A meta-analysis of the CRYSTAL and OPUS studies combining cetuximab with chemotherapy (CT) as 1st-line treatment for patients (pts) with metastatic colorectal cancer (mCRC): Results according to *KRAS* and *BRAF* mutation status

E. Van Cutsem,[1] P. Rougier,[2] C.H. Köhne,[3] C. Stroh,[4] M. Schlichting,[4] C. Bokemeyer[5]

[1] University Hospital Gasthuisberg, Digestive Oncology Unit, Leuven, Belgium; [2] Hôpital Ambroise Paré, Oncology, Boulogne, France; [3] Klinikum Oldenburg, Oncology, Oldenburg, Germany; [4] Merck KGaA, Darmstadt, Germany; [5] Universitätsklinikum Eppendorf, Department of Oncology and Hematology, Hamburg, Germany

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Abstract (updated)

Background

The CRYSTAL and OPUS studies demonstrated that adding cetuximab to CT (FOLFIRI or FOLFOX4, respectively) as 1st-line treatment for mCRC significantly reduced the risk of disease progression and increased the chance of response, compared with CT alone, in pts with *KRAS* wild-type (wt) tumors. The objective of the current meta-analysis was to evaluate overall survival time (OS), progression-free survival time (PFS) and best overall response (OR) in combined CRYSTAL and OPUS pt populations, according to *KRAS* mutation status. *BRAF* tumor mutation status will be investigated to evaluate the predictive value of downstream effectors of KRAS activity on treatment efficacy.

Materials and methods

The meta-analysis was performed on individual patient data updated for OS and *KRAS* tumor mutation status from the two randomized controlled studies for the primary clinical efficacy endpoints: PFS (CRYSTAL) and best OR (OPUS) supplemented by overall survival time. Primary definitions were employed, as provided by the individual study protocols. In both studies, the primary analysis of PFS and best OR was based on an independent radiology review committee assessment. Hazard ratios (HRs) for the treatment effect on OS and PFS were obtained by applying a Cox proportional hazards model to individual patient data that was adjusted for study and the common randomization strata, ECOG performance status. Odds ratios for the treatment effect on OR were obtained by performing a logistic regression on individual patient data using the same adjustment. Mutations in *KRAS* (codons 12/13) and *BRAF* (codon 600) were detected by mutation-specific qPCR.

Results

The meta-analysis of 845 pts with *KRAS* wt tumors demonstrated that the addition of cetuximab to CT provided a significant benefit for the primary study endpoints PFS and OR and for OS compared with pts receiving CT alone. Overall, the addition of cetuximab to CT in pts with *KRAS* wt tumors significantly reduced the risk of disease progression by 34% (HR 0.66; 95% CI: [0.55–0.80]; p<0.0001) and increased the likelihood of achieving a response by >2-fold (odds ratio 2.16; 95% CI: [1.64–2.86]; p<0.0001) compared with those pts who received CT alone. Furthermore OS was significantly longer in *KRAS* wt pts receiving cetuximab plus CT compared with those receiving CT alone (HR 0.81; 95% CI [0.69–0.94]; p=0.006). Tests on heterogeneity did not indicate a difference in the treatment effect across studies. An analysis of the impact of *BRAF* mutation status on cetuximab activity is ongoing and will be presented at a later date.

Conclusions

The meta-analysis results strengthen the findings obtained from the CRYSTAL and OPUS pt populations with *KRAS* wt tumors. Adding cetuximab to CT significantly reduces the risk of disease progression, increases the chance of response and improves OS in the 1st-line treatment of mCRC.

Background

- The *KRAS* gene is mutated in around 30% of colorectal cancer (CRC).[1]
- The randomized, controlled CRYSTAL[2] and OPUS[3] trials showed that adding the IgG1 epidermal growth factor receptor (EGFR)-targeting monoclonal antibody, cetuximab, to standard 1st-line irinotecan- or oxaliplatin-based therapy improved efficacy in patients with *KRAS* wild-type tumors.
- Meta-analyses of randomized studies form an important component of evidence-based medicine and analyses of pooled individual patient data can be useful to provide a more precise estimate of the overall treatment effects, to substantiate the effects for the population of interest, and for highlighting or confirming differences between treatments through increasing the statistical power and providing a more objective appraisal of treatment benefit.[4,5]
- The effect of tumor *KRAS* and *BRAF* (a downstream effector of *KRAS*) 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 meta-analysis of pooled data from the CRYSTAL and OPUS populations.
- Determination of the *BRAF* mutation status is ongoing and will be presented elsewhere.
- Compared to previously published study results, the ascertainment rate for *KRAS* mutation has been enhanced and the most recent survival data has been used for analysis of efficacy endpoints and tumor *KRAS* mutation status.

Objective

- The objective of this meta-analysis was to investigate the effects of tumor *KRAS* mutation status on the efficacy of cetuximab, 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

- The CRYSTAL and OPUS trials have been published previously.[2,3] Patients were randomized to receive cetuximab in combination with FOLFIRI (CRYSTAL) or FOLFOX4 (OPUS) or the standard 1st-line treatment alone.
- Additional survival data were available for the CRYSTAL and OPUS studies (see statistics below).
- For each trial, the primary analyses of PFS and OR were based on computed tomography or magnetic resonance imaging (MRI) scans as assessed by an independent radiology review committee (IRC).
- For both studies additional tumor mutation analysis was performed on material extracted from stained slides previously collected to evaluate tumor EGFR expression status.
- The presence of *KRAS* mutations at codons 12/13 were determined using a mutation-specific quantitative polymerase chain reaction (qPCR) clamping and melting curve method.[2,3]

Statistics

- The meta-analysis was performed on individual patient data from the two trials.
- CRYSTAL study data cut-offs were: PFS (IRC), OR (IRC) on the 27th July 2006, OS on the 31st May 2009, and *KRAS* on the 28th August 2009.
- OPUS study data cut-offs were: PFS (IRC), OR (IRC) on the 1st March 2007, OS on the 30th November 2008 and *KRAS* on the 12th August 2009.
- Cox's proportional hazards model and a logistic regression model stratified by the common randomization strata i.e. Eastern Cooperative Oncology Group performance status (ECOG PS) was employed to estimate the hazard ratio (HR) for the treatment effect in terms of OS, PFS and OR, respectively.
- Treatment groups were compared by a stratified log-rank test for OS and PFS and a stratified Cochran-Mantel-Haenszel test for OR.
- Sensitivity analysis comprised a random and fixed study effect model.
- Inter-study heterogeneity was assessed by testing for treatment by study interaction.

Results

Efficacy data from the CRYSTAL study

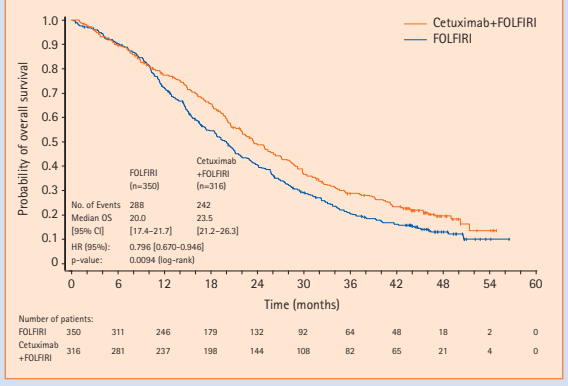
- Data from the analysis of the CRYSTAL study demonstrated that in *KRAS* wild-type patients the addition of cetuximab to FOLFIRI significantly improved OR, and PFS, and led to a significant improvement in OS compared with patients receiving FOLFIRI alone (Table 1 & Figure 1).

Table 1. Efficacy data from the CRYSTAL study

	KRAS wild-type		*KRAS* mutant	
	Cetuximab + FOLFIRI (n=316)	FOLFIRI (n=350)	Cetuximab + FOLFIRI (n=214)	FOLFIRI (n=183)
OS time				
Median OS (months)	23.5	20.0	16.2	16.7
HR	0.796		1.035	
[95% CI]	[0.670-0.946]		[0.834-1.284]	
p-value*	0.0094		0.7551	
PFS time				
Median PFS (months)	9.9	8.4	7.4	7.7
HR	0.696		1.171	
[95% CI]	[0.558-0.867]		[0.887-1.544]	
p-value*	0.0012		0.2661	
Tumor response				
OR rate (%)	57.3	39.7	31.3	36.1
Odds ratio	2.0693		0.8220	
[95% CI]	[1.5154-2.8258]		[0.5441-1.2419]	
p-value**	<0.0001		0.3475	

*Stratified log-rank p-value. **Stratified Cochran-Mantel-Haenszel test.
CI, confidence interval; HR, hazard ratio; OR, best overall response; OS, overall survival; PFS, progression-free survival.

Figure 1. Overall survival in the *KRAS* wild-type population from the CRYSTAL study



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Efficacy data from the OPUS study

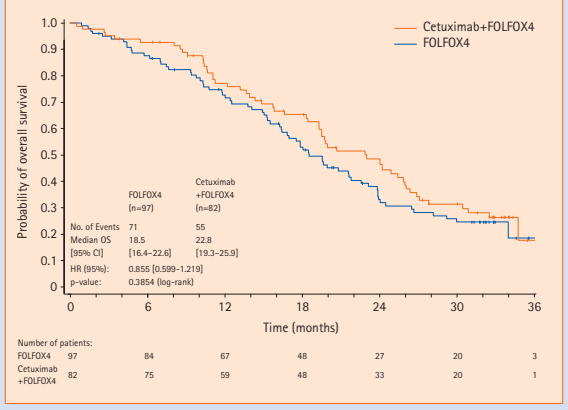
- Data from the analysis of the OPUS study demonstrated that in *KRAS* wild-type patients the addition of cetuximab to FOLFOX4 significantly improved OR, and PFS, and led to a non significant improvement in OS compared with patients receiving FOLFOX4 alone (Table 2 & Figure 2).

Table 2. Efficacy data from the OPUS study

	KRAS wild-type		*KRAS* mutant	
	Cetuximab + FOLFOX4 (n=82)	FOLFOX4 (n=97)	Cetuximab + FOLFOX4 (n=77)	FOLFOX4 (n=59)
OS time				
Median OS (months)	22.8	18.5	13.4	17.5
HR	0.855		1.290	
[95% CI]	[0.599-1.219]		[0.873-1.906]	
p-value*	0.3854		0.2004	
PFS time				
Median PFS (months)	8.3	7.2	5.5	8.6
HR	0.567		1.720	
[95% CI]	[0.375-0.856]		[1.104-2.679]	
p-value*	0.0064		0.0153	
Tumor response				
OR rate (%)	57.3	34.0	33.8	52.5
Odds ratio	2.5512		0.4591	
[95% CI]	[1.3799-4.7169]		[0.2280-0.9244]	
p-value**	0.0027		0.0290	

*Stratified log-rank test. **Stratified Cochran-Mantel-Haenszel test.
CI, confidence interval; HR, hazard ratio; OR, best overall response; OS, overall survival; PFS, progression-free survival.

Figure 2. Overall survival in the *KRAS* wild-type population from the OPUS study



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Meta-analysis of efficacy data from the CRYSTAL and OPUS studies

- A meta-analysis was performed on 845 patients with *KRAS* wild-type tumors from the OPUS and CRYSTAL studies.
- Analysis of the pooled individual patient data from the CRYSTAL and OPUS studies demonstrated that patients with *KRAS* wild-type tumors experienced more benefit in terms of OS (Figure 3), PFS (Figure 4) and OR rate (Figure 5) when receiving cetuximab plus chemotherapy compared with patients receiving chemotherapy alone.

Figure 3. Meta-analysis of pooled OS data in patients with *KRAS* wild-type tumors from the CRYSTAL and OPUS studies

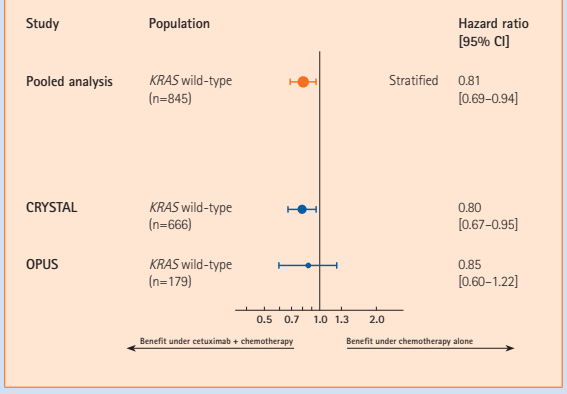


Figure 4. Meta-analysis of pooled PFS data in patients with *KRAS* wild-type tumors from the CRYSTAL and OPUS studies

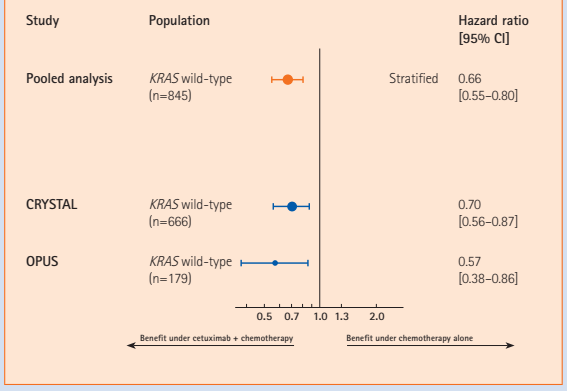
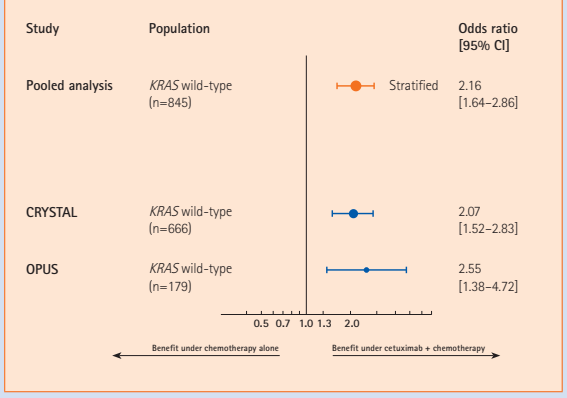


Figure 5. Meta-analysis of pooled OR data for patients with *KRAS* wild-type tumors from the CRYSTAL and OPUS studies



- The difference in the benefit obtained from receiving cetuximab plus chemotherapy in patients with *KRAS* wild-type tumors compared with those receiving chemotherapy alone was significant for each efficacy endpoint (Table 3).

Table 3. Summary of meta-analysis of efficacy endpoints in patients with *KRAS* wild-type tumors from the OPUS and CRYSTAL studies

Endpoints	HR*/Odds ratio*	[95% CI]	p-value**	Heterogeneity p-value†
OS	0.81	[0.69–0.94]	0.0062	0.70
PFS	0.66	[0.55–0.80]	<0.0001	0.33
OR	2.16	[1.64–2.86]	<0.0001	0.56

* HR of cetuximab + chemotherapy/chemotherapy-alone, odds ratio of cetuximab + chemotherapy/chemotherapy-alone.
** Likelihood ratio test on treatment effect in stratified Cox's proportional hazards model.
† Pooled (stratified): likelihood ratio test on study treatment interaction in stratified Cox's proportional hazards model.
HR, hazard ratio; OR, best overall response; OS, overall survival; PFS, progression-free survival.

- The treatment effect did not vary across studies as indicated by the non-significant p-value when testing heterogeneity.
- Results of the sensitivity analysis for fixed or random effects models were nearly identical thus confirming the robustness of the given results.

Conclusions

- In the CRYSTAL study in patients with *KRAS* wild-type tumors, the addition of cetuximab to FOLFIRI significantly improved OS compared with patients receiving FOLFIRI alone.
- In the OPUS study in patients with *KRAS* wild-type tumors, the addition of cetuximab to FOLFOX4 led to an increase in survival time of longer than 4 months although this difference was not statistically significant.
- This meta-analysis strengthens the findings from the OPUS and CRYSTAL studies in that the addition of cetuximab to chemotherapy 1st-line in patients with mCRC with *KRAS* wild-type tumors significantly improves OR and PFS.
- In the meta-analysis, a significant improvement in OS was demonstrated for patients with *KRAS* wild-type tumors receiving cetuximab plus chemotherapy compared with chemotherapy alone.
- This meta-analysis confirms the consistency of the benefit for all endpoints obtained with cetuximab added to 1st-line chemotherapy in mCRC patients with *KRAS* wild-type tumors.

References

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