Abstract O-016

Associations of Quality of Life with Adverse Events and Tumor Response in Patients with Advanced Gastric Cancer: Exploratory Analyses from RAINBOW and REGARD

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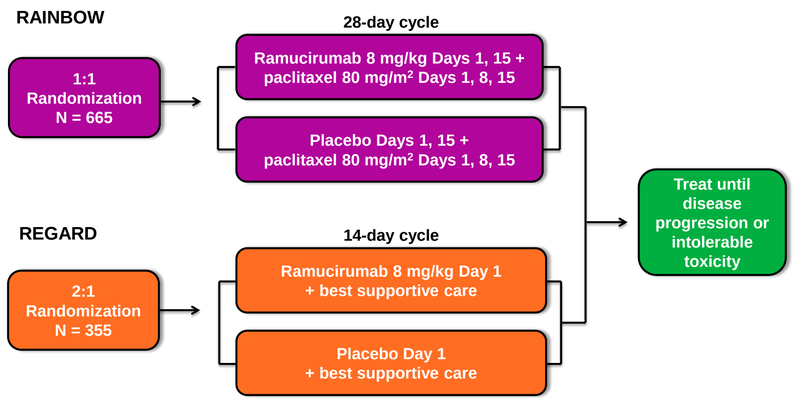
INTRODUCTION

- The European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 is a well-established Quality of Life (QoL) instrument for cancer patients, but information for gastric cancer is limited
  - Which QoL domains are most impacted in advanced gastric cancer?
  - What magnitude of change might be expected within these QoL domains?
- With no accepted standard for addressing these questions, we explored QoL changes relative to 2 clinical outcomes:
  1. Best overall response (BOR)
     - Complete Response + Partial Response vs. Stable Disease vs. Progressive Disease + Not Evaluable
  2. Treatment-emergent adverse events (TEAEs)
     - Using data from 2 phase 3 trials of ramucirumab in patients with previously treated gastric or gastroesophageal junction (GEJ) cancer
       - RAINBOW (NCT01170663)
       - REGARD (NCT00917384)

Figure 1. RAINBOW & REGARD Study Design[1,2]



- Primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), objective response rate, QoL, and safety
- Key eligibility factors:
  - Metastatic or non-resectable, locally advanced gastric or GEJ adenocarcinoma
  - Disease progression after first-line platinum- and/or fluoropyrimidine-containing chemotherapy
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1
  - Measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors
    - Version 1.1 in RAINBOW
    - Version 1.0 in REGARD

Table 1. RAINBOW & REGARD Efficacy Results[1,2]

	RAINBOW		REGARD	
Endpoint	**RAM + Pac n = 330**	**Pac n = 335**	**RAM n = 238**	**Placebo n = 117**
Median OS, months	9.6	7.4	5.2	3.8
Median PFS, months	4.4	2.9	2.1	1.3
Best overall response, n (%)				
Complete response	2 (< 1)	1 (< 1)	1 (< 1)	0
Partial response	90 (27)	53 (16)	7 (3)	3 (3)
Stable disease	172 (52)	159 (47)	108 (45)	24 (21)
Progressive disease	43 (13)	83 (25)	78 (33)	63 (54)
Not evaluable	23 (7)	39 (12)	44 (18)	27 (23)

Abbreviations: OS=overall survival; PFS=progression-free survival; Pac=paclitaxel; RAM=ramucirumab

METHODS

- Data from all treatment arms were pooled due to similar eligibility criteria and study assessments
  - Patients completed the EORTC QLQ-C30 v3.0 at baseline and every 6 weeks while on study
  - Radiologic scans were conducted at baseline and every 6 weeks to assess response
  - Adverse events, including severity grade per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.02, regardless of relationship to study drug, were collected at every visit
- QoL data were scored using the EORTC QLQ-C30 Scoring Manual with all scales/items reported with a score of 0 to 100
  - For interpretation of these analyses, higher scores represent better QoL
- Two analysis approaches:
  1. Change in QoL as predictor of clinical events
     - Odds ratios (ORs) for BOR groups (response vs. stable disease vs. other) and selected TEAE occurrence (yes vs. no) per QoL unit (point) change from baseline were estimated by logistic regression adjusted for baseline covariates and stratified by treatment and geography
       - Changes in QoL scale/item scores ≤ 20 points (in 5-point increments) were evaluated
       - OR ≤ .85 with *P* < .05 was considered meaningful
  2. Change in QoL based on change in clinical status
     - Using analysis of variance (ANOVA), changes in QoL scale/item scores from baseline were compared based on BOR group and occurrence of selected TEAEs
       - *P* < .05 was considered statistically significant
- Other considerations:
  - TEAEs selected based on incidence (> 15% in RAINBOW) and clinical symptoms evident to patient
    - Neutropenia (Grade ≥ 3)
    - Decreased appetite
    - Fatigue
    - Nausea
    - Anemia
    - Alopecia
    - Abdominal pain
    - Diarrhea
    - Vomiting
    - Pyrexia
    - Neuropathy
  - Presented results are limited to changes in QoL scale/item scores at Week 6 in order to maximize sample size
    - TEAEs were only classified as "yes" if present at Week 6 (i.e., TEAEs that resolved before Week 6 or with onset after Week 6 were classified as "no")

RESULTS

Table 2. Demographics and Baseline Clinical Characteristics

All Patients (N = 1019)[a]		All Patients (N = 1019)[a]	
Sex, n (%)		**Geographic region, n (%)[b]**	
Female	300 (29.4)	West	642 (63.0)
Male	719 (70.6)	East and Southeast Asia	249 (24.4)
Age (years)		Rest of World	128 (12.6)
Mean	59.6	**ECOG PS, n (%)[c]**	
Median (min, max)	61 (24, 87)	0	358 (35.1)
Disease measurability, n (%)		≥ 1	661 (64.9)
Measurable	845 (82.9)	**Primary tumor site, n (%)**	
Non-measurable	174 (17.1)	Gastric	792 (77.7)
Race, n (%)		GEJ	227 (22.3)
American Indian or Alaska Native	2 (0.2)	**Primary tumor present, n (%)**	
Asian	287 (28.2)	Yes	678 (66.5)
Black or African American	18 (1.8)	No	341 (33.5)
Multiple	1 (0.1)		
White	678 (66.5)		
Other	33 (3.2)		

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; GEJ=gastroesophageal junction; max=maximum; min=minimum
[a] One patient was excluded from analysis due to missing disease measurability
[b] Geographic region for RAINBOW=Asia; North America/Europe/Australia; Rest of 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, combined this patient with the ECOG PS = 1

- Baseline clinical characteristics were generally similar between studies (except for geography and race)

RESULTS (cont.)

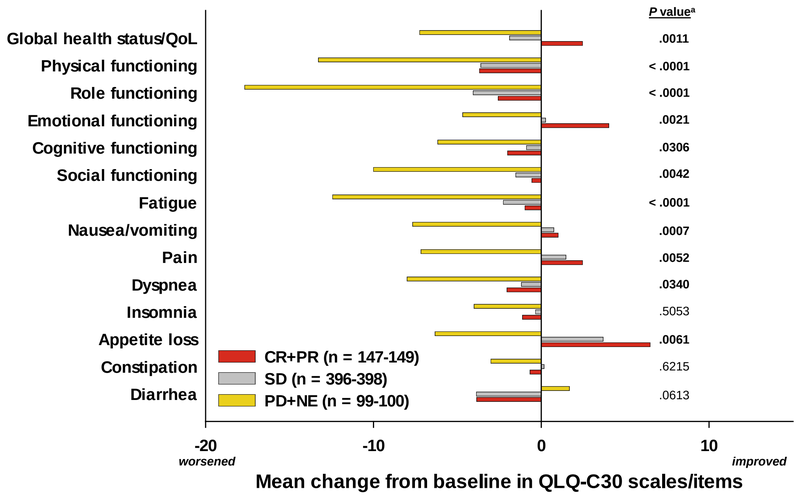
Table 3. Changes in QoL Scales/Items as Predictors of Best Overall Response

	OR (95% CI)[a] for Unit Change from Baseline at Week 6 in QLQ-C30 Scale/Item			
QLQ-C30 Scale/Item	**5-point**	**10-point**	**15-point**	**20-point**
Global health status/QoL	0.92 (0.88, 0.96)	**0.85 (0.78, 0.92)**	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)**	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)**	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)**	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)**
Fatigue	0.93 (0.90, 0.97)	0.87 (0.81, 0.94)	**0.81 (0.73, 0.91)**	0.76 (0.65, 0.88)
Nausea/vomiting	0.95 (0.91, 0.99)	0.90 (0.83, 0.97)	**0.85 (0.75, 0.96)**	0.81 (0.69, 0.94)
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)**
Dyspnea	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)
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)**
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)
Diarrhea	1.04 (1.00, 1.08)	1.07 (1.00, 1.16)	1.11 (1.00, 1.25)	1.16 (0.99, 1.34)

OR < 1 indicates that a worsening in the QoL scale/item score predicts a worse BOR outcome
Red values indicate smallest unit change with OR ≤ .85 and P < .05
[a] 95% CI that does not include 1 indicates P < .05 significance level
Abbreviations: BOR=best overall response; CI=confidence interval; OR=odds ratio; QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life

- Changes of 10 to 20 points in many scales/items distinguished among BOR groups

Figure 2. Changes in QoL Scales/Items by Best Overall Response



[a] Bold indicates statistical significance
Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life; SD=stable disease

- Disease progression was associated with significant declines in most QLQ-C30 scales/items
- Stable disease and response to treatment were associated with some improvements in a few QoL scales/items, particularly appetite loss

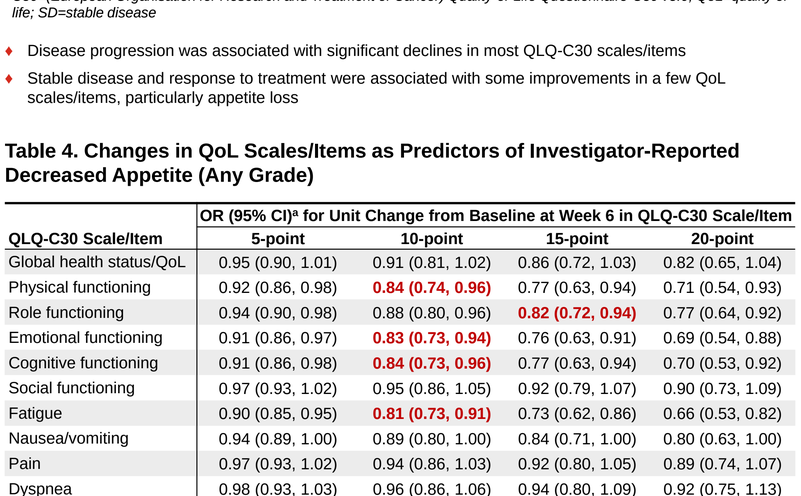
Table 4. Changes in QoL Scales/Items as Predictors of Investigator-Reported Decreased Appetite (Any Grade)

	OR (95% CI)[a] for Unit Change from Baseline at Week 6 in QLQ-C30 Scale/Item			
QLQ-C30 Scale/Item	**5-point**	**10-point**	**15-point**	**20-point**
Global health status/QoL	0.95 (0.90, 1.01)	0.91 (0.81, 1.02)	0.86 (0.72, 1.03)	0.82 (0.65, 1.04)
Physical functioning	0.92 (0.86, 0.98)	**0.84 (0.74, 0.96)**	0.77 (0.63, 0.94)	0.71 (0.54, 0.93)
Role functioning	0.94 (0.90, 0.98)	0.88 (0.80, 0.96)	**0.82 (0.72, 0.94)**	0.77 (0.64, 0.92)
Emotional functioning	0.91 (0.86, 0.97)	**0.83 (0.73, 0.94)**	0.76 (0.63, 0.91)	0.69 (0.54, 0.88)
Cognitive functioning	0.91 (0.86, 0.98)	**0.84 (0.73, 0.96)**	0.77 (0.63, 0.94)	0.70 (0.53, 0.92)
Social functioning	0.97 (0.93, 1.02)	0.95 (0.86, 1.05)	0.92 (0.79, 1.07)	0.90 (0.73, 1.09)
Fatigue	0.90 (0.85, 0.95)	**0.81 (0.73, 0.91)**	0.73 (0.62, 0.86)	0.66 (0.53, 0.82)
Nausea/vomiting	0.94 (0.89, 1.00)	0.89 (0.80, 1.00)	0.84 (0.71, 1.00)	0.80 (0.63, 1.00)
Pain	0.97 (0.93, 1.02)	0.94 (0.86, 1.03)	0.92 (0.80, 1.05)	0.89 (0.74, 1.07)
Dyspnea	0.98 (0.93, 1.03)	0.96 (0.86, 1.06)	0.94 (0.80, 1.09)	0.92 (0.75, 1.13)
Insomnia	0.97 (0.93, 1.01)	0.94 (0.86, 1.03)	0.91 (0.80, 1.04)	0.88 (0.74, 1.05)
Appetite loss	0.93 (0.90, 0.97)	0.87 (0.80, 0.93)	**0.81 (0.72, 0.90)**	0.75 (0.64, 0.87)
Constipation	0.96 (0.92, 1.00)	0.93 (0.86, 1.00)	0.89 (0.79, 1.00)	0.86 (0.73, 1.00)
Diarrhea	1.04 (0.98, 1.09)	1.07 (0.96, 1.20)	1.11 (0.94, 1.31)	1.15 (0.92, 1.44)

OR < 1 indicates that a worsening in the QoL scale/item score predicts investigator-reported decreased appetite
Red values indicate smallest unit change with OR ≤ .85 and P < .05
[a] 95% CI that does not include 1 indicates P < .05 significance level
Abbreviations: CI=confidence interval; OR=odds ratio; QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life

- Declines in most functioning scales and in the fatigue scale and appetite loss item predicted investigator-reported decreased appetite

Figure 3. Changes in QoL Scales/Items by Investigator-Reported Decreased Appetite (Any Grade)



[a] Bold indicates statistical significance
Abbreviations: QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life

- Incidence of investigator-reported decreased appetite was associated with worsened patient-reported emotional functioning and fatigue
- Absence of investigator-reported decreased appetite was associated with improved patient-reported appetite loss

Table 5. Changes in QoL Scales/Items as Predictors of Investigator-Reported Fatigue (Any Grade)

	OR (95% CI)[a] for Unit Change from Baseline at Week 6 in QLQ-C30 Scale/Item			
QLQ-C30 Scale/Item	**5-point**	**10-point**	**15-point**	**20-point**
Global health status/QoL	0.96 (0.91, 1.01)	0.92 (0.83, 1.02)	0.88 (0.76, 1.03)	0.85 (0.69, 1.04)
Physical functioning	0.95 (0.90, 1.01)	0.91 (0.81, 1.01)	0.86 (0.73, 1.02)	0.82 (0.65, 1.03)
Role functioning	0.95 (0.92, 0.99)	0.91 (0.84, 0.98)	0.87 (0.78, 0.97)	**0.83 (0.71, 0.96)**
Emotional functioning	0.96 (0.91, 1.01)	0.92 (0.83, 1.02)	0.89 (0.76, 1.03)	0.85 (0.69, 1.05)
Cognitive functioning	1.01 (0.95, 1.07)	1.02 (0.91, 1.14)	1.02 (0.87, 1.21)	1.03 (0.83, 1.29)
Social functioning	0.98 (0.94, 1.02)	0.96 (0.88, 1.04)	0.93 (0.83, 1.05)	0.91 (0.78, 1.07)
Fatigue	0.94 (0.90, 0.98)	0.88 (0.81, 0.96)	**0.83 (0.72, 0.95)**	0.78 (0.65, 0.93)
Nausea/vomiting	0.96 (0.92, 1.01)	0.93 (0.84, 1.02)	0.89 (0.77, 1.03)	0.86 (0.71, 1.04)
Pain	1.00 (0.96, 1.04)	0.99 (0.92, 1.07)	0.99 (0.88, 1.11)	0.99 (0.85, 1.15)
Dyspnea	0.97 (0.93, 1.01)	0.95 (0.87, 1.03)	0.92 (0.81, 1.05)	0.89 (0.75, 1.06)
Insomnia	0.99 (0.96, 1.03)	0.98 (0.91, 1.06)	0.97 (0.87, 1.08)	0.96 (0.83, 1.11)
Appetite loss	0.93 (0.90, 0.97)	0.87 (0.82, 0.93)	**0.82 (0.74, 0.90)**	0.76 (0.67, 0.87)
Constipation	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.94 (0.85, 1.04)	0.92 (0.80, 1.05)
Diarrhea	0.97 (0.93, 1.02)	0.94 (0.86, 1.03)	0.91 (0.79, 1.05)	0.89 (0.74, 1.07)

OR < 1 indicates that a worsening in the QoL scale/item predicts investigator-reported fatigue
Red values indicate smallest unit change with OR ≤ .85 and P < .05
[a] 95% CI that does not include 1 indicates P < .05 significance level
Abbreviations: CI=confidence interval; OR=odds ratio; QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life

- Declines in patient-reported role functioning, fatigue, and appetite loss predicted investigator-reported fatigue
- Mean changes in QoL scale/item scores were < 10 points, regardless of incidence of investigator-reported fatigue (data not shown)

Table 6. Changes in QoL Scales/Items as Predictors of Investigator-Reported Nausea (Any Grade)

	OR (95% CI)[a] for Unit Change from Baseline at Week 6 in QLQ-C30 Scale/Item			
QLQ-C30 Scale/Item	**5-point**	**10-point**	**15-point**	**20-point**
Global health status/QoL	0.94 (0.88, 1.00)	0.88 (0.77, 1.00)	0.82 (0.68, 1.00)	0.77 (0.60, 1.00)
Physical functioning	0.96 (0.89, 1.03)	0.92 (0.80, 1.05)	0.88 (0.71, 1.08)	0.84 (0.64, 1.11)
Role functioning	0.94 (0.90, 0.99)	0.89 (0.81, 0.98)	**0.84 (0.73, 0.97)**	0.80 (0.66, 0.95)
Emotional functioning	0.92 (0.87, 0.99)	**0.85 (0.75, 0.97)**	0.79 (0.65, 0.96)	0.73 (0.56, 0.95)
Cognitive functioning	0.99 (0.93, 1.07)	0.99 (0.86, 1.14)	0.98 (0.80, 1.21)	0.98 (0.74, 1.29)
Social functioning	0.97 (0.92, 1.02)	0.94 (0.85, 1.04)	0.91 (0.78, 1.06)	0.88 (0.72, 1.08)
Fatigue	0.95 (0.90, 1.01)	0.91 (0.81, 1.01)	0.86 (0.73, 1.02)	0.82 (0.66, 1.03)
Nausea/vomiting	0.89 (0.84, 0.94)	**0.79 (0.71, 0.89)**	0.71 (0.59, 0.84)	0.63 (0.50, 0.80)
Pain	0.98 (0.93, 1.03)	0.96 (0.87, 1.06)	0.94 (0.81, 1.09)	0.92 (0.76, 1.12)
Dyspnea	1.01 (0.95, 1.06)	1.01 (0.91, 1.13)	1.02 (0.86, 1.20)	1.02 (0.82, 1.27)
Insomnia	0.98 (0.94, 1.03)	0.97 (0.88, 1.06)	0.95 (0.83, 1.09)	0.93 (0.77, 1.12)
Appetite loss	0.96 (0.93, 1.00)	0.93 (0.86, 1.00)	0.89 (0.79, 1.00)	0.86 (0.73, 1.00)
Constipation	0.96 (0.92, 1.00)	0.93 (0.85, 1.01)	0.90 (0.79, 1.01)	0.86 (0.73, 1.02)
Diarrhea	0.98 (0.92, 1.04)	0.95 (0.85, 1.07)	0.93 (0.78, 1.11)	0.91 (0.72, 1.15)

OR < 1 indicates that a worsening in the QoL scale/item predicts investigator-reported nausea
Red values indicate smallest unit change with OR ≤ .85 and P < .05
[a] 95% CI that does not include 1 indicates P < .05 significance level
Abbreviations: CI=confidence interval; OR=odds ratio; QLQ-C30=(European Organisation for Research and Treatment of Cancer) Quality-of-Life Questionnaire-C30 v3.0; QoL=quality of life

- Declines in patient-reported role functioning, emotional functioning, and nausea/vomiting predicted investigator-reported nausea
- Mean changes in QoL scale/item scores were < 10 points, regardless of incidence of investigator-reported nausea (data not shown)

Other Findings

- Consistent associations using both approaches were observed for:
  - Anemia with patient-reported dyspnea
    - 15-point worsening in patient-reported dyspnea predicted incidence of anemia
    - Mean change in patient-reported dyspnea was -6 points versus -1 point for patients with anemia (*P* = .0128)
  - Investigator- and patient-reported diarrhea
    - 5-point worsening in patient-reported diarrhea predicted incidence of investigator-reported diarrhea
    - Mean change in patient-reported diarrhea was -9 points versus -1 point for patients with investigator-reported diarrhea (*P* = .0010)
- Neuropathy was associated with statistically significant differences in most of the functioning scales and with patient-reported fatigue, nausea/vomiting, and appetite loss, but changes in QoL scale/item scores did not predict incidence of neuropathy

Limitations

- Patients who had disease progression before Week 6 were not included in change-from-baseline analyses
- No adjustments were made for patients experiencing > 1 TEAE

CONCLUSIONS

- These 2 analysis approaches showed the most consistency in QoL changes for BOR and investigator-reported appetite loss
  - Disease progression was associated with declines in most QoL scales/items
  - Improvement in patient-reported appetite loss was associated with responding or stable disease and with absence of adverse events
- In this advanced gastric/GEJ cancer population, changes in clinical status were sensitive to changes in QLQ-C30 scores:
  - Changes in QoL scale/item scores of 10 to 20 points were associated with BOR
  - Changes in QoL scale/item scores of generally 10 to 15 points were associated with adverse events
- These results can be used to inform clinical trial designs and to manage patients in clinical practice

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