# Cetuximab and 1st-line chemotherapy in elderly and younger patients with metastatic colorectal cancer (mCRC): a pooled analysis of the CRYSTAL and OPUS studies

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## Background

- An analysis of pooled individual patient data from the CRYSTAL and OPUS trials demonstrated that cetuximab significantly improved the overall survival (OS), progression-free survival (PFS) and best overall response rates (ORR) when added to 1st-line treatment in patients with *KRAS* wild-type (wt) mCRC.[1]
- Although the median age of disease onset in mCRC is >70 years, elderly patients are often undertreated and their survival rates tend to be lower than those for younger patients.[2]
- We investigated the effect of age on the efficacy and safety of cetuximab combined with standard 1st-line chemotherapy in *KRAS* wt patients pooled from the CRYSTAL and OPUS studies.

## Study objectives

- To investigate the effect of patient age on the efficacy of treatment in patients with *KRAS* wt tumors using the key efficacy endpoints from the studies, PFS (OPUS) and OS (CRYSTAL), and the secondary endpoints as defined in the trials.

## Methods

- Patients were randomized to receive cetuximab in combination with FOLFIRI (CRYSTAL)[3] or FOLFOX4 (OPUS)[4] or the standard 1st-line treatment alone.
- The number of samples evaluable for *KRAS* mutation status was increased from 540/1198 (45%) previously published[3] to 1063 (89%) in the CRYSTAL study and from 233/337 (69%)[4] to 315 (93%) in the OPUS study.[1]
- Additional survival data were available for the CRYSTAL and OPUS studies (see statistics below).[1]
- For each trial:
  - Primary analyses of PFS and ORR were based on computed tomography or magnetic resonance imaging scans as assessed by an independent review committee (IRC) according to modified World Health Organization criteria
  - Additional tumor mutation analysis was performed on material extracted from stained slides previously collected to evaluate tumor epidermal growth factor receptor expression status
- *KRAS* (codons 12/13) mutations were detected using a polymerase chain reaction clamping and melting curve technique.

### Statistical considerations

- The pooled analysis was performed on individual patient data from the two trials.
- A cut off of <70 years was made for younger patients, elderly patients were ≥70 years.[5]
- CRYSTAL study data cuts-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 1 March 2007, OS on 30 November 2008.
- Treatment groups were compared in a Cox proportional hazards model for OS and PFS and in a logistic regression model for ORR that were both stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) and study effects.
- Sensitivity analyses comprised of multivariate regression analyses adjusted for baseline covariates.
- Hazard ratios (HR) and odds ratios were obtained by fitting the corresponding regression model to pooled individual patient data stratified by ECOG PS status and study.
- Heterogeneity of treatment effects across studies or across age categories were explored by likelihood ratio tests for treatment-by-age interaction and treatment-by-study interaction in the corresponding regression models.

## Results

### Patients

- Of 845 *KRAS* wt patients in the pooled analysis, 700 (83%) were <70 and 145 (17%) ≥70 years of age.
- Imbalances for some patient characteristics at baseline were noted for patients <70 and ≥70 years between the treatment groups (Table 1).

**Table 1. Patient characteristics at baseline in the pooled population**

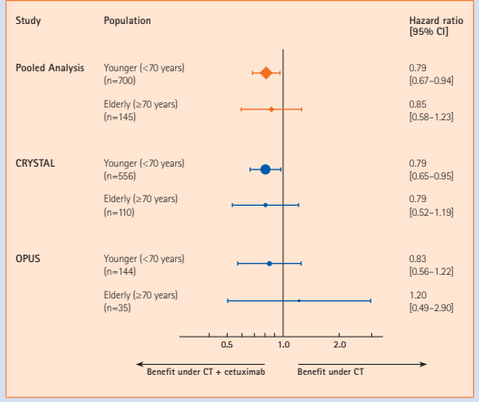
| Characteristics, n (%) | Younger (<70 years) CT n=380 | Younger (<70 years) CT + cetuximab n=320 | Elderly (≥70 years) CT n=67 | Elderly (≥70 years) CT + cetuximab n=78 |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 222 (58) | 193 (60) | 44 (66) | 45 (58) |
| Female | 158 (42) | 127 (40) | 23 (34) | 33 (42) |
| **Age, years** | | | | |
| Median | 58.0 | 58.0 | 73.0 | 73.0 |
| (range) | (19–69) | (24–69) | (70–84) | (70–79) |
| **ECOG PS** | | | | |
| 0,1 | 363 (96) | 305 (95) | 60 (90) | 74 (95) |
| 2 | 17 (4) | 15 (5) | 7 (10) | 4 (5) |
| **No. metastatic sites** | | | | |
| ≤2 | 312 (82) | 279 (87) | 58 (87) | 65 (83) |
| >2 | 62 (16) | 38 (12) | 9 (13) | 10 (13) |
| Missing | 6 (2) | 3 (0.9) | 0 | 3 (4) |
| **Liver metastasis only** | | | | |
| Yes | 86 (23) | 76 (24) | 9 (13) | 17 (22) |
| No | 294 (77) | 244 (76) | 58 (87) | 61 (78) |
| **Leukocytes** | | | | |
| ≤10,000/ mm³ | 306 (81) | 258 (81) | 54 (81) | 64 (82) |
| >10,000/ mm³ | 64 (17) | 52 (16) | 12 (18) | 12 (15) |
| Missing | 10 (3) | 10 (3) | 1 (1) | 2 (3) |
| **Alkaline phosphatase** | | | | |
| ≥300 U/L | 56 (15) | 39 (12) | 5 (7) | 4 (5) |
| <300 U/L | 309 (81) | 265 (83) | 60 (90) | 73 (94) |
| Missing | 15 (4) | 16 (5) | 2 (3) | 1 (1) |
| **LDH** | | | | |
| Upper normal limit | 151 (40) | 142 (44) | 32 (48) | 36 (46) |
| Upper normal limit | 189 (50) | 141 (44) | 27 (40) | 37 (47) |
| Missing | 40 (11) | 37 (12) | 8 (12) | 5 (6) |
| **Relevant medical history** | | | | |
| Yes | 324 (85) | 274 (86) | 65 (97) | 75 (96) |
| No | 56 (15) | 46 (14) | 2 (3) | 3 (4) |

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

### Efficacy

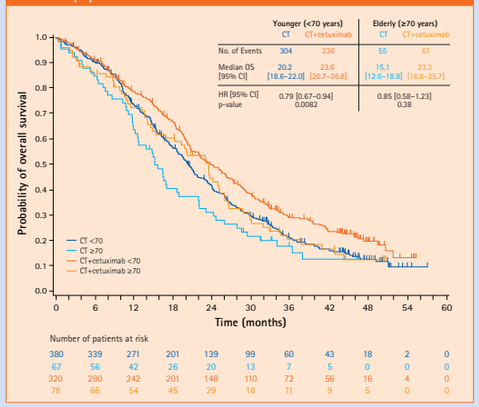
- There were no significant:
  - Treatment-by-age category interactions for OS (p=0.92), PFS (p=0.31), or ORR (p=0.22)
  - Treatment-by-study interactions for patients <70 years and ≥70 years for OS (p>0.40), PFS (p>0.19), or ORR (p>0.15)
- Efficacy by age category and treatment group is summarized (Table 2) and shown specifically for:
  - OS (Figures 1 & 2), PFS (Figures 3 & 4), and ORR (Figure 5)
- Similar findings for efficacy by age category and treatment group were found when analyses were adjusted for baseline characteristics in:
  - Patients <70 years: OS (HR 0.77), PFS (HR 0.63) and ORR (odds ratio 2.37)
  - Patients ≥70 years: OS (HR 0.78), PFS (HR 0.92) and ORR (odds ratio 1.58)
- Multivariate analyses adjusting for baseline covariates confirmed the treatment effects.

**Figure 1. Overall survival by age and treatment in the pooled population and the CRYSTAL and OPUS trials**



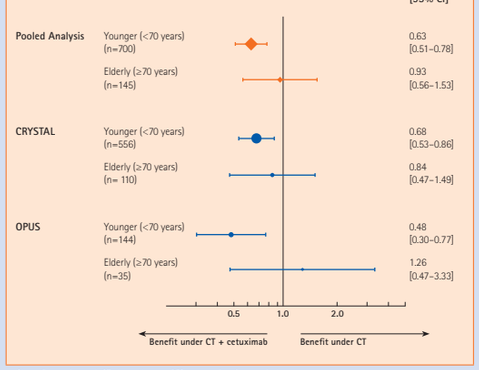

CI, confidence interval; CT, chemotherapy; OS, overall survival.

**Figure 2. Overall survival by age and treatment in the pooled population**



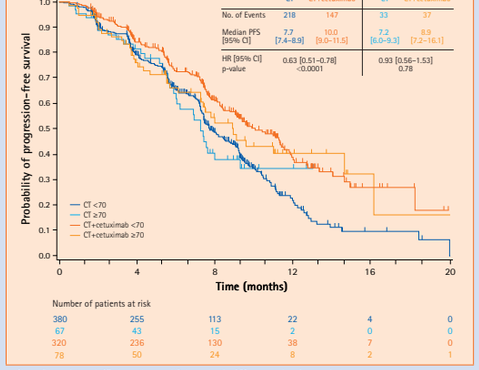

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS overall survival.

**Figure 3. Progression-free survival by age and treatment in the pooled population and the CRYSTAL and OPUS trials**



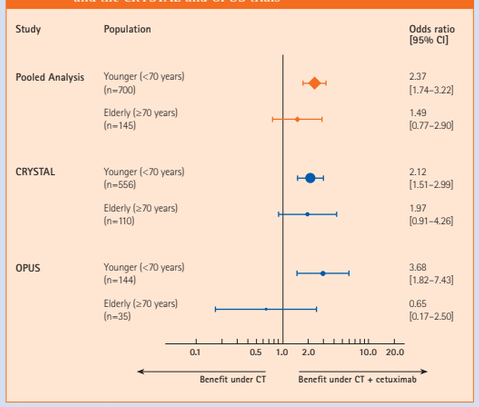

CI, confidence interval; CT, chemotherapy; PFS, progression-free survival.

**Figure 4. Progression-free survival by age and treatment in the pooled population**




CI, confidence interval; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival.

**Figure 5. Tumor response by age and treatment in the pooled population and the CRYSTAL and OPUS trials**




CI, confidence interval; CT, chemotherapy.

### Safety

- The safety profile of treatment by age category is shown in Table 3:

**Table 3. Safety in the pooled population**

| Parameters, n (%) | Younger (<70 years) CT n=380 | Younger (<70 years) CT + cetuximab n=320 | Elderly (≥70 years) CT n=67 | Elderly (≥70 years) CT + cetuximab n=78 |
|---|---|---|---|---|
| **Grade 3/4 adverse events** | | | | |
| Neutropenia | 90 (23.7) | 100 (31.2) | 24 (35.8) | 26 (33.3) |
| Diarrhea* | 30 (7.9) | 41 (12.8) | 10 (14.9) | 18 (23.1) |
| Fatigue | 18 (4.7) | 13 (4.0) | 5 (7.5) | 2 (2.6) |
| All skin toxicity | 3 (0.8) | 81 (25.2) | 1 (1.5) | 18 (23.1) |
| **60 day mortality** | 8 (2.1) | 7 (2.2) | 2 (3.0) | 1 (1.3) |

*The pooled diarrhea rate is primarily affected by the CRYSTAL trial where FOLFIRI was administered.
CT, chemotherapy.

**Table 2. Summary of the efficacy data from the pooled population**

| Characteristics | Younger (<70 years) CT n=380 | Younger (<70 years) CT + cetuximab n=320 | Elderly (≥70 years) CT n=67 | Elderly (≥70 years) CT + cetuximab n=78 |
|---|---|---|---|---|
| **OS time** | | | | |
| Median, months | 20.2 | 23.6 | 15.1 | 23.3 |
| [95% CI] | [18.6–22.0] | [20.7–26.8] | [12.6–18.8] | [16.8–25.7] |
| Hazard ratio | 0.79 | | 0.85 | |
| [95% CI] | [0.67–0.94] | | [0.58–1.23] | |
| p-value | 0.0082 | | 0.38 | |
| **PFS time** | | | | |
| Median, months | 7.7 | 10.0 | 7.2 | 8.9 |
| [95% CI] | [7.4–8.9] | [9.0–11.5] | [6.0–9.3] | [7.2–16.1] |
| Hazard ratio | 0.63 | | 0.93 | |
| [95% CI] | [0.51–0.78] | | [0.56–1.53] | |
| p-value | <0.0001 | | 0.78 | |
| **Tumor response** | | | | |
| ORR, % | 38.4 | 59.1 | 38.8 | 50.0 |
| [95% CI] | [33.5–43.5] | [53.5–64.5] | [27.1–51.5] | [38.5–61.5] |
| Odds ratio | 2.37 | | 1.49 | |
| [95% CI] | [1.74–3.22] | | [0.77–2.90] | |
| p-value | <0.0001 | | 0.23 | |

CI, confidence interval; CT, chemotherapy; PFS, progression-free survival; ORR, best overall response rate; OS, overall survival.

## Conclusions

- In this analysis of pooled individual patient data from the CRYSTAL and OPUS trials no treatment-by-age interaction was reported.
- The addition of cetuximab to standard 1st-line chemotherapy led to a significant improvement across all efficacy endpoints examined in patients <70 years of age with *KRAS* wt mCRC.
- In patients ≥70 years an improvement in efficacy from adding cetuximab to chemotherapy was observed, however this did not achieve statistical significance as compared with that seen for patients <70 years of age.
- The prognostic value of the age category regarding OS cannot be excluded.
- No marked differences in toxicity profiles between the treatment arms by patient age were found.

## References

1. Bokemeyer C, et al. J Clin Oncol 2010;28:15s (suppl;abstr 3506).
2. Papamichael D, et al. Ann Oncol 2009;20:5-16.
3. Van Cutsem E, et al. N Engl J Med 2009;360:1408-17.
4. Bokemeyer C, et al. J Clin Oncol 2009;27:663-71.
5. Goldberg R, et al. J Clin Oncol 2006;24:4085-91.

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