Biomarkers predictive for outcome in patients with metastatic colorectal cancer treated with 1st-line FOLFOX4 ± cetuximab: Updated data from the OPUS study

C. Bokemeyer,[1] I. Bondarenko,[2] J.T. Hartmann,[3] F. De Braud,[4] G. Schuch,[1] A. Zubel,[5] I. Celik,[5] P. Koralewski[6]

[1] Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2] State Medical Academy, City Clinical Hospital No. 4, Dnepropetrovsk, Ukraine; [3] Universitätsklinikum der Christian-Albrechts-Universität zu Kiel, Kiel, Germany;
[4] Istituto Europeo di Oncologica, Milano, Italy; [5] Merck KGaA, Darmstadt, Germany; [6] Oddzial Chemioterapii Wojewodzki Szpital Specjalistyczny im. L. Rydygiera, Krakow, Poland

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Background

- In the OPUS study patients with *KRAS* wild-type (*KRAS* wt) metastatic colorectal cancer (mCRC) receiving cetuximab plus FOLFOX4 displayed a significantly higher best overall response (OR), 61% vs 37%, (odds ratio 2.54, p=0.011) and a lower risk of disease progression (hazard ratio [HR] 0.57, p=0.0163) compared with patients receiving FOLFOX4 alone.[1]
- The OPUS study confirmed earlier retrospective investigations of single-arm studies suggesting that cetuximab efficacy was confined to patients with *KRAS* wt tumors.[2,3]
- The serine-threonine kinase BRAF is a direct downstream effector of KRAS. *BRAF* gene mutations have been detected in around 8% of colorectal tumors,[4] and *BRAF* mutation status has been suggested to be predictive of cetuximab efficacy in pretreated patients.[5]
- Here we report overall survival (OS), updated progression-free survival (PFS) time and OR data for patients with *KRAS* wt tumors following an increase in the number of patients for whom *KRAS* tumor mutation status could be determined.
- The impact of *BRAF* tumor mutations on cetuximab efficacy was investigated in patients with *KRAS* wt disease.

Study objectives

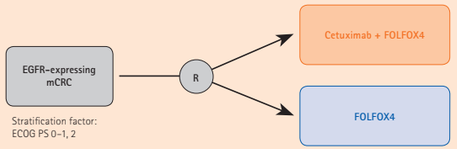
- Primary study objective:
  - Assess whether the OR of cetuximab plus FOLFOX4 was superior to that of FOLFOX4 alone
- Secondary objectives included:
  - Comparison of the treatment regimens with respect to PFS time and OS time and safety
- A retrospective subgroup analysis for associations between OR, PFS and OS times and the *KRAS*/*BRAF* mutation status of tumors.

Methods

Study design

- This was an open label randomized multicenter phase II study (Figure 1).

Figure 1. Study design[1]



FOLFOX4 (q2w)		Cetuximab
Oxaliplatin	85 mg/m² day 1	400 mg/m² initial dose then
5-FU	400 mg/m² bolus then 600 mg/m² infusion, day 1 and 2	250 mg/m² weekly
LV	200 mg/m² day 1	

Treatment until progression, symptomatic deterioration or unacceptable toxicity

5-FU, 5-fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; LV, leucovorin; mCRC, metastatic colorectal cancer; R, randomization.

Patients

- Patient inclusion and exclusion criteria have been described elsewhere.[1]

KRAS/*BRAF* tumor mutation detection

- Ascertainment of samples for *KRAS* testing was increased using tumor DNA extracted from formalin fixed paraffin embedded slide mounted sections initially prepared to evaluate tumor EGFR expression.
- *KRAS* mutations at codons 12/13 and *BRAF* (V600E) mutations were detected using the previously described polymerase chain reaction clamping and melting curve technique.[1]

Data cut-offs for analyses

- OPUS study data cut-offs were: PFS (independent review committee), OR (independent review committee), 01 March 2007, and OS, 30 November 2008.

Results

Baseline characteristics (Table 1)

- Patient tumor numbers in the ITT population (n=337) for whom *KRAS* mutation status was determined increased from 233 (69%) as previously published,[1] to 315 (93%).
- 309 (92%) patient tumors were evaluable for *BRAF* mutation status.
- *BRAF* mutations were detected in 11/309 (4%) evaluable tumor samples from the ITT population.
  - No patients were found with *KRAS* mt and *BRAF* mutant (*BRAF* mt) tumors
- 179/315 (57%) patients had *KRAS* wt tumors.
- 175 *KRAS* wt tumors were evaluable for *BRAF* mutations.
  - 164 (94%) were *BRAF* wt
  - 11 (6%) were *BRAF* mt

Table 1. Baseline and disease characteristics in patients with *KRAS* wt tumors according to *BRAF* mutation status and treatment

	KRAS wt (n=179)		*KRAS* wt/*BRAF* wt (n=164)		*KRAS* wt/*BRAF* mt (n=11)	
Characteristics, n (%) unless otherwise stated	FOLFOX4 (n=97)	Cetuximab + FOLFOX4 (n=82)	FOLFOX4 (n=92)	Cetuximab + FOLFOX4 (n=72)	FOLFOX4 (n=5)	Cetuximab + FOLFOX4 (n=6)
Gender						
Male	55 (57)	42 (51)	51 (55)	38 (53)	4 (80)	2 (33)
Female	42 (43)	40 (49)	41 (45)	34 (47)	1 (20)	4 (67)
Median age, years (range)	59 (36–82)	62 (24–75)	59 (37–82)	63 (24–75)	61 (36–74)	51 (40–74)
Age categories						
<65 years	63 (65)	46 (56)	60 (65)	39 (54)	3 (60)	5 (83)
≥65 years	34 (35)	36 (44)	32 (35)	33 (46)	2 (40)	1 (17)
ECOG PS						
0/1	86 (89)	76 (93)	82 (89)	66 (92)	4 (80)	6 (100)
Liver metastases only	23 (24)	25 (31)	23 (25)	23 (32)	0	1 (17)
Involved disease sites ≤2	75 (77)	67 (82)	74 (80)	60 (83)	5 (100)	4 (67)
Prior adjuvant chemotherapy	21 (22)	13 (16)	21 (23)	12 (17)	0	1 (17)

ECOG PS, Eastern Cooperative Group performance status; mt, mutant; wt, wild-type.

Clinical efficacy (Table 2)

- For patients with *KRAS* wt tumors the addition of cetuximab to FOLFOX4 compared with FOLFOX4 alone led to:
  - Significant improvement in OR (Figure 2), with a mean difference in the best % change of the lesion from baseline (based on WHO criteria) of 11.6
  - Significant improvement in PFS time (Figure 3)
  - Improvement in OS time although the difference between the arms was not significant (Figure 4)
- Significant interactions between treatment outcomes and *KRAS* tumor mutation status were observed for OR and PFS (<0.001) but not for OS (p=0.12).[6]
- Significant improvements in PFS and OR were also found on adding cetuximab to FOLFOX4 for patients with *KRAS* wt/*BRAF* wt tumors; the improvement in OS was not significant (Table 2).

Post-study treatment

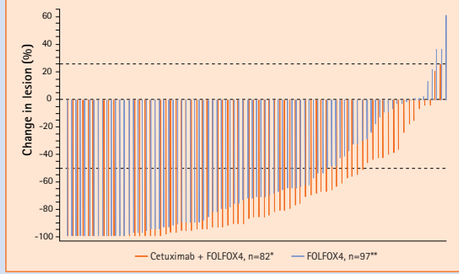
- The proportion of patients receiving post study anticancer therapy has been previously reported.[6]
- 54 (66%) patients in the cetuximab + FOLFOX4 arm and 59 (61%) in the FOLFOX4 alone arm received treatment with anticancer therapy of any kind.
  - Most frequent therapy in both arms was 5-FU/FA (41% vs 44%)
  - 10% and 16% of patients received post-study cetuximab, respectively

Table 2. Efficacy data in patients with *KRAS* wt tumors according to *BRAF* mutation status and treatment

	KRAS wt (n=179)		*KRAS* wt/*BRAF* wt (n=164)		*KRAS* wt/*BRAF* mt (n=11)	
	FOLFOX4 (n=97)	Cetuximab + FOLFOX4 (n=82)	FOLFOX4 (n=92)	Cetuximab + FOLFOX4 (n=72)	FOLFOX4 (n=5)	Cetuximab + FOLFOX4 (n=6)
Tumor response						
OR rate (%) [95%CI]	34.0 [24.7–44.3]	57.3 [45.9–68.2]	35.9 [26.1–46.5]	59.7 [47.5–71.1]	0 [0.0–52.2]	33.3 [4.3–77.7]
Odds ratio [95% CI]	2.5512 [1.3799–4.7169]		2.6491 [1.3901–5.0483]		NA NA	
p-value[a]	0.0027		0.0029		0.2207	
PFS time						
Median PFS, months [95% CI]	7.2 [5.6–7.4]	8.3 [7.2–12.0]	7.2 [5.6–7.4]	8.3 [7.3–12.7]	1.7 [0.9–7.9]	7.1 [4.2–NA]
Hazard ratio [95% CI]	0.567 [0.375–0.856]		0.556 [0.358–0.864]		0.449 [0.087–2.303]	
p-value[b]	0.0064		0.0083		0.3255	
OS time						
Median OS, months [95%CI]	18.5 [16.4–22.6]	22.8 [19.3–25.9]	19.5 [17.0–23.8]	22.8 [19.3–25.8]	4.4 [0.9–10.1]	20.7 [10.3–30.4]
Hazard ratio [95% CI]	0.855 [0.599–1.219]		0.894 [0.615–1.301]		0.104 [0.011–0.964]	
p-value[b]	0.3854		0.5582		0.0167	

[a] Stratified Cochrane-Mantel-Haenszel test; [b] Stratified log-rank test.
CI, confidence interval; mt, mutant; NA, not available; OR, best overall response; OS, overall survival; PFS, progression-free survival; wt, wild-type.

Figure 2. Tumor regression according to treatment status in patients with *KRAS* wt tumors

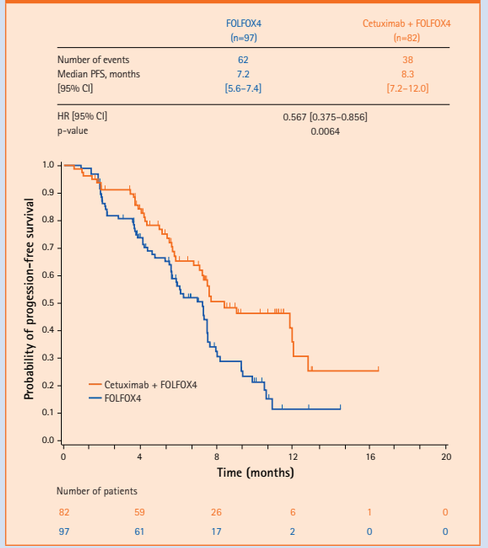


*Data are missing for 5 patients. **Data are missing for 4 patients.
wt, wild-type.

Safety data for patients with *KRAS* wt/*BRAF* wt tumor mutation status (Table 3)

- Safety data have been reported previously for the ITT[1] and *KRAS* wt[6] populations and were found to be generally similar for patients with *KRAS* wt/*BRAF* wt tumors.
- In the cetuximab + FOLFOX4 arm
  - 5 patients (7%) discontinued cetuximab only
  - 17 patients (24%) discontinued chemotherapy only
  - 8 patients (11%) discontinued both cetuximab and chemotherapy together
- In the FOLFOX4 alone arm 26 patients (28%) discontinued chemotherapy.
- 46 patients (64%) died of disease progression in the cetuximab-containing arm and 63 (68%) in the chemotherapy-alone arm. There were no cetuximab-related deaths.

Figure 3. Progression-free survival according to treatment status in patients with *KRAS* wt tumors



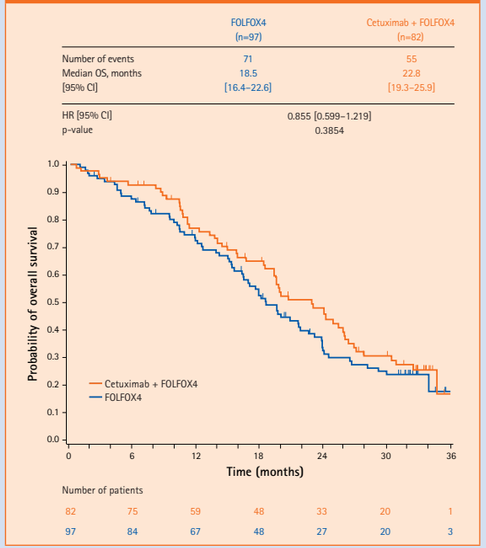
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; wt, wild-type.

Table 3. Grade 3 or 4 adverse events and special adverse events occurring in patients with *KRAS* wt tumors according to *BRAF* mutation status and treatment

	KRAS wt (n=179)		*KRAS* wt/*BRAF* wt (n=164)	
Adverse events*, n (%)	FOLFOX4 (n=97)	Cetuximab + FOLFOX4 (n=82)	FOLFOX4 (n=92)	Cetuximab + FOLFOX4 (n=72)
Any grade 3/4 event	62 (64)	67 (82)	58 (63)	72 (81)
Neutropenia	31 (32)	29 (35)	30 (33)	26 (36)
Rash**	0	9 (11)	0	8 (11)
Diarrhea**	5 (5)	7 (9)	5 (5)	5 (7)
Peripheral sensory neuropathy**	8 (8)	3 (4)	8 (9)	3 (4)
Leukopenia	5 (5)	6 (7)	5 (5)	6 (8)
Pulmonary embolism	1 (1)	4 (5)	1 (1)	4 (6)
Composite categories†, n (%)**				
Skin reactions**	0	15 (18)	0	12 (17)
Neurotoxicity associated events**	0	6 (7)	14 (15)	6 (8)
Cardiac events	0	6 (7)	0	3 (4)

*Reported in >5% of patients with *KRAS* wt tumors in either treatment arm; **No grade 4 events recorded;
† Including terms as defined in the Medical Dictionary for Regulatory Activities.
wt, wild-type.

Figure 4. Overall survival according to treatment status in patients with *KRAS* wt tumors



CI, confidence interval; HR, hazard ratio; OS, overall survival; wt, wild-type.

Conclusions

- The addition of cetuximab to FOLFOX4 in patients with *KRAS* wt tumors led to significantly longer PFS and a significantly higher OR than in patients receiving FOLFOX4 alone.
- In patients with *KRAS* wt tumors, the addition of cetuximab to FOLFOX4 in the 1st-line treatment of mCRC led to an improvement in OS compared with patients receiving FOLFOX4 alone (18.5 to 22.8 months); this difference was not statistically significant which may be due to the small sample size.
- This analysis confirms *KRAS* tumor mutation status to be a predictive factor for the efficacy of cetuximab treatment in terms of OR and PFS.
- In the OPUS study the prevalence of *BRAF* mutations in patients with *KRAS* wt tumors (11 patients) prevents conclusions being drawn on its use as a predictive or prognostic biomarker.

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