (TRAEs) in each ociperlimab dose cohort is presented in table 3. TRAEs were reported in 68.8% of patients. Three TEAEs (colitis, osteolysis, and ascites) led to treatment discontinuation; colitis was considered related to ociperlimab and tislelizumab. There were no DLTs reported in this study, and no TEAEs or TRAEs that led to death. Therefore, the maximum tolerated dose was not reached.

Antitumor activity

For analysis of disease response, partial response (PR), stable disease (SD), and progressive disease were observed in 10.0%, 40.0%, and 43.3% of patients, respectively (table 5). The patients with PR included one patient in the 450 mg dose cohort with GC/GEJC, one patient in the 900 mg dose cohort with right side epithelioid pleural mesothelioma, and one patient in the 1800 mg dose cohort with pleural mesothelioma, all of whom exhibited reductions in target lesion diameter of >50% from baseline and all of whom were immunotherapy-naïve (figure 1). The longest duration of SD at data cut-off was 126 weeks, observed in one immunotherapy-naïve patient with basal cell carcinoma who received

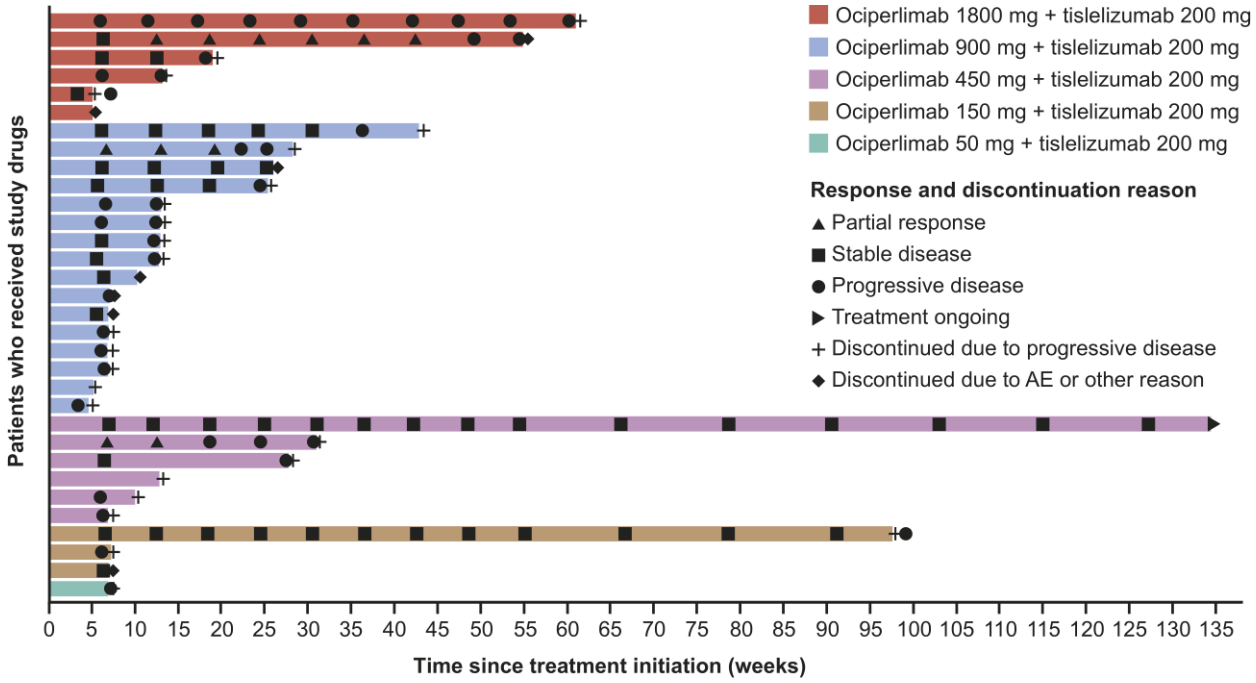

Figure 2 Disease response and duration of treatment (per RECIST V.1.1; safety analysis set). Data cut-off: September 29, 2022. The safety analysis set included all patients who received ≥1 dose of study drugs. AE, adverse event; RECIST V.1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

ociperlimab 450 mg in combination with tislelizumab 200 mg (figure 2). PD-L1 expression data were available for two of the three patients with PR, both of whom had PD-L1 expression on tumor cells of <1% (figure 1). The association between ORR and PD-L1 expression could not be formally evaluated due to limited patient numbers. DCR was 50.0% (95% CI: 31.3% to 68.7%) and median DoR was 3.6 months (95% CI: 2.8 to not evaluable).

Pharmacokinetics

The geometric mean elimination half-life of ociperlimab ranged from 7.1 to 10.9 days across the dose cohorts (online supplemental table 2). The duration of postdose PK sampling may not be sufficient for robust characterization of elimination half-life, hence reported half-life values should be interpreted with caution. Serum concentrations of ociperlimab decreased in a biexponential manner after administration (online supplemental figure 3), and ociperlimab exposures (area under the concentration–time curve and peak serum concentration) were increased approximately in proportion to the dose, at all dose levels evaluated in the study (online supplemental table 2).

Pharmacodynamics

Complete and sustained receptor occupancy of peripheral $CD8^+$ T cells was observed for all doses of ociperlimab and at all time points (online supplemental figure 4). Total Treg frequency decreased over time following a higher dose (900 mg and 1800 mg), but not at a lower dose (450 mg) of ociperlimab.[31] There were no differences observed in total $CD4^+$ and $CD8^+$ T-cell frequencies were found across doses.

Immunogenicity

At data cut-off, no patients tested positive for ADAs against ociperlimab. The incidence of treatment-emergent ADAs against tislelizumab, in combination with ociperlimab in this study (10.7%; 3/28 ADA-evaluable patients), was comparable with the ADA-positivity rate for monotherapy with tislelizumab.[14]

Recommended phase II dose

The 900 mg dose of ociperlimab in combination with tislelizumab 200 mg Q3W was selected as the RP2D following discussion with the Safety Monitoring Committee. This decision was based on the absence of dose-dependent safety events (up to 1800 mg; table 3), the preliminary efficacy from the dose escalation portion of this study (table 5; three patients experienced a PR (one each in the 450 mg, 900 mg, and 1800 mg dose cohorts)), and the DCR, which was comparable across the three dose levels. In addition, ociperlimab PK exposure in all three patients with PR was consistent with that observed at the 900 mg dose level (online supplemental figure 2), with complete TIGIT receptor occupancy observed on $CD8^+$ T cells in peripheral blood at all tested dose levels (online supplemental figure 3), supporting this dose as the RP2D.

DISCUSSION

The aim of this phase I dose escalation study was to assess the safety, tolerability, PK, and preliminary antitumor activity of ociperlimab in combination with tislelizumab in advanced solid tumors, and determine the maximum tolerated dose and RP2D. Ociperlimab plus tislelizumab

was well tolerated, and the incidence of TEAEs and TRAEs was consistent with the safety profiles of other anti-TIGIT therapies studied in combination with anti-PD-(L)1 immunotherapies, and the safety profile of tislelizumab monotherapy.[16 17 26 27] No DLT events were observed and as such the maximum tolerated dose was not reached.

Compared with other anti-TIGIT molecules, no new safety signals were identified at any dose levels, including the 1800 mg dose of ociperlimab.[26 27] Data showed that serum concentrations of ociperlimab decreased in a biexponential manner, exposures increased approximately in proportion with the ociperlimab dose, and there was complete and sustained receptor occupancy of $CD8^+$ T cells at all doses and time points.

Preliminary antitumor activity was observed in this study, with the caveat that this cohort of patients had been heavily pretreated prior to study entry. Three patients (10.0%) responded to treatment, all of whom were immunotherapy naïve and had a >50% reduction in tumor diameter from baseline. These findings were consistent with reports of preliminary antitumor activity from phase I and II studies of other anti-TIGIT mAbs in combination with anti-PD-(L)1 immunotherapies inhibitors.[26 27] However, the small number of patients enrolled into the study, the mix of immunotherapy naïve and pretreated patients, and the fact that the association with PD-L1 expression could not be assessed, must be taken into consideration. The antitumor activity of ociperlimab plus tislelizumab combination treatment with or without chemotherapy will be assessed in the dose expansion portion of the AdvanTIG-105 study in specific tumor types. Predictive biomarkers and biomarkers of resistance will be further evaluated. Such biomarker data may be particularly pertinent to further understanding the activity of anti-TIGIT plus anti-PD-(L)1 combinations, given that data emerging from phase III trials with tiragolumab plus atezolizumab in the first-line treatment of extensive-stage small cell lung cancer and PD-L1-high metastatic NSCLC did not meet its co-primary endpoint of PFS. However, at the time of this analysis, the other co-primary endpoint of OS was immature and is still under investigation.[32 33] Further investigation on the OS benefit of these combinations is warranted.

Based on the safety, PK/PD, and preliminary efficacy data, an RP2D of 900 mg ociperlimab in combination with tislelizumab 200 mg Q3W was selected. This is being further studied in China as part of the dose verification portion, and globally as part of the dose expansion portion, of this phase I study.

One of the strengths of this study included the study design, which enabled the assessment of the safety and efficacy of ociperlimab plus tislelizumab in a wide range of tumor types. This study also permitted an additional dose level of ociperlimab (1800 mg) to be assessed, in addition to the four dose levels planned.

Subsequent studies are planned to address the limitations of this study, which include the variability in baseline demographics, the small sample size, and the non-randomized, open-label nature of this study. The use of independent review of safety and tumor response will also reduce the potential for bias.

A recent study from the USA demonstrated that only ~13% of patients with advanced solid tumors respond to checkpoint inhibitors.[10] The addition of an anti-TIGIT mAb to anti-PD-(L)1 immunotherapies represents one of many strategies currently under investigation for enhancing antitumor responses.[19] The combination of tislelizumab and ociperlimab may concurrently target pathways to reduce instances of tumor immune escape.[34] The safety and antitumor efficacy shown in the dose escalation portion of this study support the continued investigation of this combination in a wide variety of solid tumor types.

CONCLUSION

In this phase I dose escalation study, ociperlimab plus tislelizumab was well tolerated in patients with advanced solid tumors and showed preliminary antitumor efficacy. The types and severity of AEs observed were consistent with tislelizumab monotherapy and the safety profiles of other anti-TIGIT mAbs currently in early clinical development. Based on the results of this phase I dose escalation study, the RP2D was determined to be 900 mg ociperlimab in combination with tislelizumab 200 mg Q3W. Phase II and phase III trials of ociperlimab in combination with tislelizumab, using this RP2D, are currently underway in a range of solid tumors, including NSCLC, small cell lung cancer, esophageal cancer, head and neck squamous cell carcinoma, and GC/GEJC.

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Competing interests SF reports: advisory board or Data Safety Monitoring Board positions with Ambrax, Akesobio, and MSD; leadership or fiduciary roles with Monash Partners Comprehensive Cancer Consortium Precision Oncology Steering Committee, Victorian Comprehensive Cancer Center Accelerating Novel Therapies Steering Committee, and BeiGene, Ltd.; sponsorship and funding to Monash Health; honoraria from Amgen; consultancy fees from Akesobio and MSD. SK reports: speaker fees from Roche, MSD, Bristol Myers Squibb, Pfizer, AstraZeneca,

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Monash Health Research Support Services, Monash Health Reference ID: RES-10-0000465A, Bellberry Human Research Ethics Committee, Ethics Reference: 2019-05-439-AC. St John of God Health Care Human Research Ethics Committee, Ethics Reference: 1734, Health and Disability Ethics Committees, Ethics reference: 2022 AM 9817. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd., will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

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