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The first-in-class bispecific antibody IBI318 (LY3434172) targeting PD-1 and PD-L1 in patients with advanced tumors: a phase Ia/Ib study

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Abstract

Background There is an unmet clinical need to enhance the response rate and safety of anti-PD-1/PD-L1-based cancer immunotherapy (IO). Herein, we presented the clinical study of IBI318 (LY3434172), a first-in-class bispecific antibody (bsAb) targeting PD-1 and PD-L1, in patients with advanced tumors.

Methods In this open-label, multicenter Phase Ia/Ib study of IBI318, the Phase Ia involved dose escalation and a safety dose expansion, while the Phase Ib focused on preliminary safety and efficacy evaluation in non-small cell lung cancer (NSCLC) and nasopharyngeal carcinoma (NPC). In Phase Ia, patients with advanced tumors received IBI318 doses ranging from 0.3 to 1200 mg every two weeks (Q2W) to determine the recommended Phase 2 dose (RP2D). In Phase Ib, NSCLC or NPC patients from five cohorts with varying treatment histories received IBI318 at the RP2D. The primary endpoint was safety and the secondary endpoints included efficacy assessed by investigators according to RECIST v1.1, pharmacokinetics, immunogenicity, and pharmacodynamics.

Results From February 11, 2019, to January 25, 2022, a total of 103 eligible patients were enrolled (Phase Ia, $n=55$; Phase Ib, $n=48$). The median follow-up was 10.1 months (range 0.7–28.6). The RP2D was determined to be 300 mg Q2W. Treatment-related adverse events (TRAEs) of any grades occurred in 88 patients (85.4%), while 10 patients (9.7%) experienced grade ≥ 3 TRAEs. The objective response rate (ORR) was 15.5% and the disease control rate (DCR) was 49.5% in all patients. In Phase Ib, the confirmed ORR was 45.5% in treatment-naïve NSCLC patients and 30.0% in IO-naïve NPC patients who had failed or were intolerant to platinum-based treatments.

Conclusions IBI318 demonstrated a favorable safety profile and preliminary efficacy in treatment-naïve NSCLC and IO-naïve NPC patients. Further clinical studies are needed to assess the full therapeutic potential of PD-1/PD-L1 dual inhibition with bsAbs.

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Background

Immune checkpoint inhibitors (ICIs) have led to significant advancements in cancer treatment [1, 2]. Several monoclonal antibodies (mAbs) targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death receptor 1 (PD-1), and its ligand PD-L1 have been approved for various malignancies, demonstrating improved efficacy and durable responses [1]. However, relatively higher response rates to anti-PD-1 monotherapy have primarily been observed in specific tumors characterized by PD-L1 expression, microsatellite instability-high (MSI-H), or a high mutational burden. For many cancers, the response rates to anti-PD-1 monotherapy remain limited [3].

Numerous efforts have been made to develop novel cancer immunotherapy (IO) strategies. Combination approaches that utilize ICIs alongside conventional chemotherapy, radiotherapy, or targeted therapies have been extensively evaluated to optimize treatment benefits across different cancer types [2]. Notably, the combination of PD-1 and CTLA-4 inhibitors has improved response rates in certain types of tumors, such as melanoma; however, this approach is also associated with increased incidences of toxicity [4].

In this context, bispecific antibodies (bsAbs), which possess two binding sites for different antigens or epitopes, have emerged as a promising alternative [5]. Compared to anti-PD-1 or anti-PD-L1 mAbs, bsAbs are expected to enhance antitumor activity while maintaining manageable safety profiles [6]. The first approved bsAb, blinatumomab (targeting CD3 and CD19), has been approved for the treatment of B-cell acute lymphoblastic leukemia [7]. More recently, cadonilimab (targeting PD-1 and CTLA-4) and Ivonescimab (targeting PD-1 and VEGF) have received approval for cervical cancer and non-small cell lung cancer (NSCLC), respectively [8, 9]. Other bsAbs targeting PD-1/CTLA-4, PD-L1/CTLA-4 and PD-L1/LAG-3 are currently under clinical development [10–12].

Within the PD-1 signaling pathway, CD80 and PD-L2 also play important roles alongside PD-1 and PD-L1 [13, 14]. Previous studies have explored the use of anti-PD-1 and anti-PD-L1 mAbs in combination for clear-cell renal cell carcinoma and other advanced solid tumors [15, 16]. It has been hypothesized that the dual inhibition of PD-1 and PD-L1 may provide additional benefits [2]. Consequently, targeting PD-1 and PD-L1 represents a rational and feasible approach to enhance antitumor activity compared to traditional anti-PD-1 and anti-PD-L1 mAbs [17].

IBI318, also known as LY3434172, is a first-in-class bsAb that targets both PD-1 and PD-L1. This fully human recombinant IgG1 antibody has a modified Fc region designed to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [17]. IBI318 can completely inhibit the PD-1 pathway by blocking the binding of PD-1 to both PD-L1 and PD-L2, as well as disrupting the interaction between PD-L1 and CD80. Bispecific molecule bridged PD-1 expressing T cells and PD-L1 expressing tumor cells would result in enhanced effector T cell activation and tumor cell killing. The preclinical study has shown an enhanced antitumor immune response with IBI318, supporting its promising profile and warranting further investigation in clinical settings [17].

In this report, we present the first clinical study of IBI318. This Phase Ia/Ib study aimed to evaluate the safety, tolerability, antitumor activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of IBI318 in patients with advanced tumors.

Methods

Study design

This open-label, multicenter study of IBI318 (NCT03875157) consisted of a Phase Ia component, which included dose escalation and a safety dose expansion, and a Phase Ib component, which involved preliminary safety and efficacy evaluation across five different cohorts. The primary endpoint was safety, with secondary endpoints including efficacy, PK, immunogenicity, and PD.

The dose escalation for IBI318 was based on the Minimum Anticipated Biological Level (MABEL), Pharmacologically Active Dose (PAD), and Human Equivalent Dose (HED). The recommended doses were formulated from a comprehensive assessment of IBI318's in vitro and in vivo activity, toxicology data, and anticipated human pharmacokinetic parameters. The proposed escalating doses were: 0.3, 1, 3, 10, 30, 100, 300, 600, and 1200 mg utilizing accelerated titration and a Bayesian interval dose-finding design known as the modified toxicity probability interval (mTPI-2) [18]. The target rate of dose-limiting toxicity (DLT) at the maximum tolerated dose (MTD) was set at 35%. The criteria and detailed escalation process are outlined in the Supplementary Methods.

Following a 28-day observation period for DLTs, patients received IBI318 intravenously every two weeks (Q2W) for up to 24 months, or until disease progression, loss to follow-up, death, intolerable toxicity, withdrawal of informed consent, or other reasons for study discontinuation, whichever occurred first. Selected safety doses ($\leq$MTD) were also expanded to include up to 10 patients per group, administered at Q2W or Q3W for the same maximum duration or until the discontinuation criteria were met.

Based on the collected data on safety, efficacy, PK, and PD, the RP2D was determined. In Phase Ib, the preliminary safety and efficacy of IBI318 were evaluated in five cohorts of patients with NSCLC or NPC. Patients received the RP2D for up to 24 months or until the same discontinuation reasons applied.

Patients

The main inclusion and exclusion criteria were: (1) age ≥ 18 years with signed informed consent; (2) an expected survival time of at least 12 weeks; (3) at least one tumor lesion according to RECIST v1.1; and (4) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients with a prior history of immunotherapy were excluded, except for Phase Ib Cohorts A and K.

The Phase Ia study included patients with histologically or cytologically confirmed, locally advanced, recurrent, or metastatic solid or hematologic tumors that were refractory or intolerant to existing standard therapies. The Phase Ib study was divided into five cohorts (A, B, C, F and K).

Cohort A consisted of NSCLC patients who had histologically or cytologically confirmed disease and had failed anti-PD-1/PD-L1 monoclonal antibody treatment. Failure was defined as disease progression following a partial response (PR) or complete response (CR), or stable disease (SD) for at least six months after immunotherapy.

Cohort B included histologically or cytologically confirmed metastatic NSCLC patients who were either intolerant to or had failed first line chemotherapy, with a PD-L1 tumor proportion score (TPS) of 1–49% and no known EGFR mutations or ALK rearrangements.

Cohort C comprised treatment-naïve NSCLC patients with histologically or cytologically confirmed recurrent or metastatic disease, a PD-L1 TPS of ≥ 50%, and no known EGFR mutations or ALK rearrangements.

Cohort F included recurrent or metastatic NPC patients who had failed or were intolerant to platinum-based chemotherapy.

Cohort K involved recurrent or metastatic NPC patients who had failed or were intolerant to platinum-based chemotherapy and had also failed anti-PD-1/PD-L1 monoclonal antibody treatment.

Safety assessments

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Treatment-related AEs (TRAEs) and immune-related AEs (irAEs) were evaluated by the investigators. Safety assessments were conducted from the time of informed consent until 90 ± 7 days after the last dose, or until the initiation of a new antitumor treatment, whichever occurred first. Patients with TRAEs that necessitated treatment continuation were monitored until AEs recovered to grade 0–1, symptoms stabilized, or informed consent was withdrawn, whichever came first.

Efficacy assessments

Treatment efficacy was evaluated by investigators using computed tomography or magnetic resonance imaging according to RECIST v1.1 criteria. The objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) were evaluated. Baseline assessments were conducted within 28 days prior to the first dose and subsequently every 6 ± 1 weeks until disease progression, the initiation of new antitumor treatment, withdrawal of informed consent, or other reasons leading to study discontinuation, whichever came first.

PK analysis

PK parameters assessed after single and multiple doses of IBI318 included maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the concentration–time curve (AUC), clearance (CL), volume of distribution (V), and elimination half-life ($t_{1/2}$). PK analysis was conducted in Phase Ia patients, encompassing dose escalation and expansion, using non-compartmental analysis (NCA).

Statistical analysis

Patients who received at least one dose of IBI318 were included for safety and efficacy analyses. Continuous variables were summarized by number of cases, mean, standard deviation, median, minimum, and maximum. Categorical variables were described by frequency and percentage. The 95% confidence interval (CI) for ORR and DCR was calculated using the Clopper-Pearson method. DOR and PFS were analyzed using the Kaplan–Meier method, with the median time and 95% CI. Statistical analyses were performed using SAS version 9.4.

Results

Patients

From February 11, 2019 to April 8, 2021, a total of 155 patients were screened, resulting in 103 eligible patients enrolled in the Phase Ia/Ib study who received treatment with IBI318 (Fig. 1). The patient characteristics are summarized in Table 1. In Phase Ia ($n = 55$), there were 31 males (56.4%) and 24 females (43.6%), with a median age of 48 years (range: 27–76). All patients had an ECOG PS of 0 ($n = 18$, 32.7%) or 1 ($n = 37$, 67.3%). Among these patients, 17 had NPC (30.9%), seven had NSCLC (12.7%),

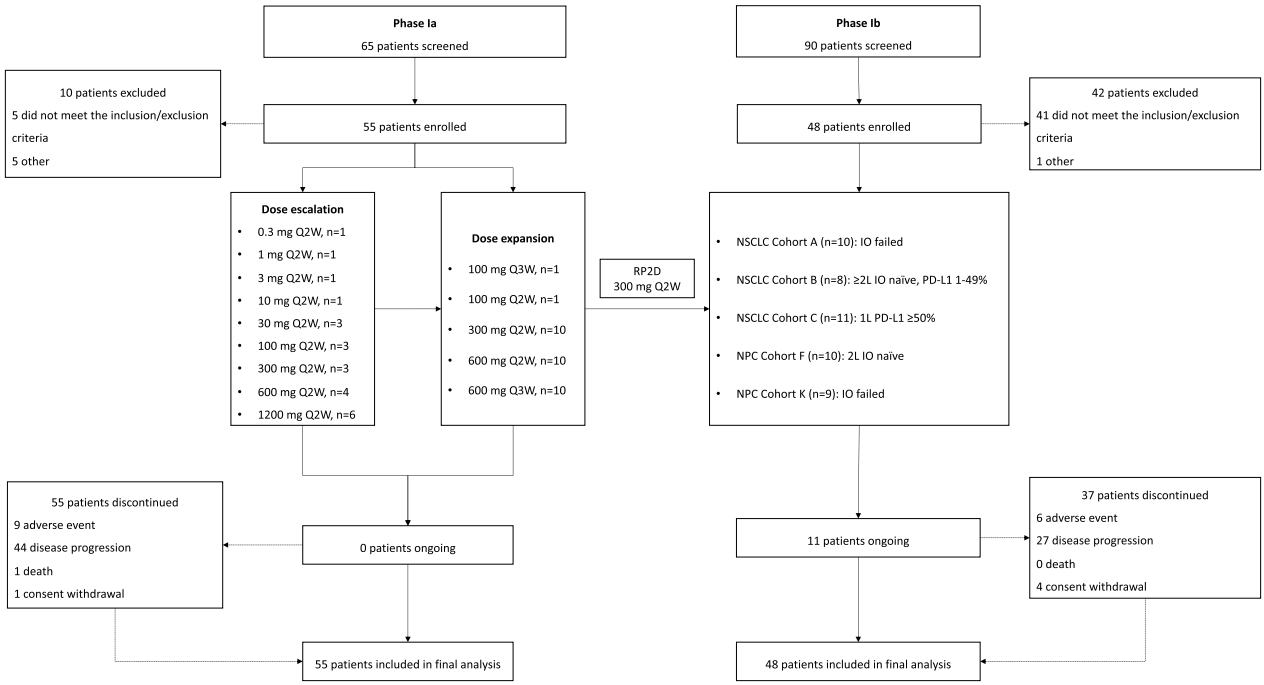

Fig. 1 Study Flowchart. Abbreviations: Non-small cell lung cancer (NSCLC), Nasopharyngeal carcinoma (NPC), Immunotherapy (IO), First line (1L), Second line (2L)

six had esophageal squamous cell carcinoma (10.9%), five had breast cancer (9.1%), three had lymphoma (5.5%), two had colon cancer (3.6%), two had pancreatic cancer (3.6%) and 13 had other tumor types (23.6%). The majority of patients were classified as stage IV ($n=51$, 92.7%), and all had received a median of two lines of prior systemic treatments.

In Phase Ib ($n=48$), patients were enrolled across five different cohorts (A, B, C, F and K) based on their treatment history. In cohort A, there were 10 NSCLC patients who had failed immunotherapy (IO-failed). In cohort B, there were eight NSCLC patients with a TPS 1–49% who had failed or were intolerant to first line chemotherapy (IO-naïve). In cohort C, there were 11 treatment-naïve NSCLC patients with a TPS ≥ 50%. In cohort F, there were 10 NPC patients who had failed chemotherapy (IO-naïve). In cohort K, there were nine NPC patients who had failed or were intolerant to chemotherapy and has also failed immunotherapy (IO-failed). The cutoff date for data collection was January 25, 2022, unless otherwise specified. The median follow-up duration was 10.1 months (range 0.7–28.6).

Determination of RP2D

The preliminary safety data for determination of RP2D was available in 37 patients treated with IBI318 at dose levels ranging from 0.3 to 1200 mg Q2W as of July 7, 2020. The safety profiles of different dose levels were shown in Supplementary Table S1. In the 300 mg dose group, no patients experienced grade ≥ 3 TRAE. In the 600 mg Q2W dose group, the incidence of grade ≥ 3 TRAEs was 14.3%, which included immune-mediated hepatitis, myocarditis, and infusion reactions. In the 1200 mg dose group, the incidence of grade ≥ 3 TRAEs increased to 33.3%, with immune-mediated hepatitis occurring in two out of six patients. Given these two DLTs at 1200 mg Q2W, the MTD of IBI318 was established at 600 mg Q2W. Preliminary efficacy was observed in patients receiving doses from 10 to 600 mg Q2W, with seven patients showing a greater than 20% reduction in target lesions. For 10 patients treated at 600 mg Q3W, no TRAEs of grade ≥ 3 were observed, and no efficacy was observed.

PK and PD analyses of 34 patients in Phase Ia indicated that 300 mg Q2W of IBI318 maintained adequate drug exposure and relatively saturated receptor occupancy (RO%) (Fig. 2A and Supplementary Figure S1). The PK data set included 21 patients in Phase Ia dose escalation and 28 patients in Phase Ia dose expansion. IBI318 concentrations in serum increased gradually to peak levels following intravenous infusion and decreased slowly afterwards. Across dose groups from 0.3 to 1200 mg, drug elimination rates decreased with escalating doses and tended to stabilize at doses ≥ 300 mg (Fig. 2B).

Table 1 Baseline Characteristics in Phase Ia/Ib Study

	Phase Ia	Phase Ib				
		Cohort A	Cohort B	Cohort C	Cohort F	Cohort K
	(*n* = 55)	(*n* = 10)	(*n* = 8)	(*n* = 11)	(*n* = 10)	(*n* = 9)
Gender, n (%)						
Male	31 (56.4)	8 (80)	7 (87.5)	10 (90.9)	10 (100)	7 (77.8)
Female	24 (43.6)	2 (20)	1 (12.5)	1 (9.1)	0	2 (22.2)
Age, years						
Median (range)	48 (27–76)	63 (49–74)	64 (51–73)	57 (46–75)	49 (35–69)	50 (32–58)
ECOG PS, n (%)						
0	18 (32.7)	0 (0)	1 (12.5)	2 (18.2)	3 (30)	3 (33.3)
1	37 (67.3)	10 (100)	7 (87.5)	9 (81.8)	7 (70)	6 (66.7)
Tumor type, n (%)						
Non-small cell lung cancer	7 (12.7)	10 (100)	8 (100)	11 (100)	0	0
Nasopharyngeal carcinoma	17 (30.9)	0	0	0	10 (100)	9 (100)
Esophageal squamous cell carcinoma	6 (10.9)	0	0	0	0	0
Breast cancer	5 (9.1)	0	0	0	0	0
Lymphoma	3 (5.5)	0	0	0	0	0
Colon cancer	2 (3.6)	0	0	0	0	0
Pancreatic cancer	2 (3.6)	0	0	0	0	0
Other	13 (23.6)	0	0	0	0	0
Tumor stage, n (%)						
III	4 (7.3)	1 (10)	1 (12.5)	0	0	0
IV	51 (92.7)	9 (90)	7 (87.5)	11 (100)	10 (100)	9 (100)
Prior lines of treatment, n (%)						
0	0	0	0	11 (100)	0	0
1	21 (38.2)	4 (40)	0	0	6 (60)	1 (11.1)
2	19 (34.5)	3 (30)	8 (100)	0	2 (20)	3 (33.3)
≥ 3	15 (27.3)	3 (30)	0	0	2 (20)	5 (55.6)
Median	2	2	2	0	1	3

After the first cycle of IBI318 administration, drug exposure, as measured by C_{max} and AUC_{inf}, increased with dose escalation from 0.3 to 1200 mg (Figure S2A and B). Body weight normalized clearance (CL/BW) decreased and stabilized at doses ≥ 300 mg (Figure S2C). Target-mediated drug disposition (TMDD) characteristics were observed at dose levels from 0.3 to 300 mg. The drug elimination profile was consistent between single and multiple doses. After cycle 1 and cycle 4 of 300 mg Q2W, the geometric means of CL/BW were 0.000266 and 0.000296 L/h/kg, respectively, while the geometric means of half-life ($t_{1/2}$) were 130.4 and 156.2 h, respectively. The average accumulation ratio of AUC_{0-336h} between cycle 1 and cycle 4 of IBI318 at 300 mg was 1.13. Detailed PK characteristics after cycles 1 and 4 are presented in Supplementary Tables S2 and S3.

An anti-drug antibody (ADA) test was performed in 21 patients in the Phase Ia dose escalation to evaluate immunogenicity. Positive ADA results were observed in 19 out of 21 patients, while negative results were noted in one patient at 300 mg and one patient at 1200 mg (Fig. 2C and Supplementary Figure S3). In dose levels from 0.3 to 100 mg, ADA-positive patients exhibited decreased drug concentration after multiple doses, leading to insufficient drug exposure. At doses ≥ 300 mg, IBI318 was able to overcome the impact of ADA, maintaining relatively stable drug exposure. Based on the safety, efficacy, PK, and PD data from Phase 1a, the RP2D was determined to be 300 mg Q2W for the subsequent Phase Ib study.

Safety

The overall safety profiles of all patients in Phase Ia and Ib, including those treated at the RP2D, are summarized in Supplementary Table S4. Across the entire cohort, TRAEs of any grades occurred in 88 patients (85.4%), while 10 patients (9.7%) experienced grade ≥ 3 TRAEs, and 12 patients (11.7%) had treatment-related serious adverse events (TRSAEs). TRAEs leading to

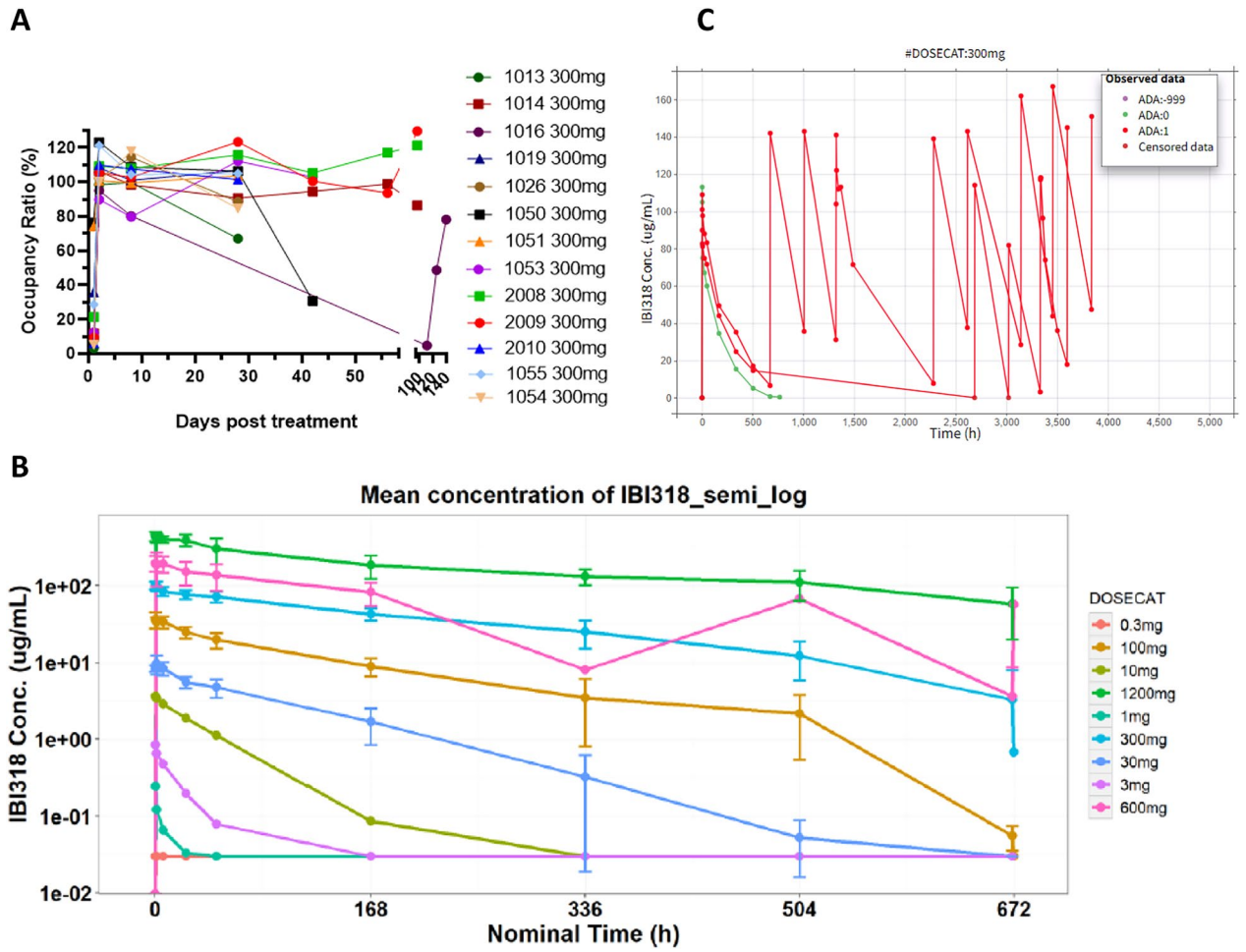

Fig. 2 Mean concentration of Different IBI318 Dose levels in Serum. **A** Mean concentration; **B** Receptor occupancy analysis of IBI318 at 300 mg; **C** Anti-drug antibody (ADA) analysis of IBI318 at 300 mg. X-axis: time (hours); Y-axis: IBI318 concentration (μg/mL); red line: ADA-positive individuals; green line: ADA-negative individuals

dose interruption and treatment discontinuation were reported in 14 (13.6%) and 10 (9.7%) patients, respectively. Importantly, no TRAEs resulted in death. Common TRAEs included increased aspartate aminotransferase ($n=16$, 15.5%), rash ($n=14$, 13.6%) and proteinuria ($n=13$, 12.6%) (Table 2). The most frequent grade ≥ 3 TRAEs were immune-mediated hepatitis ($n=4$, 3.9%) and infusion related reactions ($n=3$, 2.9%). Additionally, 36 patients (35%) had irAEs of any grade, with five patients (4.9%) experiencing grade ≥ 3 irAEs. Common irAEs included hypothyroidism ($n=6$, 5.8%), proteinuria (n = 5, 4.9%), and immune-mediated hepatitis ($n=4$, 3.9%) (Supplementary Table S5). Although increased interleukin (IL) levels occurred in three patients, cytokine release syndrome (CRS) was not observed.

In the subgroup of 61 patients receiving 300 mg Q2W, TRAEs of any grade occurred in 53 patients (86.9%), while five patients (8.2%) experienced grade ≥ 3 TRAEs and TRSAEs. TRAEs leading to dose interruption and treatment discontinuation occurred in 11 (18.0%) and four (6.6%) patients, respectively (Supplementary Table S4). irAEs of any grade were reported in 18 patients (29.5%), while grade ≥ 3 irAEs were observed in one patient (1.6%). The safety profiles at the RP2D were generally consistent with those observed across all patients (Supplementary Table S4). Among the grade ≥ 3 TRAEs, immune-mediated hepatitis ($n=4$, 3.9%), myositis ($n=1$, 1%), and myocarditis ($n=1$, 1%) were observed in the overall cohort but not in those at the RP2D (Table 2). Similar irAEs were also reported in patients at the RP2D, except for immune-mediated hepatitis and increased interleukin levels (Supplementary Table S5).

Efficacy

Among the 103 patients enrolled, the best overall responses included PR in 16 patients (15.5%), SD in 35

Table 2 Treatment-Related Adverse Events of IBI318

	Total (*N* = 103)		**300 mg Q2W (*N* = 61)**	
	Any grade	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
TRAEs, n (%)	88 (85.4)	10 (9.7)	53 (86.9)	5 (8.2)
Increased aspartate aminotransferase	16 (15.5)	0	14 (23.0)	0
Rash	14 (13.6)	0	8 (13.1)	0
Proteinuria	13 (12.6)	0	7 (11.5)	0
Asthenia	11 (10.7)	0	9 (14.8)	0
Hypothyroidism	11 (10.7)	0	6 (9.8)	0
Infusion related reaction	11 (10.7)	3 (2.9)	6 (9.8)	2 (3.3)
Pyrexia	10 (9.7)	0	5 (8.2)	0
Increased Alanine aminotransferase	9 (8.7)	0	7 (11.5)	0
Anemia	8 (7.8)	0	8 (13.1)	0
Decreased Lymphocyte count	7 (6.8)	1 (1)	7 (11.5)	1 (1.6)
Hyponatremia	6 (5.8)	0	5 (8.2)	0
Increased blood alkaline phosphatase	5 (4.9)	0	5 (8.2)	0
Increased blood creatine phosphokinase	5 (4.9)	0	4 (6.6)	0
Decreased White blood cell count	5 (4.9)	0	4 (6.6)	0
Immune-mediated hepatitis	4 (3.9)	4 (3.9)	0	0
Increased Gamma-glutamyl transferase	4 (3.9)	1 (1)	4 (6.6)	1 (1.6)
Myositis	2 (1.9)	1 (1)	1 (1.6)	0
Myocarditis	2 (1.9)	1 (1)	0	0
Diabetes mellitus	1 (1)	1 (1)	1 (1.6)	1 (1.6)

*Any grade treatment-related adverse events occurred in ≥ 5 patients, or grade ≥ 3 TRAEs occurred in ≥ 1 patients are listed

patients (34.0%), and PD in 44 patients (42.7%). The overall ORR was 15.5%, while the DCR was 49.5%. Of the 16 patients who achieved PR, responses were confirmed in 10 patients, including two patients in Phase Ia (at 10 mg Q2W and 300 mg Q2W), five patients in cohort C (treatment-naïve NSCLC) and three patients in cohort F (IO-naïve NPC). The overall confirmed ORR was 9.7% (Supplementary Table S6).

A total of 57 evaluable patients received IBI318 at the RP2D (300 mg Q2W). In this group, 12 patients achieved PR (21.1%, including nine confirmed PRs) and 21 patients had SD (36.8%) leading to an ORR of 2.1% and a DCR of 57.9%. Figure 3 shows the changes in target lesions and tumor response assessments in 55 evaluable patients with solid tumors treated with IBI318 at the RP2D in Phase Ia (two patients with lymphoma were not shown) and Phase Ib (NSCLC Cohorts A, B, and C, and NPC Cohorts F and K).

In cohort A (IO-failed NSCLC, $n = 10$), no patients achieved PR, but three had SD, and seven had PD. The duration of SD was approximately 1, 2 and 4 months respectively. In cohort B (immunotherapy-naïve NSCLC patients with a PD-L1 TPS of 1–49% who had failed or were intolerant to first-line chemotherapy, $n = 8$), one patient achieved PR in the first tumor assessment but later had PD, and three patients had SD. In cohort C (treatment-naïve NSCLC patients with a PD-L1 TPS ≥ 50%, n = 11), five patients had confirmed PR and four patients had SD, resulting in a confirmed ORR of 45.5% (95% CI: 16.8–76.6%) and a DCR of 81.8% (95% CI: 48.2–97.7%) (Supplementary Table S6). The median DOR was 3.56 months (95% CI: 2.76-NA), with a median follow-up of 9.1 months. The median PFS was 6.93 months (95% CI: 1.87-NA), with a median follow-up of 9.7 months.

(See figure on next page.)

Fig. 3 Efficacy of IBI318 at RP2D (300 mg Q2W) in Patients with Solid Tumors. **A** Best percentage change from baseline in target lesion size. Horizontal dashed lines represent a 20% increase and a 30% reduction in tumor size. **B** Percentage change in target lesions from baseline. **C**. Waterfall plots of the best percent change from baseline in target lesions in patients from Cohort C or Cohort F. *One patient had a 32% decrease in the size of the target lesion but developed new tumor lesions; therefore, the overall response was classified as progressive disease (PD). Abbreviations: Adenoid cystic carcinoma (ACC), Lymphoepithelioma-like carcinoma (LELC), Nasopharyngeal carcinoma (NPC), Non-small cell lung cancer (NSCLC), Progressive disease (PD), Partial response (PR), Stable disease (SD)

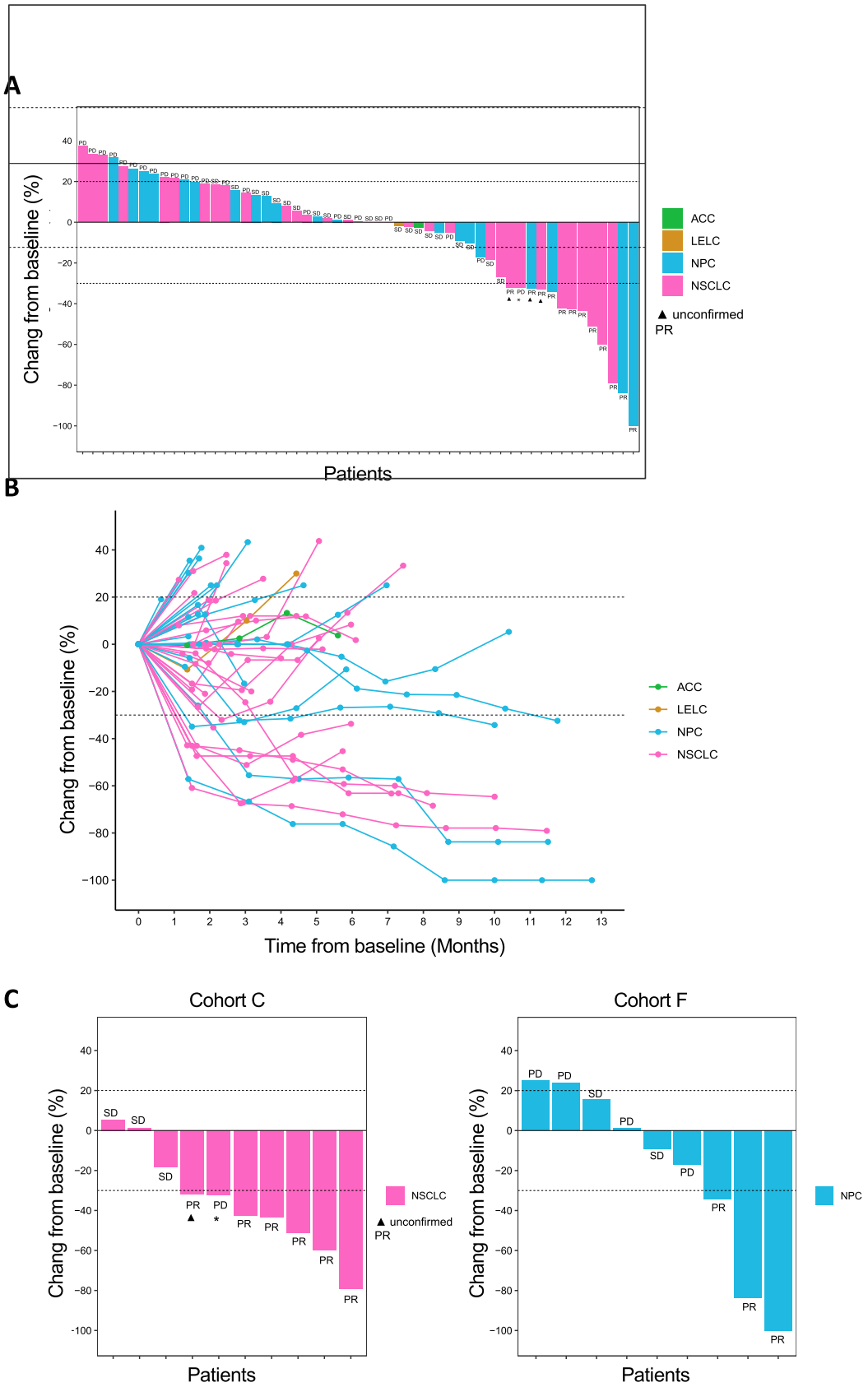

Fig. 3 (See legend on previous page.)

In cohort F (immunotherapy-naïve NPC patients who had failed chemotherapy, n = 10), three patients had confirmed PR and two patients had SD, resulting in a confirmed ORR of 30% and a DCR of 50% (Supplementary Table S6). A representative case is shown in Supplementary Figure S4A, B. Patient #1, a 36-year-old male with advanced NPC, had failed first-line treatments including chemotherapy (docetaxel, cisplatin, and fluorouracil) and radiation therapy, with a PFS of eight months. After failing subsequent treatments, including platinum-based chemotherapy, nimotuzumab, and radiotherapy, the patient received IBI318 300 mg Q2W for 15 months, achieving a best response of PR. Baseline CT imaging indicated metastases in two lung lesions and one liver lesion. After three treatment cycles, the lesions decreased, resulting in PR. After 17 treatment cycles, the lesions disappeared, resulting in CR. However, due to the persistence of non-target lesions, the overall response remained PR. After 32 cycles, the patient experienced PD, confirmed by enlargement of the non-target lesion. As of the cutoff date, the DOR for the other two patients with confirmed PR was 8.4 months and 7.1 months, with no progression reported. The median PFS for cohort F was 3.4 months (95% CI: 1.22-NA), with a median follow-up of 11.1 months.

In cohort K (immunotherapy-failed NPC patients, n = 9), six patients had SD, resulting in a DCR of 66.7% (Supplementary Table S6). Durable tumor control was observed in two patients. One patient-maintained SD for 41 weeks and achieved PR at the last tumor evaluation, though without confirmation. The second patient had a PFS of nearly 25 months (Supplementary Figure S4C). Patient #2, a 37-year-old male with advanced NPC, had failed first-line chemotherapy (gemcitabine and cisplatin) and toripalimab (a PD-1 inhibitor), with a PFS of two years. He then received IBI318 300 mg Q2W. As of the cutoff date, the patient remained at SD, though he experienced PD after 46 treatment cycles in a follow-up on January 10, 2023.

A total of 16 pts continued to use IBI318 after first progression. Among them, progression was confirmed in 11 patients at the 1st tumor assessment after the initial progression, while 3 patients at the 2nd or 3rd tumor assessment after the initial progression. Two patients remained iUPD at follow-up tumor evaluation but discontinued treatment for other reasons, such as investigator decision and patient wishes.

Discussion

The simultaneous blockade of both PD-1 and PD-L1 might lead to more comprehensive inhibition of the PD-1 signaling pathways, potentially enhancing therapeutic efficacy while minimizing the risk of resistance mechanisms. Furthermore, bispecific antibodies may alleviate the overall treatment burden by consolidating therapies into a single agent, thus improving patient compliance and safety. To this end, we designed IBI318, a bispecific antibody that blocks both PD-1 and PD- L1. To our knowledge, this is the first clinical study of a bsAb targeting both PD-1 and PD-L1. In this Phase Ia/Ib study, the results indicate that IBI318 is well-tolerated across different tumor types and showed preliminary clinical efficacy in specific patient cohorts.

The toxicity of immunotherapy is significantly different from that of conventional cytotoxic therapy or targeted drugs in many aspects. In most cases, no significant correlation between dose and safety was observed in immunotherapy, such as anti-PD-1 or anti-PD-L1 drugs. However, when evaluating anti-CTLA-4 antibodies, a dose-toxicity relationship was observed. In the phase I study of QL1706, a bifunctional PD1/CTLA4- dual blocker, DLT was also observed, reaching MTD [10]. The dual blockade mechanism of IBI318 may lead to a distinct safety profile compared to PD-1 or PD-L1 mAbs, characterized by a more pronounced immune response that could potentially result in increased adverse events, particularly at higher dose levels. Indeed, our study reached the MTD of IBI318 at 600 mg Q2W. Considering the safety, efficacy, PK, and PD data, the RP2D of IBI318 was determined to be 300 mg Q2W. In our study, any grade TRAEs occurred in 85.4% of all patients and in 86.9% of patients treated at RP2D, which is comparable to other mAbs and bsAbs targeting PD-1 or PD-L1. Notably, IB1318 demonstrated a favorable safety profile, with a low incidence of grade ≥ 3 TRAEs, reported at 9.7% among all patients and 8.2% in those at RP2D. The combination of different ICIs often raises concerns about severe adverse events or even life-threatening events. A systematic review reported an incidence of 86.8% for all-grade TRAEs and 35.9% for grade ≥ 3 TRAEs in patients receiving anti-PD-1 or anti-PD-L1 therapy plus immunotherapy [19]. In recent Phase I/II studies of combined anti-PD-1 and anti-PD-L1 therapies, the incidence of grade ≥ 3 TRAEs ranged from 20.8 to 26.2% [15, 16]. For bsAbs targeting PD-1/PD-L1 and CTLA-4, the incidence of TRAEs ranged from 74.9%−90% of patients, with grade ≥ 3 TRAEs ranging from 14 to 28% [10, 11, 20]. Common TRAEs in our study included increased aspartate aminotransferase, rash, proteinuria, asthenia, hypothyroidism, infusion related reactions, and pyrexia. Notably, gastrointestinal toxicities such as diarrhea and nausea were numerically much lower in IBI318-treated patients compared to other PD-1/PD-L1 inhibitors combined with immunotherapy (1% vs 21.1% and 1% vs 14.3%, respectively) [19].

The incidence of irAEs with IBI318 was 35% in all patients and 29.5% in those at RP2D, with only 4.9% and 1.6%, respectively, experiencing grade ≥ 3 irAEs. The most common irAEs included hypothyroidism, proteinuria, and immune-mediated hepatitis. IBI318's safety profile, particularly regarding grade ≥ 3 TRAEs and irAEs, appears favorable compared to previously reported anti-PD-1/PD-L1 mAbs and immunotherapy combinations.

We also evaluated the efficacy of IBI318 at RP2D in different patient cohorts. Patients with treatment-naïve NSCLC and a PD-L1 tumor proportion score (TPS) ≥ 50% (cohort C) had an ORR of 45.5%, which is comparable to the efficacy of anti-PD-1 mAbs. In the KEYNOTE-024 trial, previously untreated NSCLC patients with at least 50% PD-L1 expression who received pembrolizumab achieved a response rate of 44.8% with a median PFS of 10.3 months [21, 22]. However, no responses were observed in IO-failed patients (cohort A), and in cohort B (previously treated immunotherapy-naïve NSCLC patients with TPS 1–49%), one patient initially showed a partial response but later progressed. Similar findings have been reported for other bsAbs targeting PD-1 or PD-L1. For instance, the Phase I study of QL1706 (PD-1/CTLA-4 bsAb) in IO-naïve and IO-treated NSCLC patients reported ORRs of 24.2% and 1.8%, respectively. The Phase Ib/II study of cadonilimab (an anti-PD-1 and CTLA-4 bsAb) also reported limited efficacy in previously treated NSCLC patients, with an ORR of 10% in IO-naïve patients and no responses in IO-resistant patients [23].

In NPC cohorts, IBI318 achieved a confirmed ORR of 30% in previously treated, IO-naïve patients (cohort F). Studies of anti-PD-1/PD-L1 mAbs in previously treated NPC patients have reported ORRs ranging from 10 to 43% [24]. The Phase I study of QL1706 reported ORRs of 38.7% in IO-naïve and 6.3% in IO-treated NPC patients [10]. Another Phase I study of KN046 (a PD-L1/CTLA-4 bsAb) in NPC patients reported an ORR of 15.4% [11]. Consistent with previous studies, IBI318 demonstrated better efficacy in IO-naïve NPC patients. Despite limited responses in IO-failed patients (cohort K), IBI318 monotherapy showed the potential to reverse IO resistance in selected patients, with two patients achieving durable tumor control, including one with an unconfirmed PR and another with a PFS of 25 months.

IBI318's unique mechanism of action and promising therapeutic potential were demonstrated in preclinical studies. We observed stronger T-cell activation effects in preclinical studies, however, unfortunately, the expected results were not achieved in this clinical trial. Although preliminary efficacy was observed in some cohorts of our study, the overall efficacy of IBI318 monotherapy appears to be less robust than anticipated and did not achieve optimal results in reversing anti-PD-1 treatment resistance. Additionally, the overall PFS of patients is unsatisfactory, with only a few patients achieving longer DORs. In treatment-naïve NSCLC patients with PD-L1 TPS ≥ 50%, IBI318 demonstrated a median DOR of 3.56 months and a median PFS of 6.93 months, which appear shorter than those of currently approved anti-PD-1 or anti-PD-L1 mAbs. This highlights the need for further investigations into the complexity of the tumor microenvironment and the mechanisms of PD-1/PD-L1 bsAbs in vivo, as well as identifying patients who are most likely to benefit from this treatment.

One goal of drug development is to provide patients with better treatment options. Based on the concept of PD-(L)1 monoclonal antibody combination therapy, PD-(L)1 bsAbs have been developed. As a first-in-class bsAb of PD-1 and PD-L1, IBI 318 fully blocks the inhibitory receptor-ligand interactions within the PD-1 pathway, and is therefore considered a novel therapeutic strategy with enhanced anti-tumor effects compared to current PD-1 or PD-L1 mAbs [17]. Our study demonstrated a favorable safety profile for IBI318 and showed efficacy in some cohorts, but the PFS and DOR were not as good as expected. One possible explanation for this could be the high incidence of ADAs, reported at 90%, which is significantly higher than other anti-PD-1 or anti-PD-L1 antibodies, such as pembrolizumab (1.5%) and atezolizumab (54%). ADA may decrease drug concentrations in serum after multiple doses of IBI318. At doses ≥ 300 mg, IBI318 may overcome the impact of ADA on PK characteristics, maintaining relatively stable drug exposure. Administering higher doses to achieve more stable drug exposure may optimize efficacy.

Little is currently known about the clinical consequences of ADA development in biologic anti-neoplastic drugs [25]. Various factors can influence the development of immunogenicity, including the drug's origin, structure, impurities with adjuvant activity, route, dose, and frequency of administration. Lowering the incidence of ADA for IBI318 may be another direction for achieving better efficacy.

Several limitations of our study should be noted when interpreting the results of IBI318. The lack of randomization and a control group, due to the open-label and single-arm study design, may affect the robustness of the findings. Additionally, the biomarkers in our study were limited; beyond PD-L1 TPS, other biomarkers, such as tumor mutation burden or tumor immune microenvironment, may also provide valuable information.

In this Phase Ia/Ib study, IBI318, the first-in-class and the world's first bsAb targeting both PD-1 and PD-L1, was well tolerated with manageable safety profiles across all patients and demonstrated potential

anti-tumor activity in treatment-naïve NSCLC and IO-naïve NPC patients. However, the overall efficacy of IBI318 monotherapy appears to be less robust than anticipated. Among the various immunotherapy options, bsAbs represent a novel and viable approach to address unmet clinical needs. Target selection is particularly important; the design of IBI318 is a bold endeavor, and this study presents some possibilities for PD-1/PD-L1 dual inhibition with bsAbs. Many questions remain to be elucidated regarding this type of immunotherapy, and in the future, through the optimization of drug structure and biomarker selection, it may be possible to further improve efficacy and provide clinical benefits to more patients.

Abbreviations

IO	Immunotherapy
bsAb	Bispecific antibody
NSCLC	Non-small cell lung cancer
NPC	Nasopharyngeal carcinoma
Q2W	Every two weeks
RP2D	Recommended phase 2 dose
PK	Pharmacokinetics
PD	Pharmacodynamics
TRAE	Treatment-related adverse event
ORR	Objective response rate
DCR	Disease control rate
ICI	Immune checkpoint inhibitor
mAb	Monoclonal antibody
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
PD-1	Programmed cell death receptor 1
MTD	Maximum tolerated dose
ECOG PS	Eastern cooperative oncology group performance status
TPS	Tumor proportion score
TRSAE	Treatment-related serious adverse event
irAE	Immune-related adverse event

Supplementary Information

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Additional file 1.

Additional file 2.

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Conception and design: RHX and HYZ; development of methodology: DYR, RHX, and HYZ; investigation, resources, and data curation: DYR, XLW, FRL, XCH, JZ, DMJ, DZH, YQZm HMP, WJL, KYY, NX, XXL, YLC, WZ, HZ, HYZ, and RHX; analysis and interpretation of data: DYR, XLW, FRL, HYZ, and RHX; writing (review and editing): DYR, XLW, FRL, XCH, JZ, DMJ, HYZ, and RHX; study supervision: RHX and HYZ. Guarantor: RHX and HYZ. All authors contributed to manuscript editing and approved the submission of the manuscript.

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Availability of data and materials
The datasets (including de-identified individual data) generated during the current study are available from the corresponding author upon reasonable request. Requestors will need to submit a proposal to the corresponding author and sign a data access agreement to gain the data access.

Declarations

Ethics approval and consent to participate
The study protocol and all amendments were approved by the Institutional Review Boards of all participating institutions. All participants provided written informed consent. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
Xiao-Xiao Lu, Yu-Ling Chen, Wen Zhang, Hui Zhou are employees of Innovent Biologics (Suzhou) Co. Ltd. Rui-Hua Xu reports speaker fees from Bristol Myers Squibb, Roche, MerckSerono, Hutchison, Hengrui, Junshi, Qilu, CPPC, Henlius, and participates on advisory board for Astellas, MSD, AstraZeneca, Junshi, Hengrui, BeiGene. Innovent, CPPC, and Keymed.

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