Quality of life analysis in patients with \textit{KRAS} wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin

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\textbf{Abstract} \quad \textit{Background}: In the CRYSTAL study adding cetuximab to first-line FOLFIRI significantly improved outcome in patients with \textit{KRAS} wild-type metastatic colorectal cancer. Quality of life (QoL) was assessed, and associations with tumour response and survival were investigated.

\textit{Patients and methods}: The European Organization for Research and Treatment of Cancer QoL questionnaire-core 30 was used, focusing on global health status (GHS)/QoL and social functioning scales. Radiological response was assessed by an independent review committee.

\textit{Results}: QoL was evaluable in 627/666 patients (94\%) with \textit{KRAS} wild-type tumours; of these 52\% received FOLFIRI, and 48\% FOLFIRI plus cetuximab. Pattern mixture analysis revealed no significant differences for GHS/QoL ($P = 0.12$) and social functioning scores ($P = 0.43$) between the treatment arms. In additional analyses: early skin reactions in patients receiving cetuximab did not significantly affect these QoL scales, and tumour response was more common (58\% versus 40\%, $P = 0.0002$) and survival longer (Hazard ratio 1.68, $P < 0.0001$) in
asymptomatic compared with symptomatic patients at baseline. Adding cetuximab to FOLFIRI was associated with significantly higher tumour response irrespective of patient baseline symptomatic status, and enhanced symptom relief from baseline in those whose tumours had responded.

**Conclusion:** Adding cetuximab to FOLFIRI improved response rate and survival without either improving or negatively impacting on GHS/QoL and social functioning.

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1. **Introduction**

In the CRYSTAL study, adding cetuximab to first-line irinotecan and infusional fluorouracil and leucovorin (FOLFIRI) significantly improved survival (hazard ratio [HR] 0.796, \( P = 0.0093 \)), progression-free survival (PFS, HR 0.696, \( P = 0.0012 \)) and tumour response (odds ratio 2.069, \( P < 0.001 \)) compared with chemotherapy alone in patients with KRAS wild-type metastatic colorectal cancer (mCRC). Whilst the reduction of mortality and morbidity remains one of the most important goals in oncology research, therapies should ideally also lead to improvements in general health status and quality of life (QoL).

The main and most important reported side-effects associated with the combination of cetuximab with first-line chemotherapy regimens in mCRC are an increase in skin reactions and infusion-related reactions during first administration.1–4 In pretreated patients with KRAS wild-type mCRC, significant improvements in both clinical outcome and QoL scores were reported when cetuximab was combined with irinotecan or best supportive care compared with these therapies alone.5–7 Associations between efficacy and QoL were reported in the CO.17 study in this setting, where patients with objective tumour response or disease control were significantly more likely to gain improvements in QoL scores compared with patients with progressive disease.6

A number of studies have investigated associations between QoL and clinical outcome and have reported that patient QoL scores at baseline may be an independent predictor of survival in several different cancer types including mCRC.8–12 Patient QoL assessment was a secondary objective in the CRYSTAL study. The present investigation reports an analysis of QoL data collected in CRYSTAL study patients with KRAS wild-type tumours.1

2. **Patients and methods**

2.1. **Study design, treatment and objectives**

The CRYSTAL study (NCT00154102) design, patient eligibility criteria and treatment regimens have been described previously.1,2 Patients provided informed consent. This was an open-label, randomised, multicenter, phase III trial comparing FOLFIRI plus cetuximab with FOLFIRI alone. Patients were treated until disease progression or the occurrence of unacceptable toxicity. The study was carried out in accordance with the declaration of Helsinki (October 1996).

The primary objective was to examine differences in PFS between the treatment groups. The focus of the present analysis was an assessment of QoL, a secondary objective from the CRYSTAL study.

2.2. **Assessments**

Radiological response was assessed every 8 weeks by an independent review committee (IRC) until disease progression or patient withdrawal. Follow-up evaluations were performed every 3 months. Response was based on the assessment of best overall response by the IRC, as described previously.2 Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

2.3. **QoL assessments**

The European Organization for Research and Treatment of Cancer quality of life questionnaire-core 30 (EORTC QLQ-C30 [version 3.0])13 was used to assess QoL. Attention was paid to the impact of cetuximab on social functioning and global health status (GHS)/QoL.

The QLQ-C30 is a cancer specific self-administered core questionnaire of 15 multi-item or single-item scales derived from the initial 30 questions: five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning); three symptom scales (fatigue, nausea and vomiting, pain); six symptom single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and one GHS/QoL scale.

Scores were derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after linear transformation. Higher scores for the functioning and GHS/QoL scales indicated a higher level of functioning and a better QoL respectively, whereas higher scores in symptom scales represented a higher level of symptom.

QoL was assessed at randomisation, every 8 weeks before the beginning of the next treatment cycle, and at final tumour assessment. Assessment of EORTC
QLQ-C30 was conducted at each site. Only one questionnaire per patient within the QoL assessment time window was analysed (detailed in the Supplementary Material).

2.4. Statistical considerations

Analysis was performed in the KRAS wild-type evaluable for QLQ-C30 population comprising patients from the CRYSTAL intention to treat (ITT) population with KRAS wild-type tumours who had at least one evaluable QLQ-C30 questionnaire. All statistical tests were performed two-sided at the 5% level. No adjustments for multiple comparisons were made.

The null hypothesis to be tested for treatment effect on QoL was that there was no difference between the treatment groups.

The primary analysis was a pattern-mixture analysis for the GHS/QoL and social functioning which included a dropout pattern for each treatment group. A logistic regression model, including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), number of involved disease sites and liver metastases as covariables, was used to test if the dropout process was ‘missing completely at random’ (SAS Proc Logistic). The significance of QoL scores on dropout were assessed using the Wald-test.

QoL data were analysed using descriptive statistics for multi-item scales and single-item measures for each treatment group at each QoL assessment time point. Least-squares (LS) mean estimates for a treatment by time interaction, and the difference in the LS means and associated \( P \) values were obtained from an analysis of variance (ANOVA) model including covariables and a treatment by time interaction. ANOVA was used for time points where at least 20% of patients completing a baseline questionnaire remained in the population. Differences between treatment groups were assessed using the Wilcoxon non-parametric test.

Exploratory analyses included change from baseline in GHS/QoL and social functioning scores by severity of skin reactions (none versus any grade or none versus grade I versus grade II–IV). A Cochran Mantel–Haenszel non-parametric test was used to compare differences between groups. The change in reported symptoms from baseline according to tumour response and treatment was investigated. Eight single-item symptom questions from the QLQ-C30 questionnaire, considered relevant to mCRC, were included, covering the symptoms: dyspnoea, pain, fatigue, appetite loss, constipation and diarrhoea. Each item contained four response categories (not at all; a little; quite a bit; very much). Response categories were dichotomised using the following algorithm: patients at baseline were considered symptomatic if they answered ‘not at all’ or ‘a little’ to all of the symptoms questions. Analysis was performed for treatment groups on the change in symptoms in patients considered symptomatic or asymptomatic at baseline. Fisher Exact test was used to examine the association between symptomatic status at baseline and response, and between response and treatment group stratified by symptomatic status at baseline.

Survival curves and probabilities were estimated using the Kaplan–Meier method. The importance of symptomatic status at baseline as a prognostic factor on survival was tested using the Cox proportional hazards regression model with stratification for treatment arm, with significance assessed using the Wald-test.

3. Results

3.1. Patients, QoL evaluation and compliance

From the CRYSTAL ITT population \((n = 1198)\), 666 patients were KRAS wild-type and 627 of these completed at least one evaluable QLQ-C30 questionnaire. Of these patients 48% received FOLFIRI plus cetuximab and completed 1333 questionnaires, and 52% received FOLFIRI and completed 1369 questionnaires. The proportion of evaluable questionnaires in each treatment group was 80% and 76% respectively. Compliance rates with questionnaire completion by planned QoL assessment times deteriorated over time, but were similar between the treatment arms (Table 1).

Patient baseline characteristics between the CRYSTAL ITT and KRAS wild-type QLQ-C30 populations were not markedly different (Table 2).

3.2. QoL analysis

For all QLQ-C30 multi-item scales across the assessment time points, only the LS mean scores for nausea and vomiting at week 16 were significantly different in the FOLFIRI versus the FOLFIRI plus cetuximab arm (14.25 versus 9.08, \( P = 0.0014 \)). The LS means estimates for the GHS/QoL and social functioning scales were comparable between the treatment arms, remaining stable across the assessment time points (Fig. 1).

For worst post-baseline scores, for multi-item scales, only nausea and vomiting was significantly different being higher in the FOLFIRI than the combination arm (20.07 versus 15.93, \( P = 0.032 \)) (Supplementary Table S1). For single-item scales, a worse change from baseline score for dyspnoea in the FOLFIRI plus cetuximab arm compared with the FOLFIRI arm \((P = 0.020)\) was the only significant finding, which also reflected the higher incidence of dyspnoea in the combined group (10% versus 5%).
3.3. Analysis of missing data

Missing data did not occur at random (further details in Supplementary Material and Supplementary Fig. S1). Pattern-mixture analysis demonstrated no significant differences between the treatment arms for GHS/QoL ($P = 0.12$) and social functioning scores ($P = 0.43$) when accounting for different patient dropout patterns (Supplementary Table S2).

3.4. Sensitivity analysis

Wei–Lachin tests for multi-item scales confirmed no significant differences between the treatment arms at any assessment time point or overall (Supplementary Table S3).

3.5. Early skin reactions and QoL

In patients receiving FOLFIRI plus cetuximab, the mean change from baseline in GHS/QoL was 3.00 in patients without early skin reactions (week 8) compared with −1.09 and −0.51 in those with grade I and grade II–IV early skin reactions, respectively. Social functioning score worsened in patients with no skin reactions (mean −6.41) compared with a slight improvement in those with grade I (mean 1.64) and grade II–IV (mean 1.48) early skin reactions, respectively. Differences were not statistically significant (Supplementary Table S4).

3.6. Patient symptoms and tumour response

In 471 evaluable patients, the tumour response rate was significantly higher in those who were asymptomatic.
versus symptomatic at baseline (58% [162/278] versus 40% [78/193], \( P = 0.0002 \)) and remained higher in asymptomatic (versus symptomatic) patients at baseline in both those receiving FOLFIRI plus cetuximab (65% [88/136] versus 52% [46/89]) and FOLFIRI alone (52% [74/142] versus 31% [32/104]). However the addition of
cetuximab to FOLFIRI compared with FOLFIRI alone, significantly improved response rates in both asymptomatic (65% versus 52%, \( P = 0.0388 \)) and symptomatic patients at baseline (52% versus 31%, \( P = 0.0034 \)) respectively.

For patients who were symptomatic at baseline, in each treatment group, and at each assessment time point, generally more became asymptomatic if they exhibited a tumour response compared with those with unresponsive tumours (Table 3). Furthermore, symptoms were less frequently reported in responders than in non-responders (Fig. 2) Maximum symptom relief was reported earlier for patients receiving FOLFIRI plus cetuximab than with FOLFIRI alone (8 versus 16 weeks). In asymptomatic patients at baseline, more remained asymptomatic whose tumours responded, than those whose did not.

3.7. Patient symptoms and survival

Survival was significantly longer in patients asymptomatic at baseline compared with those who were symptomatic at baseline (Fig. 3, median survival 25.7 versus 16.4 months, HR 1.68, \( P < 0.0001 \)).

4. Discussion

Analysis of the CRYSTAL study data demonstrated that whilst adding cetuximab to FOLFIRI did not improve overall QoL in this setting, neither was a negative impact on QoL observed from this treatment combination. The analysis focused primarily on the EORTC QLQ-C30 GHS/QoL and social functioning scales, the latter was considered important due to the possible influence that cetuximab-related skin reactions might have on this scale.\(^1\)\(^2\) Further a large population-based study comparing long-term QoL issues between CRC patients and the general population reported social functioning as the most impaired scale.\(^16\)

Few significant differences in QoL scores were identified between the treatment arms. Nausea and vomiting scores at specific assessment time points, and for the worst post-baseline score, were significantly higher in the FOLFIRI than the combined treatment arm. In contrast, a significantly worse shift from baseline in single-item dyspnoea was reported in the FOLFIRI plus cetuximab alone arm. However, simple analyses including best and worst score summary measures do not account for patient dropout patterns and may be subject to bias. Patient compliance to QoL questionnaire completion deteriorated over time but was generally similar between the treatment arms. Patient dropout was prevalent and missing data did not occur at random, and was significantly associated with QoL scores. Patients with low QoL scores at baseline or at the previous assessment time points tended to dropout earlier. Pattern mixture analysis, taking into account missing data and patient dropout patterns, showed no significant differences in GHS/QoL and social functioning scores between the treatment arms, confirming the robustness of the data. Similar findings were reported in head and neck cancer\(^12\)\(^17\) and pre-treated patients with advanced CRC.\(^6\)

Further analysis of the CRYSTAL data suggested that the presence of skin reactions at week 8 did not significantly impact the QoL of patients treated with cetuximab. Surprisingly, the social functioning score worsened in patients with no skin reactions compared with those with early skin reactions. This may have occurred by chance partly due to the small number of patients who had no skin reactions with a change from baseline score.

In heavily pretreated patients with \( KRAS \) wild-type advanced CRC,\(^6\) cetuximab reportedly provided a significant improvement in GHS/QoL score at 8 weeks compared with best supportive care (3.2 versus −7.7, \( P = 0.02 \)). Furthermore improvements in patient QoL scores were significantly more common in patients whose tumours showed disease response or disease control compared with disease progression. This was further investigated in the first-line setting through additional analysis of the CRYSTAL data set. Tumour response was significantly higher in patients who were asymptomatic compared with those who were symptomatic at baseline. Furthermore patients symptomatic at baseline experienced more symptom relief if their tumour responded than if it did not. Whilst the association between tumour response and symptom relief appeared to be independent of treatment, adding cetuximab to FOLFIRI was associated with significantly higher tumour response, irrespective of patient baseline symptomatic status, and further enhanced and accelerated symptom relief from baseline in patients whose tumours had responded, compared with those who received FOLFIRI alone.

In advanced CRC patients treated with first-line chemotherapy, baseline social functioning score (assessed by EORTC QLQ-C30) in multivariate analysis was reported to be an independent prognostic factor for survival (HR 0.991, 95% confidence interval (95% CI) 0.987–0.996, \( P < 0.001 \)).\(^9\) These data supported earlier findings that baseline overall QoL scale (using the EORTC QLQ-C30) independently predicted survival and was a more effective prognostic indicator than performance status.\(^8\) In the present study patient survival was significantly longer in asymptomatic patients than those exhibiting symptoms at baseline. Thus, patient symptom status at baseline in this setting may be a potential prognostic indicator for both response and survival. To date the mechanism underlying the association between patient baseline QoL and prognosis is unknown.\(^9\) Studies reporting similar findings have suggested that this might reflect the patient’s early
perception of the severity of their disease. Thus baseline QoL scores may correlate with other prognostic factors such as tumour site and biology, although limited patient numbers precluded such analysis in the current study.

To our knowledge this is the first analysis of mCRC patients dichotomised by symptomatic status at baseline. The post hoc nature of this analysis, and the small number of patients examined in some subgroups, require that the data are viewed as hypothesis generating. Additional studies are needed to further investigate these relationships to better understand the impact of tumour response on patients’ perceived QoL, and the importance of the presence of disease symptoms at baseline in patient treatment decisions.

It might be expected that the improved efficacy associated with adding cetuximab to FOLFIRI in the CRYSTAL study should be associated with improved GHS/QoL and social functioning in these patients. The observation that no such association was found is likely to be due to a combination of factors. In addition to the current study, several major studies reporting an improvement in clinical outcome from the addition of a biologically-targeted agent (EGFR or VEGF monoclonal antibody) to standard first-line chemotherapy in the treatment of mCRC patients, failed to observe correspondingly marked improvements in QoL compared with the control arm. In contrast improvements in QoL have been reported in studies investigating the use of these agents in later lines of treatment. In the current study it may be that the additional cetuximab-related toxicities negate the incremental positive effect on patient QoL obtained from the enhanced tumour shrinkage and slowing of tumour progression from the treatment combination. Furthermore as patients receiving first-line chemotherapy report relatively high QoL scores, the capacity to further improve QoL might be somewhat limited in this setting in contrast with those studies reporting on later treatment lines. Indeed in the present study the highest efficacy was observed in patients asymptomatic at baseline where further improvement in QoL is difficult to achieve. Although notably, patients symptomatic at baseline demonstrated improvements in tumour response with accompanying marked symptom relief.

In summary, in the CRYSTAL study, the addition of cetuximab to first-line FOLFIRI significantly improved clinical outcome in patients with KRAS wild-type mCRC without either improving or negatively impacting on GHS/QoL and social functioning. Adding cetuximab to FOLFIRI was associated with higher tumour response in patients with or without

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### Table 3
Change in patient symptoms from baseline according to tumour response and treatment.

<table>
<thead>
<tr>
<th>Patient status</th>
<th>All treated</th>
<th>FOLFIRI</th>
<th>FOLFIRI + cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders (R)</td>
<td>Non-responders (NR)</td>
<td>R</td>
</tr>
<tr>
<td>Symptomatic at baseline Week 8</td>
<td>78 (100)</td>
<td>115 (100)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>29 (37)</td>
<td>13 (11)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>39 (50)</td>
<td>58 (50)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Missing</td>
<td>10 (13)</td>
<td>44 (38)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>36 (46)</td>
<td>17 (15)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Missing</td>
<td>28 (36)</td>
<td>24 (28)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>14 (18)</td>
<td>70 (61)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Asymptomatic at baseline Week 24</td>
<td>162 (100)</td>
<td>116 (100)</td>
<td>74 (100)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>101 (62)</td>
<td>59 (51)</td>
<td>47 (64)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>33 (20)</td>
<td>19 (16)</td>
<td>15 (20)</td>
</tr>
<tr>
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<td>28 (17)</td>
<td>38 (33)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Asymptomatic</td>
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<td>42 (36)</td>
<td>39 (53)</td>
</tr>
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<td>7 (9)</td>
</tr>
<tr>
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<td>60 (52)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>88 (54)</td>
<td>34 (29)</td>
<td>40 (54)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>27 (17)</td>
<td>8 (7)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Missing</td>
<td>47 (29)</td>
<td>74 (64)</td>
<td>23 (31)</td>
</tr>
</tbody>
</table>

Data shown are n (%).
Fig. 2. Proportion of patients symptomatic at baseline reporting symptoms over time according to tumour response status and treatment. R, responder; NR, non-responder.

Fig. 3. Overall survival in patients grouped by symptom status at baseline. *Months since start of treatment.
symptoms at baseline, and with improved and earlier symptom relief in those whose tumours had responded.

Role of the funding source

The legal sponsor of the study was Merck KGaA, Darmstadt, Germany. The sponsor was responsible for data management and statistical analysis. The clinical study was designed in collaboration with the study coordinating investigator EVC (CRYSTAL, [NCT00154102]). The subgroup analysis described in the current manuscript was carried out by the sponsor. The drafting of this manuscript was commissioned by the sponsor. The corresponding author (and all authors) had full access to all study data, and all authors made the final decision to submit the manuscript for publication.

Conflict of interest statement

C.-H.K. reports honoraria from Pfizer and Merck KGaA. G.F. reports consultant/advisory roles for Merck KGaA, Roche and BMS, honoraria from Merck KGaA, Pfizer, Roche and Novartis and research funding from Merck KGaA. P.R. reports advisory roles for Merck KGaA and has participated as a speaker or chairman of specialised symposia for Merck KGaA. D.C. reports conducting research funded by Merck KGaA. E.V.C. reports a consultant/advisory role for Merck KGaA and research funding from Merck KGaA. U.S. is an employee of Merck KGaA. At the time that this work was performed I.G. was an employee of Merck KGaA. All other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.08.023.

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