

First-in-Human Evaluation of Dual LAG-3 and PD-1 Blockade with IBI110 and Sintilimab in Advanced Solid Tumors

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Abstract

Simultaneous blockade of the immune checkpoints LAG-3 and PD-1 is thought to potentiate the effects of cancer immunotherapy by producing synergistic benefits. This study investigates the safety profile and therapeutic activity of IBI110, a novel anti-LAG-3 monoclonal antibody, when combined with sintilimab, an anti-PD-1 antibody, among Chinese individuals with advanced solid tumors. An open-label phase I clinical trial was performed, incorporating a phase Ia dose-escalation assessment of IBI110 monotherapy and a phase Ib dose-escalation evaluation of IBI110 combined with sintilimab in patients with advanced solid tumors. A phase Ib dose-expansion component was also included, in which IBI110 was administered together with sintilimab and chemotherapy to treatment-naïve patients with advanced squamous non-small cell lung cancer (sqNSCLC) or HER-2-negative gastric cancer (GC). In the phase Ia escalation, IBI110 was given as monotherapy at escalating doses of 0.01/0.1/0.3/1/3/10/, 10 and 20 mg/kg every 3 weeks (Q3W). During phase Ib escalation, IBI110 doses of 0.3/0.7/1.5/3/5/8/10 mg/kg Q3W were paired with a fixed dose of sintilimab 200 mg Q3W. In the dose-expansion stage, patients received IBI110 at the recommended phase 2 dose (RP2D) in combination with sintilimab 200 mg Q3W and standard chemotherapy. The primary endpoints focused on safety and tolerability as well as efficacy parameters such as objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) per RECIST v1.1 criteria, and overall survival (OS). Secondary objectives encompassed pharmacokinetic, pharmacodynamic, and immunogenicity analyses. Treatment-related adverse events (TRAEs) were recorded in 67.9% of participants in the phase Ia dose-escalation group (n = 28), with grade ≥ 3 events occurring in 21.4% of patients. In the phase Ib combination dose-escalation group (n = 45), TRAEs affected 75.6% of patients and grade ≥ 3 TRAEs occurred in 22.2%. No dose-limiting toxicities (DLTs) were identified across the escalation phases. The predominant TRAE was anemia (17.9%, with 3.6% grade ≥ 3) during IBI110 monotherapy in phase Ia (n = 28). In the phase Ib escalation of the combination (n = 45), increased aspartate aminotransferase was most frequent (28.9%, all grades 1-2). In the sqNSCLC dose-expansion cohort (n = 20), anemia occurred in 70.0% of patients (all grades 1-2), while decreased neutrophil count was the leading event in the GC cohort (n = 17; 64.7%, including 17.6% grade ≥ 3). The RP2D for IBI110 was established as 200 mg (equivalent to 3 mg/kg) Q3W. The ORR was 3.6% with IBI110 monotherapy and 14% with IBI110 plus sintilimab in the dose-escalation stage. In the chemotherapy-containing dose-expansion cohorts, unconfirmed and confirmed ORR values were 80.0% (95% CI: 56.3–94.3) and 75.0% (95% CI: 50.9–91.3), respectively, in sqNSCLC (n = 20), and 88.2% (95% CI: 63.6–98.5) and 70.6% (95% CI: 44.0–89.7), respectively, in GC (n = 17). Both IBI110 monotherapy and its combination with sintilimab exhibited acceptable tolerability in Chinese patients diagnosed with advanced solid tumors. The addition of IBI110 to sintilimab and chemotherapy yielded promising antitumor activity in patients with sqNSCLC and GC.

Keywords: LAG-3, PD-1, Monoclonal antibody, Non-small cell lung cancer, Gastric cancer

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Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) have become established options for the development of innovative treatments for

a wide range of cancers [1]. Although responsive patients achieve meaningful and long-lasting clinical benefits, many individuals fail to respond because of intrinsic resistance or later acquire resistance after an initial period of benefit [2]. Considerable clinical challenges therefore remain in overcoming such resistance and maximizing the therapeutic potential of ICIs. In addition to the well-characterized PD-1/PD-L1 and CTLA-4 pathways, additional immune checkpoints have been recognized as key regulators of antitumor immunity and attractive candidates for next-generation immunotherapies [3, 4]. Lymphocyte-activation gene 3 (LAG-3, also known as CD223) is an inhibitory receptor predominantly expressed on T cells and natural killer cells that modulates T-cell activity [5]. Antagonism of LAG-3 disrupts its binding to major histocompatibility complex (MHC) class II molecules, thereby reversing LAG-3-mediated suppression and augmenting T-cell-driven antitumor responses [3-5]. Simultaneous upregulation of several immune checkpoints can promote T-cell dysfunction and create an immunosuppressive tumor microenvironment, which may underlie the limited efficacy of certain ICI regimens [6]. Notably, LAG-3 and PD-1 are frequently co-expressed on T cells, where they exert cooperative inhibitory functions that facilitate tumor immune evasion [7]. Dual targeting of LAG-3, either alone or together with PD-1 blockade, therefore holds substantial promise for improving the outcomes of current immunotherapy approaches [8].

Multiple LAG-3-directed agents, including monoclonal antibodies, bispecific constructs, and soluble fusion proteins, have entered clinical development [9]. The combination of relatlimab (an anti-LAG-3 antibody) and nivolumab (an anti-PD-1 antibody) recently received regulatory approval in the United States for first-line treatment of advanced melanoma, based on the RELATIVITY-047 trial results [10, 11]. Additional early-phase trials evaluating other anti-LAG-3 antibodies in combination with anti-PD-1 agents have also been reported [12, 13]. However, the majority of LAG-3 inhibitor studies have been conducted in Western populations, leaving a gap in evidence regarding their use in Chinese patients.

IBI110 is a fully human IgG4κ monoclonal antibody engineered to specifically recognize and bind LAG-3 expressed on T cells. The current report describes the initial first-in-human clinical investigation of IBI110 in Chinese patients with advanced solid tumors, intending to characterize its safety, antitumor efficacy,

pharmacokinetic (PK), and pharmacodynamic (PD) properties when used both as a single agent and in combination with sintilimab, an anti-PD-1 monoclonal antibody.

Materials and Methods

Study design

This open-label phase I trial comprised three main components: phase Ia dose escalation of IBI110 as monotherapy, phase Ib dose escalation of IBI110 combined with sintilimab, and phase Ib dose expansion evaluating IBI110 plus sintilimab and chemotherapy in treatment-naïve patients with advanced squamous non-small cell lung cancer (sqNSCLC) or HER-2-negative gastric cancer (GC). The primary endpoints included safety and tolerability, as well as key efficacy outcomes such as objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Secondary endpoints covered pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity. Phase Ia dose escalation began with an accelerated titration approach for the lowest doses (0.01/0.1 mg/kg) and transitioned to a standard 3+3 design for higher dose levels (0.3/1/3/10/20 mg/kg). Phase Ib dose escalation followed the classic 3+3 design. Crossover from monotherapy to the combination regimen was permitted upon disease progression. Participants continued IBI110 treatment, administered either alone or with sintilimab, for a maximum of 24 months or until the occurrence of disease progression, loss to follow-up, death, unacceptable toxicity, withdrawal of consent, or any other reason for study discontinuation, whichever came first.

Patients

Enrollment in the phase Ia and Ib dose-escalation segments targeted individuals with locally advanced, recurrent, or metastatic solid tumors who had experienced treatment failure with standard regimens. The phase Ib expansion cohorts included previously untreated patients diagnosed with advanced sqNSCLC or HER-2-negative GC.

Safety assessments

Adverse events (AEs) were categorized using the Medical Dictionary for Regulatory Activities (MedDRA), and severity was graded according to the

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Investigators evaluated treatment-related adverse events (TRAEs) and immune-related adverse events (irAEs). Safety monitoring commenced at informed consent and continued for up to 90 ± 7 days after the last dose or until the start of a new anticancer therapy, whichever occurred earlier. All adverse events were monitored until they resolved to baseline status or grade 0–1, or until the investigator deemed additional follow-up unnecessary based on a sound clinical rationale (e.g., persistent findings without expected improvement).

Efficacy assessments

Investigators determined treatment response through CT or MRI scans in accordance with RECIST v1.1 and iRECIST guidelines. Baseline imaging was completed within 28 days before treatment initiation. Confirmation of the first observed complete response (CR) or partial response (PR) required repeat imaging 4 to 6 weeks later. Thereafter, tumor evaluations were scheduled every 6 weeks ± 7 days until disease progression, commencement of alternative anticancer therapy, consent withdrawal, or other events prompting study discontinuation, whichever occurred first.

Preclinical study

All preclinical experimental details are described as measurements of IBI110 affinity for LAG-3, assessment of binding activity to HEK293-hLAG-3 cells, human CD4⁺ T cells, and cynomolgus monkey peripheral blood mononuclear cells (PBMC), as well as protein- and cell-based blocking assays, LAG-3 blockade reporter assays, receptor occupancy studies in human CD4⁺ T cells, and mixed leukocyte reaction experiments.

PK and PD analysis

Blood specimens for pharmacokinetic (PK) and pharmacodynamic (PD) evaluations were collected throughout the phase Ia and Ib dose-escalation phases. Following single and repeated administrations of IBI110, the following PK parameters were characterized: 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 ($t_{1/2}$). Non-compartmental analysis (NCA) was utilized

for PK evaluation in phase Ia participants, covering both escalation and expansion stages.

Statistical analysis

The safety and efficacy populations comprised all patients who received at least 1 dose of IBI110. Continuous data were summarized using the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical data were reported as counts and percentages. The 95% confidence intervals (CIs) for ORR and DCR were derived using the Clopper-Pearson method. Survival endpoints, including DoR, PFS, and OS, were estimated using the Kaplan-Meier method, yielding median values and 95% CIs. Statistical computations were executed using SAS software version 9.4.

Results and Discussion

Preclinical study

Comprehensive preclinical evaluations, encompassing both in vitro and in vivo experiments, were carried out to characterize the pharmacological activity and safety profile of IBI110. Briefly, IBI110 demonstrated potent binding affinity toward human LAG-3 as well as cynomolgus monkey LAG-3. The antibody successfully inhibited the interaction between MHCII and LAG-3 while promoting downstream signaling events. When combined with sintilimab, IBI110 increased IL-2 release in cell-based assays and elicited more pronounced antitumor responses in animal models.

Patients

Enrollment spanned from December 4, 2019, to January 20, 2022. During this period, 28 patients participated in the phase Ia dose-escalation portion of IBI110 monotherapy, and 45 patients were included in the phase Ib dose-escalation portion of IBI110 combined with sintilimab (**Table 1**). Within the phase Ia escalation, IBI110 was administered every three weeks (Q3W) across escalating dose levels: 0.01 mg/kg ($n = 1$), 0.1 mg/kg ($n = 1$), 0.3 mg/kg ($n = 3$), 1 mg/kg ($n = 3$), 3 mg/kg ($n = 6$), 10 mg/kg ($n = 7$), and 20 mg/kg ($n = 7$). In the phase Ib escalation, IBI110 was given Q3W at doses of 0.3 mg/kg ($n = 3$), 0.7 mg/kg ($n = 3$), 1.5 mg/kg ($n = 3$), 3 mg/kg ($n = 11$), 5 mg/kg ($n = 15$), 8 mg/kg ($n = 6$), and 10 mg/kg ($n = 4$), each in conjunction with sintilimab 200 mg Q3W.

Table 1. Baseline characteristics.

Characteristic	Ib expansion GC, n = 17	Ib expansion sqNSCLC, n = 20	Ib escalation n = 45	Ia escalation n = 28
Gender, n (%)				
Male	13 (76.5)	19 (95.0)	37 (82.2)	18 (64.3)
Female	4 (23.5)	1 (5.0)	8 (17.8)	10 (35.7)
Age, years				
Median (range)	61.0 (39–73)	63.0 (52–74)	60.0 (33–74)	60.5 (35–72)
ECOG PS, n (%)				
0	3 (17.6)	4 (20.0)	14 (31.1)	14 (50.0)
1	14 (82.4)	16 (80.0)	31 (68.9)	14 (50.0)
SLD, mm				
Median (range)	42.0 (12.0–110.5)	85.5 (22.8–163.0)	61.3 (10.0–209.0)	60.8 (10.0–179.0)
Tumor types, n (%)				
Lung cancer	0	20 (100)	33 (73.3)	12 (42.9)
Colorectal cancer	0	0	2 (4.4)	3 (10.7)
Gastric cancer	17 (100)	0	1 (2.2)	2 (7.1)
Kidney cancer	0	0	0	2 (7.1)
Ovarian cancer	0	0	1 (2.2)	2 (7.1)
Melanoma	0	0	0	2 (7.1)
Other	0	0	8 (17.8)	5 (17.9)
Histology, n (%)				
Adenocarcinoma	17 (100)	0	14 (31.1)	14 (50.0)
Squamous	0	20 (100)	21 (46.7)	5 (17.9)
Other	0	0	10 (22.2)	9 (32.1)
Tumor stage, n (%)				
IIIa	0	0	5 (11.1)	1 (3.6)
IIIb	2 (11.8)	3 (15.0)	7 (15.6)	1 (3.6)
IIIc	0	2 (10.0)	2 (4.4)	0
IV	15 (88.2)	15 (75.0)	30 (66.7)	26 (92.9)
N/A	0	0	1 (2.2)	0

1. SLD: sum of the longest diameter of the target lesions

The phase Ib expansion cohort investigating IBI110 together with sintilimab and chemotherapy involved previously untreated individuals with advanced sqNSCLC or HER-2-negative GC. By October 25, 2022, the sqNSCLC group had recruited 20 patients, including 5 (25.0%) with TNM stage III disease and 15 (75.0%) with TNM stage IV disease. The median duration of IBI110 plus sintilimab administration reached 53.1 weeks (range: 6.1–70.3), at which point 10 patients (50.0%) remained on active therapy. By March 22, 2023, the GC group comprised 17 patients, including 2 (11.8%) with TNM stage III and 15 (88.2%) with TNM stage IV disease. Liver metastases were documented in 7 patients (41.2%). In this cohort, the median treatment duration with IBI110 plus sintilimab was 16.6 weeks (range: 3.1–72.1), with 3 patients (17.6%) continuing treatment. Baseline patient characteristics across the various cohorts are detailed in **Table 1**.

PK and PD

Following treatment with IBI110, either alone or in combination with sintilimab at lower doses (0.01–1.5

mg/kg), clearance decreased with increasing dose. This pattern reflects the typical nonlinear pharmacokinetics associated with target-mediated drug disposition (TMDD). Once IBI110 doses reached or exceeded 3 mg/kg (200 mg), clearance rates stabilized, resulting in linear pharmacokinetic behavior. Immunogenicity testing for anti-drug antibodies (ADA) was performed in participants from the phase Ia and Ib escalation stages. Results indicated no clinically relevant immunogenicity across the tested dose levels, with no evidence of dose dependency.

Safety

No dose-limiting toxicities (DLTs) emerged in any dosing cohort throughout the phase Ia evaluation of IBI110 monotherapy or the phase Ib assessment of IBI110 combined with sintilimab. As a result, the maximum tolerated dose was not attained. Safety data from the escalation and expansion phases are collectively presented in **Table 2**.

Table 2. Safety overview.

Parameter	Ib expansion GC, n = 17	Ib expansion sqNSCLC, n = 20	Ib escalation n = 45	Ia escalation n = 28
Treatment-related adverse events (TRAEs), n (%)	17 (100)	20 (100)	34 (75.6)	19 (67.9)
TRAEs of Grade ≥ 3, n (%)	11 (64.7)	16 (80)	10 (22.2)	6 (21.4)
Treatment-related serious adverse events (TRSAEs), n (%)	7 (41.2)	5 (25)	5 (11.1)	4 (14.3)
TRAEs leading to dose interruption, n (%)	14 (82.4)	8 (40)	6 (13.3)	2 (7.1)
TRAEs leading to treatment discontinuation, n (%)	6 (35.3)	4 (20)	0	1 (3.6)
TRAEs leading to death, n (%)	0	0	0	0
Immune-related adverse events (irAEs), n (%)	10 (58.8)	14 (70)	14 (31.1)	3 (10.7)
irAEs of Grade ≥ 3, n (%)	3 (17.6)	4 (20)	3 (6.7)	1 (3.6)

In the phase Ia escalation group, treatment-related adverse events (TRAEs) of any severity were documented in 19 patients (67.9%), and grade ≥ 3 TRAEs occurred in 6 patients (21.4%). Adverse events led to dose interruptions in 2 patients (7.1%) and to permanent discontinuation in 1 patient (3.6%). None of the TRAEs were associated with fatal outcomes. Immune-related adverse events (irAEs) developed in 3 patients (10.7%), with one case (3.6%) classified as grade ≥ 3 .

During phase Ib dose escalation, TRAEs of any grade were recorded in 34 patients (75.6%), and grade ≥ 3 events occurred in 10 patients (22.2%). There were no instances of treatment discontinuation or death attributable to TRAEs. Immune-related adverse events were experienced by 14 patients (31.1%), among whom 3 (6.7%) had grade ≥ 3 severity.

In the phase Ib expansion involving IBI110 plus sintilimab and chemotherapy for advanced sqNSCLC or HER-2-negative GC, safety outcomes were as follows. Within the sqNSCLC group (n = 20), all patients experienced TRAEs of any grade, and 16 patients (80.0%) developed grade ≥ 3 TRAEs. These events resulted in dose interruptions for 8 patients (40.0%) and treatment discontinuation for 4 patients (20.0%). No deaths were linked to TRAEs. Immune-related adverse events occurred in 14 patients (70.0%), including 4 (20.0%) with grade ≥ 3 irAEs. For the GC group (n = 17), TRAEs of any grade affected the entire cohort (100%), while grade ≥ 3 TRAEs were observed in 11 patients (64.7%). Dose interruptions occurred in 14

patients (82.4%) and discontinuations in 6 patients (35.3%). No TRAEs led to death. Immune-related adverse events were identified in 10 patients (58.8%), including 3 patients (17.6%) with grade ≥ 3 events.

Efficacy

By the data cutoff date of January 20, 2022, IBI110 monotherapy in the phase Ia dose-escalation group (n = 28) achieved an objective response rate (ORR) of 3.6% along with a disease control rate (DCR) of 25.0% (**Figure 1a**). The sole partial response (PR) occurred in a patient diagnosed with ovarian cancer who was treated at the 3 mg/kg dose. In the phase Ib dose-escalation group, 43 of 45 participants had post-baseline tumor imaging data available. Treatment with IBI110 combined with sintilimab resulted in an ORR of 14.0% and a DCR of 67.4% (**Figure 1b**). After careful review of the safety and antitumor activity data generated during the escalation phases, the recommended phase 2 dose (RP2D) was defined as IBI110 200 mg (3 mg/kg) Q3W given concurrently with sintilimab 200 mg Q3W.

In the subsequent phase Ib expansion, the RP2D of IBI110 was evaluated in combination with sintilimab and paclitaxel plus carboplatin (TP) as initial therapy for 20 patients with previously untreated advanced squamous non-small cell lung cancer (sqNSCLC). Similarly, 17 patients with previously untreated advanced HER-2-negative gastric cancer (GC) received the RP2D of IBI110 plus sintilimab combined with capecitabine and oxaliplatin (XELOX) in the first-line setting (**Table 3**).

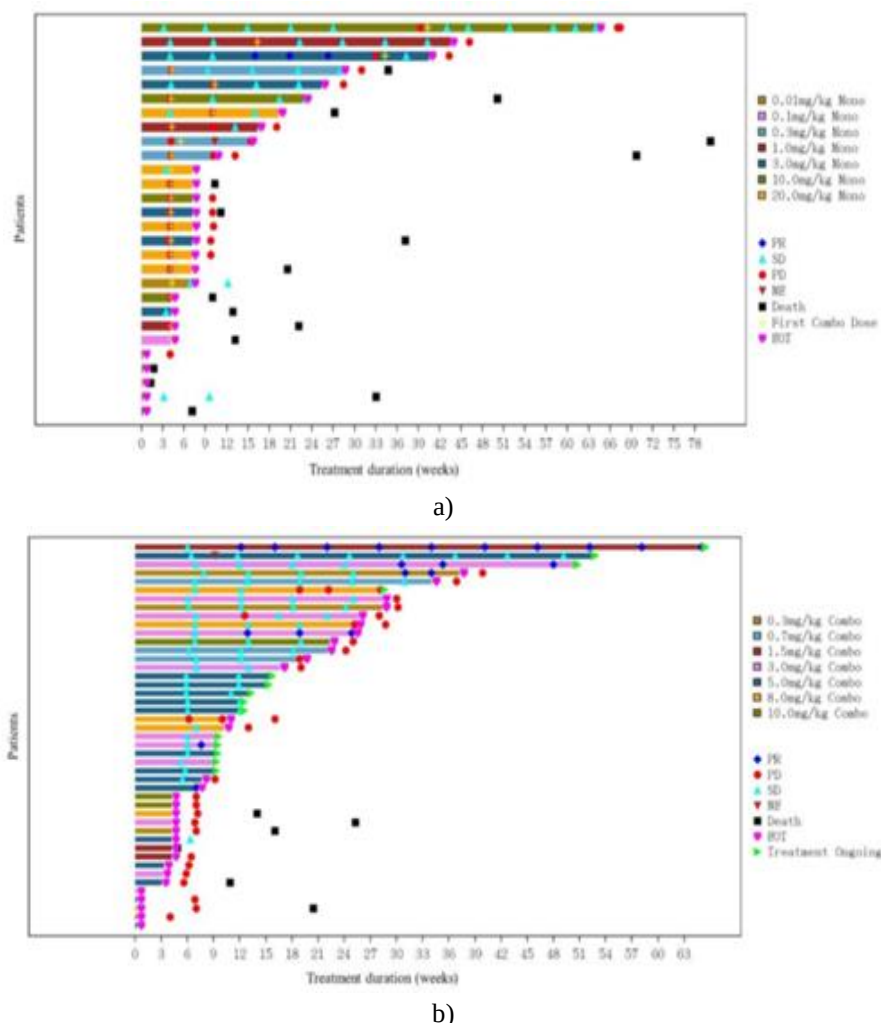


Figure 1. Waterfall plot depicting best tumor response for each patient enrolled in the phase Ia (a) and phase Ib (b) dose-escalation segments

(a) In the phase Ia portion of testing, IBI110 alone, investigator-determined best responses included partial response (PR) in a single patient and stable disease (SD) in 6 patients. Patients progressing on monotherapy were eligible to transition to the IBI110 plus sintilimab combination, during which eight patients attained stable disease. (b) For the phase Ib portion examining IBI110

plus sintilimab, 43 of 45 patients had completed at least one post-baseline tumor evaluation. Investigator-assessed best responses included partial response (PR) in 6 patients (4 with non-small cell lung cancer, 1 with small cell lung cancer, and 1 with endometrial cancer) and stable disease (SD) in 23 patients.

Table 3. Efficacy in phase Ib expansion

Endpoint	Ib expansion GC cohort (n = 17)	Ib expansion sqNSCLC cohort (n = 20)	Ib escalation IBI110 plus sintilimab (n = 43)*	Ia escalation IBI110 monotherapy (n = 28)
Confirmed best overall response, n (%)				
Partial response (PR)	12 (70.6)	15 (75.0)	3 (7.0)	1 (3.6)
Stable disease (SD)	4 (23.5)	2 (10.0)	26 (60.5)	6 (21.4)
Progressive disease (PD)	1 (5.9)	3 (15.0)	14 (32.6)	21 (75.0)
Unconfirmed ORR, % (95% CI)	88.2% (63.6–98.5)	80.0% (56.3–94.3)	14.0% (3.6–24.3)	3.6% (0–10.5)
Confirmed ORR, % (95% CI)	70.6% (44.0–89.7)	75.0% (50.9–91.3)	7.0% (0–14.6)	3.6% (0–10.5)

Disease control rate (DCR), % (95% CI)	94.1% (71.3–99.9)	85.0% (62.1–96.8)	67.4% (53.4–81.5)	25.0% (9.0–41.0)
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Note: 43 of 45 patients in phase Ib combination dose escalation had undergone at least 1 post-baseline tumor assessment as of the cutoff date

As of October 25, 2022, patients in the sqNSCLC cohort achieved unconfirmed and confirmed objective response rates (ORRs) of 80.0% (95% CI, 56.3–94.3) and 75.0% (95% CI, 50.9–91.3), respectively (**Figures 2a and 2b**). The disease control rate (DCR) was 85.0% (95% CI, 62.1–96.8). The median duration of response (DoR) had not been reached, with only 4 of 15 patients who attained confirmed responses experiencing an event. At 12

months, the DoR rate was 73.3% (95% CI, 43.6–89.1). Median progression-free survival (PFS) was not reached; 8 patients (40.0%) experienced disease progression or death. The 12-month PFS rate was 60.0% (95% CI, 35.7–77.6). Median overall survival (OS) remained unreached, with events noted in 3 patients (15%). The 12-month OS rate was 85.0% (95% CI, 60.4–94.9).

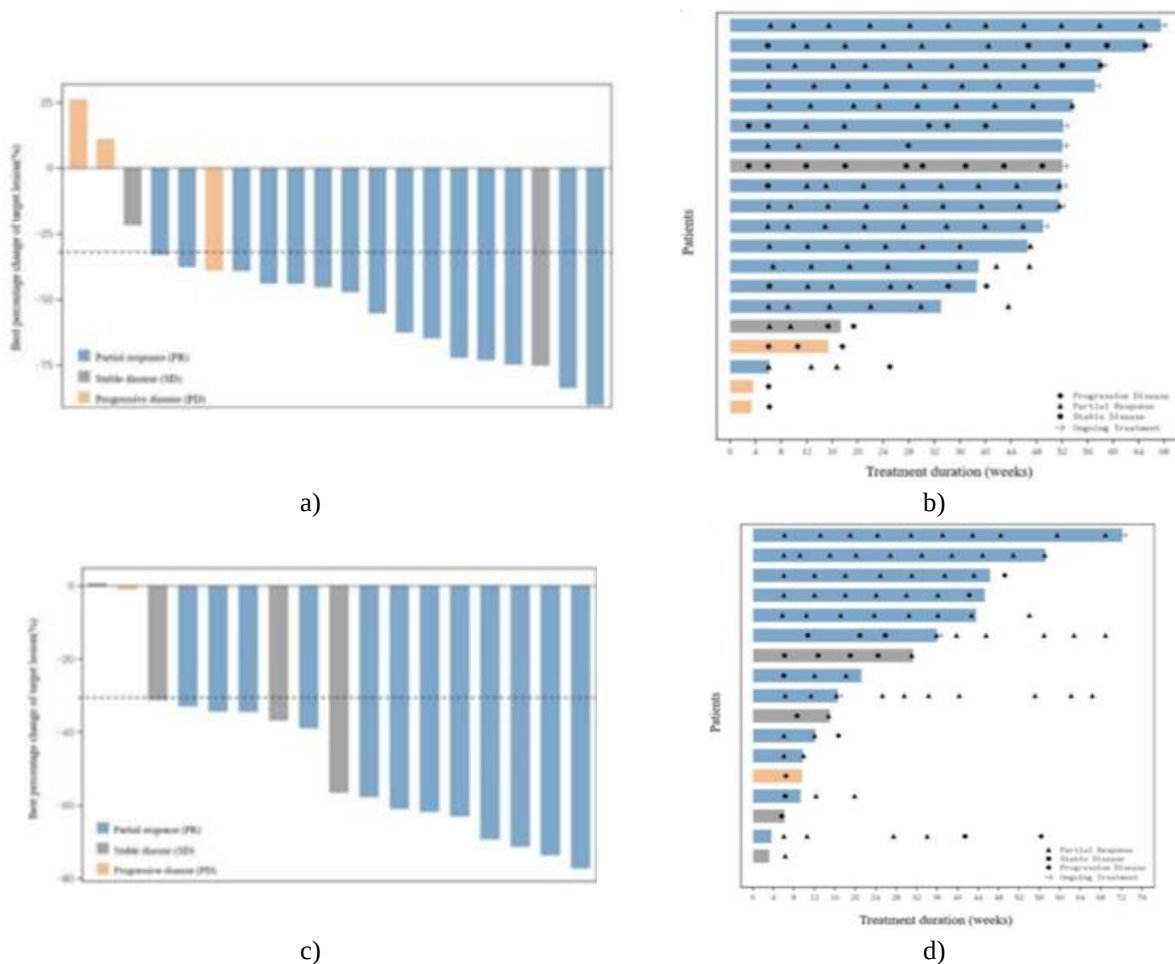


Figure 2. Antitumor efficacy of IBI110 when combined with sintilimab and chemotherapy in patients with sqNSCLC and GC

(a) Confirmed best overall response in sqNSCLC: one patient showed an 11.04% increase in the size of target lesions, and another displayed a 38.66% reduction. However, both cases were classified as progressive disease (PD) due to the appearance of new lesions, (b) Serial tumor assessments in sqNSCLC patients: one

individual presented with iUPD on the initial two evaluations and remained on treatment until iCPD was confirmed at the third assessment, (c) Confirmed best overall response in GC: one patient experienced a minimal 0.83% decrease in target lesion size, yet the overall response was progressive disease (PD) secondary

to new lesion formation, and (d) Serial tumor assessments in GC patients.

As of March 22, 2023, the GC cohort exhibited unconfirmed and confirmed objective response rates (ORRs) of 88.2% (95% CI, 63.6–98.5) and 70.6% (95% CI, 44.0–89.7), respectively (**Figures 2c and 2d**). The disease control rate (DCR) reached 94.1% (95% CI, 71.3–99.9). Median duration of response (DoR) was 10.6 months (95% CI, 2.5–14.4). After a median follow-up period of 13.1 months (95% CI, 7.1–NR), the median progression-free survival (PFS) was 12.9 months (95% CI, 3.8–15.8). Following a median follow-up of 15.8 months (95% CI, 13.4–16.6), median overall survival (OS) was 15.8 months (95% CI, 8.5–NR), with a 12-month OS rate of 70.6% (95% CI, 43.1–86.6).

In the present phase Ia/Ib clinical trial, the safety and efficacy of IBI110 were investigated in Chinese individuals with advanced solid tumors. No dose-limiting toxicities occurred in any dosing cohort during either the phase Ia monotherapy dose escalation or the phase Ib combination dose escalation with sintilimab. The recommended phase 2 dose for IBI110 was 200 mg (equivalent to 3 mg/kg), administered every 3 weeks (Q3W), either as a single agent or in combination with sintilimab at 200 mg Q3W.

Pharmacokinetic properties of IBI110 showed high similarity between monotherapy and combination with sintilimab. In patients with advanced malignancies receiving intravenous infusion, IBI110 demonstrated target-mediated drug disposition at lower doses of 0.01–1.5 mg/kg. At dose levels ≥ 3 mg/kg, exposure parameters (C_{max} and AUC) increased dose-proportionally, with stable clearance, consistent with linear pharmacokinetics. This pattern suggests the therapeutic dose range. These characteristics mirror those of relatlimab, which likewise displays target-mediated disposition at low doses and linear kinetics at higher doses [14]. LAG-3 serves as an inhibitory immune checkpoint that suppresses T-cell activation and drives T-cell exhaustion. Its soluble form (sLAG3), shed from the cell surface, provides negative regulatory feedback on immune responses. Prior research has associated baseline sLAG3 concentrations with prognosis across several malignancies [15, 16]. The current study quantified total serum sLAG3 as a marker of immune activation following therapy. Dose-dependent increases in sLAG3 levels, observed with both single-agent and combination regimens, support IBI110's capacity to stimulate immune cells. In contrast,

the RELATIVITY-020 trial involving relatlimab reported reductions in free serum sLAG3 upon treatment, indicating target occupancy, with implications distinct from the total sLAG3 assessment performed here [17].

During dose escalation, treatment-related adverse events of any severity were reported in 67.9% of participants (21.4% grades ≥ 3) in the IBI110 monotherapy arm and 75.6% (22.2% grades ≥ 3) in the combination arm—these frequencies aligned closely with those observed in trials of other LAG-3-targeted agents [11–13]. Treatment discontinuation due to adverse events was infrequent in the monotherapy escalation cohort, occurring in only one patient (3.6%). No discontinuations attributable to adverse events were recorded in the combination escalation cohort. This outcome (0%) compared favorably with higher rates documented elsewhere (14.6% for relatlimab plus nivolumab, 4.1% for ieramilimab plus spartalizumab, and 5.6% for favezelimab plus pembrolizumab) [11–13]. Safety profiles became less favorable in the phase Ib expansion stage for the squamous non-small cell lung cancer and gastric cancer cohorts, with grades ≥ 3 treatment-related adverse events affecting 80% and 64.7% of patients, respectively, and treatment discontinuation rates of 20% and 35.3%, respectively. Such increases were probably related to the incorporation of chemotherapy into the treatment regimens for these indications.

Although the overall occurrence of treatment-related adverse events was comparable, the predominant types of toxicities varied notably between studies of anti-LAG-3 antibodies. Earlier trials commonly described fatigue along with gastrointestinal side effects such as diarrhea and nausea [11–13]. In this study, patients treated with IBI110 plus sintilimab reported none of these events, whereas hepatic enzyme elevations (aspartate aminotransferase and alanine aminotransferase increases) were among the more frequent observations. Other commonly encountered treatment-related adverse events included anemia, hypothyroidism, and hypertension.

Monotherapy with IBI110 demonstrated limited antitumor activity, with a single partial response in 28 patients, yielding an objective response rate (ORR) of 3.6%. These findings align with data from earlier trials of ieramilimab and favezelimab, both of which yielded no responses when used as single agents (ORR of 0%) [12, 13]. Blockade of LAG-3 alone appears inadequate to elicit robust antitumor effects, supporting the rationale

for combined inhibition of the LAG-3 and PD-1 pathways. When IBI110 was administered alongside sintilimab in the phase Ib dose-escalation stage, an ORR of 14% was achieved among patients with diverse advanced solid tumors. This outcome is consistent with results from a separate phase I investigation of ieramilimab paired with spartalizumab, which reported an ORR of 10.7% [12]. In the setting of previously treated advanced microsatellite-stable colorectal cancer, the combination of favezelimab and pembrolizumab attained a confirmed ORR of 6.3% [13]. Notably stronger responses to dual LAG-3 and PD-1 inhibition have been documented in melanoma, a malignancy particularly responsive to immune checkpoint therapy [18]. Updated data from the RELATIVITY-047 trial showed an ORR of 43.1% with relatlimab plus nivolumab versus 32.6% with nivolumab monotherapy in patients with previously untreated unresectable or metastatic melanoma [19]. Supporting preclinical evidence from melanoma models in mice demonstrated superior tumor control and extended survival when CD8⁺ T cells lacked both PD-1 and LAG-3 [20]. Clinical studies in melanoma patients have additionally shown that relatlimab combined with nivolumab strengthens CD8⁺ T-cell receptor signaling and favors differentiation of these cells, thereby increasing their cytotoxic potential without fully reversing exhaustion [21].

In the dose-expansion cohorts, confirmed ORRs of 75% and 70.6% were achieved in patients with squamous non-small cell lung cancer (sqNSCLC) and HER-2-negative gastric cancer (GC), respectively, following treatment with IBI110, sintilimab, and chemotherapy. By comparison, the randomized phase 3 ORIENT-12 study of first-line sintilimab plus platinum-gemcitabine in advanced or metastatic sqNSCLC reported a confirmed ORR of 44.7% in the experimental arm versus 35.4% in the control arm [22]. Likewise, the phase 3 ORIENT-16 trial in untreated advanced gastric or gastroesophageal junction cancer showed an ORR of 58.2% with sintilimab plus chemotherapy compared with 48.4% for chemotherapy alone [23]. The recent open-label phase II RELATIVITY-060 study in LAG-3-positive ($\geq 1\%$) gastric/gastroesophageal junction tumors found ORRs of 48% with nivolumab, relatlimab, and chemotherapy versus 61% with nivolumab plus chemotherapy. Although no ORR advantage was observed with the triplet, subgroup analyses stratified by LAG-3 and PD-L1 status suggested potential gains in median

progression-free survival and overall survival [24]. Although response rates with IBI110 plus sintilimab and chemotherapy appear encouraging in sqNSCLC and HER-2-negative GC, direct cross-trial comparisons require careful consideration given variations in patient populations, treatment protocols, and disease entities. The potential contribution of IBI110 in specific cancers and patient subsets merits additional prospective evaluation.

Certain constraints of the current study deserve mention. Being a single-arm trial, it does not include a comparator group and involved a modest patient population. Moreover, no biomarker profiling for PD-L1 or LAG-3 expression was performed, which could have helped select individuals most likely to respond to IBI110.

Conclusion

In summary, IBI110, whether administered alone or in combination with sintilimab, demonstrated acceptable tolerability throughout the dose-escalation and expansion phases in Chinese patients with advanced solid tumors. Preliminary signs of meaningful clinical activity were noted with the combination approach. Nevertheless, larger confirmatory trials equipped with comprehensive biomarker assessments remain essential to establish its precise therapeutic utility.

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