First-line regorafenib with nivolumab and chemotherapy in advanced oesophageal, gastric, or gastro-oesophageal junction cancer in the USA: a single-arm, single-centre, phase 2 trial

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Summary

Background The addition of nivolumab to chemotherapy improves survival in patients with advanced oesophagogastric (oesophageal, gastric, or gastro-oesophageal junction) adenocarcinoma; however, outcomes remain poor. We assessed the safety and activity of regorafenib in combination with nivolumab and chemotherapy in the first-line treatment of advanced oesophagogastric adenocarcinoma.

Methods This investigator-initiated, single-arm, phase 2 trial in adult patients (aged ≥18 years) with previously untreated, HER2-negative, metastatic oesophagogastric adenocarcinoma was done at the Memorial Sloan Kettering Cancer Center (New York, NY, USA). Eligible patients had measurable disease or non-measurable disease that was evaluable (defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received FOLFOX chemotherapy (fluorouracil [400 mg/m² bolus followed by 2400 mg/m² over 48 h], leucovorin [400 mg/m²], and oxaliplatin [85 mg/m²]) and nivolumab (240 mg) intravenously on days 1 and 15, and oral regorafenib (80 mg) on days 1–21 of a 28-day cycle. Treatment was continued until disease progression (defined by RECIST version 1.1), unacceptable toxicity, or withdrawal of consent. The primary endpoint was 6-month progression-free survival in the per-protocol population (ie, all participants who received a dose of all study treatments). The regimen would be considered worthy of further investigation if at least 24 of 35 patients were progression free at 6 months. Safety was assessed in all participants who received at least one dose of any study treatment. This trial is registered with ClinicalTrials.gov, NCT04757363, and is now complete.

Findings Between Feb 11, 2021, and May 4, 2022, 39 patients were enrolled, received at least one dose of study drug, and were included in safety analyses. 35 patients were evaluable for 6-month progression-free survival. Median age was 57 years (IQR 52–66), nine (26%) patients were women, 26 (74%) were men, 28 (80%) were White, and seven (20%) were Asian. At data cutoff (March 3, 2023), median follow-up was 18·1 months (IQR 12·7–20·4). The primary endpoint was reached, with 25 (71%; 95% CI 54–85) of 35 patients progression free at 6 months. Nine (26%) of 35 patients had disease progression and one (3%) patient died; the death was unrelated to treatment. The most common adverse event of any grade was fatigue (36 [92%] of 39). The most common grade 3 or 4 adverse events were decreased neutrophil count (18 [46%]), hypertension (six [15%]), dry skin, pruritus, or rash (five [13%]), and anaemia (four [10%]). Serious treatment-related adverse events occurred in ten (26%) patients, which were acute kidney injury (three [8%]), hepatotoxicity (two [5%]), sepsis (two [5%]), dry skin, pruritus, or rash (one [3%]), nausea (one [3%]), and gastric perforation (one [3%]). There were no treatment-related deaths.

Interpretation Regorafenib can be safely combined with nivolumab and chemotherapy and showed promising activity in HER2-negative metastatic oesophagogastric cancer. A randomised, phase 3 clinical trial is planned.

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Introduction

With 1·3 million deaths annually, oesophagogastric (oesophageal, gastric, and gastro-oesophageal junction) cancer is the second-leading cause of cancer-related death globally, and its incidence is increasing among younger patients.[1,2] Approximately half of patients present with metastatic disease at the time of diagnosis. The CheckMate-649 trial[3] changed practice for patients worldwide, showing meaningful overall survival benefit with first-line nivolumab (an anti-PD-1 antibody) plus chemotherapy compared with chemotherapy alone in patients with metastatic disease. Although a proportion

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Research in context

Evidence before this study

We searched PubMed for published studies from database inception until April 1, 2023, using the search terms ("gastric cancer" OR "gastroesophageal cancer" OR "esophageal cancer") AND ("regorafenib" OR "PD-1 inhibitor" OR "PD-L1 inhibitor"). The search was restricted to clinical trials with no language restrictions. We found several trials evaluating PD-1 or PD-L1 inhibitors in combination with chemotherapy for patients with previously untreated metastatic oesophagogastric adenocarcinoma. The CheckMate 649 trial reported significantly improved overall survival with nivolumab plus chemotherapy compared with chemotherapy alone in patients with a PD-L1 combined positive score of at least 5 and in all randomised patients. Following the results of the CheckMate 649 trial in 2021, nivolumab plus fluoropyrimidine and platinum chemotherapy became standard of care for HER2-negative advanced oesophagogastric cancer. The multi-targeted tyrosine-kinase inhibitor, regorafenib, has improved outcomes in refractory, advanced oesophagogastric cancer and when administered in combination with nivolumab in the phase 1b REGONIVO trial, was found to be safe and lead to significant anti-tumour activity in heavily pre-treated patients.

Added value of this study

To our knowledge, this is the first study to evaluate the activity of regorafenib, nivolumab, and chemotherapy in patients with previously untreated metastatic oesophagogastric cancer. We also explored potential molecular determinants of response to inform future studies and identify subsets of patients most likely to benefit from this combination.

Implications of all the available evidence

The results of this study suggest that the addition of regorafenib to nivolumab and chemotherapy is safe and active in treating metastatic oesophagogastric cancer. A randomised phase 3 clinical trial of regorafenib in combination with first-line nivolumab and chemotherapy is planned.

of patients do derive long-term benefit, including 17% who are alive at 3-years, the majority develop therapeutic resistance.[4]

Resistance to immune checkpoint blockade has been linked to inadequate immune response and self-tolerance and an immunosuppressive microenvironment resulting in insufficient T-cell trafficking.[5] Low intratumoural T-cell infiltration in oesophagogastric cancer might reflect the activity of myeloid-derived suppressor cells, regulatory T cells, tumour-associated macrophages, tolerogenic dendritic cells, or transforming growth factor β, many of which are associated with immune resistance.[6,7] The efficacy of targeting each pathway in combination with PD-1 inhibitors is being explored in ongoing trials (eg, NCT05568095, NCT05111626, and NCT04662710). Ipilimumab, an anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) antibody, has been reported to modulate regulatory T cells, and although ipilimumab combined with nivolumab did not improve overall survival,[8] an exploratory biomarker analysis from CheckMate-649 showed that patients with a high regulatory T signature expression benefited from nivolumab and ipilimumab versus chemotherapy, regardless of PD-L1 expression (determined by combined positive score [CPS] status).[9]

Multi-targeted tyrosine-kinase inhibitors, such as regorafenib, activate and enhance the function of natural killer cells and $CD8^+$ T cells, while simultaneously inhibiting pathways essential to immunosuppressive tumour-associated macrophages and regulatory T cells—a process that leads to increased immune cell infiltration.[10,11] Augmentation of the tumour micro-environment is amplified when tyrosine-kinase inhibitors are administered in combination with an immune checkpoint inhibitor.[12,13] Studies of refractory oesophagogastric cancer have shown promising activity with combined PD-1 and multi-targeted tyrosine-kinase inhibitors, including regorafenib.[14,15] Regorafenib alone has also been reported to be associated with improved progression-free and overall survival compared with placebo in patients with refractory disease;[16] however, in a previous phase 2 study,[17] regorafenib with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) was insufficient to improve outcomes as a first-line treatment for oesophagogastric cancer.[17]

This phase 2 trial was designed to determine whether regorafenib can be safely combined with nivolumab and FOLFOX and whether this combination can potentiate the anti-tumour immune response sufficiently to warrant future randomised studies. We incorporated tissue-based and blood-based sample analysis to develop predictors of durable benefit for patients with oesophagogastric cancer treated with this regimen.

Methods

Study design and participants

This study was an investigator-initiated, single-arm, single-centre, phase 2 trial performed at Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY, USA). The study protocol and all amendments were approved by the MSKCC institutional review board. The study was performed in accordance with the protocol, its amendments, and Good Clinical Practice guidelines, and was overseen by MSKCC's Data and Safety Monitoring Committee. All patients provided written informed consent as per the Declaration of Helsinki principles. The study protocol and statistical analysis plan are included in the appendix.

Eligible patients were aged 18 years or older, with previously untreated histologically or cytologically

See Online for appendix

confirmed advanced oesophageal, gastric, or gastro-oesophageal junction adenocarcinoma regardless of PD-L1 expression. Key inclusion criteria included disease that was measurable or non-measurable per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, by investigator assessment, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and availability to provide a fresh or archival tumour sample to evaluate PD-L1 expression. Patients who received previous adjuvant or neoadjuvant chemotherapy or radiotherapy were eligible if 6 months or longer had elapsed between the end of treatment and study enrolment. Patients with known HER2-positive status (defined as immunohistochemistry 3+ or 2+ and fluorescence in-situ hybridisation HER2:CEP17 ratio of ≥2), untreated central nervous system metastases, peripheral neuropathy, uncontrolled hypertension despite optimal medical management, active or previously documented autoimmune disease, or history of immunodeficiency were excluded. Women who were pregnant or breastfeeding and patients who had previously received an anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody at any time were also excluded. Full eligibility criteria are presented in the protocol (appendix). Sex and ethnicity data were collected per the institutional guidelines of MSKCC. Sex and ethnicity were defined by electronic medical records.

Procedures

Patients were given nivolumab (Bristol Myers Squibb, New York, NY, USA; 240 mg flat dose) and FOLFOX chemotherapy (Memorial Sloan Kettering Cancer Center, New York, NY, USA; fluorouracil [400 mg/m² bolus followed by 2400 mg/m² over 48 h], leucovorin [400 mg/m²], and oxaliplatin [85 mg/m²]) intravenously on days 1 and 15 of a 28-day cycle with regorafenib (Bayer, Leverkusen, Germany; 80 mg) given orally on days 1–21 of the 28-day cycle. Regorafenib 80 mg was the recommended phase 2 dose.[14] At the discretion of the treating investigator, patients received an induction cycle with regorafenib and nivolumab alone for one 28-day cycle, and FOLFOX was added during cycle 2. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. All patients had a CT or MRI at baseline (within 28 days of beginning therapy) and those who started with an induction cycle of regorafenib and nivolumab had a repeat CT or MRI at week 4 to assess response to the induction phase. All patients, including those who began with an induction cycle, had imaging at week 8 and then every 8 weeks thereafter. Response and progression were evaluated per RECIST version 1.1. Toxicity and adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and laboratory evaluations were done on days 1 and 15 of each cycle. Patients were monitored for adverse events throughout follow-up and for 30 days after the last dose of study treatment. Dose reductions of regorafenib, fluorouracil, leucovorin, and oxaliplatin were permitted; dose modification of nivolumab was not. Regorafenib started at 80 mg and was only dose-reduced to 40 mg and then discontinued if necessary. No other or further reductions were permitted. Discontinuation of individual treatment components was allowed, with patients permitted to continue the other components of the combination regimen. Treatment-related adverse events leading to discontinuation were recorded in a cumulative manner throughout the duration of treatment and used to calculate the proportion of patients who discontinued treatment due to treatment-related adverse events. Criteria for removal from the study included disease progression, loss of ability to participate, withdrawal of consent, substantial deviation from the protocol or eligibility criteria, non-compliance, treatment-related adverse events, and repeated drug-related toxicity that did not resolve despite dose reduction or discontinuation. Patients who were removed from study continued to be followed up for disease progression and death. Patients who started with an induction cycle and had progression on the CT scan at week 4 before starting chemotherapy were permitted to continue on study and initiate chemotherapy.Pretreatment tumour and blood samples were collected for genomic analyses using the MSK-IMPACT assay (MSKCC, New York, NY, USA), a US Food and Drug Administration-approved capture-based next-generation sequencing assay that detects mutations, copy-number alterations, and select rearrangements in up to 505 cancer-associated genes.[18] PD-L1 immunohistochemistry was performed using clone E1L3N (Cell Signaling, Danvers MA, USA) before treatment per standard MSKCC practice. PD-L1 CPS was defined as the number of PD-L1-positive tumour cells, lymphocytes, or macrophages divided by the total number of viable tumour cells, multiplied by 100. Whole blood was collected at baseline, at the time of all imaging studies, and at end of treatment for isolation of circulating tumour DNA (ctDNA) and peripheral blood mononuclear cells, which were analysed using the MSK-Analysis of Circulating cfDNA to examine Somatic Status (MSK-ACCESS) assay (MSKCC, New York, NY, USA), a high-depth, next-generation sequencing assay with molecular barcoding technology for ultra-sensitive detection of somatic alterations in 129 genes.

Outcomes

The primary endpoint was 6-month progression-free survival (defined as the proportion of patients alive and progression free at 6 months). Secondary endpoints were safety, objective response rate (proportion of patients with complete response or partial response, per RECIST version 1.1), overall clinical benefit (defined as the proportion of patients with stable disease, partial response, or complete response), median and 12-month overall survival (calculated as the time from start of

treatment to the date of death), and median and 12-month progression-free survival (calculated as the time from start of treatment until documentation of clinical or radiological disease progression or death, whichever occurred first). Disease progression was defined according to RECIST version 1.1 as per investigator assessment, including evidence of progression in non-measurable or measurable lesions, or the development of new lesions. Prespecified exploratory outcomes included association between PD-L1 status by CPS (PD-L1 negative [CPS <1] *vs* PD-L1 positive [CPS ≥1] and PD-L1 high [CPS ≥10] *vs* PD-L1 low [CPS <10] disease; following results of CheckMate-649,[3] post-hoc analyses were performed usinga cutoff of PD-L1 CPS 5) and progression-free survival and objective response rate, as well as correlation of ctDNA clearance with progression-free and overall survival.

Statistical analysis

By use of an exact single-stage binomial design, the study sample size of 35 patients with evaluable endpoints provided 80% power to detect an improvement in the 6-month progression-free survival from the CheckMate-649 historical control of 53%[3,8] to 74%, with a type 1 error of 5%. The regimen would be considered worthy of further investigation if at least 24 of 35 patients were progression free at 6 months. Patients who received at least one dose of any study drug were included in the safety analyses. Patients who received at least one dose of all study treatments were considered evaluable for the primary endpoint. Only patients with measurable disease were considered evaluable for the secondary endpoint of objective response rate. Patients with either measurable and non-measurable disease were considered evaluable for all other secondary endpoints. Patients who came off study treatment because of toxicity before 6 months without documented progression were continually assessed at regular intervals to obtain 6 months of data. Patients who withdrew from the study and could not be followed up to the 6-month endpoint were replaced. Patients with detectable ctDNA before starting treatment were included in the exploratory ctDNA analyses.

Demographic, disease, and treatment characteristics were summarised using frequency and percentage for categorical variables, and median and either IQRs or 95% CIs for continuous variables. Analyses of the secondary endpoints of overall survival, progression-free survival, objective response rate, and overall clinical benefit included patients who received at least one dose of all study treatments. Duration of response was analysed post hoc for all patients who had a best response of complete or partial response and was defined as time of best response until date of progression. Overall survival, 6-month, median, and 12-month progression-free survival, and duration of response were estimated using Kaplan-Meier methods. Participants who were alive and free of progression at the time of analysis were censored at the date of the last evaluable tumour assessment. Responses after 4 weeks of therapy, 6-month progression-free survival, and overall survival were also evaluated in the subgroup prespecified analysis of patients who began treatment with an induction cycle. Fishers exact test was used to compare landmark survival (ie, 6-month progression-free survival). Safety was reported using descriptive statistics.

In exploratory analyses, Fisher's exact test was used to compare progression-free survival at 6 months, overall survival at 12 months, and objective response rate between PD-L1-negative and PD-L1-positive groups, as well as PD-L1 (CPS ≥10) and PD-L1 (CPS <10) groups. Post-hoc analyses were performed using a PD-L1 CPS cutoff of 5 to compare objective response rate and 6-month progression-free survival between cohorts with low PD-L1 expression (CPS <5) and high PD-L1 expression (CPS ≥5), with Fisher's exact test. To examine whether ctDNA clearance at any timepoint correlated with progression-free and overall survival, a Cox regression model was used by including ctDNA clearance as a time-dependent covariate. Additionally, 8 weeks was chosen as the preferred timepoint and the association of

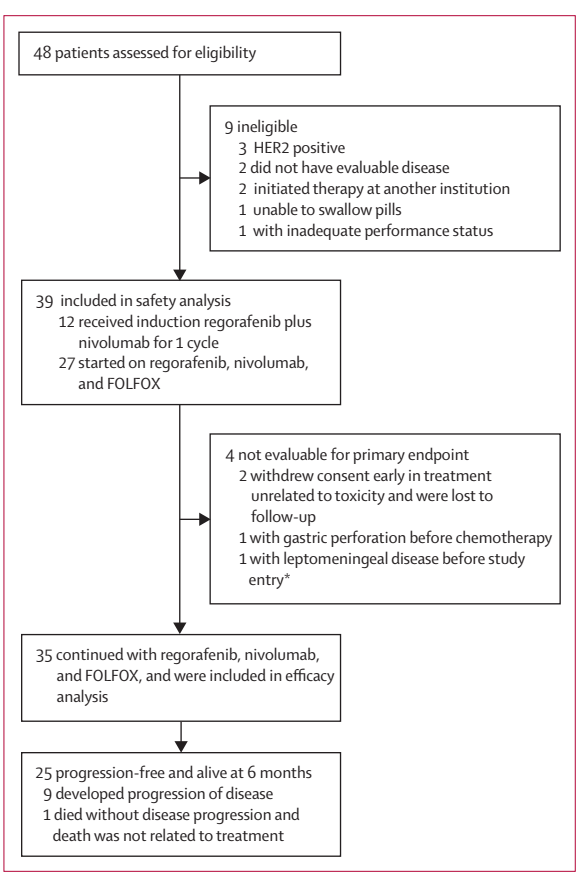

Figure 1: **Trial profile**
*Although brain imaging was not mandated per protocol, a diagnostic MRI and lumbar puncture performed after treatment initiation confirmed leptomeningeal disease, which made the patient ineligible.

	Patients (n=35)
Median age (IQR), years	57 (52–66)
Sex	
Female	9 (26%)
Male	26 (74%)
Race	
White	28 (80%)
Asian	7 (20%)
Primary tumour location	
Oesophageal	11 (31%)
Gastro-oesophageal junction	8 (23%)
Gastric	16 (46%)
ECOG performance status	
0	24 (69%)
1	11 (31%)
Disease stage	
Metastatic	29 (83%)
Recurrent disease	6 (17%)
Locally advanced, unresectable	0
Number of organs with metastases	
1	5 (14%)
≥2	30 (86%)
Sites of metastases	
Lymph nodes	30 (86%)
Liver	12 (34%)
Peritoneum	11 (31%)
Lungs	11 (31%)
Bones	6 (17%)
Pleura	3 (9%)
Soft tissue	3 (9%)
Adrenal glands	2 (6%)
Ovaries	2 (6%)
Kidneys	2 (6%)
Bladder	1 (3%)
Signet ring carcinoma	
Yes	16 (46%)
No	19 (54%)
MMR or MSI status	
MMRp/MSS	34 (97%)
MMRd/MSI-H	0
Unknown	1 (3%)
Measurable disease	29 (83%)
Non-measurable, evaluable disease	6 (17%)
Pretreatment PD-L1 status	
CPS <1 (negative)	20 (57%)
CPS ≥1 (positive)	15 (43%)
CPS ≥10 (high)	3 (9%)
CPS ≥5 (high; post-hoc cutoff)	9 (26%)

Data are n (%) unless otherwise specified. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. MMR=mismatch repair. MMRp/d=mismatch repair proficient/deficient. MSI=microsatellite instability. MSS=microsatellite stable.

Table 1: **Baseline demographic and clinical characteristics of per-protocol population**

ctDNA clearance at 8 weeks with overall survival and progression-free survival was evaluated using a Cox regression. ctDNA was identified using MSK-ACCESS, with detection defined as the presence of a tumour-matched mutation. ctDNA clearance was defined as the conversion of detectable ctDNA at baseline to undetectable ctDNA after treatment.

All statistical analyses were performed using R version 4.2.2. p values less than 0·05 were considered to be statistically significant. This study is registered with ClinicalTrials.gov, NCT04757363.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 11, 2021, and May 4, 2022, 48 patients consented to participate in the study, of whom nine were ineligible and excluded (figure 1). 39 patients began therapy and included in the safety analysis population, of whom four were found to be ineligible and not included for primary endpoint analysis as per protocol. 35 patients were included in the primary analysis among whom the median age was 57 years (IQR 52–66),

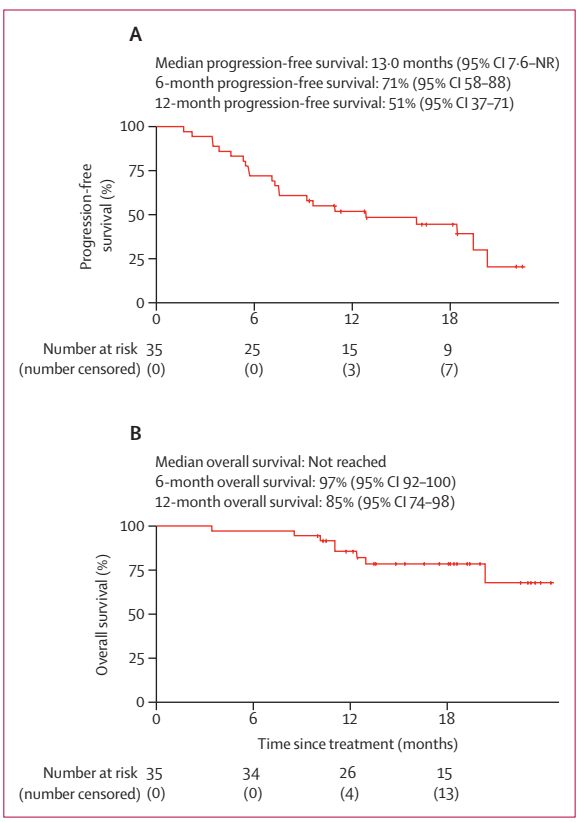

Figure 2: **Survival in the per-protocol population (n=35)**
(A) Progression-free survival. (B) Overall survival. NR=not reached.

nine (26%) patients were female, 26 (74%) were male, 28 (80%) were White, and seven (20%) were Asian (table 1).

At the time of data cutoff (March 3, 2023), median follow-up among surviving patients (n=27) was 18·1 months (IQR 12·7–20·4). At 6 months of follow up, 25 (71% [95% CI 54–85]) of 35 patients were alive and free of progression, so the study met the decision rule for the primary endpoint (binary endpoint as per the statistical design). One (3%) of 35 patients died due to causes unrelated to either treatment or disease before 6 months; nine (26%) of 35 had disease progression before 6 months. As of data cutoff, 21 (27%) of 35 patients had progression-free survival events (13 progressors and 8 deaths). Median progression-free survival was 13·0 months (95% CI 7·6 to not reached) 71% (95% CI 58–88) and 51% (37–71; figure 2A). Median overall survival was not reached, and 6-month and 12-month overall survival rates were 97% (95% CI 92–100) and 85% (74–98), respectively (figure 2B).

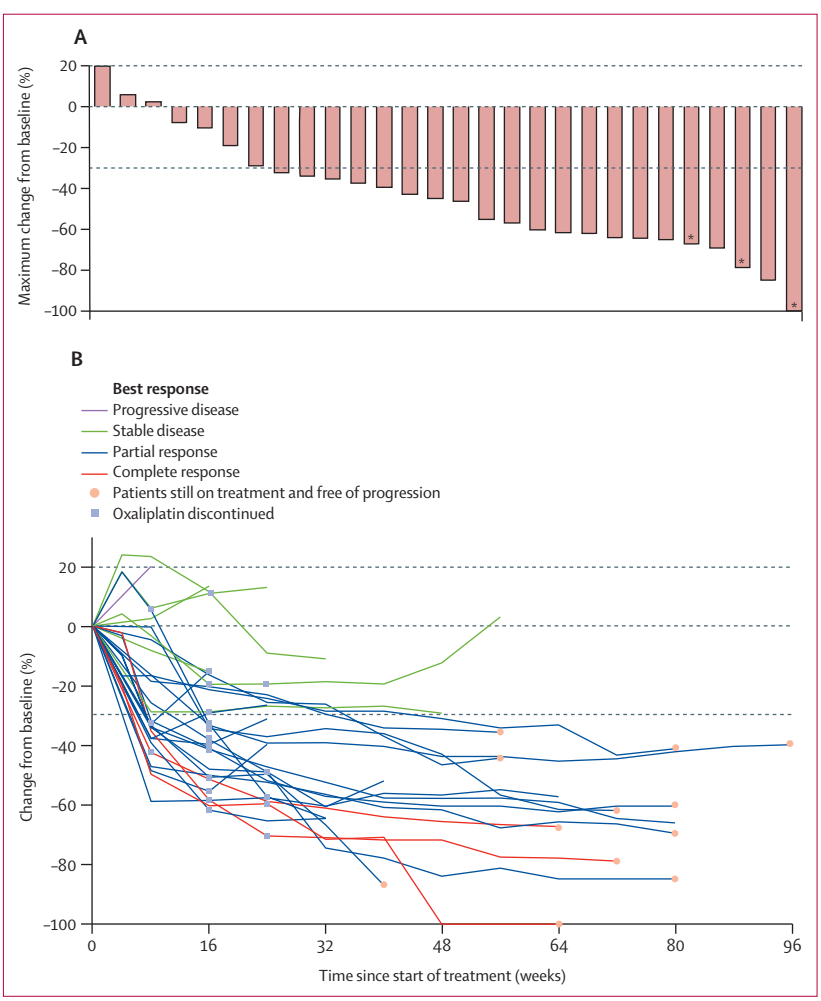

Figure 3: **Changes in tumour burden in the per-protocol population**
(A) Maximum percentage change from baseline in size of tumours. Patients with evaluable but non-measurable lesions (n=6) are not shown. (B) Percentage change from baseline over time. Growth during the induction cycle was not considered progression of disease. In panels A and B, dashed lines at 20% and –30% indicate the minimum change in tumour size for progressive disease and partial response, respectively, by Response Evaluation Criteria in Solid Tumours version 1.1. *Confirmed complete response.

Clinical benefit was observed in 34 (97% [95% CI 85–99]) of 35 patients, including six (17%) with evaluable non-measurable disease by RECIST version 1.1 criteria who had stable disease as best response. Of 29 patients with measurable disease at baseline, 22 (76%) patients had an objective response (three [10%] had a complete response and 19 [66%] had a partial response), six (21%) had stable disease, and one (3%) had progressive disease as best response (figure 3A). Among patients who had a complete or partial response as best response (n=22), post-hoc analysis showed that the median duration of response was 17·0 months (95% CI 5·7–not reached) and the median time to response was 2·1 months (95% CI 1·78–3·71; figure 3B).

In exploratory analyses by PD-L1 expression by CPS, in patients who were PD-L1 negative at baseline 12 (75% [95% CI 48–93]) of 16 with measurable disease had an objective response (two complete responses and ten partial responses) and among those who were PD-L1 positive at baseline, 10 (77% [95% CI 46–95] of 13 with measurable disease had an objective response (one complete response and nine partial responses; p>0·99). 6-month progression-free survival was 75% (95% CI 51–91; five progressors and no deaths out of 20) among patients with PD-L1-negative disease and 67% (95% CI 38–88; four progressors and one death out of 15) among patients with PD-L1-positive disease (p=0·71). Post-hoc analysis in PD-L1 high and low expression subgroups using a PD-L1 CPS cutoff of 5 also did not identify a significant difference in objective response (16 [73%; 95% CI 50–89] of 22 with measurable disease had an objective response in the PD-L1 low [CPS <5] cohort [three complete responses and 13 partial responses] *vs* 6 [86%; 95% CI 42–100] of seven with measurable disease had an objective response in the PD-L1 high [CPS ≥5] cohort [no complete responses and six partial responses]; p=0·65) or in 6-month progression-free survival (81% [21 of 26; 95% CI 61–93; five progressors and no deaths] *vs* 44% [four of nine; 95% CI 14–79; four progressors and one death]; p=0·08) between the groups.

At data cutoff, 11 (31%) of 35 patients remained on study treatment. 20 (57%) of 35 patients had progression of disease, of whom 17 (85%) received second-line therapy. Ten (59%) patients received ramucirumab and paclitaxel, three patients received fluorouracil with irinotecan (FOLFIRI) with ramucirumab, two patients received fluorouracil with nivolumab beyond progression, one patient received FOLFIRI with trastuzumab, and one patient received FOLFIRI alone. At time of data cutoff, 13 patients remain alive after disease progression, seven died due to cancer, one died from other causes, one remains on standard-of-care first-line therapy off-study, and two were lost to follow-up.

Plasma for ctDNA analysis was collected at baseline and at each imaging timepoint. 31 (89%) of 35 patients had detectable ctDNA at baseline. ctDNA analysis identified a mutational profile that was similar to tissue-based tumour sequencing (appendix pp 2–3). After starting therapy, 31 (100%) patients had a decrease in their ctDNA and 15 (48%) had clearance of ctDNA at any timepoint. Median time to clearance was 8 weeks (IQR 8–32).

Clearance of ctDNA at any timepoint was not associated with a significant reduction in all-cause mortality (hazard ratio 0·26 [95% CI 0·05–1·40]; p=0·12; appendix p 3). 15 (48%) of 31 patients had a durable ctDNA response, of whom 11 (73%) remain free of progression. 16 (52%) of 31 patients eventually had an increase in ctDNA after clearance or nadir, 14 (88%) of whom went on to develop progression of disease. Increased ctDNA preceded progression by a median of 7·6 weeks (IQR 0–16).

On the basis of the efficacy shown with regorafenib and nivolumab in heavily pretreated patients in the REGONIVO trial,[14] and to explore the activity of this biologic-only, chemotherapy-free regimen, the study allowed, per investigator discretion, an initial induction cycle of regorafenib and nivolumab alone. 11 patients in the primary efficacy group received an induction cycle. Although baseline patient and tumour characteristics were mostly similar between the induction and non-induction cohorts, in the induction cohort, all patients had an ECOG performance status of 0 (appendix pp 4–5). Ten (91%) of 11 patients in the induction cohort had measurable disease, of whom six (60%) showed a reduction in at least some target lesions (range –2·2% to –19·9%) as assessed by repeat CT scan after 3 weeks of daily regorafenib and two doses of nivolumab, and before FOLFOX chemotherapy. 6-month progression-free survival did not differ significantly between the induction and non-induction groups (82% [95% CI 48–98] *vs* 67% [45–84]; Fisher's exact p=0·45).

Adverse events occurred in 38 (97%) of 39 patients in the safety population, with the most frequent events of any grade being fatigue (36 [92%]), paraesthesia or peripheral neuropathy (30 [77%]), palmar-plantar erythrodysesthesia syndrome (26 [67%]), constipation (26 [67%]), dry skin, pruritus, or rash (25 [64%]), anorexia or dysgeusia (25 [64%]), and abdominal pain (25 [64%]) (table 2). 31 (79%) patients had an adverse event of grade 3 or worse; the most common were decreased neutrophil count (18 [46%]), hypertension (six [15%]), dry skin, pruritus, or rash (five [13%]), and anaemia (four [10%]). One patient died from respiratory failure not related to treatment or disease. Ten (26%) patients had a serious treatment-related adverse event, which were acute kidney injury (three [8%]), hepatotoxicity (two [5%]), sepsis (two [5%]), dry skin, pruritus, or rash (one [3%]), nausea (one [3%]), and gastric perforation (one [3%]). 35 (90%) patients required a dose reduction of at least one component of the regimen due to adverse events, primarily for peripheral neuropathy (n=16), decreased neutrophil count (n=16), and fatigue (n=13). One (3%) patient discontinued fluorouracil and 31 (79%) discontinued oxaliplatin due to adverse events, most

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	7 (18%)	23 (59%)	7 (18%)	1 (3%)
Any treatment-related serious adverse event	0	10 (26%)	3 (8%)	0
Fatigue	34 (87%)	2 (5%)	0	0
Paraesthesia or peripheral neuropathy	30 (77%)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	24 (62%)	2 (5%)	0	0
Constipation	26 (67%)	0	0	0
Dry skin, pruritus, or rash	20 (51%)	5 (13%)	0	0
Abdominal pain	24 (62%)	1 (3%)	0	0
Anorexia or dysgeusia	24 (62%)	1 (3%)	0	0
Decreased neutrophil count	3 (8%)	14 (36%)	4 (10%)	0
Nausea	20 (51%)	1 (3%)	0	0
Vomiting	14 (36%)	2 (5%)	0	0
Fever	15 (38%)	1 (3%)	0	0
Oral mucositis	16 (41%)	0	0	0
Cough	15 (38%)	0	0	0
Anaemia	10 (26%)	4 (10%)	0	0
Diarrhoea	14 (36%)	0	0	0
Dyspnoea	13 (33%)	1 (3%)	0	0
Hypersensitivity or infusion-related reaction	12 (31%)	0	0	0
Dysphagia	12 (31%)	0	0	0
Weight loss	11 (28%)	0	0	0
Hypertension	4 (10%)	6 (15%)	0	0
Muscle cramps or myalgias	9 (23%)	0	0	0
Increased AST or ALT	6 (15%)	2 (5%)	1 (3%)	0
Increased creatinine	5 (13%)	3 (8%)	0	0
Headache	6 (15%)	1 (3%)	0	0
Arthralgias or joint pain	7 (18%)	0	0	0
Decreased platelet count	6 (15%)	0	0	0
Alopecia	6 (15%)	0	0	0
Increased blood bilirubin	6 (15%)	0	0	0
Thromboembolic event	4 (10%)	2 (5%)	0	0
Hypokalaemia	3 (8%)	1 (3%)	0	0
Limb oedema	4 (10%)	0	0	0
Decreased white blood cell count	2 (5%)	2 (5%)	0	0
Urinary tract infection	2 (5%)	1 (3%)	0	0
Syncope	0	2 (5%)	0	0
Fall	1 (3%)	1 3(%)	0	0
Hyponatraemia	0	1 (3%)	0	0
Febrile neutropenia	0	1 (3%)	0	0
Sepsis	0	1 (3%)	0	0
Cholecystitis	0	1 (3%)	0	0
Gastric perforation	0	0	1 (3%)	0
Haematoma	0	0	1 (3%)	0
Respiratory failure	0	0	0	1 (3%)

Data are n (%). One death occurred due to an adverse event, (respiratory failure), which was determined to be unrelated to study treatment. Data are shown for adverse events of grade 1–2 that occurred in at least 10% of patients, and all grade 3–5 adverse events. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

Table 2: **Adverse events in the safety population (n=39)**

commonly due to peripheral neuropathy (14 [45%]), and after a median duration of 16 weeks (IQR 14–19). 18 (46%) patients had an immune-related adverse event due to nivolumab, and some patients reported more than one immune-related adverse event; the most common events reported were arthralgias (six [15%]), dermatitis (five [13%]), acute interstitial nephritis (three [8%]), hepatitis (three [8%]), and hypothyroidism (two [5%]). However, nivolumab was only discontinued in five (13%) patients for nephritis (three [8%]), dermatitis (one [3%]), and severe infusion reaction (one [3%]). Seven (18%) patients discontinued regorafenib and ten (26%) required dose reduction from 80 mg to 40 mg, and some patients reported more than one reason for dose reduction; the most common reasons being rash (five [13%]), palmar-plantar erythrodysesthesia syndrome (four [10%]), and fatigue (three [8%]). There were no treatment-related deaths.

Discussion

In this single-arm, phase 2 study, patients with untreated, advanced HER2-negative oesophageal, gastric, or gastro-oesophageal junction cancer were treated with the combination of regorafenib and nivolumab with FOLFOX chemotherapy, and the study reached its primary endpoint with 25 (71%) of 35 patients being progression free at 6 months. The median progression-free survival of 13·0 months, 12-month progression-free survival of 51%, and 12-month overall survival of 85% were also numerically higher than the median progression-free survival of 7·7 months, 12-month progression-free survival of 33%, and 12-month overall survival of 55% reported previously for chemotherapy plus nivolumab, the existing first-line standard.[3,8]

Outcomes were similar regardless of PD-L1 CPS status. These findings are in contrast with phase 3 trials of chemotherapy with PD-1 inhibitors, in which the benefit of treatment was greater in patients whose tumours had higher PD-L1 expression.[2,3,19] In this study, only 26% of patients had tumours with a PD-L1 CPS of at least 5, compared with 60% of patients in Checkmate-649[3] and Orient-16.[19] PD-L1 immunohistochemistry antibodies might account for these differences, because we used E1L3N for our cohort, whereas immunohistochemistry 28·8 (Agilent DAKO) was used in the Checkmate-649 trial and 22C3 (Agilent DAKO) as used in the Orient-16 trial. Patient referral might have also contributed to these differences, given that patients with tumours that were PD-L1 negative might have been disproportionately referred for this trial, whereas those with PD-L1 positive or high expression of PD-L1 might have been directed toward standard nivolumab and chemotherapy.

Adverse events were observed in most patients, and the frequency of grade 3 or worse adverse events was higher than has been reported for the combination of nivolumab and chemotherapy in CheckMate-649 (79% *vs* 60%).[3] This difference was primarily due to high rates of bone marrow suppression—namely, a relatively high rate of decreased neutrophil count (46% of patients had a grade ≥3 event *vs* 11% in CheckMate-649).[3] Notably, an additional 15% of patients in CheckMate-649 had neutropenia of grade 3 or worse, which was reported as a distinct adverse event from decreased.[3] However, the increased incidence of adverse events of grade 3 or worse in the current study could be associated with pharmacokinetic effects of regorafenib and oxaliplatin, as a similarly higher than expected rate of neutropenia was observed in our previous phase 2 study of regorafenib with FOLFOX.[17] Additionally, 79% of patients discontinued oxaliplatin due to toxicity after a median of 4 months, whereas the time to best response was 2 months, suggesting that a maintenance strategy is feasible.

In this study, ctDNA was collected in patients at baseline and longitudinally during treatment. Plasma-based ctDNA sequencing identified a similar mutational profile compared with tissue-based sequencing, but plasma-based ctDNA sequencing has the advantage of dynamic monitoring and the potential to address genomic heterogeneity among metastatic sites not assessable using a single tumour biopsy. 89% of analysable patients had detectable ctDNA at baseline and 48% had clearance of ctDNA. Moreover, given that the median time to ctDNA clearance is 8 weeks, if ctDNA monitoring is planned, our data suggest it is best to collect plasma for ctDNA evaluation before initiating therapy. Clearance of ctDNA was not found to be associated with a significant improvement in overall survival, which could be due to the small sample size. Increase of ctDNA after clearance or nadir preceded radiographical disease progression by a median of 7·6 weeks. Taken together, these data add to the growing body of evidence indicating that ctDNA might be a useful disease monitoring tool,[20–22] although larger randomised trials to validate these findings are warranted.

The first-line treatment landscape for oesophagogastric adenocarcinoma is rapidly evolving, with phase 3 trials[23,24] showing overall survival improvement with anti-claudin (CLDN) 18·2 monoclonal antibody, zolbetuximab, and chemotherapy compared with chemotherapy alone in patients with CLDN18·2-positive disease, establishing CLDN18·2 as another therapeutic target.[23,24] Despite these advances, there is still an urgent need for improved therapeutic options for patients with HER2-negative, PD-L1-negative, and CLDN18·2-negative tumours. LEAP-015 (NCT04662710) is an ongoing randomised phase 3 trial evaluating lenvatinib in combination with nivolumab and chemotherapy; however, the comparator group is chemotherapy alone without nivolumab.

Limitations of this study include its small sample size and single-arm design. Additionally, the study population was younger than the average age of patients with this disease and a high proportion received second-line therapy. However, 34% of patients had liver metastases,

31% had peritoneal metastases, and 86% of patients had at least two sites of metastatic disease, highlighting the large disease burden in this cohort. This study was also limited by the fact, that although the referenced historical control of 53% 6-month progression-free survival is based on a large multicentre study, recruitment in our trial was limited to a single centre. Therefore, a confirmatory randomised phase 3 study is necessary before this regimen could be adopted into clinical practice.

We believe that the activity observed in this study support the development of regorafenib-based combinations in future clinical trials. Given the burden of disease and symptoms experienced by many patients at the time of diagnosis, we would not recommend initiating treatment with the chemotherapy-free induction cycle. However, due to the relatively high toxicity of the quadruplet, and given that oxaliplatin's maximum benefit is typically reached within the first several months of therapy (median time to best response was 2 months), regorafenib might be best used as an addition to maintenance therapy in combination with fluoropyrimidine and nivolumab, after discontinuation of oxaliplatin. Our findings suggest that regorafenib with nivolumab and chemotherapy is safe and showed promising anti-tumour activity in patients with advanced oesophagogastric cancer. Additional biomarker work is underway to dissect the associations among neoantigen immunogenicity, immune suppression, and response to immune checkpoint blockade.

Contributors

RHM, MC, and YYJ designed the study. SLC, RHM, DC, SSJ, GYK, SBM, AD, JY, RS, DR, ZG, AA, FS, NT, HG, MAS, MS, MEL, VP, LHT, JS, DHI, and YYJ collected data. SLC, AA, FS, NT, JFC, MC, and YYJ were additionally responsible for clinical data management and quality assurance. YYJ oversaw the protocol. SLC, RHS, AA, JFC, CC, ML, MC, DBS, MFB, and YYJ analysed data. SLC, JFC, MC, RHS, MFB, and YYJ interpreted the data. All authors participated in drafting and reviewing iterations of the manuscript, and approved the final draft for submission. SLC and YYJ directly accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

SLC reports stock ownership in Pfizer, Moderna, and BioNTech. RHM reports consulting with PureTech Health, advisory board with IDEAYA Biosciences, and research funding from Nimbus Therapeutics. JFC reports an investigator role on a research study sponsored by Paige.AI. GYK reports consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, Pieris, and Zymeworks; and grants or contracts from AstraZeneca, Bristol-Myers Squibb, CARsgen, Zymeworks, Daiichi Sankyo, Oncolys, Pieris, and Adaptimmune. SBM reports honoraria from Natera, Bicara, Novartis, Basilea, Elevation Oncology, Purple Oncology, Pinetree Therapeutics, and Daiichi Sankyo; research support from Epic Sciences; grant funding from the Conquer Cancer Foundation; and research travel support from AstraZeneca outside of the submitted work. MAS reports consulting for Boston Scientific and Novo Nordisk. MEL reports ownership or equity interests with Apricity Health; intellectual property rights with John Wiley & Sons, and the Taylor & Francis Group; uncompensated provision of services for Oncoderm; and provision of services for Adgero Biopharmaceuticals, the American Academy of Dermatology, the American Society of Pediatric Hematology/Oncology, Apricity Health, AstraZeneca, Atlantic Canada Oncology Group, BGB Communications, Bicara Therapeutics, Deciphera, DelMar Pharmaceuticals, EMD Serono, GCO Global, Hoth Therapeutics, Incyte, Innovaderm Research, Johnson & Johnson, La Fonderie Ressources, La Roche-Posay, Loxo Oncology, Lutris Pharma, MJH Life Sciences, the Michigan Dermatological Society, NKMax America, NanOlogy, Novartis, Novartis Pharmaceuticals Corporation, Novocure, OnQuality Pharmaceuticals, Patient Resource, QED Therapeutics, RBC Consulting, RMEI Medical Education, Society for Immunotherapy of Cancer, Takeda Millennium, The Lynx Group, Tyra Biosciences, Varsona Pharmaceuticals, WebMD, Wolters Kluwer, and eSquared Communication Consulting. JS reports consulting for Paige.AI. MFB reports consulting for Eli Lilly and AstraZeneca (not related to this work). YYJ reports research funding from Bayer, Bristol Myers Squibb, Memorial Sloan Kettering Cancer Center Cycle for Survival, the United States Department of Defense, Eli Lilly, Fred's Team, Genentech/Roche, Merck, the National Cancer Institute, and RGENIX; advisory board or consulting with AbbVie, Amerisource Bergen, Ask-Gene Pharma, Arcus Biosciences, Astellas, Astra Zeneca, Basilea Pharmaceutica, Bayer, Bristol Myers Squibb, Clinical Care Options, Daiichi-Sankyo, Eli Lilly, Geneos Therapeutics, GlaxoSmithKline, Guardant Health, Imedex, Imugene, Lynx Health, Merck, Merck Serono, Mersana Therapeutics, Michael J Hennessy Associates, Paradigm Medical Communications, PeerView Institute, Pfizer, Research to Practice, RGENIX, Seagen, Silverback Therapeutics, and Zymeworks; and stock options in RGENIX. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data, de-identified participant data, participant data with identifiers, and a data dictionary, can be requested by qualified researchers and will be assessed by a scientific review board.

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