# Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer – the influence of *KRAS* and *BRAF* biomarkers on outcome: Updated data from the CRYSTAL trial

E. Van Cutsem,[1] I. Lang,[2] G. Folprecht,[3] M.P. Nowacki,[4] S. Cascinu,[5] I. Shchepotin,[6] J. Maurel,[7] D. Cunningham,[8] I. Celik,[9] C.H. Köhne[10]

[1] University Hospital Gasthuisberg, Leuven, Belgium; [2] National Institute of Oncology, Budapest, Hungary; [3] University Hospital Carl Gustav Carus, Dresden, Germany; [4] MSC Memorial Cancer Center, Warsaw, Poland; [5] Università Politecnica delle Marche, Ancona, Italy; [6] National Cancer Institute, Kiev, Ukraine; [7] Hospital Clinic, Barcelona, Spain; [8] The Royal Marsden NHS Foundation Trust, London, UK; [9] Merck KGaA, Darmstadt, Germany; [10] Klinikum Oldenburg, Oldenburg, Germany

ASCO GI 2010, Abstract No. 281

## Background

- In the CRYSTAL study patients with *KRAS* wild-type tumors (*KRAS* wt) had a significantly reduced risk of disease progression (Hazard ratio, 0.68, p=0.02) and an increased chance of tumor response (Odds ratio, 1.91) in the cetuximab plus FOLFIRI arm compared with the FOLFIRI arm.[1]
- The CRYSTAL trial confirmed earlier findings from randomized and single-arm studies, that cetuximab efficacy was confined to patients with *KRAS* wt tumors.[2,3,4]
- The serine-threonine kinase BRAF is a direct downstream effector of KRAS. *BRAF* gene mutations have been detected in around 8% of colorectal tumors[5] and *BRAF* mutation status has been suggested to be predictive of cetuximab efficacy in pretreated patients.[6]
- Here we report an updated analysis of the CRYSTAL study with increased follow-up time and an increased population of patients for which tumor *KRAS* mutation status has been determined.
- The impact of *BRAF* tumor mutations in patients with *KRAS* wt tumors on cetuximab efficacy was investigated.

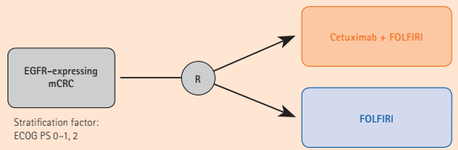
## Study objectives

- Primary study objective
  - Assess whether the progression-free survival (PFS) of patients receiving cetuximab plus FOLFIRI was superior to that of FOLFIRI alone.
- Secondary objectives
  - Comparison of the treatment regimens with respect to overall survival (OS) time, best overall response (OR) and safety.
- A retrospective subgroup analysis investigated associations between *KRAS*/*BRAF* tumor mutation status and PFS time, OR, and OS time.

## Methods

- This 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<br>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; R, randomization.

### Patients

- Main patient inclusion/exclusion criteria have been reported elsewhere.[1]

### *KRAS*/*BRAF* tumor mutation analysis

- Ascertainment of samples for *KRAS* and *BRAF* testing was increased using DNA extracted from formalin fixed paraffin embedded slide mounted sections initially prepared to evaluate tumor EGFR expression.
- *KRAS* mutations at codons 12/13 and *BRAF* (V600E) mutations were detected using the previously described polymerase chain reaction clamping and melting curve technique.[1]

### Data cut-offs for analysis

- CRYSTAL study data cut-offs were: PFS (independent review committee), OR (independent review committee) 27 July 2006, OS 31 May 2009.

## Results

### Baseline characteristics (Table 1)

- The number of patients for whom *KRAS* tumor mutation status was determined was increased from 540/1198 (45%), previously published[1] to 1063 (89%).
- The number of patients for whom *BRAF* tumor mutation status was determined was increased from 529/1198 (44%) previously reported[7] to 1000 (83%).
- *BRAF* mutations were detected in 60/1000 (6%) evaluable patient tumor samples.
  - One patient tumor was both *KRAS* mt and *BRAF* mutant (*BRAF* mt)
- 666/1063 (63%) patients had *KRAS* wt tumors.
- 625 *KRAS* wt tumors were evaluable for *BRAF* mutation.
  - 566 (91%) were *BRAF* wt
  - 59 (9%) were *BRAF* mt

Table 1. Baseline and disease characteristics in patients with *KRAS* wt tumors according to *BRAF* mutation status and treatment

| | *KRAS* wt (n=666) | | *KRAS* wt/*BRAF* wt (n=566) | | *KRAS* wt/*BRAF* mt (n=59) | |
|---|---|---|---|---|---|---|
| Characteristics, n (%) unless otherwise stated | FOLFIRI (n=350) | Cetuximab + FOLFIRI (n=316) | FOLFIRI (n=289) | Cetuximab + FOLFIRI (n=277) | FOLFIRI (n=33) | Cetuximab + FOLFIRI (n=26) |
| **Gender** | | | | | | |
| Male | 211 (60) | 196 (62) | 177 (61) | 176 (64) | 18 (55) | 15 (58) |
| Female | 139 (40) | 120 (38) | 112 (39) | 101 (36) | 15 (45) | 11 (42) |
| **Median age, years (range)** | 59 (19–84) | 61 (24–79) | 59 (19–84) | 60 (24–79) | 58 (25–75) | 65 (34–79) |
| **Age categories** | | | | | | |
| <65 years | 234 (67) | 200 (63) | 194 (67) | 177 (64) | 22 (67) | 13 (50) |
| ≥65 years | 116 (33) | 116 (37) | 95 (33) | 100 (36) | 11 (33) | 13 (50) |
| **ECOG PS** | | | | | | |
| 0/1 | 336 (96) | 303 (96) | 280 (97) | 266 (96) | 30 (91) | 26 (100) |
| 2 | 14 (4) | 13 (4) | 9 (3) | 11 (4) | 3 (9) | 0 (0) |
| **Liver metastasis only** | 72 (21) | 68 (22) | 62 (22) | 57 (21) | 4 (12) | 9 (35) |
| **Involved disease sites ≤2** | 295 (84) | 277 (88) | 247 (86) | 245 (88) | 24 (72) | 21 (81) |
| **Prior adjuvant chemotherapy** | 73 (21) | 80 (25) | 62 (21) | 75 (27) | 6 (18) | 4 (15) |

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

### Clinical Efficacy (Table 2)

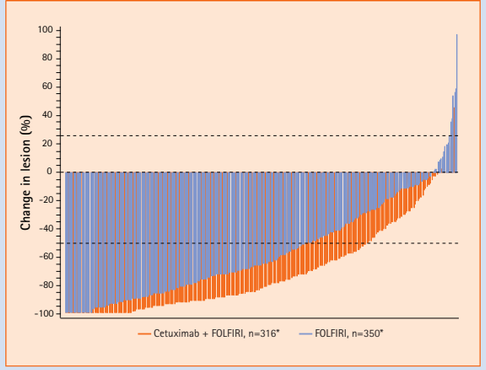
- The addition of cetuximab to FOLFIRI compared with FOLFIRI alone in *KRAS* wt patients led to:
  - Significant improvement in OS time (median follow-up time of 46.2 months vs 46.9 months, respectively; Figure 3)
  - Significant improvement in PFS time (Figure 4)
  - Significant improvement in OR (Figure 2) with a mean difference in the best % change of the lesion (based on WHO criteria) of 13.9
- Significant interactions between treatment outcomes and *KRAS* tumor mutation status were observed for all efficacy variables: tumor response (p=0.0005), PFS (p=0.003) and OS (p=0.046).[8]
- Patients with *BRAF* mt tumors were associated with poor prognosis in both treatment arms (Table 2).

Table 2. Efficacy data in patients with *KRAS* wt tumors according to *BRAF* mutation status and treatment

| | *KRAS* wt (n=666) | | *KRAS* wt/*BRAF* wt (n=566) | | *KRAS* wt/*BRAF* mt (n=59) | |
|---|---|---|---|---|---|---|
| | FOLFIRI (n=350) | Cetuximab + FOLFIRI (n=316) | FOLFIRI (n=289) | Cetuximab + FOLFIRI (n=277) | FOLFIRI (n=33) | Cetuximab + FOLFIRI (n=26) |
| **OS time** | | | | | | |
| Median OS, months | 20.0 | 23.5 | 21.6 | 25.1 | 10.3 | 14.1 |
| [95% CI] | [17.4–21.7] | [21.2–26.3] | [20.0–24.9] | [22.5–28.7] | [8.4–14.9] | [8.5–18.5] |
| Hazard ratio | 0.796 | | 0.830 | | 0.908 | |
| [95% CI] | [0.670–0.946] | | [0.687–1.004] | | [0.507–1.624] | |
| p-value[a] | 0.0093 | | 0.0549 | | 0.7440 | |
| **PFS time** | | | | | | |
| Median PFS, months | 8.4 | 9.9 | 8.8 | 10.9 | 5.6 | 8.0 |
| [95% CI] | [7.4–9.2] | [9.0–11.3] | [7.6–9.4] | [9.4–11.8] | [3.5–8.1] | [3.6–9.1] |
| Hazard ratio | 0.696 | | 0.679 | | 0.934 | |
| [95% CI] | [0.558–0.867] | | [0.533–0.864] | | [0.425–2.056] | |
| p-value[a] | 0.0012 | | 0.0016 | | 0.8656 | |
| **Tumor response** | | | | | | |
| OR rate (%) | 39.7 | 57.3 | 42.6 | 61.0 | 15.2 | 19.2 |
| [95% CI] | [34.6–45.1] | [51.6–62.8] | [36.8–48.5] | [55.0–66.8] | [5.1–31.9] | [6.6–39.4] |
| Odds ratio | 2.0693 | | 2.1750 | | 1.0842 | |
| [95% CI] | [1.5154–2.8258] | | [1.5505–3.0511] | | [0.2644–4.4456] | |
| p-value[b] | <0.0001 | | <0.0001 | | 0.9136 | |

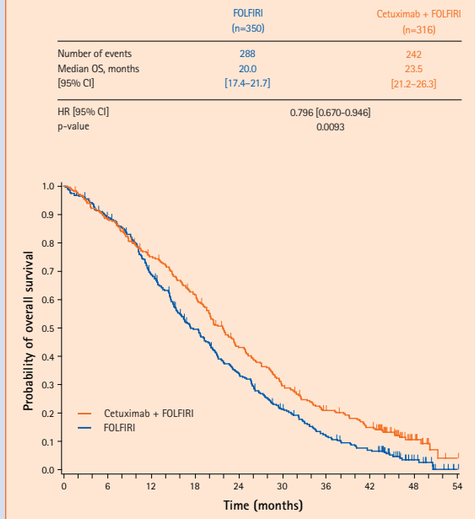
[a] Stratified log-rank test; [b] Cochran–Mantel–Haenszel test.
CI, confidence interval; mt, mutant; OR, best overall response; OS, overall survival; PFS, progression-free survival; wt, wild-type.

Figure 2. Tumor regression according to treatment status in patients with *KRAS* wt tumors



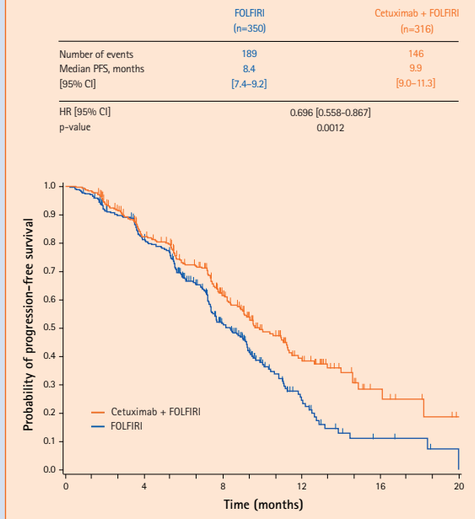

*Data for 16 patients were missing; **Data for 21 patients were missing.

Figure 3. Overall survival according to treatment status in patients with *KRAS* wt tumors




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

Figure 4. Progression-free survival according to treatment status in patients with *KRAS* wt tumors




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

## Conclusions

- This final analysis shows for the first time in a randomized study that the addition of a targeted agent (cetuximab) to FOLFIRI in the 1st-line treatment of patients with mCRC with *KRAS* wt tumors significantly improved OS compared to FOLFIRI alone.
- This final analysis confirms *KRAS* tumor mutation status to be a predictive factor across all efficacy endpoints examined for cetuximab in combination with FOLFIRI.
- The analysis suggests *BRAF* tumor mutations to be a poor prognostic factor in 1st-line mCRC.
- *BRAF* testing may not provide any additional benefit as a predictive indicator for the efficacy of cetuximab in 1st-line treatment in combination with chemotherapy.

## References

1. Van Cutsem E, et al. N Engl J Med 2009;360:1408-17.
2. Bokemeyer C, et al. J Clin Oncol 2009;27:663-71.
3. De Roock W, et al. Ann Oncol 2008;19:508-15.
4. Lièvre A, et al. J Clin Oncol 2008;26:374-9.
5. Roth A, et al. J Clin Oncol 2009 E-pub doi/10.1200/JCO.2009.23.3452.
6. Di Nicolantonio F, et al. J Clin Oncol 2008;26:5705-12.
7. Köhne C, et al. J Clin Oncol 2009;27(15s). Abstract 4068.
8. Lang I, et al. Eur J Cancer Suppl 2009;7(2):345. Abstract P-6078.

## 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.