Health-Related Quality of Life in Patients With Advanced Colorectal Cancer Treated With Cetuximab: Overall and KRAS-Specific Results of the NCIC CTG and AGITG CO.17 Trial

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ABSTRACT

Purpose
National Cancer Institute of Canada Clinical Trials Group CO.17 demonstrated the antiepidermal growth factor receptor (anti-EGFR) monoclonal antibody cetuximab improves overall and progression-free survival in patients with advanced, chemotherapy-refractory colorectal cancer (CRC), particularly in patients with wild-type KRAS tumors. This article reports the health-related quality-of-life (HRQL) outcomes from CO.17.

Patients and Methods
Patients (N = 572) with pretreated EGFR-detectable advanced CRC were randomly assigned to cetuximab and best supportive care (BSC) or to BSC alone. HRQL primary end points assessed by the EORTC QLQ-C30 were physical function (PF) and global health status (GHS); mean changes from baseline to 8 and 16 weeks were assessed. Post hoc analysis by KRAS mutation status was performed.

Results
Questionnaire compliance was 94% at baseline, but it declined differentially (67% v 47% for cetuximab v BSC at 16 weeks). PF change scores were −3.9 for cetuximab and −8.6 for BSC (P = .046) at 8 weeks and were −5.9 and −12.5 for cetuximab and BSC, respectively, (P = .002) at 16 weeks. GHS change scores were −0.5 and −7.1 (P = .008) at 8 weeks and were −3.6 and −15.2 (P = .008) at 16 weeks for cetuximab and BSC, respectively. In patients who had tumors with wild-type KRAS status, cetuximab resulted in less PF deterioration at 8 weeks (−0.7 v −7.2; P = .11) and 16 weeks (−3.4 v −13.8; P = .008) compared with BSC. Patients with wild-type status who received cetuximab experienced improved GHS at 8 weeks, whereas patients who received BSC alone deteriorated (3.2 v −7.7; P = .002). Cetuximab preserved GHS at 16 weeks (−0.2 v −18.1; P < .001). No significant differences were noted between study arms for patients with mutated KRAS tumors.

Conclusion
Cetuximab offers important HRQL and survival benefits for pretreated patients with advanced, wild-type KRAS CRC.

INTRODUCTION

Colorectal cancer (CRC) is the second-most leading cause of cancer-related death in the Western world.1 For patients with advanced CRC, chemotherapy and the vascular endothelial growth factor–targeting monoclonal antibody bevacizumab can prolong survival.2-4 However, except for a minority of patients with resectable metastases, the disease remains incurable.

Cetuximab, a murine monoclonal antibody directed against the epidermal growth factor receptor (EGFR), has activity in patients with advanced CRC. In 2007, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and Australasian Gastro-Intestinal Trials Group (AGITG) CO.17 study demonstrated that, in patients heavily pretreated for advanced CRC, treatment with cetuximab resulted in prolonged overall survival (OS; median, 6.1 v 4.6 months; hazard ratio [HR], 0.77;
KRAS, a G protein downstream of EGFR signaling, plays a pivotal role in signal transduction after EGFR activation. KRAS mutations that lead to constitutive activation of the pathway render EGFR inhibition ineffective. KRAS mutations, found in approximately 40% of CRCs, are an important predictor of benefit from EGFR targeting agents. In CO.17, benefits of cetuximab were more pronounced in patients with wild-type rather than with mutated-KRAS status (OS: median, 9.5 v 4.8 months; HR, 0.55; P < .001; PFS: HR, 0.40; P < .001; RR: 12.8 v 0%; P < .001); P values of interaction between treatment and KRAS status 0.01 for OS and less than 0.0001 for PFS. As therapeutic benefits appear isolated to patients with wild-type KRAS tumors across these studies, it is now accepted that monoclonal antibody EGFR inhibition should be limited to these patients.

Because the survival for most patients with chemotherapy-refractory CRC is short, and because of the importance of palliation of symptoms and minimization of toxicity of therapy, this study included prospective evaluation of the effect of cetuximab on health-related quality of life (HRQL). The HRQL results of CO.17, including analyses by KRAS mutation status, are reported here.

PATIENTS AND METHODS

CO.17 was a collaboration between the NCIC CTG and the AGITG conducted in Canada, Australia, New Zealand, and Singapore. Funding was provided by the NCIC CTG, the AGITG, Bristol Myers Squibb, and ImClone Systems Inc. The NCIC CTG maintained the trial database and conducted all analyses.

Patients

Included patients had advanced, pretreated, EGFR-detectable, histologically proven metastatic CRC for which no other standard anticancer therapies were available. Patients had Eastern Cooperative Oncology Group performance status (PS) scores of 0 to 2. All had prior chemotheraphy, including thymidylate synthase (TS) inhibition (fluorouracil, capcitabine, or raltrexed), and all experienced treatment failure or were considered unsuitable for treatment with both irinotecan and oxaliplatin. Additional details of the eligibility criteria have been reported previously. Participating centers received approval from their institutional ethics review boards. All patients provided written informed consent before participation.

Study Procedures

Eligible patients were randomly assigned on a 1:1 basis to receive cetuximab plus BSC or BSC alone. Cetuximab was administered at a standard dosage of 400 mg/m² intravenously (IV) over 2 hours on day one followed by 250 mg/m² IV weekly. Treatment was continued until disease progression or unacceptable toxicity occurred. BSC was defined as any and all treatments to improve symptoms and HRQL. The primary study end point was OS. Secondary end points included PFS, RR, safety, and HRQL. All patients were to complete HRQL questionnaires.

HRQL Hypothesis

In this heavily pretreated CRC population, in which deterioration in HRQL may be imminent, we hypothesized a priori that cetuximab therapy would result in a decrease in the magnitude and rate of decline in HRQL, particularly in physical functioning and overall well-being.

HRQL Assessment

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), which is a self-administered, cancer-specific, multidimensional questionnaire, was selected, because it is valid and reliable in the advanced cancer setting. This 30-item questionnaire includes five functional scales (ie, physical, role, cognitive, emotional, social), a two-item global health status (GHS) scale, three symptom scales (ie, fatigue, pain, nausea and vomiting), and six single items (ie, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). Scoring was completed according to the EORTC QLQ-C30 manual, and linear transformation was used to standardize raw scores to range between 0 and 100. Higher scores corresponded to better HRQL in functional scales and GHS and to worse HRQL in symptom scores. Missing items in a scale were handled by the methods outlined in the scoring manual.

The questionnaire was to be completed in clinic at baseline and at 4, 8, 16, and 24 weeks post-random assignment unless the patient had deteriorated to a PS of 4 or was hospitalized for end-of-life care.

Statistical Considerations

The primary HRQL analyses were defined prospectively as a comparison of the change scores from baseline to 8 and 16 weeks, respectively, for physical function (PF) and GHS scales (Wilcoxon test). These time points were chosen a priori, as the effects of cetuximab were expected to be evident by 16 weeks. Secondary HRQL analyses, defined prospectively, included comparisons of the proportion of patients with worsened PF and GHS at 8 and 16 weeks by using Fisher’s exact test and the time to deterioration in PF and GHS scales (defined as time from random assignment to a minimum 10-point worsening in the change score from baseline) by log-rank test. Exploratory analyses of change scores for all scales and items with the NCIC CTG basic approach categorized all patients for each scale or single item as having improved (ie, increase of 10 units from baseline at any time point), having worsened (ie, decrease of 10 units or more without improvement) or having remained stable (ie, change < 10 units) in the HRQL response. A 10-unit difference in change scores was predefined as clinically important. χ² testing was used to compare the distributions of HRQL response categories between arms.

HRQL outcomes were analyzed by KRAS status. Paraffin-embedded, archival tumor samples stored at a central tumor bank at Queen’s University in Kingston, Canada were assayed for KRAS mutations in a blinded fashion in the Department of Clinical Biomarkers Oncology at Bristol-Myers Squibb, NJ, and were classified as mutated or wild type on the basis of prespecified criteria. Correlation between HRQL response and objective tumor response was also sought.

HRQL analyses were based on intention to treat. All randomly assigned patients with a baseline and at least one other HRQL assessment were assessable. The Hochberg method was used to adjust for four comparisons in the primary analyses. To address data missing not at random, two sensitivity analyses were performed: primary analyses, by using pattern mixture models with missing data patterns defined on the basis of last HRQL assessment and a linear mixed model, which included treatment and a treatment-time interaction term for each pattern; and secondary analyses, which assumed that all patients with missing HRQL data had deteriorated. Differences in demographics, reported toxicities, and PS of patients with or without missing HRQL data at 8 and 16 weeks were evaluated.

RESULTS

Patient Characteristics

Five hundred seventy-two patients were randomly assigned; 287 were assigned to the cetuximab arm. Baseline characteristics were well balanced between arms. The median age was 63 years, and 77% had a PS of 1 or better. All patients had received a prior TS inhibitor: 96% received prior irinotecan, and 98% received prior oxaliplatin. Tumor KRAS mutation status was available retrospectively in 394 patients (69%). Among them, 164 (42%) had tumors with mutated KRAS.


**HRQL Compliance**

Questionnaire compliance, defined as the number of patients who completed a questionnaire at a given time point divided by the number of patients known to be alive but not deteriorated to a PS of 4 and not hospitalized for end-of-life care at that time point, is listed in Table 1. Compliance was high at baseline (>90%) but declined over time, particularly in the BSC arm.

**Baseline HRQL Results**

The study arms had comparable baseline HRQL scores (Fig 1). Balanced baseline impairment was seen in the GHS mean scores. The worst baseline symptom scale was fatigue in both arms.

**PF and GHS Change Scores**

Patients on BSC alone had a greater magnitude of worsening in their PF and GHS scores compared with cetuximab, as listed in Table 2. The mean PF change scores for the cetuximab and BSC arms were −3.9 and −8.6 (P = .046), respectively, at 8 weeks and were −5.9 and −12.5 (P = .027), respectively, at 16 weeks. The GHS change scores for the cetuximab and BSC arms were −0.5 and −7.1 (P = .008), respectively, at 8 weeks and were −3.6 and −15.2 (P < .001), respectively, at 16 weeks. Because all four P values were less than .05, the Hochberg procedure rejected all four null hypotheses, and the family-wise probability of a type I error was controlled at .05. Sensitivity analyses on the basis of pattern mixture models supported conclusions from primary analyses.

In patients with wild-type KRAS tumors, cetuximab resulted in less deterioration in mean change scores for PF at 8 weeks (−0.7 v −7.2; P = .11) and 16 weeks (−3.4 v −13.8; P = .008) compared with BSC alone. The cetuximab patients with wild-type status had a trend toward improvement in GHS mean change score at 8 weeks (P = .12), whereas those on the BSC arm had a significant deterioration (P = .009); the difference between groups was highly significant (3.2 v −7.7; P = .002). GHS mean change score remained superior in the cetuximab arm at 16 weeks (−0.2 v −18.1; P < .001). These results were also confirmed in sensitivity analyses that were based on pattern mixture models. There were no significant differences between study arms in PF or GHS for patients with mutated KRAS tumors at 8 or 16 weeks (data not shown).

More patients on BSC had worsened GHS (at least 10 points decrease) at 8 weeks (38.3 v 23.2%; P = .004) and 16 weeks (49.3 v 31.3%; P = .011), and had a trend toward worsened PF at 8 weeks (34.7 v 24.9%; P = .051 [Fisher’s exact test]) and 16 weeks (43.4 v 30.4%; P = .069). Among patients on the cetuximab arm, patients with mutated KRAS status trended toward worsened PF at 8 weeks (31.3 v 17.8%; P = .09) and 16 weeks (40.7 v 21.7; P = .08) compared with those who had wild-type KRAS status.

There were no differences in demographics or reported toxicities of patients with or without missing HRQL data at 8 and 16 weeks on either arm. However, patients with missing HRQL data were more likely to have PS 3 to 4 or missing, whereas those with HRQL data were more likely to have PS 0 to 2 (data not shown). In a sensitivity analysis in which all patients with missing data were considered to have worsened HRQL, 64.3 and 48.3% of patients who received BSC alone or cetuximab, respectively, had at least a 10-unit deterioration in PF at 8 weeks; 65.8 and 47.2% of patients experienced this at 16 weeks (all P < .001). The rates of deterioration for GHS with BSC alone or cetuximab were 84.0% and 67.7%, respectively, at 8 weeks and 85.9% and 67.3%, respectively, at 16 weeks (all P < .001).

**Time to Deterioration in HRQL**

A total of 235 patients on cetuximab and 202 on BSC had baseline and at least one postbaseline assessment for PF, and 233 on cetuximab and 200 on BSC had this for GHS. The median time before clinically important deterioration in HRQL (ie, at least 10 points decrease), as measured by the PF, was significantly longer for patients on the cetuximab compared with the BSC arm (5.4 v 3.7 months; P = .022; Fig 2A), and a trend to significance was measured by GHS (5.4 v 3.7 months;
Quality of Life With Cetuximab in Advanced Colorectal Cancer

<table>
<thead>
<tr>
<th>Table 2. Mean Health-Related Quality-of-Life Change Scores for Physical Function and Global Health Status</th>
<th>Change Score by Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 Scale by Assessment Time</td>
<td>Cetuximab + BSC</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Week 8 physical function</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>185</td>
</tr>
<tr>
<td>KRAS wild-type</td>
<td>90</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>48</td>
</tr>
<tr>
<td>Week 8 global health status</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>185</td>
</tr>
<tr>
<td>KRAS wild-type</td>
<td>88</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>48</td>
</tr>
<tr>
<td>Week 16 physical function</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>125</td>
</tr>
<tr>
<td>KRAS wild-type</td>
<td>69</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>27</td>
</tr>
<tr>
<td>Week 16 global health status</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>128</td>
</tr>
<tr>
<td>KRAS wild-type</td>
<td>70</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>28</td>
</tr>
</tbody>
</table>

NOTE. Negative change scores indicate worsening quality of life.
Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; BSC, best supportive care; SD, standard deviation.

*P value from Wilcoxon test between cetuximab and best supportive care arms.

P = .062; Fig 2B). Figures 2C to 2D demonstrate that patients on cetuximab had a longer time to deterioration when patients with KRAS wild-type were compared with mutated status for both PF (5.7 v 3.4 months; P = .01) and GHS (5.7 v 4.7 months; P = .01). No differences were seen by KRAS status in the BSC arm.

Change Scores at 8 and 16 Weeks in Other Scales and Domains

Exploratory comparisons of mean change scores of all other scale and single items at 8 and 16 weeks found statistically significant differences between patients in the cetuximab arm and BSC arm, respectively, in the following scales and items at 8 weeks (each favored cetuximab): role function (−5.0 v −12.7; P = .02), fatigue (1.2 v 8.2; P = .002), nausea (0.7 v 6.2; P = .007), pain (−0.9 v 8.4; P < .001), dyspnea (0.7 v 7.8; P = .005), sleep (−1.6 v 4.3; P = .033), financial impact (−4.5 v 2.0; P < .001); and at 16 weeks: role function (−7.5 v −23.8; P < .001), social function (−3.9 v −11.3; P = .04), fatigue (2.3 v 15.8; P < .001), nausea (0.9 v 11.3; P = .001), pain (1.1 v 13.6; P = .007), dyspnea (1.6 v 23.0; P < .001), appetite (−1.8 v 13.3; P < .001), and constipation (0.5 v 11.4; P = .02). No other differences were found.

HRQL Response Analysis

Overall HRQL response during the entire study was assessed comparing the cetuximab versus the BSC alone arm for each evaluation. All results favored the cetuximab arm, and a statistically significantly higher proportion of patients experienced improvements in at least one time point in pain (47% v 27%; P < .001), fatigue (41% v 31%; P = .04), nausea (22% v 16%; P = .01), dyspnea (22% v 13%; P = .04), and financial impact (23% v 14%; P = .003).

Analysis by KRAS status demonstrated that a higher proportion of patients with wild-type compared to mutated-KRAS status on cetuximab had improvement in GHS (40 v 19%; P = .01) and sleep (36 v 23%; P = .03). For patients in the BSC arm, KRAS wild-type status was associated with higher emotional function (P = .01) and lower financial impact (P = .04).

Correlation Between HRQL Response and Objective Tumor Response

Patients with objective tumor response and disease control were significantly more likely to have improvement in HRQL than patients with progressive disease for the following scales or items: PF, social functioning, GHS, pain, fatigue, nausea and vomiting, appetite, and diarrhea, as listed in Table 3.

DISCUSSION

Treatment with cetuximab resulted in superior HRQL compared with BSC alone. Patients who received cetuximab experienced significantly less HRQL deterioration and a longer time before clinically significant deterioration occurred. These results are important, because—although cetuximab monotherapy in heavily pretreated patients with advanced CRC results in improved OS, PFS, RR, and DCR—the magnitude of these benefits across the entire study population (ie, non–KRAS selected) was not large. Although toxicity was considered manageable, more grades 3 to 4 adverse events were recorded on the cetuximab arm compared with the BSC-alone arm,5 which needs to be considered in any deliberation regarding use of cetuximab in this setting. Patient-reported outcomes provide important information in addition to clinician-graded toxicities.21,22 HRQL results inform patients’ and clinicians’ treatment choices, particularly in advanced cancer settings. Patients and clinicians value HRQL results as part of informed decision making in oncology.23–26 Thus, our prospective analysis confirms the palliative benefits of this therapy.
This study is the first, to our knowledge, to demonstrate that selection for cetuximab therapy by wild-type KRAS status predicts for meaningful HRQL benefits. Patients with mutated KRAS status did not achieve HRQL benefits from cetuximab compared with BSC alone. However, those with wild-type KRAS status were able to maintain their HRQL with cetuximab. These HRQL findings are supportive of the improved survival and increased RR reported in the patients with wild-type KRAS status who received cetuximab.

The HRQL benefits seen in this study were statistically and clinically significant. It has been demonstrated previously that a 10% change in HRQL scores represents a perceptible and meaningful change to patients.\(^{17,18}\) In keeping with their later trajectory in the disease course, patients on CO.17 had poorer baseline HRQL scores compared with patients in other studies of advanced CRC. In another study of patients with CRC and liver metastases, some of whom were potential candidates for metastectomy, the mean baseline GHS scores were 71.7 to 79.0 (compared with 60.6 to 62.7 on CO.17), and the mean baseline PF scores were 78.3 to 87.8 (compared with 76.0 to 77.6 on CO.17).\(^{27}\) The baseline scores on CO.17 confirm that this was a population in whom disease was affecting HRQL and for whom HRQL benefits might be particularly important.

Missing data is a challenge in HRQL studies,\(^{17,28,29}\) particularly in the advanced-disease setting. This occurred in CO.17, as we sought to collect HRQL questionnaires beyond disease progression. Questionnaire compliance dropped over time, and a disproportionate level of missing data was on the BSC arm. There was also a slightly higher rate of missing data in patients with mutated versus wild-type KRAS on the cetuximab arm with no differences by KRAS status on the BSC arm (data not shown). It is clear that there are systematic differences in compliance between the treatment groups and that HRQL data were not simply missing at random.

It is important to assess the likely causes of such systematic differences, the direction, and the magnitude of bias that may result.\(^{30}\) We know that the patients in the BSC arm had worse PFS and OS. It is plausible that the patients in the BSC arm were doing more poorly medically and, thus, were less able to complete questionnaires, as has...
been found in other studies.\textsuperscript{26,31} It may be that the HRQL differences demonstrated in CO.17 are conservative. The true differences may be of greater magnitude, as the BSC arm may have had a worse HRQL than we were able to measure, as supported by our sensitivity analyses.

Because cetuximab is associated with a prominent and obvious rash, blinding was not attempted. This could bias patients’ subjective HRQL measurements. Bias could result if those on cetuximab were more likely to report HRQL improvements because they perceived they were receiving active treatment, resulting in a placebo effect. Conversely, those on BSC may have been more likely to report worsening HRQL. It is reassuring that multiple study end points (OS, PFS, RR, and across HRQL) all point to improvements with cetuximab. Our results are additionally strengthened by a priori, clinically driven, primary and secondary HRQL hypotheses.\textsuperscript{32,33} The biologic plausibility of a real HRQL effect is strengthened by the demonstration that improvements in HRQL were more likely in patients who achieved disease response. The strongest evidence that these HRQL benefits were not placebo-related comes from the findings of benefits limited to the wild-type KRAS population. At the time of the study, neither the patients nor the investigators knew the patients’ tumor mutational statuses or the clinical importance of this factor.

In conclusion, CO.17 has demonstrated that cetuximab offers clinically important survival and HRQL benefits for pretreated patients with advanced CRC. These benefits are even greater in magnitude when cetuximab use is restricted to patients with wild-type KRAS status. Cetuximab should be considered for all suitable patients who have advanced CRC with wild-type KRAS tumors. Additional research is needed to determine the best timing in the disease course to offer this treatment and whether it should be given as monotherapy, in combination with chemotherapy, or possibly with other biologics.

### Table 3. Health-Related Quality of Life Improvement According to Best Tumor Response

<table>
<thead>
<tr>
<th>Health-Related Quality-of-Life Domain/Scale</th>
<th>Best Tumor Response</th>
<th>CR + PR (n = 19)*</th>
<th>SD (n = 107)*</th>
<th>PD (n = 246)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Physical</td>
<td>4</td>
<td>21.05</td>
<td>29</td>
<td>27.10</td>
</tr>
<tr>
<td>Social</td>
<td>7</td>
<td>36.84</td>
<td>47</td>
<td>43.93</td>
</tr>
<tr>
<td>Global health status</td>
<td>11</td>
<td>57.89</td>
<td>42</td>
<td>39.62</td>
</tr>
<tr>
<td>Pain</td>
<td>10</td>
<td>52.63</td>
<td>57</td>
<td>54.29</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>63.16</td>
<td>51</td>
<td>48.11</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>4</td>
<td>21.05</td>
<td>22</td>
<td>20.75</td>
</tr>
<tr>
<td>Appétite loss</td>
<td>8</td>
<td>42.11</td>
<td>41</td>
<td>38.88</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>5.26</td>
<td>21</td>
<td>19.81</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*No. of patients who had a response and at least one change score for the global health status. Numbers for other domains or items may vary by one to three patients because of missing data.

†P values were calculated with Fisher’s exact test of complete, partial, or stable response vs progressive disease.

### Author Contributions

**Conception and design:** Heather-Jane Au, Chris J. O’Callaghan, Dongsheng Tu, Malcolm J. Moore, Derek J. Jonker

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**Expert Testimony:** None
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