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Original Research

Association of quality of life with disease characteristics and treatment outcomes in patients with advanced gastric cancer: Exploratory analysis of RAINBOW and REGARD phase III trials

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Ramucirumab;
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Abstract ***Background:*** Inadequate understanding of interpretation of quality of life (QoL) instruments leads to unsatisfactory data reporting and clinical decision-making, including in gastric cancer care.

Materials and methods: Pooled QoL data from two phase III studies of ramucirumab with or without paclitaxel in previously treated patients with gastric or gastroesophageal junction cancer were used to explore associations with clinical attributes, including tumour response, disease measurability and performance status (PS). The European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 was used in both studies. Changes in QLQ-C30 scores from baseline to week 6 as a predictor of clinical outcomes and impacts of changes in clinical status on QoL were estimated by multivariate logistic regression and analyses of variance, respectively.

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Results: Baseline QoL data were available for 989 patients. Fatigue, pain and appetite loss were prominent baseline symptoms. Disease progression resulted in worse QoL in all functional scales ($p < 0.0001$ to $p = 0.0306$), global QoL ($p = 0.0011$) and symptom scales (fatigue, $p < 0.0001$; nausea/vomiting, $p = 0.0007$; pain, $p = 0.0052$; appetite loss, $p = 0.0061$). Similar trends were seen with deterioration of PS on QoL. A 15- to 20-point change in global QoL and functional scale scores predicted change in tumour status as did change in fatigue, pain and appetite loss scores. Smaller QoL changes (5–15 points) predicted PS change. Results were similar in patients regardless of baseline disease measurability.

Conclusions: Our study underscores the importance of disease control for maintaining or improving QoL. These data could improve future trial design and routine clinical care for patients receiving therapy for previously treated gastric cancer. NCT00917384, NCT01170663.

1. Introduction

When evaluating anti-cancer therapy for patient benefit, overall survival (OS) has been regarded as the most relevant end-point in phase III randomised clinical trials (RCTs) [1]; however, assessing treatment potential can be challenging with multiple lines of therapy available. Tumour-related outcomes such as progression-free survival (PFS) and radiological objective response rate (ORR) may also be inadequate [2]. According to an individual patient data meta-analysis, PFS was not a valid surrogate for OS in advanced gastric cancer trials [3]. Many patients with advanced gastric cancer have non-measurable disease, such as peritoneal metastases or primary tumour only, so they are often not enrolled, or their data are not evaluable in studies in which the clinical end-point is ORR, requiring the presence of a measurable lesion [4–6]. This leads to systematic bias affecting generalisability of results.

Health-related quality of life (QoL) assessments are widely incorporated into phase III RCTs for solid tumours including gastric cancers [7,8]. However, poor understanding of interpretation of these instruments has meant that data were neither adequately captured nor translated into clinical decision-making [9]. In a systematic review of QoL reporting in gastric cancer trials, three-quarters of studies published between 1997 and 2017 were of limited (65%) or very limited (11%) quality [10], whereas second-line therapy and secondary publication of QoL data were significantly associated with better reporting quality [10]. The European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 is a well-established, self-reporting assessment for patients with cancer [11]. Baseline QLQ-C30 data have predicted survival in patients with advanced gastric cancer in both first-line and second-line settings [12,13]. Tumour-specific modules, such as the oesophagogastric cancer module (EORTC QLQ-OG25), were developed to supplement the QLQ-C30 [14]. During development of the EORTC QLQ-OG25, about 30% of patients had advanced disease with most having localised disease [14]; thus, using this specific module may be less relevant in advanced gastric cancer populations until after radical surgery.

Intuitively, clinicians associate disease progression with QoL deterioration and worsening symptoms. However, in a limited systematic review on solid tumours, only four studies assessed an association between disease progression and QoL: one in colorectal cancer, two in breast cancer and one in renal cell cancer [15]. PFS was significantly and positively associated with better QoL, with or without a decrease in disease-related symptoms. More recently, two studies found significant and clinically meaningful worsening of symptoms and QoL with disease progression in lung [16] and breast cancer [17]. No specific studies have evaluated this in advanced gastric cancer.

To address these knowledge gaps in gastric cancer, we used a pooled population from two global, placebo-controlled, phase III RCTs of ramucirumab alone or combined with paclitaxel of >1000 patients with previously treated gastric or gastroesophageal junction (GEJ) cancer [18,19]. We assessed 1) which QoL scales were most affected in gastric cancer patients starting second-line therapy; 2) which QoL scales were most impacted and what magnitude of change could be expected in patients who experienced disease progression compared to those who achieved disease stabilisation or objective response; 3) which QoL scales and magnitude of change could be expected with a change in performance status (PS); 4) which QoL scales were most impacted when patients experienced specific toxicities and 5) whether QoL corresponded to tumour status in patients with non-measurable compared to measurable disease.

2. Materials and methods

2.1. Data sources

REGARD (NCT00917384) and RAINBOW (NCT01170663) trials have been published previously [18,19]. Briefly, patients had Eastern Cooperative Oncology Group (ECOG) PS 0/1 and metastatic or non-resectable, locally recurrent/advanced, measurable or non-measurable gastric or GEJ cancer that had progressed despite platinum/fluoropyrimidine treatment. Treatments were ramucirumab versus placebo (REGARD) or paclitaxel plus ramucirumab versus paclitaxel plus placebo (RAINBOW). Patients completed the QLQ-C30 (version 3) at baseline and every 6 weeks while receiving study therapy. Disease measurability was assessed at baseline, and radiological tumour assessments were performed at baseline and every 6 weeks (Response Evaluation Criteria in Solid Tumours, version 1.0 for REGARD and version 1.1 for RAINBOW). PS was evaluated at baseline and before every cycle. Adverse events were collected at every visit, including severity grade as per the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.02.

The primary end-point was OS. Secondary end-points included PFS, ORR, QoL and safety. Each centre's institutional review board or ethics committee approved the study. The trials followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent. A brief summary of study outcomes is included in Supplementary Table 1.

Table 1
Patient and disease characteristics.

All patients (N = 1019)[a]	
Age, years	
Mean	59.6
Median (min, max)	61 (24–87)
Gender, male, n (%)	719 (70.6)
Race, n (%)	
White	678 (66.5)
Asian	287 (28.2)
Black or African American	18 (1.8)
American Indian or Alaska Native	2 (0.2)
Multiple	1 (0.1)
Other	33 (3.2)
Geographic region, n (%)[b]	
West	642 (63.0)
East and Southeast Asia	249 (24.4)
Rest of the world	128 (12.6)
ECOG PS, n (%)[c]	
0	358 (35.1)
1	661 (64.9)
Global QoL	
Mean (SD)	58.8 (22.0)
Primary tumour site, n (%)	
Gastric	792 (77.7)
Gastroesophageal junction	227 (22.3)
Disease measurability, n (%)	
Measurable	845 (82.9)
Non-measurable	174 (17.1)
Primary tumour present, n (%)	
Yes	678 (66.5)
No	341 (33.5)

[a] One patient was excluded from analysis due to missing disease measurability.
[b] Geographic region for RAINBOW = Asia; North America/Europe/Australia; Rest of the World; REGARD = Asia; North America/Europe/Australia/New Zealand; South and Central America/India/South Africa/Jordan/Egypt/Saudi Arabia/Lebanon.
[c] Only 1 patient had ECOG PS = 2 across both studies. This patient was combined with ECOG PS = 1 ECOG PS, Eastern Cooperative Oncology Group performance status; N, total population; n, number of patients; QoL, quality of life; SD, standard deviation.

2.2. Analytical approach

Associations between QLQ-C30 scales and radiologically assessed best overall response (BOR), PS, disease measurability and incidence of selected treatment-emergent adverse events (TEAEs) were explored. QoL data were scored using the EORTC QLQ-C30 scoring manual with all scales using a score of 0–100 [20]. Symptom scales were reversed, with higher scores representing better QoL. The financial difficulties item was not part of this analysis. Data from all treatment arms were pooled. Key end-points included change in QoL from baseline to week 6 as a predictor of clinical outcomes and effect of change in clinical status on QoL; analyses were limited to patients with both baseline and week 6 QoL data.

For most analyses, there were three clinical outcome groups for BOR: i) complete response (CR) plus partial response (PR), ii) stable disease (SD) and iii) progressive disease (PD) plus not evaluable. In analyses that included disease measurability as a dichotomous variable (measurable or non-measurable), SD was combined with CR plus PR. There were also three clinical outcome groups for PS: i) improvement by $\geq$1 levels, ii) no change and iii) worsening by $\geq$1 level. TEAEs were selected based on incidence (>15% in RAINBOW, the larger study, which had higher TEAEs rates [19]) and whether clinical symptoms would be evident to the patient. TEAEs chosen were neutropenia (grade $\geq$3), decreased appetite, fatigue, nausea, anaemia, alopecia, diarrhoea, abdominal pain, vomiting, pyrexia and neuropathy. Occurrence of TEAEs was classified as 'yes' if present at week 6 or 'no' if the TEAE either resolved before or had onset after week 6.

To assess change in QoL (week 6 compared to baseline) as a predictor of clinical outcomes, odds ratios (ORs) were estimated using covariate-adjusted logistic regression for BOR groups, PS outcome groups, and selected TEAE occurrence per QoL unit (point). The clinical outcome (i.e. BOR, PS or TEAE) was the

ordered response variable, and QoL change from baseline was the independent variable in the logistic regression model. Covariates included treatment arm, geographic region and 12 clinical and laboratory factors previously identified as significant prognostic factors for OS [21]. In these analyses, ORs <1 indicated that worsening in QoL was associated with poorer clinical outcome, and improvement in QoL was associated with better clinical outcome. To achieve statistical significance of clinical relevance, ORs should be ≤0.85 with the 95% confidence interval (CI) not including 1.

Analysis of covariance and analysis of variance were used to assess how change in clinical status affected QoL. All p-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline and QLQ-C30 completion rates

Of the 1020 randomised patients in REGARD and RAINBOW, one patient with unknown disease measurability status was excluded from these analyses. Table 1 shows baseline demographics. Baseline QLQ-C30 data were provided by 989 patients (>95% of patients in each study) and were similar in both trials. Of the patients still on study at week 6, >85% provided QLQ-C30 data in each study.

Based on mean scores at baseline, the highest levels of impairment were reported for global QoL, fatigue, pain and appetite loss. A summary of baseline QLQ-C30 scores by PS showed worse QoL for patients with PS ≥ 1 for all scales except diarrhoea (Fig. 1a). No identifiable differences in baseline QLQ-C30 scores were seen among patients based on disease measurability (Fig. 1b).

3.2. QoL changes associated with PS changes

Changes in PS were associated with statistically significant differences in changes in most QoL scales, including global QoL, all functional scales and some symptoms (Fig. 2). For all scales, positive changes in QoL were directly associated with improved PS, and deteriorated QoL was directly associated with worsened PS. Mean changes in QoL were approximately <5 points for patients with no change in PS.

Estimates of ORs characterising QoL changes from baseline to week 6 as predictors of PS changes are shown in Table 2. For all scales, ORs <1 indicated that worsened QoL may be associated with worsened PS. Based on the pre-specified criteria, changes in most scales predicted PS changes. The physical functioning scale appeared to have the closest relationship, with only a 5-point change (OR: 0.83; 95% CI: 0.78–0.88) needed to predict a change in PS. Of the other functional scales with significant findings, changes of 10–15 points predicted PS changes.

3.3. QoL changes associated with BOR

In most QoL scales, including global QoL, all functional scales and some symptoms, BOR was associated with statistically significant differences in QoL changes (Fig. 3). For patients with BOR of PD, mean scores declined in all scales except diarrhoea. For patients with BOR of PR or CR, mean scores improved for global QoL, emotional functioning, pain, appetite loss and nausea/vomiting; all other scales declined by < 5 points. Mean changes in QoL for patients with BOR of SD were <5 points. Disease stabilisation or response appeared to maintain or improve QoL, whereas disease progression led to QoL deterioration.

Estimates of ORs characterising changes in QoL from baseline as predictors of BOR are shown in Table 3. For almost all scales, ORs <1 indicated that worsening in QoL may be associated with worse tumour response outcomes. Based on the pre-specified criteria, changes in most QLQ-C30 scales of 10–20 points predicted BOR.

Examining these associations by disease measurability (Fig. 4) demonstrated similar patterns of QoL

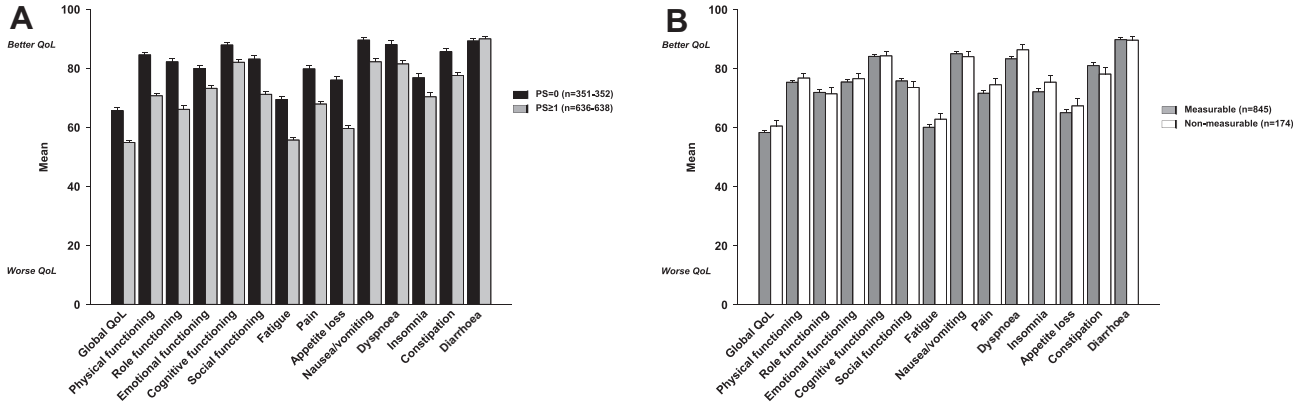

Fig. 1. QLQ-C30 scores by (a) ECOG PS and (b) disease measurability at baseline. ECOG PS, Eastern Cooperative Oncology Group performance status; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life.

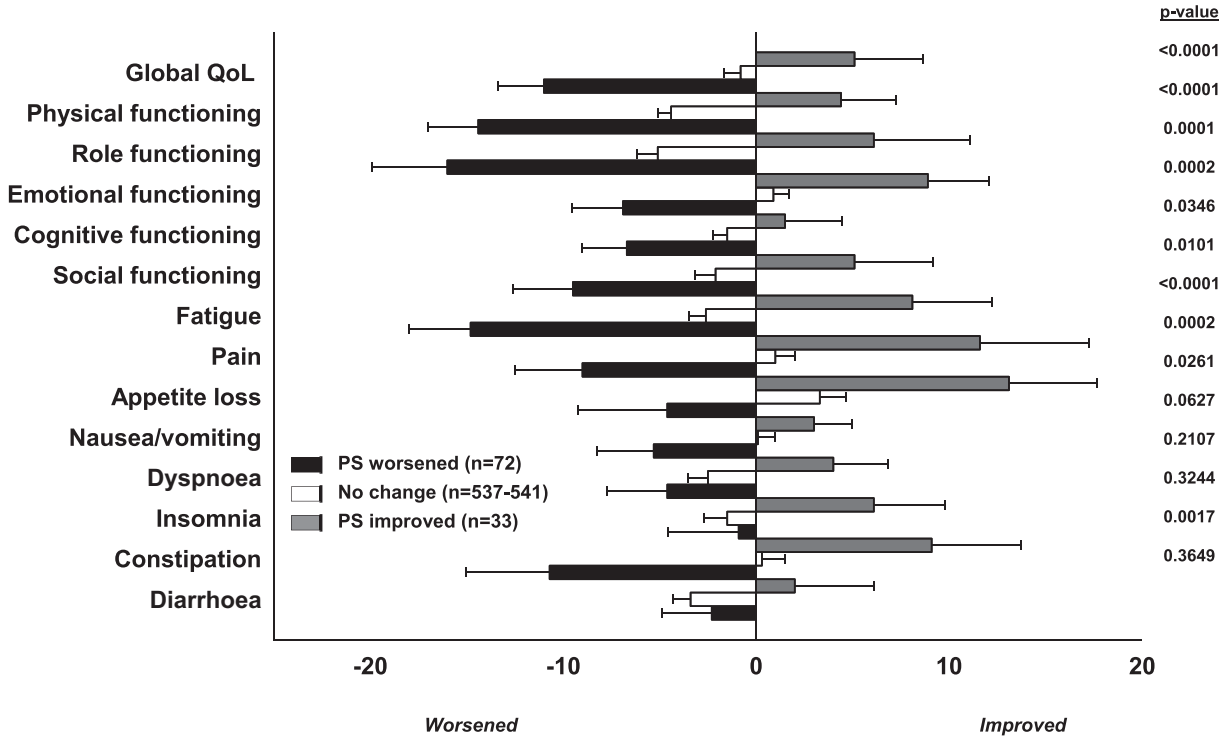

Fig. 2. Changes from baseline in QLQ-C30 scores by ECOG PS groups at week 6. ECOG PS, Eastern Cooperative Oncology Group performance status; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life.

changes. PD was associated with QoL declines in patients with measurable or non-measurable disease, and patients with non-measurable disease showed greater declines in fatigue and appetite loss. Improvement in appetite loss was seen in patients with a BOR of at least SD, regardless of disease measurability.

3.4. QoL changes associated with selected TEAEs

Statistically significant associations between changes in QoL and occurrence of TEAEs are summarised in Table 4. When changes in QoL were classified by the presence or absence of each selected TEAE, statistical differences

Table 2
Odds ratio by unit change from baseline in QLQ-C30 at Week 6 for ECOG PS group.

OR (95% CI[a]) for unit change from baseline at week 6 in QLQ-C30 score				
QLQ-C30 scale	5-point change	10-point change	15-point change	20-point
Global QoL	0.90 (0.85–0.95)	0.81 (0.72–0.90)[b]	0.72 (0.61–0.86)	0.65 (0.52–0.81)
Physical functioning	0.83 (0.78–0.88)[b]	0.69 (0.60–0.78)	0.57 (0.47–0.69)	0.47 (0.36–0.61)
Role functioning	0.91 (0.87–0.95)	0.83 (0.76–0.90)[b]	0.75 (0.66–0.86)	0.69 (0.58–0.82)
Emotional functioning	0.90 (0.85–0.95)	0.80 (0.72–0.90)[b]	0.72 (0.61–0.85)	0.64 (0.51–0.81)
Cognitive functioning	0.93 (0.88–0.99)	0.87 (0.77–0.99)	0.81 (0.67–0.98)[b]	0.76 (0.59–0.97)
Social functioning	0.94 (0.89–0.98)	0.87 (0.80–0.96)	0.82 (0.71–0.94)[b]	0.76 (0.64–0.92)
Fatigue	0.87 (0.83–0.92)	0.76 (0.69–0.84)[b]	0.67 (0.57–0.78)	0.58 (0.47–0.71)
Pain	0.92 (0.88–0.96)	0.84 (0.77–0.92)[b]	0.77 (0.67–0.88)	0.70 (0.59–0.84)
Appetite loss	0.96 (0.93–1.00)	0.93 (0.87–1.00)	0.90 (0.81–0.99)	0.86 (0.75–0.99)
Nausea/vomiting	0.92 (0.87–0.98)	0.85 (0.76–0.95)[b]	0.79 (0.67–0.93)	0.73 (0.58–0.90)
Dyspnoea	0.96 (0.92–1.01)	0.93 (0.84–1.02)	0.89 (0.78–1.03)	0.86 (0.71–1.04)
Insomnia	0.99 (0.95–1.03)	0.97 (0.90–1.05)	0.96 (0.85–1.08)	0.95 (0.81–1.11)
Constipation	0.93 (0.90–0.97)	0.87 (0.81–0.94)	0.81 (0.73–0.91)[b]	0.76 (0.65–0.88)
Diarrhoea	0.98 (0.93–1.03)	0.96 (0.86–1.06)	0.94 (0.80–1.09)	0.91 (0.75–1.12)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life.

[a] 95% CI that does not include 1 indicates $p < 0.05$ significance level.

[b] Interpretation: The lowest point change at which an association becomes statistically significant; OR $\leq$0.85 is considered meaningful. An OR = 0.85 indicates that a patient with an increase of x units in QLQ-C30 will be 15% less likely to be worsened versus stable or 15% less likely to be stable versus improved in ECOG PS.

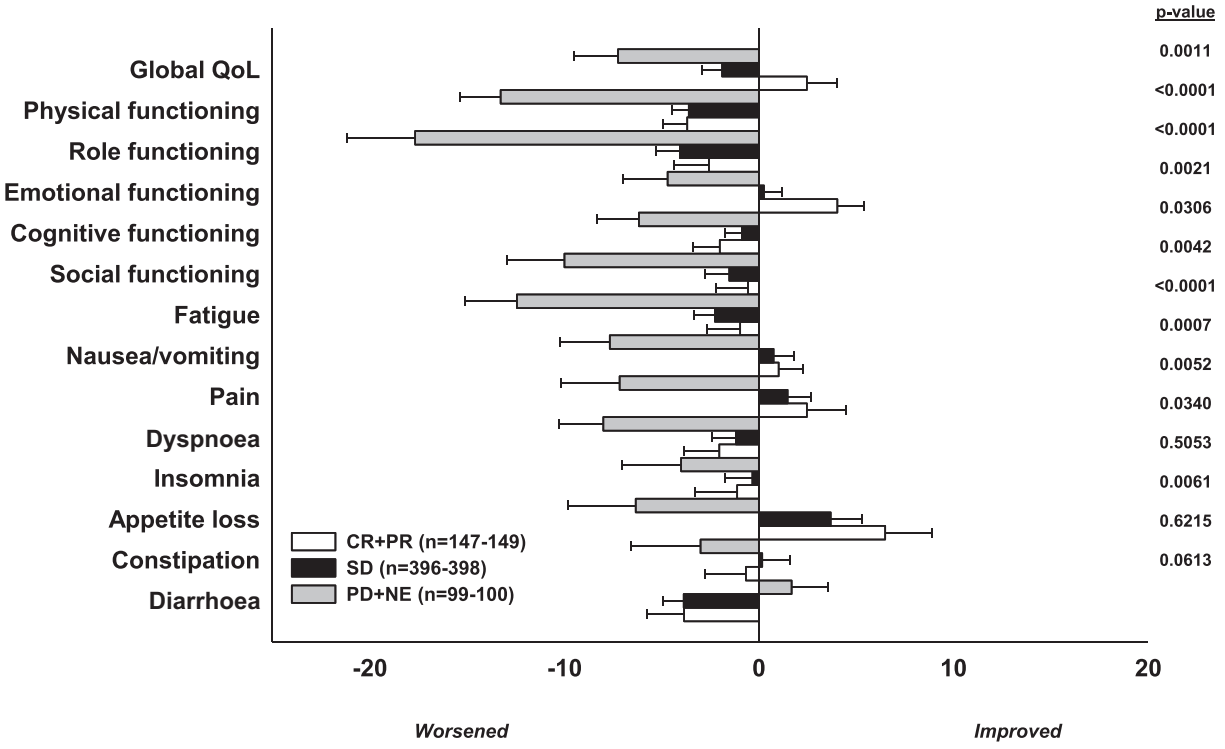

Fig. 3. Changes from baseline in QLQ-C30 scores by best overall response at week 6. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life; SD, stable disease.

Table 3
Odds ratio by unit change from baseline in QLQ-C30 at week 6 for best overall response group.

OR (95% CI[a]) for unit change from baseline at week 6 in QLQ-C30 score				
QLQ-C30 scale	5-point change	10-point change	15-point change	20-point
Global QoL	0.92 (0.88–0.96)	0.85 (0.78–0.92)[b]	0.78 (0.69–0.88)	0.72 (0.61–0.84)
Physical functioning	0.93 (0.88–0.97)	0.86 (0.78–0.94)	0.79 (0.69–0.91)[b]	0.73 (0.61–0.89)
Role functioning	0.94 (0.91–0.97)	0.88 (0.83–0.94)	0.83 (0.75–0.91)[b]	0.78 (0.68–0.88)
Emotional functioning	0.94 (0.90–0.98)	0.88 (0.81–0.96)	0.83 (0.73–0.94)[b]	0.78 (0.66–0.92)
Cognitive functioning	0.98 (0.93–1.02)	0.96 (0.87–1.05)	0.94 (0.82–1.07)	0.92 (0.76–1.10)
Social functioning	0.96 (0.93–0.99)	0.92 (0.86–0.99)	0.89 (0.80–0.98)	0.85 (0.74–0.97)[b]
Fatigue	0[b]93 (0.90–0.97)	0.87 (0.81–0.94)	0.81 (0.73–0.91)[b]	0.76 (0.65–0.88)
Pain	0.96 (0.93–0.99)	0.92 (0.86–0.98)	0.88 (0.80–0.96)	0.84 (0.74–0.95)[b]
Appetite loss	0.96 (0.93–0.98)	0.91 (0.87–0.96)	0.87 (0.81–0.94)	0.83 (0.75–0.92)[b]
Nausea/vomiting	0.95 (0.91–0.99)	0.90 (0.83–0.97)	0.85 (0.75–0.96)[b]	0.81 (0.69–0.94)
Dyspnoea	0.98 (0.94–1.01)	0.95 (0.89–1.02)	0.93 (0.84–1.03)	0.90 (0.79–1.04)
Insomnia	1.00 (0.97–1.03)	1.00 (0.95–1.06)	1.00 (0.92–1.10)	1.01 (0.89–1.13)
Constipation	0.99 (0.97–1.02)	0.99 (0.94–1.04)	0.98 (0.90–1.07)	0.98 (0.88–1.09)
Diarrhoea	1.04 (1.00–1.08)	1.07 (1.00–1.16)	1.11 (1.00–1.25)	1.16 (0.99–1.34)

CI, confidence interval; CR, complete response; NE, not evaluable; OR, odds ratio; PD, progressive disease; PR, partial response; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life; SD, stable disease.

[a] 95% CI that does not include 1 indicates $p < 0.05$ significance level.

[b] Interpretation: The lowest point change at which an association becomes statistically significant; OR $\leq$0.85 is considered meaningful. An OR = 0.85 indicates that a patient with an increase of x units in QLQ-C30 will be 15% less likely to be PD/NE versus SD or 15% less likely to be SD versus CR/PR.

were seen in only a few QoL scales. Multiple QoL scales showed worsening when investigator-reported neuropathy was present. Investigator-reported decreased appetite was associated with worsened emotional functioning and patient-reported appetite loss and fatigue (Supplementary Fig. 1). Based on the pre-specified criteria, worsening in multiple QoL scales predicted the occurrence of investigator-reported decreased appetite (Supplementary Table 2). Worsening in most patient-reported symptoms predicted the presence of similar investigator-reported TEAEs.

4. Discussion

This study analysed the largest prospective QoL database of patients receiving second-line systemic therapy

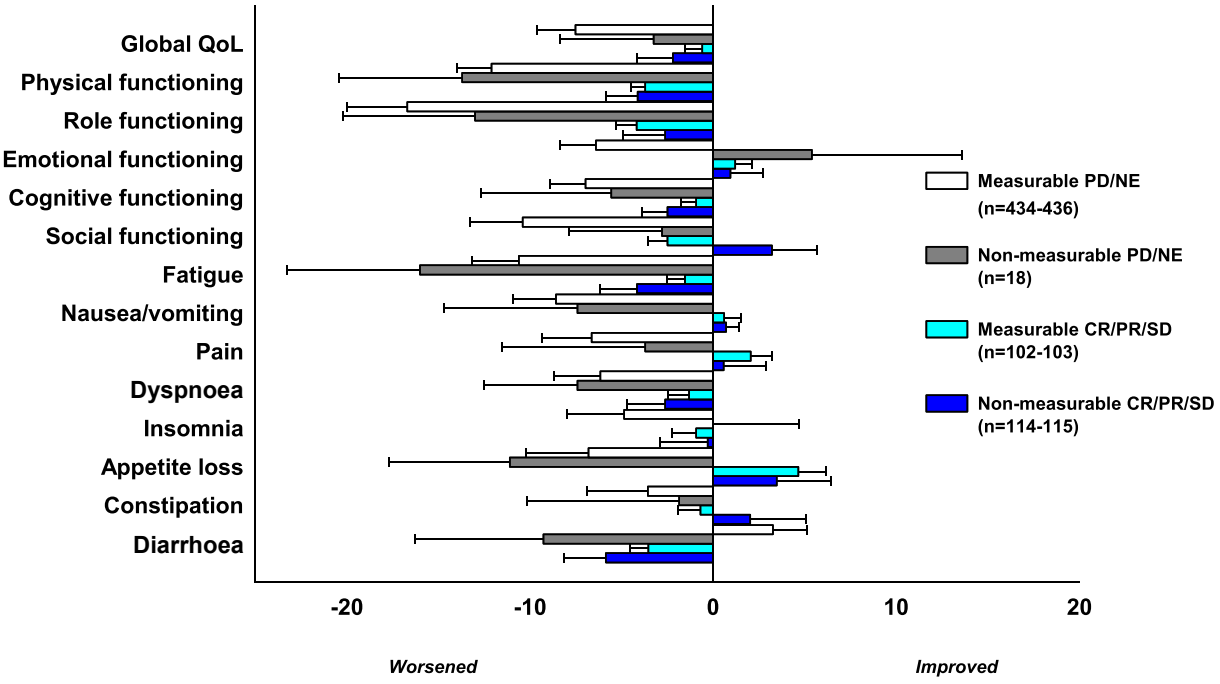

Fig. 4. Changes from baseline in QLQ-C30 scores by best overall response and by disease measurability at week 6. CR, PR and SD were combined per measurability variable; PR cannot be measured in a non-measurable disease setting, and thus all three outcomes were combined. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; QLQ-C30, Quality-of-Life Questionnaire-C30; QoL, quality of life; SD, stable disease.

for advanced gastric and GEJ cancer. At baseline, the most prominent patient-reported disease symptoms were fatigue, pain and appetite loss. Global QoL was more impaired than the functional scales. Predictably, patients with ECOG PS = 1 had worse QoL than patients with PS = 0 for almost all functional and symptom scales apart from diarrhoea. Whether patients had measurable or non-measurable disease did not impact baseline QoL, suggesting that radiologically assessed disease burden did not contribute entirely to patients' QoL. However, radiologically assessed disease progression resulted in worse QoL in all functional scales. In the second-line setting, disease stabilisation mirrored similar QoL to disease response. In future therapeutic development, achieving disease stabilisation might be a clinically meaningful goal based on QoL findings. Similar trends were seen with PS changes.

We further estimated the magnitude of changes in QoL scores associated with PS and BOR changes. As PS is a clinician's assessment of the patient's physical condition, unsurprisingly, a small change (5 points) in patient-reported physical functioning predicted a clinician-reported PS change, whereas larger changes (10–15 points) were required for global QoL and other functional scales. This suggests that PS assessment does not fully address all QoL concerns. For BOR, even larger changes (15–20 points) in global QoL and functional scale scores predicted a change in tumour status. Interestingly, similar to baseline QoL assessments, changes in fatigue, pain and appetite loss scores were the most relevant symptoms associated with tumour status change. These symptom changes may guide radiological assessment timing during routine clinical practice.

We observed an association between patient-reported symptoms and investigator-reported TEAEs, especially with decreased appetite and gastrointestinal TEAEs such as nausea, vomiting and diarrhoea. Thus, a more generic QoL instrument such as EORTC QLQ-C30 appeared to be sufficient for the assessment of important symptoms in advanced gastric cancer.

Modules for gastric or GEJ cancer include the QLQ-STO22, designed for gastric cancer [22], and the QLQ-OG25, developed to combine the QLQ-STO22 and the QLQ-OES18, a module for oesophageal cancer [23], into a single assessment for all oesophagogastric tumours [14]. The availability of these modules, however, does not necessarily translate into better assessment of patients. Studies on development and validation of the QLQ-STO22 and QLQ-OG25 included patients with gastric cancer of various disease stages undergoing different treatments [14,22,24], suggesting that the instruments may lack specificity for advanced disease. Another potential concern is the additional burden that a supplementary module may represent. Nevertheless, to the extent that data collected via these instruments can be associated with clinical outcomes, the EORTC modules can enhance use of QoL data to improve the development of treatments and patient care. A recent third-line study (INTEGRATE 1), enrolling patients with gastric and GEJ cancer, used the QLQ-C30 and the

Table 4
Association between changes from baseline in QLQ-C30 scores at week 6 and selected TEAEs.

Worsening in QLQ-C30 scale	Worsening in QoL predicted TEAEs OR ≤0.85 and 95% CI that does not include 1 based on logistic regression	TEAEs associated with changes in QLQ-C30 based on ANOVA, $p < 0.05$
Global QoL	Pyrexia (5 points)	–
Physical functioning	Decreased appetite (10 points)	Alopecia Neuropathy
Role functioning	Decreased appetite (15 points) Fatigue (20 points) Nausea (15 points) Diarrhoea (10 points)	Neuropathy
Emotional functioning	Decreased appetite (10 points)	Decreased appetite
	Nausea (10 points)	Neuropathy
Cognitive functioning	Decreased appetite (10 points)	Neutropenia (grade ≥3)
Social functioning	–	Neuropathy
Fatigue	Decreased appetite (10 points)	Decreased appetite
	Fatigue (15 points)	Neuropathy
Nausea/vomiting	Nausea (10 points) Vomiting (10 points)	Neuropathy
Pain	–	Fatigue Vomiting Abdominal pain
Dyspnoea	Anaemia (15 points)	Anaemia Abdominal pain
Appetite loss	Decreased appetite (15 points)	Decreased appetite
	Fatigue (15 points)	Neuropathy
Diarrhoea	Diarrhoea (5 points)	Anaemia Diarrhoea

ANOVA, analysis of variance; CI, confidence interval; OR, odds ratio; QoL, quality of life; TEAEs, treatment-emergent adverse events.

QLQ-STO22 [25]. Similar to our findings, fatigue, pain and appetite loss were common symptoms reported by this patient population, although body image was also considerably impaired and would not be captured with only the QLQ-C30.

A potential limitation of our study is that patients with disease progression before week 6 were excluded from change-from-baseline analyses. QoL data were also not available from all patients at the time of disease progression, and our analyses only considered the impact of one factor at a time. Although assessment of data from week 12 or later could also be informative, these may only represent select patients given that PFS for monotherapies is usually less than 4 months [26]. However, the large patient sample size and the prospective RCT nature of the studies in the same treatment setting represent important strengths.

In conclusion, fatigue, pain and appetite loss were important baseline symptoms for patients receiving second-line therapy for advanced gastric or GEJ cancer. Changes in patient-reported QoL were sensitive to changes in PS and tumour status, regardless of baseline disease measurability. For patients with non-measurable disease, QoL may be an additional tool to assess tumour status. Our study underscores the importance of disease control for maintaining or improving QoL of patients with advanced gastric cancer. Overall, our analysis provides important data to address inadequacies in the understanding of QoL in this patient population and to help improve future trial designs and routine clinical care, including the decision-making process for patients and the schedule of assessments.

Availability of data and materials

All data generated during the study are available at Eli Lilly.

Role of the funding source

This study was supported by Eli Lilly and Company, which collaborated with investigators on the design of the analyses as well as on the data collection, analysis and interpretation and the writing and preparation of this report.

Declaration of interest

Eli Lilly and Company supplied study medications and was the sponsor for the trials described herein.

Conflict of interest statement

I.C. reports receiving grant funding from Eli Lilly, Janssen-Cilag, Sanofi Oncology, Merck-Serono and Novartis; receiving honorarium from Taiho, Pfizer, Amgen and Eli Lilly and serving on an advisory board for Sanofi Oncology, Eli Lilly, Bristol Meyers Squibb, MSD, Bayer, Rocher and Five Prime Therapeutics. CF. reports a consulting role with Entrinsic Health, Genentech, Merck, Sanofi, Five Prime Therapeutics, Merrimack, Bayer, Agios, Taiho, Kew, Eli Lilly, CytomX and Bain Capital and receiving grant funding from the National Institutes of Health (grants P50 CA127003, RO1 CA118553, RO1 CA169141), the Lustgarten Foundation for Pancreatic Cancer Research and Stand Up To Cancer (SU2C) Colorectal Cancer Dream Team. AO. reports receiving grant funding from Bristol Meyers Squibb. A.B. declares no competing interest. A.L., Z.L.C. and Y.H. are all current employees and stockholders of Eli Lilly. S.E.A.B. reports an advisory role for Merck, Roche, Celgene, Eli Lilly and Nordic Pharma; ownership of IKF Klinische Krebsforschung GmbH and receiving grant funding from Sanofi, Merck, Roche, Celgene, Vifor, Medac, Hospira and Eli Lilly.

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Appendix A. Supplementary data

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