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Panitumumab in combination with modified docetaxel/cisplatin/5-fluorouracil as first-line treatment in gastric and gastroesophageal junction adenocarcinomas: a multicenter phase II study by the Hellenic Oncology Research Group

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Abstract

Background A phase I/II study to define the maximum tolerated dose (MTD) of biweekly docetaxel/cisplatin/5-fluorouracil (DCF) plus panitumumab (P), its efficacy, and tolerability as first-line treatment in advanced gastroesophageal cancer.

Methods In phase I part, patients with unresectable locally advanced or metastatic adenocarcinomas of the stomach or the gastroesophageal junction received cisplatin (40 mg/m^2 on day 1), leucovorin (400 mg/m^2 on day 1), 5-fluorouracil (400 mg/m^2 bolus on day 1), 5-fluorouracil (1000 mg/m^2/daycontinuous infusion on days 1-2), and escalated doses of docetaxel (on day 1) plus P (6 mg/kg on day 1) every 2 weeks. In phase II part, patients were treated with DCF/P at the MTD and the primary endpoint was response rate. The expected response rate was set at >40%.

Results The MTD for docetaxel in the mDCF/P was defined at 40 mg/m^2 and a total of 40 evaluable patients were enrolled in phase II study. One (2.5%) complete and 13 (32.5%) partial responses (overall response rate: 35%), as well as 16 (40%) disease stabilizations were documented. The median progression-free survival was 6.9 months (95% confidence interval [CI] 3.5-10.3) and the median overall survival was 11.3 months (95%CI 7.7-14.8). Grade 3-4 neutropenia occurred in 10 patients (25%) and febrile neutropenia in 2 (5%). Allergic reactions (grade 1-4) occurred in 9 patients (22.5%). There was 1 treatment-related death.

Conclusions mDCF/P combination was feasible, though associated with a poor toxicity profile. However, the study failed to meet its primary endpoint and was terminated prematurely due to futility.

Keywords Gastroesophageal junction cancer, docetaxel, cisplatin, 5-fluorouracil, panitumumab
ClinicalTrials.gov Identifier: NCT01716546

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Introduction

Gastric cancer represents the fifth most common malignancy worldwide, despite its recent decline in incidence due to the recognition of risk factors such as *Helicobacter pylori* infection and dietary risks [1]. At the time of diagnosis, approximately half of all patients present with unresectable, locally advanced or metastatic disease, with a median survival of 6-10 months and a 5-year survival rate of <10%.

Docetaxel, cisplatin, and 5-fluorouracil (DCF) combination is one of the most active combinations in metastatic gastric adenocarcinomas [1-6]. The V325 study in patients with metastatic gastric cancer demonstrated the superiority of the DCF triplet over the docetaxel/cisplatin doublet in terms of objective response rate, time to disease progression, overall survival (OS) and 2-year survival rate. Nevertheless, since the median survival does not exceed 1 year and the 1-year survival rate remains less than 40% [5,6], there is an unmet need to develop more effective systemic treatments to improve the patients' clinical outcome.

The identification of subgroups of patients with gastric adenocarcinomas that harbor druggable molecular alterations

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Conflict of Interest: None

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could be a useful therapeutic approach in order to improve patients' outcomes. The TOGA study proved that the addition of trastuzumab, an anti-HER2 monoclonal antibody, to the cisplatin/5-flurouracil combination could improve OS of patients with HER-2 overexpressing metastatic gastric cancer [7]. HER-2 belongs to the ErbB superfamily of tyrosine kinase receptors. The first member of this family (epidermal growth factor receptor: EGFR/HER-1) has been found to be frequently altered in several carcinomas and is related to tumorigenesis [8]. In gastric adenocarcinomas, overexpression of EGFR has been observed in up to 55% of cases [9] and its overexpression has been associated with an adverse clinical prognosis [10,11]. Therefore, since EGFR represents a targetable pathway in advanced/metastatic gastric cancer, trials were conducted with either the anti-EGFR monoclonal antibody cetuximab [12] or the tyrosine kinase inhibitor gefitinib [13], resulting in some responses. In addition, the combination of cetuximab with chemotherapy has shown substantial activity in gastric adenocarcinomas [14].

Panitumumab is a fully human IgG2 monoclonal antibody that is directed against the human EGFR; the affinity of panitumumab is approximately 60-fold greater than that of EGF. Panitumumab has been approved for use in patients with metastatic *RAS* wild-type colorectal cancer, in both the first- and second-line setting, in combination with chemotherapy, or as monotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens [15-18]. Furthermore, panitumumab has been shown to be safe and effective in the treatment of many human tumors when administered weekly, biweekly and every 3 weeks, either as monotherapy or in combination with chemotherapy.

Based on these data, a phase I/II trial was conducted by the Hellenic Oncology Research Group to evaluate the effect of panitumumab when combined with biweekly DCF (mDCF), in previously untreated patients with advanced/metastatic cancer of the stomach and the gastroesophageal junction (GEJ).

Patients and methods

Eligibility

Patients with histologically documented, inoperable, locally advanced or metastatic adenocarcinoma of the stomach and the GEJ, aged >18 years old, were eligible for the study. No prior chemotherapy for metastatic disease was allowed; adjuvant chemotherapy or chemo-radiotherapy was allowed provided that at least 6 months had elapsed since the completion of the treatment. Other key eligibility criteria were: absence of HER2 expression (score 1 by immunocytochemistry [ICH] or fluorescence *in situ* hybridization-negative for those with score 2 by ICH); measurable target lesions as defined according to the RECIST criteria (RECIST v.1.1) (patients with non-measurable disease could be enrolled only in the phase I part of the study); ECOG performance status 0-2, adequate bone marrow (defined by hemoglobin ≥8 g/dL, white blood cells ≥3×10^9/L, neutrophil count ≥1.5×10^9/L, platelets ≥100×10^9/L), renal (creatinine clearance ≥50 mL/min) and liver function tests (total bilirubin ≤1.5 times the institutional upper limit of normal, and aspartate/alanine transaminases and alkaline phosphatase ≤2.5 time the upper limit of normal); and estimated life expectancy >3 months. All patients gave written informed consent before their enrollment in the study. The protocol was approved by the Ethics and Scientific Committees of the participating institutions, as well as by the Greek National Organization for Medicines (EOF) and the National Ethics Committee (EED).

Treatment plan

The phase I part of the trial was a dose-escalation study designed to define the recommended dose of docetaxel in combination with 5-fluorouracil,Leucovorin cisplatin, and cetuximab for the second part (phase II) of the study. Patients recruited in the phase I trial were treated in cohorts of 3 (3+3 design), with escalating doses of docetaxel (30 mg/m^2 in Level 1, 35 mg/m^2 in Level 2 and 40 mg/m^2 in Level 3), while the doses of cisplatin, 5-fluorouracil, and panitumumab remained fixed. More specifically, panitumumab was administered as a 1-h iv infusion at a dose of 6 mg/kg on days 1 and 14 of each treatment cycle; docetaxel was administered as a 1-h infusion at a dose of 30-40 mg/m^2 on days 1 and 14 of each cycle; cisplatin was given at a dose of 40 mg/m^2 as a 2-h infusion on days 1 and 14 of each cycle, after adequate hydration, diuresis with mannitol or furosemide and antiemetic prophylaxis, according to the policies of each participating center; leucovorin was administered at a dose of 400 mg/m^2 on days 1 and 14, followed by bolus 5-fluorouracil infusion at a dose of 400 mg/m^2 and continuous iv infusion of 1000 mg/m^2 per day of 5-fluorouracil on days 1, 2, 14 and 15 of each cycle. Granulocyte-colony stimulating factor (G-CSF) support was administered from day 3-8. Treatment was administered every 2 weeks and one treatment cycle was completed on d28 (2 chemotherapy administrations). Maximum treatment duration was 6 (12 administrations) 4-week cycles. Patients with disease control (complete response [CR], partial response [PR], and stable disease [SD]) during the chemotherapy period received maintenance therapy with panitumumab (9 mg/kg every 3 weeks) until disease progression, intolerance, toxicity, graded according to the CTCAE v3.0 criteria [19], death, or consent withdrawal.

Three patients were enrolled at the first dose level and dose escalation proceeded if no dose-limiting toxicity (DLT) occurred in the first cycle (4 weeks). If DLT occurred in cycle 1, 3 additional patients would be enrolled to the same dose level. If less than 3 of 6 patients experienced DLT, the dose escalation would continue to the next dose level. The patients from the phase I part of the study who received the recommended doses for the phase II study were included in the phase II study and analyzed for efficacy. All patients received at least 6 chemotherapy cycles (12 administrations) at the doses initially allocated. There was no intra-patient dose escalation. All patients were followed until disease progression or death, to assess late or persistent toxicity.

Definition of DLT and maximum tolerated dose (MTD)

DLT was defined as any of the following events during the first treatment cycle: (i) hematological toxicity (febrile neutropenia, grade 4 neutropenia lasting ≥7 days, grade 3 thrombocytopenia lasting ≥7 days or grade 4 thrombocytopenia); (ii) non-hematological toxicity grade 3 or more with the exception of fatigue grade 3, which had to last for more than 7 days; (iii) failure to recover from related toxicities to grade ≤1 or baseline severity (or grade ≤2 at investigator and sponsor discretion) after delaying the next cycle up to 7 days; and (iv) failure to complete the first treatment course (≤75% of planned dose). MTD was defined as the highest dose level at which 2 out of 3 or 3 out of 6 patients experienced a DLT. The phase II part of the study would be initiated at the doses of the previous MTD level. If the MTD level corresponded to the doses of level 1 (i.e., 3 of 3, or >3 of 6 patients developing any LTD in the first cycle) the schedule and the doses of the study drugs would have to be revised.

Dose modifications

The panitumumab dose was withheld for severe skin or nail toxicities (skin toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject, skin infection requiring iv antibiotic or iv antifungal treatment, need for surgical debridement, or any skin- or nail-related serious adverse event). Panitumumab was discontinued for subjects who missed more than 2 consecutive scheduled doses because of toxicity. In patients with grade 3 and 4 neutropenia, G-CSF support was recommended on days 8 -13 in subsequent cycles. In patients with febrile neutropenia and/or grade 3 or 4 neutropenia, despite the administration of G-CSF, or grade 3-4 thrombocytopenia, subsequent cycles were administered with a 20% dose reduction in the doses of all chemotherapeutic agents.

Regarding non-hematological toxicities, 5-fluorouracil was decreased by 50% for grade 3-4 hepatotoxicity, while 5-fluorouracil and docetaxel were decreased by 25% for grade 3 diarrhea and stomatitis. For grade 3 neuropathy the doses of cisplatin and 5-fluorouracil were decreased by 25%.

If more than 2-week delay was needed for complete hematologic recovery, despite the administration of G-CSF and/or predefined doses adjustments and/or in case of persistent grade 3 or 4 non-hematologic toxicity after the completion of the two weeks of delay, the patient was withdrawn from the study and was subsequently treated at the physician's discretion.

Statistical analysis

This was a phase I/II multicenter, single-arm trial of the combination mDCF plus panitumumab in patients with locally advanced or metastatic adenocarcinomas of the stomach and GEJ. The primary endpoint of the phase I part of the study was to determine the MTD of docetaxel when given in combination with cisplatin, 5-fluorouracil and panitumumab for the subsequent phase II study. The primary endpoint of the phase II trial was to assess the efficacy and the tolerance of the regimen and to investigate whether it could achieve an objective response rate of >40% (ECIST 1.1 criteria; [20]) Secondary endpoints included the safety profile, progression-free survival (PFS) and OS. The sample size was determined based on the overall response rate, according to Fleming's two-stage minimax design [21]. According to the design, a sample of 41 patients for the first step and 28 additional patients for the second step were needed in order to prove the initial hypothesis (at least 17 objective responses in the first 41 enrolled patients) at a statistical significant level of α=0.05 (one-sided) and with a power of 80%.

PFS was defined as the interval from the date of registration into the study until disease progression or death from any cause. OS was measured from the date of registration until death from any cause. The follow-up time was measured from the day of first treatment administration to the study's cutoff date or the date of death. The PFS and OS rates were estimated using the Kaplan-Meier method, and the confidence intervals (CI) for response rates were calculated using methods for exact binomial CIs. All efficacy and toxicity results were assessed for the enrolled patients on an intention-to-treat basis. To test significant associations between continuous variables, the Mann-Whitney test was used. The chi-square test was used to test for associations between response and other dichotomous variables. Statistical significance was set at P=0.05. Tolerability was graded according to the CTCAE v3.0 criteria [19].

Results

Patient demographics

All patients in both phase I and II parts of the study were enrolled at 9 Greek hospitals. Between July 2010 and March 2012, 15 patients with locally advanced or metastatic gastric and GEJ carcinoma were enrolled in the 3 cohorts of the phase I study. Patients' baseline demographics and clinicopathological data are presented in Supplementary Table S1. At the date of data cutoff, 14 patients had discontinued or completed treatment and one was still on treatment. Seven patients (46.7%) had completed study treatment, while five (33.3%) had discontinued treatment because of disease progression and two (13.3%) because of treatment-related adverse events.

From April 2012 to January 2015, 35 additional patients were enrolled in the phase II part of the study, in addition to 6 patients from phase I who had received the recommended doses for phase II; thus, a pre-planned interim analysis was performed according to the statistical considerations. One patient did not fulfill the eligibility criteria and was excluded from the final analysis. The characteristics of patients enrolled in both the phase I and phase II parts of the study are summarized in Table 1.

Table 1 Demographic data (all patients: Phase I and II)

Demographics	N	%
Age		
Median (min-max)	51 (23-79)	
Sex		
Male	34	66.7
Female	17	33.3
ECOG performance status		
0-1	48	94.1
2	3	5.9
Grade		
1-2	22	43.1
3	29	56.9
Stage		
Locally advanced	6	11.8
Metastatic	45	88.2
Histology		
Adenocarcinoma	20	39.2
Adenocarcinoma diffuse type	16	31.4
Adenocarcinoma enteric type	13	25.5
Mixed adenocarcinoma	2	3.9
Previous surgery		
Curative intent	15	29.4
Palliative intent	2	3.9
Not done	34	66.7
Previous treatment		
Adjuvant	6	11.8
Not received	45	88.2
Primary tumor		
Pylorus	5	9.8
Body of the stomach	25	49.0
Gastroesophageal junction or antrum	21	41.2

DLT and MTD determination

At the first dose level (docetaxel: 30 mg/m^2) there was one DLT event (grade III transaminasemia); hence, 3 additional patients had to be enrolled at this dose level. In this second cohort of 3 patients one additional patient developed DLT (grade IV rash); however, the criteria for MDT (DLT at 2 of 3 or 3 of 6 patients) were not met; thus, dose escalation continued and 3 patients were enrolled at the second dose level (docetaxel: 35 mg/m^2) with no DLT events. At the third dose level (docetaxel: 40 mg/m^2) one patient presented febrile neutropenia, requiring hospitalization for intravenous antibiotics and G-CSF support; the patient recovered uneventfully after 4 days. Because of this DLT event, 3 additional patients were enrolled at this dose-level and an additional patient developed a DLT event (grade IV neutropenia); nevertheless, the MTD was not reached since DLT events occurred in only 2 of 6 patients. Therefore, the dose of 40 mg/m^2 of docetaxel was recommended as MTD for the subsequent phase II part of the study.

Efficacy

In the phase II part of the study, 40 of the 41 enrolled patients were evaluable for response (one patient did not met the eligibility criteria for metastatic or locally advanced disease after surgery). Two patients who died during the first treatment cycle were included in the analysis and were considered as progressors. One (2.5%) CR and 13 (32.5%) PR were achieved (overall response rate: 35%), while 16 (40%) patients experienced SD and 10 (25%) progressive disease. Since less than 17 responses were recorded during the first step of the phase II part of the trial, the study was terminated due to futility.

At the time of analysis, 28 patients died because of disease progression and two from other causes. The median PFS was 6.9 months (95%CI 3.5-10.3) and the median OS 11.3 months (95%CI 7.7-14.8). There was no significant difference in terms of PFS and OS survival according to the different localization of the primary tumor (data not shown).

Treatment administration and toxicity

In the phase II part of the study, a total of 326 treatment cycles were administered with a median number of 10/patient (range, 1-13). Forty-nine cycles (15%) were delayed because of hematologic (5.5%; n=18 cycles) or non-hematologic (2.1%; n=7 cycles) toxicity and for other reasons unrelated to treatment (i.e., patients' personal reasons, prescheduled imaging evaluation; n=26 cycles). The median time of delay was 7 days (range, 2-40 days). Dose reduction was required in 36 cycles (11%) because of hematologic (n=12 cycles) or non-hematologic (n=23 cycles) toxicity, or for an unknown reason (n=1 cycle; Table 2).

At the time of analysis, 39 patients (97.5%) had discontinued treatment for the following reasons: 16 patients (41%) completed treatment as per protocol (maximum treatment duration of 6 chemotherapy cycles followed by maintenance panitumumab until disease progression, toxicity, death or consent withdrawal in patients with no disease progression); 17 (42.5%) showed disease progression; four (10.3%) withdrew consent; and two (5.1%) suffered toxicity (one patient developed grade III mucositis and another presented a grade II allergic reaction during the infusion of docetaxel). There were 30 deaths due to the following reasons: disease progression (n=28), myocardial infarction occurring during the administration of the first chemotherapy cycle (n=1), and respiratory failure because of infection (n=1) occurring during the 4th treatment cycle. Fatigue, allergic reactions, hematological toxicities (neutropenia, anemia, and thrombocytopenia) and mucositis were the most common adverse events noted during the

study. With the exception of fatigue, these were also the most common serious adverse events. All adverse events and serious adverse events observed during the study are summarized in Table 3.

Discussion

The current multicenter, phase I/II study evaluated the biweekly combination of DCF/P as first-line treatment, followed by maintenance treatment with panitumumab, in patients with metastatic or non-operable/locally advanced gastric or GEJ cancer. The aims of the study were: (i) to determine the MTD of docetaxel when given in combination with CF/P; and (ii) to evaluate whether the efficacy of the regimen could justify its further exploration. During the phase I part of the study, no DLT level could be defined and the MTD level, which was used in the phase II part of the study, was considered as the highest dosage of docetaxel (40 mg/m^2) combined with the standard dose of cisplatin, 5-flurouracil, and panitumumab. However, the phase II study did not meet its primary endpoint, since during the preplanned interim analysis the number of responses achieved was less than 17 (<40%), which had been set as the lower limit for futility according to statistical considerations.

Since the initiation of this trial, two randomized phase III studies (EXPAND and REAL3) have assessed the addition of anti-EGFR antibodies to first-line chemotherapy for adenocarcinoma of the stomach and GEJ [22,23]. In both trials the addition of anti-EGFR antibodies (panitumumab or cetuximab) to a chemotherapy backbone (epirubicin/oxaliplatin/capecitabine and capecitabine/cisplatin, respectively) provided no additional benefit compared to chemotherapy alone; these results stopped any further development of panitumumab in gastric adenocarcinomas. The current study also showed that the combination of panitumumab with another chemotherapy backbone (mDCF) did not warrant further investigation in this tumor type—at least in an unselected population. Similarly, a phase II randomized study (ATTAX3), which also examined the efficacy of adding panitumumab to the docetaxel/cisplatin/5-fluorouracil regimen, showed no additional benefit for the combination [24]. Nevertheless, it should be noted that the chemotherapy regimen in the ATTAX3 study was slightly different from that used in the current study.

The poor outcome from the addition of anti-EGFR antibodies to chemotherapy in the large phase III trials was

Table 2 Compliance with treatment

Total no. of treatment cycles	326
Median no. of treatment cycles (min-max)	10 (1-13)
No. of delayed treatment cycles	49 (15%)
Due to hematologic toxicity	18
Due to non-hematologic toxicity	7
Other reasons	26
Median time of treatment cycles delay (days)	7 (2-40)
No. of treatment cycles with dose reduction	36 (11%)
Due to hematologic toxicity	12
Due to non-hematologic toxicity	23
Unknown reason	1

Table 3 Adverse events related to study treatment

Adverse events	Gr 1		Gr 2		Gr 3		Gr 4	
	N	%	N	%	N	%	N	%
Leukopenia	9	22.5	6	15.0	7	17.5	1	2.5
Neutropenia	10	25.0	3	7.5	6	15.0	4	10.0
Anemia	18	45.0	13	32.5	5	12.5	0	0
Thrombocytopenia	12	30.0	1	2.5	1	2.5	1	2.5
Nausea	7	17.5	3	7.5	0	0	0	0
Vomiting	5	12.5	1	2.5	0	0	0	0
Constipation	5	12.5	1	2.5	0	0	0	0
Diarrhea	5	12.5	9	22.5	0	0	0	0
Mucositis	10	25.0	5	12.5	2	5.0	0	0
Pancreatitis	0	0	0	0	1	2.5	0	0
Anorexia/weight loss	4	10.0	1	2.5	1	2.5	0	0
Fatigue	9	22.5	3	7.5	2	5.0	0	0
Neurotoxicity	6	15.0	0	0	0	0	0	0
Alopecia	0	0	3	7.5	0	0	0	0
Allergic reactions	6	5	2		0		1	2.5
Febrile neutropenia	0	0	0	0	0	0	2	5.0

attributed to three main reasons. The first is related to the increased gastrointestinal toxicity from the combination, which resulted in a reduced dose intensity of the chemotherapy in the experimental group [23]. In our study, no grade III gastrointestinal toxicity was noted and dose reductions were mainly attributable to hematological toxicity. It should be highlighted that the hematological toxicity was analogous to that shown in the mDCF study [25] and could not be the main reason for the failure of our study to meet its primary endpoint. In the current study, dose reduction was required in 11% cycles and delays in 15% cycles, an incidence well below those reported in the phase III trials.

The second reason for the failure of anti-EGFR antibodies in the phase III trials is a possible negative interaction with oxaliplatin, as noted in preclinical models and clinical studies [26-28]. However, this is not applicable in our study, since the chemotherapy backbone did not include oxaliplatin. Furthermore, there are no references in the literature to a possible negative interaction of docetaxel with anti-EGFR antibodies, in either clinical or preclinical studies. In contrast, the addition of panitumumab to docetaxel and cisplatin as neoadjuvant treatment for carcinomas of the distal esophagus [29] showed clinically relevant efficacy, with a significant rate of pathologically complete responses despite an increased incidence of toxicity, denoting the absence of negative interactions between these drugs.

The third reason for the failure of these agents is their use in a molecularly unselected population. The addition of anti-EGFR antibodies to chemotherapy has shown a synergistic effect in preclinical models overexpressing EGFR [30]. However, EGFR overexpression has been shown in 15% of gastric carcinomas by immunohistochemistry [10], while amplification of EGFR was noted in 1-7% of cases [31,32]. EGFR overexpression and amplification may be predictive of a response to anti-EGFR agents, as has been reported in a small phase II study [33]. Therefore, the large phase III trials (EXPAND and REAL-3) suggest that EGFR is unlikely to be a therapeutic target in most patients with esophagogastric adenocarcinomas. The biomarker analysis from these trials could demonstrate whether there is a small subgroup of patients who could derive benefit from the addition of anti-EGFR antibodies to standard chemotherapy regimens.

Notably, the study treatment was associated with a high rate of allergic reactions (27.5% grade 3-4 events); all patients recovered uneventfully. In addition, one death occurred during the first cycle of treatment because of a myocardial infarction; thus, it was considered treatment-related. The second death was due to respiratory failure because of a non-neutropenic infection occurring during the 4th cycle and was not considered treatment-related.

In conclusion, this phase II study evaluating the benefit of the addition of panitumumab to mDCF as first-line treatment in patients with advanced or metastatic gastric and GEJ adenocarcinomas did not met its primary endpoint and was terminated prematurely. These findings add to the results of large phase III trials that have shown no benefit from the addition of anti-EGFR antibodies to different chemotherapeutic backbones as first-line treatment in metastatic gastric cancer. Translational studies are required to identify specific patient subpopulations that may derive benefit from anti-EGFR treatment.

Summary Box

What is already known:

- Docetaxel, cisplatin and 5-fluorouracil (DCF) combination is one of the most active chemotherapy combinations in metastatic gastric/gastroesophageal junction (GEJ) adenocarcinomas
- EGFR represents a targetable pathway in advanced/metastatic gastric/GEJ cancer
- Panitumumab (P) is a fully human IgG2 monoclonal antibody directed against the human EGFR and currently approved for use in patients with metastatic *RAS* wild type colorectal cancer both in first and second line setting in combination with chemotherapy, or as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens

What the new findings are:

- In this phase I/II study of the combination of modified DCF (mDCF) and P in advanced gastric/GEJ cancer, the Maximum Tolerated Dose (MTD) for docetaxel in the mDCF/P combination was defined at 40mg/m2
- Overall response rate (ORR) was 35% with mDCF/P. Median progression free survival (PFS) was 6.9 months (95% CI: 3.5- 10.3) and median overall survival (OS) was 11.3 months (95% CI: 7.7-14.8)
- Grade 3-4 neutropenia occurred in 10 patients (25%) and febrile neutropenia in 2 patients (5%). Allergic reactions (grade 1-4) occurred in 9 patients (22.5%). There was 1 treatment-related death
- The combination of panitumumab with mDCF was associated with a poor toxicity profile. The study did not meet its primary endpoint of ORR and was terminated prematurely

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Supplementary Table

Supplementary Table S1 Demographic data (Phase I study)

Demographics	N=15	%
Age		
Median (min-max)	58.0 (24-73)	
Sex		
Male	8	53.3
Female	7	46.7
Performance status		
0	11	73.3
1	4	26.7
Histology		
Enteric type	8	53.4
Diffuse type	5	33.3
Unknown	2	13.3
Stage		
IIIA	1	6.7
IIIB	1	6.7
IV	13	86.7
Tumor location		
Stomach	10	66.7
Gastroesophageal junction	4	26.7
Unknown	1	6.6
Prior surgery		
Yes	7	46.7
No	8	53.3
Prior adjuvant chemotherapy	3	20.0
Prior radiotherapy (tumor bed)	2	13.3