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Clinical Trial

FOLFOX alone or combined with rilotumumab or panitumumab as first-line treatment for patients with advanced gastroesophageal adenocarcinoma (PRODIGE 17-ACCORD 20-MEGA): a randomised, open-label, three-arm phase II trial

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Abstract ***Background:*** Epidermal growth factor receptor (EGFR) and hepatocyte growth factor (HGF)/mesenchymal–epithelial transition (MET) pathways, which promote tumour growth and proliferation, are often deregulated in advanced gastroesophageal adenocarcinomas. We assessed whether adding panitumumab (an EGFR inhibitor) or rilotumumab (a HGF inhibitor) to first-line fluoropyrimidine-based and platinum-based chemotherapy (modified oxaliplatin, leucovorin and fluorouracil [mFOLFOX6]) benefits to patients with advanced gastroesophageal adenocarcinoma.
Patients and methods: This phase II, open-label, randomised, three-arm study enrolled patients ≥18 years, with advanced gastroesophageal adenocarcinoma, Eastern Cooperative Oncology Group performance status 0–1 and no known HER2 overexpression. Patients were randomly assigned (1:1:1) mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus then 2400 mg/m^2 over 46 h) alone or combined with panitumumab (6 mg/kg) or rilotumumab (10 mg/kg) every 2 weeks until limiting toxicity, patient's refusal or disease progression. The primary end-point was the 4-month progression-free survival (PFS) rate. Secondary end-points included overall survival (OS) and tolerance.
Results: The study enrolled 162 patients in 29 French centres. The median follow-up was 23.6 months (interquartile range = 16.4–29.0). The 4-month PFS rate was 71% (95% confidence interval [CI] = 57–82) with chemotherapy alone, 57% (95% CI = 42–71) combined with panitumumab and 61% (95% CI = 47–74) combined with rilotumumab. Median OS was 13.1 months (95% CI = 8.7–16.9) with chemotherapy alone, 8.3 months (95% CI = 6.2–13.2) combined with panitumumab and 11.5 months (95% CI = 7.9–17.1) combined with rilotumumab. Adverse events grade ≥III occurred less frequently with chemotherapy alone (62%) than with panitumumab (83%) and rilotumumab (89%).
Conclusions: We found no benefit in adding panitumumab or rilotumumab to mFOLFOX6 first-line chemotherapy to treat advanced gastroesophageal adenocarcinoma patients.
Trial registration: European Clinical Trials Database, number 2009-012797-12.

1. Introduction

Gastric cancer is the second leading cause of cancer death worldwide [1]. Doublet or triplet chemotherapy with a platinum-fluoropyrimidine backbone remains the mainstay of treatment for fit patients with advanced gastric cancer [2]. However, the prognosis of these tumours remains dismal, with reported median overall survival (OS) times inferior to 1 year [3–8].

Targeted therapies have been developed to counteract the deregulation of signal transduction pathways, including epidermal growth factor receptor (EGFR) and hepatocyte growth factor (HGF)/mesenchymal–epithelial transition (MET) pathways [9,10]. In advanced gastric cancer, EGFR overexpression occurs in up to 50% of patients [9,11,12]. Similarly, abnormal *HGF* and *MET* upregulation occurs in gastric cancer [10,11,13,14], with MET overexpression in 18–82% of patients [14]. Panitumumab, a monoclonal antibody targeting EGFR, is approved in advanced colorectal cancer [15]. First reports of EGFR inhibitors combined with chemotherapy showed promising results in advanced gastric cancer [12,16]. Rilotumumab, a monoclonal antibody targeting HGF, the ligand of the MET receptor, was shown tolerable and active in various advanced solid tumours [17,18].

Our study assessed the efficacy and safety of panitumumab or rilotumumab combined with 5-fluorouracil-based and oxaliplatin-based chemotherapy as first-line therapy for advanced gastroesophageal adenocarcinomas.

2. Methods

2.1. Study oversight

MEGA (MET or EGFR inhibition in gastroesophageal adenocarcinoma) was designed as a phase II, open-label, randomised, three-arm study. Patients aged ≥18 years with locally advanced (unresectable) or metastatic adenocarcinoma of the stomach, gastroesophageal junction or oesophagus, an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions were eligible. Non-inclusion criteria included prior chemotherapy for advanced disease, known HER2 overexpression (immunohistochemistry 3+ or 2 + with positive *in situ* hybridisation), known meningeal or brain metastases, and peripheral neuropathy grade ≥II. Patients were randomly assigned (1:1:1) modified oxaliplatin, leucovorin and fluorouracil (mFOLFOX6) (chemotherapy alone group), mFOLFOX6 with panitumumab (panitumumab group) or mFOLFOX6 with rilotumumab (rilotumumab group). Randomisation was stratified (minimisation method) by extent of disease (metastatic or locally advanced), histological subtype by Lauren classification [19] (diffuse, intestinal or mixed) and centre. All patients provided written informed consent before participating. The study was approved by a French ethics committee and conducted respecting the Declaration of Helsinki and good clinical practice guidelines.

2.2. Treatments

Patients received mFOLFOX6 (oxaliplatin 85 mg/m^2 in 2-h infusion; leucovorin 400 mg/m^2 in 2-h infusion; 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 infused over 46 h) alone or combined with panitumumab (6 mg/kg in 1-h infusion) or rilotumumab (10 mg/kg in 1-h infusion), every 2 weeks until limiting toxicity, patient's refusal or disease progression. At discontinuation, further treatment was at the investigator's discretion.

2.3. Assessments

Study visits occurred at baseline and then every 2 weeks and included physical examination, blood analysis and tolerance assessment. Tumour response was assessed every 8 weeks by computed tomography or magnetic resonance imaging using Response Evaluation Criteria in Solid Tumours, version 1.1 [20]. After disease progression, visits were scheduled every 2 months for up to 5 years.

2.4. End-points

The primary end-point was the 4-month progression-free survival (PFS) rate. Secondary end-points included PFS, OS, time to progression, objective response rate, duration of response, disease control rate and treatment toxicity. Adverse events were assessed by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, except peripheral neuropathy which was graded with Levi's scale [21].

2.5. Exploratory biomarker analysis

Archival tumour samples were collected at inclusion, and blood samples were collected at inclusion and on day 1 of cycle 3 before treatment administration. Exploratory studies aimed to identify predictive and prognostic biomarkers among functional or molecular alterations of the EGFR/RAS/RAF, HER2 and HGF/MET pathways. The circulating tumour cell analysis has been reported [22] and the immune cell (myeloid-derived suppressor cells, NK cells) analysis will be reported separately.

2.6. Statistical considerations

Based on a Fleming single-stage design, with a one-sided α-level of 5% and a power of 90%, with $H_0 = 40\%$ and $H_1 = 60\%$ of success (defined as a non-progression rate at 4 months), 51 evaluable patients per group were required [23]. In the experimental groups, we could conclude to efficacy if ≥ 26 successes and to inefficacy if ≥ 26 disease progressions or deaths were observed. No formal comparison between groups was planned.

Efficacy analyses were performed on the intent-to-treat population (randomised patients) and the per-protocol population (randomised patients without major protocol violations and with at least one tumour assessment after treatment start). Safety analyses were performed on the safety population (patients who received at least one dose of study treatment).

Time-to-event end-points were estimated by Kaplan–Meier methods. Subgroup analyses for PFS and OS by tumour biomarker status were performed. Baseline characteristics were compared by Kruskal–Wallis or Wilcoxon statistical tests (quantitative variables) and by Chi-square or exact Fisher's tests (qualitative variables). Biomarker prognostic and predictive values were estimated by Cox proportional hazards regression model. Treatment compliance was evaluated by dose-intensity (cumulative dose delivered/treatment duration) and relative dose-intensity per patient (dose-intensity delivered/dose intensity planned).

The statistical analysis was performed using STATA, version 13 (Texas).

3. Results

3.1. Participants

From January 2011 to August 2013, 162 patients were enrolled in 29 French centres (Fig. 1). In May 2013,

enrolment in the panitumumab group was stopped after an interim safety analysis showed an imbalance in death rates in the treatment groups.

Patient characteristics were well balanced between groups (Table 1). Most patients had a metastatic (157/162, 97%), intestinal (112/162, 69%) adenocarcinoma of the stomach (80/162, 49%) or gastroesophageal junction (50/162, 31%).

3.2. Efficacy

The median follow-up for the intent-to-treat population was 23.6 months (interquartile range [IQR] = 16.4–29.0) and was similar for the three groups (Table 2). The 4-month PFS rate was 71% (95% confidence interval [CI] = 57–82) in the chemotherapy alone group, 57% (95% CI = 42–71) in the panitumumab group and 61% (95% CI = 47–74) in the rilotumumab group. Median PFS was 5.8 months (95% CI = 5.2–7.3) in the chemotherapy alone group, 5.2 months (95% CI = 3.7–7.6) in the panitumumab group and 7.6 months (95% CI = 4.0–9.0) in the rilotumumab group (Fig. 2A and Table 2). Median OS was 13.1 months (95% CI = 8.7–16.9) in the chemotherapy alone group, 8.3 months (95% CI = 6.2–13.2) in the panitumumab group and 11.5 months (95% CI = 7.9–17.1) in the rilotumumab group (Fig. 2B and Table 2). These results were confirmed on the per-protocol population (Supplementary Table S1).

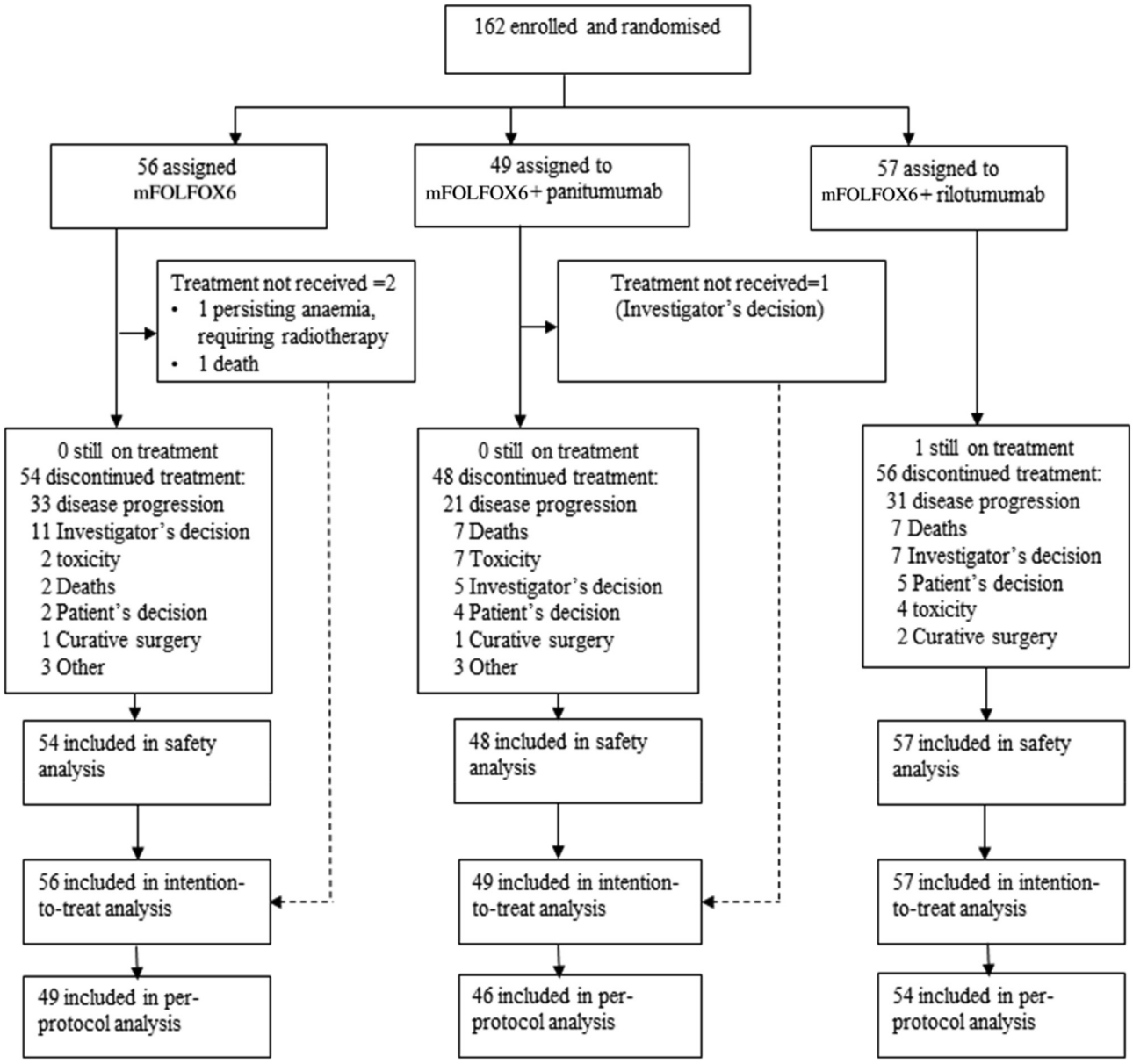


Fig. 1. Trial profile. mFOLFOX6, oxaliplatin, leucovorin and fluorouracil.

Table 1
Patient characteristics—intent-to-treat population.

Characteristic	mFOLFOX6 (n = 56)	mFOLFOX6 + panitumumab (n = 49)	mFOLFOX6 + rilotumumab (n = 57)
Age (years)	64 (57–69)	64 (51–71)	65 (58–70)
Sex			
Male	39 (70%)	33 (67%)	37 (65%)
Female	17 (30%)	16 (33%)	20 (35%)
ECOG performance status			
0	20 (36%)	16 (33%)	17 (30%)
1	36 (64%)	33 (67%)	39 (70%)
Primary tumour location			
Stomach	26 (46%)	24 (49%)	30 (53%)
Gastroesophageal junction	18 (32%)	13 (27%)	19 (33%)
Oesophagus	12 (21%)	12 (24%)	8 (14%)
Tumour type			
Intestinal	40 (71%)	33 (67%)	39 (68%)
Diffuse	10 (18%)	10 (20%)	12 (21%)
Mixed	6 (11%)	6 (12%)	6 (11%)
Disease stage at enrolment			
Metastatic	53 (95%)	49 (100%)	55 (96%)
Synchronous metastases	43 (81%)	40 (82%)	45 (82%)
Locally advanced	3 (5%)	0	2 (4%)
Prior curative-intent surgery	11 (20%)	12 (25%)	18 (32%)

Data are n (%) or median (IQR).
mFOLFOX6, modified oxaliplatin, leucovorin and fluorouracil; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

3.3. Treatment compliance and safety

Patients received a median of 10.5 (range 1–31) cycles in the chemotherapy alone group, nine (2–31) in the panitumumab group and 11 (1–51) in the rilotumumab group (Supplementary Table S2). A relative dose-intensity equal or superior to 80% for FOLFOX was achieved in 52% of patients in the chemotherapy alone group, 48% in the panitumumab group and 35% in the rilotumumab group. Treatment modifications were most frequent in the rilotumumab group. Treatment was discontinued because of disease progression in 61% of patients in the chemotherapy alone group, 44% in the panitumumab group and 55% in the rilotumumab group.

Adverse events grade ≥III occurred less frequently in the chemotherapy alone group (62%) than in the panitumumab group (83%) and in the rilotumumab group (89%) (Table 3). Serious adverse events occurred in 37 (66%) patients in the chemotherapy alone group, 40 (82%) in the panitumumab group and 53 (93%) in the rilotumumab group. Four suspected unexpected severe adverse reactions were reported: two in the panitumumab group (unknown cause of death and colonic perforation with peritonitis) and two in the rilotumumab group (interstitial pneumopathy and left transient hemiparesis).

Four patients died of treatment-related adverse events in the panitumumab group (from interstitial lung disease, colonic perforation, gastrointestinal obstruction and unknown) and two in the rilotumumab group (from gastrointestinal haemorrhage and pulmonary embolism). Two further patients died from adverse events, not considered treatment related: one in the chemotherapy alone group and one in rilotumumab group.

3.4. Exploratory biomarker analysis

Patient baseline characteristics were similar between the 100 patients (62%) evaluable for at least one tumour biomarker and the non-evaluable remainder (Supplementary Table S3). 55/91 patients (60%) had MET overexpression (immunohistochemistry), 3/99 (3%) had *MET* amplification, 13/92 (14%) had HER2 overexpression or amplification (13/92, 14%), 7/72 (10%) had *KRAS*-mutated tumours, no patient had a *NRAS*-mutated tumour and only 1/72 patients had a *BRAF*-mutated tumour (Supplementary Table S4). Patients with HER2-positive tumours had longer median PFS (hazard ratio [HR] = 0.51, 95% CI = 0.27–0.97, p = 0.03) and OS (HR = 0.35, 95% CI = 0.15–0.78, p = 0.004) (Supplementary Fig. S1). *KRAS* mutations or MET overexpression had no prognostic effect on survival. *KRAS*, HER2 and MET tumour statuses did not predict response to therapy.

4. Discussion

Our results indicate that adding panitumumab or rilotumumab to fluoropyrimidine-platinum doublet

Table 2
Efficacy outcomes—intent-to-treat population.

Endpoint	mFOLFOX6 (n = 56)	mFOLFOX6 + panitumumab (n = 49)	mFOLFOX6 + rilotumumab (n = 57)
Median follow-up (months) (IQR)	23.5 (14.4–29.9)	23.6 (17.5–27.6)	25.5 (16.4–29.0)
4-month progression-free survival rate (95% CI)	71 (57–82)	57 (42–71)	61 (47–74)
Time-to-event outcomes			
Time to progression (months)	5.9 (5.3–7.3)	5.2 (3.7–7.6)	7.6 (4.0–9.0)
Progression-free survival (months)	5.8 (5.2–7.3)	5.2 (3.7–7.6)	7.6 (4.0–9.0)
Overall survival (months)	13.1 (8.7–16.9)	8.3 (6.2–13.2)	11.5 (7.9–17.1)
Objective response rate	29 (52)	21 (43)	28 (49)
Complete response	1 (2)	3 (6)	5 (9)
Partial response	28 (50)	18 (37)	23 (40)
Stable disease	12 (21)	17 (35)	18 (32)
Progressive disease	9 (16)	7 (14)	7 (12)
Non-evaluable	0	1 (2)	0
Not assessed	6 (11)	3 (6)	4 (7)
Disease control rate	41 (73)	38 (78)	46 (81)
Duration of response (months)			
Objective response	5.7 (3.8–7.8)	6.4 (3.8–11.3)	8.0 (3.9–10.7)
Stable disease	5.8 (4.8–8.4)	4.6 (3.3–8.4)	7.3 (3.7–8.9)

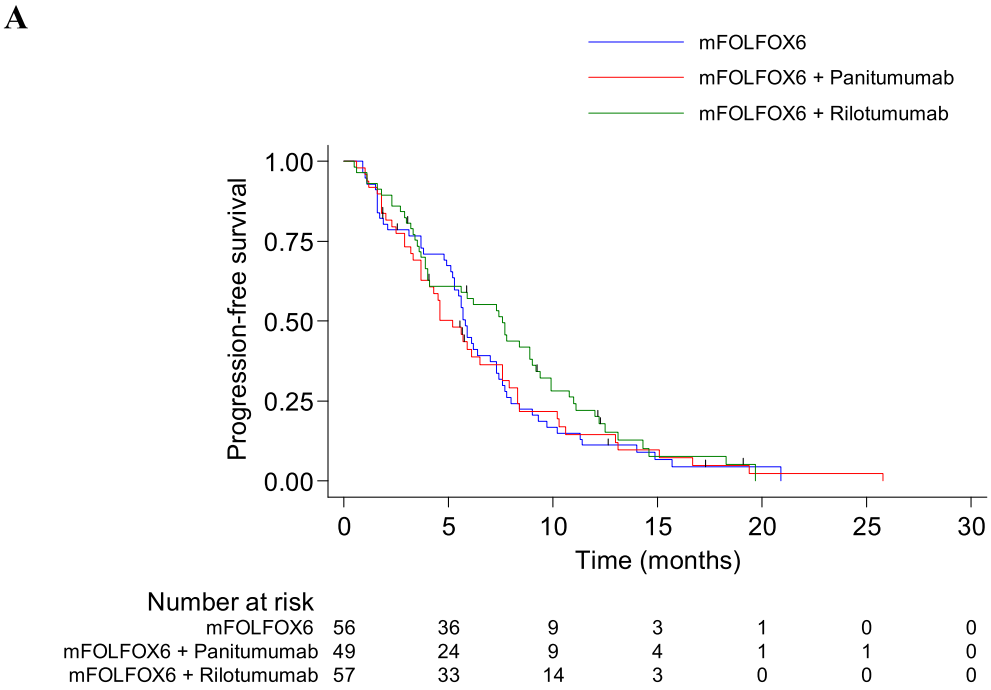
Data are n (%) or median (95% CI) unless otherwise specified.
mFOLFOX6, modified oxaliplatin, leucovorin and fluorouracil; CI, confidence interval; IQR, interquartile range.

chemotherapy does not improve first-line therapy efficacy in advanced gastroesophageal adenocarcinoma patients. No benefit in 4-months PFS and OS was observed in adding panitumumab or rilotumumab to mFOLFOX6. The median OS, 13.1 months, with chemotherapy alone corresponds with the 8.6–12.6 months reported in other phase II trials using FOLFOX alone in this setting [24–26].

Our results agree with other studies combining chemotherapy with EGFR antibodies (panitumumab [3] and cetuximab [4]) and HGF/MET pathway antibodies (rilotumumab [5,6] and onartuzumab [7,8]). In the REAL3 study, adding panitumumab to epirubicin, oxaliplatin and capecitabine (modified EOC regimen) was detrimental with respect to PFS and OS [3]. The authors argue that reducing the oxaliplatin and capecitabine dosages in the combined therapy (for toxicity management) may reduce chemotherapy efficacy. In our study, the mFOLFOX6 dosage was not reduced in the panitumumab group. However, the relative dose-intensity of mFOLFOX6 was lower in the rilotumumab group. In the EXPAND study, adding cetuximab to capecitabine and cisplatin (XP regimen), without chemotherapy dose-intensity reduction, gave no benefit in PFS, OS or objective response rate [4]. The chemotherapies used in the EXPAND and REAL3 studies have been questioned because results in advanced colorectal cancer suggest a possible negative interaction between cetuximab and oxaliplatin with oral 5-FU (capecitabine) but not infusional 5-FU [27]. In the RILOMET-1 study, rilotumumab was added to epirubicin, cisplatin and capecitabine (ECC regimen) [5]. The study terminated early, because more deaths due to disease progression were observed with rilotumumab. OS, PFS and objective response rate were worse in the rilotumumab group. Finally, adding the MET antibody onartuzumab to FOLFOX did not improve PFS [7].

Adverse events were more frequent and more severe in the panitumumab and rilotumumab groups than in the chemotherapy alone group. Although targeted therapies generally have acceptable safety profiles, their combination with chemotherapy seems to increase the chemotherapy's cytotoxic effects. Our study's open-label design may have increased the reporting of adverse events in the targeted therapy groups. However, panitumumab and rilotumumab (to lesser degree) are known to induce frequent skin toxicity, which precludes blinding.

Tumour MET expression was not considered during enrolment, even though high MET expression levels in gastroesophageal adenocarcinoma have been associated with poorer prognosis [13,14]. However, no prognostic or predictive effects on survival were associated with MET-positive tumours, in line with the results of the RILOMET-1 [5] and METGastric phase III studies [8]. These results are at variance from those of the earlier randomised phase II study of rilotumumab plus ECC, in which patients with MET-positive tumours harboured a worse survival in the chemotherapy alone group but derived clinical benefit in the rilotumumab group [6], underlining the unreliability of MET overexpression as assessed by immunohistochemistry in the available randomised studies. Of note, the METGastric study [8] closed early because a parallel phase II study failed to identify an obvious predictive cut-off for MET expression intensity [7]. The absence of a biomarker able to identify the patients whose tumours are strictly driven by aberrant *MET* activity might have contributed to the



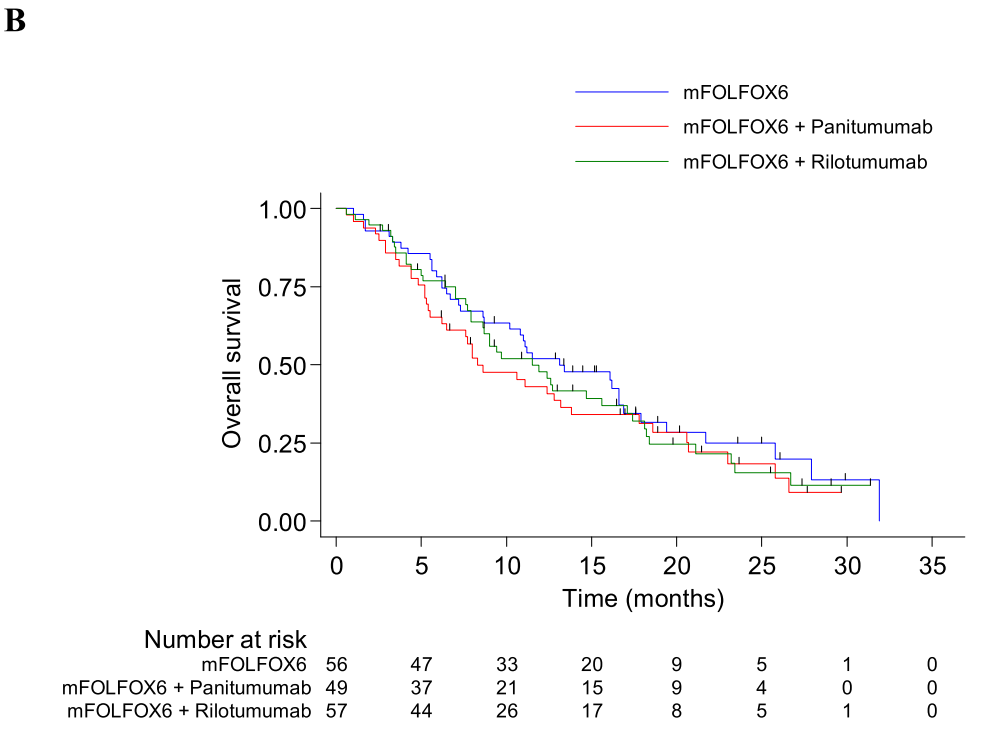


Fig. 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) in the intent-to-treat population. mFOLFOX6, modified oxaliplatin, leucovorin and fluorouracil.

failure of MET-targeted agents in gastroesophageal cancer. *MET* amplification, which harbours the strongest evidence for predictive benefit from anti-MET therapy via receptor-specific inhibitors [28], accounted for only 3% of patient in our study. By contrast, the more ubiquitous MET overexpression in the absence of gene amplification, which accounted for 60% of the patients in our study, may be a consequence rather than the cause of the cell transformation, and other aberrant signalling pathways afford tumour cells to easily circumvent the effects of isolated MET inhibition in these patients [29]. Thus, MET overexpression might not

Table 3
Adverse events—safety population.

	mFOLFOX6 (n = 54)				mFOLFOX6 + panitumumab (n = 48)				mFOLFOX6 + rilotumumab (n = 57)			
Worst grade (NCI-CTCAE version4.0)	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5
Any adverse event	20 (38)	24 (45)	8 (15)	1 (2)[a]	8 (17)	26 (54)	10 (21)	4 (8)[b]	6 (11)	41 (72)	7 (12)	3 (5)[c]
SAEs/patients (%)			90/37 (66)			144/40 (82)				140/53 (93)		
Haematological	37 (70)	11 (21)	4 (8)	0	24 (50)	17 (35)	5 (10)	0	35 (61)	16 (28)	4 (7)	0
Haemoglobin	47 (89)	2 (4)	0	0	38 (79)	4 (8)	1 (2)	0	46 (81)	1 (2)	2 (4)	0
Leucocytes	20 (38)	4 (8)	0	0	14 (29)	2 (4)	0	0	24 (42)	1 (2)	1 (2)	0
Neutrophils	21 (40)	10 (19)	4 (8)	0	17 (35)	9 (19)	4 (8)	0	22 (39)	13 (23)	3 (5)	0
Platelets	26 (49)	1 (2)	0	0	23 (48)	1 (2)	0	0	41 (72)	1 (2)	0	0
Infection/febrile neutropenia	3 (6)	1 (2)	0	0	4 (8)	5 (10)	0	1 (2)	5 (9)	5 (9)	0	0
Febrile neutropenia	NA	0	0	0	NA	3 (6)	0	0	NA	1 (2)	0	0
Infection with grade III–IV neutropenia	0	0	0	0	0	1 (2)	0	0	0	0	0	0
Infection without neutropenia	3 (6)	0	0	0	3 (6)	1 (2)	0	0	5 (9)	1 (2)	0	0
Other infection	0	1 (2)	0	0	1 (2)	2 (4)	0	1 (2)	1 (2)	3 (5)	0	0
Neurological	35 (66)	8 (15)	1 (2)	0	36 (75)	3 (6)	0	0	31 (54)	20 (35)	0	0
Peripheral neuropathy	34 (64)	8 (15)	1 (2)	0	36 (75)	3 (6)	0	0	30 (53)	19 (33)	0	0
Gastrointestinal	39 (74)	7 (13)	2 (4)	0	27 (56)	15 (31)	2 (4)	1 (2)	34 (60)	14 (25)	2 (4)	1 (2)
Diarrhoea	21 (40)	2 (4)	0	0	21 (44)	7 (15)	0	0	27 (47)	1 (2)	0	0
Nausea	30 (57)	2 (4)	0	0	30 (63)	3 (6)	0	0	39 (68)	4 (7)	0	0
Vomiting	15 (28)	2 (4)	0	0	15 (31)	4 (8)	1 (2)	0	24 (42)	2 (4)	0	0
Constipation	16 (30)	0	0	0	16 (33)	3 (6)	0	0	25 (44)	1 (2)	0	0
Mucositis	19 (36)	1 (2)	0	0	19 (40)	2 (4)	0	0	16 (28)	0	1 (2)	0
Dermatological	15 (28)	1 (2)	0	0	33 (69)	9 (19)	0	0	27 (47)	1 (2)	0	0
Rash	4 (8)	1 (2)	0	0	33 (69)	5 (10)	0	0	14 (25)	1 (2)	0	0
Paronychia	1 (2)	0	0	0	7 (15)	2 (4)	0	0	1 (2)	0	0	0
Hand-foot syndrome	7 (13)	0	NA	NA	9 (19)	0	NA	NA	6 (11)	0	NA	NA
Alopecia	6 (11)	NA	NA	NA	5 (10)	NA	NA	NA	8 (14)	NA	NA	NA
Other	6 (11)	0	0	0	29 (60)	5 (10)	0	0	15 (26)	0	0	0
Cardiovascular	5 (9)	3 (6)	0	0	7 (15)	2 (4)	3 (6)	0	10 (18)	6 (11)	2 (4)	1 (2)
Venous thromboembolism	4 (8)	1 (2)	0	0	1 (2)	0	1 (2)	0	9 (16)	0	0	0
Cerebrovascular event	0	0	0	0	0	0	1 (2)	0	0	0	0	0
Other	1 (2)	1 (2)	0	0	5 (10)	1 (2)	1 (2)	0	2 (3.5)	5 (9)	1 (2)	0
General	36 (68)	13 (25)	0	1 (2)	21 (44)	16 (33)	1 (2)	3 (6)	30 (53)	23 (40)	0	1 (2)
Asthenia	39 (74)	3 (6)	0	0	31 (65)	8 (17)	0	0	41 (72)	8 (14)	0	0
Anorexia	20 (38)	3 (6)	0	0	18 (38)	2 (4)	0	0	14 (25)	7 (12)	0	0
Weight loss	21 (40)	0	0	0	21 (44)	1 (2)	0	0	17 (30)	0	0	0
Oedema	4 (8)	1 (2)	0	0	6 (13)	0	0	0	20 (35)	2 (4)	0	0
Infusion-related reaction	1 (2)	1 (2)	0	0	1 (2)	0	0	0	0	0	0	0
Fever (without neutropenia)	6 (11)	0	0	0	12 (25)	0	0	0	15 (26)	1 (2)	0	0
Laboratory	36 (68)	10 (19)	1 (2)	0	35 (73)	7 (15)	2 (4)	0	38 (67)	16 (28)	0	0
Hyperglycaemia	2 (4)	0	0	0	3 (6)	0	0	0	4 (7)	2 (4)	0	0
Hypomagnesaemia	4 (8)	0	0	0	18 (38)	0	0	0	12 (21)	0	0	0
Hypophosphataemia	4 (8)	1 (2)	0	0	17 (37)	0	0	0	14 (25)	1 (2)	0	0

Data are number (%).
SAE, serious adverse event; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
[a] Performance status deterioration.
[b] Gastrointestinal obstruction, colonic perforation, interstitial lung disease, unknown (1 each).
[c] Gastrointestinal haemorrhage, performance status deterioration, pulmonary embolism (1 each).

be an appropriate target for MET-directed drugs in the majority of patients with gastroesophageal cancer and other solid tumours [10,29]. Furthermore, the reported rates of gastroesophageal cancer cases considered MET-positive by immunohistochemistry ranged widely from 4% to 63% [30], because of different scoring criteria, tissue processing techniques, storage methods and antibodies [31], as in the RILOMET-1 [5] and METGastric studies [8]. MET-targeted agents might also be ineffective in gastroesophageal cancer by exerting off-target effects. It has been shown experimentally that neutrophil-specific deletion of *MET* impairs recruitment of neutrophils to tumours, leading to enhanced tumour growth [32]. A way to overcome this might be the development of biclonal antibodies against MET and another target, expressed on cancer cells but not on neutrophils.

Our exploratory analyses evaluated PFS and OS according to tumour biomarker status (*HER2*, *KRAS*, *NRAS*, *BRAF* or *MET*). HER2 status did not predict

survival. However, HER2-positive tumours patients had longer median PFS and OS, as in the EXPAND study [4]. The prognostic value of HER2 expression in gastric cancer is controversial since some studies have shown no association [3], while others associated HER2 expression with a poorer outcome [9,33]. This may be because of differences in HER2 testing (different primary antibodies and scoring methods) and false HER2-negatives due to intratumour heterogeneity of HER2 expression in gastric cancer [34]. As reported, *NRAS* and *BRAF* mutations and *MET* amplification were rare [13,35]. *KRAS* mutant status had no prognostic or predictive value in any group. In fact, in patients with wild-type *KRAS* tumours, adding panitumumab to mFOLFOX6 decreased survival, as in the REAL3 study [3].

When we designed our study, a strong rationale existed for adding a targeted therapy to chemotherapy for treating advanced gastroesophageal adenocarcinoma patients. However, substantial evidence now shows that adding an anti-EGFR or anti-HGF/MET to first-line fluoropyrimidine-based and platinum-based chemotherapy for advanced gastroesophageal adenocarcinomas does not improve treatment efficacy and is thus not recommended.

Conflict of interest statement

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Appendix A. Supplementary data

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