ILUSTRO: Phase II Multicohort Trial of Zolbetuximab in Patients with Advanced or Metastatic Claudin 18.2–Positive Gastric or Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Purpose: Zolbetuximab, an IgG1 monoclonal antibody, binds to claudin 18.2 (CLDN18.2) and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. We sought to examine zolbetuximab combinations in CLDN18.2-positive HER2-negative gastric/gastroesophageal junction (G/GEJ) adenocarcinoma.

Patients and Methods: This phase II study assessed efficacy and safety of zolbetuximab, alone or with modified FOLFOX6 (mFOLFOX6) or pembrolizumab, in CLDN18.2-positive advanced/metastatic G/GEJ adenocarcinoma. Patients received zolbetuximab as monotherapy in third/later-line (Cohort 1A, $n = 30$), with mFOLFOX6 in first-line (Cohort 2, $n = 21$), or with pembrolizumab in third/later-line (Cohort 3A, $n = 3$) treatment. The primary endpoint for Cohort 1A was objective response rate (ORR). Key secondary endpoints were ORR (Cohorts 2 and 3A), overall survival (OS; Cohort 1A), and progression-free survival (PFS) and safety (all cohorts).

Results: ORR was 0% in Cohorts 1A and 3A, and 71.4% [95% confidence interval (CI), 47.82–88.72] in Cohort 2. Median PFS was 1.54 months (95% CI, 1.31–2.56) in Cohort 1A, 2.96 months (95% CI, 1.48–4.44) in Cohort 3A, and 17.8 months (95% CI, 8.05–25.69) in Cohort 2. Median OS in Cohort 1A was 5.62 months (95% CI, 2.27–11.53). Gastrointestinal adverse events occurred across cohorts [nausea, 63%–90% (grade ≥ 3, 4.8%–6.7%) and vomiting, 33%–67% (grade ≥ 3, 6.7%–9.5%)].

Conclusions: Zolbetuximab plus mFOLFOX6 demonstrated promising efficacy in previously untreated patients with CLDN18.2-positive G/GEJ adenocarcinoma. These data support the first-line development of zolbetuximab in patients whose tumors are CLDN18.2-positive. Across cohorts, zolbetuximab treatment was tolerable with no new safety signals.

Introduction

Gastric/gastroesophageal junction (G/GEJ) adenocarcinoma are a leading global cause of cancer-related death (1). Current frontline standard therapy achieves a median progression-free survival (PFS) of 4 to 7 months and median overall survival (OS) of 9 to 14 months among patients with HER2-negative advanced disease (2). Fluoropyrimidine and platinum-based chemotherapy regimens, including modified FOLFOX6 [mFOLFOX6; leucovorin (folinic acid), fluorouracil (5-FU), and oxaliplatin; median PFS, approximately 6.0 months], are a global standard for advanced/metastatic G/GEJ adenocarcinoma (3–5). Standard second-line or subsequent-line therapy includes chemotherapy with or without ramucirumab (4). Third-line or subsequent-line nivolumab is a standard therapy in some countries, including Korea, Japan, and Taiwan (6). The 5-year survival rate for advanced disease is roughly 6%, highlighting the need for novel approaches (7).

Biomarker-directed therapy, when combined with chemotherapy, has improved survival for patients with advanced/metastatic G/GEJ adenocarcinoma, when compared with chemotherapy alone (8, 9). The monoclonal antibody trastuzumab, combined with chemotherapy, is a standard of care first-line treatment option for

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Translational Relevance

This phase II trial enrolled patients with claudin 18.2–positive advanced/metastatic gastric/gastroesophageal junction (G/GEJ) adenocarcinoma. First-line zolbetuximab plus modified FOLFOX6 (mFOLFOX6) showed promising efficacy [objective response rate, 71.4% {95% confidence interval (CI), 47.82–88.72}; median progression-free survival, 17.8 months (95% CI, 8.05–25.69)]. There was limited activity in third-line or later-line treatment with zolbetuximab alone or with pembrolizumab. No new safety signals were observed with zolbetuximab alone or with mFOLFOX6 or pembrolizumab. Results showed that enrollment in a biomarker-enriched trial based on claudin 18.2 expression is feasible in advanced/metastatic G/GEJ adenocarcinoma; this knowledge informed the design of two positive phase III studies. This ongoing trial is enrolling patients with claudin 18.2–positive advanced/metastatic G/GEJ adenocarcinoma to assess outcomes of first-line zolbetuximab plus mFOLFOX6 and nivolumab. Use of biomarker-selected treatment strategies is increasing and understanding zolbetuximab activity in biomarker subsets (e.g., programmed death-ligand 1 combined positive score strata, HER2, and FGFR2) is important for future studies.

patients with HER2-positive G/GEJ adenocarcinoma (10). The anti–programmed cell death protein-1 (anti–PD-1) antibodies nivolumab and pembrolizumab (only GEJ cancer) are approved in several countries for first-line combination chemotherapy in advanced disease (10). In Europe, the use of immune checkpoint inhibition is largely restricted to patients with programmed death-ligand 1 (PD-L1)-positive G/GEJ tumors, particularly those with a combined positive score of ≥5 (10, 11). The magnitude of benefit for PD-1 inhibitors is related to the expression of PD-L1; patients with low or absent PD-L1 expression derive little or no treatment benefit (12, 13). The relationship between patient outcomes and PD-L1 expression highlights the clinical importance of optimal biomarker selection in advanced/metastatic G/GEJ adenocarcinoma (4, 14, 15).

Claudin 18.2 (CLDN18.2) is a tight junction protein expressed exclusively on gastric epithelial cells in normal tissues (16). CLDN18.2 is maintained during malignant transformation, but as cells lose their polarization, CLDN18.2 may become more accessible on the surface of G/GEJ adenocarcinoma (17), making it available to monoclonal antibodies as a largely cancer-restricted target. CLDN18.2 is prevalent in G/GEJ adenocarcinoma and its expression is maintained in metastases (16, 18). Zolbetuximab is a chimeric immunoglobulin G1 monoclonal antibody that specifically binds to CLDN18.2 and mediates tumor cell death through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC; ref. 19). Preclinical studies demonstrated that tumor cell lines exposed to chemotherapy were sensitized to ADCC and CDC and that chemotherapeutic agents can upregulate CLDN18.2 expression (19). Xenografted mice treated with zolbetuximab plus chemotherapy had improved antitumor activity when compared with zolbetuximab alone or chemotherapy alone, consistent with cooperative or synergistic activity (17). As clinical validation of this preclinical observation, zolbetuximab demonstrated encouraging antitumor activity in patients with CLDN18.2-positive G/GEJ adenocarcinoma (20, 21). In the phase II FAST study, survival of patients with CLDN18.2-positive HER2-negative G/GEJ adenocarcinoma was significantly prolonged for those who received first-line zolbetuximab combined with EOX (epirubicin, oxaliplatin, and capecitabine) versus EOX alone ($P < 0.0005$ for PFS and OS) in patients with CLDN18.2-positive advanced G/GEJ adenocarcinoma, particularly those with a higher CLDN18.2 expression cutoff (20). Recent data from phase II studies demonstrated that zolbetuximab plus fluoropyrimidine- and platinum-based chemotherapy regimens significantly improved PFS and OS in patients with CLDN18.2-positive HER2-negative advanced/metastatic G/GEJ adenocarcinoma (22, 23). The current study assessed the efficacy and safety of zolbetuximab as a single agent and combined with either mFOLFOX6 or pembrolizumab in patients with CLDN18.2-positive advanced/metastatic G/GEJ adenocarcinoma.

Patients and Methods

Study design and patients

This phase II nonrandomized study assessed efficacy of zolbetuximab in patients with advanced/metastatic G/GEJ adenocarcinoma whose tumors have high or intermediate CLDN18.2 expression. High CLDN18.2 expression was defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining and intermediate CLDN18.2 expression was defined as ≥50% but <75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining. Study cohorts were established for zolbetuximab monotherapy and zolbetuximab combination therapy (Supplementary Fig. S1). Cohort 1A enrolled patients with high CLDN18.2 expression to receive third-line or later zolbetuximab monotherapy. Cohort 2 enrolled patients with high CLDN18.2 expression and HER2-negative status (determined by local or central testing) to receive first-line zolbetuximab plus mFOLFOX6. Cohort 3A enrolled patients with high or intermediate CLDN18.2 expression to receive third-line or later zolbetuximab plus pembrolizumab.

Patients were required to have measurable disease per investigator assessment (Cohort 1A and Cohort 2) or measurable and/or nonmeasurable disease per local assessment (radiologically evaluable, Cohort 3A) based on RECIST (version 1.1) criteria. Patients in Cohort 1A and Cohort 3A were required to have experienced disease progression during or after at least 2 prior regimens for their advanced disease, including fluoropyrimidine and platinum-containing chemotherapy (and HER2-targeted therapy if appropriate). Patients in Cohort 2 received no prior treatment for their advanced or metastatic disease. Neoadjuvant and/or fluorouracil (5-FU)-containing adjuvant chemotherapy was permitted if treatment occurred >6 months before enrollment. Complete inclusion/exclusion criteria can be found in the protocol.

In all cohorts, zolbetuximab was administered via intravenous infusion (2-hour minimum) at an 800 mg/m^2 loading dose and then at 600 mg/m^2 every 3 weeks thereafter. Zolbetuximab treatment started on Cycle 1, Day 1 in Cohort 1A and Cohort 3A and on Cycle 1, Day 3 in Cohort 2 [to allow pharmacokinetic (PK) assessment of 5-FU and oxaliplatin]. In Cohort 2, mFOLFOX6 was administered every 2 weeks as oxaliplatin 85 mg/m^2 with leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2) followed by 5-FU as a 400 mg/m^2 bolus then via continuous infusion of 2,400 mg/m^2 over 46 to 48 hours. In Cohort 3A pembrolizumab 200 mg was administered every 3 weeks. All patients received antiemetic premedication, including but not limited to NK-1 and 5-HT3 receptor blockers.

Treatment continued until disease progression, intolerable toxicity, start of another anticancer treatment, or other treatment discontinuation criteria were met. Patients without disease progression could receive pembrolizumab for up to 24 months.

The study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonization Good Clinical Practice guidelines, and applicable laws and regulations. All patients provided written informed consent. In addition, all human investigations were performed after approval by an institutional review board.

Assessments

The primary objective of the study was to determine the objective response rate (ORR) with zolbetuximab as a single agent in Cohort 1A, as assessed by independent review per RECIST v1.1. Secondary efficacy endpoints were assessed for zolbetuximab monotherapy and zolbetuximab combined with either mFOLFOX6 or pembrolizumab. ORR of zolbetuximab combination therapy (with mFOLFOX6 or pembrolizumab) was assessed by independent review and ORR with zolbetuximab monotherapy and combination therapy (with mFOLFOX6 or pembrolizumab) was assessed by the investigator. Disease control rate [DCR, the proportion of patients with a complete response (CR) or partial response (PR; ≥ 4 weeks), stable disease (SD), or non-CR/non-progressive disease (≥ 35 days from first dose) per RECIST v1.1], duration of response, and PFS were assessed with monotherapy and combination therapy (mFOLFOX6) by independent review and by the investigator. OS was assessed with zolbetuximab as a single agent (Cohort 1A). Safety and tolerability of zolbetuximab monotherapy and combination therapy were evaluated by monitoring safety parameters, including adverse events (AE), electrocardiograms, vital signs, Eastern Cooperative Oncology Group performance status, and laboratory assessments. Immunogenicity was assessed by evaluating the proportion of patients (all cohorts) positive for antidrug antibodies (ADA) after receiving zolbetuximab.

PK parameters were assessed for zolbetuximab and included area under the concentration–time curve over the dosing interval (AUC_{tau}) and maximum concentration (C_{max}). Dose-normalized C_{max} and dose-normalized AUC over 24 hours (AUC_{24h}) were assessed for oxaliplatin (total and free platinum) and 5-FU; dose-normalized AUC over 5 hours (AUC_{5h}) was assessed for 5-FU. PK parameters assessed for pembrolizumab included concentrations after end of infusion and trough concentrations. The PK assessment schedule is presented in the Supplementary Data.

Health-related quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC-QLQ-C30), EORTC-QLQ Oesophago-Gastric Module (EORTC-QLQ-OG25), Global Pain questionnaire, and EuroQoL Five Dimensions Questionnaire, 5-level version (EQ-5D-5L). The health-related quality of life assessment schedule is presented in the Supplementary Data.

Statistical analysis

Planned sample sizes were expected to provide adequate early efficacy and safety data in Cohort 1A ($n = 20$), sufficient PK data for zolbetuximab, oxaliplatin, and 5-FU in Cohort 2 ($n = 12$), and data on safety and tolerability of dose level in Cohort 3A [$n = 3$–12 depending on dose-limiting toxicities (DLT)]. The full analysis population included all patients who received at least 1 dose of zolbetuximab and had at least 1 posttreatment disease assessment. The safety population included all patients who received at least 1 dose of zolbetuximab. The PK population was a subset of the safety population and included patients for whom at least 1 concentration value was available for analysis. Time to event endpoints were estimated using the Kaplan–Meier method and medians and 95% confidence intervals (CI) are reported. Descriptive statistics were used to summarize PK parameters. AEs were graded using the US NCI's Common Terminology Criteria for Adverse Events.

Data availability

Upon request, and subject to certain criteria, conditions, and exceptions, Astellas will provide access to anonymized patient level data from completed Astellas sponsored Phase I to IV interventional clinical studies conducted for its products. Where available, the following anonymized patient level data and information is provided for each clinical study: Raw dataset, Analysis ready dataset, Protocols with any amendments or addenda, Annotated case report form, Statistical analysis plan, Dataset specifications and Clinical study report. Additional data may be available upon request. Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials by submitting an enquiry at https://clinicalstudydatarequest.com/Submission.aspx?groupid=ENQUIRY. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

Results

Patients

From study initiation until data cutoff (August 20, 2018 to May 3, 2021), 54 patients from 14 study sites had enrolled in the study [Cohort 1A, $n = 30$; Cohort 2, $n = 21$; Cohort 3A, $n = 3$ (Cohort 3A enrollment had been completed at data cutoff); Supplementary Table S1]. Of the 351 valid CLDN18.2 IHC results generated from tumor samples submitted during prescreening/screening, 36.8% (129/351) and 9.4% (33/351) were positive for CLDN18.2 with strong to moderate membranous CLDN18 staining in ≥ 75% of tumor cells and 50% to < 75% of tumor cells, respectively. All patients (100%) in Cohorts 1A and 2 and 66.7% of patients in Cohort 3A were in the high CLDN18.2 expression category (**Table 1**). Additional patient demographics are shown in **Table 1**. Representativeness of the study population in the context of real-world populations is described in Supplementary Table S2.

At data cutoff of May 3, 2021, 20 of 21 (95.2%) patients had discontinued zolbetuximab and mFOLFOX6 and all patients had discontinued zolbetuximab plus pembrolizumab and zolbetuximab monotherapy. Median duration of zolbetuximab treatment was 22 days (range, 1–589) in Cohort 1A, 231 days (range, 1–839) in Cohort 2, and 45 days (range, 44–64) in Cohort 3A.

Efficacy

Cohort 1A – third-line or later zolbetuximab monotherapy

On the basis of independent review, the ORR was 0% (**Table 2**); 3 patients had tumor size reduction with zolbetuximab monotherapy (Supplementary Fig. S2A). DCR was 44.4% (95% CI, 25.48–64.67). Of 20 evaluable patients, 6 (30%) patients had a best overall response of SD (by independent review), 5 (25%) of whom experienced tumor shrinkage (Supplementary Fig. S3A). At data cutoff, 26 (86.7%) of patients either had disease progression (per independent review) or had died. Median PFS was 1.54 months (95% CI, 1.31–2.56; **Fig. 1**).

On the basis of investigator review, there were 3 confirmed PRs, which yielded an ORR of 11.1% (95% CI, 2.45–30.15). DCR was 44.4% (95% CI, 26.59–66.63). Median PFS was 1.48 months (95% CI, 1.28–2.56).

At data cutoff, 24 patients in Cohort 1A had died. Median OS was 5.62 months (95% CI, 2.27–11.53); the 18-month OS rate was 23.62% (95% CI, 9.78–40.83). Median follow-up time was 28.35 months (95%

Table 1. Patient characteristics and disease demographics in the safety population.

	Cohort 1A Zolbetuximab Monotherapy ($n = 30$)	Cohort 2 Zolbetuximab + mFOLFOX6 ($n = 21$)	Cohort 3A Zolbetuximab + Pembrolizumab ($n = 3$)
Sex, *n* (%)			
Male	20 (66.7)	12 (57.1)	1 (33.3)
Female	10 (33.3)	9 (42.9)	2 (66.7)
Race, *n* (%)			
White	15 (50.0)	8 (38.1)	0
Black or African American	0	1 (4.8)	0
Asian	11 (36.7)	9 (42.9)	3 (100)
Missing	4 (13.3)	3 (14.3)	0
Ethnicity, *n* (%)			
Hispanic or Latino	3 (10.0)	0	0
Not Hispanic or Latino	23 (76.7)	18 (85.7)	3 (100)
Missing	4 (13.3)	3 (14.3)	0
Age (years)			
Median (min–max)	59.5 (32.0–79.0)	63.0 (36.0–74.0)	65.0 (58.0–74.0)
CLDN18.2 expression, *n* (%)			
Intermediate (≥50% and <75%)	0	0	1 (33.3)
High (≥75%)	30 (100)	21 (100)	2 (66.7)
Tumor location, *n* (%)			
Proximal	13 (43.3)	9 (42.9)	1 (33.3)
Distal	11 (36.7)	5 (23.8)	2 (66.7)
Unknown	6 (20.0)	7 (33.3)	0
Tumor type, *n* (%)			
Diffuse	16 (53.3)	12 (57.1)	2 (66.7)
Intestinal	9 (30.0)	7 (33.3)	0
Mixed	1 (3.3)	0	1 (33.3)
Other	4 (13.3)	2 (9.5)	0
Location of first metastasis, *n* (%)			
Abdominal cavity	1 (3.3)	0	0
Bone	3 (10.0)	2 (9.5)	0
Liver	8 (26.7)	3 (14.3)	1 (33.3)
Lung	3 (10.0)	0	0
Lymph node	3 (10.0)	4 (19.0)	2 (66.7)
Peritoneum	8 (26.7)	8 (38.1)	0
Rectum	1 (3.3)	0	0
Retroperitoneum	1 (3.3)	1 (4.8)	0
Stomach	0	1 (4.8)	0
Other	0	1 (4.8)	0
Prior cancer medication, *n* (%)			
Platinum-based chemotherapy	4 (13.3)	0	0
Oxaliplatin-based chemotherapy	18 (60.0)	3 (14.3)	3 (100)
Irinotecan	7 (23.3)	0	0
S1	2 (6.7)	1 (4.8)	3 (100)
Docetaxel	3 (10.0)	2 (9.5)	0
Ramucirumab	8 (26.7)	0	3 (100)
Paclitaxel	11 (36.7)	0	3 (100)
Ramucirumab with paclitaxel	5 (16.7)	0	0
Nivolumab	1 (3.3)	0	0
Pembrolizumab	2 (6.7)	0	0
Trastuzumab	1 (3.3)	0	0
Other	27 (90.0)	3 (14.3)	0
Prior gastrectomy, *n* (%)	12 (40.0)	4 (19.0)	0

Abbreviations: max, maximum; min, minimum.

CI, 18.89–28.75). When stratified by previous gastrectomy, median OS was 6.64 months (95% CI, 1.68–15.15) and 2.86 months (95% CI, 2.00–11.53) for gastrectomy and no gastrectomy, respectively. By Lauren classification, median OS was 9.89 months (95% CI, 1.91–21.45) with diffuse type and 5.62 months (95% CI, 2.27–15.15) with intestinal type.

Cohort 2 – first-line zolbetuximab plus mFOLFOX6

On the basis of independent review, ORR was 71.4% (95% CI, 47.82–88.72; **Table 2**). The best overall response was PR in 15 patients (71.4%; Supplementary Fig. S2B). The DCR was 100% (95% CI, 83.89–100). Median duration of response was 15.9 months (95% CI, 5.4 to not evaluable). Of 18 evaluable patients, 3 (17%) patients had a best overall

Table 2. Tumor responses per independent review in the full analysis population.

	Cohort 1A Zolbetuximab Monotherapy ($n = 27$[a])	Cohort 2 Zolbetuximab + mFOLFOX6 ($n = 21$)	Cohort 3A Zolbetuximab + Pembrolizumab ($n = 3$)
Best overall response, *n* (%)[b]			
Confirmed CR	0	0	0
Confirmed PR	0	15 (71.4)	0
Unconfirmed CR	0	0	0
Unconfirmed PR	0	1 (4.8)	0
Stable disease	6 (22.2)	2 (9.5)	1 (33.3)
Non-CR/non-progressive disease	6 (22.2)	3 (14.3)	1 (33.3)
Progressive disease	12 (44.4)	0	1 (33.3)
Not evaluable	3 (11.1)	0	0
ORR (confirmed)			
ORR, *n* (%)	0	15 (71.4)	0
95% CI (%)[c]	(0.00–12.77)	(47.82–88.72)	(0.00–70.76)
ORR (confirmed and unconfirmed)			
ORR, *n* (%)	0	16 (76.2)	0
95% CI (%)[c]	(0.00–12.77)	(52.83–91.78)	(0.00–70.76)
DCR (confirmed)			
DCR, *n* (%)[d]	12 (44.4)	21 (100.0)	2 (66.7)
95% CI (%)[c]	(25.48–64.67)	(83.89–100.00)	(9.43–99.16)
DCR (confirmed and unconfirmed)			
DCR, *n* (%)[d]	15 (55.6)	21 (100.0)	2 (66.7)
95% CI (%)[c]	(35.33–74.52)	(83.89–100.00)	(9.43–99.16)

Note: Patients included in the full analysis population received at least 1 dose of zolbetuximab and had at least 1 posttreatment disease assessment.
[a]Of 30 patients, 3 patients were excluded because no postbaseline scan was available per the definition of the full analysis population. Among the 27 patients in the full analysis population, 3 patients received postbaseline scans, but results were not evaluable. Those 3 patients were included in the analysis per the statistical analysis plan.
[b]The definition of best overall response followed RECIST v1.1. Confirmed CR/PR must have been confirmed by 2 scans a minimum of 4 weeks apart. When SD (or non-CR/non-progressive disease) was believed to be the best response, the assessment was to be at least 35 days from first dose date. For calculation of percentage, denominator included total number of participants in all categories in best overall response, except not evaluable.
[c]Using exact method based on binomial distribution (Clopper-Pearson).
[d]Confirmed DCR was defined as the proportion of participants who have a best overall response of CR or PR (≥4 weeks), SD or non-CR/non-progressive disease (≥35 days from first dose date).

response of SD (by independent review), 2 of whom experienced tumor shrinkage. Fifteen (83%) patients had a best overall response of PR, 12 (67%) of whom experienced tumor shrinkage of at least 50% (Supplementary Fig. S3B). At data cutoff, 10 patients (47.6%) had experienced disease progression or died; median PFS was 17.8 months (95% CI, 8.05–25.69; **Fig. 1**) and the 12-month PFS rate was 58.6% (95% CI, 31.92–77.90).

On the basis of investigator review, ORR was 57.1% (95% CI, 34.02–78.18); 12 patients had confirmed PRs. The DCR was 100% (95% CI, 83.89–100). Median duration of response was 4.2 months (95% CI, 3.9–19.5). Seventeen patients (81.0%) experienced PFS events (disease progression or death); median PFS was 8.38 months (95% CI, 6.05–14.19).

Cohort 3A – third-line or later zolbetuximab plus pembrolizumab

On the basis of independent review and investigator review, there were no CRs or PRs in Cohort 3A (**Table 2**). The DCR was 66.7% (95% CI, 9.43–99.16) by independent review and 100% (95% CI, 29.24–100) by investigator review. Median PFS was 2.96 months by independent review (**Fig. 1**) and investigator review.

Safety

The most frequent reasons for zolbetuximab discontinuation were progressive disease (70.0%) and AEs (10.0%) in Cohort 1A and progressive disease in Cohort 2 (71.4%) and Cohort 3A (100%).

Cohort 1A – zolbetuximab monotherapy

Commonly reported AEs of any grade in Cohort 1A were nausea (63.3%), abdominal pain (40.0%), vomiting (36.7%), asthenia (26.7%), decreased appetite (23.3%), anemia (20.0%), and pyrexia (20.0%; **Table 3**). Nausea and vomiting, considered AEs of special interest, were primarily grade 1 or 2. Fifteen (50.0%) patients in the cohort experienced an AE of grade ≥3. The most reported grade 3 AEs were anemia, abdominal pain, and hypertension ($n = 3$ each); grade 4 AEs were acute coronary syndrome, cardiac arrest, and posterior reversible encephalopathy syndrome ($n = 1$ each). Grade ≥3 nausea and vomiting each were reported in 6.7% of patients (Supplementary Table S3). Grade ≥3 AEs deemed related to zolbetuximab were reported in 7 (23.3%) patients; hypertension was the only grade ≥3 AE that occurred in 3 or more patients (Supplementary Table S3).

Twelve (40.0%) patients experienced an AE that led to a dose interruption of zolbetuximab; the AEs reported in 2 or more patients were nausea ($n = 9$), vomiting ($n = 4$), and hypertension ($n = 2$). Five patients discontinued zolbetuximab due to 8 AEs ($n = 1$ acute coronary syndrome, cardiac arrest, intestinal obstruction, anaphylactic reaction, drug hypersensitivity, sepsis, posterior reversible encephalopathy syndrome, and pulmonary embolism). During the study period, 3 patients died due to AEs. Causes of death were intestinal obstruction ($n = 1$) and sepsis ($n = 2$), none of which were considered related to zolbetuximab.

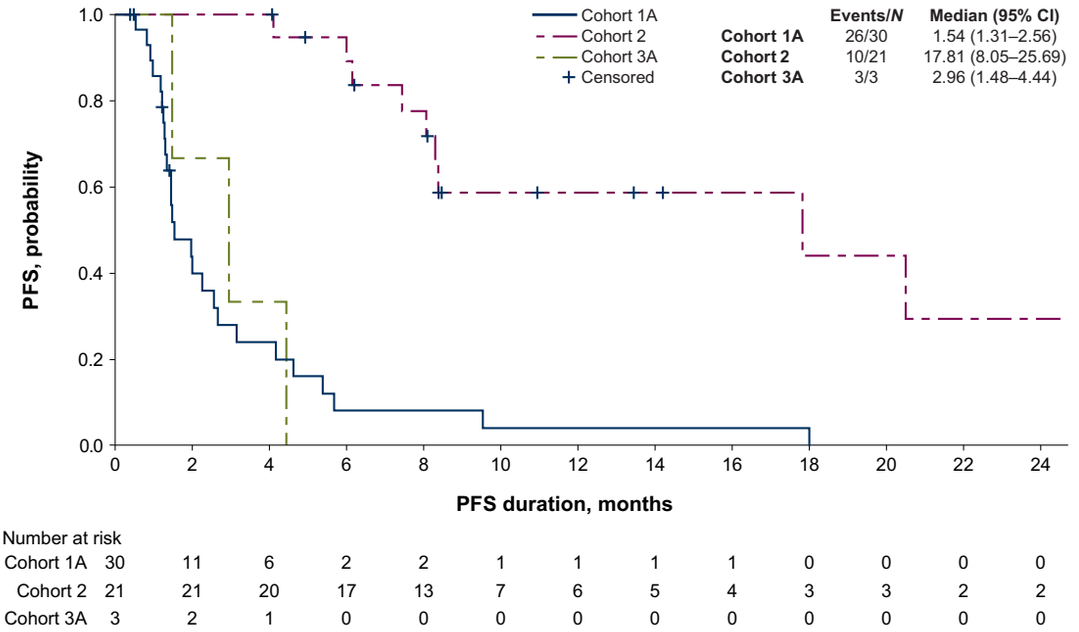

Figure 1.

PFS based on Independent Review in the Safety Population (Kaplan–Meier). Cohort 1A, zolbetuximab monotherapy ($n = 30$); Cohort 2, zolbetuximab + mFOLFOX6 ($n = 21$); Cohort 3A, zolbetuximab + pembrolizumab ($n = 3$).

Cohort 2 – zolbetuximab plus mFOLFOX6

Any-grade AEs reported in ≥20% of patients were nausea (90.5%); vomiting (66.7%); decreased neutrophil count and decreased appetite (42.9% each); neutropenia, diarrhea, and fatigue (38.1% each); abdominal pain and peripheral sensory neuropathy (33.3% each); constipation and pyrexia (28.6% each); and anemia, weight decrease, back pain, and myalgia (23.8% each; **Table 3**). Nausea and vomiting (AEs of special interest) were primarily grade 1 or 2. Twenty (95.2%) patients experienced AEs that were grade ≥ 3 (Supplementary Table S3). The grade ≥3 AEs that occurred in 3 or more patients were neutropenia (grade 3, $n = 5$; grade 4, $n = 1$), decreased neutrophil count (grade 3, $n = 6$; grade 4, $n = 1$), hypertension (grade 3, $n = 3$), and peripheral sensory neuropathy (grade 3, $n = 3$). Grade ≥3 nausea and vomiting were reported in 4.8% and 9.5% of patients, respectively (Supplementary Table S3). Fourteen (66.7%) patients experienced grade ≥3 AEs deemed related to zolbetuximab; those that occurred in 3 or more patients were neutropenia (grade 3, $n = 4$; grade 4, $n = 1$), decreased neutrophil count (grade 3, $n = 4$; grade 4, $n = 1$), and hypertension (grade 3, $n = 3$).

Eleven (52.4%) patients experienced an AE that led to a dose interruption of zolbetuximab. Four patients discontinued zolbetuximab as a result of 7 AEs ($n = 1$ each: abdominal pain, dysphagia, nausea, vomiting, hypokalemia, meninges metastasis, and dyspnea). No patient died due to an AE during the study.

Cohort 3A – zolbetuximab plus pembrolizumab

All 3 patients in Cohort 3A experienced AEs of any grade (**Table 3**). The most frequently reported were nausea, constipation, pyrexia, and decreased appetite ($n = 2$ each), and all other AEs were reported in 1 patient each. Nausea and vomiting (AEs of special interest) were grade 1 or 2. No immune-related AEs were reported. No DLTs were reported in the 3 DLT-evaluable patients, so additional patients were not enrolled into the cohort per the study plan. One (33.3%) patient experienced an AE of grade ≥ 3 (grade 4 decreased neutrophil count) that was related to zolbetuximab (Supplementary Table S3). One patient had their zolbetuximab dose interrupted to manage pyrexia. No patient discontinued zolbetuximab due to AEs. No patient died during the study.

Immunogenicity

Across the cohorts, 44 patients had immunogenicity data and 3 (6.8%) patients with a negative baseline tested positive for ADAs after receiving zolbetuximab. Among the ADA-positive patients, 2 were in Cohort 1A and 1 was in Cohort 2. In Cohort 1A, 1 of the patients was ADA-positive on Day 1 of Cycles 2 and 3 and the other patient was ADA-positive on Day 1 of Cycle 2 and at the 30-day safety follow-up visit. In Cohort 2, the patient was ADA-positive on Day 1 of Cycle 2 then ADA-negative at subsequent visits. Time from the earliest ADA-positive assessment to progressive disease per independent review was 24 and 25 days for the 2 patients in Cohort 1A and 101 days for the patient in Cohort 2.

PK parameters

Zolbetuximab exposure (C_{max} and AUC_{tau}) was generally comparable across the cohorts (Supplementary Fig. S4A–S4C), indicating that coadministration with mFOLFOX6 or pembrolizumab did not impact zolbetuximab PK. Geometric mean (GM) C_{max} and AUC_{tau} after the first dose of zolbetuximab in each cohort ranged from 426 to 470 μg/mL and from 1,770 to 2,870 day•μg/mL, respectively (Supplementary Table S4). After multiple doses of zolbetuximab, GM C_{max} was 354 and 365 μg/mL in Cohort 1A and Cohort 2, respectively; GM AUC_{tau} was 2,490 and 2,210 day•μg/mL, respectively (Supplementary Table S4).

Coadministration of zolbetuximab with oxaliplatin appeared to increase the dose-normalized AUC_{24h} of total platinum and free platinum by approximately 10% to 16% (Supplementary Table S5).

Table 3. Any grade (in ≥3 patients in any treatment cohort) and grade ≥3 AEs in the safety population.

	Cohort 1A Zolbetuximab Monotherapy ($n = 30$), n (%)		Cohort 2 Zolbetuximab + mFOLFOX6 ($n = 21$), n (%)		Cohort 3A Zolbetuximab + Pembrolizumab ($n = 3$), n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	30 (100)	15 (50.0)	21 (100)	20 (95.2)	3 (100)	1 (33.3)
Blood and lymphatic system disorders						
Anemia	6 (20.0)	3 (10.0)	5 (23.8)	2 (9.5)	0	0
Neutropenia	0	0	8 (38.1)	6 (28.6)	0	0
Gastrointestinal disorders						
Nausea	19 (63.3)	2 (6.7)	19 (90.5)	1 (4.8)	2 (66.7)	0
Abdominal pain	12 (40.0)	3 (10.0)	7 (33.3)	2 (9.5)	0	0
Vomiting	11 (36.7)	2 (6.7)	14 (66.7)	2 (9.5)	1 (33.3)	0
Constipation	5 (16.7)	0	6 (28.6)	0	2 (66.7)	0
Diarrhea	3 (10.0)	0	8 (38.1)	1 (4.8)	1 (33.3)	0
Dyspepsia	3 (10.0)	0	3 (14.3)	0	0	0
Hematemesis	3 (10.0)	1 (3.3)	0	0	0	0
Dysphagia	1 (3.3)	0	3 (14.3)	1 (4.8)	0	0
Stomatitis	0	0	4 (19.0)	0	0	0
General disorders and administration site conditions						
Asthenia	8 (26.7)	1 (3.3)	3 (14.3)	0	0	0
Pyrexia	6 (20.0)	1 (3.3)	6 (28.6)	2 (9.5)	2 (66.7)	0
Fatigue	2 (6.7)	0	8 (38.1)	1 (4.8)	0	0
Laboratory investigations						
Decreased neutrophil count	2 (6.7)	0	9 (42.9)	7 (33.3)	1 (33.3)	1 (33.3)
Weight decreased	1 (3.3)	0	5 (23.8)	0	0	0
Platelet count decreased	0	0	3 (14.3)	1 (4.8)	0	0
Metabolism and nutrition disorders						
Decreased appetite	7 (23.3)	0	9 (42.9)	1 (4.8)	2 (66.7)	0
Hypokalemia	0	0	3 (14.3)	2 (9.5)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	3 (10.0)	0	5 (23.8)	0	0	0
Myalgia	1 (3.3)	0	5 (23.8)	1 (4.8)	0	0
Muscle spasms	0	0	3 (14.3)	0	0	0
Nervous system disorders						
Dizziness	1 (3.3)	0	3 (14.3)	1 (4.8)	0	0
Paresthesia	1 (3.3)	0	3 (14.3)	1 (4.8)	0	0
Peripheral sensory neuropathy	1 (3.3)	0	7 (33.3)	3 (14.3)	0	0
Neuropathy, peripheral	0	0	4 (19.0)	2 (9.5)	0	0
Respiratory, thoracic, and mediastinal disorders						
Cough	3 (10.0)	0	2 (9.5)	0	0	0
Skin and subcutaneous tissue disorders						
Pruritus	1 (3.3)	0	4 (19.0)	0	0	0
Vascular disorders						
Hypertension	4 (13.3)	3 (10.0)	3 (14.3)	3 (14.3)	1 (33.3)	0

Coadministration of zolbetuximab with oxaliplatin appeared to increase the dose-normalized C_{max} of free platinum (by approximately 30%), but not total platinum. Although the sample size was small, the apparent increase in total platinum and free platinum exposure after coadministration with zolbetuximab did not appear to change the safety profile of mFOLFOX6 and was not deemed to be clinically significant (24, 25).

Concomitant administration of zolbetuximab with 5-FU did not affect the systemic exposure of 5-FU (Supplementary Table S5). Zolbetuximab did not appear to affect the PK parameters of pembrolizumab (data not shown).

Health-related quality of life

Mean changes over time did not indicate a worsening of health-related quality of life, as assessed using the EORTC-QLQ-C30, EORTC-QLQ-OG25, Global Pain, and EQ-5D-5L questionnaires. Neither increases nor decreases from baseline in global pain were clinically relevant. Results of the EQ-5D-5L 5-point-scale questionnaire indicated a good health state for the patients. Most patients reported positive results for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Discussion

The paradigm of biomarker-directed therapies continues to evolve in G/GEJ adenocarcinoma. This nonrandomized multi-cohort phase II trial was designed to examine zolbetuximab across multiple lines of therapy and with multiple drug combinations in CLDN18.2-expressing patients to inform further development. Although the activity in the primary efficacy cohort (Cohort 1A) was limited (ORR, 0%), the antitumor response (independent review ORR, 71.4%) and median PFS (17.8 months) with the combination of zolbetuximab plus

mFOLFOX6 (Cohort 2) are encouraging and compare favorably with results of other frontline biomarker-selected trials (26, 27). It should be noted that difference between median duration of response by independent review (15.9 months, 15 responders with 53% censoring rate) and investigator review (4.2 months, 12 responders with 25% censoring rate) was likely a result of small sample size and the effect of censoring on duration of response estimation by the Kaplan–Meier method. Patients enrolled in the current study had advanced/metastatic G/GEJ adenocarcinoma with high or intermediate CLDN18.2 expression (in ≥75% of tumor cells in Cohorts 1A and 2 and in ≥50% of tumor cells in Cohort 3A) determined using a validated IHC assay. The previously reported phase IIa MONO study, which evaluated zolbetuximab monotherapy in previously treated (≥1 line of chemotherapy) patients with advanced/metastatic CLDN18.2-positive [moderate to strong (2+/3+) membrane staining intensity in ≥50% of tumor cells] G/GEJ adenocarcinoma, showed an ORR of 9% (PR, $n = 4$) among 43 assessable patients (21). The randomized phase II FAST study demonstrated the ability of an enriched population (higher CLDN18.2 expression) to increase the magnitude of benefit from zolbetuximab (20). The FAST study evaluated first-line zolbetuximab combined with EOX in patients with advanced G/GEJ adenocarcinoma and moderate to strong CLDN18.2 membrane staining intensity in ≥40% of tumor cells (2+/3+ staining intensity using the CLAUDETECT18.2 assay; ref. 20). When a more stringent CLDN18.2 expression cutoff of ≥70% was analyzed, the PFS benefit was significantly longer with zolbetuximab plus EOX versus EOX alone (9.0 vs. 5.7 months; $P < 0.0005$), consistent with a relationship between biomarker expression and zolbetuximab activity. Results of the current study have added to these data by demonstrating the safety and clinical activity of zolbetuximab combined with mFOLFOX6, which is the most commonly used frontline chemotherapy regimen.

The relevance of CLDN18.2 as a targetable biomarker in gastric cancers is being assessed in different treatment strategies. Early results of a phase I trial showed promising antitumor activity and an acceptable safety profile with CLDN18.2-specific chimeric antigen receptor T cell (CAR-T) treatment of patients with CLDN18.2-positive gastrointestinal cancers (28). A humanized immunoglobulin G1 monoclonal antibody against CLDN18.2 and an anti-CLDN18.2 antibody-drug conjugate have also shown promising antitumor activity and acceptable safety profiles in early phase studies of patients with gastrointestinal cancers (29, 30). Studies assessing safety and antitumor activity of a novel bispecific antibody against CLDN18.2 and a novel CLDN18.2-targeted CAR-T therapy in patients with solid tumors, including gastrointestinal tumors, are underway (31, 32). These therapeutic strategies have the potential to enhance the treatment landscape for patients with CLDN18.2-positive gastrointestinal cancers.

Differential activity among biomarker strata has been observed in trials that stratified patients by HER2 and PD-L1 expression level. In subgroup analyses from the first ToGA trial, patients with the highest degree of HER2 positivity and/or amplification had the best clinical outcomes (27). Similarly, in the recent frontline CheckMate-649 trial, both antitumor response and survival were improved in the highest biomarker strata [patients who were PD-L1–positive with combined positive score (CPS) > 5; ref. 14]. Analogous trends were observed in the frontline phase III KEYNOTE-590 trial where patients with CPS ≥ 10 derived the largest degree of benefit (12, 33). We have leveraged an improved biomarker understanding to limit Cohorts 1A and 2 to high CLDN18.2 expression (defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining), which also served as the basis for selecting patients in the phase III zolbetuximab trials [GLOW, zolbetuximab plus capecitabine/oxaliplatin (NCT03653507) and SPOTLIGHT, zolbetuximab plus mFOLFOX6 (NCT03504397)]. Primary analysis showed that both trials met their primary endpoint of PFS and key secondary endpoint of OS, with clinically and statistically significant benefit in both endpoints (22, 23). Median PFS with zolbetuximab plus mFOLFOX6 was 17.8 months (95% CI, 8.05–25.69) in the current study ($n = 21$) and 10.61 months (95% CI, 8.90–12.48) in the SPOTLIGHT study ($n = 283$; ref. 23). Baseline characteristics of patients in the zolbetuximab plus mFOLFOX6 groups were similar between studies. The safety profile of zolbetuximab plus mFOLFOX6 was assessed in the larger SPOTLIGHT population and was consistent with that in the current study. Commonly reported AEs with zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6 were nausea (81.0% vs. 60.8%), vomiting (64.5% vs. 34.5%), and decreased appetite (47.0% vs. 33.5%). The proportion of patients who experienced serious AEs was similar in both treatment groups (44.8% vs. 43.5%).

Safety data from the current study are consistent with the known safety profile for zolbetuximab. Results of the FAST study showed that the most commonly reported AEs with zolbetuximab combined with EOX were gastrointestinal and generally of mild to moderate intensity (20). Anemia and neutropenia were slightly more frequently reported among patients who received zolbetuximab and EOX versus EOX alone (20). Gastrointestinal AEs were commonly reported across all 3 cohorts in the current study, and most cases were grades 1 to 2. Fewer than 20% of patients in any cohort discontinued treatment with zolbetuximab due to an AE. No new safety signals were observed within any of the treatment cohorts. Notably, the safety profile does not include longer-duration AEs, such as immune-related events observed with anti–PD-1 agents. In addition, zolbetuximab combinations did not have a negative impact on global health-related quality of life.

The exposure of zolbetuximab was generally comparable across the cohorts, indicating that coadministration with mFOLFOX6 or pembrolizumab did not affect zolbetuximab PK. Concomitant administration with zolbetuximab did not affect the systemic exposure of 5-FU, but appeared to slightly increase the exposure of platinum. The apparent increase in total platinum and free platinum exposure after coadministration with zolbetuximab did not appear to change the safety profile of mFOLFOX6 and was not deemed to be clinically significant. Although the number of patients in Cohort 3A was small ($n = 3$), pembrolizumab exposure appeared to be comparable to that reported in the literature (34), indicating that zolbetuximab did not impact pembrolizumab PK.

Although limited by sample size and study design (single-arm study), our work with zolbetuximab combined with mFOLFOX6 provides early insight into the promising efficacy of this combination in frontline treatment of patients with CLDN18.2-positive G/GEJ adenocarcinoma. The encouraging results observed with zolbetuximab plus mFOLFOX6 supported findings from nonclinical studies (17, 19). Preliminary findings from ongoing clinical studies show high CLDN18.2 prevalence in advanced/metastatic G/GEJ adenocarcinoma, suggesting application to a larger proportion of patients. Demonstrating single-agent biologic activity for monoclonal antibodies in heavily pretreated patients with G/GEJ adenocarcinoma has been difficult. Similarly, we observed limited zolbetuximab monotherapy activity in third- or later-line treatment.

Overall, results of the current study provided preliminary efficacy and safety data to support the ongoing phase III zolbetuximab studies (NCT03504397 and NCT03653507) designed to confirm the benefit of adding zolbetuximab to frontline fluoropyrimidine/platinum

chemotherapy. Building upon the strategy of combining monoclonal antibodies with anti–PD-1 agents and chemotherapy in first-line G/GEJ adenocarcinoma, the study reported here has added an additional cohort assessing the triple combination of zolbetuximab, mFOLFOX6, and nivolumab (NCT03505320).

Authors' Disclosures

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Note

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