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CLDN18.2–targeting antibody–drug conjugate IBI343 in advanced gastric or gastroesophageal junction adenocarcinoma: a phase 1 trial

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Aberrant expression of claudin18.2 (CLDN18.2) has frequently been observed in gastric and gastroesophageal junction (G/GEJ) adenocarcinoma, making it a promising therapeutic target for this aggressive cancer. While a monoclonal antibody targeting CLDN18.2 has been approved for G/GEJ adenocarcinoma, antibody–drug conjugates (ADCs) have also emerged as therapeutic modalities. IBI343 is an ADC consisting of a fully humanized anti-CLDN18.2 monoclonal antibody conjugated to exatecan via site-specific glycol conjugation and a cleavable linker with a drug-to-antibody ratio of 4. Here we present the results from a phase 1 dose escalation and dose expansion study of the IBI343 ADC. A total of 127 patients were enrolled and dosed (19 in the escalation phase and 108 in the expansion phase). Dose-limiting toxicities occurred in two of six participants at a dose of 10 mg kg^{-1}, including one with myelosuppression (grade 4) and one with both neutropenia (grade 4) and febrile neutropenia (grade 3). Minimal gastrointestinal adverse events (grade ≥3) were observed and no interstitial lung disease was reported. The recommended phase 2 dose of IBI343 was determined to be 6 mg kg^{-1} every 3 weeks with a confirmed objective response rate of 29% and median progression-free survival of 5.5 months in CLDN18.2-high (2+/3+ ≥ 75%) G/GEJ adenocarcinoma. IBI343 was well tolerated, with a manageable safety profile and promising efficacy in G/GEJ adenocarcinoma. Further research is required to understand optimal sequencing, and biomarker-informed combination therapy, in G/GEJ tumors given the development of multiple therapies targeting CLDN18.2 in addition to human epidermal growth factor receptor 2 and programmed cell death 1 ligand 1. ClinicalTrials.gov registration: NCT05458219.

Gastric cancer ranks fifth in both incidence and mortality among all cancer types worldwide, with 968,350 new cases (4.9%) and 659,853 deaths (6.8%) in 2022 (ref. 1). It remains a substantial public health challenge globally, with a particularly high disease burden observed in East Asia[2,3]. In China, gastric cancer is the fifth most common cancer type (358,700 new cases) and was the third leading cause of cancer deaths (260,400 deaths) in 2022, accounting for nearly 40% of the total incidence and mortality rates worldwide[4]. Despite recent advances in immune checkpoint inhibitors and human epidermal growth factor receptor 2 (HER2)-directed therapy, there is a substantial unmet clinical need in the treatment of unresectable or metastatic gastric and gastroesophageal junction (G/GEJ) adenocarcinoma. In most individuals who are HER2-negative and mismatch-repair-proficient, current clinical trial data report a median overall survival (OS) of 10–15 months and an objective response rate (ORR) of 45–60% for first-line therapy[5–7]. For second-line treatments, the median OS and ORR decline

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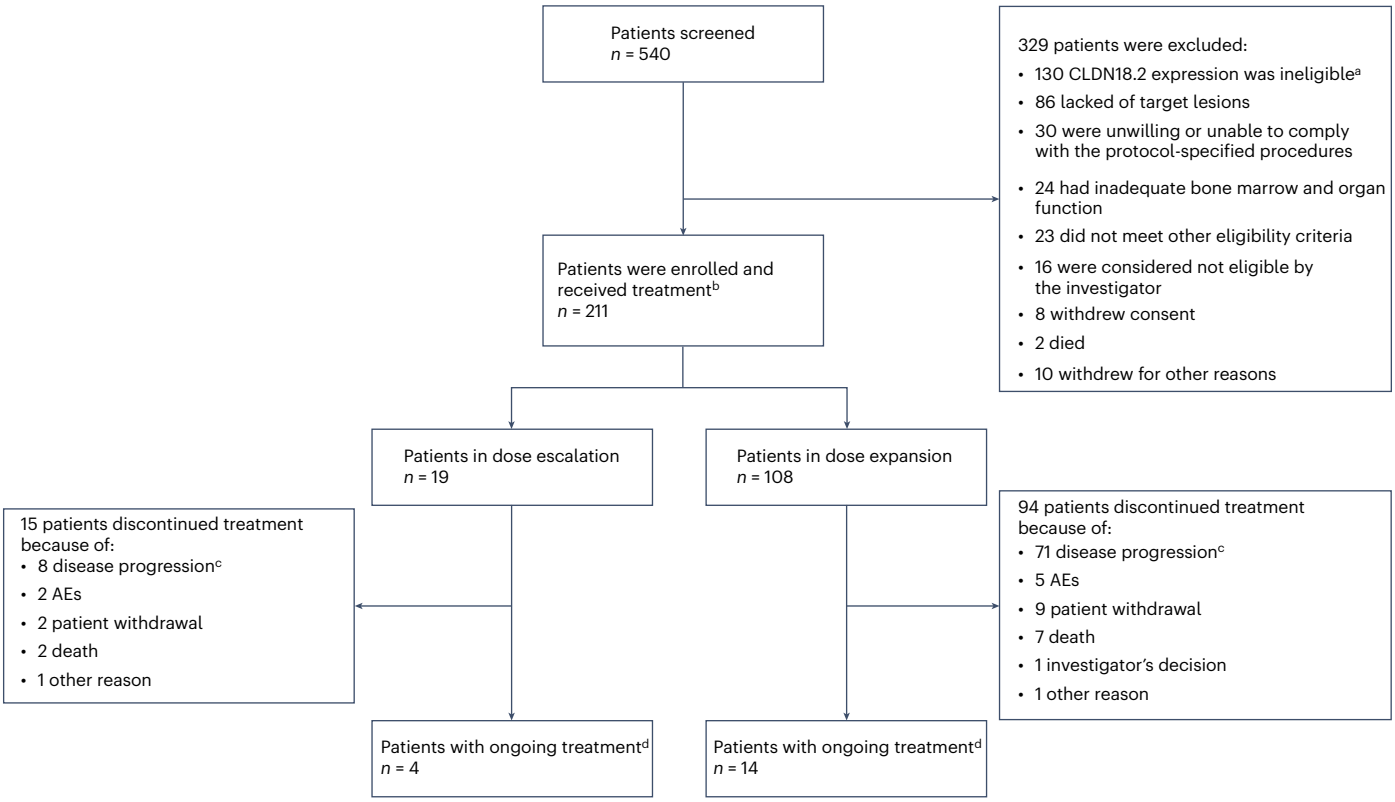

Fig. 1 | CONSORT diagram. AE, adverse events. [a]CLDN18.2-positive expression defined as 1% or more tumor cells with membranous staining of any intensity in tumor tissue using immunohistochemistry (IHC) and measured with the VENTANA CLDN18 (43-14A) IHC assay. [b]Nineteen participants from the dose escalation phase and 108 participants with G/GEJ adenocarcinoma from the dose expansion phase. [c]Participants with either disease progression or clinical deterioration. [d]As of the cutoff date of 30 June 2024.

to 5–10 months and 20–30%, respectively[8]. Few individuals proceed to receive third-line therapy or beyond, reflecting the great need for new and more effective therapies.

Claudin18.2 (CLDN18.2) is a tight junction protein that is commonly expressed in both healthy and malignant gastric mucosa[9]. Upon malignant transformation, the CLDN18.2 epitope is exposed on the tumor cell surface, leading to structural and functional damage in epithelial and endothelial cells and disrupted cell adhesion. As such, aberrant expression and overexpression of CLDN18.2 makes it an appealing therapeutic target for solid tumors, particularly gastrointestinal tumors[9]. CLDN18.2 expression occurs in approximately 80% of gastric cancers and 60% of pancreatic ductal adenocarcinomas[10]. Zolbetuximab, a monoclonal antibody (mAb) targeting CLDN18.2, was approved in Japan in March 2024 and by the US Food and Drug Administration (FDA) in October 2024 for individuals with CLDN18.2-positive (≥75% of tumor cells with moderate-to-strong CLDN18.2 membranous staining) and HER2-negative G/GEJ adenocarcinoma[11,12]. Results from two randomized, controlled, phase 3 trials—GLOW and SPOTLIGHT—indicated that zolbetuximab plus capecitabine and oxaliplatin or modified folinic acid (or levofolinate), fluorouracil and oxaliplatin regimen significantly improved progression-free survival (PFS) and OS in individuals with CLDN18.2-positive, HER2-negative G/GEJ adenocarcinoma[13–15]. In addition, other treatments targeting CLDN18.2, including bispecific antibodies[16,17], chimeric antigen receptor (CAR) T cells[18,19] and antibody–drug conjugates (ADCs)[20] have also shown potential in treating individuals with CLDN18.2-positive G/GEJ adenocarcinoma and pancreatic ductal adenocarcinoma in phase 1 studies. ADCs integrate the targeting capabilities of the mAb and the cytotoxic effects of the payload to deliver targeted therapy directly to cancer cells, thus achieving precise and potent antitumor activity[21]. Currently, several ADCs targeting HER2, trophoblast cell surface antigen 2 and nectin cell adhesion molecule 4 have been developed, with promising efficacy across different tumors[20]. However, hematological toxicities related to the payload and life-threatening interstitial lung disease (ILD) are commonly reported toxicities of currently approved first-generation ADCs that affect the durability of therapy and the quality of life of individuals[20].

IBI343 is a fully humanized anti-CLDN18.2 mAb conjugated to exatecan (a topoisomerase inhibitor payload) via site-specific glycol conjugation and a cleavable linker with a drug-to-antibody ratio (DAR) of 4 (refs. 22,23). As a next-generation ADC, IBI343 features unique IgG1 Fc silencing, which attenuates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)[22,23]. Here we report the clinical results of IBI343, including safety, efficacy and pharmacokinetics, from the phase 1 dose escalation in participants with advanced solid tumors and the dose expansion study of IBI343 monotherapy in participants with G/GEJ adenocarcinoma.

Results

Participants and treatment

The first participant was enrolled on 26 October 2022 and the study is ongoing. As of 30 June 2024, 540 patients were screened and 211 patients were enrolled to receive IBI343 monotherapy. Most screening failures were due to CLDN18.2 expression. This Article includes 19 participants from the dose escalation phase and 108 participants with G/GEJ adenocarcinoma from the dose expansion phase (Fig. 1). During dose escalation (Extended Data Table 1), 19 participants received IBI343 monotherapy intravenously at a dose of 0.3 mg kg^{-1} ($n = 1$), 1 mg kg^{-1} ($n = 1$), 3 mg kg^{-1} ($n = 5$), 6 mg kg^{-1} ($n = 3$), 8 mg kg^{-1} ($n = 3$) or 10 mg kg^{-1} ($n = 6$) once every 3 weeks (Q3W). During dose expansion, 108 participants with G/GEJ adenocarcinoma received IBI343 monotherapy intravenously at a dose of 6 mg kg^{-1} ($n = 60$), 8 mg kg^{-1}

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Table 1 | Baseline characteristics of participants

	Dose escalation	Dose expansion			
	0.3–10 mg kg^{-1} (*n*=19)	6 mg kg^{-1} (*n*=60)	8 mg kg^{-1} (*n*=32)	Other (*n*=16)	Total (*n*=108)
Age (years)					
Median	59	55.5	59.5	58.5	57
Range (min–max)	44–84	25–80	33–77	31–73	25–80
Sex, *n* (%)					
Male	8 (42.1)	37 (61.7)	20 (62.5)	10 (62.5)	67 (62.0)
Female	11 (57.9)	23 (38.3)	12 (37.5)	6 (37.5)	41 (38.0)
Ethnicity, *n* (%)					
East Asian	13 (68.4)	60 (100)	31 (96.9)	16 (100)	107 (99.1)
White	6 (31.6)	0	1 (3.1)	0	1 (0.9)
Eastern Cooperative Oncology Group, *n* (%)					
PS 0	1 (5.3)	8 (13.3)	8 (25.0)	2 (12.5)	18 (16.7)
PS 1	18 (94.7)	52 (86.7)	24 (75.0)	14 (87.5)	90 (83.3)
CLDN18.2 expression, *n* (%)[a]					
Low (2+/3+ < 40%)	2 (22.2)	8 (14.3)	0	2 (14.3)	10 (10.0)
Moderate (2+/3+: 40–74%)	3 (33.3)	17 (30.4)	12 (40.0)	4 (28.6)	33 (33.0)
High (2+/3+ ≥ 75%)	4 (44.4)	31 (55.4)	18 (60.0)	8 (57.1)	57 (57.0)
Missing	10	4	2	2	8
Tumor type, *n* (%)					
Gastric cancer	8 (42.1)	54 (90.0)	28 (87.5)	13 (81.3)	95 (88.0)
GEJ cancer	0	6 (10.0)	4 (12.5)	3 (18.8)	13 (12.0)
Other	11 (57.9)	0	0	0	0
Common sites of metastasis, *n* (%)					
Distant lymph nodes	8 (42.1)	38 (63.3)	21 (65.6)	5 (31.3)	64 (59.3)
Peritoneum	10 (52.6)	29 (48.3)	10 (31.3)	4 (25.0)	43 (39.8)
Liver	9 (47.4)	22 (36.7)	15 (46.9)	3 (18.8)	40 (37.0)
Prior treatment lines, *n* (%)					
First-line	4 (25.0)	13 (21.7)	12 (37.5)	4 (25.0)	29 (26.9)
Second-line	8 (50.0)	24 (40.0)	13 (40.6)	9 (56.3)	46 (42.6)
Third-line and beyond	4 (25.0)	23 (38.3)	7 (21.9)	3 (18.8)	33 (30.6)
Missing	3	0	0	0	0

[a]CLDN18.2: positive expression defined as 1% or more tumor cells with membranous staining of any intensity in tumor tissue identified using IHC and measured with the VENTANA CLDN18 (43-14A) IHC assay. CLDN18.2 expression levels were categorized based on central laboratory measurement. Eight participants in the dose expansion phase were classified as missing; all exhibited moderate-to-high CLDN18.2 expression (2+/3+ ≥ 40%) as measured using local testing and were deemed eligible to enroll. PS, performance status.

(*n* = 32) and other dose levels (*n* = 16). The baseline characteristics of participants enrolled in the dose escalation and dose expansion phases are shown in Table 1.

In the dose expansion cohorts with G/GEJ adenocarcinoma (Table 1), CLDN18.2 expression status could be evaluated in 100 of 108 participants as measured using the Ventana CLDN18 (43-14A) IHC assay[24]. Of these participants, 57 (57.0%) had high expression (2+/3+ ≥ 75%), 33 (33.0%) had moderate expression (2+/3+: 40–74%) and 10 (10.0%) had low expression (2+/3+ < 40%). For all participants with G/GEJ adenocarcinoma (*n* = 116, including eight participants with gastric cancer from the dose escalation phase), the median treatment duration was 18.0 weeks (range = 3.0–64.0).

Safety

Safety was assessed as a primary endpoint. During dose escalation, dose-limiting toxicity (DLT) was evaluated in 17 of 19 participants. One participant discontinued the study due to consent withdrawal and one participant had a thromboembolism and was deemed as DLT unevaluable by the safety evaluation team. No DLTs were observed at the dose levels of 0.3 mg kg^{-1} (*n* = 1), 1 mg kg^{-1} (*n* = 1), 3 mg kg^{-1} (*n* = 3), 6 mg kg^{-1} (*n* = 3) and 8 mg kg^{-1} (*n* = 3); DLTs were observed in two of six participants treated at 10 mg kg^{-1}, including one participant with myelosuppression (grade 4) and one participant with both neutropenia (grade 4) and febrile neutropenia (grade 3). The maximum tolerated dose (MTD) of IBI343 monotherapy was determined to be 8 mg kg^{-1}.

The safety profiles of participants with G/GEJ adenocarcinoma are presented in Tables 2 and 3. Among all participants with G/GEJ adenocarcinoma (*n* = 116, including eight participants with gastric cancer from the dose escalation phase), treatment-emergent adverse events (TEAEs) occurred in 113 participants (97.4%) while 77 participants (66.4%) had grade 3 and higher TEAEs. Treatment-related adverse events (TRAEs) occurred in 107 participants (92.2%) while 61 participants (52.6%) had grade 3 and higher TRAEs. The most common TEAEs (≥35%) were a decrease in white blood cell count (67.2%, including 25.9% with grade 3 and higher TEAEs), anemia (64.7%, including 16.4% with grade 3 and higher TEAEs), a decrease in neutrophil count (58.6%,

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Table 2 | Safety profile of IBI343 in participants with G/GEJ adenocarcinoma

AEs, *n* (%)	6 mg kg^{-1} (*n*=62)	8 mg kg^{-1} (*n*=34)	Total (*n*=116)[a]
TEAE	62 (100)	34 (100)	113 (97.4)
TEAE grade ≥3	39 (62.9)	28 (82.4)	77 (66.4)
TRAE	61 (98.4)	31 (91.2)	107 (92.2)
TRAE grade ≥3	26 (41.9)	27 (79.4)	61 (52.6)
TEAE leading to dose interruption	33 (53.2)	21 (61.8)	62 (53.4)
TRAE leading to dose interruption	24 (38.7)	17 (50.0)	48 (41.4)
TEAE leading to dose reduction	5 (8.1)	11 (32.4)	19 (16.4)
TRAE leading to dose reduction	4 (6.5)	11 (32.4)	18 (15.5)
TEAE leading to permanent discontinuation	4 (6.5)	2 (5.9)	6 (5.2)
TRAE leading to permanent discontinuation	0	1 (2.9)	1 (0.9)
TEAE leading to death	3 (4.8)	3 (8.8)	7 (6.0)
TRAE leading to death	0	0	0

[a]Eight participants with gastric cancer from the dose escalation phase were included, with two participants treated at a dose of 6 mg kg^{-1}, two participants treated at a dose of 8 mg kg^{-1} and four participants treated at a dose of 10 mg kg^{-1}.

including 28.4% with grade 3 and higher TEAEs), decreased appetite (46.6%, including 2.6% with grade 3 and higher TEAEs), nausea (41.4%, including 1.7% with grade 3 and higher TEAEs), hypoalbuminemia (37.9%, all grade 1–2) and a decrease in platelet count (35.3%, including 5.2% with grade 3 and higher TEAEs). Other common TEAEs (≥20%) are presented in Table 3. No ILD of any grade was observed.

In all participants with G/GEJ adenocarcinoma, TEAEs and TRAEs leading to dose interruption occurred in 62 (53.4%) participants and 48 (41.4%) participants, respectively. TEAEs and TRAEs leading to dose reduction occurred in 19 (16.4%) and 18 (15.5%) participants, respectively. TEAEs and TRAEs leading to treatment discontinuation occurred in six (5.2%) participants and one (0.9%) participant, respectively. TEAEs leading to death occurred in seven (6.0%) participants with none deemed to be treatment-related. As presented in Tables 2 and 3, compared to a dose of 6 mg kg^{-1}, numerically higher incidences of grade 3 and higher TEAEs (82.4% versus 62.9%) and TRAEs (79.4% versus 41.9%) were observed at a dose of 8 mg kg^{-1}. Participants treated at a dose of 8 mg kg^{-1} also had numerically higher incidences of grade 3 and higher hematological toxicities than a dose of 6 mg kg^{-1}, including a decreased white blood cell count (41.2% versus 19.4%), anemia (32.4% versus 8.1%) and a decreased neutrophil count (47.1% versus 22.6%).

Efficacy

The ORR and disease control rate (DCR) of IBI343 were evaluated in the evaluable population. This population included participants who completed two cycles of treatment and had at least one tumor assessment after the first dose of the study drug, or who prematurely discontinued the study drug because of disease progression, death or an AE. Table 4 shows the best overall response in participants with G/GEJ adenocarcinoma with high expression of CLDN18.2 (2+/3+ ≥ 75%) treated at doses of 6 mg kg^{-1} and 8 mg kg^{-1} as well as their prior treatment histories.

At a dose of 6 mg kg^{-1}, 31 participants with high expression of CLDN18.2 were evaluated. Among them, 15 had partial responses (PRs), including nine participants with confirmed PRs and one participant awaiting confirmation (Fig. 2a). The unconfirmed and confirmed ORRs were 48.4% (95% confidence interval (CI) = 30.2–66.9) and 29.0% (95% CI = 14.2–48.0), respectively. The DCR was 90.3% (95% CI = 74.2–98.0). In nine participants with a confirmed response (Fig. 2b), the median duration of response (DOR) was 5.6 months (95% CI = 2.8–7.0). The subgroup analyses of confirmed ORRs are shown in Extended Data Fig. 1. In participants with G/GEJ adenocarcinoma with high CLDN18.2 expression treated at a dose of 6 mg kg^{-1} (n = 31), the median follow-up was 10.6 months (95% CI = 9.7–11.5) for PFS and OS (Extended Data Figs. 2 and 3). The median PFS was 5.5 months (95% CI = 4.1–7.0). OS data were not mature with the current median OS of 10.8 months (95% CI = 6.8–NC) and events occurring in 48.4% of participants. After the data cutoff, the response of the remaining one participant was confirmed on 26 July 2024; the confirmed ORR was updated to 32.3% (95% CI = 16.7–51.4).

At a dose of 8 mg kg^{-1}, 17 participants with high expression of CLDN18.2 were evaluated. Among them, nine had PRs, including eight participants with confirmed PR (Fig. 2c). As shown in Table 4, the unconfirmed and confirmed ORRs were 52.9% (95% CI = 27.8–77.0) and 47.1% (95% CI = 23.0–72.2), respectively. The DCR was 88.2% (95% CI = 63.6–98.5). In eight participants with a confirmed response (Fig. 2d), the median DOR was 5.7 months (95% CI = 2.7–NC). The subgroup analyses of the confirmed ORRs are shown in Extended Data Fig. 4. Of all participants with G/GEJ adenocarcinoma with high CLDN18.2 expression treated at a dose of 8 mg kg^{-1} (n = 19, including one participant from the dose escalation phase and 18 participants from the dose expansion phase), the median follow-up was 8.1 months (95% CI = 7.6–8.5) for PFS and OS (Extended Data Figs. 2 and 3). The median PFS was 6.8 months (95% CI = 2.8–7.5); the median OS was not reached, with events occurring in 36.8% participants.

Efficacy of IBI343 in participants with G/GEJ adenocarcinoma with moderate (2+/3+: 40–74%) and moderate-to-high (2+/3+ ≥ 40%) expression of CLDN18.2 are shown in Extended Data Table 2. For participants with moderate-to-high expression of CLDN18.2 (2+/3+ ≥ 40%) that could be evaluated, the ORR was 38.8% (95% CI = 25.2–53.8) at a dose of 6 mg kg^{-1} (n = 49, including one participant from the dose escalation phase and 48 patients from the dose expansion phase) with a confirmed response in 13 of 19 responders; it was 44.8% (95% CI = 26.4–64.3) at a dose of 8 mg kg^{-1} (n = 29, excluding one participant from the dose escalation phase without a target lesion), with a confirmed response in 12 of 13 responders. Ten participants in the dose expansion had low expression of CLDN18.2 (2+/3+: 1–39%). However, no response was observed in these participants. For all patients with G/GEJ adenocarcinoma that could be evaluated, the best changes in the target lesions are shown in Extended Data Fig. 5.

Clinical pharmacology

IBI343 demonstrated linear pharmacokinetics (PK) across the dose range of 0.3–10 mg kg^{-1} with no evidence of target-mediated drug disposition. At the proposed dose of 6 mg kg^{-1} Q3W, the half-life was approximately 2 weeks, supporting the 3-week dosing interval. The stability of the linker payload was demonstrated by (1) molar ratios of the IBI343 peak (C_{max}) and the trough (C_{trough}) concentrations to the free payload exceeding more than 60-fold and more than 100-fold at a dose of 6 mg kg^{-1}, respectively; (2) near-constant DAR in cynomolgus macaques over 21 days after dosing (versus a 69% DAR decline (average DAR from 7–8 to 2.5 at day 21) for trastuzumab deruxtecan in monkeys[25]); and (3) a strong correlation ($r \geq 0.85$) between ADC and total antibody (TAB) exposure metrics (C_{max}, area under the curve, C_{trough}) in participants, confirming minimal payload loss in vivo. This high ADC–TAB correlation—driven by DAR stability and limited payload dissociation—allowed interchangeable use of TAB as a surrogate exposure marker for exposure–response analyses, simplifying bioanalysis and modeling. Importantly, the sustained DAR ensured that each antibody efficiently delivered its payload

Table 3 | Common TEAEs (≥20%) of IBI343 in participants with G/GEJ adenocarcinoma

Preferred terms, *n* (%)	6 mg kg^{-1} (*n*=62)		8 mg kg^{-1} (*n*=34)		Total (*n*=116)[a]	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
White blood cell count decreased	41 (66.1)	12 (19.4)	27 (79.4)	14 (41.2)	78 (67.2)	30 (25.9)
Anemia	39 (62.9)	5 (8.1)	25 (73.5)	11 (32.4)	75 (64.7)	19 (16.4)
Neutrophil count decreased	34 (54.8)	14 (22.6)	26 (76.5)	16 (47.1)	68 (58.6)	33 (28.4)
Appetite decreased	26 (41.9)	3 (4.8)	19 (55.9)	0	54 (46.6)	3 (2.6)
Nausea	27 (43.5)	1 (1.6)	16 (47.1)	1 (2.9)	48 (41.4)	2 (1.7)
Hypoalbuminemia	27 (43.5)	0	14 (41.2)	0	44 (37.9)	0
Platelet count decreased	26 (41.9)	4 (6.5)	12 (35.3)	2 (5.9)	41 (35.3)	6 (5.2)
Aspartate aminotransferase increased	15 (24.2)	0	11 (32.4)	2 (5.9)	31 (26.7)	2 (1.7)
Weight decreased	16 (25.8)	2 (3.2)	8 (23.5)	1 (2.9)	30 (25.9)	3 (2.6)
Hypokalemia	15 (24.2)	4 (6.5)	10 (29.4)	1 (2.9)	29 (25.0)	6 (5.2)
Vomiting	17 (27.4)	1 (1.6)	9 (26.5)	1 (2.9)	29 (25.0)	3 (2.6)
Alanine aminotransferase increased	14 (22.6)	4 (6.5)	8 (23.5)	1 (2.9)	27 (23.3)	5 (4.3)
Constipation	11 (17.7)	0	8 (23.5)	0	24 (20.7)	0

[a]Eight participants with gastric cancer from the dose escalation phase were included, with two participants treated at a dose of 6 mg kg^{-1}, two participants treated at a dose of 8 mg kg^{-1} and four participants treated at a dose of 10 mg kg^{-1}.

to target tissues, maximizing target engagement and therapeutic efficacy while minimizing off-tumor toxicity—a dual mechanism that enhances the therapeutic index.

Population PK simulations demonstrated continuous and dose-proportional exposure across a dosage range of 3–10 mg kg^{-1} Q3W, forming a broad and continuous exposure spectrum. This expansive exposure distribution provided a robust foundation for characterizing exposure–response relationships and guiding dose selection. PK profiles for TAB and payload were well characterized by two-compartment models with linear clearance, the latter incorporating a first-order conversion rate from ADC to payload. No demographic or clinical covariates (for example, age, sex, CLDN18 expression, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine clearance) significantly influenced ADC, TAB or payload PK. The absence of time-dependent PK variability, coupled with sustained clinical efficacy and safety across cycles, suggested a negligible immunogenicity impact on PK, safety or efficacy.

As shown in Extended Data Fig. 6a–d, the TAB exposure metrics (C_{max}, area under the curve, C_{trough}) significantly correlated with G3 hematological toxicities, these commonly being leukopenia, anemia and neutropenia as well as gastrointestinal disorders, with a relatively flat exposure–safety relationship at doses ≤6 mg kg^{-1} and a steep toxicity increase at doses >6 mg kg^{-1}. Efficacy analyses demonstrated a plateau in response rates in the 3–6 mg kg^{-1} dose range (Extended Data Fig. 6e), whereas disease control was exposure-dependent and maximized at a dose of 6 mg kg (Extended Data Fig. 6f), providing justification for the choice of 6 mg kg^{-1} as the recommended phase 2 dose (RP2D).

Integrated PK, exposure–response, safety and efficacy data supported a dose of 6 mg kg^{-1} Q3W as the RP2D, balancing sustained therapeutic exposure, manageable toxicity and maximized clinical benefit. Immunogenicity risk was low based on stable exposure and clinical outcomes. Phased anti-drug antibody monitoring will further validate this profile.

Table 4 | Efficacy of IBI343 in participants with G/GEJ adenocarcinoma and high expression of CLDN18.2 (2+/3+ ≥ 75%)

Efficacy in the evaluable population[a]	6 mg kg^{-1} (*n*=31)	8 mg kg^{-1} (*n*=17)[b]
Prior irinotecan, *n* (%)	6 (19.4)	5 (29.4)
Prior immunotherapy, *n* (%)	28 (90.3)	12 (70.6)
Prior gastrectomy, *n* (%)	14 (45.2)	8 (47.1)
Best overall response, *n* (%)		
PR[c]	15 (48.4)	9 (52.9)
SD	13 (41.9)	6 (35.3)
PD	3 (9.7)	1 (5.9)
Not assessed[d]	0	1 (5.9)
Unconfirmed ORR (95% CI)	48.4% (30.2–66.9)	52.9% (27.8–77.0)
Confirmed ORR (95% CI)	29.0% (14.2–48.0)	47.1% (23.0–72.2)
DCR (95% CI)	90.3% (74.2–98.0)	88.2% (63.6–98.5)

[a]Efficacy in the evaluable population included participants who completed two cycles of treatment and had at least one tumor assessment after the first dose of the study drug, or who prematurely discontinued the study drug because of disease progression, death or an AE. [b]Nineteen participants were treated at a dose of 8 mg kg^{-1}. Among them, one participant from the dose escalation phase without target lesions, and one participant from the dose expansion phase, had a short treatment duration without tumor assessment after baseline before the data cutoff; therefore, they were not included in the evaluable population (*n*=17). [c]PR confirmed in nine of 15 participants treated at a dose of 6 mg kg^{-1}, and in eight of nine participants treated at a dose of 8 mg kg^{-1}. [d]One participant was not assessed for tumor response because of sudden death unrelated to cancer. PD, progressive disease; SD, stable disease.

Discussion

The development of therapies targeting CLDN18.2 has increased rapidly over the last few years with the clinical development of mAbs, bispecific antibodies, ADCs and CAR T cells[9]. In this study, we report a next-generation CLDN18.2-targeting ADC, IBI343, which demonstrated a manageable safety profile and promising efficacy in a phase 1 study. Despite the numerically higher ORR and longer PFS observed at a dose of 8 mg kg^{-1}, the safety profile at a dose of 6 mg kg^{-1} was more favorable with significantly lower rates of treatment interruption and discontinuation (occurring at 38.7% and 6.5% at a dose of 6 mg kg^{-1} versus 50% and 32.4%, respectively at the higher dose of 8 mg kg^{-1}). During the clinical pharmacology analysis, the exceptional DAR stability of IBI343—reinforced by interchangeable ADC/TAB exposure metrics—positions it as a next-generation ADC with antibody-like PK and a widened therapeutic index. Considering the safety, efficacy and clinical pharmacology

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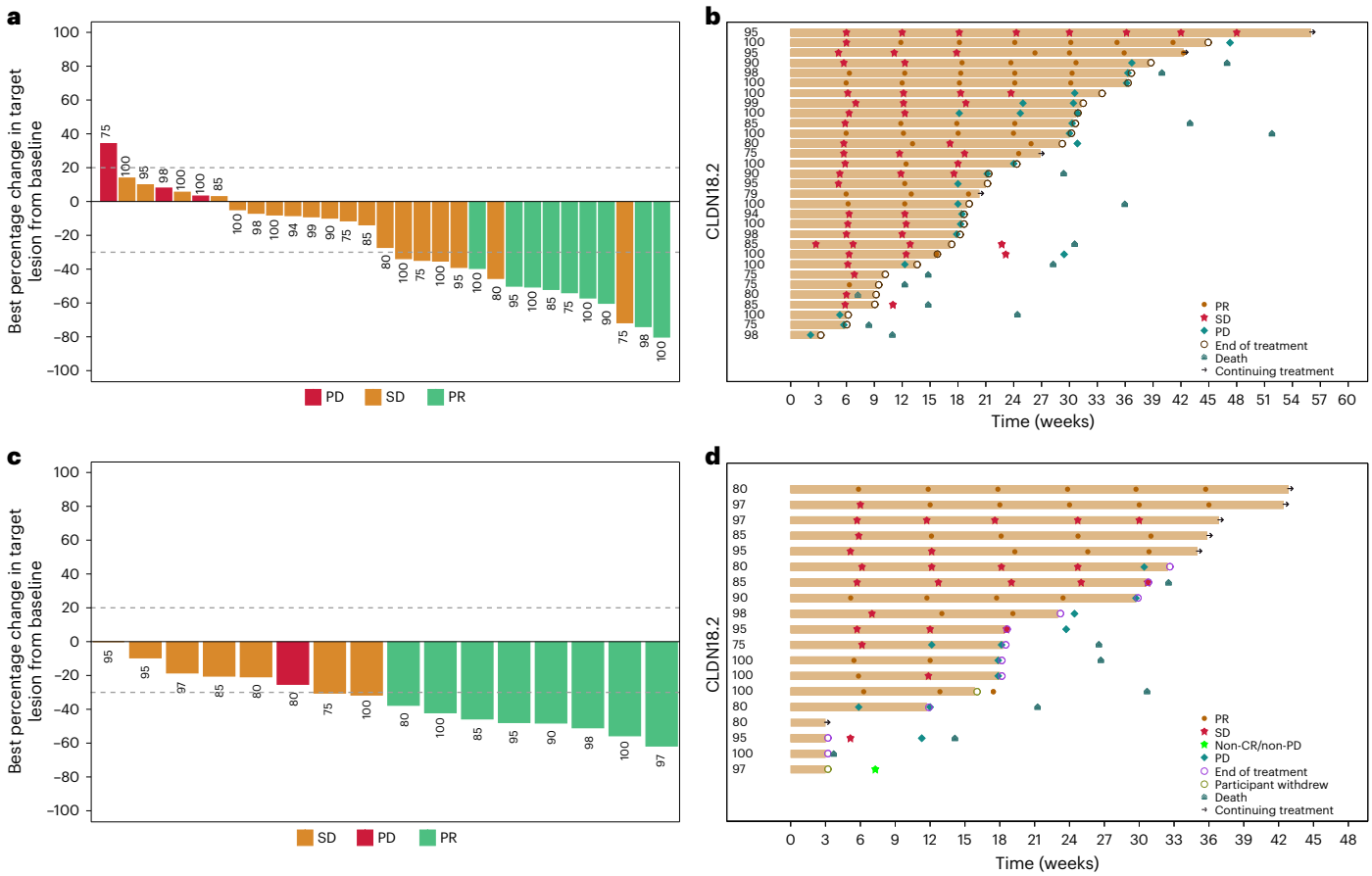

Fig. 2 | Efficacy of IBI343 in participants with G/GEJ adenocarcinoma with high expression of CLDN18.2 (≥75%). a, Waterfall plot showing the best change in target lesion in evaluable participants treated at a dose of 6 mg kg^{-1} (n = 31). The percentage of CLDN18.2 expression is indicated for each participant; PR indicates participants with a confirmed response. **b**, Swimmer plot showing the duration of treatment and the timing of the tumor response of each participant treated at a dose of 6 mg kg^{-1} (n = 31). The percentage of CLDN18.2 expression is indicated for each participant. **c**, Best change in target lesion in evaluable participants treated at a dose of 8 mg kg^{-1} (n = 16, excludes one participant in the evaluable population who died before tumor assessment). The percentage of CLDN18.2 expression is indicated for each participant. PR indicates participants with a confirmed response. **d**, Swimmer plot showing the duration of treatment and the timing of the tumor response of each participant during the study (n = 19, includes one participant from the dose escalation phase and 18 participants from the dose expansion phase) treated at a dose of 8 mg kg^{-1}. The percentage of CLDN18.2 expression is indicated for each participant. CR, complete response.

data, a dose of 6 mg kg^{-1} was selected as the RP2D of IBI343 to ensure treatment tolerance and the durability of the therapy. Our preliminary results reinforce the paradigm of CLDN18.2 as a validated and important therapeutic target in the treatment of upper gastrointestinal cancers and the importance of quantitative CLDN18.2 testing as a biomarker to guide treatment selection.

On-target, off-tumor toxicities relating to CLDN18.2 therapies frequently include nausea and vomiting because of organ-specific expression of CLDN18.2 in the stomach; these are particularly problematic for individuals with G/GEJ adenocarcinomas. In the phase 2a MONO study of zolbetuximab monotherapy in individuals with advanced G/GEJ adenocarcinoma or esophageal adenocarcinoma, the most common TEAEs were nausea (63%, including 15% G3–4) and vomiting (57%, including 22% G3–4) while 20% of participants discontinued because of TEAEs[26]. Per protocol, mandatory prophylactic antiemetics were not required in the MONO study. In the phase 3 GLOW trial, zolbetuximab plus capecitabine and oxaliplatin showed a similar safety profile, with the most common TEAEs being nausea (68.5%, including 8.7% ≥G3) and vomiting (57%, including 12.2% ≥G3)[13]. These gastrointestinal AEs may in part be associated with ADCC or CDC, induced by the functional active Fc regions of CLDN18.2 mAbs[9]. IBI343 is the first CLDN18.2-targeting ADC that features a Fc-silenced design to reduce on-target, off-tumor gastrointestinal toxicities[22,23]. The glycan-based conjugation technology enables IBI343 to achieve site-specific conjugation of its payload to the *N*-glycans (N297) of the anti-CLDN18.2 antibody, thereby strategically reducing the binding affinity of IBI343 to Fc gamma receptors and significantly decreasing the induction of ADCC and CDC activities[22,23].

There are important difference in the design of the ADC in the recently published phase 1 trial of CLDN18.2-targeting ADC CMG901 in patients with G/GEJ cancer[27] compared to IBI343. Unlike IBI343, which is Fc-silenced with a topoisomerase payload, CMG901 is non-Fc-silenced with a microtubule-disrupting monomethyl auristatin E payload[27]. Common TEAEs in the dose expansion phase of CMG901 were vomiting (36% G1–2, 10% G3+) and nausea (53% G1–2, 4% G3) despite mandatory six-drug prophylaxis, including dexamethasone, neurokinin-1 receptor antagonist, 5-hydroxytryptamine type 3 receptor antagonist (5-HT3) receptor antagonist and H_1 and H_2 antagonists[20,27]. In contrast, numerically lower rates of nausea and vomiting (25% any grade of vomiting, 2.6% G3+, 41% any grade of nausea, 1.7% G3+) were seen for IBI343 despite the exatecan topoisomerase payload, which contributes to gastrointestinal toxicity. The lower rates of gastrointestinal side effects observed with IBI343 may relate to the recommended four-drug antiemetic prophylaxis (neurokinin-1 receptor antagonist, 5-HT3 receptor antagonist, dexamethasone and proton pump inhibitor), or the unique Fc silencing design of IBI343. Given the prevalence of nausea and vomiting in CLDN18.2-directed therapies, aggressive and proactive management with antiemetics during administration is

important to ensure tolerability, especially when given in combination with chemotherapy.

Safety profiles across IBI343 and other ADCs are reflective of both payload and antibody-directed, on-target toxicities. Hypoalbuminemia, another known on-target toxicity occurred in 37.9% of participants without grade 3 or higher events, compared to 61% of participants in the CMG901 trial. In our study, only 5% participants discontinued IBI343 because of a TEAE. The most common TEAE was exatecan-payload-related hematological toxicity[28,29], including decreased white blood cell count (67.2%), anemia (64.7%) and neutropenia (58.6%). Importantly, granulocyte colony-stimulating factor was not given prophylactically but was used to manage participants experiencing significant neutropenia affecting dosing intensity. Unlike other ADCs, ILD was not observed in our study to date with a median time on treatment of 4.5 months. As reported in a pooled analysis of trastuzumab deruxtecan monotherapy studies, overall incidence of drug-related ILD or pneumonitis was 15.4%, including 3.5% with G3 and higher events[28], with a median time to adjudicated ILD onset of 5.4 months (range: <0.1–46.8 months). With the non-Fc-silenced CMG901 molecule, 6% of participants experienced G1–2 pneumonitis[27]. Although a longer follow-up is required, no cases of late ILD have been observed to date in this trial. This suggests the importance of Fc silencing as an important mechanism to reduce on-target, off-tumor toxicities that can be potentially life-threatening and dose-limiting, as observed across ADCs independent of the antibody target.

In participants with G/GEJ adenocarcinoma in the expansion phase of the trial with high expression of CLDN18.2 (2+/3+ ≥ 75%), with the same cutoff and assay which was used in the zolbetuximab trials, IBI343 monotherapy showed promising efficacy signals that were superior compared to benchmark efficacy of second-line and third-line chemotherapy. Notably, more than 70% participants in our study had prior two (42.6%) or three or more (30.6%) lines of treatment at enrollment. In third-line settings and beyond, IBI343 compared favorably against trifluridine and tipiracil (ORR of 4% and median PFS of 2.0 months)[30] and nivolumab (ORR of 11.2% and median PFS of 1.6 months)[31]. As for other treatments targeting CLDN18.2, zolbetuximab monotherapy had an ORR of 9% in participants with G/GEJ adenocarcinoma with moderate-to-strong CLDN18.2 expression (≥50%) in the phase 2a study[26]. The successful outcomes of the GLOW and SPOTLIGHT trials led to the approval of the zolbetuximab plus chemotherapy regimen in Japan and FDA approval in October 2024 for first-line treatment of gastric cancer, validating the rationale of targeting CLDN18.2 (refs. 13,14). As for CMG901, despite differences in the definition of CLDN positivity and the IHC assay used, comparable efficacy was observed in 107 participants treated in dose expansion between 2.2 and 3.0 mg kg^{-1} with an ORR of 29%, DCR of 63% and median PFS of 3.7 months. The promising findings on IBI343 and other ADCs/mAbs further validates CLDN18.2 as an efficacious and clinically relevant therapeutic target in G/GEJ adenocarcinoma. As such, a multicenter, randomized, open-label, phase 3 study of IBI343 monotherapy versus chemotherapy of the investigators' choice in patients with previously treated, high CLDN18.2 expression (2+/3+ ≥ 75%), HER2-negative G/GEJ adenocarcinoma is being initiated (G-HOPE-001 trial; ClinicalTrials.gov registration: NCT06238843).

As reported in different clinical studies, the degree of CLDN18.2 expression in the current study was a predictive biomarker of efficacy in G/GEJ adenocarcinoma[13,14,18,19]. In the dose expansion phase, we enrolled participants with different CLDN18.2 expression levels (≥1% tumor cells with membranous staining of any intensity, similar to the phase 1 study of zolbetuximab[32]) to encompass a broader patient population. Both SPOTLIGHT and GLOW, as well as the present IBI343 trial, used the Ventana 43-14A IHC assay with identical cutoff for defining high expression (≥75%), while the trial of CT041 CAR T cells used the clone 14F8 IHC assay but with the same cutoff. The CMG901 trial used a CLDN18.2-specific EPR19202-244 antibody (Abcam) with a positivity threshold of 5% or more tumor cells with 2+ intensity in dose expansion. A global study investigated the analytical comparability of different CLDN18.2 assays and demonstrated the reliability of IHC testing for CLDN18.2 expression in gastric cancer samples when using commercially available platforms such as the Ventana 43-14A assay[24]. IBI343 now joins a suite of active targeted therapies in G/GEJ adenocarcinoma, many of which have pathological overlap. The correlation between IHC expression and response seen in IBI343 is consistent with the relationship between HER2 expression and response with trastuzumab deruxtecan as reported in the biomarker analyses of the DESTINY-Gastric01 study, which showed a dose-dependent relationship between HER2 expression using IHC, RNA expression using RNA sequencing and HER2 amplification in circulating tumor DNA, but a negative effect on response when co-mutations in *EGFR*, *MET* and *FGFR2* are present[33]. It is paramount that baseline biomarker testing including CLDN18.2, PD-L1 and HER2 is done routinely alongside comprehensive genomic sequencing in G/GEJ adenocarcinoma and that trials in biomarker-directed therapy are progressed to better understand optimal combinations and sequencing with uniformity of assays and thresholds for positivity across populations and jurisdictions.

Several limitations of this phase 1 trial should be noted. As a single-arm study that mainly enrolled Chinese participants, the efficacy of IBI343 should be interpreted with caution when extrapolating the data to other contexts considering potential variations in patient demographics, CLDN18.2 expression levels and treatment regimens across different populations. As such, ongoing dose optimization is underway in the phase 1 trial excluding China. The efficacy signals seen with IBI343, while promising and consistent with the CMG901 trial, need to be validated in larger randomized settings and with longer follow-up. Interestingly, in the zolbetuximab trials, the addition of zolbetuximab to chemotherapy prolonged PFS and OS without a significant increase in radiological response rates[34]. This contrasts with ADCs where the ORR typically correlates with PFS and OS and may reflect the mechanism of mAbs inducing ADCC and CDC to delay tumor progression, while ADCs use the cytotoxic payload present to achieve greater tumor volume shrinkage. Furthermore, the study does not include participant-reported outcome measures, such as quality of life (QoL), which may provide additional evidence for the long-term tolerability and QoL benefits of IBI343. Therefore, QoL measures have been included in the phase 3 G-HOPE-001 study. In addition, an exploratory analysis of biomarkers, including CLDN18.2, HER2 and PD-L1, may be informative in identifying subsets of patients who are most likely to benefit from IBI343 versus checkpoint inhibitors or other targeted therapies.

Future directions include exploring the efficacy of IBI343 in combination with checkpoint inhibitors and the optimal sequencing of anti-CLDN18.2 therapy, particularly after other CLDN18.2-targeting agents. In the present study, one participant received prior anti-CLDN18.2 therapy and achieved a PR after treatment with IBI343, indicating that IBI343 may still have antitumor activity even in patients receiving prior anti-CLDN18.2 therapy. In the ongoing phase 3 study (G-HOPE-001), receipt of prior anti-CLDN18.2 therapy is allowed. However, biopsy will be repeated to make ensure that tumors retain sufficient CLDN18.2 expression for enrollment after prior anti-CLDN18.2 treatments, including zolbetuximab. Combination therapy with IBI343 and checkpoint inhibitors is of interest given the promising efficacy observed between ADCs and checkpoint inhibitors in urothelial cancer[35], and the potential for ADC-stimulated dendritic cell activation and synergy with checkpoint inhibitors, which may improve the durability of response without overlapping toxicities[36].

In conclusion, IBI343 monotherapy was well tolerated, with a manageable safety profile and low gastrointestinal AEs; it showed promising efficacy in individuals with G/GEJ adenocarcinoma with moderate-to-high CLDN18.2 expression. The ongoing phase 3 multicenter, randomized, controlled study and future studies of IBI343 in

combination with other treatments, particularly immunotherapy, may provide more evidence supporting IBI343 as a new treatment option for G/GEJ adenocarcinoma and other solid tumors expressing CLDN18.2.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03783-8.

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Methods

Study oversight

The study protocol received approval from the institutional review boards and ethics committees at all participating sites. This study is registered at ClinicalTrials.gov (registration: NCT05458219) and was conducted in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki (2013) and relevant local regulatory policies. Written informed consent was obtained before patient enrollment.

Study design

This phase 1, multicenter, open-label study of IBI343 was conducted in 32 centers across China and Australia and included a dose escalation phase recruiting participants with solid tumors and a dose expansion phase recruiting participants with G/GEJ adenocarcinoma. IBI343 was administered via intravenous infusion on day 1 of a 21-day cycle (Q3W) with a four-agent prophylactic antiemetic regimen, including a neurokinin-1 receptor antagonist, 5-HT3, dexamethasone and a proton pump inhibitor. The primary endpoints of this phase 1 study included the safety and tolerability of IBI343 and the MTD, as well as the RP2D of IBI343. The secondary endpoints included the preliminary efficacy of IBI343, assessed through the ORR, DCR, DOR and PFS as evaluated by the investigator, and OS. A detailed study protocol is available in the Supplementary Information.

During the dose escalation phase, 14–30 participants who could be evaluated for DLT were planned to be enrolled to accurately estimate the MTD. The starting dose of IBI343 was set at 0.3 mg kg^{-1} based on nonclinical pharmacology and toxicology data, with five dose levels planned for evaluation (0.3, 1, 3, 6 and 10 mg kg^{-1}). An accelerated dose titration design was used for the first two dose levels (0.3 mg kg^{-1} and 1 mg kg^{-1}), followed by a traditional '3 + 3' dose escalation design for the remaining dose levels. If more than one participant in a cohort of six or fewer participants had a DLT at 6 mg kg^{-1}, then a dose level of 4.5 mg kg^{-1} would be explored. If more than one participant in a cohort of six or fewer participants had a DLT at 10 mg kg^{-1}, then a dose of 8 mg kg^{-1} would be initiated. After the 21-day DLT observation window, participants continued to receive IBI343 Q3W until disease progression, intolerable toxicity, withdrawal of consent or until treatment duration reached 24 months, whichever occurred first. The MTD was defined as the highest dose level of the study drug at which a minimum of six evaluable participants were treated, with no more than one of six evaluable participants experiencing a DLT during the first treatment cycle of the dose escalation phase.

During the dose expansion phase, 2–4 doses were planned to be selected. Approximately 6–60 participants were planned to be enrolled in each dose expansion group. Approximately 40–140 participants for each tumor type were planned. In the present study, participants with G/GEJ adenocarcinoma were enrolled at several expansion cohorts across dose levels deemed sufficiently well tolerated as determined by the investigators and sponsor and in line with FDA dose optimization requirements. The RP2D was determined based on the MTD along with overall assessment of safety and efficacy data at all dose levels evaluated during dose escalation and expansion. Additionally, the RP2D was supported by a minimum of six evaluable participants at that dose level, with acceptable tolerability observed in at least five of six participants.

Participants

The dose escalation cohorts enrolled participants with histologically or cytologically documented locally advanced unresectable or metastatic solid tumor regardless of CLDN18.2 expression. The dose expansion cohorts enrolled participants with pathologically documented locally advanced unresectable or metastatic G/GEJ adenocarcinoma with CLDN18.2-positive expression defined as 1% or more tumor cells with membranous staining of any intensity in tumor tissue using IHC as measured with the VENTANA CLDN18 (43-14A) assay. Other key inclusion criteria for both dose escalation and dose expansion phases were: (1) patients aged 18 years and older; (2) refractory or intolerable to standard treatment or where no standard therapy was available; (3) at least one measurable lesion per Response Evaluation Criteria in Solid Tumors v.1.1; (4) Eastern Cooperative Oncology Group performance status of 0 or 1; (5) anticipated life expectancy of 12 weeks or more; and (6) adequate bone marrow and organ function (detailed in the study protocol). Key exclusion criteria included participants having received previous antitumor therapy within 4 weeks or 5 half-lives of the antitumor regimens before the first administration of IBI343, whichever was shorter.

Safety assessment

AEs were coded using the Medical Dictionary for Regulatory Activities v.26.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0. Safety assessments began at the time of the informed consent and continued for 30 days after the last dose of IBI343. TRAEs were evaluated by the investigators. All AEs were monitored until the participant either recovered to baseline or grade 0–1, or until the investigator determined that further follow-up was not necessary for valid reasons (such as the inability to recover or improve). If an AE could not be resolved, a reasonable explanation was documented.

Efficacy assessment

Tumor response was assessed by the investigator or a qualified designee in accordance with Response Evaluation Criteria in Solid Tumors v.1.1, using contrast-enhanced computed tomography or magnetic resonance imaging. For participants suspected of having brain metastases during screening, brain imaging was required. For those without brain metastases at baseline, routine brain imaging assessments were not necessary during the study. The same imaging technique was consistently used for each participant throughout the study. If necessary, alternative imaging techniques for other body regions could be conducted as baseline references. Baseline evaluations were performed within 28 days before the first dose of IBI343. If imaging was conducted within 28 days before the first dose, and it met the study quality requirements, it could be used as baseline imaging. Tumor imaging evaluations were conducted every 6 weeks (±7 days) for the first 48 weeks after the initial administration of IBI343, after which evaluations occurred every 12 weeks (±7 days).

Statistical analysis

Continuous data were summarized using counts, means, s.d., medians, and maximum and minimum, while discrete data were characterized using frequencies and percentages. The 95% CIs for the ORR and DCR were calculated using the Clopper–Pearson method. Time-to-event endpoints, including DOR, PFS and OS, were analyzed using the Kaplan–Meier method; median time to event(s) and the 95% CI for the median were provided. Subgroup analyses of confirmed ORRs were conducted based on several baseline characteristics, such as sex, age, previous lines of therapy, prior irinotecan treatment, primary tumor site, presence of bone or peritoneal metastases, history of gastrectomy, number of metastatic sites and prior immunotherapy. Data were collected with TrialMaster v.5.0. Statistical analyses were carried out using SAS v.9.4.

Clinical pharmacology analysis

PK parameters were analyzed using noncompartmental analysis with PKanalix 2023R1 (Lixoft). Population PK analysis was performed using Monolix 2023R1 (Lixoft) for compartmental model development and covariate screening, with simulations conducted in Simulx 2023R1 (Lixoft). Exposure–safety and exposure–efficacy relationships were assessed using logistic regression models implemented in R v.4.1.1 (R Foundation for Statistical Computing).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data supporting the findings of this study are available in the paper and the Supplementary Information. Reasonable requests for additional data sharing should be directed to the corresponding author and will be evaluated in accordance with the data access and sharing policy of the Human Genetic Resource Administration of China.

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Author contributions

The manuscript was written by J.L. and critically reviewed and revised by the other authors. All authors contributed to the analysis and interpretation of the data. The authors confirm the accuracy and completeness of the data and adherence to the trial protocol.

Competing interests

J.L. declares honoraria from Merck Sharp & Dohme and Specialised Therapeutics, consulting or advisory roles for Starpharma and Greywolf Therapeutics, research funding from Starpharma, ViroCure, Corvus Pharmaceuticals, Relay Therapeutics, ALX Oncology, IDEAYA Biosciences, Innovent Biologics, Greywolf Therapeutics, Merck Sharp & Dohme, Regeneron, Bristol Myers Squibb, AbbVie and AVEO, and travel, accommodation and expenses from Starpharma, ImmVirX, Merck Sharp & Dohme and Innovent Biologics. Y.L., X.Z., Y.G. and H.Z. are employees of Innovent Biologics. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03783-8.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03783-8.

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Peer review information *Nature Medicine* thanks Mithat Gonen, Sarbajit Mukherjee and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ulrike Harjes, in collaboration with the *Nature Medicine* team.

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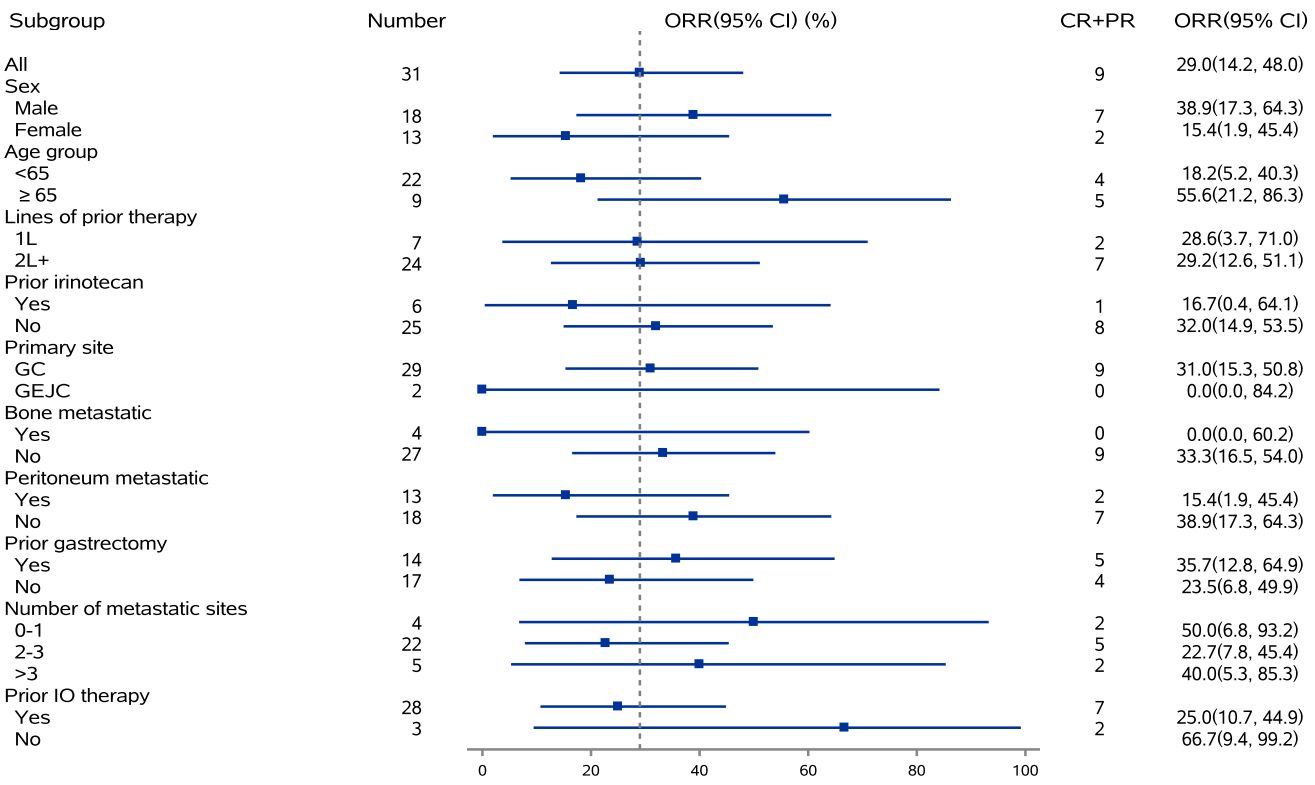
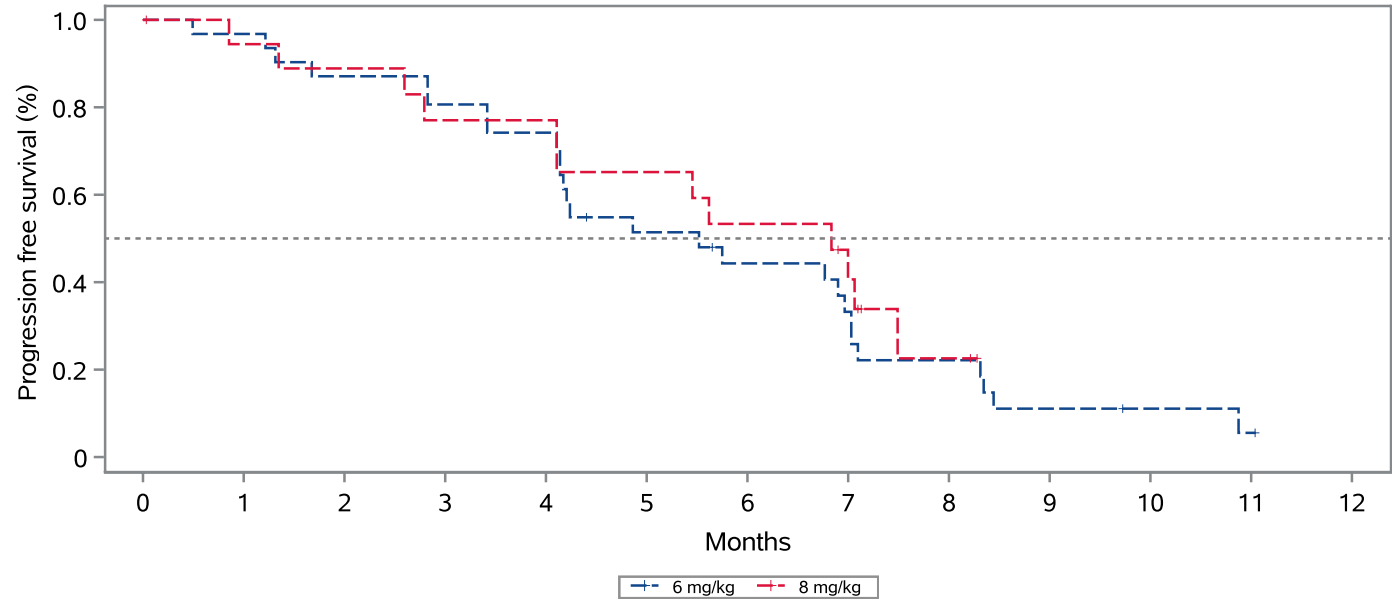


Extended Data Fig. 1 | Subgroup analysis of ORR in G/GEJ adenocarcinoma patients with high expression of CLDN 18.2 (≥ 75%) treated at 6 mg/kg. Abbreviations: treatment lines (L), gastric cancer (GC), gastroesophageal junction cancer (GEJC), immuno-oncology (IO).

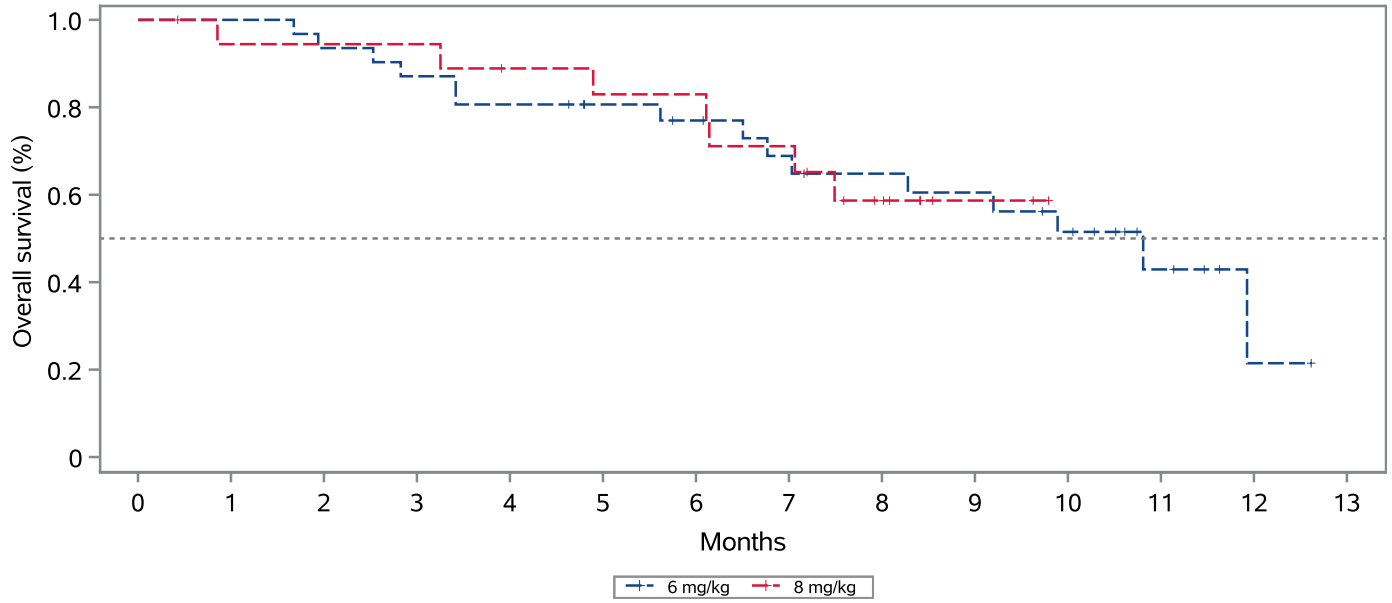
https://doi.org/10.1038/s41591-025-03783-8



At risk													
6 mg/kg	31	30	27	25	23	15	12	9	6	3	2	1	0
8 mg/kg	19	17	15	13	13	11	9	6	2	0			

Extended Data Fig. 2 | PFS in G/GEJ adenocarcinoma patients with high expression of CLDN 18.2 (≥ 75%). PFS at 6 mg/kg (n = 31) and 8 mg/kg (n = 19), including 1 patient treated at 8 mg/kg from dose escalation.

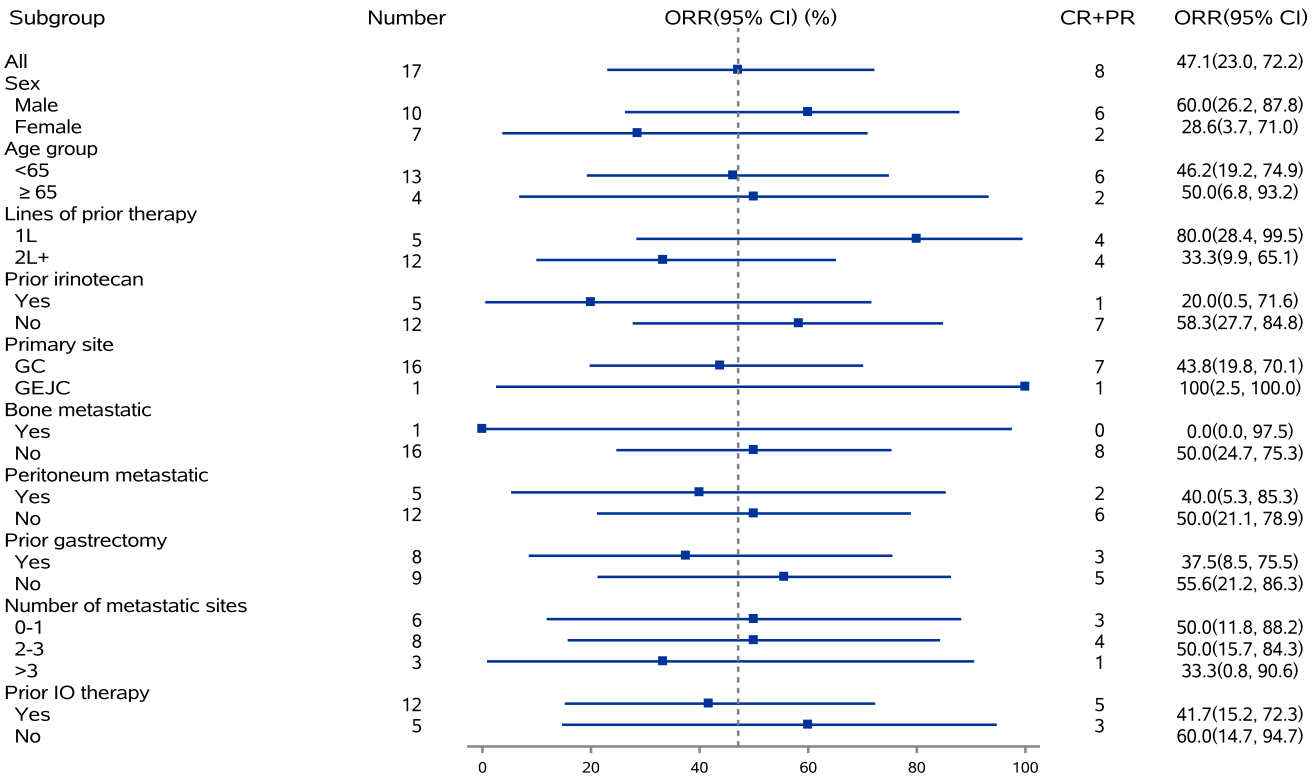
https://doi.org/10.1038/s41591-025-03783-8



At risk														
6 mg/kg	31	31	29	27	25	22	20	17	15	14	11	5	1	0
8 mg/kg	19	17	17	17	15	14	14	12	7	2	0			

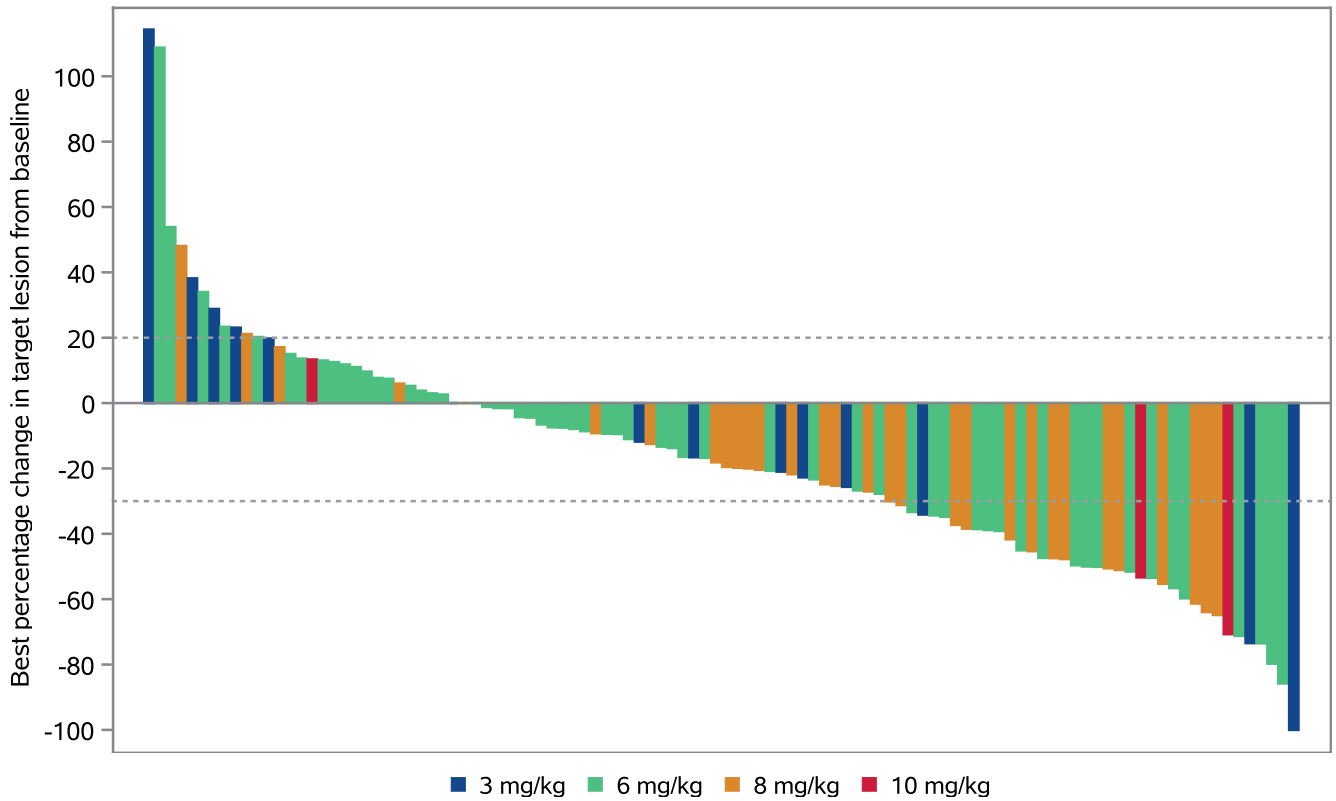
Extended Data Fig. 3 | OS in G/GEJ adenocarcinoma patients with high expression of CLDN18.2 (≥ 75%). OS at 6 mg/kg (n = 31) and 8 mg/kg (n = 19), including 1 patient treated at 8 mg/kg from dose escalation.

https://doi.org/10.1038/s41591-025-03783-8



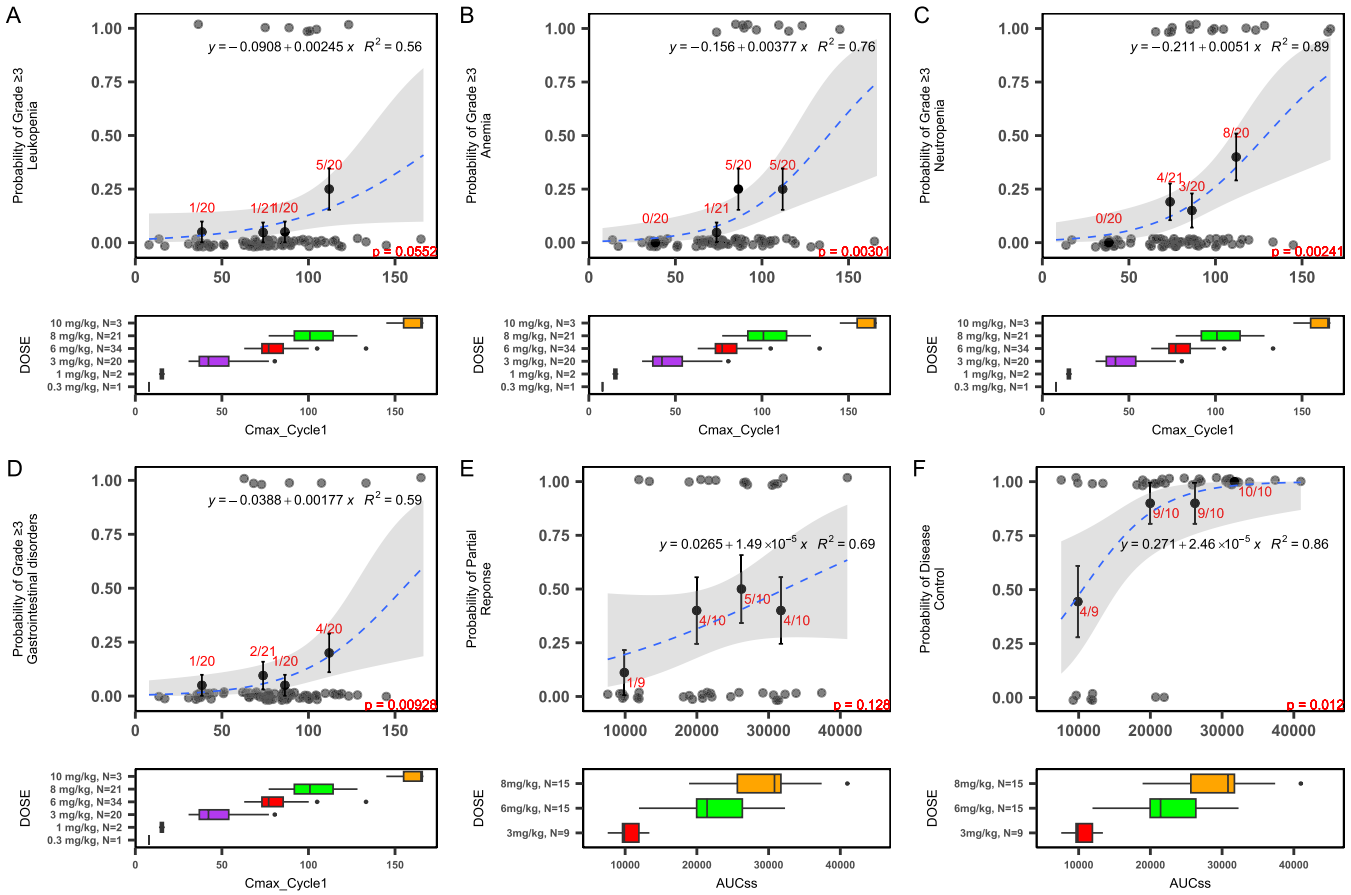
Extended Data Fig. 4 | Subgroup analysis of ORR in G/GEJ adenocarcinoma patients with high expression of CLDN 18.2 (≥ 75%) treated at 8 mg/kg. Abbreviations: treatment lines (L), gastric cancer (GC), gastroesophageal junction cancer (GEJC), immuno-oncology (IO).

https://doi.org/10.1038/s41591-025-03783-8



Extended Data Fig. 5 | Efficacy of IBI343 in all evaluable patients with G/GEJ adenocarcinoma.

https://doi.org/10.1038/s41591-025-03783-8



Extended Data Fig. 6 | IBI343 exposure-safety and efficacy relationship. Probability of≥G3 Leukopenia vs total antibody C_{max_cycle1} (**a**), ≥G3 Anemia vs total antibody C_{max_cycle1} (**b**), ≥G3 neutropenia vs total antibody C_{max_cycle1} (**c**), ≥G3 Gastrointestinal disorders vs total antibody C_{max_cycle1} (**d**), Probability of partial response vs total antibody AUC_{ss} (**e**) and disease control vs total antibody AUC_{ss} (**f**): = 1 for responder; = 0 for non-responder. Dashed line refers to predicted probability by a linear logistic regression model. The shaded area refers to its 95% confidence interval. The grey small circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P × (1 − P) /N)] for quantiles (at 100× (1/q) th percentiles) of exposures (plotted at the median value within each quantile). Formula is listed in top right corner; p value of intercept is listed in lower right corner. Bottom panel: box plot of exposure metrics at 0.3, 1, 3, 6, 8, 10 mg/kg.

https://doi.org/10.1038/s41591-025-03783-8

Extended Data Table 1 | Baseline characteristics of participants in dose escalation

	0.3 mg/kg (n=1)	1 mg/kg (n=1)	3 mg/kg (n=5)	6 mg/kg (n=3)	8 mg/kg (n=3)	10 mg/kg (n=6)
Age, years						
Median	67	79	64	61	45	57
Range (min-max)	67-67	79-79	57-77	53-84	44-59	50-61
Sex, n(%)						
Male	0	1(100)	1(20.0)	2(66.7)	1(33.3)	3(50.0)
Female	1(100)	0	4(80.0)	1(33.3)	2(66.7)	3(50.0)
Race, n(%)						
East Asian	0	0	2(40.0)	2(66.7)	3(100)	6(100)
Caucasian	1(100)	1(100)	3(60.0)	1(33.3)	0	0
ECOG, n(%)						
PS 0	0	0	1(20.0)	0	0	0
PS 1	1(100)	1(100)	4(80.0)	3(100)	3(100)	6(100)
CLDN 18.2 expression, n (%)						
Low (2+/3+ < 40%)	0	0	0	1(50.0)	1(50.0)	0
Moderate (2+/3+: 40%-74%)	0	0	0	1(50.0)	0	2(40.0)
High (2+/3+≥75%)	0	0	0	0	1(50.0)	3(60.0)
Missing	1	1	5	1	1	1
Tumor type, n(%)						
Prostate cancer	0	0	1(20.0)	0	0	0
Ovarian cancer	0	0	2(40.0)	0	0	0
Endometrial cancer	0	0	0	1(33.3)	0	0
Colorectal cancer	1(100)	0	0	0	0	0
Gastric cancer	0	0	0	2(66.7)	2(66.7)	4(66.7)
Biliary tract cancer	0	0	0	0	0	1(16.7)
Pancreas cancer	0	1(100)	2(40.0)	0	1(33.3)	1(16.7)
Prior treatment lines, n(%)						
1	0	0	0	1(50.0)	1(33.3)	2(33.3)
2	0	0	3(60.0)	1(50.0)	0	4(66.7)
3	0	0	0	0	2(66.7)	0
5	0	0	1(20.0)	0	0	0
6	0	0	1(20.0)	0	0	0
Missing	1	1	0	1	0	0

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Extended Data Table 2 | Efficacy of IBI343 in evaluable patients with G/GEJ adenocarcinoma and different CLDN 18.2 expression cutoffs

CLDN 18.2 expression*	6 mg/kg		8 mg/kg	
	moderate (n=18)	moderate to high (n=49)	moderate (n=12)	moderate to high (n=29)
Best overall response, n (%)				
Partial response (PR)	4 (22.2)	19 (38.8)	4 (33.3)	13 (44.8)
Stable disease (SD)	11 (61.1)	24 (49.0)	5 (41.7)	11 (37.9)
Progressive disease (PD)	2 (11.1)	5 (10.2)	2 (16.7)	3 (10.3)
Not evaluable (NE)*	0	0	1 (8.3)	1 (3.4)
Not assessed (NA)**	1(5.6)	1 (2.0)	0	1 (3.4)
unconfirmed ORR (95% CI)	22.2% (6.4, 47.6)	38.8% (25.2, 53.8)	33.3% (9.9, 65.1)	44.8% (26.4, 64.3)
confirmed ORR (95% CI)	22.2% (6.4, 47.6)	26.5% (14.9, 41.1)	33.3% (9.9, 65.1)	41.4% (23.5, 61.1)
DCR (95% CI)	83.3% (58.6, 96.4)	87.8% (75.2, 95.4)	75.5% (42.8, 94.5)	82.8% (64.2, 94.2)

*Efficacy in the evaluable population included patients who completed 2 cycles of treatment and had at least one tumor assessment after the first dose of study drug, or who prematurely discontinued study drug due to disease progression or death or AE. CLDN 18.2 expression cutoffs: moderate (2+/3+: 40-74%), moderate to high (2+/3+≥ 40%). **PR confirmed in 13 of 19 patients treated at 6 mg/kg, and in 12 of 13 patients treated at 8 mg/kg.

nature portfolio

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
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☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	TrialMaster V5.0
Data analysis	Statistical analyses were carried out using SAS version 9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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Data supporting the findings of this trial are available within the manuscript and the supplementary materials. Reasonable requests for additional data sharing should be directed to the corresponding author and will be evaluated in accordance with the data access and sharing policy of Human Genetic Resource Administration of China.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex (Male & Female) was described as baseline characteristics of the patients in results-patients and treatments, Table 1 and Supplementary Table S1. Sex was also used in subgroup analysis of ORR as shown in Supplementary Figure S3.
Reporting on race, ethnicity, or other socially relevant groupings	Race (East Asian & Caucasian) was described as baseline characteristics of the patients in results-patients and treatments, Table 1 and Supplementary Table S1.
Population characteristics	Baseline characteristics of the patients were described in results-patients and treatments, Table 1 and Supplementary Table S1.
Recruitment	Patients were evaluated by the investigators or staff at the study sites. Recruitment was limited to locations or regions where the study being conducted. Written informed consent was obtained prior to patient enrollment.
Ethics oversight	The study protocol received approval from the institutional review board and ethics committee at all participating sites.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size was based on the typical 3+3 design as well as clinical considerations for safety and efficacy as detailed in the study protocol.
Data exclusions	Patients excluded for this study were presented in the CONSORT diagram (Figure 1). Exclusion criteria are detailed in the study protocol.
Replication	All relevant experiments in lab and statistical analyses reported in this study can be replicated.
Randomization	not applicable for this single-arm study
Blinding	not applicable for this open-label study

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT05458219
Study protocol	Study protocol is available in supplementary materials
Data collection	Patients were enrolled in China and Australia. The first patient was enrolled on October 26th, 2022 and the study is ongoing. As of June 30th, 2024, a total of 540 patients were screened and 211 patients were enrolled to receive IBI343 monotherapy. This report includes 19 patients from the dose escalation phase and 108 patients with G/GEJ adenocarcinoma from the dose expansion phase (Figure 1).
Outcomes	The primary endpoints of this phase 1 study included the safety and tolerability of IBI343 and the maximum tolerated dose (MTD) as well as the recommended Phase 2 dose (RP2D) of IBI343. The secondary endpoints included the preliminary efficacy of IBI343, assessed through objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) as evaluated by the investigator, and overall survival (OS).

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*