Original Article

Gefitinib and celecoxib in advanced metastatic gastrointestinal tumors: a pilot feasibility study

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Background: This pilot, open-label study examined the safety and tolerability (primary objective) and efficacy (secondary objective) of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in combination with celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, in patients with advanced or refractory gastrointestinal (GI) tumors of epithelial origin.

Methods: Patients were administered gefitinib (250 mg/day) plus celecoxib (400 mg twice daily). In the event of toxicity, dose interruptions were permitted and a single celecoxib dose reduction was allowed.

Results: Thirty patients (median age 60 years) with primary colorectal (25 patients), pancreatic (3 patients), esophageal (1 patient), or gall bladder (1 patient) tumors were recruited, 29 of whom had received prior chemotherapy. Adverse events (AEs) were generally mild and consisted mainly of acne, diarrhea, and nausea. Few severe AEs were noted. There were no withdrawals or deaths due to AEs. Dose reductions for celecoxib were reported for five patients, in three cases due to toxicity. Stable disease was confirmed in 12 patients (40%), with progressive disease in 18 patients (60%).

Conclusions: After study completion, safety issues relating to the long-term use of COX-2 inhibitors have been raised. However, in this pilot study, the combination of gefitinib and celecoxib was generally well tolerated in patients with advanced GI cancer.

Keywords: Gefitnib; celecoxib; gastrointestinal cancer (GI cancer)

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Introduction

Gastrointestinal (GI) cancer (cancer of esophagus, stomach, intestines, liver, or pancreas) is a major health problem. Approximately 3.25 million people are diagnosed with the disease each year worldwide (1), with Brazil accounting for nearly 2% of these cases (1). The majority of GI tumors are epithelial in origin, and most patients present with advanced (regional or distant) disease (~60% patients for colorectal and esophageal cancer) with poor prognoses and low survival rates (2). Despite advances in surgery, radiotherapy, and chemotherapy, treatment for most patients is palliative. Indeed, the life expectancy for patients with advanced gastric cancer (with or without chemotherapy) is only 6 to 9 months (3). Chemotherapy for advanced GI cancer has some advantage over best supportive care (BSC), including improved quality of life; however, survival does not increase dramatically, with overall survival ranging from 6.0 to 12.0 months with chemotherapy *vs.* 2.5 to 5.0 months with BSC (4-9). For patients with advanced colorectal cancer with distant spread, 5-year survival is only 11% (10). There is a clear need for alternative treatment options that are

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effective in advanced GI cancers.

Increasing knowledge of the molecular events underlying carcinogenesis, tumor growth, and metastasis has provided new targets for therapy, including the epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2). Elevated levels of EGFR and COX-2, both of which mediate events involved in tumorigenic processes, were observed in GI tumors (11-15). Increased EGFR expression was shown to correlate with more aggressive GI disease and poor survival in several studies (11,12,14-19). Similarly, COX-2 was found to be associated with poor prognosis and tumor recurrence in GI tumors (20-24). Indeed, COX-2 was also shown to promote angiogenesis and inhibit apoptosis in gastric tumor biopsies (25). As such, it was hypothesized that simultaneous inhibition of EGFR and COX-2 signaling pathways may be a novel treatment option capable of producing synergistic antitumor effects in patients with GI tumors.

Gefitinib (IRESSA®; AstraZeneca, Macclesfield, UK) is an orally active EGFR tyrosine kinase inhibitor. Phase I trials of gefitinib monotherapy demonstrated some activity in advanced GI cancer (26-29), with stable disease observed in several patients with colorectal and esophageal tumors. A phase II study also found that treatment with gefitinib (250 or 500 mg/day) was associated with disease control in 13/75 (18.3%) patients with metastatic gastric adenocarcinoma (30). In another phase II study, gefitinib (250 or 500 mg/day) was associated with a median progression-free and overall survival of 1.9 and 6.3 months, respectively, in patients with recurrent colorectal adenocarcinoma (31). Interestingly, an *in vitro* study conducted in human colon cancer cells showed that when gefitinib was combined with the COX-2 inhibitor SC-236, the two agents had a cooperative antiproliferative effect (32). This effect was accompanied by a reduction in the expression of COX-2 and angiogenic growth factors, such as vascular endothelial growth factor.

Celecoxib (Celebrex®; Pfizer Inc., New York, NY, USA) is a selective COX-2 inhibitor that has demonstrated potent suppression of colon polyps, which can lead to the development of colorectal cancer. However, enrollment in follow-up trials was inadequate and, as a result, regulatory requirements were not fulfilled and celecoxib was withdrawn in the USA and Europe as an adjunct to standard care in patients with familial adenomatous polyposis (33). The different mechanisms of action of gefitinib and celecoxib, together with *in vitro* evidence that suggests the two agents have a cooperative antiproliferative effect (30), provide a rationale for clinical evaluation of their combination. As such, we investigated the efficacy and tolerability of gefitinib in combination with celecoxib in patients with advanced or refractory GI tumors of epithelial origin.

Methods

Patient population

The study population consisted of adults (aged ≥18 years) with advanced or refractory, stage III/IV, histologically or cytologically confirmed GI tumors of epithelial origin (i.e., esophageal, gall bladder, colorectal, or pancreatic). Refractory patients had received previous treatment including ≥1 chemotherapeutic regimen with or without previous radiotherapy. However, patients with untreated advanced disease could participate if they were considered unsuitable for, or if they had refused, conventional chemotherapy. Patients with ≥1 measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤3, and a life expectancy of >12 weeks were eligible.

Patients were ineligible to participate in the study in the event of: any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease); active duodenal or gastric ulcers; any other co-existing malignancy or malignancy diagnosed within the past two years (with the exception of basal cell carcinoma or cervical cancer *in situ*); unresolved chronic toxicity greater than Common Toxicity Criteria (CTC) grade 2 from prior therapies (except alopecia); evidence of incomplete healing from previous oncologic or other surgery, or any known hematologic bleeding dyscrasias; any contraindication to the use of celecoxib; pregnancy or breastfeeding. In addition, patients undergoing concomitant treatment with phenytoin, carbamazepine, barbiturates, rifampicin, or St John's Wort were not eligible to participate. Furthermore, except for the study drugs, use of systemic treatments known to have an effect on GI tumors was not permitted during the trial. Radiotherapy, however, could be used outside the measurable lesions if necessary for symptomatic or healing purposes.

Patients were also excluded if any of the following laboratory parameters were recorded during screening: absolute neutrophil count $<1.0\times10^9$/L; platelets $<100\times10^9$/L; hemoglobin <9.0 g/dL; serum bilirubin >1.25 times the upper limit of normal (ULN); serum creatinine >1.8 mg/dL or creatinine clearance <60 mL/min; alanine aminotransferase or aspartate aminotransferase >2.5 times the ULN if no

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demonstrable liver disease, or >5.0 times the ULN in the presence of liver metastases.

Study design

This AstraZeneca-sponsored study (1839IL/0086) was a pilot, open-label, non-comparative, phase I/II study conducted at several centers in Brazil. The primary objective was to examine the safety and tolerability of the combination of gefitinib (250 mg/day) and celecoxib [400 mg twice daily (bid)] in advanced or refractory GI tumors. Secondary outcomes included the efficacy of the treatment regimen [objective response rate, disease control rate, progression-free survival (PFS), overall survival, duration of response] and the safety of combination therapy. An exploratory objective evaluated the association between tumor EGFR and COX-2 immuno-expression and tumor response. The trial was conducted in accordance with Good Clinical Practice and the ethical principles outlined in the revised Declaration of Helsinki. Local ethics committee approval was obtained before study initiation and all participants gave written, informed consent.

Eligible patients were administered gefitinib and celecoxib, both given orally, from day 1 until disease progression, unacceptable toxicity, or withdrawal. Wherever possible, patients were followed up for ≥6 months after the start of trial therapy, with assessment on day 15 and then every 28 days thereafter.

Safety and tolerability measures

The nature, incidence, and severity of adverse events (AEs) were recorded throughout the study. Routine hematology, biochemistry, and physical examinations were carried out during the seven days before study entry and during the treatment phase on day 1, day 15, and every 28 days thereafter. Urinalysis was performed as necessary. Both AEs and laboratory parameters were assessed using National Cancer Institute CTC version 2.0. Causality was assigned by the investigators.

In cases where toxicity was unacceptable, dose interruptions (≤14 days) were used as the first approach to manage toxicity. Repeat dose interruptions were permitted but if toxicity recurred on re-challenge and further interruptions were not considered to be sufficient to resolve toxicity, patients were either withdrawn from the study (for gefitinib-related toxicities) or underwent a dose reduction (for celecoxib-related toxicities). A single celecoxib dose reduction (from 400 to 200 mg bid) was permitted in patients experiencing recurring toxicity (> grade 2) to celecoxib. However, if serious GI toxicity was observed, celecoxib was discontinued and patients could continue on gefitinib monotherapy.

Efficacy measures

Objective tumor response (complete or partial response) was evaluated using RECIST within the 3 weeks prior to study entry, 6 weeks after the start of therapy, and every 12 weeks thereafter until disease progression. Patients were considered to have controlled disease if the RECIST criteria for complete response, partial response, or stable disease were at any time satisfied at or before trial closure. The duration of response was defined as the number of days from the first documented response until death/progression or the last on-study tumor assessment. Likewise, time to progression (TTP) was defined as the number of days from start of treatment on day 1 until disease progression/death or the last tumor assessment. Overall survival time was defined as the number of days from the first day of treatment until death or the last tumor assessment.

EGFR and COX-2 immunohistochemical assessment

Tumor EGFR and COX-2 immuno-expression was determined from biopsies taken at baseline (archived paraffin-embedded samples were permitted). Biopsy samples (≥2 mm^2) underwent fixation in 4% neutral buffered formalin for 8 to 16 hours at room temperature followed by routine specimen dehydration using graded ethanols to xylene (or chloroform). Samples were then embedded longitudinally in paraffin under vacuum at 60 ℃. In the event that paraffin-embedded tumor biopsies could not be provided, 5 μm thick sections were cut from tumor biopsies and applied to ten positively charged glass slides.

EGFR protein expression was assessed at the central laboratory by immunohistochemistry using the EGFR pharmDx kit (DAKO, Glostrup, Denmark), and a staining intensity of 0 to 3+. For the purpose of statistical analyses, staining intensities of 0 or 1+ were considered negative, and scores of 2+ or 3+ were considered positive for EGFR protein expression.

Immunohistochemistry for COX-2 was performed using a murine anti-COX-2 monoclonal antibody (clone 33, BD Transduction Laboratories, Lexington, KY, USA) at a dilution of 1:100. Samples were incubated for 16 hours at

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Table 1 Patient demographics	
No. patients	30
Median age [range], years	60 [24-77]
Gender, n [%]	
Male	17 [57]
Female	13 [43]
ECOG performance status, n [%]	
0	14 [47]
1	13 [43]
2	3 [10]
Prior therapy, n [%]	
Radiotherapy	7 [23]
Chemotherapy	
1	2 [7]
2	12 [40]
3	14 [47]
4	1 [3]
GI tumor type, n [%][a]	
Colorectal	25 [83]
Pancreatic	3 [10]
Esophageal	1 [3]
Gall bladder	1 [3]
Site of metastatic disease, n [%]	
Liver	22 [73]
Lung	10 [33]
Other	3 [10]
Lymph nodes	2 [7]
Primary tumor	3 [10]
Skin/soft tissue	1 [3]
Adrenal	1 [3]
Mediastinal lymph nodes	1 [3]

[a]Tumor type data were collected retrospectively. ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal.

4 ℃, amplified using an avidin-biotin-peroxidase system, with antigen recovery performed under pressure (3.30 min) in sodium citrate solution (pH 6.0). The extension of stromal and tumoral COX-2 staining was assessed in a semiquantitative manner from 0 to 3+, where 0 and 1+ were considered negative and 2+ or 3+ were considered positive.

Statistical analysis

This was a pilot feasibility study and no formal statistical power calculations were performed. Nevertheless, a sample size of 30 patients was considered sufficient to examine the primary objective given that any event with an underlying incidence of 8% has a probability in excess of 90% of occurring in at least one patient out of 30.

The intent-to-treat population (i.e., all patients who enrolled and received study medication) was used to analyze efficacy parameters. Median duration of response, TTP, and overall survival were summarized using Kaplan-Meier methods along with the appropriate 95% confidence interval (CI). Tolerability outcomes were described using standard summary statistics.

Results

Patients

In total, 30 patients were enrolled into the study between December 2002 and April 2003 and their demographic characteristics are summarized in *Table 1*. Colorectal carcinoma was the most common primary GI tumor (83% of patients). Twenty-nine patients had received prior chemotherapy, with the majority receiving at least two previous regimens. Nearly one quarter of patients had also received prior radiotherapy. ECOG performance status was 0 to 1 in 90% of patients. All enrolled patients received at least one dose of gefitinib and celecoxib, and the median duration of treatment throughout the study was 70 days (range, 13 to 290 days).

Treatment

Interruptions in gefitinib and celecoxib therapy were required in 17 (56.7%) and 17 (56.7%) patients, respectively. Only six patients (20.0%) required dose interruption because of toxicity related to gefitinib (diarrhea, acne, and erythema). Eleven patients (36.7%) required interruption in celecoxib therapy due to toxicity (hepatitis, vomiting, nausea, and gastric pain). Eleven patients required interruption in gefitinib therapy and six patients required interruption in celecoxib therapy for reasons other than toxicity, such as disease progression, surgery, and non-related toxicity. Five patients had their dose of celecoxib reduced (three cases due to toxicity, one case due to mental confusion, and one case due to patient misunderstanding of required dosing).

Safety and tolerability

In total, 28 patients (93%) experienced ≥1 AE during the

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Table 2 Drug-related AEs occurring in ≥5% of patients (and all grade 3/4 AEs)

AE[a] n [%]	Gefitinib related		Celecoxib related	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Acne	11 [37]	1 [3]	1 [3]	0 [0]
Diarrhea	10 [33]	1 [3]	3 [10]	0 [0]
Stomatitis	4 [13]	0 [0]	4 [13]	0 [0]
Skin desquamation	4 [13]	0 [0]	2 [7]	0 [0]
Nausea	3 [10]	0 [0]	4 [13]	0 [0]
Rash	2 [7]	0 [0]	0 [0]	0 [0]
Pruritus	2 [7]	0 [0]	0 [0]	0 [0]
Abdominal pain	1 [3]	0 [0]	2 [7]	0 [0]
Vomiting	1 [3]	0 [0]	2 [7]	0 [0]
Hypotension	0 [0]	1 [3]	0 [0]	0 [0]
Upper abdominal pain	0 [0]	0 [0]	3 [10]	0 [0]
Hepatitis	0 [0]	0 [0]	0 [0]	1 [3]
Folliculitis	0 [0]	1 [3]	0 [0]	0 [0]

[a]A patient could have ≥1 AE. AE, adverse event.

study, most of which were mild to moderate in severity (*Table 2*). AEs were considered related to gefitinib in 20 (67%) patients and celecoxib in 11 (36.7%) patients. The most frequent AEs considered related to gefitinib were grade 1/2 acne and diarrhea. The most frequent AEs considered related to celecoxib were grade 1/2 stomatitis, nausea, diarrhea, and upper abdominal pain. Twelve patients (40%) experienced CTC grade 3/4 AEs (including fatigue, hepatitis, chest pain, pneumonia, perineal abscess, diarrhea, vomiting, hypertension, and abdominal pain). However, grade 3/4 AEs were considered by the investigator to be possibly related to gefitinib in only two patients; both grade 3 acne and folliculitis in one patient; and both grade 3 diarrhea and hypotension in one patient. One patient experienced grade 3 celecoxib-related hepatitis.

Of the three patients who required a reduction in the dose of celecoxib due to toxicity, one had a history of gastric sensitivity (dose was halved to 200 mg bid). No patients were withdrawn and there were no deaths due to AEs.

Efficacy

All 30 patients were included in the intent-to-treat population and were evaluable for efficacy. Twelve patients (40%) were classified as having stable disease during follow-up and 18 patients (60%) had progressive disease. The median TTP was 69 days (95% CI: 49-97) (*Figure 1A*).

Sixty percent of the patients (95% CI: 43-78) were alive at six months. The median overall survival time was 241 days; however, the 95% CI could not be estimated for this value due to censored data (*Figure 1B*).

EGFR and COX-2 immuno-expression: relationship with tumor response

EGFR and COX-2 immuno-expression was evaluable for 20 and 21 patients, respectively. There was no significant association between either EGFR or COX-2 immuno-expression and TTP (data not shown) or overall survival (*Figure 2*).

Discussion

These data represent the only known clinical evaluation of gefitinib and celecoxib given in combination to patients with advanced/refractory GI cancer. While the results demonstrate that the regimen is feasible and well tolerated, disease control was only achieved in 12 patients (40%) who had confirmed stable disease for ≥8 weeks, and no patients were classified as complete or partial responders. In this study, an exploratory analysis failed to detect an association between either EGFR or COX-2 immuno-expression and TTP or survival.

In NSCLC, *EGFR* mutation has been shown to be a key predictive factor for the efficacy of gefitinib (34-36). To date, there is limited evidence on the role of activating

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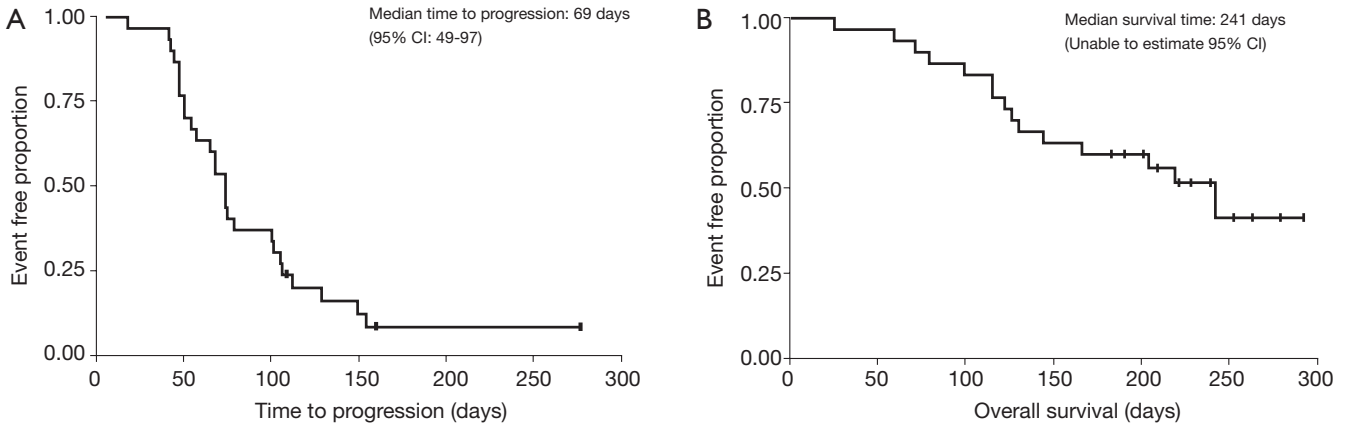

Figure 1 (A) TTP and (B) overall survival in 30 patients with GI tumors treated with gefitinib (250 mg/day) and celecoxib (400 mg bid). bid, twice daily; CI, confidence interval; GI, gastrointestinal; TTP, time to progression.

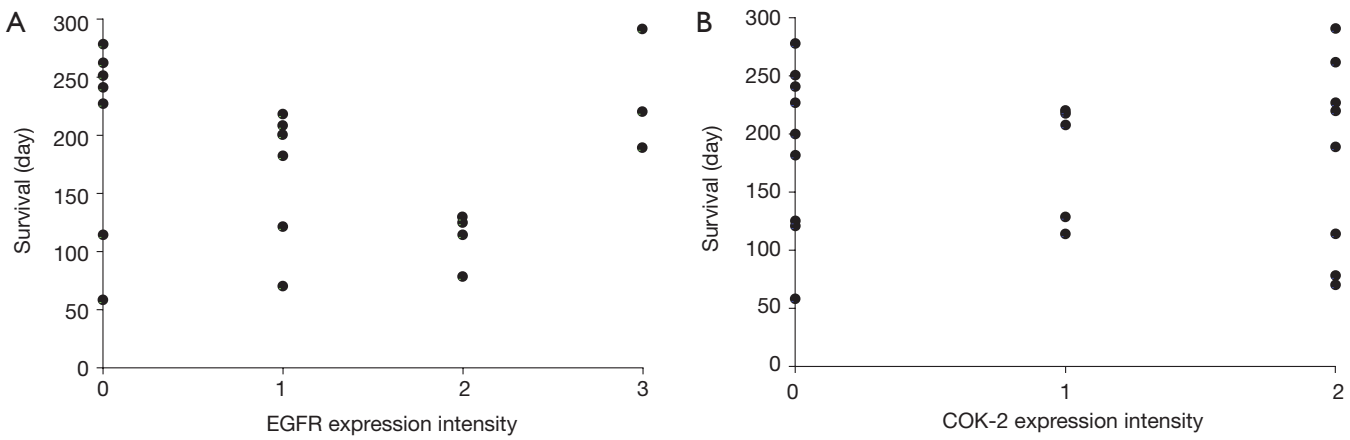

Figure 2 (A) EGFR and (B) COX-2 immuno-expression, and overall survival in patients with GI tumors. COX-2, cyclo-oxygenase-2; EGFR, epidermal growth factor receptor; GI, gastrointestinal.

EGFR mutations in determining response to gefitinib in colorectal cancer, and activating *EGFR* mutations are rare in colorectal cancer and do not seem to confer sensitivity to combination chemotherapy with gefitinib (37). Cetuximab, an anti-EGFR monoclonal antibody, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer in combination with irinotecan; however, EGFR expression has been shown by some investigators to be unreliable and lack predictive value for survival in colorectal cancer (38,39). *EGFR* gene-copy number as determined by fluorescence *in situ* hybridization may be a potentially predictive tool for response rate and TTP with cetuximab (40,41), although some investigators failed to find a relationship between EGFR amplification and response rate, PFS, and overall survival with either cetuximab or gefitinib (42,43). Recent studies have indicated that the benefits of cetuximab in terms of response rates, PFS, and/or overall survival are limited to patients with wild-type K-Ras (44).

The celecoxib dose chosen for this study was 400 mg bid, a dose that had been previously recommended for patients with familial adenomatous polyposis based on data from a small study (n=77) that showed greater reductions in colorectal polyps (P=0.003) and polyp burden (P=0.001) compared with placebo over six months (45). In our study, three patients required a reduction in celecoxib dose to 200 mg bid for reasons of toxicity.

Since the completion of this study, rofecoxib and valdecoxib (the COX-2 inhibitors) were withdrawn from clinical use due to an apparent increased risk of serious thromboembolic AEs (including myocardial infarction and

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stroke) with long-term use compared with placebo (46). Two meta-analyses examined the cardiovascular risks of celecoxib and other non-steroidal anti-inflammatory drugs (NSAIDs) (47,48). The first analysis, which examined the incidence of cardiovascular events in randomized controlled studies of COX-2 inhibitors and traditional NSAIDs, found an increased risk of cardiovascular events with COX-2 inhibitors (47). However, the increased cardiovascular risk with celecoxib was observed only at doses ≥400 mg/day. The second analysis, which included observational rather than randomized studies, did not find an increased risk of cardiovascular events with celecoxib at doses commonly used in clinical practice (approximately 200 mg/day) (48). A more recent network meta-analysis indicated that celecoxib is associated with an increased risk of myocardial infarction and of cardiovascular death compared with placebo; however, the low event rates in the included trials meant that the estimates of rate ratios were imprecise, with wide credibility intervals, and statistical significance was not reached (49). A large study involving 20,000 patients with arthritis, either with or at risk of developing cardiovascular disease, is attempting to establish the true risk: benefit profile of celecoxib compared with traditional NSAIDs [Prospective Randomized Evaluation of Celecoxib Integrated Safety *vs.* Ibuprofen Or Naproxen (PRECISION); NCT00346216] (50). Recently, celecoxib has been withdrawn from use in familial adenomatous polyposis, in the USA and European markets, due to inadequate enrollment in follow-up clinical trials and concerns that any long-term benefits of treatment had not been shown to outweigh the increased risk of cardiovascular and GI side effects (33). Any further trials in this setting should therefore include careful follow-up of all patients, particularly if the 400 mg bid regimen is utilized, and interim toxicity and safety analyses should be integrated into the study design.

The combination of gefitinib and celecoxib used in this study was generally well tolerated. The most frequent AEs attributed to gefitinib were mild to moderate acne and diarrhea, while for celecoxib they were abdominal/upper abdominal pain, nausea, stomatitis, and diarrhea. These AEs were typical of each drug in terms of nature, incidence, and severity.

Although only limited activity was reported in this study, there have been other previous studies that have investigated the use of gefitinib in GI tumors. The combination of gefitinib (250 mg/day) and celecoxib (400 mg bid) has been evaluated in 15 chemonaïve patients with squamous-cell carcinoma (n=3) or adenocarcinoma (n=12) of the esophagus (51). Of the 14 patients who were evaluable for efficacy after two months, three patients (21%) had stable disease and remained in follow-up after a mean of 5.5 months (one patient had been lost to follow-up).

Gefitinib monotherapy (500 mg/day) has been evaluated in two phase II trials in patients with advanced esophageal cancer, with promising results. Response rates of 3% and 11% were reported, along with disease control rates of 31% and 37% (52,53). In both of these studies, the most common drug-related AEs were diarrhea [58% (52) and 59% (53)] and rash [47% (52) and 52% (53)].

Twenty-five (83%) of the 30 patients enrolled in the current study had colorectal cancer. Only limited data are available for gefitinib as a treatment for colorectal cancer, with several phase II studies of gefitinib in combination with standard treatment approaches (54,55). In the intent-to-treat population of one study of gefitinib in combination with capecitabine and oxaliplatin, three patients had a complete response, 14 had a partial response, and 11 had stable disease (55). Furthermore, in a phase II study of gefitinib in combination with the standard treatment option FOLFOX-4 in patients with advanced disease, 31 of 43 patients had a complete or partial response (54).

While studies in advanced NSCLC have found no difference in response rates between 250 and 500 mg/day doses of gefitinib (56,57), data from 75 patients with advanced GI cancers have indicated that the higher dose may be more effective, with disease control achieved in 13.9% and 22.9% of patients randomized to receive gefitinib 250 and 500 mg/day, respectively; median TTP was 0.9 and 1.6 months, respectively (30). While there were no statistically significant differences between the groups for either parameter, further investigations into the most appropriate dose for gefitinib to treat patients with advanced GI tumors are warranted.

In summary, this pilot, open-label, exploratory trial investigated the use of gefitinib plus celecoxib, a novel treatment combination, in patients with advanced GI tumors. The results of this study are encouraging for a population in whom care is generally palliative, and several other studies have shown promising activity with gefitinib in this setting. Nevertheless, there is still much to understand about the mode of action of EGFR and COX-2 inhibitors and how best to combine the agents with existing chemotherapeutic regimens. Moreover, the optimal dose for gefitinib in this setting remains undetermined and a definitive outcome regarding the long-term safety issues

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with COX-2 inhibitors is awaited.

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