

ORIGINAL ARTICLE

A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study

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Background: Claudin 18.2 (CLDN18.2) is physiologically confined to gastric mucosa tight junctions; however, upon malignant transformation, perturbations in cell polarity lead to CLDN18.2 epitopes being exposed on the cancer cell surface. The first-in-class monoclonal antibody, zolbetuximab (formerly known as IMAB362), binds to CLDN18.2 and can induce immune-mediated lysis of CLDN18.2-positive cells.

Patients and methods: Patients with advanced gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinomas with moderate-to-strong CLDN18.2 expression in $\geq 50\%$ of tumour cells received zolbetuximab intravenously every 2 weeks for five planned infusions. At least three patients were enrolled in two sequential cohorts (cohort 1300 mg/m²; cohort 2600 mg/m²); additional patients were enrolled into a dose-expansion cohort (cohort 3600 mg/m²). The primary end point was the objective response rate [ORR: complete and partial response (PR)]; secondary end points included clinical benefit [ORR+stable disease (SD)], progression-free survival, safety/tolerability, and zolbetuximab pharmacokinetic profile.

Results: From September 2010 to September 2012, 54 patients were enrolled (cohort 1, $n = 4$; cohort 2, $n = 6$; cohort 3, $n = 44$). Three patients in cohort 1 and 25 patients in cohorts 2/3 received at least 5 infusions. Antitumour activity data were available for 43 patients, of whom 4 achieved PR (ORR 9%) and 6 (14%) had SD for a clinical benefit rate of 23%. In a subgroup of patients with moderate-to-high CLDN18.2 expression in $\geq 70\%$ of tumour cells, ORR was 14% ($n = 4/29$). Treatment-related adverse events occurred in 81.5% ($n = 44/54$) patients; nausea (61%), vomiting (50%), and fatigue (22%) were the most frequent.

Conclusions: Zolbetuximab monotherapy was well tolerated and exhibited antitumour activity in patients with CLDN18.2-positive advanced gastric or GEJ adenocarcinomas, with response rates similar to those reported for single-agent targeted agents in gastric/GEJ cancer trials.

ClinicalTrials.gov number: NCT01197885.

Key words: gastric cancer, gastro-oesophageal junction adenocarcinoma, CLDN18.2, zolbetuximab, IMAB362

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide [1, 2]. In patients with locally advanced incurable, recurrent, or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma, first-line treatment with fluoropyrimidine- and platinum-based combination therapy is standard of care [3, 4]. Recently, single-agent treatments targeting antigens expressed on tumour cells (cetuximab, trastuzumab) or in the tumour microenvironment (nivolumab, pembrolizumab, ramucirumab) have been evaluated in patients with gastric/GEJ cancer with modest benefit; objective response rates (ORR) ranged between 3% [5, 6] and 11% [7, 8].

The tight junction protein claudin 18.2 (CLDN18.2) has been identified as a promising target for the treatment of gastric/GEJ adenocarcinoma [9]. CLDN18.2 is typically buried in the tight junction supramolecular complex, largely inaccessible to monoclonal antibodies (mAbs). However, malignant transformation leads to disruptions in tight junctions that expose CLDN18.2 epitopes on the surface of tumour cells [9].

Zolbetuximab is a chimeric IgG1 mAb that binds to CLDN18.2 on the surface of tumour cells and induces cancer cell death through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Based on data from a first-in-human study (NCT00909025) in patients with previously treated advanced gastric/GEJ adenocarcinoma, a dose range of 300–600 mg/m² was selected for further evaluation [10].

This phase II study (NCT01197885) examined zolbetuximab monotherapy in patients with recurrent or refractory locally advanced or metastatic CLDN18.2-positive (CLDN18.2⁺) gastric, GEJ, or oesophageal adenocarcinoma. The primary objective was to evaluate ORR at week 11/12; secondary objectives included safety, tolerability, immunogenicity, and pharmacokinetic (PK)

profile of zolbetuximab monotherapy given as repeated intravenous (i.v.) infusions.

Methods

Patients

Adult patients ≥ 18 years old with histologically confirmed metastatic, refractory or recurrent gastric, GEJ, or oesophageal adenocarcinoma who had received ≥ 1 prior line of chemotherapy, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0 [11]) were centrally assessed for CLDN18.2 expression. Only patients with moderate or strong (2+/3+) CLDN18.2 membrane staining intensity in $\geq 50\%$ of tumour cells were eligible. Additional inclusion/exclusion criteria are provided in the [supplementary material](#), available at *Annals of Oncology* online.

Procedures

This was an international, open-label, phase II study, conducted from September 2010 through September 2012. Patients were consecutively enrolled in three cohorts. Cohorts 1 and 2 were small lead-in cohorts to assess the feasibility of repeated administration of zolbetuximab monotherapy at two dose levels (300 mg/m² as safety run-in and 600 mg/m² as targeted dose). Cohort 3 was a larger dose-expansion arm of the 600 mg/m² dose. All cohorts were recruited sequentially.

All patients were scheduled to receive i.v. infusions of zolbetuximab every 2 weeks for up to five infusions. Patients who completed five infusions of zolbetuximab at the highest dose level (600 mg/m²) could continue study treatment until progression if they had documented complete response (CR), partial response (PR), or stable disease (SD) based on investigator assessment per RECIST v1.0. Additional details regarding study procedures are provided in the [supplementary material](#), available at *Annals of Oncology* online.

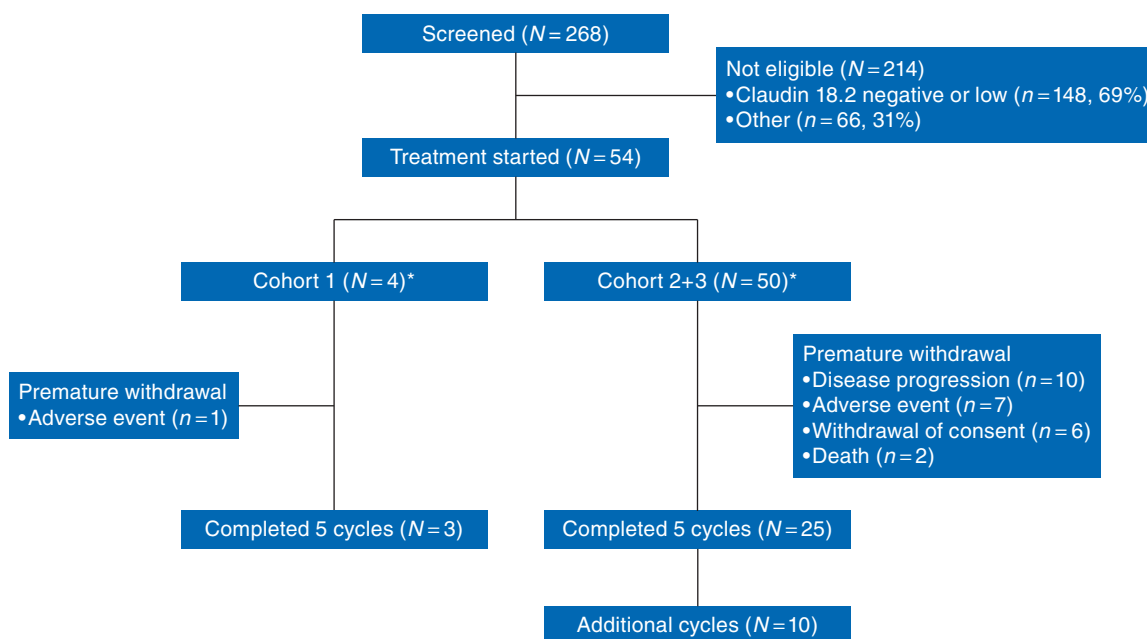


Figure 1. Patient's disposition. *Three patients from cohort 1 and 40 patients from cohorts 2+3 were included in the full analysis set, which was defined as the set of patients who received at least one dose of medication and for whom any efficacy data were available.

Table 1. Patient's baseline demographic and disease characteristics

	Cohort 1300 mg/m² (n = 4)	Cohorts 2/3600 mg/m² (n = 50)	All patients (N = 54)
Sex, n (%)			
Female	3 (75%)	14 (28%)	17 (32%)
Male	1 (25%)	36 (72%)	37 (69%)
Age, years, median (range)	62 (45–66)	60 (35–77)	60 (35–77)
ECOG performance status, n (%)			
0	2 (67%) ^a	19 (48%)	21 (49%)
1	1 (33%) ^a	21 (53%)	22 (51%)
Location of primary tumour, n (%)			
Oesophagus	0	1 (2%)	1 (2%)
GEJ	1 (25%)	23 (46%)	24 (44%)
GEJ, stomach	0	2 (4%)	2 (4%)
Stomach	3 (75%)	24 (48%)	27 (50%)
Histological subtype, n (%)			
Intestinal	0	20 (40%)	20 (37%)
Diffuse	2 (50%)	20 (40%)	22 (41%)
Mixed	0	4 (8%)	4 (7%)
Unknown	2 (50%)	6 (12%)	8 (14%)
Time since diagnosis, months, median (range)	17.9 (3.8–21.9)	14.5 (0.2–93.3)	15.4 (0.2–93.3)
HER-2 status, n (%)			
Positive	0	12 (24%)	12 (22%)
Negative	2 (50%)	26 (52%)	28 (52%)
Unknown	2 (50%)	12 (24%)	14 (26%)
Prior gastrectomy, n (%)	2 (50%)	27 (54%)	29 (54%)
Number of metastatic sites, median (range)	3.5 (1–5)	2.0 (1–6) ^b	2.0 (1–6)
Prior treatment with fluoropyrimidine and platinum			
Fluoropyrimidine	2 (50%)	34 (68%)	36 (67%)
Platinum	1 (25%)	21 (42%)	22 (41%)
Unknown	2 (50%)	12 (24%)	14 (26%)
Measurable disease, n (%)			
Yes	4 (100%)	47 (94%)	51 (94%)
No	0	3 (6%)	3 (6%)

Data presented as n (%) or median (range).

^aPercentage calculated from number of patients with non-missing data (n = 3).

^bData from 46 patients.

GEJ, gastro-oesophageal.

Outcomes and assessments

The primary objective of the study was to determine the ORR (CR + PR) of zolbetuximab after 11–12 weeks of treatment. Secondary objectives included assessment of best overall response, overall clinical benefit rate (CR + PR + SD), progression-free survival (PFS), PK profile of zolbetuximab after multiple doses, immunogenicity of zolbetuximab, and safety/tolerability profile of zolbetuximab. Response was evaluated by computed tomography or magnetic resonance imaging of target and non-target lesions and assessed by RECIST criteria version 1.0 [11] or 1.1 [12]. Treatment-emergent adverse events (TEAEs) were assessed by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. Additional information related to outcomes and assessments can be found in the [supplementary material](#), available at *Annals of Oncology* online.

Statistical analysis

Safety/tolerability end points were analysed in patients who received ≥ 1 administration of zolbetuximab at any dosage. PK parameters were

evaluated by dose levels and the PK analysis set included patients who had received ≥ 1 dose of study medication and for whom PK measures were available. Antitumour activity was assessed in the full analysis set (FAS), defined as patients who received ≥ 1 dose of study medication and for whom any efficacy data upon treatment are available, and on a subpopulation of patients whose tumours expressed high CLDN18.2 levels ($\geq 2+$ in $\geq 70\%$ tumour cells). ORR was assessed based on the point estimate and 95% confidence interval; OS and PFS were estimated using the Kaplan–Meier method. More about the statistical analyses and sample size calculation can be found in the [supplementary material](#), available at *Annals of Oncology* online.

Study oversight and data sharing

This study was designed by Ganymed Pharmaceuticals GmbH, in collaboration with the investigators, and was conducted in accordance with the Declaration of Helsinki ethical principles, Good Clinical Practices, principles of informed consent, and requirements of public registration of clinical trials (ClinicalTrials.gov Identifier, NCT01197885). Site-specific institutional review boards approved the protocol. Written informed

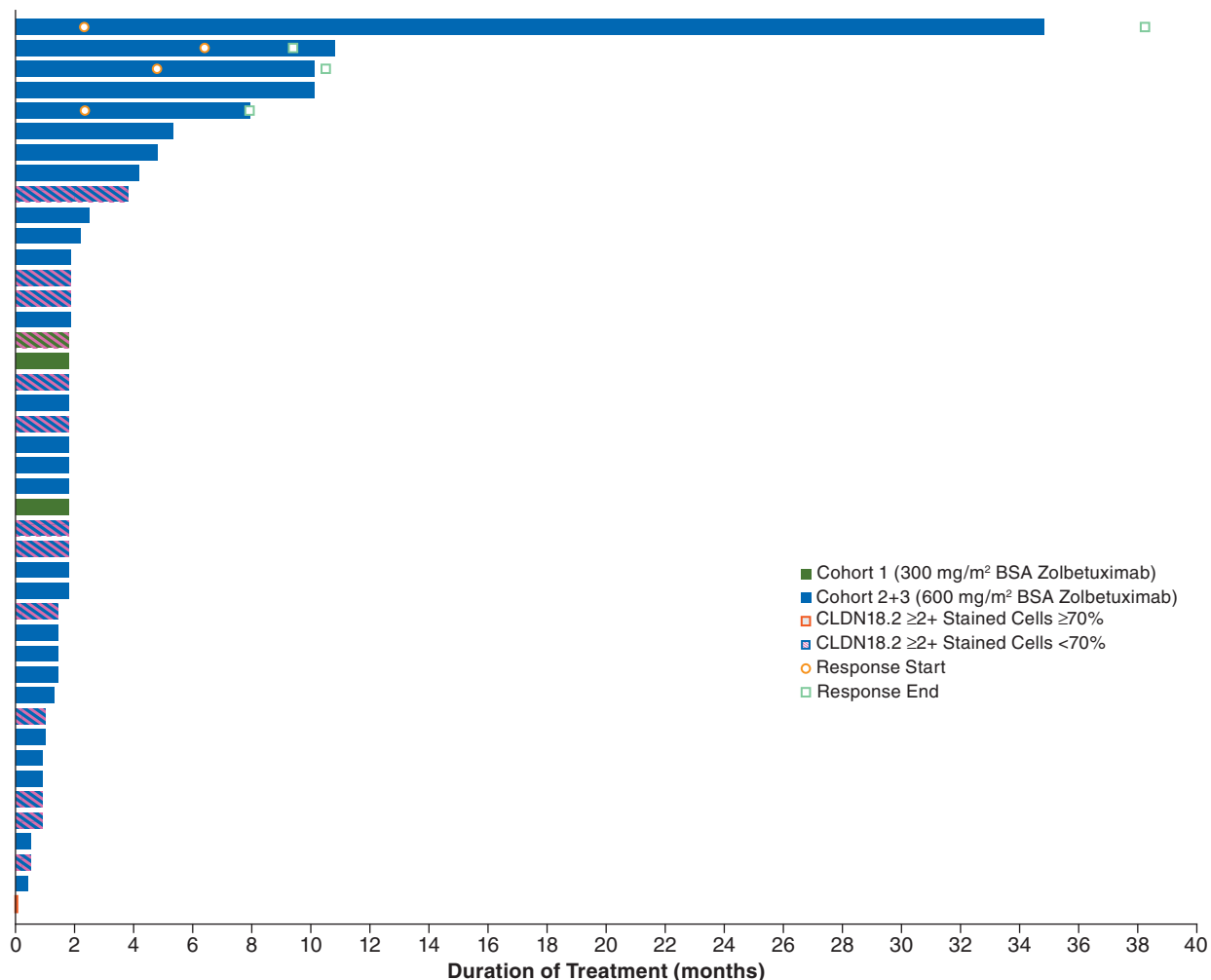


Figure 2. Duration of treatment and response with zolbetuximab. Duration of response for each individual patient. One patient had a prolonged response and received >70 infusions.

consent was obtained from each patient at enrolment. Statistical analyses were carried out by the statistical team at Astellas Pharma, Inc.

Studies conducted with product indications or formulations that remain in development are assessed after study completion to determine whether Individual Participant Data can be shared. The plan to share Individual Participant Data is based on the status of product approval or termination of the compound, in addition to other study specific criteria described on www.clinicalstudydatarequest.com under ‘Sponsor Specific Details for Astellas’.

Results

Study disposition

Between 3 September 2010, and 24 September 2012, 268 patients were screened. Of these, 54 patients were eligible and four received 300 mg/m² zolbetuximab in cohort 1, and 50 received 600 mg/m² zolbetuximab in cohorts 2 and 3. A total of 26 patients (cohort 1, $n = 1$; cohorts 2 and 3, $n = 25$) discontinued treatment before completing five infusions. The remaining 28 patients

($n = 3$, cohort 1; $n = 25$, cohorts 2 and 3) received ≥ 5 infusions of zolbetuximab (Figure 1). Ten patients were treated beyond week 11; additional treatments ranged from 3 to >70 infusions (median 8.5). Patient demographics and baseline disease characteristics were similar across all cohorts (Table 1).

Antitumour activity

Antitumour activity was assessable in 43 patients; however, at week 11/12, disease assessment was available for only 29 patients (300 mg/m², $n = 3$; 600 mg/m², $n = 26$). Across 43 assessable patients, ORR was 9% ($n = 4$) and clinical benefit rate was 23% ($n = 10$). All patients treated with zolbetuximab 300 mg/m², for whom efficacy data were available, experienced progressive disease (Figures 2 and 3; [supplementary Figure S1](#), available at *Annals of Oncology* online). At week 11/12, 2 of the 26 (8%) response-assessable patients who received 600 mg/m² achieved a PR and seven (27%) achieved SD (Table 2); two additional patients achieved PR after the week 11/12 evaluation. Among patients who responded to zolbetuximab, median duration of response was 24.6 weeks (range 13.1–156.1 weeks). Data for OS and

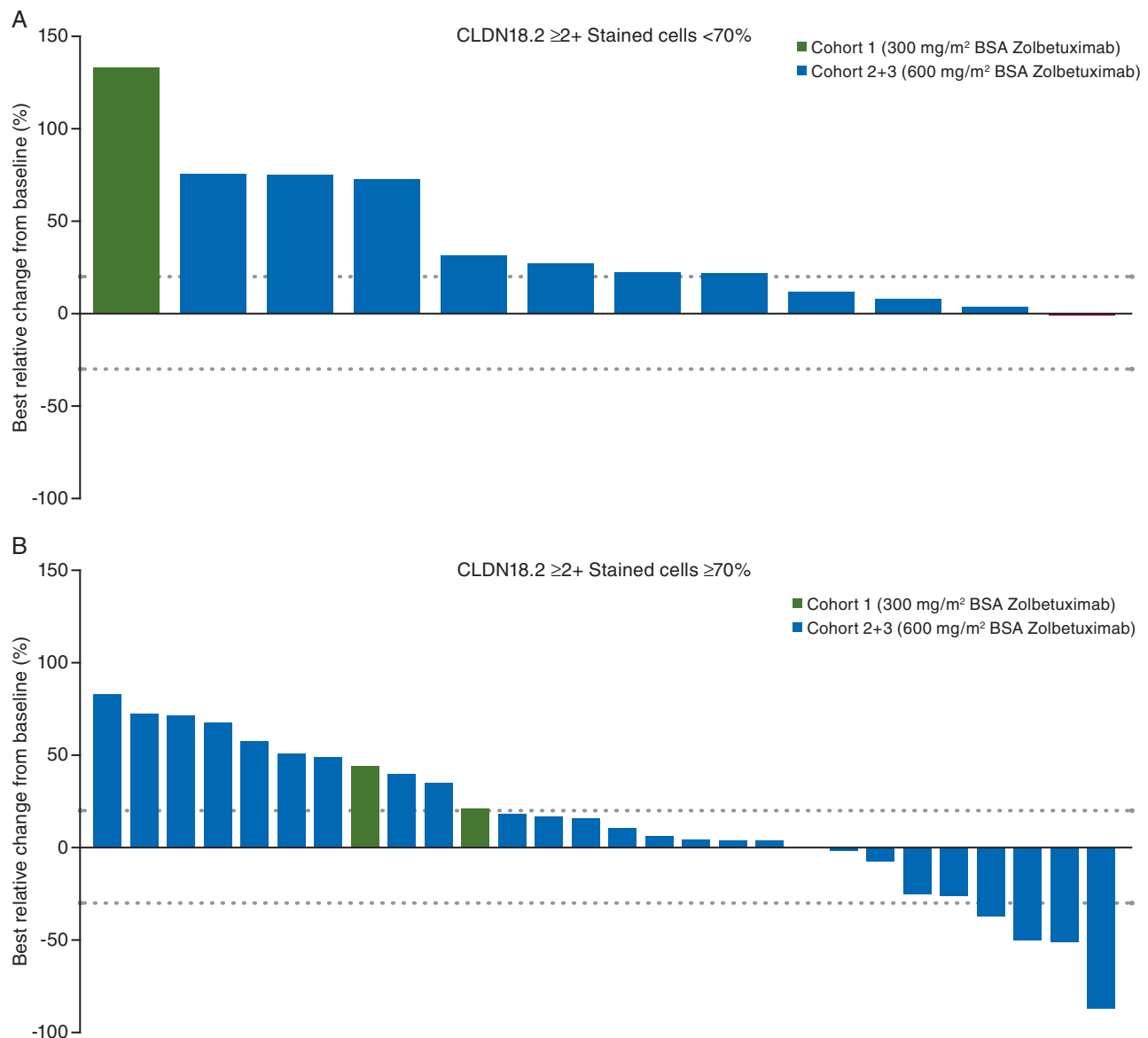


Figure 3. Best percentage change from baseline in tumour size with zolbetuximab in patients with gastric, GEJ, and oesophageal adenocarcinomas. Tumour diameter changes from baseline for each individual patient with (A) $< 70\%$ and (B) $\ge 70\%$ tumour cells stained for CLDN18.2. Note: tumour diameter data were available only for 40 of the 43 subjects in the FAS population (12 in A, 28 in B).

PFS are presented in [supplementary Figures S2 and S3](#), available at *Annals of Oncology* online. Of the 10 patients who achieved clinical benefit (CR + PR + SD), 9 (90%) had moderate-to-high CLDN18.2 expression in $\ge 70\%$ of tumour cells. In a subgroup analysis of patients with moderate-to-high CLDN18.2 expression in $\ge 70\%$ of tumour cells ($n = 29$), four patients (14%) achieved PR and five patients (17%) had SD as their best overall response (Table 2).

Safety and tolerability profile

TEAEs were reported in 52 of 54 (96%) patients; 44 patients (82%) experienced a TEAE that was considered related to zolbetuximab. Eleven patients (20%) discontinued the study due to TEAEs [abdominal pain, abdominal pain upper, decreased appetite, drug hypersensitivity, fatigue, inadequate diet, malignant

neoplasm progression, pneumonia, vertigo, vomiting, weight decreased ($n = 1$ for each), nausea ($n = 2$), and general physical health deterioration ($n = 2$)].

TEAEs occurring in $\ge 10\%$ of patients are shown in Table 3. Nausea, vomiting, fatigue, and decreased appetite were the only events considered related to zolbetuximab in $\ge 10\%$ of the total population. The majority of reported TEAEs were grade 1 or 2; grade 3 vomiting was reported in 12 patients (22%) and grade 3 nausea in eight patients (15%). Grade 4 events occurred in two patients: dyspnoea ($n = 1$) and diarrhoea ($n = 1$). Five patients experienced serious treatment-related AEs (TRAEs): grade 3 nausea and vomiting; grade 2 nausea and vomiting; grade 2 haematemesis ($n = 1$ for each), and grade 3 vomiting ($n = 2$). All patients who experienced serious TRAEs received the 600 mg/m² dose, except for one who had only grade 3 vomiting.

Table 2. Clinical response observed with zolbetuximab

	All FAS patients (N = 43)				FAS patients with CLDN18.2 ≥70% (N = 29)				
	Cohort 1 (300 mg/m ²) (n = 3)		Cohorts 2/3 (600 mg/m ²) (n = 40)		Cohort 1 (300 mg/m ²) (n = 2)		Cohorts 2/3 (600 mg/m ²) (n = 27)		Total (N = 29)
	Response at week 11/12 ^a n = 3	Best overall response n = 3	Response at week 11/12 n = 26	Best overall response n = 40	Response at week 11/12 n = 2	Best overall response n = 2	Response at week 11/12 n = 20 ^a	Best overall response n = 27	Best overall response N = 29
Complete response	0	0	0	0	0	0	0	0	0
Partial response	0	0	2 (8%)	4 (10%)	0	0	2 (10%)	4 (15%)	4 (14%)
Stable disease	0	0	7 (27%)	6 (15%)	0	0	6 (30%)	5 (19%)	5 (17%)
Progressive disease	3 (100%)	3 (100%)	17 (65%)	28 (70%)	2 (100%)	2 (100%)	12 (60%)	17 (63%)	19 (66%)
Not assessable	0	0	0	2 (5%)	0	0	0	1 (4%)	1 (3%)

Data presented as n (%).

^aOnly 29 patients provided disease assessment at week 11/12.

Table 3. Treatment-emergent adverse events occurring in ≥10% patients in all patients treated set (N = 54)

	Any grade	Grade 3 or 4	Grade 5
Nausea ^a	34 (63%)	8 (15%)	–
Vomiting	31 (57%)	12 (22%)	0
Fatigue	23 (43%)	2 (4%)	0
Decreased appetite	16 (30%)	2 (4%)	0
Constipation	14 (26%)	0	0
Peripheral oedema	12 (22%)	1 (2%)	0
Asthenia	12 (22%)	4 (7%)	0
Diarrhoea	14 (26%)	3 (6%)	0
General physical health deterioration	10 (19%)	1 (2%)	3 (6%)
Dyspnoea	8 (15%)	6 (11%)	0
Abdominal pain upper	8 (15%)	0	0
Weight decreased	8 (15%)	0	0
Abdominal pain	7 (13%)	2 (4%)	0
Ascites	7 (13%)	3 (6%)	0
Sleep disorder	7 (13%)	1 (2%)	0
Anaemia	6 (11%)	1 (2%)	0
Pleural effusion	6 (11%)	1 (2%)	0
Malignant neoplasm progression	6 (11%)	0	5 (9%)
Tumour pain	6 (11%)	2 (4%)	0

Data presented as n (%).

^aNo grade 4 or 5.

Nausea and vomiting were the most common TEAEs, and occurred early during infusion of zolbetuximab. Given the organ-specific expression of CLDN18.2 in the stomach, the frequency of these events was analysed post hoc in relation to prior gastrectomy. Patients without prior gastrectomy were more likely to report nausea and vomiting (Figure 4A). Incidence of these TEAEs decreased over time as patients were exposed to repeated zolbetuximab infusions (Figure 4B and C). No confirmed antidrug antibody reactivity was detected in any patient during this study.

Zolbetuximab PK profile

The PK profile of zolbetuximab was assessed in samples from 44 patients after first infusion; zolbetuximab exposure (defined as AUC and C_{max}) was generally dose-proportional (supplementary Figure S4 and Table S1, available at *Annals of Oncology* online).

Discussion

CLDN18.2 has been identified as a promising target for antibody-mediated cancer immunotherapy due to two key features: CLDN18.2 has a restricted expression profile in normal tissue and CLDN18.2 epitopes become exposed/accessible in malignant tissues, rendering them targetable by parenterally administered mAbs [9]. In preclinical models, zolbetuximab selectively binds to CLDN18.2⁺ cells and identifies them for immune-mediated destruction, primarily by ADCC and CDC.

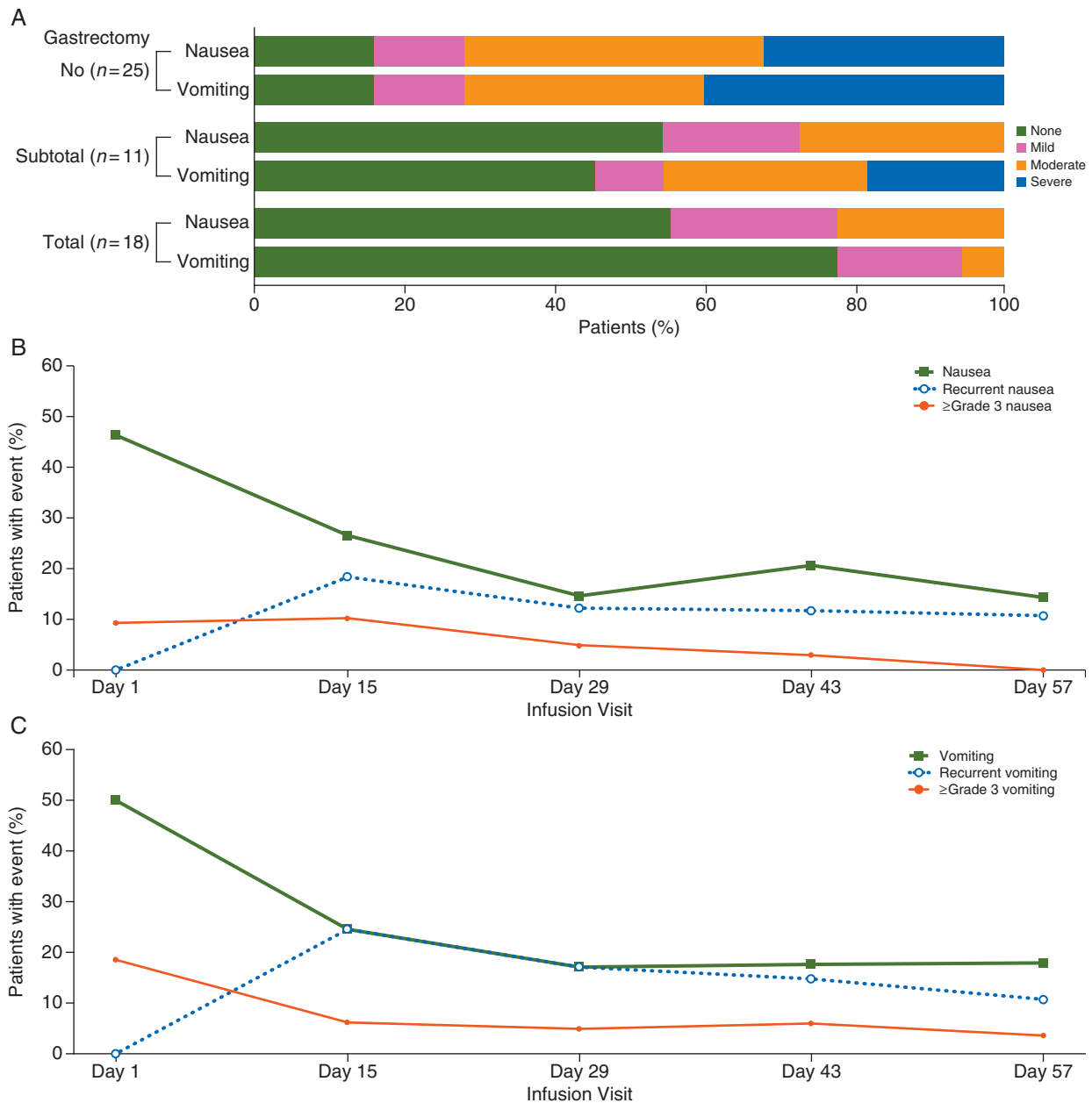


Figure 4. Treatment-emergent nausea and vomiting during treatment with zolbetuximab: (A) nausea and vomiting by gastrectomy status; (B) nausea by treatment cycle, first five doses of zolbetuximab; (C) vomiting by treatment cycle, first five doses of zolbetuximab. Patients were scheduled to receive i.v. infusions of zolbetuximab every 2 weeks for up to five infusions before potentially qualifying for continued treatment; nausea (B) and vomiting (C) events that occurred during continued treatment are not shown in this figure.

In the current study, patients were required to have $\geq 50\%$ CLDN18.2⁺ in tumour cells, as demonstrated by IHC analysis. Interestingly, all four responders had $\geq 70\%$ CLDN18.2⁺ in tumour cells, suggesting a possible correlation between CLDN18.2 expression and therapeutic benefit.

Currently, the majority of first- and second-line therapies for gastric/GEJ cancers utilize chemotherapy regimens [13]. Nonclinical data have shown that chemotherapeutic agents can enhance zolbetuximab-induced ADCC [14, 15]. That observation, coupled with the antitumour activity observed in this study, suggests that zolbetuximab may be an effective addition to

chemotherapy. Indeed, a phase II trial (FAST; NCT01630083) has shown, in patients with CLDN18.2⁺ advanced gastric/GEJ cancer, combining zolbetuximab with EOX chemotherapy confers a survival benefit over EOX alone [16].

The nausea and vomiting observed in this study were more frequent and/or severe in patients without prior gastrectomy and were managed by pausing or slowing infusion of zolbetuximab. Possible explanations for this include target-specific organ toxicity based on a drug-related pharmacodynamic mechanism, a higher antigen load in the stomach with the primary tumour still present, or the absence of an intact stomach as an effector

organ for vomiting. In general, these gastric toxicities were manageable and decreased in frequency and/or severity with repeated drug administration. Considering this, the safety of repeated infusions of zolbetuximab for gastric and GEJ cancers was established in this study. The small number of oesophageal cancer cases in the study precludes any conclusion in this disease population.

Generalisability of this trial's results is challenging due to small sample size. Furthermore, this study did not include diverse ethnicities; given that GC is far more prevalent among Asian populations [1] and that there may be ethnic differences in the pathology of GC [17, 18], this study cannot inform whether zolbetuximab may exhibit different levels of activity across different ethnicities. Patients enrolled in this study had moderate to strong CLDN18.2 expression. As such, this study cannot address how patients with lower CLDN18.2 expression may respond to zolbetuximab.

Gastric cancer remains a highly lethal malignancy and current therapies have limited applicability and benefit, partly due to a lack of prevalent, selective targets. This study validates CLDN18.2 as a target for immune-mediated antitumour therapy, and supports further investigation of zolbetuximab, particularly in combination with chemotherapy, as a potential treatment for patients with advanced GC. Clinical development of zolbetuximab is ongoing and phase III studies are planned.

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