Early tumor shrinkage for the prediction of efficacy of cetuximab in metastatic colorectal cancer (mCRC): analysis from the CRYSTAL study

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ESMO 2010, Abstract No. 596P

Background

- We have previously shown that early tumor shrinkage predicts long-term outcome in chemorefractory mCRC treated with cetuximab either as monotherapy or in combination with chemotherapy in unselected patients in the BOND trial,[1] and in selected patients with *KRAS* wild-type tumors (wt).[2]
- Therefore early tumor shrinkage may be a hallmark of epidermal growth factor receptor (EGFR) inhibition, and may have the potential to be used as an on treatment marker of efficacy for EGFR-targeted agents.
- In contrast in the AVF2107 and N9741 trials objective response did not predict the outcome benefit from 1st-line treatment with standard chemotherapy either alone or in combination with bevacizumab.[3]
- In the CRYSTAL study the addition of cetuximab to 1st-line FOLFIRI significantly improved overall survival (OS) (Hazard ratio [HR], 0.796, p=0.0093) in patients with *KRAS* wt tumors.[4]
- An investigation of tumor shrinkage at first radiological evaluation as a predictor of long-term outcome in *KRAS* wt patients in the 1st-line setting in the CRYSTAL study was therefore carried out.

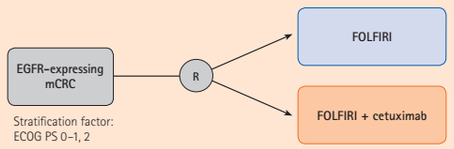
Study objectives

- The primary objective of this analysis was to investigate whether the occurrence of early tumor shrinkage at week 8 of 1st-line treatment was associated with superior long-term outcome in patients from the CRYSTAL trial treated with cetuximab.

Methods

- The CRYSTAL study was an open-label, randomized, multicenter, phase III study (Figure 1).

Figure 1. Study design



FOLFIRI (q2w)		Cetuximab
Irinotecan	180 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.

- Relative changes in tumor size from baseline were computed from the baseline and 8-week radiological evaluation 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 progression-free survival (PFS) and OS in patients with early tumor shrinkage, stratified by treatment and *KRAS* tumor mutation status.
- *KRAS* mutations at codons 12/13 were detected using the previously described polymerase chain reaction clamping and melting curve technique.[5]

Results

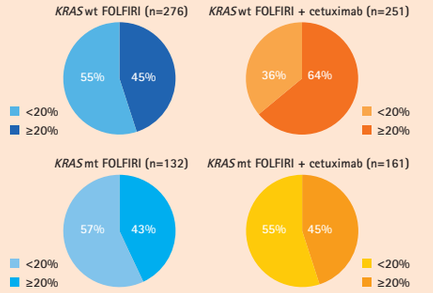
Patients

- The intention to treat population (ITT) included 1198 mCRC patients.
- Radiological evaluation at week 8 (range 7–9) was available for central review in 931 of these patients:
  - Absence of data was mainly due to evaluation occurring too early (5-7 weeks) in 77 patients or too late (9-11 weeks) in 88 patients
- *KRAS* tumor mutation status was available for 1063 (89%) patients.
- Both *KRAS* mutation status and radiological evaluation at week 8 was available from 820 (68%) patients:
  - 527/820 (64%) were *KRAS* wt

Early tumor shrinkage and treatment outcome

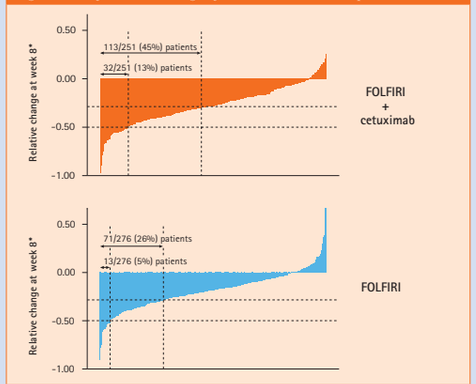
- A time-dependent receiver operating curve analysis identified the best cut-off to use as a predictive variable for outcome to be a ≥20% tumor shrinkage at week 8.
- Early tumor shrinkage was most common in patients with *KRAS* wt tumors receiving FOLFIRI plus cetuximab (Figures 2 & 3).
- Early tumor shrinkage was associated with significantly improved PFS and OS in *KRAS* wt patients treated with FOLFIRI plus cetuximab (Table 1, Figures 4 & 5) and for PFS with FOLFIRI (Table 2, Figure 6) but not for OS in patients treated with FOLFIRI (Table 2, Figure 7).
- Early tumor shrinkage did not provide additional benefit for OS for patients with *KRAS* mutant tumors.

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



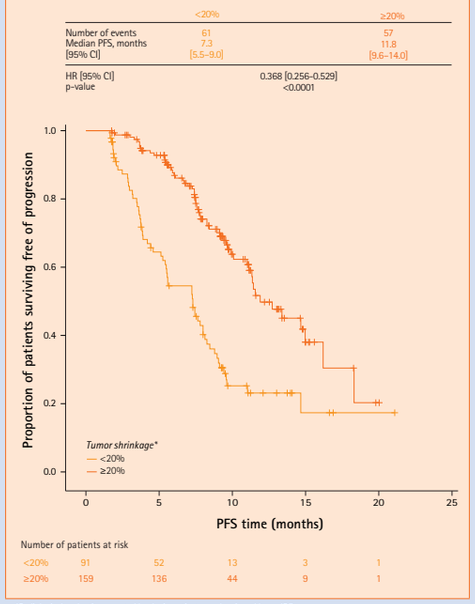
mt, mutant; wt, wild-type.

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



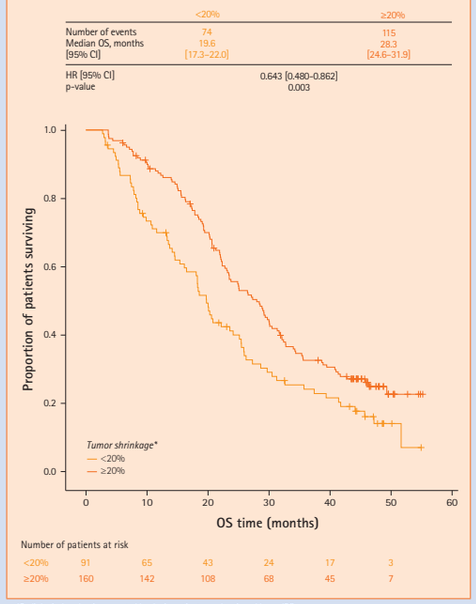
*Radiological evaluation reported by the investigator and reviewed by an IRC.
IRC, independent review committee; wt, wild-type.

Figure 4. Early tumor shrinkage and progression-free survival in *KRAS* wt patients treated with FOLFIRI + cetuximab at week 8



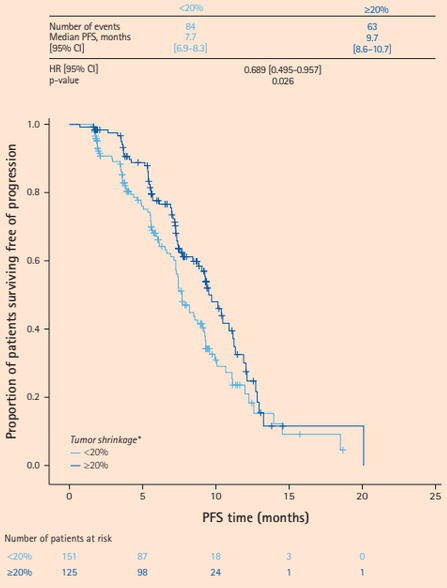
*Radiological evaluation reported by the investigator and reviewed by an IRC.
CI, confidence interval; IRC, independent review committee; PFS, progression-free survival; wt, wild-type.

Figure 5. Early tumor shrinkage and overall survival in *KRAS* wt patients treated with FOLFIRI + cetuximab at week 8



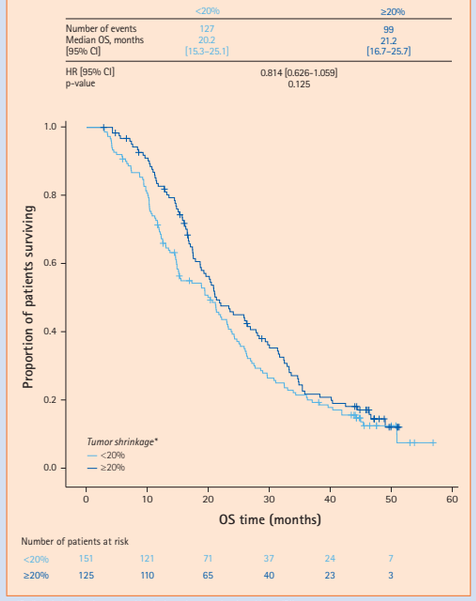
*Radiological evaluation reported by the investigator and reviewed by an IRC.
CI, confidence interval; IRC, independent review committee; OS, overall survival; wt, wild-type.

Figure 6. Early tumor shrinkage and progression-free survival in *KRAS* wt patients treated with FOLFIRI at week 8



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

Figure 7. Early tumor shrinkage and overall survival in *KRAS* wt patients treated with FOLFIRI at week 8



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

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

	Early tumor shrinkage	
	<20% n=91	≥20% n=160
PFS time		
Median, months [95% CI]	7.3 [5.5–9.0]	11.8 [9.6–14.0]
Hazard ratio [95% CI] p-value*	0.368 [0.256–0.529] <0.0001	
OS time		
Median, months [95% CI]	19.6 [17.3–22.0]	28.3 [24.6–31.9]
Hazard ratio [95% CI] p-value*	0.643 [0.480–0.862] 0.003	

*Log-rank.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

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

	Early tumor shrinkage	
	<20% n=151	≥20% n=125
PFS time		
Median, months [95% CI]	7.7 [6.9–8.3]	9.7 [8.6–10.7]
Hazard ratio [95% CI] p-value*	0.689 [0.495–0.957] 0.026	
OS time		
Median, months [95% CI]	20.2 [15.3–25.1]	21.2 [16.7–25.7]
Hazard ratio [95% CI] p-value*	0.814 [0.626–1.059] 0.125	

*Log-rank.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Conclusions

- In the CRYSTAL study early tumor shrinkage (≥20% at week 8) was experienced in 64% of *KRAS* wt patients treated with FOLFIRI plus cetuximab in the 1st-line setting.
- In these patients this early tumor shrinkage translated to a long-term clinical benefit of 28.3 months median OS.
- In patients treated with FOLFIRI alone, early tumor shrinkage led to significantly improved PFS but not OS.

References

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Acknowledgments

The study was sponsored by Merck KGaA Darmstadt, Germany. The authors would like to thank the patients and all investigators, including the study teams at each of the participating centers and at Merck KGaA, Darmstadt. Editorial assistance in the preparation of this poster was provided by Dr Paul Hoban, Cancer Communications and Consultancy Ltd, funded by Merck KGaA, Darmstadt, Germany.