Impact of early tumor shrinkage on long-term outcome in metastatic colorectal cancer (mCRC) treated with FOLFOX4 with or without cetuximab: lessons from the OPUS trial

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Impact of early tumor shrinkage on long-term outcome in metastatic colorectal cancer (mCRC) treated with FOLFOX4 with or without cetuximab: lessons from the OPUS trial

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Background

- The measurement of early tumor shrinkage has been reported to predict long-term outcome in mCRC treated with irinotecan-based chemotherapy + cetuximab.[1,2]
- This association was observed both in chemorefractory patients[1] and in patients treated 1st-line from the CRYSTAL study.[2]
- In the CRYSTAL study early tumor shrinkage (≥20% tumor shrinkage at week 8):
  - Translated into long-term clinical benefit of 28.3 months median overall survival (OS) in patients with *KRAS* wild-type (wt) tumors treated with FOLFIRI + cetuximab
  - Prolonged progression-free survival (PFS) in *KRAS* wt patients treated with FOLFIRI alone
- This observation suggests that early tumor shrinkage has a profound impact on the course of the disease; it is not known however if this is true when other accompanying chemotherapeutic regimens are used.
- In the OPUS study, in patients with *KRAS* wt tumors, the addition of cetuximab to FOLFOX4 significantly improved PFS (median time 8.3 vs 7.2 months, hazard ratio [HR] 0.567, p=0.0064) and tumor response (57% vs 34%, odds ratio 2.551, p=0.0027), compared with FOLFOX4 alone. OS was also increased (median time 22.8 vs 18.5 months, HR 0.855, p=0.39) although the difference between the treatment arms was not significant.[3]
- An investigation into the effects of early tumor shrinkage on clinical outcome when using FOLFOX4 as the chemotherapeutic regimen was therefore carried out in patients treated 1st-line in the OPUS study.

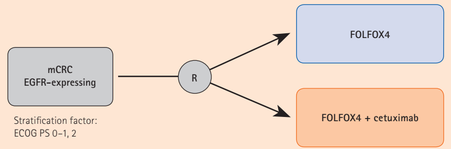
Study objective

- The primary objective of this retrospective analysis was to compare the ability of early tumor shrinkage (≥20% shrinkage at week 8) to predict long-term outcome in patients treated with FOLFOX4 with or without cetuximab.

Methods

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

Figure 1. Study design



FOLFOX4 (q2w)		Cetuximab (q1w)
Oxaliplatin	85 mg/m² day 1	400 mg/m² initial dose then
5-FU	400 mg/m² bolus then	250 mg/m² weekly
	600 mg/m² infusion, day 1 and 2	
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.

- *KRAS* mutations at codons 12/13 were detected using a polymerase chain reaction clamping and melting curve technique.[3]
- Relative changes in tumor size from baseline were computed from the baseline and 8-week radiological evaluations reported by the investigator and reviewed by an independent review committee.
- Changes in tumor size were expressed as relative change of the sum of the longest diameter of the target lesions.
- Kaplan-Meier curves were computed for PFS and OS in patients with early tumor shrinkage, stratified by treatment and *KRAS* tumor mutation status.
- A time-dependent receiver operating curve analysis had previously identified the best cut-off to use as a predictive variable for outcome to be ≥20% tumor shrinkage at week 8.[2]

Results

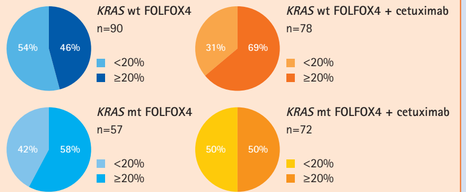
Patients

- The intention to treat population (ITT) included 337 mCRC patients.
- Radiological evaluation at week 8 (range 7–9) was available for central review in 317 of these patients:
  - Absence of data was due to early death in 13 patients, early surgery in one patient and protocol violation in six patients
- *KRAS* tumor mutation status was available for 300 (89%) of the ITT patients:
  - 130 (44%) were *KRAS* mutant
  - 170 (56%) were *KRAS* wt
- Both *KRAS* tumor mutation status and radiological evaluation at week 8 was available for 297 (88%) patients.

Early tumor shrinkage and outcome

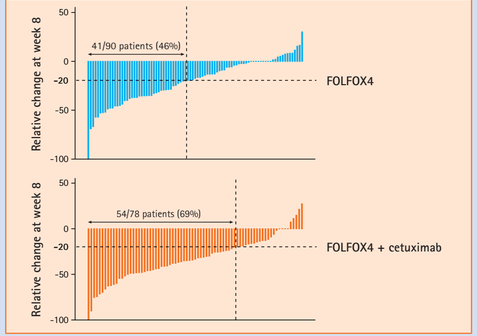
- Early tumor shrinkage occured more frequently in patients with *KRAS* wt tumors receiving FOLFOX4 + cetuximab (Figures 2 & 3).
- Early tumor shrinkage was associated with significantly better PFS and OS in *KRAS* wt patients treated with FOLFOX4 + cetuximab (Table 1, Figures 4 & 5) but not in patients treated with FOLFOX4 (Table 2, Figure 6 & 7).
- Early tumor shrinkage, compared with <20% shrinkage, in patients with *KRAS* mutant tumors treated with FOLFOX4 + cetuximab, was associated with significantly better PFS (median time 7.5 vs 4.0 months, HR 0.45, 95% confidence interval [CI] [0.26–0.79]) but not with significantly longer OS (median time 15.4 vs 12.7 months, HR 0.73, 95% CI [0.43–1.23]). However, in patients with *KRAS* mutant tumors treated with FOLFOX4 there was no association between early tumor shrinkage and outcome parameters.

Figure 2. Early tumor shrinkage according to *KRAS* mutation status and treatment



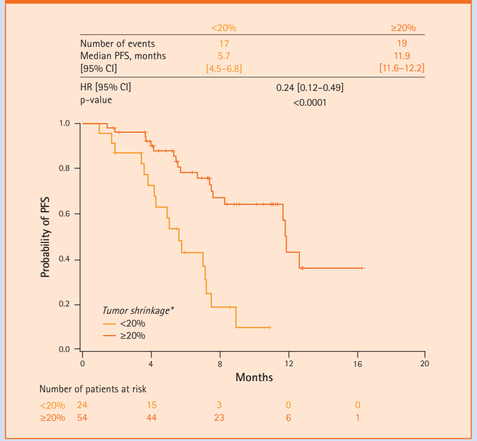
mt, mutant; wt, wild-type.

Figure 3. Early tumor shrinkage according to treatment in *KRAS* wt patients*



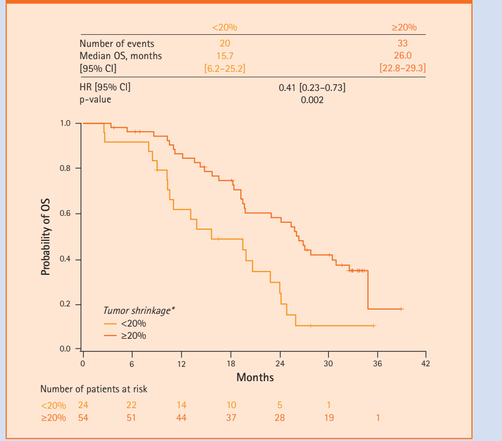
*Radiological evaluation reported by the investigator and reviewed by an independent review committee.
wt, wild-type.

Figure 4. Early tumor shrinkage and progression-free survival in *KRAS* wt patients treated with FOLFOX4 + cetuximab



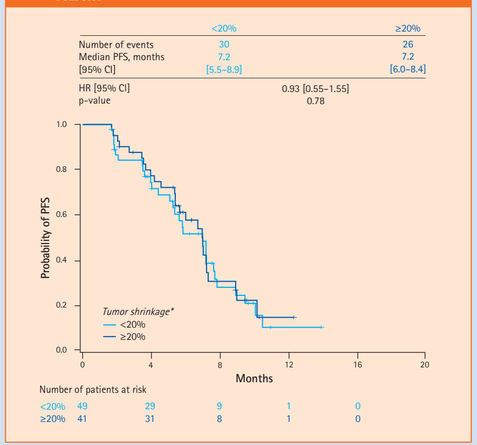
*Radiological evaluation reported by the investigator and reviewed by an independent review committee.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; wt, wild-type.

Figure 5. Early tumor shrinkage and overall survival in *KRAS* wt patients treated with FOLFOX4 + cetuximab



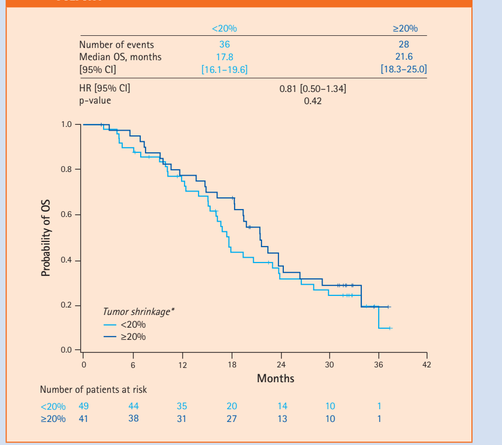
*Radiological evaluation reported by the investigator and reviewed by an independent review committee.
CI, confidence interval; HR, hazard ratio; OS, overall survival; wt, wild-type.

Figure 6. Early tumor shrinkage and progression-free survival in *KRAS* wt patients treated with FOLFOX4



*Radiological evaluation reported by the investigator and reviewed by an independent review committee.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; wt, wild-type.

Figure 7. Early tumor shrinkage and overall survival in *KRAS* wt patients treated with FOLFOX4



*Radiological evaluation reported by the investigator and reviewed by an independent review committee.
CI, confidence interval; HR, hazard ratio; OS, overall survival; wt, wild-type.

Table 1. Early tumor shrinkage and survival in *KRAS* wt patients treated with FOLFOX4 + cetuximab

	Tumor shrinkage	
	<20% n=24	≥20% n=54
PFS		
Median, months [95% CI]	5.7 [4.5–6.8]	11.9 [11.6–12.2]
HR [95% CI] p-value*	0.24 [0.12–0.49] <0.0001	
OS		
Median, months [95% CI]	15.7 [6.2–25.2]	26.0 [22.8–29.3]
HR [95% CI] p-value*	0.41 [0.23–0.73] 0.002	

*Log-rank.
HR, hazard ratio; OS, overall survival; PFS, progression-free survival; wt, wild-type.

Table 2. Early tumor shrinkage and survival in *KRAS* wt patients treated with FOLFOX4

	Tumor shrinkage	
	<20% n=49	≥20% n=41
PFS		
Median, months [95% CI]	7.2 [5.5–8.9]	7.2 [6.0–8.4]
HR [95% CI] p-value*	0.93 [0.55–1.55] 0.78	
OS		
Median, months [95% CI]	17.8 [16.1–19.6]	21.6 [18.3–25.0]
HR [95% CI] p-value*	0.81 [0.50–1.34] 0.42	

*Log-rank.
HR, hazard ratio; OS, overall survival; PFS, progression-free survival; wt, wild-type.

Conclusions

- In the OPUS trial, early tumor shrinkage was experienced in 69% of patients with *KRAS* wt tumors treated with 1st-line FOLFOX4 + cetuximab.
- In these patients, this early tumor shrinkage translated to a long-term clinical benefit of 26 months median OS.
- In patients treated with FOLFOX4 alone, early tumor shrinkage does not confer significant benefit in terms of PFS or OS.
- Based on this and the previous CRYSTAL analysis the association between early tumor shrinkage and better long-term outcome, in patients with *KRAS* wt tumors, is unrelated to the background chemotherapeutic regimen and appears to be specific for cetuximab.

References

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3. Bokemeyer C, et al. Ann Oncol 2011; Jan 12 [Epub ahead of print].

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