Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial

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Summary

Background Since the 1990s, fluorouracil-based adjuvant chemotherapy has significantly reduced the risk of tumour recurrence in patients with stage III colon cancer. We aimed to assess whether the addition of cetuximab to standard adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy (FOLFOX4) in patients with stage III colon cancer improved disease-free survival (DFS).

Methods For this open-label, randomised phase 3 study done in nine European countries, we enrolled patients through an interactive voice response system to the central randomisation centre, with a central stratified permuted block randomisation procedure. We randomly assigned patients with resected (R0) stage III disease (1:1) to receive 12 cycles of FOLFOX4 twice a week with or without cetuximab. Patients were stratified by N-status (N1 *vs* N2), T-status (T1-3 *vs* T4), and obstruction or perforation status (no obstruction and no perforation *vs* obstruction or perforation or both). A protocol amendment (applied in June, 2008, after 2096 patients had been randomly assigned to treatment-restricted enrolment to patients with tumours wild-type at codons 12 and 13 in exon 2 of the *KRAS* gene (*KRAS* exon 2 wild-type). The primary endpoint was DFS. Analysis was intention to treat in all patients with *KRAS* exon 2 wild-type tumours. The study is registered at EudraCT, number 2005-003463-23.

Findings Between Dec 22, 2005, and Nov 5, 2009, 2559 patients from 340 sites in Europe were randomly assigned. Of these patients, 1602 had *KRAS* exon 2 wild-type tumours (intention-to-treat population), 791 in the FOLFOX4 plus cetuximab group and 811 in the FOLFOX4 group. Median follow-up was 3·3 years (IQR 3·2–3·4). In the experimental and control groups, DFS was similar in the intention-to-treat population (hazard ratio [HR] 1·05; 95% CI 0·85–1·29; p=0·66), and in patients with *KRAS* exon 2/*BRAF* wild-type (n=984, HR 0·99; 95% CI 0·76–1·28) or *KRAS* exon 2-mutated tumours (n=742, HR 1·06; 95% CI 0·82–1·37). We noted heterogeneous responses to the addition of cetuximab in preplanned subgroup analyses. Grade 3 or 4 acne-like rash (in 209 of 785 patients [27%] *vs* four of 805 [<1%]), diarrhoea (113 [14%] *vs* 70 [9%]), mucositis (63 [8%] *vs* 10 [1%]), and infusion-related reactions (55 [7%] *vs* 30 [4%]) were more frequent in patients treated with FOLFOX4 plus cetuximab than in those patients who received FOLFOX4 alone.

Interpretation The addition of cetuximab to FOLFOX4 did not improve DFS compared with FOLFOX4 alone in patients with *KRAS* exon 2 wild-type resected stage III colon cancer. This trial cannot conclude on the benefit of cetuximab in the studied population, but the heterogeneity of response suggests that further investigation of the role of FOLFOX4 plus cetuximab in specific patient subgroups is warranted.

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Introduction

Surgical resection offers a potential cure for patients with colon cancer; however, after resection of stage III tumours, up to 50% of patients develop recurrence and die from metastatic disease.[1] Since the 1990s, the risk of tumour recurrence has been reduced with fluorouracil-based adjuvant chemotherapy.[2–4] Findings of the MOSAIC study[5] showed significant improvements in disease-free survival and overall survival in patients with stage III colon cancer receiving infused fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) compared with fluorouracil and leucovorin alone, with 5-year disease-free survival (DFS) of 66·4% and 6-year overall survival of 72·9% in the experimental group. This degree of benefit was confirmed by the NSABP C-07 study[6,7] in patients receiving FLOX (bolus fluorouracil, leucovorin, and oxaliplatin) compared with bolus fluorouracil and leucovorin alone.

The addition of VEGF and EGFR antibodies to standard first-line chemotherapy regimens has significantly improved clinical outcomes in patients with metastatic colorectal cancer.[8–12] In the OPUS[9] and PRIME studies,[10,12] the clinical benefit reported from combination of an EGFR antibody with chemotherapy was restricted to patients with tumours wild-type at *KRAS* codons 12 and 13 in exon 2 (*KRAS* exon 2 wild-type); patients with tumours mutated at these loci (*KRAS* exon 2 mutated tumours)

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were harmed by EGFR antibodies.[9,10,12] In studies of chemorefractory metastatic colorectal cancer, patients with *KRAS* exon 2 mutations were resistant to EGFR antibodies.[13–15]

In patients with resectable stage III colon cancer, an interim analysis of the NCCTG N0147 phase 3 study[16] reported a failure to improve 3-year DFS when cetuximab was added to the modified sixth version of FOLFOX (mFOLFOX6). The addition of bevacizumab to oxaliplatin-based chemotherapy also did not prolong DFS in two large randomised studies in this setting.[17,18]

The Pan-European Trials in Alimentary traCt Cancer (PETACC-8) study investigated FOLFOX4 with or without cetuximab given to patients after curative resection of stage III colon cancer. This study came after a promising phase 2 study in metastatic colorectal cancer, which reported impressive response and disease control rates, suggesting a potential synergistic effect of this new treatment combination.[19] A protocol amendment to PETACC-8 was approved on June 17, 2008, to restrict enrolment to patients with *KRAS* exon 2 wild-type tumours, and the sample size was expanded. We did a planned interim analysis of efficacy and the final safety analysis in this patient population, including pre-planned subgroup analyses, and analysis of patients with *KRAS* exon 2 mutated tumours enrolled before the protocol amendment.

Methods

Study design and participants

We did this open-label randomised, controlled, multinational phase 3 study in patients aged between 18 and 75 years with pathologically confirmed stage III colon

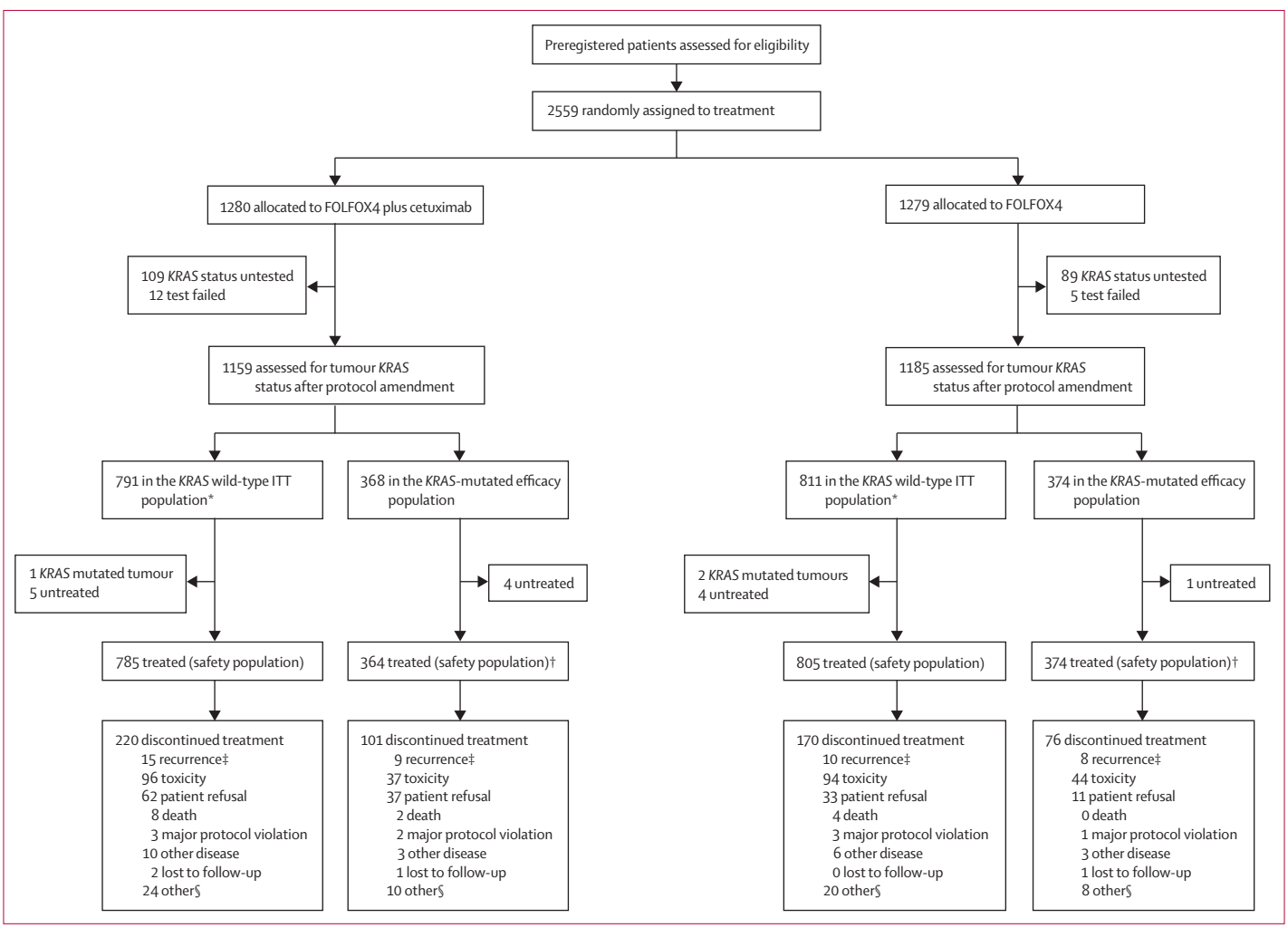

***Figure 1*: Trial profile**

ITT=intention to treat. *The *KRAS* exon 2 wild-type intention-to-treat population contained three patients with *KRAS*-mutated tumours accidently randomly assigned after the protocol amendment: one in the FOLFOX4 plus cetuximab group and two in the FOLFOX4 group. †In the safety population, in the FOLFOX4 plus cetuximab group, four patients with *KRAS* exon 2-mutated tumours were excluded because they were not treated, and one patient with a *KRAS* exon 2 mutated tumour randomly assigned after the protocol amendment was included (but excluded from the *KRAS* exon 2-mutated efficacy population). In the FOLFOX4 group, one patient with a *KRAS* exon 2-mutated tumour was untreated and excluded from the safety population, and one with a *KRAS* exon 2-mutated tumour randomly assigned after the protocol amendment was included in the safety population (but excluded from the *KRAS* exon 2-mutated efficacy population). ‡Recurrence included disease recurrence and second primary colon cancer or death due to disease recurrence. §Other included investigator decision, sponsor decision, error, and other.

adenocarcinoma. Other main inclusion criteria were: a *KRAS* exon 2 wild-type tumour (following the June 17, 2008, protocol amendment), curative (R0) resection at least 28 days before the start of treatment and between 14 and 56 days before randomisation, WHO performance status 0 or 1, life expectancy of 5 years or longer, adequate

	KRAS exon 2 wild-type ITT population		*KRAS* exon 2-mutated efficacy population	
	FOLFOX4 plus cetuximab (n=791)	FOLFOX4 (n=811)	FOLFOX4 plus cetuximab (n=368)	FOLFOX4 (n=374)
Sex				
Men	468 (59%)	468 (58%)	208 (57%)	196 (52%)
Women	323 (41%)	343 (42%)	160 (43%)	178 (48%)
Age (years)				
Median (range)	60·0 (19·0–75·0)	60·0 (21·0–75·0)	61·0 (23·0–74·0)	61·0 (26·0–75·0)
≤70 years	715 (90%)	738 (91%)	324 (88%)	327 (87%)
>70 years	76 (10%)	73 (9%)	44 (12%)	47 (13%)
WHO PS				
0	621 (79%)	637 (79%)	292 (79%)	298 (80%)
1	139 (18%)	136 (17%)	61 (17%)	60 (16%)
≥2*	1 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)
Missing	30 (4%)	35 (4%)	14 (4%)	15 (4%)
Pathological staging				
pT classification				
pT1–3	628 (79%)	668 (82%)	294 (80%)	280 (75%)
pT4	161 (20%)	142 (18%)	74 (20%)	94 (25%)
Missing	2 (<1%)	1 (<1%)	0	0
pN classification				
pN1	486 (61%)	510 (63%)	237 (64%)	239 (64%)
pN2	305 (39%)	301 (37%)	131 (36%)	135 (36%)
Bowel obstruction or perforation, or both	147 (19%)	146 (18%)	74 (20%)	80 (21%)
Type of surgery†				
Open	540 (68%)	557 (69%)	269 (73%)	279 (75%)
Laparoscopic	251 (32%)	252 (31%)	99 (27%)	92 (25%)
Unknown	0	2 (<1%)	0	3 (1%)
Tumour localisation				
Left	499 (63%)	517 (64%)	200 (54%)	203 (54%)
Right	286 (36%)	284 (35%)	159 (43%)	161 (43%)
Both	5 (1%)	4 (<1%)	9 (2%)	6 (2%)
Missing	1 (<%)	6 (<1%)	0	4 (1%)
Histopathology grade				
G1–2	632 (80%)	641 (79%)	305 (83%)	301 (80%)
G3–4	148 (19%)	160 (20%)	59 (16%)	67 (18%)
Missing	11 (1%)	10 (1%)	4 (1%)	6 (2%)
BRAF mutation status				
Wild-type	492 (62%)	492 (61%)	..	..
Mutated	79 (10%)	71 (9%)	..	..
Non-informative	34 (4%)	34 (4%)	..	..
Missing	186 (24%)	214 (26%)	..	..
EGFR expression status			..	..
Detectable	391 (49%)	405 (50%)	211 (57%)	211 (56%)
Undetectable	345 (44%)	349 (43%)	129 (35%)	138 (37%)
Missing	55 (7%)	57 (7%)	28 (8%)	25 (7%)

Data are n (%) unless otherwise stated. ITT=intention to treat. FOLFOX4=adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy. PS=performance status. *One patient randomly assigned to receive FOLFOX4 had WHO PS 3. †Patients could receive different types of surgery; if they received open and laparoscopic surgery, laparoscopic was not counted.

***Table 1*: Patient baseline and tumour characteristics in the *KRAS* populations**

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haematological and organ function, carcinoembryogenic antigen less than 1·5 times the upper limit of normal after surgery, and signed written informed consent.

When the trial was conceived in 2004, CT scanning was not standard for baseline patient assessment in all participating countries and therefore was recommended, but not mandatory, for patients being considered for entry into the trial.

Main patient exclusion criteria were: previous chemotherapy, abdominal or pelvic irradiation; major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study treatment; metastatic spread at baseline; rectal cancer located within 15 cm from the anal verge by endoscopy or under the peritoneal reflection at surgery or having received radiation therapy before surgery; presence of inflammatory bowel disease; known hypersensitivity reaction to study treatments; clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high-risk of uncontrolled arrhythmia; previous cancer in the past 5 years except basal cell carcinoma of the skin or in-situ carcinoma of the cervix, or both; history of or present evidence of CNS disease or peripheral neuropathy of grade 1 or higher (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 3.0), and pregnancy or breastfeeding.

The study was done in accordance with the Declaration of Helsinki (amended 2000) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice and approved by the appropriate Ethics Committees.

	KRAS exon 2 wild-type safety population		*KRAS* exon 2-mutated safety population	
	FOLFOX4 plus cetuximab (N=785)	FOLFOX4 (N=805)*	FOLFOX4 plus cetuximab (N=364)	FOLFOX4 (N=374)
Cetuximab				
Treatment duration (weeks)	24·0 (13·0–26·6)	2·1	N/A	..
Number of infusions (IQR)	23·0 (12·0–24·0)	2·0	23·0 (13·0–24·0)	..
RDI				..
80–90%	168 (21%)	0	72 (20%)	..
>90%	442 (56%)	1 (<1%)	216 (59%)	
Missing	2 (<1%)	0	2 (1%)	..
Dose reductions				
1	73 (9%)	..	37 (10%)	..
≥2	18 (2%)	..	14 (4%)	..
Missing	34 (4%)	..	14 (4%)	..
Oxaliplatin				
Treatment duration (weeks)	24·0 (18·0–26·0)	24·1 (20·0–27·0)	N/A	N/A
Number of infusions (IQR)	11·0 (8·0–12·0)	11·0 (9·0–12·0)	N/A	N/A
RDI				..
80–90%	259 (33%)	275 (34%)	113 (31%)	131 (35%)
>90%	337 (43%)	291 (36%)	142 (39%)	129 (34%)
Missing	2 (<1%)	0	0	0
Dose reductions				
1	255 (32%)	286 (36%)	136 (37%)	144 (39%)
≥2	33 (4%)	38 (5%)	19 (5%)	6 (2%)
Missing	2 (<1%)	0	0	0
Fluorouracil†				
Treatment duration (weeks)	24·9 (23·9–27·0)	25·7 (23·9–28·0)	N/A	N/A
Number of infusions	24·0 (22·0–24·0)	24·0 (24·0–24·0)	24·0 (22·0–24·0)	24·0 (24·0–24·0)
RDI				
80–90%	212 (27%)	204 (25%)	88 (24%)	109 (29%)
>90%	312 (40%)	300 (37%)	137 (37%)	125 (33%)
Missing	2 (<1%)	0	0	0
Dose reductions				
1	200 (25%)	193 (24%)	104 (29%)	93 (25%)
≥2	156 (20%)	170 (21%)	78 (21%)	71 (19%)
Missing	2 (<1%)	0	0	0

Data are median (IQR) or n (%). FOLFOX4=adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy. N/A=not available. RDI=relative dose intensity.*One patient given FOLFOX4 plus cetuximab received two cetuximab injections; therefore, the median treatment duration with cetuximab was 2·1 and the median number of infusions was 2·0 in the FOLFOX4 alone group. †Values calculated from the combination of fluorouracil bolus and continuous infusions.

***Table 2*: Treatment exposure in the *KRAS* safety populations**

Randomisation and masking

We randomly assigned (1:1) eligible patients to receive FOLFOX4 plus cetuximab or FOLFOX4 alone. Patients were enrolled through an interactive voice response system by the central randomisation centre. A central stratified permuted block randomisation procedure was used. Stratification factors were N status (N1 *vs* N2), T-status (T1-3 *vs* T4), and obstruction and perforation status (no obstruction and no perforation *vs* obstruction or perforation). The study was open-label in nature.

Procedures

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with or without weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic effect, any disease recurrence, or withdrawal of consent.

Tumour assessment included abdominal and pelvic imaging (CT, MRI, or as minimal requirement ultrasound) and a thoracic CT scan or at least chest radiograph, done at screening and at least every 6 months (within 4 weeks) after surgery for the first 5 years and then every year (within 4 weeks). Recurrence was established either histologically or by imaging.

We coded adverse events with the Medical Dictionary for Regulatory Activities (MedDRA version 14.0). Toxic effects were graded according to the NCI-CTCAE (version 3.0). Detection of tumour *KRAS* (codons 12 and 13) and *BRAF*

(V600E) mutations, and EGFR expression were done centrally (*KRAS* testing done at U755 INSERM, Paris, France, and EGFR staining done at Clermont Ferrand and Boulogne). *KRAS* testing was done in real time to establish eligibility for all patients following the protocol amendment restricting the trial population to *KRAS* exon 2 wild-type patients. All *KRAS* testing was done on DNA extracted from formalin-fixed paraffin-embedded sections after macro-dissection. The presence of *KRAS* mutations was established by an allelic discrimination assay. Both *KRAS* and *BRAF* tumour mutations were detected as described previously (appendix).[14,20] EGFR expression was established by immunohistochemistry on deparaffinised tumour sections fixed on slides with the EGFR pharmDX kit (DAKO Glostrup, Denmark) according to the manufacturer's guidelines on a DAKO autostainer.

Outcomes

The primary endpoint was DFS in patients with *KRAS* exon 2 wild-type tumours, analysed in the intention-to-treat population comprising all patients with *KRAS* exon 2 wild-type tumours. DFS was defined as the interval from randomisation to locoregional or metastatic recurrence, the appearance of a secondary colon or rectal cancer, or death, whichever occurred first.

Secondary endpoints included: overall survival (including 5-year and 7-year survival), treatment compliance, the identification of prognostic and predictive factors for relapse or treatment efficacy or both, and the safety profile. Overall survival was defined as the time from randomisation to death.

Statistical analysis

For sample size calculations for the *KRAS* exon 2 wild-type intention-to-treat population, in patients already enrolled before the protocol ammendment on June 17, 2008 (n=2096), we expected the occurrence of evaluable patients with *KRAS* exon 2 wild-type tumours to be at least 46% (n=957). The null hypothesis was that DFS was equal in the two treatment groups. A 25% reduction in the risk of disease recurrence or death (hazard ratio 0·75) was the target (alternative hypothesis) in these patients when cetuximab was added to adjuvant chemotherapy, requiring 566 events for detection, with a two-sided log-rank test with type I error rate of α=5% for a power of 90% (β=10%). After June 17, 2008, a further 450 patients with *KRAS* exon 2 wild-type tumours were planned for enrolment in the period November, 2008, to June, 2009. Therefore, our total anticipated sample size was 1407 patients with *KRAS* exon 2 wild-type tumours.

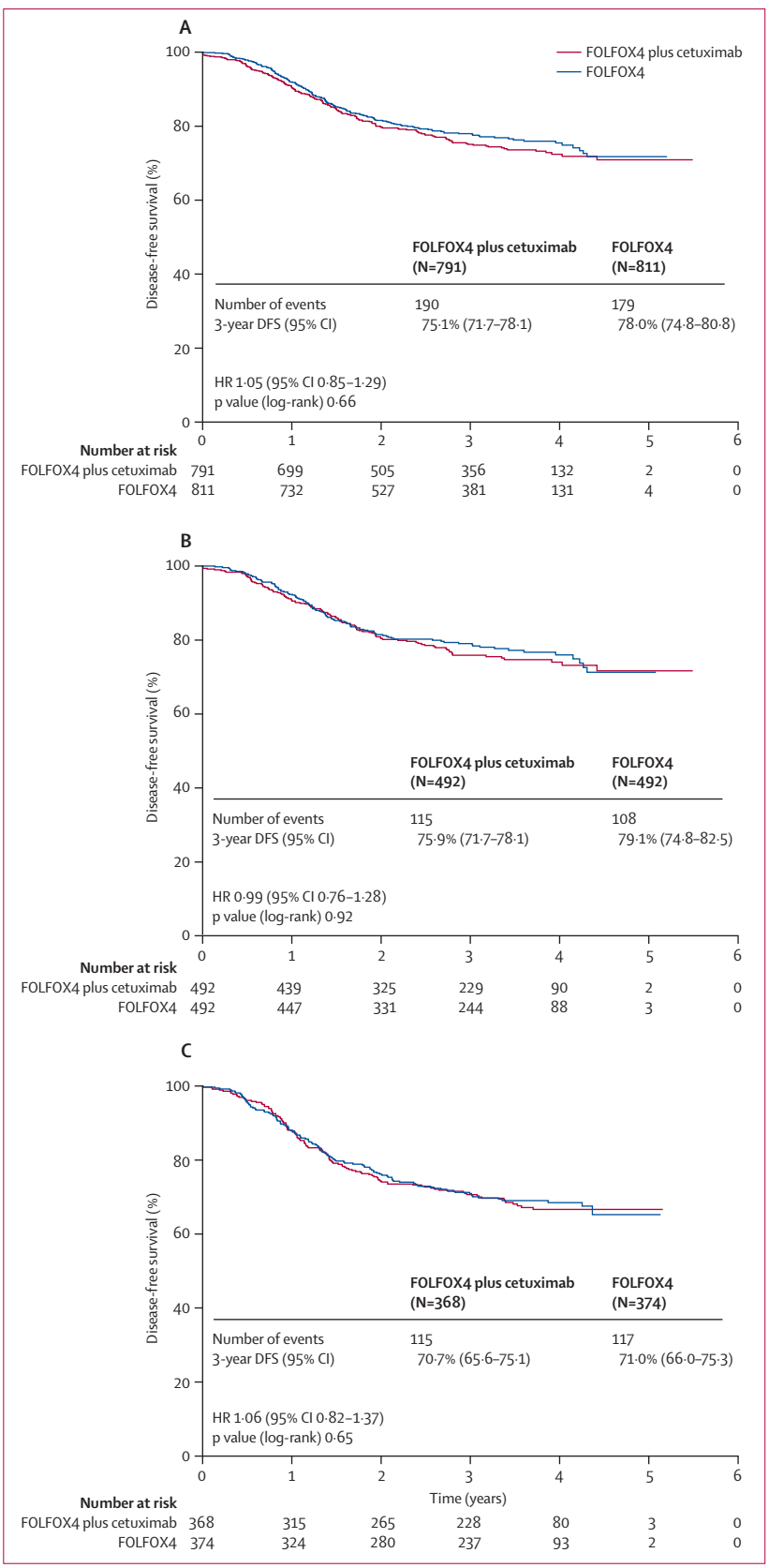
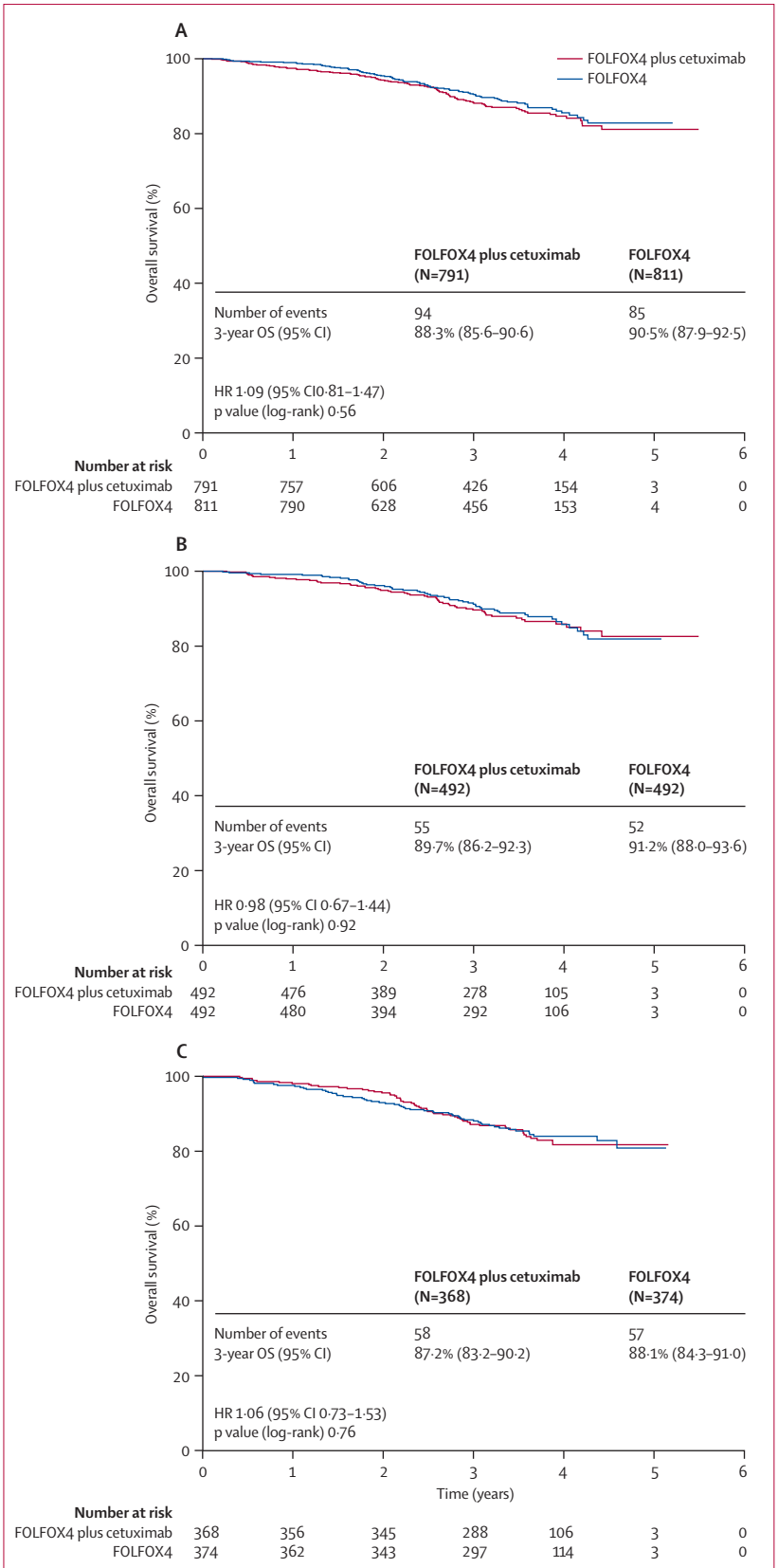


Figure 2: **Kaplan-Meier curves for disease-free survival according to study treatment**

(A) In patients in the *KRAS* exon 2 wild-type intention-to-treat population. (B) In patients with KRAS exon 2 wild-type and *BRAF* wild-type tumours. (C) In patients with *KRAS* exon 2-mutated tumours. DFS=disease-free survival. HR=hazard ratio.



An interim analysis was planned to reject the null hypothesis early if a strong and convincing treatment effect in favour of the combined therapy was recorded. The interim analysis of DFS was planned when 368 events (information fraction 0·65) were reported in the intention-to-treat *KRAS* exon 2 wild-type population; expected at roughly 5·7 years after start of randomisation. We used an α-spending function approach with Pocock boundaries to preserve the overall α=5% level and to specify the nominal significance levels.[21]

All efficacy analyses were intention to treat and were described in a statistical analysis plan before the database was frozen. The *KRAS* exon 2 wild-type population comprised all patients with *KRAS* exon 2 wild-type and the mutated safety population comprised all patients with *KRAS* exon 2 mutated tumours who received at least one dose of any study treatment, according to the treatment received. The *KRAS* exon 2 mutated efficacy population comprised all patients with *KRAS* exon 2 mutated tumours who were randomly assigned before the protocol amendment, in the treatment group assigned at randomisation.

We estimated DFS and overall survival with the Kaplan-Meier technique[22] (primary analysis) and compared survival with a stratified two-sided log-rank test.[23] Analyses were stratified according to randomisation factors. A Cox proportional hazards model accounted for confounding variables or imbalances in prognostic factors and stratification variables (pre-specified in the statistical analysis plan) in the treatment effect estimation.[24]

Pre-planned subgroup analyses investigated the homogeneity of treatment effect for DFS and overall survival across the following subgroups defined by EGFR expression status: *KRAS* and *BRAF* mutation, sex, N category, T category, and obstruction. Analyses were done with SAS (version 9.1.3).

The study is registered at EudraCT, number 2005-003463-23.

Role of the funding source

The study was funded by Fédération Francophone de Cancérologie Digestive, which was responsible for the study design, data collection, the statistical analysis, data interpretation and writing the report. Merck KGaA provided cetuximab and financial support for study management; Sanofi-Aventis provided financial support for the provision of oxaliplatin to Belgian sites when necessary. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

***Figure 3*: Kaplan-Meier curves for overall survival according to study treatment**

(A) In patients in the *KRAS* exon 2 wild-type intention-to-treat population. (B) In patients with *KRAS* exon 2 wild-type and *BRAF* wild-type tumours. (C) In patients with *KRAS* exon 2 mutated tumours. HR=hazard ratio. OS=overall survival.

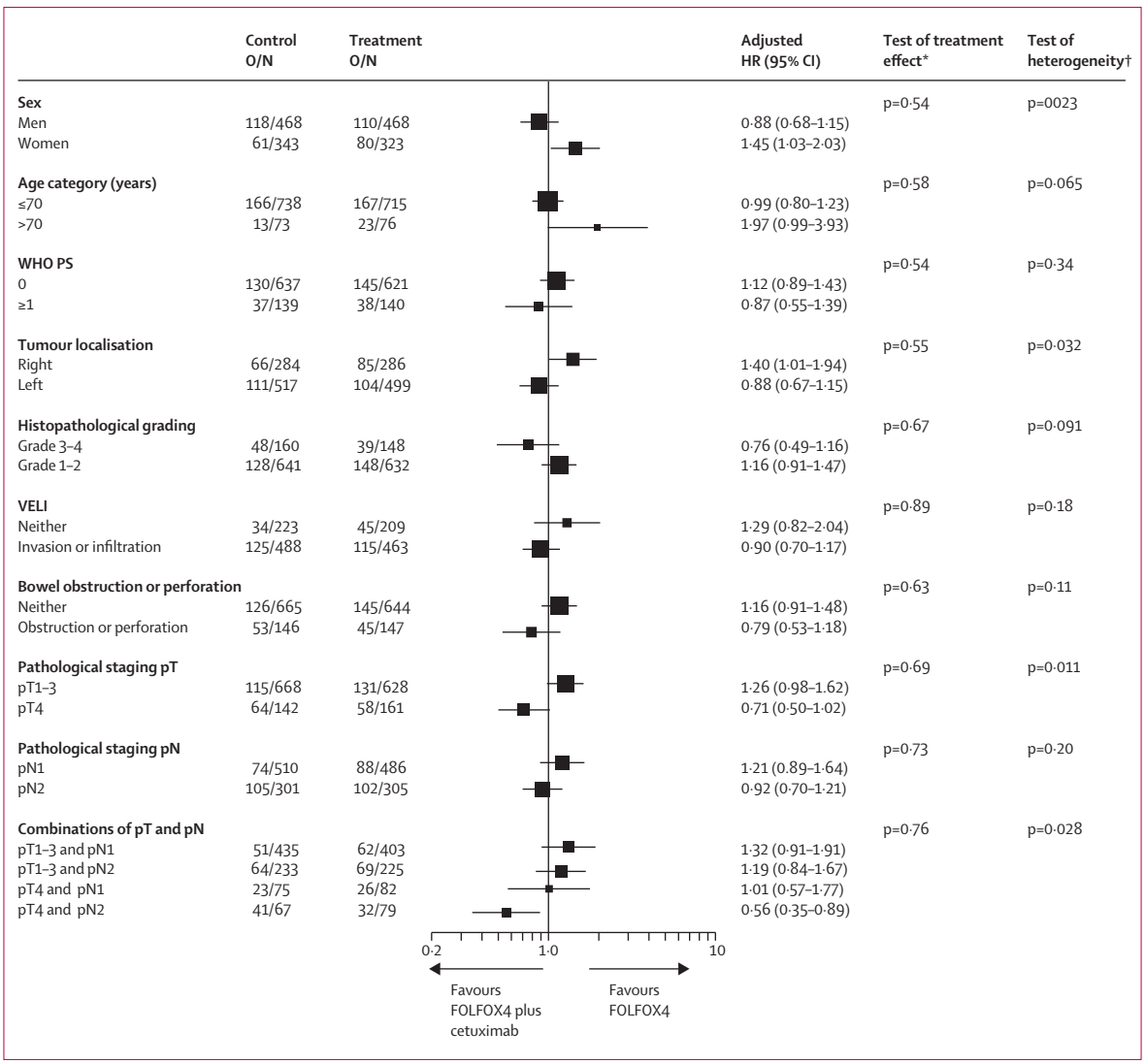


Figure 4: **Forest plot of hazard ratios for disease-free survival in patient subgroups of the *KRAS* exon 2 wild-type intention-to-treat population**
O=number of events. N=number of patients. PS=performance status. VELI=vascular invasion or lymphatic infiltration. FOLFOX4=adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy.* With a univariate Cox proportional hazards model with treatment as covariate and the subgroup and stratifications factors used at randomisation in the model.† With the Cochran *Q* test.

Results

Between Dec 22, 2005, and Nov 5, 2009, 2559 patients were enrolled from 340 sites in Europe and randomly assigned to treatment (2096 were randomised before June 17, 2008). Of these, 1602 comprised the *KRAS* exon 2 wild-type intention-to-treat population, with 791 (49%) allocated to receive FOLFOX4 with cetuximab and 811 (51%) to FOLFOX4 only. Among patients randomly assigned before the protocol amendment, 1881 of 2096 (90%) were retrospectively screened for *KRAS* mutations, and 742 of 1881 (39%) had *KRAS* exon 2 mutated tumours (*KRAS* exon 2 mutated population). Figure 1 shows the trial profile.

The cutoff date for the interim analysis was June 30, 2011, after the 368 DFS events needed to trigger the planned interim efficacy analysis had occurred. Table 1 shows baseline characteristics in the *KRAS* exon 2 wild-type and mutant populations between the treatment groups (table 1). Although CT scans were not mandatory 91% (722/791) of patients in the FOLFOX4 plus cetuximab group and 89% (725/811) of patients in the FOLFOX4 group (p=0·49) had both baseline and follow-up CT scans. In the *KRAS* exon 2 wild-type intention-to-treat population, 796 of 1602 (50%) patients tumours expressed EGFR, and 150 of 1602 (9%) had *BRAF* mutations (1202 were screened for *BRAF* mutations).

Table 2 summarises treatment exposure in the *KRAS* safety populations. In the *KRAS* exon 2 wild-type safety population, the median number of cetuximab infusions was 23 and 610 of 785 (78%) patients received 80% or more

of the planned dose. In both treatment groups most patients received more than 80% of the planned dose of oxaliplatin and fluorouracil. One cetuximab dose reduction was recorded in 73 of 785 patients (9%) with 18 patients reporting two or more dose reductions. Dose reductions for oxaliplatin and fluorouracil were similar between the treatment groups. 96 of 785 (12%) patients who received FOLFOX4 plus cetuximab and 94 of 805 (12%) who received FOLFOX4 discontinued treatment because of toxic effects (figure 1). Treatment exposure in the *KRAS* exon 2 mutated safety population was similar for that reported for the patients with *KRAS* wild-type tumours.

Median follow-up for DFS in the *KRAS* exon 2 wild-type intention-to-treat population was 3·3 years (IQR 3·2–3·4). DFS was not significantly different between the FOLFOX4 plus cetuximab and FOLFOX4 groups (HR 1·05; 95% CI 0·85–1·29; p=0·66), 3-year DFS was 75·1% (95% CI 71·7–78·1) and 78·0% (74·8–80·8), respectively (figure 2). We recorded no significant differences in overall survival between the experimental and control groups (HR 1·09; 95% CI 0·81–1·47; p=0·56; figure 3).

DFS and overall survival were not markedly different between treatment groups in the subgroup of patients with both *KRAS* exon 2 and *BRAF* wild-type tumours or in patients with *KRAS* exon 2 mutated tumours (figures 2 and 3). In further subgroup analyses of the *KRAS* exon 2 wild-type intention-to-treat population, DFS differed by treatment in favour of chemotherapy alone in women (heterogeneity p=0·023) and those with right-sided tumours (heterogeneity p=0·032; figure 4), whereas chemotherapy plus cetuximab treatment was favoured in patients with pT4/N2 disease (heterogeneity p=0·028; figures 4 and 5). DFS was similar between the treatment groups in patients with tumours with detectable EGFR expression (HR 1·22; 95% CI 0·92–1·62; p=0·17), and in those in which EGFR was undetectable (0·89; 0·63–1·23; p=0·46). We recorded no marked differences in DFS according to treatment for patients with *KRAS* exon 2 mutated tumours (appendix).

Table 3 shows adverse events in the *KRAS* exon 2 wild-type safety population. We recorded more grade 3 and 4 adverse events in the cetuximab plus FOLFOX4 group than in 805 patients from the FOLFOX4 group, including diarrhoea (121 [15%] *vs* 73 [9%] patients), and decreased appetite (13 [15%] *vs* four [0·5%] patients), and special composite categories of acne-like rash (209 [27%] *vs* four [1%] patients), mucositis (63 [8%] *vs* ten [1%] patients) and infusion-related reactions (55 [7%] *vs* 30 [4%] patients; table 4). The safety profile in the *KRAS* exon 2-mutated safety population was similar to that reported for the *KRAS* exon 2 wild-type safety population (table 4 and appendix). In patients with *KRAS* exon 2 wild-type tumours, ten grade 5 adverse events possibly related to treatment (from randomisation to 30 days after the last treatment dose) were reported; in seven patients treated with FOLFOX4 plus cetuximab (sudden death, bronchopneumonia and sepsis, pneumonia, diabetes mellitus inadequate control, ischaemic stroke, pulmonary embolism, and pulmonary fibrosis) and in three patients treated with FOLFOX4 alone (death, pulmonary embolism, and respiratory failure). In patients with *KRAS* exon 2-mutated tumours, three deaths in the FOLFOX4 plus cetuximab group, and one in patients receiving FOLFOX4 alone were potentially treatment related.

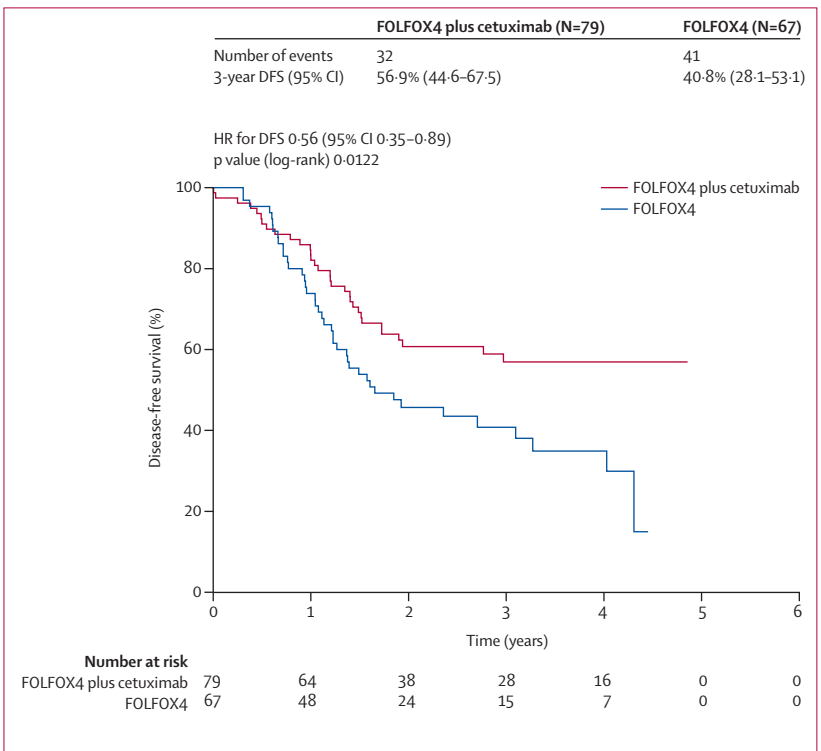


***Figure 5*: Kaplan-Meier curve for disease-free survival according to study treatment in patients with *KRAS* exon 2 wild-type pT4 and pN2 tumours**
DFS=disease-free survival. HR=hazard ratio.

Discussion

In this interim analysis of the PETACC-8 study, the addition of cetuximab to FOLFOX4 after curative resection of *KRAS* exon 2 wild-type stage III colon cancer did not improve DFS or overall survival compared with FOLFOX4 alone (panel). We recorded no unexpected adverse events, and safety profiles were similar to those previously reported for these agents.[9,16] The results are consistent with those recently reported in the NCCTG N0147 study, which did not detect an improvement in DFS from addition of cetuximab to mFOLFOX6 in the adjuvant treatment of patients with stage III colon cancer (3-year DFS 74·6% *vs* 75·1%).[16] The PETACC-8 and NCCTG NO147 adjuvant trials were similar in their design except for the age limit (75 years in PETACC-8 and no age limit in NCCTG NO147), and the associated chemotherapy regimens (FOLFOX4 based on the MOSAIC study in PETACC-8 and mFOLFOX6 in NCCTG NO147).

These findings contrast with those from the OPUS and PRIME studies in which the addition of an EGFR antibody to first-line FOLFOX4 in patients with *KRAS* exon 2 wild-type metastatic colorectal cancer significantly improved clinical outcome.[9,10,12] Furthermore, in these studies, the combination of FOLFOX4 with cetuximab (HR 1·720, 95% CI 1·104–2·679; p=0·0153)[9] or panitumumab (1·29, 1·04–1·62; p=0·02)[10,12] was detrimental for progression-free survival in patients with *KRAS* exon 2-mutated tumours. An analysis of patients

	FOLFOX and cetuximab (N=785)				FOLFOX (N=805)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Any (at least one)	149 (19%)	503 (64%)	132 (17%)	8 (1%)	271 (33%)	409 (51%)	124 (15%)	4 (<0·5%)
Neutropenia*	255 (32%)	207 (26%)	71 (9%)	0	297 (37%)	208 (26%)	88 (11%)	0
Febrile neutropenia	4 (0·5%)	17 (2%)	4 (0·5%)	0	2 (<0·5%)	13 (2%)	3 (<0·5%)	0
Leucopenia†	91 (12%)	8 (1%)	1 (<1%)	0	118 (15%)	5 (1%)	1 (<0·5%)	
Thrombocytopenia‡	481 (61%)	12 (2%)	4 (0.5%)	0	576 (72%)	23 (3%)	0	0
Anaemia§	445 (57%)	4 (0·5%)	0	0	480 (60%)	1 (<0·5%)	0	0
Cardiac arrest	0	0	0	1 (<0·5%)	0	0	0	0
Conjunctivitis	89 (11%)	1 (<0·5%)	0	0	37 (5%)	0	0	0
Abdominal pain	113 (14%)	10 (1%)	1 (<1%)	0	148 (18%)	3 (<0·5%)	1 (<0·5%)	0
Constipation	235 (30%)	4 (0·5%)	1 (<1%)	0	236 (29%)	4 (0·5%)	0	0
Diarrhoea	370 (47%)	113 (14%)	8 (1%)	0	427 (53%)	70 (9%)	3 (<0·5%)	0
Nausea	434 (55%)	12 (2%)	1 (<0·5%)	0	510 (63%)	18 (2%)	0	0
Vomiting	214 (27%)	17 (2%)	1 (<0·5%)	0	263 (32%)	5 (1%)	0	0
Asthenia	443 (56%)	57 (7%)	2 (<0·5%)	0	463 (58%)	43 (5%)	2 (<0·5%)	0
Mucosal inflammation	355 (45%)	57 (7%)	2 (<0·5%)	0	279 (35%)	9 (1%)	1 (<0·5%)	0
Pyrexia	140 (18%)	5 (1%)	0	0	131(16%)	4 (0·5%)	0	0
Death (unclear cause)	0	0	0	0	0	0	0	1 (<0·5%)
Sudden death	0	0	0	1 (<0·5%)	0	0	0	0
Bronchopneumonia	1 (<0·5%)	1 (<0·5%)	1 (0·5%)	1 (<0·5%)	0	0	0	0
Pneumonia	2 (<0·5%)	4 (<0·5%)	0	1 (<0·5%)	3 (<0·5%)	3 (<0·5%)	0	0
Sepsis	1 (<0·5%)	4 (0·5%)	0	0	1 (<0·5%)	1 (<0·5%)	1 (<0·5%)	1 (<0·5%)
ALT increased	189 (24%)	12 (15%)	1 (<0·5%)	0	152 (19%)	10 (1%)	0	0
AST increased	203 (26%)	5 (1%)	1 (<0·5%)	0	173 (21%)	4 (0·5%)	0	0
ALP increased	112 (14%)	3 (<0·5%)	0	0	128 (16%)	2 (<0·5%)	0	0
GGT increased	111 (14%)	21 (3%)	1 (<0·5%)	0	113 (14%)	23 (3%)	1 (<0·5%)	0
Decreased appetite	190 (24%)	12 (15%)	1 (<0·5%)	0	154 (19%)	4 (0·5%)	0	0
Hypokalaemia	56 (7%)	19 (2%)	5 (1%)	0	29 (4%)	9 (1%)	1 (<0·5%)	0
Diabetes mellitus inadequate control	1 (<0·5%)	1 (0·5%)	0	1 (<0·5%)	0	1 (<0·5%)	0	0
Dysgeusia	145 (18%)	1 (<0·5%)	0	0	157 (20%)	0	0	0
Ischaemic stroke	0	0	0	1 (<0·5%)	0	0	1 (<0·5%)	0
Neuropathy (peripheral)	531 (68%)	112 (14%)	8 (1%)	0	578 (72%)	138 (17%)	7 (1%)	0
Epistaxis	121 (15%)	0	0	0	103 (13%)	0	0	0
Pulmonary embolism	2 (<0·5%)	6 (1%)	6 (1%)	1 (<0·5%)	2 (<0·5%)	4 (0·5%)	3 (<0·5%)	1 (<0·5%)
Pulmonary fibrosis	0	1 (<0·5%)	0	1 (<0·5%)	0	0	0	0
Respiratory failure	0	0	1 (<0·5%)	0	0	0	0	1 (<0·5%)
Alopecia	140 (18%)	3 (<0·5%)	0	0	149 (19%)	0	0	0
Dermatitis acneiform	513 (65%)	191 (24%)	3 (<0·5%)	0	22 (3%)	3 (<0·5%)	0	0
Dermatitis allergic	84 (11%)	18 (2%)	0	0	64 (8%)	6 (1%)	0	0
Dry skin	168 (21%)	9 (1%)	0	0	24 (3%)	0	0	0
Nail disorder	215 (27%)	34 (4%)	1 (<0·5%)	0	21 (3%)	0	0	0
Hand-foot syndrome	182 (23%)	26 (3%)	2 (<0·5%)	0	76 (9%)	8 (1%)	1 (<0·5%)	0
Skin fissures	136 (17%)	12 (2%)	0	0	8 (1%)	0	0	0

Data are n (%) of grade 1–2 (≥10%) in either treatment group, grade 3 or 4 (≥3%), and grade 5 adverse events. FOLFOX4=adjuvant oxaliplatin, fluorouracil, and leucovorin chemotherapy. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma glutamyl transferase. Listed are preferred terms. *Neutrophil count decreased. †White blood cell count decreased. ‡Platelet count decreased. §Haemoglobin decreased (MedDRA [version 14.0]).

***Table 3*: Adverse events in the *KRAS* exon 2 wild-type safety population**

with *KRAS* exon 2 mutated tumours in the PETACC-8 study showed no difference in DFS or overall survival between the treatment groups. Similar findings in *KRAS* exon 2 mutated tumours were reported from the NCCTG N0147 adjuvant trial.[16] Therefore, although clinical outcome was not improved, there was no evidence that combination of cetuximab with FOLFOX4 was detrimental for outcome in patients with *KRAS* exon 2 mutated colon tumours in this setting, despite concerns raised about cetuximab in combination with oxaliplatin-based regimens in the treatment of patients with metastatic disease.[9,25]

The reasons for the apparent discrepancies between the treatment efficacy in adjuvant and metastatic settings are unclear but might be due to differences in the biology of the micro-metastases, which are the intended targets of adjuvant treatment, compared with the biology of established metastases treated in the metastatic setting.[16,26,27] Given that about 90% of patients had a CT scan, we do not think that a lack of standardised imaging is an issue. However, non-detectable, small metastatic lesions might have been present in the T4/N2 subgroup of patients, which could explain the efficacy of cetuximab in this subgroup with high frequency of relapse. Recently reported biomarker analysis in the PETACC-3 study further highlights the heterogeneity of patients with stage III disease in terms of molecular and baseline characteristics, together with their clinical outcome.[28]

The findings from the primary analysis were investigated in patient subgroups of the *KRAS* exon 2 wild-type intention-to-treat population. We noted *BRAF* mutations in about 9% of patients with *KRAS* exon 2 wild-type tumours. *BRAF* tumour mutations have been implicated in resistance to cetuximab in later treatment lines, and with poor prognosis in patients with metastatic colorectal cancer.[8,29] Data from the PETACC-3 study suggest that a *BRAF* mutation might also be a marker of poor prognosis in the adjuvant setting.[30] In the PETACC-8 study, when patients with *BRAF*-mutated tumours were excluded from the analysis, patients with both *KRAS* exon 2 and *BRAF* wild-type tumours received no benefit from the addition of cetuximab to FOLFOX4 in terms of DFS and overall survival.

Recently, in addition to tumour mutations at *KRAS* codons 12 or 13 (exon 2), those at other loci in *KRAS* exons 2 to 4, or any loci in exons 2 to 4 of *NRAS* were reported to identify patients who did not benefit from EGFR antibodies in the metastatic setting.[12,31] As far as we are aware, no data are available for the value of mutations at these other *RAS* loci in the adjuvant setting, but this will be a priority for the continuing translational work in the PETACC-8 and NCCTG NO147 studies.

Further subgroup analyses revealed that female patients and those with right-sided tumours had better DFS with FOLFOX4 alone than with FOLFOX4 plus cetuximab. By contrast, in patients with more advanced disease (pT4/N2 tumours), DFS was improved with cetuximab plus FOLFOX4 compared with FOLFOX4 alone. Although such data should be treated cautiously (partly because of the small number of patients studied), the heterogeneity of treatment efficacy suggests that further investigation of the role of FOLFOX4 plus cetuximab in certain patient subgroups (eg, those with pT4/N2 disease) is warranted. Associations between patient sex and tumour site with molecular prognostic biomarkers including tumour microsatellite instability status and *BRAF* mutations have been described,[30] and warrant further investigation in this setting. Patients with primary tumours located on the right colon derived much less benefit for progression-free survival than did patients with left-sided tumours.[32] By contrast, the improved outcome noted when cetuximab was added to FOLFOX4 in patients with pT4/N2 tumours might suggest that these patients resemble those with advanced disease, with the characteristics of their tumour

	***KRAS* exon 2 wild-type safety population**		***KRAS* exon 2-mutated safety population**	
	FOLFOX4 plus cetuximab (N=785)	FOLFOX4 (N=805)	FOLFOX4 plus cetuximab (N=364)	FOLFOX4 (N=374)
Acne-like rash	209 (27%)	4 (<1%)	106 (29%)	0
Neurotoxicity	127 (16%)	152 (19%)	57 (16%)	69 (18%)
Mucositis	63 (8%)	10 (1%)	36 (10%)	3 (1%)
Infusion-related reactions	55 (7%)	30 (4%)	11 (3%)	21 (7%)
Thromboembolic events (venous)	22 (3%)	13 (2%)	10 (3%)	5 (1%)

Data are n (%) of special adverse events occurring in ≥3% of patients in either treatment group.

***Table 4*: Grade 3 and 4 special adverse events in the *KRAS* exon 2 wild-type and *KRAS* exon 2-mutated safety populations**

Panel: Research in context

Systematic review

When treated by surgery alone, approximately 50% of patients with resected stage III colon cancer will experience tumour recurrence and will die from their disease. Treatment with adjuvant chemotherapy can significantly reduce this risk, and at the time of the study design the standard adjuvant treatment for patients in this setting was FOLFOX4. The design of the phase 3 PETACC-8 intergroup study was specifically influenced by an analysis of the literature on existing chemotherapy regimens for the treatment of patients in this setting, and the introduction of the EGFR antibody cetuximab in combination with first-line FOLFOX4 chemotherapy in the treatment of patients with metastatic colorectal cancer. The existing evidence was identified by a search of published work (PubMed), from inception, using search terms "colon cancer" "adjuvant chemotherapy (oxaliplatin, 5-FU)". The aim was to examine cetuximab as a potential addition to the treatment armamentarium for stage III colon cancer patients in the adjuvant setting.

Interpretation

Our findings show that addition of cetuximab to FOLFOX4 in the treatment of patients with *KRAS* exon 2 wild-type resected stage III colon cancer provided no benefit compared with chemotherapy alone. However, the positive outcomes for the subgroups of patients with more advanced disease opens the possibility of further trials in specific patient populations. Molecular classification of this heterogeneous disease, with respect to candidate predictive biomarkers, might be needed before substantial improvements in treatment outcome are to be made in this setting.

cells making them more responsive to EGFR antibodies compared with other patients with less locoregional involvement receiving adjuvant treatment.

Finally, we noted a non-significant indication of a detrimental effect of FOLFOX4 plus cetuximab in patients older than 70 years. Age-related differences in treatment efficacy in patients with stage III colon cancer receiving oxaliplatin-based chemotherapy have been previously reported.[7] In the NCCTG N0147 study, in patients with *KRAS* exon 2 wild-type tumours, the addition of cetuximab to mFOLFOX6 in patients older than 70 years was associated with reduced treatment exposure, increased toxic effects, and worse outcome, compared with mFOLFOX6 alone.[16] Similarly, in the PETACC-8 study, treatment exposure was reduced, and premature treatment discontinuation was increased in patients older than 70 years compared with those aged 70 years or younger, especially in the FOLFOX4 plus cetuximab group, but this finding was not recorded for female patients or those with right-sided tumours (data not shown). These findings support the view that elderly patients in this setting are less tolerant to more intensive treatments.[7,16]

The addition of cetuximab to FOLFOX4 led to more reported grade 3 and 4 adverse events, mainly skin-related toxic effects, diarrhoea, and mucositis, compared with FOLFOX4 alone. Toxicity profiles for patients with *KRAS* exon 2 wild-type compared with *KRAS* exon 2 mutated tumours were generally similar, and comparable with those described in previous studies in which this treatment combination was used.[9,16] Mortality during the 6 months after randomisation was less than 1% in both treatment groups in these patient groups and was in accordance with what is generally recorded in studies of colon cancer adjuvant therapy.[6,16,18,33]

In summary, in this interim analysis of the PETACC-8 study, the addition of cetuximab to FOLFOX4 did not improve DFS or overall survival in patients with *KRAS* exon 2 wild-type resected stage III colon cancer. Large collections of blood and tissue samples from PETACC-8 and other recent adjuvant trials should be used in collaborative translational studies in the further characterisation of these patients to generate improvements in clinical outcome in the adjuvant setting.

Contributors

JTai, JTab, EM, GF, JT, LC (statistics), EVC, PR, LB, JFE, and PL-P contributed to the study concept and design. JTai, JTab, JTha, JB, LB, LP, LC, and EVC, contributed to study coordination and governance. JTai, GF, JB, RS, LB, J-FE, PL-P, and CL, contributed to data collection (including literature searches). JTai, JTab, EM, J-LVL, JB, LP, EVC, PR, and EM, contributed to the provision of patients and or study materials. JTai, JTab, EM, FS, GF, JTha, JB, LC, EVC, PR, RS, PL-P, and CL contributed to data analysis and or interpretation. HB was responsible for tumour *KRAS* and *BRAF* mutation analysis and J-FE reviewed histology. JTai, JTab, GF, EVC, J-LVL, and RS contributed to manuscript writing. A medical writer, Paul Hoban, drafted and amended a first draft of the manuscript under the guidance of JTai and FS. This was subsequently expanded by P Hoban into a full manuscript that was amended after a series of comments and discussions from the authors. The final version of the manuscript has been approved by all authors and the study sponsor.

Declaration of interests

JTai has received grants from Merck and Sanofi relating to the submitted work, plus grants and personal fees from Merck, Sanofi, Roche Genentech, Pfizer, and Amgen; JTab has received honoraria for presentations from Amgen, Merck KGaA, Novartis, Roche, and Sanofi, and provides advisory support to Amgen, Imclone, Lilly, Merck KGaA, Millennium, Novartis, Roche, Sanofi, Celgene, Chugai, and Taiho; EM has received clinical study participation grants from Fédération Française de Cancérologie Digestive relating to the submitted work; GF has received grants and personal fees from Merck KGaA, and personal fees from Sanofi; JT has received grants and personal fees from Merck and personal fees from Sanofi relating to the submitted work; JB has received personal fees for supporting the following advisory boards: Roche, Sanofi, Merck Serano, and Amgen; LP has received fees from Fédération Française de Cancérologie Digestive relating to the submitted work, plus travel and conference reimbursements from Merck, invitations to annual meetings from Roche and Amgen, and departmental and educational grants from Roche Denmark, and has previously been a member of a national advisory board for Roche, Denmark; EVC has received research grants paid to his university from Merck Serono both related to and outside of the submitted work; PR has received data monitoring support grants from Fédération Française de Cancérologie Digestive relating to the submitted work, and grants and personal fees from Sanofi and Lilly for symposia and advisory boards, personal fees from Merck Serono, Ipsen, Amgen, and Pfizer for symposia and personal fees and non-financial support from Keocyte for symposia and advisory boards and for help for meeting organisation; RS has declared lectures and advisory roles with Merck KGaA; LB has received grants from Merck-Serono relating to the submitted work while chairman of Fédération Française de Cancérologie Digestive; J-FE has received grants from Fédération Française de Cancérologie Digestive for the collection of tumour material and for DNA extraction relating to the submitted work, plus honoraria for participation of advisory board from Merck; PL-P has received personal fees from Merck-Serono, Amgen and Sanofi, related to the submitted work, plus additional personal fees from Integragen, Pfizer and Boerhinger Ingelheim, and grants from Raindance. FS, J-LVL, HB, LC, and CL declare no competing interests.

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