Efficacy, Tolerability, and Biomarker Analyses of Once-Every-2-Weeks Cetuximab Plus First-Line FOLFOX or FOLFIRI in Patients With *KRAS* or All *RAS* Wild-Type Metastatic Colorectal Cancer: The Phase 2 APEC Study

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Abstract

The nonrandomized phase 2 APEC trial investigated first-line once-every-2-weeks cetuximab plus chemotherapy (investigator's choice of FOLFOX or FOLFIRI) studied patients with *KRAS*/*RAS* wild-type metastatic colorectal cancer. We observed an activity and safety profile similar to that reported in prior first-line pivotal studies involving weekly cetuximab, suggesting that once-every-2-weeks cetuximab is effective and tolerable as first-line therapy.

Background: In patients with *KRAS* wild-type (wt) metastatic colorectal cancer (mCRC), outcomes with first-line chemotherapies are improved by adding weekly cetuximab. The APEC study investigated first-line once-every-2-weeks cetuximab plus chemotherapy for patients with *KRAS* wt mCRC; additional biomarker subgroups were also analyzed. **Patients and Methods:** APEC was a nonrandomized phase 2 trial conducted in the Asia-Pacific region. Patients (n = 289) received once-every-2-weeks cetuximab with investigator's choice of chemotherapy (FOLFOX or FOLFIRI). The primary end point was best confirmed overall response rate (BORR); progression-free survival (PFS) and

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overall survival (OS) were secondary end points. Early tumor shrinkage (ETS) and depth of response (DpR) were also evaluated. **Results:** In the *KRAS* wt population, BORR was 58.8%, median PFS 11.1 months, and median OS 26.8 months. Expanded *RAS* mutational analysis revealed that patients with *RAS* wt mCRC had better outcomes (BORR = 64.7%; median PFS = 13.0 months; median OS = 28.4 months). The data suggest that ETS and DpR may be associated with survival outcomes in the *RAS* wt population. Although this study was not designed to formally assess differences in outcome between treatment subgroups, efficacy results appeared similar for patients treated with FOLFOX and FOLFIRI. There were no new safety findings; in particular, grade 3/4 skin reactions were within clinical expectations. **Conclusion:** The observed activity and safety profile is similar to that reported in prior first-line pivotal studies involving weekly cetuximab, suggesting once-every-2-weeks cetuximab is effective and tolerable as first-line therapy and may represent an alternative to weekly administration.

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Keywords: Depth of response, Dosing schedule, Early tumor shrinkage, Erbitux, mCRC

Introduction

The anti–epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab has been approved for the first-line treatment of patients with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC). The addition of weekly cetuximab at a dose of 250 mg/m^2 (after an initial dose of 400 mg/m^2) to standard first-line infusional 5-fluorouracil (5-FU)-based chemotherapy regimens including oxaliplatin (FOLFOX [oxaliplatin, folinic acid, 5-FU]) or irinotecan (FOLFIRI [5-FU, folinic acid, irinotecan]) improves clinical outcome in patients with *KRAS* wt or *RAS* wt mCRC, as demonstrated in the randomized OPUS and CRYSTAL studies, respectively.[1-5]

Cetuximab has a mean half-life of 112 hours, and pharmacokinetic data suggest similar steady-state bioavailability for the standard weekly schedule of cetuximab (250 mg/m^2) and a once-every-2-weeks dose of 500 mg/m^2.[6] It is therefore plausible that cetuximab could be administered according to a once-every-2-weeks dosing schedule. Recent clinical evidence supports the activity and tolerability of such a regimen at a dose of 500 mg/m^2.[7-10] Such a dosing schedule would potentially be more convenient to patients, particularly due to the 2-week dosing cycles utilized for FOLFOX and FOLFIRI.

In light of these prior observations, a multicenter, nonrandomized phase 2 APEC study was conducted to assess the efficacy and safety of 500 mg/m^2 cetuximab once-every-2-weeks combined with FOLFOX or FOLFIRI as first-line treatment for patients with *KRAS* wt mCRC. To reflect the outcome in the population for which cetuximab is currently approved, we also performed exploratory subgroup analyses based on expanded *RAS* mutational status (*KRAS* and *NRAS* exons 2-4). Further analyses considered *BRAF* and *PIK3CA* mutational testing, EGFR expression status, and the potential association between early tumor shrinkage (ETS) and depth of response (DpR) with survival outcomes. Because FOLFOX and FOLFIRI have shown similar efficacy in patients with mCRC,[11] including when used in combination with cetuximab,[12,13] the study design included a nonrandomized allocation to either chemotherapy regimen, based on investigator's choice.

Patients and Methods

Study Design and Patients

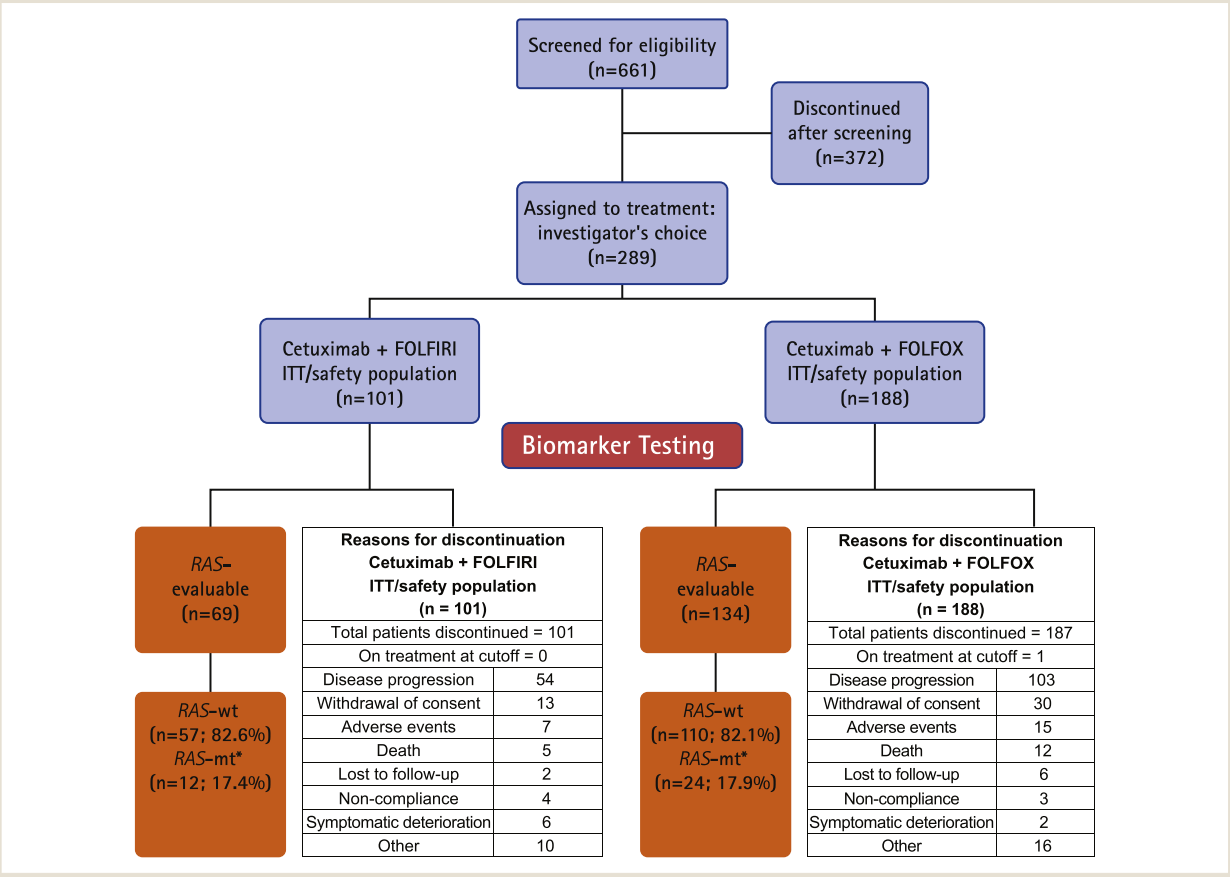
APEC (NCT00778830) was a multicenter, nonrandomized, open-label phase 2 exploratory trial carried out in the Asia-Pacific region. APEC included adult patients (aged ≥ 18 years) from the Asia-Pacific region with *KRAS* wt metastatic adenocarcinoma of the colon or rectum. *KRAS* wt was defined as no detected mutations in *KRAS* exon 2 (codon 12/13). Eligible patients were required to have a life expectancy of ≥ 12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, presence of ≥ 1 bidimensionally measurable index lesion, and written informed consent. Patients were excluded if they had known or suspected brain metastasis and/or leptomeningeal disease; previous treatment with chemotherapy for colorectal cancer (excluding adjuvant therapy terminated > 6 months previously); or radiotherapy, surgery (excluding prior diagnostic biopsy), or any investigational drug in the 30 days before the start of treatment in this study.

All patients received cetuximab (500 mg/m^2) on the first day of every 14-day treatment cycle over 120 minutes for the first infusion, 90 minutes at the second infusion, and 60 minutes at the subsequent infusions. According to investigator's choice, patients received either FOLFOX (oxaliplatin 100 mg/m^2, folinic acid (FA) 200 mg/m^2 L-form or 400 mg/m^2 racemic, then 5-FU as a 400 mg/m^2 intravenous bolus and a 2400 mg/m^2 continuous infusion over 46 hours) or FOLFIRI (irinotecan 180 mg/m^2, FA 200 mg/m^2 L-form or 400 mg/m^2 racemic, then 5-FU as a 400 mg/m^2 intravenous bolus and a 2400 mg/m^2 continuous infusion over 46 hours) (Figure 1). Treatment was planned to continue until the disease progressed, unacceptable toxicity was reported, or consent was withdrawn; when chemotherapy was discontinued, continuation of cetuximab as a maintenance regimen (until disease progression) was to be considered. After the end of study treatment, information on further anticancer treatment and survival was collected every 3 months.

Outcomes

Because all patients in the intention-to-treat (ITT) population received ≥ 1 dose of study treatment, efficacy analyses and safety assessments were conducted on the ITT population, which was defined as all patients with *KRAS* wt mCRC who received ≥ 1 dose of either study treatment (n = 289). The primary end point was the best overall confirmed response rate (BORR); response to treatment was assessed every 8 weeks by radiologic imaging according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.0.

Figure 1 APEC Study Profile. *Includes Patients With *KRAS* Exon 3/4 Mutations, *NRAS* Exon 2/3/4 Mutations, and New *KRAS* Exon 2 Mutations Identified by NGS



Reasons for discontinuation Cetuximab + FOLFIRI ITT/safety population (n = 101)	
Total patients discontinued = 101	
On treatment at cutoff = 0	
Disease progression	54
Withdrawal of consent	13
Adverse events	7
Death	5
Lost to follow-up	2
Non-compliance	4
Symptomatic deterioration	6
Other	10

Reasons for discontinuation Cetuximab + FOLFOX ITT/safety population (n = 188)	
Total patients discontinued = 187	
On treatment at cutoff = 1	
Disease progression	103
Withdrawal of consent	30
Adverse events	15
Death	12
Lost to follow-up	6
Non-compliance	3
Symptomatic deterioration	2
Other	16

Abbreviations: FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; ITT = intention-to-treat; mt = mutant; NGS = next-generation sequencing; wt = wild type.

Secondary end points were progression-free survival (PFS), overall survival (OS), and safety. In assessing the potential relationship of documented adverse events (AEs) to the study drugs (ie, cetuximab and/or chemotherapy), it was assumed that the AE was related to the study drugs unless the investigator definitively reported that the AE was unrelated to the study drugs.

The number of patients who underwent metastatic surgery, together with information on the localization of metastases removed and outcome of surgery with respect to residual tumor after surgery (R0, R1, R2, not evaluable), was evaluated in an exploratory analysis. In case of resection of $>$ 1 metastasis, the worst outcome of surgery defined overall status.

All patients with an available tumor size evaluation at baseline and week 8 (n = 269) were considered for an exploratory analysis of the potential association between ETS and survival outcomes (PFS and OS). ETS was categorized as $\geq$ 20% decrease in the sum of longest diameters of target lesions between baseline and posttreatment week 8.

A total of 159 patients with *RAS* wt mCRC were considered evaluable for an exploratory analysis of DpR, including its potential association with efficacy outcomes (PFS as well as OS). Evaluable patients were those who had quantitative tumor size assessments available from baseline and at least 1 postbaseline visit. DpR was defined as the extent of maximal tumor shrinkage (sum of tumor diameters at nadir divided by sum of tumor diameters at baseline) and was expressed as a percentage. Assessments were performed every 8 weeks by computed tomography or magnetic resonance imaging according to RECIST 1.0.

Expanded RAS *Testing and Exploratory Biomarker Analysis*

Expanded *RAS* (*KRAS* and *NRAS* exons 2-4; including retesting of *KRAS* exon 2) mutational status was assessed by Ion Torrent (Life Technologies, Thermo Fisher Scientific Life Sciences, Waltham, MA) next-generation sequencing (NGS). *RAS* wt was defined as no mutations in *KRAS* and *NRAS* exons 2-4; *RAS* mutant (mt) was defined as $\geq$ 1 mutation in exons 2-4 of *KRAS* and/or *NRAS*. Upon retesting via NGS, *KRAS* exon 2 mutations were detected in 10 patients from the *KRAS* wt ITT population, potentially owing to the higher sensitivity of NGS compared with the direct sequencing method initially used to screen patients for eligibility. These 10 patients were included, along with patients with *KRAS* exon 3-4 and *NRAS* exon 2-4 mutations, in the *RAS* mt population during the exploratory analysis.

Table 1 Baseline Demographics in *KRAS* wt and *RAS* wt Populations

Characteristic	*KRAS* wt (ITT) Population, n (%)			*RAS* wt Populationn (%)		
	Total (n = 289)	Cetuximab + FOLFOX (n = 188)	Cetuximab + FOLFIRI (n = 101)	Total (n = 167)	Cetuximab + FOLFOX (n = 110)	Cetuximab + FOLFIRI (n = 57)
Sex						
Male	185 (64.0)	119 (63.3)	66 (65.3)	108 (64.7)	72 (65.5)	36 (63.2)
Female	104 (36.0)	69 (36.7)	35 (34.7)	59 (35.3)	38 (34.5)	21 (36.8)
Age, years						
<65	215 (74.4)	145 (77.1)	70 (69.3)	131 (78.4)	88 (80.0)	43 (75.4)
≥65	74 (25.6)	43 (22.9)	31 (30.7)	36 (21.6)	22 (20.0)	14 (24.6)
Region						
East Asia	167 (57.8)	94 (50.0)	73 (72.3)	86 (51.5)	46 (41.8)	40 (70.2)
Australia	29 (10.0)	21 (11.2)	8 (7.9)	25 (15.0)	17 (15.5)	8 (14.0)
South Asia	31 (10.7)	19 (10.1)	12 (11.9)	15 (9.0)	10 (9.1)	5 (8.8)
Southeast Asia	62 (21.5)	54 (28.7)	8 (7.9)	41 (24.6)	37 (33.6)	4 (7.0)
Ethnic origin						
Asian	259 (89.6)	167 (88.8)	92 (91.1)	141 (84.4)	92 (83.6)	49 (86.0)
Caucasian	29 (10.0)	21 (11.2)	8 (7.9)	26 (15.6)	18 (16.4)	8 (14.0)
Other	1 (0.3)	0	1 (1.0)	0	0	0
Leukocytes						
≤10,000/mm^3	233 (80.6)	146 (77.7)	87 (86.1)	136 (81.4)	85 (77.3)	51 (89.5)
>10,000/mm^3	39 (13.5)	31 (16.5)	8 (7.9)	22 (13.2)	18 (16.4)	4 (7.0)
Missing	17 (5.9)	11 (5.9)	6 (5.9)	9 (5.4)	7 (6.4)	2 (3.5)
Primary tumor site						
Colon	157 (54.3)	106 (56.4)	51 (50.5)	96 (57.5)	68 (61.8)	28 (49.1)
Rectum	117 (40.5)	72 (38.3)	45 (44.6)	59 (35.3)	34 (30.9)	25 (43.9)
Colon + rectum	15 (5.2)	10 (5.3)	5 (5.0)	12 (7.2)	8 (7.3)	4 (7.0)
Metastatic site						
Liver only	85 (29.4)	55 (29.3)	30 (29.7)	54 (32.3)	33 (30.0)	21 (36.8)
Other metastasis	203 (70.2)	133 (70.7)	70 (69.3)	112 (67.1)	77 (70.0)	35 (61.4)
No metastases	1 (0.3)	0	1 (1.0)	1 (0.6)	0	1 (1.8)
Prior therapy						
Adjuvant	87 (30.1)	40 (21.3)	47 (46.5)	10 (6.0)	5 (4.5)	5 (8.8)
Neoadjuvant	14 (4.8)	9 (4.8)	5 (5.0)	1 (0.6)	1 (0.9)	0

Abbreviations: FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; wt = wild type.

Mutational status of *BRAF* and *PIK3CA* was assessed retrospectively by pyrosequencing. EGFR expression was assessed by immunohistochemistry using an EGFR pharmDx Kit (Dako, Glostrup, Denmark; Agilent Technologies, Santa Clara, CA) with a cutoff point of ≥ 5% of tumor cells exhibiting a staining intensity of ≥ 1+ for defining EGFR-detectable (< 5% was defined as EGFR-undectable).

Statistical Analysis

The primary analysis was planned to be performed in the ITT *KRAS* wt population. The study design did not plan for direct or statistical comparison between the FOLFOX and FOLFIRI treatment subgroups, as this comparison was not supported by randomization. The response rate from the overall population, as well as each treatment subgroup, and its 95% confidence interval (CI) was calculated using the Clopper-Pearson method. Estimates for the secondary efficacy variables PFS and OS were described applying the Kaplan-Meier method. All analyses were performed using SAS 9.1 or later software (SAS Institute, Cary, NC).

The sample size determination was not based on power considerations for a statistical test but on the confidence limit approach to ensure adequate precision of estimates. Based on the results from the CRYSTAL and OPUS studies,[1,2,4,5] a precision of estimates with 55% as the expected BORR in each of the 2 treatment subgroups was selected. A length of the 2-sided 95% CI (not exceeding 10 percentage points in each direction from the point estimate) was used as a reasonable precise estimate of the BORR for each of the 2 treatment subgroups if ≥ 96 patients received that specific combination treatment.

Results

Patient Populations

The first patient entered our study in February 2009, and the last patient's final treatment visit was in April 2014. In total, 289

Table 2 Efficacy in *KRAS* wt, *RAS*-Evaluable, *RAS* wt, and *RAS* mt Populations

Characteristic	*KRAS* wt (ITT)			*RAS* Evaluable			*RAS* wt			*RAS* mt		
	Total (n = 289)	Cetuximab + FOLFOX (n = 188)	Cetuximab + FOLFIRI (n = 101)	Total (n = 203)	Cetuximab + FOLFOX (n = 134)	Cetuximab + FOLFIRI (n = 69)	Total (n = 167)	Cetuximab + FOLFOX (n = 110)	Cetuximab + FOLFIRI (n = 57)	Total (n = 36)	Cetuximab + FOLFOX (n = 24)	Cetuximab + FOLFIRI (n = 12)
BORR (95% CI), %	58.8 (52.9-64.6)	61.2 (53.8-68.2)	54.5 (44.2-64.4)	60.6 (53.5-67.4)	60.4 (51.6-68.8)	60.9 (48.4-72.4)	64.7 (56.9-71.9)	62.7 (53.0-71.8)	68.4 (54.8-80.1)	41.7 (25.5-59.2)	50.0 (29.1-70.9)	25.0 (5.5-57.2)
Median PFS (95% CI), months	11.1 (9.3-11.8)	11.1 (9.0-12.7)	11.1 (8.1-14.8)	11.1 (9.3-13.5)	11.1 (8.8-13.6)	12.7 (9.3-15.2)	13.0 (11.1-14.8)	13.3 (9.8-14.8)	12.8 (9.7-15.4)	7.4 (5.5-7.5)	7.3 (3.7-7.7)	7.4 (5.5-35.3)
Median OS (95% CI), months	26.8 (23.4-29.7)	27.0 (22.8-30.1)	26.6 (21.5-33.8)	27.5 (23.4-30.8)	27.6 (23.0-31.2)	27.5 (21.8-34.0)	28.4 (24.4-32.3)	27.8 (23.2-31.8)	28.7 (23.1-37.9)	22.1 (16.6-30.1)	22.1 (9.2-34.2)	24.0 (14.9-34.0)

Abbreviations: BORR = best confirmed overall response rate; FOLFRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; ITT = intention-to-treat; mt = mutant; OS = overall survival; PFS = progression-free survival; wt = wild type.

patients comprised the ITT (*KRAS* wt) population. The 5 countries with the highest participation were China (21.1%), Taiwan (15.9%), South Korea (13.1%), Australia (10.0%), and India (8.0%). In the *KRAS* wt population, 188 patients (65.1%) were treated with cetuximab plus FOLFOX, and 101 patients (34.9%) received cetuximab plus FOLFIRI.

Additional biomarker testing within the *KRAS* wt ITT population was conducted to assess the potential influences of mutations in *RAS* (*KRAS* and *NRAS* exons 2-4). Among the tumors from 203 evaluable patients, 167 (82.3%) were found to be *RAS* wt, defined as having no detectable mutations in exons 2-4 of *KRAS* and *NRAS*. The frequencies of *BRAF* and *PIK3CA* mutations were low (5.5% for *BRAF*; 3.5% and 1.0% for *PIK3CA* exons 9 and 20, respectively) (Supplemental Table 1; available in the online version). Due to the small number of patients with *BRAF* and *PIK3CA* mutations, the *BRAF/PIK3CA* mt groups were combined in our subsequent analyses.

Within the *KRAS* wt population, the baseline characteristics of the 2 treatment subgroups were generally well balanced. However, several exceptions existed, including the percentage of patients who were aged $\geq$ 65 years (22.9% FOLFOX and 30.7% FOLFIRI), baseline leukocyte count $>$ 10,000/mm^3 (16.5% FOFOX and 7.9% FOLFIRI), and prior adjuvant therapy (21.3% FOLFOX and 46.5% FOLFIRI; previous oxaliplatin exposure in the adjuvant setting may have contributed to an increased frequency of investigator's choice of FOLFIRI in this study). Baseline characteristics of the *RAS* wt population were broadly similar to those of the *KRAS* wt population (Table 1).

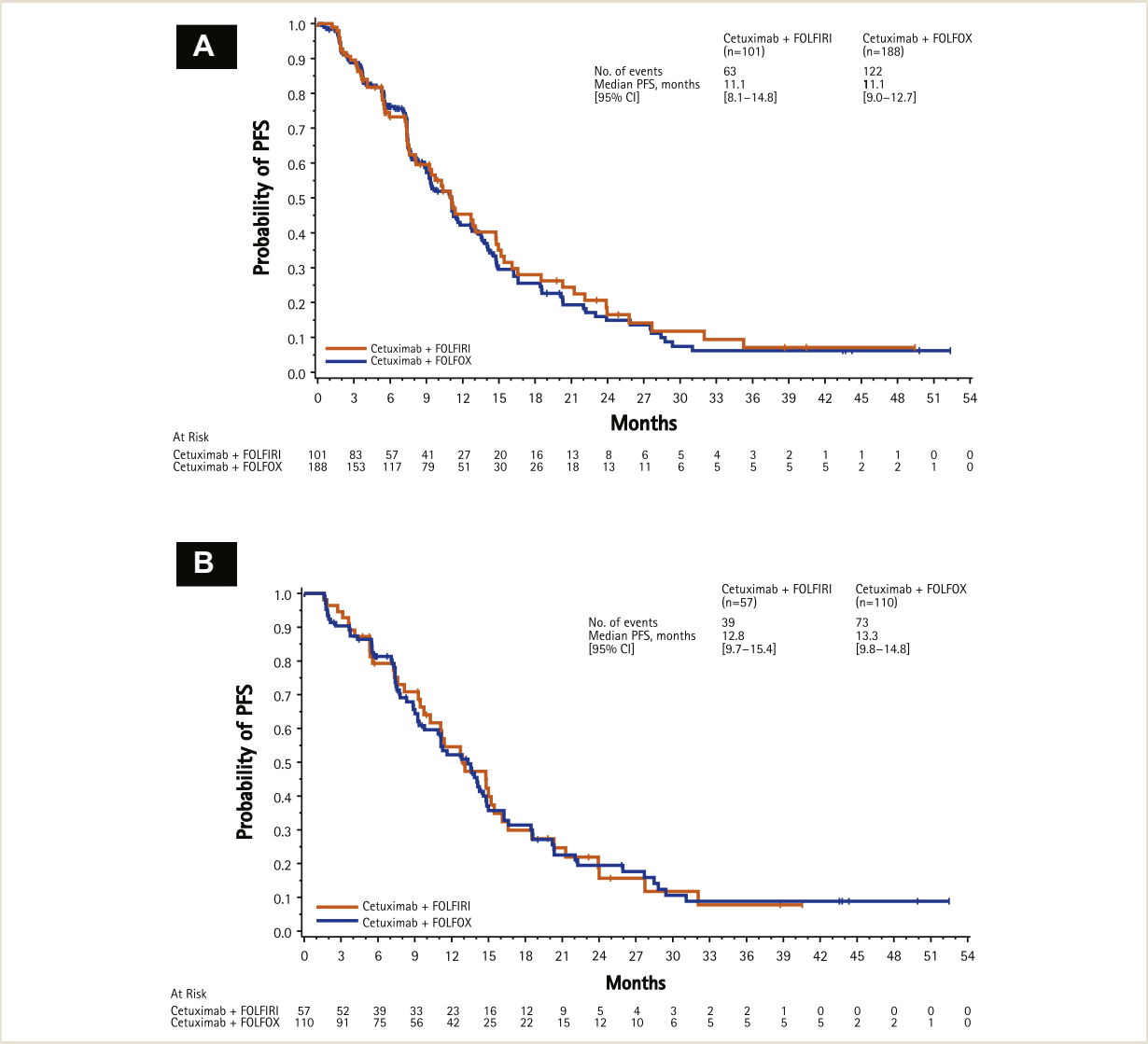
Exposure to cetuximab and chemotherapy (irinotecan or oxaliplatin plus 5-FU), as measured by relative dose intensity, was similar between the 2 treatment subgroups (Supplemental Table 2; available in the online version). Furthermore, cetuximab relative dose intensity was $\geq$ 80% in the majority of patients in the *KRAS* wt, *RAS* wt, *RAS* mt, and *RAS*-evaluable populations ($>$ 70% of patients in each population), with no major differences between the populations (data not shown). The median duration of cetuximab treatment was relatively long ($\approx$7.5 months; 32.1 weeks in the FOLFOX subgroup and 33.3 weeks in the FOLFIRI subgroup) and exceeded the median duration of chemotherapy administration (25.4 weeks for oxaliplatin; 32.0 weeks for irinotecan; and 27.8 weeks and 32.0 weeks for 5-FU in the FOLFOX and FOLFIRI subgroups, respectively), suggesting that investigators followed the recommendation to use cetuximab as maintenance therapy after withdrawal of chemotherapy (Supplemental Table 3; available in the online version).

Efficacy

Key efficacy measures for both the *KRAS* wt and *RAS* wt populations are summarized in Table 2. The *KRAS* wt and *RAS*-evaluable populations were comparable.

In the *KRAS* wt population, BORR, the primary end point of the study, was 58.8% (95% CI, 52.9-64.6); further refinement of the most appropriate patient pool via expanded *RAS* analysis revealed a BORR of 64.7% (95% CI, 56.9-71.9) in the *RAS* wt population. Consistent with the relatively long median duration of treatment, median PFS was 11.1 months (95% CI, 9.3-11.8) and 13.0 months (95% CI, 11.1-14.8) in the *KRAS* wt and *RAS* wt populations, respectively. Median OS in the *KRAS* wt population was 26.8

Figure 2 Progression-Free Survival (A, B) and Overall Survival (C, D) According to Treatment Subgroup in *KRAS* wt (A, C) and *RAS* wt (B, D) Populations



Abbreviations: FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; OS = overall survival; PFS = progression-free survival; wt = wild type.

months (95% CI, 23.4-29.7); in the *RAS* wt population, median OS was further improved (28.4 months [95% CI, 24.4-32.3]) (Table 2 and Figure 2). The survival rate in the *KRAS* wt population was 33% at 36 months and 23% at 48 months (36% and 26%, respectively, in the *RAS* wt population).

As anticipated, BORR, median PFS, and median OS were relatively low in patients with *RAS* mt mCRC, as compared with patients with *RAS* wt mCRC (Table 2).

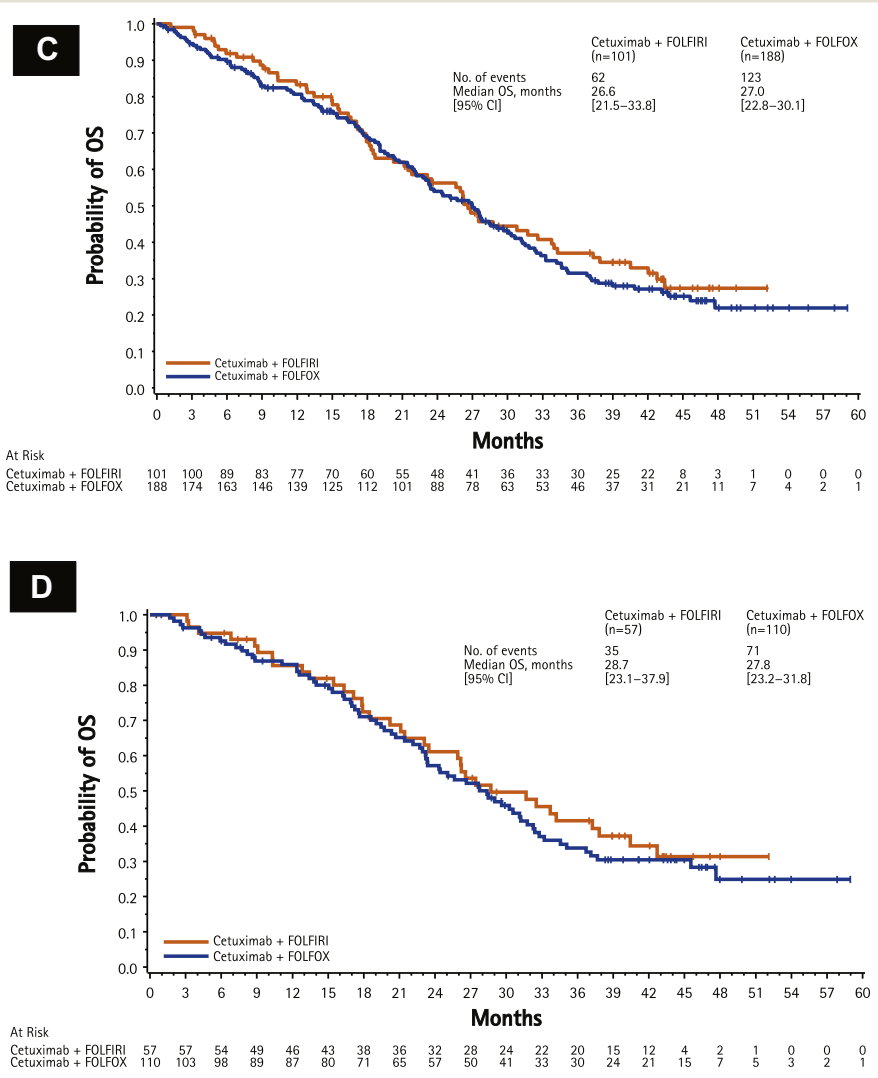
The study was not designed to assess differences in outcomes based on treatment subgroup. However, as expected, efficacy results were similar for patients treated with FOLFOX versus FOLFIRI in both the *KRAS* wt and *RAS* wt populations (Table 2 and Figure 2).

Post–first-line anticancer treatment was received by 59.2% of the *KRAS* wt population. The most common post–first-line treatment administered was chemotherapy (52.2%), and relatively few patients (≤ 20.8%) received post–first-line biologics (Supplemental Table 4; available in the online version).

We also sought to address efficacy within a biomarker subpopulation defined by *BRAF* and *PIK3CA* mutational status. Among 203 evaluable patients, 175 were wt at both *BRAF* and *PIK3CA*, 15 with *BRAF* mt and *PIK3CA* wt, 12 were *BRAF* wt and *PIK3CA* mt, and 1 was *BRAF* mt and *PIK3CA* mt. *BRAF/PIK3CA* wt patients appeared to have numerically improved outcomes compared with patients with *BRAF* mt and/or *PIK3CA* mt tumors; however, definitive conclusions were precluded by the limited number of patients with *BRAF/PIK3CA* mutations in our study (Supplemental Table 5; available in the online version).

Additional biomarker efficacy subanalyses were conducted on the basis of EGFR expression. Among 154 evaluable patients, 124 had detectable EGFR expression versus 30 with undetectable

Figure 2 continued



EGFR expression. There were no major differences in outcome between the EGFR subgroups, although caution is required when interpreting these analyses due to the small number of patients in some subgroups (Supplemental Table 6; available in the online version).

During the study, 31 patients (10.7%) underwent surgery with curative intent (24 [12.8%] in the FOLFOX subgroup and 7 [6.9%] in the FOLFIRI subgroup). The R0 resection rate was 10.0% (29 of 289) in the *KRAS* wt population (22 [11.7%] in the FOLFOX subgroup and 7 [6.9%] in the FOLFIRI subgroup). Palliative surgery was undertaken in 5 additional patients (1 in the FOLFOX subgroup and 4 in the FOLFIRI subgroup). Thus, a total of 36 patients in the *KRAS* wt population underwent on-study surgery for metastases. The R0 resection rate was 10.8% (18 of 167) within the *RAS* wt population (15 [13.6%] in the FOLFOX subgroup and 3 [5.3%] in the FOLFIRI subgroup), and a total of 23 patients (13.8%) underwent on-study surgery for metastases.

Assessment for ETS was evaluable in 269 and 159 patients in the *KRAS* wt and *RAS* wt populations, respectively. Overall, 76.2% (205 of 269) of the evaluable patients with *KRAS* wt mCRC achieved ETS, whereas ETS occurred in 81.8% (130 of 159) of evaluable patients with *RAS* wt mCRC. In patients with *KRAS* wt and *RAS* wt mCRC, ETS was associated with longer PFS and OS; there were no major differences between the FOLFOX and FOLFIRI subgroups (Table 3).

The extent of tumor shrinkage was similar between the FOLFOX and FOLFIRI treatment subgroups; among patients whose disease did not progress, tumor size continued to decrease as the duration of treatment increased (Supplemental Figure 1; available in the online version). 159 patients with *RAS*-wt mCRC were evaluable for DpR: median DpR was 62.2% (interquartile range [IQR], 39.1-80.0) within the overall DpR-evaluable population; within the FOLFOX (n = 103) and FOLFIRI (n = 56) treatment subgroups, median DpR was 62.2% (IQR, 40.0-80.7) and 62.5%

Table 3 Association of PFS and OS With Early Tumor Shrinkage in *KRAS* wt and *RAS* wt Populations

Population	Total		Cetuximab + FOLFOX		Cetuximab + FOLFIRI	
	ETS (≥20%)	ETS (<20%)	ETS (≥20%)	ETS (<20%)	ETS (≥20%)	ETS (<20%)
KRAS wt (ITT)						
n	205	64	134	38	71	26
Median OS (95% CI), months	30.1 (27.2-33.8)	16.4 (11.1-21.5)	29.1 (25.7-32.8)	16.9 (8.8-22.8)	31.7 (26.3-40.5)	15 (9.6-18.7)
Median PFS (95% CI), months	12.7 (11.1-14.2)	5.5 (3.6-7.4)	11.8 (11.1-14.2)	6.3 (3.6-7.7)	12.7 (10.3-15.2)	4.1 (2.4-5.9)
RAS wt						
n	130	29	83	20	47	9
Median OS (95% CI), months	30.3 (26.3-33.2)	16.4 (10.3-31.2)	29.7 (24.5-32.8)	16.9 (8.2-37.2)	31.7 (26.0-40.5)	15.5 (3.3-NE)
Median PFS (95% CI), months	14.0 (11.2-14.9)	7.5 (3.6-16.6)	14.0 (11.1-16.2)	7.7 (1.9-16.6)	13.0 (10.3-15.4)	5.3 (1.6-NE)

Abbreviations: ETS = early tumor shrinkage; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; NE = not estimable; OS = overall survival; PFS = progression-free survival; wt = wild type.

(IQR, 38.1-79.0), respectively. The median time to tumor size nadir was 5.9 months (95% CI, 5.6-7.6) within the overall DpR-evaluable population; median time to nadir was 5.9 months (95% CI, 5.6-7.6) and 7.4 months (95% CI, 5.1-9.2) within the FOLFOX and FOLFIRI treatment subgroups, respectively. Notably, there appeared to be an association between the extent of DpR and time to tumor size nadir: patients experiencing a deeper response seemed to achieve maximal tumor shrinkage later than

Table 4 AEs (≥5% Grade 3/4) in *KRAS* wt and *RAS* wt Populations

AE	*KRAS* wt (ITT), n (%)				*RAS* wt, n (%)			
	Cetuximab + FOLFOX (n = 188)		Cetuximab + FOLFIRI (n = 101)		Cetuximab + FOLFOX (n = 110)		Cetuximab + FOLFIRI (n = 57)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	180 (95.7)	151 (80.3)	99 (98.0)	75 (74.3)	108 (98.2)	91 (82.7)	57 (100)	47 (82.5)
Neutropenia	101 (53.7)	73 (38.8)	56 (55.4)	36 (35.6)	64 (58.2)	47 (42.7)	35 (61.4)	22 (38.6)
Rash	115 (61.2)	29 (15.4)	55 (54.5)	4 (4.0)	70 (63.6)	16 (14.5)	38 (66.7)	4 (7.0)
Peripheral neuropathy	63 (33.5)	20 (10.6)	4 (4.0)	0	43 (39.1)	12 (10.9)	3 (5.3)	0
Diarrhea	81 (43.1)	16 (8.5)	59 (58.5)	12 (11.9)	46 (41.8)	9 (8.2)	35 (61.4)	9 (15.8)
Paronychia	49 (26.1)	14 (7.4)	33 (32.7)	10 (9.9)	32 (29.1)	11 (10.0)	18 (31.6)	7 (12.3)
Peripheral sensory neuropathy	34 (18.1)	12 (6.4)	1 (1.0)	0	19 (17.3)	7 (6.4)	1 (1.8)	0
Hypokalemia	33 (17.6)	11 (5.9)	23 (22.8)	11 (10.9)	21 (19.1)	8 (7.3)	17 (29.8)	9 (15.8)
Mucosal inflammation	54 (28.7)	11 (5.9)	15 (14.9)	2 (2.0)	36 (32.7)	5 (4.5)	7 (12.3)	1 (1.8)
Stomatitis	52 (27.7)	8 (4.3)	31 (30.7)	9 (8.9)	33 (30.0)	4 (3.6)	20 (35.1)	6 (10.5)
Palmar–plantar erythrodysesthesia syndrome	30 (16.0)	8 (4.3)	11 (10.9)	2 (2.0)	16 (14.5)	6 (5.5)	7 (12.3)	2 (3.5)
Fatigue	48 (25.5)	6 (3.2)	21 (20.8)	4 (4.0)	33 (30.0)	5 (4.5)	15 (26.3)	3 (5.3)
Hypophosphatemia	6 (3.2)	4 (2.1)	4 (4.0)	3 (3.0)	3 (2.7)	2 (1.8)	4 (7.0)	3 (5.3)
Dermatitis acneiform	21 (11.2)	3 (1.6)	12 (11.9)	5 (5.0)	16 (14.5)	2 (1.8)	6 (10.5)	4 (7.0)
Hyperglycemia	5 (2.7)	3 (1.6)	4 (4.0)	3 (3.0)	4 (3.6)	2 (1.8)	4 (7.0)	3 (5.3)
Leukopenia	28 (14.9)	3 (1.6)	24 (23.8)	6 (5.9)	18 (16.4)	1 (0.9)	17 (29.8)	6 (10.5)
Vomiting	65 (34.6)	3 (1.6)	38 (37.6)	5 (5.0)	33 (30.0)	2 (1.8)	25 (43.9)	3 (5.3)
Intestinal obstruction	2 (1.1)	2 (1.1)	6 (5.9)	4 (4.0)	1 (0.9)	1 (0.9)	5 (8.8)	4 (7.0)
Composite Categories of Special Interest								
Acnelike rash	150 (79.8)	35 (18.6)	76 (75.2)	11 (10.9)	91 (82.7)	18 (16.4)	46 (80.7)	10 (17.5)
Infusion-related reactions	23 (12.2)	9 (4.8)	1 (1.0)	0	12 (10.9)	5 (4.5)	1 (1.8)	0
Cardiac events	7 (3.7)	3 (1.6)	10 (9.9)	3 (3.0)	5 (4.5)	2 (1.8)	9 (15.8)	3 (5.3)
Septic events	4 (2.1)	4 (2.1)	4 (4.0)	4 (4.0)	3 (2.7)	3 (2.7)	3 (5.3)	3 (5.3)

Inclusion and sorting of AEs was based on grade 3/4 AEs that were observed in ≥ 5% of patients in either treatment subgroup in either population.
Abbreviations: AE = adverse event; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; ITT = intention-to-treat; wt = wild type.

patients with a less deep response (Supplemental Figure 2; available in the online version). Furthermore, the data suggest that there was a relationship between the extent of DpR and PFS/OS (Supplemental Figure 3; available in the online version).

Safety

Neutropenia was the most common grade 3/4 AE in both treatment subgroups of the *KRAS* wt population. Grade 3/4 infusion-related reactions occurred in 4.8% of patients receiving cetuximab plus FOLFOX and in none of those receiving cetuximab plus FOLFIRI. Grade 3/4 acne-like rash occurred in 18.6% and 10.9% of patients receiving cetuximab in combination with FOLFOX and FOLFIRI, respectively (Table 4).

Serious AEs (SAEs) were experienced by 34.0% of patients treated with FOLFOX plus cetuximab and 36.6% of patients receiving FOLFIRI plus cetuximab in the *KRAS* wt population; pyrexia (3.7%) was the most common SAE among patients in the FOLFOX treatment subgroup, whereas intestinal obstruction (5.0%) was the most frequent SAE in the FOLFIRI treatment subgroup; the only other SAEs that occurred with $\geq$ 3% incidence in either treatment subgroup of the *KRAS* wt population were febrile neutropenia and diarrhea in the FOLFOX subgroup and neutropenia, diarrhea, pyrexia, hypokalemia, and deep vein thrombosis in the FOLFIRI subgroup. Within the *KRAS* wt population, 11.7% and 16.8% of patients in the FOLFOX and FOLFIRI subgroups experienced AEs leading to the permanent discontinuation of cetuximab, respectively. Skin and subcutaneous tissue disorders were responsible for permanent discontinuation of cetuximab in 2.7% and 3.0% of patients in the FOLFOX and FOLFIRI treatment subgroups, respectively. Oxaliplatin was permanently discontinued before confirmation of progressive disease in 33.5% of patients receiving FOLFOX, while irinotecan was permanently discontinued in 15.8% of patients receiving FOLFIRI. There were 4 deaths reported in the study; 2 of them were categorized as due to disease complication with no evidence of progression, the third one (interstitial pneumonitis) as being reasonably related to cetuximab plus FOLFOX combination as assessed by the investigator, and the last one as treatment related due to unexplained death with missing relationship.

The safety profile of cetuximab plus chemotherapy in both *RAS* wt treatment subgroups was comparable with that described above for the *KRAS* wt population. No new safety findings were identified (Table 4).

Discussion

The APEC study has shown that once-every-2-weeks cetuximab with either FOLFOX or FOLFIRI is effective as a first-line therapy for mCRC in this Asia-Pacific study population. The observed median OS for the *KRAS* wt and *RAS* wt populations is similar to those reported in prior first-line pivotal studies involving weekly cetuximab plus FOLFOX or FOLFIRI that enrolled mainly white patients.[2,5,14-16]

Cetuximab compliance in the APEC study was high, and the overall occurrence of AEs, including grade 3/4 acneiform skin reactions, was similar to historical rates for the weekly administration schedule of cetuximab plus chemotherapy and chemotherapy alone.[2,5]

Notably, the CECOG CORE 1.2.002 study has shown that the efficacy and safety of cetuximab in combination with FOLFOX4 is similar when administered weekly versus once every 2 weeks in patients with *KRAS* wt mCRC.[7,14] These observations are further substantiated by data from the OPTIMIX and NORDIC 7.5 studies demonstrating the efficacy and tolerability of a once-every-2-weeks cetuximab regimen.[8,9] Accordingly, once-every-2-weeks cetuximab may represent an alternative to weekly administration.

Although this was not a randomized study and no formal statistical hypotheses were planned to be evaluated between treatment subgroups, as expected, the data suggest that cetuximab can be effectively combined with either chemotherapy regimen (FOLFOX or FOLFIRI). These findings are consistent with the CRYSTAL, OPUS, FIRE-3, and CALGB 80405 trials.[2,5,15-17] Furthermore, the safety profile within both treatment subgroups of the *KRAS* wt and *RAS* wt populations was comparable, and no new safety findings were identified.

Rates of mutation in *RAS* (*KRAS/NRAS* exons 2-4), *BRAF*, and *PIK3CA* were consistent with those of previous studies,[2,5,18] suggesting that the mutation frequencies of these genes appear to be similar between Asians and whites. In accordance with our expectations, BORR, median PFS, and median OS were relatively low in patients with *RAS* mt mCRC, as compared with patients with *RAS* wt mCRC. Furthermore, relative to the *KRAS* wt population, the efficacy of cetuximab was numerically improved in the *RAS* wt population, demonstrating that expanded testing of *RAS* mutational status reveals a population of patients with better clinical outcomes. These results underline the importance of expanded *RAS* testing to select patients most likely to benefit from therapy with cetuximab.

A prognostic role for *BRAF* and *PIK3CA* in mCRC has been suggested previously, although the potential predictive value of these 2 biomarkers remains controversial.[19,20] In our study, there appeared to be a trend toward improved outcomes in the *BRAF/PIK3CA* wt population compared with the mt populations; however, further studies with larger numbers of patients with *BRAF/PIK3CA* mt tumors are needed to provide a conclusive result.

Prior studies have indicated that patients with EGFR-undetectable mCRC can respond to cetuximab.[21,22] Although the relatively small number of patients in certain subgroups is a limitation of the present study, our results appear to be broadly consistent with these previous observations.

Although the number of patients in certain subgroups of our study was relatively small, our results suggest that patients with ETS or high DpR may have derived increased benefit, in terms of PFS and OS, from cetuximab plus chemotherapy. These findings are similar to earlier subgroup analyses of analogous pivotal studies involving weekly cetuximab, as ETS has been correlated with improved long-term outcome in patients with *KRAS/RAS* wt mCRC treated with weekly cetuximab in the CRYSTAL and OPUS (at 8 weeks) as well as the FIRE-3 (at 6 weeks) trials[23,24]; similarly, extent of DpR has been associated with survival outcomes in CRYSTAL, OPUS, and FIRE-3.[24,25]

Our data further suggest that there are patients with *RAS* wt mCRC who may benefit from the continuation of treatment with cetuximab plus FOLFOX or FOLFIRI rather than treatment breaks (eg, upon ETS) to achieve maximal tumor reduction. Indeed, in our study, the median duration of cetuximab treatment was relatively

long (≈7.5 months) and exceeded the median duration of chemotherapy administration (especially in the subgroup treated with FOLFOX and less pronounced in the FOLFIRI subgroup; Supplemental Table 3; available in the online version). The relatively long median PFS observed here (11.1 months in the *KRAS* wt population) is therefore noteworthy and consistent with the results of COIN-B,[26] suggesting that patients may derive benefit from the use of cetuximab as a maintenance regimen.

Conclusion

The present observations suggest that cetuximab plus FOLFOX or FOLFIRI in a once-every-2-week regimen is effective and tolerable as first-line therapy in this Asia-Pacific study population. Thus, once-every-2-weeks cetuximab may represent an alternative to weekly administration in patients with *KRAS* wt or *RAS* wt mCRC.

Clinical Practice Points

- A chemotherapy doublet (either FOLFOX or FOLFIRI) plus weekly cetuximab represents standard-of-care first-line therapy for patients with *KRAS*/*RAS* wt mCRC. Indeed, the safety and efficacy of such a weekly regimen in patients with *KRAS*/*RAS* wt mCRC has been firmly established by the pivotal first-line CRYSTAL and OPUS studies.
- The present nonrandomized phase 2 trial investigated whether the well-tolerated beneficial treatment effect observed in patients with *KRAS*/*RAS* wt mCRC on adding weekly cetuximab to first-line chemotherapy persisted when the regimen was administered according to a once-every-2-weeks dosing schedule.
- Our findings suggest an activity and safety profile for 500 mg/m^2 cetuximab once every 2 weeks plus chemotherapy is similar to that reported in prior first-line pivotal studies involving weekly administration of 250 mg/m^2 after an initial dose of 400 mg/m^2.
- Accordingly—consistent with observations from the CECOG CORE 1.2.002, NORDIC 7.5, and OPTIMIX trials—the impact of the present study on future clinical practice is empirical validation of the effectiveness and tolerability of once-every-2-weeks cetuximab plus first-line chemotherapy in patients with *KRAS*/*RAS* wt mCRC, suggesting that a once-every-2-weeks dosing schedule may represent an alternative to weekly administration.
- Our study further establishes that cetuximab can be effectively combined with either FOLFOX or FOLFIRI, a finding that is supported by data from the CRYSTAL, OPUS, FIRE-3, and CALGB 80405 trials.

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Disclosure

F.B. is an employee of Merck KGaA, Darmstadt, Germany. S.C. is an employee of Merck Serono, Mumbai, India. These authors disclose the following relationships with Merck KGaA: G.C. has received research funding, L.S. has received honoraria, T.P. has provided consulting, B.M. has received honoraria, and R.L. has provided consulting. The other authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clcc.2016.08.005.

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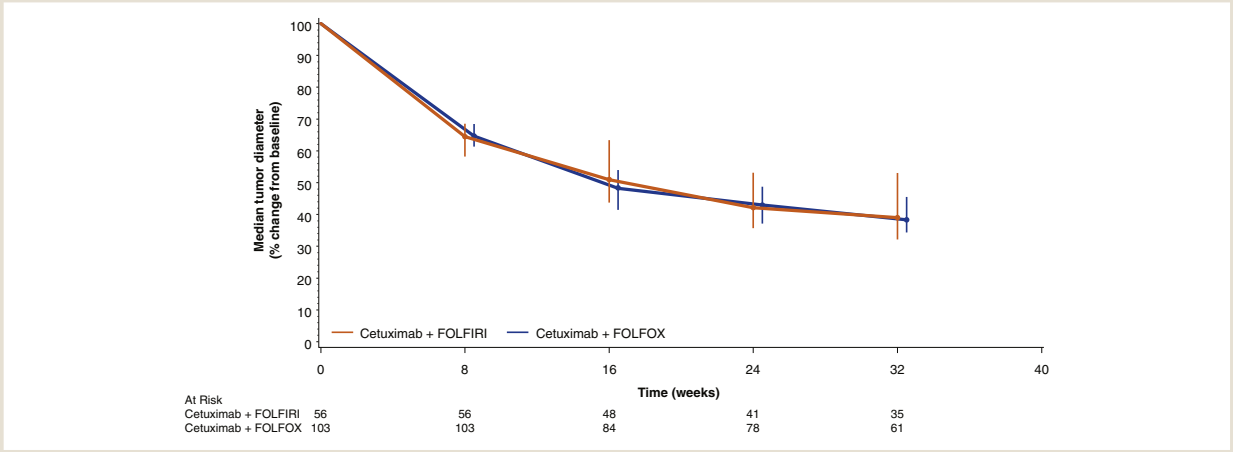
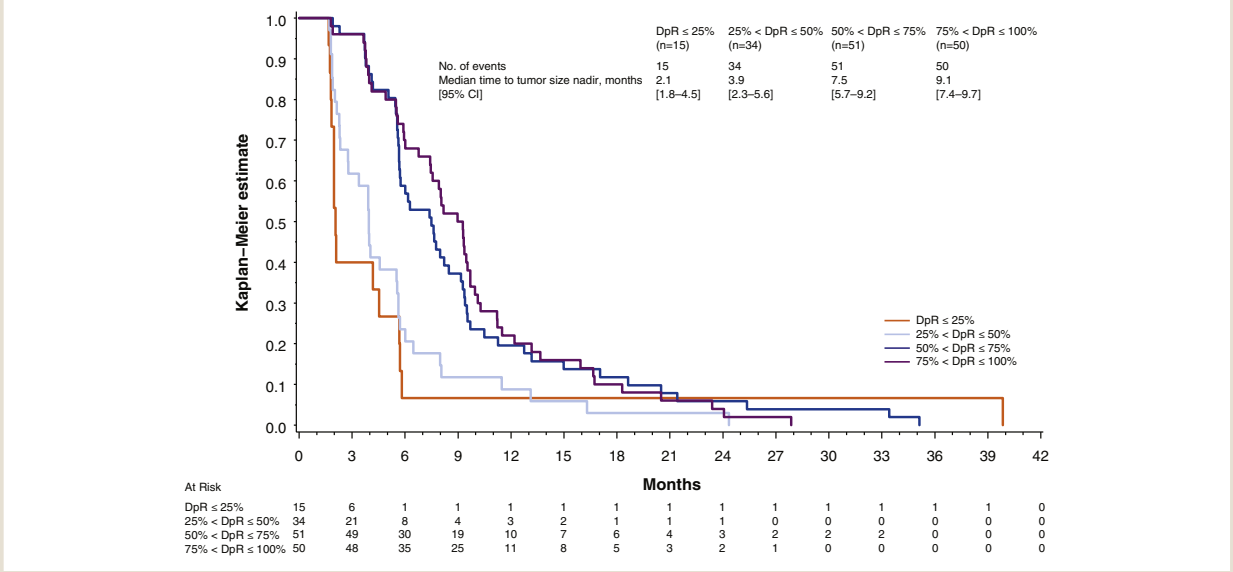
Supplemental Figure 1 Extent of Tumor Shrinkage in Nonprogresssing Patients Within *RAS* wt Population



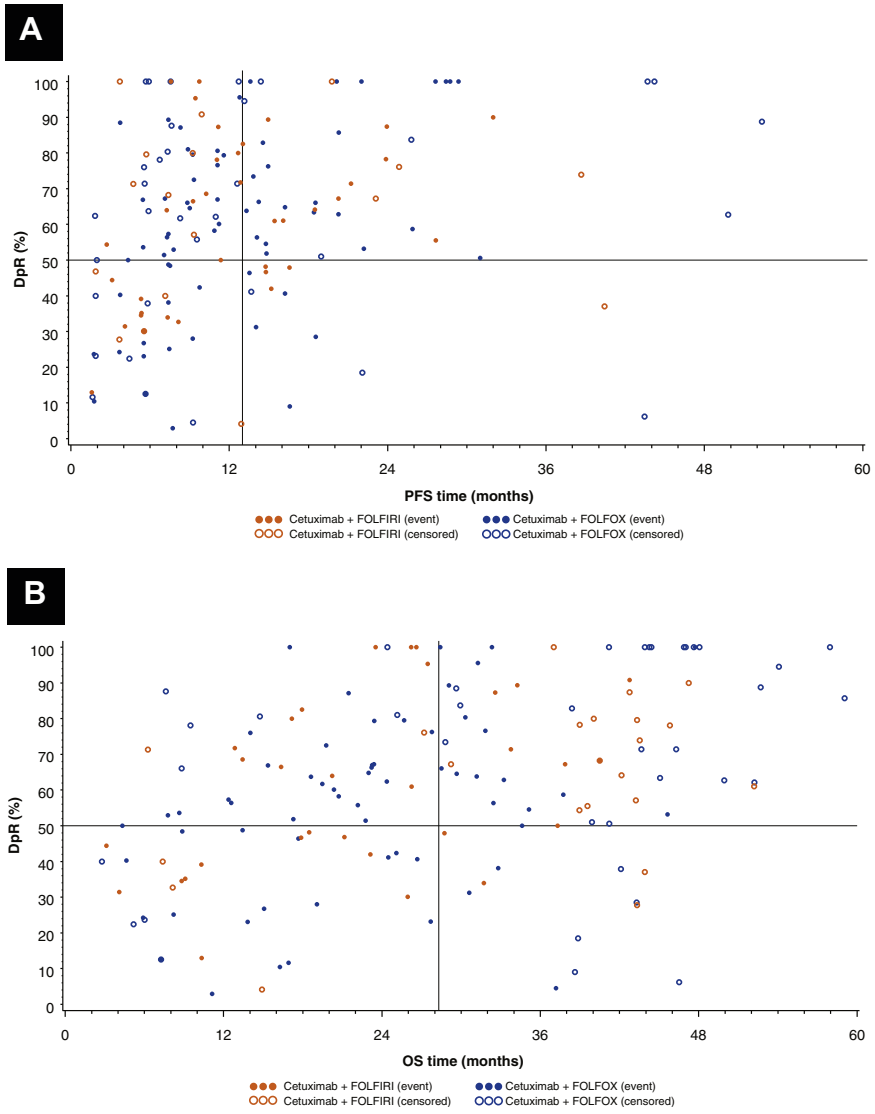
Abbreviations: FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; wt = wild type.

Supplemental Figure 2 Association Between Extent of DpR and Time to Tumor Size Nadir in *RAS* wt Population



Abbreviations: DpR = depth of response; wt = wild type.

Supplemental Figure 3 Relationship Between Extent of DpR and PFS (A) and OS (B) in *RAS* wt Population. Crosshairs Denote Median DpR (%) and PFS/OS Time (Months)



Abbreviations: DpR = depth of response; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; OS = overall survival; PFS = progression-free survival; wt = wild type.

Supplemental Table 1 Rate of Biomarker Mutation Detection

Mutation	Total (n = 289)[a,b]	Cetuximab + FOLFOX (n = 188)[a,b]	Cetuximab + FOLFIRI (n = 101)
***KRAS*, n (%)**			
Exon 2	10 (3.5)	6 (3.2)	4 (4.0)
Exon 3	6 (2.1)	4 (2.1)	2 (2.0)
Exon 4	7 (2.4)	4 (2.1)	3 (3.0)
***NRAS*, n (%)**			
Exon 2	5 (1.7)	4 (2.1)	1 (1.0)
Exon 3	9 (3.1)	7 (3.7)	2 (2.0)
Exon 4	0	0	0
***BRAF*, n (%)**	16 (5.5)	10 (5.3)	6 (5.9)
***PIK3CA*, n (%)**			
Exon 9	10 (3.5)	7 (3.7)	3 (3.0)
Exon 20	3 (1.0)	2 (1.1)	1 (1.0)
***BRAF* mt and/or *PIK3CA* mt, n (%)**	29 (10.0)	19 (10.1)	10 (10.0)
EGFR, n			
Evaluable	154	100	54
Detectable	124	81	43
Undetectable	30	19	11

Abbreviations: EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; mt = mutant; wt = wild type.
[a]One patient had 2 *RAS* mutations; the total number of patients with *RAS* mt mCRC was 36.
[b]One patient had 2 *BRAF* and/or *PIK3CA* mutations; the total number of patients with *BRAF* mt and/or *PIK3CA* mt mCRC was 28.

Supplemental Table 2 Treatment Exposure in *KRAS* wt Population

Relative Dose Intensity	Cetuximab + FOLFOX (n = 188), n (%)	Cetuximab + FOLFIRI (n = 101), n (%)
Cetuximab		
<60%	6 (3.2)	2 (2.0)
60%-80%	36 (19.1)	24 (23.8)
80%-90%	33 (17.6)	21 (20.8)
≥90%	113 (60.1)	54 (53.5)
Irinotecan		
<60%		12 (11.9)
60%-80%	—	41 (40.6)
80%-90%		19 (18.8)
≥90%		29 (28.7)
Oxaliplatin		
<60%	21 (11.2)	
60%-80%	76 (40.4)	—
80%-90%	33 (17.6)	
≥90%	58 (30.9)	
5-FU		
<60%	28 (14.9)	15 (14.9)
60%-80%	79 (42.0)	38 (37.6)
80%-90%	27 (14.4)	18 (17.8)
≥90%	54 (28.7)	30 (29.7)

Abbreviations: 5-FU = 5-fluorouracil; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; wt = wild type.

Supplemental Table 3 Duration of Treatment (Weeks) in *KRAS* wt Population

Therapy	Cetuximab + FOLFOX (n = 188)	Cetuximab + FOLFIRI (n = 101)
Cetuximab		
Median	32.1	33.3
Q1-Q3	16.1-50.9	16.4-52.0
Irinotecan		
Median	—	32.0
Q1-Q3		16.1-47.1
Oxaliplatin		
Median	25.4	—
Q1-Q3	15.9-31.9	
5-FU		
Median	27.8	32.0
Q1-Q3	16.9-41.6	16.1-46.1

Abbreviations: 5-FU = 5-fluorouracil; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; wt = wild type.

Supplemental Table 4 Post–First-Line Treatments Received in *KRAS* wt Population

Therapy	Total (n = 289), n (%)	Cetuximab + FOLFOX (n = 188), n (%)	Cetuximab + FOLFIRI (n = 101), n (%)
Any Anticancer Therapy	171 (59.2)	110 (58.5)	61 (60.4)
Post–First-Line Therapy			
Radiotherapy	37 (12.8)	19 (10.1)	18 (17.8)
Chemotherapy	151 (52.2)	103 (54.8)	48 (47.5)
Surgery	33 (11.4)	17 (9.0)	16 (15.8)
Other[a]	60 (20.8)	37 (19.7)	23 (22.8)
No. of Further Lines of Therapy			
≤2	142 (49.1)	89 (47.3)	53 (52.5)
>2	29 (10.0)	21 (11.2)	8 (7.9)
Combination Therapy	131 (45.3)	87 (46.3)	44 (43.6)
Chemotherapy + radiotherapy	4 (1.4)	1 (0.5)	3 (3.0)
Chemotherapy + surgery + other[a]	2 (0.7)	2 (1.1)	0
Chemotherapy + other	44 (15.2)	30 (16.0)	14 (13.9)
Chemotherapy combination only	113 (39.1)	72 (38.3)	41 (40.6)

Abbreviations: FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; wt = wild type.
[a]Includes biologics cetuximab, bevacizumab, regorafenib, panitumumab, and INC280 (clinical trial drug).

Supplemental Table 5 Efficacy in *BRAF/PIK3CA*-Evaluable Subpopulations

Therapy	Evaluable	*BRAF* wt, *PIK3CA* wt	*BRAF* and/or *PIK3CA* mt	*BRAF* wt, *PIK3CA* mt	*BRAF* mt, *PIK3CA* wt	*BRAF* mt, *PIK3CA* mt
Total						
n	203	175	28	12	15	1
BORR (95% CI), %	59.1 (52.0-65.9)	61.1 (53.5-68.4)	46.4 (27.5-66.1)	58.3 (27.7-84.8)	33.3 (11.8-61.6)	100.0 (2.5-100.0)
PFS (95% CI), months	11.1 (9.2-13.5)	11.5 (10.3-14.6)	7.4 (5.5-7.8)	7.5 (5.6-13.5)	6.4 (3.7-7.8)	5.5 (NE)
OS (95% CI), months	26.7 (23.3-30.1)	28.7 (26.2-32.8)	13.8 (8.6-17.9)	17.7 (12.8-26.0)	9.0 (4.6-17.9)	8.6 (NE)
Cetuximab + FOLFOX						
n	134	116	18	8	9	1
BORR (95% CI), %	59.0 (50.1-67.4)	61.2 (51.7-70.1)	44.4 (21.5-69.2)	75.0 (34.9-96.8)	11.1 (0.3-48.2)	100.0 (2.5-100.0)
PFS (95% CI), months	11.0 (8.3-13.6)	11.5 (9.3-14.9)	7.4 (3.7-7.8)	8.3 (2.6-13.5)	4.6 (1.6-7.7)	5.5 (NE)
OS (95% CI), months	26.7 (22.2-30.3)	28.5 (23.4-33.2)	11.1 (4.6-17.7)	17.7 (2.6-25.7)	6.9 (2.8-11.1)	8.6 (NE)
Cetuximab + FOLFIRI						
n	69	59	10	4	6	0
BORR (95% CI), %	59.4 (46.9-71.1)	61.0 (47.4-73.5)	50.0 (18.7-81.3)	25.0 (0.6-80.6)	66.7 (22.3-95.7)	NE
PFS (95% CI), months	11.4 (8.1-14.9)	11.4 (9.3-15.4)	7.3 (5.3-14.8)	5.9 (5.6-.)	11.0 (5.3-.)	NE
OS (95% CI), months	26.6 (21.5-33.8)	28.7 (23.5-37.3)	18.2 (8.8-26.0)	20.5 (12.8-42.8)	18.2 (8.8-.)	NE

Abbreviations: BORR = best confirmed overall response rate; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; mt = mutant; NE = not estimable; OS = overall survival; PFS = progression-free survival; wt = wild type.

Supplemental Table 6 Efficacy in EGFR-Evaluable Subpopulations

Therapy	Evaluable	EGFR Detectable	EGFR Undetectable
Total			
n	154	124	30
BORR (95% CI), %	53.9 (45.7-62.0)	56.5 (47.3-65.3)	43.3 (25.5-62.6)
PFS (95% CI), months	11.1 (8.3-13.6)	11.1 (8.1-14.1)	11.1 (5.5-22.1)
OS (95% CI), months	28.4 (24.4-33.8)	28.7 (23.7-34.6)	27.8 (18.2-37.7)
Cetuximab + FOLFOX			
n	100	81	19
BORR (95% CI), %	56.0 (45.7-65.9)	58.0 (46.5-68.9)	47.4 (24.4-71.1)
PFS (95% CI), months	11.1 (7.7-14.2)	11.1 (7.5-14.2)	11.1 (7.7-23.0)
OS (95% CI), months	28.5 (23.7-34.2)	31.3 (23.7-35.2)	27.8 (16.9-31.8)
Cetuximab + FOLFIRI			
n	54	43	11
BORR (95% CI), %	50.0 (36.1-63.9)	53.5 (37.7-68.8)	36.4 (10.9-69.2)
PFS (95% CI), months	11.1 (7.4-16.6)	11.0 (7.4-16.6)	22.1 (2.4-27.7)
OS (95% CI), months	26.8 (17.2-40.5)	26.8 (16.6-37.3)	26.2 (5.3-NE)

Abbreviations: BORR = best confirmed overall response rate; EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = oxaliplatin/folinic acid/5-fluorouracil; NE = not estimable; OS = overall survival; PFS = progression-free survival.