Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma†

S.-E. Al-Batran1*, E. Van Cutsem2, S. C. Oh3, G. Bodoky4, Y. Shimada5, S. Hironaka6, N. Sugimoto7, O. N. Lipatov8, T.-Y. Kim9, D. Cunningham10, P. Rougier11, K. Muro12, A. M. Liepa13, K. Chandrawansa14, M. Emig15, A. Ohtsu16 & H. Wilke17

1Institute of Clinical Cancer Research (IKF), UCT-University Cancer Center, Frankfurt, Germany; 2University Hospitals Gasthuisberg, Leuven, Belgium; 3Korea University Guro Hospital, Seoul, South Korea; 4Szent László Hospital, Budapest, Hungary; 5Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; 6Department of Clinical Trial Promotion, Chiba Cancer Center, Chiba, Japan; 7Department of Clinical Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; 8Izmirlar cosmetic and surgical oncology, Izmir, Turkey; 9Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; 10Royal Marsden Hospital, Sutton, UK; 11Hôpital Européen Georges Pompidou, Université Paris VI, Paris, France; 12Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; 13Eli Lilly and Company, Indianapolis, Indiana, USA; 14Bayer HealthCare, Whippany, NJ, USA; 15Eli Lilly and Company, Bad Homburg, Germany; 16Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Chiba, Japan; 17Department of Oncology, Klinikum Essen Mitte Center of Palliative Care, Muenster University Clinic, Essen, Germany

Received 4 September 2015; revised 17 November 2015; accepted 18 December 2015

Background: The phase III RAINBOW trial demonstrated that the addition of ramucirumab to paclitaxel improved overall survival, progression-free survival, and tumor response rate in fluoropyrimidine–platinum previously treated patients with
advanced gastric/gastroesophageal junction (GEJ) adenocarcinoma. Here, we present results from quality-of-life (QoL) and performance status (PS) analyses.

**Patients and methods:** Patients with Eastern Cooperative Oncology Group PS of 0/1 were randomized to receive ramucirumab (8 mg/kg i.v.) or placebo on days 1 and 15 of a 4-week cycle, with both arms receiving paclitaxel (80 mg/m²) on days 1, 8, and 15. Patient-reported outcomes were assessed with the QoL/health status questionnaires EORTC QLQ-C30 and EQ-5D at baseline and 6-week intervals. PS was assessed at baseline and day 1 of every cycle. Time to deterioration (TtD) in each QLQ-C30 scale was defined as randomization to first worsening of ≥10 points (on 100-point scale) and TtD in PS was defined as first worsening to ≥2. Hazard ratios (HRs) for treatment effect were estimated using stratified Cox proportional hazards models.

**Results:** Of the 665 patients randomized, 650 (98%) provided baseline QLQ-C30 and EQ-5D data, and 560 (84%) also provided data from ≥1 postbaseline time point. Baseline scores for both instruments were similar between arms. Of the 15 QLQ-C30 scales, 14 had HR < 1, indicating similar or longer TtD in QoL for ramucirumab + paclitaxel. Treatment with ramucirumab + paclitaxel was also associated with a delay in TtD in PS to ≥2 (HR = 0.798, P = 0.0941). Alternate definitions of PS deterioration yielded similar results: PS ≥ 3 (HR = 0.656, P = 0.0508), deterioration by ≥1 PS level (HR = 0.802, P = 0.0444), and deterioration by ≥2 PS levels (HR = 0.608, P = 0.0063). EQ-5D scores were comparable between treatment arms, stable during treatment, and worsened at discontinuation.

**Conclusion:** In patients with previously treated advanced gastric/GEJ adenocarcinoma, addition of ramucirumab to paclitaxel prolonged overall survival while maintaining patient QoL with delayed symptom worsening and functional status deterioration.

**ClinicalTrials.gov:** NCT01170663.

**Key words:** quality of life, gastric cancer, GEJ cancer, ramucirumab, EORTC QLQ-C30, EQ-5D

---

**introduction**

There were approximately 1.4 million new cases of gastric and gastroesophageal cancer worldwide in 2012 [1]. The associated 2012 mortality rate of 1.1 million [1] reflects the frequent late-stage detection and incurability of metastatic disease. While the majority of patients progress within 6 months following first-line therapy [2], many remain candidates for second-line treatment. Recent open-label phase III studies comparing single-agent, second-line taxanes or irinotecan versus best supportive care (BSC) have demonstrated incremental improvement in survival for patients with advanced gastric/gastroesophageal junction (GEJ) cancer [3–5]. Single-agent ramucirumab, a human IgG1 monoclonal antibody against the vascular endothelial growth factor receptor-2 (VEGFR-2), improved median survival for patients with advanced gastric/GEJ cancer versus BSC in the REGARD trial [6]. Ramucirumab prevents VEGF ligand binding to the VEGFR-2 and subsequent receptor-mediated pathway activation in endothelial cells, thus interfering with tumor-required angiogenesis, slowing its growth [7].

The RAINBOW trial [8] showed the addition of ramucirumab to second-line paclitaxel treatment extended median survival of advanced gastric/GEJ cancer patients by 2.3 months [9]. Median progression-free survival (PFS) was prolonged by 1.5 months, and tumor response rate and disease control rate were likewise improved.

Since advanced gastric/GEJ cancer is an incurable condition, treatments aim to not just prolong survival, but to maintain patients’ quality of life (QoL). Hence, the survival benefit observed in RAINBOW should also be considered along with the QoL of these patients treated with ramucirumab + paclitaxel.

While some data exist on QoL in the first-line setting [10, 11], QoL data associated with the second-line treatment are sparse. Docetaxel second-line therapy versus BSC was shown to maintain global QoL and to reduce some symptoms [5]. Previously reported results for the RAINBOW study indicated QoL was maintained during ramucirumab + paclitaxel treatment [8]. Additional RAINBOW analyses are presented here, detailing the impact of second-line ramucirumab + paclitaxel treatment on the QoL of advanced gastric/GEJ cancer patients.

**methods**

**study design**

The design of the global, randomized, double-blind phase III RAINBOW trial has been previously published [8] and is summarized in the supplement, available at Annals of Oncology online.

**patient-reported outcomes and performance status assessment**

Patient-reported outcomes (PROs) were assessed using the European Organisation for Research and Treatment of Cancer QoL questionnaire (EORTC QLQ-C30, version 3.0) [12] and the EuroQol five dimensions health status questionnaire (EQ-5D-3L) [13]. The EORTC QLQ-C30 is a self-administered, cancer-specific QoL instrument that assesses global health status, functioning, symptoms, and toxicities. The EQ-5D is a nonspecific and standardized instrument for self-reported health status. PROs were evaluated at baseline, every 6 weeks (±3 days) following the first dose of study therapy until radiographic documentation of progressive disease, and at the end-of-therapy visit. The PRO instruments were to be completed at the beginning of the clinic visit, before any extensive contact with investigative staff occurred.

Before every cycle, at the end of treatment, and at 30-day follow-up, Eastern Cooperative Oncology Group (ECOG) performance status (PS) [14] was evaluated.
statistical considerations

All analyses were based on the intent-to-treat population. For both PRO instruments, compliance at each assessment time point was defined as the number of patients who completed the PRO instrument divided by the expected number of patients at that time point; the expected number of patients at any postbaseline visit was equal to the number of patients who were alive and without disease progression.

The EORTC QLQ-C30 instrument was scored according to EORTC guidelines [15], such that all scales reported from 0 to 100, with higher functioning and global scores representing better QoL and higher symptom scores representing greater symptom burden. Prespecified analyses of response and time to deterioration (TtD) were carried out on the QLQ-C30 data. In these analyses, a change of at least 10 points in each of the scales was considered clinically meaningful [16]. Hence, the QLQ-C30 TtD was defined as the time from randomization to the first deterioration of ≥10 points from baseline. If no deterioration was observed, censoring occurred at the date of the last QLQ-C30 assessment. QLQ-C30 TtD was compared between the treatment arms using a log-rank test. The TtD hazard ratio (HR) and 95% confidence interval were estimated using the Cox proportional hazards model [17] with assigned treatment and baseline score as covariates. The impact of adjusting for independent baseline factors was also examined, considering those factors previously identified as significant for PFS in the RAINBOW population (gender, weight loss in prior 3 months, number of metastatic sites, and liver metastases) [8]. Sensitivity analyses using deteriorations of ≥5, 15, and 20 points were also carried out.

The QLQ-C30 response analysis characterized each postbaseline assessment as Improved or Deteriorated if change was ≥10 points, and Stable if change was <10 points for each of the scales. The proportion of patients in each treatment arm with Improved/Stable scores versus Deteriorated/Off-Study/No Data at each time point was compared using the Fisher’s exact test.

The EQ-SD index scores (calculated based on UK weights) [18] and the visual analog scale (VAS) scores were examined using summary statistics for each assessment time by treatment arm, including change from baseline.

ECOG PS TtD was defined as the time from the date of randomization to the date when ECOG PS score of ≥2 was observed for the first time; censoring occurred at the date of the last ECOG PS assessment if no deterioration was observed. ECOG PS TtD was compared between the treatment arms using a log-rank test and presented using Kaplan–Meier graphs. The HR was estimated using the Cox proportional hazards model. Additional analyses were carried out by using different definitions of deterioration and included a change in ECOG PS to ≥3, a change of ≥1 level from baseline, and a change of ≥2 levels from baseline.

Adjustments for multiplicity were not made in these analyses; however, a level of 0.05 was used as the threshold for presenting results.

results

The global, double-blind, phase III RAINBOW trial enrolled 665 patients: 330 randomized to ramucirumab + paclitaxel and 335 to the placebo + paclitaxel. The demographic, disease, and pretreatment characteristics were generally balanced between treatment arms and reflective of the population of patients with advanced gastric cancer enrolled in clinical trials (supplementary Table S1, available at Annals of Oncology online).

The completion rates of the QLQ-C30 were high, with 650 (98%) of patients completing at least one assessment. On the basis of expected assessments, percentage compliance was >80% at the early assessment times on both treatment arms (Table 1). The completion rates for the EQ-5D were nearly identical to those for QLQ-C30. The number of expected PRO instruments to be completed at each scheduled assessment decreased over time due to the decrease in the number of patients who remained on study therapy, more markedly in the placebo + paclitaxel arm.

As detailed in Table 2, baseline scores were similar in both treatment arms for the 15 QLQ-C30 scales and the EQ-5D instrument. The QLQ-C30 role functioning scale revealed a higher degree of baseline impairment than other functional scales. Likewise, fatigue, appetite loss, pain, and insomnia symptom scales showed that patients experienced these symptoms at baseline to a greater degree than other symptoms.

QLQ-C30 TtD analysis

The analysis of QLQ-C30 TtD data showed that QoL deterioration during the course of the study was delayed for patients on the ramucirumab + paclitaxel arm. HRs derived from comparing TtD assessments for each of the 15 QLQ-C30 outcomes were <1.

Table 1. EORTC QLQ-C30 compliance by scheduled assessment

| Time point (weeks) | Ramucirumab + paclitaxel (N = 330) | Placebo + paclitaxel (N = 335) |
|--------------------|-----------------------------------|--------------------------------|
|                    | No. of patients expected to complete QLQ-C30 | Compliance (%) | No. of patients expected to complete QLQ-C30 | No. of completed QLQ-C30 | Compliance (%) |
| 0 (Baseline)       | 330                               | 322 | 97.6 | 335 | 328 | 97.9 |
| 6                  | 280                               | 243 | 86.8 | 248 | 221 | 89.1 |
| 12                 | 200                               | 174 | 87.0 | 145 | 125 | 86.2 |
| 18                 | 143                               | 119 | 83.2 | 91  | 76  | 83.5 |
| 24                 | 93                                | 70  | 75.3 | 53  | 43  | 81.1 |
| 30                 | 76                                | 57  | 75.0 | 36  | 22  | 61.1 |
| 36                 | 50                                | 35  | 70.0 | 26  | 18  | 69.2 |

*Compliance at each assessment time point was defined as the number of patients who completed the QLQ-C30 divided by the expected number of patients at that time point. The expected number of patients at any postbaseline visit was equal to the number of patients who were alive and without disease progression.

*On both arms, failure to administer accounted for 30%–32% of the missing assessments; subject decision (too ill, too inconvenient, did not understand language, violation of privacy) accounted for 9%–14% of the missing assessments; 54%–61% of the assessments were missing for other, unspecified reasons.
Table 2. Summary of baseline QLQ-C30 and EQ-5D scores

|                  | Ramucirumab + paclitaxel (N = 330) | Placebo + paclitaxel (N = 335) |
|------------------|----------------------------------|---------------------------------|
|                  | n| Mean (SD) | n| Mean (SD) |
| QLQ-C30<sup>a</sup> | | | | |
| Global QoL/health status | 322 | 61.5 (22.0) | 326 | 58.0 (22.0) |
| Functional scales | | | | |
| Physical functioning | 322 | 76.9 (20.5) | 327 | 76.5 (20.8) |
| Role functioning | 322 | 71.8 (29.6) | 327 | 72.7 (29.3) |
| Emotional functioning | 322 | 75.7 (22.1) | 327 | 76.8 (21.9) |
| Cognitive functioning | 322 | 83.9 (18.7) | 327 | 84.0 (18.7) |
| Social functioning | 322 | 77.5 (26.5) | 326 | 73.8 (26.2) |
| Symptom scales | | | | |
| Fatigue | 322 | 39.1 (24.4) | 328 | 39.5 (23.9) |
| Nausea and vomiting | 322 | 14.1 (22.2) | 328 | 14.0 (21.4) |
| Pain | 322 | 27.2 (29.0) | 328 | 27.3 (27.8) |
| Dyspnea | 321 | 15.2 (23.7) | 328 | 16.3 (23.6) |
| Insomnia | 322 | 27.5 (29.8) | 327 | 26.4 (29.3) |
| Appetite loss | 322 | 34.7 (33.6) | 328 | 34.2 (32.4) |
| Constipation | 322 | 18.5 (26.8) | 327 | 21.7 (28.4) |
| Diarrhea | 322 | 10.5 (18.7) | 327 | 9.1 (18.9) |
| Financial impact | | | | |
| Financial difficulties | 322 | 23.9 (29.8) | 326 | 24.1 (31.2) |
| EQ-5D<sup>b</sup> | | | | |
| Index | 323 | 0.74 (0.23) | 323 | 0.73 (0.25) |
| VAS | 318 | 65.2 (20.9) | 324 | 63.2 (20.1) |

<sup>a</sup>Scores range 0–100. High scores represent better QoL for functional scales and global QoL/health status, and low scores represent less burden for symptom scales and financial impact. Few patients reported ceiling/floor effects that did not allow for deterioration. Rates were similar between arms.

<sup>b</sup>Index score range: −0.59 to 1; VAS score range 0–100, with high scores representing good health status.

QLQ-C30, quality-of-life questionnaire; EQ-5D, EuroQol five dimensions questionnaire; QoL, quality of life; SD, standard deviation; VAS, visual analog scale.

---

**Figure 1.** Time to deterioration in EORTC QLQ-C30 scales. Hazard ratios are shown for time to deterioration for each of the EORTC QLQ-C30 scales in the ramucirumab + paclitaxel group, when compared with the placebo + paclitaxel arm. Horizontal bars represent 95% confidence limits. CI, confidence interval; HR, hazard ratio; N, number of patients with deterioration; PBO, placebo; PTX, paclitaxel; RAM, ramucirumab.
patients classiﬁed as Off-study/No data than the ramucirumab + paclitaxel arm patients experienced ‘Stable’ or ‘Improved’ QoL parameters at each assessment, compared with placebo + paclitaxel patients. Comparison of the two treatment arms produced a \( P < 0.05 \) for all scales, at most time points. Among those patients that were classiﬁed as ‘Deteriorated’, the ramucirumab + paclitaxel arm had a greater percentage of patients—an issue addressed in the discussion. In the placebo arm, across all time points, each scale had a greater number of patients classiﬁed as Off-study/No data than the ramucirumab + paclitaxel arm patients. Among patients with a tumor response, there were higher percentages of stable/improved QLQ-C30 scores across all time points, regardless of treatment arm (data not shown).

**EQ-5D**

For both EQ-5D index and VAS, the mean baseline scores were similar between the treatment arms (Table 2). During the treatment period, the mean scores remained consistent with the baseline scores and comparable between the treatment arms; the change from baseline score was within ±0.05 for the index and within ±4.0 for the VAS for both arms (supplementary Figure S2, available at *Annals of Oncology* online). However, notable changes were observed at the end of treatment for both the index (supplementary Figure S2A, available at *Annals of Oncology* online) and the VAS (supplementary Figure S2B, available at *Annals of Oncology* online) for both of the treatment arms. These values were lower than the baseline indicating poorer health status at the time of treatment discontinuation.

**ECOG PS TtD analysis**

Treatment with ramucirumab + paclitaxel was associated with a delay in TtD of PS to \( \geq 2 \) (HR = 0.798, log-rank \( P = 0.0941 \)) (Figure 2A). Additional analyses were carried out using alternate deﬁnitions of PS deterioration with similar results: PS \( \geq 3 \) (HR = 0.656, \( P = 0.0508 \)), deterioration by \( \geq 1 \) PS level (HR = 0.802, \( P = 0.0444 \)), and deterioration by \( \geq 2 \) PS levels (HR = 0.608, \( P = 0.0063 \)) (Figure 2B–D). The analyses must be interpreted with caution due to the high censoring rate (\( \geq 50\% \)).

**Discussion**

This detailed analysis of the QoL and ECOG PS data from the RAINBOW study demonstrates that the survival beneﬁt associated with second-line ramucirumab + paclitaxel was achieved while maintaining the QoL of these patients with advanced gastric/GEJ adenocarcinoma.

The functioning (role functioning) and symptoms (pain, fatigue, appetite loss, and insomnia) scales are closely related to the advanced gastric/GEJ cancer disease state had the poorest baseline scores in the RAINBOW study. While baseline scores for these scales were comparable between the two treatment arms, the patients treated with ramucirumab + paclitaxel demonstrated a similar or longer TtD in the functioning and worsening of symptoms compared with the patients treated with placebo + paclitaxel. The symptoms of constipation and dyspnea, as well as ﬁnancial difﬁculties, had an HR close to 1 consistent with their limited relevance in the context of gastric/GEJ cancer, the interventions, and a clinical trial setting.

Diarrhea, an adverse event reported with the ramucirumab + paclitaxel combination, was the only QoL symptom with a non-favorable HR, an observation noted in other clinical trials. Since even low-grade diarrhea may have a negative impact on QoL [19], clinicians might well proactively inform patients of symptom management options.

At all on-therapy assessment time points, a higher percentage of patients in the ramucirumab + paclitaxel arm were classiﬁed as Improved/Stable compared with those in the placebo + paclitaxel arm for all QLQ-C30 parameters. Although the ramucirumab + paclitaxel arm generally had a greater percentage of patients classiﬁed as ‘Deteriorated’, the placebo + paclitaxel arm had a higher percentage of patients in the combined ‘Deteriorated/No data’ groups. The higher percentage of patients on the placebo arm in this combined grouping is due to the earlier discontinuation of treatment among placebo + paclitaxel arm patients compared with the ramucirumab + paclitaxel arm patients, in most cases due to disease progression. One can argue that those patients who discontinued likely had deteriorated QoL; hence, these discontinued patients without data at a given assessment time point could be considered more like those classiﬁed as ‘Deteriorated.’ Since such assumptions remain debatable in QoL research, and since patient attrition translates into a steady decline in available data, especially in the less-effective arm, QoL response analyses in rapidly progressing cancer patients should be interpreted with caution.

The analysis of TtD in PS corroborates that ramucirumab treatment maintains the health of patients for a longer period. Patients treated with ramucirumab + paclitaxel experienced a delay in TtD of PS over those treated with placebo + paclitaxel. The preservation of patients’ functional status is a key goal and may allow for them to receive further treatment and additional beneﬁt.

The EQ-5D results were consistent with other results in that they indicate that progressive disease has the greatest impact on QoL. However, as expected, this generic tool did not differentiate between treatment arms. Despite the limited usefulness of these data in clinical practice, health state utility data are worthwhile to collect and report for economic evaluations.
Patients with metastatic gastric/GEJ cancer seek to preserve their QoL during second-line treatment. The QLQ-C30 results presented here demonstrate that the combination of ramucirumab + paclitaxel prolongs survival while maintaining patient QoL, lengthening the TTD of symptoms and functions, and slowing PS deterioration. These robust and detailed QoL data could inform clinical decision making and provide patients with more detailed information about the functional and symptomatic impact of treatment. These results support the recommendation of paclitaxel + ramucirumab for previously treated gastric/GEJ cancer if a taxane is indicated and if there are no ramucirumab contraindications.

acknowledgements

The authors thank the patients, investigators, and institutions involved in this study. They also thank Jiangang Jameson Cai and Zhanghlin Cui for statistical analysis support, Anastasia Perkowski for editorial support, and Mary Dugan Wood for writing assistance.

funding

This work was supported by Eli Lilly and Company (there is no grant number). The study sponsor provided the study drug and collaborated with the investigators to design the study; collect, analyze, and interpret the data; and write this report. The corresponding author had access to study data, and all authors approved submission for publication.

disclosure

PR, HW, and S-E A-B report speaker honoraria and an Advisory Board position. EVC and S-E A-B report a Lilly commercial research grant. DC reports his institution receives funding from some non-Eli Lilly pharmaceutical companies. GB reports an Advisory Board position. YS reports speaker honoraria. AML and PR, HW, and S-E A-B report speaker honoraria and an Advisory Board position. EVC and S-E A-B report a Lilly commercial research grant. DC reports his institution receives funding from some non-Eli Lilly pharmaceutical companies. GB reports an Advisory Board position. YS reports speaker honoraria. AML and
ME are employees of Eli Lilly and Company. KC was an employee of Eli Lilly when this work was performed. All remaining authors have declared no conflicts of interest.

references

1. Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr, accessed on 16 May 2015.

2. Price TJ, Shapiro JD, Segelov E et al. Management of advanced gastric cancer. Expert Rev Gastroenterol Hepatol 2012; 6: 199–209.

3. Thuss-Patience PC, Kretzschmar A, Bichev D et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011; 47: 2306–2314.

4. Kang JH, Lee SI, Lim DH et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012; 30: 1513–1518.

5. Ford HER, Marshall A, Bridgewater JA et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15: 78–86.

6. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224–1235.

7. Spratlin JL, Cohen RB, Eadens M et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010; 28: 780–787.

8. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a global, phase III randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy. J Clin Oncol 2014; 32(suppl 3): abstr LBA7.

9. Al-Batran SE, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. Cancer 2010; 116: 2511–2518.

10. Saloh T, Bang YJ, Gotovkin EA et al. Quality of life in the trastuzumab for gastric cancer trial. Oncologist 2014; 19: 712–719.

11. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365–376.

12. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199–208.

13. Oken MM, Creech RH, Torney DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655.

14. Fayers PM, Aaronson NK, Bjordal K et al. on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual, 3rd Edition. European Organisation for Research and Treatment of Cancer. Brussels: EORTC, 2001. ISBN: 2-9300 64-22-6.

15. Osoba D, Rodrigues G, Mylès J et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139–144.

16. Cox DR, Snell EJ. Analysis of Binary Data, 2nd edition. Chapman & Hall: London, 1989.

17. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35: 1095–1108.

18. Al-Batran SE, Hozaeel W, Tauchert FK et al. The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoLTax). Ann Oncol 2015; 26: 1244–1248.