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Outcome according to metastatic site in patients with *KRAS* wt tumors: analysis from the CRYSTAL and OPUS studies

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Background

- The randomized phase III CRYSTAL study demonstrated that the addition of cetuximab to 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) as 1st-line therapy resulted in significant improvements in overall survival (OS), progression-free survival (PFS) and response in patients with *KRAS* wild-type (wt) metastatic colorectal cancer (mCRC).[1,2]
- The randomized phase II OPUS study demonstrated that the addition of cetuximab to 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) as 1st-line therapy resulted in significant improvements in PFS and response in patients with *KRAS* wt mCRC.[3,4]
- We hypothesized that patients with mCRC who had metastases limited to the liver (liver-limited disease; LLD) might have a different response to treatment when compared with those patients who had extra-hepatic disease (non-LLD).

Study objective

The aim of this subgroup analysis was to investigate the efficacy of chemotherapy + cetuximab compared with chemotherapy alone in the 1st-line treatment of patients with *KRAS* wt mCRC according to whether they had LLD or non-LLD at study entry.

Methods

- Patients were randomized to receive cetuximab in combination with FOLFIRI (CRYSTAL)[1] or FOLFOX4 (OPUS)[3] or the standard 1st-line chemotherapy regimen alone.
- Treatment was continued until disease progression, symptomatic deterioration or the occurrence of unacceptable toxicity.
- In each study the primary analyses of PFS and best overall response were based on radiological scans as assessed by an independent review committee (IRC) according to modified World Health Organization criteria.
- In a retrospective subgroup analysis, patients in the CRYSTAL and OPUS studies with *KRAS* wt tumors were grouped according to whether metastatic lesions were detectable at study entry only in the liver (LLD), or whether they were detectable within and/or outside the liver (non-LLD).
- For each study, for each treatment arm, best overall response rates (ORRs), R0 resection rates, PFS and OS were compared for LLD vs non-LLD patient groups.
- These parameters were also analyzed according to treatment arm for LLD and non-LLD patient groups in each study.
- CRYSTAL study data cut-offs were: PFS (IRC), ORR (IRC) on 27 July 2006, OS on 31 May 2009.
- OPUS study data cut-offs were: PFS (IRC), ORR (IRC) on 01 March 2007, OS on 30 November 2008.
- Patient subgroups were compared using Cox proportional hazards models for OS and PFS and a logistic regression model for ORR and R0 resection. Stratified hazard ratios (HRs), odds ratios and p-values were presented according to the study-specific randomization strata.
- Due to the exploratory nature of this analysis, multiplicity adjustments were not performed. P-values should be considered as descriptive statistical measures.

Results

- Of 666 patients in the CRYSTAL study with *KRAS* wt tumors, 140 (21%) had LLD and 526 (79%) had non-LLD.
- Of 179 patients in the OPUS study with *KRAS* wt tumors, 48 (27%) had LLD and 131 (73%) had non-LLD.
- Efficacy data for both studies for patients with *KRAS* wt tumors according to treatment arm and site of metastatic disease are summarized in Tables 1 & 2.
- In both the CRYSTAL and OPUS studies, response rates were significantly higher for patients with *KRAS* wt tumors in the chemotherapy + cetuximab compared with chemotherapy alone arms (Table 1 & Figure 1):
  - Resection rates were also higher in the chemotherapy + cetuximab arms, although the difference in R0 resection reached significance only for CRYSTAL study patients (Table 1 & Figure 1; overall rate in the CRYSTAL study 7.9% vs 4.6%, odds ratio 1.82, p=0.063; R0 rate 5.1% vs 2.0%, odds ratio 2.65, p=0.027)

Table 1. Efficacy in each treatment arm in patients with *KRAS* wt tumors according to metastatic site*

	CT			CT + cetuximab		
CRYSTAL	All n=350	LLD n=72	Non-LLD n=278	All n=316	LLD n=68	Non-LLD n=248
Response						
ORR, %	39.7	44.4	38.5	57.3	70.6	53.6
Odds ratio [95% CI]		1.28 [0.75–2.16]			2.02 [1.12–3.66]	
p-value†		0.36			0.019	
R0 resection						
Rate, %	2.0	5.6	1.1	5.1	13.2	2.8
Odds ratio [95% CI]		5.89 [1.24–27.96]			4.92 [1.69–14.31]	
p-value†		0.013			0.002	
PFS						
Median, months	8.4	9.2	8.1	9.9	11.8	9.5
HR [95% CI]		0.82 [0.56–1.21]			0.71 [0.46–1.10]	
p-value†		0.32			0.127	
OS						
Median, months	20.0	27.7	17.4	23.5	27.8	22.5
HR [95% CI]		0.62 [0.46–0.84]			0.74 [0.54–1.03]	
p-value†		0.002			0.071	
OPUS	n=97	n=23	n=74	n=82	n=25	n=57
Response						
ORR, %	34.0	39.1	32.4	57.3	76.0	49.1
Odds ratio [95% CI]		1.25 [0.47–3.34]			2.81 [0.97–8.21]	
p-value†		0.66			0.055	
R0 resection						
Rate, %	3.1	4.3	2.7	7.3	16.0	3.5
Odds ratio [95% CI]		1.48 [0.13–17.12]			4.67 [0.79–27.47]	
p-value†		0.76			0.068	
PFS						
Median, months	7.2	7.9	6.0	8.3	11.9	7.6
HR [95% CI]		0.46 [0.23–0.95]			0.57 [0.26–1.21]	
p-value†		0.031			0.138	
OS						
Median, months	18.5	23.9	16.4	22.8	26.3	19.8
HR [95% CI]		0.48 [0.26–0.89]			0.61 [0.33–1.14]	
p-value†		0.016			0.115	

*Stratified hazard and odds ratios are for LLD vs non-LLD groups; †Cochran–Mantel–Haenszel test; ‡stratified log-rank test.
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LLD, liver-limited disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

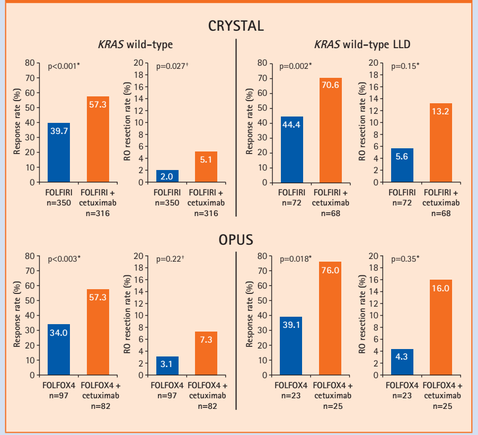
- For patients with *KRAS* wt LLD compared with non-LLD, in both the CRYSTAL and OPUS studies (Table 1, Figures 2 & 3):
  - Tumor response was improved (significantly for CRYSTAL patients in the FOLFIRI + cetuximab group)
  - R0 resection was enhanced (significantly for both treatment groups of the CRYSTAL study)
  - PFS time was prolonged (significantly for OPUS patients in the FOLFOX4 alone group)
  - OS times were prolonged with differences significant for patients in the chemotherapy alone groups of both studies
- For patients with *KRAS* wt LLD in both the CRYSTAL and OPUS studies, response was significantly improved for those in the chemotherapy + cetuximab compared with chemotherapy alone groups (Figure 1):
  - The highest R0 resection rates were seen in patients with *KRAS* wt LLD in the chemotherapy + cetuximab groups of both studies, with 2.3-fold (CRYSTAL) and 3.7-fold (OPUS) increases in rates compared with the chemotherapy alone groups (Table 1 & Figure 1)
- For patients with *KRAS* wt LLD, PFS was prolonged in both studies for patients randomized to chemotherapy + cetuximab compared with chemotherapy alone (Table 2):
  - CRYSTAL: median 11.8 vs 9.2 months, stratified HR 0.56, p=0.035
  - OPUS: median 11.9 vs 7.9 months, stratified HR 0.64, p=0.39
- In patients with *KRAS* wt non-LLD, the addition of cetuximab to chemotherapy:
  - Significantly improved OS in CRYSTAL study patients (median OS improved by 5.1 months; Figure 4)
  - Prolonged OS in OPUS study patients (median OS improved by 3.4 months; Figure 5)
  - Significantly improved PFS in both studies (Table 2)

Table 2. Efficacy according to treatment arm for patients with *KRAS* wt tumors grouped by metastatic site*

	LLD		Non-LLD	
CRYSTAL	CT n=72	CT + cetuximab n=68	CT n=278	CT + cetuximab n=248
PFS				
Median, months	9.2	11.8	8.1	9.5
HR [95% CI]	0.56 [0.32–0.97]		0.74 [0.58–0.94]	
p-value†	0.035		0.012	
OS				
Median, months	27.7	27.8	17.4	22.5
HR [95% CI]	0.85 [0.57–1.28]		0.79 [0.65–0.95]	
p-value†	0.44		0.013	
OPUS	n=23	n=25	n=74	n=57
PFS				
Median, months	7.9	11.9	6.0	7.6
HR [95% CI]	0.64 [0.23–1.79]		0.59 [0.37–0.93]	
p-value†	0.39		0.023	
OS				
Median, months	23.9	26.3	16.4	19.8
HR [95% CI]	0.93 [0.44–2.00]		0.80 [0.54–1.21]	
p-value†	0.86		0.29	

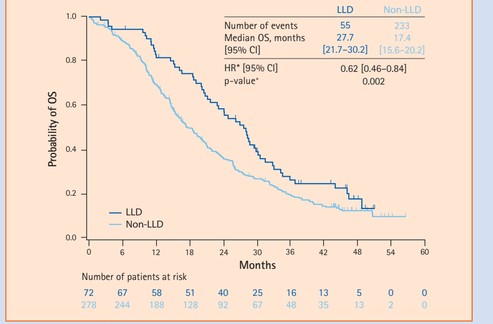
*Stratified hazard ratios are for CT + cetuximab vs CT groups; †stratified log-rank test.
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; PFS, progression-free survival.

Figure 1. Response and R0 resection rates according to treatment



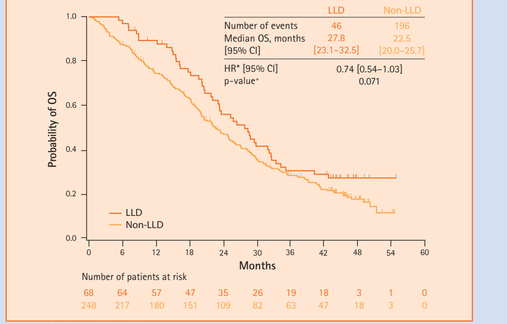
*Fisher's exact test; †Cochran–Mantel–Haenszel test.
LLD, liver-limited disease.

Figure 2. Overall survival according to metastatic site in CRYSTAL study patients with *KRAS* wt tumors randomized to FOLFIRI



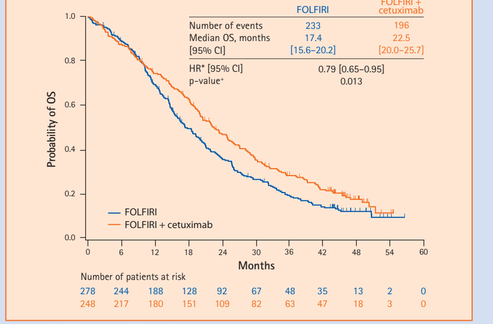
*Stratified HR for LLD vs non-LLD; †stratified log-rank test.
CI, confidence interval; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; wt, wild-type.

Figure 3. Overall survival according to metastatic site in CRYSTAL study patients with *KRAS* wt tumors randomized to FOLFIRI + cetuximab



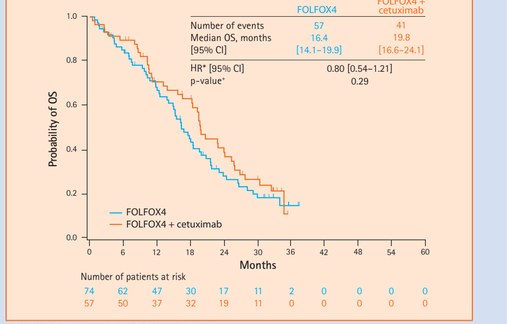
*Stratified HR for LLD vs non-LLD; †stratified log-rank test.
CI, confidence interval; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; wt, wild-type.

Figure 4. Overall survival according to treatment in CRYSTAL study patients with *KRAS* wt, non-LLD



*Stratified HR for FOLFIRI + cetuximab vs FOLFIRI; †stratified log-rank test.
CI, confidence interval; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; wt, wild-type.

Figure 5. Overall survival according to treatment in OPUS study patients with *KRAS* wt, non-LLD



*Stratified HR for FOLFOX4 + cetuximab vs FOLFOX4; †stratified log-rank test.
CI, confidence interval; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; wt, wild-type.

Conclusions

- For patients with *KRAS* wt mCRC who receive standard 1st-line chemotherapy, OS was significantly longer for those with LLD compared with non-LLD:
  - LLD may be a baseline characteristic associated with good prognosis in this patient group
- In patients with *KRAS* wt tumors, the addition of cetuximab to chemotherapy:
  - Significantly increased R0 resection rates in patients who received FOLFIRI + cetuximab
  - Increased R0 resection rates in patients with LLD who received FOLFIRI + cetuximab (2.3-fold) or FOLFOX4 + cetuximab (3.7-fold)
  - Significantly improved PFS and OS in non-LLD patients who received FOLFIRI + cetuximab
  - Significantly improved PFS in non-LLD patients who received FOLFOX4 + cetuximab
- The addition of cetuximab to chemotherapy as 1st-line treatment for mCRC improves clinical outcome in patients with both LLD and non-LLD.

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