Cetuximab with chemotherapy as 1st-line treatment for metastatic colorectal cancer: A meta-analysis of the CRYSTAL and OPUS studies according to *KRAS* and *BRAF* mutation status

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ASCO GI 2010

Background

- The randomized, controlled CRYSTAL[1] and OPUS[2] trials showed that adding cetuximab to standard 1st-line irinotecan- or oxaliplatin-based therapy improved efficacy in patients with *KRAS* wild-type (wt) metastatic colorectal cancer (mCRC).
- The serine-threonine kinase BRAF is a direct downstream effector of KRAS. *BRAF* gene mutations have been detected in 8% of CRC tumors[3] and *BRAF* mutation status has been suggested to be predictive of cetuximab efficacy in pretreated patients with mCRC.[4]
- The effect of tumor *KRAS* and *BRAF* mutation status on progression-free survival (PFS), best overall response (OR) and overall survival (OS) in patients receiving cetuximab plus standard 1st-line chemotherapy was investigated further in this updated pooled analysis of individual patient data from the CRYSTAL and OPUS populations presented at ECCO 2009.[5]
- The ascertainment rate for *KRAS* mutation status in the CRYSTAL and OPUS studies has been enhanced from the published studies and the most recent survival data has been used for analysis of efficacy endpoints and tumor *KRAS* and *BRAF* mutation status.

Study objectives

- To investigate the effects of tumor *KRAS* and *BRAF* mutation status on the efficacy of cetuximab in patients with *KRAS* wt tumors using the key efficacy endpoints from the two trials: PFS (CRYSTAL) and OR (OPUS), and the secondary endpoints as defined in the trial protocols.

Methods

- Patients were randomized to receive cetuximab in combination with FOLFIRI (CRYSTAL)[1] or FOLFOX4 (OPUS)[2] or the standard 1st-line treatment alone.
- The number of samples evaluable for *KRAS* mutation status was increased from 540/1198 (45%) previously published[1] to 1063 (89%) in the CRYSTAL study and from 233/337 (69%)[2] to 315 (93%) in the OPUS study.
- The number of samples evaluable for *BRAF* mutation status was increased from 529/1198 (44%) previously reported[6] to 1000 (83%) in the CRYSTAL study and 309 (92%) in the OPUS study.
- In the CRYSTAL and OPUS studies, 625 and 175 *KRAS* wt tumors respectively, were evaluable for *BRAF* mutation status.
- Additional survival data were available for the CRYSTAL and OPUS studies (see statistics below).
- For each trial:
  - Primary analyses of PFS and OR rate were based on computed tomography or magnetic resonance imaging scans as assessed by an independent radiology review committee (IRC) according to modified WHO criteria.
  - Additional tumor mutation analysis was performed on material extracted from stained slides previously collected to evaluate tumor EGFR expression status.
  - *KRAS* (codons 12/13) and *BRAF* (V600E) mutations were detected using a polymerase chain reaction clamping and melting curve technique.

Statistical considerations

- The pooled analysis was performed on individual patient data from the two trials.
- CRYSTAL study data cut-offs were: PFS (IRC), OR (IRC) on 27 July 2006, OS on 31 May 2009.
- OPUS study data cut-offs were: PFS (IRC), OR (IRC) on 01 March 2007, OS on 30 November 2008.
- Treatment groups were compared in a Cox proportional hazards model for OS and PFS and in a logistic regression model for OR that were both adjusted for study effects and stratified by Eastern Cooperative Oncology Group performance status.
- Inter-study heterogeneity was assessed by testing for individual treatment effect estimates across the studies.

Results

Baseline characteristics

Table 1. Patient and disease characteristics at baseline in patients with *KRAS* wt tumors pooled from the CRYSTAL and OPUS studies

Characteristics, n (%) unless otherwise stated	*KRAS* wt (n=845)		*KRAS* wt/*BRAF* wt (n=730)		*KRAS* wt/*BRAF* mt (n=70)	
	CT (n=447)	Cetuximab + CT (n=398)	CT (n=381)	Cetuximab + CT (n=349)	CT (n=38)	Cetuximab + CT (n=32)
Gender						
Male	266 (60)	238 (60)	228 (60)	214 (61)	22 (58)	17 (53)
Female	181 (40)	160 (40)	153 (40)	135 (39)	16 (42)	15 (47)
Median age, years (range)	59 (19–84)	61 (24–79)	59 (19–84)	61 (24–79)	59 (25–75)	64 (34–79)
Age categories						
<65 years	297 (66)	246 (62)	254 (67)	216 (62)	25 (66)	18 (56)
≥65 years	150 (34)	152 (38)	127 (33)	133 (38)	13 (34)	14 (44)
ECOG PS						
0/1	423 (95)	379 (95)	363 (95)	332 (95)	34 (90)	32 (100)
Liver metastases only	95 (21)	93 (23)	85 (22)	80 (23)	4 (11)	10 (31)
Involved disease sites ≤2	370 (83)	344 (86)	321 (84)	305 (87)	25 (66)	25 (78)
Prior adjuvant chemotherapy	90 (20)	85 (21)	83 (22)	87 (25)	6 (16)	5 (16)

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

Clinical efficacy (Table 2)

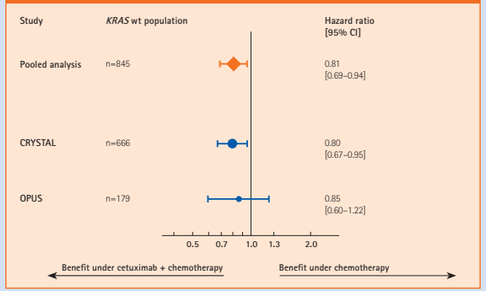
- Patients with *KRAS* wt tumors experienced more benefit in terms of OS (Figure 1 & 4), PFS (Figure 2 & 5) and OR (Figure 3) when receiving cetuximab plus chemotherapy compared with chemotherapy alone.

Table 2. Efficacy data from the pooled analysis of patients with *KRAS* wt tumors according to *BRAF* mutation status

	KRAS wt (n=845)		*KRAS* wt/*BRAF* wt (n=730)		*KRAS* wt/*BRAF* mt (n=70)	
	CT (n=447)	Cetuximab + CT (n=398)	CT (n=381)	Cetuximab + CT (n=349)	CT (n=38)	Cetuximab + CT (n=32)
OS time						
Median OS, months [95% CI]	19.5 [17.8–21.1]	23.5 [20.7–25.7]	21.1 [19.5–23.6]	24.8 [22.1–27.0]	9.9 [5.7–13.6]	14.1 [8.8–18.5]
Hazard ratio[a] [95% CI] p-value[b] (heterogeneity p-value[c])	0.81 [0.69–0.94] 0.0062 (0.6996)		0.84 [0.71–1.00] 0.0479 (0.6980)		0.62 [0.36–1.06] 0.0764 (0.0478)	
PFS time						
Median PFS, months [95% CI]	7.6 [7.4–8.4]	9.6 [8.9–11.3]	7.7 [7.4–9.0]	10.9 [9.2–11.9]	3.7 [2.1–7.9]	7.1 [3.7–9.1]
Hazard ratio[a] [95% CI] p-value [b] (heterogeneity p-value[c])	0.66 [0.55–0.80] <0.0001 (0.3332)		0.64 [0.52–0.79] <0.0001 (0.3362)		0.67 [0.34–1.29] 0.2301 (0.3778)	
Tumor response						
OR rate, %	38.5	57.3	40.9	60.7	13.2	21.9
Odds ratio[a] [95% CI] p-value [b] (heterogeneity p-value[c])	2.16 [1.64–2.86] <0.0001 (0.5568)		2.27 [1.68–3.07] <0.0001 (0.5891)		1.60 [0.45–5.67] 0.4606 (0.1727)	

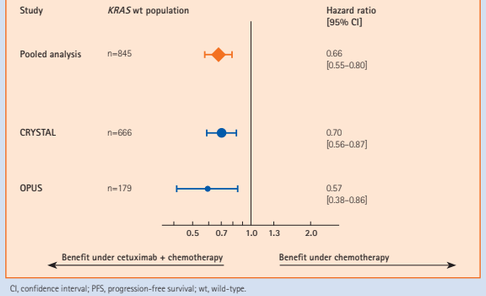
[a] Hazard ratios <1 for OS and PFS and odds ratios >1 for OR indicate a benefit for the addition of cetuximab to chemotherapy compared with chemotherapy alone.
[b] Likelihood ratio test on treatment effect in stratified Cox's proportional hazards model.
[c] Pooled (stratified) likelihood ratio test on study treatment interaction in stratified Cox's proportional hazards model.
CI, confidence interval; CT, chemotherapy; OR, best overall response; OS, overall survival; PFS, progression-free survival; mt, mutant; wt, wild-type.

Figure 1. Analysis of pooled OS data in patients with *KRAS* wt tumors



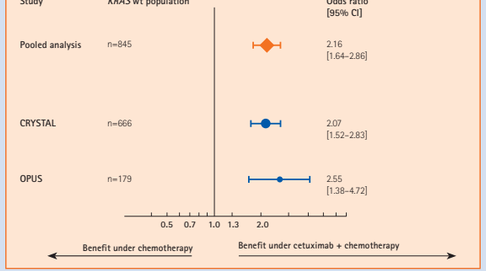
CI, confidence interval; OS, overall survival; wt, wild-type.

Figure 2. Analysis of pooled PFS data in patients with *KRAS* wt tumors



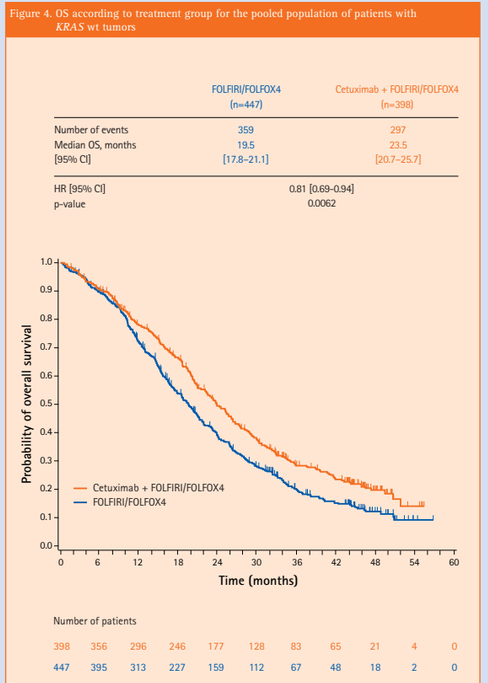
CI, confidence interval; PFS, progression-free survival; wt, wild-type.

Figure 3. Analysis of pooled OR data in patients with *KRAS* wt tumors



CI, confidence interval; OR, best overall response; wt, wild-type.

Figure 4. OS according to treatment group for the pooled population of patients with *KRAS* wt tumors



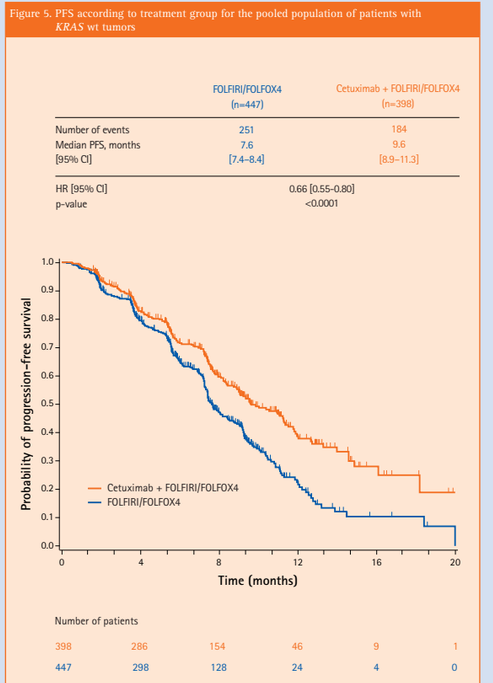
CI, confidence interval; HR, hazard ratio; OS, overall survival; wt, wild-type.

- Results of sensitivity analyses for fixed or random effect models were nearly identical thus confirming the robustness of the data.

Conclusions

- In this pooled analysis a significant improvement in OS time was demonstrated for patients with *KRAS* wt tumors receiving cetuximab plus chemotherapy compared with chemotherapy alone.
- This analysis strengthens the findings from the CRYSTAL and OPUS studies that the addition of cetuximab to 1st-line chemotherapy in patients with *KRAS* wt mCRC significantly improves OR and PFS.
- The cetuximab treatment effect does not vary by *BRAF* mutation status. Patients with *BRAF* mutations also appear to benefit from cetuximab.
- The pooled analysis confirms the consistency of the benefit across all endpoints obtained with cetuximab added to 1st-line chemotherapy in patients with *KRAS* wt mCRC.

Figure 5. PFS according to treatment group for the pooled population of patients with *KRAS* wt tumors



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

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Acknowledgments

The authors would like to thank patients, investigators, co-investigators and the study teams at each of the participating centers and at Merck KGaA, Darmstadt, Germany.