Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial

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Abstract

AIM: To investigate efficacy and safety of cetuximab combined with two chemotherapy regimens in patients with unresectable metastatic colorectal cancer (mCRC).

METHODS: Randomized patients received cetuximab with 5-fluorouracil (5-FU), folinic acid (FA) and oxaliplatin (FOLFOX) 6 (arm A, n = 74) or 5-FU, FA and irinotecan (FOLFIRI) (arm B, n = 77). KRAS mutation status was determined retrospectively in a subset of tumors (n = 117).

RESULTS: No significant difference was found between treatment arms A and B in the progression-free survival (PFS) rate at 9 mo, 45% vs 34%; median PFS, 8.6 mo vs 8.3 mo (hazard ratio [HR] = 1.06); overall response rate (ORR) 43% vs 45% [odds ratio (OR) = 0.93] and median overall survival (OS), 17.4 mo vs 18.9 mo (HR = 0.98). Patients with KRAS wild-type tumors demonstrated improved PFS (HR = 0.55, P = 0.0051), OS, (HR = 0.62, P = 0.0296) and ORR (53% vs 36%) and in arm A, improved PFS (HR = 0.49, P = 0.0196), OS (HR = 0.48, P = 0.0201) and ORR (56% vs 45%).
INTRODUCTION

Colorectal cancer (CRC) accounted for 529,000 deaths worldwide in 2002\[1\]. Up to 25% of CRC patients present with metastatic disease (mCRC) with five-year survival rates of approximately 10% reported\[2,3\]. The standard treatment for unresectable mCRC has been to administer first-line 5-fluorouracil (5-FU) with folinic acid (FA)\[4,5\], with improvements in clinical outcome being demonstrated for infusional 5-FU/FA combined with oxaliplatin (FOLFOX)\[6,7\] or irinotecan (FOLFIRI)\[8,9\]. However safety profiles differ, with grade 3/4 neutropenia and neurotoxicity more common with FOLFOX, and grade 3/4 mucositis and nausea/vomiting more common with FOLFIRI.

Cetuximab [Erbitux, developed by Merck KGaA Darmstadt, Germany (under license from Imclone, NY USA)] is an immunoglobulin G1 monoclonal antibody that specifically targets the epidermal growth factor receptor (EGFR), competitively inhibiting ligand binding and ligand-dependent downstream signaling\[10,11\]. Cetuximab first gained approval for use in Europe and the United States in the treatment of EGFR-expressing mCRC following failure of irinotecan-containing regimens\[12\]. More recently, the randomized CRYSTAL study demonstrated improved progression-free survival (PFS) in EGFR-expressing mCRC patients receiving FOLFIRI plus cetuximab compared with FOLLIRI alone\[13\]. In addition, the phase II OPUS trial reported a trend towards improved overall response rate (ORR) in EGFR-expressing mCRC patients receiving FOLFOX4 plus cetuximab compared with FOLFOX4 alone\[14\].

An accumulating body of data from studies of chemoresistant mCRC patients receiving cetuximab as monotherapy or in combination with chemotherapy suggests that clinical responses are confined to those patients whose tumors do not harbor mutations in codons 12 or 13 of the KRAS gene (KRAS-WT). The KRAS gene encodes a GDP/GTP binding protein which, following ligand binding to receptor tyrosine kinases including EGFR, activates downstream intracellular signaling cascades promoting cellular growth and proliferation\[15-21\]. KRAS mutations (in codons 12 or 13) occur in 40%-50% of CRCs and circumvent the cellular requirement for receptor activation of the KRAS protein\[20,21\]. Metastatic colorectal tumors harboring KRAS mutations are therefore hypothesized to be refractory to EGFR-targeting monoclonal antibodies.

Data from retrospective analyses of the CRYSTAL and OPUS studies confirmed that the efficacy of cetuximab in combination with FOLFOX or FOLFIRI was restricted to patients with KRAS-WT wild-type tumors\[13,14\], indicating tumor KRAS mutation status to be a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy.

In the current Central European Co-operative Oncology Group (CECOG)-sponsored randomized phase II trial, the efficacy and safety of cetuximab in combination with either FOLFOX6 or FOLFIRI was investigated first-line in patients with mCRC. In addition, a retrospective subgroup analysis of clinical outcome according to tumor KRAS mutation status was performed.

MATERIALS AND METHODS

Main patient eligibility criteria

Patients (≥ 18 years old) with histologically confirmed adenocarcinoma of the colon or rectum, with metastatic disease unsuitable for resection with curative-intent, an Eastern Co-operative Oncology Group (ECOG) performance status < 2, and adequate organ function were eligible for inclusion.

Exclusion criteria included: previous chemotherapy for metastatic disease; prior EGFR-targeted therapy; adjuvant chemotherapy with oxaliplatin or irinotecan (5-FU-based adjuvant chemotherapy was allowed provided the chemotherapy treatment-free interval was > 6 mo). Patients with brain metastases; concurrent malignancy and those with a previous malignancy within the last 5 years (excluding non melanoma skin cancer and in situ carcinoma of cervix); coronary artery disease or a history of myocardial infarction within 12 mo of study entry; pre-existing neuropathy > grade 1; intestinal occlusion or a history of inflammatory bowel disease; a > grade 3 allergic reaction to study treatment components; those

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undergoing surgery (excluding biopsy) or irradiation within 4 wk of study entry were also excluded, as were pregnant or lactating patients.

The study was approved by independent ethics committees at each center and was conducted in accordance with the principles of the Declaration of Helsinki and the Note for Guidance on Good Clinical Practice. All patients provided written informed consent.

**Study design**

This was a two-arm randomized multicenter, open-label, parallel-group phase II study involving 28 participating centers across 13 countries (CECOG/CORE1.2.001). Eligible patients were centrally randomized 1:1, using a minimization technique, stratifying patients according to study site, the number of organs involved and prior neo-adjuvant/adjuvant therapy. Patients received cetuximab (400 mg/m² initial infusion day 1, then 250 mg/m² weekly), then either in arm A: oxaliplatin (day 1, 100 mg/m²) with FA [400 mg/m² (racemic) or 200 mg/m² (L-form)] plus 5-FU (400 mg/m² bolus plus 2400 mg/m² as a 46-h continuous infusion) every 2 wk (FOLFOX6), or in arm B: irinotecan (180 mg/m²) with the 5-FU/FA regimen described (FOLFIRI). Patients received 6 mo of combination therapy, after which cetuximab was continued. Study treatment was discontinued in the case of progressive disease (PD). Patient follow-up was every 12 wk until treatment end or clinical cut-off date. The primary endpoint was PFS at 9 mo, secondary endpoints included ORR, PFS at 3, 6 and 12 mo, overall survival and safety.

**Dose modifications**

Dose reductions, treatment delays and the omission of a maximum of two consecutive doses of cetuximab were permitted in cases of grade 3 skin reactions. Two dose reductions for irinotecan or oxaliplatim were permitted after which the drug was discontinued (in either case cetuximab could be continued). Dose reductions were permanent.

**Assessments**

Computed tomography or magnetic resonance imaging of chest, abdomen and pelvis was performed at baseline and weeks 6, 12, and every 12 wk thereafter during treatment, and at the end of the study or upon PD. PFS rate was defined as the percentage of patients in each arm alive and free of tumor progression at analysis from the time of randomization, using response evaluation criteria in solid tumors (RECIST). Tumor response was evaluated according to RECIST guidelines. Survival was defined as time from randomization until death (patients lost to follow-up were censored at the time they were last determined to be alive). Adverse events (AEs) were assessed at treatment visits using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) and coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 10.1).

Tumor DNA was extracted and purified from formalin-fixed paraffin-embedded tissues as previously described.[48] The presence of KRAS mutations in co-
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Table 1 Patient characteristics at baseline

| Characteristic                      | ITT population | KKRAS population | KKRAS mutant |
|-------------------------------------|----------------|------------------|--------------|
|                                     | FOLFOX6 plus cetuximab (n = 77) | FOLFOX6 plus cetuximab (n = 34) | KRAS wild-type |
|                                     | FOLFOX6 plus cetuximab (n = 74) | FOLFOX6 plus cetuximab (n = 28) | KRAS mutant |
| Gender, n (%)                       | Male           | 43 (56)          | 22 (65)      | 11 (48) |
|                                     | Female         | 34 (44)          | 12 (35)      | 12 (52) |
|                                     | Age (yr)       | 62.0 (54-67)     | 62.5 (55-67) | 64.0 (56-68) |
|                                     | Median (Q1-Q3) | 62.5 (54-68)     | 64.0 (56-68) | 62.5 (54-70) |
|                                     | < 65, n (%)    | 46 (60)          | 19 (56)      | 13 (57) |
|                                     | > 65, n (%)    | 31 (40)          | 15 (44)      | 10 (43) |
|                                     | ECOG PS, n (%) | 0                | 20 (59)      | 13 (57) |
|                                     | 1              | 46 (60)          | 17 (61)      | 14 (44) |
|                                     | Primary tumor location, n (%) | 31 (40) | 14 (41) | 10 (43) |
|                                     | Colon          | 52 (68)          | 26 (76)      | 13 (57) |
|                                     | Rectum         | 25 (32)          | 8 (24)       | 10 (43) |
|                                     | Metastasis, n (%) | 45 (58) | 17 (50) | 16 (70) |
|                                     | Organs with metastases, n (%) | 59 (77) | 28 (82) | 17 (74) |
|                                     | >2             | 18 (23)          | 6 (18)       | 6 (26) |
|                                     | 1              | 16 (21)          | 3 (9)        | 6 (26) |
|                                     | Intestine/bowel| 12 (16)          | 3 (9)        | 6 (26) |
|                                     | Liver          | 66 (86)          | 30 (88)      | 20 (87) |
|                                     | Lung           | 27 (35)          | 11 (32)      | 8 (35) |
|                                     | Lymph nodes    | 28 (38)          | 18 (64)      | 16 (70) |
|                                     | Chest          | 7 (9)            | 2 (6)        | 3 (13) |
|                                     | Abdomen        | 22 (29)          | 9 (26)       | 5 (22) |
|                                     | Bone           | 2 (3)            | 0 (0)        | 2 (9) |
|                                     | Other          | 10 (13)          | 5 (15)       | 2 (9) |
|                                     | Duration of disease, mo | 5 (14-14) | 1.9 (1-15) | 1.8 (1-3) |
|                                     | CRC, median (Q1-Q3) | 1.2 (1-2) | 1.1 (1-2) | 1.3 (1-2) |
|                                     | mCRC median (Q1-Q3) | 1.4 (1-2) | 1.1 (1-2) | 1.3 (1-2) |
|                                     | EGFR status, n (%) | 1.4 (1-2) | 1.1 (1-2) | 1.3 (1-2) |
|                                     | Detectable     | 43 (56)          | 21 (62)      | 17 (74) |
|                                     | Undetectable   | 17 (22)          | 10 (29)      | 5 (22) |
|                                     | Non evaluable  | 17 (22)          | 3 (9)        | 2 (9) |
|                                     | Prior treatment, n (%) | 63 (82) | 31 (91) | 19 (83) |
|                                     | At least 1 therapy | 14 (18) | 9 (26) | 2 (9) |
|                                     | Adjuvant chemotherapy | 61 (79) | 30 (88) | 18 (78) |
|                                     | Surgery        | 8 (10)           | 3 (9)        | 3 (13) |
|                                     | Other          | 5 (7)            | 2 (7)        | 2 (6) |

Metastases detected within 1 mo of tumor diagnosis; Patients with >1 metastasis per organ site, the organ site was counted once only; Three patients included with rectal cancer received neoadjuvant therapy; Value determined from 76 patients. Patients receiving FOLFOX6 plus cetuximab (arm A) and those receiving FOLFOX6 plus cetuximab (arm B). ITT: Intention to treat; FOLFIRI: 5-fluorouracil (5-FU) folinic acid (FA) and oxaliplatin; FOLFOX: 5-FU FA and irinotecan; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; Q1-Q3: Interquartile range; mCRC: Metastatic colorectal cancer.

(ITT) population defined as all randomized patients who received at least one dose of study medication, which was the same as the safety population. Time to event data were analyzed using the Kaplan-Meier method. Standard errors were calculated using Greenwood's formula and the hazard ratio (HR) for PFS between both treatment groups and corresponding 95% CIs was calculated using an unadjusted Cox proportional hazard model. Differences in survival were tested using the log-rank test. Estimates of ORR in each treatment group, odds ratios and associated 95% CIs were calculated using the Cochran-Mantel-Haenszel procedure.

The study was initiated and patient recruitment finished (2006) before the evidence from a randomized trial that KRAS tumor mutation was associated with clinical outcome in patients treated with cetuximab in combination with chemotherapy was first presented. Subsequently a retrospective analysis of efficacy and safety was performed in the subgroup of patients with available tumor material that was evaluable for KRAS mutation status (wild-type vs mutant). Exploratory Cox proportional hazard models and logistic regression models were used to investigate the impact of KRAS mutation status on PFS, overall survival and ORR across the treatment groups adjusted for other significant confounding factors. A significance level of 0.2 was used to enter a factor into the model and a significance level of 0.10 was used for removing a factor from the model. Following an update of survival time, all information available by December 16th 2008 was considered for survival analyses. All calculations...
were performed with SAS release 8.2 (SAS Institute, Cary, NC USA).

RESULTS

Patient demographics

Patients were enrolled between July 2005 and July 2006; patient disposition is shown in Figure 1. Four patients randomized to receive cetuximab plus FOLFIRI withdrew their consent prior to treatment, with 151 patients subsequently receiving treatment. Reasons for discontinuing the study treatment were similar for both treatment arms.

Patient characteristics at baseline were generally well balanced between treatment groups (Table 1). KRAS mutation status was evaluable in 117/151 (77%) patient tumors; of these, KRAS mutations were detected in 55/117 (47%) patient tumors. Baseline characteristics of the KRAS subpopulation were representative of those of the ITT population (Table 1).

Table 2  Treatment exposure in the safety population

| Characteristic                      | FOLFOX6 plus cetuximab (arm A, n = 77) | FOLFIRI plus cetuximab (arm B, n = 74) |
|-------------------------------------|----------------------------------------|----------------------------------------|
| Exposure to cetuximab (Q1-Q3)      |                                        |                                        |
| Median duration, wk                 | 28.0 (17-46)                           | 29.1 (13-46)                           |
| Median number of infusions          | 26.0 (14-40)                           | 26.0 (12-42)                           |
| Relative dose intensity, %          |                                        |                                        |
| Only initial dose                   | 4 (5)                                  | 3 (4)                                  |
| < 60%                               | 2 (3)                                  | 3 (4)                                  |
| 60% to < 80%                        | 15 (19)                                | 8 (11)                                 |
| 80% to < 90%                        | 21 (27)                                | 20 (27)                                |
| ≥ 90%                               | 35 (45)                                | 40 (54)                                |
| Exposure to chemotherapy (Q1-Q3)   |                                        |                                        |
| Median duration, wk                 | 25.1 (19-28)                           | 25.5 (14-28)                           |
| Median number of cycles             | 12 (7-12)                              | 12 (6-12)                              |
| Relative dose intensity, %          |                                        |                                        |
| Oxaliplatin                         |                                        |                                        |
| No dose                             | 1 (1)                                  | 74 (100)                               |
| < 60%                               | 4 (5)                                  |                                        |
| 60% to < 80%                        | 24 (31)                                |                                        |
| 80% to < 90%                        | 22 (29)                                |                                        |
| ≥ 90%                               | 26 (34)                                |                                        |
| Irinotecan                          |                                        |                                        |
| No dose                             | 77 (100)                               | 2 (3)                                  |
| < 60%                               |                                        | 3 (4)                                  |
| 60% to < 80%                        |                                        | 18 (24)                                |
| 80% to < 90%                        |                                        | 13 (18)                                |
| ≥ 90%                               |                                        | 38 (51)                                |
| Bolus 5-FU                           |                                        |                                        |
| No dose                             | 1 (1)                                  | 2 (3)                                  |
| < 60%                               | 1 (1)                                  | 2 (3)                                  |
| 60% to < 80%                        | 28 (36)                                | 19 (26)                                |
| 80% to < 90%                        | 19 (25)                                | 14 (19)                                |
| ≥ 90%                               | 28 (36)                                | 37 (50)                                |
| Continuous infusion 5-FU            |                                        |                                        |
| No dose                             | 1 (1)                                  | 2 (3)                                  |
| < 60%                               | 1 (1)                                  | 3 (4)                                  |
| 60% to < 80%                        | 21 (27)                                | 14 (19)                                |
| 80% to < 90%                        | 13 (17)                                | 11 (15)                                |
| ≥ 90%                               | 41 (53)                                | 44 (59)                                |
| Dose reductions, n (%)              |                                        |                                        |
| Cetuximab                           | 9 (12)                                 | 5 (7)                                  |
| Chemotherapy                        | 25 (32)                                | 17 (23)                                |
| Treatment delays, n (%)             |                                        |                                        |
| Any cetuximab                       |                                        |                                        |
| ≥ 3 d                               | 59 (77)                                | 47 (64)                                |
| ≥ 16 d                              | 12 (16)                                | 8 (11)                                 |
| Any chemotherapy                    |                                        |                                        |
| ≥ 3 d                               | 59 (77)                                | 51 (69)                                |
| ≥ 14 d                              | 25 (32)                                | 15 (20)                                |
| Treatment discontinuation, n (%)    |                                        |                                        |
| Cetuximab                           | 13 (17)                                | 9 (12)                                 |
| Chemotherapy                        | 9 (12)                                 | 4 (5)                                  |

Table 3  Efficacy in the ITT population

| Characteristic                      | FOLFOX6 plus cetuximab (arm A, n = 77) | FOLFIRI plus cetuximab (arm B, n = 74) |
|-------------------------------------|----------------------------------------|----------------------------------------|
| PFS                                 |                                        |                                        |
| Events, n (%)                       | 61 (79)                                | 59 (80)                                |
| Median1, mo (95% CI)                | 8.6 (6.3-9.7)                          | 8.3 (7.4-8.7)                          |
| Log rank P-value                    | 0.7375                                 |                                        |
| Hazard ratio (95% CI)               | 1.06 (0.74-1.52)                      |                                        |
| PFS rate1, % (95% CI)               |                                        |                                        |
| 3 mo                                | 92 (85-98)                             | 78 (68-88)                             |
| 6 mo                                | 69 (58-80)                             | 69 (58-80)                             |
| 9 mo                                | 45 (33-58)                             | 34 (23-46)                             |
| 12 mo                               | 18 (8-27)                              | 18 (8-27)                              |
| Overall survival                    |                                        |                                        |
| Events, n (%)                       | 54 (70)                                | 50 (68)                                |
| Median1, mo (95% CI)                | 17.4 (14.9-22.6)                      | 18.9 (14.7-23.9)                      |
| Logrank P-value                     | 0.9230                                 |                                        |
| Hazard ratio (95% CI)               | 0.98 (0.67-1.44)                      |                                        |
| Survival rate1, % (95% CI)          |                                        |                                        |
| 9 mo                                | 79 (70-88)                             | 79 (70-89)                             |
| 12 mo                               | 70 (60-80)                             | 71 (60-81)                             |
| 18 mo                               | 46 (35-57)                             | 53 (42-65)                             |
| 24 mo                               | 33 (22-44)                             | 38 (26-50)                             |
| Best overall response, n (%)        |                                        |                                        |
| CR                                  | 2 (3)                                  | 6 (8)                                  |
| PR                                  | 31 (40)                                | 27 (36)                                |
| SD                                  | 31 (40)                                | 24 (32)                                |
| PD                                  | 6 (8)                                  | 9 (12)                                 |
| NE                                  | 7 (9)                                  | 8 (11)                                 |
| Objective response rate, n (%)      | 33 (43)                                | 33 (45)                                |
| 95% CI                              | 32-55                                  | 33-57                                  |
| Odds ratio (95% CI)                 | 0.93 (0.49-1.77)                      |                                        |

1Dose reductions, treatment delays and discontinuations due to adverse events.

1Median time and rates are based on Kaplan-Meier estimates; 2Hazard ratio and corresponding 95% CI based on unadjusted Cox proportional hazard model: hazard rate FOLFIRI plus cetuximab divided by hazard rate FOLFOX6 plus cetuximab. CR: Complete response; NE: Not evaluable; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

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that for the safety population. The proportion of patients experiencing dose reductions, delays in treatment, and treatment discontinuations for cetuximab or chemotherapy in each treatment arm by KRAS mutation status was not markedly different and was comparable with that found in the safety population.

**Efficacy**

Efficacy data for the ITT population are summarized in Table 3. The 9-mo PFS rate was 11% higher in arm A than arm B (45% vs 34%); however, the 95% CI for the difference was -6% to 28%, indicating no significant difference. The risk of disease progression (Figure 2A), death (Figure 3A) and the ORR were also similar between treatment arms.

The influence of tumor KRAS mutation status on clinical outcome is summarized in Table 4. The 9-mo PFS rate was higher and the risk of disease progression was significantly reduced in patients with KRAS wild-type tumors compared with those with KRAS mutations (Figure 2B). A significant improvement in survival (Figure 3B) and an increase in ORR were also demonstrated in patients with KRAS wild-type tumors compared with KRAS mutated tumors. In multivariate analyses of the KRAS evaluable population using Cox proportional hazard models (baseline characteristics and acne-like rash), only KRAS tumor mutation status (wild-type vs mutant) was identified as a significant prognostic indicator for prolonged PFS (HR = 0.55, \( P = 0.006 \)), while KRAS mutation status (wild type vs mutant, HR = 0.51, \( P = 0.003 \)), prior adjuvant/neo-adjuvant therapy (no vs yes, HR = 0.32, \( P < 0.001 \)) and acne-like rash during the first 6 wk (grade 2-3 vs grade 0-1, HR = 0.47, \( P = 0.004 \)) were significant independent prognostic indicators for prolonged overall survival.

In treatment arm A, the 9-mo PFS rate in patients with KRAS wild-type tumors was higher and the PFS time was significantly longer compared with patients with KRAS mutated tumors (Table 4, Figure 2C). In arm B, the 9-mo PFS rate was also higher in KRAS wild-type patients, although the PFS time was not significantly different compared with patients with KRAS mutated tumors (Figure 2D, Table 4). Similarly, in treatment arm A, survival time was significantly higher in patients with KRAS wild-type tumors compared with tumors with KRAS mutations (Figure 3C, Table 4). In both treatment arms the ORR was higher in patients with KRAS wild-type tumors compared with KRAS mutated tumors (Table 4).

In treatment arm A vs B; median PFS was 8.2 vs 8.4 mo
in patients with EGFR-detectable tumors \((n = 43\ vs\ n = 46)\), and 11.0 mo vs 8.1 mo in patients with EGFR-undetectable tumors \((n = 17\ vs\ n = 12)\). Median OS was also comparable by EGFR tumor status between the treatment groups. In arm A vs arm B, median OS was 15.5 mo vs 21.6 mo in patients with EGFR-detectable tumors and 23.3 mo vs 17.6 mo in patients with EGFR-undetectable tumors.

**Adverse events**

The number of patients experiencing serious AEs was balanced between the treatment groups (27% in arm A vs 28% in arm B). The frequencies of the most common treatment emergent AEs (TEAEs) in arm A vs arm B were: neutropenia (47% vs 36%); nausea (40% vs 26%); diarrhea (44% vs 58%); rash (36% vs 34%); vomiting (26% vs 23%); stomatitis (22% vs 18%); dermatitis acneiform (21% vs 23%); anorexia (22% vs 20%); pyrexia (22% vs 20%). Peripheral neuropathy was reported only in arm A (13%).

Grade 3/4 TEAEs related to study treatment (Table 5) were slightly higher in arm A than in arm B. Grade 4 neutropenia occurred more frequently in patients in arm A than in patients in arm B. The incidence of the special AEs, acne-like rash and infusion-related reactions (composite categories), was not significantly different between the treatment groups (Table 5).

Fifty-four deaths (70%) were reported for patients in arm A and 50 deaths (68%) in arm B. Ten deaths (13%) occurred on-treatment or within 60 d after the last dose in arm A and six (8%) in arm B. None of these deaths were assessed as being due primarily to treatment. Progressive disease and death related to disease complications were the most common reasons for death in both treatment groups.

The frequencies of serious AEs by KRAS tumor mutation status and treatment group were similar across the 4 groups (29%-31%). The only noteworthy finding was the relatively low incidence of related grade 3/4 AEs in KRAS wild-type patients treated with FOLFOX6 plus cetuximab (36%) in comparison to the other 3 groups (56%-71%), mainly due to a lower incidence of neutropenia (Table 5). However, the low sample size in the subgroup analysis should be taken into account, when considering this finding.

**DISCUSSION**

No significant differences in efficacy were found for cetuximab combined with FOLFIRI or FOLFOX6 in the first-line treatment of mCRC. Efficacy data in the current study are comparable with those reported from the corresponding arms of the CRYSTAL (median PFS value of 7.2 mo) and OPUS studies (median PFS value of 7.2 mo and an ORR of 46%)\[13\].

The KRAS evaluable population was representative of the ITT population. The KRAS tumor mutation status in patients receiving FOLFIRI plus cetuximab, KRAS wild-type \((n = 28)\) vs KRAS mutation \((n = 32)\).
frequency (47%) was similar to that previously reported for mCRC\textsuperscript{[13,14,27].} Across the treatment groups, PFS and overall survival were significantly improved and there was an increased chance of a tumor response in patients with KRAS wild-type tumors compared with KRAS mutant tumors; differences in PFS and survival appeared to increase over time. Multivariate analysis also confirmed that tumor KRAS mutation status is a prognostic marker for PFS and overall survival after adjustment by other independent predictors such as acne-like rash in the first 6 wk.

Patients with KRAS wild-type tumors receiving cetuximab plus FOLFOX6 demonstrated significantly improved PFS and overall survival and an increased chance of tumor response compared with patients with KRAS mutant tumors. Similar findings were reported in the OPUS study in patients receiving cetuximab plus FOLFOX4, where patients with KRAS wild-type tumors had a reduced risk of disease progression (HR 0.45, \( p = 0.0009\)) and a higher response rate (61% vs 37%) compared with those with tumor mutations\textsuperscript{[14].} However in the present study for patients receiving FOLFIRI plus cetuximab, no significant benefit was apparent with regard to PFS, survival or ORR according to KRAS tumor mutation status. This contrasts somewhat with the CRYSTAL study, where a significant clinical benefit was associated with the addition of cetuximab to FOLFIRI in patients with KRAS wild-type tumors, but not in patients with KRAS mutant tumors\textsuperscript{[13].} This non-significance may be due to the comparatively small sample size in the KRAS subgroup analysis in the present study compared with the CRYS- TAL study\textsuperscript{[13].} It should also be noted that the difference in the predictive power of KRAS tumor mutation status in patients receiving FOLFOX with cetuximab compared with those receiving FOLFIRI with cetuximab described here is consistent with the KRAS analysis from CRYSTAL and OPUS studies\textsuperscript{[13,14,20].} Furthermore, FOLFIRI and cetuximab were given until disease progression in the CRYSTAL study, whereas FOLFIRI was given for 6 mo and cetuximab until progression in the present study. Within this context it is noteworthy that the PFS curves cross after 6 mo in the FOLFIRI subgroup.

In the absence of chemotherapy-alone control arms, the present study was not able to accurately assess the influence of KRAS mutation status on clinical outcome for cetuximab or chemotherapy-alone as individual treatment components. The influence of KRAS tumor mutation status on patients treated with 5-FU-based chemotherapy remains controversial. The MRC FOCUS study of mCRC patients randomized to receive first-line 5-FU, 5-FU plus irinotecan or 5-FU plus oxaliplatin, reported that patients whose tumors harbored KRAS tumor mutations displayed significantly worse survival than those with KRAS wild-type.

### Table 4  Efficacy in the KRAS population

| Parameter | KRAS population | FOLFOX6 plus cetuximab (arm A) | FOLFIRI plus cetuximab (arm B) |
|-----------|-----------------|--------------------------------|-------------------------------|
|           | KRAS wild-type  | KRAS mutation (\( n = 55\)) | KRAS wild-type (\( n = 23\)) | KRAS mutation (\( n = 32\)) |
| PFS       |                 |                               |                               |                               |
| Events, n (%) | 46 (74)          | 47 (85)                      | 26 (87)                      | 20 (71)                      |
| Median, mo (95% CI) | 8.9 (7.3-11.1) | 7.8 (6.4-8.4)              | 9.1 (8.3-11.1)              | 7.2 (5.5-9.7)              |
| Logrank P-value | 0.0051          |                               | 0.0196                      | 0.1737                      |
| HR (95% CI) | 0.55 (0.36-0.84) |                               | 0.49 (0.27-0.91)           | 0.66 (0.36-1.21)           |

PFS rate, % (95% CI)

| Events, n (%) | 3 mo | 6 mo | 9 mo | 12 mo | Overall survival | Events, n (%) | Median, mo (95% CI) | Logrank P-value | HR (95% CI) | Survival rate, % (95% CI) |
|--------------|------|------|------|-------|------------------|--------------|--------------------|----------------|------------|---------------------------|
|              | 81 (70-91) | 70 (58-82) | 49 (35-62) | 29 (17-41) | 37 (60)         | 20.8 (16.6-26.9) | 0.0296 | 0.0201 | 0.62 (0.40-0.96)          |
|              | 88 (80-97) | 70 (57-83) | 26 (14-39) | 11 (2-20) | 45 (82)         | 15.9 (14.4-18.9) | 0.7160 | 0.1737 | 0.5608 (0.39-1.40)        |

Best overall response, n (%)

| CR | FR | SD | PD | NE | ORR, n (%) | 95% CI | Odds ratio (95% CI) |
|----|----|----|----|----|-----------|-------|-------------------|
| 6 (10) | 24 (44) | 14 (23) | 8 (13) | 7 (11) | 12 (23) |
| 1 (2) | 19 (35) | 26 (47) | 6 (11) | 3 (5) | 3 (9) |
| 2 (6) | 17 (30) | 9 (26) | 3 (9) | 3 (9) | 2 (6) |
| - | 7 (30) | 12 (52) | 3 (13) | 1 (4) | 1 (4) |
| 4 (14) | 5 (36) | 5 (18) | 5 (18) | 4 (14) | 14 (50) |
| 1 (3) | 12 (38) | 14 (44) | 3 (9) | 2 (6) | 13 (41) |
| 19.9 (11.9-na) | 18.9 (14.5-23.9) | 7 (30) | 10 (36) | 4 (14) | 14 (50) |

Odds ratio (95% CI) 1.99 (0.95-4.18) 2.90 (0.95-8.84) 1.46 (0.53-4.07)
Table 5  Grade 3/4 adverse events related to study treatment and special adverse event categories in the safety and KRAS populations \( n \) (%)

| Adverse event | FOLFIRI plus cetuximab (arm A) | FOXL6 plus cetuximab (arm B) | Grade 3/4 | Grade 4 | Grade 3/4 | Grade 4 |
|---------------|-------------------------------|-------------------------------|-----------|--------|-----------|--------|
| Safety population\( ^2 \) | Any related AE | 48 (62) | 12 (16) | 37 (50) | 6 (8) |
| Neutropenia | 22 (29) | 9 (12) | 15 (20) | 4 (5) |
| Diarrhea | 7 (9) | - | 9 (12) | - |
| Rash | 5 (6) | - | 3 (4) | - |
| Dermatitis acniform | 4 (5) | - | - | 2 (3) |
| Special AE categories | Skin reactions\( ^3 \) | 11 (14) | - | 6 (8) | - |
| Acne-like rash\( ^1 \) | 10 (13) | - | 6 (8) | - |
| Infusion-related reactions\( ^4 \) | 5 (6) | 2 (3) | 1 (1) | 1 (1) |
| Allergy/anaphylaxis | 5 (6) | 2 (3) | 1 (1) | 1 (1) |
| KRAS wild-type population\( ^1 \) | Any related AE | 24 (71) | 5 (15) | 10 (36) | 1 (4) |
| Neutropenia | 12 (35) | 3 (9) | 3 (11) | 1 (4) |
| Diarrhea | 3 (9) | - | 2 (7) | - |
| Dermatitis acniform | 3 (9) | - | - | - |
| Mucosal inflammation | 3 (9) | - | - | - |
| Rash | 2 (6) | - | - | - |
| Neutropathy peripheral | 2 (6) | - | - | - |
| Hypersensitivity | 2 (6) | 1 (3) | - | - |
| Special AE categories | Skin reactions\( ^3 \) | 6 (18) | - | 1 (4) | - |
| Acne-like skin rash\( ^1 \) | 5 (15) | - | 1 (4) | - |
| Infusion-related reactions\( ^4 \) | 2 (6) | 1 (3) | - | - |
| Allergy/anaphylaxis | 2 (6) | 1 (3) | - | - |
| KRAS mutation population\( ^2 \) | Any related AE | 14 (61) | 4 (17) | 18 (56) | 4 (13) |
| Neutropenia | 6 (26) | 3 (13) | 9 (28) | 2 (6) |
| Diarrhea | 3 (13) | - | 4 (13) | - |
| Thrombocytopenia | 2 (9) | - | - | - |
| Rash | 1 (4) | - | 2 (6) | - |
| Mucosal inflammation | - | - | 2 (6) | - |
| Dehydration | - | - | - | - |
| Special AE categories | Skin reactions\( ^3 \) | 2 (9) | - | 3 (9) | - |
| Acne-like rash\( ^1 \) | 2 (9) | - | 3 (9) | - |
| Infusion-related reactions\( ^4 \) | 2 (9) | 1 (4) | 1 (3) | 1 (3) |
| Allergy/anaphylaxis | 2 (9) | 1 (4) | 1 (3) | 1 (3) |

\( ^1 \)Grade 3/4 adverse events occurring in ≥ 5% of patients in either treatment group in each population are reported; \( ^2 \)Safety population: 77 patients received FOLFIRI plus cetuximab in arm A, 74 patients received FOLFOX6 plus cetuximab in arm B; \( ^3 \)Composite categories. Skin reactions include the terms: acne\( ^2 \), acne pustular\( ^3 \), cellulitis, dermatitis acniform\( ^4 \), dry skin\( ^5 \), erysipelas, erythema\( ^5 \), face edema, folliculitis\( ^5 \), hair growth abnormal, hypertrichosis, nail bed infection, nail disorder, nail infection, paronychia, pruritus\( ^5 \), rash\( ^6 \). Of these, all terms marked with an asterisk constituted the acne-like rash subset of the skin reaction category. Infusion-related reactions refer to special adverse event categories, including the MedDRA preferred terms: acute myocardial infarction, acute respiratory failure, anaphylactic reaction, **anaphylactic shock, **anaphylactoid reaction, **anaphylactoid shock, **angina pectoris, apnea, bronchial obstruction, bronchospasm, cardiac failure, cardiopulmonary failure, chills, clonus, convulsion, cyanosis, drug hypersensitivity, **dyspnea, dyspnea at rest, dyspnea exacerbated, dyspnea exertional, epilepsy, hyperpyrexia, hypersensitivity, **hypotension, **hypoxia, infusion-related reaction, loss of consciousness, myocardial infarction, myocardial ischemia, orthopnea, pyrexia, respiratory distress, respiratory failure, shock, sudden death, syncope. A double asterisk refers to those included regardless of when they occurred, all other terms were included only if the onset of the adverse event occurred on the same day as the first administration of cetuximab; \( ^1 \)Patients with KRAS wild-type tumors: 34 in arm A, 28 in arm B; \( ^2 \)Patients whose tumors harbored KRAS mutations: 23 in arm A, 32 in arm B. AE: Adverse event.

type tumors (HR = 1.24, \( p = 0.08 \))\(^{28}\). In contrast, in patients treated in the FOLFOX6-alone arm in the CRYS-TAL trial, KRAS mutation status was not associated with clinical outcome. Furthermore, in the large PETACC-3 trial of stage II and III colon cancer patients treated with adjuvant chemotherapy, KRAS tumor mutation status was found not to be of prognostic value\(^{28}\). The data from the present study lends support to the findings from retrospective analyses of randomized trials that demonstrated a lack of efficacy of cetuximab (either in combination with chemotherapy or best supportive care) in the treatment of mCRC. Patients with KRAS mutant tumors\(^{13,14,19}\), adding to the view that KRAS tumor mutation status is predictive of resistance to EGFR-targeted antibodies.

No marked difference in efficacy between the treatment groups for patients with EGFR-undetectable and EGFR-detectable tumors was found. Whilst this result should be treated with caution given the low numbers of EGFR-undetectable patients, the efficacy of cetuximab in combination with chemotherapy in EGFR-undetectable tumors has been reported previously\(^{30,31}\).

The combination of FOLFIRI with cetuximab was generally better tolerated than FOLFOX6 plus cetuximab with regard to grade 3/4 related AEs, and the frequency of study withdrawal being slightly higher in the latter group. The observed chemotherapy toxicity profiles are similar to those previously reported\(^{13}\). AEs associated with cetuximab were typically acne-like skin rash, which was observed with both chemotherapy combinations. KRAS mutation status did not appear to markedly influence the toxicity profiles of either treatment regimen as would be expected and as previously reported\(^{28}\).

In summary, this CECOG study shows that combinations of cetuximab with either FOLFOX6 or FOLFIRI have similar efficacies and acceptable toxicity profiles, in the first-line treatment of patients with unresectable mCRC. Analyses of tumor KRAS mutation status demonstrated cetuximab in combination with chemotherapy to have an increased treatment effect on tumor response, overall survival and PFS in patients with KRAS-wild-type tumors compared with those with KRAS-mutated tumors. Whether there is a stronger predictive effect of KRAS mutation status in patients treated with cetuximab plus FOLFOX6 compared with cetuximab plus FOLFIRI requires further investigation.

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COMMENTS

Background
The standard first-line treatment for patients with metastatic colorectal cancer (mCRC) is a combination of 5-fluorouracil (5-FU) and folinic acid (FA) with either irinotecan or oxaliplatin. The addition of cetuximab, a new class of drug known as biological therapeutics, to both these regimens has led to an increase in efficacy in some studies. This is even more pronounced in patients who do not carry a mutation in the KRAS gene (some 60% of the CRC population). No direct comparison has been made between the efficacy of these two regimens and the current study was undertaken to address this.

Research frontiers
Cetuximab is one of a number of biological therapeutics which have the potential to improve the outcome of patients with mCRC. However, as with all treatments, some patients respond well to this therapy while others do not. The current research hotspot is to identify key biomarkers which will predict the treatment to which patients are more likely to respond. The KRAS gene is one such biomarker and many others are under investigation.

Innovations and breakthroughs
A number of studies have produced encouraging results for combinations of cetuximab with various regimens containing 5-FU, FA and irinotecan or 5-FU, FA and oxaliplatin for the first-line treatment of mCRC. The current CCGCOG study was important in that it directly compared cetuximab combined with 5-FU/FA and irinotecan (FOLFIRI) and 5-FU/FA and oxaliplatin (FOLFOX) and showed that there was no statistical difference in efficacy between the two regimens in this setting. Efficacy data in the current study are also comparable with those reported from the corresponding arms of the CRySTAL (cetuximab plus FOLFIRI) and OPUS studies (cetuximab plus FOLFOX). Of further interest is the retrospective analysis of KRAS data, which demonstrated that the 9-mo PFS rate was higher and the risk of disease progression was significantly reduced in patients receiving cetuximab in combination with chemotherapy who had KRAS wild-type tumors compared with those with KRAS mutations.

Applications
The results of this study suggest that cetuximab plus FOLFIRI and cetuximab plus FOLFOX are equally effective in treating patients with mCRC. The data consolidate the view that cetuximab in combination with standard chemotherapy should be tailored to patients with KRAS wild-type mCRC. Whether there is a stronger predictive effect of KRAS mutation status in patients treated with cetuximab plus FOLFOX compared with cetuximab plus FOLFIRI requires further investigation.

Peer review
This is a well written manuscript which describes the effect of cetuximab combined with FOLFOX or FOLFIRI. The authors report that in general, in patients with KRAS wild-type tumors the treatment was more effective compared with patients with KRAS mutated tumors.

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