Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

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Summary

Background Zolbetuximab, a monoclonal antibody targeting claudin-18 isoform 2 (CLDN18.2), has shown efficacy in patients with CLDN18.2-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. We report the results of the SPOTLIGHT trial, which investigated the efficacy and safety of first-line zolbetuximab plus mFOLFOX6 (modified folinic acid [or levofolinate], fluorouracil, and oxaliplatin regimen) versus placebo plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma.

Methods SPOTLIGHT is a global, randomised, placebo-controlled, double-blind, phase 3 trial that enrolled patients from 215 centres in 20 countries. Eligible patients were aged 18 years or older with CLDN18.2-positive (defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative (based on local or central evaluation), previously untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma, with radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria in Solid Tumors version 1.1; an Eastern Cooperative Oncology Group performance status score of 0 or 1; and adequate organ function. Patients were randomly assigned (1:1) via interactive response technology and stratified according to region, number of organs with metastases, and previous gastrectomy. Patients received zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus mFOLFOX6 (every 2 weeks) or placebo plus mFOLFOX6. The primary endpoint was progression-free survival assessed by independent review committee in all randomly assigned patients. Safety was assessed in all treated patients. The study is registered with ClinicalTrials.gov, NCT03504397, and is closed to new participants.

Findings Between June 21, 2018, and April 1, 2022, 565 patients were randomly assigned to receive either zolbetuximab plus mFOLFOX6 (283 patients; the zolbetuximab group) or placebo plus mFOLFOX6 (282 patients; the placebo group). At least one dose of treatment was administered to 279 (99%) of 283 patients in the zolbetuximab group and 278 (99%) of 282 patients in the placebo group. In the zolbetuximab group, 176 (62%) patients were male and 107 (38%) were female. In the placebo group, 175 (62%) patients were male and 107 (38%) were female. The median follow-up duration for progression-free survival was 12·94 months in the zolbetuximab group versus 12·65 months in the placebo group. Zolbetuximab treatment showed a significant reduction in the risk of disease progression or death compared with placebo (hazard ratio [HR] 0·75, 95% CI 0·60–0·94; p=0·0066). The median progression-free survival was 10·61 months (95% CI 8·90–12·48) in the zolbetuximab group versus 8·67 months (8·21–10·28) in the placebo group. Zolbetuximab treatment also showed a significant reduction in the risk of death versus placebo (HR 0·75, 95% CI 0·60–0·94; p=0·0053). Treatment-emergent grade 3 or worse adverse events occurred in 242 (87%) of 279 patients in the zolbetuximab group versus 216 (78%) of 278 patients in the placebo group. The most common all-grade adverse events with zolbetuximab plus chemotherapy were nausea, vomiting, and decreased appetite. Treatment-related deaths occurred in five (2%) patients in the zolbetuximab group versus four (1%) patients in the placebo group. No new safety signals were identified.

Interpretation Targeting CLDN18.2 with zolbetuximab significantly prolonged progression-free survival and overall survival when combined with mFOLFOX6 versus placebo plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Zolbetuximab plus mFOLFOX6 might represent a new first-line treatment in these patients.

Lancet 2023; 401: 1655–68

Published **Online** April 14, 2023 https://doi.org/10.1016/S0140-6736(23)00620-7

This online publication has been corrected. The corrected version first appeared at thelancet.com on December 12, 2023

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Funding Astellas Pharma, Inc.

Introduction

Gastric and gastro-oesophageal junction adenocarcinomas are among the malignancies with the highest unmet medical needs, with the highest incidence rates in Asia, Latin America, and eastern Europe.[1–3] The standard first-line chemotherapy for patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma has been platinum–fluoropyrimidine chemotherapy, including mFOLFOX6 (modified folinic acid, fluorouracil, and oxaliplatin regimen), resulting in a median overall survival duration of about 1 year.[2–8]

Combining targeted therapies with chemotherapy can improve survival, although there are few validated molecular targets in this disease.[9] In the approximately 15% of patients with human epidermal growth factor receptor 2 (HER2)-positive disease, trastuzumab is approved in combination with chemotherapy.[2,4–8] Checkpoint inhibition with nivolumab is approved as a first-line treatment in combination with chemotherapy in some countries; however, the efficacy of this treatment is mainly in patients with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) of 5 or more.[2,4,7,8,10,11] There is an unmet need for additional targeted therapies to prolong survival in the large population of patients with HER2-negative disease, many of whom have a PD-L1 CPS less than 5.[6,9,12,13]

Research in context

Evidence before this study

At the time of publication of this study, to our knowledge, there were no non-immunotherapy, biomarker-based therapies approved for the first-line treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. We used Ovid to search Embase on Feb 3, 2023, using the terms ("claudin 18" OR "CLDN18") AND ("stomach cancer" OR "gastroesophageal junction") AND ("phase 2 clinical trial" OR "phase 3 clinical trial"), with no language or time restrictions. We filtered the results by articles with no time restrictions, and conference abstracts published within the past 3 years. We removed results related to the current study, conference abstracts reporting the same study or later published as articles, reviews, editorials, a phase 1 study, and a study in patients with locally advanced resectable gastric cancer. Our search yielded four studies with efficacy and safety data. Three studies evaluated zolbetuximab: the phase 2a MONO study of zolbetuximab monotherapy showed restricted antitumour efficacy, with a manageable safety profile in patients with claudin-18 isoform 2 (CLDN18.2)-positive tumours; the phase 2b FAST study of zolbetuximab plus chemotherapy showed improved progression-free survival and overall survival versus chemotherapy, with a manageable safety profile in patients with CLDN18.2-positive tumours; and the phase 2 ILUSTRO study (cohort 2) of zolbetuximab plus chemotherapy showed a median progression-free survival of 13·7 months and an objective response in 63% of patients, with a manageable safety profile in patients with CLDN18.2-positive, HER2-negative tumours. A phase 1b–2 study evaluated a CLDN18.2-specific chimeric antigen receptor T-cell therapy and showed promising anti-tumour efficacy with a manageable safety profile in patients with CLDN18.2-positive tumours.

Added value of this study

With over 550 patients randomly assigned in the SPOTLIGHT trial, first-line zolbetuximab plus chemotherapy showed improved progression-free survival and overall survival versus placebo plus chemotherapy in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. To our knowledge, SPOTLIGHT is the first global, phase 3 study to examine the efficacy and safety of the addition of CLDN18.2-targeted therapy (ie, zolbetuximab) to standard chemotherapy (ie, mFOLFOX6 [modified folinic acid, fluorouracil, and oxaliplatin regimen]) in gastric or gastro-oesophageal junction adenocarcinoma and to show prolonged survival with a CLDN18.2-targeted therapy. Nearly 40% of screened patients had tumours that met the definition of CLDN18.2 positivity used in this study. Although nausea and vomiting leading to discontinuation were more frequent with zolbetuximab plus chemotherapy versus placebo plus chemotherapy, the safety profile was manageable in the context of the significant benefits for both progression-free and overall survival.

Implications of all the available evidence

The SPOTLIGHT trial addresses a high unmet need for additional biomarker-targeted therapies to improve survival outcomes in patients with previously untreated, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma for whom, other than immunotherapy, no advances have been reported in over a decade. The results of SPOTLIGHT suggest that CLDN18.2 tumour positivity defines a large population of patients whose survival is prolonged by targeted therapy with zolbetuximab plus chemotherapy, and that zolbetuximab could represent a new potential first-line therapy in combination with chemotherapy in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma.

Claudin-18 isoform 2 (CLDN18.2) is a tight junction protein that is normally expressed exclusively in gastric mucosa cells.[14,15] CLDN18.2 expression is retained in most gastric and gastro-oesophageal junction adenocarcinoma cells and is the dominant CLDN18 isoform expressed in both normal and malignant gastric cells.[12,15–20] During malignant transformation, cell polarity is lost and CLDN18.2 might become exposed on the surface of gastric and gastro-oesophageal junction adenocarcinoma cells, which might render CLDN18.2 more accessible to antibodies.[15–21] Therefore, CLDN18.2 is a promising emerging therapeutic target.[15–21]

Zolbetuximab is a first-in-class chimeric immunoglobulin G1 monoclonal antibody that targets and binds to CLDN18.2.[15,20] This binding mediates cell death of CLDN18.2-positive gastric and gastro-oesophageal junction adenocarcinoma cells via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[20,22,23] The phase 2b FAST study suggested that zolbetuximab improves progression-free survival and overall survival when combined with first-line chemotherapy versus chemotherapy alone in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma; the survival benefit was enhanced in patients whose tumours had higher CLDN18.2 expression compared with those with lower CLDN18.2 expression.[16]

Here, we report the results of the SPOTLIGHT trial, which investigated the efficacy and safety of first-line zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma.

Methods

Study design and patients

SPOTLIGHT is a global, randomised, placebo-controlled, double-blind, phase 3 trial that enrolled patients from 215 centres in 20 countries (appendix p 4). The trial was done in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The protocol and all amendments were approved by the appropriate institutional review board or ethics committee at each participating institution. All patients provided written informed consent before entering the trial.

Eligible patients were aged 18 years or older with CLDN18.2-positive (defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining, determined by central immunohistochemistry using the investigational VENTANA CLDN18 [43-14A] RxDx Assay [Roche Diagnostic Solutions; Tucson, AZ, USA]), HER2-negative (based on local or central evaluation), previously untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma, with radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group performance status score of 0 or 1; and adequate organ function. Additional eligibility criteria are listed in the appendix (pp 165–68). In SPOTLIGHT, the patient selection assay was switched from a manual immunohistochemistry test used in the FAST study (Claudetect 18.2; Ganymed Pharmaceuticals; Mainz, Germany) to the VENTANA CLDN18 (43-14A) RxDx Assay (both assays use the CLDN18 [43-14A] antibody). The cutoff for CLDN18.2 positivity was adapted (from ≥70% in FAST to ≥75% in SPOTLIGHT) to best identify a similar patient population using the new test.

Sex was reported by study site staff through an interactive response technology system with the options male or female.

As an ad-hoc analysis, PD-L1 immunohistochemistry was investigated using the Dako PD-L1 IHC 28-8 pharmDx assay on the available remaining tumour samples.

Randomisation and masking

Enrolled patients were randomly assigned (1:1) to zolbetuximab plus mFOLFOX6 or placebo plus mFOLFOX6 by masked site staff via interactive response technology by block randomisation (block sizes of two) and stratified according to region (Asia *vs* non-Asia), number of organs with metastases (0–2 *vs* ≥3), and previous gastrectomy (yes *vs* no). The randomisation list and study drug masking were maintained by the interactive response technology system. The funder, investigators, clinical staff, and patients remained masked to treatment throughout the study. Zolbetuximab and placebo were identical in appearance and form and were provided to the investigator or designee by an unmasked pharmacist and administered in identical volumes, routes, and schedules to maintain masking.

Procedures

Patients received either an intravenous infusion of zolbetuximab 800 mg/m² (cycle 1, day 1) followed by 600 mg/m² (cycle 1, day 22, and days 1 and 22 of subsequent cycles) plus intravenous infusion of mFOLFOX6 (folinic acid 400 mg/m², or optionally in Japan, levofolinate 200 mg/m²; fluorouracil 400 mg/m² bolus followed by 2400 mg/m² in a 46-h to 48-h infusion; and oxaliplatin 85 mg/m²; on days 1, 15, and 29) or placebo plus mFOLFOX6, for four 42-day cycles. Patients without disease progression continued beyond four cycles with zolbetuximab or placebo plus, at the investigator's discretion, folinic acid (or optionally in Japan, levofolinate) and fluorouracil. Treatment continued until disease progression, development of toxic effects, start of another anticancer treatment, or other discontinuation criteria were met, as specified in the protocol.

See Online for appendix

The radiological tumour response was assessed by imaging at screening, then every 9 weeks in the first 54 weeks, and every 12 weeks thereafter until disease progression or the start of another anticancer treatment. During follow-up, survival was assessed at least every

12 weeks. Patients completed health-related quality-of-life assessments, including the European Organization for Research and Treatment of Cancer QLQ-C30, QLQ-OG25, and Global Pain and the EuroQOL Five-Dimensions Questionnaire, at screening, then every 3 weeks while on treatment, at treatment discontinuation, and at 30 days and 90 days after treatment discontinuation.

Outcomes

The primary endpoint was progression-free survival per RECIST version 1.1, as determined by an independent review committee. Key secondary endpoints were overall survival and time to confirmed deterioration; statistical hypothesis testing for time to confirmed deterioration in key patient-reported outcomes is pending the clinically meaningful threshold obtained from the ongoing exit survey study per protocol and will be disclosed in a subsequent publication. Additional secondary endpoints were objective response and duration of response per RECIST version 1.1 as determined by an independent review committee, safety and tolerability of zolbetuximab, additional patient-reported outcomes, and pharmacokinetics and immunogenicity of zolbetuximab; additional patient-reported outcome data will also be disclosed in a subsequent publication. As an ad-hoc analysis, objective response per RECIST version 1.1 was assessed in patients with measurable lesions. Adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, were monitored throughout the trial and for 90 days after treatment discontinuation. Adverse event preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

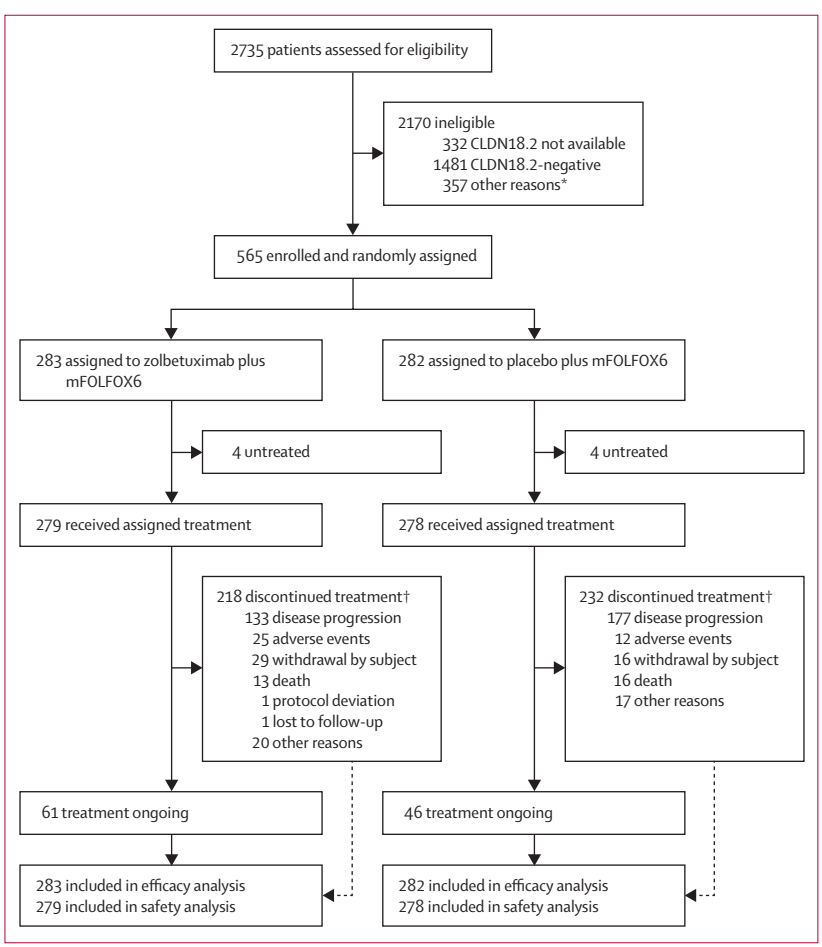


Figure 1: **Trial profile**
CLDN18.2=claudin-18 isoform 2. mFOLFOX6=modified folinic acid, fluorouracil, and oxaliplatin regimen. *Represents patients whose tumours were CLDN18.2-positive but who failed screening for other reasons, including withdrawal by patient, laboratory findings, human epidermal growth factor receptor 2 expression status, and Eastern Cooperative Oncology Group performance status score. †If a patient discontinued from both zolbetuximab or placebo and mFOLFOX6 on the same day, all reasons for discontinuation are summarised; therefore, the sum of the values for individual reasons for discontinuation is more than 218 for the zolbetuximab group and more than 232 for the placebo group.

Statistical analysis

The Kaplan-Meier method was used to estimate the distribution of progression-free survival, overall survival, and duration of response, and a stratified log-rank test was used to assess between-group differences. A Cox proportional hazard model, stratified according to region (Asia *vs* non-Asia), number of organs with metastases (0–2 *vs* ≥3), and previous gastrectomy (yes *vs* no), was used to estimate hazard ratios (HRs) and corresponding 95% CIs. The Cochran-Mantel-Haenszel test was used to assess between-group differences in objective response rate. Prespecified multiplicity adjustment methods were used to control the overall one-sided type I error rate at 0·025. Efficacy boundaries were calculated for the interim overall survival analysis based on the information fraction at the time of analysis. The reported 95% CIs describe the precision of the point estimates and might not correspond to the significance of the test.

We planned to include 550 patients in the study. The sample size analysis was done by a statistician at the protocol development stage. The final analysis of progression-free survival was planned for when 300 patients had disease progression or died, to provide 93% power to detect a between-group difference with an assumed median progression-free survival of 9 months versus 6 months (HR 0·67) with zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6, at an overall one-sided significance level of 0·025. A 10% dropout rate was considered in the sample size calculation for the progression-free survival analysis. Based on the planned event number, the statistically significant boundary for the progression-free survival analysis was an HR of 0·80. To strictly control the one-sided type I error rate at 0·025, overall survival was tested only if the null hypothesis for progression-free survival was rejected. An interim analysis of overall survival was planned at the final progression-free survival analysis, and a final analysis of overall survival was planned after 396 deaths to provide 81% power to detect a between-group difference with an assumed median overall survival of 14·7 months versus

11 months (HR 0·75) with zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6, at an overall one-sided significance level of 0·025. A 5% dropout rate was considered in the sample size calculation for the interim overall survival analysis. Based on the planned event number, the statistically significant boundary for the interim overall survival analysis was an HR of 0·78. At the time of the interim overall survival analysis, a one-sided level of significance of 0·0135 was used with an 82·3% information fraction. The study enrolled around 14 patients per month. The study accrual window was from Oct 29, 2018 (first patient randomly assigned), to April 1, 2022 (last patient randomly assigned). The assumed study duration was from June 21, 2018, to Sept 9, 2022 (approximately 51 months).

Progression-free survival, overall survival, objective response, and duration of response were assessed in the full analysis set, which comprised all randomised patients. Safety was assessed in the safety analysis set, which comprised all randomised patients who received at least one dose of any study drug (ie, zolbetuximab, placebo, or mFOLFOX6).

Full details of analyses are provided in the statistical analysis plan in the appendix (pp 617–62).

Sample size calculations were done with East version 6.4. Statistical data analyses were done with SAS version 9.3 or later. An independent data monitoring committee reviewed safety and efficacy data. The study is registered with ClinicalTrials.gov, NCT03504397.

Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between June 21, 2018, and April 1, 2022, 2735 patients were screened (figure 1). Of the 2403 patients assessable for CLDN18.2 status, 922 (38%) met the cutoff for CLDN18.2 positivity. Among HER2-negative patients assessable for CLDN18.2 status (2004 [83%] of 2403 patients), 839 (42%) met the cutoff for CLDN18.2 positivity. 565 patients were randomly assigned to receive either zolbetuximab plus mFOLFOX6 (283 patients; the zolbetuximab group) or placebo plus mFOLFOX6 (282 patients; the placebo group). At least one dose of treatment was administered to 279 (99%) of 283 patients in the zolbetuximab group and 278 (99%) of 282 patients in the placebo group. In the zolbetuximab group, 218 patients discontinued treatment and in the placebo group, 232 patients discontinued treatment. The most common reason for treatment discontinuation was disease progression (133 [48%] patients in the zolbetuximab group and 177 [64%] patients in the placebo group). All enrolled patients were assessed for efficacy.

The median age of the patients was 61·0 years (IQR 50·0–69·0). 429 (76%) of 565 patients presented

	Zolbetuximab plus mFOLFOX6 group (n=283)	Placebo plus mFOLFOX6 group (n=282)
Age, years	62·0 (51·0–69·0)	60·0 (50·0–69·0)
Sex		
Male	176 (62%)	175 (62%)
Female	107 (38%)	107 (38%)
Region		
Asia	88 (31%)	89 (32%)
Non-Asia	195 (69%)	193 (68%)
Ethnicity		
Hispanic or Latino	36 (13%)	37 (13%)
Not Hispanic or Latino	225 (80%)	213 (76%)
Missing	22 (8%)	32 (11%)
Organs with metastases		
0–2	219 (77%)	219 (78%)
≥3	64 (23%)	63 (22%)
Location of metastases*		
Lymph node	101 (36%)	109 (39%)
Peritoneum	94 (33%)	76 (27%)
Liver	62 (22%)	75 (27%)
Lung	36 (13%)	33 (12%)
Bone	28 (10%)	23 (8%)
Abdominal cavity	19 (7%)	17 (6%)
Ovary	16 (6%)	19 (7%)
Previous gastrectomy		
Yes	84 (30%)	82 (29%)
No	199 (70%)	200 (71%)
Primary site		
Stomach	219 (77%)	210 (74%)
Gastro-oesophageal junction	64 (23%)	72 (26%)
Lauren classification		
Diffuse	82 (29%)	117 (41%)
Intestinal	70 (25%)	66 (23%)
Mixed	31 (11%)	13 (5%)
Unknown	49 (17%)	40 (14%)
Other	50 (18%)	42 (15%)
Missing	1 (<1%)	4 (1%)
ECOG performance status score		
0	125 (44%)	115 (41%)
1	153 (54%)	163 (58%)
2†	1 (<1%)	0
Missing‡	4 (1%)	4 (1%)
Measurable disease		
Yes	211 (75%)	211 (75%)
No	72 (25%)	71 (25%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. mFOLFOX6=modified folinic acid, fluorouracil, and oxaliplatin regimen. *Locations of metastases which were identified in at least 5% of patients in either treatment group are presented. †Baseline measurements were reported at cycle 1 day 1, at which time these patients had an ECOG performance status score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment. ‡Baseline measurements were reported at cycle 1 day 1; patients reported as missing did not receive any treatment, thus no baseline was defined per statistical analysis plan. However, at screening these patients had an ECOG performance status score of 0 or 1, and were thus eligible for enrolment.

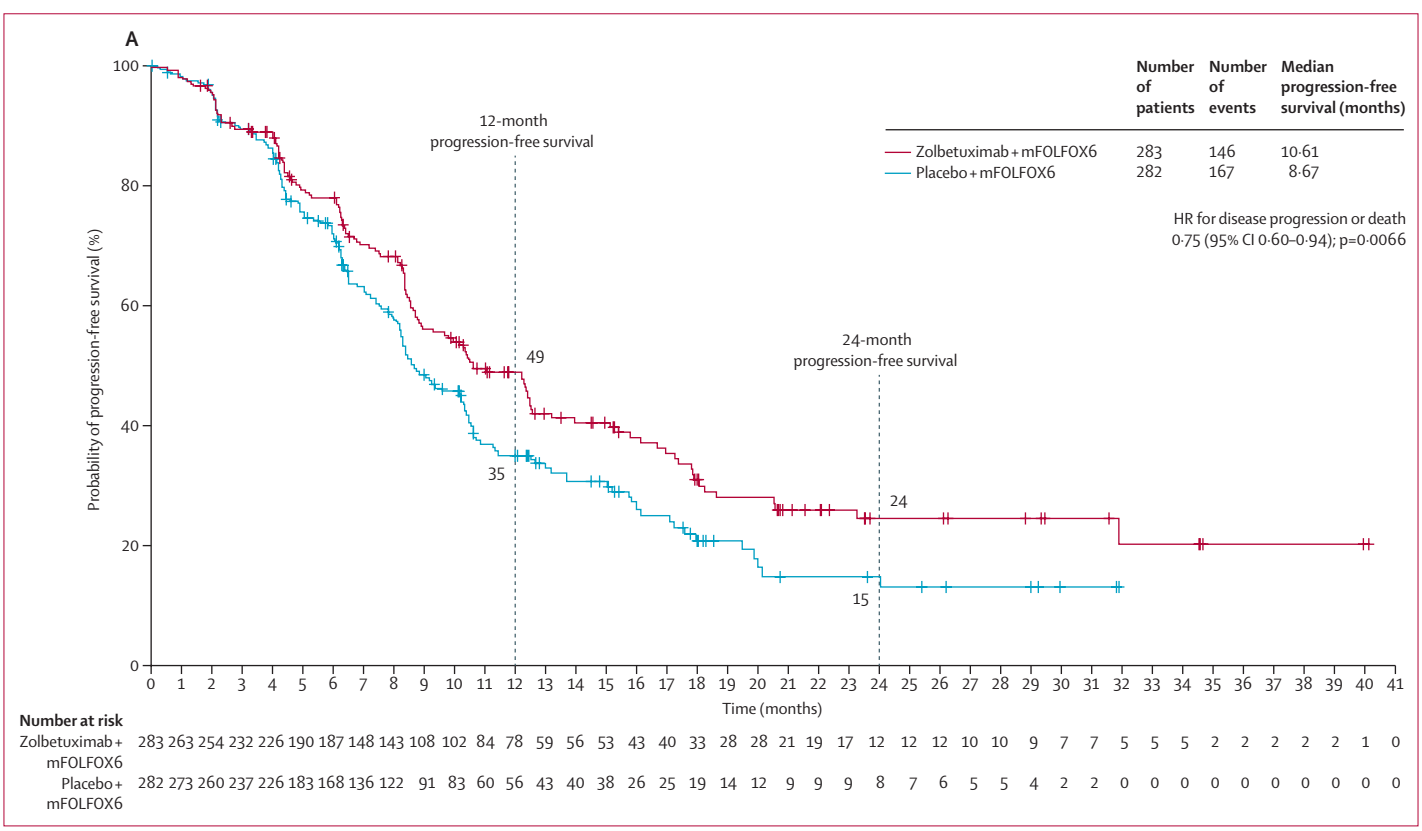
Table 1: **Baseline demographic and clinical characteristics of patients in the full analysis set**

with gastric adenocarcinoma and 136 (24%) patients presented with gastro-oesophageal junction adenocarcinoma. In the zolbetuximab group, 176 (62%) patients were male and 107 (38%) were female. In the placebo group, 175 (62%) patients were male and 107 (38%) were female. Demographic and baseline characteristics were generally similar between the two study groups, except for disease histology (table 1). A PD-L1 CPS of 5 or more was observed in 41 (13%) of 311 assessed patients.

The median follow-up duration for progression-free survival was 12·94 months in the zolbetuximab group versus 12·65 months in the placebo group. Zolbetuximab treatment showed a significant reduction in the risk of disease progression or death compared with placebo (HR 0·75, 95% CI 0·60–0·94; p=0·0066). The median progression-free survival was 10·61 months (95% CI 8·90–12·48) in the zolbetuximab group versus 8·67 months (8·21–10·28) in the placebo group (figure 2A; appendix p 5). The estimated 12-month progression-free survival was 49% (95% CI 42–55) in the zolbetuximab group versus 35% (28–42) in the placebo group, and the 24-month progression-free survival was 24% (17–32) in the zolbetuximab group versus 15% (9–22) in the placebo group. Progression-free survival was prolonged across most prespecified subgroups; because of the small sample size, no conclusions on progression-free survival can be drawn for gastro-oesophageal junction adenocarcinoma (figure 2B). Progression-free survival per investigator assessment as a sensitivity analysis was also significantly improved by zolbetuximab (appendix p 23).

The median follow-up for overall survival was 22·14 months in the zolbetuximab group versus 20·93 months in the placebo group. By the interim analysis, 326 (58%) of 565 patients had died: 149 (53%) of 283 patients in the zolbetuximab group versus 177 (63%) of 282 patients in the placebo group. Zolbetuximab treatment showed a significant reduction in the risk of death versus placebo (HR 0·75, 95% CI 0·60–0·94; p=0·0053 [prespecified criteria for superiority based on number of events, p=0·0135]). The median overall survival was 18·23 months (95% CI 16·43–22·90) in the zolbetuximab group versus 15·54 months (13·47–16·53) in the placebo group (figure 3A; appendix p 5). The estimated 12-month overall survival was 68% (95% CI 61–73) in the zolbetuximab group versus 60% (54–66) in the placebo group, and the 24-month overall survival was 39% (32–46) in the zolbetuximab group versus 28% (22–35) in the placebo group. Overall survival was also prolonged across most prespecified subgroups; because of the small sample size, no conclusions on overall survival can be drawn for gastro-oesophageal junction adenocarcinoma (figure 3B).

In the full analysis set, an objective response (complete or partial) was observed in 135 (48%, 95% CI 42–54) of



(Figure 2 continues on next page)

B

	Zolbetuximab + mFOLFOX6		Placebo + mFOLFOX6		Hazard ratio (95% CI)
	Number of events/ number of patients	Median progression-free survival (months)	Number of events/ number of patients	Median progression-free survival (months)	
Age (years)					
≤65	94/181	11·04	106/181	8·94	0·77 (0·58–1·02)
>65	52/102	10·61	61/101	8·57	0·71 (0·49–1·04)
≤75	138/267	10·61	154/260	8·44	0·74 (0·59–0·93)
>75	8/16	8·34	13/22	10·41	0·96 (0·39–2·34)
Sex					
Male	95/176	10·61	106/175	8·94	0·78 (0·59–1·02)
Female	51/107	11·04	61/107	8·38	0·71 (0·49–1·03)
Region					
Asia	45/88	12·55	47/89	8·21	0·56 (0·37–0·85)
Non-Asia	101/195	9·69	120/193	9·36	0·85 (0·65–1·11)
Number of metastatic sites					
0–2	107/219	12·35	123/219	9·20	0·73 (0·56–0·94)
≥3	39/64	8·11	44/63	8·18	0·84 (0·55–1·30)
Previous gastrectomy					
No	106/199	9·30	117/200	8·57	0·81 (0·62–1·05)
Yes	40/84	12·42	50/82	9·26	0·62 (0·41–0·94)
Primary site					
Stomach	109/219	12·22	126/210	8·38	0·69 (0·53–0·89)
Gastro-oesophageal junction	37/64	8·77	41/72	8·94	1·02 (0·65–1·59)
Lauren classification					
Diffuse	40/82	12·48	64/117	10·28	0·76 (0·51–1·13)
Intestinal	41/70	10·28	46/66	6·57	0·58 (0·38–0·89)
Mixed or other	49/81	9·79	35/55	8·67	0·93 (0·60–1·43)
Country					
Japan	12/32	18·07	17/33	8·28	0·48 (0·23–1·01)
Non-Japan	134/251	10·41	150/249	8·74	0·79 (0·63–1·00)
China	12/19	8·54	10/17	6·24	0·50 (0·20–1·26)
Non-China	134/264	11·04	157/265	9·07	0·75 (0·60–0·95)
Race					
White	77/140	8·94	82/134	10·15	0·93 (0·68–1·27)
Asian	47/96	13·96	51/97	8·21	0·53 (0·35–0·79)
Tobacco history					
Never	75/142	10·35	82/137	8·25	0·74 (0·54–1·01)
Current	15/26	10·28	14/25	8·67	1·00 (0·48–2·09)
Former	56/113	12·32	70/118	9·76	0·71 (0·50–1·02)

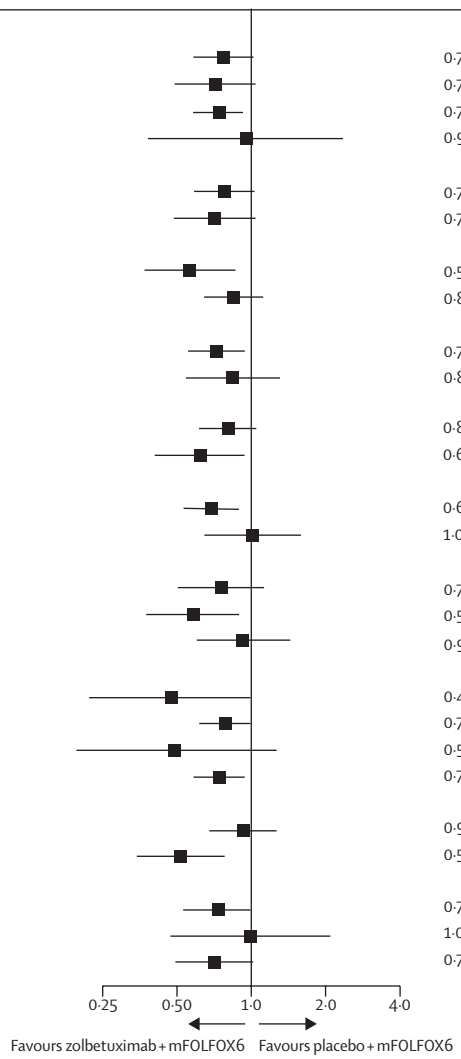


Figure 2: **Progression-free survival in the full analysis set**
(A) Kaplan-Meier plot by treatment group. (B) Subgroup analyses by treatment group. HR=hazard ratio. mFOLFOX6=modified folinic acid, fluorouracil, and oxaliplatin regimen.

283 patients in the zolbetuximab group versus 134 (48%, 42–54) of 282 patients in the placebo group. The median duration of response was 9·00 months (95% CI 6·87–10·25) in the zolbetuximab group versus 8·05 months (6·47–10·81) in the placebo group (appendix p 6). As an ad-hoc analysis, in patients with measurable disease, an objective response was observed in 128 (61%, 95% CI 54–67) of 211 patients in the zolbetuximab group versus 131 (62%, 55–69) of 211 patients in the placebo group. The median duration of response was 8·51 months (95% CI 6·80–10·25) in the zolbetuximab group versus 8·11 months (6·47–11·37) in the placebo group (appendix p 7). As a sensitivity analysis in the full analysis set, an objective response, as evaluated by the investigator, was observed in 150 (53%, 95% CI 47–59) of 283 patients in the zolbetuximab group versus 124 (44%, 38–50) of 282 patients in the placebo group. The median duration of response was 9·00 months (95% CI 7·49–10·25) in the zolbetuximab group versus 6·80 months (6·21–8·31) in the placebo group (appendix p 8).

Subsequent anticancer therapies were received by 135 (48%) of 283 patients in the zolbetuximab group versus 148 (53%) of 282 patients in the placebo group. Types of therapies were similar between the two arms (appendix p 9).

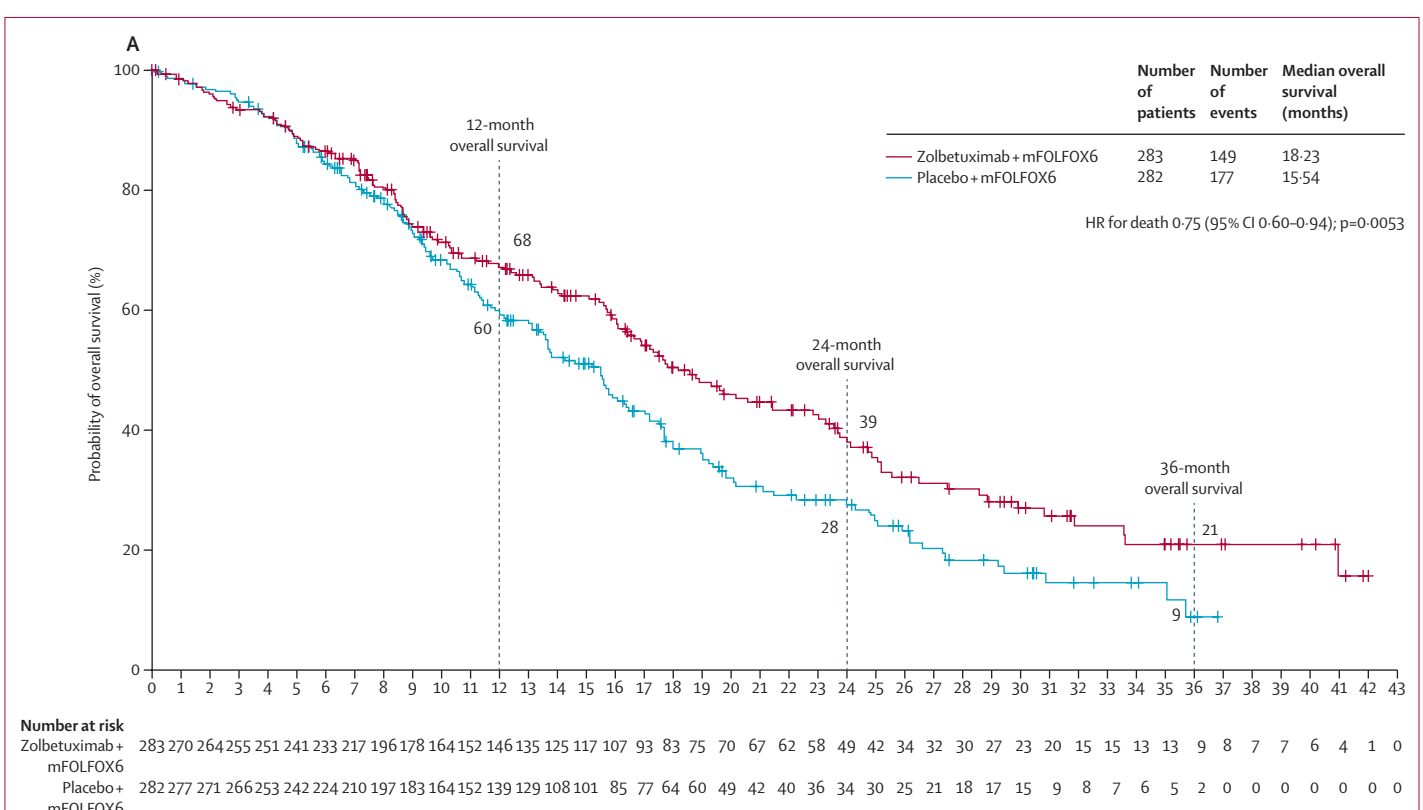
The median duration of exposure for each treatment component is reported in the appendix (p 10); the median

duration of exposure was 6·2 months (IQR 2·5–12·0) for the zolbetuximab group and 6·4 months (3·7–10·3) for the placebo group. Treatment-emergent grade 3 or worse adverse events occurred in 242 (87%) of 279 patients in the zolbetuximab group versus 216 (78%) of 278 patients in the placebo group (table 2). The most common all-grade adverse events with zolbetuximab plus chemotherapy were nausea, vomiting, and decreased appetite (table 2). Nausea, vomiting, and decreased appetite were also the only all-grade treatment-emergent adverse events with a greater than 10% difference in incidence in patients in the zolbetuximab group versus patients in the placebo group (table 2; appendix p 11). The incidences of nausea and vomiting in patients with or without previous gastrectomy are reported in the appendix (p 12). Incidences of nausea, vomiting, and decreased appetite were most common during the first treatment cycle and decreased thereafter (appendix pp 24–25). Treatment-related adverse events by preferred terms are reported in the appendix (p 13). Treatment-related adverse events led to discontinuation of zolbetuximab in 38 (14%) of 279 patients and discontinuation of placebo in 6 (2%) of 278 patients (table 2). Treatment-related grade 5 adverse events (leading to death) occurred in five (2%) patients in the zolbetuximab group versus four (1%) patients in the placebo group (table 2; appendix p 14). Treatment-emergent adverse events of special interest are listed in the appendix (pp 15–22). Nausea led to discontinuation of any study drug in 18 (6%) of 279 patients in the zolbetuximab group versus three (1%) of 278 patients in the placebo group, and vomiting led to discontinuation of any study drug in 20 (7%) of 279 patients in the zolbetuximab group versus one (<1%) of 278 patients in the placebo group.

Discussion

In this study, the addition of zolbetuximab to standard chemotherapy significantly improved progression-free survival and overall survival in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. To our knowledge, this is the first phase 3 study to show a survival improvement after CLDN18.2-targeted therapy in any tumour type. Longitudinal assessments showed that the overall survival benefit in patients receiving zolbetuximab versus placebo was maintained over time. Survival continues to be followed up in patients who remain on study.

The anticipated median progression-free survival was 9 months with zolbetuximab plus mFOLFOX6 versus 6 months with placebo plus mFOLFOX6; the anticipated median overall survival was 14·7 months with zolbetuximab plus mFOLFOX6 versus 11 months with placebo plus mFOLFOX6. The longer than anticipated median progression-free survival and overall survival in patients in



(Figure 3 continues on next page)

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	Zolbetuximab + mFOLFOX6		Placebo + mFOLFOX6		Hazard ratio (95% CI)
	Number of events/ number of patients	Median overall survival (months)	Number of events/ number of patients	Median overall survival (months)	
Age (years)					
≤65	89/181	20·24	112/181	15·57	0·74 (0·56–0·98)
>65	60/102	16·16	65/101	15·28	0·76 (0·53–1·09)
≤75	138/267	18·86	165/260	15·54	0·71 (0·57–0·90)
>75	11/16	9·76	12/22	15·64	1·32 (0·58–3·00)
Sex					
Male	98/176	17·38	113/175	15·57	0·76 (0·58–1·00)
Female	51/107	23·75	64/107	15·28	0·73 (0·50–1·05)
Region					
Asia	47/88	21·49	59/89	17·74	0·64 (0·44–0·95)
Non-Asia	102/195	16·99	118/193	13·73	0·80 (0·61–1·04)
Number of metastatic sites					
0–2	110/219	19·68	129/219	15·84	0·77 (0·59–0·99)
≥3	39/64	16·43	48/63	12·02	0·67 (0·44–1·03)
Previous gastrectomy					
No	109/199	16·95	125/200	14·32	0·84 (0·65–1·09)
Yes	40/84	24·80	52/82	15·74	0·58 (0·38–0·87)
Primary site					
Stomach	111/219	20·24	135/210	13·83	0·67 (0·52–0·86)
Gastro-oesophageal junction	38/64	15·80	42/72	16·39	1·07 (0·69–1·67)
Lauren classification					
Diffuse	46/82	20·63	75/117	15·84	0·77 (0·53–1·11)
Intestinal	38/70	22·90	48/66	13·83	0·55 (0·36–0·85)
Mixed or other	48/81	16·13	34/55	14·69	0·99 (0·64–1·54)
Country					
Japan	23/32	23·10	27/33	17·71	0·71 (0·41–1·25)
Non-Japan	126/251	17·87	150/249	14·69	0·76 (0·60–0·96)
China	9/19	16·16	9/17	12·25	0·91 (0·36–2·32)
Non-China	140/264	18·86	168/265	15·57	0·74 (0·59–0·92)
Race					
White	81/140	16·13	81/134	15·28	0·95 (0·70–1·29)
Asian	49/96	23·33	65/97	16·53	0·57 (0·39–0·83)
Tobacco history					
Never	70/142	18·96	87/137	13·47	0·68 (0·49–0·93)
Current	15/26	19·35	15/25	15·57	0·82 (0·40–1·69)
Former	64/113	17·81	74/118	15·84	0·81 (0·58–1·13)

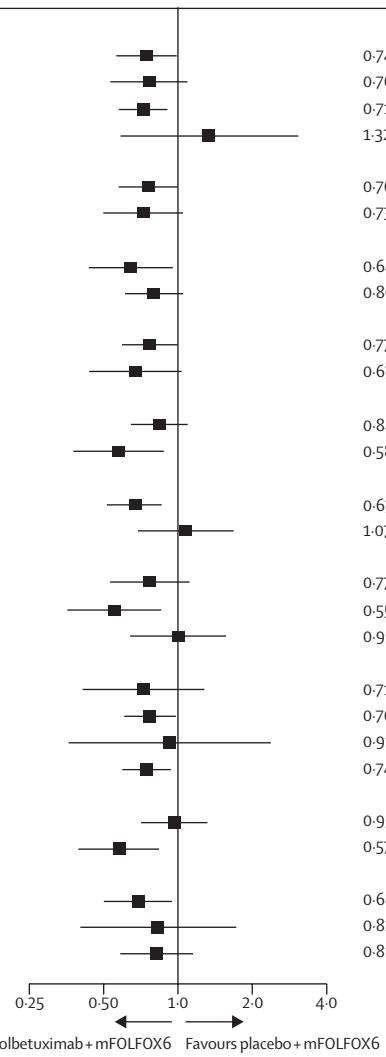

Figure 3: **Overall survival in the full analysis set**
(A) Kaplan-Meier plot by treatment group. (B) Subgroup analyses by treatment group. HR=hazard ratio. mFOLFOX6=modified folinic acid, fluorouracil, and oxaliplatin regimen.

the placebo group might have been partly due to the distribution of patients from various countries—there were more patients from Japan and Korea in SPOTLIGHT compared with other global studies (eg, CheckMate 649).[10] Similarly, in the ATTRACTION-4 study in patients in Japan, South Korea, and Taiwan, the median overall survival of the control group was longer than in the global CheckMate 649 study.[10,24] Another phase 3 study of zolbetuximab plus chemotherapy in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GLOW; NCT03653507) has completed enrolment, but trial patients continue to be followed up. This study has different distributions of patients from various countries compared with SPOTLIGHT, and might provide additional insights into the survival outcomes in the control groups in this patient population. Although the median difference in progression-free survival was less than the 3 months expected per statistical assumptions, this might have been affected by the longer than expected median progression-free survival in the placebo group. The longer than anticipated median progression-free survival and overall survival in patients in the placebo group might also have contributed to the delayed separation of the survival curves of patients between the two treatment groups. Other possible explanations include early discontinuation of patients in the zolbetuximab group because of increased

	Zolbetuximab plus mFOLFOX6 group (n=279)		Placebo plus mFOLFOX6 group (n=278)	
	All grade	Grade ≥3	All grade	Grade ≥3
All treatment-emergent events	278 (>99%)	242 (87%)	277 (>99%)	216 (78%)
Treatment-emergent serious events	125 (45%)	..	121 (44%)	..
Treatment-emergent events leading to discontinuation of any study drug	120 (43%)	..	106 (38%)	..
Treatment-related events leading to discontinuation of any study drug	106 (38%)	..	82 (29%)	..
Treatment-emergent events leading to discontinuation of zolbetuximab or placebo	55 (20%)	..	30 (11%)	..
Treatment-related events leading to discontinuation of zolbetuximab or placebo	38 (14%)	..	6 (2%)	..
Treatment-emergent events leading to death	..	22 (8%)	..	24 (9%)
Treatment-related events leading to death	..	5 (2%)	..	4 (1%)
Treatment-emergent events* by preferred terms				
Nausea	230 (82%)	45 (16%)	169 (61%)	18 (6%)
Vomiting	188 (67%)	45 (16%)	99 (36%)	16 (6%)
Decreased appetite	131 (47%)	16 (6%)	93 (33%)	9 (3%)
Diarrhoea	110 (39%)	12 (4%)	122 (44%)	9 (3%)
Peripheral sensory neuropathy	106 (38%)	11 (4%)	118 (42%)	15 (5%)
Neutropenia	102 (37%)	79 (28%)	94 (34%)	65 (23%)
Anaemia	100 (36%)	24 (9%)	104 (37%)	26 (9%)
Constipation	99 (35%)	3 (1%)	112 (40%)	2 (1%)
Neutrophil count decreased	95 (34%)	69 (25%)	91 (33%)	69 (25%)
Fatigue	78 (28%)	17 (6%)	91 (33%)	14 (5%)
Asthenia	74 (27%)	20 (7%)	64 (23%)	7 (3%)
Abdominal pain	67 (24%)	12 (4%)	82 (29%)	6 (2%)
Stomatitis	58 (21%)	7 (3%)	57 (21%)	3 (1%)
Weight decreased	55 (20%)	5 (2%)	54 (19%)	2 (1%)
Pyrexia	54 (19%)	1 (<1%)	48 (17%)	1 (<1%)
White blood cell count decreased	50 (18%)	8 (3%)	46 (17%)	16 (6%)
Hypokalaemia	50 (18%)	16 (6%)	41 (15%)	10 (4%)
Oedema peripheral	49 (18%)	2 (1%)	26 (9%)	0
Aspartate aminotransferase increased	49 (18%)	4 (1%)	44 (16%)	7 (3%)
Abdominal pain upper	47 (17%)	4 (1%)	32 (12%)	0
Paraesthesia	44 (16%)	6 (2%)	46 (17%)	4 (1%)
Hypoalbuminaemia	43 (15%)	11 (4%)	17 (6%)	2 (1%)
Dysgeusia	41 (15%)	1 (<1%)	40 (14%)	0
Platelet count decreased	40 (14%)	3 (1%)	49 (18%)	6 (2%)
Dizziness	36 (13%)	0	27 (10%)	1 (<1%)
Alanine aminotransferase increased	34 (12%)	2 (1%)	47 (17%)	7 (3%)
Back pain	34 (12%)	0	30 (11%)	0
Headache	31 (11%)	2 (1%)	35 (13%)	1 (<1%)
Hypertension	31 (11%)	15 (5%)	22 (8%)	10 (4%)
Hypocalcaemia	30 (11%)	6 (2%)	9 (3%)	0
Insomnia	29 (10%)	1 (<1%)	25 (9%)	0
Thrombocytopenia	28 (10%)	4 (1%)	45 (16%)	4 (1%)
Cough	28 (10%)	0	28 (10%)	0
Dyspnoea	20 (7%)	3 (1%)	32 (12%)	6 (2%)

Data are n (%). For cells with no data, events were not reported by severity. mFOLFOX6=modified folinic acid, fluorouracil, and oxaliplatin regimen. *The all-grade events reported here occurred in ≥10% of patients in either treatment group.

Table 2: **Adverse events in the safety analysis set**

nausea and vomiting or a potential role of the mechanism of action of zolbetuximab in inducing the innate immune system through antibody-dependent cellular cytotoxicity. Nevertheless, the significant improvement in progression-free survival and overall survival supports the clinical value of zolbetuximab. Given this was a selected patient population, it is important to consider the possible role of CLDN18.2 as a prognostic factor. However, data from two large retrospective studies that used the same diagnostic antibody and cutoff for CLDN18.2 positivity as SPOTLIGHT showed no relationship between CLDN18.2 status and survival outcomes.[12,13]

The magnitude of the benefit in progression-free survival and overall survival in patients in the zolbetuximab group compared with the placebo group is statistically significant and clinically meaningful. The FAST study[16] suggested that the addition of zolbetuximab to chemotherapy improves progression-free survival (HR 0·38, 95% CI 0·23–0·62) and overall survival (0·50, 0·33–0·74) in patients whose tumours expressed high levels of CLDN18.2. FAST was a small (n=252) phase 2b study that was designed for proof of concept, and was done from 2012 to 2014 across 49 study sites in European countries only.[16] By contrast, SPOTLIGHT is a pivotal, phase 3 study with enrolment more than twice that of FAST, done across 215 global study sites. SPOTLIGHT also used a more prevalent chemotherapy regimen, mFOLFOX6, whereas FAST used a chemotherapy regimen of epirubicin, oxaliplatin, and capecitabine.[16] These attributes could have contributed to the different magnitude of clinical benefit and treatment effect observed in SPOTLIGHT compared with FAST.

The longer survival outcomes with zolbetuximab versus placebo were observed across most prespecified subgroups. Although patients with gastro-oesophageal junction adenocarcinoma derived less benefit from zolbetuximab than did patients with gastric adenocarcinoma, this is a relatively small subgroup, and interpretation should be made with caution.

The objective response rates and duration of response, as assessed by an independent review committee in patients with measurable lesions, were similar in patients receiving zolbetuximab or placebo. Improving response rates is a relevant treatment effect in gastric and gastro-oesophageal junction adenocarcinoma to alleviate disease-related symptoms. The effect of zolbetuximab on alleviation of disease-related symptoms will be further explored in future research when time to confirmed deterioration and patient-reported outcome data from SPOTLIGHT are mature. In the phase 2a MONO study,[17] among patients receiving 600 mg/m² zolbetuximab monotherapy, at week 11 of 12, two (8%) of 26 patients had a partial response and seven (27%) of 26 patients had stable disease, suggesting that a major treatment effect of zolbetuximab is disease stabilisation, as opposed to reduction in tumour size. In the FAST study,[16] the objective response rate with zolbetuximab plus chemotherapy was 39%, compared with 25% with chemotherapy alone. The differences in the study attributes of SPOTLIGHT and FAST might contribute to the differences in observed objective responses. Although similar between treatment groups, the response rate was high in patients with measurable lesions in SPOTLIGHT. Although the possible effect of zolbetuximab in promoting disease control versus tumour shrinkage is an appealing possibility, a succinct explanation remains unclear. The prolonged progression-free survival and overall survival outcomes in SPOTLIGHT were not dependent on objective tumour responses, as observed previously, and reflect a significant and meaningful clinical benefit for patients treated with zolbetuximab versus placebo. In SPOTLIGHT, there was a discordance in tumour response evaluations between central and investigator reviews; however, the HRs for progression-free survival were similar between central and investigator reviews. Similarly, in the phase 3 RAINFALL study in patients with metastatic gastric or gastro-oesophageal junction adenocarcinoma,[25] there was discordance in tumour response evaluations between central and investigator reviews after treatment with ramucirumab plus cisplatin and capecitabine versus placebo plus cisplatin and capecitabine.

In the phase 2b FAST study,[16] patients whose tumours expressed higher levels of CLDN18.2 had a greater benefit from zolbetuximab plus chemotherapy compared with the lower expression subgroup. Based on these results, a patient population with a similarly high cutoff for CLDN18.2 positivity was selected for SPOTLIGHT. The relationship between CLDN18.2 expression and other relevant biomarkers has been explored in other studies.[12] Data from a retrospective study that used the same diagnostic antibody and CLDN18.2-positivity cutoff as SPOTLIGHT showed there were no clear differences in the prevalence of select biomarkers, including HER2, PD-L1, and mismatch repair between CLDN18.2-positive and CLDN18.2-negative patients: 17 (15%) of 117 tested CLDN18.2-positive tumour samples and 35 (15%) of 233 tested CLDN18.2-negative tumour samples were HER2-positive; 21 (18%) of 117 tested CLDN18.2-positive tumour samples and 50 (21%) of 233 tested CLDN18.2-negative tumour samples had a PD-L1 CPS of 5 or more.[12] In SPOTLIGHT, 41 (13%) of 311 assessed patients had a PD-L1 CPS of 5 or more. The results of SPOTLIGHT support CLDN18.2 as a promising molecular target and biomarker that is expressed in a high proportion of tumours in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Collectively, these data appear to indicate CLDN18.2 as a novel biomarker that defines a new biomarker-driven subgroup for zolbetuximab-based therapy.

In this study, the most common treatment-emergent adverse events after zolbetuximab treatment were nausea, vomiting, and decreased appetite; this profile is consistent with previous phase 1 and 2 studies of

zolbetuximab.[16,17,20] Nausea, vomiting, and decreased appetite were the only treatment-emergent adverse events with a more than 10% difference between treatment groups; no new safety signals were identified. Nausea and vomiting might have contributed to the greater proportion of patients who discontinued zolbetuximab compared with placebo because of treatment-related adverse events. Although the overall rate of treatment-emergent adverse events in patients receiving zolbetuximab was similar between patients with and without previous gastrectomy, a higher proportion of patients without previous gastrectomy had vomiting compared with patients with previous gastrectomy. Nausea, vomiting, and decreased appetite were most common during the first and second infusions; infusion rate guidelines, infusion interruptions, and antiemetics were used to manage these events, but additional future research might be needed to further characterise these toxic effects. The significantly prolonged survival benefits and manageable safety profile in this study indicate a favourable benefit–risk profile for zolbetuximab plus mFOLFOX6.

This study had some limitations. The sample size of the study is insufficient to draw any definitive conclusions from subgroup analyses, and interpretations of these data must be made with caution. There was a higher proportion of patients with diffuse histology in the placebo group compared with the zolbetuximab group and, by contrast, a higher proportion of patients with mixed disease histology in the zolbetuximab group compared with the placebo group; however, a survival benefit was observed regardless of histology. In SPOTLIGHT, patients received zolbetuximab every 3 weeks, and mFOLFOX6 every 2 weeks. Although this led to increased clinic visits for patients, the phase 3 dose for zolbetuximab was based on the proof of concept FAST study, and mFOLFOX6 is a widely accepted standard of care that is administered every 2 weeks. The administration of zolbetuximab in combination with a second widely accepted standard of care, CAPOX (capecitabine and oxaliplatin), which is administered every 3 weeks, is being evaluated in the GLOW study. Thus, two widely followed standard-of-care regimens across various participating countries have been included in the phase 3 SPOTLIGHT and GLOW studies to allow evaluation of zolbetuximab in combination with these regimens. Additionally, administration of zolbetuximab plus nivolumab and chemotherapy (mFOLFOX6) every 2 weeks is being evaluated in the ILUSTRO study (NCT03505320).

In conclusion, treatment with zolbetuximab plus mFOLFOX6 led to a clinically meaningful and significant benefit in progression-free survival and overall survival compared with placebo plus mFOLFOX6 in patients with previously untreated, CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. The results of SPOTLIGHT support that CLDN18.2 defines a large population of patients whose survival might be significantly prolonged by targeted therapy with zolbetuximab plus mFOLFOX6. Platinum–fluoropyrimidine chemotherapy is a standard first-line therapy for the large population of patients with HER2-negative disease; many of these patients also have disease with a PD-L1 CPS less than 5.[4,7,8] Based on the results of SPOTLIGHT, zolbetuximab should be considered as an option for first-line therapy in combination with chemotherapy in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Zolbetuximab is being tested in other studies in CLDN18.2-positive gastric and pancreatic adenocarcinomas.

Contributors

KS, FL, Y-JB, PE, DI, MAS, EVC, R-HX, JY, DM, PB, AA, JWP, MO, and JAA contributed to the conception and design of the study in collaboration with Astellas Pharma. KS, FL, Y-JB, PE, DI, MAS, EVC, R-HX, GA, JX, JC, RP-C, Y-KK, JY, DM, PB, AA, JWP, MO, and JAA acquired the study data. JY, DM, PB, AA, JWP, and MO analysed and interpreted the study data. KS, JY, DM, PB, AA, JWP, and MO accessed and verified the study data. All authors had access to the study data, participated in reviewing the manuscript, and provided final approval to submit the manuscript for publication.

Declaration of interests

KS reports research funding from Astellas Pharma, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharmaceutical, MSD, Amgen, Eisai, and Medi Science; consulting fees from Eli Lilly, Bristol Myers Squibb, Takeda Pharmaceutical, Pfizer, Ono Pharmaceutical, Novartis, AbbVie, Daiichi Sankyo, Taiho Pharmaceutical, GSK, Amgen, Boehringer Ingelheim, MSD, Astellas Pharma, Guardant Health Japan, and Janssen Pharmaceuticals; and payment or honoraria from Bristol Myers Squibb, Takeda Pharmaceutical, and Janssen Pharmaceuticals. FL reports research funding from Astellas Pharma; consulting fees from Amgen, Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, MSD, Novartis, and Roche Holding; payment or honoraria from Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Elsevier, Falk Foundation, Incyte Corporation, Medscape, MedUpdate, Merck, MSD, Novartis, Roche Holding, Servier Laboratories, Springer Nature, and Streamed Up; support for travel or meeting attendance from Bristol Myers Squibb; and participating on data safety monitoring boards or advisory boards for BioNTech. Y-JB reports research funding from Astellas Pharma, Genentech, Roche Holding, Merck Serono, Daiichi Sankyo, MSD, Amgen, and BeiGene; and consulting fees from MSD, Daiichi Sankyo, ALX Oncology, Hanmi Pharmaceutical, Merck Serono, Astellas Pharma, Samyang Biopharm Corporation, and Daewoong Pharmaceutical. PE reports research funding from Astellas Pharma; and consulting fees from ALX Oncology, Arcus Biosciences, Astellas Pharma, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Chimeric Therapeutics, Celgene, Coherus BioSciences, Daiichi Sankyo, Five Prime Therapeutics, IDEAYA Biosciences, Istari Oncology, Legend Biotech, Eli Lilly, Loxo Oncology, Merck, Novartis, Ono Pharmaceutical, Servier Laboratories, Taiho Pharmaceutical, Takeda Pharmaceutical Company, Turning Point Therapeutics, Xencor, and Zymeworks. DI reports research funding from Astellas Pharma; consulting fees from Amgen, Bayer, Astellas Pharma, Merck, Daiichi Sankyo, Natera, Taiho Pharmaceutical, Bristol Myers Squibb, Eli Lilly, Roche Holding, and AstraZeneca; and participating on data safety monitoring boards or advisory boards for MacroGenics and Merck. MAS reports research funding from Astellas Pharma, Merck, Bristol Myers Squibb, and Oncolys BioPharma; and serving a leadership or judiciary role in board, society, committee, or advocacy groups for the American Society of Clinical Oncology Leadership Council. EVC reports research funding from Astellas

Pharma, Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Ipsen, Eli Lilly and Company, MSD, Merck, Novartis, Roche Holding, and Servier Laboratories; and consulting fees from AbbVie, Array BioPharma, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Halozyme, GSK, Helsinn Healthcare, Incyte, Ipsen, Janssen Pharmaceuticals, Eli Lilly, MSD, Merck, Mirati Therapeutics, Novartis, Laboratoires Pierre Fabre, Roche Holding, Seagen, Servier Laboratories, Sirtex Medical, Terumo Corporation, Taiho Pharmaceutical, TRIGR, and Zymeworks. R-HX reports research funding from Astellas Pharma. GA reports research funding from Astellas Pharma; consulting fees from Amgen, AstraZeneca, Bristol Myers Squibb, Merck, MSD, and Novartis; and payment or honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, MSD, and Novartis. JX reports study funding from Astellas Pharma. JC reports study funding from Astellas Pharma, Merck, and Eterna Therapeutics; consulting fees from Eli Lilly, Merck, AstraZeneca, Foundation Medicine, Daiichi Sankyo, MacroGenics, Amgen, Ono Pharmaceutical, Bristol Myers Squibb, Astellas Pharma, Turning Point Therapeutics, Silverback Therapeutics, Novartis, Coherus BioSciences, Geneos Therapeutics, Roche Holding, and Guardant Health; payment or honoraria from Merck and Bristol Myers Squibb; and participating on data safety monitoring boards or advisory boards for Yiviva. RP-C reports research funding from Astellas Pharma; consulting fees from Roche Holding, Eisai, and Bristol Myers Squibb; payment or honoraria from Bristol Myers Squibb, Servier Laboratories, and AstraZeneca; and receiving support for travel or meeting attendance from Eli Lilly. Y-KK reports research funding from Astellas Pharma; and consulting fees from Daehwa Pharma, ALX Oncology, Zymeworks, Amgen, Novartis, MacroGenics, Blueprint Medicines, Surface Oncology, Bristol Myers Squibb, and Merck. JY, DM, PB, JWP, and MO are full-time employees of Astellas Pharma. AA is a full-time employee and stock holder of Astellas Pharma. JAA reports study funding from Astellas Pharma, Bristol Myers Squibb, Merck, Zymeworks, Taiho Pharmaceutical, Delta-Fly Pharma, ProLynx, Daiichi Sankyo, Leap Therapeutics, Turning Point Therapeutics, Lanova Pharma, and Gilead Sciences; consulting fees from Bristol Myers Squibb, Merck, Astellas Pharma, Taiho Pharmaceutical, Zymeworks, BeiGene, AstraZeneca, Amgen, Novartis, Gilead Sciences, Servier Laboratories, Arcus Biosciences, and GRAIL; support for travel or meeting attendance from Daiichi Sankyo, Bristol Myers Squibb, Aadi Bioscience, and Merck; and participating on data safety monitoring boards or advisory boards for Beigene.

Data sharing

On request, and subject to certain criteria, conditions, and exceptions, Astellas will provide access to anonymised patient-level data from completed Astellas-sponsored phase 1 to 4 interventional clinical studies conducted for products and indications that have been approved in any country and for terminated compounds. Approval must have been granted by the agencies of the main regions of the USA, EU, and Japan. If approval is sought in only one or two regions, approval must have been granted by those agencies. Where available, the following anonymised patient-level data and information are 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. Additionally, data might be available on request. Researchers can request access at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

Acknowledgments

This study was funded by Astellas Pharma. We thank the patients, caregivers, investigators, and site staff who participated in the study. We thank study managers Julie Donnelly, Sini Koshy Hunt, and Archita Shrivastava, and steering committee members Sunnie Kim, Samuel Klempner, Sara Lonardi, and Jeffrey Raizer. We thank Sean Moran, Cari Beckman, Jannine McDonald, Shruti Arora, Judith Pugh, Margarita Kouzova, Lizhen Pang, and the CLDN18 project team at Roche Tissue Diagnostics for their fruitful collaboration in assay development, clinical trial implementation, and technical review of the manuscript. Medical writing and editorial support were provided in accordance with the Good Publication Practice 2022 Update and the International Committee of Medical Journal Editors guidelines by Ann Ferguson from Oxford PharmaGenesis (Newtown, PA, USA) and were funded by Astellas Pharma.

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