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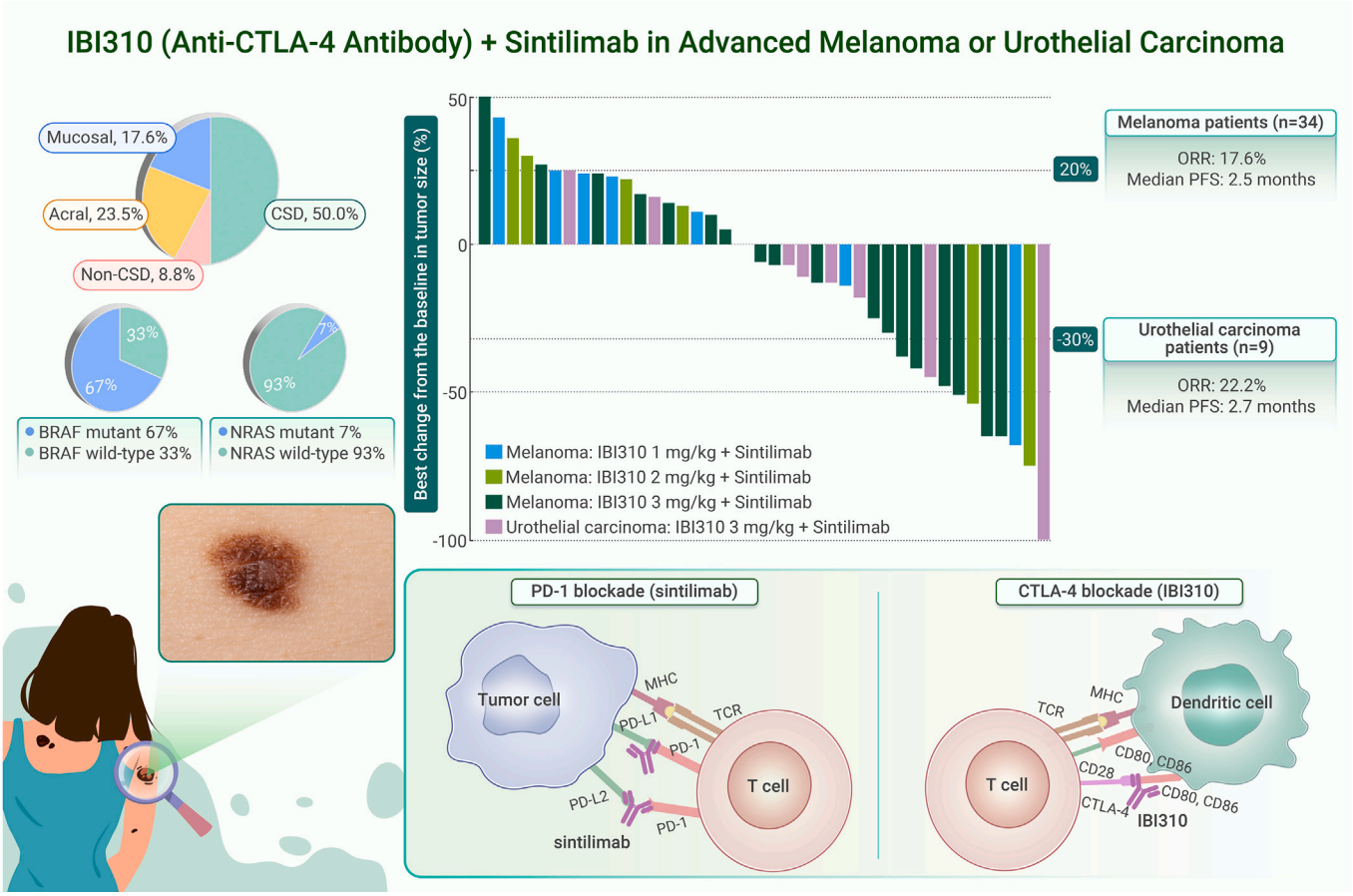
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Great differences exist in melanoma characteristics between Caucasian and Asian populations.
- We evaluated cytotoxic T lymphocyte antigen 4 and programmed cell death-1 blockades in melanoma in China.
- IBI310 (an anti-cytotoxic T lymphocyte antigen 4 antibody) alone or combined with sintilimab was well tolerated.
- Favorable antitumor activity was observed in Chinese patients with advanced melanoma.

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IBI310 (anti-CTLA-4 antibody) monotherapy or in combination with sintilimab in advanced melanoma or urothelial carcinoma

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IBI310 is a recombinant fully human IgG1 antibody against cytotoxic T lymphocyte antigen 4. This study was conducted to evaluate IBI310 monotherapy or combination therapy with sintilimab in the patients with advanced melanoma or urothelial carcinoma (UC). Patients in phase 1a received IBI310 at 0.3/1/2/3 mg/kg intravenously (IV) every 3 weeks (Q3W) following the accelerated titration and 3 + 3 escalation design. Patients in phase 1b received IBI310 (1/2/3 mg/kg IV, Q3W) plus sintilimab (200 mg IV, Q3W) for four cycles, followed by sintilimab maintenance therapy. The phase 1b expansion of IBI310 plus sintilimab was performed in patients with advanced melanoma or UC. Overall, 53 patients were enrolled, including 10 patients with melanoma in phase 1a, 34 with melanoma, and 9 with UC in phase 1b. Overall, 94.3% of patients (50/53) experienced at least one treatment-related adverse event (TRAE) with most being grade 1–2; 26.4% of patients (14/53) experienced grade 3 or higher TRAEs. In phase 1a, the disease control rate (DCR) was 50.0% (95% confidence interval [CI], 18.7%–81.3%). In phase 1b, the objective response rate (ORR) and DCR were 17.6% (95% CI, 6.8%–34.5%) and 44.1% (95% CI, 27.2%–62.1%), respectively, for melanoma, and were 22.2% (95% CI, 2.8%–60.0%) and 66.7% (95% CI, 29.9%–92.5%), respectively, for UC. IBI310 monotherapy or combination therapy with sintilimab was well tolerated with favorable antitumor activity across patients with advanced melanoma and UC.

INTRODUCTION

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a molecule expressed on the surface of activated $CD4^+$ and $CD8^+$ T cells, the targeting of which could induce its inhibitory signals.[1-3] To date, there is only one anti-CTLA-4 monoclonal antibody (mAb), ipilimumab (a fully human mAb against CTLA-4) that has been approved for the treatment of several types of human malignancy.[4,5]

Melanoma has long been acknowledged as a type of immunogenic cancer.[6] Its mortality rate is high, with a 5-year survival rate of less than 5% for advanced patients in China.[7,8] Ipilimumab combination therapy with nivolumab (a mAb against programmed death-1 [PD-1]) has profoundly changed the clinical management of advanced melanoma in western countries, with a 5-year survival rate of more than 50%.[9] However, previous melanoma immunotherapies with anti-CTLA-4 were mainly conducted in western countries, where the cutaneous subtype of melanoma accounts for 90% of cases.[10-13] By comparison, both acral and mucosal melanomas are predominant subtypes in Asian countries (approximately 70%).[14-16] Clinical evidence derived from Asian patients is urgently demanded due to the difference in genetic background and clinical efficacy among melanoma subtypes.

IBI310 is a recombinant fully human IgG1 mAb against CTLA-4 that consists of the same amino acid sequence as ipilimumab. Sintilimab is an IgG4 anti-PD-1 antibody, with potent blocking interaction of PD-1 and its ligands,[17,18] and has been approved for the treatment of several human malignancies in China. Here we report the initial dose escalation and expansion study of IBI310, including safety, tolerability, and antitumor activity of IBI310 monotherapy or combination therapy with sintilimab in patients with advanced melanoma or urothelial carcinoma (UC).

RESULTS

Patients characteristics

Between October 2018 and February 2021, 53 patients were enrolled in this study, with the majority being males, Eastern Cooperative Oncology Group (ECOG) 1 and metastatic disease (Table 1). The phase 1a part enrolled 10 patients (6 mucosal melanoma, 2 acral melanoma, and 2 non-chronic sun damaged [NCSD] melanomas). The phase 1b IBI310 combination therapy part enrolled 34 patients with melanoma (6 mucosal melanoma, 8 acral melanoma, 17 NCSD melanoma, and 3 chronic sun-damaged melanoma [CSD]) in three dose cohorts including IBI310 1 mg/kg (n = 7), 2 mg/kg (n = 7), and 3 mg/kg (n = 20), and 9 patients with UC in the IBI310 3 mg/kg cohort.

The median treatment duration was 4 cycles (range, 2–7) in phase 1a and 3.5 cycles (range, 1–4) among the 34 patients with melanoma in phase 1b, and 3.0 (range, 1–4) among the 9 patients with UC. Overall, as of data cutoff (July 9, 2021), 44 patients discontinued treatment mainly due to disease progression (24/44, 54.5%); nine patients remained under study treatment. The median follow-up was 8.25 months (range, 1.3–23.85 months) in phase 1a and 10.2 months (range, 1.4–27.8 months) in phase 1b.

Safety and tolerability profile

No dose-limiting toxicities (DLTs) were reported. IBI310 monotherapy and combination therapy with sintilimab were well tolerated in patients with advanced melanoma or UC. Adverse events by dose level were summarized in Table 2.

In phase 1a, treatment-related adverse events (TRAEs) of any grade occurred in 9 of the 10 patients (90.0%), with the most common TRAEs being pruritus (50.0%), increased blood thyroid-stimulating hormone (20.0%), decreased thyroxine free (20.0%), asthenia (20.0%), and decreased appetite (20.0%) (Table 3). Grade 3 or higher TRAEs occurred only in one patient with increased gamma-glutamyl transferase. Three patients (30.0%) experienced immune-related AEs (irAE). No AE leading to study drug discontinuation or interruption, or death occurred.

Among the 34 patients with advanced melanoma in phase 1b, 32 patients (94.1%) experienced TRAEs (Table 2); the most common TRAEs (Table 3) were increased alanine aminotransferase (41.2%), pruritus (41.2%), rash (38.2%), increased aspartate aminotransferase (35.3%), hyperthyroidism (35.3%), and hypothyroidism (35.3%). Grade 3 or higher TRAEs occurred in 7 patients (20.6%); the most frequent grade 3 or higher TRAE was immune-mediated enterocolitis (5.9%). irAEs were reported in 31 patients (91.2%). Infusion reaction occurred in 1 patient (2.9%), with dyspnea and flushing. AE led to treatment discontinuation in six patients (16.7%). One patient (2.9%) died due to suspected disease progression, which was not treatment related according to the investigator's assessment.

Among the nine patients with UC in phase 1b, all subjects experienced at least one TRAE (Table 2). The most common TRAEs (Table 3) were pruritus (66.7%), asthenia (55.6%), increased thyroxine free (44.4%), increased tri-iodothyronine free (44.4%), and pyrexia (44.4%). Grade 3 or higher TRAE occurred in six patients (66.7%). All patients experienced irAEs (incidence of grade ≥3 irAE: 66.7%). Infusion reaction was observed in one patient (11.1%) who showed symptoms of chills, pyrexia, temperature intolerance, and rash. AEs led to IBI310 or sintilimab discontinuation in three patients (33.3%). One patients (11.1%) died due to cardiac arrest, which was not treatment related as per the investigator's assessment.

Table 1. Patient demographics and baseline disease characteristics

Characteristics	Phase 1a	Phase 1b	
n (%)	**Melanoma (n = 10)**	**Melanoma (n = 34)**	**UC (n = 9)**
Age (median years, range)	55.5 (44–66)	52.0 (26–68)	58.0 (39–65)
Gender			
Male	5 (50.0%)	16 (47.1%)	8 (88.9%)
Female	5 (50.0%)	18 (52.9%)	1 (11.1%)
ECOG performance status			
0	0	2 (5.9%)	3 (33.3%)
1	10 (100.0%)	32 (94.1%)	6 (66.7%)
Subtype of melanoma			
Non-CSD	2 (20.0%)	17 (50.0%)	/
CSD	0	3 (8.8%)	/
Acral	2 (20.0%)	8 (23.5%)	/
Mucosal	6 (60.0%)	6 (17.6%)	/
Stage			
III	1 (10%)	3 (8.8%)	1 (11.1%)[a]
IV	9 (90.0%)	31 (91.2%)	7 (77.8%)
Metastasis stage at baseline			
M0	1 (10.0%)	3 (8.8%)	2 (22.2%)
M1	9 (90.0%)	31 (91.2%)	7 (77.8%)
Gene mutation status			
BRAF mutation	/	14/21 (66.7%)	/
CKIT mutation	/	0/29 (0%)	/
NRAS mutation	/	2/30 (6.7%)	/
PD-L1 expression			
TPS ≥1%	/	5 (14.7%)	1 (11.1%)
TPS <1%	/	9 (26.5%)	0
Not available	/	20 (58.8%)	8 (88.9%)
Prior line of treatment			
0	0	17 (50.0%)	2 (22.2%)
1	6 (60.0%)	11 (32.4%)	6 (66.7%)
≥2	4 (40.0%)	6 (17.6%)	1 (11.1%)
Previous treatment			
Chemotherapy	6 (60.0%)	8 (23.5%)	7 (77.8%)
Radiotherapy	3 (30.0%)	3 (8.8%)	2 (22.2%)
Surgery	10 (100.0%)	33 (97.1%)	9 (100.0%)
Anti-VEGF therapy	7 (70.0%)	7 (20.6%)	3 (33.3%)
Targeted therapy	1 (10.0%)	6 (17.6%)	0
Immunotherapy	0	17[b] (50.0%)	1[c] (11.1%)
other[d]	2 (20.0%)	2 (5.9%)	0

The staging was classified according to the eighth edition of the American Joint Committee on Cancer (AJCC) melanoma staging system.
CSD, melanomas on skin with chronic sun-induced damage; non-CSD, melanomas on skin without chronic sun-induced damage.
[a]The stage of one patient with UC was TxN0M0.
[b]Including 16 patients with immunomodulator therapy and 1 patient with cellular immunotherapy.
[c]One patient with cellular immunotherapy.
[d]Including traditional Chinese medicine and oncolytic virus therapy. /Indicates data are not available. Percentages might not sum to 100 because of rounding.

Table 2. Summary of adverse events in all patients

	Patients with melanoma in phase 1a					Patients with melanoma in phase 1b				Patients with UC in phase 1b
	0.3 mg/kg (n = 1)	1 mg/kg (n = 3)	2 mg/kg (n = 3)	3 mg/kg (n = 3)	Total (n = 10)	1 mg/kg (n = 7)	2 mg/kg (n = 7)	3 mg/kg (n = 20)	Total (n = 34)	3 mg/kg (n = 9)
Any TRAE	1 (100)	3 (100)	2 (66.7)	3 (100)	9 (90.0)	7 (100)	7 (100)	18 (90.0)	32 (94.1)	9 (100)
Grade ≥3 TRAE	0	0	0	1 (33.3)	1 (10.0)	0	1 (14.3)	6 (30.0)	7 (20.6)	6 (66.7)
TRSAE	0	0	0	0	0	0	0	6 (30.0)	6 (17.6)	5 (55.6)
TRAE leading to treatment discontinuation	0	0	0	0	0	1 (14.3)	0	5 (25.0)	6 (17.6)	3 (33.3)
TRAE leading to death	0	0	0	0	0	0	0	0	0	0
Immune-related adverse event	0	0	0	3 (100)	3 (30.0)	6 (85.7)	7 (100)	18 (90.0)	31 (91.2)	9 (100)
Grade ≥3 immune-related adverse event	0	0	0	1 (33.3)	1 (10.0)	0	0	5 (25.0)	5 (14.7)	6 (66.7)
Infusion reaction	0	0	0	0	0	0	0	1 (5.0)	1 (2.9)	1 (11.1)

Data are presented as number (%). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

TRSAE, treatment-related serious adverse events.

Efficacy

Among the 10 patients with advanced melanoma in phase 1a, no patients achieved a complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator's assessment (Table 4; Figure 1A). one (1/3), two (2/3), and two (2/3) patients had best overall response of stable disease in the 1, 2, and 3 mg/kg dose cohorts, respectively (Table S1). Overall, DCR was 50.0% (95% confidence interval [CI], 18.7%–81.3%). Consistent results were observed per immune-based RECIST (iRECIST) (Table S2). The overall median progression-free survival (PFS) was 1.9 months (95% CI, 1.2 to NA). A numerically higher median PFS was observed in the 3 mg/kg cohort with 8.5 months versus 1.2, 1.3, and 2.6 months for the IBI310 0.3, 1, and 2 mg/kg cohorts, respectively. The overall median overall survival (OS) was 14.9 months (95% CI, 6.2 to NA).

Among the 34 patients with advanced melanoma in phase 1b, objective clinical response was observed at every dose level (Table S1) and across acral, mucosal, and NCSD melanomas (Table S3). The overall objective response rate (ORR) was 17.6% (95% CI, 6.8%–34.5%) per RECIST v1.1, with one confirmed CR and five confirmed PR (Table 4; Figure 1B). Durable response was observed (Figure 1C) in five patients (>300 days); four patients maintained response as of the data cutoff date. Per iRECIST, the overall immune objective response rate (iORR) was 20.6% (95% CI, 8.7–37.9), with one immune complete response (iCR) and six immune partial response (iPR) (Table S2). DCR was 44.1% (95% CI, 27.2%–62.1%); four patients with stable disease had decreased target lesions. The overall median time to response (TTR) was 2.6 months (range, 1.3–11.1 months); the median TTR was numerically shorter in IBI310 3 mg/kg plus sintilimab cohort (1.3 months; range, 1.3–2.7 months) than in the other two dose cohorts (6.0 months [range, 6.05–6.05 months] for IBI310 1 mg/kg + sintilimab and 6.9 months [range, 2.6–1.1 months] for IBI310 2 mg/kg + sintilimab). The overall median PFS was 2.5 months (95% CI, 1.2–3.9 months). The IBI310 3 mg/kg plus sintilimab dose cohort showed a numerically longer median PFS (2.9 months; 95% CI, 1.2–4.3 months) than the other two dose cohorts (1.2 months [95% CI, 1.2 to NA months] and 1.3 months [95% CI, 1.2 to NA months], respectively). The median PFS was 2.6 months (95% CI, 1.2–3.9 months) for the subgroup of BRAF mutation versus 4.6 months (95% CI, 1.2–23.3 months) for the subgroup of BRAF wild type. The median duration of response (DOR) and OS were not reached.

Subgroup analysis for ORR was performed for the 34 patients with advanced melanoma in phase 1b. Generally, age, gender, ECOG status, melanoma subtypes, prior lines of treatment, and levels of PD-L1 expression did not seem to play significant roles (Figure S1). Of note, the ORR for patients with a tumor proportion score (TPS) of 1% or higher was 40.0% (2/5) versus 11.1% (1/9) for patients with a TPS of less than 1%. The ORR was 30.0% (3/10) for the previously untreated patients. The ORR for patients with the BRAF mutation was 14.3% (2/14) versus 28.6% (2/7) for patients with BRAF wild type.

For the nine patients with advanced UC in phase 1b, the ORR was 22.2% (95% CI, 2.8%–60.0%) per RECIST v1.1, including one CR (11.1%) and one PR (11.1%) (Table 4). These two patients continued response as of data cutoff (Figure 1C). The DCR was 66.7% (95% CI, 29.9%–92.5%). Consistent results were observed per iRECIST (Table S2). The median TTR was 2.0 months (range, 1.5–2.5 months). The median PFS was 2.7 months (95% CI, 1.3 to NA). The median DOR and OS were not reached.

Pharmacokinetics and immunogenicity

The first dose and multiple dose pharmacokinetic (PK) profiles of IBI310 alone or in combination with sintilimab were characterized from 28 patients including 1, 9, 9, and 9 patients treated with IBI310 0.3 mg/kg, 1 mg/kg, 2 mg/kg, and 3 mg/kg dose levels with or without sintilimab, respectively.

The IBI310 serum concentration reached the maximal serum concentration (C_{max}) as the infusion finished and was slowly eliminated from the circulation. IBI310 exposure parameters (C_{max} and AUC_{0-504h}) increased in a dose-proportional manner from 0.3 to 3 mg/kg, and clearance (CL) was stable among the dose levels. Hence, IBI310 exhibited a linear PK profile within the dose levels of 0.3–3 mg/kg. Accumulation of IBI310 was observed when given as a multi-dose infusion, with an accumulation index of 0.82–2.29 (cycle 4). PK parameters were consistent between IBI310 alone and in combination with sintilimab (Tables S4 and S5). The serum concentrations of IBI310 over time derived from 0.3–3 mg/kg dose levels at cycle 1 and cycle 4 are presented in Figure 2.

No positive anti-drug antibody (ADA) against IBI310 was identified as of the data cutoff date.

DISCUSSION

This study is the first of a CTLA-4 inhibitor conducted exclusively in Chinese patients. IBI310 was generally well tolerated with a safety profile consistent with other anti-CTLA-4 antibodies, as well as PK characteristics. Favorable clinical responses were observed in advanced melanoma, including acral, mucosal and NCSD subtypes, and advanced UC.

Most of the recent melanoma immunotherapies with CTLA-4 blockade were mainly conducted in the cutaneous subtype of CSD in western countries, while less is known about patients with acral and mucosal melanomas in Asia.[19] Great differences exist in genomic alteration and drug efficacy between acral or mucosal and cutaneous melanomas.[8,15] It was reported that immunotherapy is less effective in treating acral and mucosal melanomas as compared with CSD melanoma, which is probably caused by their distinct tumorigenesis mechanism and lesser immunogenic properties.[20] In this study, Chinese subjects with different melanoma subtypes were prospectively enrolled. The results demonstrated that IBI310 alone or in combination with sintilimab had an acceptable safety profile and promising antitumor activity. For IBI310 monotherapy in

Table 3. Most common TRAEs in the patients with advance melanoma or UC in phase 1b

	Patients with melanoma in phase 1a (n = 10)		Patients with melanoma in phase 1b (n = 34)		Patients with UC in 1lb (n = 9)	
TRAEs in ≥10% of patients with melanoma[a]	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Alanine aminotransferase increased	1 (10.0)	0	14 (41.2)	1 (2.9)	3 (33.3)	1 (11.1)
Pruritus	5 (50.0)	0	14 (41.2)	0	6 (66.7)	0
Rash	1 (10.0)	0	13 (38.2)	0	3 (33.3)	0
Aspartate aminotransferase increased	0	0	12 (35.3)	1 (2.9)	3 (33.3)	0
Hyperthyroidism	0	0	12 (35.3)	0	2 (22.2)	0
Hypothyroidism	0	0	12 (35.3)	0	2 (22.2)	0
Vitiligo	0	0	11 (32.4)	0	0	0
Blood thyroid-stimulating hormone increased	2 (20.0)	0	11 (32.4)	0	2 (22.2)	0
Blood creatine phosphokinase increased	0	0	9 (26.5)	0	0	0
Thyroxine free decreased	2 (20.0)	0	9 (26.5)	0	3 (33.3)	0
Thyroxine free increased	1 (10.0)	0	9 (26.5)	0	4 (44.4)	0
Blood thyroid-stimulating hormone decreased	0	0	7 (20.6)	0	2 (22.2)	0
Bilirubin conjugated increased	0	0	6 (17.6)	0	0	0
Tri-iodothyronine free increased	0	0	6 (17.6)	0	4 (44.4)	0
Amylase increased	0	0	5 (14.7)	0	0	0
Tri-iodothyronine free decreased	0	0	5 (14.7)	0	2 (22.2)	0
Blood bilirubin increased	0	0	4 (11.8)	0	0	0
White blood cell count decreased	0	0	4 (11.8)	0	0	0
Pyrexia	1 (10.0)	0	4 (11.8)	1 (2.9)	4 (44.4)	1 (11.1)
Blood glucose increased	1 (10.0)	0	2 (5.9)	0	0	0
Gamma-glutamyltransferase increased	1 (10.0)	1 (10.0)	2 (5.9)	0	0	0
Hepatic function abnormal	1 (10.0)	0	1 (2.9)	1 (2.9)	0	0
Asthenia	2 (20.0)	0	1 (2.9)	0	5 (55.6)	0
Decreased appetite	2 (20.0)	0	0	0	0	0
Protein urine present	1 (10.0)	0	0	0	0	0

TRAE was related to any study drug. Adverse events were classified according to *Medical Dictionary for Regulatory Activities* and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
[a]Listed by decreasing order in patients with melanoma in phase 1b.

advanced melanoma, no CR or PR was observed, although the DCR of patients receiving IBI310 monotherapy was numerically higher than that of patients receiving ipilimumab monotherapy (50.0% vs. 28.5%).[10] This may be partially attributed to the small sample size in the present phase 1 study compared with phase 2/3 ipilimumab studies (>100 patients were enrolled in each study).[10,13,21] It was noteworthy that the five melanoma patients with a TPS 1% or greater showed an ORR of 40.0%, while those with a TPS of less than 1 exhibited an ORR of 11.1% (Figure S1). This indicated that higher PD-L1 expression might be associated with better antitumor activity in IBI310-sintilimab combination therapy.

IBI310 alone or in combination with sintilimab displayed an acceptable safety profile of 3 mg/kg every 3 weeks (Q3W). Its overall safety profile was similar to that observed in other anti-CTLA-4 inhibitors.[10,11,21,22] No new safety signals were identified. Melanoma patients receiving IBI310-sintilimab combination therapy (20.6%) were observed to have a relatively lower incidence of grade 3 or higher TRAEs compared with those receiving nivolumab and ipilimumab in the CheckMate-067 study (55.0%).[17] This might be ascribed to the administration of relatively lower doses of IBI310 in this study. Nevertheless, making comparisons across studies should be done cautiously, considering the different study designs, sample sizes, and baseline characteristics. In this study, common TRAEs were mild to moderate in severity and manageable with supportive care.

Among patients with advanced melanoma, the incidence and severity of irAE seemed to be associated with IBI310 dose, and its incidence was higher in IBI310-sintilimab combination therapy (any grade irAE, 91.2%; grade ≥3 irAE, 14.7%) compared with IBI310 monotherapy (any grade irAE, 30.0%; grade ≥3 irAE, 10.0%). Immunogenicity data showed that ADA was negative at baseline and follow-up in melanoma patients.

The incidence of grade 3 or higher TRAEs was higher in patients with UC compared with that in patients with melanoma. This might be attributable to the poorer baseline condition of UC patients (eg, more heavily pretreated), too small sample size (with only nine UC patients) and different AE spectra between melanoma and UC. The optimal IBI310 dose level for advanced UC warrants further exploration to improve the safety profile while retaining antitumor activity.

Combination immunotherapy with nivolumab and ipilimumab showed significant antitumor activity for advanced melanoma. The ORR was 52% for previously untreated melanoma patients with BRAF mutation and 61% and 57.6% for those with BRAF-wild tumors in Checkmate-069[13] and Checkmate-067 studies, respectively.[21] In this study, combination immunotherapy with IBI310 and sintilimab also demonstrated promising antitumor activity with an ORR of 30.0% (3/10) for previously untreated melanoma patients (Figure S1). For IBI310 monotherapy in previously treated advanced melanoma, no CR or PR was observed, although the DCR of patients receiving IBI310 monotherapy

Table 4. Antitumor activity per RECIST v1.1

	Phase 1a	Phase 1b	Phase 1b
	Melanoma (n = 10)	Melanoma (n = 34)	UC (n = 9)
ORR			
N (%)	0	6 (17.6%)	2 (22.2%)
95% CI	(0.0, 30.8)	(6.8, 34.5)	(2.8, 60.0)
Best overall confirmed response, n (%)			
CR	0	1 (2.9%)	1 (11.1%)
PR	0	5 (14.7%)	1 (11.1%)
Stable disease	5 (50.0%)	9 (26.5%)	4 (44.4%)
Progressive disease	5 (50.0%)	17 (50.0%)	3 (33.3%)
Not available	0	2[a] (5.9%)	0
DCR			
N (%)	5 (50.0%)	15 (44.1%)	6 (66.7%)
95% CI	(18.7, 81.3)	(27.2, 62.1)	(29.9, 92.5)

[a]The efficacy data were not available in these two patients who were lost to follow-up during a local coronavirus disease 2019 outbreak.

was numerically higher than that of patients receiving ipilimumab monotherapy (50.0% vs. 28.5%).[10] The difference in clinical response may be partially due to divergent baseline characteristics of patients and smaller sample sizes in this phase 1 study.[10,13,21] Additionally, as previously reported, acral and mucosal melanomas are less responsive to immunotherapy than CSD melanoma.[20] Further studies in a larger patient population will help to clarify the efficacy of IBI310-sintilimab combination immunotherapy in these target patients.

The limitations of the present study lie in the non-randomized and open-label design with a small sample size wherein the data had inherent limitations. In conclusion, IBI310 alone or in combination with sintilimab showed an acceptable safety profile, with no new safety signals identified. The promising antitumor activity of IBI310-sintilimab combination therapy was observed in patients with advanced melanoma and UC.

MATERIALS AND METHODS

Patients

Key eligible criteria were patients with 18–70 years of age with advanced, recurrent or metastatic melanoma or UC, at least one measurable disease per the RECIST v1.1 criteria, ECOG performance status of 0 or 1, and adequate organ function. Patients who were previously exposed to any anti-CTLA-4, anti-PD-1, or anti-PD-L1/2 antibodies were excluded.

Study design and treatment administration

This single-center and open-label phase 1 study contained two parts: phase 1a (IBI310 monotherapy dose-escalation) and 1b (IBI310-sintilimab combination dose escalation and expansion). It was aimed at evaluating the safety, tolerability, PK, and antitumor activity of IBI310 alone or in combination with sintilimab. The study protocol and amendments gained the approval of the Institutional Review Board and Ethics Committee of Peking University Cancer Hospital. Registered in ClinicalTrials.gov (NCT03545971), the present study was performed according to the protocol and subsequent amendments, the Declaration of Helsinki, and Good Clinical Practice Guidelines. Written, informed patient consent was obtained before enrollment.

In phase 1a, patients who suffered from locally advanced, recurrent or metastatic melanoma and had failed standard therapy were enrolled. IBI310 was administered intravenously (IV) Q3W, and the dose escalation followed an accelerated titration design (0.3 mg/kg), and then a 3 + 3 escalation design (1, 2, or 3 mg/kg). The observation period of DLT was 21 days. DLT refers to a treatment-associated grade 3 or above AEs or a laboratory abnormality observed within 21 days after the first dosing. If no DLT was observed, three patients would be assigned to receive the first dose of 1, 2, or 3 mg/kg IBI310. Escalation to the next dose could only be allowed when no DLT was detected in the initial three patients. In contrast, additional patients were enrolled up to six patients if one patient experienced DLT. Dose escalation would not continue if DLT occurred in two or more patients among the six patients. After the observation of DLT, patients could continue to receive IBI310 at the intended dose level for an additional three cycles. They were allowed to continue IBI310 therapy (every 12 weeks) if the investigator considered that patients benefited from the treatment per RECIST v1.1.

Any IBI310 monotherapy dose level (excluding 0.3 mg/kg) that was considered tolerable after DLT observation in phase 1a could be entered in phase 1b. IBI310-sintilimab dose escalation followed a 3 + 3 escalation design. In phase 1b, patients with locally advanced, recurrent or metastatic, unresectable melanoma were administrated with 1, 2, or 3 mg/kg IBI310 (Q3W, IV) plus sintilimab (200 mg, Q3W, IV) for up to 4 cycles, followed by sintilimab maintenance therapy (200 mg, Q3W, IV). The treatment was continued until progressive disease, intolerable toxicity, withdrawal of consent, loss to follow-up, death, a maximum of 24 months of treatment, or any other reasons requiring for treatment discontinuation, whichever occurred first. Any IBI310-sintilimab dose level that demonstrated tolerable after the 42-day DLT observation could be expanded in advanced melanoma or UC (patients with advanced, recurrent or metastatic, unresectable UC who had failed standard therapy or were intolerant of platinum-based therapy) for further evaluation of safety, pharmacokinetics, pharmacodynamics, and clinical activity. Subjects with UC were enrolled solely into the IBI310 3 mg/kg plus sintilimab dose cohort.

Study endpoints and assessment

The primary objective was to assess the safety and tolerability of IBI310 monotherapy or combination therapy with sintilimab. The secondary objective was to assess PK characteristics and antitumor efficacy of the IBI301 monotherapy or combination therapy, including ORR, DCR, TTR, DOR, PFS, and OS.

A safety and tolerability assessment was performed up to 90 days after the last dose and was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0. Efficacy was assessed by investigators based on RECIST v1.1 and iRECIST at screening, every 6 weeks until the initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, death, or completion of the study, whichever occurred first.

PK parameters including area under the concentration-time curve, C_{max}, and CL, the volume of distribution, and elimination half-life were estimated. Blood samples for PK assessment were collected 1 h prior to dosing, 0 and 1 h after the end of infusion, and serially at 6, 24, 48, 168, 336, and 504 h after the initiation of IBI310 infusion at the first (for IBI310 alone and in combination with sintinimab) or fourth (for IBI310 alone) dose. The serum concentration of IBI310 was determined using a validated ELISA method. Immunogenic responses to IBI310 were examined for ADA formation. Serum samples were collected 1 h prior to dosing on cycles 1, 2, and 4, and at 90 days after the last dosing. A validated, semi-quantitative electrochemiluminescence method was applied to detect ADAs against IBI310 in human serum.

Statistical analysis

All statistical analyses were conducted using SAS version 9.2 (or higher). The safety was evaluated in the safety analysis set (patients who received at least one dose of IBI310). Patient characteristics and efficacies were evaluated in the full analysis set (patients who met all included criteria and received at least one dose of IBI310). DLTs were determined from the DLT set (patients who experienced a DLT or completed the DLT observation). The PK profile was established from the PK analysis set (patients who had received at least the first dose of IBI310/sintilimab and provided PK samples as per protocol). Study data were all summarized via descriptive statistics. The 95% CIs of ORR and DCR were calculated using the Clopper-Pearson method. The estimation of TTR, DOR, OS, and PFS was done using the Kaplan-Meier method, and the 95% CI of median time was calculated using the Brookmeyer and Crowley method.

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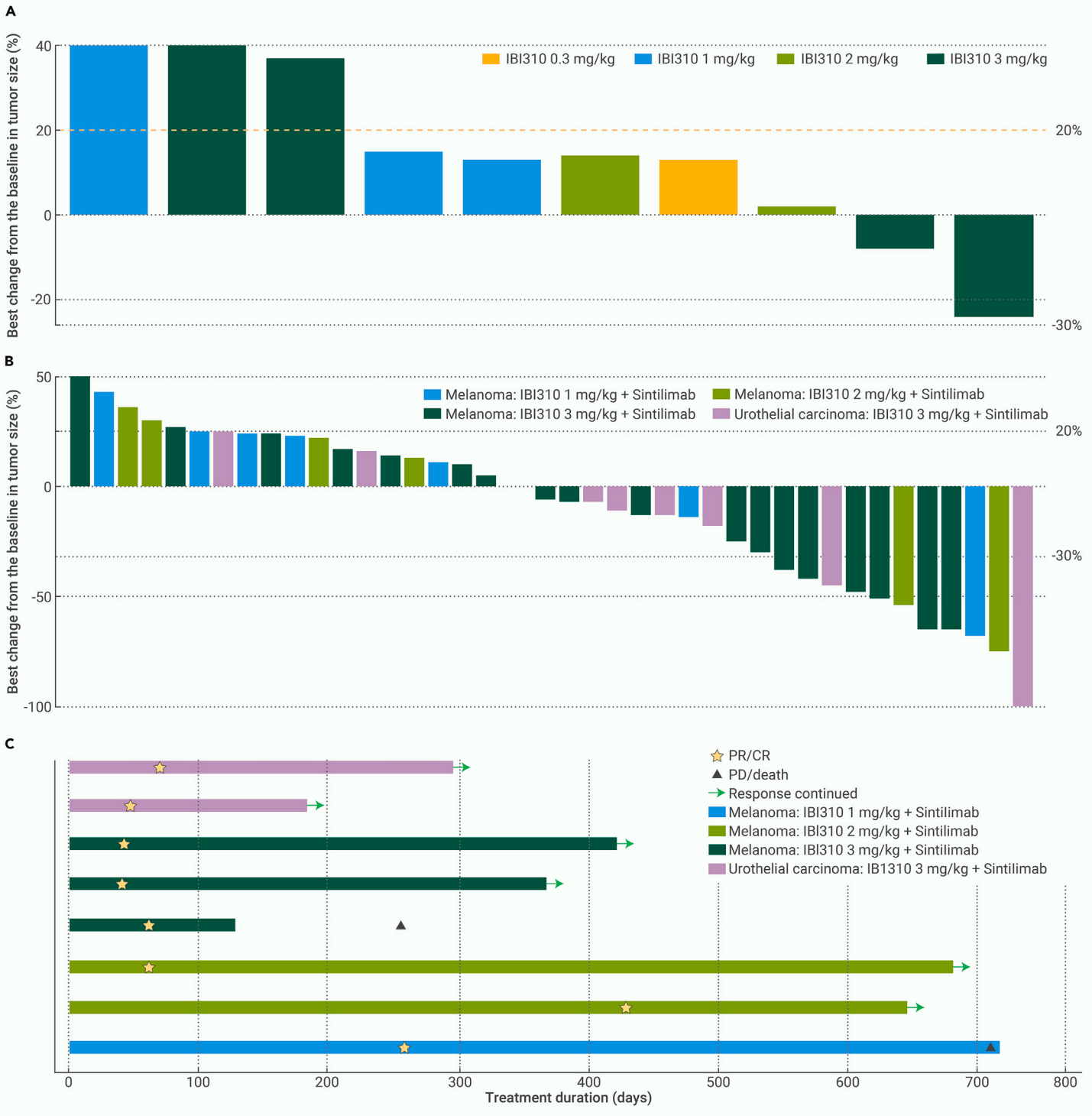

Figure 1. Antitumor activity Waterfall plot of best percentage reduction in tumor burden from baseline for IBI310 alone (A) and for IBI310 in combination with sintilimab (B). DOR for patients with objective clinical response (C). Clinical response was evaluated using RECIST v1.1 by investigators. PD, progressive disease.

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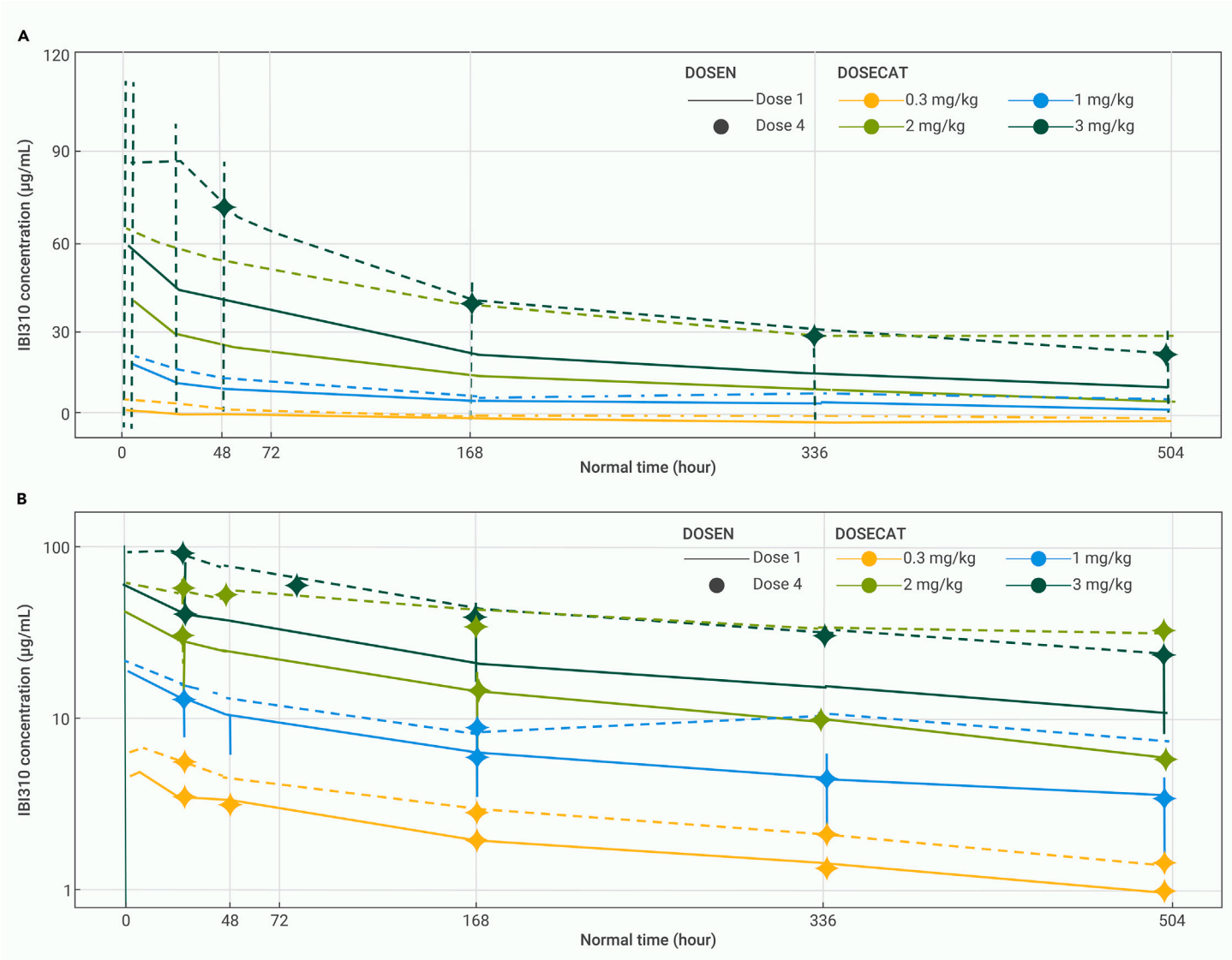

Figure 2. The mean serum concentration-time curve (mean ± SD) of IBI310 in Chinese patients with advanced cancer The mean concentration-time curve is presented in linear ordinate (A) and logarithmic ordinate (B); the solid line and dot-dashed line represent the mean concentration-time curve after administration of IBI310 in Cycle 1 and Cycle 4, respectively.

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AUTHOR CONTRIBUTIONS

B.L., C.C., and J.G. contributed to the study design. B.L., C.C., J.L., Y.Y., L.S., Z.C., L.M., X.Wang, B.T., X.Y., S.L., L.Z., X.Wei, and J.G. contributed to patient enrollment and data acquisition. Q.G. did the statistical analysis. All authors contributed to the data interpretation and medical reviewing. B.L., J.L., C.C., Y.Y., and J.G. drafted the manuscript. All authors contributed to critical manuscript revision and provided approval to submit the manuscript for publication.

DECLARATION OF INTERESTS

J.G. serves consulting/advisory roles in Merck Sharp & Dohme, Roche, Bayer, Novartis, Simcere Pharmaceutical Group, Shanghai Junshi Biosciences, and Oriengene. Y.S., S.Z., and Q.G. reported being employees of Innovent Biologics, Inc.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.1016/j.xinn.2024.100638.

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