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Phase 1a dose escalation study of ivonescimab (AK112/SMT112), an anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors

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ABSTRACT

Background Studies showed that vascular endothelial growth factor (VEGF) inhibitors could improve therapeutic efficacy of PD-1/PD-L1 antibodies by transforming the immunosuppressive tumor microenvironment (TME) into an immunoresponsive TME. Ivonescimab is a first-in-class, humanized tetravalent bispecific antibody targeting PD-1 and VEGF-A simultaneously. Here, we report the first-in-human, phase 1a study of ivonescimab in patients with advanced solid tumors.

Methods Patients with advanced solid tumors were treated with ivonescimab 0.3, 1, 3, 10, 20 or 30 mg/kg intravenously every 2 weeks using a 3+3+3 dose escalation design. Dose expansion occurred at 10 and 20 mg/kg in selected tumor types. The primary objective was to assess the safety and tolerability, and to determine the maximum tolerated dose (MTD). The secondary objectives included pharmacokinetics, pharmacodynamics and preliminary antitumor activity based on Response Evaluation Criteria in Solid Tumors V.1.1.

Results Between October 2, 2019 and January 14, 2021, a total of 51 patients were enrolled and received ivonescimab. Two dose-limiting toxicities were reported at 30 mg/kg. The MTD of ivonescimab was 20 mg/kg every 2 weeks. Grade≥3 treatment-related adverse events (TRAEs) occurred in 14 patients (27.5%). The most common TRAEs of any grade were rash (29.4%), arthralgia (19.6%), hypertension (19.6%), fatigue (17.6%), diarrhea (15.7%) and pruritus (11.8%). The most common grade≥3 TRAEs were hypertension (7/51, 13.7%), alanine aminotransferase increased (3/51, 5.2%), aspartate aminotransferase increased (2/51, 3.9%) and colitis (2/51, 3.9%). Of 47 patients who had at least one postbaseline assessment, the confirmed objective response rate was 25.5% (12/47) and disease control rate was 63.8% (30/47). Among 19 patients with platinum-resistant ovarian cancer, 5 patients (26.3%) achieved partial response (PR). Efficacy signals were also observed in patients with mismatch repair proficient (pMMR) colorectal cancer, non-small cell lung cancer, and both MMR deficient and pMMR endometrial cancer.

Conclusions Ivonescimab demonstrated manageable safety profiles and promising efficacy signals in multiple solid tumors. Exploration of alternative dosing regimens of ivonescimab monotherapy and combination therapies is warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A combination of programmed death 1/programmed death ligand (PD-L1) inhibition and vascular endothelial growth factor (VEGF) inhibition provides clinical benefit but increases the risk of toxicity.

WHAT THIS STUDY ADDS

⇒ Ivonescimab (AK112) is a first-in-class, humanized tetravalent bispecific antibody targeting PD-1 and VEGF-A simultaneously. This is the first-in-human phase 1a study demonstrating that ivonescimab is safe and tolerable. The maximum tolerated dose of 20 mg/kg every 2 weeks was determined during dose escalation. Treatment-related adverse events (TRAEs) occurred in 38 patients (74.5%), and grade≥3 TRAEs occurred in 14 patients (27.5%). Efficacy signals were observed in several types of solid tumors, with a confirmed objective response rate of 25.5% and disease control rate of 63.8%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports that ivonescimab has manageable safety profiles, promising efficacy signals. Several studies with ivonescimab monotherapy or combination therapy with chemotherapy in a variety of solid cancers such as lung cancer, triple negative breast cancer, head and neck squamous cell carcinoma, colorectal cancer are ongoing.

Trial registration number NCT04047290.

INTRODUCTION

Treatment strategies combining immune checkpoint inhibitors (ICIs) have become an increasingly common strategy to overcome the limited efficacy of ICI monotherapy.[1] Preclinical have shown that in addition to the known antiangiogenic effects, vascular endothelial growth factor (VEGF) inhibitors exhibit synergistic effects with ICIs in the tumor microenvironment (TME), and they

can improve therapeutic efficacy of PD-1/PD-L1 antibodies by normalizing tumor blood vessels, increasing T-cell infiltration, and decreasing activity of immunosuppressive cells (myeloid-derived suppressor cells, Tregs and tumor-associated macrophages).[2–4] These synergistic effects may improve the antitumor activity of ICIs by transforming the immunosuppressive TME into an immunoresponsive TME.

The efficacy of combining anti-PD-1/PD-L1 inhibitors with VEGF inhibitors has been evaluated in many studies. In the IMpower150 study, compared with bevacizumab plus chemotherapy (BCP), the combination of atezolizumab and BCP revealed survival improvement in patients with metastatic non-squamous non-small cell lung cancer (NSCLC), while ACP failed to demonstrated overall survival (OS) improvement versus BCP.[5 6] In the IMbrave 150 trial, the combination of atezolizumab plus bevacizumab improved OS and progression-free survival (PFS) over sorafenib in unresectable hepatocellular carcinoma (HCC).[7] In a phase II trial, nivolumab and bevacizumab combination also showed promising activity with an objective response rate (ORR) of 28.9% in all patients with relapsed ovarian cancer, including 40.0% in platinum-sensitive and 16.7% in platinum-resistant patients.[8] These studies suggest that the antitumor efficacy of a combination strategy is promising and possibly synergistic in various solid tumors.

However, despite this benefit, the overlapping toxicities of combining such agents should be carefully considered. An observational study which included 15,872 patients with NSCLC from the Food and Drug Administration adverse events (AEs) reporting system database showed that the combination of PD-(L)1 inhibitors with bevacizumab provided a survival benefit but significantly increased the risk of various toxicities, and combination therapy was an independent risk factor for fever, neutropenia, nephritis, and immune thrombocytopenic purpura.[9] New approaches are, therefore, needed to facilitate enhanced blockade of PD-1 and VEGF with a favorable toxicity profile. Given that there is significant coexpression of both VEGF and PD-1 in the TME,[4] simultaneous blockade of PD-1 and VEGF with a bispecific antibody might offer a more targeted enrichment of the antibody.

Ivonescimab is a first-in-class, humanized tetravalent bispecific antibody targeting PD-1 and VEGF-A simultaneously. Preclinical studies showed that ivonescimab could specifically bind to human PD-1 and VEGF-A with high affinity.[10] In vivo pharmacology studies demonstrated that ivonescimab could significantly inhibit tumor growth in a dose-dependent manner in HCC827 xenograft mouse model.[10]

Here, we reported the first-in-human (FIH) phase 1a study of ivonescimab, which evaluated the safety, pharmacokinetics (PK), pharmacodynamics and clinical activity of ivonescimab in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT04047290).

METHODS

Study design and patients

This was an FIH, phase 1a, multicenter trial which was conducted in six sites in Australia and included dose-escalation and dose-expansion portions. The primary objectives of this study were to assess the safety and tolerability, dose-limiting toxicities (DLTs), and to determine the maximum tolerated dose (MTD) or maximum administered dose. The secondary objectives included assessing the PK, pharmacodynamics as well as preliminary antitumor activity of ivonescimab when administered as a single agent in patients with advanced solid tumors.

Eligible patients had histologically or cytologically confirmed advanced or metastatic solid tumors that were refractory or had relapsed after standard therapies, or for which no effective standard therapy was available. Key inclusion criteria were measurable disease according to Response Evaluation Criteria in Solid Tumors V.1.1, Eastern Cooperative Oncology Group performance status score of 0 or 1, adequate organ function, and life expectancy of ≥12 weeks. Key exclusion criteria included the presence of active brain metastases, active or prior documented autoimmune disease, clinically significant cardiovascular disease, history of gastrointestinal perforation, surgery and wound healing complications, and hemorrhagic events.

Study procedure

Ivonescimab was administered intravenously on day 1 and day 15 of each 28-day treatment cycle until disease progression, consent withdrawal or intolerable toxicity occurred. A single-subject cohort was enrolled at the starting dose of 0.3 mg/kg, after which a 3+3+3 design was used in the dose escalation phase, with a minimum of three DLT-evaluable patients at each dose level and a maximum of nine patients at each dose level. The dose levels tested in the escalation phase were 0.3, 1, 3, 10, 20 and 30 mg/kg administered every 2 weeks to determine the MTD. DLT was defined as grade≥3 drug-related toxicity that occurred within the 28-day DLT-evaluation period. Further specific DLT definitions and exceptions can be found in online supplemental data. The MTD was defined as the highest dose level with a DLT incidence of less than 33.3%. Based on the efficacy signals observed during dose escalation phase, two cohorts receiving doses of 10 and 20 mg/kg were expanded in selected tumor types including microsatellite stable (MSS)/proficient mismatch repair (pMMR) colorectal cancer, ovarian cancer, endometrial cancer (deficient MMR (dMMR) or pMMR) and mesothelioma.

Safety assessments mainly included the incidence and severity of AEs, serious AEs, DLTs, abnormal laboratory parameters. AEs were recorded during treatment period and up to 90 days after the last dose of ivonescimab. The grading of AEs was conducted according to the National Cancer Institute Common Terminology Criteria for Adverse Event V.5.0.

Tumor response was evaluated every 8 weeks for the first 12 months, then every 12 weeks thereafter, until confirmed objective disease progression, initiation of new anticancer therapy, withdrawal of consent, or death. Following the completion of treatment, patients were followed up for survival every 3 months until death, withdrawal of consent, lost to follow-up, or the end of study.

Pharmacokinetics

Blood samples for PK analysis were collected on day 1 (predose, end of infusion (EOI), and 3 hours after the EOI on day 1, days 2, 3, 8 and 15 (predose) in cycles 1 and 3. Predose and EOI PK samples were collected on day 1 and 15 in cycle 2, on day 1 in cycles 4 and 6. Predose samples were collected on day 1 of cycle 8 and every other cycles thereafter. Serum concentrations of ivonescimab were determined using ELISA method.

Pharmacodynamics

Pharmacodynamic biomarkers included PD-1 receptor occupancy (RO) on peripheral circulating CD3+T cells and serum free VEGF. Blood samples for RO were collected on day 1 (predose), 2 and 8 in cycle 1, day 1 (predose) of each cycle thereafter. Blood samples for RO were tested using flow cytometry analysis and the RO was calculated by mean fluorescence intensity. Blood samples for serum free VEGF (not ivonescimab bound VEGF) were collected on day 1 (predose), 2 and 8 in cycle 1, day 1 (predose) of every 2–3 cycles thereafter. All serum samples were tested using a human $VEGF_{165}$ kits (R&D) to measure the levels of free VEGF.

Statistical analysis

The safety analysis population included all enrolled patients who received any amount of ivonescimab. Response-related endpoints for efficacy were analyzed in patients who received any amount of ivonescimab, had measurable disease at baseline, and had at least one postbaseline tumor assessment. Descriptive statistics were used to analyze demographic, safety, PK, PD biomarker, and response data.

RESULTS

Patient characteristics

Between October 2, 2019 and June 14, 2021, a total of 51 patients were enrolled. As of the data cut-off on June 7, 2022, the median duration of follow-up was 12.8 months and 12 patients (23.5%) were still on treatment. Given the efficacy signals and potential on-target toxicities observed at 10 mg/kg dose level, dose expansion was conducted at 10 mg/kg and 20 mg/kg (figure 1).

The majority of enrolled patients had received extensive prior treatment, with 62.7% of patients having received ≥3 lines of therapy. Among the patients, 35.3%

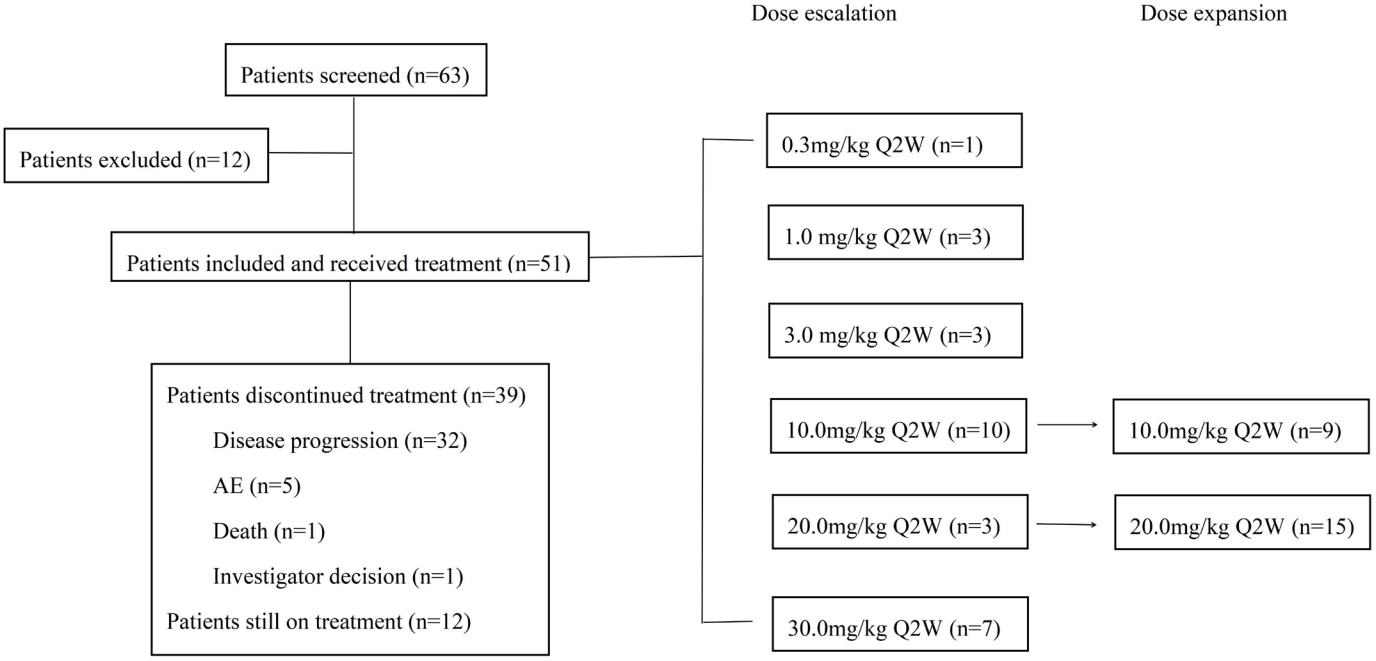

Figure 1 Patient flow diagram. (A) In dose escalation phase, one patient each in 10 mg/kg and 20 mg/kg dropped off within the first cycle and thus deemed non-DLT evaluable. One patient in 10 mg/kg experienced recurrent colitis. Although the event did not meet the DLT definition; DEC deemed it as a notable TRAE and determined to enroll more patients in 10 mg/kg dose escalation cohort before further escalation. (B) In dose expansion phase, 10 mg/kg every 2 weeks was initially expanded for additional enrolment in patients with pMMR colorectal cancer given the one responder observed at 3 mg/kg. Considering the efficacy signal observed in dose escalation cohorts, ovarian cancer, endometrial cancer and mesothelioma was recommended for further expansion by DEC in both 20 mg/kg and 10 mg/kg to select the optimal dose moving forward. AE, adverse event; DLT, dose-limiting toxicity; pMMR, mismatch repair proficient; TRAE, treatment-related adverse event; DEC, dose escalation committee.

had previously received antiangiogenic therapy, and 29.4% had received immunotherapy (table 1). The enrolled patients represented a variety of tumor types, including epithelial ovarian cancer (37.3%), colorectal cancer (17.6%) and mesothelioma (7.8%).

Safety and tolerability

All 51 treated patients were included in the safety analysis. During dose escalation, no DLTs were observed at the first five dose levels. At the 30 mg/kg cohort, two DLTs were observed in six DLT-evaluable patients. One patient experienced a DLT of grade 1 myocarditis, characterized by an asymptomatic elevation of troponin I and led to study drug discontinuation. Troponin I level returned to normal range after corticosteroid treatment. The second DLT was a grade 3 hypertension which occurred in a patient with pre-existing history of hypertension. The patient recovered within 2 weeks after receiving antihypertensive medication. The MTD for ivonescimab was 20 mg/kg every 2 weeks.

Treatment-related AEs (TRAEs) occurred in 38 patients (74.5%). The most common TRAEs of any grade were rash (29.4%), arthralgia (19.6%), hypertension (19.6%), fatigue (17.6%), diarrhea (15.7%), pruritus (11.8%) and aspartate aminotransferase increased (11.8%). TRAEs of grade≥3 were reported in 14 patients (27.5%). No grade≥3 infusion-related reactions occurred. There were no TRAEs leading to death. The details of TRAEs can be found in table 2.

Immune-related toxicities and anti-VEGF related toxicities were of special interest in this study. Pruritus, rash and hypothyroidism were the most commonly reported toxicities of potential immune-related cause, with all being grade 1 or 2 in severity. Five patients experienced grade≥3 hepatotoxicity which was characterized by elevated transaminase levels and normal bilirubin. These events were effectively managed with corticosteroids. Four of them were successfully rechallenged and one patient was not retreated due to disease progression. Three patients experienced colitis (two grade 3 and one grade 2), which were all managed with corticosteroids but two cases had led to treatment discontinuation. One patient on 20 mg/kg experienced grade 3 glomerulonephritis which was managed with corticosteroids and supportive therapy. No further doses of ivonescimab were given to this patient due to disease progression. One case of grade 2 synovitis in 10 mg/kg cohort also led to treatment discontinuation.

Hypertension is considered as an on-target toxicity of anti-VEGF therapies, which was observed at ≥10 mg/kg dose levels and was the most common TRAE with grade≥3 (13.7%, 7/51) in this study. All cases were effectively managed with antihypertensive drugs. Proteinuria was observed in three patients (5.9%) including the patient who experienced glomerulonephritis. No patient experienced grade≥3 cardiovascular event. No gastrointestinal perforation or notable hemorrhage events were observed.

Table 1 Baseline characteristics

Characteristic	No of patients (N=51)
Age, years	
Median (range)	63 (30, 76)
Sex, n (%)	
Male	18 (35.3)
Female	33 (64.7)
Race, n (%)	
White	42 (82.4)
Asian	8 (15.7)
Other	1 (2.0)
ECOG performance status, n (%)	
0	33 (64.7)
1	18 (35.3)
Prior therapies, n (%)	
0	2 (3.9)
1	10 (19.6)
2	7 (13.7)
≥3	32 (62.7)
Prior antiangiogenic therapy, n (%)	18 (35.3)
Prior Bevacizumab, n (%)	16 (31.4)
Prior anti-VEGF TKI, n (%)	2 (3.9)
Prior immunotherapy, n (%)	15 (29.4)
Tumor types, n (%)	
Epithelial ovarian cancer	19 (37.3)
High-grade serous	13 (25.5)
Clear cell	3 (5.9)
Other	3 (5.9)
Colorectal cancer	9 (17.6)
Mesothelioma	4 (7.8)
Endometrial cancer	3 (5.9)
NSCLC	2 (3.9)
Chondrosarcoma	2 (3.9)
Pancreatic cancer	2 (3.9)
Anal cancer	1 (2.0)
Duodenal adenocarcinoma	1 (2.0)
Esophageal cancer	1 (2.0)
Granulosa cell tumor	1 (2.0)
Hepatocellular carcinoma	1 (2.0)
HNSCC	1 (2.0)
Medullary thyroid carcinoma	1 (2.0)
Small cell ovarian cancer	1 (2.0)
Upper gastrointestinal adenocarcinoma	1 (2.0)
Renal cell carcinoma	1 (2.0)

Continued

Table 1 Continued

Characteristic	No of patients (N=51)

ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Efficacy

Antitumor response was observed at dose levels of ≥3 mg/kg every 2 weeks. Among four patients who did not have postbaseline imaging, three of them were due to rapid clinical deterioration and one was due to non-related AE (myocardial infarction). Of 47 patients who had at least one postbaseline assessment, the confirmed ORR was 25.5% (12/47) and the disease control rate (DCR) was 63.8% (30/47). Objective response was observed in patients with platinum-resistant ovarian cancer (PROC), endometrial cancer (both pMMR and dMMR), pMMR colorectal cancer, small cell ovarian cancer, pleural mesothelioma and anal cancer. Among these responders, three patients had received prior ICI therapy and two patients had received prior bevacizumab treatment. The best overall response and duration of treatment for all patients are shown in figure 2.

Among 19 patients with PROC, 68.4% had received ≥3 lines of prior therapy. Five patients achieved PR, three of whom had high-grade serous pathology and two had clear cell pathology, resulting in an ORR of 26.3%. Higher ORR was observed at 20 mg/kg compared with that at 10 mg/kg (30.0% vs 14.3%). Prolonged stable disease (SD) for more than 12 months was observed in four patients who had received prior bevacizumab treatment (online supplemental table S1).

Among nine patients with MSS/pMMR colorectal cancer, 88.9% had received ≥3 lines of prior therapy. One patient treated at 3 mg/kg achieved PR and two patients achieved SD, with duration of 8 and 16 weeks, respectively. The patient who achieved PR had received three lines of prior therapy including bevacizumab.

Three patients with endometrial cancer were enrolled. One patient with dMMR tumor achieved PR, another patient with pMMR tumor achieved PR and experienced a durable response for about 1 year. The third patient with unknown MMR status achieved SD for 16 weeks with 8.5% reduction in tumor burden.

Two patients with NSCLC were enrolled. Both patients were previously heavily treated and PD-1 refractory. One patient had sustained SD (−16.5%) for about 11 months, and the other experienced disease progression.

Pharmacokinetics

As shown in figure 3A,B, following single-dose and multiple-dose intravenous administrations of ivonescimab, serum concentration of ivonescimab increased in a dose-dependent manner. The PK parameters were summarized in online supplemental tables S2 and S3. After the first dosing, C_{max} for 0.3, 1, 3, 10, 20, and 30 mg/kg every 2 weeks ivonescimab was 8.90, 16.9±2.10, 77.8±2.19, 240±73.8, 511±125, and 672±250 µg/mL, and area under the serum concentration-time curve (AUC) from 0 hour to the last measurable concentration (AUC_{0-t}) was 27.1, 64.3±5.92, 409±145, 1220±465, 2790±770, and 3580±1270 day*µg/mL, respectively. After the fifth dosing, $C_{max,\ ss}$ for 1, 10, 20, and 30 mg/kg every 2 weeks ivonescimab was 23.3, 68.9, 355±103, 679±137, and 1010±80.3 µg/mL, and $AUC_{0-\tau}$ at steady-state ($AUC_{0-\tau,\ ss}$) was 95.9, 2240±770, 4380±976, and 6100±690 day*µg/mL, respectively.

The apparent mean terminal half-life after the first dose was 3.66, 3.40±0.340, 4.53±2.59, 6.13±1.85, 6.60±2.05, and 6.03±1.36 days for 0.3, 1.0, 3.0, 10.0, 20.0, and 30.0 mg/kg every 2 weeks doses, respectively.

Pharmacodynamics

After multiple doses of ivonescimab, RO remained at a high level in all the five cohorts (0.3, 1.0, 3.0, 10.0, 20.0, and 30.0 mg/kg every 2 weeks), and sustained saturation (>80%) was observed at doses of 3.0 mg/kg every 2 weeks and higher (figure 4A). Serum-free VEGF level decreased rapidly by 80%–95% in all cohorts after 24 hours following the first dose of ivonescimab (figure 4B). Rebound increase in free VEGF levels was observed in some dose levels and the interpretation of the results was limited due to high individual variation.

DISCUSSION

In this study, we evaluated the safety and efficacy of ivonescimab, a novel anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors. Two DLTs were observed out of 6 patients at 30 mg/kg every 2 weeks. Thus, the MTD of ivonescimab was determined to be 20 mg/kg every 2 weeks per protocol. A higher response rate was observed with ivonescimab 20 mg/kg compared with 10 mg/kg in PROC (ORR 30.0% vs 14.3%) while the safety profile was comparable between these two dose levels. This preliminary finding of dose response was further explored and confirmed in the phase 1b and phase 2 studies of ivonescimab as monotherapy or in combination with chemotherapy in NSCLC.[11 12]

Toxicity profiles in our study were consistent with previous studies investigating the combination of PD-(L)1 inhibitors with bevacizumab.[7 13–16] No new or unexpected toxicities were observed, with rash (29.4%), arthralgia (19.6%), hypertension (19.4%) and fatigue (17.6%) being the most common TRAEs. Lower rates of grade≥3 TRAEs (27.5%) and TRSAEs (5.9%) were observed compared with the data reported in previous studies. The most common grade≥3 TRAE was hypertension (7, 13.7%), which was comparable with the results in bevacizumab studies.[17] Hypertension was the most common anti-VEGF related AE (any grade: 19.6%, grade≥3: 13.7%), all cases occurred in patients receiving dose levels ≥10 mg/kg, and the majority of grade≥3 hypertension occurred in patients with a prior history of hypertension. The commonly

Table 2 Summary of treatment-related adverse event (TRAEs)

	0.3–3 mg/kg Q2W (N=7)		10 mg/kg Q2W (N=19)		20 mg/kg Q2W (N=18)		30 mg/kg Q2W (N=7)		Total (N=51)	
Event, n (%)	**Any**	**Grade≥3**	**Any**	**Grade≥3**	**Any**	**Grade≥3**	**Any**	**Grade≥3**	**Any**	**Grade≥3**
TRAEs	5 (71.4)	1 (14.3)	14 (73.7)	6 (31.6)	14 (77.8)	5 (27.8)	5 (71.4)	2 (28.6)	38 (74.5)	14 (27.5)
Treatment-related SAEs	0	–	1 (5.3)	–	1 (5.6)	–	1 (14.3)	–	3 (5.9)	–
TRAEs leading to drug discontinuation	0	–	2 (10.5)	–	1 (5.6)	–	1 (14.3)	–	4 (7.8%)	–
TRAEs leading to death	0	–	0	–	0	–	0	–	0	–
TRAE of any grade in ≥5% of patients or any grade ≥3										
Rash*	1 (14.3)	0	7 (36.8)	0	5 (27.8)	0	2 (28.6)	0	15 (29.4)	0
Arthralgia	1 (14.3)	0	5 (26.3)	0	4 (22.2)	0	0	0	10 (19.6)	0
Hypertension	0	0	4 (21.1)	3 (15.8)	4 (22.2)	2 (11.1)	2 (28.6)	2 (28.6)	10 (19.6)	7 (13.7)
Fatigue	1 (14.3)	0	4 (21.1)	0	3 (16.7)	0	1 (14.3)	0	9 (17.6)	0
Diarrhea	0	0	3 (15.8)	0	5 (27.8)	0	0	0	8 (15.7)	0
Pruritus	0	0	2 (10.5)	0	2 (11.1)	0	2 (28.6)	0	6 (11.8)	0
Aspartate aminotransferase increased	0	0	1 (5.3)	1 (5.3)	4 (22.2)	1 (5.6)	1 (14.3)	0	6 (11.8)	2 (3.9)
Alanine aminotransferase increased	0	0	1 (5.3)	1 (5.3)	3 (16.7)	2 (11.1)	1 (14.3)	0	5 (9.8)	3 (5.2)
Headache	0	0	1 (5.3)	0	2 (11.1)	0	1 (14.3)	0	4 (7.8)	0
Hypothyroidism	1 (14.3)	0	1 (5.3)	0	2 (11.1)	0	0	0	4 (7.8)	0
Infusion related reaction	0	0	1 (5.3)	0	3 (16.7)	0	0	0	4 (7.8)	0
Hyperthyroidism	1 (14.3)	0	0 (0.0)	0	1 (5.6)	0	1 (14.3)	0	3 (5.9)	0
Colitis	0	0	1 (5.3)	1 (5.3)	2 (11.1)	1 (5.6)	0	0	3 (5.9)	2 (3.9)
Mucosal inflammation	0	0	0 (0.0)	0	3 (16.7)	0	0	0	3 (5.9)	0
Proteinuria	0	0	1 (5.3)	0	1 (5.6)	0	1 (14.3)	1 (14.3)	3 (5.9)	1 (2.0)
Hepatitis	0	0	2 (10.5)	1 (5.3)	0	0	0	0	2 (3.9)	1 (2.0)
Stomatitis	1 (14.3)	1 (14.3)	0	0	0	0	0	0	1 (2.0)	1 (2.0)
Glomerulonephritis	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (2.0)	1 (2.0)
Neutropenia	0	0	1 (5.3)	1 (5.3)	0	0	0	0	1 (2.0)	1 (2.0)

The relatedness of the adverse event to treatment was determined by the investigators.
*Rash included rash, rash macular, rash maculopapular, lichen planus and drug eruption on preferred term level.
Q2W, every 2 weeks; SAE, serious adverse event.

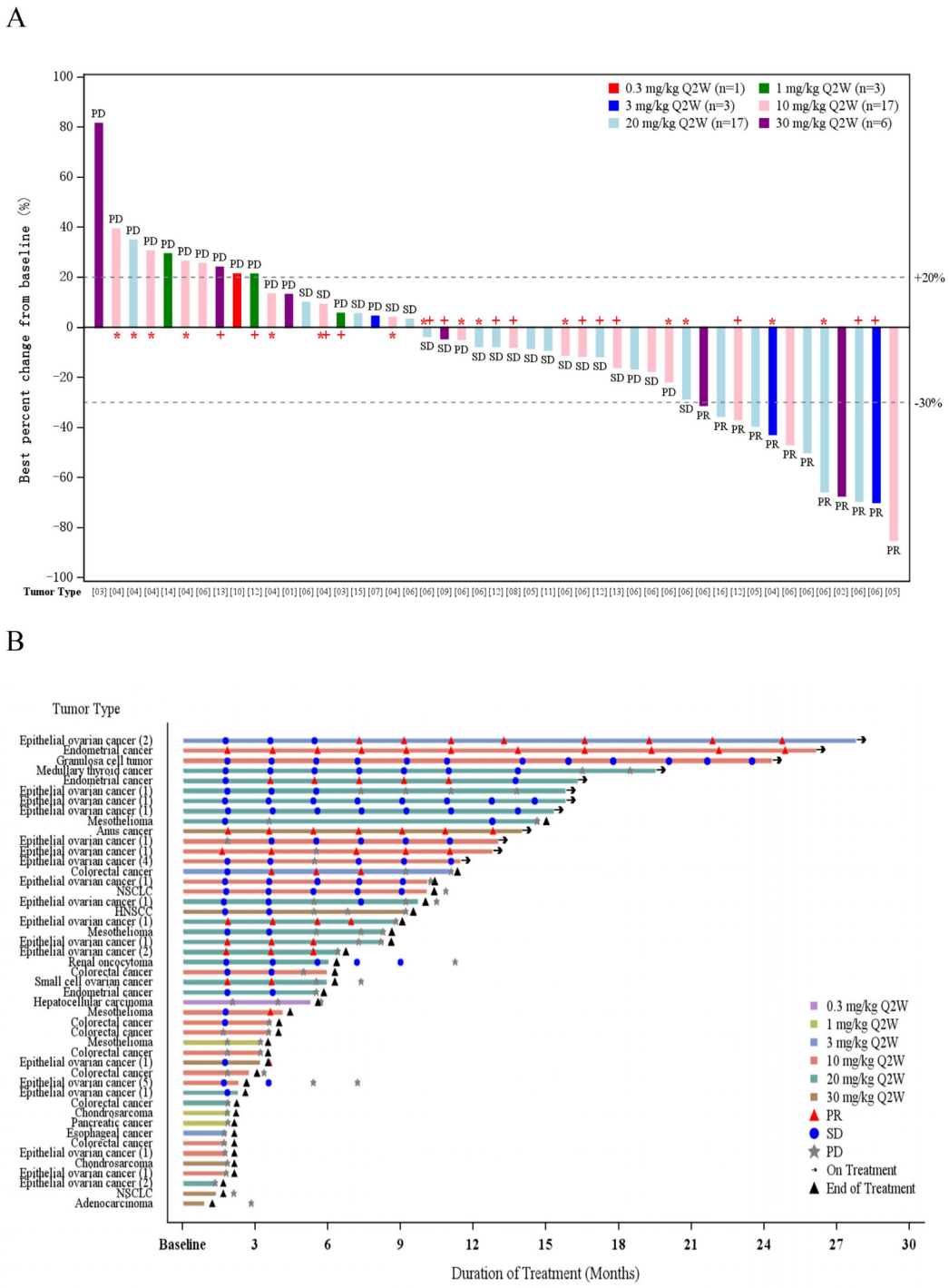

Figure 2 (A) Maximum change from baseline of target lesions in all evaluable patients. Four patients discontinued before any disease assessment and are not included in the plot. (B) Duration of treatment in all evaluable patients. (01)=adenocarcinoma, (02)=anus cancer, (03)=chondrosarcoma, (04)=colorectal cancer, (05)=endometrial cancer, (06)=epithelial ovarian cancer, (07)=esophageal cancer, (08)=granulosa cell tumor, (09)=HNSCC, (10)=hepatocellular carcinoma, (11)=medullary thyroid cancer, (12)=mesothelioma, (13)=NSCLC, (14)=pancreatic cancer, (15)=renal oncocytoma, (16)=small cell ovarian cancer. Epithelial ovarian cancer: (1) high-grade serous; (2) clear cell; (3) mucinous; (4) endometrioid; (5) serous (grade unknown). *Previous bevacizumab; +Previous immunotherapy. NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma.

observed immune-related toxicities were pruritus, rash and hypothyroidism, similar to that reported with anti-PD-1/PD-L1 monotherapy. Although grade≥3 hepatotoxicity and recurrent colitis occurred, all these AEs were manageable with corticosteroids. No gastrointestinal perforation or arterial thromboembolism was observed. No grade≥2 hemorrhage events were observed which was a known adverse reaction to bevacizumab.

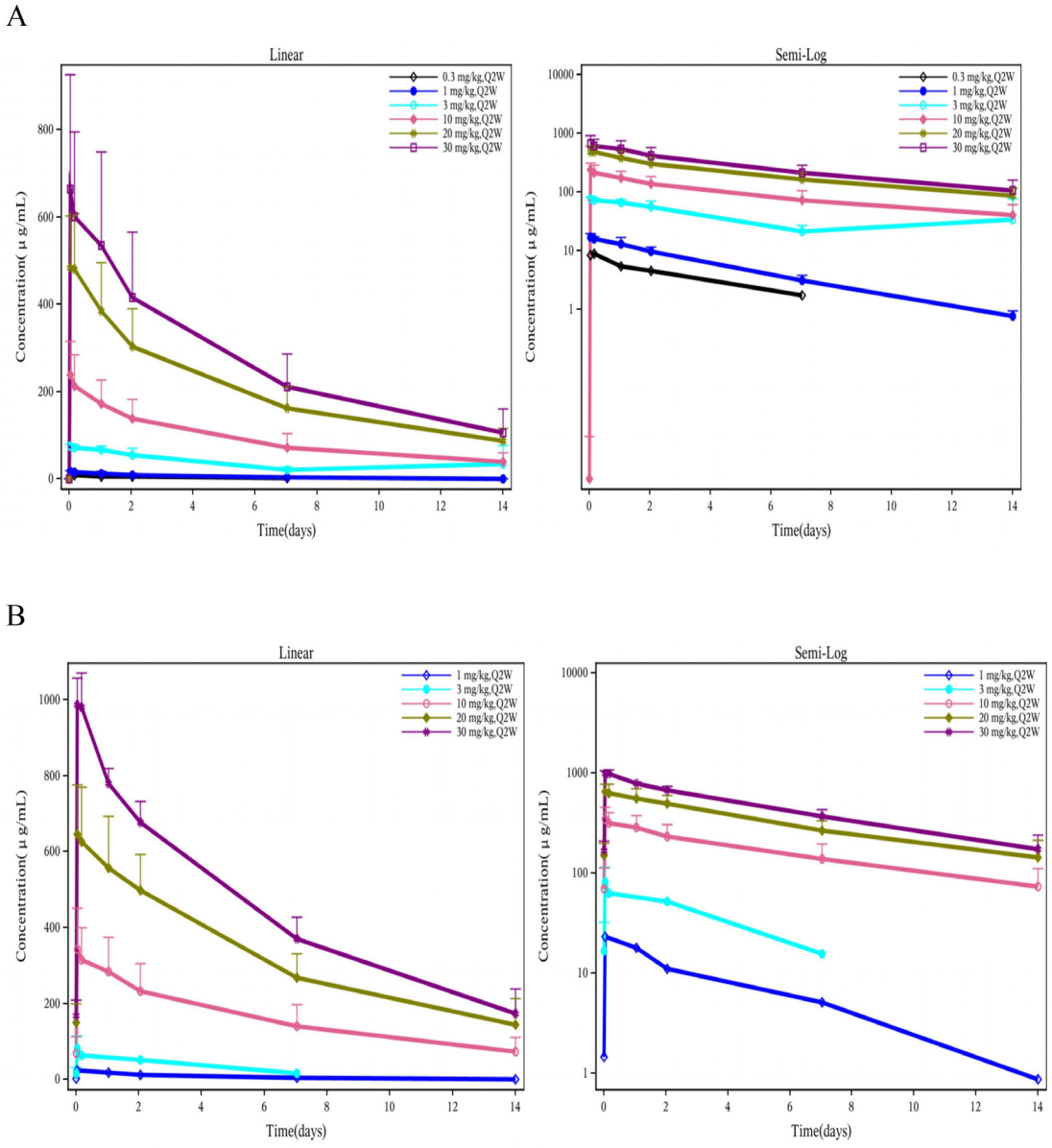

Figure 3 (A) Serum concentration-time curve after the first dose of ivonescimab. (B) Serum concentration-time curve after the fifth dose of ivonescimab. Visit days are presented on the x-axis, ivonescimab concentration on the y-axis, data represent the mean and SD of patients.

The favorable safety profile of ivonescimab may be attributed to the unique characteristics of the bispecific antibody itself and its potential retention in tumors. Preclinical studies have demonstrated that when a high density of VEGF antigen is present, the PD-1 binding activity of ivonescimab is significantly enhanced. This property of ivonescimab may contribute to its increased accumulation and retention in tumor tissues.[10]

Most patients in this study were heavily pretreated, with 62.7% of patients having received ≥3 lines of therapy, including receipt of prior antiangiogenic therapy in 35.3% patients, and prior ICI therapy in 29.4% patients. Ivonescimab showed preliminary efficacy signals in multiple tumor with ORR 25.5% and DCR 63.8%, even though the study enrolled most patients with tumor types that have historically not been known to respond to single-agent immunotherapy (eg, serous ovarian cancer, MSS colorectal cancer, and other cancers). Of note, among 19 heavily pretreated patients with PROC, the ORR was 26.3% with nine patients having a PFS of >6 months. A higher response rate was observed at 20 mg/kg (30.0%, n=10,) vs 10 mg/kg (14.3%, n=7). Currently, PROC represents a high unmet medical need with limited treatment options available.[18] Results from single-agent anti-PD-(L)1 therapy were disappointing with an ORR of less than 10%.[19 20] Combination of nivolumab plus bevacizumab has demonstrated activity in patients with relapsed ovarian cancer with modest improvement in ORR (16.7%) in platinum-resistant patients.[8]

Nine patients with MSS/pMMR colorectal cancer were enrolled in this study—one achieved PR and two achieved SD with an ORR of 11.1% and DCR of 33.3%. MSS/pMMR

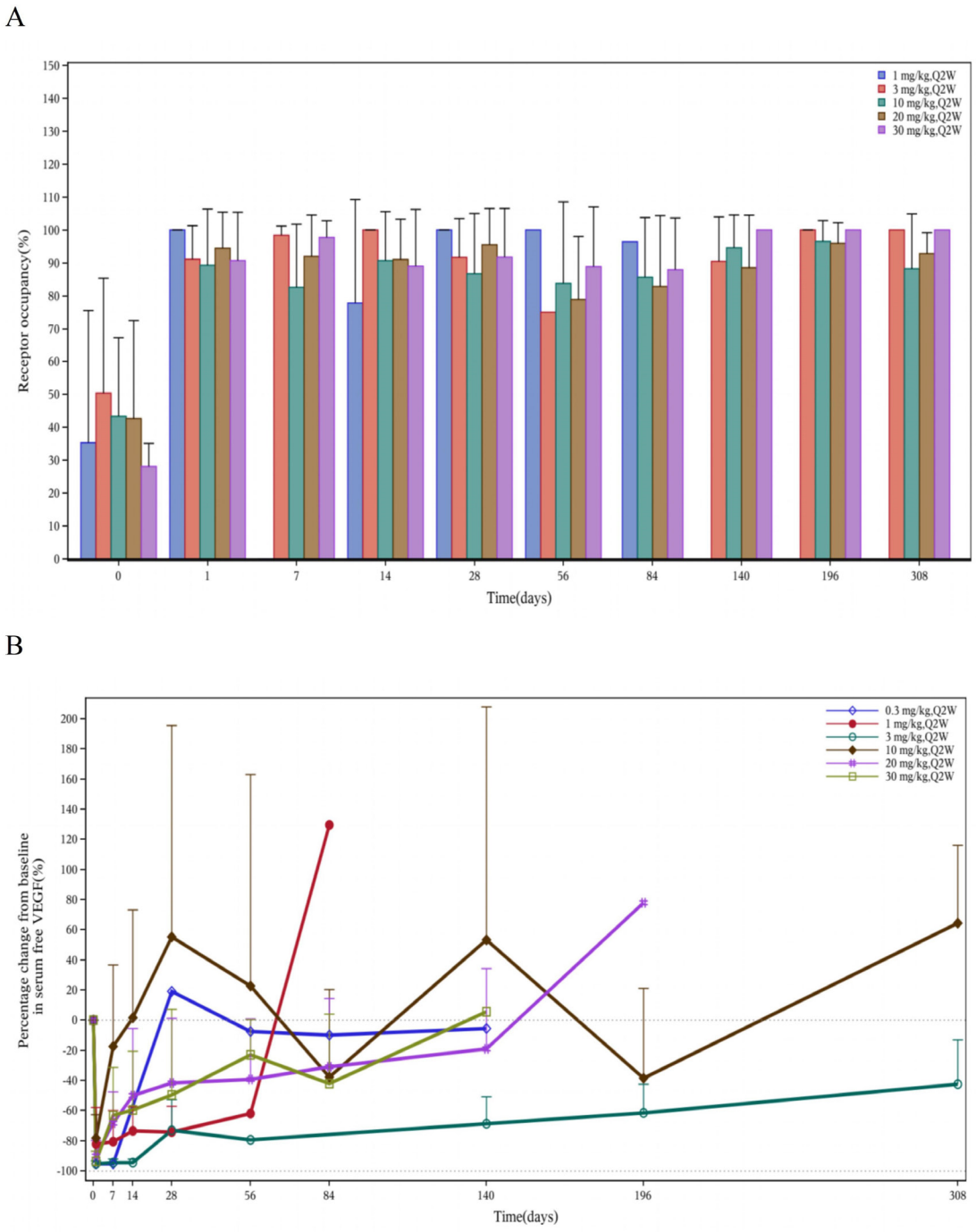

Figure 4 (A) Receptor occupancy (RO) following multiple doses of ivonescimab. (B) Percentage change from baseline in serum free VEGF level following multiple doses of ivonescimab. Visit days are presented on the x-axis, percentage of RO on the y-axis in (A), percentage change from baseline in serum free VEGF on the Y axis in (B), data represent the mean+SD for each dose cohort. VEGF, vascular endothelial growth factor.

CRC has shown resistance to anti-PD-1 treatment,[21 22] and immunotherapy-based combination therapies are being explored. In a randomized clinical trial, patients with MSS CRC could benefit more from the addition of atezolizumab to capecitabine and bevacizumab therapy.[23] In our study, an ORR of 11.1% is encouraging in MSS/pMMR CRC patients treated with ivonescimab monotherapy. Identifying the subtypes of MSS CRC patients who can benefit from the combination of immunotherapy and anti-VEGF therapy is an important direction to be explored in further studies.

The combination of pembrolizumab and lenvatinib has emerged as an effective treatment in patients with metastatic endometrial cancer. KEYNOTE 775 randomized patients with pretreated endometrial cancer to either pembrolizumab and lenvatinib or chemotherapy and led to prolonged survival with the combination of anti-PD-1 and VEGF therapy, however, AEs of grade ≥3

occurred in 88.9% of the patients who received combination therapy.[24] A single-arm, phase 1b/2 trial had demonstrated a high ORR of 38% in previously treated endometrial cancer patients who received lenvatinib plus pembrolizumab, but the incidence of grade 3/4 TRAEs was 69.4% in the same population.[25] The combination of atezolizumab plus bevacizumab has also been investigated in a phase II trial, among 57 patients with recurrent endometrial cancer, the ORR reached 30% regardless of MMR status, grade≥3 TRAEs reported in 29% of patients, which was lower than lenvatinib plus pembrolizumab.[26] In our study, among three patients with recurrent endometrial cancer, all three cases demonstrated clinical meaningful responses including 2 PR and 1 SD. Grade≥3 TRAEs occurred in 27.5% of all 51 patients. This encouraging result suggests that ivonescimab has the potential to be a viable treatment option for endometrial cancer.

Furthermore, our study demonstrated that patients who had previously received bevacizumab or anti-PD-(L)1 therapy, could still benefit from ivonescimab treatment, evidenced by observed PR or prolonged SD, especially in PROC, pMMR colorectal cancer, and NSCLC. Several studies involving ivonescimab monotherapy or in combination with chemotherapy in various solid cancers are ongoing (NCT04736823, NCT04900363, NCT04870177). Four phase 3 studies in NSCLC have been initiated (NCT05184712, NCT05499390, NCT05899608, NCT05840016). One limitation to this study was the lack of biomarker analyses which was important to identify correlations with treatment efficacy. The biomarker analysis will be performed in other studies.

In summary, ivonescimab demonstrated manageable safety and tolerability profile. Preliminary efficacy data showed encouraging efficacy signals in solid tumors patients with heavily pretreated disease, including patients who had progressed after prior ICI and anti-VEGF therapy.

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